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## VOLUME DELLE RELAZIONI, COMUNICAZIONI ORALI E POSTER

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# INDICE

## RELAZIONI

# I farmaci antinfiammatori

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I pazienti con malattia renale cronica (CKD) presentano un rischio cardiovascolare che può essere elevato, molto elevato oppure "estremo". Incidenza e prevalenza di eventi cardiovascolari (CV), infatti, sono significativamente più alte nei pazienti con stadio di CKD dal primo al quinto, in maniera progressivamente crescente ed ulteriormente amplificata dalla presenza di albuminuria o franca proteinuria. Questo è vero a tale punto che la causa principale di morte nella popolazione nefropatica è la malattia CV e non quella renale in fase terminale [1].

In questo contesto, la CKD è nota per causare l'insorgenza uno stato pro-infiammatorio che – a sua volta – è in grado di innescare e contribuire in modo significativo al processo aterogenetico. In accordo con questo assunto, negli ultimi anni l'inibizione della flogosi è stata identificata come un obiettivo chiave nella prevenzione CV, mentre diversi studi hanno dimostrato l'efficacia di varie strategie dirette contro diversi mediatori pro-infiammatori. Cardine terapeutico di molti tra questi studi è la colchicina, il cui bersaglio è l'inflammasoma NLRP3. Al dosaggio di 0.5 oppure 1 mg/die l'assunzione orale di colchicina è associata ad una riduzione significativa dell'incidenza di infarto del miocardio, ictus ischemico e mortalità CV in pazienti con patologia coronarica [2]. In accordo con ciò, le evidenze emerse dagli studi randomizzati e controllati COLCOT (mostrato nella figura sottostante), COPS, LoDoCo e LoDoCo2, in cui sono stati arruolati complessivamente oltre 10.000 pazienti, hanno portato all'inserimento della colchicina nell'aggiornamento del 2021 delle raccomandazioni ESC per la prevenzione CV [3].

Questo anche se la mortalità per tutte le cause non sembra essere influenzata in maniera consistente dalla colchicina. Gli studi che abbiamo citato, pertanto, indicano certamente una strada, assai promettente anche per la stessa colchicina, ma anche che il percorso da fare è ancora denso di interrogativi.

Nella stessa direzione – affascinante, ma ancora da illuminare in diversi angoli bui – d'altra parte, vanno i dati dello studio CANTOS. In questo studio, infatti, è stato studiato un anticorpo monoclonale diretto verso l'IL-1β (canakinumab), con una protezione vascolare tanto evidente quanto proporzionale all'entità della riduzione dei livelli di IL-6 e di hsPCR ottenuta grazie al trattamento [4,5[]. Malgrado questo brillante risultato, le infezioni gravi erano significativamente più comuni nel braccio canakinumab rispetto a quello placebo. Pertanto, pur rilevando una riduzione delle neoplasie fatali canakinumab versus placebo (p=0.02), persistono taluni dubbi sulla sua sicurezza nel lungo periodo.

Per tutta questa serie di motivi, grande speranza ed immensa attesa è rivolta all'inibizione diretta di IL-6 operata da ziltivekimab, anticorpo monoclonale che – a differenza delle molecole attualmente in uso per il trattamento di patologie infiammatorie croniche quali l'artrite reumatoide (tocilizumab e sarilumab) – è diretto contro il ligando dell'IL-6 e non contro il recettore dell'IL-6 o la stessa citochina. Questo tipo di azione – se si vuole più "discreto" – permetterebbe di massimizzare i benefici anti-aterogenetici e minimizzare gli effetti negativi già visti con canakinumab e metotressato. In accordo con ciò, nello studio randomizzato e controllato di fase 2 RESCUE sono già stati valutati

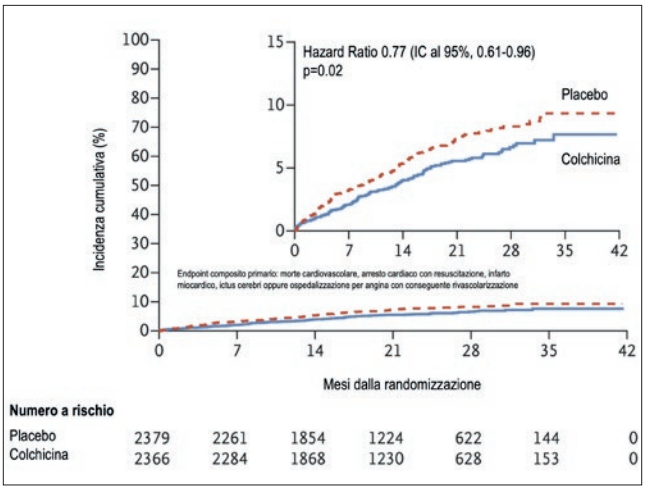


**Figura:** Studio Colchicine Cardiovascular Outcomes Trial (COLCOT). Il trattamento con colchicina riduce in maniera significativa l'endpoint composito primario versus placebo in pazienti reduci da un recente (30 giorni) infarto miocardico.

gli effetti di ziltivekimab (somministrato per via sottocutanea ogni 4 settimane) in una popolazione affetta da CKD e con elevati livelli di hsPCR. L'outcome primario, la modifica della PCR ad alta sensibilità a 12 settimane, è stato raggiunto pienamente, con una riduzione mediana del 77% nel gruppo che assumeva ziltivekimab al dosaggio di 7,5mg, all'88% nel gruppo che assumeva 15mg ed al 92% nel gruppo che assumeva 30 mg rispetto al placebo (riduzione del 4%) [6]. Tali riduzioni si mantenevano per tutte le 24 settimane di follow-up. Dal punto di vista della sicurezza, non sono stati riportati eventi avversi gravi e gli eventi avversi lievi erano sovrapponibili tra trattamento attivo e trattamento con placebo. Pertanto, visti i risultati del RESCUE è stato progettato un nuovo studio (ZEUS, NCT05021835), rivolto ai pazienti con malattia CV, elevati livelli di hsPCR e CKD. Outcome composito primario sarà il tempo al primo episodio cardiovascolare maggiore (morte cardiovascolare, infarto miocardico non fatale o ictus non fatale).

In conclusione, le evidenze sul ruolo ateroprotettivo di alcuni farmaci anti-infiammatori sono sin qui incoraggianti, ma anche gravate da diversi dubbi, soprattutto relativi alla sicurezza. Il paziente nefropatico, in questo senso, è particolarmente "fragile", caratterizzato come è da un misto di difetto nella risposta immune ed attivazione della flogosi pro-aterogenetica [7]. Auspicabilmente, nel prossimo futuro saranno proprio questi pazienti quelli che trarranno i maggiori benefici dalla correzione del cosiddetto rischio infiammatorio [8].

**Bibliografia**


1. Jankowski J., Floege J., Fliser D, Böhm M, Marx N; Cardiovascular disease in chronic kidney disease: pathophysiological insights and therapeutic options; Circulation 2021,143:1157-1172
2. Samuel M., Tardif J.C., Bouabdallaoui N., Khairy P., Dubé M.P., Blondeau L. et al; Colchicine for secondary prevention of cardiovascular disease: a systematic review and meta-analysis of randomized controlled trials; Can J Cardiol 2021,37:776–785
3. Visseren F.L.J., Mach F., Smulders Y.M., Carballo D., Koskinas K.C., Bäch M., et al; 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice; Eur Heart J 2021,42:3227-3337
4. Ridker P.M., Everett B.M., Thuren T, MacFayden J.G., Chang W.H. Ballantyne C., et al; CANTOS Trial Group; Antiinflammatory therapy with canakinumab for atherosclerotic disease; N Engl J Med 2017,377:1119–1131
5. Ridker P.M., MacFayden J.G., Everett B.M., Libby P., Thuren T, Glynn R.J., CANTOS Trial Group; Relationship of C-reactive protein reduction to cardiovascular event reduction following treatment with canakinumab: a secondary analysis from the CANTOS randomised controlled trial; Lancet 2018,391:319–328
6. Ridker P.M., Devalaraja M., Baeres F.M.M., Engelmann M.D.M., Hovingh G.K., Ivkovic M., et al; IL-6 inhibition with ziltivekimab in patients at high atherosclerotic risk (RESCUE): a double-blind, randomised, placebo-controlled, phase 2 trial; Lancet 2021, 397: 2060–2069
7. Piscitani L., Del Pinto R., Basili A., Tunno M., Ferri C. Humoral Immune Response to COVID-19 Vaccination in hemodialysis patients: a retrospective, observational case-control pilot study; High Blood Press Cardiovasc Prev 2022,29:163-167
8. Del Pinto R., Pietropaoli D., Monaco A., Desideri G., Ferri C., Grassi D. Non-pharmacological strategies against systemic inflammation: molecular basis and clinical evidence; Curr Pharm Des 2020,26:2620-2629

# RAASi/ARNi nel HFrEF: quali scelte e perché

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L'inibizione del sistema renina-angiotensina-aldosterone (RAAS) rappresenta sin dai primi anni '90 un caposaldo del trattamento farmacologico dello scompenso cardiaco a ridotta frazione d'eiezione (HFrEF). Diversi studi hanno infatti dimostrato come l'impiego di farmaci inibitori del RAAS sia in grado di ridurre la mortalità per cause cardiovascolari e i ricoveri per scompenso cardiaco [1,2].

Più recentemente lo scenario terapeutico è stato integrato dalla disponibilità di una nuova classe farmacologica che combina l'inibizione del RAAS, tramite il blocco del recettore per l'angiotensina II, a quella della neprilisina, potenziando gli effetti vasodilatatori, natriuretici, antifibrotici dei peptidi natriuretici atriali. Nello studio "proof-of-concept" PARADIGM-HF il sacubitril/valsartan, il prototipo della classe farmacologica degli ARNi (angiotensin receptor-neprilysin inhibitors), ha dimostrato infatti una superiorità in termini di riduzione del 20% dell'outcome composito di mortalità cardiovascolare e scompenso cardiaco rispetto all'ACE inibitore enalapril ed on top della terapia standard dello scompenso cardiaco [3].

L'efficacia del sacubitril/valsartan è stata confermata in maniera indipendente dall'età, dal sesso, dalla provenienza geografica, dall'eziologia dello scompenso cardiaco e dall'impiego di altri farmaci in associazione, sia in pazienti ambulatoriali che ospedalizzati per una riacutizzazione di scompenso cardiaco [4,5]. Inoltre, il sacubitril/valsartan ha dimostrato una tollerabilità sovrapponibile a quella di ACE inibitori ed ARB, in assenza di un aumento significativo di end-point di sicurezza quali insufficienza renale ed iperpotassiemia, ad eccezione di un'incidenza leggermente più elevata di ipotensione [4,5].

Sulla base di questi risultati, sin dal 2016 le Linee Guida Europee hanno introdotto l'impiego del sacubitril/valsartan nel trattamento del HFrEF, anche se come farmaco di seconda-terza linea in pazienti già in trattamento con un ACE inibitore o un ARB [6].

Le più recenti Linee Guida del 2021 hanno rivoluzionato l'algoritmo terapeutico nella gestione del HFrEF, prevedendo l'impiego del sacubitril/valsartan come farmaco di prima scelta già nelle prime fasi del trattamento anche in pazienti "de-novo", in associazione con un beta-bloccante, un antagonista dei recettori per i mineralocorticoidi e un inibitore di SGLT2 [7]. Questo tipo di approccio basato sull'impiego di farmaci in grado di migliorare gli outcome di malattia e con effetti sinergistici ha pertanto sostituito il precedente concetto di introduzione "stepwise" dei farmaci, guidata soprattutto dalla persistenza di sintomi [7]. In maniera concorde, anche le Linee Guida Americane del 2021 indicano il sacubitri/valsartan come terapia di prima linea nei pazienti con HFrEF, raccomandando l'impiego di ACE inibitori e ARB nel caso in cui il trattamento con ARNi non venga tollerato[8].

Nonostante questo tipo di raccomandazioni, solo una percentuale limitata di pazienti con HFrEF (34-76% a seconda dei registri) riceve al momento una terapia con ARNi [9].

Un grande sforzo deve essere compiuto dalla comunità medica per implementare l'utilizzo di strategie terapeutiche sempre più efficaci nel ridurre i principali outcome nei pazienti affetti da HFrEF, evitando inerzia terapeutica e sospensioni troppo affrettate dei trattamenti in corso.

Per rendere possibile l'introduzione e la titolazione della terapia con sacubitri/valsartan può essere consigliata la riduzione del dosaggio di tutti quei farmaci che non influenzano il decorso del HFrEF e che viceversa hanno effetti sui valori di pressione arteriosa, quali calcio-antagonisti, diuretici e nitroderivati [2,4].

**Bibliografia**

1. Basso N, Terragno NA. History about the discovery of the renin-angiotensin system. Hypertension. 2001 Dec 1;38(6):1246-9
2. Filardi PP, Paolillo S, Indolfi C, Agostoni P, Basso C, Barillà

F, et al. Position paper della Società Italiana di Cardiologia: Il blocco del sistema renina-angiotensina-aldosterone (RAAS) nel paziente con scompenso cardiaco – Parte I: Dalla scoperta del RAAS ai trial clinici [Position paper of the Italian Society of Cardiology: The renin-angiotensin-aldosterone system (RAAS) blockade in heart failure patients - Part I: From RAAS identification to clinical trials]. G Ital Cardiol (Rome). 2022 Mar;23(3):217-228.

3. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al; PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014 Sep 11;371(11):993-1004
4. Volpe M, Bauersachs J, Bayés-Genís A, Butler J, Cohen-Solal A, Gallo G, et al. Sacubitril/valsartan for the management of heart failure: A perspective viewpoint on current evidence. Int J Cardiol. 2021 Mar 15;327:138-145
5. Gallo G, Volpe M, Battistoni A, Russo D, Tocci G, Musumeci MB. Sacubitril/Valsartan as a Therapeutic Tool Across the Range of Heart Failure Phenotypes and Ejection Fraction Spectrum. Front Physiol. 2021 Aug 23;12:652163
6. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al.; ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016 Jul 14;37(27):2129-2200
7. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al.; ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021 Sep 21;42(36):3599-3726
8. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022 May 3;145(18):e895-e1032
9. Simpson J, Benson L, Jhund PS, Dahlström U, McMurray JJV, Lund LH. "Real World" Eligibility for Sacubitril/Valsartan in Unselected Heart Failure Patients: Data from the Swedish Heart Failure Registry. Cardiovasc Drugs Ther. 2019 Jun;33(3):315-322

# Variazioni di uricemia come effetto ancillare di farmaci cardiovascolari e prognosi CV: una lezione da imparare?

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La stretta associazione tra l'aumento dei livelli sierici di acido urico (SUA) e l'incidenza di innumerevoli patologie cardiovascolari e non quali l'insufficienza cardiaca, l'ipertensione arteriosa sistemica, la malattia renale cronica e il diabete mellito tipo II è ormai nota e ampiamente documentata dalla letteratura scientifica attualmente disponibile. Il valore oltre al quale si osserva un aumento dell'incidenza di patologie cardiovascolari risulterebbe addirittura inferiore (5.0 mg/dL negli uomini e 4.5 mg/dL nelle donne) rispetto alla soglia limite utilizzata classicamente nella patologia gottosa [1]. A tale valore statico, tuttavia, sta progressivamente subentrando un parametro dinamico, ovvero la variabilità dei valori di SUA nel tempo: nel lavoro di Tian et al. si evince come vi sia non solo un'associazione lineare tra il valore basale di SUA e il rischio di mortalità per tutte le cause (HR 1.42, 95% CI, 1.20-1.60; $p < 0.0001$), ma che dal quartile di popolazione con la minor variabilità di SUA a quello con la variabilità maggiore vi sia un aumento significativo del rischio di mortalità per tutte le cause da 6.71 a 8.19 su 1000 individui ogni anno ($p < 0.0001$) [2]. È interessante notare come il rischio di mortalità per tutte le cause aumenti sia nei soggetti con ampie diminuzioni dei livelli di SUA (HR 1.28, 95% CI, 1.14-1.44) sia nei soggetti con cospicui aumenti di SUA (HR 1.18, 95% CI, 1.05-1.32). Risulta dunque fondamentale che i clinici ricordino in che modo innumerevoli farmaci utilizzati nella terapia di pazienti affetti da malattie cardiovascolari esercitino, in maniera differente, un effetto sui livelli di SUA, come riportato di seguito: i farmaci ACE inibitori e i bloccanti del recettore dell'angiotensina possiedono un blando effetto uricosurico; anche gli inibitori della neprilisina hanno un effetto analogo e inibiscono inoltre la sintesi di urato; i beta bloccanti possiedono effetti inconsistenti su tale versante, mentre i diuretici come i tiazidici e lo spironolattone aumentano i livelli di SUA, interferendo con la clearance renale dell'acido urico [3]. Nello studio LIFE [4] viene comparata l'efficacia di losartan vs atenololo nel prevenire l'incidenza di fibrillazione atriale in una popolazione di ipertesi; il protocollo prevedeva la misurazione dei livelli di SUA alla prima visita e successivamente ad ogni follow-up annuale: la variazione temporale dei livelli di SUA è risultata essere un forte predittore dell'incidenza di fibrillazione atriale (HR 1.19 per 1 mg/dL, 95% CI, 1.12-1.26, $p < 0.0001$), indipendentemente dall'effetto protettivo conferito dal sartano. Il losartan si è dimostrato infatti efficace, rispetto all'atenololo, nel ridurre del 33% l'incidenza di FA con simili risultati in termine di valori pressori (HR 0.75, 95% CI, 0.61-0.93, $p = 0.007$). Anche l'aumento dei livelli di SUA, rispetto al braccio con atenololo, è risultato inferiore nei soggetti in terapia con losartan4, dato in linea con l'attività uricosurica di tale molecola.

L'effetto sull'iperuricemia relata all'assunzione di diuretici è stato indagato nello studio URRAH [5]: i tassi di mortalità per tutte le cause, morte per cause cardiovascolari e incidenza di eventi cardiovascolari sono risultati analoghi nei soggetti con iperuricemia in maniera indipendente dall'utilizzo o meno di diuretici; ciò dimostra come l'aumento di SUA esprima un significato prognostico similare sia quando è da attribuirsi ad un'aumentata produzione, sia nei casi in cui una quota di SUA sia legata ad un aumentato riassorbimento tubulare.

Oltre ai "classici" farmaci sopracitati utilizzati nei pazienti con patologie cardiovascolari, gli inibitori di SGLT2 (SGLT2i) stanno ottenendo un'importanza sempre maggiore in differenti contesti, grazie alle proprietà pleiotropiche che esercitano in aggiunta all'evidente effetto glicosurico che li caratterizza. In una metanalisi del 2018 su un totale di 34.941 pazienti, Zhao et al. hanno valutato l'effetto di empagliflozin, canagliflozin, dapagliflozin, ipragliflozin, luseogliflozin e tofogliflozin sulla riduzione di SUA in una popolazione di soggetti affetti da diabete mellito tipo II: rispetto al braccio di controllo, gli SGLT2i hanno determinato una riduzione media del valore di SUA pari a -37.73 μmol/L (95% CI, -40.51, -34.95) [6]. Il razionale alla base dell'effetto uricosurico parrebbe essere dovuto, almeno in parte, all'aumentato efflusso di acido urico nel tubulo prossimale per azione del trasportatore GLUT9, secondario all'aumentata concentrazione tubulare di glucosio [7]. Nello studio EMPEROR-Reduced3, in una popolazione di pazienti affetti da insufficienza cardiaca a frazione d'eie-

zione ridotta (HFrEF), indipendentemente dalla presenza di diabete mellito tipo II, empagliflozin ha determinato una riduzione del SUA a quattro settimane dall'inizio del trattamento se comparato a placebo (-1.12 +/- 0.04 mg/dL, p < 0.0001), mantenendo tale risultato per tutta la durata del successivo follow-up; questo dato riveste particolare importanza soprattutto in considerazione della prognosi negativa che caratterizza i pazienti con ampie variabilità di SUA. Gli effetti di empagliflozin sull'endpoint composito primario e il rischio di ospedalizzazione per scompenso cardiaco si sono rivelati indipendenti dai livelli di SUA (HR 0.76, 95% CI 0.65-0.88, p < 0.001); tuttavia, è stata osservata una significativa riduzione nella mortalità per eventi cardiovascolari e per tutte le cause nei pazienti con livelli di SUA più elevati, effetto non riscontrato nei pazienti con livelli di SUA minori. È possibile dunque ipotizzare come l'effetto protettivo di empagliflozin sia maggiore nei pazienti con livelli più elevati di stress ossidativo, aumentato catabolismo e stato pro-infiammatorio, ovvero stati di disequilibrio metabolico espressi dall'aumentata concentrazione di SUA. Ricordiamo, tuttavia, come al singolo valore di SUA debba essere preferita la variazione dinamica di tale parametro nel tempo [8], così come il concetto di esposizione cumulativa: l'abbandono dei parametri statici a favore della variabilità temporale, associata ad una sempre maggiore conoscenza degli effetti metabolici ancillari dei farmaci utilizzati quotidianamente dai clinici consentirà, in un futuro prossimo, di stratificare al meglio il rischio cardiovascolare dei pazienti individuando precocemente i soggetti maggiormente a rischio, consentendo dunque di instaurare una terapia personalizzata su misura.

**Bibliografia**


1. Borghi, C., Bentivenga, C. & Cosentino, E. R. Uric acid and risk of myocardial infarction. A dynamic duo. Int. J. Cardiol. 320, 23–24 (2020).
2. Tian, X. et al. Changes in serum uric acid and the risk of cardiovascular disease and all-cause mortality in the general population. Nutr. Metab. Cardiovasc. Dis. 31, 1401–1409 (2021).
3. Doehner, W. et al. Uric acid and sodium-glucose cotransporter-2 inhibition with empagliflozin in heart failure with reduced ejection fraction: the EMPEROR-reduced trial. Eur. Heart J. 1–13 (2022). doi:10.1093/eurheartj/ehac320
4. Zacks, E. S. et al. Time-varying serum uric acid predicts new-onset atrial fibrillation in treated hypertensive patients. The LIFE Study. Explor. Med. 3, 128–138 (2022).
5. Maloberti, A. et al. Relationships between diuretic-related hyperuricemia and cardiovascular events: Data fromthe URic acid Right forheArt Health study. J. Hypertens. 39, 333–340 (2021).
6. Zhao, Y. et al. Effects of sodium-glucose co-transporter 2 (SGLT2) inhibitors on serum uric acid level: A meta-analysis of randomized controlled trials. Diabetes, Obes. Metab. 20, 458–462 (2018).
7. Chino, Y. et al. SGLT2 inhibitor lowers serum uric acid through alteration of uric acid transport activity in renal tubule by increased glycosuria. Biopharm. Drug Dispos. 35, 391–404 (2014).
8. Borghi, C. & Piani, F. Uric Acid and Risk of Cardiovascular Disease: A Question of Start and Finish. Hypertension 1219–1221 (2021). doi:10.1161/HYPERTENSIONAHA.121.17631

# La fibrosi epatica

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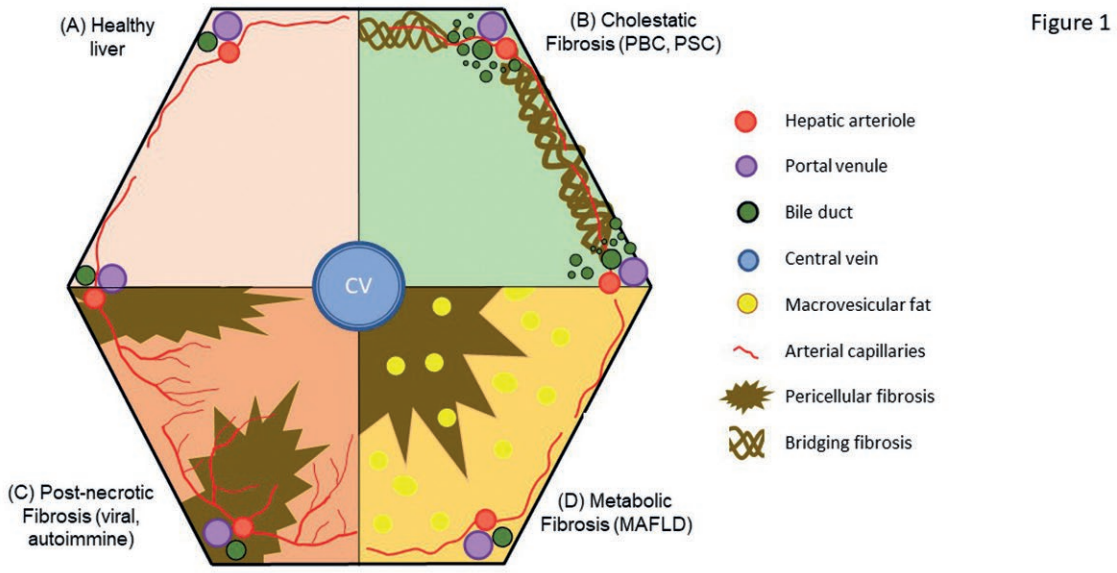
Genericamente, la fibrosi epatica, analogamente ad altre forme di fibrosi d'organo conseguenti a malattie croniche infiammatorie, e' caratterizzata dalla cronicizzazione di un processo di riparazione del danno tissutale in cui la componente parenchimale viene significativamente sostituita da un'espansione della matrice extracellulare (ECM) di tipo fibrillare. Questo risultato, che in genere viene raggiunto dopo molti anni di malattia cronica, non rappresenta necessariamente la peggiore evenienza. Infatti, la fibrosi rappresenta il miglior compromesso per assicurare una continuita' nella struttura del tessuto al prezzo di una diminuzione delle sue capacita' funzionali associata a conseguenze meccaniche negative (riduzione dell'elasticita'). In termini altrettanto generici, si assume anche la fibrosi epatica della malattie croniche del fegato (MCF) si sviluppi con gli stessi meccanismi cellulari e molecolari indipendentemente dall'eziologia (virale, metabolica, tossica, autoimmune e colestatica). Tuttavia, esistono delle importanti caratteristiche dipendenti dall'eziologia responsabile del danno epatico che appaiono cruciali per la comprensione dell'evoluzione verso la cirrosi nelle diverse MCF e della potenziale reversibilita' della fibrosi in seguito ad appropriato trattamento [1] **(Figura 1)**. La fibrosi definita "biliare", tipica delle malattie colestatiche (colangite biliare primitiva e colangite sclerosante primitiva), origina dallo spazio portale ed e' associata alla co-proliferazione di dotti biliari e miofibroblasti portali con lo sviluppo di setti fibrosi con andamento porto-portale con interessamento del lobulo epatico e della vena centrolobulare solo in fase avanzata. In contrasto, la fibrosi definita "post-necrotica", tipica dell'epatitite cronica virale (da HBV e HCV), segue un percorso porto-centrale in conseguenza della cosiddetta "bridging fibrosis" tra lo spazio portale e la vena centrolobulare. Il precoce coinvolgimento della vena centrolobulare e una significativa neo-angiogenesi determinano un piu' rapido sviluppo di ipertensione portale. Infine, la fibrosi con distribuzione pericellulare e perisinusoidale a partire dalla zona centrolobulare e' tipica delle epatopatie alcolica e metabolica. Questi distinti modelli di

Figure 1




(A) Healthy Liver, (B) Cholestatic fibrosis with biliary proliferation and porto-portal fibrosis, (C) Post-necrotic fibrosis with porto-central fibrosis and sinusoidal arterialization, (D) Steatotic liver with pericentral fibrosis

sviluppo fibrogenico sono dovuti a diversi fattori ed in particolare: 1. la localizzazione del danno nel lobulo epatico; 2. la relativa concentrazione di fattori profibrogenici e 3. Il prevalente meccanismo profibrogenico. Inoltre, i diversi modelli implicano la partecipazione di diversi tipi cellulari nel processo.

Studi effettuati negli ultimi 30 anni hanno sostanziato il ruolo delle cellule stellate epatiche (HSC) come principali effettori cellulari della fibrosi epatica [2,3]. Le HSC sono periciti fegato-specifici che acquisiscono un permanente fenotipo miofibroblastico profibrogenico in seguito alla loro attivazione conseguente al danno della ECM periepatocitaria, allo stress ossidativo, e al reclutamento di cellule infiammatorie. Le HSC attivate sono a loro volta sorgente di fattori pro-infiammatori che portano allo stabilirsi di un circolo vizioso in cui la co-stimolazione di cellule infiammatorie e fibrogeniche promuove l'accumulo di ECM fibrillare.

Le piu' recenti acquisizioni riguardano lo studio delle caratteristiche biochimiche e biomeccaniche della ECM del fegato fibrotico e cirrotico (matrisoma) che rivelano caratteristiche distinte in diverse MCF e rappresentano una base molto promettente per la scoperta di marcatori diagnostici esclusivi per ogni MCF e di specifici target per lo sviluppo di farmaci antifibrotici [4,5].

**Bibliografia**

1. Hall A, Germani G, Isgro G, Burroughs AK, Dhillon AP. Fibrosis distribution in explanted cirrhotic livers. Histopathology 2012;60:270-277.
2. Parola M, Pinzani M. Liver fibrosis: Pathophysiology, pathogenetic targets and clinical issues. Molecular Aspects of Medicine 2019; 65:37–55.
3. Friedman SL, Pinzani M. Hepatic fibrosis 2022: Unmet needs and a blueprint for the future. Hepatology 2022;75:473-488.
4. Mazza G, Al-Akkad W, Telese A, Longato L, Urbani L, Robinson B, et al. Rapid production of human liver scaffolds for functional tissue engineering by high shear stress oscillation-decellularization. Sci Rep 2017;7:5534.
5. Mazza G, Telese A, Al-Akkad W, Frenguelli L, Levi A, Marrali M, et al. Cirrhotic Human Liver Extracellular Matrix 3D Scaffolds Promote Smad-Dependent TGF-beta1 Epithelial Mesenchymal Transition. Cells 2019;9.

# Microbiota intestinale, alimentazione e salute

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Il microbiota intestinale (MI) è composto da trilioni di microrganismi che colonizzano l'intestino e che si sono evoluti in simbiosi con l'organismo. Tale ecosistema esercita funzioni nutritive, metaboliche ed immunologiche, con un contributo diretto o indiretto sull'omeostasi immunitaria ed infiammatoria di tutto l'organismo. La disbiosi intestinale, vale a dire il disequilibrio della normale composizione del MI - con conseguente alterazione funzionale e metabolica - è una condizione associata a numerose patologie croniche. [1] Negli anni è emersa la correlazione tra disbiosi intestinale e malattie del tratto gastroenterico, tra cui le malattie infiammatorie intestinali (colite ulcerosa e malattia di Crohn), la sindrome dell'intestino irritabile e il cancro del colon. [1,2] In ambito neurologico, numerosi lavori scientifici hanno suggerito che il MI è coinvolto nello sviluppo di malattie neuropsichiatriche, come il disturbo dello spettro autistico, la schizofrenia, la sindrome ansioso-depressiva, il disturbo da deficit di attenzione/iperattività e l'epilessia, e neurodegenerative, come la malattia di Parkinson e di Alzheimer. [3] Nonostante l'incidenza di malattie metaboliche sia fortemente condizionata da fattori genetici e ambientali, numerose di queste patologie, tra cui l'obesità, il diabete e la steatosi epatica non alcolica, sono fortemente correlate ad alterazioni del MI. Inoltre, il MI e i suoi metaboliti, come la trimetilammina-N-ossido (Trimethylamine N-oxide, TMAO), gli acidi biliari e gli acidi grassi a catena corta (Short-chain fatty acids, SCFA), possono influenzare l'insorgenza di patologie cardiovascolari, come l'ipertensione e l'aterosclerosi.[1] La scoperta dell'asse microbiota-intestino-cervello, ha inoltre rivoluzionato molti aspetti della medicina nelle ultime due decadi, mettendo in evidenza come il MI sia un regolatore fondamentale di questi processi. Infatti, esso è in grado di comunicare con il cervello in maniera diretta, attraverso il sistema nervoso neuroenterico e il nervo vago, oppure indirettamente, stimolando il rilascio e la produzione di ormoni, sintetizzando metaboliti neurotrasmettitori (SCFA, amminoacidi, serotonina, triptofano, catecolamine e acido gamma-amino-butirrico) in grado di influenzare l'integrità della barriera ematoencefalica a partire dai componenti alimentari e modulando il sistema immunitario locale e sistemico. A sua volta, le afferenze centrali, provenienti dal sistema nervoso e dall'asse ipotalamo-ipofisi-surrene in risposta a stimoli ambientali (come ad esempio lo stress), possono influenzare la composizione microbica intestinale e la permeabilità della barriera intestinale. Numerosi altri fattori possono influenzare il MI, come la modalità di parto, le infezioni, l'allattamento, l'uso di antibiotici, lo stress, la genetica dell'ospite e l'età [2]. Un ruolo prioritario nella modulazione del MI è dato dalla nutrizione. La composizione della dieta e le abitudini alimentari condizionano in maniera significativa l'ecosistema intestinale, e, di conseguenza, lo stato metabolico e immunitario. In estrema sintesi, l'adozione di uno stile alimentare basato sui principi della dieta mediterranea comporta una modulazione positiva della composizione microbica intestinale con una riduzione dello stato infiammatorio e un equilibrio della risposta immunitaria, attraverso la produzione di metaboliti quali gli SCFA.[4] Al contrario, una dieta ricca di grassi saturi e zuccheri raffinati, tipica dello stile occidentale (Western-type diet) comporta un potenziamento della risposta infiammatoria e immunologica attraverso la produzione di metaboliti tossici (es. TMAO), la riduzione di popolazioni microbiche considerate benefiche e l'aumento della permeabilità intestinale. La dieta moderna è tuttavia caratterizzata non solo da singoli nutrienti e gruppi di alimenti, ma anche da additivi alimentari naturali e artificiali che hanno un impatto diretto sul microbiota intestinale.

Giorno dopo giorno, le abitudini alimentari legate alla provenienza geografica degli individui influenzano il loro microbiota intestinale in termini di composizione e funzione. Negli ultimi decenni sono poi emerse nuove abitudini alimentari, come diete vegetariane, vegane, senza glutine, chetogeniche e di altro tipo che il nostro ecosistema intestinale non aveva mai affrontato prima. Tali scelte sono spesso considerate salutari, a prescindere da una effettiva indicazione clinica e da un controllo medico. Queste nuove scelte dietetiche potrebbero modulare il microbiota intestinale e barriera intestinale con potenziale impatto sul metabolismo e sull'intero stato immunologico. D'altra parte, le restrizioni dietetiche nella frequenza dei pasti e/o nelle

dimensioni delle porzioni potrebbero influenzare la composizione e la funzione del microbiota intestinale, rappresentando potenziali terapie efficaci nella prevenzione della disbiosi e nel ritardare l'insorgenza di malattie cronico-degenerative. Il rapporto tra microbiota intestinale, abitudini alimentari e salute è, pertanto, un orizzonte innovativo e affascinante che offre al medico di oggi incredibili potenzialità di ricerca e applicazione clinica.

**Bibliografia**

1. Chen Y, Zhou J, Wang L. Role and Mechanism of Gut Microbiota in Human Disease. 2021 Frontiers in cellular and infection microbiology;11:625913
2. Cryan JF, O'Riordan KJ, Cowan CSM, Sandhu K V, Bastiaanssen TFS, Boehme M et al. The Microbiota-Gut-Brain Axis. 2019 Physiological reviews;99:1877–2013
3. Cenit MC, Sanz Y, Codoñer-Franch P. Influence of gut microbiota on neuropsychiatric disorders. 2017 World journal of gastroenterology;23:5486–98
4. Rinninella E, Cintoni M, Raoul P, Ianiro G, Laterza L, Ponziani FR et al. Diet-Induced Alterations in Gut Microbiota Composition and Function [Internet]. 2022 In: Glibetic MBT-CGM. Oxford: Elsevier; page 354–73

# Salvare il muscolo nel malato oncologico

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I pazienti con malattia oncologica in fase avanzata spesso presentano problemi nutrizionali, tra cui malnutrizione, sarcopenia (cioè perdita di funzione e massa muscolare) e cachessia (cioè perdita di peso caratterizzata da un continuo declino della massa muscolare scheletrica, con o senza perdita di massa grassa) [1–3]. Tuttavia, ci sono evidenze crescenti che anche i pazienti con malattia in fase iniziale [non metastatica] manifestano problemi nutrizionali [4], tra cui perdita di peso involontaria ed esaurimento muscolare, che possono avere un impatto prognostico negativo sul lungo termine. Diversi studi hanno evidenziato la prevalenza della malnutrizione e/o dell'esaurimento muscolare già al momento della diagnosi di neoplasia [4–7]. Nello studio multicentrico italiano PreMiO, tra i pazienti naïve al trattamento, il 2,7% di quelli con malattia in stadio 1 erano malnutriti al momento della diagnosi aumentando al 15,2% di quelli con malattia allo stadio 4. La prevalenza di aumentato rischio di malnutrizione alla diagnosi è stata del 20,1% nei pazienti con malattia di stadio 1, che saliva al 42,7% nei pazienti con malattia allo stadio [4]. La perdita di peso è un criterio utilizzato per la definizione della malnutrizione e si verifica indipendentemente dal tipo o dallo stadio del cancro ed è associato a sopravvivenza più breve. In un recente, ampio studio che ha incluso 12.253 pazienti neoplastici a rischio di perdita di peso, è stata chiaramente dimostrata una correlazione tra ridotta assunzione di cibo e infiammazione (misurata utilizzando livelli di proteina C-reattiva [CRP]) e sopravvivenza [8].

Per quanto riguarda il tessuto muscolare, è stato dimostrato che una bassa massa muscolare aumenta il rischio di tossicità dose-limitante durante la terapia antineoplastica sistemica [9-18]. Pertanto, impedendo la somministrazione di un regime ottimale, la perdita di massa muscolare può compromettere direttamente l'efficacia e gli esiti dei trattamenti antitumorali [14,19,20]. Per questi motivi, la valutazione nutrizionale, che includa anche la composizione corporea, deve essere effettuata per tutti i pazienti con diagnosi di cancro indipendentemente dal loro stadio di malattia e devono essere monitorati durante tutto il percorso di trattamento e oltre, con l'obiettivo di ottimizzare i risultati riducendo al contempo gli effetti collaterali del trattamento. Il riconoscimento precoce dei problemi nutrizionali è la chiave per evitare che i pazienti siano o diventino "unfit" per i trattamenti specifici per la malattia di base [21,22]. Il mantenimento di un adeguato stato nutrizionale, oltre a migliorare la capacità del paziente di tollerare la terapia antineoplastica, è associato ad una riduzione delle complicanze post-chirurgiche dopo l'intervento chirurgico e ha un impatto positivo sugli esiti a lungo termine, compresa la sopravvivenza [23–27]. Ne consegue che vi è una chiara necessità di un approccio standardizzato per valutare e monitorare lo stato nutrizionale, al fine di massimizzare l'efficacia e ridurre al minimo il rischio di tossicità dei trattamenti.

Da tempo viene invocato che lo screening nutrizionale, la valutazione, il trattamento e il monitoraggio dello stato nutrizionale e della composizione corporea divengano parte integrante del percorso di diagnosi e cura oncologiche, tuttavia i percorsi nutrizionali in oncologia sono ancora molto scarsamente implementati [28–31] La sfida dei prossimi anni è quindi non solo quella di stabilire quando e da chi dovrebbe essere svolto questo compito, ma anche di come realizzare il processo in modo fattibile ed efficace all'interno di una pratica oncologica routinaria e consolidata [31].

## Bibliografia

1. Baracos VE. Cancer-associated malnutrition. Eur J Clin Nutr. 2018;72:1255–9.
2. Baracos VE, Martin L, Korc M, et al. Cancer-associated cachexia. Nat Rev Dis Primers. 2018;4:17105.
3. Bossi P, Delrio P, Mascheroni A, et al. The spectrum of malnutrition/cachexia/sarcopenia in oncology according to different cancer types and setting: A narrative review. Nutrients. 351 2021;13:1980.
4. Muscaritoli M, Lucia S, Farcomeni A, et al. Prevalence of malnutrition in patients at first medical oncology visit: the PreMiO study. Oncotarget. 2017;8:79884–96.
5. Alvaro Sanz E, Garrido Sile M, Rey Fernandez L, et al. Nutritional risk and malnutrition rates at diagnosis of cancer in patients treated in outpatient settings: Early intervention protocol.

Nutrition. 2019;57:148–53.
6. Hebuterne X, Lemarie E, Michallet M, et al. Prevalence of malnutrition and current use of nutrition support in patients with cancer. J Parent Ent Nutr. 2014;38:196–204.
7. Wie GA, Cho YA, Kim SY, et al. Prevalence and risk factors of malnutrition among cancer patients according to tumor location and stage in the National Cancer Center in Korea. Nutrition. 2010;26:263–8.
8. Martin L, Muscaritoli M, Bourdel-Marchasson I, et al. Diagnostic criteria for cancer cachexia: reduced food intake and inflammation predict weight loss and survival in an international, multicohort analysis. J Cachexia Sarcopenia Muscle. 2021;12:1189–1202.
9. Antoun S, Baracos VE, Birdsell L, et al. Low body mass index and sarcopenia associated with dose-limiting toxicity of sorafenib in patients with renal cell carcinoma. Ann Oncol. 2010;21:1594–8.
10. Cushen SJ, Power DG, Teo MY, et al. Body composition by computed tomography as a predictor of toxicity in patients with renal cell carcinoma treated with sunitinib. Am J Clin Onc: Cancer Clinical Trials. 2017;40(1):47–52.
11. Huillard O, Mir O, Peyromaure M, et al. Sarcopenia and body mass index predict sunitinib372 induced early dose-limiting toxicities in renal cancer patients. Br J Cancer. 2013;108:1034–41.
12. Massicotte MH, Borget I, Broutin S, et al. Body composition variation and impact of low skeletal muscle mass in patients with advanced medullary thyroid carcinoma treated with vandetanib: results from a placebo-controlled study. J Clin Endocrinol Metab. 2013;98:2401–8.
13. Mir O, Coriat R, Blanchet B, et al. Sarcopenia predicts early dose-limiting toxicities and pharmacokinetics of sorafenib in patients with hepatocellular carcinoma. PLoS One. 2012;e37563.
14. Palmela C, Velho S, Agostinho L, et al. Body composition as a prognostic factor of neoadjuvant chemotherapy toxicity and outcome in patients with locally advanced gastric cancer. J Gastric Cancer. 2017;17(1):74–87.
15. Prado CMM, Baracos VE, McCargar LJ, et al. Body composition as an independent determinant of 5-fluorouracil-based chemotherapy toxicity. Clin Cancer Res. 2007;13:3264–8.
16. Prado CMM, Baracos VE, McCargar LJ, et al. Sarcopenia as a determinant of chemotherapy toxicity and time to tumor progression in metastatic breast cancer patients receiving capecitabine treatment. Clin Cancer Res. 2009;15:2920–6.
17. Surov A, Pech M, Gessner D, et al. Low skeletal muscle mass is a predictor of treatment related toxicity in oncologic patients. A meta-analysis. Clin Nutr. 2021;40:5298–310.
18. Wendrich AW, Swartz JE, Bril SI, et al. Low skeletal muscle mass is a predictive factor for chemotherapy dose-limiting toxicity in patients with locally advanced head and neck cancer. Oral Oncol. 2017;71:26–33.
19. Barret M, Malka D, Aparicio T, et al. Nutritional status affects treatment tolerability and survival in metastatic colorectal cancer patients: results of an AGEO prospective multicenter study. Oncology. 2011;81:395–402.
20. Parsons HA, Baracos VE, Dhillon N, et al. Body composition, s 395 ymptoms, and survival in advanced cancer patients referred to a phase I service. PLoS One. 2012;7:e29330.
21. Muscaritoli M, Molfino A, Gioia G, et al. The "parallel pathway": a novel nutritional and metabolic approach to cancer patients. Intern Emerg Med. 2011;6(2):105–12.
22. Cardenas D, Toulson Davisson Correia MI, Ochoa JB, et al. Clinical nutrition and human rights. An international position paper. Clin Nutr. 2021;40:4029–36.
23. Bargetzi L, Brack C, Herrmann J, et al. Nutritional support during the hospital stay reduces mortality in patients with different types of cancers: secondary analysis of a prospective randomized trial. Ann Oncol. 2021;32:1025–33.
24. Gonzalez-Rodriguez M, Villar-Taibo R, Fernandez-Pombo A, et al. Early versus conventional nutritional intervention in head and neck cancer patients before radiotherapy: Benefits of a fast-track circuit. Eur J Clin Nutr. 2021;75:748–53.
25. Prado CM, Laviano A, Gillis C, et al. Examining guidelines and new evidence in oncology nutrition: a position paper on gaps and opportunities in multimodal approaches to improving patient care. Support Care Cancer. 2021;30:3073–83.
26. Ravasco P, Monteiro Grillo I, Camilo M. Dietary individualized counselling benefits in colorectalcancer: the long term follow-up of a randomized controlled trial of nutritional therapy. Am J Clin Nutr. 2012;96:1346–53.
27. Tan S, Meng Q, Jiang Y, et al. Impact of oral nutritional supplements in post-discharge patients at nutritional risk following colorectal cancer surgery: A randomized clinical trial. Clin Nutr. 2021;40:47–53.
28. Arends J, Strasser F, Gonella S, et al. Cancer cachexia in adult patients: ESMO Clinical Practice Guidelines. ESMO Open. 2021;6:1000092.
29. Rauh S, Antonuzzo A, Bossi P, et al. Nutrition in patients with cancer: a new area for medical oncologists? A practising oncologist's interdisciplinary position paper. ESMO Open. 2018;3:e000345.
30. Mohile SG, Dale W, Somerfield MR, et al. Practical assessment and management of vulnerabilities in older patients receiving chemotherapy: ASCO guideline for geriatric oncology. J Clin Oncol. 2018;36:2326–47.
31. Yalcin S, Gumus M, Oksuzoglu B, et al. Nutritional aspect of cancer care in medical oncology patients. Clin Ther. 2019;41:2382–96.

# Disturbi funzionali gastrointestinali

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È opinione comune che errori di alimentazione siano coinvolti nel determinismo di una larga parte dei disturbi digestivi funzionali. Pazienti affetti da dispepsia e/o sindrome dell'intestino irritabile riportano quasi invariabilmente sintomi indotti o aggravati dall'ingestione dei pasti. Pertanto i pazienti da soli, su consiglio medico o con il supporto di indagini diagnostiche non sempre attendibili (ma molto diffuse e costose in ambienti privati) seguono diete di eliminazione generalmente inutili e potenzialmente dannose. D'altro canto dati scientifici consistenti dimostrano che i contenuti del canale alimentare (secrezioni digestive, alimenti, microbiota), attraverso una barriera mucosa non adeguatamente impermeabile (leaky gut) stimolano importanti reazioni del sistema immunitario di sottomucosa (il principale sistema immunitario del corpo umano) con conseguente rilascio di citochine che irritano le terminazioni nervose del sistema nervoso enterico (con alterazione delle funzioni digestive) e delle fibre nervose autonomiche afferenti (con stimolazione del sistema nervoso centrale che, sotto l'influsso di fattori psico-sociali, porta alla percezione dei sintomi). Nei casi più severi l'attivazione immunitaria indotta da alimenti "irritanti" è tanto grave da indurre anche sintomi extra-digestivi quali dolori somatici diffusi (spesso interpretati come fibromialgia), cefalea, emicrania, confusione mentale, disturbi mnesici, ecc.

La dispepsia è caratterizzata da sintomi suggestivi di problematiche gastro-duodenali e, in assenza di patologie organiche, sistemiche o metaboliche, viene definita funzionale. Se ne riconoscono 2 sottogruppi: dispepsia simil-ulcerosa o epigastric pain syndrome (EPS) e dispepsia simil motoria o postprandial distress syndrome (PDS) che solo in una minoranza di casi si possono manifestare contemporaneamente. EPS si sovrappone ampiamente alla patologia da reflusso e dati fisiopatologici suggeriscono di evitare alimenti noti per stimolare la secrezione acida gastrica e/o ridurre la pressione dello sfintere esofageo inferiore quali pasti abbondanti / iperlipidici, cioccolata, menta, bevande ricche di caffeina, alcoolici (soprattutto è da sconsigliare il vino bianco), ma trial clinici controllati non sono disponibili. PDS, come dice il nome, è tipicamente scatenata dall'assunzione di pasti che inducono sazietà precoce e/o ripienezza postprandiale. Circa il 30% di questi pazienti presenta un rallentato svuotamento gastrico dei cibi solidi (in questo caso si parla di gastroparesi). Negli altri casi incapacità del fondo gastrico di rilasciarsi in seguito all'ingestione del pasto o ipersensibilità viscerale indotta da infiammazione eosinofila della mucosa duodenale sono possibili fattori patogenetici. Anche questi pazienti si giovano di pasti ipocalorici/ipolipidici e l'esperienza clinica suggerisce inoltre di limitare solidi indigeribili (fibre vegetali insolubili) e solidi digeribili di grandi dimensioni (da preferire macinati) perché rallentano lo svuotamento gastrico. Nell'ipotesi che l'infiltrato eosinofilo sia secondario ad una condizione allergica sono state tentate diete di eliminazione con risultati insoddisfacenti

La sindrome dell'intestino irritabile (IBS) è caratterizzata da dolore addominale e alterazioni dell'alvo in senso stitico (IBS-C) o diarroico (IBS-D) o misto (IBS-M) che spesso si associano a gonfiore/tensione addominale. In una rilevante percentuale di casi si è osservata un'elevata infiltrazione mastocitaria in stretto contatto con le terminazioni nervose della sottomucosa, suggestiva anche in questo caso di possibili meccanismi di tipo allergico. Numerosi trial clinici controllati dimostrano l'efficacia di diete a basso contenuto di alimenti fermentabili (Fermentable, Oligo-, Di-, Mono-saccharides And Polyols), note con il termine low-FODMAP. E' comunque noto da tempo che lattosio e fibre vegetali sono mal tollerati in un'elevata percentuale di pazienti e le diete low-FODMAP non fanno altro che confermare questa secolare esperienza clinica. In particolare, in Italia, almeno il 60% degli adulti ha un deficit di lattasi geneticamente indotto. Anche il glutine è ritenuto possibile causa di sintomi digestivi ed extra-digestivi in pazienti non-celiaci, anche se i confini di tale patologia (non-celiac gluten sensitivity, o NCGS) restano al momento sfumati e i trial clinici soffrono della difficoltà di impostare adeguate condizioni di doppio-cieco. Le fibre vegetali (frutta, verdura, cibi integrali) sono alimenti benefici e favoriscono le evacuazioni in soggetti sani, ma sono mal digerite e risultano irritanti

con conseguente aggravamento del dolore addominale in soggetti con disturbi digestivi. Inoltre, possono addirittura aggravare la stipsi in pazienti con inertia coli e insufficiente idratazione.

La differenza tra intolleranza ed allergia risiede nell'attivazione del sistema immunitario (con coinvolgimento in particolare di eosinofili e mastociti) che è tipica delle seconde, mentre avviene solo in casi estremi nelle prime. A tale proposito è bene tenere a mente alcuni aspetti importanti nella pratica clinica: 1) i test di intolleranza alimentare riconosciuti scientificamente sono esclusivamente test del respiro per carboidrati ed anche questi hanno importanti limitazioni; in caso di incertezza diete alternate di eliminazione / reinserimento di un singolo alimento (es. lattosio) possono essere dirimenti; 2) anche i test per la diagnosi di allergia (rast, prick, patch) hanno sensibilità e specificità non ottimali, pur rappresentando il gold standard diagnostico; 3) i test allergologici dovrebbero essere mirati allo studio non solo degli alimenti, ma anche degli inalanti e dei possibili contaminanti chimici degli alimenti (metalli, conservanti, coloranti, aromatizzanti).

Infine si deve ricordare che l'essere umano appartiene ad una specie animale onnivora e che l'esclusione di qualsiasi alimento dalla dieta non è privo di conseguenze negative potenzialmente anche rilevanti e certamente oggi non completamente note, per cui, come sempre, è necessario valutare bene il rapporto rischio / beneficio.

**Bibliografia**


1. Stanghellini V, Chan FKL, Hasler WL, et al. Gastroduodenal disorders. Gastroenterology 2016;150:1380–92.
2. Barbara G, Feinle-Bisset C, Ghoshal UC, Quigley EM, Santos J, Vanner S, et al. The Intestinal Microenvironment and Functional Gastrointestinal Disorders. Gastroenterology. 2016:S0016-5085
3. Barbaro MR, Cremon C, Fuschi D, Marasco G, Palombo M, Stanghellini V, et al. Pathophysiology of Diverticular Disease: From Diverticula Formation to Symptom Generation. Int J Mol Sci. 2022;23(12):6698.
4. Barbaro MR, Cremon C, Wrona D, Fuschi D, Marasco G, Stanghellini V, et al. Non-Celiac Gluten Sensitivity in the Context of Functional Gastrointestinal Disorders. Nutrients. 2020;12(12):3735.
5. Grover M, Farrugia G, Stanghellini V. Gastroparesis: a turning point in understanding and treatment. Gut. 2019;68(12):2238-2250
6. Stanghellini V, Tosetti C, Benedetto E, Condoluci M, De Bastiani R, Cogliandro Ret al. Nickel sensitization in patients with gastro-esophageal reflux disease. United European Gastroenterol J. 2016 Apr;4(2):184-90.
7. De Giorgio R, Ruggeri E, Stanghellini V, Eusebi LH, Bazzoli F, Chiarioni G. Chronic constipation in the elderly: a primer for the gastroenterologist. BMC Gastroenterol. 2015;15:130.
8. Camilleri M, Stanghellini V. Current management strategies and emerging treatments for functional dyspepsia. Nat Rev Gastroenterol Hepatol. 2013;10(3):187-94.
9. Tack J, Müller-Lissner S, Stanghellini V, Boeckxstaens G, Kamm MA, Simren M, et al. Diagnosis and treatment of chronic constipation--a European perspective. Neurogastroenterol Motil. 2011;23(8):697-710.

*RELAZIONI - OBESITÀ: ASPETTI INNOVATIVI DI UNA "NUOVA" MALATTIA INTERNISTICA*

# Il tessuto adiposo sano e quello malato

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L'organismo umano contiene un voluminoso organo endocrino denominato "Organo Adiposo" **(Figura 1)** [1]. Esso risulta composto da due tipi diversi di tessuto adiposo: il bianco (WAT) e il bruno (BAT). Il WAT (con cellule sferiche grandi e un unico vacuolo lipidico) accumula l'energia assunta coi pasti e la distribuisce nel periodo di digiuno tra un pasto e l'altro assicurando la sopravvivenza. Il WAT accumula energia tramite l'assunzione del cibo. Per assumerlo è necessario cercarlo e ingerirlo. In condizione avverse (es: preistoria) per cercare il cibo è necessaria una forte motivazione istintuale. Nel 1994 si scopre che il WAT produce un ormone: la leptina [2]. La leptinemia è proporzionale alla quantità di WAT. Quando le scorte si riducono la leptinemia si abbassa e ciò costituisce uno stimolo irrefrenabile per la ricerca di cibo. Esseri umani con mutazione del gene (senza l'ormone) diventano massivamente obesi. La somministrazione dell'ormone a questi soggetti risolve l'obesità, ma nella maggior parte dei casi i pazienti con obesità hanno alti livelli di leptina nel sangue e sviluppano leptino-resistenza [3]. Il recettore per l'ormone si trova nel centro ipotalamico della sazietà e diffuso in tutto il sistema limbico (responsabile del comportamento istintivo): ciò implica che l'ormone svolge un ruolo essenziale nell'indurre il comportamento della ricerca del cibo [4]. Il WAT, a digiuno, produce anche un secondo ormone: asprosina. Soggetti senza asprosina mangiano pochissimo anche se sono magrissimi, quindi con bassi livelli di leptinemia [5]. Quindi il WAT produce la leptina che induce alla ricerca del cibo e l'asprosina che ne determina la sua assunzione.

Il BAT (composto da cellule piccole poligonali con lipidi multiloculari) ha un'azione opposta a quella del bianco:

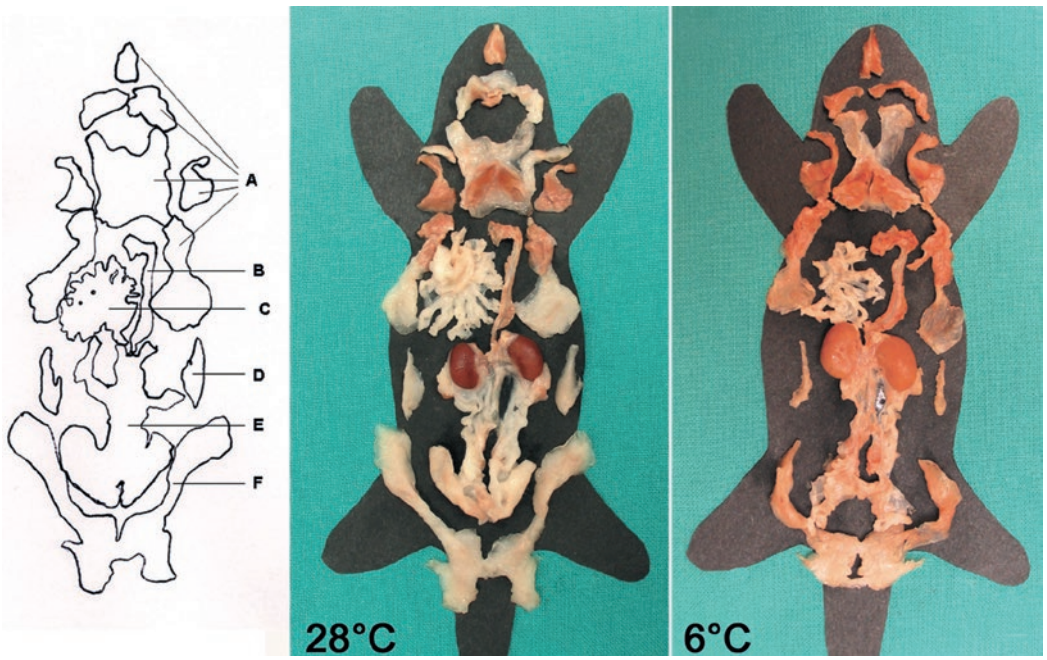


**Figura 1:** Organo adiposo di topo dissecato a temperatura ambiente (sinistra) e dopo 10 giorni di esposizione al freddo (destra). Nota che dopo l'esposizione al freddo aumenta la componente bruna dell'organo. Nello schema: A: sottocutaneo anteriore, B: viscerale mediastinico, C: viscerale mesenterico, D: viscerale retroperitonele, E: viscerale addomino-pelvico, F: sottocutaneo posteriore. Da Murano et al Adipocytes 2:121-130, 2005 con permesso. Barra: 2 cm.

brucia i grassi per produrre calore [1]. Anche questa azione è essenziale alla sopravvivenza perché le nostre cellule lavorano solo a 37°C e la temperatura ambientale in cui viviamo è spesso al di sotto di tale livello. Lo stimolo fisiologico per attivare il grasso bruno è la temperatura al di sotto della termoneutralità (circa 22°C). Numerosi studi hanno dimostrato una nuova particolare proprietà dei tessuti adiposi: la trans differenziazione [6]. Essi cioè, in condizioni fisiologiche particolari, possono convertirsi l'uno nell'altro: in caso di cronica esposizione al freddo il WAT si può convertire in BAT per incrementare la termogenesi **(Figura 1)**. In caso di bilancia energetica positiva il BAT si può convertire in WAT per incrementare la riserva energetica. Il problema principale dell'obesità è dovuto all'eccessiva espansione delle cellule adipose che, per accumulare i lipidi, diventano ipertrofiche. L'ipertrofia innesca meccanismi che portano alla morte le cellule del WAT. Quindi si formano detriti cellulari che devono essere riassorbiti (eliminati). Le cellule spazzino dell'organismo (macrofagi) entrano nel WAT infiammandolo e si distribuiscono attorno ai detriti delle cellule adipose ipertrofiche morte formando le cosiddette crown-like structures (CLS)[7-8] **(Figura 2)**. Poiché i detriti sono assai voluminosi il processo di riassorbimento diventa cronico e durante tale processo, come effetto collaterale, i macrofagi producono sostanze (TNFa, IL-6, Resistina, miR-155 ed altre) che vanno ad interferire con la funzione del recettore dell'insulina (insulino-resistenza) e, a lungo andare, determinano il crollo nella produzione dell'insulina stessa e favorendo lo sviluppo del diabete (tipo2). Il WAT viscerale è più fragile (meno espansibile) e determina maggiore infiammazione da cui la sua maggiore pericolosità clinica. Nel topo farmaci in grado di trasformare il grasso bianco in bruno sono efficaci nella terapia dell'obesità e delle malattie correlate [9]. Le industrie farmaceutiche sono attualmente impegnate nel trasferire tali risultati agli esseri umani e nuovi farmaci in questo senso hanno iniziato nuovi trials clinici [10].

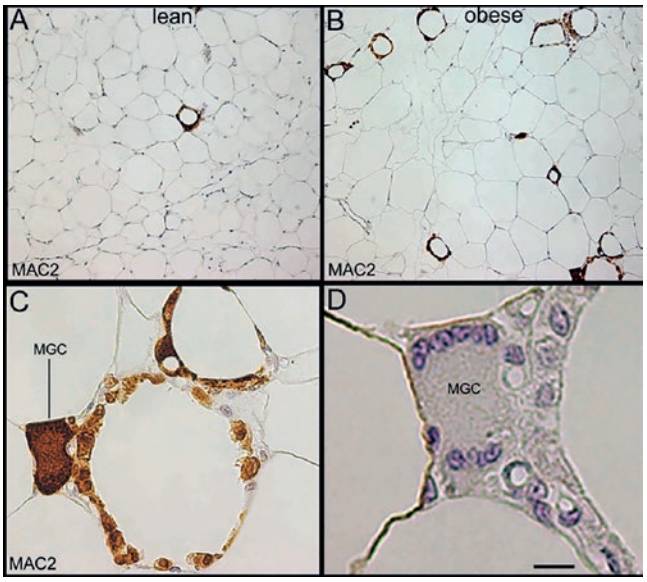


**Figura 2:** Macrofagi MAC2 positivi formano crown-like structures (CLS) attorno ai residui di adipociti ipertrofici morti (7). CLS sono più abbondanti nei tessuti obesi (B,C). Talora I macrofagi formano cellule giganti multinucleate (MGC) in C e D. Bar: 100 mm for A, B, 28 mm for C, and 10 mm for D. Da Cinti S et al J Lipid Res. 2005;46(11):2347-55 con permesso.

In conclusione quindi il nuovo concetto di organo adiposo endocrino costituito dai due tessuti bianco e bruno che cooperano fisiologicamente e sono provviste di proprietà plastiche offrono nuove prospettive terapeutiche per obesità, diabete T2 e altre malattie correlate.

## Bibliografia

1. Cinti S. Adipose Organ Development and Remodeling. Compr Physiol. 2018 Sep 14;8(4):1357-1431. doi: 10.1002/cphy.c170042. PMID: 30215863.
2. Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. Nature. 1994 Dec 1;372(6505):425-32. doi: 10.1038/372425a0. Erratum in: Nature 1995 Mar 30;374(6521):479. PMID: 7984236.
3. Maffei M, Halaas J, Ravussin E, Pratley RE, Lee GH, Zhang Y et al Leptin levels in human and rodent: measurement of plasma leptin and ob RNA in obese and weight-reduced subjects. Nat Med. 1995 Nov;1(11):1155-61. doi: 10.1038/nm1195-1155. PMID: 7584987.
4. De Matteis R, Cinti S. Ultrastructural immunolocalization of leptin receptor in mouse brain. Neuroendocrinology. 1998 Dec;68(6):412-9. doi: 10.1159/000054391. PMID: 9873205.
5. Romere, C.; Duerrschmid, C.; Bournat, J.; Constable, P.; Jain, M.; Xia, F. et al Asprosin, a Fasting-Induced Glucogenic Protein Hormone. Cell 2016, 165, 566–579.
6. Cinti S. Transdifferentiation properties of adipocytes in the adipose organ. Am J Physiol Endocrinol Metab. 2009 Nov;297(5):E977-86. doi: 10.1152/ajpendo.00183.2009. Epub 2009 May 19. PMID: 19458063.
7. Cinti, S.; Mitchell, G.; Barbatelli, G.; Murano, I.; Ceresi, E.; Faloia, E. et al Adipocyte death defines macrophage localization and function in adipose tissue of obese mice and humans. J. Lipid Res. 2005, 46, 2347–2355.
8. Camastra, S.; Vitali, A.; Anselmino, M.; Gastaldelli, A.; Bellini, R.; Berta, R. et al Muscle and adipose tissue morphology, insulin sensitivity and beta-cell function in diabetic and nondiabetic obese patients: Effects of bariatric surgery. Sci. Rep. 2017, 7, 9007.
9. Danforth, E., Jr.; Himms-Hagen, J.H. Obesity and diabetes and the beta-3 adrenergic receptor. Eur. J. Endocrinol. 1997, 136, 362–365.
10. O'Mara, A.E.; Johnson, J.W.; Linderman, J.D.; Brychta, R.J.; McGehee, S.; Fletcher et al Chronic mirabegron treatment increases human brown fat, HDL cholesterol, and insulin sensitivity. J. Clin. Invest. 2020, 130, 2209–2219

*RELAZIONI - OBESITÀ: ASPETTI INNOVATIVI DI UNA "NUOVA" MALATTIA INTERNISTICA*

# Obesità: malattia funzionale o strutturale del SNC

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Il SNC partecipa alla regolazione dell'alimentazione e del bilancio energetico. Nel corso dell'evoluzione il cervello ha subito enormi cambiamenti strutturali e funzionali, con preponderante sviluppo di funzioni superiori e della corrispondente rete di collegamento con le regioni cerebrali subcorticali. Il comportamento alimentare risulta pertanto da una integrazione complessa di segnali omeostatici ed edonici, con un coinvolgimento importante delle facoltà cognitive.

Studi di imaging hanno evidenziato che il paziente con obesità si caratterizza per alterazioni dei sistemi dopaminergico, oppioide e cannabinoide e delle reciproche interazioni [1-4]. Questi neuromodulatori sono legati al piacere, alla gratificazione e all'affettività. L'attuale evidenza suggerisce che il paziente con obesità sia sollecitato verso una maggiore ricerca di questi stimoli. Le proiezioni dopaminergiche traferirebbero l'informazione alle regioni prefrontali [funzione esecutiva], diminuendone il metabolismo glucidico ed il controllo inibitorio, traducendo la motivazione in azione [3]. Questi aspetti funzionali non sono presenti in tutti i pazienti, a parità di indice di massa corporea [5] e possono cambiare in funzione della durata e/o della gravità dell'obesità, sottolineando l'importanza di un approccio individuale. Il metabolismo cerebrale del glucosio rappresenta un punto di incontro fra regolazione edonica e omeostatica, in cui la sensibilità insulinica sembra interagire con i sistemi oppioide, cannabinoide e dopaminergico [4, 6].

I riscontri strutturali più frequentemente associati all'incremento dell'indice di massa corporea comprendono l'assottigliamento della corteccia frontale e di quella temporale [7] e la riduzione della densità della materia cerebrale, coerenti con una compromissione del controllo inibitorio e mnemonico. Alcune osservazioni nelle sindromi amnestiche umane e in modelli murini di neurodegenerazione suggeriscono che il danno strutturale del SNC modifichi il rapporto fra comportamento alimentare e accumulo di massa grassa, effetto che potrebbe indebolire l'identificazione di una predizione o associazione. La terapia cronica con insulina intranasale nel modello murino [8] esercita neuroprotezione e ripristina il comportamento alimentare, con evidenti ripercussioni periferiche. Nell'uomo la sensibilità insulinica risulta correlata con le alterazioni strutturali del SNC e la singola somministrazione intranasale di insulina influenza il metabolismo periferico ed il comportamento alimentare [9] in maniera diversa negli uomini rispetto alle donne e nei soggetti normopeso rispetto ai pazienti con obesità.

Le osservazioni disponibili sono in larga parte trasversali e focalizzate in maniera alternativa sulla struttura o sulla funzione del SNC, limitando la possibilità di confrontarne la coesistenza, la frequenza e la sequenza di compromissione. L'identificazione di processi cerebrali che siano causa primaria di obesità-comune, ricercata in soggetti a rischio per radici familiari o [poli]geniche, ha prodotto risultati controversi, anche a causa della difficoltà di definire un momento di esordio del sovrappeso. Inoltre, come innanzi illustrato, il rapporto causale e sequenziale fra alterazioni del SNC e obesità è sfuggente laddove un appetito aumentato non si traduca in un proporzionale incremento di peso e laddove il SNC sia coinvolto in misura diversa in persone con lo stesso indice di massa corporea. La comprensione della causa-prima richiede pertanto ancora uno sforzo considerevole di osservazione longitudinale, personalizzata e olistica. Di contro, gli studi di prevenzione e cura dimostrano un effetto della neuroprotezione sul consumo di cibo, sul peso corporeo e sulle complicanze dell'obesità ed un reciproco effetto del trattamento dell'obesità [con dieta o chirurgia] sulla struttura e sulla funzione cerebrali [ad esempio 1, 2, 5, 10], offrendo prospettive in ambito di trattamento nutrizionale, ormonale e probiotico rapidamente testabili.

## Bibliografia

1. Burghardt PR, Rothberg AE, Dykhuis KE, Burant CF, Zubieta J-K. Endogenous Opioid Mechanisms Are Implicated in Obesity and Weight Loss in Humans J Clin Endocrinol Metab. 2015;100(8):3193-201.
2. Karlsson HK, Tuominen L, Helin S, Salminen P, Nuutila P, Nummenmaa L. Mesolimbic opioid-dopamine interaction

is disrupted in obesity but recovered by weight loss following bariatric surgery. Transl Psychiatry. 2021;11(1):259.
3. Volkow ND, Wang G-J, Telang F, Fowler JS, Thanos PK, Logan J, et al. Low dopamine striatal D2 receptors are associated with prefrontal metabolism in obese subjects: possible contributing factors. Neuroimage. 2008 ;42(4):1537-43.
4. Kantonen T, Pekkarinen L, Karjalainen T, Bucci M, Kalliokoski K, Haaparanta-Solin M, et al. Obesity risk is associated with altered cerebral glucose metabolism and decreased μ-opioid and CB 1 receptor availability. Int J Obes (Lond). 2022;46(2):400-407.
5. Guzzardi MA, Garelli S, Agostini A, Filidei E, Fanelli F, Giorgetti A, et al. Food addiction distinguishes an overweight phenotype that can be reversed by low calorie diet. Eur Eat Disord Rev. 2018;26(6):657-670.
6. Kullmann S, Blum D, Jaghutriz BA, Gassenmaier C, Bender B, Häring HU. Central Insulin Modulates Dopamine Signaling in the Human Striatum. J Clin Endocrinol Metab. 2021;106(10):2949-2961.
7. Opel N, Thalamuthu A, Milaneschi Y, Grotegerd D, Flint C, Leenings R, et al. Brain structural abnormalities in obesity: relation to age, genetic risk, and common psychiatric disorders: Evidence through univariate and multivariate mega-analysis including 6420 participants from the ENIGMA MDD working group. Mol Psychiatry. 2021;26(9):4839-4852.
8. Sanguinetti E, Guzzardi MA, Panetta D, Tripodi M, De Sena V, Quaglierini M, et al. Combined Effect of Fatty Diet and Cognitive Decline on Brain Metabolism, Food Intake, Body Weight, and Counteraction by Intranasal Insulin Therapy in 3×Tg Mice. Front Cell Neurosci. 2019;13:188.
9. Schneider E, Spetter MS, Martin E, Sapey E, Yip KP, Manolopoulos KN, et al. The effect of intranasal insulin on appetite and mood in women with and without obesity: an experimental medicine study. Int J Obes (Lond). 2022;46(7):1319-1327.
10. Michaud A, Dadar M, Pelletier M, Zeighami Y, Garcia-Garcia I, Iceta S, et al. Neuroanatomical changes in white and grey matter after sleeve gastrectomy. Neuroimage. 2020;213:116696.

*RELAZIONI - OBESITÀ: ASPETTI INNOVATIVI DI UNA "NUOVA" MALATTIA INTERNISTICA*

# Obesità e disturbi dell'alimentazione: una coesistenza problematica e interagente

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L'obesità è la più frequente condizione medica osservata nelle persone con disturbi dell'alimentazione. Coesiste frequentemente con il disturbo da binge-eating e con alcuni casi di bulimia nervosa. L'obesità può precedere la comparsa di un disturbo dell'alimentazione, rappresentando a volte un fattore di rischio per il suo sviluppo o essere la conseguenza degli episodi ricorrenti di abbuffata. L'obesità e i disturbi, quando coesistono, tendono a interagire negativamente tra loro e a rendere più difficile il trattamento.

**Prevalenza**

Tra i pazienti che chiedono un trattamento per l'obesità, circa il 9% soddisfa i criteri diagnostici per il disturbo da binge-eating. Tuttavia, nella stessa popolazione, la presenza di episodi di abbuffata è stata riportata in circa il 29%. Non esistono dati attendibili sulla prevalenza della bulimia nervosa nell'obesità, ma la coesistenza delle due condizioni non sembra essere molto frequente.

**Fattori di rischio**

Studi caso-controllati e di coorte hanno rivelato che l'obesità pre-morbosa e familiare è un fattore di rischio per la bulimia nervosa e il disturbo da binge-eating. È stato ipotizzato che lo stigma del peso presente nei paesi occidentali metta le persone con obesità ad aumentato rischio di ricevere commenti critici sulla loro forma del corpo e sul loro peso e a subire la discriminazione da parte di altre persone. Queste esperienze negative aumentano la probabilità di interiorizzare l'"ideale di magrezza" e di sviluppare l'eccesiva valutazione del peso e della forma del corpo (cioè, giudicare il proprio valore prevalentemente o in alcuni casi esclusivamente in termini di peso, forma del corpo e loro controllo). Quest'ultima, considerata la psicopatologia nucleare della maggior parte dei disturbi dell'alimentazione, favorisce l'adozione di regole alimentari rigide ed estreme, spesso implicate nell'insorgenza e nel mantenimento degli episodi di abbuffata e delle altre caratteristiche dei disturbi dell'alimentazione.

**Interazioni tra obesità e disturbi dell'alimetntazione**

L'obesità e i disturbi dell'alimentazione interagiscono negativamente tra loro attraverso tre meccanismi principali:

1. Gli episodi di abbuffata promuovono l'aumento di peso.
2. L'eccesso di peso aumenta le preoccupazioni per il peso e la forma del corpo e incoraggia l'adozione di una dieta ferrea e di altri comportamenti estremi di controllo del peso che, a loro volta, aumentano il rischio di episodi di abbuffata.
3. L'eccesso di peso è spesso associato a livelli ridotti di attività fisica e ad un aumentato rischio di avere stati emotivi negativi che possono mantenere gli episodi di abbuffata.

**Conseguenze cliniche**

L'obesità, quando coesiste con il disturbo da binge-eating, è caratterizzata da un peggioramento della comorbilità medica e della disabilità fisica. Gli studi, controllati per l'età, il genere, l'educazione, l'indice di massa corporea e la salute psicologica hanno evidenziato che le persone con disturbo da binge-eating hanno una maggiore frequenza della sindrome metabolica e del rischio cardiometabolico rispetto a quelli senza storia di disturbo dell'alimentazione.

**La perdita di peso è indicata?**

La perdita di peso è sempre controindicata quando l'obesità coesiste con la bulimia nervosa, perché la restrizione dietetica mantiene la psicopatologia del disturbo dell'alimentazione aumentando le preoccupazioni per l'alimentazione, la frequenza degli episodi di abbuffata e l'intensità dell'eccessiva valutazione del peso e della forma del corpo.

Quando l'obesità coesiste con il disturbo da binge-eating non esiste una controindicazione assoluta alla perdita di peso. Le ricerche più recenti, infatti, hanno confermato che nel disturbo da binge-eating, non solo una moderata e flessibile restrizione dietetica non aumenta la frequenza degli episodi di abbuffata, ma, al contrario, produce in media una loro diminuzione. Tuttavia, mentre i trattamenti psicologici disponibili per il disturbo da binge-eating sono efficaci

nel ridurre la frequenza degli episodi di abbuffata, il loro impatto sulla perdita di peso a lungo termine nei pazienti con obesità ed episodi di abbuffata è modesto.

Recentemente è stato sviluppato un trattamento, in corso di valutazione, che integra le procedure della terapia cognitivo comportamentale migliorata (CBT-E) dei disturbi dell'alimentazione per affrontare i meccanismi di mantenimento degli episodi di abbuffata con quelle della CBT dell'obesità (CBT-OB), che aiuta il paziente a raggiungere una moderata e salutare perdita di peso. Dopo una prima fase finalizzata ad aiutare il paziente a regolarizzare l'alimentazione, il trattamento affronta in modo integrato e personalizzato i processi di mantenimento che agiscono nel paziente (vedi Figura), rendendolo così adatto alle varie presentazioni cliniche del disturbo da binge-eating associato all'obesità.

## Bibliografia


- Cooper Z, Calugi S, Dalle Grave R. Controlling binge eating and weight: A treatment for binge eating disorder worth researching? Eat Weight Disord. 2019;25(4):1105-9. doi: 10.1007/s40519-019-00734-4.
- Dalle Grave R, Calugi S. Cognitive behavior therapy for adolescents with eating disorders. New York: Guilford Press; 2020.
- Dalle Grave R, Sartirana M, Calugi S. Complex cases and comorbidity in eating disorders. Assessment and management. Cham, Switzerland: Springer Nature; 2021.
- Dalle Grave R, Sartirana M, El Ghoch M, Calugi S. Treating obesity with personalized cognitive behavioral therapy. Cham: Springer; 2018.


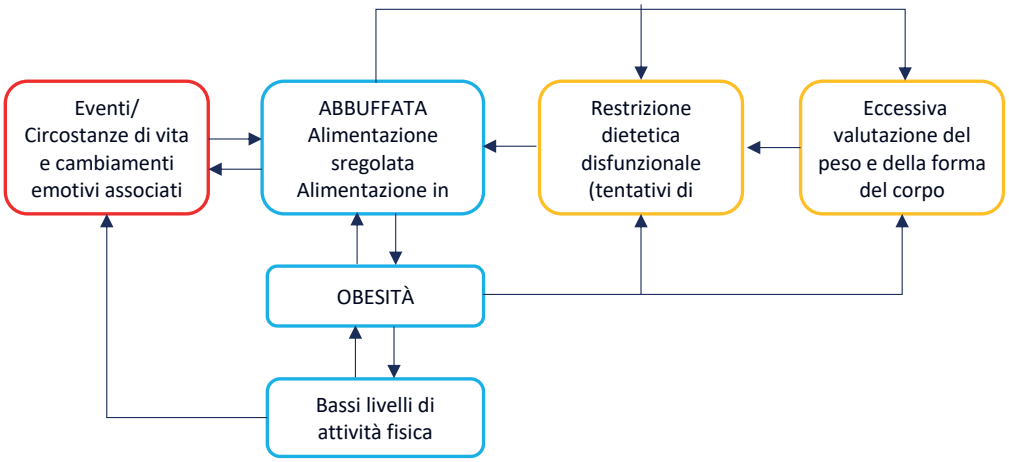


**Figura:** Meccanismi di mantenimento del disturbo da binge-eating e dell'obesità

*RELAZIONI - OBESITÀ: ASPETTI INNOVATIVI DI UNA "NUOVA" MALATTIA INTERNISTICA*

# NAFLD o MAFLD?

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L'acronimo NAFLD (Nonalcoholic Fatty Liver Disease) comprende un ampio spettro di condizioni caratterizzate da accumulo intraepatico di grasso (prevalentemente trigliceridi) in più del 5% degli epatociti all'esame istologico ovvero, alla risonanza magnetica epatica, con un segnale di contenuto di grasso superiore al 5.6% [1, 2]. La prevalenza della NAFLD, ritenuta oggi la patologia epatica più frequente, ha raggiunto globalmente livelli epidemici (27%) e tende ad aumentare. Anche se nella maggior parte dei pazienti la NAFLD ha un decorso lentamente progressivo, in circa il 20% dei casi può evolvere verso forme più gravi (nonalcoholic steatohepatitis, NASH) caratterizzate da degenerazione tipo "ballooning" dell'epatocita, necrosi, infiammazione e fibrosi, sino alla cirrosi ed epatocarcinoma. La presenza e la severità della malattia dipendono da diversi fattori quali la presenza di polimorfismi genici coinvolti nel metabolismo lipidico, comorbidità metaboliche (ad es. diabete), stili di vita inadeguati (diete ad alto contenuto di grassi e zuccheri semplici, consumo di fruttosio, sedentarietà [3]) **(Figura 1)**, alterazioni del microbiota intestinale [4]. Le interazioni tra questi fattori rendono difficile una diagnosi eziopatogenetica precisa o il disegno di trial clinici. Sicuramente il termine NAFLD presuppone l'assenza di cause secondarie di steatosi epatica quali consumo di alcool >21 e >14 drinks/settimana nell'uomo e nella donna, rispettivamente [5], epatiti virali, farmaci epatotossici, morbo di Wilson, nutrizione parenterale totale e digiuno prolungato. La NAFLD si associa ad obesità morbigena in circa il 90% dei casi, ad obesità e dislipidemia in oltre l'80% dei casi [6], ad ipertensione arteriosa nel 70% dei casi e a diabete mellito tipo 2 in circa il 50% dei casi. In questo senso, la NAFLD diventa una manifestazione epatica di una patologia sistemica e cresce all'aumentare di stili di vita inadeguati, obesità, insulino-resistenza e in generale della sin-

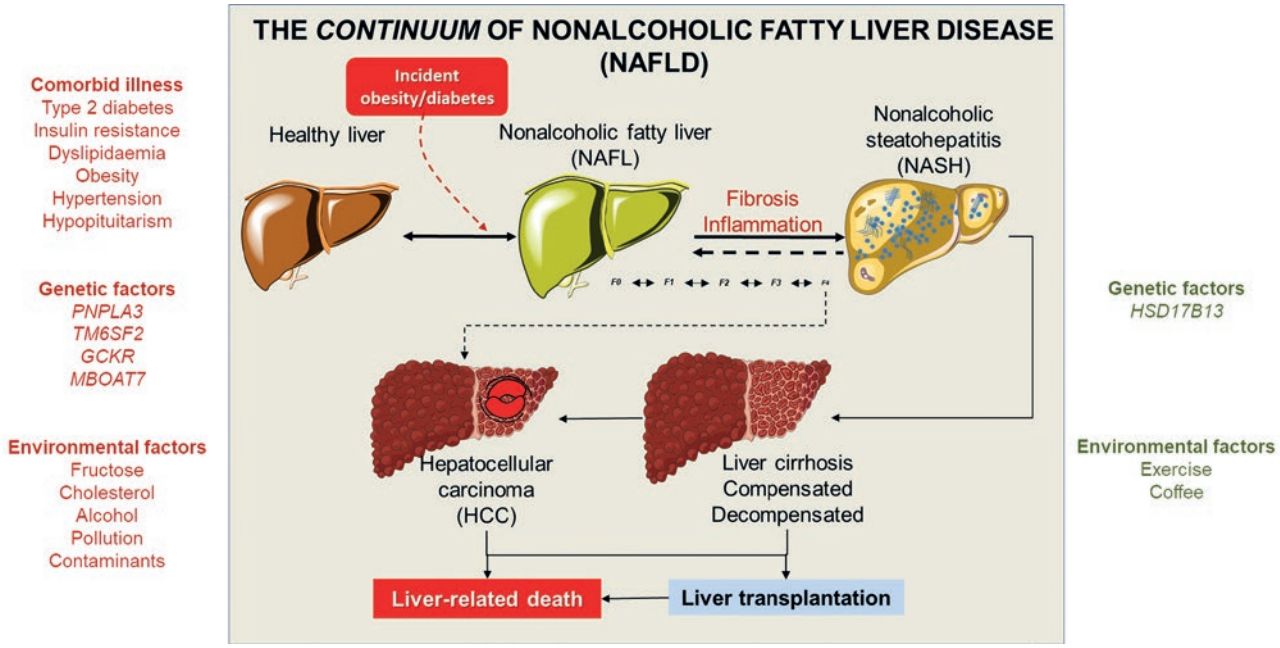


**Figura 1:** Sequenze che partecipano alla storia naturale della NAFLD. Entro ceri limiti la fibrosi è reversibile. A sinistra in rosso i fattori predisponenti, a destra in verde i fattori protettivi. Modificato da Powell et al, 2021 [3]

drome metabolica. In considerazione delle sue implicazioni fisiopatologiche sistemiche, la storia naturale della NAFLD non riguarda solo il danno epatico ma anche complicanze cardiovascolari come la fibrillazione atriale, il diabete, la patologia renale cronica e neoplasie extraepatiche.

In una metanalisi che ha esaminato 20 studi per complessivi circa 49.000 pazienti diabetici in diverse aree geografiche del mondo [7] le prevalenze di NAFLD e NASH erano rispettivamente al 68% ed al 37%, con riscontro di fibrosi avanzata (f3-f4) nel 17% dei pazienti sottoposti a biopsia. È anche da sottolineare che il 10-30% di soggetti non obesi possono presentare una NAFLD del soggetto magro, con le stesse implicazioni sistemiche e di rischio. Tali osservazioni rendono insufficiente il termine NAFLD che si basa sulla esclusione di condizioni morbigene ("non alcolica"). Negli scorsi anni tale terminologia ha causato confusione e incertezze anche nei pazienti con NAFLD, i quali ignorano di essere affetti da epatopatia fino al 96% dei casi. È necessaria una terminologia che indichi ciò che la patologia steatosica epatica rappresenta realmente in senso fisiopatologico, piuttosto ciò che "non rappresenta". Per questo, dal 2020 si è proposto di rinominare la NAFLD con l'acronimo MAFLD (Metabolic dysfunction Associated Fatty Liver Disease) [8]. MAFLD accomuna pazienti con steatosi che presentino almeno una tra le seguenti condizioni: sovrappeso-obesità, diabete mellito tipo 2 o evidenza di alterazioni metaboliche **(Figura 2)**[9]. Il termine permette una migliore classificazione dei soggetti affetti, e soprattutto di quelli a più elevato rischio cardiovascolare e renale. Una recente metanalisi e review sistematica ha esaminato un pool di oltre 3 milioni di individui, riscontrando una prevalenza di MAFLD del 38.8% in obesi, del 29.8% in non-obesi e del 5.4% in soggetti normopeso. Anche in questi due ultimi gruppi esiste una significativa associazione tra MAFLD, ipertensione e diabete [10]. L'impiego del temine MAFLD consente an che una migliore comprensione dei meccanismi fisiopatologici alla base della patologia e una maggiore realizzazione del rischio da parte della popolazione target. Riconoscere una MAFLD offre inoltre migliori possibilità terapeutiche, anche grazie a collaborazioni multidisciplinari tra internisti, cardiologi, epatologi, endocrinologi, nutrizionisti e medici di comunità. L'attenzione deve comunque restare alta anche per i casi di steatosi epatica apparentemente non metabolica. In questo campo sono indispensabili studi orientati alla patogenesi, al rischio e storia naturale della steatosi epatica, patologia la cui rilevanza clinica è ancora largamente sottovalutata e priva di una terapia definitiva. Poiché sono soprattutto obesità e sindrome metabolica a guidare la storia naturale della M(N)AFLD, i presidi terapeutici più immediati, in attesa di nuove strategie, rimangono i corretti stili di vita che includono raggiungimento/mantenimento del peso corporeo ideale con dieta appropriata e contrasto alla sedentarietà.

## Bibliografia

1. Portincasa P, Krawczyk M, Smyk W, Lammert F, Di Ciaula A. COVID-19 and non-alcoholic fatty liver disease: Two

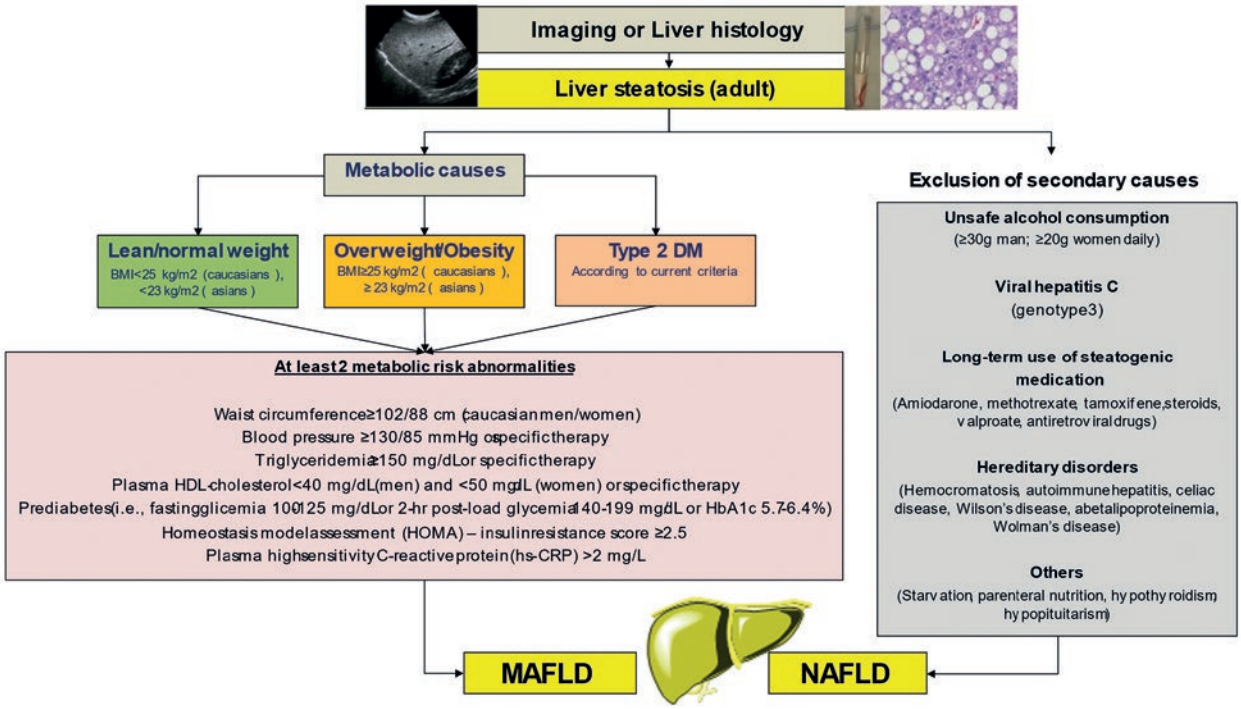


**Figura 2:** Il flowchart illustra le fasi essenziali richieste per porre una diagnosi "positiva" di MAFLD rispetto alla diagnosi di NAFLD che presuppone l'esclusione di cause secondarie. Modificato da Eslam et al. [9].

intersecting pandemics. European journal of clinical investigation. 2020;50:e13338.
2. Targher G, Tilg H, Byrne CD. Non-alcoholic fatty liver disease: a multisystem disease requiring a multidisciplinary and holistic approach. The lancet Gastroenterology & hepatology. 2021;6:578-88.
3. Powell EE, Wong VW, Rinella M. Non-alcoholic fatty liver disease. Lancet. 2021;397:2212-24.
4. Di Ciaula A, Bonfrate L, Portincasa P. The role of microbiota in nonalcoholic fatty liver disease. European journal of clinical investigation. 2022;52:e13768.
5. Di Ciaula A, Baj J, Garruti G, Celano G, De Angelis M, Wang HH, et al. Liver Steatosis, Gut-Liver Axis, Microbiome and Environmental Factors. A Never-Ending Bidirectional Cross-Talk. J Clin Med. 2020;9:2648.
6. Yarnoz-Esquiroz P, Olazaran L, Aguas-Ayesa M, Perdomo CM, Garcia-Goni M, Silva C, et al. 'Obesities': Position statement on a complex disease entity with multifaceted drivers. European journal of clinical investigation. 2022:e13811.
7. Younossi ZM, Golabi P, de Avila L, Paik JM, Srishord M, Fukui N, et al. The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: A systematic review and meta-analysis. Journal of hepatology. 2019;71:793-801.
8. Mendez-Sanchez N, Bugianesi E, Gish RG, Lammert F, Tilg H, Nguyen MH, et al. Global multi-stakeholder endorsement of the MAFLD definition. The lancet Gastroenterology & hepatology. 2022;7:388-90.
9. Eslam M, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez M, et al. A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. Journal of hepatology. 2020;73:202-9.
10. Chan KE, Koh TJL, Tang ASP, Quek J, Yong JN, Tay P, et al. Global Prevalence and Clinical Characteristics of Metabolic-associated Fatty Liver Disease: A Meta-Analysis and Systematic Review of 10 739 607 Individuals. The Journal of clinical endocrinology and metabolism. 2022;107:2691-700.

*RELAZIONI - OBESITÀ: ASPETTI INNOVATIVI DI UNA "NUOVA" MALATTIA INTERNISTICA*

# Il tessuto adiposo in oncologia: oltre l'obesità

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Il tessuto adiposo rappresenta un organo chiave nella regolazione dell'omeostasi energetica dell'organismo. Sono stati individuati due tipi principali di tessuto adiposo: il tessuto adiposo bianco (WAT) e il tessuto adiposo bruno (BAT) [1]. Il WAT è formato da cellule che presentano al loro interno un'unica grande goccia citoplasmatica in grado di accumulare e rilasciare grassi. In aggiunta alla funzione di "storage" lipidico, il WAT svolge funzioni di carattere endocrino, tra cui la secrezione di peptidi ed ormoni quali la leptina, l'adiponectina e di diverse citochine pro-infiammatorie (ad es. il TNF-alpha) [1]. Il BAT è composto da adipociti "bruni", caratterizzati da un elevato numero di mitocondri che, utilizzando glucosio e trigliceridi come substrato, generano calore. Oltre ai due principali tipi di adipociti, all'interno del WAT sono presenti adipociti con un fenotipo intermedio tra quello "bianco" e "bruno", chiamati "beige". Questi, se sottoposti a stimolazione β-adrenergica, a basse temperature, possono assumere attività termogenica [1, 2].

Un'alterata funzionalità del tessuto adiposo si associa a diverse condizioni cliniche a volte apparentemente opposte l'una dall'altra, come l'obesità e la cachessia.

Il WAT, responsabile dello storage lipidico, in condizioni di obesità diventa spesso ipertrofico e ciò è correlato a quadri clinici di dislipidemia, infiammazione e insulino-resistenza [2]. Tali alterazioni metaboliche, come l'infiammazione e l'insulino-resistenza, sono comuni anche in condizioni di cachessia associata a una sottostante neoplasia [2, 3]. In particolare, la cachessia neoplastica è definita come "una sindrome multifattoriale caratterizza dalla progressiva perdita di massa muscolare e tessuto adiposo, dovuta ad un consumo energetico alterato secondario alla presenza di neoplasia" **(Figura 1)** [3, 4]. La presenza del tumore induce il rilascio di citochine pro-infiammatorie (TNF alpha, IL-1, IL-6, IFN-gamma) e altri fattori circolanti in grado di favorire i processi catabolici nei tessuti periferici, principalmente muscolo scheletrico e tessuto adiposo [3]. Relativamente a quest'ultimo recenti dati di letteratura ne sot-

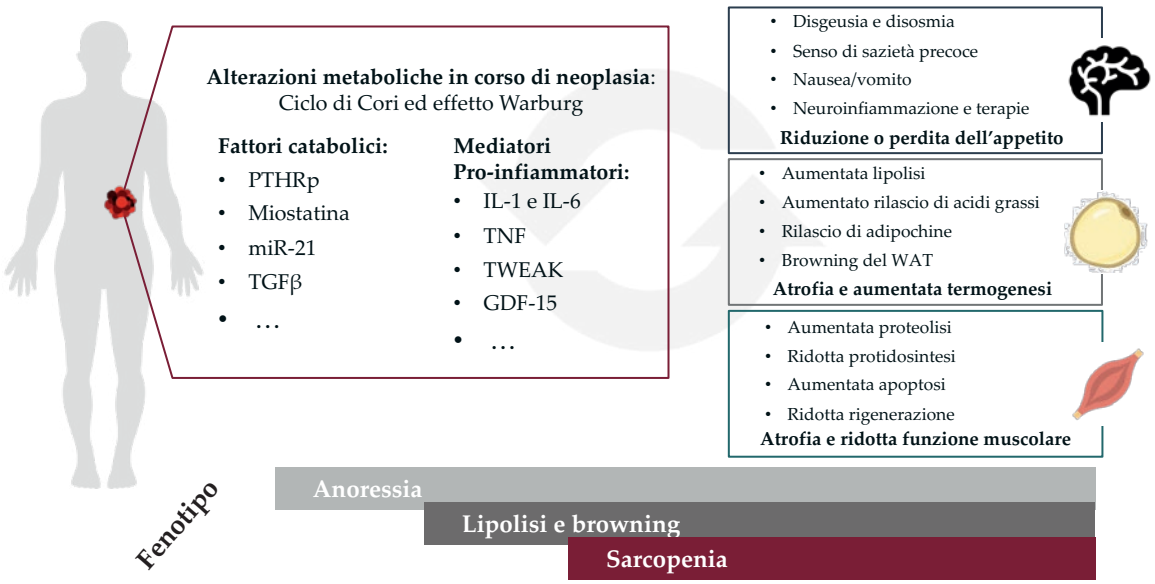


**Figura 1**

tolineano il ruolo chiave nelle modificazioni metaboliche della spesa energetica in corso di tumore. I due principali meccanismi coinvolti nell'alterazione del tessuto adiposo nei modelli sperimentali e nell'uomo, ritenuti svolgere un ruolo eziopatogenetico nella cachessia, sono principalmente la lipolisi e il fenomeno del "browning" del WAT [5, 6] **(Figura 2)**. Questi meccanismi comporterebbero un aumentato rilascio in circolo di acidi grassi liberi e di intermedi della lipolisi, favorendo il processo di insulino-resistenza e atrofia del tessuto adiposo.

Nei pazienti con cachessia neoplastica l'attività di hormone sensitive lipase (HSL) e adipose triglyceride lipase (ATGL), enzimi chiave della lipolisi, è incrementata [2]. In aggiunta, il processo di browning del WAT (i.e., il fenomeno della modificazione degli adipociti in beige nel WAT) sembrerebbe rappresentare un evento particolarmente rilevante per i processi catabolici durante patologia neoplastica, attraverso l'aumentata attività termogenica di tale tessuto [2].

Oggetto di interesse scientifico è, inoltre, la matrice extracellulare del tessuto adiposo, che sia in condizioni di obesità che di cachessia neoplastica sembrerebbe essere particolarmente fibrotica, probabilmente in seguito a stimolazione dei fibroblasti da parte di cellule infiammatorie, quali i macrofagi [2, 7].

Chiarire i meccanismi della disregolazione metabolica del tessuto adiposo in corso di neoplasia rappresenta un importante target per la diagnosi e le terapie della cachessia, al fine di migliorare lo stato metabolico-nutrizionale dei pazienti neoplastici e la risposta alle terapie anti-tumorali, inoltre con lo scopo di impattare positivamente sulla prognosi e la qualità di vita.

## Bibliografia


1. M.Cypess, M.D., Ph.D. Reassessing Human Adipose Tissue. N Engl J Med 2022;386:768-79. doi: 10.1056/NEJMra2032804
2. Vegiopoulos A, Rohm M, Herzig S. Adipose tissue: between the extremes. EMBO J. 2017 Jul 14;36(14):1999-2017. doi: 10.15252/embj.201696206
3. Baracos VE, Martin L, Korc M, et al. Cancer-associated cachexia. Nat Rev Dis Primers. 2018 Jan 18;4:17105. doi: 10.1038/nrdp.2017.105
4. Fearon K, Strasser F, Anker SD, et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol. 2011;12:489-95. doi: 10.1016/S1470-2045(10)70218
5. Molfino A, Imbimbo G, Muscaritoli M. Role of metabolic changes of adiposity in cancer. Trends Endocrinol Metab. 2021;32:957. doi: 10.1016/j.tem.2021.08.007.
6. Molfino A, Belli R, Imbimbo G, et al. Evaluation of Browning Markers in Subcutaneous Adipose Tissue of Newly Diagnosed Gastrointestinal Cancer Patients with and without Cachexia. Cancers (Basel). 2022 Apr 12;14(8):1948.
7. Molfino A, Carletti R, Imbimbo G, et al. Histomorphological and inflammatory changes of white adipose tissue in gastrointestinal cancer patients with and without cachexia. J Cachexia Sarcopenia Muscle. 2022;13:333-342. doi: 10.1002/jcsm.12893.


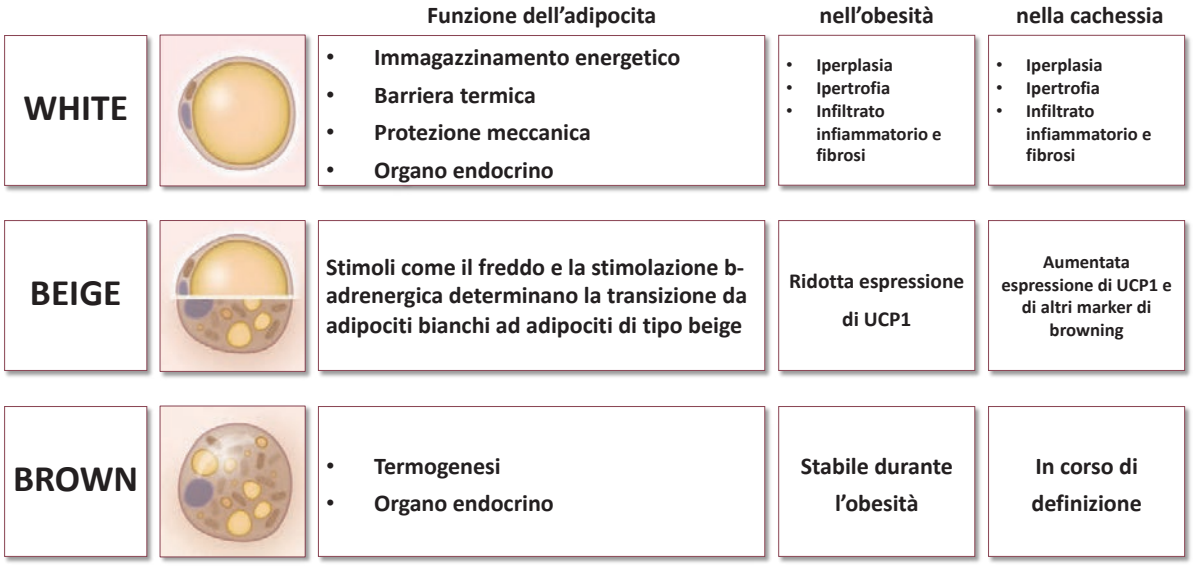


**Figura 2**

# Utilizzo della terapia antiaggregante in prevenzione primaria: i risultati dei trial clinici

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L'assunzione cronica di acido acetilsalicilico (ASA) a basse dosi in prevenzione cardiovascolare primaria ha rappresentato, per oltre un ventennio, una sorta di "dogma" terapeutico per i soggetti considerati ad elevato rischio cardiovascolare. Addirittura vi è una pletora di soggetti, tutt'altro che esigua, che assume arbitrariamente ASA a scopo antitrombotico senza prescrizione medica.

Già sul finire dell'ultimo decennio sono cominciati ad apparire dati in letteratura, in forma di meta-analisi di dati individuali, che gettavano un'ombra sull'effettiva utilità di ASA in prevenzione primaria [1]. Negli ultimi 5 anni molti altri risultati di trials clinici e meta-analisi semberebbero aver fornito supporto numerico a tali dubbi, fino ad indurre le società internazionali [2,3], da sempre indirizzanti il "mainstream" scientifico, a riconsiderare drasticamente le principali indicazioni all'utilizzo di ASA nelle più recenti edizioni delle linee guida estese nell'anno appena trascorso.

Si è trattato di un abbaglio? Oppure la letteratura veramente ci suggerisce di cambiare atteggiamento? I tre principali trials clinici in questione, da cui sarebbero emerse tali evidenze, meritano di essere letti nel dettaglio.

Lo studio ARRIVE [4] ha randomizzato pazienti di età superiore a 55 anni e con rischio cardiovascolare elevato all'utilizzo di ASA 100 mg vs placebo per un periodo medio di circa 5 anni. Si è osservata una riduzione di significativa di circa il 45% di IMA non fatali (number needed to treat 145), mentre non vi erano effetti significativi sull'insorgenza di stroke, TIA ed eventi anginosi. Di entità relativamente simile in termini assoluti (NNT 216), risultava essere il numero degli eventi emorragici (gastrointestinali e cerebrali), sebbene nella grande maggioranza le emorragie digestive erano lievi o moderate. Interessante notare come in questo trial l'incidenza di eventi nel gruppo controllo era significativamente inferiore rispetto a quanto atteso (i soggetti arruolati dovevano avere un rischio cardiovasolare elevato) e decisamente più in linea con un livello di rischio lieve o intermedio.

Lo studio ASCEND [5] ha arruolato soggetti diabetici per un periodo di circa 7 anni. In questo caso, il beneficio in termini di riduzione di eventi cardiaci appariva ancora più esiguo di quanto osservato nello studio ARRIVE e non raggiungeva la significatività statistica. Sebbene vi fosse un debole trend significativo quando gli eventi trombotici venivano accorpati in un end-point composito, decisamente superiori risultavano le emorragie cerebrali ed emorragie digestive gravi (+33%, NNT 160) nei trattati vs gruppo placebo. Anche in questo caso le incidenze reali di eventi trombotici risultavano inferiori a quanto atteso.

Lo studio ASPREE [6] si è rivolto ad una popolazione over 70, anch'essi arruolati ad ASA vs placebo. Anche in questo caso risultava piuttosto esiguo il numero delle morti cardiovascolari ed addirittura vi era un eccesso significativo di morti da ogni causa nel gruppo trattato con ASA rispetto a placebo, in gran parte queste ultime rappresentate da morti per neoplasia. Dato, quest'ultimo, assolutamente soprendente ed in controtendenza rispetto agli studi osservazionali che avevano individuato ASA come potenziale agente protettivo nei confronti dell'insorgenza del cancro del colon.

In generale i risultati dei trial clinici convergono, in maniera più o meno concorde, su tre punti principali: 1. L'efficacia di ASA nel ridurre gli eventi di natura cardiaca o cardiovascolare è esigua, sebbene significativa; essa è controbilanciata, pressochè in eugual misura, da un elevato rischio di eventi emorragici maggiori che ne restringe il beneficio clinico effettivo. 2- Rischio trombotico ed emorragico riconoscono, in larga parte, gli stessi fattori di rischio (es. età avanzata, insufficienza renale e pressione arteriosa). Ciò rende difficile, ed in alcuni casi impossibile, scorporare in ogni singolo paziente l'entità di tali rischi, anche se ciò costituirebbe senza ombra di dubbio l'unica strategia valida ed appropriata. 3- Negli ultimi 20 anni il rischio cardiovascolare si è progressivamente ridotto, anche per effetto di altri interventi preventivi efficaci (es. profilassi primaria con statine negli ipercolesterolemici). La concomitante

riduzione dell'incidenza di eventi ha ancor più "diluito" il beneficio legato alla profilassi con ASA. Tale approccio terapeutico, tuttavia, rimane assolutamente valido in forma di principio, in quanto fondato su solide basi razionali. La possibilità di manipolare il rischio emorragico del paziente attraverso opzioni farmacologiche mirate, la ricerca di nuove molecole di pari efficacia e maggior sicurezza rispetto ad ASA, ed una strategia più effiace per la predizione del rischio cardiovascolare nel singolo individuo rappresentano, al momento, le principali linee di ricerca e sviluppo per gli anni futuri.

**Bibliografia**


1. Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet. 2009;373:1849-1860
2. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M et al, 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2021;42:3227-3337
3. Davidson KW, Barry MJ, Mangione CM, Cabana M, Chelmow D, Coker TR et al. Aspirin Use to Prevent Cardiovascular Disease: US Preventive Services Task Force Recommendation Statement. JAMA. 2022;327:1577-1584
4. Gaziano JM, Brotons C, Coppolecchia R, Cricelli C, Darius H, Gorelick PB et al. Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease ARRIVE.: a randomised, double-blind, placebo-controlled trial. Lancet. 2018;392:1036-1046
5. Bowman L, Mafham M, Wallendszus K, Stevens W, Buck G, Barton J et al. Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus. N Engl J Med. 2018;379:1529-1539
6. McNeil JJ, Nelson MR, Woods RL, Lockery JE, Wolfe R, Reid CM et al. ASPREE Investigator Group. Effect of Aspirin on All-Cause Mortality in the Healthy Elderly. N Engl J Med. 2018;379:1519-1528

# Biomarcatori strumentali di danno aterosclerotico: hanno un valore aggiuntivo?

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La malattia cardiovascolare è la principale causa di morte del mondo e questo sottolinea l'importanza della prevenzione cardiovascolare primaria, prima che si manifestino eventi cardiovascolari fatali e non. Gli sforzi per migliorare l'identificazione dei soggetti a maggior rischio di sviluppare un primo evento cardiovascolare si sono in gran parte concentrati su nuovi parametri – biomarcatori – con un significativo valore predittivo di malattie cardiovascolari [1]. Ad oggi sono stati proposti centinaia di biomarcatori, la maggior parte dei quali derivanti dalla misurazione dei livelli plasmatici di alcune sostanze. Molti di essi hanno mostrato una buona associazione statistica con l'incidenza di eventi successivi, ma in generale, solo un modesto miglioramento del valore predittivo dei punteggi attuali [2]. Al contrario, la valutazione dell'aterosclerosi subclinica, con varie modalità, ha chiaramente dimostrato un beneficio aggiuntivo sostanziale [3]. Nell'ultimo decennio, numerose evidenze scientifiche hanno evidenziato il ruolo della valutazione dell'aterosclerosi subclinica mediante biomarcatori strumentali di imaging non invasivo; tra questi, di maggior risvolto nella pratica clinica sono la valutazione di aterosclerosi coronarica mediante il coronary artery calcium (CAC) score e di aterosclerosi carotidea e femorale mediante ecocolordoppler. I principali studi prospettici di coorte quali il MESA, Heinz Nixdorf e Rotterdam hanno soprattutto evidenziato che il CAC score è un valido biomarcatore strumentale nella riclassificazione del rischio cv nei pazienti asintomatici in prevenzione primaria, soprattutto nei soggetti a rischio cv intermedio [4–6]**(Tabella 1)**. Inoltre, lo studio condotto da Yeboah pubblicato su JACC ha evidenziato che tra vari fattori di rischio non tradizionali (PCR, ABI index e familiarità per eventi cardiovascolari precoci) il CAC score era l'unico a migliorare la valutazione del rischio cv [7]. Infine, Folsom ha evidenziato nello studio MESA che CAC score prediceva meglio gli eventi cv rispetto alla valutazione dello spessore medio-intimale [8]. La presenza di aterosclerosi carotidea e femorale riveste un ruolo di rilievo soprattutto per quanto riguarda sono la valutazione del "carico aterosclerotico" (atherosclerotic burden); infatti, diverse evidenze scientifiche hanno dimostrato che il danno aterosclerotico in diversi siti facilmente esplorabili nella pratica clinica quale il distretto carotideo e femorale sia associato ad un aumentato rischio di eventi cardiovascolari e di mortalità, sia in soggetti in prevenzione primaria che in prevenzione secondaria. In linea con tali evidenze scientifiche, le linee guida europee 2019 delle Società Europea di Cardiologia e della Società Europea di Aterosclerosi cosi come la Task Force Europea di pre-

| Studi | % Riclassificazione | Numero di soggetti | Età, anni | Follow-up, anni |
|---|---|---|---|---|
| **MESA** | | 5878 | 62.2 | 5.8 |
| FRS 0%–6% | 11.6 | | | |
| FRS 6%–20% | 54.4 | | | |
| FRS > 20% | 35.8 | | | |
| NRI | 25 | | | |
| **Heinz Nixdorf** | | 4487 | 45–75 | 5.0 |
| FRS < 10% | 15.0 | | | |
| FRS 10%-20% | 65.6 | | | |
| FRS > 20% | 34.2 | | | |
| NRI | 22.4 | | | |
| **Rotterdam** | | 2028 | 69.6 | 9.2 |
| FRS < 10% | 12 | | | |
| FRS 10%-20% | 52 | | | |
| FRS > 20% | 34 | | | |
| NRI | 19 | | | |
| I dati sono presentati come medie e percentuali. CAC = coronary artery calcium, MESA = Multi-Ethnic Study of Atherosclerosis, FRS = Framingham Risk Score, NRI = net reclassification index, | | | | |

**Tabella 1:** Riclassificazione del rischio cardiovascolare mediante l'utilizzo del CAC score.

venzione cardiovascolare (2021) hanno raccomandato la valutazione del carico aterosclerotico (coronarico mediante CAC e carotideo/femorale mediante ecocolordoppler) nel migliorare la stratificazione cardiovascolare della popolazione, specie in prevenzione primaria [9,10]

**Bibliografia**


1. Osei AD, Blaha MJ. Combining Biomarkers and Imaging for Short-Term Assessment of Cardiovascular Disease Risk in Apparently Healthy Adults: A Paradigm-Shifting Approach? J Am Heart Assoc [Internet]. 2020 Aug 4 [cited 2022 Aug 27];9(15). Available from: https://pubmed.ncbi.nlm.nih.gov/32698709/
2. Kremers B, Wübbeke L, Mees B, Ten Cate H, Spronk H, Ten Cate-Hoek A. Plasma Biomarkers to Predict Cardiovascular Outcome in Patients With Peripheral Artery Disease: A Systematic Review and Meta-Analysis. Arterioscler Thromb Vasc Biol [Internet]. 2020 [cited 2022 Aug 27];40(9):2018–32. Available from: https://pubmed.ncbi.nlm.nih.gov/32640905/
3. Castellon X, Bogdanova V. Screening for subclinical atherosclerosis by noninvasive methods in asymptomatic patients with risk factors. Clin Interv Aging [Internet]. 2013 May 27 [cited 2022 Aug 27];8:573–80. Available from: https://pubmed.ncbi.nlm.nih.gov/23761967/
4. Erbel R, Möhlenkamp S, Moebus S, Schmermund A, Lehmann N, Stang A, et al. Coronary risk stratification, discrimination, and reclassification improvement based on quantification of subclinical coronary atherosclerosis: the Heinz Nixdorf Recall study. J Am Coll Cardiol. 2010 Oct;56(17):1397–406.
5. Elias-Smale SE, Proença RV, Koller MT, Kavousi M, Van Rooij FJA, Hunink MG, et al. Coronary calcium score improves classification of coronary heart disease risk in the elderly: the Rotterdam study. J Am Coll Cardiol [Internet]. 2010 Oct 19 [cited 2022 Aug 27];56(17):1407–14. Available from: https://pubmed.ncbi.nlm.nih.gov/20946998/
6. Polonsky TS, McClelland RL, Jorgensen NW, Bild DE, Burke GL, Guerci AD, et al. Coronary artery calcium score and risk classification for coronary heart disease prediction. JAMA [Internet]. 2010 Apr 28 [cited 2022 Aug 27];303(16):1610–6. Available from: https://pubmed.ncbi.nlm.nih.gov/20424251/
7. Yeboah J, Young R, McClelland RL, Delaney JC, Polonsky TS, Dawood FZ, et al. Utility of Nontraditional Risk Markers in Atherosclerotic Cardiovascular Disease Risk Assessment. J Am Coll Cardiol. 2016 Jan;67(2):139–47.
8. Folsom AR, Kronmal RA, Detrano RC, O'Leary DH, Bild DE, Bluemke DA, et al. Coronary Artery Calcification Compared With Carotid Intima-Media Thickness in the Prediction of Cardiovascular Disease Incidence<subtitle>The Multi-Ethnic Study of Atherosclerosis (MESA)</subtitle> Arch Intern Med. 2008 Jun;168(12):1333.
9. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020 Aug 31;41(1):111–88.
10. Visseren FLJ, MacH F, Smulders YM, Carballo D, Koskinas KC, Bäck M, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J [Internet]. 2021 Sep 7 [cited 2022 Aug 27];42(34):3227–337.

# Lp(a) e rischio cardiovascolare: questione di kringle

**Giuseppe Mandraffino**



La lipoproteina(a) (Lp(a)) è una lipoparticella costituta da una molecola di Apo(a) legata ad una molecola di ApoB100, individuata per la prima volta nel 1963 da Berg e poi successivamente meglio caratterizzata dal punto di vista biochimico nel 1974 dallo stesso gruppo di ricerca. È noto ormai da tempo che i valori plasmatici di Lp(a) siano fortemente condizionati da aspetti genetici ereditabili. In effetti, studi più recenti hanno confermato che i livelli di Lp(a) siano geneticamente determinati per oltre il 90%; solo come esempio, per giustificare i livelli plasmatici di altre lipoproteine è necessario valutare l'arrangiamento di oltre 160 geni. Il gene per Apo(a) presenta delle caratteristiche assai peculiari: la sequenza appare strettamente correlata a quella che codifica per il plasminogeno, tanto da convincere diversi ricercatori che si tratti dello stesso gene duplicato in un'epoca primordiale per la vita umana, e poi successivamente andato incontro a diverse mutazioni sino ai giorni nostri. Come il gene del plasminogeno, infatti, presenta delle sequenze specifiche caratteristiche, definite kringle (K), che nel gene per Apo(a) sarebbero andate delete a parte KIV e KV; KIV si presenta con diverse varianti, identificate da numeri che vanno da 1 a 10; in particolare il numero di ripetizioni KIV-2 sembra essere strettamente – ed in modo non-lineare - associato ai valori plasmatici. Inoltre, KIV-2 può presentarsi con sequenze differenti; il numero di SNPs individuati a cario di questa regione cresce ogni giorno, così come le associazioni tra le varianti ed i valori plasmatici. Queste evidenze confermano in maniera inequivocabile lo strettissimo controllo genico di questa particolare lipoparticella.

I valori plasmatici di Lp(a) sono stati associati con diversi aspetti della malattia cardiovascolare; se inizialmente era stato prospettato un contributo di Lp(a) nel determinismo della malattia aterosclerotica e nella stenosi valvolare aortica solamente per livelli estremamente elevati di L(a), il suo ruolo è oggi dimostrato secondo una associazione di tipo continuo.

Studi di associazione GWAS (GenomeWide Association Studies) hanno confermato che Lp(a) ha un ruolo causale nella malattia coronarica aterosclerotica, nella degenerazione valvolare aortica, nello scompenso cardiaco e nella malattia aterosclerotica periferica.

Per contro, la stessa tipologia di approccio ha permesso di sottolineare come soggetti con varianti genetiche che condizionano sin dalla nascita bassi livelli plasmatici di Lp(a) presentino un rischio significativamente inferiore di andare in contro a: stroke (-13%), malattia renale cronica (-9%), stenosi valvolare aortica (-37%), scompenso cardiaco (-17%), arteriopatia obliterante cronica periferica (-31%), e coronaropatia aterosclerotica (-29%).

Una relazione particolare che merita una menzione a parte è rappresentata dalla associazione dei valori di Lp(a) con la malattia diabetica; ridotti valori di Lp(a) sono risultati predittivi di sviluppo di diabete mellito tipo2, e d'altro canto è infrequente che pazienti diabetici presentino elevati valori plasmatici di Lp(a). Un dato interessante correla i valori di Lp(a) con il grado di sensibilità insulinica, ed è stato suggerito che il miglioramento dello stato di insulinoresistenza possa essere associato ad un incremento significativo delle concentrazioni di Lp(a).

Benchè oramai non vi siano dubbi sul ruolo patogenico di Lp(a), ad oggi le opzioni terapeutiche sono assai limitate; non sono ancora disponibili per l'impiego clinico terapie specificatamente disegnate per ridurre i valori plasmatici Lp(a), sebbene alcune molecole siano attualmente in fase di sviluppo.

Le statine – pietra angolare nel trattamento del rischio cardiovascolare - non modificano favorevolmente i livelli di Lp(a). La niacina riduce in media i livelli del 20% e gli inibitori di CETP del 20-40%; tuttavia, non è stato dimostrato alcun beneficio cardiovascolare. Per contro, gli anticorpi monoclonali che inibiscono PCSK9 in hanno dimostrato di ridurre in media le concentrazioni del 25%, candidandosi a terapia di riferimento nel paziente ipercolesterolemico

con Lp(a) elevata. L'aferesi lipoproteica può ridurre i valori anche del 75%, con una riduzione media interdialitica di circa il 35%. Vi sono poi farmaci innovativi, come gli oligonucleotidi antisenso (ASO): il mipomersen, un ASO che inibisce la traduzione del mRNA ApoB, riduce Lp(a) di 20-30%. Ma il futuro potrebbe essere rappresentato da una nuova molecola in studio ormai da diversi anni, attualmente identificata come APO(a)LRx: riconosce specificatamente mRNA per Apo(a) ed ha dimostrato riduzioni fin'oltre 80% negli studi di fase2. Per adesso, modificare il RCV nei pazienti con elevati valori di Lp(a) vuol dire soprattutto controllare nel migliore modo possibile gli altri determinanti del RCV con al migliore terapia oggi disponibile.

**Bibliografia**


- Bartoli-Leonard F, Turner ME, Zimmer J, Chapurlat R, Pham T, Aikawa M, Pradhan AD, Szulc P, Aikawa E. Elevated lipoprotein(a) as a predictor for coronary events in older men. J Lipid Res. 2022 Aug;63(8):100242. doi: 10.1016/j.jlr.2022.100242. Epub 2022 Jun 18. PMID: 35724702; PMCID: PMC9304778.
- Clarke, R., Peden, J. F., Hopewell, J. C., Kyriakou, T., Goel, A., Heath, S. C., et al. (2009) Genetic variants associated with Lp(a) lipoprotein level and coronary disease. N. Engl. J. Med. 361, 2518–2528.
- Emdin, C. A., Khera, A. V., Natarajan, P., Klarin, D., Won, H. H., Peloso, G. M., et al. (2016) Phenotypic characterization of genet- ically lowered human lipoprotein(a) levels. J. Am. Coll. Cardiol. 68, 2761–2772.
- Kamstrup, P. R., and Nordestgaard, B. G. (2016) Elevated lipoprotein(a) levels, LPA risk genotypes, and increased risk of heart failure in the general population. JACC Heart Fail. 4, 78–87.
- Kronenberg F, Mora S., Stroes E, Ference B, Arsenault B, Berglund L, et al; Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society consensus statement. European Heart Journal (2022) 0, 1–22 https://doi.org/10.1093/eurheartj/ehac361.
- Kronenberg, F. (2016) Human genetics and the causal role of lipoprotein(a) for various diseases. Cardiovasc. Drugs Ther. 30, 87–100
- Langsted A, Nordestgaard BG. Antisense Oligonucleotides Targeting Lipoprotein(a). Curr Atheroscler Rep. 2019 May 20;21(8):30. doi: 10.1007/s11883-019-0792-8. PMID: 31111240.
- Nordestgaard, B. G., and Langsted, A. (2016) Lipoprotein (a) as a cause of cardiovascular disease: insights from epidemiology, genetics, and biology. J. Lipid Res. 57, 1953–1975
- Thanassoulis, G., Campbell, C. Y., Owens, D. S., Smith, J. G., Smith, A. V., Peloso, G. M., et al. (2013) Genetic associations with valvular calcification and aortic stenosis. N. Engl. J. Med. 368, 503–512

# I farmaci per terapia cellulare avanzata: loro produzione ed inquadramento regolatorio

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Un settore della biomedicina che sta offrendo importanti opportunità per la terapia di patologie fino ad ora incurabili è quello dei *prodotti di terapia cellulare avanzata* (ATMP). Il Regolamento (CE) n. 1394/2007 [1] disciplina gli ATMP destinati ad essere immessi in commercio ed integra quanto già stabilito nella Direttiva 2001/83/CE [2]. Esso classifica i prodotti di terapia avanzata in prodotti di terapia genica, *prodotti di terapia cellulare somatica e prodotti dell'ingegneria tissutale*. Esso introduce il concetto di *rilevante manipolazione* e si riferisce ad attività quali l'espansione cellulare *in vitro*, la modificazione genetica, la differenziazione/attivazione con fattori di crescita. La definizione di rilevante manipolazione ha permesso di distinguere fra ATMP e trapianto di tessuti e cellule umani. Oltre alle tre precedenti classi, è stata anche definita la *terapia avanzata combinata* che definisce come ATMP un prodotto che incorpora uno o più dispositivi medici.

Gli ATMP sono farmaci [3]e in Italia devono essere prodotti in Officine Farmaceutiche autorizzate dall' Agenzia Italia del Farmaco secondo gli standard definiti dalle Buone Pratiche di Fabbricazione (GMP) [4]. Il loro utilizzo sperimentale deve sottostare alle norme specifiche sulla sperimentazione clinica secondo quanto previsto dal Regolamento (CE) n. 536/2014 [5]. Di nota, agli ATMP è stato riservato un modello alternativo di autorizzazione d'uso rappresentato dall' *Hospital Exemption* [6] ovvero l'uso non ripetitivo limitato a singoli pazienti in mancanza di valida alternativa terapeutica, nei casi di urgenza ed emergenza che pongono il paziente in pericolo di vita o di grave danno alla salute. In questa direzione, le *cell factory* ospedaliere stanno acquisendo un ruolo sempre più rilevante nella produzione e nella sperimentazione clinica degli ATMP. È importante sottolineare che *l'Hospital Exemption* non deve sostituire una sperimentazione clinica controllata ma solo concedere l'accesso ad una terapia innovativa in caso di *unmet clinical need*.

Le GMP per gli ATMP [4] sono il documento chiave per l'organizzazione di una *cell factory* per la produzione di ATMP in termini di organizzazione del personale, sistema di assicurazione della qualità, laboratori di produzione, di controllo di qualità e criteri di rilascio del prodotto finito. Il personale gioca un ruolo cruciale nella produzione di ATMP, dove le attività umane sono preponderanti a causa della natura biotecnologica del prodotto e delle difficoltà di automazione. Inoltre, ogni sito di produzione deve avere almeno una Persona Qualificata con provata esperienza in biologia cellulare, biotecnologia, lavorazione cellulare. Deve dotarsi inoltre un Responsabile di Produzione ed un Responsabile del Controllo di Qualità. Poiché gli ATMP non possono essere sterilizzati in modo terminale, devono essere fabbricati in asepsi in un'area di classe A-GMP situata in una ambiente di classe B-GMP (*background*).

Gli ATMP sono caratterizzati da variabilità biologica e da una farmacodinamica e farmacocinetica solo parzialmente definibili. In questo scenario, il processo di produzione deve essere solidamente convalidato. In particolare, la convalida dei metodi analitici va eseguita secondo le linee guida stabilite dall' *International Council on Harmonization* [7].

In conclusione, gli ATMP si pongono quale nuova frontiera della medicina. Rimangono tuttavia molte questioni aperte riguardo il costo e la rimborsabilità, la loro produzione ed utilizzo in ambito ospedaliero piuttosto che industriale, la complessità del processo produttivo e di sperimentazione clinica. Questioni che diventa sempre più urgente risolvere a livello legislativo e tecnico in considerazione del numero crescente di ATMP in sperimentazione o già in pratica clinica.

## Bibliografia

1. Regolamento (Ce) N. 1394/2007 del Parlamento Europeo e del Consiglio del 13 novembre 2007 sui medicinali per terapie avanzate recante modifica della Direttiva 2001/83/CE e del Regolamento (CE) N. 726/2004.
2. Direttiva 2001/83/CE del Parlamento Europeo e del Consiglio del 6 novembre 2001 recante un codice comunitario relativo ai medicinali per uso umano.
3. Ciccocioppo R., Comoli P., Astori G., Del Bufalo F., Prapa

M., Dominici M., Locatelli F. Developing cell terapies as drug products. Br J Pharmacol. 2021 Jan;178(2):262-279. doi: 10.1111/bph.15305. Epub 2020 Dec 9.
4. European Commission. Guidelines on Good Clinical Practice specific to Advanced Therapy Medicinal Products (2019).
5. Regolamento (CE) N. 536/2014 del Parlamento Europeo e del Consiglio del 16 aprile 2014 sulla sperimentazione clinica di medicinali per uso umano e che abroga la Direttiva 2001/20/CE.
6. DECRETO 16 gennaio 2015. Disposizioni in materia di medicinali per terapie avanzate preparati su base non ripetitiva. (GU Serie Generale n.56 del 09-03-2015).
7. ICH Topic Q 2 (R1). Note for guidance on validation of analytical procedures: text and methodology (CPMP/ICH/381/95).

# L'introduzione di soluzioni di telemedicina nel percorso di cura e assistenza dei pazienti

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È ormai un fatto acquisito come la pandemia Covid abbia definitivamente reso la telemedicina una modalità accettata e diffusa per l'erogazione di servizi sanitari, come complemento delle attività in presenza. La "Survey sulle soluzioni di telemedicina implementate dalle aziende sanitarie" [1], condotta alla fine del 2021 dall'Osservatorio sulla Telemedicina Operativa [2] dell'ALTEMS [3], l'Alta Scuola di Economia e Management sui Sistemi Sanitari dell'Università Cattolica del Sacro Cuore, ha fotografato 278 scenari implementati da 128 aziende su tutto il territorio nazionale

Considerata l'esigenza di estrema rapidità nell'implementazione, le soluzioni realizzate si sono basate su strumenti e tecnologie molto differenti (a partire dal semplice contatto telefonico) e sono state in gran parte circoscritte al supporto a singole attività di cura ed assistenza, indipendentemente dal contesto complessivo del percorso di cura del paziente.

L'obiettivo principale, adesso, deve quindi essere quello di "mettere a sistema" quanto realizzato sotto la spinta dell'emergenza, per integrare le soluzioni realizzate all'interno dei processi clinico-assistenziali e poter capitalizzare sui risultati raggiunti utilizzandoli come base per i successivi passi di evoluzione digitale del sistema sanitario, nell'ottica della continuità del percorso di cura del paziente.

Le piattaforme nazionali e regionali previste entro i prossimi tre anni nell'ambito del PNRR [4] rappresenteranno, quando operative, l'infrastruttura di riferimento comune con la quale dovranno integrarsi i singoli contesti. Queste piattaforme implementeranno un modello di riferimento generico per le varie attività e quindi, da sole, non potranno soddisfare le esigenze peculiari dei singoli centri e patologie ("one size does not fit all"), garantendo quanto evidenziato anche dal DM 77 del 22.05.2022: ***"le prestazioni di telemedicina non sostituiscono completamente le prestazioni assistenziali tradizionali, ma le integrano per migliorarne efficacia, efficienza, appropriatezza e sostenibilità"***.

In altre parole, la telemedicina non deve ridursi ad un prodotto tecnologico e/o ad una attività autonoma, alternativa e scollegata con le attività in presenza, ma deve costituire una risorsa aggiuntiva, complementare alle attività tradizionali e praticabile qualora le condizioni del paziente lo consentano. A seconda delle esigenze e delle opportunità, che possono variare nel corso del tempo ed a fronte dello stato di salute del paziente, deve quindi essere possibile erogare prestazioni in presenza e/o in telemedicina, assicurando la continuità e la coerenza del percorso di cura e l'integrità del quadro clinico del paziente in modo da assicurare la completezza e la sicurezza della decisione medica **(Figura 1)**.


**Figura 1:** La prestazione in telemedicina deve rispecchiare lo stesso processo clinico-organizzativo e fare uso degli stessi strumenti informatici e/o manuali usati in presenza

Gli scenari risultanti devono quindi tener conto dei requisiti delle specifiche patologie e contesti clinico-organizzativi esistenti nonché essere integrati con i sistemi informatici già in uso (prenotazione, lista di lavoro, cartella clinica, prescrizione, refertazione, rendicontazione) sia a livello aziendale che regionale. Solo così si possono evitare frammentazioni nei dati (si pensi alle cartelle cliniche specialistiche, diverse per ogni patologia e per ogni Centro), assicurando la coerenza del processo clinico-organizzativo e l'uniformità nella cura del paziente indipendentemente dal setting: in presenza o in telemedicina.

Con questo obiettivo, considerando la molteplicità e la diversità delle esigenze, l'introduzione della telemedicina nel percorso di cura in uno specifico Centro e per una specifica patologia deve iniziare necessariamente con l'analisi del processo clinico-organizzativo attualmente in essere, identificando quelle attività che possono essere eseguite -e nel caso ottimizzate- tramite una interazione remota con il paziente.

Come in tutte le iniziative di cambiamento, questa evoluzione non è un processo semplice né immediato: prima ancora degli aspetti tecnologici, fondamentali sono la gradualità di introduzione nei contesti già operativi, la formazione e il cambiamento culturale sia negli operatori sanitari che nei pazienti (che assumono un ruolo diverso, molto più proattivo) e la possibilità di introdurre rapidamente in corso d'opera miglioramenti ed ottimizzazioni individuabili solo dall'esperienza sul campo, sia dal punto di vista clinico-organizzativo che relativamente ai benefici per i pazienti.

Sulla base dei risultati positivi ottenuti dall'iniziativa "Telemedicina Subito!" [5] condotta fin dall'inizio della pandemia dall'Osservatorio sulla Telemedicina Operativa dell'ALTEMS in collaborazione con circa 40 aziende sanitarie, la metodologia per introdurre soluzioni di telemedicina efficaci e coerenti nei diversi percorsi di cura dei pazienti è caratterizzata da una fase iniziale che non richiede la realizzazione e/o l'acquisizione di nuovi sistemi tecnologici, ma piuttosto:

a) la gestione del processo clinico organizzativo all'interno dei centri (prenotazione, lista di lavoro, cartella clinica, prescrizione, refertazione, rendicontazione) nelle stesse modalità e con gli stessi strumenti -informatici e cartacei- attualmente in uso;
b) la gestione delle interazioni con il paziente e fra gli operatori sanitari mediante un sistema di comunicazione, che sia in grado -con le necessarie garanzie di sicurezza- di supportare in modo integrato le interazioni audio/video e lo scambio di documenti secondo i requisiti individuati, evitando l'uso di strumenti frammentati ed insicuri (es. mail, sms, WhatsApp) e senza creare condizionamenti e/o richiedere interventi sui sistemi attualmente in uso.

Tale sistema di comunicazione può essere facilmente individuato dall'Azienda in uno dei tanti già disponibili (Skype, Zoom, Teams, Gmeet), che forniscono le necessarie garanzie di sicurezza, che sono immediatamente disponibili (anche gratuitamente) e che sono già in gran parte

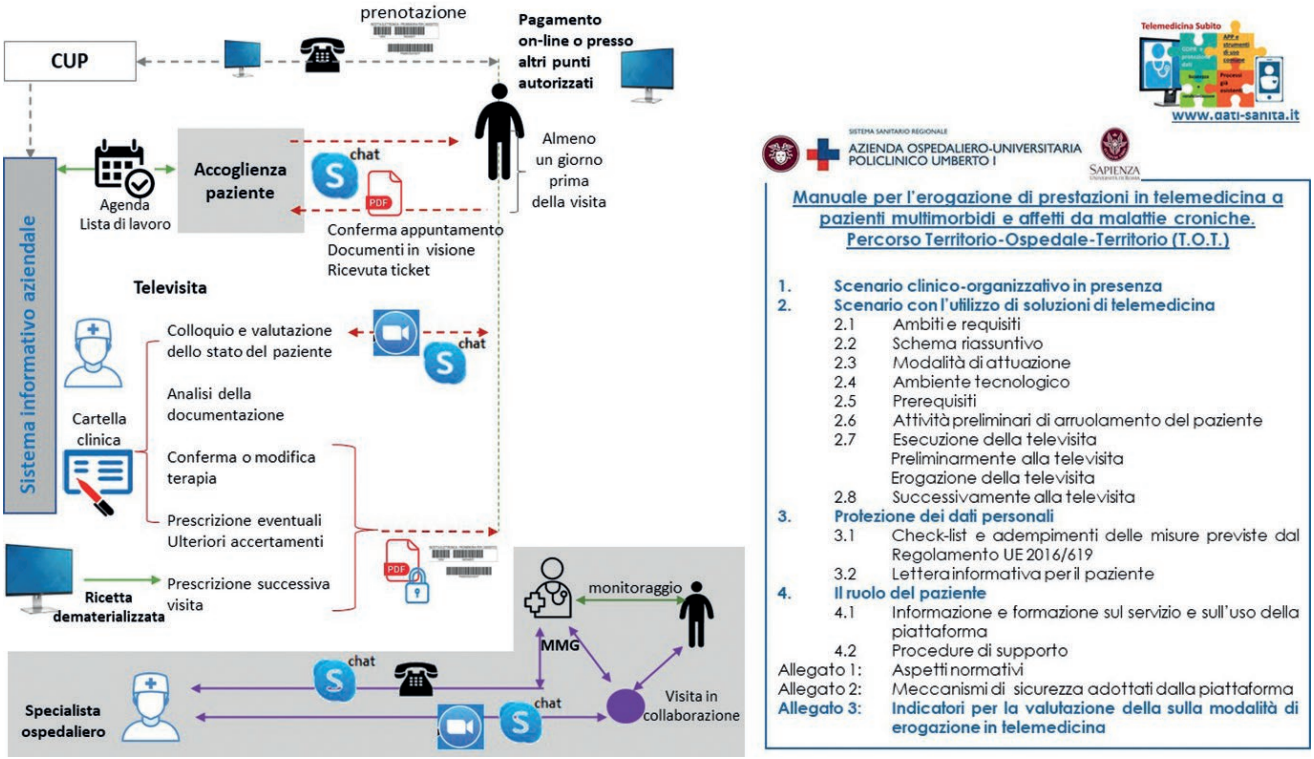


**Figura 2:** a telemedicina nel percorso Territorio-Ospedale-Territorio

conosciuti da operatori sanitari e pazienti, riducendo così le difficoltà della formazione iniziale.

Solo a seguito di una tale attività e della sperimentazione "sul campo" è possibile individuare le singole specificità e requisiti e selezionare di conseguenza le soluzioni tecnologiche più adatte nei singoli centri, nel rispetto delle indicazioni nazionali e regionali.

Va infine sottolineato come questo approccio, che affianca al processo in presenza uno strumento tecnologico finalizzato alla sola interazione con il paziente e senza archiviazione di dati in contesti separati, non solo assicuri la necessaria immediatezza e flessibilità nella messa a punto del nuovo modello (permettendo quindi di erogare rapidamente le prestazioni ai pazienti), ma consentirà anche la semplice sostituzione del sistema di comunicazione con le piattaforme e sistemi regionali e/o aziendali man mano che queste saranno disponibili, capitalizzando senza costi e/o impegni aggiuntivi sull'esperienza acquisita e sull'organizzazione implementata.

Come esempio di questa strategia, si può citare il progetto condotto in collaborazione fra il "Centro di medicina predittiva per la prevenzione e gestione delle malattie croniche" del Policlinico Umberto I di Roma, l'ALTEMS e l'ALAMA l'"Associazione Liberi dall'Asma, dalle Malattie Allergiche, Atopiche, Respiratorie e Rare", finalizzato alla introduzione di soluzioni di telemedicina nella collaborazione Ospedale-Territorio a favore di pazienti multimorbidi ed affetti da patologie croniche, come schematizzato in **Figura 2**.

## Bibliografia

1. https://www.dati-sanita.it/wp/telemedicina/survey-sulle-soluzioni-di-telemedicina-implementate-dalle-aziende-un-approccio-multidimensionale-per-lanalisi-e-la-valutazione-delle-soluzioni-di-telemedicina/
2. https://www.dati-sanita.it/wp/telemedicina/osservatorio-telemedicina/
3. https://altems.unicatt.it/altems-laboratori-e-osservatori-i-sistemi-informativi-sanitari-per-il-governo-dell-organizzazione
4. https://www.agenas.gov.it/comunicazione/primo-piano/2061-agenas-pubblica-l%E2%80%99avviso-per-la-piattaforma-nazionale-di-telemedicina
5. https://www.dati-sanita.it/wp/telemedicina/telemedicina-subito/#

*RELAZIONI - L'ANGOLO DELLE MALATTIE RARE: SHERLOCK HOLMES' CORNER*

# Parestesie progressive in paziente operato di cuffia dei rotatori

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Si tratta di un paziente che abbiamo avuto modo di osservare alcuni anni fa, il cui caso è tornato alla nostra attenzione per la comparsa di analoghi sintomi nel figlio. Il soggetto, di sesso maschile, 68 anni, ritirato dal lavoro (ex imbianchino), veniva ricoverato circa venti anni fa per algoparestesie a tipo formicolio, ingravescenti da 18 mesi, localizzate alle mani bilateralmente, maggiori a sinistra, con irradiazione a guanto, in assenza di altri sintomi associati. All'anamnesi: familiarità per cerebrovasculopatie (genitori deceduti per ictus); fumatore (20 sigarette/die dai 14 anni); ipertensione arteriosa normale-alta non in trattamento; tre anni prima ricovero per broncopolmonite; un anno prima comparsa di impotenza funzionale della spalla sinistra con diagnosi di rottura della cuffia dei rotatori per cui effettuava poco dopo intervento chirurgico. Tuttavia le parestesie avevano continuato a peggiorare. L'esame obiettivo all'ingresso era sostanzialmente normale ad eccezione della presenza di un soffio sistolico (2/6) su tutti i focolai all'auscultazione cardiaca e di una lieve riduzione diffusa del murmure vescicolare a quella del torace. All'esame obiettivo neurologico: difficoltosa la marcia a tandem, al Romberg lievi oscillazioni multidirezionali, presenza di fascicolazioni spontanee al deltoide e al bicipite bilateralmente, ipotrofia e deficit di forza arto superiore sinistro da esiti dell'intervento sulla cuffia dei rotatori, deficit del deltoide destro e del bicipite bilateralmente; ipoevocabilità dei riflessi osteo-tendinei, con inevocabilità dei bicipitali, ipoestesia TTD a calza e algoparestesie a guanto bilaterali. Venivano effettuati esami ematochimici, emocromo, elettroforesi proteica, VES, PCR, sierologia per sifilide, HCV e HBV: nella norma; ECG: frequenti extrasistoli sopraventricolari, BBdx, blocco fascicolare anteriore sinistro; RMN colonna cervicale: spondilolistesi C4-C5 (grado 1), spondilodiscoartrosi diffusa e protrusione discale C4-C5 e C6-C7; pletismografia arteriosa delle dita delle mani: nella norma; ecocardio-doppler transtoracico: ipertrofia ventricolare sinistra con cinesi globale e segmentale conservata, insufficienza mitralica lieve-media, lieve ingrandimento atriale sinistro, insufficienza tricuspidale lieve, ipertensione polmonare lieve, ectasia del bulbo aortico e dell'aorta ascendente. Infine l'elettromiografia (neurografia sensitiva, motoria e muscoli) mostrava reperti indicativi di polineuropatia sensitivo-motoria assonale, che fu la diagnosi di dimissione. L'elettromiografia veniva ripetuta e risultava invariata a distanza di tre mesi. Dopo circa un anno comparivano dispnea da sforzo ingravescente, edemi declivi e infine aumento di volume dell'addome. Il paziente si recava pertanto in Pronto Soccorso e veniva nuovamente ricoverato. Eseguiva ECG: ritmo da fibrillazione atriale 84 bpm, BBdx, anomalie dell'onda T sospette per ischemia anterolaterale; CKMB e TnT: nella norma. (NT pro BNP all'epoca non disponibile); radiografia del torace: lieve edema interstiziale diffuso, soffusione pleurica basale destra e versamento pleurico sinistro; ecocardio-doppler transtoracico: marcata ipertrofia ventricolare sinistra e destra con aspetto compatibile con malattia infiltrativa, disfunzione ventricolare sinistra lieve, atrio sinistro lievemente ingrandito (55 ml in 4C) e atrio destro significativamente ingrandito (130 ml in 4C), insufficienza mitralica lieve e tricuspidale severa con ipertensione polmonare moderata. Si impostava terapia e.v. con furosemide 20 mg qid e orale con spironolattone 25 mg qd, metoprololo 25 mg bid, acetilsalicilato di lisina 160 mg qd, pantoprazolo 20 mg qd, ramipril 5 mg qd, assistendo a miglioramento dei sintomi e riduzione del versamento pleurico. Si decideva di effettuare un cateterismo cardiaco con coronarografia (negativa) e biopsia miocardica: l'esame istologico evidenziava la presenza di sostanza amiloide. La biopsia del nervo surale eseguita a completamento mostrava riduzione della densità di fibre ed evidenti fenomeni di degenerazione simil-walleriana, indicativi per una neuropatia assonale con fenomeni degenerativi in atto. Veniva dimesso con diagnosi di amiloidosi cardiaca. In assenza di terapie specifiche all'epoca il paziente proseguiva trattamenti sintomatici e a causa dell'evolversi della malattia giungeva ad exitus dopo circa quattro anni. L'amiloidosi da transtiretina (ATTR) è causata dall'instabilità di questa proteina tetramerica per fattori genetici (mutazioni del tetramero, m-TTR) o degenerativi (wild-type TTR), con deposizione di monomeri di TTR negli organi vitali [1]. Si distingue dall'altra principale forma di amiloidosi (AL) causata dal deposito di catene leggere delle immunoglobuline che ha diversa eziologia, alcune differenze clini-

che e diverso trattamento. La forma familiare più comune di ATTR, che determina polineuropatia, colpisce meno di 1:100.000 in Europa, sebbene in alcune aree particolari mutazioni siano molto più comuni (esistendo più di 100 mutazioni patogene) [2]. Le "red flags" cliniche per la diagnosi di amiloidosi sono illustrate nella tabella 1 (3-5). I progressi nell'imaging cardiovascolare hanno recentemente facilitato la diagnosi di ATTR, eludendo spesso la necessità di una biopsia tissutale invasiva: la risonanza magnetica cardiaca con LGE, la scintigrafia ossea con 99mTc-PYP o 99mTc-DPD e 99mTc-HMDP, la PET/SPECT sono validi strumenti per la caratterizzazione della malattia e per la differenziazione dei sottotipi di amiloidosi (AL vs ATTR) [6-8]. Di pari passo al miglioramento della diagnostica si è assistito alla scoperta di nuove efficaci terapie contro l'ATTR: tra le altre, diflunisal e tafamidis sono molecole in grado di stabilizzare il tetramero della transtiretina; patisiran (siRNA) e inotersen (oligonucleotide antisenso, ASO) inibiscono l'espressione del gene sia di m-TTR sia di wt-TTR [7-8]. Ciò ha accresciuto l'interesse della comunità scientifica verso la necessità di identificare tempestivamente i pazienti che potrebbero trarre vantaggio da uno screening sistematico per ATTR **(Tabella 2)** e dall'impiego mirato dei nuovi agenti terapeutici. A vent'anni di distanza quindi dalla storia del nostro paziente, il figlio, di anni 60, è giunto alla nostra osservazione per la comparsa di parestesie distali alle mani, in assenza di segni di disautonomia, di scompenso cardiaco, di proteinuria e/o nefropatia; l'ECG e l'ecocardiogramma sono normali. La disponibilità di strumenti meno invasivi per la diagnosi e soprattutto di terapie che possano modificare la storia naturale della malattia ci impongono di avviare subito le indagini genetiche, ora possibili, e di avviare il paziente a controlli seriati, meglio se da parte di team multidisciplinare dedicato, o nde evitare se possibile quanto accaduto al suo genitore.

## Bibliografia


1. Manganelli F, Fabrizi GM, Luigetti M, Mandich P, Mazzeo A, Pareyson D: Hereditary transthyretin amyloidosis overview. Neurol Sci 2020; https://doi.org/10.1007/s10072-020-04889-2. Online ahead of print.
2. D'Aguanno V, Ralli M, Artico M, Russo FY, Scarpa A, Fiore M et al. Systemic amyloidosis: a contemporary overview. Clin Rev Allergy Immunol 2020; 59: 304-322. https://doi.org/10.1007/s12016-019-08759-4
3. Maurer MS, Bokhari S, Damy T, Dorbala S, Drachman BM, Fontana M et al: Expert consensus recommendations for the suspicion and diagnosis of Transthyretin Cardiac


| |
|---|
| ❖ sindrome del tunnel carpale specie se bilaterale, |
| ❖ stenosi del canale vertebrale (specialmente nelle wt-ATTR) |
| ❖ neuropatia sensitivo-motoria periferica di origine indeterminata |
| ❖ disautonomia (ipotensione ortostatica, alvo alterno, alterazione della sudorazione, ecc.) |
| ❖ rottura spontanea di tendini (bicipite) |
| ❖ epatomegalia |
| ❖ proteinuria non diabetica fino alla s. nefrosica |
| ❖ macroglossia e porpora periorbitale (forme AL, ) |
| ❖ manifestazioni cardiache:<br>- Scompenso destro (epatomegalia, ascite, edemi declivi)<br>- Scompenso biventricolare specialmente a frazione di eiezione preservata<br>- Cardiomiopatia ipertrofica o stenosi aortica a basso gradiente/flusso di neodiagnosi nell'anziano<br>- Intolleranza a betabloccanti, ACE inibitori, sartani, ARNI<br>- Comparsa disturbi della conduzione atrioventricolare ed intraventricolare/necessità di pacemaker associate a ispessimento del ventricolo sinistro<br>- Aritmie atriali senza causa riconosciuta<br>- Bassi voltaggi, pattern simil-infartuale, frammentazione del QRS e discordanza con il grado di ispessimento ventricolare all'ECG<br>- Comparsa di pressione normale/bassa in soggetto iperteso |

**Tabella 1:** Red flags per la diagnosi di ATTR

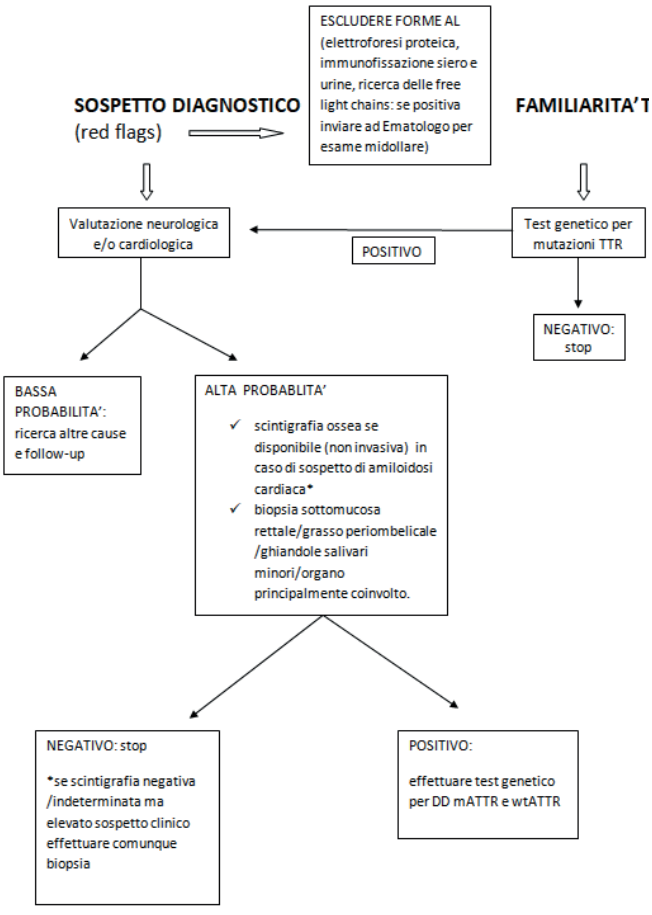


**Tabella 2**

# Covid 19: update sul trattamento con antivirali

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Dall'inizio della pandemia da COVID-19 una grande varietà di terapie antivirali è stata sistematicamente valutata nella speranza dell'ottenimento di un reale beneficio nel real world; tuttavia attualmente sono pochi i farmaci antivirali ad avere dati sostenuti da evidenze scientifiche **(Figura 1)**. Remdesivir è un analogo nucleotidico che inibisce la RNA polimerasi in SARS-CoV-2 ed è attualmente l'unico antivirale raccomandato per i pazienti ospedalizzati e può essere utilizzato anche in pazienti ambulatoriali con un regime di 3 giorni. ACTT-1 era un RCT in doppio cieco che includeva 1059 pazienti ospedalizzati con COVID-19 e ha riscontrato che i pazienti che ricevevano remdesivir avevano un recupero mediano di 10 giorni, rispetto ai 15 giorni di quelli che non ricevevano il farmaco (rate ratio per il recupero 1,29 - IC 95% 1.12-1.49). Questo beneficio è stato osservato principalmente in coloro che richiedevano ossigeno supplementare a basso flusso ma non altri trattamenti delle vie aeree [1]. Un secondo studio che includeva 584 pazienti ospedalizzati con COVID-19 moderato ha rilevato che un ciclo di 5 giorni di remdesivir era associato a un miglioramento dello stato clinico rispetto al placebo (OR 1,65 - IC 95% 1,09-2,48), mentre il decorso di 10 giorni non ha mostrato differenze rispetto al placebo [2]. Lo studio dell'OMS Solidarity che ha coinvolto 11.330 adulti in 30 paesi non ha riscontrato differenze in termini di mortalità, durata della ventilazione o durata della degenza ospedaliera in pazienti randomizzati a remdesivir per 10 giorni rispetto ad altri standard di cura [3]. Lo studio DisCoVeRy, un RCT di fase 3 che includeva 857 pazienti in 48 siti europei, non ha riscontrato alcun beneficio (in termini di stato clinico) a 15 giorni nei pazienti ospedalizzati con COVID-19 confermato, malattia di qualsiasi durata ed evidenza di polmonite ipossica o necessità di supplementazione di ossigeno che ricevevano remdesivir per 10 giorni più standard di cura rispetto allo standard di cura [4]. Le linee guida IDSA raccomandano condizionatamente l'uso di remdesivir in pazienti (ambulatoriali o ospedalizzati) con COVID-19 da lieve a moderato che sono a rischio di progressione verso una malattia grave, indipendentemente dalla necessità di ossigeno supplementare [5]. Il NIH raccomanda remdesivir nei pazienti ospedalizzati che richiedono ossigeno supplementare e come terapia di terza linea in ambito ambulatoriale [6].

Nirmatrelvir/ritonavir è una combinazione di un inibitore della proteasi (nirmatrelvir) e un booster farmacocinetico (ritonavir). E' attualmente la terapia raccomandata di prima linea per i pazienti ambulatoriali che soddisfino i criteri per il trattamento6. I dati più interessanti derivano da un'analisi ad interim della fase 2/3 dello studio EPIC-HR

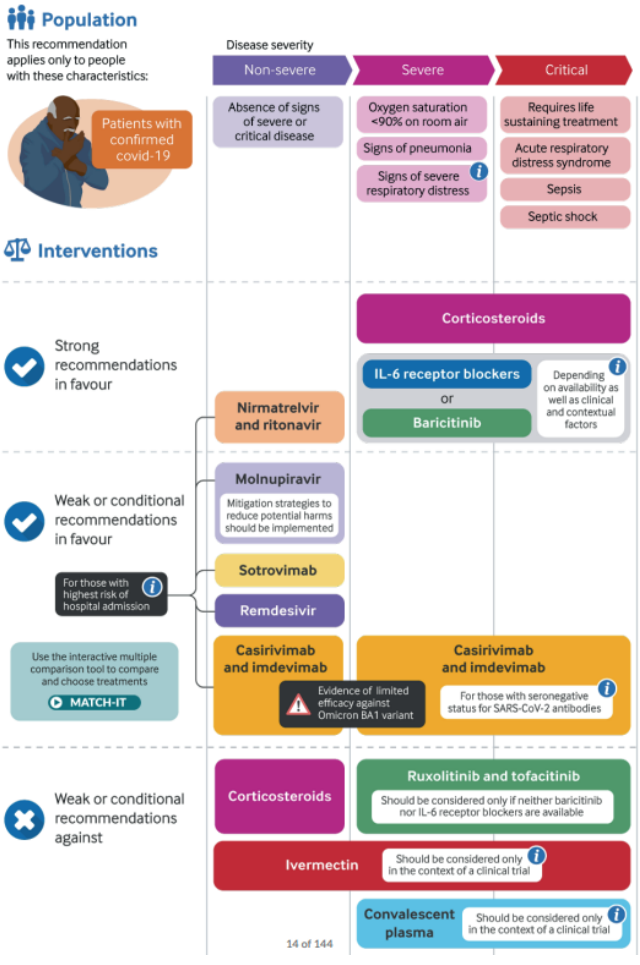


**Figura 1:** Raccomandazioni terapeutiche stratificate per severità della malattia da COVID19

che includeva 2246 pazienti ambulatoriali adulti non vaccinati con COVID-19 con esordio dei sintomi non più di 5 giorni prima della randomizzazione e almeno un fattore di rischio per malattia grave. I pazienti sono stati randomizzati a ricevere 300 mg di nirmatrelvir e 100 mg di ritonavir rispetto al placebo due volte al giorno per 5 giorni. È stato riscontrato che i pazienti trattati con nirmatrelvir/ritonavir entro 3 giorni dall'esordio dei sintomi avevano un rischio ridotto di ospedalizzazione e morte rispetto a quelli che avevano ricevuto placebo (-6,32 %; IC 95% -9,04 -3,59), con 0 decessi nei gruppi di trattamento rispetto a 7 decessi nel gruppo placebo. La carica virale era inferiore nei gruppi di trattamento quando il trattamento è stato iniziato entro 3 giorni dall'esordio dei sintomi (0,8% vs. 7%, p <0,0001). L'incidenza di eventi avversi è stata simile tra i gruppi. I pazienti senza caratteristiche ad alto rischio hanno anche dimostrato tassi ridotti di ospedalizzazione e diminuzione della carica virale [7]. In uno studio osservazionale nel mondo reale che includeva oltre 180.000 pazienti (vaccinati e non vaccinati) con un test SARS-CoV-2 positivo e fattori di rischio per la progressione verso una malattia grave, il trattamento con nirmatrelvir-ritonavir è stato associato a una diminuzione della progressione vs. malattia grave o morte a 28 giorni rispetto a nessun trattamento (HR 0,54, IC 95% 0,39-0,75)[8].

Molnupiravir è un analogo nucleosidico che inibisce la replicazione di SARS-CoV-2, approvato per l'uso in soggetti di età superiore ai 18 anni. Le indicazioni includono pazienti ambulatoriali sintomatici da 5 giorni o meno, ad alto rischio di progressione verso malattia grave. Uno studio di controllo randomizzato internazionale di fase 3 ha riportato risultati ad interim con 775 pazienti che hanno dimostrato un rischio ridotto di ricovero ospedaliero o di morte con molnupiravir (7,3% vs. 14,1%, p = 0,0012), senza decessi nel gruppo che ha ricevuto molnupiravir [9]. Un RCT di fase 3, in doppio cieco, ha valutato molnupiravir in 1433 pazienti ambulatoriali non vaccinati entro 5 giorni dall'insorgenza di segni o sintomi di COVID-19 e almeno un fattore di rischio per una malattia grave. Gli autori hanno riscontrato una riduzione dell'ospedalizzazione e della morte a 29 giorni nel gruppo molnupiravir rispetto al placebo (- 3,0%; IC 95% da -5,9 a -0,1)[10].

**Bibliografia**


1. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19 - final report. N Engl J Med 2020;383(19):1813-1826.
2. Spinner CD, Gottlieb RL, Criner GJ, et al. Effect of Remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19: a randomized clinical trial. JAMA 2020;324(11):1048-1057.
3. WHO Solidarity Trial Consortium, Pan H, Peto R, et al. Repurposed antiviral drugs for Covid-19 - interim WHO Solidarity trial results. N Engl J Med 2021;384(6):497-511,
4. Ader F, Bouscambert-Duchamp M, Hites M, et al. Remdesivir plus standard of care versus standard of care alone for the treatment of patients admitted to hospital with COVID-19 (DisCoVeRy): a phase 3, randomised, controlled, open-label trial. Lancet Infect Dis 2021;S1473–3099(21)00485–0.
5. Bhimraj A, Morgan RL, Shumaker AH, et al. Infectious diseases society of america guidelines on the treatment and management of patients with COVID-19. Infectious Diseases Society of America 2022. Updated February 22, 2022. Available at https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/
6. The COVID-19 Treatment Guidelines Panel's Statement on Therapies for High-Risk Non hospitalized Patients With Mild to Moderate COVID-19. National Institutes of Health 2021. Available at https://files-covid19treatmentguidelines-nih-gov.bvsp.idm.oclc.org/guidelines/section/section_166.pdf
7. Pfizer Announces Additional Phase 2/3 Study Results Confirming Robust Efficacy of Novel COVID-19 Oral Antiviral Treatment Candidate in Reducing Risk of Hospitalization or Death. Pfizer 2021. https://www.pfizer.com/news/press-release/press-release-detail/pfizer-announces-additional-phase-23-study-results
8. Najjar-Debbiny R, Gronich N, Weber G, et al. Effectiveness of Paxlovid in Reducing Severe COVID-19 and Mortality in High Risk Patients. Clin Infect Dis 2022;ciac443.
9. Merck and Ridgeback's Investigational Oral Antiviral Molnupiravir Reduced the Risk of Hospitalization or Death by Approximately 50 Percent Compared to Placebo for Patients with Mild or Moderate COVID-19 in Positive Interim Analysis of Phase 3 Study. Merck 2021. https://www.merck.com/news/merck-and-ridgebacks-investigational-oral-antiviral-molnupiravir-reduced-the-risk-of-hospitalization-or-death-by-approximately-50-percent-compared-to-placebo-for-patients-with-mild-or-moderat/
10. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, MOVe-OUT Study Group, et al. Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients. N Engl J Med 2021;10.1056/NEJMoa2116044.

*RELAZIONI - SIMPOSIO - LE VACCINAZIONI NEI PAZIENTI FRAGILI E NEGLI IMMUNOCOMPROMESSI*

# Vaccinazione anti-herpes zoster e anti-SarsCov-2 nel paziente con sclerosi sistemica progressiva

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La sclerosi sistemica (SSc) è una malattia cronica autoimmune del tessuto connettivo che coinvolge cute, sistema vascolare ed organi interni, in particolare esofago, tratto gastroenterico, polmoni, cuore e reni. La prevalenza varia da 7 a 700 casi per milione in tutto il mondo [1]. La patogenesi della SSc è multifattoriale con base genetica, con età di incidenza soprattutto fra i 30 ed i 50 anni, e con frequenza circa sette volte maggiore nelle donne. [2]. Gli anti-Scl70 sono in genere presenti nelle forme con interessamento cutaneo diffuso e con fibrosi polmonare, gli anti-centromero sono più frequenti nelle forme con interessamento cutaneo limitato e con ipertensione polmonare isolata. Nel 90% dei pazienti questa malattia si presenta con il fenomeno di Raynaud [3]. La SSc viene classificata in forma diffusa (dSSc) e limitata (lSSc) in base al coinvolgimento cutaneo. I pazienti con coinvolgimento renale ed interstiziale polmonare vengono trattati con farmaci immunosoppressori che rappresentano un altro forte fattore di rischio per malattie trasmissibili. Le infezioni opportuniste sono una delle principali cause sia di ricovero ospedaliero sia di mortalità nei pazienti sclerodermici [4]. I vaccini rappresentano uno dei mezzi più sicuri ed efficaci per il controllo delle malattie. Fra le vaccinazioni raccomandate nei pazienti con SSc prendiamo in considerazione quelle verso i virus herpes zoster e Sars-Cov-2.

**1. Vaccinazione verso herpes zoster**

L'herpes zoster (HZ) è una malattia virale causata dalla riattivazione del virus latente della varicella-zoster nei gangli dei nervi cranici o delle radici dorsali ed è caratterizzata da un'eruzione dermatomale vescicolare dolorosa e da nevralgia post-erpetica. I pazienti immunocompromessi possono sviluppare malattia cutanea disseminata e necrosi esterna della retina acuta o progressiva. Alcuni studi di coorte hanno dimostrato un tasso di infezione più elevato nell'SSc rispetto alla popolazione generale [5]. La somministrazione di un vaccino vivo attenuato HZ (Zostavax) riduce il rischio di HZ tra gli individui immunocompetenti di età pari o superiore a 50 anni, ma non è indicato nei pazienti immunocompromessi che potrebbero sviluppare un'infezione primaria da varicella [6]. Le attuali linee guida suggeriscono la sua somministrazione almeno 4 settimane prima di iniziare un farmaco immunosoppressore. Utile la valutazione del sierostato prima della somministrazione per limitare il rischio di un'infezione primaria da varicella. Un nuovo vaccino zoster adiuvante a subunità ricombinante non vivo (Shingrix) è disponibile in alcuni paesi europei e potrebbe sostituire il vaccino vivo attenuato evitando il rischio di infezione iatrogena. Studi comparativi hanno dimostrato un migliore profilo di sicurezza e una maggiore efficacia di Shingrix rispetto al vaccino vivo attenuato [7].

**2. Vaccinazione verso Sars-Cov-2**

Con oltre 250 milioni di casi, la pandemia causata da SARS-CoV-2 rappresenta a livello globale un grande onere per le comunità [8] Circa la metà dei pazienti reumatologici (46%) che ha contratto l'infezione ha necessitato di ricovero ospedaliero ed il 10% di ventilazione invasiva. La vaccinazione verso il Sars-Cov2 è fra quelle fortemente raccomandate dal momento che l'infezione può avere un'evoluzione severa con conseguente ospedalizzazione e causare l'exitus nei soggetti con malattie croniche inclusa la SSc. La mortalità è peraltro più frequente nel genere femminile. La somministrazione di farmaci immunosoppressori convenzionali e biologici possono ridurre l'efficacia della risposta alle vaccinazioni, pertanto è raccomandata la somministrazione di una terza dose di vaccino a differenza di una dose "booster" prevista nella popolazione generale sana [9,10]. Per l'efficacia stimata complessivamente più elevata, i vaccini mRNA sono fortemente raccomandati per i pazienti fragili. Nella tabella 1 sono descritti i diversi tipi di vaccino verso il Sars-Cov2.

**3. Raccomandazioni**

È raccomandata la somministrazione di alcune vaccinazioni nei pazienti con SSc per ridurre il rischio di complicanze severe delle vie aeree (vedi tabella 1).

| Vaccinazione | Livello di raccomandazione |
|---|---|
| Sars-Cov2 | Fortemente raccomandato |
| Influenza | Fortemente raccomandato |
| S. Pneumoniae | Fortemente raccomandato |
| N. Meningitidis | Fortemente raccomandato |
| H.Influentiae | Fortemente raccomandato |
| Difteria-tetano-pertosse (dTp) | Fortemente raccomandato |
| HAV | Raccomandato |
| HBV | Raccomandato |
| HZV | Raccomandato |
| HPV | Raccomandato |

**Tabella 1**

## Bibliografia


1. Elhai M, Avouac J, Walker UA, Matucci-Cerinic M, Riemekasten G, Airò P, et al; EUSTAR co-authors. A gender gap in primary and secondary heart dysfunctions in systemic sclerosis: a EUSTAR prospective study. Ann Rheum Dis. 2016;75(1):163-9.
2. Khedoe P, Marges E, Hiemstra P, Ninaber M, Geelhoed M. Interstitial Lung Disease in Patients With Systemic Sclerosis: Toward Personalized-Medicine-Based Prediction and Drug Screening Models of Systemic Sclerosis-Related Interstitial Lung Disease (SSc-ILD). Front Immunol. 2020;11:1990.
3. Alba MA, Velasco C, Simeón CP, Fonollosa V, Trapiella L, Egurbide MV, et al; RESCLE Registry. Early- versus late-onset systemic sclerosis: differences in clinical presentation and outcome in 1037 patients. Medicine (Baltimore). 2014;93(2):73-81.
4. Nagaraja V, Matucci-Cerinic M, Furst DE, Kuwana M, Allanore Y, Denton CP, et al. Current and Future Outlook on Disease Modification and Defining Low Disease Activity in Systemic Sclerosis. Arthritis Rheumatol. 2020;72(7):1049-1058.
5. Hsu CY, Ko CH, Wang JL, Hsu TC, Lin CY. Comparing the burdens of opportunistic infections among patients with systemic rheumatic diseases: a nationally representative cohort study. Arthritis Res Ther. 2019;21(1):211.
6. Ansaldi F, Trucchi C, Alicino C, Paganino C, Orsi A, Icardi G. Real-World Effectiveness and Safety of a Live-Attenuated Herpes Zoster Vaccine: A Comprehensive Review. Adv Ther. 2016;33(7):1094-104.
7. Maltz F, Fidler B. Shingrix: A New Herpes Zoster Vaccine. P T. 2019;44(7):406-433.
8. WHO. Coronavirus (COVID-19) Dashboard. Available online: https://covid19.who.int/ (accessed on 25 November 2021).
9. Comirnaty and Spikevax: EMA Recommendations on Extra Doses Boosters—European Medicines Agency. Available online: https://www.ema.europa.eu/en/news/comirnaty-spikevax-ema-recommendations-extra-doses-boosters (accessed on 25 November 2021).
10. Murdaca G, Noberasco G, Olobardi D, Lunardi C, Maule M, Delfino L, et al. Current Take on Systemic Sclerosis Patients' Vaccination Recommendations. Vaccines (Basel). 2021;9(12):1426.

*RELAZIONI - SIMPOSIO - IL FUMO: UN FATTORE DI RISCHIO MODIFICABILE*

# Le difficoltà della cessazione dal fumo e le resistenze al cambiamento

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Quando si parla di resistenze al cambiamento ci si riferisce a quelle difficoltà legate ad un comportamento che o deve essere interrotto o orientarsi verso una nuova direzione, come ad esempio interrompere un'abitudine insalubre come il fumo.
Tutti gli esseri viventi tendono a cercare e mantenere un loro equilibrio, il cosiddetto equilibrio omeostatico, che viene ricercato dal soggetto in quanto gli permette di sperimentare benessere.
Tale stato viene percepito come piacevole tanto da non poter fare a meno di agire o interrompere il comportamento che lo produce per ricercarne gli effetti, anche se questi si rivelano poi dannosi. E' il caso dell'abuso di sostanze, dei comportamenti a rischio e delle disfunzionalità, che si protraggono nel tempo creando le cosiddette resistenze al cambiamento. Regina tra le resistenze è la dipendenza al fumo, sia fisica che psicologica, che alimenta il cosiddetto meccanismo di ricompensa del fumatore.
Le resistenze ci interessando da vicino quando si manifestano a sostegno di un bisogno individuale: rimanere nella propria zona di comfort, evitare emozioni faticose come la paura del cambiamento, scongiurare il passato intriso di aspettative e tentativi precedenti fallimentari, tendere al perfezionismo o all'auto-sabotaggio.
Tuttavia prima o poi il cambiamento diventa una necessità non più procrastinabile e, in un'ottica darwiniana, chi non si adatta è destinato a soccombere.
Quali gli strumenti trasversali ad ogni disciplina medica che si possono impiegare in favore del cambiamento del paziente sono:

1. Promuovere una relazione di fiducia tra medico-paziente, caratterizzata dalla reciprocità nel rapporto di alleanza terapeutica
2. Stimolare il livello di responsabilità del paziente nella presa di decisioni che hanno impatto sulla salute in coordinamento con il professionista o la rete multidisciplinare
3. Utilizzare una comunicazione efficace di tipo suggestivo ed evocativo, rivolta sia a fattori consci stimolando il livello di consapevolezza dl paziente, sia a quelli inconsci motivazionali. L'intento è quello che il paziente attribuisca dei significati specifici rispetto all'interpretazione trasformata simbolica della realtà che lo circonda.
4. Fornire un insieme di soluzioni, strategie e metodi pratici che possono supportare l'utente nel cambiamento.

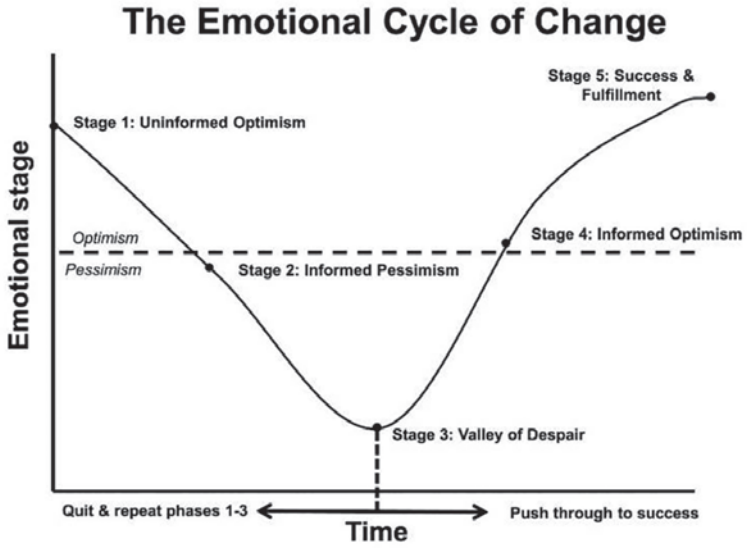


**Figura 1:** The Emotional Cycle of Change. Tratto da: Kelley D, Conner D. Emotional Cycle of Change. Annual Handbook for Group Facilitators (1979).

Da un lato il paziente dall'altro il medico devono quindi trovare una sorta di azione sinergica di collaborazione dove il professionista si fa carico dei dubbi, delle perplessità, degli stati emotivi, delle paure, delle necessità, delle aspettative e dei sogni che accompagnano la dimensione del cambiamento del paziente per fronteggiare le resistenze che impattano sullo stato di salute del paziente e sulla sua Qualità di Vita [1].
In virtù di quanto discusso per promuovere la cessazione dell'abitudine al fumo si invita allo studio delle Linee Guida Ministeriali OSSFAD dell'Istituto Superiore di Sanità [3] e qualora la situazione lo richieda si suggerisce di fare rete multidisciplinare con altri professionisti della salute a seconda della complessità del caso, soprattutto quando alcuni comportamenti riguardano stati di comorbilità psicologico-psichiatrica o gravi livelli di diepndenza.
Quando ci si trova di fronte ad un paziente che presenta determinate caratteristiche il fattore tempo è determinante. In effetti il cambiamento e la capacità di fronteggiarlo non possono essere svincolati dalla condizione clinica che si riscontra nel paziente. Differente è sia l'intervento del clinico che la capacità di reattività del soggetto, in base anche al tempo a disposizione per adattarsi: ad esempio in presenza di una diagnosi di carcinoma maligno, il paziente deve far ricorso a tutte le sue risorse interne per velocizzare l'elaborazione situazionale e significare la realtà, al fine di agire in modo proattivo ed adattivo. L'esigenza del medico diventa quindi quella di collimare le necessità clinico-terapeutiche-preventive con la capacità di cambiare del soggetto.
Nell'Annual Handbook for Group Facilitators del 1979 due ricercatori americani, Don Kelley e Daryl Conner, parlarono per la prima volta di Emotional Cycle of Change (Ciclo Emotivo del Cambiamento) [4].
Nei loro studi i due ricercatori notarono che la maggior parte degli individui, che avevano deciso volontariamente di cambiare qualcosa, avevano attraversato una serie di fasi emotive comuni.

A livello psicologico si riscontrano una serie di specifici momenti emotivi caratteristici man mano che il tempo passa. In particolare nella fase 2 di "Pessimismo Giustificato" subentrano tutta una serie di possibili sintomi di origine emotiva che portano l'utente a vivere nella cosiddetta "Valle della disperazione". Riconoscere questa fase è particolarmente importante per sostenere adeguatamente il paziente nel fronteggiare sentimenti di ansia, depressione, panico, rabbia oppure sintomi psicosomatici.
Qualche tips di neuroscienze per fronteggiare il cambiamento:

1. Le abitudini sono difficili da eliminare, più facili da sostituire
2. I cambiamenti non devono essere radicali, in quanto non sono sostenibili
3. La volontà di cambiare è la conditio sine qua non si possa farlo
4. La parola «impossibile» non può esistere, stimolare l'ottimismo
5. Le contromisure suggerite devono essere rapide, accessibili, immediatamente disponibili, semplici
6. Godere delle piccole conquiste quotidiane, da cui trarre energia per nuove conquiste

Per sostenere i pazienti al cambiamento è importante sintonizzarsi sulla sfera emotiva del paziente, nel rispetto dei suoi tempi e dei suoi strumenti, per arricchire le sue risorse atte a fronteggiare il cambiamento. Dire: "Cambia!" non è sufficiente, la motivazione al cambiamento non si riduce ad un mero trasferimento di informazioni, pertanto è necessario coltivare il tempo dell'accoglienza e della comunicazione efficace che è tempo di cura.

**Bibliografia**

1. Gangale M, Ghianda L. Comunicazione emozionale in odontoiatria. Milano: Quintessenza, 2020.
2. Gangale M. La motivazione al paziente parodontale. Dental Cadmos, 2016;8(84):494-504.
3. Linee Guida cliniche per promuovere la cessazione dell'abitudine al fumo. Osservatorio Fumo, A.col e Droga. Ministero della Salute e Istituto Superiore di Sanità. Aggiornamento 2008. https://www.salute.gov.it/imgs/C_17_pubblicazioni_832_allegato.pdf
4. Kelley D, Conner D. Emotional Cycle of Change. Annual Handbook for Group Facilitators (1979).

# Il trattamento del dolore nel paziente oncologico

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Il dolore rimane un sintomo molto importante in oncologia da indagare e valutare in relazione alla stadiazione della patologia oncologica, per una differenziazione tra dolori causati dalla malattia neoplastica e dalla sua progressione, dolori causati dalle terapie che possono cronicizzarsi, o indipendenti dalla malattia e dalle terapie.

Il dolore causato dalla malattia neoplastica non guaribile e dalla sua progressione, rimane uno dei bisogni clinici più rilevanti del percorso assistenziale oncologico e di cure palliative di questi pazienti che interessa almeno il 70% di tutti i pazienti. Considerando che il cancro sta ormai diventando la prima causa di morte nei paesi ad alto reddito, e non solo, il ruolo delle cure palliative e del controllo del dolore assume una rilevanza fondamentale per assicurare una qualità della vita adeguata a questi pazienti. La valutazione del dolore in queste condizioni cliniche deve partire da una visione multidimensionale del sintomo nel quadro clinico complessivo che secondo la definizione scolastica del "dolore totale" tenga conto delle componenti fisiche, psicologiche, sociali e spirituali della sofferenza.

La gestione del dolore nel paziente con cancro avanzato si avvale di linee guida di primo livello che (World Health

| Outcomes | Bakitas et al, 2009 | Temel et al, 2010 | Zimmermann et al, 2014 | Bakitas et al, 2015 | Maltoni et al, 2016 | Temel et al, 2016 | Groenvold et al, 2017 | Vanbutsele et al, 2018 |
|---|---|---|---|---|---|---|---|---|
| QOL | **+** | **+** | **+** | = | **+** | **+** | = | **+** |
| Physical Symptoms | = | **+** | **+** | = | **+** | na | **=/+** (nausea) | = |
| Depression | **+** | **+** | na | = | = | **+** | = | = |
| Patient satisfaction with care | na | na | **+** | na | = | na | na | na |
| Caregiver outcomes | = burden | na | **+ satisfaction with care** = QOL | **+ mood** = QOL | na | **+ mood** =/+ QOL | na | not yet reported |
| EOL care/ service use | = | **+** | na | = | +/= | na | na | na |
| Survival | = | **+** | na | **+** | na | na | = | = |

**Tabella:** Studi clinici randomizzati controllati sulla efficacia di cure palliative precoci in ooncologia le variabili di risultato con un effetto positivo dimostrato dal trial sono contraddistinte da un segno + (EOL = end of life care, QOL = quality of life).

Organization 1986, Caraceni 2012, Fallon et al 2020) che prevedono l'uso sequenziale di analgesici : FANS, paracetamolo , oppioidi deboli , oppioidi forti e adiuvanti. La somministrazione orale e transdermica di oppioidi come ossicodone, morfina e fentanyl si rende necessaria nella grande maggioranza di questi pazienti e richiede: titolazione individuale del dosaggio, assistenza e monitoraggio continuo con frequenti rivalutazioni, controllo preventivo di alcuni effetti collaterali come la stipsi e verifica con una valutazione standardizzata e multidimensionale della incidenza di sintomi e complicazioni. Questo tipo di intervento farmacologico integrato con il percorso clinico oncologico nelle fasi ambulatoriali precoci della patologia offre un controllo adeguato del dolore all'80% dei pazienti (Ventafridda et al 1987) .

Il dolore e la prognosi oncologica sono anche determinanti a indicare per questi pazienti il ricorso all'invio a cure palliative precoci, cioè simultanee con la fase terapeutica e quindi ambulatoriali. Sono oggi disponibili studi clinici controllati (Haun et al 2017) che hanno dimostrato l'efficacia delle cure palliative precoci, in diverse popolazioni di pazienti con cancro avanzato, sulla qualità della vita, il controllo dei sintomi psicologici, il benessere dei familiari e l'utilizzo delle risorse sanitarie alla fine della vita come l'accesso tempestivo agli hospice e la limitazione del ricorso a pronto soccorsi e ospedalizzazioni.

Si può quindi concludere che attenzione e competenza nel controllo del dolore sono elementi essenziali di una visione delle cure del malato con cancro avanzato che coinvolge le competenze oncologiche e delle cure palliative, in stretta collaborazione con la medicina di base e del territorio, per realizzare percorsi clinici e assistenziali centrati sul paziente e integrati tra risorse ospedaliere, domiciliari e territoriali.

La tabella riassume gli studi clinici controllati attualmente disponibili.

**Bibliografia**


- World Health Organization Cancer Pain Relief World Health Organization Geneve 1986
- Fallon M, Giusti R, Aielli F, Hoskin P, Rolke R, Sharma M, Ripamonti CI; ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Management of cancer pain in adult patients: ESMO Clinical Practice Guidelines. Ann Oncol. 2018
- Caraceni A, Hanks G, Kaasa S, Bennett MI, Brunelli C, Cherny N et al ; European Palliative Care Research Collaborative (EPCRC); European Association for Palliative Care (EAPC). Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC. Lancet Oncol. 2012 Feb;13(2):e58-68.18
- Ventafridda V, Tamburini M, Caraceni A, De Conno F, Naldi F. A validation study of the WHO method for cancer pain relief. Cancer. 1987 Feb 15;59(4):850-6.
- Haun MW, Estel S, Rücker G, Friederich HC, Villalobos M, Thomas M, Hartmann M. Early palliative care for adults with advanced cancer. Cochrane Database Syst Rev. 2017 Jun 12;6(6)

# Gli inibitori di PCSK9 nella pratica clinica: uno sguardo oltre gli RCT

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Solide evidenze scientifiche hanno dimostrato il ruolo del colesterolo contenuto nelle lipoproteine a bassa densità (LDL-C) come principale fattore causale nello sviluppo dell'aterosclerosi [1]. L'avvento della terapia con statine negli anni '90 ha consentito una riduzione senza precedenti del rischio cardiovascolare (CV) e questi farmaci dovrebbero essere considerati uno dei maggiori progressi della medicina contemporanea. Tuttavia, nonostante la comprovata efficacia di questi farmaci, non sempre si riesce a raggiungere l'obbiettivo terapeutico [2]. Tale problematica è ulteriormente gravata dalla scarsa aderenza alla terapia con statine da parte dai pazienti a causa di effetti avversi di tipo muscolare. Le conseguenze cliniche derivanti dal sotto-trattamento sono particolarmente gravose per i pazienti ad alto e altissimo rischio CV, in particolare quelli affetti da ipercolesterolemia familiare (FH) [3]. La successiva introduzione della terapia combinata statina-ezetimibe, tuttavia, ha portato effetti modesti sulla riduzione di LDL-C e sugli esiti clinici nei pazienti ad alto ed altissimo rischio [4]. Più recentemente, gli inibitori della pro-proteina convertasi subtilisina/kexina tipo 9 (PCSK9i) hanno dimostrato efficacia nella riduzione di LDL-C, nella prevenzione di eventi CV e dell'aterosclerosi subclinica [5-8]. PCSK9 è una proteina riconosciuta per il suo ruolo chiave nel metabolismo del LDL-C [9]. Il legame di PCSK9 al recettore delle LDL promuove la degradazione del recettore, riducendo così la rimozione delle particelle di LDL [7].

Studi clinici su larga scala hanno dimostrato in maniera univoca e significativa che gli PCSK9i producono una riduzione del 50-60% di LDL-C quando aggiunti alla terapia con statine-ezetimibe [10]. È importante sottolineare, che negli studi clinici non sono stati osservati effetti avversi gravi dell'inibizione di PCSK9 e i tassi di interruzione erano generalmente simili tra i gruppi di trattamento e quelli trattati con placebo. Sulla base di questi risultati di studi clinici, gli anticorpi monoclonali PCSK9i, evolocumab ed alirocumab, sono stati approvati dalle organizzazioni di regolamentazione a livello globale per l'uso da parte di pazienti ad alto ed altissimo rischio CV che non raggiungono i target di LDL-C e da coloro che presentano documentata intolleranza alle statine. I PCSK9i sono stati inoltre inseriti tra le opzioni terapeutiche delle più recenti linee guida delle società scientifiche per la gestione dell'ipercolesterolemia[1].

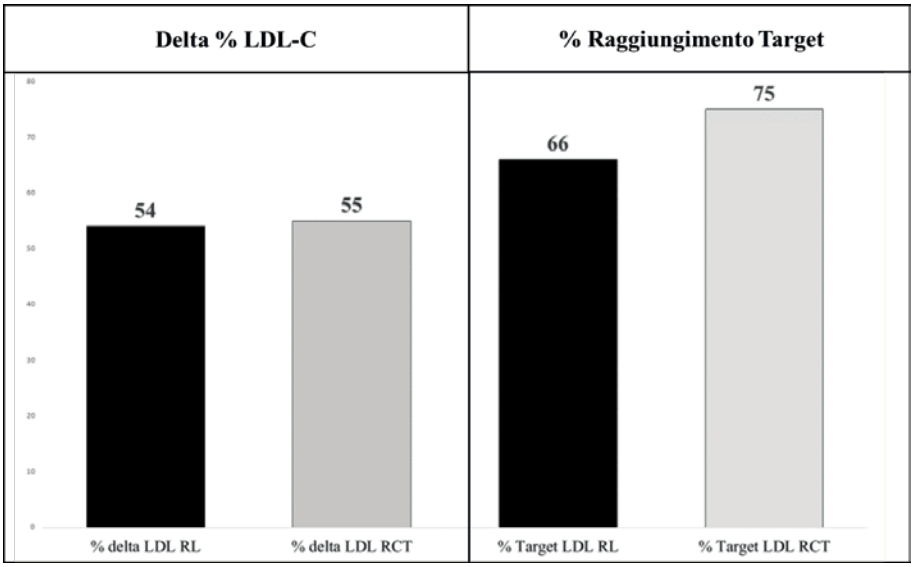
Tuttavia, gli studi clinici sono progettati per testare l'efficacia e la sicurezza di una nuova terapia in circostanze ideali. In contrasto ai dati provenienti dalle situazioni ideali dei trial clinici randomizzati, la pratica clinica è influenzata da molteplici fattori confondenti come l'aderenza variabile del paziente, la presenza di co-morbilità, i trattamenti concomitanti. Pertanto, le evidenze derivate da un contesto di "pratica clinica" sono state riconosciute come un modo per far luce su una conoscenza più completa dell'efficacia di un trattamento. Diversi studi osservazionali, comprese alcune esperienze italiane, si sono occupati di valutare l'efficacia e la sicurezza dei PCSK9i in un contesto di "real world practice". Dalla revisione sistematica di tali studi, che hanno incluso un totale di 13673 pazienti (55% con malattia cardiovascolare e 27% con FH), trattati con PCSK9i si evince che la riduzione percentuale media di LDL-C è stata del 54%. La percentuale media di raggiungimento del target LDL-C < 70 mg/dl (1,8 mmol/L) è stata del 66%, mentre la percentuale media di raggiungimento del target LDL-C < 55 mg/dl (1,44 mmol/L) è stata del 43%. Il profilo di aderenza alla terapia risulta molto alto (> 80%). Il tasso medio di interruzione della terapia è stata di circa il 10%. Il profilo di tollerabilità del farmaco è molto alto e la percentuale media di pazienti che hanno riportato eventi avversi è di circa il 17% prevalentemente di natura lieve, solo 1 studio ha riportato eventi avversi classificati come gravi. Tali risultati sono in linea con quelli riscontrati nei trial clinici randomizzati. Infatti, negli studi clinici e negli studi di estensione in aperto, i PCSK9i hanno ridotto il LDL-C di circa il 50%–60% quando aggiunti alla terapia con statine-ezetimibe e hanno consentito a circa il 65%–85% dei pazienti di raggiungere un LDL-C < 70 mg/dl (1,8 mmol/L) con riduzione degli eventi CV [4]. I tassi di interruzione e la percentuale di pazienti che hanno riportato effetti collaterali sono

stati generalmente simili tra i pazienti che hanno ricevuto i PCSK9i e il placebo [4]. I PCSK9i sono sempre più utilizzati nella pratica clinica e, alla luce delle più recenti evidenze, l'agenzia italiana del farmaco (AIFA) ha ampliato i criteri di rimborsabilità per i pazienti in prevenzione secondaria aumentando la quota di pazienti che avranno accesso a tale terapia con i benefici connessi alla riduzione degli eventi CV.

In conclusione, i dati provenienti dagli studi di "real world practice" dimostrano che i risultati degli studi di intervento sui PCSK9i vengono mantenuti quando questi farmaci sono prescritti in un contesto di pratica clinica. Nel complesso, il tasso di raggiungimento del target LDL-C rappresenta ancora un problema importante nei pazienti con altissimo profilo di rischio CV, nonostante l'elevato profilo di efficacia che abbiamo raggiunto con l'impego di terapie di associazione che comprendono l'uso di PCSK9i.

## Bibliografia


1. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. European heart journal. 2020;41:111-88.
2. Duell PB, Gidding SS, Andersen RL, Knickelbine T, Anderson L, Gianos E, et al. Longitudinal low density lipoprotein cholesterol goal achievement and cardiovascular outcomes among adult patients with familial hypercholesterolemia: The CASCADE FH registry. Atherosclerosis. 2019;289:85-93.
3. Iannuzzo G, Buonaiuto A, Calcaterra I, Gentile M, Forte F, Tripaldella M, et al. Association between causative mutations and response to PCSK9 inhibitor therapy in subjects with familial hypercholesterolemia: A single center real-world study. Nutr Metab Cardiovasc Dis. 2022;32:684-91.
4. Stoekenbroek RM, Hartgers ML, Rutte R, de Wijer DD, Stroes ESG, Hovingh GK. PCSK9 inhibitors in clinical practice: Delivering on the promise? Atherosclerosis. 2018;270:205-10.
5. Giugliano RP, Pedersen TR, Park JG, De Ferrari GM, Gaciong ZA, Ceska R, et al. Clinical efficacy and safety of achieving very low LDL-cholesterol concentrations with the PCSK9 inhibitor evolocumab: a prespecified secondary analysis of the FOURIER trial. Lancet. 2017;390:1962-71.
6. Schwartz GG, Steg PG, Szarek M,t Bhatt DL, Bittner VA, Diaz R, et al. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. The New England journal of medicine. 2018;379:2097-107.
7. Di Minno MND, Gentile M, Di Minno A, Iannuzzo G, Calcaterra I, Buonaiuto A, et al. Changes in carotid stiffness in patients with familial hypercholesterolemia treated with Evolocumab(R): A prospective cohort study. Nutr Metab Cardiovasc Dis. 2020;30:996-1004.
8. Di Minno A, Gentile M, Iannuzzo G, Calcaterra I, Tripaldella M, Porro B, et al. E ndothelial function improvement in patients with familial hypercholesterolemia receiving PCSK-9 inhibitors on top of maximally tolerated lipid lowering therapy. Thromb Res. 2020;194:229-36.
9. Anesi A, Di Minno A, Calcaterra I, Cavalca V, Tripaldella M, Porro B, et al. An Untargeted Lipidomic Analysis Reveals Depletion of Several Phospholipid Classes in Patients with Familial Hypercholesterolemia on Treatment with Evolocumab. Biomedicines. 2021;9.
10. Zhang XL, Zhu QQ, Zhu L, Chen JZ, Chen QH, Li GN, et al. Safety and efficacy of anti-PCSK9 antibodies: a meta-analysis of 25 randomized, controlled trials. BMC Med. 2015;13:123.


LDL: low density lipoprotein; %: percentuale; RL: real Life; RCT: randomized controlled trial

*LDL-C < 70 mg/dl (1,8 mmol/L) [1]

**Figura:** Confronto della stima della riduzione percentuale media del LDL-C e del raggiungimento del target di LDL-C nei pazienti ad alto rischio*: confronto tra gli di real world practice e nei trial clinici randomizzati.

*RELAZIONI - LETTURE*

# La gestione in urgenza delle emorragie in pazienti trattati con anticoagulanti inibitori del Xa

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La terapia anticoagulante è la chiave del trattamento e della prevenzione degli eventi trombotici. La sua principale complicanza è l'insorgenza di emorragie maggiori che devono prevedere un rapido intervento di reverse del loro effetto; tale situazione si può anche verificare per quei pazienti che non sanguinano ma che necessitano di un intervento chirurgico o di una procedura in urgenza. Ad oggi più opzioni terapeutiche sono disponibili per il trattamento anticoagulante a lungo termine e sono rappresentate dagli anti vitamina K (VKA) e dagli anticoagulanti orali diretti (DOAC) (Apixaban, Dabigatran, Edoxaban e Rivaroxaban). Questi ultimi hanno certamente aumentato le opzioni terapeutiche disponibili, ma il loro uso si associa comunque ad un rischio di emorragia che si attesta intorno al 5% in base ai risultati dei trial disponibili in letteratura [1] e dei registri; pertanto conoscere quali metodiche sono disponibili per intervenire in tali condizioni è di essenziale importanza per il clinico.

Tra le varie strategie disponibili c'è da sottolineare come il plasma fresco congelato (FFP) non venga raccomandato da quasi nessuna linea guida; gli alti volumi da infondere per garantire un effetto emostatico, oltre ai tempi relativamente lunghi necessari alla loro infusione, rendono tale trattamento poco fruibile in situazione di emergenza e a rischio di eventi avversi legati proprio al sovraccarico di volume [2]. Solo in quelle condizioni dove è necessario un supporto al circolo per il trattamento dello shock emorragico il FFP può essere preso in considerazione, anche se il suo effetto sul reverse dell'anticoagulazione resta controverso [3]. Per quanto concerne l'approccio terapeutico ai pazienti in trattamento con DOAC che presentano un'emorragia maggiore da sottoporre ad una strategia di reverse la maggioranza delle linee guida suggerisce l'uso degli antidoti specifici e solo quando questi non sono disponibili l'impiego dei plasma derivati come il complesso protrombinico attivato a 3 o a 4 fattori (PCC 3-F o PCC-4F). Sebbene questi ultimi vengano impiegati off-label per anni sono stati l'unica opzione terapeutica disponibile. Il meccanismo d'azione mediante il quale esplicano la loro attività nei confronti dei DOAC non è del tutto noto; per lo più sono stati infatti testati su volontari sani. Recentemente alcuni trial clinici hanno dimostrato che il 4F-PCC garantisce un efficacia clinica nel controllo delle emorragie nei pazienti in trattamento con DOAC paragonabile a quello osservato nel controllo delle emorragie da VKA, con un incidenza di eventi trombotici peraltro inferiore [4-5]. La dose da impiegare varia tra le 25 e le 50UI pro/kg in base alla gravità e al sito dove l'emorragia si presenta. Le varie linee guida lasciano poco spazio all'impiego del Fattore VII attivato ricombinante (rFVIIa) come strategia di reverse, che dovrebbe essere considerata solo quando le altre opzioni terapeutiche non hanno funzionato [2]. L'impiego di antidoti specifici recentemente introdotti (Idarucizumab per il Dabigatran e Andexanet-alfa per Rivaroxaban e Apixaban) hanno rivoluzionato le possibilità a disposizione dei clinici tanto da essere stati inseriti a pieno titolo in numerose linee guida. Andexanet alfa è una proteina ricombinante con una struttura simile a quella del fattore Xa endogeno ma è biologicamente inattiva. E' stato studiato in un trial dedicato (ANNEXA-4) [6] in pazienti che assumevano Rivaroxaban e Apixaban e presentavano un evento emorragico maggiore con concentrazioni di farmaco almeno superiori ai 75 ng/ml. Il trattamento ha dimostrato un decremento dell'attività dei livelli mediani di fattore Xa del 92% per entrambi i DOAC testati oltre ad un buon controllo delle emorragie a 12 ore dall'infusione con una mortalità pari al 14% ed un tasso di eventi trombotici del 10%, la maggioranza dei quali è avvenuta in pazienti che non avevano potuto reintrodurre una terapia anticoagulante. In base a questi dati anche l'ultimo consenso di esperti pubblicato dall'ACC [7] raccomanda l'impiego di tale strategia per il reverse in caso di emorragia maggiore dei due farmaci succitati. Va comunque notato come, ad oggi, l'FDA non abbia approvato l'uso dell'Andexanet-alfa per le procedure chirurgiche in emergenza visto che il suo impiego nel peri-procedurale non è stato sufficientemente studiato. A tal riguardo va considerato che il farmaco necessita, dopo il bolo iniziale, di una infusione successiva la cui durata ottimale non è del tutto chiara soprattutto per procedure di lunga durata. Il farmaco

inoltre non è approvato per il trattamento dei pazienti in Edoxaban; per quanto nel trial dedicato [6] alcuni pazienti fossero stati arruolati, il loro piccolo numero non consente di trarre conclusioni definitive. Per questo motivo, quando ci si trova a dover agire su un'emorragia maggiore con tale farmaco viene raccomandato di ricorrere alla dose maggiore suggerita dalla scheda tecnica, indipendentemente dal momento dell'ultima assunzione e dalla dose di farmaco [8].

Concludendo attualmente esistono antidoti specifici per i DOAC che consentono, in situazione di emergenza, di effettuare un rapido ed efficace reverse del loro effetto. Qualora però questi non siano fruibili si mantiene comunque l'indicazione all'uso del PCC, preferibilmente a 4 fattori.

Per una rassegna delle principali linee guida sull'argomento si rimanda ad una recente revisione [9]. Il principale riferimento resta comunque la guida pratica della Società europea di aritmologia (EHRA) [10]

**Bibliografia**


1. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta- analysis of randomised trials. Lancet. 2014; 383: 955–62.
2. Burnett AE, Mahan CE, Vazquez SR, Oertel LB, Garcia DA, Ansell J. Guidance for the practical management of the direct oral anticoagulants (DOACs) in VTE treatment. J Thromb Thrombolysis. 2016; 41: 206–32.
3. Steffel J, Verhamme P, Potpara TS, et al. The 2018 European Heart Rhythm Association practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J. 2018; 39: 1330–93.
4. Tran H, Joseph J, Young L, et al. New oral anticoagulants: a practical guide on prescription, laboratory testing and peri-procedural/bleeding management. Australasian Society of Thrombosis and Haemostasis. Intern Med J. 2014; 44: 525–36.
5. Muller M, Eastline J, Nagler M, Exadaktylos AK, Sauter TC. Application of prothrombin complex concentrate for reversal of direct oral anticoagulants in clinical practice: indications, patient characteristics and clinical outcomes compared to reversal of vitamin K antagonists. Scand J Trauma Resusc Emerg Med. 2019; 27: 48.
6. Connolly SJ, Crowther M, Eikelboom JW, Gibson CM, Curnutte JT. Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors N Engl J Med 2019; 380:1326-35
7. Tomaselli GF, Mahaffey KW, Cuker A, Dobesh PP, Doherty JU, Eikelboom JW. 2020 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on oral anticoagulants JACC 2020; 76: 594-622
8. Cuker A, Burnett A, Triller D, et al. Reversal of direct oral anticoagulants: guidance from the anticoagulation forum. Am J Hematol. 2019; 94:697–709.
9. Milling TJ, Pollack CV. A review of guidelines on anticoagulation reversal across different clinical scenarios – Is there a general consensus? Am J Emerg Med 2020; 38: 1890-1903
10. Steffel J, Collins R, Antz M, et al. 2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation. Europace. 2021; 23:1612-76.

# COMUNICAZIONI ORALI

## 1. INDIVIDUAL PATHS AND DIGITIZATION: A NEW APPROACH FOR THE MANAGEMENT OF CHRONICITY

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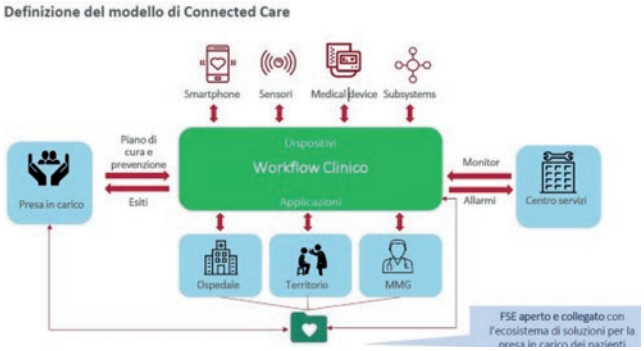
The spread of diseases chronic, which increased during the pandemic and their incidence on health expenditure has increased awareness of the urgency of rethinking e therefore to innovate the organizational models of healthcare. The patient referred to is a person, usually elderly, often suffering from multiple chronic diseases incident at the same time (comorbidity or multimorbidity), whose care needs are determined not only by factors related to clinical conditions, but also by other determinants (socio-family status, environmental status, accessibility to care etc.). The presence of multiple pathologies requires the intervention of various figures professional. The population over 65 represents 23.6% of the population but it absorbs 55.4% of healthcare costs.
A care system oriented to the management of chronicity must program its own evaluation system orienting it on the patient-person and his individual "global" health project built through a personalized and shared "Pact of Care". Connected care puts the citizen-patient at the center of system by creating organizational models that favor the integration of care between the hospital and the local area and enable patient empowerment.
The Connected Care model designed like this:
1. allows you to share information between the different actors of the different care models involved in the patient care process,
2. governs the global "taking charge" of patients,
3. identifies the Electronic Health Record as a tool main way of gathering information and communicating between operators of the system and with the citizen / patient;
4. transforms technology to support the prevention and treatment of citizens / patients, conveying information to Service Centers for the monitoring of care plans and clinical and health data.
The PNRR is a great opportunity to overcome the weaknesses that emerged during the health crisis and start planning post-emergency health right away. Restarting "connected" means using digital to promote more effective collaboration between all players in the health ecosystem e model health services on the needs of citizens / patients in support of healthcare professionals.




## 2. A ROLE FOR A PALLIATIVE CARE SERVICE IN THE MANAGEMENT OF FRAGILE COMORBID PATIENTS IN A PRIMARY CARE HOSPITAL

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**Background:** Palliative care represents the set of therapeutic, diagnostic and assistance interventions, aimed both at the patient and at his family, focused on inclusive care of patients whose underlying disease, characterized by an unstoppable evolution and from a poor prognosis, no longer responds to specific treatments. (Law n.38 / 1 Art. 2-Definitions)
Majority of frail patients who resort to hospitalization are discharged at home without any form of follow-up care and left on they own in the management of their disease.

**Patients and Methods:** Starting from October 2021, a Fragility and Palliative Care (FCP) Outpatient Clinic is active at the Montichiari Hospital, which aims to improve frail patients' quality of life and, when possible, preventing inappropriate recourse to the hospital setting.
After first assessment, patients may be followed, according to they needs, by follow-up visits, phone interview or day hospice (with related procedures such es paracentesis, thoracentesis or blood cell transfusions)
**Results:** In its first 150 days of activity, the FCP ambulatory in Montichiari took care of a total of 27 patients (mean age: 82 ± 9 years, of which 18 males with mean age of 80 ± 8 years and 9 females with mean age of 86 ± 11 years), for an average period of 82 ± 54 days.
Of these patients, 19 were affected by malignant neoplasm, while 8 were admitted for different conditions. Palliative care was initiated simultaneously with cancer therapy in 16% of patients.
At the time of admission, comorbidities, excluding malignancies (heart disease, COPD / asthma, chronic renal failure, arterial hypertension, diabetes mellitus) were 1.5 per patient (see table for details).
The average value of Zarit index was 22 ± 12 (mild to moderate burden of care).
A total of 10 patients, (27%), died during the follow-up period, while 17 (63%) are still actively followed. Six of patients who died were successfully addressed to a hospice service.
On average, there were 142 accesses to the service, of which 44 in presence and 98 telephone assessments; the day hospice service was needed 20 times, with a total of 17 transfusions of concentrated red blood cells, 5 paracentesis and 1 thoracentesis.
Therapy needed to achieve adequate pain control included NSAIDs in 15% of cases, acetaminophen in 56%, corticosteroids in 33%, minor opioids in 4%, major opioids in 37%, other pain-modulating drugs in 8% of cases. The most used major opioid was oxycodone per os (average dose 37 mg / day), followed by fentanyl patch (average 62 mcg / h).
We traced the cumulative number of hospital admissions of our patients before being taken in charge by our FCP service; the number was significantly higher both when the 5 months prior to taking charge are considered, compared to the 5 months of service activity (31 vs 17 with an average of 1.2 ± 1.5 vs 0.7 ± 0.9) with p = 0.005, and when the previous accesses of the last year compared to the time of taking in charge are considered (44 vs 26 with an average of 1.8 ± 1.6 vs 0.7 ± 0.9; p = 0.004).
**Conclusions:** Although numbers are still small, these preliminary data seem to highlight a significant role for a frailty and palliative care service in a primary care hospital (with a relevant role for phone interviews): the reduction in the number of hospitalizations translates into an improvement in the quality of life (both by granting prolonged home staying and preventing classical consequences of hospital admission such as infections, delirium, falls, etc.) as well as a reduction of economic burden for healthcare system.

| | YES | | NO | |
|---|---|---|---|---|
| **Neoplasm** | 19 | 70% | 8 | 30% |
| **Heart disease** | 12 | 44% | 15 | 56% |
| **Hypertension** | 15 | 56% | 12 | 44% |
| **Diabetes mellitus** | 5 | 19% | 22 | 81% |
| **CKD** | 7 | 26% | 20 | 74% |
| **COPD** | 2 | 7% | 25 | 93% |

## 3. WHEN THE BEST IS THE ENEMY OF THE GOOD: WHEN TO TREAT?

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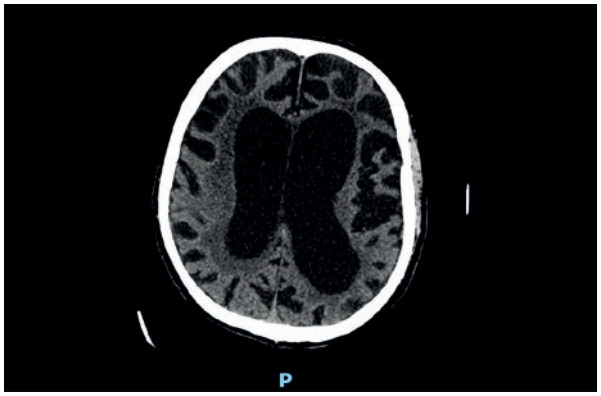
The patient, a 65-year-old man, has a history of fronto-temporal dementia due to progranulin deficiency (see brain TC) with complete functional dependence in the basic activities of daily life, bed rest syndrome, dysphagia and chronic inhalation with the need for an indwelling Conveen type catheter and positioning of percutaneous endoscopic gastrostomy. We also report a positive history for extrapyramidal syndrome, right pulmonary nodularity in radiological follow-up, multiple hospitalizations for hypersecretive bronchitis and urinary tract infections. The patient entered the emergency room for fever and diarrhea. In our ward, he appeared alert, mutated, not

contactable. There was edema in the lower limbs and hyperemia of the right knee. Thoraco-abdominal objectivity was normal. Vital signs showed low-grade fever. The patient was, however, haemodynamically stable. Blood chemistry tests showed increased inflammation indices and bacterial serology and faecal culture tests were negative. A single blood culture was positive for Candida parapsilosis. During hospitalization, several instrumental investigations were performed, with evidence of bilateral pulmonary thickening, abundant bronchial secretions and bilateral pleural effusion. Therefore, the patient was treated with steroid therapy, broad-spectrum antibiotic (meropenem and vancomycin) and antifungal (caspofungin), with good clinical-laboratory response.

The present clinical case reflects on a situation that we often find in hospital wards, facing clinical, ethical, management and communication problems with patients and / or family members. Frequently, multi-morbid patients are hospitalized with a long history of infectious causes. There is often a lack of a global and shared approach between the territorial care systems and the acute hospital, for a correct management of the patient's clinical status and the optimization of resources, a rational management of therapies, an overall vision to limit the multiple increasing resistance to antibiotics. Exams, cultural isolations, antibiograms are often more important than the patient. There is no reflection if the therapy I'm using is actually therapeutic and curative for the patient or whether it represents a brief parenthesis of asymptomaticity before the next infection, possibly fatal. Therefore, it is also necessary to the real importance of care pathways that allow the home management of terminal phases of patients with chronic degenerative pathology or neoplasia.




## 4. DIAGNOSTIC AND PROGNOSTIC PERFORMANCE OF URINARY NEUTROPHIL GELATINASE-ASSOCIATED LIPOCALIN IN PATIENTS WITH CIRRHOSIS AND ACUTE KIDNEY INJURY

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**Background and Aims:** Acute Kidney Injury (AKI) commonly occurs in patients with decompensated cirrhosis. Neutrophil Gelatinase-associated Lipocalin (NGAL) is a novel urinary biomarker that could help in discriminating between different etiologies of AKI. The aim of this study was to investigate the ability of urinary NGAL (uNGAL) in: (1) the differential diagnosis of AKI, (2) predicting the response to treatment with terlipressin and albumin in patients with Hepatorenal Syndrome (HRS)-AKI and (3) predicting in-hospital and 90-day mortality.

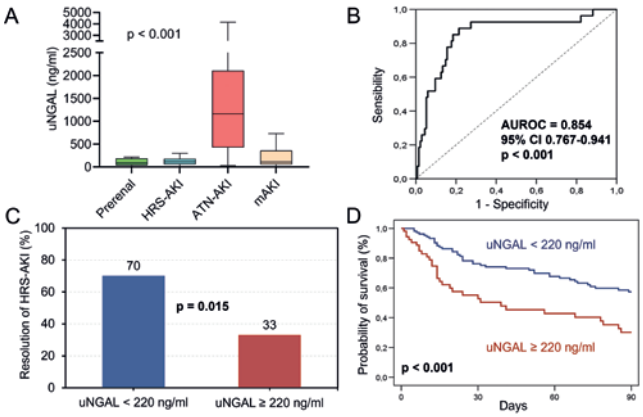
**Method:** We included cirrhotic patients with AKI not solved within 48 hours, who were consecutively admitted from 2015 to 2020 at the University Hospital of Padova. uNGAL and standard urinary biomarkers were measured. Data on the type of AKI, AKI treatment, resolution of AKI were collected during the hospitalization and patients were followed up until transplant, death or 90 days.

**Results:** We enrolled 162 patients (mean age: 62 ± 10 years, male: 77%; alcoholic etiology: 48%; Mean MELD: 25 ± 8). Thirty-five patients (22%) had hypovolemic AKI, 64 (39%) HRS-AKI, 27 (17%) acute tubular necrosis (ATN)-AKI and 36 (22%) a mixed form of AKI (mAKI). uNGAL values were significantly higher in patients with ATN-AKI than in patients with other types of AKI (1162 [423-2105] vs 109 [52-192] ng/ml; p < 0.001; Fig. A). uNGAL showed a high discrimination ability in predicting ATN-AKI (AUROC = 0.854; [95% CI = 0.767-0.941]; p < 0.001; Fig. B) and the best threshold was 220 ng/ml (sensitivity 89%; specificity 78%).

Sixty-two patients with HRS-AKI were treated with terlipressin and albumin. Among them, patients with uNGAL ≥ 220 ng/ml had a significantly lower rate of response to terlipressin and albumin (33 vs 70%; p = 0.015; Fig. C). After adjusting for serum creatinine, uNGAL ≥ 220 ng/ml was independently associated with a higher risk of non-response (aOR=4.55, 95% CI=1.28– 16.67; p= 0.02).

In multivariable analysis (adjusted for age, MELD, ACLF, leukocytes and type of AKI) uNGAL was an independent predictor of in-hospital mortality (aOR = 1.74 [95% CI = 1.26-2.38]; p = 0.001) and 90-day mortality (aHR = 1.32 [95% CI = 1.13-1.55]; p = 0.001). Probability of survival was significantly lower in patients with uNGAL ≥ 220 ng/ml (57% vs 30%; p < 0.001; Fig. D).

**Conclusion:** uNGAL is an excellent biomarker for the differential diagnosis of AKI in cirrhosis, it predicts response to treatment with terlipressin and albumin in patients with HRS-AKI and is an independent predictor of mortality.




## 5. PROPROTEIN CONVERTASE SUBTILISIN/KEXIN TYPE 9 (PCSK9) LEVELS AND THROMBOTIC EVENTS IN PRIMARY ANTIPHOSPHOLIPID SYNDROME. THE MULTICENTER ATHERO-APS STUDY.

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**Background:** The proprotein convertase subtilisin/kexin type 9 (PCSK9) is emerging as a novel cardiovascular risk factor. Levels of PCSK9 in thrombotic primary antiphospholipid syndrome (PAPS) have never been investigated.

**Methods:** Cross sectional comparison of baseline characteristics of 91 PAPS patients enrolled in the multicenter ATHERO-APS cohort study. PCSK9 levels were categorized into tertiles and the association with arterial and recurrent thrombosis were assessed by univariable and multivariable regression analysis.

**Results:** Median age was 51 years and 71.4% (n=65) were women. Overall, 33% (n=30) experienced an arterial event while 31% (n=28) had recurrent thrombotic events. Median PCSK9 levels were 1243 (1100-1650) pg/ml. Patients in the third PCSK9 tertile (>1458 pg/ml) showed a higher prevalence of dyslipidemia, lupus anticoagulant positivity and a history of pre-

vious arterial and recurrent thrombosis than patients in the first and second tertile. PCSK9 levels were higher in arterial than venous thrombosis (1502 vs. 1180 pg/ml, p=0.002), and in patients with recurrent vs isolated thrombosis (1680 vs. 1150 pg/m, p<0.001). High plasma PCSK9 levels were associated with a 4-fold increase risk for arterial events and with a 10-fold increase risk for recurrent thrombosis after adjustment for confounding factors.
**Conclusion:** These preliminary data suggest that PCSK9 levels are increased in PAPS patients with arterial and recurrent thrombosis. Its role as a possible therapeutic target in PAPS needs further studies.

## 6. HELIOS-A: STUDY OF VUTRISIRAN IN PATIENTS WITH HATTR AMYLOIDOSIS

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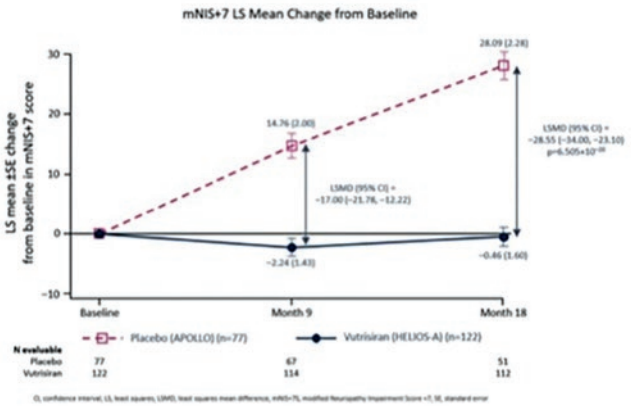
**Introduction:** Hereditary transthyretin-mediated amyloidosis (hATTR) is a fatal, multisystem disease. Vutrisiran, an investigational RNA interference therapeutic that targets variant and wild-type TTR, was assessed in the Phase 3, HELIOS-A study (NCT03759379).
**Methods:** Patients with hATTR amyloidosis with polyneuropathy were randomized (3: 1) to vutrisiran (25 mg subcutaneous injection every 3 months) or patisiran (0.3 mg/kg intravenous infusion every 3 weeks), a reference comparator. The placebo group (n=77) from the APOLLO study was the external control. The primary endpoint: change from baseline in neuropathy (mNIS+7) at Month 9, versus external placebo.
**Results:** 164 patients randomized (vutrisiran, n=122; patisiran, n=42). As reported previously, at 9 months vutrisiran significantly improved mNIS+7 versus external placebo (Figure); improvement was maintained until 18 months (secondary endpoint). Vutrisiran met all other secondary endpoints, with significant improvements in quality of life (Norfolk QOL-DN) and gait speed (10-meter walk test) at Months 9 and 18, and in nutritional status (mBMI) and disability (R-ODS) at Month 18, versus external placebo. Vutrisiran achieved robust, sustained TTR reduction across 18 months, which was non-inferior to patisiran. Most adverse events with vutrisiran were mild or moderate, with no drug-related discontinuations or deaths.
**Discussion:** Vutrisiran significantly improved multiple important disease-relevant endpoints, versus external placebo, and demonstrated an acceptable safety profile.
**Conclusion:** Vutrisiran may provide benefit across important hATTR amyloidosis disease manifestations.




## 7. AI-SCORE (ARTIFICIAL INTELLIGENCE-SARS COV2 RISK EVALUATION): A FAST, OBJECTIVE AND FULLY AUTOMATED PLATFORM TO PREDICT THE OUTCOME IN COVID-19 PATIENTS

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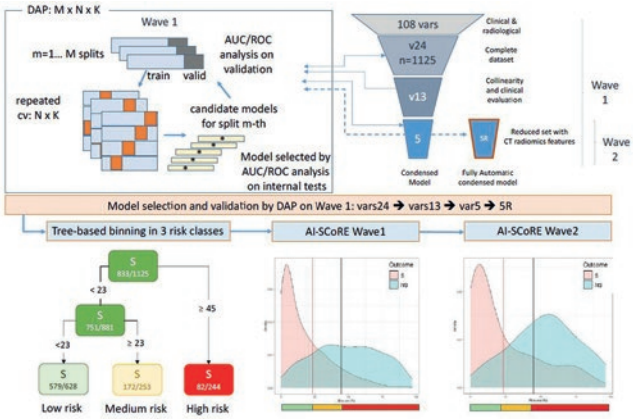
**Background:** The implementation of effective automated tools for a risk stratification of Covid-19 patients at the onset of symptoms is pivotal for a better allocation of patients and health resources. To this aim we developed and prospectively validated a rapid, reliable, objective and user-friendly AI platform.
**Methods:** Our study comprised two cohorts. A first one (Retrospective training cohort) included 1575 adults affected by COVID-19 admitted to Emergency Departments during the first wave (Wave 1) of pandemic (February 16th to April 29th, 2020) from 16 centers in Northern Italy. A second one (Prospective external validation cohort) included 213 adults affected by COVID-19, enrolled during the second wave (Wave 2) of pandemic (October 14th to December 31th, 2020). 107 clinical and CT variables obtained at patients' hospital admission were analyzed in the training cohort. A rigorous AI model selection framework was adopted to select predictive models based on a limited set of clinical and CT objective and automated data. Predictive performances were assessed in terms of AUC (area under the receiver operator curve). A web-mobile interface was developed using Microsoft PowerApps environment and cloud services. The study is registered with ClinicalTrials.gov, NCT04834934.




**Findings:** After data cleaning, the final cohort included 1125 patients (292 non-survivors, 26%) and 24 variables. Logistic was selected as the best performing machine learning model according to the best outcome prediction performance in a model including a subset of 5 variables (Var5, mean AUC = 0.834, sdAUC = 0.007), and in models including a set of 24 and 13 variables (Var24, AUC=0.839 sdAUC= 0.009 and Var13: AUC=0.840, sdAUC=0.0093), respectively. The final risk score was based on age, sex,

saturation, and two CT features. In order to obtain a risk score easy and straight to compute, the extraction of CT variables in Var5 model (well-aerated parenchyma and total cardiovascular thoracic calcium) was automatized. The fully automated Var5 model showed an AUC=0.842 (DeLong 95% CI: 0.816-0.867) estimated on the full Wave1 and was used to build a 0-100 scale risk score (AI-SCoRE). Classification tree identified 3 risk classes in AI-SCoRE: low risk (≥0,<23), medium risk (≥23,< 45) and high risk (≥45, ≤100) with a mortality rate of 8%, 32%, and 66%, respectively. The predictive performance was confirmed in the external validation cohorts (overall AUC 0.808; 95% CI: 0.7402-0.8766)
**Interpretation:** AI-SCoRE risk stratification of COVID-19 patients, based on an algorithm built on automated and objective variables, may support clinical decision making, improving patients' management and resources allocation.

## 8.OBESITY AND OVERWEIGHT ARE LINKED TO AN INCREASED DUODENAL ABUNDANCE OF SODIUM/GLUCOSE CO-TRANSPORTER 1 AND GLUCOSE TRANSPORTER 5

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Augmented dietary sugar intake is involved in the pathogenesis of obesity and its related disorders. In the proximal intestine, dietary monosaccharides glucose and galactose are transported from the lumen of the intestine into enterocytes by the sodium/glucose co-transporter-1 (SGLT-1), whereas fructose enters into the enterocytes by the glucose transporter 5 (GLUT-5). All the three monosaccharides are transferred from the intracellular compartment of enterocytes to the bloodstream across the basolateral membrane by the glucose transporter 2 (GLUT-2). Recent evidence indicates that subjects with obesity, as compared to those with normal weight, exhibit increased intestinal glucose absorption along with higher duodenal mRNA levels of SGLT-1, without differences in GLUT-2 mRNA levels. However, whether subjects with overweight or obesity display higher duodenal protein levels of SGLT-1 and GLUT-2 remains to be firmly established. Additionally, no studies have explored the link between obesity and an augmented intestinal abundance of the fructose carrier GLUT-5. To address this issue, we assessed duodenal protein abundance of SGLT-1, GLUT-5 and GLUT-2 by western blot in a cohort of 50 non-diabetic subjects who underwent to a complete anthropometrical and biochemical characterization, including an oral glucose tolerance test (OGTT), and an upper gastrointestinal endoscopy with duodenal mucosa biopsies. Study participants were stratified on the basis of their BMI values as follow: normal weight (n=11), overweight (n=15) and obese (n=24). We found that subjects with overweight and obesity exhibit progressively increased duodenal protein levels of SGLT-1 (+10 and +20% respectively, P= 0.04) and GLUT-5 (+10 and +30% respectively, P=0.01) as compared to those with normal weight. Conversely, no differences in duodenal GLUT-2 abundance was found amongst the three study groups. By performing univariate analyses, we found that duodenal SGLT-1 and GLUT-5 protein levels were positively correlated with BMI, waist circumference, 1h post-load plasma glucose, 1h and 2h post-load insulin levels. Furthermore, a positive relationship was detected between intestinal GLUT-5 levels and serum concentration of uric acid (r=0.40; P=0.04), which is a product of fructose metabolism known to be involved in the pathogenesis of obesity and its complications. In conclusion, our findings demonstrate that overweight and obesity conditions are associated to increased duodenal levels of SGLT-1 and GLUT-5, thus suggesting that inhibition of intestinal SGLT-1 and/or GLUT-5 may be a valuable strategy for prevention and treatment of obesity and its related disorders.

## 9. HELIOS-A: 18-MONTH EXPLORATORY CARDIAC RESULTS FROM THE PHASE 3 STUDY OF VUTRISIRAN IN PATIENTS WITH HEREDITARY TRANSTHYRETIN-MEDIATED AMYLOIDOSIS

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**Background:** Hereditary transthyretin-mediated (hATTR) amyloidosis, also known as ATTRv amyloidosis, is a fatal, multisystem disease that presents with progressive polyneuropathy and/or cardiomyopathy. HELIOS-A (NCT03759379) assessed the efficacy of vutrisiran, an investigational RNA interference therapeutic, in patients with hATTR amyloidosis with polyneuropathy.
**Purpose:** To evaluate the effect of 18 months of vutrisiran treatment on exploratory cardiac endpoints in the HELIOS-A Phase 3 study.
**Methods:** Patients were randomised (3: 1) to vutrisiran (25 mg SC, q3m) or patisiran (0.3 mg/kg IV, q3w), a reference comparator. The APOLLO placebo group (n=77) was an external control. Primary endpoint was change from baseline in the modified Neuropathy Impairment Score +7 (mNIS+7) at 9 months, vs. external placebo. Exploratory cardiac endpoints included change from baseline in NT-proBNP levels, echocardiography parameters, and technetium (Tc) scintigraphy parameters at 18 months. A prespecified cardiac subpopulation was included (baseline left ventricular wall thickness ≥1.3 cm and no medical history of aortic valve disease or hypertension).
**Results:** HELIOS-A enrolled 164 patients and the primary endpoint was met. In the cardiac subpopulation (n=40/122 vutrisiran; n=36/77 placebo), 18 months of vutrisiran treatment significantly improved NT-ProBNP levels vs. external placebo (adjusted geometric fold change ratio: 0.49; p=0.0004) and demonstrated a trend towards improvement in echocardiographic parameters vs. external placebo (including a significant difference in cardiac output [least squares mean difference: 0.41; p=0.043]). Of the 122 vutrisiran-treated patients, 99mTc scintigraphy assessment was captured for 64 vutrisiran-treated patients at baseline, 35 (54.7%) of whom had Perugini grade ≥2 (moderate/intense) cardiac uptake of 99mTc. Among patients with evaluable scintigraphy parameters repeated at 18 months (evaluable patients), heart-to-contralateral lung ratio and normalised LV total uptake on scintigraphy improved (decrease from baseline) in 64.6% (31/48) and 68.1% (32/47), respectively, at 18 months. Of the evaluable patients, 28.1% (16/57) had an improvement (reduction from baseline) in Perugini grade of cardiac uptake, 68.4% (39/57) had no change in grade, and 3.5% (2/57) worsened in grade. Of evaluable patients with baseline Perugini grade ≥2, the proportion with improvement in heart-to-contralateral lung ratio and normalised LV total uptake was 76.9% (20/26) and 100% (25/25) respectively. No cardiac safety concerns were identified with vutrisiran treatment.
**Conclusions:** In this exploratory analysis, vutrisiran treatment was associated with a positive impact on NT-ProBNP levels and echocardiographic parameters vs. external placebo in the cardiac subpopulation. Vutrisiran treatment also reduced cardiac uptake of 99mTc potentially suggesting reduction in cardiac amyloid, although the clinical significance of this is not yet clear.

## 10. INHIBITION OF COMPLEMENT C1S BY SUTIMLIMAB IN PATIENTS WITH COLD AGGLUTININ DISEASE: EFFICACY AND SAFETY RESULTS FROM THE RANDOMIZED, PLACEBO-CONTROLLED PHASE 3 CADENZA STUDY

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**Background:** Cold agglutinin disease (CAD) is a serious and rare autoimmune hemolytic anemia. Clinical manifestations include complement-mediated chronic hemolytic anemia and profound fatigue. Sutimlimab is a first-in-class humanized IgG4 monoclonal antibody that selectively inhibits the classical complement pathway at C1s. In the single-arm CARDINAL study (NCT03347396), sutimlimab halted hemolysis, and improved hemoglobin (Hb) and quality of life in patients with CAD and a recent history of transfusion. CADENZA (NCT03347422) is a 26-week (Part A) randomized, double-blind, placebo-controlled Phase 3 study with open-label extension (Part B) to assess sutimlimab in patients with CAD with no recent transfusion history. We herein report efficacy and safety results from CADENZA Part A.

**Methods:** Patients were enrolled with confirmed CAD diagnosis, screening Hb ≤10 g/dL, bilirubin above normal, transfusion independence ≥6 months, and ≥1 CAD symptom. Patients were then randomized 1: 1 to receive sutimlimab (body weight <75 kg, 6.5 g; ≥75 kg, 7.5 g; N=22) or placebo (N=20) on Days 0 and 7, followed by biweekly infusions. The composite primary endpoint (sutimlimab vs placebo, compared using the Cochran-Mantel-Haenszel method) was the proportion of patients with Hb increase ≥1.5 g/dL against baseline at the treatment assessment timepoint (TAT; mean of Weeks 23, 25, and 26) and avoidance of transfusion and study-prohibited CAD therapy (Weeks 5–26). Secondary endpoints included markers of hemolysis, Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-Fatigue), and pharmacodynamic outcomes. Safety was evaluated.

**Results:** The composite primary endpoint criteria were met by a total of 16 (73%) sutimlimab patients, compared with three (15%) placebo patients (odds ratio, 15.9 [95% confidence interval, 2.9–88.0; P<0.001]). One (5%) patient in the sutimlimab arm and four (20%) patients in the placebo arm received transfusions from Weeks 5 to 26. At TAT, 16 (73%) sutimlimab patients and two (10%) placebo patients had Hb ≥2 g/dL from baseline. Sutimlimab, but not placebo, rapidly increased mean Hb and FACIT-Fatigue, and normalized mean bilirubin by Week 1, which were sustained to TAT (Figure). At TAT, the least squares mean (standard error) difference in Hb and FACIT-Fatigue between sutimlimab and placebo was 2.6 (0.4) g/dL (P<0.001) and 8.9 (2.5) points (P<0.001). Sutimlimab yielded improvements in additional hemolysis markers, decreased lactate dehydrogenase levels and reticulocyte counts, and increased haptoglobin levels, from baseline to TAT (not seen with placebo). For the sutimlimab patients, incidence of solicited symptomatic anemia symptoms reduced from baseline to Week 26 across all components; incidences of weakness and shortness of breath were reduced in the placebo arm (Figure). Observed improvements in anemia, hemolysis, and fatigue for sutimlimab patients coincided with normalized C4 levels and near-complete classical pathway inhibition, with reductions in classical pathway activity (Wieslab) and CH50 levels. C1q levels remained unchanged from baseline to Week 26, suggesting pro-phagocytic functions of C1q were unaffected by sutimlimab. Placebo arm pharmacodynamic outcomes were unaffected. Twenty-one (96%) sutimlimab patients and 20 (100%) placebo patients experienced ≥1 treatment-emergent adverse event (TEAE). Three sutimlimab patients (14%) and one placebo patient (5%) had one or more serious TEAE; one serious TEAE of cerebral venous thrombosis was assessed as sutimlimab-related by the investigator. No deaths were reported. Serious infections, but no meningococcal infections, were reported. There were no serious TEAE of hypersensitivity or anaphylaxis, no TEAEs suggestive of the development or worsening of autoimmune disease, or systemic lupus erythematosus reported in either group. Three sutimlimab patients (none in placebo) discontinued from study due to a TEAE: acrocyanosis and Raynaud's phenomenon (n=1), increased blood IgM (n=1), and infusion-related reaction (n=1). TEAEs reported more frequently in the sutimlimab arm than in placebo arm, with a difference of ≥3 patients between groups, were hypertension, headache, Raynaud's phenomenon, rhinitis, and acrocyanosis. Two sutimlimab patients developed transient, low-titer, treatment-emergent anti-drug antibodies, which did not correlate with pharmacokinetics or clinical response, suggesting that the immunogenicity risk of sutimlimab is low.

**Conclusion:** Sutimlimab, but not placebo, rapidly halted hemolysis, markedly increased Hb, and improved quality of life in patients with CAD. Sutimlimab was generally well tolerated, and the immunogenicity risk appears low. Results from CADENZA, the first placebo-controlled trial in CAD, alongside the single-arm CARDINAL study, support targeting C1s for treatment of CAD.

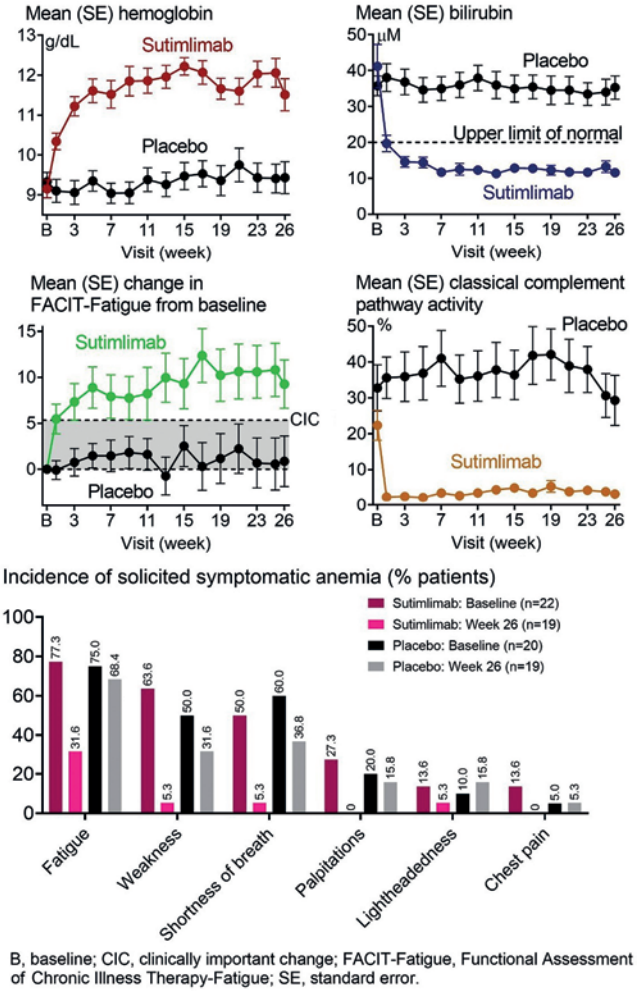


**Figure.** Effects of sutimlimab and placebo on hemoglobin, bilirubin, FACIT-fatigue, classical complement pathway activity and incidence of solicited symptomatic anemia.

## 11. HMGB1 IS HIGHLY EXPRESSED IN VESSEL WALL OF COVID-19 PULMONARY EMBOLISM: A POST-MORTEM STUDY

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**Introduction:** Cardiovascular disease is one of the main complications in COVID-19 patients with an impact on disease outcome. A frequent complication is pulmonary embolism (PE). This mostly relates to a prothrombotic state due to endothelitis. Molecular mechanisms are still far from being clarified. A possible mechanism is related to damage-associated molecular patterns (DAMPs) and, in particular, the high-mobility group box 1 (HMGB1).
Purpose of the study was to evaluate the immune cell infiltration and HMGB1 expression in COVID-19 PE tissue samples.
**Methods:** We evaluated 6 COVID-19 patients who died for chronic pulmonary embolism (CPE, 3M, 3F, aged 70.86±11.83). As controls, we used data collected from 20 patients with COVID negative PE who died before December 31, 2019 (8F, 12M, aged 75.94±18.84). All patients underwent a complete physical examination, pulmonary computerized tomography, laboratory tests, d-dimer and blood gas analysis at the time of diagnosis. Echocardiogram was evaluated at the ward admission. Died patients underwent a post-mortem analysis of tissues. Histological analysis was performed to evaluate vessel wall patho-morphology. Immunohistochemiistry was performed using anti- CD3+, -CD4+, -CD8+, -CD15+ and -HMGB1 mAbs.
**Results:** No differences between the two groups were observed for laboratory tests, d-dimer, and left and right heart echocardiography variables. In COVID-19 patients, CPE was associated with an increased HMGB1 expression ($p<0.05$). No differences were found in CD3+, CD4+, and CD8+ T cells, while the CD15+ cells (e.g., neutrophils) were more frequent in COVID-19 CPE ($p<0.05$). HMGB1 increase was three fold that of CD15+ (Spearman r -0.66 for CPE and -0.79 for controls) suggesting that CD15+ cells may undergo necrosis during COVID-19 CPE, thus shedding neutrophil extracellular traps (NETs) that contribute to HMGB1 increase.
**Conclusions:** Our data indicate that the COVID-19 CPE does not have different histopathological patterns and that inflammatory infiltration overlaps with that of non COVID-19 patients. HMGB1 and CD15+ cells are the only markers overexpressed in COVID-19 CPE and might suggest a possible mechanism involved in disease progression.

## 12. ERYTHROCYTOSIS AND FAMILIARITY: COEXISTENCE OF MULTIPLE MUTATIONS

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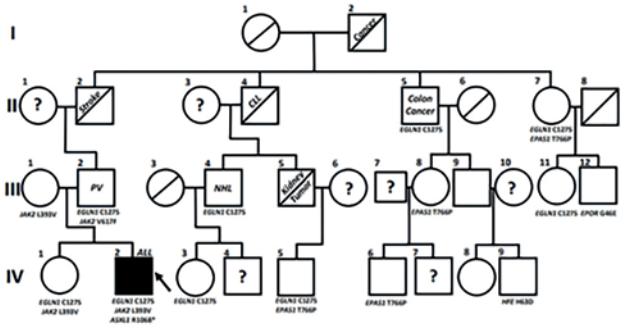
**Introduction:** Idiopathic Erythrocytosis (IE) and rare Hereditary Erythrocytosis (HE), characterized by haemoglobin (Hb) and hematocrit (HT) above the normal range, are purely studied. The recent availability of NGS offers new opportunities in the study of erythrocytosis and we report here an interesting venetian family in which patients have various mutations in erythrocytosis-associated genes.
**Methods:** Our NGS gene panel comprehends the following genes: JAK2, EGLN1, EPOR, FTL, FTH, ASXL1, HFE, HFE2, TFR2, HAMP, SLC40A1, SLC11A2, VHL, BPMG, EPAS1. We used bioinformatics tools to analyse data and Sanger Sequencing to validate the germline mutations.
The proband (IV.2) is a 24 years old man with Hb 173 g/L and HT 50% observed 6 months after the end of his treatment for acute lymphocytic leukemia (ALL). His 61 years old father suffers for PV (Hb 187 g/L, HT 55%, GB 12 x 109/L, plts 488 x 109/L). We re-evaluated with NGS these 2 patients and we studied 14 of their relatives belonging to 3 different generations (Fig 1).
**Results:** The proband inherited his mother JAK2L393V germinal mutation and his father EGNL1C127S (Tibetan mutation); his sister has the same bio-molecular pattern but not erythrocytosis. The patient carries also ASXL1 R1068[1] somatic mutation. We found EGNL1C127S mutation in 7 relatives, in 2 showing polyglobulic face and border line Hb and HT. Interestingly, in 2 subjects with normal cells counts, EGNL1C127S was associated with EPAS1T766P mutation. We found also a normal subject with EPORG46E mutation.
**Conclusions:** In our family different mutations in erythrocytosis-associated genes were found as well as rare germinal JAK2 mutations and somatic ASXL1 mutation responsible for epigenetic modifications. The Tibetan mutation is present in 9 out of the 16 evaluated subjects. It appears to be benign, but we surmise that it can play a role in the genesis of erythrocytosis at least when associated with other biomolecular alterations. In fact, in the proband it is associated with JAK2 germinal mutation and in 2 other subjects, with signs of erythrocytosis, with EPAS1 mutations known to be responsible for hereditary erythrocytosis. The JAK2L393V germline mutation, may precede the acquisition of the JAK2V617F, and the ASXL1R1068[1] is possibly related to patient's previous leukemia. In conclusion, this study suggests that multiple genes erythrocytosis may explain some erythrocytosis even in the same family.




## 13. ANTI-TUMORAL EFFECT OF PXD-101 ON OSTEOSARCOMA CELL LINES

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**Introduction:** Osteosarcoma is a highly heterogeneous bone tumor and even though surgical and chemotherapy are available for patients, new therapeutic approaches are needed to treat chemoresistance, recurrence and metastases. Our study aims to investigate the antitumor activity of the histone deacetylase inhibitor PXD-101 on low aggressive Saos-2, non-metastatic HOS and metastatic 143B cell lines.
**Methods:** XTT colorimetric assay was used to measure the cell viability and to calculate the concentration of PXD-101 able to reduce 50% cell viability. Fluorescence-activated cell sorting (FACS) analysis was performed to evaluate proliferation, cell cycle and apoptosis. The wound healing assay was used to measure cell migration. Gene and protein expression was evaluated by Real-Time RT-qPCR and western blotting analysis, respectively.
**Results:** The PXD-101 concentration able to reduce 50% of cell viability (GI50) was 4.63 μM in Saos-2, 3.31 μM in HOS and 6.02 μM in 143B cells. The GI50 concentrations were therefore applied in all further experiments. The treatment with PXD-101 in Saos-2, HOS and 143B cells decreased cell viability in a dose dependently manner. Moreover, PXD-101 reduced the proliferation in osteosarcoma cell lines [Proliferative rate. Saos-2, Vehicle: 3.64±0.42, PXD-101: 2.47±0.11. $p<0.01$; HOS, Vehicle: 7.77±0.39, PXD-101: 3.04±0.46. $p<0.001$; 143B, Vehicle: 3.18±0.37, PXD-101: 2.05±0.16. $p<0.01$], as confirmed by cell cycle analysis [Relative cell population at the S phase (%). Saos-2, Vehicle: 42.16±2.56, PXD-101: 36.38±3.71. $p<0.05$; HOS, Vehicle: 19.70±4.40, PXD-101: 7.53±1.70. $p<0.0001$; 143B, Vehicle: 25.63±3.64, PXD-101: 7.30±3.05. $p<0.0001$], and induced cell apoptosis in a time dependently manner. In addition, PXD-101 inhibited about 30% the migration ability of Saos-2, HOS and 143B cells. These features were associated with a significant reduction of mRNA and protein expression of osteoblast markers (ALP, RUNX2, OSTERIX) in the human osteosarcoma Saos-2 and HOS cell lines.
**Conclusions:** Taken together, our study reveals the antitumor activity of PXD-101 in Saos-2, HOS and 143b cells suggesting a new potential therapeutic approach for osteosarcoma.

## 14. REDUCED INCRETIN EFFECT IS AN EARLY SIGN OF DIABETES APPEARANCE. A STUDY IN A HUMAN MODEL OF B-CELL MASS REDUCTION.

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**Background:** In type 2 diabetes (T2D) patients, the incretin effect is impaired and contributes to only 20-35% of insulin response to oral glucose. The main reason appears to be impairment of the insulinotropic effect of the incretin hormones, GIP and GLP-1. However, the cause of the defective incretin effect is unclear and whether its impairment is a consequence of reduced incretin hormone secretion or reduced β-cell activity (defective beta-cell receptor expression/post-receptor defects secondary to diabetes) is still debated. Here, we evaluate changes in GLP-1 levels and differential beta-cell response to oral vs intravenous stimuli in nondiabetic humans before and after partial pancreatectomy. We also investigate protein expression related to modulation of GLP-1-induced insulin secretion in surgical pancreas biopsies.
**Materials and Methods:** To investigate changes in in vivo GLP-1 and incretin effect, we enrolled 33 nondiabetic patients (M/F: 15/18; Age: 62±15; BMI: 26.5±4.3) scheduled for pancreatoduodenectomy (PD). All subjects underwent a 2-h hyperglycemic clamp (HC), an 830 kcal mixed meal test (MMT), and an oral glucose tolerance test (OGTT) before and after surgery. β-cell glucose sensitivity (βCGS) was calculated as the ratio of insulin secretion and glucose increments, during both the hyperglycemic clamp and the mixed meal test. We applied high performance liquid chromatography-mass spectrometry (HPLC-MS) analysis to islets isolated by laser capture microdissection (LCM) from samples obtained during surgery. We performed qualitative and quantitative analysis to detect differential protein expression among the 3 groups.
**Results:** Based on post-surgery OGTT, we divided subjects into 3 groups based on glucose tolerance after PD: normal glucose tolerance (post-NGT), impaired glucose tolerance (post-IGT), or diabetes (post-DM). Before surgery, post-IGT subjects had increased GLP-1 secretion during MMT compared to other 2 groups (GLP-1 AUC: post-IGT 9795±1119 vs post-NGT 5319±1022 vs post-DM 5419±1440, P<0.05). A similar βCGS was observed in the 3 groups following i.v. glucose administration during HC stimulation (post-NGT 97.2±17.7 vs post-IGT 76.4±9.12 vs post-DM 72.7±11.8 pmol·min-1m-2·mM-1, P=0.2). However, a scaled reduction in βCGS was observed in post-IGT and post-DM following MMT (post-NGT 218±45.0 vs post-IGT 102±20.2 vs post-DM 92.3±22.8 pmol·min-1m-2·mM-1, P=0.01). Proteomic analysis showed reduced expression of proteins regulating GLP-1-stimulated insulin secretion in IGT and DM subjects: Rap1 was expressed only in post-NGT group (p<0.01), while IQGA1 was significantly reduced in IGT and DM, compared to NGT group (p=0.03) and correlated inversely with glucose AUC during OGTT (r=-0.57, P=0.03) and HOMA-IR (r=-0.78, P<0.001).
**Conclusions:** Our data show that GLP-1 secretion tends to increase in early stage beta-cell dysfunction, possibly compensating impaired beta-cell function in subjects at risk of impaired glucose tolerance and diabetes. Our findings seem to suggest that poor glucose metabolism and insulin resistance are linked to in-situ impairment of islet sensitivity to GLP-1.

## 15. PALMITOYLETHANOLAMIDE (PEA) IN PERSISTENT DEPRESSION, CHRONIC PAIN AND FATIGUE IN PATIENTS RECOVERED FROM COVID-19

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**Background:** Coronavirus disease 2019 (COVID-19) leaves behind sequelae following recovery as part of the so called long-COVID syndrome. Survivors frequently complain about chronic pain, fatigue, depression, and reduced quality of life even months after acute disease resolution. Reflecting the still unclear pathogenesis of these manifestations, targeted therapeutic interventions for the neuropsychological alterations persisting beyond acute COVID-19 are lacking. Palmitoylethanolamide (PEA) belongs to the endocannabinoid family, a group of fatty acid amides. PEA has analgesic and anti-inflammatory effects and has been found to improve chronic pain and fatigue in adult patients with different underlying clinical conditions. It is conceivable that PEA may have be effective in the management of the neuropsychological manifestations of long-COVID.
**Objective:** The aim of the present study was to investigate whether PEA has an effect on chronic pain, fatigue, depression, and quality of life in patients with long-COVID.
**Methods:** In this retrospective study, we enrolled patients previously hospitalized for COVID-19, who underwent the 3- and 6-month post-discharge evaluations at the COVID-19 Follow-up Outpatient Clinic of San Raffaele University Hospital and who were proposed a 3-month treatment with PEA by the examining physician based on altered neuropsychological status. At both the 3- and 6-month visits, all patients underwent neuro-psychological assessment through validated scales for depression (Zung Self-Depression Rating Scale, ZSDS), quality of life (general Visuo-Analogue Scale, VAS), fatigue (Fatigue Severity Scale, FSS, and Strength, Assistance in walking, Rise from a chair, Climb stairs, and Falls questionnaire, SARC-F) and chronic pain (VAS pain). To assess changes in all scales during the follow-up period, scores at 6 months were subtracted scores obtained at 3 months in a pairwise manner. For the purpose of the analysis, global improvement was defined as an improvement of at least one unit in at least three of the mentioned scales.
**Results:** A total of 98 patients were enrolled. Of these, 57 accepted to take PEA while 41 refused it and were used as controls.
The two cohorts did not differ in terms of age, sex, pre-existing comorbidities (i.e. arterial hypertension, coronary artery disease, diabetes mellitus, chronic obstructive pulmonary disease, chronic kidney disease and active cancer), length of hospital stay, and rate of transfer to the Intensive Care Unit (ICU).
No differences in the neuropsychological status (general VAS, ZSDS, FSS, VAS pain and SARC-F) were found prior to PEA initiation between patients who then received PEA and those who did not.
In the overall population, global improvement was reached in 17 out of 98 (17.3%) patients, of whom 14 (24.6%) in the PEA cohort and 3 (7.3%) in the group not taking PEA, this difference being statistically significant (p<0.05). PEA treatment was effective in improving depression (ZSDS) and fatigue (FSS). Specifically, ZSDS and FSS scores significantly decreased between the 3- and 6-month evaluations in patients who took PEA compared with patients who refused therapy (both p<0.05). Accordingly, the proportions of patients experiencing improvement in depression (51% vs. 27%, respectively) and fatigue (37% vs. 15%, respectively) were significantly higher among patients who took PEA compared with those who did not (both p <0.05). No differences in chronic pain and quality of life were detected between patients who received PEA and those who refused treatment.
To investigate whether PEA treatment predicts neuropsychological improvement from 3 to 6 months post-discharge, multivariable logistic regression analyses predicting global improvement were performed within the entire cohort (n=98). PEA treatment emerged as being a significant predictor of global improvement independently of age, sex and neuropsychological status prior to therapy (all p<0.05).
**Conclusions:** Our results suggest that PEA is effective in improving depression and fatigue when administered during the post-acute phase of COVID-19, while no effect on chronic pain and quality of life was detected. Moreover, PEA therapy significantly predicts neuro-psychological improvement independently of age, sex and baseline evaluation. Among patients taking PEA, those with worse baseline fatigue and lower quality of life most likely benefit from PEA treatment.

## 16. ASSESSMENT OF HEART RATE VARIABILITY (HRV) IN SUBJECTS WITH TYPE 2 DIABETES MELLITUS WITH AND WITHOUT DIABETIC FOOT: CORRELATIONS WITH ENDOTHELIAL DYSFUNCTION INDICES AND MARKERS OF ADIPO- INFLAMMATORY DYSFUNCTION

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**Background:** Some studies have suggested that patients with diabetes and foot complications have worse cardiovascular and cerebrovascular risk profiles, higher degrees of endothelial dysfunction and arterial stiffness and a higher inflammatory background than patients with diabetes without diabetic foot complications. Patients with diabetes mellitus have an alteration in the sympathovagal balance as assessed by means of heart rate variability (HRV) analysis, which is also related to the presence of endothelial dysfun-

ction. Other studies suggest a possible role of inflammation coexisting with the alteration in the sympathovagal balance in favor of the atherosclerotic process in a mixed population of healthy subjects of middle and advanced age.
**Aims:** The aim of this study was to evaluate the degree of alteration of sympathovagal balance, assessed by HRV analysis, in a cohort of patients with diabetes mellitus with diabetic foot and in control subjects without diabetic foot compared with a population of healthy subjects and the possible correlation of HRV parameters with inflammatory markers and endothelial dysfunction indices.
**Methods:** We enrolled all patients with diabetic ulcerative lesions of the lower limb in the Internal Medicine with Stroke Care ward of P. Giaccone University Hospital of Palermo between September 2019 and July 2020. 4-hour ECG Holter was performed. The following time domain HRV measures were analyzed: average heart rate, square root of the mean of successive differences of NN (RMSSD), standard deviation or square root of the variance (SD), and standard deviation of the means of the NN intervals calculated over a five-minute period (SDANN/5 min). The LF/HF ratio was calculated, reactive hyperemia was evaluated by endo-PAT, and serum levels of vaspine and omentin-1 were assessed by blood sample collection.
**Results:** 63 patients with diabetic foot, 30 patients with diabetes and without ulcerative complications and 30 patients without diabetes were enrolled. Patients with diabetic ulcers showed lower mean diastolic blood pressure values than healthy controls, lower MMSE scores corrected for age, lower serum levels of omentin-1, lower RHI values, higher body weight values and comparable body height values, HF% and LF/HF ratio values. We also reported a negative correlation between the RHI value and HRV indices and the expression of increased parasympathetic activity (RMSDD and HF%) in subjects with diabetic foot and a statistically significant positive correlation with the LF/HF ratio and the expression of the sympathovagal balance.
**Discussion:** Patients with diabetic foot show a higher degree of activation of the parasympathetic system, expressed by the increase in HF values, and a lower LF/HF ratio. Our findings may corroborate the issue that a parasympathetic dysfunction may have a possible additive role in the pathogenesis of other vascular complications in subjects with diabetic foot.

## 17. EFFICACY AND SAFETY OF GIVOSIRAN IN PATIENTS WITH ACUTE HEPATIC PORPHYRIA: 36-MONTH RESULTS OF THE PHASE 3 ENVISION RANDOMISED CLINICAL TRIAL

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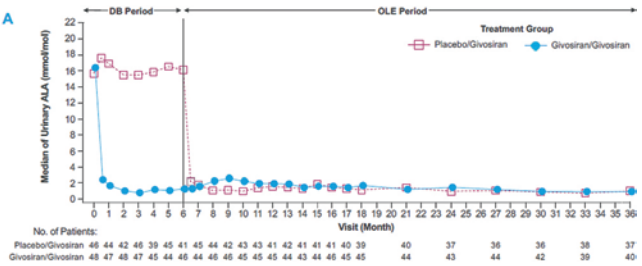
**Background and Aims**: Acute hepatic porphyrias (AHPs) are caused by defects in hepatic heme biosynthesis leading to accumulation of neurotoxic heme intermediates 5-aminolevulinic acid (ALA) and porphobilinogen (PBG). AHP is characterized by acute disabling and sometimes life-threatening neurovisceral attacks that can become recurrent in some patients. Givosiran treatment in the open-label extension (OLE) period of the ENVISION study (NCT03338816) led to sustained clinical benefit, with >75% of patients attack-free at 21-24 months (M). Data from the 36M analysis are reported here.
**Method:** ENVISION is a phase 3, randomised, placebo-controlled trial in patients ≥12 years old with AHP who had experienced ≥2 attacks requiring hospitalization, urgent care, or intravenous hemin at home in the past 6M, with a 6M double-blind (DB) period followed by a 30M OLE period.
**Results:** Of 94 patients enrolled, 93 patients entered the OLE period. Givosiran treatment led to sustained lowering of median urinary ALA to near-normal levels and to lowering of PBG levels by >90% in the continuous givosiran and placebo crossover groups at 36M. Continued givosiran treatment also led to a sustained reduction in attacks and hemin use in both groups. The proportion of patients with 0 attacks per 3M interval improved over the OLE period, with 86% of patients in the continuous givosiran group and 92% of patients in the placebo crossover group attack-free at 33-36M. Similarly, the proportion of patients with 0 days of hemin use improved over the OLE period, with no days of hemin use in 88% of patients in the continuous givosiran group and 90% of patients in the placebo crossover group at 33-36M. Exploratory measures showed further improvements in quality of life and activities of daily living during the OLE versus the DB period (Short Form 12-Item Health Survey, EuroQol visual analogue scale, and Porphyria Patient Experience Questionnaire). Most common treatment-related adverse events (AEs) (>10%) were injection-site reactions (ISRs), nausea, and fatigue. Six patients discontinued study drug due to AEs; 4 of these patients discontinued due to treatment-related AEs.
**Conclusion:** Long-term givosiran treatment provides sustained benefit to patients with AHP, maintaining reduced frequency of attacks and hemin use and further improving physical functioning and quality of life. Most common treatment-related AEs were ISRs, nausea, and fatigue

**Figure. Urinary ALA and PBG Levels**

**A, Median ALA levels over time. B, Median PBG levels over time.** OLE data for 1.25 mg/kg and 2.5 mg/kg are pooled. Reference ranges: ALA (ULN, 1.47 mmol/mol Cr), PBG (ULN, 0.14 mmol/mol Cr).
ALA, delta-aminolevulinic acid; Cr, creatinine; DB, double-blind; OLE, open-label extension; PBG, porphobilinogen; ULN, upper limit of normal.




## 18. METABOLIC AND CARDIAC MORPHO-FUNCTIONAL IMPROVEMENTS AFTER PCSK9 INHIBITORS ADMINISTRATION

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Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) is mainly produced by the liver and secreted into the bloodstream, but it is also expressed in extrahepatic tissues, like heart. PCSK9 plays a key role in cholesterol's metabolism regulation through the degradation of low-density lipoprotein receptor (LDLR). Recent studies suggest its possible role in cardiovascular (CV) diseases, promoting vascular inflammation, platelet activation, reactive oxygen species generation and atherosclerotic plaque formation. Furthermore, higher TG/HDL ratio has recently emerged as a marker of increased atherosclerotic extension and it can identify subjects with higher CV risk profile. Global longitudinal strain (GLS), global myocardial work efficiency (GWE), reservoir (PALS) and pump (PACS) atrial function evaluated by speckle-tracking echocardiography are able to identify early sub-clinical ventricular and atrial cardiomyopathy, that may preceed heart failure and atrial fibrillation development. In the last years, PCSK9 inhibitors have been introduced as innovative therapies for LDL plasma levels' reduction, showing strong CV protection. The aim of our study was to investigate, at baseline and after 6-months follow-up, PCSK9 inhibitors' effects in patients with established coronary artery disease (80% treated with CABG or PCI) who were statin-intolerant and/or not reaching the target of LDL-C <55 mg/dl using the maximum tolerated drugs' dosage. We enrolled 30 patients who completed the six month follow-up (24 male and 6 female, mean age 66+8 years old), 97% showed hypertension, 70% chronic kidney disease II-III stage, 67% polidistrectual atherosclerosis, 50% type 2 diabetes mellitus (T2DM), 20% OSAS-COPD, 15% atrial fibrillation and 20% chronic heart failure NYHA class II-III. All subjects underwent main anthropometric and

hemodynamic parameters evaluation, blood chemistry analysis, oxidative stress markers assessment, and advanced echocardiogram at baseline and after six months of treatment. The serum values of oxidative stress markers (NOX-2) and platelet activation (Sp-selectin) were assessed with ELISA sandwich. Echocardiographic recordings were performed using an E-95 Pro ultrasound system (GE Technologies). For all continuous variables, comparisons between baseline (T0) and post-treatment values (T6) were performed using paired Student's t test. A linear correlation analysis was performed to compare PALS, PACS, GWE, E/e' and CDK-EPI expressed as Δ variation and different covariates. There were no significant differences among the population regarding systolic blood pressure, heart rate and glycemia after six month of therapy. As expected, lipid profile was greatly improved in all the subjects, reaching the target of LDL-C <55 mg/dl. We obtained a statistically significant reduction of total-cholesterol (Δ= -32%, p<0.0001), LDL-C (Δ= -60%, p<0.0001), TG (Δ= -26%, p<0.0001), TG/HDL ratio (Δ= -27%, p<0.0001); an increase of HDL-C (Δ= +9%, p=0.001) and an improvement of glomerular filtrate evaluated by CKD-EPI (Δ= +6%, p=0.007). We observed a statistically significant reduction of NOX-2 (Δ= -27%, p<0.0001) and Sp-selectin (Δ= -36%, p<0.0001). Concerning echocardiographic parameters, we obtained a statistically significant increase of PALS (Δ= +16.9%, p<0.0001), PACS (Δ= +21%, p<0.0001), GWE (Δ= +9.7%, p<0.0001), GLS (Δ= +24%, p<0.0001) and a statistically significant reduction of global wasted work (GWW) (Δ= -15%, p<0.0001), left atrial volume index (LAVI) (Δ= - 8%, p<0.0001) and E/e' ratio (Δ= -19%, p<0.0001) respectively. The linear correlation analysis showed that ΔPACS was significantly and inversely correlated with ΔTG/HDL (r=-0.406, p=0.013) and ΔNOX-2 (r= -0.416, p=0.011); ΔPALS was significantly and inversely correlated with TG/HDL (r= -0.473, p=0.004) and ΔNOX-2 (r= -0.435, p=0.008); ΔE/e' was significantly and directly correlated with ΔTG/HDL (r=0.654, p<0.0001) and ΔNOX-2 (r=0.438, p=0.008); ΔGWE was inversely correlated with ΔNOX-2 (r= -0.422, p=0.01). Our study demonstrated for the first time that PCSK9 inhibitors are able to reduce left ventricular filling pressure, to increase atrial function (reservoir and pump) and global cardiac performance. Furthermore, PCSK9 inhibitors are able to increase CKD-EPI after six months of treatment in high CV risk population. Our results could be partially explained with a reduction of oxidative stress markers, inflammation and cardio-lipotoxicity, probably linked to a modulation of PCSK9's heart expression and its toxic effect on CV and renal function. In addition, we observed a TG/HDL ratio's reduction related to cardiometabolic and lipid profile improvement. Further studies are necessary to better investigate systemic benefit in a larger population with longer follow-up.

## 19. PROGNOSTIC IMPACT OF HYPOCHROMIC ERYTHROCYTES IN PATIENTS WITH PULMONARY ARTERIAL HYPERTENSION

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**Background:** Iron deficiency affects up to 50% of patients with pulmonary arterial hypertension (PAH) but iron markers such as ferritin and serum iron are confounded by several non-disease-related factors like acute inflammation and diet. The aim of this study was to identify a new marker for iron deficiency and clinical outcomes in PAH patients.
**Methods:** In this single-center, retrospective study we assessed indicators of iron status and clinical parameters specifying the time to clinical worsening (TTCW) and survival in PAH patients at time of initial diagnosis and at 1-year follow-up using univariable and multivariable analysis.
**Results:** In total, 150 patients were included. The proportion of hypochromic erythrocytes > 2% at initial diagnosis was identified as an independent predictor for a shorter TTCW (p = 0.0001) and worse survival (p = 0.002) at initial diagnosis as well as worse survival (p = 0.016) at 1-year follow-up. Only a subset of these patients (64%) suffered from iron deficiency. Low ferritin or low serum iron neither correlated with TTCW nor survival. Severe hemoglobin deficiency at baseline was significantly associated with a shorter TTCW (p = 0.001).
**Conclusions:** The presence of hypochromic erythrocytes > 2% was a strong and independent predictor of mortality and shorter TTCW in this cohort of PAH patients. Thus, it can serve as a valuable indicator of iron homeostasis and prognosis even in patients without iron deficiency or anemia. Further studies are needed to confirm the results and to investigate therapeutic implications.
Keywords: Iron deficiency, Anemia, Hypochromic erythrocytes, Pulmonary arterial hypertension

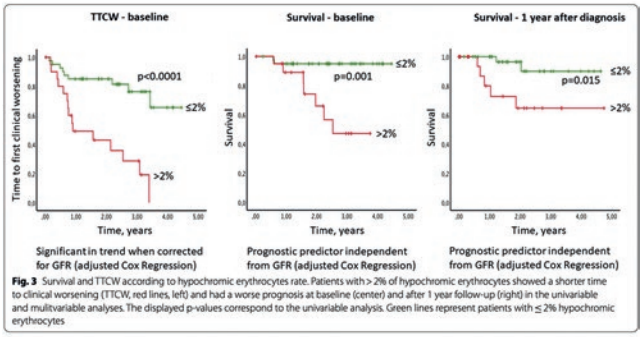

**Fig. 3** Survival and TTCW according to hypochromic erythrocytes rate. Patients with > 2% of hypochromic erythrocytes showed a shorter time to clinical worsening (TTCW, red lines, left) and had a worse prognosis at baseline (center) and after 1 year follow-up (right) in the univariable and multivariable analyses. The displayed p-values correspond to the univariable analysis. Green lines represent patients with ≤ 2% hypochromic erythrocytes

## 20. WOMAN DON'T… STAND UP

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We report the case of a 56-year-old woman referred to our Emergency Department complaining acute nucal headache triggered by the orthostatic position, associated to flushing, nausea and vomiting. Symptoms started three days before and were rapidly worsening; she denied fever, new-onset neurologic defects or recent trauma. Her past history was notably for systemic hypertension and recent eradication of asymptomatic HCV infection, without evidence of chronic liver disease. The physical examination confirmed the absence of other neurological abnormalities (in particular no meningeal signs) with inability to maintain orthostasis.
In the suspicion of vascular brain accident, an angiography computed tomography was performed without relevant findings, so the patient was hospitalized in our Internal Medicine ward.
A magnetic resonance of brain and complete spinal tract revealed diffused leptomeningeal thickening with post-contrastrographic enhancing and perimedullary extradural fluid amount of liquor, extending from cervical to sacral region. These findings were consistent with the clinical suspicion of liquor hypotension syndrome. After a mutidisciplinary discussion (neurologist and neuroradiologist) a conservative approach was taken with indication for absolute bed rest, fluid administration and analgesics.
Three weeks after admission the patient was discharge with a good tollerance to orthostatic position. However, at the post-discharge visit one-month later she complained mnesic problems and the radiological examination showed the presence of bilateral subdural haematomas, so an epidural blood-patch was needed.
Liquor hypotension syndrome usually occurs after trauma of meningeal layers (p.e. lumbar puncture); anyway, literature reports that up to half of patients could not have previous trauma. Spontaneous liquor hypotension is a very unusual cause of headache with a typical clinical feature that must be known and suspected.

## 21. IMMUNOHISTOCHEMICAL EVALUATION OF THE EXPRESSION OF SPECIFIC MEMBRANE ANTIGENS IN PATIENTS WITH PANCREATIC DUCTAL ADENOCARCINOMA UNDERGOING SURGERY

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**Background and Aims**: Pancreatic cancer is one of the most lethal malignancies in the population with a 5-year survival rate of only 8% and a poor response to oncological treatments. Hence, an early detection remains the most important prognostic criteria. However, the lack of validated disease biomarkers makes timely diagnosis challenging in most cases. Cell membrane and surface proteins play a crucial role in several routes of oncogenesis and tissue differentiation, as well as facilitating adhesion and metastasis. This study aimed to evaluate the expression of six membrane antigens on pancreatic cancer cells (CA 19.9, MUC1, MUC4, Mesothelin, Annexin A10, and Glypican-1) and its relashionship with clinical, laboratory, histological data and oncological outcomes, in terms of overall survival (OS) and disease free survival (DFS).
**Materials and Methods:** Surgical samples of 50 consecutive patients with pancreatic ductal adenocarcinoma (PDAC) undergoing pancreaticoduodenectomy were collected. Exclusion criteria were neoadjuvant therapy and history of other malignances. Immunohistochemical staining for CA 19.9, MUC1, MUC4, Mesothelin, Annexin A10, and Glypican-1 using monoclonal antibodies was performed. The antigen expression was evaluated blindly by two different pathologists and classified according to Histoscore (H-score). The score was obtained considering immunostaining intensities (strong 3+, intermediate 2+, weak 1+, or no 0) and percentage of positive cells of the tumour (H-score = [0 × percentage of immunonegative tumour cells] + [1 × percentage of weakly stained tumour cells] + [2 × percentage of intermediately stained tumour cells] + [3 × percentage of strongly stained tumour cells]). The maximum possible H-score was 300. H-score for tumoral, ductal and acinar tissues was calculated. The patients were followed after surgery and clinical and laboratory data were collected.
**Results:** Median follow-up was 21,5 months. During the follow-up period, in 23 patients (47%) PDAC recurred, with a median DFS of 15 months, and 18 patients (36%) deceased, with a median OS of 21.5 months. Immunostaining for CA 19.9 and MUC1 showed a significantly higher expression in neoplastic tissue compared with non-tumoral ductal and acinar tissues ($p<0.001$). Moreover, the intensity of CA 19.9 and MUC1 staining of neoplastic tissue was very high, with mean H-score of 270 and 210 respectively. The expression of MUC4, Mesothelin, Annexin-10 and Glypican-1 were significantly different between normal and pathologic tissue ($p<0.001$), resulting completely absent in normal tissue and expressed in cancer cells in various percentages.
Neutrophil count > 4.8x10^9/L and CA 19.9 H-score > 270 were found to be significantly correlated with OS ($p=0.02$ and $p=0.05$, respectively) and DFS ($p=0.04$ and 0.05, respectively) in univariate analysis and, in multivariate analysis, they were confirmed to be independent predictor variables for OS.
**Conclusions:** CA 19.9 and MUC1 are highly expressed in PDAC cells. The histological expression of CA 19.9 may predict prognosis, in terms of OS, in patients with PDAC. MUC4, Mesothelin, Annexin-10 and Glypican-1 are selectively expressed by neoplastic tissue compared with non-tumoral pancreatic tissues and may represent a potential histological biomarker of disease.

## 22. IS IT JUST ANOTHER ANEMIA? WHEN LUMPING THE TROUBLES MEANS TO CRACK THE CASE

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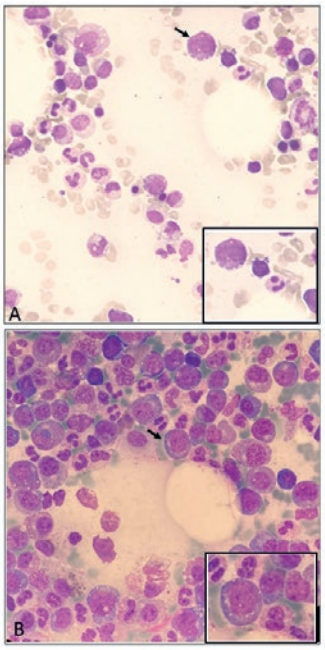
A 77 year-old caucasian male was admitted to the Hematology Unit with a septic shock. His past medical history revealed a multilineage MDS classified as very-low risk according to the Revised International Prognostic Staging System at the diagnosis six years before, which was kept without treatment until three years before when, due to worsening cytopenias (Hb 85 g/L, platelets 62x109/L), he was prescribed azacytidine. While on azacytidine treatment, he reached transfusion indipendece but started suffering from recurrent polychondritis involving nose and ears, whose flares had been treated successfully with steroid therapy. Along with polychondritis he also had uveitis and erythema nodosum. Serologic investigations showed ANA positivity (titer 1: 160, homogeneous pattern). He also was on therapy with digoxin and beta-blocker for parossistic atrial fibrillation, while anticoagulation had been stopped because of worsening thrombocytopenia. At time of admission red blood-cells transfusion dependency was 4-7 units per month, occasionally he also needed platelets tranfusions although one month before he was started on steroids because antiplatelet autoantibodies positivity was found. Azacytidine was stopped after 48 cycles, when the patient was admitted to our department with hemodinamic instability and fever. At hospital admission, complete blood cell count revealed severe macrocytic anemia (Hb 67 g/L, range 135-175 g/L; MCV 97 fL, range 80-94 fL) with severe thrombocytopenia (platelets 18x109/L, range 130-400 x 109/L) and normal WBC (6.27x109/L, range 4.80-10.80 x 109/L) with normal formula. C-reactive protein was raised (7.9 mg/dL, cut-off 0.5 mg/dL) with negative procalcitonin, normal renal function and high ferritin levels (30448 mg/L, range 30-400 mg/L) with slightly increased Interleukin-6 level (18.7 ng/L, cut-off < 10ng/L). Triglycerides and coagulation factors were normal. PCR for Epstein-Barr virus DNA in peripheral blood revealed an elevated number of copies (41486 copies/mL, cut-off < 250 copies/mL). CT scan showed bilateral ground glass areas and pleural effusions and splenomegaly (160 mm). The patient was initially treated with intravenous fluids, vasoactive amines and broad-spectrum antibiotics. During hospitalization, medical efforts have focused on treatment a suspected underlying infectious state that could, in turn, have triggered an autoinflammatory condition such as Hemophagocytic Lymphohistiocytosis. Bone marrow examination was carried out but it did not reveal features evocative for this syndrome. Subsequently, the occurrence of bilateral pulmonary infiltrates raised the question of Pneumocystis jirovecii pneumonia and although it had not been possible to obtain a microbiologic diagnosis, treatment with antibiotics and steroids was started reaching clinical stability. At that point, in light of patient's past medical history and the suspicion of an auto-inflammatory disorder, his hematological history was re-assessed taking into account the newly described VEXAS syndrome: it was found that the bone marrow at MDS diagnosis already carried vacuoles in 1.5 and 1.8% of erythroid and myeloid cells respectively (Fig. 2A,C), a proportion which increased to 4.8 and 9.8% at the last assessment (Fig. 2B,C).




| Differences in BM cellularity between diagnosis and last examination | | |
|---|---|---|
| | February 2015 | June 2021 |
| Cell type | % cellularity | % cellularity |
| Erythroid series | 31,2 | 7,4 |
| Myeloid series | 52,5 | 70 |
| Myeloid precursors | 19,4 | 37,8 |
| Granulocytes | 32,7 | 29,8 |
| Blasts | 0,4 | 2,4 |
| Lymphocytes | 10,4 | 8 |
| Monocytes | 5,2 | 5,2 |
| Plasma cells | 0,4 | 9,4 |
| Vacuolated myeloid cells (% of myeloid cells) | 1,8 | 9,8 |
| Vacuolated erythroid cells (% of erythroid cells) | 1,5 | 4,8 |

Furthermore, at the latter point, his blast percentage also increased, and he was found to have increased number of plasmacells, some of which bi-nucleated. In 2020, five years after MDS diagnosis, a Next generation sequencing (NGS) of a targeted panel of myeloid genes in peripheral blood cells revealed a mutation in DNAMethyltransferase3Alpha (DNMT3A). The DNMT3A mutation was re-assessed and was found to be present at a clonal level (Fig. 2D). UBA1 gene mutation analysis showed a subclonal p.Met-41Thr mutation (NM_003334.4: C.122T>C) (Fig. 2D) and a diagnosis of

VEXAS syndrome was made. Later in the course, the patient had further infectious complications and due to worsening heart function he was started on a palliative care pathway and died in hospice 6 years after his initial MDS diagnosis.
VEXAS syndrome is a clonal, non-neoplastic syndrome linked to somatic mutations of the UBA1 gene in the myeloid compartment. The main clinical features are recurrent fever, relapsing polychondritis, pulmonary and skin involvement, macrocytic anemia, and bone marrow vacuolization restricted to myeloid and erythroid precursor cells. In our patient the DNMT3A mutation was clonal throughout the disease course, while the UBA1 mutation appeared subclonal, and later increased its prevalence, in parallel with a shift in disease phenotype: polychondritis, worsening cytopenias, pulmonary involvement and increased in blast percentage. This would suggest that the UBA1 mutation arose in a permissive DNMT3A-mutated genetic background, and its development may have changed the natural history of the disease. Notably, azacytidine was effective in treating the MDS, but had no effect on the autoimmune manifestations of the disease, which responded to steroid therapy. Message for the Internist: in a patient with anemia and history of recurrent polychondritis, keep VEXAS in mind!

## 23. A CHALLENGING CASE OF WERNICKE'S ENCEPHALOPATHY

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**Introduction:** Wernicke's encephalopathy (WE) is defined by Central Nervous System damage after exhaustion of B-vitamin reserves, in particular thiamine. It is characterized by a triad of symptoms (ophthalmoplegia, ataxia, confusion) which generally develops over a few days or weeks. Even if it is commonly attributed to malnourished people with alcohol misuse, WE can be caused also by a variety of diseases, such as eating malabsorption disorders, bariatric surgery or cancer.
A 83-year-old woman was admitted in September 2021 to our ward of Internal Medicine for worsening of her cognitive impairment and for a pneumonia ab ingestis. Her son explained that her cognitive status got progressively worse after the death of her husband the previous year and that she was not following a balanced diet at home, but denied the consumption of benzodiazepines or alcohol. The patient's personal history was unremarkable except for severe hypoacusis.At the emergency department at physical examination she was drowsy, not responding to verbal and tactile stimuli. She showed spasticity to the four limbs and her heartbeat was arrhythmic with several extrasystoles. She was feverish and tachypneic (30 acts/min) and she showed low peripheral blood saturation (89%) in ambient air. Blood tests at admission showed signs of infection (WBC 18250, RCP 8.67 ng/dL) because of the pneumonia so that low flow oxygen and an antibiotic therapy with piperacillin/tazobactam were started and the patient was then transferred to our unit. During hospitalization the 10-days antibiotic course was completed, with biochemical response (WBC 9500, RCP 1,5 ng/dL), with progressive weaning off oxygen and fever disappearance. However, since her cognitive and vigilance status did not improve despite the resolution of the infection, a brain CT scan was required and showed mesial hypodensity of the thalamus and of the posterior cingulate cortex bilaterally. To better investigate these alterations, a brain MRI was performed and showed diffuse hypointensities in T1 sequence and hyperintensities in T2 sequence, especially in the talami, the medulla, the cerebellar vermis and in the fronto-parietal cortex, associated to diffuse several petechiae. These results turned out suggestive for metabolic damage and were attributed to Wernicke's encephalopathy. In order to define its etiology, several investigations were performed: blood tests showed a slight deficiency in vitamin B12 and folates (150 ng/L and 1.6 ng/L respectively) but excluded thyroid disfunction; an upper endoscopy ruled out coeliac disease and autoimmune atrofical gastritis as causes of malabsorption. Finally, an empirical therapy with high dosage of tiamine, B12 vitamine and folates was started. An initial improvement of her vigilance and cognitive impairment was obtained but still the patient appeared disoriented, not able to execute simple orders and her spasticity did not get better. After several days, the patient's son accidentally reported that in the past the patient had been genetically tested for Leber disease mutations and that she was an heteroplasmic carrier of the 3460G>A mutation in MT-ND1 gene, compatible with Leber plus Syndrome. This clinical entity includes patients with clinical signs of Leber hereditary optic neuropathy (LHON) in association to other severe neurological disorders (such as spasticity, movement disorders, multiple sclerosis-like illness…) or systemic abnormalities, including cardiac or bone ones. Indeed, our patient underwent the genetic test since one of her daughters suffered from juvenile blindness and the other one had severe skeleton deformities. Genetic mutations which characterize Leber plus Syndrome alter the normal mitochondrial function of oxidative phosphorylation. In fact, it is believed that altered apoptosis and creation of reactive oxygen species (ROS) in neuronal cells may be involved in the genesis of the disease, by damaging neuronal bio energetical metabolism and causing cell degeneration.Target therapy is constituted by ibedenone, which interacts with mitochondrial electron transport chain and enhances cellular respiration, and coenzyme Q, a great antioxidant agent which protects cells from ROS damage.Therefore, a final diagnosis of Wernicke's encephalopathy in Leber plus disease was made and a therapy with ibedenone and coenzyme Q was started, leading to a mild and progressive improvement in patient's neurological state.
**Conclusion:** We report a rare case of Wernicke's encephalopathy in a patient mutated for Leber plus Syndrome, which features include LHON and other neurological, cardiac and skeletal abnormalities. LHON and the variant Leber plus are hereditary diseases caused by mutations in mitochondrial DNA. Despite the patient was characterized only by a slight malnutrition status, possibily this condition could have triggered a bio energetical imbalance in her cerebral tissue, which was genetically impaired by her heteroplasmic mutation. In fact, even if she showed a progressive improvement of her neurological status during hospitalization, she never totally recovered.

## 24. SEX-SPECIFIC DIFFERENCES IN MYOCARDIAL GLUCOSE METABOLIC RATE IN NON-DIABETIC, PRE-DIABETIC AND TYPE 2 DIABETIC SUBJECTS

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**Background:** Evidence has shown that women with type 2 diabetes (T2DM) have a higher excess risk for cardiovascular disease (CVD) than their male counterparts. In subjects with both T2DM and prediabetes was observed a myocardial insulin resistance, considered a causal factor in the development of CVD. However, it is not yet defined whether exist sex-related differences in myocardial insulin resistance in diabetic and prediabetic subjects. In order to address this issue, we evaluated sex-related differences in myocardial glucose metabolic rate (MRGlu) in normal glucose tolerant (NGT), pre-diabetic and type 2 diabetic subjects.
**Patients and Methods:** Sex-related differences in myocardial glucose metabolic rate were examined in 57 subjects with NGT (n=20), prediabetes (n=11), and T2DM (n=26). Myocardial MRGlu was evaluated using dynamic cardiac 18F-FDG PET combined with euglycemic hyperinsulinemic clamp, which allows to assess peripheral insulin sensitivity normalized for lean body mass (MFFM) and to standardize metabolic and hormonal conditions during PET. The 18F-FDG PET imaging procedure started 60 minutes after the insulin infusion. The insulin-glucose infusion continued throughout the PET imaging sequence, maintaining euglycemia by continuous adjustment of the glucose infusion rate according to the glucose levels of the arterialized blood samples collected every 5 min.
**Results:** Women with prediabetes and T2DM exhibited greater relative differences in whole-body insulin-stimulated glucose disposal and myocardial MRGlu than men with prediabetes and T2DM when compared with their NGT counterparts. As compared with women with NGT (25.74±6.91 mmol/min/100g), women with prediabetes exhibited a 35% decrease in myocardial MRGlu (16.77±7.29 mmol/min/100g; P=0.01) and those with T2DM a 75% decrease (6.66±7.00 mmol/min/100g; P=0.005). Conversely, as compared with men with NGT (28.39±5.4 mmol/min/100g), only men with T2DM exhibited a 41% reduction in myocardial MRGlu (16.91±10.1 mmol/min/100g; P=0.007), while no significant difference was observed with men with prediabetes. The statistical test for interaction between sex and glucose tolerance on myocardial MRGlu (P<0.0001) was significant suggesting a sex-specific association.
**Conclusions:** Our data suggest that an impairment in myocardial glucose metabolic rate is an early alteration already observed in women with prediabetes at risk for type 2 diabetes. The sex-specific myocardial insulin resistance could be an important key factor responsible for the greater effect of T2DM on the excess risk of cardiovascular disease in women than in men.

## 25. EFFECTS OF LONG-TERM ALBUMIN ADMINISTRATION ON THE MANAGEMENT OF HYPONATREMIA IN OUTPATIENTS WITH CIRRHOSIS AND ASCITES: POST-HOC ANALYSIS OF THE ANSWER TRIAL DATABASE

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**Introduction:** . Hyponatremia is the most frequent electrolyte disorder in patients with decompensated cirrhosis. It associates with severe complications of the disease (e.g., favoring or aggravating hepatic encephalopathy) and elevated mortality. In a recent trial, human albumin (HA) administration slightly increased serum sodium levels in patients with cirrhosis hospitalized because of acute decompensation. So far, however, no data are available on the effects of long-term HA administration.
**Aims:** To determine whether long-term human albumin administration could help in correcting and preventing of hyponatremia in outpatients with decompensated cirrhosis and ascites.
**Methods:** We performed a post-hoc analysis on the intention-to-treat population (431 patients) enrolled in the ANSWER trial, grouping patients according to their baseline serum sodium levels. The cumulative incidence of hyponatremia correction within 3 months was calculated according to the Kaplan-Meier method. Moreover, incidence rates (IRs) and IR ratios (IRRs) of at least moderate hyponatremia (<130 mmol/l) during a follow-up of 18 months were calculated.
**Results:** 149 (35%) patients presented hyponatremia (<135 mmol/l) at baseline (74 vs 75 in the standard medical treatment [SMT] and in the SMT+HA arms, respectively). 116 of them (78%) had mild hyponatremia (≥130 and <135 mmol/l), while 33 (22%) had at least moderate hyponatremia (<130 mmol/l). Patients with hyponatremia had higher Child-Pugh and MELD scores as compared to patients with normal natremia at inclusion. Hyponatremic patients randomized to receive long-term HA did not differ from those randomized to SMT. Normalization of hyponatremia (≥135 mmol/l) was reached more frequently and faster in SMT+HA than SMT group, as expressed by the cumulative correction rate of hyponatremia after three months: 71% vs 44% in the SMT+HA and the SMT groups, respectively (P=0.006). Long-term HA was also effective in preventing episodes of hyponatremia, as the incidence rate of at least moderate hyponatremia was significantly lower in the SMT+HA than in SMT arm (IR 0.554 [95% CI 0.389-0.767] and 2.262 [95% CI 1.839-2.754], respectively), leading to an incidence rate ratio (IRR) of 0.245 (95% CI 0.167-0.359) (P<0.001).
**Conclusions:** This is the first prospective controlled clinical trial showing that HA administration to hyponatremic patients with cirrhosis and ascites is associated with a higher rate of serum sodium normalization and a lower incidence of moderate-to-severe hyponatremia, compared with SMT. Our findings show that long-term HA administration could be an effective intervention in managing hyponatremia in outpatients with decompensated cirrhosis and ascites.

## 26. TEMPORAL PROFILE OF SEROLOGICAL RESPONSE TO COVID-19 VACCINES IN A COHORT OF PATIENTS HOSPITALIZED IN INTERNAL MEDICINE

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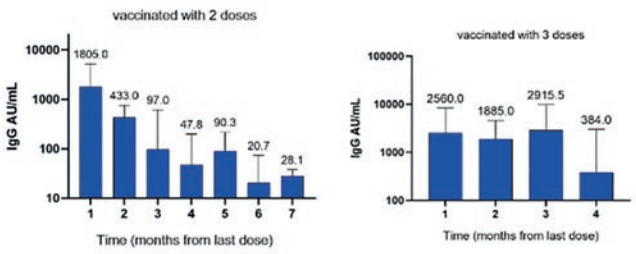
**Introduction:** Older adults have been severely affected by SARS-CoV-2 infection(1). Age >65 years and chronic diseases such as diabetes and obesity have been described as the most important risk factors for hospitalisation and death(2). Therefore, in order to protect the most vulnerable population, in Italy, older adults and frail people were prioritised in the COVID-19 vaccination programme.
**Methods:** An observational study was conducted on a cohort enrolled between August 2021 and April 2022 at the Department of Internal Medicine, University Centre for Liver Disease Research and Treatment (C.U.R.E.), Liver Unit, University of Foggia, Italy. We collected data of serological responses to two or three doses of SARS-CoV-2 vaccines (Spikevax, Comirnaty, AstraZeneca vaccine, Janssen vaccine) in 400 patients, with or without previous SARS-CoV-2 infection, hospitalised in a Unit of Internal Medicine. The antibody titers against SARS-CoV-2 were measured according to quantitative chemiluminescent serological test (LIAISON® SARS-CoV2 IgM and S1/S2 IgG, DiaSorin, Saluggia, Italy) performed on LIAISON®XL (DiaSorin,Saluggia, Italy). Data were expressed in median ± inter quartile range(IQR).To define antibody concentrations at different timepoints from the last immunization, the IgG titers, between patients at different times from the last vaccine dose, were compared.
**Results:** The participants were similar in terms of comorbidities (chronic obstructive pulmonary disease, diabetes mellitus, coronary artery disease,hypertension,and hyperlipidaemia). The median age was 77 years (IQR 64-84), 62%(248) were male, 37%(152) were female. Analysing hospitalized patients who received only two vaccine doses, after one month from the last dose, the IgG median concentration was 1805 AU/mL(IQR 224,8-5200AU/mL). The concentration dropped in patients at two months from last dose (median 433AU/mL;IQR 206,3-761AU/mL). In patients hospitalised at six months from two-doses immunization the median IgG was already near to the detection threshold (IgG median 20AU/mL; IQR 6,7–73,4AU/mL). Accordingly, we observed that in patients with two doses, after three months the 21,3% of patients already showed negative serology. This percentage progressively grew, so that after seven months, 41,7% of patients was IgG-negative. Patients, who were previously infected with SARS-CoV-2 and subsequently received two vaccine doses, showed higher antibody concentrations at one month (IgG median 2950AU/mL; IQR 1067–6610AU/mL) and at the second month (IgG median 962,5AU/mL; IQR 530–2060AU/mL). Subjects, who received three doses, showed a higher antibody response and higher sustained titers (IgG median 2560AU/mL; IQR 648,3-8398AU/mL at one month; IgG median 2916AU/mL; IQR 233,5-9870AU/mL at the third month), with a significant decrease at month 4 (IgG median 384AU/mL; IQR 250-3005AU/mL). IgG concentrations were even higher in patients previously infected and then vaccinated with three doses (IgG median at one month 8000AU/mL;IQR 4910-30200AU/mL). Comparing the first month antibody response in all participants,we found that patients getting SARS-CoV-2 infection after receiving two or three vaccine doses, presented the highest humoral immunogenicity (IgG median 15200AU/mL; IQR 1160-23700AU/mL). Previously infected patients with consequent two or three doses of vaccine followed. Lowest antibody level was found in uninfected older adults with two doses.
**Conclusion:** The association between neutralizing antibody level after SARS-CoV-2 vaccination and protection against COVID-19 has been demonstrated by several studies(3). We have here reported the temporal profile of anti-SARS-CoV-2 IgG concentrations in a cohort of patients hospitalised in a Unit of Internal Medicine. We proved that two vaccine doses in this patient class do not guarantee a long-term protection. Three doses induce a higher and longer sustained serological response, although the significant titer reduction after 4 month imposes a monitoring in the following months. These results suggest that the typical population of patients hospitalised in internal medicine, presents an important decrease of antibody concentrations along time, becoming more susceptible to new infection. This patient category is usually represented by older adults

with high risk of hospitalization for all causes and potentially susceptible to severe COVID-19. The possibility of an early administration of a 4th vaccine dose in these subjects should be considered. Our data in patients with double immunization (vaccine and infection) suggest that a 4thvaccine dose should induce a higher antibody response and a longer serological protection also in older multimorbid patients.




## 27. GLUCAGON INDUCES THE HEPATIC EXPRESSION OF INFLAMMATORY MARKERS THROUGH TRAF2/NF-KB PATHWAY AND NLRP3 INFLAMMASOME

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**Background:** Glucagon exerts multiple hepatic actions including stimulation of glycogenolysis, and gluconeogenesis. The liver has also a crucial role in chronic inflammation being involved in the synthesis of cytokines, and acute phase proteins, and hepatic inflammation is thought to contribute to insulin resistance and hyperglycemia. However, whether glucagon affects hepatic expression of pro-inflammatory cytokines and acute-phase reactants is unknown.
**Methods:** To address this issue, we evaluated 132 adults not-affected by type 2 diabetes, who underwent anthropometrical and biochemical evaluation, and a 75-g OGTT. In order to generate a suitable animal model in which to evaluate the in vivo activity of glucagon, we have utilized male CD1 mice treated in equal volumes with vehicle or glucagon (1 μg/h via an osmotic minipump), for 4 weeks A third group of male littermates injected with glucagon in the same way, was administered a glucagon receptor antagonist (GRA-II, 1 μM) in the drinking water throughout the duration of the study. To estimate the expression levels of inflammatory markers and the phosphorylation status of intracellular pathways, we employed HepG2 cells treated with increasing concentrations of glucagon for 24h.
**Results:** Herein, we report a positive relationship between fasting glucagon levels and circulating cytokines IL-1β (r=0.252, p=0.042), and IL-6 (r=0.230, p=0.026) and acute phase proteins fibrinogen (r=0.193, p=0.031), complement C3 (r=0.227, p=0.024), and hsCRP (r=0.230, p=0.012), in individuals without diabetes. In the murine model we observed that 4 week continuous treatment with glucagon induced a significant increase in circulating IL-1β (p=0.02), and IL-6 (p=0.001), which was countered by the contingent administration of the glucagon receptor antagonist GRA-II. Consistent with these results, when we performed a Western blot analysis on the protein fraction of the livers of the sacrificed animals, we detected a significant increase in the activation of inflammatory pathways, such as the phosphorylation of NF-κB (p<0.02) and protein expression of NLRP3 (p<0.02), both required for the synthesis and maturation of cytokines and acute phase proteins, and phosphorylation of STAT3 (p<0.01), which directly regulates the expression of fibrinogen, downstream the activation of IL-6 receptor. In HepG2 cells, we found that glucagon dose-dependently stimulated the expression of IL-1β, and IL-6 (p<0.002, for both) along with fibrinogen (p<0.01), complement C3 (p<0.01), and CRP (p<0.01) in vitro. The glucagon-induced increase in cytokines expression was inhibited by preincubating cells with the glucagon receptor antagonist GRA-II. Glucagon stimulated the activation of NLRP3 inflammasome (p<0.01) and its downstream effector caspase-1 (p<0.05), which are involved in the activation of proIL-1β. Moreover, we found that glucagon stimulated TRAF2 phosphorylation leading to NF-κB activation (p<0.01), which is the canonical pathway involved in IL-6 expression, and STAT3 (p<0.01), which is required for the transcription of fibrinogen and under the direct control of IL-6. Finally, when the cells were pre-treated with LMT-28, a small molecule inhibitor of IL-6 receptor activation, the ability of glucagon to induce fibrinogen expression was hindered.
**Conclusion:** These results suggest that glucagon has pro-inflammatory effects that may help to elucidate the mechanism by which glucagon contributes to hyperglycemia in addition to the well known stimulatory effect on hepatic gluconeogenesis.

## 28. ASYMPTOMATIC DEEP VENOUS THROMBOSIS IN HOSPITALIZED ACUTELY ILL MEDICAL PATIENTS: RISK FACTORS AND THERAPEUTIC IMPLICATIONS.

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**Background:** Acutely ill medical patients experience deep venous thrombosis (DVT) during the hospitalization, however the time course of DVT is still unclear.
**Objectives:** To evaluate risk factors in hospitalized acutely ill medical patients for asymptomatic DVT (ADVT) and symptomatic DVT (SDVT) within 48 hours from admission and at discharge; to compare prophylactic treatment with (group A) and without (group B) low-molecular weight heparin (LMWH).
**Patients and Methods:** Consecutively-hospitalized acutely ill medical patients underwent duplex color compression ultrasonography (CUS) of proximal lower limb veins within 48h from admission and at discharge to screen for ADVT and to document SDVT. Primary end-point of this multicentric study was the incidence of all DVT. Biographical characteristics at hospitalization, D-Dimer and IMPROVE-DD score at entry and at discharge were analyzed by univariate and multivariate analysis to identify variables associated with DVT and were compared between groups.
**Results:** Of 2,100 patients (1002 females, 998 males, age 71±16) included, 58 (2.7%) (31 females, 27 males, age 77±14) had ADVT at admission. A binary logistic regression analysis showed that age (O.R.: 1.03, 95%C.I. 1.007-1.05, p=0.008), thrombophilia (O.R.: 10, 95%C.I. 3-34, p<0.001) and active cancer (O.R.: 2.3, 95%C.I. 1.3-4.1, p=0.005) were independently associated with ADVT at admission. The median length of hospitalization was 10 days [interquartile range: 6-15]. During the hospital stay, 6 patients (0.3%) with a negative CUS at admission experienced DVT (2 SDVT and 4 ADVT). On admission and at discharge, risk factors between all patients and patients with DVT during hospitalization (n=64) were not different. In the subgroup of patients (n=1118) in which D-dimer was measured at admission, elevated D-Dimer and higher IMPROVE-DD score were associated with ADVT at admission (n=37) and with all DVT (n=42) at discharge. Patients of group A presented the following risk factors compared to patients of group B: older age, reduced mobility, acute infection, kidney failure, heart or respiratory failure, previous myocardial infarction or stroke and hypertension.
**Conclusions:** The incidence of ADVT and of SDVT was high (3%) at the moment of hospital admission of acutely ill medical patients. Advanced age, active cancer, thrombophilia, elevated D-dimer and IMPROVE-DD score greater than 2.5 were risk factors for ADVT and they should be analyzed upon hospitalization in order to decide treatment with LMWH. The benefit of anticoagulant treatment at therapeutic doses needs to be investigated in

patients with ADVT and specific risk factors.

| | NEGATIVE CUS AT ADMISSION | POSITIVE CUS AT ADMISSION | P |
|---|---|---|---|
| N. | 2042 | 58 | - |
| Age (years) | 71±16 | 77±14 | **0,009** |
| Age > 70 years, n (%) | 1181 (57,8%) | 43 (74,1%) | **0,013** |
| Female, n (%) | 971 (47,8%) | 31 (53,4%) | 0,399 |
| BMI (Kg/m2) | 27±5 | 26±4 | 0,083 |
| Current Smoking, n (%) | 461 (22,6%) | 15 (25,9%) | 0,557 |
| Diabetes, n (%) | 532 (26%) | 12 (20,7%) | 0,358 |
| Hypertension, n (%) | 1275 (62,4%) | 34 (58,6%) | 0,554 |
| Myocardial infarction or STROKE, n (%) | 298 (14,6%) | 4 (6,9%) | 0,099 |
| Acute infection, n (%) | 652 (31,9%) | 25 (43,1%) | 0,073 |
| Pneumonia, n (%) | 300 (14,7%) | 10 (17,2%) | 0,589 |
| Active Cancer, n (%) | 306 (15%) | 15 (29%) | **0,003** |
| Previous VTE, n (%) | 78 (3,8%) | 5 (8,6%) | 0,064 |
| Reduced mobility, n (%) | 549 (26,9%) | 21 (36,2%) | 0,115 |
| Thrombophilia, n (%) | 15 (0,7%) | 4 (6,9%) | **<0,0001** |
| Kidney failure, n (%) | 399 (19,5%) | 9 (15,5%) | 0,445 |
| Heart or respiratory failure, n (%) | 470 (23%) | 19 (32,8%) | 0,083 |
| Dyslipidemia, n (%) | 682 (33,4%) | 14 (24%) | 0,140 |
| D-dimer (ng/mL)* | 1510±1473 | 3255±1495 | **<0,0001** |
| Albumin (g/L) | 40±9 | 35±5 | 0,245 |
| Hormone therapy, n (%) | 81 (4%) | 3 (5,2%) | 0,644 |
| Antiplatelet therapy, n (%) | 796 (39%) | 26 (44,8%) | 0,373 |

**Table 1:** Clinical characteristics of the population with positive and negative CUS at admission. Data are reported as mean±SD for continuous variables and % for categorical variables.

| | Patients with LMWH prophylaxis | Patients without LMWH prophylaxis | P |
|---|---|---|---|
| N | 251 | 1532 | - |
| Age (years) | 77±13 | 70±16 | **<0,001** |
| Age > 70 years, n (%) | 184 (73%) | 866 (56%) | **<0,001** |
| Female, n (%) | 130 (52%) | 710 (46%) | 0,110 |
| BMI (Kg/m2) | 26±5 | 27±5 | 0,23 |
| Current Smoking, n (%) | 54 (21%) | 339 (22%) | 0,824 |
| Diabetes, n (%) | 68 (7%) | 391 (25%) | 0,598 |
| Hypertension, n (%) | 173 (69%) | 945 (62) | **0,028** |
| Myocardial infarction or STROKE, n (%) | 53 (21%) | 215 (14%) | **0,004** |
| Acute infection, n (%) | 103 (41%) | 477 (31%) | **0,002** |
| Pneumonia, n (%) | 69 (27%) | 194 (13%) | **<0,001** |
| Active cancer, n (%) | 48 (19%) | 221 (14%) | 0,054 |
| history of VTE, n (%) | 15 (6%) | 52 (3.4%) | 0,127 |
| Reduced mobility, n (%) | 178 (70%) | 328 (21%) | **<0,001** |
| Thrombophilia, n (%) | 2 (0.7%) | 12 (0.7%) | 0,982 |
| Kidney failure, n (%) | 66 (26%) | 294 (19%) | **0,009** |
| Heart or respiratory failure, n (%) | 91 (36%) | 330 (21%) | **<0,001** |
| | | | |
| D-dimer (ng/mL)* | 1933±1506 | 1451±1399 | **<0,0001** |

**Table 2:** Clinical characteristics of patients with and without LMWH prophylaxis. Data are reported as mean±SD for continuous variables and % for categorical variables.

*AURELIO study group: Cacciafesta M., Casciaro M. A., Morelli S., Accapezzato D., Rossi E., Proietti Bocchini V., Longo R., Cosenza M., Battaglia S., Pirillo L. S., Capozza A., Summa M. L., Taccari F., Alfano A., Bagnato C., Filoni D., Mereu E., Schipa C., Caltabiano C., Usai L..

## 29. A CASE OF NON-INFECTIOUS TRICUSPID VALVE ENDOCARDITIS

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An 81-year-old male patient was admitted to the ward for lower extremity edema. The patient had a history of pneumonia in the six months prior to hospitalization and atrial fibrillation. He also reported receiving steroids therapy for continuous episodes of low-grade fever after the pneumonia. Blood tests performed two weeks before admission showed anemia and elevated serum creatinine. An echocardiogram performed 3 days before admission showed severe tricuspid regurgitation. Clinical examination revealed arrhythmia with tricuspid and mitral systolic murmur, crackles at the base of the right lung, and lower extremity edema. An electrocardiogram showed atrial fibrillation. Blood tests showed normocytic anemia (Hb 9 g/dl; MCV 90.2 fl), renal insufficiency (serum creatinine 2.93 mg/dl), C-reactive protein 22.7 mg/l, NTproBNP 7742 pg/ml, troponin I 31 ng/l, serum albumin 29 g/l. Other laboratory results included a negative stool blood test, low reticulocyte index, normal levels of ferritin (166 ng/ml), folic acid, vitamin B12, aptoglobin, LDH, TSH, total iron-binding capacity, indicating an anemia of chronic disease. In addition, 24-hour urine collection showed the presence of proteinuria in the non-nephrotic range, and urine was positive for malformed red blood cells. An echocardiography revealed right atrium and ventricle enlargement, severe tricuspid regurgitation with fibrotic retraction of the contralateral leaflet and rupture of tricuspid chordae and no apparent pulmonary hypertension. Lung CT-scan images showed evidence of solid noncalcified micronodules and early interstitial disease. Abdominal ultrasonography showed normal liver and spleen parenchyma with enhanced echogenicity of the cortical kidney. Venous ultrasonography revealed no thrombotic events. To rule out an infective endocarditis, repeated blood cultures were negative. Serological detections of Coxiella burnetii, Legionella pneumophila, Mycoplasma pneumoniae, Chlamidia pneumoniae, Brucella spp were negative. To evaluate the presence of a systemic disease, immunologic tests were assessed. Abnormal laboratory findings included hypocomplementemia (C3 level 79 mg/dl, normal range 90 mg/dl to 180 mg/dl), elevated antinuclear antibodies levels (fine speckled pattern) and a positive lupus anticoagulant test, while P-ANCA, c-ANCA, HCV and HBV antibodies, cryoglobulinemia, circulating immune complexes were negative. To rule out a vasculitis disease, the patient was subjected to a renal biopsy, which revealed a pauci-immune crescentic necrotizing glomerulonephritis associated with acute tubulointerstitial nephritis. ANCA-negative microscopic polyangiitis (MPA) associated with noninfectious endocarditis was diagnosed based on clinical, laboratory and histological findings. The rheumatologist recommended starting treatment with high doses of methylprednisone and cyclophosphamide. After initiation, hemoglobin (12 g/dl) and creatinine (1.82 mg/dl) levels improved. After a multidisciplinary discussion by the Heart Team of our hospital, the indication for surgery treatment of tricuspid regurgitation was determined.
MPA is a necrotizing vasculitis that primarily affects small-sized arteries. It is also known as ANCA-associated vasculitis (AAV) due to its close association with antineutrophil cytoplasmic autoantibody (ANCA). A negative ANCA test does not rule out the diagnosis of MPA. Despite the clinical and histological features of ANCA-associated vasculitis, some ANCA-negative patients may have MPO-ANCA that is undetectable by routine laboratory testing because it is masked by circulating fragments of enzymatically degrading ceruloplasmin, that may be elevated in patients with active disease. The most commonly affected organs are the kidneys and lungs. Necrotizing and crescentic glomerulonephritis and diffuse alveolar hemorrhage are the main clinical manifestations. MPA rarely affects large vessels such as the aorta, and heart valve involvement is rare. Proper assessment of organic tricuspid regurgitation requires progressive exclusion of infectious and noninfectious causes. As with infective endocarditis, severe valvular regurgitation associated with progressive ventricular dysfunction and heart failure indicates a surgical treatment.

## 30. RESPONSE TO ANTI-SARS-COV-2 PRIMARY CYCLE AND BOOSTER DOSE VACCINE IN PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY

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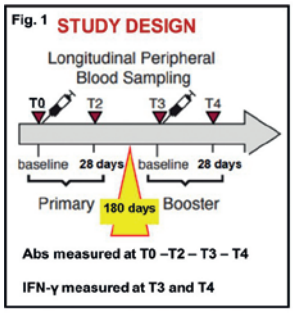
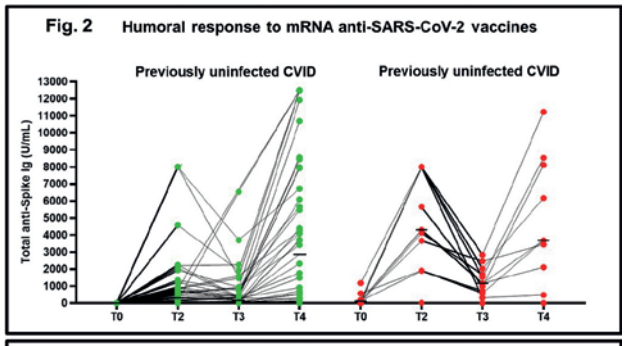
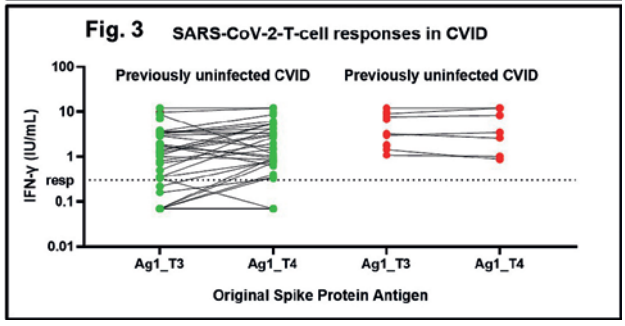
**Introduction:** Patients with Primary Immunodeficiencies (PIDD) are at high risk to develop severe complication even after usual pathogens. Prevention of infections with either primary and secondary prophylaxis is of main importance. After December 2020, the first two vaccines based on mRNA technology (BNT162b2, Pfizer-BioNTech and mRNA-1273, Moderna) were available and received emergency use authorization to contain the global SARS-CoV-2 pandemic infection. PIDD patients have been prioritized

in the mass-immunization campaign for receiving these mRNA vaccines, despite they have not been involved in the trials for validation study neither it was known the efficacy of these vaccines in this population.
**Aim:** This study aims to evaluate the immune response after mRNA anti-SARS-CoV-2 vaccines in patients with common variable immune deficiencies (CVID) along time.
**Patients and Methods:** We enrolled 60 CVID patients diagnosed according to ESID criteria. They have been vaccinated with mRNA vaccines anti-SARS-CoV-2 according to the Regional vaccination program. The quantitative detection of serum Ig against the SARS-CoV-2 Spike (S) protein receptor binding domain and a quantitative IFN-gamma production as a surrogate of the T-cell response have been measured. Study design is shown in figure 1. Analyses have been performed with Stata16 (StataCorp. 2019) and with IBM SPSS Statistics (SPSS Inc. Chicago, IL version 27.0). Graphics have been created with GraphPad.
**Results:** We analysed 60 CVID patients: 14 underwent primary cycle anti-SARS-CoV-2 vaccination with Pfizer-BioNTech (BNT162b2) and 46 with Moderna (mRNA-1273) vaccines. All the patients use to receive replacement therapy and tests of the infused immunoglobulin products showed no detectable levels of anti-Spike Ig until T3. The figure 2 shows results dividing patients between the SARS-CoV-2 uninfected from the previously infected ones, who got COVID-19 before the first vaccine dose. There was 11 previously infected CVID.
The figure 3 shows the SARS-CoV-2-T-cell responses before and after the third booster vaccine dose. Responder (resp) cutoff is set at 0.30 IU/mL (black dotted line). There is reported the comparison between the previously uninfected and infected patients. At T3, all the patients had just received 2-doses of vaccine.
**Conclusions:** The CVID patients' levels of anti-SARS-CoV-2 Ig dropped significantly at T3. The booster dose produced an antibody response in severals. This strengthens the indication for the 2nd booster, while for those who did not respond to the third dose, monoclonal prophylaxis is recommended. The 78.3% of had a positive T-cells response (Ag1) at T3, almost always unchanged at T4, consisting with the maintenance of the T-cell response over time.




## 31. GLOMERULAR HYPERFILTRATION IS A MARKER OF CARDIOVASCULAR DAMAGE AND FIBROSIS SEVERITY OF NONALCOHOLIC FATTY LIVER DISEASE

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**Background:** Nonalcoholic steatosis (NAFLD) represents a risk factor for the development of cardiovascular disease and chronic kidney failure (CKD), early expressed by glomerular hyperfiltration. However, whether there is a direct correlation between glomerular filtrate, different degrees of NAFLD and cardiovascular risk is not described in the literature.
**Aim:** To determine the correlation between glomerular hyperfiltration, the degree of nonalcoholic steatosis and the main indicators of cardiovascular risk.
**Methods:** 133 patients with NAFLD diagnosed by abdominal ultrasound and Fibroscan CAP, were enrolled. The degree of steatosis and stiffness in all subjects were assessed by Fibroscan echoSense with CAP module. Glomerular filtration rate (eGFR) was estimated using the 2021CKD-EPI formula. Two different classes were defined on the basis of filtrate: normal (eGFR: <110 and > 60 mL/min) (neGFR) and hyperfiltration (eGFR≥110 mL/min) (heGFR). For cardiovascular risk, echocardiogram and Pulse Wave velocity (PWV) were taken into account. Main anthropometric and biochemical indexes are recorded.
**Results:** Of the133 enrolled patients, 111 were in neGFR group while 22 in heGFR. Overall patients had a mean age of 53 years ±12 SD. The two groups did not show statistically significant differences for age, sex, arterial blood pressure or body mass index. On the other hand, the heGFR group was characterized by a worse cardiovascular and hepatic profile compared to neGFR. In particular, the heGFR group showed at echocardiographyc evaluation an average of Left ventricular mass index (LVMi) and Tricuspid annular plane excursion (TAPSE) values of 90.1 g/m2 and 24.8 mm, respectively, compared with the neGFR, which presented an LVMi of 75 g/m2 and a TAPSE of 22.6 mm, respectively ($p<0.006$, $p<0.082$). With regard to cardiovascular assessment, heGFR patients had a mean PWV of 8.5 m/sec, compared with the other with a mean of 7.7 m/sec ($p<0.056$). Respect liver profile, within the group with heGFR hyperfiltration, there was a mean stiffness and steatosis grade of 7.3 kPa and 1.8, respectively, compared with normal eGFR with 5.8 kPa and 1.5, respectively. ($p<0.099$, $p<0.041$). Finally, the lipid profile, and in particular the HDL values were statistically significantly better in the heGFR group (mean HDL value of 1.56 mmol/ vs 1.38 mmol/L, $p<0.056$); triglyceride 0.96 mmol/L vs 1.22 mmol/L, $p<0.025$).
**Conclusions:** The group of patients with glomerular hyperfiltration was characterized by a worse cardiovascular indices and a worse liver profile. Therefore, glomerular hyperfiltration could represent an early marker of liver damage and increased cardiovascular risk in patients with non-alcoholic steatohepatitis.

## 32. BRADYCARDIA ASSOCIATED WITH REMDESIVIR IN PATIENTS WITH SARS-COV2 -PNEUMONIA: THE EXPERIENCE OF THE INTERNAL MEDICINE UNITS IN MILAN

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Several cases of Remdesivir-associated bradycardia have been recently reported during its administration in patients with SARS-CoV-2 infection. However, there are few studies evaluating the cardiac toxicity of Remdesivir in COVID-19 patients and little is known about the prognostic factors of Remdesivir-associated bradycardia.
We aimed to assess the experience of several internal medicine units to evaluate the occurrence of Remdesivir-related bradycardia in patients hospitalized for SARS-CoV2 pneumonia and the factors associated with it. In a retrospective, multicenter study, we enrolled patients admitted to Internal Medicine Units for COVID-19-pneumonia in Milan. We evaluated 71 patients who received Remdesivir (RDV group) and 54 controls matched for sex, age and oxygen therapy on admission who did not receive Remdesivir (CTR group). The mean heart rate recorded in the first two days of hospitalization was considered the baseline heart rate value (HRb). Heart rate values relative to the 5-day treatment and the 5-day post-treatment were considered for RDV group, while heart rate values relative to 10 days of hospitalization following the baseline assessment were considered for the CTR group. ΔHR values were calculated as maximum heart rate drop versus HRb. Regression analysis was performed between ΔHR and HRb, age, sex, baseline alanine aminotransferase levels (bALT) and concurrent therapies.
The RDV group experienced a significantly higher incidence of bradycardia compared with the CTR group (40/71, 56% vs 18/54, 33%, p=0.011). In RDV group, patients with sinus bradycardia were characterized by lower HRb and higher ALT values at the baseline with respect to RDV patients who did not experience bradycardia. Moreover, higher ΔHR values in RDV group compared to CTR group was observed, after correction for age, sex, baseline alanine aminotransferase levels (ALT) and concurrent therapies. The greatest drop of heart rate was found on the third and sixth days from the start of RDV administration, with maximum reduction on the sixth day. Multiple linear regression analysis was performed to find predictive factors of ΔHR in RDV group, considering age, sex, β-blockers assumption, HRb and the ALT values at the admission. We observed a significant positive relationship between ΔHR and HRb and between ΔHR and ALT values at the admission.
Among the mechanisms that could justify these adverse cardiac effects of RDV there is its active metabolite GS-443902 which is similar to adenosine triphosphate and has been shown to reduce the automaticity of the sinus node, resulting in sinus bradycardia. Furthermore, the acute bradycardia observed after the administration of the first dose and the nadir reached on day 6 at the completion of 5 days therapy, could be explained by the pharmacokinetics of the antiviral drug. In fact, although remdesivir does not accumulate in the organism, its metabolite GS-443902 reaches steady state around day 4 and accumulates by ~ 2-fold after multiple once daily dosing. This mechanism could be exacerbated by hepatic dysfunction as suggested by the relationship between ΔHR and ALT values at the admission.

## 33. LEAN MAFLD SUBJECTS WITH METABOLIC DYSREGULATION ARE AT HIGHER RISK OF HEPATIC AND CARDIOVASCULAR DISEASE COMPARED TO OVERWEIGHT AND DIABETIC MAFLD ONES

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**Introduction:** Recently a new definition of non-alcoholic fatty liver disease (NAFLD) has been proposed, namely metabolic associated fatty liver disease (MAFLD). MAFLD shares the presence of hepatic steatosis with NAFLD but it can comprise also patients with other liver diseases or alcohol consumption as long as with hepatic fat (diagnosed by histology, imaging or blood biomarkers) one of these three criteria is present: (1)body mass index (BMI)>25 kg/m2; (2) type 2 diabetes (T2DM); (3) metabolic dysregulation in patients with normal BMI, classified as "lean", defined by at least two features among enlarged waist circumference, hypertension, increased triglycerides, low high-density lipoprotein cholesterol, prediabetes, insulin resistance, and high-sensitivity C-reactive protein ≥ 2 mg/dL. MAFLD exposes patients to hepatic and cardiovascular (CV) complications, and data from literature even report an increased risk of advanced liver disease, CV events and mortality in patients affected by MAFLD compared to NAFLD. However, which features of MAFLD definition specifically impacts on the hepatic and cardiovascular disease has never been explored. In addition, no data has been reported on the association between MAFLD and subclinical CV damage. Therefore, the aim of our study is to evaluate if there is a different impact of the three features of MAFLD on the hepatic and CV (both clinical and subclinical) disease in a cohort of MAFLD subjects.
**Material and Methods:** 371 NAFLD subjects (69% males, mean age 52+12 ys) attending the Metabolic and Liver Disease outpatient clinic of the Policlinico Hospital of Milan presented one of the three criteria of MAFLD definition and were thus enrolled. Liver disease was evaluated by ultrasound to detect and grade hepatic steatosis and by Fibroscan to diagnose fibrosis (by liver stiffness measurement: LSM>8.7/7.2 kPa M/XL probe defined advanced fibrosis). Cardiovascular disease was evaluated by carotid Doppler Ultrasound and radiofrequency (intima-media thickness-IMT>0.9 mm; presence of carotid plaques; carotid stiffness as pulse wave velocity-PWV), by transthoracic echocardiography (epicardial adipose tissue: EAT>9.5/7.5 mm male/females considered as increased) and by history of previous CV events. Genotyping for PNPLA3, TM6SF2 and MBOAT7 was performed in 216 subjects.
**Results:** In the cohort of MAFLD patients, 291 (79%) had BMI>25 without other metabolic alterations, 57(15%) had BMI>25 and T2DM and 22 (6%) had BMI<25 with metabolic dysregulation. No subjects presented isolated T2DM. Moderate to severe steatosis was present in the 67% of the cohort, whereas advanced fibrosis in 11% by LSM>8.7/7.2 kPa M/XL probe. Increased IMT was detected in 223 (60%) patients, carotid plaques in 93 (35%), whereas EAT >9.5/7.5 mm male/females in 115 (31%). Mean pulse wave velocity was 7.9+1.8 m/s and history of CV events was found in 7 (3%) subjects. Evaluating hepatic and CV disease according to the three different features of MAFLD, moderate to severe steatosis (94% in group 3 vs 68% in group 2 vs 64% in group 1, p=0.02) and carotid plaques (59% in group 3 vs 42% in group 2 vs 32% in group 1, p=0.02) were more prevalent in patients with BMI<25 and metabolic dysregulation (group 3) compared to the other two groups (group 1: BMI >25 without other metabolic alterations; group 2: BMI>25 and T2DM). No difference in the prevalence of hepatic fibrosis was found across the three groups, as well as in IMT, carotid stiffness, EAT or prevalence of previous CV events. Likewise, no difference in polymorphisms distribution was observed in the cohort according to the different metabolic groups. In multivariate analysis (adjusted for age, sex, smoking, anti-hypertensive therapy and statins use), having BMI<25 with metabolic dysregulation remained an independent risk factor for moderate to severe steatosis (OR 9.4, CI 95 1.2-76.7, p=0.04) and for carotid plaques (OR 3.8, CI 95 1.2-12.7, p=0.02), whereas no association was found for the other groups.
**Conclusions:** MAFLD patients present a high prevalence of severe steatosis, advanced fibrosis and subclinical CV alterations. Notably, among all features characterizing MAFLD definition, metabolic dysregulation in lean individuals seems to play a key role in the onset of both hepatic and CV disease, at a greater extent compared to the effect of overweight or T2DM. This stresses on the need of a careful screening for complications and metabolic alterations in MAFLD patients, especially in lean subjects.

## 34. LONG COVID-19 AFTER HOSPITAL DISCHARGE IN FRAIL AND ROBUST PATIENTS

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**Background:** A motley post-acute symptomatology may develop after COVID 19, irrespectively of the acute disease severity, age and comorbidities. Frail individuals have reduced physiological reserves, and manifested a worse COVID-19 course, during the acute setting. However, it is still unknown, whether frailty may subtend some long COVID-19 manifestations. We explored the prevalence of long COVID-19 disturbs, in COVID-19 survivals.
**Methods:** Observational study. Patients aged 65 or older followed up 1, 3 and 6 months after hospitalization for COVID-19 pneumonia.
**Results:** 382 patients. Frail patients, were more malnourished (median Mini Nutritional Assessment Shor Form score 8 versus 9, p = 0.001), at higher risk of sarcopenia (median SARC-F score 3 versus 1.5, p = 0.003)

and manifested a worse physical performance (median Short Physical Performance Battery (SPPB) score 10 versus 11, p = 0.007) than robust individuals, after hospital discharge following SARS-CoV-2 pneumonia. Frailty was a significantly associated with i) confusion, as a presenting symptom of COVID-19 (OR 77.84, 95% C.I. 4.23 – 1432.49, p = 0.003), ii) malnutrition (MNA-SF: adjusted B -5.63, 95% C.I. -8.39 - -2.87, p < 0.001), risk of sarcopenia (SARCF: adjusted B 9.11, 95% C.I. 3.10 – 15.13, p = 0.003), impaired muscle performance (SPPB: B -3.47, 95% C.I. – 6.33 – 0.61, p =0.02), complaints in mobility (adjusted OR 1674200.27, 95% C.I. 4.52 - 619924741831.25, p=0.03), in self-care (adjusted OR 553305.56, 95% C.I. 376.37 - 813413358.35, p< 0.001), and in performing usual activities of daily living (OR 71.57, 95% C.I. 2.87 - 1782.53, p=0.009) at 1-month follow-up, ii) dyspnea (mMRC: B 4.83, 95% C.I. 1.32 – 8.33, p= 0.007) and risk of sarcopenia (SARCF: B 7.12, 95% C.I. 2.17 - 12.07, p=0.005) at 3-month-follow-up and of iii) difficulties in self-care (OR 2746.89, 95% C.I. 6.44 - 1172310.83, p=0.01) at the 6-month-follow-up. In a subgroup of patients (78 individuals) the prevalence of frailty increased at the 1 month follow up compared to baseline (p = 0.009).

**Conclusion:** The precocious identification of frail COVID-19 survivors, who manifest more motor and respiratory complaints during the follow up, could improve the long-term management of these COVID-19 sequelae.

## 35. LYMPHOID INTERSTITIAL PNEUMONIA IN ADULTS (LIP)

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A 72-year-old woman was admitted to the Emergency Department for two weeks of fatigue and dyspnea and a few days of fever. She has a history of rheumatic polymyalgia for over 10 years, under corticosteroid therapy up to a month before admission and MGUS on follow-up. The examination of the chest reveals bilateral crackles. Blood tests showed high C-Reactive Protein (PCR) and Erythrocyte Sedimentation Rate (ESR). The serum protein electrophoresis showed the presence of two monoclonal spikes in the gamma zone. Blood gas analysis reveal mild hypoxemia. The chest X-ray showed thickening of the bronchial walls and pulmonary interstitium. The patient was transferred to our Internal Medicine ward for further investigation. We performed a contrast high resolution chest CT (HRCT) showing multiple cystic formations, with peribronvovascular, periscissural and subpleural distribution. The presence of "ground glass" areas was most evident in the upper lobes, middle lobe and in the lingula, with bronchiectasis and bronchiolectasis. The history of rheumatic disease and monoclonal gammopathy, the clinical manifestations and radiological findings, guided the diagnosis for a form of lymphocytic interstitial pneumopathy (LIP) (image 1). Thus, glucocorticoid therapy was administered with Metilprednisolone 20 mg ev die. During hospitalization, we asked the patient if she had any further symptoms and she refferred xerostomia and xerophthalmia, increasing the suspicion of Sjogren's syndrome. Antibody screen was obtained with Antinuclear antibodyes (ANA), anti-DNA antibodie and ENA screen including anti-Ro/SSA and anti-La/SSB antibodies, and they were all negative. Shirmer's test and tears break up time were found abnormal. Salivary gland biopsy confirm the diagnosis of Sjogren's syndrome. The negativity of the autoantibodies was interpreted as a consequence of glucocorticoids therapy before the hospitaliization. Furthermore up to 20% of cases of Sjogren's syndrome have a normal antibody. After the introduction of glucocorticoid therapy there was a progressive improvement in symptoms. The patient was discharged home completely asymptomatic.The patient was evaluated after six months and performed lung function tests that documented a mild reduction in DLCO (56%). HRCT showed disease stability. Therefore, glucocorticoids were gradually tapered and a steroid-sparing drug was introduced (Hydroxychloroquine 200 mg 1 cp / day). Lymphoid interstitial pneumonia (LIP) is an uncommon form of interstitial lung disease wich represents one entity within a spectrum of lymphoproliferative disorders that can involve the lung. According to the American Thoracic Society/ European Respiratory Society (ATS/ERS) classification, LIP is characterized by an extensive alveolar septal infiltration of lymphocytes, plasma cells and other lymphoreticular elements. The cause of lymphoid interstitial pneumonia (LIP) is unknown. LIP is associated with rheumatic diseases as Sjögren's syndrome (1/4 of reported cases of LIP), often with a marked monoclonal or polyclonal gammopathy.It is also described in patients with common variable immunodeficiency and in persons infected with HIV virus (suggesting a possible viral etiology). However, less than 20% of cases of LIP have no clear underlying cause. The differential diagnosis of lymphoid interstitial pneumonia (LIP) includes IgG4-related disease. IgG4-RD is associated with a variety of patterns on HRCT and in addition, sicca symptoms can be seen with both Sjögren's syndrome and IgG4-related disease, thus making it important to exclude this diagnosis. The serum IgG4 in our patient found to be normal. Cough and dyspnea are the most common presenting symptoms of LIP. Other symptoms/signs include: fever, pleuritic chest pain, fatigue and arthralgias. Laboratory tests including serologic test (eg, ANA or anti-Ro/SSA and anti-La/SSB antibodies if Sjögren's syndrome is suspected) and testing for HIV infection. The measurement of antibodies against HIV antigens in our patient was negative. LIP has a varied radiographic appearance; on HRCT, ground-glass attenuation, centrilobular nodules, and interstitial thickening are frequently seen with a lower lobe predominance. Lung cysts occur in 68-82% of patients with LIP and can be helpful in the differential diagnosis with NSIP.In patients with LIP, pulmonary function testing may shows reduced lung volumes (eg, FVC, TLC) and DLCO. Bronchoalveolar lavage findings are nonspecific, so a definitive diagnosis requires a lung biopsy. Controlled clinical trials have not been reported for LIP. Information on treatment comes from case reports and case series. Patients with LIP complicating rheumatic disease respond well to oral glucocorticoids (GC). If patients have progressive disease despite systemic GC, other immunosuppressive agents can be used. The proper duration of therapy is not known. The natural history and prognosis of lymphoid interstitial pneumonia (LIP) are poorly understood. Controlled clinical trials are needed to better understand the etiology, duration of therapy and the natural history and prognosis of the disease.

## 36. THE IMPACT OF SARCOPENIA AND GENETIC PREDISPOSITION ON METABOLIC AND CARDIOVASCULAR ALTERATIONS IN A COHORT OF NON-CIRRHOTIC MAFLD PATIENTS

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**Background and Aims**: In 2020 a consensus panel proposed the use of metabolic dysfunction-associated fatty liver disease (MAFLD) term as a more inclusive definition of fatty liver instead of non-alcoholic fatty liver disease (NAFLD). MAFLD is defined by the presence of hepatic steatosis associated with at least one metabolic comorbidity, without excluding other causes of liver disease such as alcohol consumption or viral infections, and it is associated with increased risk of cardiovascular disease (CVD) and progressive liver damage. Sarcopenia is defined as a loss of skeletal muscle strength, mass and function and bioelectrical impedance analysis (BIA) is a non-invasive and validated tool for its diagnosis through the skeletal muscle index (SMI), calculated as the ratio between the skeletal mass and the height squared. Also, sarcopenia is a predictor of CVD and it has been mainly reported in cirrhotic patients, but its prevalence and association with CVD in the early stages of liver diseases and particularly MAFLD has not been defined yet. Finally, the I148M PNPLA3 variant is the major genetic determinant of NAFLD and it seems to be related to increased visceral fat, as demonstrated primarily in murine models of liver steatosis. Nevertheless, its role in MAFLD patients and particularly in the onset and progression of sarcopenia has not been clarified yet.

**Aims**: to define 1) prevalence of sarcopenia by BIA and association with anthropometric parameters in non-cirrhotic MAFLD patients; 2) the relationship between sarcopenia, liver disease and subclinical CV damage 3) the interaction between I148M PNPLA3 variant and sarcopenia in the same cohort.

**Methods:** 316 consecutive non-cirrhotic MAFLD patients (mean age 52 ys, 64% male) were enrolled. For all patients, anthropometric parameters (BMI; waist circumference-WC, considered increased for value ≥102/88 cm men/ women) and sarcopenia by BIA (SMI≤10.75/6.75 kg/m2 men/woman) were evaluated, as long as carotid intima-media thickness (cIMT) (increased for values >0.9mm) and carotid plaques by ultrasound. In addition, all patients underwent an echocardiography to quantify the epicardial fat (EFT) (increased for values≥9.5/7.5 mm men/ women). Finally, liver fibrosis was diagnosed by liver stiffness measurement (LSM ≥7/6.2 kPa M/XL probe diagnosed fibrosis≥F2) at Fibroscan®. In a subgroup of 114 patients, genotyping

for PNPLA3 was performed. For all patients alcohol consumption expressed as g alcohol/day was assessed.
**Results:** Sarcopenia was present in 36% of MAFLD cohort and sarcopenic patients were more prevalently male (92%vs47%, p<0.001) and presented lower indexes of adiposity as lower BMI (27.7vs30.8, p<0.001), lower percentage of patients with increased WC (24%vs76%, p<0.0014) and lower prevalence of increased EFT (16%vs40%, p<0.001). As for CV damage, in the sarcopenic group a higher prevalence of cIMT>0.9 mm (42%vs29%, p=0.03) was reported, whereas no differences in the prevalence of carotid plaques was observed between groups. As for liver disease, no differences in LSM values were observed between sarcopenic and non-sarcopenic patients. Sarcopenic MAFLD patients had higher prevalence of wild type PNPLA3 genotype compared to non-sarcopenic ones (51%vs27%, p=0.04). Notably, PNPLA3 mutated allele in homozygous form was more prevalent in patients with increased EFT (p=0.01), significant liver fibrosis (p=0.04) and carotid plaques (p=0.02), whereas no difference in BMI and WC were found according to PNPLA3 genotype.
At multivariate analysis, male sex was an independent risk factor for sarcopenia (OR 16.8, CI 95% 6.5-43.2, p<0.001), whereas increased BMI (OR 0.3, CI 95% 0.2-0.5) and WC (OR 0.7, CI 95% 0.6-0.9) resulted protective factors. Interestingly, in multivariate analysis adjusted for age, sex, BMI, WC, EFT and increased cIMT, there was an independent association between sarcopenia and increased cIMT (OR 6.6, CI 95% 1.9-23.3), for the presence of sarcopenia.
**Conclusions:** Sarcopenia is highly prevalent in young, male non-cirrhotic MAFLD patients and it is associated with subclinical atherosclerotic damage, despite lower visceral obesity and BMI. In addition, there is a high prevalence of PNPLA3 wild type form in sarcopenic patient, in line with our finding of the association of PNPLA3 I148M variant with increased EFT, a marker of visceral adiposity. Therefore, physicians need to emphasize the crucial role of nutrition and physical activity in patients with MAFLD, especially men, to prevent loss of skeletal muscle and progression of CVD. An assessment of PNPLA3 could also help stratifying the risk of developing sarcopenia.

## 37. COVID IN THE ELDERLY: ONE YEAR LATER

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**Background and Aim:**
Despite early observational studies have shown an increased risk for hospitalization and mortality in the elderly affected by COVID-19 (C-19), few studies specifically regarded the very elderly.
This study represents the long-term follow-up of our previous study and aims to determine the one-year mortality rate in patients aged >80 years and that were hospitalized for C-19 during the Second Wave (SW) in a Spoke Hospital of the Varese province (Galmarini Hospital, Tradate) in northern Italy.
**Methods:** The initial data was collected from 26th October 2020 to 22th May 2021. Our C-19 ward capacity was of 76 patients. All the data was anonymized; age, sex, discharge modality, length of hospitalization (LOH), main diagnoses etc. were gathered and coded.
According to our hospital network organization, the patients admitted were mostly elderly and not eligible for invasive treatment. Standard therapy was intravenous steroids, deep vein thrombosis prophylaxis and O2 therapy.
We divided the elderly patients in two groups, Discharged and Not-Survived, focusing specifically on patients >80 years. Main discharge modalities were at home or to post-acute C-19 settings.
Follow-up was carried out through telephone calls which aimed to find out patients' vital status and overall health status. If patients had died we defined the date of death through their relatives.
**Results:** The total number of patients admitted to our ward was 1,116 (mean age 76.9 yrs, range 18-99), 835 pts (74.8%) were discharged, 281 pts (25.2%) died.
Focusing on the patients >80 years, we admitted 525 pts (50.6%, mean age 86.6, range 80-99) of these 210 (40%, males 94, females 116, mean age 87.8, range 80-99) died; 315 (60%, mean age 85.9, range 80-98) were discharged.
The mean age was significantly (p<0.0001) lower in the Discharged group compared to the Not-survived patients.
In the Discharged group, the length of hospitalization (LOH) had a weak positive significant correlation with age (r=0.12, p=0.00001).
93 patients (29.5%, mean age 84.4 years, males 46.2%) were discharged at home; 209 patients (66.3%, mean age 85.7 years, males 38.8%) were discharged to a post-acute C19 setting; nine patients (2.9%, mean age 86 years, males 33.3%) were discharged to a nursing home; four patients (1.3%, mean age 80 years, males 25%) were discharged to a rehabilitation facility.
At one year from discharge, 126 patients (40%) were lost to follow-up. Of the remaining 189 patients, 74 of them (39.2%, males 44.6%) had died. The mean age was significantly higher in the patients who had died compared to the patients alive at follow-up (respectively 87.2 vs 84.9 years; p<0.0009).
The LOH was similar in patients who had died, in those who had survived and those lost at follow-up at the one-year (13.2, 13.2 and 13.4 days respectively).
Amongst those who died before follow-up the mean survival was of 90.1 days; no statistically significant difference in survival was found between the two genders (105.3 vs 77.9 days respectively).
We have also recorded the length of the follow-up telephone calls: no statistically significant difference was found between the length of the calls made to the relatives of those who had died and the patients who had survived at follow-up (mean follow-up call duration 95 sec vs 89 sec; p>0.05).
**Conclusions:** At one-year follow-up, 39.1% of the elderly patients that had been discharged alive after C-19 hospitalization, were dead. No similar follow-up has been found in literature concerning elderly patients.
Nevertheless, our study has many limitations: firstly, the elderly patients admitted to our ward were patients who had no indications to invasive forms of therapy, therefore, our study population could not reflect the real-life elderly population as a whole. No information regarding comorbidities were acquired during this study.
Last but not least, there was a huge number of patients (40%) lost at follow-up and some of these may have died.

## 38. MULTICENTRIC OBSERVATIONAL STUDY ON SAFETY AND TOLERABILITY OF COVID 19 VACCINES IN PATIENTS WITH ANGIOEDEMA WITH C1 INHIBITOR DEFICIENCY: DATA FROM THE ITALIAN NETWORK ON HEREDITARY AND ACQUIRED ANGIOEDEMA (ITACA)

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**Background:** Angioedema with C1 inhibitor deficiency is a rare disease characterized by recurrent and unpredictable attacks of angioedema without hives, with heterogeneous phenotypes in terms of frequency, severity and site of attacks. The genetic form is a rare autosomal dominant disorder due to C1-inhibitor deficiency (type I) or dysfunction (type II). The acquired form is often associated with hematologic neoplasms or antibodies against C1 inhibitor, causing excessive consumption or inactivation of C1 inhibitor. The inadequate control of the contact system causes excessive bradykinin formation with localized and transient increase in vascular permeability, resulting in angioedema attacks. Eliciting factors of the attacks include trauma, emotional factors, medical procedures and infections. Few studies on the safety of COVID-19 vaccines in a small population of patients with angioedema with C1 inhibitor deficiency were performed and suggested that mRNA vaccines potentially represent an eliciting factor of angioedema attacks. Aim of the study was to collect data on safety, tolerability and recurrency of acute angioedema attacks in a large population of patients following COVID vaccines
**Methods:** Adult patients with angioedema due to C1 inhibitor deficiency followed by reference centers of the Italian Network for Hereditary and Acquired Angioedema (ITACA) were enrolled in this study. Patients received nucleoside-modified mRNA COVID vaccines (BNT162b2 by BioNTech/Pfizer and mRNA-1273 by Moderna) and vaccines with adenovirus vector (ChAdOx1 nCoV-19 vaccines by AstraZeneca and Ad26.COV2.S by Johnson & Johnson). Data on the onset of acute attacks in the 72 hours following different COVID-19 vaccination were collected. The frequency of attacks in the following 6 months after COVID-19 vaccination compared with previous rate of attacks.
**Results:** Between March 2020 and February 2022, 183 patients (101 females) with angioedema due to C1-INH deficiency received Covid 19 vaccines in a

controlled medical setting in 8 ITACA centers (Ancona, Aosta, Civitanova, Firenze, Messina, Milano, Salerno, Torino). Eighty-nine percent of patients had hereditary angioedema. 83 patients were on long term prophylaxis. In this cohort the mean attack rate was 0.89/months. The majority of patients received mRNA vaccines (172 patients). About 5% of patients received vaccines with adenovirus vector: Astra Zeneca and Johnson & Johnson were given respectively to 8 and 1 patients. No severe adverse reactions were reported. The most common adverse reactions were arm pain at the site of injection and fever. A total of 45 attacks of angioedema occurred within 72 hours following the COVID-19 vaccine administration. All attacks were associated to the administration of mRNA vaccines and only one attack occurred after vaccination with Astra Zeneca. The majority of attacks (62%) were abdominal attacks. One patient reported a laryngeal attack occurring after the administration of first dose of Pfizer. Hospitalization was not required and all the attacks were successfully treated with specific treatment for acute angioedema attacks, Icatibant or plasma derived C1-inhibitor. There was no difference in the monthly rate of attacks following the vaccination, both in patients on LTP and in those using on demand approach.
**Conclusions:** Our results show that adult patients with angioedema due to C1 inhibitor deficiency can be safely vaccinated against Covid 19. Our data suggest that Covid 19 vaccines, in particular those produced with mRNA technology, might elicit an angioedema attack. Patients with angioedema due to C1 inhibitor deficiency should be vaccinated in a controlled medical setting and should always have available on demand therapies.

## 39. NON-THROMBOTIC INFLAMMATORY VENOUS INVOLVEMENT IN A PATIENT WITH SWEET'S SYNDROME, SUGGESTING A COMPLEX AUTOINFLAMMATORY DISEASE

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Sweet's syndrome, also known as acute febrile neutrophilic dermatosis, is a rare autoinflammatory condition characterized by fever, leucocytosis, tender erythematous skin lesions and diffuse upper dermal infiltrate of mature neutrophils. It can be associated with various systemic diseases, such as cancer, immunological disorders and others. Systemic corticosteroids are the mainstay treatment of Sweet's syndrome; other possible pharmacological strategies may include: colchicine, iodide, indomethacin, tacrolimus, dapsone, pentoxifylline and new biological drugs, such as anti-interleukin-1 receptor antagonist.
Sweet's syndrome may involve extracutaneous organs, even large arteries and small vessels, all of which presenting a sterile neutrophilic inflammation. To date, there is no data on the venous manifestations of Sweet's syndrome. However, venous involvement has been reported in VEXAS syndrome, a complex adult autoinflammatory disease also including Sweet syndrome and interstitial lung disease, due to a somatic mutation of UBA1, the major E1 enzyme that initiates ubiquitylation.
Hereby, we describe the case of a 71-year-old man was admitted to our Hospital for worsening general conditions, fever, anuria, and a tender skin eruption on both arms and legs of new onset. He reported a diagnosis of ulcerative colitis associated with Sweet's Syndrome seven years earlier. At the time of admission, the patient was being treated with anakinra 100 mg/thrice a week and colchicine 0.5 mg/day, the latter discontinued at the recommendation of the general practitioner due to the onset of diarrhea.
Physical examination revealed tender erythematous nodules with a serpiginous pattern on both arms and legs, following the superficial veins vascular course and suggesting an acute recrudescence of Sweet's syndrome. Chest CT scan and hemogasanalysis showed an interstitial lung disease. Laboratory findings showed an elevation of acute phase proteins (C reactive protein [CRP] 16.2 mg/L), erythrocyte sedimentation rate [ESR] 51 mm (0-30), leucocytosis (8.88 x10^9/L) and signs of acute kidney injury (creatinine 2.28 mg/dL). A doppler ultrasound (DUS) examination of the upper and lower extremity showed a diffuse wall thickening of the superficial venous system with no sign of thrombosis, suitable for vascular inflammatory disease, involving the right cephalic vein, left basilic vein, left great saphenous vein and right small saphenous vein (Figure 1). Therefore, the diagnosis of Sweet's syndrome recurrence with inflammatory vascular injury was made. In marrow aspirate vacuoles of myeloid cells were not detected.
Systemic steroid therapy with metilprednisolone 40 mg/day was started, and colchicine 0.5 mg/day was reintroduced. Patient's clinical conditions gradually improved; DUS was repeated four weeks later, showing the resolution of the venous wall thickening. There were no further episodes of phlebitis.
Our case shows an atypical exacerbation of a previously known Sweet's syndrome, with an unusual and diffuse involvement of superficial veins. DUS provide information about the perivascular distribution of the inflammatory process, which appears as a hypoechoic cuff around the vein. The superficial venous involvement was responsible for the cutaneous lesions, which differed from the typical pattern of Sweet's syndrome and reflected the vascular inflammatory process.
Rapid and complete resolution of lesions after steroid treatment, which is one of the minor diagnostic criteria for Sweet's syndrome, further confirmed the clinical suspicion. The venous biopsy is not necessary in the context of an already known Sweet syndrome, therefore DUS results useful to evaluate vessels anatomy and the lesions distributions on arms and legs, ensuring correspondence with rash. Nonetheless, the lack of histological analysis of the vascular lesions represents the main limitation of our case.
As our patient presented all clinical markers of VEXAS syndrome, a vacuole search in myeloid precursors in bone marrow were not found.
In conclusion, this report provides the DUS evidence of non-thrombotic inflammatory venous disease in Sweet's Syndrome, and the response to high-dose intravenous glucocorticoids.

## 40. CARDIOVASCULAR RISK OF SORAFENIB-TREATED PATIENTS: SIMPLE SCORES ARE BETTER THAN COMPLEX ALGORITHMS

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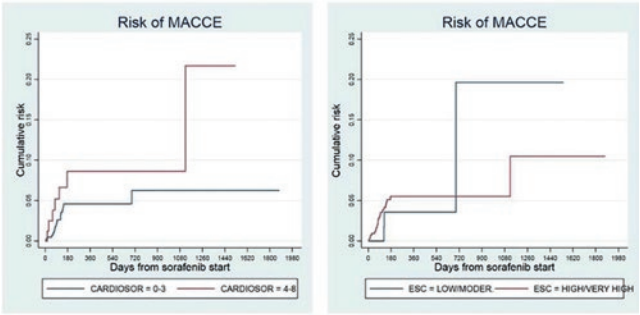
**Background and Aims**: Antineoplastic agents targeting the VEGF-VEGFR pathway are associated with an increased risk of major adverse cardiac and cerebrovascular events (MACCE). These events often cause permanent drug discontinuation and worsening of the quality of life. The identification of at-risk subjects is of particular relevance in the case of hepatocellular carcinoma (HCC), for which antiangiogenic TKIs are currently used and the anti-VEGF bevacizumab will become part of a frontline combination therapy.
We verified the ability of the European Society of Cardiology (ESC) score for TKI and the recently proposed CARDIOSOR score (Carballo-Folgoso, 2021) in predicting MACCE in sorafenib-treated patients.
**Method:** retrospective analysis of prospectively collected data of the ARPES database (508 pts from 5 centers). All patients received sorafenib for unresectable HCC from 2012 to 2018. Evolutive events after sorafenib start (including the occurrence of MACCE) were available for all patients. The ability of both scores in predicting MACCE was verified using a competing risk regression, in which any non-cardiovascular death was considered as a competing event.




**Results:** Median age at the sorafenib start was 69 years (IQR 62-74), the majority of patients were males (85.6%). During the follow-up, we observed MACCE in 24 (4.7%) patients. The most frequent MACCE were: cerebrovascular accidents (n=10), heart failure (n=5), coronary syndrome (n=4), pulmonary embolism (n=3), sudden cardiac death (n=1), cardiac syncope (n=1).

According to the ESC risk score the study population was classified as follows: veryhigh/high (n=120, 20.1%), medium (n=335, 65.9%), low (n=71, 14.0%). The CARDIOSOR score was <4 in 426 pts (83.9%), 4 in 64 patients (12.6%), >4 in 18 pts (3.6%). The threshold of the latter score to define high-risk was lowered to 4, as too few patients had higher scores.
The concordance between the ESC and CARDIOSOR scores was very low (Cohen k= 0.061). The ESC score was not able to predict MACCE (high/very high vs moderate/low risk: HR 1.188, 95% CI 0.354-3.986, p=0.780), the CARDIOSOR score came close to the threshold of statistical significance (score 0-3 vs 4-8: HR 2.013, 95% CI 0.932-4.970).
**Conclusion:** Even if neither score was fully validated by our data, the CARDIOSOR score appears better suited to assess the risk of MACCE in HCC patients receiving sorafenib, despite considering far less variables.

## 41. A CASE OF SPONTANEOUS PNEUMOTHORAX AS CLINICAL PRESENTATION OF A RARE DISEASE

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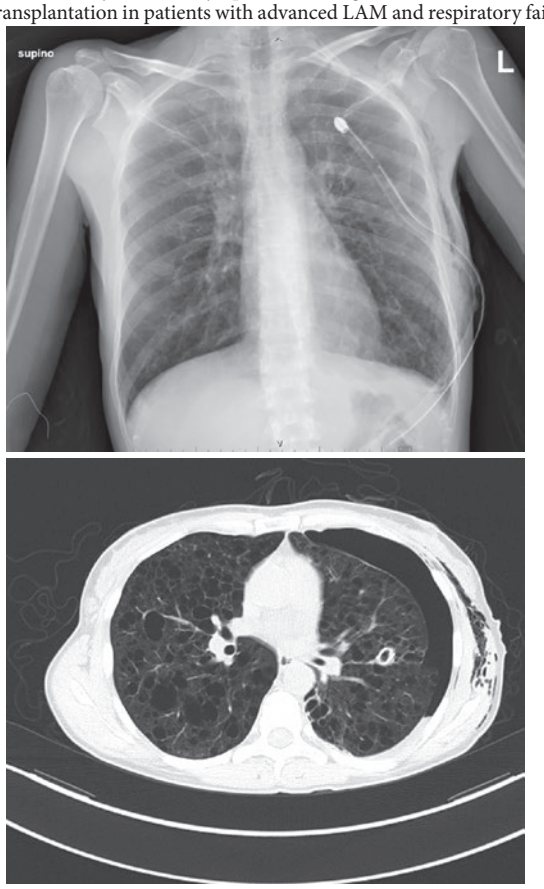
We describe the case of a 51-year-old woman admitted to the High Care Internal Medicine Unit of the IRCCS Fondazione Ca' Granda Ospedale Maggiore Policlinico due tospontaneous pneumothorax with positivity at molecular swab for Sars-CoV2.The patient was admitted to the Emergency Department for worsening dyspnoea and chest pain; Five days before, during a tennis match, she felt unwell and two days later she reported sudden chest pain. Shedidn't suffer from any additional comorbiditie, her family history was negative,and reported a history of tobacco smoking. Her lifestyle was active, and she never recorded physical problem.At physical examination the patient was alert, with tachidyspnoea and visible engagement of respiratory accessory muscles, pale and dry skin.On thorax auscultation breath sounds were significantly reduced in the left side.Patient's arterial blood gasses showed slight hypoxemia with respiratory alkalosis. The EKG was normal, biochemical values were unremarkable, whereas at lung sliding was absent in the left lung at chest ultrasound. The diagnosis of pneumothorax (PNX) was then confirmed by achest X-raysr. A high-resolution computed tomography was carried out andunexpectedly it showed bilateral walled, diffuse, round cysts, without lobar predominance and PNX in the left lung. The imaging was suspicious for lymphangioleiomyomatosis (LAM).A chest tube drainage was positioned and the patient was then transferred to our Unit.Eight days later a new chest X-ray showed re-expansion of the lung and the absence of PNX; this findingdisagreed with our daily examination by bed-side US-guided approach, during which we didn't find any pleural sliding in the anterior left hemithorax, rising the suspicion for persistence PNX.This was confirmed by a total-body CT scan made in order to exclude other disease localisation, sinceLAM is often characterised by renal angiomyolipomas and lymphatic complications Main disease was confined to the lung and PNX resolved after twelve days.The patient was then discharged with an out-patient pneumological follow-up.In our opinion this case is interesting for many reasons: the clinical presentation of a rare disease, its diagnostic work-up and the importance of bed-side ultrasonography as a reliable tool for dynamic evaluation of PNX, which is sometimes more sensitive than chest X-rays.LAM is characterised by a diffuse lung cystic disease, renal angiomyolipomas and lymphatic complications. We have two types of disease: first type is sporadic LAM; second type is LAM associated with the mutations of the TSC1 and TSC2 genes, responsible for tuberous sclerosis complex. These mutations lead to inappropriate LAM cell growth and proliferation. Abnormal smooth muscle cells destroy lung parenchyma resulting in progressive dyspnoea and PNX.
In LAM patients, we can also observe blockage of the thoracic duct or of one of its branches resulting in chylothorax. Common side findings are unilateral and asymptomatic renal angiomyolipomas. When they break, patients report a palpable abdominal mass or pain.LAM is predominant in white females and the age range can extend from pre-adolescent to elderly. Female sex hormones play a key role in LAM. In fact, there is an exacerbation of LAM during pregnancy, during the use of hormonal contraception or menstruation, so during situations of high exposure to female sex hormones. The incidence of PNX in LAM is 1000 times higher than in the general population and relapses are frequent.Diagnostic work-up is based on high-resolution computer tomography (HRCT). As in our case, diagnosis is often incidental, and imaging is performed for other indications. VEGF-D plays a key role in diagnosis. It is a growth factor that binds to VEGF receptor 3 and its levels are elevated in the serum of the most of patients with LAM disease.To screen out other causes, blood tests are useful. These include alpha1-antitrypsin and connective tissue disease screening. Disease management is based on pharmacotherapy with an mTOR inhibitor, like sirolimus or everolimus in cases with impaired lung capacity. PNX is treated according to standard guidelines and in case of recurrence pleurodesis is recommended.The management of renal angiomyolipomas is based on follow up, with surveillance imaging every 1-2 years and surgery is recommended only in case of symptomatic or big tumours.The last choice is lung transplantation in patients with advanced LAM and respiratory failure.




## 42. THE PROGNOSTIC ROLE OF INTERATRIAL BLOCK AMONG COVID-19 PATIENTS HOSPITALIZED IN MEDICINE WARDS

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**Introduction:** Some abnormal electrocardiographic findings were independently associated with increased mortality in patients admitted for COVID-19; however, no studies have focussed on the prognosis impact of the interatrial block (IAB) in this clinical setting. The aim of our study was to assess the prevalence and clinical implications of IAB, both partial and advanced, in hospitalizedCOVID-19 patients.
**Materials:** We retrospectively evaluated 300 consecutive COVID-19 patients (63.22 ± 15.16 years; 70% males) admitted to eight Italian Hospitals from February 2020 to April 2020 who underwent twelve lead electrocardiographic recording at admission. The study population has been dicho-

tomized into two groups according to the evidence of IAB at admission, both partial and advanced. The differences in terms of ARDS in need of intubation, in-hospital mortality, and thromboembolic events (a composite of myocardial infarction, stroke and transient ischaemic attack) have been evaluated.
**Results:** The presence of IAB was noticed in 64 patients (21%). In the adjusted logistic regression model, the partial interatrial block was found to be an independent predictor of ARDS in need of intubation (HR: 1.92; p: 0.04) and in-hospital mortality (HR: 2.65; p: 0.02); moreover, the advanced interatrial block was an independent predictor of thrombotic events (HR: 7.14; p < 0.001).
**Conclusions:** Among COVID-19 patients hospitalized in medical wards, the presence of interatrial block is more frequent than in the general population and it might be useful as an early predictor for increased risk of incident thrombotic events, ARDS in need of intubation and in-hospital mortality.

## 43. ASPIRIN EXPOSURE AS A PRIMARY PREVENTION STRATEGY IN WOMEN AND MEN WITH CONTROLLED HYPERTENSION AND THE RISK OF CLINICAL OUTCOMES

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**Background:** The added value of aspirin in primary or long-term secondary prevention when major cardiovascular risk factors are controlled has been recently questioned, and sex-specific data is sparse. We tested the association of aspirin use with incident cardiovascular events and all-cause mortality in high-risk hypertensive women and men with treated hypertension enrolled in the Systolic Blood Pressure Intervention (SPRINT) trial.
**Methods:** This is a post-hoc analysis of SPRINT, a multicenter, two-arm, randomized clinical trial comparing intensive (<120 mmHg) and standard (<140 mmHg) systolic blood pressure (BP) lowering strategies in nondiabetic, non-stroke high-risk hypertensive patients, with a median follow-up of 3.26 years. Herein, a primary prevention cohort was derived by excluding participants with baseline cardiovascular disease (CVD). Individuals with chronic kidney disease (CKD) were excluded owing to increased ischemic and hemorrhagic risk. Participants were included if valid baseline and consistent in-trial information on aspirin use (ie, the exposure) was available. Exposed and not exposed participants were 1: 1 propensity-matched for randomization group, sex, age category, Black race, and having ever smoked. The risk of cardiovascular events (ie, the primary outcome, including adjudicated myocardial infarction, non–myocardial infarction acute coronary syndrome, stroke, acute heart failure, and CVD death) and all-cause mortality based on the exposure (expressed as hazard ratios [HR] with 95% CIs) were progressively adjusted for residual, noncollinear confounders (ie, age at randomization, current smoking status, serum creatinine level, and triglyceride level). A subgroup analysis based on sex was performed.
**Results:** 2664 participants in SPRINT (N. 1332/group; 29.3% women; 24.5% ≥75 years) were analyzed. Individuals in the exposed group were older, had increased BMI and better lipid profiles, and were more likely to have never smoked and to be taking a statin. No between-group differences in history of peptic ulcer, chronic liver disease, or daily nonsteroidal anti-inflammatory drug use were recorded. Exposure was associated with a nonsignificant decreased risk of all-cause death (HR 0.84, 95% CI 0.53-1.30; p=0.45) and with an increased risk of the primary outcome (HR 2.30, 95% CI 1.31-3.90; p=0.004). In the subgroup analysis, the HR for the primary outcome was 2.33 (95% CI 1.09-4.56) in women and 1.5 (95% CI 0.95-2.38) in men (p for interaction 0.36).
**Conclusions:** The modern management of hypertension may have redefined the benefit associated with aspirin as a primary prevention strategy in an experimental cohort of high-risk male and female individuals with hypertension and without diabetes or CKD. The use of multiple antihypertensive drugs, the downwards redefinition of BP targets, and the improvement of additional cardiovascular prevention strategies were likely paramount to drive the reduction of the CVD risk in the examined context. Long-term data on aspirin use in combination with emerging therapies for cardiovascular prevention may clarify the future role of this pivotal drug in similar clinical settings.

## 44. "STUPENDOUS NIGHTMARE"

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The pandemic storm has profoundly disrupted our existence by confronting us with fear and uncertainty and has revolutionized the way we work, interpret relationships with patients, families and colleagues.
We found it useful to collect the thoughts of fellow doctors and nurses engaged in the care activities in a COVID department in order to facilitate the exchange of reflections and the elaboration of experiences that are often too demanding to be managed in solitude. To this end, we have dedicated a collection box in a dedicated area of the department kitchen where those who were available could insert a sheet with a sentence between December 2020 and March 2021 that represented their impressions at that time.
The adhesion between doctors and nurses was very good (over 80% participated); in order to structure their reflections in a more relevant way, we have developed with a young film artist a project entitled "stupendous nightmare" which saw the transformation of thoughts into a short film that describes their hellish "journey". In addition, some non-professional painters were invited to give voice to individual reflections with their representations.
We believe that this project represents a narrative medicine experience that can offer operators a tool for sharing and processing their experiences during the pandemic and at the same time represents an "inverse" version of the narrative medicine experience that sees the operator opening up with their own experiences to patients in order to foster the relationship of care

## 45. PROGNOSTIC MARKERS OF MORTALITY IN ELDERLY PEOPLE WITH COVID-19

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**Background:** Covid-19 is an infectious disease caused by the Sars-CoV2 virus, initially manifested as an endemic outbreak in the city of Wuhan (China) starting from December 2019 and then spread all over the world (1). The most frequent clinical manifestations are cough, fever, pharyngodynia, asthenia and myalgia (2), minor symptoms are inappetence, nausea, anosmia and ageusia (3).
Risk factors associated with Covid-19 infection with poor prognosis include advanced age (> 65 years), cardiovascular disease, chronic respiratory disease, diabetes and obesity.
**Aim:** purpose of this study is to identify prognostic markers of mortality in elderly patients with Sars Cov2 pneumonia.
**Methods:** this is a retrospective observational study of a cohort of 188 over 65-year old patients (118 male and 70 female; mean age 71,3 ± 12 years; age > 80: 43 patients (22.8%)) admitted to the Emergency Room of Policlinico Riuniti of Foggia from January to May 2021, with positive molecular nasopharyngeal swab for Sars Cov2, symptoms and radiological signs of pneumonia. 67 patients died up to 3 months after admission to the Emergency Room.
For each patient we collected the following data: age, sex, vital signs, comorbidities, ECG, complete blood count, PT sec and PT%, D-dimer, fibrinogen, INR, GOT, GPT, gamma GT, ALP, creatinine, eGFR formula K- DOQI, BUN, glycemia, CK-MB, myoglobin, high sensitivity troponin I, serum protein elcetroforesis, calcium, ESR, CRP, PCT.
Comparisons between deceased and non-deceased subjects were performed using Chi-squared test and Student's T-test when appropriate. Logistic regression analyzed the predictivity of variables on death events. P-value < 0.05 was considered significant.
**Results:** Our study showed a higher prevalence of comorbidities in the group of deceased, with a significant association for chronic kidney disease (32 deceased (47.7%) vs 27 non-deceased (22.6%); p-value 0.0004), ischemic heart disease (28 deceased (43%) vs 24 non-deceased (20%); p-value 0.0008), severe cognitive impairment (ADL <6) (12 deceased (17.9%) vs 12 non-deceased (9.9%); p-value 0.004), dyslipidemia (37 deceased (56.9%) vs 44 non-deceased (36.6%); p-value 0.008), arterial hypertension (59 deceased (90.7%) vs 93 non-deceased (77.5%); p-value 0.02), diabetes mellitus (25 deceased (38.4%) vs 29 non-deceased (24.1%); p-value 0.04), known neoplasms.
Moreover, the deceased group showed older age (76.33 ± 1.48 vs 68.53 ±1 non-deceased; p value 0,000013), higher respiratory rate, creatinine, GOT (66,89 ± 9.55 vs 46.72± 3.47 non-deceased; p value 0,018), CRP, troponin I hs and CPK-MB levels significantly higher. SpO2 in ambient air, platelet

count, lymphocyte count, monocyte%, hemoglobin and hematocrit were significantly lower in deceased patients.
Therefore, we analyzed the impact of most significantly altered parameters in the deceased group on outcome (death) with a logistic regression in order to correct for confounding factors such as sex and age, showing that parameters such as SpO2 in ambient air, creatinine values, lymphocyte counts, GOT and CK-Mb values were significant prognostic indicators.
Then we performed a logistic regression considering all these prognostic markers of mortality simultaneously in order to evaluate their independent predictive capacity on death event: advanced age (p value <0.00001), SpO2 in ambient air (p value 0.02), lymphocyte count (p value 0.01) and GOT (p value 0.003) were confirmed as excellent prognostic independent markers of mortality.
**Conclusion:** Parameters such as lymphocyte count, muscle creatine kinase and GOT proved to be excellent independent markers of mortality in a population of over 65-year-old admitted to emergency for COVID-19.
**Bibliography:** 1) Ralph R, Lew J, Zen T, et al. 2019-nCoV (Wuhan virus) a novel Coronavirus: human-to-human transmission, travel-related cases, and vaccine readiness. J Infect Develop Countries, 2020: 14.01: 3-17 - 2)Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA, 202, 323. 11: 1061-1069. - 3) American Academy of Otolaryngology - Head and Neck Surgery. AAO-HNS: anosmia, hyposmia and dysgeusia symptoms of coronavirus disease. World Journal of Otorhinolaryngology-Head and Neck Surgery, 2020.

## 46. PERICARDITIS AFTER COVID-19 VACCINATION: A CASE SERIES

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**Background:**. COVID-19 vaccination campaigns successfully impacted on viral spreading and in particular on clinical course of the disease, showing a remarkable reduction of hospitalization and admission in intensive care units. However, secondary to a highly extended vaccination program, several local and systemic adverse events associated with mRNA COVID-19 vaccines have been reported. Pericarditis and myocarditis are examples of cardiac complications related to these vaccines. A small but increased risk for development of pericarditis after COVID-19 vaccination is shown in population-based studies. Regulatory Agencies, including AIFA, are actually monitoring cases of pericarditis after COVID-19 vaccination. In particular, cases of pericarditis have occurred after mRNA COVID-19 vaccination (mostly secondary to vaccination with Moderna than Pfizer-BioNTech), especially in male adolescents and young adults, more often after the second dose. The incidence is approximately of 1-2 cases/100.000.
Aim of our study was to study the clinical profile of pericarditis occurred within 30 days after COVID-19 vaccines in patients attending our pericardial disease clinic.
**Setting:** We present a case series of patients who developed pericarditis after COVID-19 vaccination in the Department of Internal Medicine at Fatebenefratelli Hospital in Milan, followed from December 1st, 2021 to April 15th, 2022.
**Methods:** We analyzed twenty-five cases of patients vaccinated with COVID-19 vaccines who developed a pericarditis within 30 days after vaccination.
**Results:** Twenty-five individuals, of which 18 (72%) were women and 7 (28%) were males, had vaccine related pericarditis. Two patients were vaccinated with AstraZeneca, 2 with Moderna, the remaining with Pfizer-BioNTech. Median age was of 42 years. One subject developed transient constrictive effusive pericarditis, while another required treatment of pericarditis with Anakinra, switched to Canakinumab after severe skin reactions, because of failure of therapeutic response to first-line treatments; these two patients required hospital admission. In the remaining cases clinical symptoms associated with post-vaccines pericarditis were mild and didn't require hospitalization.
Chest pain was reported in 100% of cases, whereas pericardial effusion (in one case larger than 10 mm) was evidenced in 30% of subjects. Eighty percent of patients experienced tachycardia, whereas 90% reported asthenia. An increase in indices of inflammation (CRP) was documented in 50% of patients, usually mild.
With regard to therapy, 90% of patients were treated with NSAIDs (low-dose), 95% with colchicine, while 48% of cases required treatment with low-dose steroids (5mg prednisone); 48% of cases were treated with beta-blockers or ivabradine for tachycardia.
**Discussion:** COVID-19 vaccination induces a particular form of pericarditis, often insidious and troublesome, but with good prognosis. In fact, vaccine-induced pericarditis is mostly mild and don't require hospitalization. The clinical phenotype showed less typical chest pain, often normal indices of inflammation and little or no instrumental changes, but patients often experimented tachycardia and functional limitation. Regarding therapy, we used NSAIDs, or low-dose colchicine. Low doses of cortisone (e.g., prednisone 5mg a day) were useful in the presence of marked asthenia or systemic symptoms. Beta-blockers or ivabradine were used in the presence of tachycardia.
**Conclusion:** Clinical course of pericarditis occurring after COVID-19 vaccination is usually mild and doesn't require hospitalization, even if associated symptoms can be troublesome, similar to what sometimes occurs in so-called "long-COVID," e.g., those complaints that persist or appear after virologic cure. In this way, these forms of pericarditis may impair quality of life of the patients.
Keywords: pericarditis; COVID-19 vaccination.

## 47. PROGNOSTIC ACCURACY OF STANDARD CHEST-X-RAY AND LUNG ULTRASOUND IN COVID-19 PNEUMONIA: A COMPARISON BETWEEN TWO DIAGNOSTIC TOOLS

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**Background:** Chest radiography (CXR) and lung ultrasound (LUS) have been largely used as first evaluation tools during COVID-19 pandemic. Several studies evaluated the role of CXR or LUS alone and as part of clinical scores in diagnosis, assessing severity and monitoring COVID-19 pneumonia, as they may represent a more affordable and harmless alternative to chest CT scan which is considered the reference standard. However, comparison between the prognostic accuracy of CXR and LUS is still lacking.
**Objectives:** To compare the prognostic accuracy of CXR and LUS performed at admission in predicting need for ventilation, and death from any cause in hospitalized patients with COVID-19 pneumonia.
**Materials and Methods:** We conducted a single center retrospective observational cohort study enrolling patients admitted from February 2020 to April 2020 for COVD-19 pneumonia to two Internal Medicine Units converted into COVID19 medium-intensity care units at Luigi Sacco Hospital ASST Fatebenefratelli-Sacco, Milan, Italy. The primary outcome was to compare the prognostic accuracy of CXR and LUS performed at admission in predicting the composite outcome of non invasive mechanical ventilation, endotracheal intubation and death from any cause in hospitalized patients with COVID-19 pneumonia. The secondary outcome was to evaluate the inter-observer reliability for Brixia score between the expert radiologist and an internal medicine resident after a short training session made by an expert radiologist. We included patients >=18 years old, with a SARS-Cov2 infection confirmed by a positive RT-PCR assay on nasopharyngeal swab with radiological and/or clinical signs of pneumonia. CXR and LUS had to be performed within 48 hours from Emergency Department (ED) admission. CXR was evaluated by Brixia Score, while LUS was evaluated by LUS score. Briefly, to calculate Brixia score, lungs were divided into 6 zones (3 zones for each side); 0 to 3 points were assigned to each zone according to lung abnormalities observed (0= no lung abnormalities; 1= interstitial infiltrates; 2= interstitial and alveolar infiltrates with interstitial predominance; 3= interstitial and alveolar infiltrates with alveolar predominance), obtaining a total score ranging from 0 to 18. To calculate LUS score lungs were divided in 12 zones (6 zones for each side) and 0 to 3 points were assigned to each zone according to lung abnormalities observed (0=regular pleural line, presence of A lines; 1= at least 3 separate B-lines in at least one scan of the region; 2= multiple, confluent B-lines; 3= presence of at

least one parenchymal consolidation with major axis >1 cm), obtaining a score ranging from 0 to 36. The left anterior-inferior zone was then excluded because of the presence of the heart which may alter LUS interpretation, leaving a total of 11 zones and a score ranging from 0 to 33. Receiver operating characteristic (ROC) curve analyses were performed to describe the accuracy of the two scores to predict the primary outcome. Sensitivity and specificity with their 95% CIs were calculated according to pre-specified cut offs proposed in literature (Brixia score >= 8/< 8; LUS score >= 9/< 9). Cohen's Kappa statistics was used to calculate the inter-observer reliability.
**Results:** A total of 140 patients were included in the analysis (mean age 62 y, 56% males). The composite outcome of death, intubation or non-invasive ventilation occurred in 49 patients (35%), with 15 deaths (11%), 10 endotracheal intubation (7%) and 43 non invasive-mechanical ventilation (31%). Age, sex, dyspnoea and PaO2/FiO2 upon presentation, LUS and Brixia scores at admission were significantly associated with the primary outcome on univariate model, but significance persisted on multivariate analysis only for PaO2/FiO2, Brixia and LUS scores. The ROC curve analysis for the composite outcome demonstrated an AUC of 0.783 and 0.876 for LUS and Brixia score respectively. Considering death and/or intubation alone, AUC was 0.789 for LUS and 0.805 for Brixia score. Sensitivity and specificity for the composite outcome were 46.9% (IC95% 34.8-59.1%) and 95.6% (IC95% 90.3-98.2%) for Brixia score (LR+ 10.68, IC95%: 7.90-14.43, LR- 0.56, IC95%: 0.41-0.75) and 89.8% (IC95% 83.3-94.1%) and 52.7% (IC95% 44.2-61.2%) for LUS score (LR+ 1.90, IC95% 1.52-2.36, LR- 0.19, IC95% 0.16-0.24). The secondary analysis of inter-observer reliability for Brixia score demonstrated a weighted Cohen's Kappa of 0.59 (IC95% 0.53-0.66) between the expert radiologist and the internal medicine resident after training.
**Conclusions:** Our analysis demonstrated a similar prognostic accuracy of LUS and CXR scores at admission in predicting mortality or need for invasive or non invasive mechanical ventilation in hospitalized patients with COVID 19 pneumonia. LUS could be a useful tool for identifying patients at risk of worse outcome in settings where Chest X Ray is not immediately available or for monitoring during hospital stay. There was an acceptable concordance between an expert radiologist and an internal medicine resident after a short training program in CXR evaluation.

## 48. TYG BUT NOT HOMA-IR PREDICTS CARDIOVASCULAR EVENTS IN PATIENTS WITH NONALCOHOLIC FATTY LIVER DISEASE

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**Background and Aim:** Nonalcoholic fatty liver disease (NAFLD) is the most common liver disease worldwide and its prevalence steadily grow. The spread of NAFLD in Western countries is strongly associated with the increasing prevalence of obesity and type 2 diabetes due to the changing lifestyle and dietary habits. Some authors consider NAFLD as the hepatic manifestation of metabolic syndrome. Aim of the study was to investigate which of Triglycerides and glucose index (TyG) and Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) indexes better predicts cardiovascular events in NAFLD patients.
**Methods:** the present study is a post-hoc analysis of Plinio Study (Progression of LIver Damage and Cardiometabolic Disorders in Non-alcoholic Fatty Liver Disease: an Observational Cohort Study. ClinicalTrials.gov Identifier: NCT04036357). Plinio study includes dysmetabolic patients investigated for the presence of NAFLD. TyG index (ln[Fasting triglyceride (mg / dl) x Fasting glucose (mg / dl)] / 2) and HOMA-IR (Fasting insulin (mg/dl)[1]Fasting glucose (mg/dl)/405) were calculated as insulin resistance scores. NAFLD fibrosis score (NFS) was calculated as noninvasive markers of liver fibrosis. Data on incident Major Adverse Cardiovascular Events (MACEs) were collected during the follow-up.
**Results:** Plinio study included 1039 patients, 826 with NAFLD (79.5%) and 213 without NAFLD (20.5%). Patients with NAFLD had higher median TyG Index (4.8 ± 0.3 vs 4.6 ± 0.2, p<0.001) and HOMA-IR (4.1 ± 3.4 vs 1.6 ± 1.7, p<0.001). Among patients with NAFLD, those with positive NFS (n=34) had higher median TyG (4.9 ± 0.3 vs 4.7 ± 0.3, p<0.001) and median HOMA-IR (6.0 ± 4.4 vs 3.6 ± 2.4, p<0.01) in comparison to those with negative NFS (n=398). Patients with NAFLD were followed-up for a median of 43 [21-70] months yielding 3307 person-years of observation. During the follow-up were observed 57 MACEs. HOMA-IR didn't predict MACEs, while TyG index did (III tertile vs. I tertile HR: 2.14, p<0.05) after adjustment for age, sex, obesity and diabetes.
**Conclusions:** unlike the HOMA-IR, TyG index predicts cardiovascular events in NAFLD patients, and its use could help identify patients in need of more careful cardiovascular prevention.
OK 48 abstract.

# POSTER

## ALLERGOLOGIA, IMMUNOLOGIA CLINICA

### 1. CELIAC DISEASE: UNDERDIAGNOSED DISEASE?

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A 45-year-old woman referred to the internal clinic department for relapsing episodes of anterior uveitis about six months; relapsed after ocular topical steroid discontinuation and got substantial benefit after oral steroid introduction (prednisone 25 mg / day) for about a week.
She reported sicca syndrome and occasional episodes of diarrhea for many years, with a history of Hashimoto's tyroditis and endometriosis.
Systemic objectivity was normal.
Blood tests showed a slight increase in ESR (46 mm / h) and iron deficiency.
Approximately 80 causes of uveitis have been described and these can be classified into five groups:
- bacterial
- parasitic
- viral
- fungal

Epidemiology varies according to genetic and ethnic factors (e.g., Human Leukocyte Antigen (HLA)-B27, sarcoidosis,etc.), environmental factors (e.g., tuberculosis in endemic countries).
The investigations allowed to formulate the diagnosis of celiac disease (CD). The positivity of IgA anti-tissue transglutaminase antibody and endomysial antibodies suggested the hypothesis of celiac disease. The CD diagnosis was confirmed by upper endoscopy with histological analysis of duodenum's multiple biopsies.
Several ocular symptoms and disorders have been associated with CD and are a result of defective intestinal absorption and immunological mechanisms. These include nyctalopia, dry eye, cataract, thyroid-associated orbitopathy, uveitis, central retinal vein occlusion and neuro-ophthalmic manifestations. In addition, CD-related ocular disease may represent the first manifestation of CD.
In our patient a gluten-free diet resulted in a compete resolution of uveitis.

### 2. UN UNUSUAL COEXISTENCE OF SYSTEMIC LUPUS ERYTHEMATOSUS AND PRIMARY BILIARY

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Lupus erythematosus is a worldwide chronic autoimmune disease that can affect any organ or tissue. However, hepatic involvement has never been considered as a primary organic manifestation in SLE. In fact, 25-50% of patients with lupus may present alterations in the liver function tests. This association may be accounted for the existence of liver damage associated with SLE alone (lupus hepatitis) or for the occurrence of an overlap syndrome with autoimmune liver diseases (autoimmune hepatitis, primary biliary cholangitis) or for the co-existence of non-autoimmune liver diseases (viral hepatitis, drug-induced hepatitis). Several cases of liver function abnormalities in patients with lupus have been reported in literature, but data on the co-existence of hepatic diseases are actually rare. We report a clinical case of a 73-year-old woman with SLE and no history of alcohol, drug or hepatotoxic substance abuse, with negative serological studies for viral hepatitis, who presents clinical signs and symptoms of liver disease. Serological investigations and histological confirmation have defined a picture of primary biliary cholangitis. This case emphasizes the importance of study liver involvement in patients with SLE, although this is not considered in the current guidelines.
Here we report the case of a 73 years old woman with SLE, acquired thrombophilia, antiphospholipid syndrome, osteoporosis and papulosis lymphomatoid who initially presents tachycardia, asthenia and general malaise. Upon arriving at our emergency department, her vital signs were as follows: body temperature 36 °C; pulse 125bpm; blood pressure 125/75, SpO2 97% on room air. Physically, she looked asymptomatic, without lymphadenopathy or neck mass palpable. The chest expanded symmetrically and the breathing sounds were clear; her heart sounds were regular without an audible murmur; the abdomen was soft and the bowel sounds were normal. No cyanosis or pitting edema over the extremities was noted. Laboratory tests revealed an increase in the levels of: ALT (445 U/L), AST (151 U/L), GGT (1474 U/L), ALP (389 U/L), total bilirubin (3.31 mg/dL), direct bilirubin (2.42 mg/dL), amylase (208 U/L) lipase (151 U/L), RT-PCR (3.87 mg/dL) and creatinine (1.67 mg/dL; ClCr 95 mmol/L). Under the impression of cholestatic hepatitis, she was admitted for further observation and treatment. The cause of the cholestatic hepatitis was considered: anti-hepatitis A virus immunoglobulin M (IgM), anti-hepatitis B core antigen IgM, hepatitis B surface antigen, anti-hepatitis C virus antibody, Epstein-Barr virus/cytomegalovirus immunoglobulin G, herpes simplex virus for viral hepatitis were negative. Abdominal ultrasonography revealed normal biliary systems and biliary sludge in the common bile duct has been found in MRCP. Autoimmune disease was diagnosed by antinuclear antibody (ANA) titer positivity; ENA anti RNP positivity (61 U/L); anti- mitochondrial (AMA) titer positivity (1: 160) and low C4 levels (12 mg/dL) as well as negative IgG4 (0.46 g/L), negative anti LKM, negative C-ANCA and negative P-ANCA. The pathological report of the liver biopsy showed features of chronic, nonsuppurative, destructive cholangitis of the small interlobular bile ducts which were compatible with primary biliary cholangitis. After admission, ursodeoxycholic acid was administered, replaced with obeticholic acid for the occurrence of diarrhea and vomiting.
The purpose of this case report is to demonstrate the importance of liver involvement in patients with SLE. Data in literature are scarce but we can conclude that not only kidney, but also liver is often a target of systemic lupus erythematosus. For that reason biochemical liver tests should be systematically carried out in these patients in order to optimize the therapy and the quality of life.

### 3. RITIRATO

### 4. MIXED CRYOGLOBULINEMIA SYNDROME (MCS) DUE TO UNTREATED HEPATITIS C: CASE REPORT

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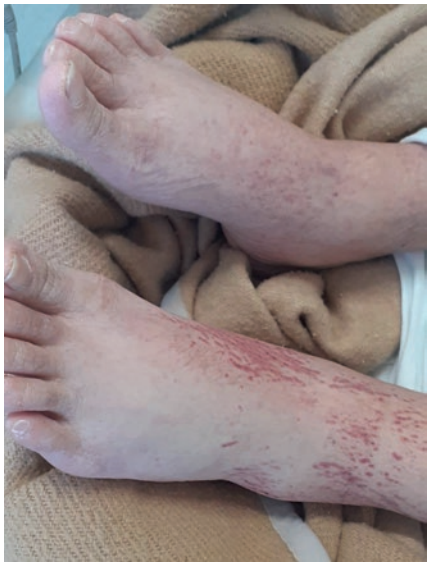
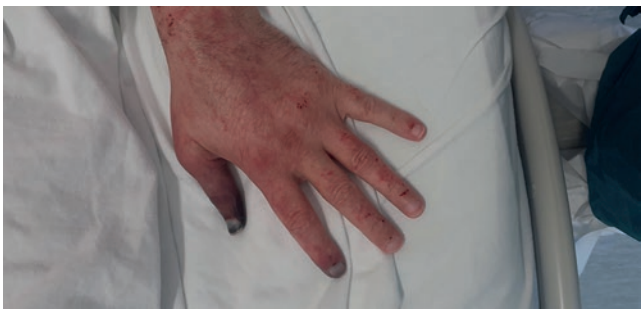
Cryoglobulinemia is a rare disease characterized by the production of monoclonal or polyclonal immunoglobulins that precipitate in cold temperature. Cryoglobulins differ in their composition, which has an impact on the clinical presentation and the underlying disease that triggers cryoglobulin formation. Cryoglobulinemia is categorized into two main subgroups: type I, which is seen exclusively in clonal hematologic diseases, and type II/III, which is called "mixed cryoglobulinemia" and it is seen in hepatitis C virus infection and systemic diseases such as B-cell lineage hematologic malignancies and connective tissue disorders. Clinical presentation is broad and varies between types but includes arthralgia, purpura, skin ulcers, glomerulonephritis, and peripheral neuropathy.
**Case Report:** We describe a case of a 45-year-old man with a non-cirrhotic hepatitis C virus infection presenting with weakness, arthralgias, purpuric rash with bilateral peripheral sensorimotor polyneuropathy, renal impairment and cardiac failure (Fig.1). Musculoskeletal manifestations were expressed with arthralgias and proximal interphalangeal and metacarpophalangeal articulations, with exacerbation on exposure to cold temperature (Fig.2).The initial laboratory investigation revealed decreased renal function (creatinine 5 mg/dL and a glomerular filtration rate of 25 mL/min.Laboratory investigations revealed severe proteinuria (4 g/day), low serum albumin level, and cryoglobulinemia. Computed tomography showed massive pleural effusion and ascites.Serum HCV RNA was detected by qualitative PCR and HCV genotype 1 was identified. Serum HBV DNA was undetectable by hybridization. Serologies for HBV,HIV, and Epstein-Barr virus were negative. Anti-DNA, antinuclear, anti-SSA/RO, anti-SSB, anti-neutrophil cytoplasmic, anti-Jo1, anti-SCL 70, and anti-ENA antibodies and lupus erythematosus cells were all normal or negative. The protein profile showed a monoclonal gammopathy of uncertain significance, to rule out the hypothesis of progression of MGUS, a bone biopsy was performed, no significant alterations.A elevated rheumatoid factor (318 IU/mL), positive cryoglobulins (cryocrit 2%, IgG polyclonal and IgM monoclonal), hypocomplementaemia (C4: 1.6mg/dL, C3: 85mg/dL) and the diagnosis of type II mixed cryoglobulinemia was made, and all systems were explored in detail to determine its involvement. At cardiac ultrasound absence of cavity

dilation, preserved global systolic function.The electromyogram showed signs compatible to severe sensory-motor polyneuropathy with greater lower limb involvement. A kidney biopsy was performed and the histology revealed leucocytoclastic vasculitis. The investigation was compatible with a severe type II mixed cryoglobulinemia with multisystemic involvement. Initial management with immunosuppressive therapy with glucocorticoids to control symptoms and simultaneous nefrosic syndrome treatment was required. Antiviral treatment need to control the severity of systemic manifestations was not available because of an acute hemorrhagic neurological complication.

**Discussion:** Cryoglobulins are found in 25%–30% of patients with HCV, but only 10%–15% of these patients develop clinically significant disease, with different ranges of symptoms. The spectrum of manifestations ranges from mild to severe disease, which may include typical purpuric skin lesions, other organ involvement and lymphoproliferative disorders. Wide spread vasculitis involving medium-small arteries, capillaries and venules with multiple organ involvement: skin, kidney, lungs, central nervous system, and gastrointestinal tract. The severe skin involvement occurs in only about 2% of cases and is due to vasculitis with fibrinoid necrosis and inflammation of the vessel wall and perivascular space.





## 5. ONE DIAGNOSIS MAY NOT BE ENOUGH: AN UNUSUAL CAUSE OF RELAPSING UNILATERAL PLEURAL EFFUSION

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V.S., a 73-year-old man, was hospitalised in our Internal Medicine Department for dyspnoea due to relapsing right pleural effusion, associated with persistent skin rash and hepato-splenomegaly of unknown origin.
His medical history was relevant for multiple diseases (arterial hypertension, type 2 diabetes, chronic ischaemic heart disease, previous paroxysmal supra ventricular tachycardia (PSVT), dyslipidaemia, bronchial asthma, OSAS, previous HBV-related hepatitis, chronic anaemia) requiring polypharmacotherapy (metformin, cardioaspirin, verapamil, doxazosin, irbesartan, simvastatin, esomeprazole, cholestyramine, folic acid, ferrous solfate, idroxizin, salmeterole/fluticasone, semaglutide, insulin). Since some months, the patient had been reporting night low-grade fever, skin rash and weight loss. An abdominal ultrasonography showed enlarged liver with irregular margins, splenomegaly (18 cm) and increased calibre of the portal vein (18 mm). A total-body CT scan with contrast was subsequently performed and showed moderate right pleural effusion and minimal pericardial and ascitic effusion (peri-hepatic and peri-splenic). The patient was admitted in a Pneumology Department of another Hospital, where a diagnostic and therapeutic thoracentesis was performed concluding for a hypereosinophilic pleural fluid (47%), in the absence of hyperosinophilia on peripheral blood. The culture tests as well as the research of parasites in blood and stool samples resulted negative. Autoimmune screening revealed only isolated ANA positivity (homogeneous pattern, titre 1: 160) and a PET-CT scan was also normal.
After the admission to our Internal Medicine Department, the cutaneous problem was diagnosed as contact eczema due to the use of various topical preparations with secondary scratching injuries; topical steroid therapy was administered with complete regression of skin lesions.
Given the recurrence of right monolateral pleural effusion, diagnostic and therapeutic thoracentesis was repeated, with confirmation of isolated hyperosinophilia on pleural fluid, although in reduction compared to the previous analysis (eosinophil count from 47% to 14%); microbiological and cytological analyses resulted negative. Since infectious and oncological causes had been already excluded, we completed the diagnostic work-up to define other potential causes of hypereosinophilic pleural effusion. After review of potential pharmacological iatrogenic causes, the possible role of simvastatin was identified, and the drug was immediately discontinued.
The analyses carried out on bone marrow biopsy and aspiration excluded onchoematological causes; haematopoietic cellularity was normal-for-age, with hyperplasia of the eosinophilic series.
On the hepatological side, given the high hepatic stiffness values detected with fibroscan, we hypothesized a possible metabolic liver cirrhosis, decompensated in terms of minimal ascites and possible right liver hydrothorax. However, the biochemical characteristics of pleural effusion were compatible with an exudate, thus making this hypothesis unlikely.
On the immuno-rheumatological side, the autoimmune panel confirmed the positivity of ANA with a homogeneous pattern titre 1: 320 and anti-dsDNA positivity. All the other tests resulted normal (C3-C4, ENA, p-/c-ANCA, AMA, ASMA, anti-Tg, anti-TPO). Craniofacial CT-scan was negative for nasal polyps, excluding hypereosinophilic vasculitis. Conversely, anti-histone antibodies were positive, suggesting the hypothesis of a drug-induced Lupus. Among the patient's usual drugs, statins were reported as being a possible risk factor for such side effect, although with a "low risk" causality.
Therefore, we report a case of monolateral pleural effusion secondary to serositis in the context of suspected drug-induced Lupus, in a patient with metabolic liver cirrhosis and past-HBV infection. We started diuretic therapy (canrenone and furosemide) in combination with low-dose oral steroid, which allowed us to obtain a complete regression of the unilateral pleural effusion. A revaluation of autoantibodies has been also planned.
In conclusion, this very rare case of drug induced Lupus and pleural effusion underlines the crucial role of the Specialist in Internal Medicine in defining the etiologies of complex clinical cases with multi-organ involvement. While skin rash was a confounder, hepato-splenomegaly could be easily explained by liver cirrhosis, but only the diagnosis of drug-induced Lupus allowed to correlate the immunological status to the relapsing eosinophilic pleural exudate.

## 6. DUPILUMAB FOR THE TREATMENT OF REFRACTORY EOSINOPHILIC ESOPHAGITIS: A MULTICENTER REAL-LIFE OBSERVATIONAL STUDY

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**Introduction:** Eosinophilic esophagitis (EoE) is a rare chronic immunologic disorder of the esophagus. Protonic pump inhibitors and oral steroid formulations (StF) currently represent the main therapeutic options, but usually patients have high rates of recurrence and consequent negative impact on their quality of life. Dupilumab is a monoclonal antibody which targets the interleukin-4 receptor and showed to be efficacious in a phase 2 trial in EoE.1 The phase 3 trial is still ongoing and currently no data are available from real-life settings.
**Aims and Methods:** The primary aim of this multicenter observational study was to compare clinical benefit between patients with EoE treated for 6 months with Dupilumab or StF in a real-life setting. Secondary aims included the comparison of endoscopic and histological changes after therapy, the quality of life and adverse events between the two groups. All consecutive patients with an established diagnosis of EoE referring since 2020 to two outpatient Clinics (Treviso and Padua) and with a follow-up of at least 6 months were considered eligible. Dupilumab was prescribed for off-label use at standard doses (600 mg at time 0 and then 300 mg weekly for 6 months) to patients with EoE refractory to conventional therapies. Patients' demographic and clinical characteristics were collected at baseline and during follow-up, with control visits planned every three months. Straumann Dysphagia Instrument (SDI) patient reported outcome (PRO), EoE Endoscopic Reference Scoring System (EREFS), the number of eosinophils per high power field (HPF) and Adult Eosinophilic Esophagitis Quality of Life (EoE-QOL-A) score were used to assess clinical, endoscopic and histologic activity and to investigate quality of life of patients at baseline and 6 months after therapies. All adverse events were recorded. The protocol was approved by the local Ethic Committee.
**Results:** Seventeen patients were included in the study (mean age 24.5 ± 11.6 years, 16 males). Five patients received Dupilumab and 12 were treated with StF (9 with viscous budesonide and 3 with oral fluticasone). Baseline characteristics were similar between the 2 groups, except for previous admission to the Hospital (p=0.009) and disease duration (p=0.001) that were significantly more frequent and longer, respectively, in the Dupilumab group. There were no differences in terms of comorbid atopic diseases, IgE levels, blood eosinophil count, previous exclusion diet and baseline clinical, endoscopic and histologic scores. After 6 months, patients treated with Dupilumab showed statistically significant reduction of the SDI PRO score (mean±SEM SDI PRO at baseline 2.6±1.2 and at 6 months 0.0±0.0, p=0.033) compared to patients conventionally treated (SDI PRO at baseline 2.7±0.7 and at 6 months 1.7±0.7). Also, endoscopic activity after 6 months was significantly different between the 2 groups with lower scores in patients receiving Dupilumab (mean±SEM ERESF score at 6 months were 1.8±0.4 in StF group and 0.2±0.2 in Dupilumab group, p=0.042). The esophageal intraepithelial eosinophil count at 6 months was significantly reduced in patients treated with Dupilumab compared to StF (0.4±0.4 and 22.9±7.1 eosinophils/HPF, respectively, p=0.009). No significant changes were found in the mean EoE-QOL-A score after treatment. Only two adverse events were reported in the StF group: a case of esophageal candidiasis and an episode of food impaction resolved by urgent endoscopy.
**Conclusions:** Our study confirms that Dupilumab may represent a valid therapeutic option in refractory EoE, improving clinical, endoscopic and especially histological activity of the disease.

## 7. STAPHYLOCOCCUS AUREUS IN COMPLICATED ECZEMATOUS DERMATITIS WITH DIFFERENT CLINICAL OUTCOMES: THE ADVANTAGE OF ANAKINRA VS STEROID IMMUNE TREATMENT

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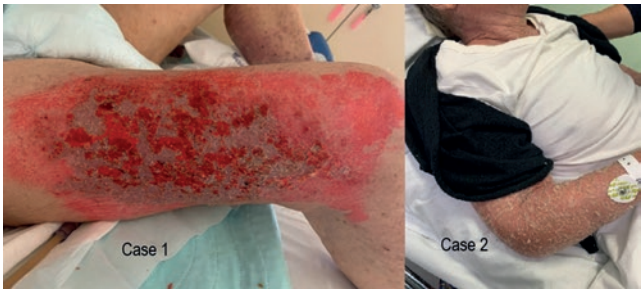
Staphylococcus aureus (SA) is a common pathogen colonizing the anterior nose of around 30% of healthy individuals and represents a major cause of bloodstream infections mostly in patients with dermatologic diseases. SA triggers both innate and adaptive immune system contributing to both T helper 1 and 2 responses, shifting the balance of the various arms of immune response to allow its own survival. We present two clinical cases in which the different picture depends on the expression of virulence factors by SA. Case 1: man, 87 y.o., with low-grade fever, diarrhea (since 5 days) and diffuse itching maculopapular rash, with focal blistering and scratching injuries. Previous history (P.H.): kidney failure (stage III), Therapy: amlodipine. Physical examination (P.E.): alert, oriented, no relevant alterations except for body temperature 37.3°C and eczematous dermatitis all over the body with edematous areas on the lateral surface of the left leg and right thigh (Fig.1) confirmed by biopsy. Laboratory tests were normal except for IgE 1108 mg/dL and CRP 15.9 mg/L. Two days after starting methylprednisolone 40 mg qd the patient developed high-grade fever, altered mental status and hypotension (qSOFA 2/3). Blood cultures, skin and nasal swabs were positive for methicillin-sensitive SA (MSSA) with the same antibiogram in all specimens and oxacillin was started. An increase in specific IgE anti-TSST (6.83 U/mL, n.v.< 0.1 U/mL) was found. A week later, the patient complained chest pain and echocardiogram showed acute pericarditis (moderately severe circumferential effusion with systolic collapse of the right atrium and mild diastolic collapse of the right ventricle free wall). After 5 days of therapy with ibuprofen and colchicine without clinical improvement, we started the IL-1 receptor antagonist anakinra (100 mg/day). After 48 hours the pain resolved, inflammatory markers improved and the echocardiogram showed the reduction of the pericardial effusion without signs of collapse of the right heart. A pericardiocentesis was avoided and the patient was discharged after 5 days (Sicignano L. Intern Emerg Med. 2021;16(5): 1391-1394). Case 2: woman, 72 y.o., with a diffuse erythroderma-like itching erythema (Fig.1) and ulcers in her oral cavity, started after stopping linezolid prescribed during the last hospital stay for urinary infection. P.H.: type 2 diabetes, kidney failure (stage III), nephrectomy (renal cancer), multiple recent hospitalizations for infections (SA, Candida, Acinetobacter), many drug adverse skin reactions. Therapy: atorvastatin, furosemide, pantoprazole, diltiazem, aspirin. P. E.: alert, oriented, no relevant alterations. Laboratory tests: hemoglobin 9 g/dL, creatinine 3 mg/dL, albumin 22 g/L, procalcitonin 1.44 ng/mL, CRP 261 mg/L, LDH 312 UI/L, total IgE 1710 mg/dL. Multiple microbiological specimens were collected. Dermatologist adviced high-dose IV steroid pulses. CRP decreased but blood culture resulted positive for MSSA. Anti-SA specific toxins IgE analysis showed significant increase in enterotoxin B IgE (62 UI/mL, n.v.< 0.1 U/mL) and enterotoxin C IgE (19.60 U/m, n.v.< 0.1 U/mL). In spite of Cefazoline treatment, cough and dyspnea soon appeared; arterial hemogasanalysis and chest X-ray showed hypoxemia and bilateral pleural effusion with right basal pneumonia, whereas blood tests showed CRP 23.1 mg/L, NT-proBNP 12569 pg/mL, and WBC 14500 cells/mm3. Oxygen and furosemide were added. A cardiac arrest occurred three days later. After successful resuscitation, she was transferred to the Intensive Care Unit but died a few hours later. The analysis of the microbial blood samples showed a polymicrobial positivity, including MSSA, Gram- spp, and Candida spp.




**Discussion:** Case 1: The immediate improvement of the pericardial effusion after anakinra (together with antibiotic) supports the Th-1 mechanism; indeed an initial phase with low SA-related TSST-1 production and prevalent Th-2 response (with an increase in total IgE and anti-TSST-1 specific IgE) and a following expansion of TSST-1-producing SA strain (or a reduction of the not-producing one) support high levels of circulating toxin and strong Th-1 response. Case 2: An enterotoxin-producing strain, given the increase in anti-staphylococcal enterotoxin B- and enterotoxin C-specific IgE, is consistent with prevalent Th-2 response, Clinical and laboratory findings during invasive SA infection may be misleading: in the initial phase signs and symptoms could be subtle as inflammatory markers could be higher than expected, may be due to the chronic immunomodulatory effect of SA (possible Th-2 mechanism shifting and tolerance induced by SA itself). In the late phase of the invasive infection, our patient had a transient improvement of blood values despite a clinical deterioration, suggesting the

need of starting antibiotic therapy as soon as there is a suspicion of involvement of SA regardless inflammatory marker elevation. The comparison of the different immunomodulatory approaches shows a better outcome and risk/benefit advantage of anakinra approach, if appropriate, over the common steroid approach.

## 8. IMMUNOGLUBULIN REPLACEMENT THERAPY IN PATIENTS WITH HAEMATOLOGICAL MALIGNANCIES DURING COVID-19 PANDEMIC

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**Introduction:** Secondary antibody deficiency (SAD) is common in patients with haematological malignancies (HM), expecially multiple myeloma (MM) and chronic lymphocytic leukaemia (CLL). SAD results in higher risk of infections, that represent the leading cause of death in those patients. Therefore, Immunoglobulin replacement therapy (IgRT) appears a logical approach to reduce the risk of infections. IgRT is generally administered either intravenously (IVIg), or subcutaneously (SCIg). The advantages of SCIg include the possibility for the patient to self-administer the preparations at home, no need of systemic pre-medication, the gradual absorption with slower catabolism and decreased incidence of systemic adverse events (AEs).
**Objectives:** IgRT refers to the liquid plasma component of blood that contains immunoglobulins or antibodies, pooled from thousands of plasma donations by plasmapheresis. COVID-19 infection reduced plasma donations and increased the cost of transporting and distribution of IgRT. Due to this reduction of availability emergency-related, many patients who are treated with SCIg replacement therapy were obliged to change kind of Ig. We assess the security and efficacy of the treatment with SCIg with the aim of evaluate the efficacy and emergence of any adverse events related to the use of different type of IgRT.
**Methods:** 44 evaluable patients with SAD (19 females -F-, 25 males -M-) have been enrolled in this observational, single-center study conducted from 2016 to 2021. 11 pts were affected by MM (3 F, 8 M), 12 by Non Hodgking Lymphoma -LNH- (7 F, 5M), 5 by CLL (1 F, 4 M), 16 were affected by non-oncologic diseases. During the period of the study 2 patients died for Sars-CoV-2 infection (1 affected by CLL treated with IVIg and 1 affected by MM treated with SCIg), and 2 patients died for other infections (both affected by MM and treated by SCIg). No one of this group of patients switched type of SCIg.
Between March 2020 and December 2021, a total of 6 patients switched to another type of SCIg (3 affected by CLL, 2 by MM and 1 by LNH). No one patient switched from SCIg to IVIg. All patients gave their written informed consent for the data collection, and ethical clearance was obtained from the Local Ethics Committee.
**Results:** The evaluation of symptoms and site of infection was interchangeably assessed by all authors.
Regarding AEs, only two patients require the discontinuation of the SCIg infusion because of grade IV AE: one of them experienced uncontrolled hypertension, and one showed a bilateral subconjunctival hemorrhage. No patient experienced new infections neither frequency variation of administration needing.
No differences were observed in patients who were non-responding to antineoplastic therapy or in those with frailty, in which reduction of doses of anti-neoplastic therapy was necessary.
Patients receiving SCIg consistently reported improvements in health-related quality of life measures, including improvements in their feeling of general well-being and in the impact of disease on both their own and their family's activities.
**Discussion and Conclusions:** Epidemiological data underlies no differences between different types of SCIg during COVID-19 pandemic period. Our report confirms that SCIg showed to be safe, cost-effective, and compatible with good health-related quality of life (HRQoL) in patients with SAD. Local reactions are usually mild and do not affect the good tolerability of the treatment.
In this observational trial, we evaluated the efficacy, safety and HRQoL during IgRT with different preparations of SCIg in a cohort of HM patients or other non-neoplastic diseases with SAD. Our data demonstrate that SCIg are an effective and valuable replacement treatment in those regardless of any type of Ig nor in case of switch of type of SCIg.

## 9. ANTI IL5 R-ALFA THERAPY AS A STEROID SPARING OPTION IN A CASE OF AUTOIMMUNE HEPATITIS WITH EOSINOPHILIC INFILTRATION AND SEVERE EOSINOPHILIC ASTHMA.

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Increasing evidence suggests that various chronic autoimmune and metabolic conditions are caused or exacerbated by inflammatory tissue damage. Leaky intestinal barrier and gut dysbiosis contribute to disease onset, progression and exacerbations in inflammatory diseases such as type 1 or 2 diabetes, obesity, arthritis, multiple sclerosis, ankylosing spondylitis, autoimmune hepatitis and systemic lupus erythematosus.
We describe the case of T.B., a 61-year-old woman with severe asthma, nasal polyposis, and chronic follicular gastritis who was admitted to our hospital because of acute abdominal pain 3 years ago.
Laboratory data revealed increased liver enzymes (ALT 465 UI/L), blood hypereosinophilia (3,320 Eo/mmc), and positive antinuclear antibodies (ANA) and of anti-LKM antibodies (1: 40), in the absence of anti-neutrophil cytoplasmic antibodies (ANCA).
The patient underwent liver biopsy which showed portal/periportal predominantly lymphohistiocytic infiltrate with associated MUM1 positive plasma cells, especially at the interface, with moderate eosinophilic granulocytosis, diffuse lymphocytic cholangitis, lobular hepatocytic pycnosis and necroinflammatory foci.
Based on clinical, laboratory and histopathological data, she was diagnosed with type I autoimmune liver disease.
Immunosuppressive therapy with oral prednisone 37.5 mg/day and azathioprine 100 mg/day was started, but with episodes of biochemical reactivation after corticosteroid treatment tapering.
After achieving a complete remission, and discontinuation of steroid therapy, the patient presented an episode of chest pain. The patient was hospitalized, and diagnosed with acute pericarditis. Infectious or autoimmune etiologies were excluded.
Taken into account the high rate of circulating and tissue eosinophils and the poor control of asthma symptoms, therapy with the monoclonal anti-interleukin-5 receptor (IL-5R) antibody benralizumab was started.
No consensus exists on how to reduce oral corticosteroids after the initiation of biologics in severe asthma. The reduction of daily oral corticosteroid dosages by 5 mg every 4 weeks, maintaining asthma control and adrenal function status, is suggested by recent evidence. A similar scheme was used in this case. After 8 months, the patient achieved a good control of both asthma and abdominal symptoms; no exacerbations occurred. As expected, eosinophils count was recorded after three months of therapy.
Moreover, therapy with benralizumab allowed the complete withdrawal of immunosuppressive therapy with azathioprine with good control of autoimmune liver disease, which is currently in biochemical and histological remission.
No further episodes of pericarditis were reported.

Benralizumab is an interleukin-5 receptor alpha-directed cytolytic monoclonal antibody. The inhibition of interleukin-5 receptor allows both circulating and tissue eosinophils decrease, for this reason the therapeutic choice fell on benralizumab.

## 10. NEVER DROP YOUR GUARD: STATIN-INDUCED IMMUNE-MEDIATED NECROTIZING MYOPATHY

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**Case Report:** A 70-year-old woman was admitted to our Department because of rhabdomyolysis. She complained of pain and muscle weakness especially in thighs and shoulders and reported mild dysphagia without dyspnea. NSAIDs provide limited benefit. The laboratory exams showed: creatinine 0.49 mg/L, CK 5309 U/L, total bilirubin 1.4 mg/dL, direct bilurubin 0.4 mg/L, AST 206 U/L, ALT 259 U/L, troponin T 159 ng/L, normality of hemochrome, ESR and CRP. The patient was affected by hypercholesterolemia and has been taking statins for 8 years: rosuvastatin was stopped after 5 years for myalgia without CK elevation; then atorvastatin was started; at the moment, she was taking atorvastatin at very low dosage (only 5 mg).

Ad admission: total cholesterol 177 mg/dL, LDL cholesterol 89 mg/dL, HDL cholesterol 61 mg/dL, triglycerides 136 mg/dL. Anamnesis revealed: autoimmune hypothyroidism, Gilbert's syndrome. During the hospitalization the patient was treated with hydration, therapy with atorvastatin was stopped; abdominal US, ECG, echocardiography and chest X-rays were performed. Polymyositis (i.e. PM-DM), polymyalgia rheumatica, infectious diseaseas and tumours were excluded. Electromyography detected signs of diffuse myopathy, hallmarks of denervation in proximal regions and pseudomyotonia. The biopsy of vastus lateralis showed cellular necrosis, abscence of inflammatory infiltrate, a small number of degenerating fibers with vacuolization phenomena, normal endomysium, expression of MHC I on the membranes and complement terminal complex deposition on the surface of some fibers and capillary vessels. Anti-HMGCR (hydroxy-methylglutaryl-coenzime A reductase) assay revealed strongly positive antibodies (343 CU, normal value <20). The patient was therefore treated with prednisone 50 mg (1 mg/Kg/day) with poor results (CK >3000 U/L) and then with intravenous immunoglobulins (0.4 g/Kg/day for 5 days). An abdominal and thoracic CT excluded tumors and therefore paraneoplastic syndromes. Azathioprine 50 mg was eventually started. In the next months, the clinical status and EMG findings markedly improved, with normalization of CK values and reduction of anti-HMGCR antibodies (88 CU): prednison was tapered and stopped after 18 months; after 2 years the patient was taking azathioprine at the dosage of 25 mg/day. In absence of lipid-lowering therapy, the exams show dyslipidemia (total cholesterol 244 mg/dL, LDL cholesterol 143 mg/dL, HDL cholesterol 74 mg/dL, triglycerides 132 mg/dL) and CK 124 U/L. Diagnosis (muscle biopsy, anti-HMGCR assay) and therapeutic regimen management was done in collaboration with a Hub Center (Department of Neurology, University of Verona).

**Discussion:** Statin drugs are generally considered safe and effective and widely used to reduce cardiovascular risk. Myalgia and self-limiting myopathy are common - up to 10-15% in clinical practice-, typically observed in the first weeks and usually heal with the suspension of the therapy. Association with other immune or pre-existing muscolar diseases and conditions (i.e. polymiosytis-dermatomyositis, isolated iperCKemia) and concomitant therapy has to be considered. Statin-induced mmune-mediated necrotizing myopathy is very rare, accounting only for 2-3: 100000 users, can appear years after the start of treatment and can even appear or persist years after cessation of therapy. CK can be extremely high (more than 10 times to more than 50 the upper limit of normal). Three subtypes of IMNM are recognized: anti-3-hydroxy-3-methylglutaryl-coenzime A reductase (anti-HMGCR) autoantibodies, anti-signal recognition particle (anti-SRP) antibodies, anti-HMGCR/SRP-negative. In anti-HMGCR myopathy the immune system can become sensitized to increased levels of HMG-CoA reductase - that is uptoregulated by statins - and this results in a injury to the cells that express this enzime. Hystologically, foci of necrosis are associated with regenerating fibers and lymphocyte infiltration is very limited. MHC class I and membrane attack complex deposition on the sarcolemma of non-necroting fibers is observed. IMNM is a potentially life-threatening disease and has to be treated with corticosteroids, intravenous immunoglobulins, long-term immunosuppressant therapy (i.e. azathioprine, methotrexate) or a combination of them. Laboratory exams - also with measurement of levels of autoantibodies - and EMG may be therefore required to establish the duration of treatment with immunosuppressive agents. Cardiovascular risk assessment models have to be used and lipid-lowering drugs other than statins have to be considered.

**References:**

- Mammen AL. Statin-Associated Autoimmune Myopathy. NEJM 2016, 374: 664.
- Stroie OP et al. Statin-induced immune-mediated necrotizing myopathy: an increasingly recognized inflammatory myopathy. Cureus 2020, 12: e7963.
- Babu S, Li Y. Statin induced necrotizing autoimmune myopathy. J Neurol Sci 2015, 351: 13.
- Mammen AL et al. Autoantibodies against 3-hydroxy-3-methylglutaryl-coenzyme A reductase in patients with statin-associated autoimmune myopathy. Arthritis Rheum 2011, 63: 713.
- Abd TA, Jacobson TA. Statin-induced myopathy: a review and update. Expert Opin Drug Saf 2011, 10: 373.

## 11. TYPE 1 KOUNIS-ZAVRAS SYNDROME PRESENTING WITH CARDIAC ARREST

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Prof. Manetti R., U.O. di Clinica Medica, Università degli Studi di Sassari, Dott.ssa Sircana M. C., U.O. di Clinica Medica, Università degli Studi di Sassari Type 1 Kounis-Zavras syndrome presenting with cardiac arrest A twenty-eight year old student with chest pain that started an hour earlier after a slight effort presented to the emergency room on December 22nd 2020. The pain was continuous, dull, oppressive, retrosternal, with back and right arm radiation, accompanied by profuse sweating and nausea. A few hours before the event, he had taken one Ketorolac 10 mg tablet/day to alleviate sinus headaches, as he used to do in the week of the exam session. Before admission he was also taking the following chronic therapy: Salbutamol inhaler (1-2 puffs 100 mcg per day when needed for shortness of breath), Diltiazem 120 mg RP 1 cps/day, Atorvastatin 40 mg 1 cps/day. The young man reported medical history of G6PDH deficiency, chronic rhinosinusitis with nasal polyps, NSAIDs-induced anaphylactic reactions (bronchospasm and laryngeal edema following consumption of Ibuprofen and Diclofenac) as well as recent onset of asthma triggered by dust mite exposure. The patient had been hospitalized in November 2020 for a vasospastic myocardial infarction presenting with NSTEMI, which occurred after chronic abuse of nasal decongestants (Naphazoline) in association with chronic low dose Ketorolac consumption (he was also taking bronchodilators). He complained of retrosternal pain for an hour after taking the last dose of Naphazoline, repolarization abnormalities were detected in ECG, laboratory tests showed elevated troponin (1200 pg/ml) and hypercholesterolemia, coronary arteries were not obstructed and cardiac ultrasound showed mid-apical segments hypokinesia, cardio-RM was negative. The disorder was interpreted as myocardial infarction with normal coronary arteries induced by nasal decongestants abuse and he was discharged from the Cardiac Care Unit asymptomatic with normal heart function a few days later, with the following prescribed home therapy: Diltiazem 120 mg RP 1/day and Atorvastatin 40 mg 1/day as well as strong recommendation to absolutely avoid nasal vasoconstrictors. Upon arrival to the Emergency Care Unit on December 22nd, his heart rate was 55 bpm (sinus bradycardia), systolic blood pressure was 100/70 mmHg, no signs of hemodynamic decompensation, Killip 1. ECG displayed repolarization abnormalities in the anterolateral leads, characterized by hyperacute T waves in the anterior leads (V3-V4). He subsequently developed ST segment elevation in aVR with ST segment depression in the remaining leads. Toxicological tests were negative. Serum troponin I was 2392 pg/ml. Echocardiography revealed mid-apical segments akinesia, the left ventricular ejection fraction measured 40%. Mild mitral valve insufficiency, right and left heart sections normal, no pericardial effusion. The coronary artery angiography showed multivessel vasospasms (with normal coronary arteries), causing near-complete occlusion of anterior and posterior interventricular arteries. The patient was in cardiopulmonary arrest with ventricular fibrillation and cyanotic, so he was defibrillated twice with 200 J and intracoronary nitroglycerin was administered, with restoration of sinus rhythm. Blood analysis showed results within normal ranges, as regarded complete blood count and markers of renal and liver function, except for mild eosinophilia. To exclude myocarditis, a cardio-RM was performed, which was negative. During the subsequent hospitalization, which was spent regularly in the absence of complications, the medical therapy was optimized and the patient had left the hospital asymptomatic with normal ECG, normal echocardiography with an ejection fraction of 62%. The disorder was interpreted as allergy associated myocardial infarction. He was discharged with the following therapy: Isosorbide monohydrate 50 mg 1/day, Cardioaspirin 1/day, Diltiazem 120 mg RP 1/day and Atorvastatin 40 mg 1/day. After the allergy visit, a Kounis syndrome induced by Ketorolac was suspected, so the drug was absolutely contraindicated in this patient and other drugs were added: Fluticasone 100 mcg/day (200 mcg/day during asthma exacerbations), Beclomethasone nasal spray. Mepolizumab was then added to steroid therapy with improved sino-nasal symptoms and asthma control. Cardioaspirin was suspended due to the onset of bronchospasm. The patient was vaccinated against house dust mite. This type I Kounis syndrome case with ST-segment elevation myocardial infarction complicated by cardiac arrest was successfully treated in the acute setting with myocardial infarction management alone. Intramuscular Epinephrine was not administered as the anaphylactic reaction was not immediately recognizable and no intravenous Epinephrine was administered to treat the cardiac arrest as it resolved with defibrillation, thus preserving the heart from further vasospastic injuries.

## 12. A PECULIAR CASE OF MASSIVE PLEURAL AND PERICARDIAL EFFUSION

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**Introduction:** . We describe the challenging case of a woman with pericardial and left pleural effusion who was admitted to our Internal Medicine ward in March 2022.
**Case Report:** A 84-year-old woman presented to our emergency department with a six-months history of mild intermittent fever associated with fatigue, increasing dyspnea in the course of the last month, and worsening of pre-existing edema.
Her previous medical history was significant for hypertension, chronic kidney disease, type 2 diabetes mellitus and chronic ischemic heart disease. On admission to our ward the patient was alert and comfortable at rest, her vital signs were stable. Dyspnea occurred with minimal activity. Her oxygen saturation was 90% breathing room air, so that oxygen therapy was started. Examination of the chest and heart revealed a systolic murmur and no pathological lung sounds.
Laboratory tests displayed increased inflammation markers, impaired kidney function, normal liver function and mild increase of beta-2-microglobuline. All the microbiological analyses tested negative. Chest radiography and CT scan showed evidence of a basal left pneumonia associated with massive pleural effusion. Empiric Antibiotic therapy was started with good biochemical response and decrease of dyspnea. However, sporadic mild fever endured.
Chest ecography confirmed the massive left pleural effusion, which was still present despite resolution of pneumonia and no microbiological evidence of other infections. Ecocardiography showed a normal cardiac funcition, no major valvular insufficiency, and a pericardial effusion, with no haemodynamic consequences.
Diuretic therapy was introduced with no significant clinical response.
In order to investigate the cause of the persistent pleural effusion, the patient underwent a lung scintigraphy which excluded pulmonary thrombosis. In addition, thoracentesis was performed. Pleural fluid had characteristics of transudate, and its analysis revealed no evidence of infections or tumoral cells. Despite an initial decrease, pleural effusion manifested again, therefore a thoracic drainage was placed, with daily putput of about 500cc. Analyses on pleura fluid were repeated, confirming its transudative nature. Citofluorimetry was negative for lymphoproliferative disorders.
Moreover, the detailed analysis of renal function confirmed kidney failure with severe proteinuria 2.5g/24h, probably due to uncontrolled diabetes.
A neoplastic origin of pleural effusion was also excluded by PET, CT scan, and mammography.
The autoimmune screening revealed a positivity for antinuclear antibodies (ANA) 1: 320 with an omogenous pattern (i.e., ring rods), while extractable nuclear antigen antibodies (ENA), double stranded DNA antibodies (dsDNA), anti-neutrophil cytoplasmic antibodies (ANCA) tested negative. Complement components were normal.
In the hypotesis of an underlying sierositis unleashed by the lung infection, despite no significant vascular arterial uptake demonstrated by total body FDG-PET, high dose steroid therapy was started. At the same time, diuretic therapy was enhanced.
The subsequent clinical observation showed a general improvement. A reduction of pleural effusion was observed, thereforer the thoracic drainage was removed without further formation of massive effusion. Furthermore, swelling in the legs, ankles and feet decreased and the patient's weight went from 89 kg to 77 kg. Finally urinary protein excretion decreased to 0.8g/24h.
**Conclusions:** Our patient presented with anasarca status of unknown origin. Possible causes like heart and liver failure, tumors or vasculitides were excluded. According to the nephrologist, even the significant protein dispersion could not justify the amount of monolateral pleural effusion.
A clinical diagnosis of autoimmune parainfectious pleuropericarditis was made, and it was corroborated by apparent response to corticosteroid therapy.

## 13. A CASE OF ELDERLY MAN WITH COUGH, DYSPNEA AND HEMOPTYSIS: NOT ONLY INFECTION OR CANCER

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Microscopic polyangiitis is a necrotizing vasculitis that mainly affects capillaries, venules or arterioles, manifesting in most cases as necrotizing glomerulonephritis and/or pulmonary capillaritis. The prevalence of microscopic polyangiitis (MPA) ranges from 9.0 to 94.0 cases per million. Recent studies, compared to previous ones from 1980s, have shown a shift of the incidence peak from 55-64 to 75-84 years of age. Antineutrophil cytoplasmic autoantibody (ANCA) positivity is present in >90 percent of patients with MPA. Here we describe a case of MPA in an elderly patient with history of renal disease.
**Case report:** on 17th of October 2021, during the second wave of COVID-19 pandemic, a 79 years old male patient presented at the emergency department of our hospital because of acute-onset dyspnea, asthenia and persistent cough for about a month. His previous medical history showed type 2 diabetes, previous HBV infection, rapidly progressive CKD suspect for IgA nephropathy, arterial hypertension, a previous urothelial carcinoma treated with surgery and in a maintenance therapy with Bacillus Calmette-Guérin. On the examination bibasilar pulmonary crackles were observed, with legs edema and a systolic murmur. Blood analysis showed: creatinine 8.6 mg/dL (normal values (n.v.) 0.78-1.18), CPK 191 UI/L (n.v. 38-174), C-reactive protein 5.08 mg/dL (n.v. < 0.5), white blood count 9600/mmc (n.v. 4800-10800), haemoglobin 7.7 g/dL (n.v. 13.5 – 17.5). The ECG showed signs of overload, while the chest x-ray showed a right basal lung consolidation. A CT scan of the thorax was performed, revealing multiple ground-glass consolidations on both the lungs, a right pleural effusion and a 1 cm pericardial effusion. Nasal swab and bronchial aspirate for SARS-CoV-2 were negative, as well as urinary antigens for Legionella pneumophila and Streptococcus pneumoniae and a multiplex nasopharyngeal swab for upper nasal airways viruses.
Due to the end-stage renal disease, a Kimal catheter was positioned in the right jugular vein for emergency hemodialysis, associated with high-dose diuretic therapy and fluid restriction; later on, after clinical stabilization, it was substituted with a Split Stream dialysis catheter. Meanwhile, we documented the presence of mild hemoptysis since the acceptance; the patient revealed the onset of this symptom some months prior. Considering this information, in association with the CT findings and the history of rapidly progressive CKD, we performed a complete autoimmune panel which showed positivity for anti-myeloperoxidase ANCA antibodies (56 UI/mL, n.v. 0-5.97), leading to the diagnosis of active MPA. An induction therapy with methylprednisolone 1-gram dose alternate days with prednisone 1 mg/Kg was started, followed by a prednisone 1 mg/Kg daily dose of maintenance. We assisted to a rapid resolution of the dyspnea and hemoptysis, as well as an improvement of the lung lesions at the CT. In consideration of the induced immunosuppression, and in anticipation of biological therapy with rituximab, prophylactic therapy with lamivudine for the HBV infection was started, and an interferon gamma release array was performed, resulting positive; for this reason, prophylactic therapy with isoniazid was implemented and rituximab infusion was delayed for about a month. The patient was discharged on 3rd of November and remained asymptomatic during the follow-up; the blood analysis performed at 4 months, after two infusions of 1 gram of rituximab, showed negativization of anti-MPO antibodies, normal levels of C-reactive protein as well as a significative improvement of creatinine (5 mg/dL), although with the necessity of long-term hemodialysis.
**Conclusions:** although MPA and other vasculitides are rare conditions, it is important to consider them in the differential diagnosis of elderly patients, in particular in presence of constitutional symptoms such as fever, fatigue, anorexia, or weight loss along with clinical evidence of rapidly progressive acute kidney injury, upper or lower respiratory tract involvement or multiple mononeuropathy. The suspicion should be confirmed by laboratory detection of ANCA positivity, although its negativity isn't sufficient to rule it out. The goal of the therapy is to achieve complete long-term remission, defined by absence of any clinical manifestation that are considered secondary to ongoing active vasculitis. In case of life-threatening disease, as in our patient, an induction regimen of glucocorticoids in combination with either rituximab or cyclophosphamide is indicated, followed by a maintenance therapy through rituximab, azathioprine, methotrexate, or mycophenolate based on patient-specific factors.

## COVID-19

### 14. CEREBROSPINAL FLUID LEAK AFTER REPETITIVE NASAL SWAB TEST: CASE REPORT

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**Introduction:** Diagnostic tests such as RT-PCR are used to detect active cases and therefore to prevent the spread of the infection. The U.S Centers for Disease Control and Prevention recommends a nasal swab test, however, a throat swab test or a saliva sample is also acceptable for the RT-PCR test. To date, only one case has been reported with cerebrospinal fluid (CSF) rhinorrhea due to nasal swab testing for COVID-19. We present a 53-year-old male patient with CSF rhinorrhea due to repetitive nasal swab testing for COVID-19. The aim of this report is to inform the medical community about the potential risks of frequent nasal swabbing and raise awareness on the importance of using other sampling methods for befitting cases.
**Case report:** A 53-year-old male was admitted with a right-sided rhinorrhea and headache. The patient had been tested for COVID-19 four times within the span of the previous month. Following the first swab test, the patient reported some minor fluid leak from his right nasal cavity. Three days after the last nasal swab test, the dripping developed into massive fluid leak following a sneeze. The patient had a medical history of a minor head trauma which occurred 4 years ago, however, the patient did not seek any medical assistance and did not suffer from any symptoms. The physical examination showed leakage of a clear fluid from the right nasal cavity. We have suspected a CSF leak due to the fluid's characteristics and amount. The CT scan detected normal neural parenchyma along with pneumocephalus. The paranasal sinus CT showed intracranial air passage which was directly related to right superior nasal meatus and proved the physician's suspicions of a CSF Leak. Only a paranasal and cerebral CT scan could be performed for screening since performing a prone positioned MRI resulted in an increase in pneumocephalus and rhinorrhea. The patient was admitted to the hospital for an endoscopic transnasal surgery. During the surgery, a bone defect was identified at the right fovea ethmoidalis. The defect was repaired with synthetic dura mater and was supported with a nasoseptal flap. The operation was conducted without any complications and the patient was admitted for post-operative care. The patient did not report any complaints or discomfort and is doing fine 2 months after the procedure. Paranasal sinuses CT: a) coronal bone window, showing intracranial air passage from small bony defect in right foveal ethmoidalis (thin arrow) b) axial bone window, diffuse pneumocephalus c) axial B-FFE sequence, CSF collection in prone position leveling in the right maxillary sinus (thin arrow).
**Discussion:** CSF leaks are usually divided into non-traumatic and traumatic. Traumatic leaks are more commonly encountered and can be iatrogenic following anterior skull base and endoscopic sinus surgery (ESS) or non-iatrogenic due to skull base trauma. CSF rhinorrhea stays a rare complication of ESS with a less than 1% occurrence-rate. To our knowledge, there has been only one case of an iatrogenic unilateral CSF rhinorrhea due to RT-PCR sampling method which was used for COVID-19 diagnosis and the patient was a 40- year-old woman with a nasal operation history, encephalocele and pseudomeningocele. Our case had repetitive and frequent nasopharyngeal swab sampling and had a history of minor head trauma 4 years prior to his first RT-PCR testing. We speculate that the unilateral right-sided CSF leak was primarily caused by repetitive nasal swab testing, unlike the previously reported case who had predisposing factors such as undiagnosed congenital skull base defect. The certainty of our speculation stays limited since no medical report or radiological imagery of the minor head trauma which occurred 4 years ago was available for further inspection. However, the fact that the patient was never diagnosed with a congenital skull base defect and did not require any medical assistance or show any symptoms following the past trauma strengthen our position on the case. Even though nasal swab sampling has become a reliable source of a diagnostic tool during COVID-19 pandemic, this case of CSF leak shows that nasopharyngeal swab testing can lead to iatrogenic outcomes due to its invasiveness. A less invasive approach such as saliva or throat swab samplings could be safer and preferable in such cases. A recent study from Yale School of Medicine comparing nasal swab samples to saliva specimens suggested that more SARS-CoV-2 RNA copies in the saliva specimens are detected than in the nasopharyngeal swab specimens and they have at least similar sensitivity in the detection of SARS-CoV-2 during the course of hospitalization, thus making the saliva sampling method more viable in susceptible cases. This report aims to encourage the medical community to question the patients' pre-existing conditions and medical history in order to assess the risk of adverse effects of nasal swab sampling prior to the procedure and use another sampling method if such risks are present.
**Conclusion:** The Authors presented a CSF leaks case report after repetitive nasal swab testing for SARS.CoV2.

### 15. VITT SYNDROME: CASE REPORT

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**Introduction:** COVID-19 is an ongoing global pandemic caused by SARS-CoV-2. COVID-19 vaccines were developed after being carefully evaluated in clinical trials, and play an important role in management of COVID-19. However, reports have emerged of a small number of vaccine recipients developing an unusual thrombocytopenia and thrombosis. Researchers have speculated an immune response that resembles a rare reaction to heparin for development of thrombocytopenia and thrombosis. This case reflects a very similar presentation of vaccine-induced immune thrombotic thrombocytopenia (VITT).
**Case Presentation:** A 55-year-old fit and well woman presented with intermittent headaches associated with eye floaters and vomiting. His symptoms started 72 hours after having the first dose of ChADOx1 nCOV-19 vaccine. She tried simple analgesia with no benefit and his headache persisted for 10 days. No personal or family history of thromboembolic events. On arrival, he complained of mild headache with no neurological deficits and normal funduscopy. His bloods showed raised D-dimer, low platelets and fibrinogen. His CT of the head was normal and CT venogram confirmed significant cerebral venous sinus thrombosis (CVST). After liaising with haematology, he was started on LMWH and intravenous immunoglobulins (IVIg) (1 g/kg). Her platelets and clotting profile was regularly monitored and samples for platelets factor 4 (PF4) antibodies were sent off (subsequently positive). 24 hours after the first dose of LMWH, she developed severe headache and vomiting. Neurological examination showed left-sided homonymous hemianopia. Repeat CT of the head revealed an acute 5.3×3.2 cm parenchymal haemorrhage in the right parietal lobe. Haematology advised high-dose steroids with proton pump inhibitors (PPI) cover. She was continued on IVIg but his Glasgow Coma Scale (GCS) continued to drop and required intubation and emergency decompressive craniotomy. She required an external ventricular drain as her intracranial pressures were difficult to control. Her treatment was: 1. IVIg (1 g/kg) OD (once a day) initiated immediately. 2. No anticoagulation with after discussing bleeding risks. 4. Prednisolone 80 mg OD (1 mg/kg) with PPI cover.
**Discussion:** ChAdOx1 nCOV-19 is a recombinant adenovirus vector vaccine developed by Oxford University. It is marketed with a trade name Vaxzevria (previously AstraZeneca COVID-19 vaccine, AstraZeneca). Researchers have proposed a possible mechanism for development of thrombocytopenia and thrombosis after receiving ChADOx1 nCOV-19 which suggests that it is an immune response that resembles a drug heparin which is an anticoagulant. Researches have categorised this syndrome as VITT. They have also suggested an association with PF4 antibodies and advised to have a low threshold for ELISA testing for PF-4 heparin antibodies in patients with suspected VITT. Although there is an association with VITT and PF-4 antibodies, we need further studies to assess whether these antibodies are induced by vaccine cross-reacting with PF4 and platelets or strong inflammatory stimulus of the vaccine itself. ASH has published guidelines for diagnosis and management for VITT. They have advised anticoagulating with non-heparin- based therapies and urgent use of IVIg (1 g/kg). They also advised to consider steroids if there is a delay in initiating IVIg and correct fibrinogen level with fibrinogen concentrate or cryoprecipitate if it drops to less than 1.5 g/L.3 It is mandatory for all the cases of thrombosis and thrombocytopenia post vaccination to be reported to the AIFA through online card reporting. We treated our patient as advised by the haematology team and was started on IVIg and LMWH but unfortunately patient developed a life-threatening bleed which required urgent surgical intervention. blurred vision, persistent headache, seizures, unexplained pinprick rash, persistent abdominal pain, and shortness of breath, leg swelling, confusion or bruising beyond injection site.
**Conclusions:** The Authors presented a VITT syndrome case report

## 16. A NEW EARLY PREDICTOR OF FATAL OUTCOME FOR COVID-19 IN AN ITALIAN EMERGENCY DEPARTMENT: THE MODIFIED QUICK-SOFA

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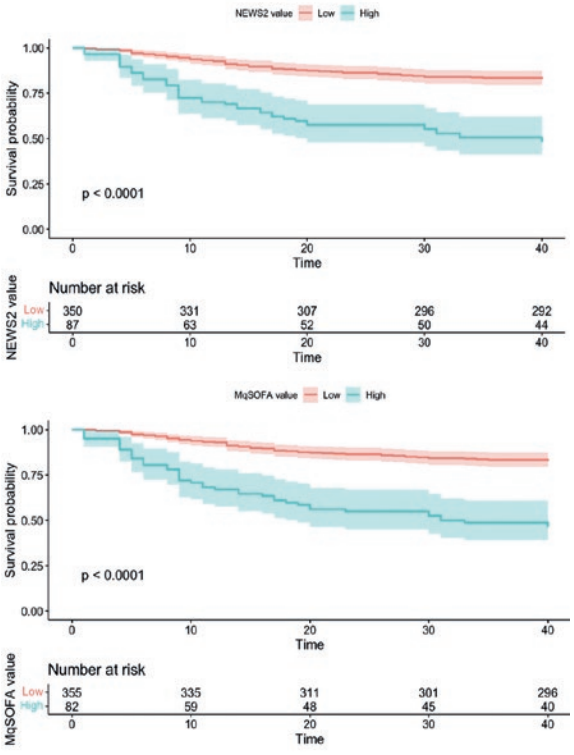
**Introduzione:** Dal 2019 il nuovo SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) sta causando una pandemia in rapida diffusione. Questa pandemia ha avuto origine in Cina, e si è diffusa rapidamente in tutto il mondo, causando oltre 450 milioni di casi ed oltre 6 milioni di decessi. Il presente studio mira a confrontare un quickSOFA modificato (MqSOFA) con NEWS-2 per prevedere la mortalità intraospedaliera (IHM), quella a 30 giorni e capire se questi due score sono in grado di predire l'intensità di cura che i pazienti affetti da COVID-19 necessiteranno.
**Materiali e Metodi:** Tutti i pazienti valutati da Marzo a Ottobre 2020 presso il Pronto Soccorso dell'Ospedale Sant'Anna di Ferrara con infezione da SARS-CoV-2 clinicamente sospetta sono stati inclusi retrospettivamente in questo studio e valutati con MqSOFA e NEWS-2. Al nostro database sono state applicate analisi di regressione statistica e logistica.
**Risultati:** Sono stati inizialmente reclutati un totale di 3359 record individuali. Di questi, 2716 pazienti sono stati esclusi per negatività del tampone nasofaringeo e 206 per mancanza di dati riguardanti i parametri vitali; in questo modo 437 pazienti sono risultati idonei per lo studio. I dati hanno mostrato che MqSOFA e NEWS-2 sono in grado di predire ugualmente sia la mortalità intraospedaliera (p <0.001) che quella a 30 giorni (p <0.001). Incidenze più elevate di malattia coronarica, insufficienza cardiaca congestizia, incidenti cerebrovascolari, demenza, malattia renale cronica e cancro sono state riscontrate nel gruppo deceduto rispetto a quello sopravvissuto. Né NEWS-2 né MqSOFA sono stati in grado di predire in maniera accurata il setting di ricovero che i pazienti avrebbero necessitato.
**Conclusioni:** In questo studio abbiamo confermato che MqSOFA non è inferiore a NEWS-2 nel predire la IHM e quella a 30 giorni. Tuttavia, rispetto a NEWS-2, MqSOFA è risultato più semplice e quindi più adatto all'impiego nel dipartimento di emergenza. Entrambi gli score non sono stati in grado di predire il setting di ricovero più idoneo per il paziente.




## 17. IMPAIRED FLOW-MEDIATED DILATION IN CONVALESCENT COVID-19

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**Background:** Endothelial dysfunction has a role in acute COVID-19, contributing to systemic inflammatory syndrome, acute respiratory distress syndrome and vascular events of the acute phase of disease. Evidence regarding COVID-19 middle- and long-term consequences on endothelial function, however, is still lacking. Our study aimed to evaluate if COVID-19 severity could significantly affect the endothelial function after three months from the acute phase.
**Methods:** We assessed endothelial function in outpatients with previous COVID-19 three months after negative SARS-CoV-2 molecular test by measuring flow-mediated dilation (FMD) in patients categorized according to a two-levels ("hospitalised" and "non-hospitalised") and a four-levels COVID-19 severity scale ("home care", "hospital, no oxygen", "hospital, oxygen", "hospital requiring high-flow nasal cannula, non-invasive ventilation, invasive mechanical ventilation or extracorporeal membrane oxygenation"). FMD difference among COVID-19 severity categories was assessed with analysis of variance; we further clarified the relationship between FMD and previous COVID-19 severity with multivariate logistic models.
**Results:** Among 658 consecutive COVID-19 subjects, we observed a significant linear trend of FMD reduction with the increase of the COVID-19 category (p<0.0001). The presence of endothelial dysfunction was more frequent among hospitalized patients (78,3%) in respect to home-care patients (21.7%;p<0.0001). Increasing COVID-19 severity was associated with increased endothelial dysfunction risk (OR: 1.354;95%CI: 1.06-1.71;p=0.011) at multivariate binary logistic analysis. FMD showed a significant direct correlation with partial pressure of oxygen at blood gas analysis (p=0.004), P/F ratio (p=0.004), FEV1 (p=0.008) and six minutes walking distance (p=0.0001).
**Conclusions:** Hospitalized COVID-19 subjects showed an impaired endothelial function three months after the acute phase that correlated with lung function impairment. Further studies are needed to evaluate if these subjects are at higher risk of developing pulmonary disease or future cardiovascular events.

## 18. A LEFT SHOT PLAYED BY ANXIETY: TAKO-TSUBO SYNDROME ONSET IN A FEMALE PATIENT WITH BILATERAL INTERSTITIAL PNEUMONIA DUE TO COVID 19 INFECTION

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**Introduction:** Tako-Tsubo cardiomyopathy or syndrome (TTS) constitutes an acute and reversible form of heart failure, first described in 1991, with a prognosis not as favorable as initially considered. Although high levels of circulating catecholamines have been implicated as one of the main mechanisms underlying the disease, the exact pathophysiological cascade has not yet been precisely defined. Several possible, not mutually exclusive, mechanisms have been proposed. The chain of events underlying the disease seems to be articulated first of all through the activation of the hypothalamic-pituitary-adrenal axis, then with the increase in circulating catecholamines and finally with the consequent cardiovascular responses. The syndrome was described for the first time in Japan in 1991. A characteristic of this

form is the transient balloon-like modification of the left ventricular apex, probably due to stimuli of neurogenic origin, originating from acute stress such as threats to one's life or important emotional separations. This deformation, visible with imaging techniques such as ventriculography, echocardiography or magnetic resonance, causes the left ventricle to take the shape of a basket (tsubo) used by Japanese fishermen for octopus fishing (tako), hence the name of Tako-Tsubo syndrome!
**Case Report:** A 61-year aged woman already submitted to the first administration of anti-COVID 19 RNA vaccine (Pfizer), positive to Covid 19 infection since the last weeks (Ta-Coronavirus COVID-19 PCR Delta AY.4.2 positive) and treated at home on oral prednisone, antibiotics, Low Molecular Weight Heparin LMWH subcutaneously (sc), was admitted to our Department for shortness of breath and sudden chest pain, precordial discomfort, cardiopalmus onset in the last hours. At history hypertension on sartans and autoimmune thyroiditis at 49 years; coeliac disease diagnosed at 50 y on gluten free diet; fibromyalgia, few cigarettes daily smoker since her youth. She presented febrile, tachypnoic and hypoxic. Lung auscultation revealed bibasilar crackles and at cardiac evaluation there were no presence of pathological heart sounds; normal B.P.110/60 mmHg, H.R. 95 B/min, T 38°C, oxygen saturation 94%, RR 18 br/min. At EKG there was slight ST and V1-V2 T-waves changes. Laboratory tests were significant for elevated serum inflammatory markers: C-reactive protein (217 mg/L; RR <3 mg/L), ferritin (1427 ng/mL; RR 28–365 ng/mL), erythrocyte sedimentation rate (84 mm/hour; RR 0–20) and interleukin-6 (IL-6; 67 pg/mL; RR ≤5 pg/mL, elevated D-dimer (3.45 μg/mL), slight leukocytosis, IgM-Ab anti-Covid 19 test positive, while negative were myocardial enzymes with troponin and myoglobin (troponin I(<0.015 ng/mL). Chest-X-ray showed signs of bilateral pneumonitis and thorax CT-scan confirmed the presence of bilateral, patchy peripheral ground-glass opacities with a crazy paving pattern, focal consolidations and mild pleural effusions. She underwent emergent coronary angiography due to haemodynamic instability, which revealed non-obstructive coronary arteries and apical ballooning on ventriculography consistent with Tako-Tsubo syndrome. The estimated left ventricular (LV) ejection fraction was 50%. Due to ventriculogram findings and negative troponin the most likely diagnosis remained Tako-Tsubo syndrome based on the patients apical ballooning on ventriculogram and patent coronary arteries on angiography. The patient was treated on beta-blocker and ACE inhibitors, diuretics and oxygen with nasal cannula and additional therapy was started on Casirivimab/Imdevimab 1200 mg in a single intravenously (iv) administration and Remdesevir 200 mg iv at the first day and 100 mg iv from the second day to the fifth, due to the evidence of a hyperinflammatory state and likely cytokine storm. So, she clinically improved within two weeks with normalization of all laboratory findings and echocardiogram parameters and was discharged without medical symptoms and 20 days later, she resulted Ta-Coronavirus COVID-19 PCR negative. One month later, she was still in healthy.
**Discussion:** Tako-Tsubo syndrome or stress cardiomyopathy is a syndrome characterized by transient regional systolic dysfunction of the LV and ECG changes that mimic acute myocardial infarction in the absence of angiographic evidence of obstructive coronary artery disease or acute plaque rupture. There are limited data regarding precipitating factors and the pathogenesis has not yet well understood. It has been reported that bacterial sepsis are the most frequent cause of Tako-Tsubo syndrome, while cases of TTS attributed to viral infections are rare. It has been hypothesized that SARS-CoV-2 as well as other viruses could elicit an exuberant systemic immune response with a cytokine release syndrome (CRS) characterized by elevated inflammatory markers with consequent myocyte injury.

## 19. AN UNFORGETTABLE BIRTHDAY: MYOCARDITIS AS A COMPLICATION OF COVID 19 INFECTION ONSET WITH BILATERAL INTERSTITIAL PNEUMONIA IN AN ELDERLY PATIENT…

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**Introduction:** Since the beginning of the pandemic, the infection caused by the new coronavirus SARS-CoV-2 has proved capable of causing serious consequences not only in the respiratory but also in the heart, with complications, such as arrhythmias and decompensation, persisting even after recovery.
It is not clear whether these consequences are directly attributable to the virus or whether they are the effect of a series of defensive reactions implemented by the body to eradicate the virus. So, it is known that the virus damages the heart, but the molecular mechanisms that create this damage are not known, and for this reason we have no currently targeted drugs able to guarantee more effective cardio-protection. Given all this, myocarditis which clinically presents with fatigue, breath-shortness, palpitations, tachycardia-arrhythmia, chest pain, fever, joint pain and is an inflammatory disease of the myocardium due to autoimmune disorders (rheumatoid arthritis and SLE), exogenous agents, infections (viral, bacterial, parasite or fungal), in the last year has recognized its origin in Covid 19 viral injury!
**Case Report:** A 90-year aged woman patient, already submitted to the first administration of anti-Covid 19 RNA vaccine (Pfizer) and afflicted with bilateral interstitial pneumonitis related to Covid 19 infection (Delta AY.4.2) in the last weeks (Ta-Coronavirus COVID-19 PCR positive) treated on oral prednisone, antibiotics, Low Molecular Weight Heparin subcutaneously (LMWH sc) and Oxygen, was admitted to our Department for sudden chest pain, precordial discomfort, cardiopalmus onset in the last hours. At history, allergic asthma since her youth, severe arthritis; no-smoker. At cardiac evaluation: no presence of pathological heart sounds; normal B.P.110/60 mmHg, H.R. 85 B/min, T 37°C, oxygen saturation 89%, at EKG slight ST and V1-V2 T-waves changes. Chest-X-ray showed signs of bilateral pneumonitis. Thorax CT-scan showed out bilateral, patchy peripheral ground-glass opacities with a crazy paving pattern, focal consolidations and mild pleural effusions. Cardiac imaging with echocardiography showed myocardial hypokinesis of apex and septum and slight systolic dysfunction (FE 50%) as in acute myocarditis and magnetic resonance imaging (MRI) detected a reduced biventricular function. MRI additionally showed myocardial oedema and late gadolinium enhancement. Laboratory data pointed out leukocytosis, positive myocardial enzymes with troponin and myoglobin; the IgM-Ab anti-Covid 19 test resulted positive. Treated on Casirivimab/Imdevimab 1200 mg in a single intravenously (iv) administration and Remdesevir 200 mg iv only the first day and 100 mg iv from the second day to tenth, corticosteroids, beta-blocker and ACE inhibitors, diuretics, antibiotics, LWMH sc, non- invasive ventilation (NIV), fluid restriction and low salt diet and rest, she gradually improved with normalization of all laboratory findings and echocardiogram parameters. 20 days later, she resulted Ta-Coronavirus COVID-19 PCR negative and one month later, she was still in healthy and celebrated her birthday (91 y!).
**Discussion:** SARS-CoV-2 has resulted in a viral pandemic whose rapid spread and high mortality rate have exposed susceptible individuals to unpredictable symptoms. Known virulence risk factors for SARS-CoV-2 are advanced age, a state of malnutrition and the presence of concomitant cardiovascular diseases, while COVID-19 can lead to myocardial diseases, vasculitis and athero-thrombotic manifestations. Cardiovascular diseases therefore represent a risk factor and a common complication during infection. The cardiovascular sequelae begin with the viral binding to ACE2 in the lower airways with damage to the alveolar cells, right from the start, altering the diffusion of oxygen through the capillary alveolar membrane thus preventing the correct oxygenation of the tissues. During the worsening of the respiratory phase, the immune response in the lungs impairs the integrity of the alveolar-capillary barrier, with plasma components seeping into the alveolar cavity along with immune cells. The cytokine storm is the origin for the systemic phase. Surprisingly, even patients with mild respiratory symptoms can experience cardiovascular implications such as: acute myocarditis/pericarditis, Tako-Tsubo syndrome and acute myocardial infarction. All that said, we should probably expect a further increase in cases of myocarditis in the coming months as a complication of the Covid 19 viral insult, the signs of which must therefore not be underestimated as long as the Covid 19 pandemic with its various mutationes rages!

## 20. COVID-19 HAPPY HYPOXEMIA. CASES REPORT.

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**Introduction:** COVID-19 has a wide spectrum of clinical severity, data classifies cases as mild (81%), severe (14%), or critical (5%). Many patients present with pronounced arterial hypoxemia yet without proportional signs of respiratory distress, they not even verbalize a sense of dyspnea. This phenomenon is referred as silent or happy hypoxemia. In patients with COVID-19, the severity of hypoxemia can be an important predictor that the patient is at risk of requiring admission to the intensive care unit.

**Cases Report:** Patient AS, a 71-year-old man, with fever 38.3°C, tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and coronavirus disease (COVID-19) was diagnosed after Thorax Angio-CT. While the patient was receiving 4 L/min oxygen by nasal cannula, his oxygen saturation as measured by pulse oximetry (SpO2) was 78%, and arterial blood gas revealed oxygen tension (PaO2) of 67 mm Hg, carbon dioxide tension (PaCO2) of 41 mm Hg, and oxygen saturation (SaO2). of 75%. On questioning, he consistently denied any difficulty with breathing. On examination, he was comfortable and not using accessory muscles of respiration. Comorbidities included diabetes mellitus, hypertension. in the 5th day of hospitalization, while remaining asymptomatic, arterial hemogasanalysis showed PCO2 values of 27 mmHg, PaO2 values of 70 mmHg, oxyhemoglobin saturation values of 73. Thorax Angio-CT was repeated showing bilateral segmental pulmonary embolism. Patient CD, a 65-year-old man, with fever (38.1°C), tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and COVID-19 was diagnosed after Thorax Angio-CT. While the patient was receiving 2 L/min oxygen by nasal cannula, his oxygen saturation as measured by pulse oximetry (SpO2) was 75%, and arterial blood gas revealed oxygen tension (PaO2) of 73 mm Hg, carbon dioxide tension (PaCO2) of 40 mm Hg, and oxygen saturation (SaO2). of 74%. On questioning, he consistently denied any difficulty with breathing. On examination, he was comfortable and not using accessory muscles of respiration. Comorbidities included diabetes mellitus. On the 6th day of hospitalization, while remaining asymptomatic, arterial hemogasanalysis showed PCO2 values of 25 mmHg, PaO2 values of 71 mmHg, oxyhemoglobin saturation values of 74. Thorax Angio-CT was repeated showing bilateral segmental pulmonary embolism. Patient GP, a 56-year-old man, with fever (37.8°C), tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and coronavirus disease (COVID-19) was diagnosed after Thorax Angio-CT. While the patient was receiving 4 L/min oxygen by nasal cannula, his oxygen saturation as measured by pulse oximetry (SpO2) was 77%, and arterial blood gas revealed oxygen tension (PaO2) of 79 mm Hg, carbon dioxide tension (PaCO2) of 43 mm Hg, and oxygen saturation (SaO2). of 79%. On questioning, he consistently denied any difficulty with breathing. On examination, he was comfortable and not using accessory muscles of respiration. Comorbidities included hypertension. On the 7th day of hospitalization, while remaining asymptomatic, arterial hemogasanalysis showed PCO2 values of 22 mmHg, PaO2 values of 75 mmHg, oxyhemoglobin saturation values of 78%. Thorax Angio-CT was repeated showing bilateral segmental pulmonary embolism.
**Discussion:** A shift in the oxygen dissociation curve is a confounding factor. Fever, prominent with COVID-19, causes the curve to shift to the right; any given PaO2 will be associated with a lower SaO2. These shifts produce substantial desaturations without change in chemoreceptor stimulation (because carotid bodies respond only to PaO2 and not SaO2). Tobin links silent hypoxemia with the development of thrombi within the pulmonary vasculature. Increased thrombogenesis has been noted in patients with COVID-19. Thrombosis within the pulmonary vasculature can cause severe hypoxemia, and dyspnea is related to pulmonary vascular obstruction and its consequences. Dyspnea can also arise from the release of histamine or stimulation of juxtacapillary receptors within the pulmonary vasculature. No biological mechanism exists, however, whereby thrombosis in the pulmonary vasculature cause blunting of dyspnea (producing silent hypoxemia). The happy hypoxia condition is based on the fact that the bulbar chemoreceptors, responsible for the transmission of the signal to the medulla oblongata and cortex inherent in the sensation of dyspnea, are sensitive to PaO2 and not to SaO2. The three COVID patients, being febrile, shift the dissociation curve to the right, maintain high levels of PaO2 with low levels of SaO2 without stimulating the chemoreceptors. Happy, hypoxic, normocapnic. After a few days, our three patients are still happy and hypoxic but they become hypocapnic and not due to tachypnea, but due to a V / Q ratio altered by pulmonary microembolism without having time to open the arteriovenous shunts. All this before IL6-mediated capillary damage to the alveolus occurs.
**Conclusions:** The authors presented a case report of patients with COVID-related interstitial pneumonia associated with a condition of happy hypoxia.

## 21. FIBROSIS-4 (FIB-4) INDEX AND MORTALITY IN COVID-19 PATIENTS ADMITTED TO THE EMERGENCY DEPARTMENT

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**Objective:** Liver damage worsens the prognosis of coronavirus 19 disease (COVID-19). However, the best strategy to stratify mortality risk according to liver damage has not been established. The aim of this study is to test the predictive value of the validated Fibrosis-4 (FIB-4) Index and compared it to liver transaminases and to the AST-to-Platelet ratio index (APRI).
**Methods:** Multicenter cohort study including 992 consecutive COVID-19 patients admitted to the Emergency Department. FIB-4 >3.25 and APRI >0.7 were used to define liver damage. Multivariable Cox regression and ROC curve analysis for mortality were performed. Secondary endpoints were 1) need for high-flow oxygen and 2) mechanical ventilation.
**Results:** 240 (24.2%) patients had a FIB-4 >3.25. FIB-4 >3.25 associated with an increased mortality (n=119, log-rank test p<0.001 and adjusted hazard ratio (HR) 1.72 (95% Confidence Interval [95%CI] 1.14-2.59, p=0.010). ROC analysis for mortality showed that FIB-4 (AUC 0.734, 95%CI 0.705-0.761) had a higher predictive value than AST (p=0.0018) and ALT (p<0.0001). FIB-4 >3.25 was also superior to APRI >0.7 (AUC 0.58, 95%CI 0.553-0.615, p=0.0008). Using an optimized cut-off >2.76 (AUC 0.689, 95%CI 0.659-0.718, p<0.0001), FIB-4 was superior to FIB-4 >3.25 (p=0.0302), APRI >0.7 (p<0.0001), AST >51 (p=0.0119) and ALT >42 (p<0.0001). FIB-4 was also associated with high-flow oxygen use (n=255, HR 1.69, 95%CI 1.25-2.28, p=0.001) and mechanical ventilation (n=39, HR 2.07, 95%CI 1.03-4.19, p=0.043).
**Conclusion:** FIB-4 score predicts mortality better than liver transaminases and APRI score. FIB-4 score may be an easy tool to identify COVID-19 patients at worse prognosis in the Emergency Department.

## 22. DETERMINANTS OF COVID-19 RELATED MORTALITY IN AN INTERNAL MEDICINE SETTING

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**Background:** Few data are available regarding the clinical characteristics and outcomes of patients hospitalised in internal medicine wards due to COVID-19 in Italy. Though internal medicine practitioners have been rapidly and heavily involved in the management of the pandemic, relevant patient outcomes have been partially described.
**Aims:** The main aim of this study was to evaluate the in-hospital mortality of the index hospital stay due to COVID-19 in the Internal Medicine Department of our hospital by analysing its associated factors.
**Methods:** This was a monocentric, retrospective, and observational study, named SMACORE. All 540 patients admitted between March and December 2020 (i.e., first and second waves) to the Internal Medicine Department of Fondazione IRCCS Policlinico San Matteo in Pavia, were included in the study. Data were collected and semi-anonymised and entered in the REDCap database. A laboratory diagnosis of SARS-CoV2-related infection was made according to the nasopharyngeal swab (molecular test) on bronchoalveolar lavage. We included socio-demographic data (age, sex), body mass index, main comorbidities including hypertension, cardiovascular disease (i.e., coronary heart disease, peripheral vascular disease, and heart failure), metabolic diseases (e.g., diabetes mellitus, obesity), chronic obstructive pulmonary disease, chronic kidney disease, neoplastic and onco-haematological disease, psychiatric diseases, dementia, and bed confinement status. The symptoms investigated and included in this study upon admission were fever, cough, pulse rate, and respiratory rate. Finally, the day of discharge, if present, was recorded, along with the outcome death. The length of stay was calculated in days, considering the admission day as the beginning of the observation and the discharge day or death as the end of study.
**Results:** The overall mean hospitalization length was 14 days (IQR 9-22). During an overall observation period of 9500 days, 146 deaths (27%) were reported, with a mortality rate of 10.9 per 100 people/week. Figure 1 shows the overall Kaplan Meier survival curve (upper part) and by other clinical variables which turned out to be significantly associated with death (lower part). Of note, most deaths occurred within the first 14 days of hospitalisation, while, thereafter, the slope of deaths diminishes. Having more than >2 comorbidities, cardiovascular disease, hypertension, and dementia were all associated with an increased mortality rate, whereas having mild dysp-

noea was a protective factor (as compared to moderate or severe dyspnoea). At multivariable analysis, among the various factors investigated, only an age >70 years (p=0.001) was associated with the outcome in-hospital death (Table 2), while comorbidities did not influence this outcome.

**Conclusions:** In our internal medicine ward, we found an in-hospital mortality rate due to COVID-19 of 10.9 per 100 persons/week, with mortality-related factors being an age >70 years, hypertension, multimorbidity, cardiovascular disease, and dementia. The mean hospitalization time was 14 days, possibly reflecting the high mortality burden.

**Table 1.** Vital signs, presenting symptoms and comorbidities at admission

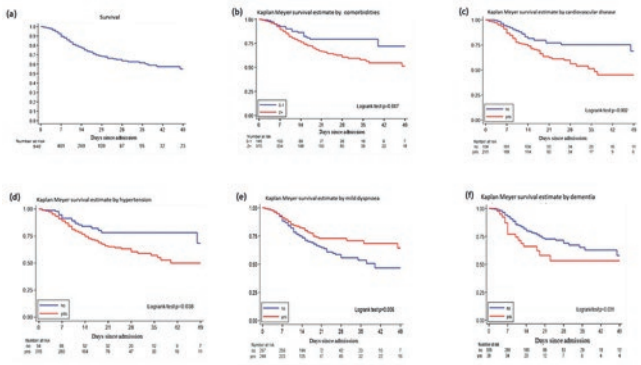
| Vital signs | | |
|---|---|---|
| | Median (IQR) | |
| Fever (°C) | 37 (36 -38) | |
| HR (beats/minute) | 88 (78 - 100) | |
| BF (breaths/minute) | 20 (17 - 25) | |
| Comorbities at admission | | |
| | n | % |
| At least 1 comorbidity | 469 | 89.5 |
| ≥2 chronic diseases | 378 | 72.1 |
| Hypertension | 322 | 77.2 |
| Cardiovascular disease | 217 | 52.4 |
| COPD | 48 | 13.5 |
| Interstitial disease | 10 | 2.8 |
| Asthma | 10 | 2.8 |
| Obesity | 66 | 18.8 |
| Presenting symptoms | | |
| | n | % |
| Fever | 300 | 73.71 |
| Cough | 148 | 47.59 |
| Fatigue | 147 | 49.16 |
| Dyspnoea | 258 | 66.32 |

Abbreviations. BF, Breath Frequency; COPD, Chronic Obstructive Pulmonary Disease; HR, Heart Rate IQR, interquartile range.

**Table 2.** Multivariable analysis for factors associated with death

| Variable | Hazard ratio | 95% confidence interval | p-value |
|---|---|---|---|
| Age ≥70 (vs<70) | 3.82 | 2.10-6.93 | <0.001 |
| Mild dyspnoea | 0.89 | 0.56-1.42 | 0.619 |
| Bed confinement | 1.19 | 0.23-5.99 | 0.837 |
| Cardiovascular disease | 1.34 | 0.82-2.18 | 0.239 |
| Chronic kidney disease | 0.78 | 0.37-1.62 | 0.499 |
| Dementia | 1.13 | 0.50-2.56 | 0.771 |
| Diabetes mellitus | 0.98 | 0.59-1.63 | 0.947 |
| Hypertension | 1.23 | 0.69-2.17 | 0.480 |
| Obesity | 0.45 | 0.16-1.28 | 0.133 |
| Psychiatric disease | 1.26 | 0.60-2.68 | 0.543 |
| Onco-haematological disease | 1.98 | 0.97-4.04 | 0.062 |

Of note, the absence of each variable was considered as "base".



## 23. THE HEAVY RESPIRATORY, PHYSICAL AND PSYCHOLOGICAL BURDEN OF SARS-COV-2 RELATED PNEUMONIA REQUIRING HIGH-OXYGEN FLOW

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**Introduction:** Coronavirus disease 2019 (COVID-19) pandemic represents a major clinical problem not only in terms of deaths: there is evidence of significant clinical sequelae of the disease that may impair both life length and its quality.

**Patients and Methods:** The aim of the present study was to assess the long-term consequences of moderate to severe SARS-CoV-2-related pneumonia in a subset of hospitalized patients requiring high-flow oxygen treatment. This prospective follow-up cohort study included 45 patients with confirmed COVID-19 admitted to a medical ward at the Montichiari Hospital, Brescia, Italy from November 2020 to April 2021 Patients had COVID-19 related pneumonia with respiratory failure and needed at least treatment with an inspired fraction of oxygen of 40% (of them, 59% were treated with Venturi mask and 41% needed non-invasive ventilation).

Patients underwent a clinical assessment with standard laboratory testing, chest CT scan, lung function tests with DLCO, and evaluation of vital parameters after a mean of 382 days after hospital discharge. A quality-of-life questionnaire was administered to each willing patient.

**Results:** While standard laboratory testing showed a substantial normalization of all measured indexes (namely circulating white blood cells, granulocytes, monocytes, lymphocytes, and haemoglobin, c-reactive protein (CRP), ferritin, plasma creatinine and electrolytes, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma glutamyl transferase (γGT)), we found persistence of radiological alterations (i.e. ground-glass opacities, irregular linear/reticular opacities) in 61% of patients;, mean Tiffenau index (FEV1/FVC) was reduced, although not clearly pathologic (79%) and 38% of patients showed a mild to moderate reduction in CO lung diffusion (DLCO).

Interestingly, 54% of subjects showed concomitant presence of radiologic alterations AND persistence of dyspnoea OR reduction in CO lung diffusion while 21% had all three concomitant conditions, compatible with the diagnosis of lung fibrosis.

Overall, a total of 75% patients had some degree of functional or structural alteration of respiratory apparatus.

We also evaluated quality of life thorough a structured questionnaire: after more than one year 62% of the patients still lamented fatigue, 62% effort dyspnoea, 12% anorexia, 29% dysgeusia or anosmia, 31% insomnia and 43% anxiety.

Main population data and results.

**Conclusions:** In conclusion, our preliminary data seem to demonstrate that SARS-CoV-2-related pneumonia requiring any degree of high flow of oxygen (no matter if administered with Venturi mask or NIV) has a heavy long-term burden, both in terms of persistence of functional and structural pulmonary damage (which may be progressive and evolve to a more severe degree in the future) and of burden on overall quality daily life.

| Main population data | |
|---|---|
| Age (mean±SD) | 63±11 |
| M/F | 13/32 |
| Days of follow-up (mean±SD) | 382±47 |
| Comorbidities (mean±SD) | 1.7±0.4 |
| N° of medications (mean±SD) | 2.0±0.2 |

| Main strumental data | |
|---|---|
| Radiological alterations (%) | 61% |
| FEV1/FVC % (mean±SD) | 79±5 |
| DLCO % (of predicted; mean±SD) | 86±14 |
| CO diffusion alteration (%) | 38% |
| Pulmonary fibrosis (%) | 21% |

| Biochemistry | Mean±SD |
|---|---|
| WBC (10^3/µl) | 7.4±2.2 |
| Neutrophils (10^3/µl) | 5.4±3.3 |
| Lymphocytes (10^3/µl) | 2.6±0.9 |
| Monocytes (10^3/µl) | 0.8±1.4 |
| Hb (g/dl) | 14.6±1.3 |
| Platelets (10^3/µl) | 244±64 |
| PCR (mg/L) | 3.7±5.3 |
| AST (U/L) | 24±8 |
| ALT (U/L) | 30±13 |
| Ferritin (µg/L) | 242±289 |
| Creatinine (mg/dl) | 1.0±0.2 |

| Quality of life | Yes | | No | |
|---|---|---|---|---|
| Persisting Fever (n, %) | 0 | 0% | 44 | 100% |
| Fatigue (n, %) | 27 | 61% | 17 | 39% |
| Effort dyspnea (n, %) | 27 | 61% | 17 | 39% |
| Anorexia (n, %) | 9 | 20% | 35 | 80% |
| Insomnia (n, %) | 13 | 30% | 31 | 70% |
| Anxiety (n, %) | 13 | 30% | 31 | 70% |
| Dysgeusia and/or anosmia (n, %) | 20 | 45% | 24 | 55% |

## 24. RELATIONSHIPS BETWEEN DIFFERENT DEGREES OF OXYGEN SUPPLEMENTATION AND LONG-TERM CONSEQUENCES IN MODERATE TO SEVERE COVID-19: A RETROSPECTIVE ANALYSIS

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**Background:** Many efforts for coronavirus disease 2019 (COVID-19) are directed towards prevention, early diagnosis, and effective treatment, but long-lasting effects observed in patients with 'Long COVID' are far from being completely understood. Long COVID can be categorized into two stages depending on the duration of prolonged symptoms: the 'post-acute COVID' which includes symptoms lasting from 3 to 12 weeks and 'chronic COVID' in which symptoms last more than 12 weeks.(1)
To date, few data are present in Literature about the possible pathophysiology, risk factors, and treatments of long COVID (2). In this study we investigate the relationship between the different degrees of oxygen supplementation in the acute phase and the presence of long-term consequences.
**Patients and Methods:** The aim of this retrospective analysis was to investigate long-term consequences of moderate to severe SARS-CoV2 related pneumonia in two groups of hospitalized patients which required different oxygen support.
The first group included 39 patients who needed to be treated during acute phase up to an inspired fraction of oxygen (FiO2) of 35% with nasal cannulas or Venturi Mask (VM).
The second group included 42 patients who needed at least a 40% FiO2 provided by VM or a non-invasive ventilation or oro-tracheal intubation.
Long-term consequences have been evaluated through a follow-up program including a quality-of-life phone interview, standard laboratory tests, chest x-ray and/or chest computed tomography, spirometry with evaluation of the Diffusing capacity of the Lungs for Carbon Monoxide (DLCO).
**Results:** No significant differences in age, sex, comorbidities (heart disease, hypertension, diabetes mellitus, COPD, CKD, neoplasm), ongoing home therapy (ACE-I, ATII-antagonist, statins, anti-platelet or anti-coagulant drugs, immunomodulant drugs, steroids) were detected between groups.
Standard laboratory tests showed a substantial normalization of all measured indexes: circulating white blood cells, granulocytes, monocytes, lymphocytes, and haemoglobin, c-reactive protein (CRP), ferritin, plasma creatinine and electrolytes, aspartate aminotransferase (AST), alanine aminotransferase (ALT) in both groups.
Follow-up radiological alterations were present in 25,6% (10/39) in the first group and in 69,0% (29/42) in the second group.
Respectively 23,1% (9/39) and 52,4% (22/42) of patients in the first and the second group presented both radiological alterations and persistent dyspnea or an alteration of DLCO.
The three conditions together were described in only one patient (2,6%) of the first group and in 7 patients (16,7%) of the second group.
An alteration of DLCO was found in 48,0% (16/39) of the first group, while the frequency in the second group was 38,1% (16/42).
As for symptoms, we analyzed the presence of fever, dyspnea, asthenia, loss of appetite, dysgeusia, insomnia and anxiety. They were similar between the two groups except for dyspnea (30,8% vs 61,9%) and anxiety (12,8% vs 45,2%).
**Discussion:** The outcome of our statistical analysis has highlighted a significant difference in the presence of fibrosis between the two groups, with a higher frequency in patients who needed high flow oxygen support during COVID-19 acute phase (p=0,03). Although a trend was present, DLCO reduction wasn't statistically significant between the two groups (p value=0,09) while there was a strong significance in the presence of radiological alterations (p<0,001). A possible explanation of DLCO outcome was the different timing for DLCO evaluation, closer to the acute phase for the first group (because of their lower need of oxygen supplementation). Moreover, dyspnea and anxiety were significantly more frequent in patients who needed higher flow oxygen support, NIV or intubation (respectively p<0,005 and p<0,001). **Conclusions:** In our retrospective analysis the presence of fibrosis and radiological alterations appears to be related to oxygen need, with a possible role of increased disease severity and pulmonary involvement during the acute phase. Our analysis reports that some long covid symptoms (such as dyspnea and anxiety) are more frequent in patients who needed high flow oxygen support; on the other hand, asthenia, loss of appetite, insomnia, dysgeusia are similar between the groups. This confirms that long covid symptoms may go beyond improvements in pulmonary radiological and functional examination. (3)
Further studies are necessary to better understand risk factors, markers, pathophysiology, and appropriate management of post-covid pulmonary fibrosis and long-covid symptoms.
**References:** 1) Ahmad, M. S. et al. "LONG COVID": An insight. Eur. Rev. Med. Pharmacol. Sci. 25, 5561–5577 (2021).2).Yong, S. J. Long COVID or post-COVID-19 syndrome: putative pathophysiology, risk factors, and treatments. Infect. Dis. (Auckl). 53, 737–754 (2021).Arnold, D.T. et al. Patient outcomes after hospitalisation with COVID-19 and implications for follow-up: Results from a prospective UK cohort. Thorax 76, 399–401 (2021).

| DEMOGRAPHIC DATA | First Group Treatment up to FiO2 35% | Second Group Treatment above FiO2 40% | P-value (T-test) |
|---|---|---|---|
| Average age (years) | 64 ± 12 | 62 ± 10 | NS |
| Sex (M / F) (n° of patients) | 21 / 18 | 31 / 11 | NS |
| Heart disease | 15% (6/39) | 36% (14/42) | NS |
| Hypertension | 49% (19/39) | 55% (23/42) | NS |
| Diabetes | 18% (7/39) | 26% (10/42) | NS |
| COPD | 5% (2/39) | 3% (1/42) | NS |
| Charlson Comorbidity Index | 2.4 ± 1.8 | 2.5 ± 1.4 | NS |

| QUALITY OF LIFE | First Group Treatment up to FiO2 35% | Second Group Treatment above FiO2 40% | P-value (T-test) |
|---|---|---|---|
| Anxiety | 12.8% (5/39) | 45.2% (19/42) | 0.001 |
| Asthenia | 46.2% (18/39) | 59.5% (25/42) | NS |
| Dysgeusia | 15.4% (6/39) | 31.0% (13/42) | NS |
| Dyspnea | 30.8% (12/39) | 61.9% (26/42) | 0.0045 |
| Fever | 0.0% (0/39) | 0% (0/42) | NS |
| Insomnia | 25.6% (10/39) | 28.6% (12/42) | NS |
| Loss of appetite | 12.8% (5/39) | 33.0% (8/42) | NS |

| INSTRUMENTAL DATA | First Group Treatment up to FiO2 35% | Second Group Treatment above FiO2 40% | P-value (T-test) |
|---|---|---|---|
| Radiological alterations | 25.6% (10/39) | 69.0% (29/42) | <0.001 |
| Radiological alterations + Dyspnea / DLCO alterations | 23.1% (9/39) | 52.4% (22/42) | 0.006 |
| Radiological alterations + Dyspnea + DLCO alterations | 2.6% (1/39) | 16.7% (7/42) | 0.031 |
| DLCO alterations | 48.0% (16/39) | 38.1% (16/42) | 0.09 |

| BIOCHEMISTRY | First Group Treatment up to FiO2 35% | Second Group Treatment above FiO2 40% | P-value (T-test) |
|---|---|---|---|
| WBC (10³/μl) | 6.7 ± 2.1 | 7.2 ± 2.1 | NS |
| Neutrophils (10³/μl) | 3.7 ± 1.6 | 3.8 ± 1.2 | NS |
| Lymphocytes (10³/μl) | 2.3 ± 1.3 | 2.6 ± 1.0 | NS |
| Monocytes (10³/μl) | 0.5 ± 0.2 | 0.8 ± 1.4 | NS |
| Hb (g/dl) | 13.6 ± 1.2 | 14.0 ± 1.3 | <0.001 |
| Platelets (10³/μl) | 224.2 ± 65.5 | 239.1 ± 57.2 | NS |
| PCR (mg/l) | 2.5 ± 3.4 | 3.4 ± 4.9 | NS |
| AST (u/l) | 24.3 ± 8.7 | 24.4 ± 9.5 | NS |
| ALT (u/l) | 23.1 ± 11.6 | 29.9 ± 13.2 | 0.02 |
| Ferritin (ng/ml) | 148.2 ± 120.6 | 207 ± 165 | NS |
| Creatinine (mg/dl) | 1.0 ± 0.2 | 1.0 ± 0.2 | NS |

## 25. TITLE: STATIN THERAPY MAY PROTECT AGAINST ACUTE KIDNEY INJURY IN PATIENTS HOSPITALIZED FOR INTERSTITIAL SARS-COV2 PNEUMONIA

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**Background and Aims**: COVID-19-associated acute kidney injury (AKI) represents an independent risk factor for all-cause in-hospital death in patients with COVID-19. Chronic statin therapy use is highly prevalent in individuals at risk for severe COVID-19. Our aim is to assess whether patients under treatment with statins have a lower risk of AKI and in-hospital mortality during hospitalization for interstitial SARS-CoV2 pneumonia.
**Methods and Results:** Our study is a prospective observational study on 269 consecutive patients admitted for COVID-19 pneumonia at the Internal Medicine Unit of IRCCS Sant'Orsola Hospital in Bologna, Italy. We compared the clinical characteristics between patients receiving statin therapy (n=65) and patients not treated with statins and we assessed if chronic statin use was associated with a reduced risk for AKI, all-cause mortality, admission to ICU, and disease severity. Statin use was associated with a significant reduction in the risk of developing AKI (OR 0.47, IC 0.23 to 0.95, p 0.036) after adjustment for age, sex, BMI, hypertension, diabetes, and chronic kidney disease (CKD). Additionally, statin use was associated with reduced C-reactive protein (CRP) levels (p 0.048) at hospital admission. No significant impact in risk of all-cause mortality (HR 1.98, IC 0.71 to 5.50, p 0.191) and ICU admission (HR 0.93, IC 0.52 to 1.65, p 0.801) was observed with statin use, after adjustment for age, sex, BMI, hypertension, diabetes, and CKD (Figure 1).
**Conclusion:** The present study shows a potential beneficial effect of statins in COVID-19-associated AKI. Furthermore, patients treated with statins before hospital admission for COVID-19 may have lower systemic inflammation levels.

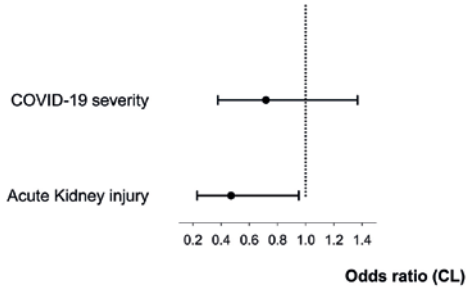


**Figure 1.** Logistic regression for outcomes associated with statin use.

## 26. COVID-19 VACCINE INDUCED MYOCARDITIS: A NEW DIAGNOSTIC REALITY

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To date, 10 billion doses of Covid-19 vaccine have been administered worldwide. Although its side effects are mild and self-limiting, there is an increased cases of myocarditis after SARS CoV-2 mRNA vaccines (Pfitzer BioNTech/Spikevax-Moderna). The pathogenetic mechanism has not been well defined: it is believed there is an exaggerated innate and acquired autoimmune response as a potential trigger of myocardial inflammation. Based on the latest update of the Pharmacovigilance Committee, the European Medicines Agency (EMA) underlines that the development of myocarditis after SARS CoV-2 vaccine remains a very rare event: the incidence of myopericarditis is around 1/10 thousand, predominantly affects young males within the first 14 days after the injection of second dose of SARS CoV-2 mRNA vaccines and clinical manifestations are mild and readily resolvable in a few days.
Our clinical case concerns a young adult of 36 years old who goes to the emergency room for persistent chest pain. He reported having received the first dose of SARS CoV-2 vaccination-Spikevax, 4 days before the onset of symptoms. In his medical history: previous sars cov-2 infection, hypertension, obesity, dyslipidemia. Blood tests on admission showed troponin I (hsI) 3585ng/ml, C-Reactive Protein (CRP) 6.4 mg/dl, procalcitonin levels 0.13 ng/ml, quantitative test for SARS CoV-2 antigen by nasopharyngeal swab sample on were negative. At the electrocardiography: sinus rhythm with right bundle block and the echocardiogram showed normal biventricular systolic function in the absence of significant valvulopathies. Therefore, on the basis of the symptoms, the rise in phlogosis indices and troponin, in the absence of echocardiographic and electrocardiographic alterations, in the suspicion of myocarditis, he was admitted to Subintensive Medicine. During his hospitalization he was subjected to non-invasive multiparametric monitoring and coronary tomography which excluded myocardial ischemia. Blood tests at 48 hours showed a reduction of Troponin I levels 1684ng/ml and CRP 2.5mg/dl, the echocardiogram remained unchanged therefore on the third day he was discharged with a diagnosis of "myocarditis due to SARS CoV-2 vaccination" and usual home therapy was confirmed. We re-evaluated the patient after 15 days with a cardiac magnetic resonance imaging (C-MRI) that showing edema and myocardial hyperemia with two Lake Louise criteria: therefore we confirmed the diagnosis of vaccine induced myocarditis
Myocarditis after SARS CoV-2 vaccines is a rare adverse event which, with the implementation of the vaccination campaign and its extension to younger classes, has incresed myocarditis cases. It mainly affects adolescents and young adults 14 days after the injection of the second dose of the vaccine, however, as our case shows, they can also occur after the first injection. Mild forms are more frequent and, if the systolic function is normal, the evolution is benign and discharge can be early. A recent study published at The Lancet Respiratory confirms that the incidence of myocardial inflammation due to SARS CoV-2 vaccine is comparable to the incidence of myocarditis for other vaccinations (influenza vaccine/smallpox). This underline how myocarditis are not a prerogative of the SARS CoV-2 vaccine, due to an immune-mediated reaction by our body to the spike protein, but also of an autoimmune inflammatory response secondary to the administration of other vaccines. The incidence of SARS CoV-2 myocarditis is even more amplified by the underestimation of myocarditis cases in the pre-pandemic era due to subclinical forms that did not require medical evaluation.

## 27. A RARE COMPLICANCE AFTER COVID-19 VACCINE

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With the aim of tackling the COVID19 pandemic, the world scientific community, one year after the virus was identified in Wuhan, authorized the use of viral vector and mRNA vaccines against SARSCoV2 infection. Although they have high immunogenic efficacy, have also be reported moderate-severe adverse reactions. Among these were also included the "interstitial lung disease-drug induced "(DI-ILD). In this abstract we present the story of two patients L.A. 70-year-old and A.A 51-year-old who access to Emergency Department at Ospedali Riuniti Ancona for fever, dyspnoea, cough and desaturation which occurred four days after the injection of the second dose of COVID-19 Pfizer/BioNTech Comirnaty vaccines. In they past clinical history: chronic obstructive pulmonary disease, prostatectomy for neoplasm, hypertension and diabetes mellitus, respectively. They denied exposure to tobacco smoke/dust inhalation and drug allergies. They also reported that they had not made any changes to the intake of home medications in the last six months.
Blood tests in the emergency room showed: leukocytosis, procalcitonin 0.85 and 0.07 respectively, CRP 14.8 and 12.3 respectively and hypoxemia, quantitative test for SARS CoV-2 antigen by nasopharyngeal swab sample on admission were negative. Chest computed tomography (CT) showed, respectively, "consolidation thickening with bilaterally ground glass halo" and "smooth thickening of the interlobular septa and soft areas with bilaterally diffused ground glass at both central and peripheral locations". Therefore, they were admitted to Subintensive Medicine. Here they underwent oxygen therapy with the use of high-flow nasal cannulas with FiO2 45% and 50%, lung ultrasound with calculation of the LUS score, which was 10 and 8 respectively, search for CMV- DNA, Antibodies anti rickettsia, chlamydia, mycoplasma, legionella and research of the urine antigens of legionella and pneumococcus results negative, culture examination of sputum negative. Therefore, in the suspicion of pneumonia induced by SARS CoV-2 vaccination, steroid therapy with methylprednisone 20 mg/day was started, and, only for L.A was started also antibiotic therapy with levofloxacin 500 mg x2/day. Excluding other pathologies, Brain Natriuretic Peptide (BNP) and troponin were also measured and found to be within normal limits. At a distance of 2 and 4 days from hospitalization, there was resolution of symptoms, improvement of peripheral saturation with progressive reduction of oxygen requirements, normalization of blood tests, improvement of the radiological picture, CT and ultrasound (LUS at discharge, respectively 2 and 6). Both discharged after 5 days with diagnosed of: " COVID-19 vaccine induced interstitial pneumoniae" and tapering steroid therapy for 10 days. In anticipation of the administration of the III dose of same vaccine we suggested premedication with prednisone 5 mg from the day before to 7 days after vaccination.
Interstitial pneumonia is a frequent cause of acute respiratory failure and can result from a large group of etiological agents such as: viral, bacterial and fungal infections, autoimmune diseases, exposure to dust, drugs (aspirin, amiodarone, NSAIDs, ACEI, antidepressants, chemotherapy) and vaccines. In particular, drug-induced pneumonia or vaccine-induced pneumonia in our case is a diagnosis of exclusion and guided by short time between the inoculation of the vaccine/administration of the drug and the onset of symptoms. Similarly to the series collected by Park et all (2022), the onset was rapid, a few days after inoculation of the second dose of the vaccine, the severity of respiratory failure is variable and with it the resolution of the clinical-radiographic picture after immediate initiation of respiratory and pharmacological support therapy by administering high-dose intravenous corticosteroids. In fact, in our patients, the early steroid treatment allowed a rapid resolution of the interstitial pneumonia due to the Covid-19 Pfizer/BioNTech Comirnaty vaccine, reducing the rate of hospitalization,mortality and morbidity.

## 28. COVID-19 DISEASE-TRIGGERED AUTOIMMUNITY. A CASE REPORT

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**Background:** Evans syndrome is an autoimmune disorder characterized by two or more forms of cytopenia, most frequently involving autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia. Several studies demonstrated that COVID-19 disease, characterized by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-Cov2), can trigger an inappropriate immune response and stimulates an autoantibodies production in genetically predisposed patients.
**Case report:** A 74-year-old man, vaccinated for Sars-Cov2, was admitted to our Hospital because of COVID-19 pneumonia. His past medical history included type 2 diabetes, dyslipidemia, permanent atrial fibrillation and

mechanical aortic valve replacement on chronic treatment with warfarin. Moreover, the patient reported a history of iron-deficiencient anemia and mild chronic thrombocytopenia. At the time of Hospital admission, the patient was awake and well oriented. The respiratory rate was 16 breaths/min and the oxygen saturation was 98% during oxygen supplementation by 28% Venturi mask. On examination, minimal jaundice was present on skin and sclera. The abdomen was soft and nontender, with mild hepatomegaly. The urine was hyperchromic. At routine admission laboratory tests an intravascular hemolytic anemia was detected (Hb 7 g/dL, Reticulocytes 3.34%, Total Bilirubin 3.88 mg/dL, Indirect Bilirubin 2.89 mg/dL, ALT 25 U/L, LDH 635U/L, haptoglobin <7.8 mg/dL) and low platelet count (PLT 36,000 μL) with normal coagulation tests. In order to exclude a microangiopathic hemolytic anemia, a peripheral blood smear was performed; that excluded the presence of schistocytes or other forms of cellular abnormalities. The direct and indirect Coombs tests resulted positive for IgG class pan-reactive autoantibodies, thus confirming the autoimmune nature of the hemolytic anemia. Considering the simultaneous presence of thrombocytopenia, the diagnosis of Evans syndrome came first. Prednisolone 1 mg/Kg/body weight/day was started as initial first-line therapy. Moreover, bearing in mind the bad prognosis of Evans syndrome, intravenous immunoglobulin for five days was added. In order to exclude secondary causes of Evans syndrome, autoimmunity tests were performed, which identified positivity for ANA (1: 160, granular pattern) and negativity for ENA. In addition, lymphocyte typing showed severe reduction of circulating T-lymphocytes CD3+, together with both CD4+ and CD8+ subsets decrease, as well as reduction of absolute value of peripheral B-lymphocytes (CD19+). A thoracic and abdominal CT scan excluded solid tumors but showed the presence of several millimetric splenic hypodense lesions of uncertain meaning. In order to better characterize the before mentioned splenic lesions, it was considered to deepen the diagnostics by performing PET. Unfortunately, in the following days, the hemolytic anemia and thrombocytopenia further worsened despite the initial therapy (PLT 17,000 μL, Hb 6.8 g/dL, Total Bilirubin 2.24 mg/dL, Indirect Bilirubin 1.68 mg/dL, AST 17 U/L, LDH 419 U/L, Haptoglobin <7.2 mg/dL). An immunosuppressive approach with rituximab or cyclophosphamide was considered but, taking into account positivity for Sars-Cov2, albeit asymptomatic for respiratory disease, we decided to delay the beginning of immunosuppression after recovery from SARS-Cov2 infection. During the hospitalization, the patient was given blood transfusions and steroid therapy. Despite the therapy, one month after Sars-Cov2 positivity the anemia was unmodified and transfusions resulted contraindicated because of no blood compatibility. Finally, the patient suddenly died, leaving the diagnostic process incomplete.

**Conclusions:** Evans syndrome is associated with a worse prognosis than that of primary warm AIHA. It is mandatory to identify secondary causes of Evans syndrome, in order to treat the triggering cause and consequently restore the hematologic disorder. SARS-Cov2 infection, while triggering autoimmunity, is also a potentially lethal condition, due to pneumonia and respiratory failure. Therefore, it may be difficult to balance the need for immunosuppression against the risk of worsening infection. Literature is still poor of evidence regarding the clinical management of inflammatory processes associated with COVID-19 disease. A better characterization of immune response following SARS-Cov2 infection is still an unmet need, that would help focusing on the link between COVID-19 and autoimmunity, so favoring the development of clinical guidelines.

## 29. RISK FACTORS FOR SPONTANEOUS MUSCLE HEMATOMA IN PATIENTS WITH SEVERE COVID-19

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**Background:** The clinical features of Coronavirus disease 19 (COVID-19) are highly variable and systemic, covering a large spectrum of illness from asymptomatic infection to a severe form with respiratory failure and coagulation abnormalities, with both hypercoagulability and spontaneous hemorrhages. Spontaneous muscle hematoma (SMH) is a rare and life-threatening complication of severe COVID-19. This retrospective study aims to evaluate risk factors for SMH in COVID-19 patients admitted to the Department of Intensive Care Unit (ICU).

**Methods:** Medical records of all patients with COVID-19 referring from March 11th, 2020 to July 31th, 2021 to the Department of ICU of Federico II University of Naples, Italy, were analyzed. Clinical and laboratory characteristics were compared between COVID-19 patients with SMH and without SMH.

**Results:** From 11th March, 2020 to 31th July, 2021 99 patients (61 males, 61.6%; mean age 66.80 ± 14.04 years) were referred to ICU because of COVID-19. Of them, 6 patients (6.1%; 3 males, 50.0%; mean age 65.84 ± 3.37 years) developed SMH during the hospitalization (14.5 ± 9.2 days, mean, after the admission). Increased risk for SMH during the infection was observed in patients with type 2 diabetes mellitus [OR 14.38 (1.60 – 129.31), $p < 0.01$] and peripheral artery disease [OR 14.37 (1.60 – 129.31), $p < 0.01$]. Among laboratory parameters evaluated at admission in ICU, SMH patients showed significantly higher values of Interleukin-6, procalcitonin and creatine kinase. The OR for the occurrence of SMH in patients with more than 3 risk factors was 8.33 (95% C.I. 1.14 – 49.01; $p < 0.04$).

**Conclusion:** The study identified parameters associated with the risk of SMH. These parameters are also known to predict a poor outcome in COVID-19 patients, and so commonly evaluated at the admission in ICU. The presence of more than 3 of these risk factors identifies COVID-19 patients at higher risk of SMH.

## 30. ACUTE KIDNEY INJURY IS ASSOCIATED WITH INCREASED IN-HOSPITAL MORTALITY AND WITH IMPAIRMENT OF KIDNEY, LUNG AND MOTOR FUNCTION 1 YEAR AFTER DISCHARGE FOR COVID-19

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**Background:** AKI is the most frequent complication after respiratory failure in COVID-19. AKI increases mortality risk, length of hospital stay and healthcare costs with possibile progression toward CKD.

**Study Aims:** 1) evaluation of AKI incidence in 1020 COVID-19 hospitalized patients; 2) comparison of AKI incidence in COVID-19 vs. pre-pandemic period; 3) establishment of out-patient follow-up for monitoring kidney, lung, motor and immune function; 4) creation of a biobank for biomarker discovery studies.

**Methods:** AKI incidence was calculated matching laboratory and administrative data of 26214 hospitalized patients in 2018-2019 and in 1020 COVID-19 patients in 2020-2021: KDIGO algorithms were applied for AKI grading. After 12 months from discharge, 232 COVID AKI patients and relative controls matched for age and gender were evaluated for kidney (eGFR, biomarkers of tubular damage NGAL, CCl-14, DKK-3), lung (DLCO, CT scan) and neuro-motor (SPPB, 2-min walking test, post-traumatic stress test-IES) function.

**Results:** Before pandemic, in-hospital AKI incidence was 18% (10% KDIGO 1, 5% KDIGO 2, 3% KDIGO 3): median age of AKI patients was 69. In-hospital mortality was 3.5 % in non-AKI group vs. 15% in AKI group in accordance with KDIGO stages. In COVID patients, AKI incidence increased to 37% (20% KDIGO 1,11% KDIGO 2, 6% KDIGO 3): median age of patients was 54. In-hospital mortality was 31 % in the AKI group. After 12 months from hospital discharge, COVID AKI patients showed a persistent reduction of respiratory function (severe DLCO impairment <60%) related to the extent of CT scan abnormalities. AKI patients also presented motor function impairment and a worse post-traumatic stress response. GFR reduction was 1.8 ml/min in non AKI vs. 9.7 ml/min in AKI COVID patients not related to age. Urinary DKK-3 and CCL-14 were also higher in the AKI group.

**Conclusion:** AKI incidence was significantly increased during COVID-19 in respect to pre-pandemic period with an association with higher mortality in class 2-3 KDIGO. In the post-COVID follow-up, AKI was associated with lung and neuro-motor function impairment and a sudden GFR decline concomitant to the persistence of tubular injury biomarkers. These results suggest the importance of a nephrological and multidisciplinary follow-up of frail patients who developed AKI during hospitalization for COVID-19

## 31. ANXIETY, STRESS AND DEPRESSION IN COVID-19 SURVIVORS FROM AN ITALIAN COHORT OF HOSPITALIZED PATIENTS: RESULTS FROM A 1-YEAR FOLLOW-UP.

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**Background:** Mental health-related symptoms can persist over time beyond the most common respiratory clinical features of COVID-19, A recent meta-analysis underlined that mental health sequalae may be relevant for COVID-19 survivors, and reported the following prevalence rates: 20% for Post-Traumatic Stress Disorder, 22% for anxiety, 36% for psychological distress and 21% for depression. In the context of a multi-disciplinary follow-up project, we already investigated the mid-term (4 months) psychiatric outcomes in a sample of COVID-19 survivors. Patients were re-assessed after 1-year since hospital discharge.
**Methods:** Follow-up conducted after 1 year involved 196 individuals recovered from COVID-19. Patients were assessed with a multi-disciplinary approach; including both a clinical interview performed by an experienced psychiatrist, trained in the use of the Mini-International Neuropsychiatric Interview to assess the presence of anxiety, stress and depressive symptoms and the following self-administered questionnaires: Beck Anxiety Inventory, Beck Depression Inventory-II, Resilience Scale for Adults, Impact of Event Scale, COVID-19 Peritraumatic Distress Index.
**Results:** Anxiety (p<0.0001) and depressive (p<0.0003) symptoms registered at the clinical interview showed a significant improvement from the 4-months to the 12-months follow-up. Logistic regression model showed that female gender (p=0.006), arterial hypertension (p=0.01), obesity (0.04), anxiety (p<0.0001) and depressive (p=0.02) symptoms at 4-months follow-up were associated with persistence of anxiety symptoms at 12 months. At logistic regression analysis female gender (p=0.02) and depressive symptoms at 4-months follow-up (p=0.01) were associated with depressive symptoms after 12 months.
**Conclusions:** Severity of the disease in the acute phase, in our study, was not a determining factor in identifying subjects at risk of developing clinically relevant anxiety and depression as a consequence of COVID-19 disease. Findings from the logistic regressions suggest that the factors most affecting depression and anxiety in COVID survivors after 12 months were female gender, the presence of anxiety and depression after 4 months and some physical symptoms, not necessarily COVID-related. Impact of infection and consequent hospitalization for COVID-19 did no longer represent a relevant issue for depressive symptoms, compared to other general factors.

## 32. DOES USE OF NON-INVASIVE VENTILATION IMPACT ON PULMONARY LONG-TERM OUTCOME OF SARS-COV-2 RELATED PNEUMONIA REQUIRING HIGH-OXYGEN FLOW?

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**Introduction and Background:** Coronavirus disease represents a challenging condition not only for its heavy burden of lives taken during acute phase (25% during the first pandemic outbreak and of 10.9% during the second/third outbreak in our ward), but even for its only partially understood sequelae in time, which can heavily impact on life quality and duration of patients.
In a previous study we assessed short-term consequences of SARS-Co-V-2-related pneumonia, also in relation to radiologic/laboratory/clinical indices of risk at baseline (1) and found that more than 25% of patients showed radiological abnormalities and/or an altered diffusing capacity of the lung for carbon monoxide (DLCO) at spirometry.
In an ongoing study, we focused on patients with COVID-19 pneumonia that required high-flow oxygen supplementation and found that more than 75% of them had persistent radiological abnormalities and/or an altered DLCO at spirometry even after more than one year follow-up. At least 20% of them showed some degree of pulmonary fibrosis.
During the 2020 and 2021 outbreak of SARS-CoV-2 pandemic there was a shortage of hospital bed in intensive care unit, so non-invasive ventilation (NIV) was widely used continuously for several days (and sometimes weeks). This prolonged use of NIV raised the concern that a positive-pressure ventilation could lead to pulmonary damage and long-term health-care related sequelae.
**Patients and Methods:** We tried to address this topic by comparing two groups of patients, one treated with high-flow oxygen (at least 40% of inspired fraction of oxygen) and the other with NIV with at least 8 cmH2O positive pression and for a mean period of 5 days.
The NIV group and the Venturi mask (VM) group were respectively of 20 and 24 patients.
Patients were invited to a follow-up program at a mean of 382 ± 47 days (all patients) including a quality of life phone interview, standard laboratory testing, lung function tests with DLCO, computed tomography (CT) scan of the chest and a final clinical assessment. A quality-of-life questionnaire was administered to each willing patient.
**Results:** There were no significant differences in age, sex and comorbidities (heart disease, hypertension, diabetes mellitus, COPD, CKD, neoplasm) nor in ongoing home therapy (ACE-I; ATII-antagonist; statins, anti-platelet or anti-coagulant drugs, immuno-modulating drugs, steroids).
Vital parameters as well as radiologic and biochemical data did not show any significant differences; administered treatment during hospital staying was not different as well.
After statistical analysis, we did not find any significant differences between patients treated with NIV or VM in terms of number or characteristic of radiological alterations, persistence of dyspnoea, reduction in CO lung diffusion at spirometry or biochemical data (see table).
**Conclusions:** Although with the limitations due to retrospective nature of the study and the small number of the sample, patients undergoing NIV (who are expected to have a more severe disease) did not show a worse outcome in terms of pulmonary disease compared to patients treated with VM alone.
Further and wider studies are needed, but preliminary data seem to support safety and efficacy of prolonged NIV treatment in COVID-19 pneumonia (even in the long-term outcome)

| | VM | NIV | Significance |
|---|---|---|---|
| Age | 65±9 | 61±14 | NS |
| M/F (%) | 6/14 | 8/15 | NS |
| Days of follow-up | 392±52 | 368±42 | NS |
| Comorbidities | 2.0±0.2 | 2.1±0.3 | NS |
| N° of medications | 1.2±0.1 | 1.3±0.1 | NS |

| | VM | NIV | Significance |
|---|---|---|---|
| Radiological alterations (%) | 57 | 58 | NS |
| FEV1/FVC % | 79±5 | 78±6 | NS |
| DLCO % (of predicted) | 87±13 | 83±15 | NS |
| DLCO/VA | 4.20±0.79 | 4.28±0.65 | NS |
| Dispnoea (%) | 58 | 62 | NS |

| | VM | NIV | Significance |
|---|---|---|---|
| WBC (10^3/µl) | 7.5±2.4 | 7.4±2.3 | NS |
| Neutrophils (10^3/µl) | 4.1±1.9 | 3,8±1.3 | NS |
| Lymphocytes (10^3/µl) | 2.5±0.9 | 2.7±1.1 | NS |
| Monocytes (10^3/µl) | 0.7±0.3 | 1.1±2.1 | NS |
| Hb (g/dl) | 14.4±1.2 | 14.6±1.5 | NS |
| Platelets (10^3/µl) | 289±85 | 247±50 | NS |
| PCR (mg/L) | 5.3±7.3 | 1.8±1.6 | NS |
| AST (U/L) | 26±11 | 24±7 | NS |
| ALT (U/L) | 34±16 | 27±11 | NS |
| Ferritin (µg/L) | 306±315 | 210±307 | NS |
| Creatinine (mg/dl) | 1.0±0.3 | 1.0±0.2 | NS |

## 33. FOLLOW-UP OF OLDER AND YOUNGER PATIENTS AFTER SARS-COV-2 RELATED PNEUMONIA: WHAT DIFFERENCES IN SEQUELAE?

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**Background:** Coronavirus disease 2019 (COVID-19) pandemic represents a major clinical problem in term of deaths; moreover, there is evidence of significant clinical sequelae of the disease that may impair both life length and quality.
In a previous retrospective study conducted in our ward, we have found that elder people payed a significantly heavier toll in term of deaths compared to younger patients (33% older that 65 years vs 25% of younger died during

first wave and 15% vs 10.5% during the second/third wave in our ward).
It is widely accepted that patients affected by moderate to severe COVID-19 often show long term sequelae ranging from pulmonary fibrosis to dementia, dermatologic and immunologic alterations. Psychological burden is heavy as well (e.g. anxiety, insomnia, chronic fatigue).
**Patients and Methods:** In this study we compared consequences over time in younger and older patients, using the traditional cut-off of 65 years of age. A group of 84 patients (48 younger and 36 older than 65 years), underwent a clinical assessment with standard laboratory testing, chest CT scan, lung function tests with diffusing capacity of the lungs for carbon monoxide (DLCO), and evaluation of vital parameters after a mean time from hospital discharge of 267 days.
A quality-of-life questionnaire was administered to each willing patient, evaluating persistence of fever of unspecified origin, fatigue, effort dyspnoea, anorexia, insomnia, anxiety, dysgeusia or anosmia. Patients with an established diagnosis of dementia were excluded from the study.
**RESULTS:** See table for more detailed results. Standard laboratory testing showed a normalization of all measured indexes (circulating white blood cells, granulocytes, monocytes, lymphocytes, and hemoglobin, c-reactive protein (CRP), ferritin, plasma creatinine and electrolytes, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma glutamyl transferase (γGT)) in both groups.
Persistence of non-specific radiological alterations (i.e. ground-glass opacities, irregular linear/reticular opacities) was more pronounced in elder group (69% vs 35%), while DLCO reduction was present in both groups in a similar feature (45% vs 42%). Effort dyspnoea persisted at follow-up visit in 47% of adults and 56% of elder patients, but difference did not reach statistical significance (p=0.12). There was no significant difference in mean Tiffenau index (FEV1/FVC) nor in other spirometry parameters.
Interestingly, 18% of elder patients and 15% of younger showed concomitant presence of non-specific radiological alterations, persistence of dyspnoea and DLCO reduction OR CT scan alterations typical of pulmonary fibrosis. The difference between groups, anyway, did not reach statistical significance (p=0.71).
The quality of life questionnaire showed a significant difference between groups in persisting fatigue (69% elder VS % 44 adult patients; p=0.02) and anxiety (46% elder VS 19 % adult patients; p=0.02).
**Conclusions:** Our preliminary data show a substantial normalization of laboratory data and don't detect a significant difference in global spirometry parameters as well as in CO diffusion. While a higher amount of nonspecific radiological alterations is present in older patients, diagnosis of pulmonary fibrosis is similar in both groups. Overall, nine months after discharge, organic alterations between groups seem to be similar.
On the other side, it is confirmed that psychological burden is present and persistent for a long time-span and it is much heavier in elder people. This fact should be taken in consideration when approaching these patients, for instance by providing a Geriatric counselling at the time of discharge from the hospital. Patients should be instructed as well to seek help in case of persistence of psychological discomfort.

**Main demographic data**

| | Adult | Elder | Significance |
|---|---|---|---|
| Age | 55±8 | 74±6 | < 0.001 |
| M/F (%) | 31/17 | 22/14 | NS |
| Days of follow-up | 272±128 | 240±143 | NS |
| Hearth disease | 17% | 36% | 0.05 |
| Hypertension | 40% | 69% | 0.006 |
| Type 2 diabetes | 19% | 25% | NS |
| COPD/Athsma | 3% | 4% | NS |

**Quality of life questionnaire**

| | Adults | Elder | Significance |
|---|---|---|---|
| Persisting Fever | 0% | 0% | NS |
| Effort dyspnea | 40% | 57% | NS |
| Fatigue | 44% | 69% | 0,02 |
| Anorexia | 21% | 11% | NS |
| Insomnia | 21% | 26% | NS |
| Anxiety | 19% | 46% | 0,01 |
| Dysgeusia or anosmia | 21% | 26% | NS |

**Spirometry, radiological alterations,**

| | Adult | Elder | Significance |
|---|---|---|---|
| Radiological alterations (%) | 35 | 69 | 0,002 |
| FEV1/FVC % | 79±9 | 80±4 | NS |
| DLCO alteration | 42% | 45% | NS |
| DLCO % (of predicted) | 79±9 | 89±18 | NS |

**Laboratory data**

| | Adult | Elder | Significance |
|---|---|---|---|
| WBC (10^3/µl) | 7.1±2.0 | 7.1±2.4 | NS |
| Neutrophils (10^3/µl) | 3.8±1.4 | 3,8±1.7 | NS |
| Lymphocytes (10^3/µl) | 2.5±0.8 | 2.4±1.5 | NS |
| Monocytes (10^3/µl) | 0.8±1.3 | 0.6±0.3 | NS |
| Hb (g/dl) | 14.34±1.2 | 13.9±1.5 | NS |
| Platelets (10^3/µl) | 239±66 | 229±62 | NS |
| PCR (mg/L) | 2.9±4.4 | 3.0±4.9 | NS |
| AST (U/L) | 24±8 | 25±7 | NS |
| ALT (U/L) | 28±13 | 25±13 | NS |
| Ferritin (µg/L) | 208±241 | 187±213 | NS |
| Creatinine (mg/dl) | 1.0±0.3 | 1.0±0.2 | NS |

## 34. ANALYSIS OF PROGNOSTIC FACTORS IN COVID-19 HOSPITALIZED PATIENTS: AN ITALIAN SINGLE-CENTER PROSPECTIVE STUDY

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**Introduction:** COVID-19 clinical presentation ranges from asymptomatic infection to an inflammatory cytokine storm with multi-organ failure and fatal outcomes. The identification of high-risk patients for severe disease is crucial in order to plan an early treatment and intensive follow-up.
**Aim:** we aimed at investigating negative prognostic factors in a group of patients hospitalized for COVID-19.
**Methods:** 181 patients (83 men and 98 women, age 69.50±15.75 years) were enrolled. Each patient received a work-up including medical history, clinical examination, arterial blood gas analysis, laboratory blood tests, feasible ventilatory support required during hospital stay, intensive care setting required, duration of illness and length of hospital stay (>or<25 days). For the assessment of the severity of COVID-19, four main indicators were considered: 1) the intensive care unit (ICU) admission 2)the hospitalization lenght >25 days; 3)the need of non-invasive ventilation (NIV); 4) death.
**Results:** The independent risk factor associated with the ICU admission were: male gender (p=0.02), gamma glutamyl transpeptidase elevation (p=0.014), C reactive protein elevation (p=0.09) at hospital admission and direct oral anticoagulant home therapy (p=0.048); for hospital length >25 days: early corticosteroid therapy (p=0.026) d-dimer elevation at hospital admission (p=0.009), the presence of at least three comorbidities (p=0.038); for NIV treatment: ferritin and C reactive protein elevation at hospital admission (p=0.006 and p=0.008 respectively), body overweight (p<0.01) and early corticosteroid therapy (0.018); for in-hospital death: body overweight (p=0.012), age (p=0.047), antiplatelet therapy (p=0.03), creatinine values elevation (p=0.025).
**Conclusion:** the presence of the above factors may be useful to identify patients at high risk of developing a severe COVID-19 that need an early treatment and intensive follow-up.

## 35. CLINICAL PREDICTION MODELS IN HOSPITALIZED PATIENTS WITH COVID-19: A RETROSPECTIVE COHORT STUDY

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**Background:** Clinical spectrum of novel coronavirus disease (COVID-19) ranges from asymptomatic infection to severe respiratory failure. We aimed at validating clinical models to predict prognosis in hospitalized patients with COVID-19.
**Methods:** Consecutive patients with acute confirmed COVID-19 pneumonia hospitalized at 5 Italian non- intensive care unit [ICU] centers during the 2020 outbreak were included. Validated prognostic scores for pneumonia and/or sepsis and specific COVID-19 scores were calculated for each patient and their accuracy compared in predicting in-hospital death and the composite of death and orotracheal intubation.
**Results:** During hospital stay, 302 of 1044 included patients presented critical illness (28.9%), and 226 died (21.6%). Nine out of 34 items included in different prognostic scores were identified as predictors. The discrimination was acceptable for the majority of scores and was poor for the remainder. A high negative predictive value was observed for REMS (100.0%) and 4C (98.7%) scores; the positive predictive value was poor overall, ROX-index

having the best value (75.0%).
**Conclusions:** Despite the growing interest in prognostic models, their performance in patients with COVID-19 is modest. The 4C, REMS and ROX-index may have a role to select high and low risk patients at admission. However, simple predictors as age and PaO2/FiO2 ratio can also be useful to inform decision making.

## 36. FIRST CASE OF KIKUCHI-FUJIMOTO DISEASE ASSOCIATED WITH HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AFTER THE BNT162B2 MRNA COVID-19 VACCINATION

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Kikuchi-Fujimoto disease (KD) is a self-limiting histiocytic necrotizing lymphadenitis. KD pathogenesis is unknown, although it is believed to be a consequence of an aberrant immune response of T cells and histiocytes to an immunogenic antigen, following infections, hematological malignancies, autoimmune diseases, hematopoietic stem cells or organ transplantation. Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening hyperinflammatory state, brought on by uncontrolled histiocytes, macrophages and T-cell activation, which have also been occasionally observed after BNT162b2 vaccination. KD and HLH present overlapping pathogenesis and symptoms, and their association has been previously described in children and adult patients. A case of KD following administration of the BNT162b2 mRNA COVID-19 vaccine was recently reported. Here, we report the first case of KD associated with HLH following the BNT162b2 mRNA COVID-19 vaccination.
A 38-year-old previously healthy woman was admitted to the hospital with a history of a fever of 40° C for more than 10 days, associated with chills and fatigue. She presented with a diffuse cutaneous eruption of erythematous papules, that were subsequently confluent. She was previously treated with antibiotics (amoxicillin and clavulanic acid, followed by teicoplanin and doxycycline), with no improvement. The first dose of the vaccine was administered two months after giving birth to a healthy baby. Three weeks before the onset of fever, the patient received a second dose of the BNT162b2 mRNA COVID-19 vaccine, inoculated in the same left arm as the first dose. At hospital admission, her nasopharyngeal swab for SARS CoV-2 PCR was negative; SARS CoV-2 IgG antibodies were positive (>2.080 BAU/mL; cut-off: 33.8 BAU/mL; LIAISON SARS-CoV-2 TrimericS IgG, Diasorin, Saluggia, Italy). Her physical exam was normal except for the cutaneous rash and multiple enlarged tender lymph nodes in the left axillary zone, confirmed by a contrast-enhanced computed tomography (CT) exam.Laboratory tests showed bi-cytopenia with leukopenia and anemia (neutrophil count, 0.9 x 10 9 /L; lymphocyte count, 0.3 x 10 9 /L, hemoglobin, 9.8 g/L), increased lactate dehydrogenase and transaminase levels, high serum ferritin levels (500 µg/L), mild hypertriglyceridemia (225 mg/dL) and normal fibrinogen. Her serum soluble interleukin-2 receptor (IL-2R) level was increased to 2.610 U/mL (normal value 223-710) and her natural killer (NK) cell count was low (<35 cells/µL, normal value 200-400). IL-6, IL-8 and IL-10 levels were normal, but the tumor necrosis factor(TNF) level was increased. Further analysis did not show ongoing infections of HCV, HBV hepatitis virus, HIV, Toxoplasma, Rubeovirus, Brucella, Leptospirosis, Bartonella, Chlamydia, Morbillivirus, Mycoplasma or Yersinia. The tuberculosis Quantiferon test was also negative. Epstein Barr virus (EBV), Parvovirus B19, Cytomegalovirus, JC virus and Herpes-6 DNA were also absent.Antinuclear antibodies (ANA), antibodies to double-stranded DNA (anti-dsDNA), and antibodies to extractable nuclear antigens (anti-ENA) were absent, and rheumatoid factor test was negative. Both complement C3 and C4 serum levels were normal. The patient underwent a bone marrow aspiration and trephine procedure and an excisional lymph node biopsy of the left axillary was additionally performed.
A diagnosis of HLH was confirmed based on the fulfilment of six out of eight criteria HLH-2004 diagnostic criteria. The bone marrow aspiration showed hemophagocytis. Histopathological examination of the lymph node revealed histiocytic necrotizing lymphadenitis, characterized by paracortical, well-circumscribed necrotic areas with karyorrhexis and fibrin deposits. Immunohistochemistry revealed numerous CD68-positive histiocytes as well as several CD3-positive T cells and few CD20-positive B cells. All these features are considered typical of KD.
The patient was promptly initiated on steroids (methylprednisolone 1 mg/kg i.v.), according to the recommended treatment for HLH. Sudden fever lysis was observed and clinical conditions improved. Methyl-prednisone was substituted with prednisone (1 mg/day) at hospital discharge 1 week later. This schedule was maintained for a further 2 weeks, changed to half dosage for 3 more weeks, then tapered in the following 3 weeks. IL-2R levels decreased to 1.170 U/mL and 740 U/mLafter 2 and 3 weeks of steroid treatment, respectively, and reached normal levels (460 U/mL) after 4 weeks. NK cells also returned to normal levels. The patient is doing well and follow-up is still ongoing.
In conclusion, we described the first case of KD associated with HLH following COVID-19 vaccination. This is a rare event and does not compromise the safety and efficacy of the BNT162b2 mRNA vaccine in the fight against COVID-19. Physicians should be aware of rare systemic inflammatory reactions that require an early diagnosis and treatment.

## 37. IMPACT OF POST-COVID-19 OUTPATIENT CLINIC ON PATIENTS' QUALITY OF LIFE AND POST-HOSPITALIZATION MORTALITY

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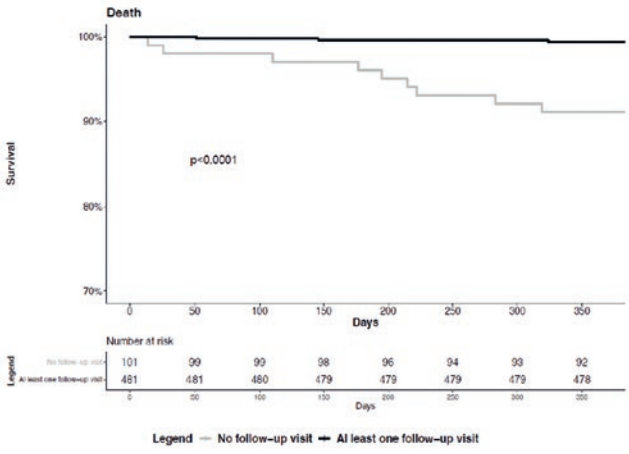
**Background:** Coronavirus Disease 2019 (COVID-19) may leave behind clinical manifestations beyond recovery from acute disease as part of the so-called "long-COVID syndrome". Long-COVID deeply impacts patients' quality of life (QoL). Several healthcare centres developed outpatient services for the management of COVID-19 survivors with persisting symptoms. However, whether post-discharge monitoring influences patients' perspective of general status and post-discharge mortality remains to be determined.
**Objective:**The aim of the present study was to investigate the utility of post-COVID-19 outpatient management in terms of QoL and mortality at 1 year post-discharge.
**Methods:** All patients who were proposed post-COVID follow-up at the outpatient clinic of San Raffaele University Hospital from April, 2020, to September, 2020 were enrolled. All patients, including both those who performed at least one post-COVID visit and those who refused follow-up, received a phone call by a physician of the outpatient clinic 1 year after discharge and were interrogated about their QoL. Post-discharge mortality was assessed by searching the patient within National Healthcare System records. Follow-up visits were programmed at 4 weeks, 3 months and 6 months after discharge. Data were collected during the visits and during the phone. QoL was quantified through the EuroQol-5 Dimensions-5 Levels (EQ-5D-5L) questionnaire, which queries health status in the subdomains of mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each item may range from 1 to 5, with 1 representing no problems and 5 extreme problems. Multivariate logistic regression analyses were performed to investigate the impact of follow-up on mortality risk after correction for age, comorbidities, sex and length of hospital stay.




**Results:** From April, 2020, to September, 2020, 603 patients were discharged alive from San Raffaele University Hospital. All of them were proposed post-COVID follow-up clinic. Of these, 483 (80.1%) performed at least 1 follow-up visit (visit cohort), while 120 (19.9%) did not due to several reasons (non-visit cohort). All 603 patients were phone called at 1 year after

discharge. Of these, 414 (69%) answered, while 189 (31%) did not. Among the 414 responders, 367 (89%) performed at least one visit, while 47 (11%) did not. The visit cohort was younger and had a shorter length of stay (both p<0.05). Moreover, they were more frequently admitted to the intensive care unit and had a lower cumulative number of comorbidities (both p<0.05). Total EQ-5D score had a tendency to be lower in the visit group, indicating a better QoL (p 0.08). Specifically, significantly lower scores were observed in the items of personal care (p <0.05) and daily activities (p <0.01). Investigation about the impact of the follow-up clinic on mortality showed that the rate of mortality after hospitalization was significantly lower in patients who participated at follow-up visits (0.8%) compared with those who refused follow-up (8.9%, p<0.0001), excluding patients who died immediately after discharge or prior to the programmed follow-up visit date and those affected by critical illnesses or bed-ridden. Multivariate logistic regression analyses revealed that post-discharge follow-up was a significant protective factor for mortality independent of age, sex, number of comorbidities and length of hospital stay.
**Conclusions:** In our cohort, outpatient follow-up of COVID-19 survivors improved patients' QoL and protected from post-hospitalization mortality. Our findings suggest that monitoring of COVID-19 patients should not end with hospital discharge, especially for those with more severe acute disease.

## 38. THE EXPERIENCE OF SAN RAFFAELE UNIVERSITY HOSPITAL IN MANAGING COVID-19 IN AN OUTPATIENT SETTING

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A leading problem linked to the SARS-CoV-2 pandemic is the management of a high number of patients simultaneously accessing to Emergency Departments. A proportion of such patients presents with mild to moderate COVID-19 symptoms not warranting urgent care or hospital admission. Such cases are compatible with outpatient treatment by primary care practitioners. Nevertheless, the weakness of Italian primary care infrastructure led to the impossibility for general pratictioners to manage these patients. As a possible solution to this problem, the health policy makers of Lombardy Region together with major hospitals in Milan launched in November 2020 an integrated approach of health care delivery called mild-to-moderate COVID-19 outpatient clinic (MMCO).
MMCO is addressed to patients with COVID-19 who need a specialist evaluation, due to pre-existing risk factors or mild to moderate clinical manifestations, but do not strictly require a hospitalization.
COVID-19 patients are referred to our service by General Practitioners (GPs), Emergency Department physicians (EDs) or Hospital Specialists (HS).
We hereby report the activity of the MMCO at San Raffaele University Hospital in the November 2021-March 2022 timespan. A total of 386 patients were treated. Most of the patients (61.6%) were referred by HS, usually haematologists or oncologists; the rest were referred by GPs (24.6%) and EDs (12.4%).
The prevalent comorbidities of patients referred by HS differed from the ones referred by GPs and EDs. In the first group, active neoplasm and immunosuppression for any reason (eg organ transplant, autoimmune disease) were prevalent, while in the second one, advanced age (>65 years), obesity (Body Mass Index – BMI>30 kg/m2) and chronic obstructive pulmonary disease (COPD) were more represented.
The first visit at MMCO comprises a physical examination with vital sign assessment and measurement of anthropometric parameters. An accurate patient's history, including information about the onset, the severity and the type of symptoms of COVID-19, is collected.
Lung assessment relies on Lung UltraSound (LUS) imaging. LUS is performed at bedside and represents a sensitive method to evaluate lung parenchymal abnormalities, which are quantified using the Lung UltraSound Score (LUSS, range 0-36), a semi-quantitative score to measure the lung aeration loss, associated with mortality and severity of COVID-19.
Arterial blood gas analysis, electrocardiography at rest and blood exams are performed at the first visit and repeated, if necessary, in follow up visits.
Most patients included in the study were male (58%) and median age was 60 years, with a median BMI of 25.5 kg/m2. Approximately half of the patients (45.8%) were current or ex-smokers.
At the first visit the median peripheral blood oxygen saturation measured by pulse oximetry was 98.0%, while the one determined with arterial blood analysis was 95.7%. The median LUSS was 3.7.
At MMCO there is the possibility to administer to eligible patients specific and early therapies, including anti-SARS-CoV-2 monoclonal antibodies and antiviral therapies, like Remdesivir and Nirmatrelvir/Ritonavir, with strict monitoring by health personnel.
Remdesivir (Veklury®) is a direct-acting nucleotide pro-drug inhibitor of the SARS-CoV-2 RNA-dependent RNA-polymerase, while Nirmatrelvir/ritonavir (Paxlovid®), is an orally bioavailable SARS-CoV-2 main protease inhibitor. These therapies have been approved for patients with symptom onset within the previous 5-7 days and at risk of disease progression.
In the evaluated timespan, 95 patients were treated with Veklury at the MMCO, with a median age of 64 years. More than half of the patients were referred by HS and were eligible for the therapy due to primary or acquired immunosuppression. Other indications were obesity or cardiac disease. Most of the patients had no adverse effects, except 2 patients with nausea and 1 patient with angioedema, leading to administration interruption.
Paxlovid was administered to 26 patients at the MMCO in the evaluated timespan. Patient had a median age of 55 years, and were mostly referred by HS (80.7%). Eligibility criteria were immunosuppression, obesity or cardiac disease. There were no significant adverse events. A commonly reported complaint was that of dysgeusia following drug intake.
MMCO is an innovative healthcare pathway to optimize the management of COVID-19 patients while sparing resources for the other patients, who had been sacrificed during the first wave. MMCO fills a gap existing between the two extremes of an insufficient home care capacity offered by GPs and a hospitalization or ED admission that would be on the other hand improper. MMCO also allows to deliver appropriate early treatment.
The purpose of our work is to describe the MMCO's activity and its potential benefits as such an approach could be proposed also for patients with other chronic conditions like COPD or Heart Failure (Ambulatory Care Sensitive Conditions) that would be in specific cases amenable to outpatient treatment if promptly recognised.
(Menchi S. and Pata G. equally contributed to this work)

## 39. BAMLANIVIMAB AND ETESEVIMAB WERE EFFECTIVE TO REDUCE LUNG DAMAGE IN COVID-19 PATIENTS EVALUATED WITH LUNG ULTRASOUND: A SINGLE CENTER EXPERIENCE

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**Background:** COVID-19 induces a robust systemic inflammation. Worldwide researchers spent many efforts to find a useful and easy tool to evaluate these patients. Lung ultrasound (LUS) was identified as an important diagnostic tool since the beginning of pandemic. At the same time, many resources have been used to identify adequate treatment. Bamlanivimab and Etesevimab were the first mAbs combination used to prevent worsening of respiratory disease in the mild COVID patients.
**Aim:** We evaluated COVID-19 patients with LUS who were were treated with Bamlanivimab and Etesevimab.
**Material and Methods:** We studied 15 patients (9 M, 6 F, aged 64,50±7,26) with mild COVID disease, who did not require home oxygen treatment. Diagnosis was confirmed by molecular nose-throat swab test. All patients were not affected by pulmonary disease and were office patients. They were admitted to receive Bamlanivimab and Etesevimab as a single day infusion treatment to prevent further COVID worsening. Admission for the mAbs therapy was decided in line with the Italian Drug Agency (AIFA) rules at the time of approval. LUS was performed before the drug was given (T0) and after three months (T1). We compared LUS at T1 in outpatients who were comparable for admittance criteria to mAbs treatment but did not experience it, and came to our COVID-office for a follow-up visit after recovery. The same operator performed all LUS.
**Results:** All patients became SARS-CoV-2 negative within a month of treatment but patients who experienced mAbs presented an earlier recovery (mAbs 13.85±7.91 vs no mAbs 21.65 ± 7.08 days, p<0.05). One patient was hospitalized after treatment for arrhythmia and heart failure. LUS at T0 was 8,23±6,46. At T1 we found a significant decrease in LUS in the mAbs group (4.75 ± 4.48, p<0.05). We found also a significant decrease in LUS of mAbs patients compared to those who did not experience this treatment (mAbs

4.75 ± 4.48 vs no mAbs 7.11 ± 4.63 p<0.05).
**Discussion:** Early treatment on SARS-CoV-2 virus is effective to achieve a better recovery of disease and to reduce lung involvement after three months as evaluated with LUS. This ultrasound method results also effective for evaluation and follow-up of lung involvement in the COVID-19 patients.

## 40. NATURAL LANGUAGE PROCESSING FOR COVID-19 OUTCOMES PREDICTION IN THE EMERGENCY DEPARTMENT

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**Background:** More than two years after the pandemic outbreak, clinical deterioration of COVID-19 patients is still a challenging event to predict. Numerous machine learning (ML)-based models were developed to predict COVID-19 outcomes. Most predictors used were mainly related to imaging or laboratory data, and only a few integrated unstructured data from electronic medical records (EMRs). In this setting, natural language processing (NLP) is a useful technique, enabling the analysis of medical charts written by clinicians. NLP has already been used during the pandemic for detection and diagnosis and patient features extraction. We hypothesized that integrating structured and unstructured data in a prediction model may yield valuable prognostic predictions regarding mortality and ICU admission in patients with COVID-19.
**Aim:** To develop artificial neural networks (ANNs) capable of using information from medical records, laboratory data, and radiological reports from the emergency department (ED) to predict COVID-19 patients' 30-day mortality and ICU admission.
**Methods:** We considered the EMRs of 15599 patients evaluated at the ED of Humanitas Research Hospital (HRH) and San Raffaele Hospital (SRH), in the Milan area, between February 20 and May 5, 2020. Data collected from each center was processed by two separate groups of algorithms and merged into a single dataset. Each group of algorithms performed data anonymization, preparation, and preprocessing. Once the datasets were merged, patients without covid-19 were selected to train, validate and test the language model. Patients with covid-19 were used to train and evaluate a tabular model, whose input data consisted of selected numeric predictors (i.e., age, creatinine, C-reactive protein, hemoglobin, and platelets), and a text-tabular model, whose input data was both numeric and text predictors (i.e., patient history, physical exam, and radiology reports). The predictive performance of each model was assessed by evaluating both discrimination (i.e., area under the curve [AUC], Matthew's correlation coefficient [MCC]) and calibration (expected calibration error [ECE]). The MCC computed for each model on test sets was compared using a paired t-test.
**Results:** We included 1296 patients with COVID-19 to train, validate and test the ANNs. Of these, 252 died within 30 days, and 158 were transferred to the ICU. The performances of the tabular and text-tabular models in the test set are summarized in the table below.

| Model | Specificity | Recall | Precision | NPV | F1-score | MCC | AUC |
|---|---|---|---|---|---|---|---|
| **30-day Mortality** | | | | | | | |
| Tabular | 0.75 ± 0.06 | 0.77 ± 0.09 | 0.43 ± 0.04 | 0.93 ± 0.02 | 0.55 ± 0.03 | 0.43 ± 0.04 | 0.84 ± 0.02 |
| Text-tabular | 0.78 ± 0.07 | 0.74 ± 0.08 | 0.46 ± 0.06 | 0.93 ± 0.02 | 0.56 ± 0.04 | 0.44 ± 0.04 | 0.84 ± 0.02 |
| **ICU admission** | | | | | | | |
| Tabular | 0.71 ± 0.06 | 0.70 ± 0.11 | 0.25 ± 0.03 | 0.95 ± 0.01 | 0.37 ± 0.04 | 0.29 ± 0.05 | 0.79 ± 0.04 |
| Text-tabular | 0.72 ± 0.08 | 0.67 ± 0.11 | 0.25 ± 0.03 | 0.94 ± 0.01 | 0.36 ± 0.03 | 0.28 ± 0.05 | 0.79 ± 0.04 |

As to 30-day mortality prediction, the text-tabular MCC was slightly greater than that of the tabular model (p= 0.43), suggesting a tendency toward a more robust prediction capability. Nevertheless, the tendential advantage of the text-tabular model was not highlighted in ICU admission prediction. Performances of the text-tabular models could have been decreased by the recent discovery of the disease, thus limiting the amount of prognostic information written as natural language in EMRs. Furthermore, transferal to ICU is a far more challenging prediction due to confounding factors such as the availability of beds and mechanical ventilators. The mean ECE of the text-tabular model predicting death outcome was 0.10 ± 0.06 vs. 0.10 ± 0.07 of the simple tabular model, thus making the prediction estimates acceptably accurate.
Limitations of the present study were the computational time required to train, validate and test each model in addition to the limited number of data and the absence of an external validation cohort. Moreover, the interpretability of models is limited due to the intrinsic nature of ANNs.
**Conclusions:** Our findings suggest the possible usefulness of NLP, not only for classification but also for predictive purposes, in evaluating the outcome of patients affected by COVID-19. Further studies will be necessary to improve the predictive accuracy of the proposed model and confirm its external validity and generalizability, also in light of the epidemiological evolution of the pandemic.

## 41. CARDIOVASCULAR RISK AND OUTCOMES IN THE POST-COVID SYNDROME

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**Background and Aims**: The aim of this prospective observational study conducted on 1782 consecutive patients with previous COVID- 19 infection was to assess whether cardiovascular risk correlates with the incidence of symptoms and changes in respiratory function parameters in the post-COVID syndrome. The association between estimated cardiovascular risk and the severity of the acute disease course in the context of acute COVID-19 disease was also considered.
**Methods:** A prospective observational study was conducted using the "Post-acute COVID-19 Day Hospital Unit registry - Fondazione Policlinico Universitario Agostino Gemelli IRCCS of Rome, Italy", a prospective single-center observational registry that includes outpatients with previous COVID-19 undergoing an accurate medical evaluation in the post-acute phase of the disease through a complete clinical and multidisciplinary evaluation.
**Results:** In patients with previous COVID-19 a high cardiovascular risk is associated with an increased risk of hospitalization for COVID-19, (p <0.0001, chi-square test). A high or very high cardiovascular risk is associated with an increased prevalence of severe clinical manifestations of previous COVID-19 and ICU hospitalization (p <0.0001, chi-square test). Post-COVID dyspnea was significantly associated with cardiovascular risk (p = 0.049, chi-square test). The interaction between global cardiovascular risk and the severity of previous COVID- 19 was significantly associated in predicting both P/F and DLCO and dyspnea (p <0.0001)in the multivariate test, indicating an additional effect between previous severity of COVID-19 and cardiovascular risk in predicting these three outcomes.
**Conclusions:** Our study demonstrate a statistically significant association between cardiovascular risk, severity of the COVID-19 acute disease course, post-COVID-19 symptoms, P/F ratio and DLCO in post-COVID.

## 42. "SHABOO" – RELATED ACUTE PSYCHOSIS IN A COVID-19 PATIENT: A CLINICAL CHALLENGE

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In December 2020, a 53-year-old Philippine man was admitted to the Emergency Room (ER) of our Hospital for psychomotor agitation. He was accompanied by his wife, who was interviewed in his stead. She explained that in the two previous days he had become obsessed with the idea of having contracted Covid-19 with subsequent appearance of insomnia,

underfeeding and final onset of psychomotor disturbance with aggressive behaviour, which persuaded her to alert the Emergency Service. She reported that he had cough for two days but no fever. The patient had a history of diabetes mellitus and chronic HBV infection; he was on therapy with insulin and tenofovir. He had no personal or familiar history of psychiatric illness. She also denied any substance abuse and excluded recent trauma.
On admission patient's vital signs were normal: blood pressure 147/87 mmHg, heart rate 77 beats/minute, oxygen saturation 97% on room air, temperature 36°C. He appeared agitated, aggressive and uncollaborative, exhibiting purposeless movements of limbs. On neurological examination pupils were normal and no meningeal signs or focal abnormalities were found. The remaining examination was unremarkable.
Laboratory investigations showed elevation of serum C-reactive protein with normal blood cell count, blood glucose 260 mg/dl, creatine phosphokinase 291 U/ l. Other biochemical laboratory values were normal, as well as routine toxicological tests that resulted negative. Electrocardiogram showed normal sinus rhythm. SARS-CoV-2 nasopharyngeal swab resulted positive. Head CT scan was negative and chest X-ray revealed slight bilateral pulmonary opacities in middle and lower lobes. Lumbar puncture to rule out CNS infection was unsuccesful due to severe agitation hence empirical therapy with acyclovir was started. Additional urine samples were collected and sent to the poison control center of Pavia for further investigations. The patient was transferred to our Internal Medicine Covid-19 Unit.
During the first days of hospital stay the patient was persistently agitated, delusional and confused, requiring sedative therapy with intravenous benzodiazepines and promazine. He was re-evaluated by neurologist and underwent electroencephalogram that showed diffuse low voltage activity suspect for toxic-dysmetabolic damage. After few days of hospitalization, we received the poison control center report on urine samples, which revealed the presence of methamphetamine and amphetamine in urine, undetected by the routine toxicological screening performed in the ER. In a thorough interview, the patient's wife admitted his occasional inhalation of an ethnic drug named "shaboo", a common name for synthetic methamphetamine crystals diffused among Philippine community. Antiviral therapy was stopped.
In the first days of hospitalization patient was febrile, due to concomitant SARS-CoV2 infection. Severe behavioral impairment with delusion, aggressiveness, and persistent refusal to eat led to the need of enteral nutrition via nasogastric tube and intravenous fluid administration.
Despite improvements in laboratory examinations and resolution of fever, the drug associated delirium did not resolve. After multidisciplinary discussion with neurologist and psychiatrist we started a therapy with haloperidol, in the hypothesis of acute psychosis induced by methamphetamine intoxication.
After about a week, he developed sudden onset of catatonic state with plastic hypertonia due to combined effect of dopaminergic pathway drug-induced damage and neuroleptic antagonism. We discontinued haloperidol and continued treatment with benzodiazepine alone.
In the following three weeks we documented progressive improvement in state of consciousness, firstly with marked fluctuations, then with recovery in attention and orientation. For episodic agitation mirtazapine was added to benzodiazepine. Hospital stay was prolonged by occurrence of catheter-related urinary infection, hospital-acquired pneumonia and haemorrhagic shock from gastrointestinal bleeding.
The patient was discharged at home after 41 days of hospitalization, having regained his usual cognitive skills and behaviour.
Our case illustrates prolonged neuropsychiatric symptoms following "shaboo" consumption in the context of SARS-CoV2 infection. "Shaboo" is considered an ethnic drug, popular among Philiphine and Chinese abusers. Given its relatively low cost it has become popular among workers because of its stimulant effects. Its catabolites may not be detected in a standard toxicological examination; therefore, suspicion of drug abuse must always remain high in the presence of agitated delirium of unknown etiology. The role of concurrent SARS-CoV2 infection in our case is unclear: viral infection and methamphetamine consumption could have interacted to provoke central nervous system prolonged effects.

## 43. PRONE POSITIONING FOR PATIENTS WITH SARS-COV-2-RELATED RESPIRATORY FAILURE IN NON-INTENSIVE CARE UNIT

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**Background:** Prone positioning (PP) is an established and commonly used lung recruitment method for intubated patients with severe acute respiratory distress syndrome, with potential benefits in clinical outcome. The role of PP outside the intensive care unit (ICU) setting is debated.
We aimed at describing the use and potential benefits of PP in non-intubated patients with acute respiratory failure related to COronaVIrus Disease-19 (COVID-19)-pneumonia.
**Methods:** Consecutive adult patients with COVID-19-related respiratory failure were included in a prospective collaborative cohort and classified based on the severity of respiratory failure by the partial arterial oxygen pressure to fraction of inspired oxygen ratio (PaO2/FiO2) and on clinical severity by the quick Sequential Organ Failure Assessment (qSOFA) score. Primary study outcome was the composite of in-hospital death or ICU admission within 30 days from hospitalization.
**Results:** PP was used in 114 of 536 study patients (21.8%), more commonly in patients with lower PaO2/FiO2 or receiving non-invasive ventilation and less commonly in patients with known comorbidities. A primary study outcome event occurred in 163 patients (30.4%) and was in-hospital death in 129 (24.1%). PP was not associated with death or ICU admission (HR 1.15, CI 95% 0.78-1.72) and not with death (HR 1.03, CI 95% 0.62-1.69); PP was an independent predictor of ICU admission (HR 2.55, 95%CI 1.50-4.32). The severity of respiratory failure and non-invasive ventilation were independent predictors of death or ICU admission at 30 days. The lack of association between PP and death or ICU admission was confirmed at propensity score matching analysis.
**Conclusion:**PP is used in a not negligible proportion of non-intubated patients with COVID-19-related severe respiratory failure and is not associated with death but with ICU admission. The role of PP in this setting requires evaluation in randomized studies.

## 44. TWO-YEAR POST-COVID-19 DISABILITY IN PATIENTS TREATED WITH NON-INVASIVE VENTILATION

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-related disease (COVID-19) is a systemic disorder characterised by prominent respiratory symptoms and associated with high rates of short-term morbidity and mortality. Patients with severe COVID-19 and respiratory failure often require advanced life support including invasive mechanical ventilation. Non-invasive mechanical ventilation (NIV) possibly in combination with respiratory physiotherapy has also proved effective in ameliorating patient outcomes and compensate for the lack of available ventilators during pandemic surges. Post-COVID-19 physical and psychological sequelae have been described in patients surviving the acute phase of the infection. However, little is known about the impact of the disease on respiratory function and quality of life of patients with most severe manifestations in the long-term.
To address this issue, we screened a cohort of 108 patients hospitalised during 2020 (first pandemic wave in Italy) and treated with NIV (with or without subsequent need for intubation). We performed telephone interviews to assess respiratory functional status and quality of life through validated questionnaires (the 1-10 Borg's scale, the Euro Quality 5 Dimensions 3 Levels, the telephone version of the Mini Mental State Examination, MMSE, EQ5D) and a 0-100 numerical rating scale (NRS). Anxiety and depression symptoms were measured through the Hospital Anxiety and Depression Scales (HADS) with eight as the cutoff of significance. We also assessed the presence of post-traumatic stress disorder through the PCL5 instrument of the Diagnostic and Statistical Manual of Mental Disorders, with a score of 33 as diagnostic cutoff. Patients were overall evaluated at 2 years post discharge from the hospital for Covid-19 disease and comparisons with patients' status at six months were also performed.
One patient died after discharge due to cancer, 11 refused to be contacted after discharge, and 38 were lost to follow up. Fifty-eight patients (49 males,

nine females) responded to the questionnaire. The median (interquartile range, IQR) age of these patients was 61 (55-72) years. Additional hospitalisations (all for non-COVID-19-related causes) were reported by 12/46 (26%) patients with available data. The NRS for global health after two years from COVID-19 was 80 (70-85) points. Forty-five subjects (78%) had no dyspnoea at rest, and 20 (34%) after physical effort. However, at intraindividual comparison, pre- and post-effort Borg's scales were significantly worse at two years than at six months from discharge (p<0.001 and p=0.001 respectively). There was no correlation among Borg's scale levels after two years, demographics, anthropometrics, clinical, laboratory and radiological features at time of admission for COVID-19. Specifically there was no association with previous comorbidities. Borg's scale levels did not differ among active or former smokers. Pre- and post-effort Borg's scale levels were significantly correlated with patient general NRS (rho=-0.392; p=0.002; rho=-0.590; p<0.001, respectively), EQ5D measures of movement (rho=0.410; p=0.001; rho=0.333; p=0.010, respectively), activity (rho=0.380; p=0.003; rho=0.368; p=0.004, respectively), anxiety (rho=0.322; p=0.013; rho=0.473; p<0.001, respectively) and self-care (rho=0.412; p=0.001; rho=0.437; p<0.001, respectively) and HADS scores for depression (rho=0.338; p=0.009; rho=0.446; p<0.001, respectively). EQ5D pain scores and HADS anxiety scores selectively correlated with Borg's scale after effort (rho= 0.268; p=0.041 and rho= 0.302; p=0.021). Impaired motricity as per the EQ5D correlated with the first PaO2/FiO2 ratio after NIV start (rho=0.331; p=0.014). Four patients (7%) showed alterations in MMSE. Disability in daily activity, self-care and movement as per the EQ5D were reported by eight (14%), five (9%) and ten (17%) patients respectively. Twenty-five subjects (43%) reported EQ5D alterations in terms of pain and 16 (28%) in terms of anxiety. Consistently, 10 subjects (17%) had a HADS-anxiety≥8, while nine (16%) had HADS-depression≥8. Five patients (9%) had a PCL5 score above the diagnostic cutoff for PTSD.

These data suggest that a non-negligible fraction of patients with severe COVID-19 still has physical and mental disability after two years from hospital discharge. Although COVID-19 disease seems to predominantly affect the respiratory tract leaving shortness of breath in a substantial proportion of survivors, it may also worsen self-perceived health status and capability to perform daily activities. In addition, some patients still experience psychological distress two years after COVID-19, which may in some cases match the criteria for a post-traumatic stress disorder. Taken together, these data suggest the necessity to consider COVID-19 disease not only as an acute illness requiring hospitalization, but a chronic disorder persisting two years after the resolution of the acute phase, affecting patients both physically and mentally.

## 45. CPAP EFFECTIVENESS IN COVID-19 PATIENTS WITH HYPOXEMIC ACUTE RESPIRATORY FAILURE: THE CHALLENGING ROLE OF PAO2/FIO2

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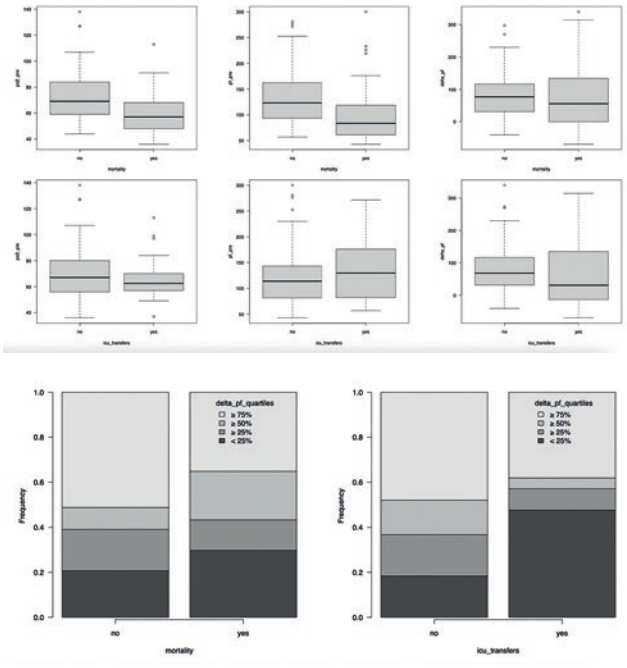
**Background:** and aim: Coronavirus disease 2019 (COVID-19) has overwhelmed national healthcare systems worldwide. Approximately 15% of patients develop severe disease that requires oxygen support and 5% have critical disease with complications such as hypoxemic acute respiratory failure (hARF), acute respiratory distress syndrome (ARDS), sepsis and septic shock, thromboembolism, and/or multiorgan failure. The prompt recognition of clinical deterioration when a patient with respiratory distress is failing to respond to standard oxygen therapy and the adequate preparation to provide advanced oxygen/ventilatory support are essential, especially in time of limited resources. Continuous positive airway pressure (CPAP) may be a strategy to reduce the need for invasive mechanical ventilation (IMV) in Intensive Care Units (ICUs), but the absence of evidence to support the use of non-invasive respiratory systems (CPAP, High Flow Nasal Oxygen, Non-Invasive Positive Pressure Ventilation) in patients with COVID-19 led to significant variability both in international guidelines and clinical practice. The principal outcomes considered to define CPAP effectiveness are mortality and IMV rate. The wide percentages of CPAP success/unsuccess could be explained by different ICU admission and IMV criteria, including do-not-resuscitation orders, different definitions of respiratory deterioration, different settings of application and cohorts characteristics. The aim of this study is to analyse the role of PaO2/FiO2 as predictor of CPAP failure considering in-hospital mortality and ICU-transfers for IMV as primary outcomes.

**Materials and Methods:** We investigated 134 patients with hARF due to COVID-19 interstitial pneumonia admitted to the High Care Internal Medicine Unit of IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico (Milan) between February and April 2020 managed with CPAP according to standardized medical and respiratory in-hospital protocols modelled on international ongoing indications. The diagnosis of COVID-19 interstitial pneumonia was based on positive chest imaging and SARS-CoV-2 infection was confirmed by PCR assay for nasopharyngeal swab specimens. Data about clinical characteristics, treatment, physiological parameters and arterial blood gas analysis (ABG) at admission and within 12 hours were registered and the percentage change of PaO2/FiO2 (D PaO2/FiO2) was calculated. In-hospital mortality and ICU-transfers for IMV were considered as split dismal outcomes.

**Results:** Out of the 134 patients enrolled, 75.4% were male, the median age was 67.5 (29-94) years; at admission the median PaO2/FiO2 was 115 (43-300) and pO2 66 (36-138) mmHg, median CPAP days of treatment had been 6 (1-40). The overall in-hospital mortality was 29.9%, ICU-transfers rate was 19.4%. Non survivors were older [77.5 (51-94) vs 65 (29-91) years, p < 0.001] and showed significant differences in PaO2/FiO2 [83.5 (43-300) vs 123 (57-280), p < 0.001] and pO2 [57 (36-113) vs 69 (44-138) mmHg, p < 0.001] at admission. Patient transferred to ICU, instead, were younger [63 (29-79) vs 68.5 (30-94) years, p = 0.005] but didn't show differences in PaO2/FiO2 [129.7 (57.0-271.4) vs 114.0 (43.0-300), p = 0.177] and pO2 [62 (37-113) vs 67 (36-138) mmHg, p = 0.535] at admission. Matching mortality and ICU transfers as a composite poor outcome, CPAP days of treatment had been fewer [4 (1-15) vs 7 (1-40), p < 0.001] either for non survivors or patients transferred to ICU. Considering D PaO2/FiO2 within 12 hours after starting CPAP and stratifying the percentage difference into quartiles, no evidences were found for mortality (D PaO2/FiO2 < 25% in 29.7% vs 20.7% and ≥ 50% in 56.8% vs 61% of non survivors and survivors, respectively, p = 0.531), while the lack of improvement was a significant predictor for ICU-transfers (D PaO2/FiO2 < 25% in 47.6% vs 18.4% and ≥ 50% in 42.9% vs 63.3% of patients transferred to ICU and non-transferred, respectively, p = 0.024).




**Conclusions:** In COVID-19 patients PaO2/FiO2 had an important role to define respiratory failure and the need of respiratory support, by enabling practitioners of different backgrounds and specialties to share objective data in a common language, but its role should not be overestimated. The severity of hARF (according to PaO2/FiO2 and PaO2) could predict in hospital mortality but it is no relevant to identify the need of mechanical ventilation due to CPAP failure. Management of non-invasive ventilation requires multiple and rapid adjustments at bedside depending on patients' response and the early D PaO2/FiO2 after starting CPAP can be a better indicative factor for subsequent ICU-transfers and IMV than baseline PaO2/FiO2. However, a correct ABG results interpretation must be associated to vital signs trends (tachycardia, hemodynamic deterioration and worsening dyspnoea/tachypnoea) and to high-risk factors (i.e. older age and comorbidities) because numbers can support but not replace clinical judgement.

## 46. ONGOING MYCOPHENOLATE TREATMENT IMPAIRS ANTI-SARS-COV-2 VACCINATION RESPONSE IN PATIENTS AFFECTED BY CHRONIC INFLAMMATORY AUTOIMMUNE DISEASES OR LIVER TRANSPLANTED, RESULTS OF THE RIVALSA PROSPECTIVE COHORT

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Vaccines are the most effective means to prevent the potentially deadly effects of SARS-CoV-2 infection, but not all vaccinated individuals get the same degree of protection. Patients undergoing chronic immunosuppressive therapy due to autoimmune diseases or liver transplant, for example, may show impaired anti-SARS-CoV-2 antibody response after vaccination. We performed a prospective observational study with parallel arms, aiming a) to evaluate seroconversion after anti-SARS-CoV-2 mRNA vaccine administration in different subgroups of patients receiving immunosuppressive treatment for rheumatological or autoimmune diseases or to prevent organ rejection after liver transplantation and b) to identify negative predictors of IgG anti-SARS-CoV-2 development.
Out of 437 eligible patients, 183 individuals were enrolled at the Rheumatology and Hepatology tertiary units at Novara University Hospital: 52 of them were healthy subjects while among the 131 patients, 30 had a diagnosis of spondyloarthritis, 25 had autoimmune hepatitis, 10 were liver transplantation recipients, 23 suffered from connective tissue diseases (10 of them were overlap with other diseases), 40 were treated for rheumatoid arthritis and 5 had vasculitis. Moreover, all patients were receiving chronic immunosuppressive therapy.
The immunogenicity of mRNA COVID-19 vaccines was evaluated by measuring IgG anti-SARS-CoV-2 antibody titers before vaccination and after 10, 30 and 90 days since the first dose administration.
Of the selected cohort of patients, 23.7% did not develop any detectable anti-SARS-CoV-2 IgG after a complete mRNA-based primary cycle vaccination. At univariate analysis, independent predictors of an absent antibody response to vaccine were an history of liver transplantation (OR 11.5, 95% CI 2.5-53.7, p=0.0018), the presence of a comorbid active neoplasia (OR 26.4, 95% CI 2.8- 252.4, p=0.0045), an ongoing immunosuppressive treatment with mycophenolate (MMF) (OR 14.0, 95% CI 3.6-54.9, p=0.0002) or with calcineurin inhibitors (OR 17.5, 95% CI 3.1-99.0, p=0.0012). At multivariate analysis, only treatment with MMF (OR 24.8, 95% CI 5.9-103.2, p<0.0001) and active neoplasia (OR 33.2, 95% CI 5.4-204.1, p=0.0002) were independent predictors of seroconversion failure. These findings suggest that MMF dose reduction or suspension may be required to optimize vaccine response in these patients.

## 47. BASELINE PLASMA SARS-COV-2 RNA DETECTION PREDICTS AN ADVERSE COVID-19 EVOLUTION IN MODERATE TO SEVERE HOSPITALIZED PATIENTS

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**Background:** SARS-CoV-2 is a single-stranded RNA virus, known to be the causative agent of COVID-19. As the resulting disease shows a very heterogeneous range of clinical manifestations, the identification of early biomarkers allowing patients stratification according to the expected disease severity is still an unmet clinical need.
**Methods:** In this observational prospective cohort study, 137 consecutive patients, testing positive for SARS-CoV-2 infection by nasopharyngeal swab RT-PCR or antigenic test, were enrolled to evaluate their plasma viral load at the time of hospitalization.
**Results:** Even if all of them had a molecular diagnosis of COVID-19, only 29 patients showed a detectable plasma SARS-CoV-2 RNAemia. Such viremic patients also showed other clinical and laboratory finding alterations (increased troponin I, IL-6, RDW-CV and creatinine levels along with decreased platelet count and glomerular filtration rate). A plasma detectable RNA viral load predicted in hospital death or ICU admission with an odds ratio of 3.53 (C.I. 1.44-8.64, p=0.0058), while the lack of a detectable viral load was associated with a faster recovery, with an odds ratio of 4.06 (C.I. 1.72-9.59, p=0.0014). These findings were confirmed in multivariate models including age, sex and baseline National Early Warning Score 2 and arterial oxygen tension over inspired oxygen fraction ratio.
**Conclusion:** Our data thus suggest that plasma viral RNA load at the time of hospital admission could represent a useful independent biomarker allowing early patients' stratification according to the expected disease evolution, and driving clinical decisions tailored on the specific needs of the individual patient.

## 48. TWO FORMS OF PERICARDITIS AFTER SARS-COV-2 VACCINATION

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Nowadays, approximately 11.5 billion doses of Sars-CoV-2 vaccines have been administered worldwide. Vaccines have contributed to reduction of morbidity and mortality rates related to Sars-CoV-2 disease, however they have not been exempted from reports of complications, such as the onset of pericarditis.
In our case report we have included patients who had access to our Pericarditis Center, located inside the Internal Medicine of the Papa Giovanni XXIII Hospital in Bergamo, affected from pericarditis and subjected to vaccination for Sars-Cov2 in the 30 days prior to arise of symptoms.
We reported a series of 12 patients, mainly women (83,3%) and 43 years old on average. In all cases they developed symptoms following the administration of Pfizer-BioNTech mRNA vaccine (BNT162b2), most after the second dose (1 after the first, 8 after the second and 3 after the third dose).
Basing on the clinical presentation, it has been possible to split the subjects into two subgroups: "typical" and "atypical" forms of pericarditis.
The first subgroup included five cases (41,7%) with typical presentation, i.e. with chest pain typical for pericarditis, high inflammation indices, presence of pericardial effusion and / or typical electrocardiographic changes. Two of these patients already had at least one history of pericarditis. This group of patients had an excellent response to the administered therapy: NSAIDs and colchicine. Furthermore two patients had to add low-dose steroids and one patient developed a cortisone-dependent form and colchicine resistant, for which anakinra was introduced.
The remaining seven cases (58,3%) belong to the subgroup of "atypical" pericarditis. In fact, the patients presented atypical chest pain, dull inflammatory markers, absence of electrocardiographic alterations; in addiction the echocardiogram described hyperechogenicity of the pericardial sheets or minimal pericardial effusion for which they were labeled as pericarditis. These patients continued to experience retrosternal discomfort for several weeks / months following diagnosis, refractory to treatment with anti-inflammatory agents and colchicine or with a minimum response. Collaterally they manifested a set of symptoms as palpitation (in particular nocturnal), breathlessness, fatigue, worsening anxiety, concentration reduction and poor memory. They described a reduced quality of life with a difficulty in continuing their employment. We excluded identifiable causes of thoracic pain including infectious, autoimmune, neoplastic, metabolic disease. In two cases cardio-magnetic resonance excluded myocardial or pericardial inflammation. The treatment aimed at symptom control: bisoprolol to reduce tachycardia, low doses of glucocorticoids or paracetamol or tramadol / tapentadolo to reduce thoracic pain, amitriptyline to reduce anxiety and headache, citalopram to reduce depressive sensation.
Our data confirm that pericarditis is a rare complication of the Sars-Cov 2 vaccine (since the start of the vaccination compaign we have visitated 182 patients, of which only 12 have developed vaccine-induced pericarditis).

We identified two post-vaccination pericarditis phenotypes, one typical and one atypical. The same phenotypes have also been described in the literature for pericarditis after Sars-Cov2 infection. Hence, we speculate these cases of atypical pericarditis can be contextualized within the clinical spectrum of long COVID, sustained by the vaccination, due to the persistence of viral nucleic acid in the pericardium without virus replication (1).
**References:** 1. Carubbi,F.; Alunno,A.; Leone, S.; Di Gregorio, N.; Mancini, B.; Viscido, A.; Del Pinto, R.; Cicogna, S.; Grassi, D.; Ferri, C. Pericarditis after SARS-CoV-2 Infection: Another Pebble in the Mosaic of Long COVID?Viruses 2021, 13,1997.

## 49. SARS-COV2 VACCINES: SHADOWS AND LIGHTS.

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In last year, wide scientific attention has been focused on adverse events related to SARS-CoV2 vaccines. In a study performed on English population, an increased hospitalization was recorded because of haemostatic disorders and vascular events after a short time lapse from the administration of a first dose of vaccine. However, the same study shows that risk of most of these events is substantially higher and longer in patients with SARS-CoV2 infection than in vaccinated people. Several theories were proposed to explain mechanism underlying onset of adverse events related to vaccines, among which the production of anti-PD4 antibodies inducing platelets aggregation and/or pro-inflammatory cascade activation.
**Case Report:** Man, 57yo entered ER for syncopal episode with loss of sphincterial control and body left side motor deficits during an amateur football match. Patient was soporous but easily awakened by verbal stimulation, with spontaneous motility at four limbs. He received third dose SARS-CoV2 vaccine six days before. Despite absence of anginal symptoms, ECG demonstrated a STEMI in DII-DIII-aVF, echocardiographic examination confirmed inferior and posterolateral walls akinesia. Furthermore, a head CT scan and a CT Angiography of the Aorta was performed. Head CT scan showed presence of a cerebral lesion in right temporo-parietal area with peripheral oedema and intralesional micro bleeding, while CT angiography showed multiple diffuse arterial thrombotic lesions, due to possible thromboembolic mechanism with a pulmonary lesion in right upper lobe with two enlarged thoracic lymphadenopathies, both findings of unclear aetiology. Considering the complexity of clinical case associated and concomitant impossibility of performing a coronary angiography, patient was admitted to our Internal Medicine Department. Blood chemistry tests showed progressive increase of myocardial necrosis markers associated with thrombocytosis and neutrophilic leukocytosis. Crossing blood chemistry and instrumental tests, following exams were required to enlighten a possible acquired and/or inherited conditions of increased thrombotic risk: oncological and autoimmunity markers, genetic thrombophilic screening, specific genetic mutations to rule out a myeloproliferative disease, all tested negative. At resolution of haemorrhagic infarction confirmed by the head-CT, patient was discharged after that anticoagulant and antiplatelets therapy were started, recommending periodic follow-up. DISCUSSION Arterial thromboembolic events onset few days after vaccine administration seemed to suggest a close correlation between the two events, which issue was sustained by various case reports in literature. The event was reported to Hospital pharmacovigilance. SARS-Cov-2 vaccines are essential to overcome the pandemic, therefore it is important to continue to be vigilant for possible emerging complications. Others dates and longer follow-up are needed to verify pathophysiology of thromboembolic events and relationship between thromboembolic events and mRNA vaccines administration. Systematic safety monitoring of COVID-19 vaccines is essential to ensure that benefits are superior to risks.

## 50. COVID-19 AND SARS COV2. WE LEARN THAT THERE'S STILL SO MUCH MORE TO LEARN

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**Background:** Current COVID-19 pandemic exposes health staff to a new and potentially fatal disease
**Case History:** Male, 36yo, entered ER referring worsening asthenia, feeling non-specifically unwell for 7 days, recent history of SARS-CoV-2 infection with interstitial pneumonia requiring hospitalization two weeks prior admission. Blood tests showed severe anemia (Hb 4gr/dl), mild hyperbilirubinemia, markedly raised LDH, positive direct/indirect Coombs' reaction. Autoimmune hemolytic anemia was suspected because of symptomatic anemia, evidence of ongoing hemolysis on blood tests, history of a viral infection. Chest XRay and CT pulmonary angiogram were negative for features suggestive of Covid-19 but highlighted lower right lobar pneumonia. Nasopharyngeal molecular swab was negative, while antibody test showed high titer G Immunoglobulin, confirming recent infection. He was initially treated with high doses steroids (1 gr/Kg bw) as well as antibiotics for pneumonia; but, due to lack of efficacy, on the fourth day we started EV immunoglobulins, obtaining gradual improvement in Hb towards baseline and tests normalization.
**Discussion:** SARS-CoV2 infection frequently meets complications; although the pathophysiology underlying COVID-19 remains poorly understood, evidence argues for hyperinflammatory syndrome and/or various autoimmune disorders, which may appear after pneumonia recovery, highlighting need of medium and long-term follow up, to identify possible presentations of COVID-19 complications.

## 51. HEREDITARY SPHEROCYTOSIS: IS SARS-COV2 INFECTION A NEW TRIGGER OF HEMOLYTIC CRISIS ?

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Hereditary spherocytosis (HS) is a common inherited disorder, most commonly transmitted in an autosomal dominant manner, characterized by hemolytic anemia. This condition is caused by mutations in some of several genes, such as the ANK1, EPB42, SLC4A1, SPTA1 and SPTB genes that encode for five erythrocytes membrane proteins. Primary lesion is loss of membrane surface area, leading to reduced deformability due to defects in some of these proteins. Erythrocytes do not have the usual shape, but appear more sphere-shaped and this change makes these more frail than usual, causing their rupture. Clinically, the disease manifests itself depending on various mutations of genes that encode membrane proteins, their various functional consequences, and the mode of inheritance.Signs and symptoms can range from mild to severe and may include jaundice, anemia, splenomegaly and gallstones. Splenectomy is curative but should be undertaken only after careful assessment of the risks and benefits. HS may be diagnosed based on clinical features, screening tests (including extended complete blood count), osmotic fragility or EMA (eosin-5'maleimide) test, and finally, plasma membrane electrophoresis, which will reveal the deficient protein. Many conditions, such as infections, can induce hemolytic crisis in patients with HS. A 18-year woman with a positive family history for spherocytosis (father) and multiple sclerosis (mother) presented to the emergency department with a history of fever for five days. She was treated at home with ibuprofen and azithromycin without response. She also referred a SARS-CoV2 infection 15 days before the admission. Clinical examination and laboratory study revealed significant mucocutaneous jaundice and anemia. Peripheral blood smear test showed the presence of 70% of lymphoid habitus cells, 25% of neutrophils and 5% of monocytes. Immunomorphology and flow cytometry showed increase of T- cells CD3+, exclusively consisting of CD8+ cells (T-cytotoxic), and increased T the expression of CD38+ and HLA-DR+, probably meaning an inflammatory process. Laboratory examinations revealed high levels of hemolysis index with total bilirubin 5.42 mg/dL, direct bilirubin 2.72 mg /dL, LDH 908 U/L, haptoglobin < 7.2 mg/dL. We found also liver cytolysis (AST 254 U/L; ALT 264 U/L). Complete blood count showed WBC 10.840/ µL, LYMPH 7.720/ µL, NEUT 2.520/ µL, HGB 7.6 g/dL, HCT 23 %, MCV 103.7 fL, MCH 34.5 ρg, MCHC 33.3 g/dL, PLT 235.000/ µL, Retyculocites 11.95%. On the first day of hospitalization in our Unit showed pharyngodynia, pain at the left hypochondrium and left latero-cervical tumefaction. By the abdominal ultrasound examination 3rd grade splenomegaly and vascular congestion were identified (ø 19.4 cm, area 150cm2). Moreover she underwent further haematological evaluation confirming the presence of spherocytes. She was negative for hepatitis viruses, measles virus, Cytomegalovirus, Toxoplasma, Rubella, Streptococcus Beta-Haemolytic Group A pharyngeal carriage,

celiac disease, G6PDH Test, direct and indirect Coombs Test. The Epstein Barr Virus (EBV) immunoglobulins resulted positive (EBV Igm VCA > 160 U/mL). During the hospitalization the patient was treated with rehydrating therapy, folic acid and subjected to clinical, laboratory and ultrasound monitoring, and we observed an improvement of the blood cells with a decrease in haemolysis parameters (WBC 4.450/ µL, LYMPH 2.930/ µL, NEUT 1.040/ µL, HGB 9 g/dL, HCT 27.4 %, MCV 104.6 fL, MCH 34.2 ρg, MCHC 32.7 %, PLT 330.000/ µL, Retyculocites 9.17 %). Thanks to clinical improvement, it was decide to the patient's discharge and follow-up in on outpatient setting. In patients with HS anemia haemolytic crisis after viral infections, aplastic crisis due to parvovirus B19 or megalobastic crisis due to folic acid defieency can be observed. We hypothesized that both SARS-CoV2 and EBV infections could trigger hemolysis, that in our patient was the first manifestation. Our case report highlights the importance of monitoring patients at risk of hemolysis during the pandemia, and brings to the fore that SARS-Cov2 infection could represent a new important trigger of hemolytic crises in those patients with erythrocyte membrane abnormalities.

## 52. EFFECTS OF CHRONIC ASSUMPTION OF LOW DOSE OF ASPIRIN IN SARS-COV2 PNEUMONIA. A RETROSPECTIVE ANALYSIS FROM THE SIMI-COVID-19 STUDY OF THE ITALIAN SOCIETY OF INTERNAL MEDICINE (SIMI)

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**Background:** SARS- CoV2 virus, spread worldwide, had had dramatic consequences through the development of acute respiratory distress syndrome (ARDS), massive thrombosis and pulmonary embolism, reliable for patients' death. In COVID-19, platelets are generated with a procoagulant phenotype and could cause thrombosis in the pulmonary and systemic vascular network. Aspirin (ASA) as well known, is an antiaggregant drugs able to inhibits the effects of platelets. However, currently, in literature there are systematic reviews that suggest a possible benefit in low-dose aspirin (LDA) use in prevention and treatment of ARDS, and in reverse, others have shown any association with the patients' outcome.
**Materials and Patients:** Through the nationwide cohort multicentre study of Italian Society of Internal Medicine (SIMI), we conducted a retrospective study to verify the role of chronic assumption of ASA on death outcome in adult COVID-19 patients admitted in Internal Medicine Units (IMU). Of the 3044 COVID-19 patients at 41 referral hospitals across Italy from February 3rd to May 8th 2020, we randomly matched for age, 500 patients (250 in LDA group and 250 in no LDA group). Demographics, comorbidities, organ dysfunction, treatment, and outcomes including death were assessed.
**Results:** 59.4 % were male, mean age was 75.9 ±9.9. 28% of the population enrolled died for any causes during the hospitalization. LDA group patients had a higher proportion of cardiovascular comorbidity, 41.5% suffered from ischemic heart disease, 78.7% arterial hypertension, 21.1% cerebrovascular disease history, 36.5% diabetes and 38.4% dyslipidemia, all these proportions being significantly different from the no-LDA group. In LDA group the patients died more (32.4% vs 23.6%, p=0.028), with a reduction in intensive care unit (ICU) transfers (10.2% vs 18.1%, p=0.05) due to the hight mortality. In a logistic regression model, LDA use showed an increased risk of death along with male gender and increasing age, with an OR of 1.94 (95%CI: 1.20-3.13, p=0.007).
**Discussion:** Our analysis documented that LDA is associate with a worse outcome, in particular with death. However, this retrospective study documented that LDA was in use in population with many comorbidities, reinforcing the idea that the outcome is link with the pre comorbidities. Specific randomized trials are necessary to clarify the role of LDA in prevention of ARDS or mortality reduction

## 53. A PILOT STUDY OF THE EFFICACY AND ECONOMICAL SUSTAINABILITY OF ACUTE COVID-19 PATIENT MANAGEMENT IN AN OUTPATIENT SETTING

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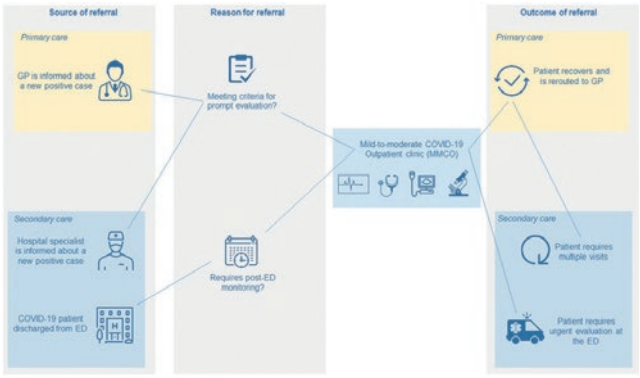
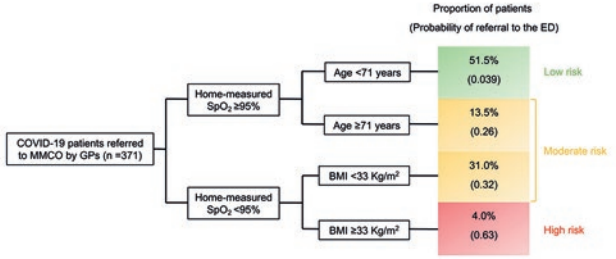
**Objective:** To report a preliminary experience of outpatient management of patients with Coronavirus disease 2019 (COVID-19) through an innovative approach of healthcare delivery (Fig. 1). On the heels of the first pandemic wave and with the belief that some measure had to be taken to avoid system collapse, health policy makers of Lombardy region in Italy at the beginning of the second wave designed an integrated approach of healthcare delivery, called "Hot Spot" or "Mild-to-moderate COVID-19 outpatient clinic" (MMCO), based on the strict, bidirectional collaboration with GPs and the ED. One year after the introduction of this novel service, here we describe our preliminary experience of patient management at two MMCOs of the metropolitan city of Milan, specifically those of San Raffaele University Hospital and Luigi Sacco University Hospital. Moreover, we provide an evidence-based tool for patient classification into risk groups by the GP beforehand, to identify patients deserving early ED referral with the aims of optimizing patient management and spare resources (Fig. 2).
**Patients and Methods:** Patients evaluated at the MMCOs from 1 October 2020 to 31 October 2021 were included. Patients were referred by general practitioners (GPs), Emergency Department (ED) physicians or hospital specialists (HS) in case of moderate COVID- 19. A classification and regression tree (CART) model predicting ED referral by MMCO physicians was developed to aid GPs identify those deserving immediate ED admission. Cost-effectiveness analysis was also performed.




**Results:** A total of 660 patients were included. The majority (70%) was referred by GPs, 21% by the ED and 9% by HS. Patients referred by GPs had more severe disease as assessed by peripheral oxygen saturation (SpO2), ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO2/FiO2), C-reactive protein (CRP) levels and interstitial involvement at lung ultrasound. Among them, 18% were addressed to the ED following MMCO assessment. CART analysis identified three independent predictors, namely home-measured SpO2, age and body mass index (BMI), that robustly divide patients into risk groups of COVID-19 severity. Home-measured SpO2 <

95% and BMI ≥ 33 Kg/m2 defined the high-risk group. The model yielded an accuracy (95% CI) of 83 (77– 88)%. Outpatient management of COVID-19 patients allowed the national healthcare system to spare 1,490,422.05 € when compared with inpatient care.
**Conclusion:** Mild-to-moderate COVID-19 outpatient clinics were effective and sustainable in managing COVID-19 patients and allowed to alleviate pressure on EDs and hospital wards, favoring effort redirection toward non-COVID-19 patients. This patient-centered, sustainable and flexible approach would ensure continuity of care through a 360-degree assistance and possibly serve as a template beyond COVID-19 outbreak.
MM and RDL equally contributed to this work




## 54. EVALUATION OF POST-COVID SYMPTOMS IN HOSPITALIZED SUBJECTS: GENDER AND AGE DIFFERENCES

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**Background:** A growing number of subjects who have recovered from COVID-19 are reporting several symptoms that can last weeks to months. The major efforts of healthcare professionals and researchers is moving to identify, classify, and understand the sequelae of COVID-19.
We aimed to evaluate the Post- COVID symptoms at 1 week, 1 month and 3 months after discharge of subjects hospitalized with COVID-19.
**Methods:** we enrolled 94 subjects (M: F=43: 51, age 61 ± 14 yrs; BMI=28 ± 6 kg/mt2) hospitalized at two Units of Internal Medicine of Bari (Clinica Medica "A. Murri" e Medicina Interna Ospedaliera COVID) from January 2021 to April 2021. The following features were assessed: lenght of hospitalization, days of COVID-19 positivity, comorbidities, COVID-19 severity scoring (0-5) during hospitalization, symptoms post discharge (i.e., myalgia/arthralgia, fatigue, respiratory symptoms, gastrointestinal symptoms, memory impairment, anxiety/depression, headache, anosmia /ageusia).
**Results:** The lenght of hospitalization was 13 ± 10 days. The number of days of COVID-19 positivity was 27 ± 13, and was positively correlated with the length of hospitalization and the COVID-19 severity scoring (n=94, r= 0.47, p< 0.001; r=0.23, p= 0.03, respectively). The median of the COVID-19 severity scoring was 3 ± 1 SD. According to symptoms, after 1 week myalgia/arthralgia was reported by 39% of subjects (VAS 6.7 cm ± 2.7 SD), the fatigue by 78% (VAS 6.4 ± 2.6 SD), the respiratory symptoms by 60% (VAS 10 ± 7.5 SD), gastrointestinal symptoms by 36% (VAS 8.5 ± 6 SD), memory impairment by 23% (VAS 6.5 ± 2.7 SD), anxiety/depression by 40% (VAS 6.4 ± 2.7 SD), headache by 12% (VAS 6 ± 2.7 SD), anosmia /ageusia by 30% (VAS 5.8 ± 2.8 SD). The severity of symptoms and the percentage of affected subjects decreased at the three time points. According to sex and age, the severity of memory impairment was greater in older females than older males (6.5±1.3 cm SD vs 2± 0.2 SD, P=0.002). The severity of anxiety/depression was greater in females (<65 yrs) than males (<65 yrs) (7.6 ± 2.5 cm vs 4.3± 1.6 SD, P=0.01). The severity of respiratory symptoms was higher in subjects with age <65 yrs than in those with age >65 yrs. The severity of fatigue was greater in females with age <65 yrs than males with age <65 yrs (6.7 ± 1.9 SD vs 4.4 ± 2.2 SD, P= 0.03).
**Conclusions:** A wide range of symptoms affect subjects with a previous hospitalization for COVID-19 infection also after 3 months, and it is clear that age and sex contribute to the severity and perpetuation of the syndrome.

## 55. GLUCOCORTICOID TREATMENT IN PATIENTS WITH COVID-19 PNEUMONIA: DIFFERENCES BETWEEN COVID-19 SURVIVORS AND NON-SURVIVORS

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**Background:** in COVID-19, the lung is the most affected organ, and the exaggerated release of proinflammatory cytokines can result in a cytokine storm that could lead to death. Glucocorticoids (GCs) have anti-inflammatory and immunomodulant properties. Since the RECOVERY trial, systemic GCs are routinely used in the treatment of COVID-19 requiring oxygen support.
**Objectives:** The aim of our study was to assess differences in GC therapy between COVID-19 survivors and non-survivors.
**Methods:** this was a prospective observational study part of the COVID-BioB study, a large observational study carried out at San Raffaele Hospital in Milan, Italy. We recruited laboratory confirmed COVID-19 pneumonia cases admitted to our Hospital from September 4th to November 24th 2020. We excluded patients without pneumonia, admitted for other reasons and subsequently diagnosed with superimposed SARS-CoV-2 infection. For each patient, we calculated the cumulative GC dose administered during hospitalization, which was converted into methylprednisolone dose equivalent (MPD).
**Results:** 160 patients were included in the present analysis. Mean age was 61 years (IQR 51.9-76.5), 102 (63.7%) were male, median body mass index (BMI) was 26.4 kg/m2 (IQR 23.8-30.4), 87 (54.3%) patients had hypertension, 21 (13.1%) had diabetes. Thirteen (8.1%) patients developed critical illness requiring Intensive Care Unit (ICU) admission. We compared survivors (n: 128) vs. non-survivors (n: 32) who required oxygen and GC therapy during hospitalization. Upon admission, non-survivors were older (79 vs. 59 years, p<0.001), had lower BMI (24 vs. 27 kg/m2, respectively; p=0.008), greater inflammatory burden (CRP, IL-6 [41.2 vs. 18.8 ng/mL, respectively; p=0.006]) and worse respiratory function (PaO2/FiO2 205 vs. 295, respectively; p=0.001) than COVID-19 survivors. The Charlson Comorbidity Index (CCI) was higher in non-survivors (p<0.001). The time from symptom onset to initiation of steroid therapy was significantly shorter (4.0 vs. 6.5 days, respectively; p=0.003), with a higher proportion of patients who were started on steroid therapy within 10 days of symptom onset in non-survivors vs. survivors (93.8% vs. 77.3%, respectively; p=0.040). The median daily MPD was greater (33.4 vs. 32.0 mg/day, respectively; p=0.045) in non-survivors, as was the cumulative MPD in the first 10 days of therapy (183 vs. 128 mg, respectively; p=0.021). The proportion of patients who were administered doses higher than currently recommended (a cumulative MPD of 320mg, equivalent to dexamethasone 6 mg/daily for 10 days) was high, and similar between groups (59% vs. 68%, p=0.358). Median treatment duration was 10 days in both groups, indicating that half of patients were treated for longer than recommended. At the univariate analysis, a later initiation of steroid therapy was protective (HR 0.84, 95% C.I. 0.75;0.95), whereas both the MPD cumulative dose (HR 14.8, 95% C.I. 3.03–72.72), and the MDP daily dose per kg of body weight (HR 1.004, 95% C.I. 1.001;1.008) in the first 10 days of therapy showed a significant correlation with mortality At the multivariable Cox regression analysis, only the MDP daily dose per kg of body weight remained a statistically significant predictor of mortality after correction for comorbidities (CCI) and disease severity (PaO2/FiO2). Finally, non-survivors exhibited higher rates of hyperglycaemia (53% vs. 32%, p=0.026), pulmonary embolism (13% vs. 1%), and tended to have more bacterial infections (22% vs. 10%, p=0.076).
**Conclusion:** We found that, in a real-life setting, a large proportion of COVID-19 patients are administered higher than recommended GC doses, often exceeding the recommended treatment duration. Although this might increase the risk of GC-related complications, it does not appear to influence mortality. After correction for comorbidities and disease severity, the MDP daily dose per kg of body weight, but not the cumulative dose in the first 10 days of therapy, was a significant predictor of mortality. Although these data need to be confirmed, it is possible that weight-based dosing needs to be adopted in patients with COVID-19.

## 56. A COMPARISON OF FIRST AND SECOND WAVES AMONG HOSPITALIZED PATIENTS WITH SARS COV 2 INFECTION ADMITTED TO A DEDICATED INTERNAL MEDICINE WARD

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**Objective:** Substantial differences exist between the first (2020 -2021) and the second (2021-2022) COVID – 19 wave in terms of patients' characteristics and disease outcomes, which are mostly driven by the start of widespread vaccination programs at the beginning of 2021 and the consequent high prevalence of fully vaccinated patients during the second wave. The aim of this analysis was to compare outcomes of Sars-Cov2 infections between the two waves and according to patients' characteristics at the diagnosis.
**Methods:** Subjects admitted to the hospital who were positive for Sars-Cov2 infection during the first (December 2020 to May 2021) and second (December 2021 to March 2022) waves were included. The setting was an Internal Medicine ward in the University Hospital "Policlinico Umberto I" in Rome, Italy. Demographics, comorbidities, treatment, and disease's outcomes were recorded. Parameters considered were differences among hospitalized patients in the first vs. second wave in terms of age, comorbidities (i.e. arterial hypertension, diabetes, dyslipidemia, chronic heart disease, autoimmune diseases, cancer) at the admission, presence / absence of COVID - 19 related pneumonia at the HRCT imaging, severity of respiratory symptoms, need of oxygen therapy support. Moreover, we recorded the reason of hospitalization by evaluating the existence of typical COVID-19 respiratory manifestations as fever and dyspnea upon arrival to the Emergencies Department.
**Results:** The first group included 166 patients, hospitalized between December 2020 and May 2021, with a mean age of 66 ±16.5 years (82 females) none of them was vaccinated. Patients admitted in the same ward during the second wave from December 2021 to March 2022, were older with respect to the first wave (mean age: 72 ±16.82; p = 0.0077) (n = 83 females), 51 (61%) of them were vaccinated.
Regarding oxygen therapy support, it was higher in the first group (n = 111; 67%) with respect to the second group (n = 41; 48%) (p = 0.008).
Concerning comorbidities, in the first sample 28 out of 166 patients (16%) were affected by diabetes mellitus, 24 (14%) were oncologic patients and 89 (53%) had arterial hypertension. In the second sample, only 9 out of 83 (10%) were affected by diabetes mellitus (p = 0.2), 16 (19%) were oncologic patients (p = 0.3) and 40 (48%) were affected by arterial hypertension (p = 0.4). Remarkably, 127 patients out of 166 (76%) had COVID 19 pneumonia in the first wave, while only 29 (34%) had COVID 19 pneumonia among the 83 people of the second sample (p = 0.00001).
Moreover, the reason of hospitalization was also significantly different between the two groups. A higher number of people in the first group (n = 93; 56%) had fever as a presenting symptom, unlike those in the second group (n = 26; 31%) (p = 0.0002), as well as a higher number of patients manifested dyspnea in the first group as initial symptom (n = 67; 40%) with respect to the number of patients in the second group (n=21; 25%) (p= 0.02).
In addition, 21 people were transferred in an intensive care unit (ICU) department in the first group. Conversely, none of the patients in the second group needed an ICU hospitalization.
Lastly, the length of hospital stay (LOS) the was also different: in the first group was of 15 ±10.44 days while in the second group was of 11 ±8.17 days (p=0.0025). However, in the second group, including both vaccinated and non-vaccinated subjects, the mean LOS was 11.98 ± 8.9 days for vaccinated people (61%), while, for non-vaccinated patients (39%) the mean LOS was 13.75 ± 11.6 days (p > 0.05).
**Conclusions:** In our Internal Medicine ward and during the first wave, when vaccination programs had not been implemented yet, a higher number of patients with a lower mean age required hospital care for COVID – 19 compared to the second wave of COVID – 19 pandemic. Moreover, in the first group, respiratory symptoms were more severe, requiring more oxygen therapy and intensive care treatments with respect to the second group. Comorbidities such as diabetes, hypertension and neoplasms had a major impact concerning the progress of COVID – 19 disease and symptoms in the first group of patients compared to the second group. These differences may be likely attributable to the massive vaccine campaign adopted in Italy. Further studies are needed to identify other factors that may have contributed to the more favorable course of the Sars Cov – 2 infections during the second wave.

## 57. A CASE OF SERONEGATIVE RHEUMATOID ARTHRITIS. CHLAMYDIA PNEUMONIAE OR VACCINE ANTI SARS-COV 2: WHAT IS THE CULPRIT?

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**Background:** Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease based on a breakdown of immune tolerance. Prevalance of RA in USA and in European countries rages between 0,5-1%, and the annual incidence is estimated to be approximately 5-50/100.000.
**Case Report:** A 50-year-old woman with hypertension and a history of carpal tunnel surgery, accessed the emergency room for serotin fever, migratory arthralgia and edema of hands and feet, which occurring about 10 days after the first dose of SARS-CoV2 mRNA vaccine by Pfizer. In the months before, the patient accessed several hospitals for the same symptoms. Given a diagnosed Chlamydia Pneumoniae bronchopneumonia she was treated with antibiotic and corticosteroid therapy, with benefit effects on joint pain and swelling. Before entering our hospital ANGIO-CT was performed because of very high D-Dimer levels, but pulmonary embolism was excluded. Anemia (Hb 7.8) had been corrected by blood transfusion and EGDS showed the presence of a hiatus hernia and a hyperemic gastropathy of the antrum. The patient was then referred to our department of Internal Medicine for further diagnostic investigations.
During hospitalization, blood tests detected normocytic anemia (Hb 10.7 g/dL, serum iron 14 mg/dL, serum ferritin 387.5 ng/dL, serum transferrin 153 mg/dL), increase of inflammatory markers with CRP 229 mg/L, ESR 128 mm, D-dimer 3328 ng/L, fibrinogen 823 mg/dl, interleukin-6 286.7 pg/mL; electrolytes, liver and kidney function, as well as LDH, CPK and PCT 0.03 resulted normal.
Moreover serological tests for TORCH agents, measles, EBV, HCV, HBV, Salmonella Typhi and Paratyphi, Brucella, Borrelia, Leishmania, Rickettsia and Treponema P. were negative. b-D-glucan, urine and blood cultures for bacteria and mycetes did not show any growth. Molecular swab for SARS-Cov2 was also performed with negative results. Only anti-Chlamydia Pneumoniae IgA and IgG antibodies resulted positive, confirming the etiology of the pneumonia.
Negative was the search for serum auto-antibodies.
Echocardiogram excluded systolic disfunction as well as segmentary myocardial hypokinesis Steroid terapy improved joint pain and myalgia.
**Conclusion:** Active Chlamydia Pneumoniae infection or SARS CoV2 mRNA vaccine administration: what is the trigger of arthritis exacerbation? In literature there are reports of other vaccines (against tetanus, rubella, hepatitis B, influenza) and other infectious agents triggering rheumatoid arthritis, but causality has never been proven and an association has never been so far reported in large controlled studies.
It is assumed that molecular mimicry is one of the mechanisms by which infectious or chemical agents my induce autoimmunity, but this has not been so far proven in rheumatoid arthritis. Could it be the case?

## 58. HYPERTENSION AND COVID-19: INCIDENCE AND EVOLUTIVE RISK IN PATIENTS WITH DIFFERENT BLOOD PRESSURE CONTROL

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**Background and Aims**: Hypertension is a known risk factor itself for the development of several diseases. The interaction between SARS-Cov-2 infection and blood pressure control has been investigated with discordant results. We therefore aim: 1) to verify the protective role of adequate blood pressure control in patients with SARS-CoV-2 infection and 2) to evaluate the progression of COVID-19 in three categories of patients: normotensive, hypertensive treated with proper blood pressure control and untreated hypertensive patients.
**Methods and Result:** This is a prospective observational study on 269 consecutive patients admitted for COVID-19 pneumonia at the Internal Medi-

cine Unit of IRCCS Sant'Orsola Hospital in Bologna, Italy between January 2021 and March 2021.
The study population was divided into three groups: normotensive (112 patients), treated hypertensive (135 patients) and untreated hypertensive (22 patients). Patients were followed until the end of the hospitalization. We evaluated three endpoints: mortality, admission in ICU and composite outcome (mortality /admission to intensive care).
Untreated hypertensive patients had an almost three times greater risk of admission to intensive care compared to treated hypertensive patients (OR 2.6; IC 95% 1.01- 6.9; $p < 0.05$). Considering the composite endpoint (mortality/admission to intensive care), untreated hypertensive patients present a double risk compared to normotensive and treated hypertensive patients (OR 1.8;IC 95% 0.7-4.5;p=0.1).
Moreover, untreated hypertensive patients with another risk factor (heart condition and/or diabetes mellitus) have a 3 times greater risk of admission to intensive care and/or death compared to normotensive patients with the same risk factors (OR 3.03; IC 95% 0.6 – 14.7; $p = 0.1$). In the hypertensive population with comorbidities (heart disease and/or diabetes mellitus), we observed that untreated hypertensive patients have a four-fold increased risk of admission to intensive care and/or death compared to treated hypertensive patients (OR 4.3; IC 95% 1.00 – 18.5; $p < 0.04$).
**Conclusions:** A proper blood pressure control determines a lower risk of admission into ICU compared to untreated hypertensive patients. Therefore, hypertension is associated with an increased risk of mortality and admission to intensive care, for which untreated hypertensive patients have and increased risk compared to normotensive and treated hypertensive patients. In conclusion, this study confirms the protective role of an adequate blood pressure control in the evolution of COVID-19 disease.

## 59. NEUTROPHIL-TO-LYMPHOCYTE-RATIO (NLR) IS INVERSELY RELATED TO PAO2/FIO2 (P/F) IN COVID-19 PATIENTS: A FURTHER PROOF OF IMMUNOLOGIC DERANGEMENT ASSOCIATED WITH TYPE 1 RESPIRATORY FAILURE

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**Introduction and Aim:** Type 1 respiratory failure in COVID-19 disease recognizes a complex pathophysiology.
We aimed to evaluate not only the predictive role of various bio-humoral parameters on mortality or admission to Intensive Care Unit (ICU) in COVID-19 hospitalized patients, but also the pathophysiological chain leading to the worsening of the disease. In this context we considered the role of the relationship between PaO2/FiO2 ratio and neutrophil-to-lymphocyte ratio (NLR).
**Methods:** In this retrospective two-center observational survey, 411 subjects were selected among 512 patients who were consecutively admitted to two hospitals (Cannizzaro, S. Marco) in Catania, Italy, with a reliable diagnosis of SARS-CoV2 obtained by rRT-PCR from September 2020 to May 2021. Patients on previous chronic treatment with drugs affecting leukocyte count were excluded.
Neutrophil-to-lymphocyte ratio (NLR), derived neutrophil-to-lymphocyte ratio (d-NLR), platelet-to-lymphocyte ratio (PLR), and C-reactive protein (CRP) of patients with COVID-19 were compared. The Receiver Operating characteristic (ROC) Curve was built to determine the predictive thresholds for these bio-markers, and their prognostic values were assessed by multivariate COX regression models. We analyzed the correlation between P/F ratio and NLR and assessed their strength and direction using Spearman's rank correlation coefficients. In order to derive the best cut-off of P/F ratio and to test its specificity and sensitivity, the ROC curve was also plotted.
**Results:** The median age of our sample was 72 years (interquartile range: 70-75). A higher prevalence of male sex was observed (237). Hypertension, diabetes and ischemic heart disease were the most common comorbidities. At baseline, 120 patients were on low flow oxygen therapy, 66 on high flow oxygen therapy, 136 on non-invasive mechanic ventilation. P/F showed a significant decrease along these three groups ($p < 0.000001$).
A comparison between ROC curves was made in order to test the prognostic performance of NLR, d-NLR, PLR, and CRP for predicting in-hospital mortality of COVID-19 patients. NLR showed the largest area under the curve (AUC) (0.772), followed by d-NLR (0.756), CRP (0.676) and PLR (0.570). The difference between NLR and CRP AUCs ($p = 0.0173$), as well as that between NLR and PLR ($p < 0.0001$), were statistically significant. The best cut-off of NLR established by the Youden index at 11.38 had a sensitivity of 72.9% and a specificity of 71.9% (AUC = 0.772, $p < 0.0001$). Linear regression analysis showed an inverse relationship between NLR and P/F ratio at baseline ($r = 0.39$; $p < 0.0001$).
Two Cox regression models were built in order to obtain Hazard Ratios of the main markers, adjusted for the main confounders. The model 1 was adjusted for sex and age, while model 2 included main comorbidities and P/F ratio. NLR was independently associated with mortality. In model 1, for each increase of 1 unit in the standard deviation of NLR, the risk of mortality increased by 45% in the whole sample. In model 2, for each increase of 1 unit in the standard deviation of NLR, the risk of mortality increased by 60% in the whole sample.
Regarding the prediction of ICU admission, Cox regression analysis showed that NLR largely predicted the risk of ICU admission (HR: 3.9597, $p < 0.0001$). A ROC curve built for P/F ratio expressed as a continuous variable showed an acceptable predictive power of ICU admission: the best cut-off of P/F ratio established by the Youden index at 185 had a sensitivity of 89.7% and specificity of 53.9% (AUC = 0.738, $p < 0.0001$). The independent association of NLR with ICU admission, however, disappeared when P/F was included in the model. This means that NLR and P/F are associated in the same pathophysiological chain, where the weight of NLR is entirely captured by P/F, likely because NLR behavior is linked to the worsening of P/F, which, in turn, characterizes Type 1 respiratory failure.
**Conclusions:** Early assessment of factors predicting the worsening of type 1 respiratory failure in COVID-19 patients, such as baseline NLR and P/F, is useful for risk stratification. The assessment of NLR values could help an early identification of type 1 respiratory failure's worsening.

## 60. OUTCOME PREDICTION OF SARS-COV-2 INFECTION THROUGH MACHINE LEARNING BASED ALGORITHMS

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**Background and Objective:** We devised and evaluated the performances of several machine learning (ML) classifiers, fed with routine clinical and laboratory analyses, in order to support physicians in decision making process on patients affected by coronavirus disease 2019 (COVID-19).
**Materials and Methods:** Our observational retrospective study collected data from a cohort of 779 COVID-19 patients presenting to Emergency Department (ED) of three hospitals of the Lazio-Abruzzo area (Italy).
**Results:** We devised several models from both: the complete dataset with missing data and the subset of complete cases. The AUCs for the classifiers used to predict safe discharge were 0.94 and 0.89, respectively. The AUCs for the classifiers devised for disease severity were 0.89 and 0.83, whereas the AUCs regarding mortality were 0.87 and 0.84.
**Discussion:** The results of our study are consistent with the scientific literature that reports several prognostic prediction models, accomplishing significant performances to forecast safe discharge from ED and severe clinical course of COVID-19.
**Conclusions:** Here we propose several excellent prediction models addressed to patients with incomplete immunization for SARS-CoV-2 infection. The models are also incorporated into a decision support system currently used in our institution. We do not suppose that ML could replace physicians and human decision process, but we conceive that the integration of prediction models in emergency care routine could improve healthcare assistance and have a significant impact on SARS-CoV-2 inpatient and outpatient outcomes.

## 61. ADDRESSING MICROVASCULAR DISEASE IN COVID-19 SURVIVORS BY SIMULTANEOUS MEASURE OF DIFFUSING CAPACITY FOR CARBON MONOXIDE AND NITRIC OXIDE

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The prevalence of pulmonary sequelae among COVID-19 survivors varies according to the severity of the acute phase. The impairment of diffusion capacity is the most common abnormality of lung function. Even if the crucial role of microvascular disease has been widely explored in the acute phase of COVID-19, little is known about the relevance of this mechanism of lung injury during convalescence. Pulmonary diffusing capacity can be separated into its two components: the membrane diffusing capacity (Dm) and the component related to the pulmonary capillaries (Vc) According to Roughton and Forster equation (1/DLCO=1/DM+1/θCO·VC), where θ is the specific transfer conductance of CO in blood, simultaneous measurements of diffusing capacity of the lung for carbon oxide (DLCO) and nitric oxide (DLNO) allow the assessment of both components. Nitric oxide has a more rapid (about 300-fold) uptake rate by intracapillary haemoglobin compared to carbon monoxide. Given these properties, DLNO is more sensitive to changes in Dm, while DLCO mainly reflects red cell conductance and Vc. The physiological significance and clinical implications are that, in patients affected by pulmonary vascular disease the loss of capillary vasculature mainly affect DLCO, determining a higher DLNO/DLCO ratio; conversely, in patients with interstitial lung disease, membrane thickening mostly determines a reduction in DLNO determining a lower DLNO/DLCO ratio. In this paper we explore the changes in DLNO and DLCO as an assessment of the potential microvascular damage underling COVID-19 pulmonary sequelae. Between May 04th 2020 and September 16th 2021 we included 199 adult patients with confirmed SARS-CoV-2 infection. We obtained pulmonary function tests and comprehensive medical evaluation starting around 3 months post discharge. All PFTs were conducted by using Jaeger MasterScreen PFT Analyzer Unit (JLAB software version 5.3.0, CareFusion, Italy) at the Unit of Respiratory Medicine of IRCCS San Raffaele Hospital, Milan, Italy. Logistic regression analysis were used to identify predictors abnormal DLNO/DLCO ratio among all available variables. Of the entire cohort, 19 patients had a mild COVID infection and were managed at home, 70 patients had a moderately severe disease requiring oxygen support, 54 patients had severe disease requiring non-invasive mechanical ventilation (NIV) or high flow nasal cannula (HFNC) and 56 patients had a critical disease requiring ICU admission and mechanical ventilation. Median (interquartile range, IQR) age was 64 (56-73) years and most patients were male (72%). Main comorbidities were Arterial Hypertension (47%), Obesity (28%) and Diabetes mellitus (18%). Respectively 11%, 5% and 6% of the patients had a history of Chronic Obstructive Pulmonary Disease (COPD), Asthma and Obstructive Sleep Apnea Syndrome (OSAS). Ninety patients had a history of smoking (45%). Patients were hospitalised for a median of 24 (12 – 41) days. The interpretation of PFT showed a total amount of 22 obstructive patterns (11%), 61 restrictive pattern (31%) and 111 DLCO impairment (56%). DLNO impairment was instead observed in 167 patients (84%). Median value of DLCO was 69,2% (53,4 – 83,35), and Kco (DLCO/VA) was normal with a median value of 92,1% (80,4 – 109,3). Overall, DLNO appeared more compromised in comparison to DLCO, with a median of 49,4% (40,2 – 61,3) observed. DLCO impairment was higher in severe and critical groups (p=0,001). Conversely, there were no differences in DLNO impairment between the different groups. 6MWT were performed on 105 patients. A significant positive correlation was observed between DLCO, DLNO and travelled distance of 6MWT at 1 month evaluation (Spearman's rho, Rs 0,294, p=0,03; Rs 0,323, p=0,02). Median DLNO/DLCO ratio was 3,75 (3,42 – 4,18) and resulted significantly higher in critical group compared to the other sub-groups of hospitalised patients (p< 0,001). Pulmonary capillary blood volume, Vc (%), was significantly reduced in critical disease compared to mild and moderate (p=0,005), but similar between severe and critical group. Conversely, there were no differences between groups in the membrane component of diffusion capacity, Dm (%). Alveolar volume, Va (%), was significantly reduced in patient with critical disease compared to mild disease (p=0,04). Longer hospitalisation and lower PaO2/FiO2 ratio at the admission were associated with poorer Vc (%) and Dm (%) (Rs -0,495, p< 0,001; Rs -0,335, p<0,001), and with a higher DLNO/DLCO ratio (Rs 0,325, p< 0,001; Rs -0,414, p< 0,001). No correlation was observed between DLNO/DLCO ratio and Va (%) (Rs -0,119, p=0,112). In the multivariable logistic regression, critical disease and hospital length of stay emerged as independent factor in predicting higher DLNO/DLCO ratio. Our findings suggest that patients discharged after severe COVID-19 have a higher amount of microvascular damage compared to the other groups, thus sustaining the role of simultaneous measurement of DLCO and DLNO in the assessment of COVID-19 related lung injury at follow up evaluation.

## 62. ON FIELD EFFICACY OF THE VACCINATION CAMPAIGN AGAINST SARS-COV-2 AMONG AUTOIMMUNE INFLAMMATORY RHEUMATIC DISEASES PATIENT ACROSS ITALY, PARTIAL DATA

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Systemic sclerosis is a chronic immune-mediated disease characterized by high mortality, especially for patients with diffuse cutaneous form. It has been estimated that around one in 10000 people are affected, worldwide, with a reported female/male ratio ranging from 3: 1 to 8: 1. Etiology is complex and still unclear but some environmental factors (e.g. chemicals, chemotherapy, and silicone implant) combined with genetic and epigenetic susceptibility play a role. It may present at any age, but the most frequent peak is between 20 and 50 years or even after, till 69 years. Systemic lupus erythematosus is a chronic autoimmune disease that may involve any organ caused by an aberrant autoimmune response. Its prevalence ranges from 9 to 241 per 100,000 people, and its incidence ranges from 0.3 to 23.2 per 100,000 person-years, with a trend of a constant increase. The 10-year survival rate is about 70%. The introduction of Systemic Lupus International Collaborating Clinics (SLICC) criteria, being more sensitive, made its incidence increase. Etiology is challenging in comprehending a mix of genetic factors, environmental influences, female hormones, gender, epigenetic factors, socioeconomic factors, and immune cell regulations. The coronavirus disease 2019 (COVID-19) pandemic, caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused an increase in hospitalization for pneumonia with the multiorgan disease. Oxygen supplementation was needed in more than 75% of hospitalized patients. In frail patients, e.g. elderly, the case-fatality rate for COVID-19 reached 304.9 per 1000 cases in the US. In patients hospitalized in intensive care units, the case fatality rate was as high as 40%. In this scenario, SARS-CoV-2 vaccines, distributed in the largest vaccination campaign in human history, had a major impact on reducing hospitalization and death by COVID-19. This effectiveness was of great importance in frail patients, like autoimmune disease patients comprehending Systemic Sclerosis and Systemic lupus erythematosus, and other diseases.
This multicentric study was conducted between January 2021 and February 2022 and involved five Italian centers: Ancona, Bari, Genova, Salerno, and Verona. Here data of followed-up patients, afflicted mainly by SSc, LES but also other autoimmune diseases, were collected and organized in a shared database in accordance with Helsinki's declaration. The main focus of this research was data was to start investigating vaccine coverage rates, SARS-CoV-2 positivity, and on-field vaccine efficacy against the infection, hospitalization, and death.
A descriptive statistical analysis was conducted to better describe the population and afterward, the correlation of vaccine effectiveness against several endpoints such as virus positivity, hospitalization, and death was calculated for the cohort with a p<0,01. Cumulative survival against the different

outcomes was represented using Kaplan-Meier Curves.
A cohort of 413 patients was gathered. The main clinical condition was systemic sclerosis with a percentage of 63,9% of all patients. Lupus Erythematosus Systemic was the second most represented group with the 8,2%. All further data are summarized in table 1.
The cohort was divided between vaccinated and not vaccinated. Patients were considered vaccinated seven days after completing the cycle of COVID-19 vaccine, patients were considered not vaccinated in absence of a vaccination record or whether the test was collected prior to the eighth day after the completion of the vaccine schedule.
Among 413 patients 58 (14,0%) were not vaccinated while 355 (86,0%) formed the vaccinated group. The majority of patients were vaccinated using Pfizer-BioNTech COVID-19 vaccine (n=344; 96,9% of the vaccines). The vaccinated group was found less likely to contract SARS-Cov-2 infection with a odds ratio of OR=0,197 (IC 95%: 0,01-0,372; p<0,0001) and less likely to encounter death as an outcome with a odds ratio of OR=0,18 (IC 95 %: 0,059-0,559; p=0,003). The vaccination campaign showed a vaccine efficacy of 80,3% against the infection and of 82% against SARS-CoV-2 related deaths.
The following images show the Kaplan Meyer survival curves of the vaccinated and not vaccinated group in relation to infection (fig.1) and death (fig.2). Further analysis will be carried on to better assess correlations between vaccination and different outcomes.

Table 1

| Condition | Number of patients | % |
|---|---|---|
| Systemic sclerosis | 264 | 63,9% |
| Lupus Erythematosus Systemic | 34 | 8,2% |
| Rheumatoid arthritis | 12 | 2,9% |
| Antiphospholipid syndrome | 10 | 2,4% |
| Other condition | 93 | 22,5% |

Fig.1

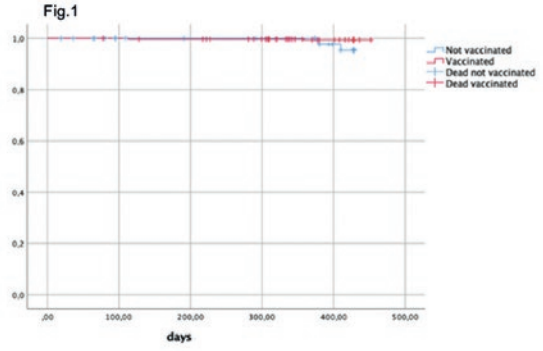
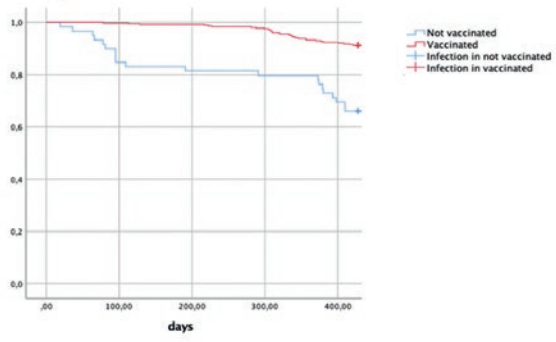



Fig.2




## 63. INFLAMMATORY CYTOKINES RESPONSE TO SARS-COV-2 VIRUS INFECTION: THE CLINICAL SCENERY

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**Introduction:** Since the first cases of Sars-CoV-2 infections, it was realized that the worse outcome is associated to an exaggerated inflammatory response of the host to the virus infection. It is now well established that the rapid evolution to an acute respiratory distress syndrome (ARDS) is strictly related to cytokines storm which is the main trigger of the huge lung injury observed in ARDS. The cytokines serum concentration, as measured at the admission at the Emergency Department, is suggestive of poorer prognosis of the patients. In this framework IL-6 and Il-18 play a major role as triggers of inflammatory programs that reflect in a significant increase of acute phase proteins, C reactive protein (CRP) and ferritin, respectively. In particular, the role of IL-18 and its effective decoy receptor binding protein (IL-18BP) are analysed and discussed, also in view of a possible therapeutic approach to downgrade the immune system reaction.
**Materials and Methods:** The authors carried out an analysis of the serum concentrations of IL-6 (n.r. 0-46 pg/mL), IL-18 (n.r. 70-490 pg/mL), IL-18BP (n.r. 2000-3000 pg/mL), IFN-g, as well as the main inflammatory molecules routinely evaluated in the clinical setting (CRP (n.r. <0.5 mg/dL), Ferritin (n.r. 30-400 ng/mL), D-dimer dimer (n.r. < 500ng/mL)), on a subset of 85 COVID-19 related pneumonia patients admitted to the Emergency Medicine Unit.
The laboratory values patients were divided in different classes according to a value of the P/F ratio less than 300 or to a severe outcome (decease/ARSD). The ARSD was evaluated on the basis of CT.
All the quantities have been measured at the admittance time.
**Results:** The average age of the enrolled 85 patients was 58 ± 19 (53.6% were male).
The table shows the mean values and the standard deviations of all the measured variables with the statistical significance.

| | P/F>300 (N=45) | P/F<300 (N=40) | p-value | No Severe Outcome (N=55) | Severe Outcome (N= 35) | p-value |
|---|---|---|---|---|---|---|
| IL-6 | 17.8 (19.2) | 78.6 (54.7) | 0.001 | 36.3 (42) | 66.9 (52.6) | 0.005 |
| IL-18 | 477 (354) | 583 (301) | 0.19 | 491 (301) | 538 (299) | 0.485 |
| IL-18BP | 2157 (1170) | 3489(1804) | 0.001 | 2360 (1288) | 3325 (1288) | 0.005 |
| IFN-g | 8.9 (38) | 13.6 (39) | 0.631 | 7.2 (30.1) | 13.7 (41.4) | 0.415 |
| CRP | 3.18 (6.9) | 8.15 (7.03) | 0.006 | 4.87 (6.53) | 6.71 (7.3) | 0.242 |
| Ferritin | 497 (473) | 1218 (1434) | 0.006 | 653 (656) | 1222 (1410) | 0.014 |
| D-Dimer | 555.6 (348) | 1422 (1108) | 0.001 | 760 (716) | 1111 (1061) | 0.080 |

**Conclusions:** The serum concentrations of the routinely inflammation parameters (CRP, ferritin, D-dimer) are significantly associated with the clinical presentation, to support the pathogenic role of inflammatory process on the lung injury and clinical evolution.
The values of IL-6 and IL-18 confirm their pro-inflammatory action and the association to the clinical outcome is quite good, even if the statistical significance of IL-18 is less sound.
The IL-18BP displays a weak correlation to the IL-18 and its role needs further investigations to clarify the underlying molecular mechanisms.
In conclusion, the results obtained confirm the fundamental function of the pro-inflammatory cytokines in the disease and leave space to further research and to the improvement of new therapeutic strategies.

## 64. THE INFLUENCE OF SARS-COV2 ON THE EMERGENCY DEPARTMENT'S ACTIVITY IN EMILIA ROMAGNA REGION

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**Background:** Clinical studies showed a significant reduction in emergency room accesses during the previous SARS and MERS epidemics of about -10% and -33% respectively (1). A similar manifestation was also documented at the beginning of the SARS-CoV-2 pandemic in many countries around the word (1-3). In Italy, at the end of March 2020, the reduction was estimated at 70% compared to the previous two years (4).
**Aim of the study:** To evaluate the reduction in the accesses to Emilia Romagna emergency rooms (ER) during SARS-CoV-2 pandemic.
**Methods:** All emergency room accesses of the Emilia-Romagna region during 2020 and 2021, maintained in the regional database and classified by reason of access and severity, were considered. The 2019 was used as the non-pandemic reference year.

**Results:** We observed a reduction in access to the ER during 2020 compared to 2019 (-32,2%). Although this reduction was evident in all severity categories, the largest one was relative to less severe cases classified as "patient with deferrable urgency" (-34.2%) and "patient with no urgency" (-36.9%). We observed a recovery in access to the ER in 2021 compared to 2020 (+13.1%), mainly for cases classified as "patients with no urgency" (+138,7%). These data were in contrast with all the other categories showing a further decrease. However, the increase of activity during the 2021 was not sufficient to reach the pre-pandemic numbers of access (difference 2021–2019: -23.3%). All the categories of severity showed a reduction, with the exception of those classified as "patient with no urgency" which presented a significant increase (+50.7%).
**Conclusion:** At the beginning of the pandemic, the chaotic sanitary emergency could justify the severe reduction in health services. However, our results underline that the ER activity continues to be lacking compared to pre-pandemic standards even after one year from the start of the pandemic, resulting in a lack of health care. In our opinion, it is possible that this is due to the inability of the Italian health system to respond to the emergency situation's needs. In fact, our health system enjoys a precarious condition with numerous weaknesses, especially at the territorial level. In absence of adequate assistance, the population tends to refer to the ER even for non-urgent problems. The observed results confirm the lack of territorial organization, given the increase, greater in 2021 for cases of lesser severity, which should be managed in other settings, out of the ER. Covid-19 pandemic has triggered the existing problems, and we have to learn the lessons and operate a reorganization of the health system to make it more efficient and capable of responding to future emergencies.

## 65. EARLY TREATMENT WITH MONOCLONAL ANTIBODIES AND ANTIVIRAL DRUGS IN SARS-COV-2 INFECTION OF PRIMARY IMMUNODEFICIENCIES PATIENTS

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**Background:** Primary immunodeficiency patients (PIDD) may have a reduced or absent humoral and cellular response to vaccination due to their underlying immune defects. Early treatment with monoclonal antibodies (mAbs) and/or antiviral drugs is a valuable tool in this population.
**Aim:** We aim to assess safety and clinical outcomes of early treatment for COVID-19 among patients with PIDD.
**Methods:** We retrospectively reviewed all PIDD patients who received an early treatment with mAbs (bamlanivimab/etesevimab or sotrovimab) or antiviral drugs (remdesevir or paxlovid) for COVID-19, according to the Italian National Health System indications, from 25-11-2021 to 30-04-2022 in a large tertiary hospital in Milano. Outcomes included frequency of adverse drug reaction (ADR), duration of molecular swab positivity, duration of symptoms, reinfections, emergency department access, hospital or intensive care unit admission, and mortality in the 14 days following treatments administration.
**Results:** Early treatment was administered to 32 PIDD patients (21 CVID, 1 XLA, 3 AD-HIES, 1 CGD, 1 complement deficiency, 1 Good Syndrome, 3 Unclassified PAD, 1 selective IgA deficiency with bronchiectasis). Antivirals (paxlovid or remdesevir) plus mAbs (bamlanivimab/etesevimab or sotrovimab) were administrated to 10 patients, 8 patients received only antivirals (mainly because mAbs were not available) and 14 patients received only mAbs.
Overall, one subject reported ADR that needed stopping antiviral treatment. Median time from the start of treatment to SARS-CoV-2 nasopharyngeal molecular swab negativity ranged from one week to more than 6 weeks, while symptoms solved in 2-4 days after the treatment. During the observation period of 6 months after treatment administration, nobody was hospitalized for causes related to COVID-19 nor died. One patient had a new SARS-CoV-2 infection 15 weeks after the administration of mAbs for the first SARS-CoV-2 infection and was treated with antiviral.
**Conclusions:** Antivirals and mAbs treatments administered in the early stages of COVID-19 have minimal ADRs and favourable outcomes in PIDD patients.

## 66. PREDICTORS AND OUTCOMES OF DELIRIUM IN THE EMERGENCY DEPARTMENT IN COVID-19 PATIENTS

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**Background:** respiratory infections can be complicated by acute brain failure. We assessed delirium prevalence, predictors and outcomes in COVID-19 emergency department (ED) patients.
**Methods:** observational study at the San Raffaele ER between the 26th February 2020 and 30th May 2020. Inclusion criteria: age > 18 years, positive molecular nasopharyngeal swab for SARS-CoV-2. The Chart-Based Delirium Identification Instrument (CHART-DEL) was used to assess retrospectively delirium. Univariable and multivariable logistic regression analyses were used to evaluate delirium predictors. Univariable binary logistic regression analyses, linear regression analyses and Cox regression analyses were used to assess the association between delirium and clinical outcomes. Age and sex adjusted models were then run for the significant predictors of the univariable models.
**Results:** among the 826 included patients 123 cases (14.9%) of delirium were retrospectively detected through the CHART-DEL method. Delirious patients were older (76.9 vs 61.3 years, $p < 0.001$) and were more frequently institutionalized (26% vs 3.1%, $p < 0.001$). Age (OR 1.06, 95% C.I. 1.04–1.09, $p < 0.001$), dementia (OR 17.5, C.I. 7.27–42.16, $p < 0.001$) epilepsy (OR 6.96, 95% C.I. 2.48–19.51, $p < 0.001$) and the number of chronic drugs (1.09, 95% C.I. 1.01–1.17, $p = 0.03$) resulted significant predictors of delirium. Delirium was associated with an increased in-hospital mortality (adjusted HR 2.16, 95% C.I. 1.55–3.03, $p< 0.001$) and with a reduced probability of being discharged at home (adjusted OR 0.39, 95% C.I. 0.25 – 0.61, $p < 0.001$).
**Conclusions:**
Chart review identified frequently ED delirium in COVID-19 patients. Age, dementia, epilepsy and polypharmacy were significant predictors of ED delirium. Delirium was associated with an increased in-hospital mortality and with a reduced probability of being discharged home after hospitalization. The implementation of delirium screening tools in the ED should be promoted to confirm our retrospective findings.

## 67. RITIRATO

## 68. PREVENTION IS BETTER THAN HEALING: PRELIMINARY DATA FROM THE CASTELLI-EARLY-COV 19 (CEC-19) OBSERVATIONAL STUDY

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**Background:** Since April 2021, at Internal Medicine of Castelli Hospital started the administration of early anti-COVID-19 therapies.
**Materials and Methods: .** Initially only Monoclonal Antibodies (MAbs) were available; lately the oral antiviral (OA) therapy Molnupiravir. These drugs are reserved to positive patients, with recent symptoms onset and affected by risk factors for development of severe bilateral interstitial pneumonia.
**Results:** 271 patients were treated with MAbs (M/F 142/129, median age 63, SD 13.87, IQR 18). Risk factors 50 patients obese (BMI>30), 187 with cardio-cerebrovascular diseases, 35 uncompensated diabetes mellitus, 83 chronic lung diseases, 45 immunosuppresed, 6 neurological disorders; 105 had more than 1 risk factor. Until now, 196 patients reached one month

follow-up; 10 were hospitalized for COVID-19 complications, 7 discharged, 1 is still hospitalized, 2 died. Among the remaining 186 patients, 11 were still positive, but clinically recovered; the remaining 175 were healed and negative. To date 28 patients were treated with Molnupiravir (M/F 14/14, median age 64, DS 15.4, IQR 21). 8 obese, 21 cardio-cerebrovascular disorders, 10 chronic lung diseases, 3 uncompensated diabetes mellitus, 1 immunosuppressed. At one week follow-up no adverse effect nor hospitalization were reported.
**Conclusions:** Early treatment of SARs Cov 2 appears to be well tolerated and able to avoid hospitalizations of patients at risk. This result allows us to hypothesize a saving of about 4500 € per patient treated with Monoclonals and about 5000 € with Antivirals. treatment.

## 69. ALTERATIONS OF LIPID PROFILE OBSERVED IN COVID-19 PATIENTS

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**Introduction:** It seems that during SARS-CoV-2 infection, total cholesterol, LDL-C, and HDL-C values decrease and lipids could play a fundamental role in viral replication.
**Methods and Aim:** We performed a retrospective analysis of 118 hospitalized patients with COVID-19, comparing pre- infection lipid profile (53 patients) to those measured on admission. Our aim was to evaluate whether SARS-CoV-2 infection could be involved in lipid profile alterations and study possible correlations with disease severity and clinical outcome.
**Results:** Median baseline values at the admission time were: total cholesterol 136.89 ±
42.73 mg/dL, LDL-C 81.53 ± 30.35 mg/dL, HDL-C 32.36 ± 15.13 mg/dL triglycerides
115.00 ± 40.45 mg/dL and non-HDL-C 104.53 ± 32.63 md/dL. Median values of pre- infection total cholesterol and HDL-C were significantly higher (total cholesterol 158.43 ±
45.18 mg/dL; HDL-C 44.08 ± 17.76 mg/dL) than those measured at the admission time (p value < 0.05). The C-reactive protein (CRP) was negatively correlated with LDL-C (p = 0.013) and HDL-C (p = 0.05).
**Conclusion:** Our data suggest a possible relation between COVID-19 and lipid profile with a negative correlation between CRP, LDL-C, and HDL-C values, thus proposing the hypothesis that lipid lowering could follow the rising of the COVID-19 inflammatory state.

## 70. SARS-COV-2 INFECTION, REMDESIVIR AND MRNA VACCINE: ALL POSSIBLE CAUSES IN A CASE OF MYOCARDITIS

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**Introduction:** COVID-19 remains a global public health emergency. Although the lungs initially appeared to be the main target of infection, the concept of systemic illness is now accredited. Systemic involvement is frequently encountered, especially in people with cardiovascular diseases and other comorbidities. Ever since the beginning of the COVID-19 pandemic, international efforts have been directed to the development of therapeutic strategies and effective vaccines. Among treatments, the only antiviral drug approved is remdesivir, an adenosine analog but with a significantly longer half-life than adenosine. It seems have cardiotoxic and proarrythmyc effects in patients with heart disease. While tolerance to COVID-19 vaccination is considered satisfactory, a phenomenon of myocarditis, although rare, is becoming a safety concern in mRNA COVID-19 vaccination. Myocarditis is a myocardial tissue inflammatory disease.
It may be due by viral agents, but several toxic substances, drugs and systemic immune-mediated diseases can be guilty. Rarely it can also be secondary to vaccines.
**Case Presentation:** On the 2nd of January 2022, a 75-years-old man with silent medical history, was evaluated by our Emergency Department because of fever and worsening dyspnea for five days. He got Sars-CoV-2 completed vaccination course (two Astrazeneca doses on July 2021 and booster dose with Moderna on December 2021).
At clinical examination the patient had reduced vescicular murmur with crackles at the lung bases, legs oedema and desaturation in ambient air (SpO2 70%, FiO2 21%). The electrocardiogram (EKG) evidenced sinus rhythm 88 bpm without repolarization anomalies, while the chest X-ray interstitial pneumonia with bilateral pleural effusion. Laboratory parameters reported normal blood count, potassium 4.4 mmol/L, [3.5-5.5] creatinine 0.97 [0.5-1.1] mg/dL, CRP 2.7 [<0.5] mg/dL, high-sensitive troponine 1073 [0-44] ng/L, BNP 808 [0-100] ng/L and D-Dimer 3994 [<500] FEU. Chest-CT ruled out pulmonary embolism. Third generation Sars-CoV-2 swab resulted positive and the patient was so admitted to our COVID-Medical Department for viral pneumonia and first episode of acute heart failure. We started treatment with intravenous steroids and diuretics, LMWH at prophylactic dose, high flow oxygen by Venturi Mask then reduced to low flow. Initial improvement was rapidly provided by biochemical and clinical parameters. As indicated by Infectious disease Specialist, remdesivir therapy was administrated. After the second infusion, patient had bradycardia and an EKG showed low rate atrial fibrillation (AF) with slightly prolonged QT interval. Echocardiography showed reduced systolic function (FE 46%) with anterior interventricular septum akinesia and posterior wall hypokinesia, mild biatrial dilatation and no signs of pericardial effusion. The patient remained completely asymptomatic, despite hypotension and bradyarrythmia. Under continuous cardiac rhythm monitoring, remdesivir treatment was then carefully completed and direct oral anticoagulation (DOAc) was started. Once discharged and become COVID-19 negative, the patient was re-evaluated by outpatient Cardiologist: EKG confirmed AF with normalized QTc and echocardiography showed systolic function improvement (FE 58%), mild mitral valve insufficiency and atrial dilatation.
**Discussion:** The cardiac injury can be due by different etiologies. The viral infection itself can lead to myocarditis. Remdesivir can cause profound hypotension, bradycardia, prolonged QT interval and it can also shorten atrial action potential and refractioriness leading to AF. In this case report, after possibly drug accumulation, on the third day of administration, hypotension and bradyrrythmia were recorded. The same temporal connection could be identified between the onset of myocarditis and the booster dose vaccination. In case of Moderna vaccine, one hypothesis considered that low levels of dsRNA present in COVID-19 mRNA vaccine preparations could be, alone or in addition to other predisposing factors, at the origin of the still unexplained cases of myocarditis following vaccination.
The cardiotoxic effects are usually more frequent in people with cardiovascular diseases, but in this case, the patient had no known diseases, even though the echocardiography revealed structural abnormalities.
**Conclusion:** Myocarditis is a myocardial tissue inflammatory disease with a heterogeneous aetiology. In Sars-CoV-2 pandemic, this phenomenon has been described as a clinical manifestation of the viral infection itself, but also as a side effect of mRNA vaccines. It's mandatory to investigate cardiological personal history. In this case the patient had unknown heart disease and we can't exclude a synergic effect of all these factors in the onset of the myocarditis. In addition, in people with known cardiovascular disease and COVID-19 infection, who undergo to remdesivir treatment, continuous cardiac rhythm monitoring is recommended.

## 71. ALBUMIN AND DEMENTIA IN COVID-19: A LINK WITH MORTALITY?

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**Background:** decreased serum albumin levels are associated with increased thrombotic events and mortality in COVID-19 patients. The association between serum albumin levels with dementia and mortality in elderly patients with COVID-19 is still unclear.

**Objective:** to evaluate the behavior of albumin in patients with Covid-19 and dementia and its impact with mortality.
**Methods:** this is an observational cohort study performed in Italian hospitals that hospitalized COVID-19 patients. Hospitals that enrolled COVID-19 patients were from Rome Sapienza University and Perugia. We included in this study 225 adults (65 ≥ years), patients with laboratory confirmed COVID-19 and severe acute COVID-19 related pneumonia consecutively hospitalized in medical words from March 2020 to March 2021. COVID-19 was diagnosed on the basis of the WHO interim guidance.
**Results:** patients with dementia (n=75) had lower serum albumin and C-reactive protein (CRP) and higher D-dimer values. Dead patients had a higher prevalence of dementia and D-dimer levels values, but lower serum albumin and P/F ratio. Bivariate analysis showed that serum albumin correlated only with D-Dimer (Rs: -0.287,p<0.001) and PaO2/FiO2(P/F) ratio (Rs: 0.241,p<0.001) in the overall population.
In the subgroup of patients with dementia the only variables associated with serum albumin were D-Dimer (Rs: -0.319,p=0.005), P/F ratio (Rs: 0.284,p=0.01) and CRP (Rs: -0.429,p=0.02); no correlation was observed between albumin and AST (Rs: 0.141,p=0.348), ALT (Rs: 0.048,p=0.751) and creatinine (Rs: 0.132,p=0.261).
In the overall population, logistic regression analysis showed that dementia (OR: 3.1;B: 1.152, S.E.: 0.356, 95% C.I.: 1.5-6.3; p=0.001), serum albumin levels (OR: 0.923;B: -0.080, S.E.: 0.038, 95% C.I.: 0.86-0.99; p=0.03) and P/F ratio (OR: 0.995;B: -0.005, S.E.: 0.002, 95% C.I.: 0.991-0.998; p=0.005) were associated with mortality in COVID-19 patients.
**Conclusion:** we provide evidence that hospitalized elderly patients with dementia and COVID-19 have low albumin levels that could contribute to increase mortality.

**Table 1. Clinical characteristics of patients with and without dementia.**

| Table n.1 | No Dementia | Dementia | p |
|---|---|---|---|
| Population of the study | 75 | 150 | - |
| Females n (%) | 36 (48) | 71 (47) | 0.925 |
| Age years (median [IQR]) | 83±7 | 81±7 | 0.02 |
| Clinical characteristics | No Dementia | Dementia | p |
| Smokers (%) | 5 (6) | 27 (18) | 0.117 |
| COPD (%) | 9 (12) | 29 (19) | 0.706 |
| Diabetes (%) | 15 (20) | 40 (26) | 0.295 |
| Hypertension (%) | 93 (25.9) | 262 (44.4) | <0.001 |
| CAD (%) | 15 (20) | 25 (16) | 0.281 |
| Stroke (%) | 14 (18) | 15 (10) | 0.056 |
| Tumors (%) | 8 (12) | 16 (10) | 0.393 |
| Dyslipidemia (%) | 7 (9) | 23 (15) | 0.271 |
| Serum Albumin g/dl | 31.8±4.8 | 33.2±4.9 | 0.04 |
| D-DIMER ng/ml (median [IQR]) | 2459±1668 | 1885±1450 | 0.009 |
| CRP mg/L | 8 [2, 17] | 29 [12, 117] | <0.001 |
| P/F ratio | 257±100 | 81±7 | 0.02 |
| SpO2 (median [IQR]) | 93.6±5 | 94.1±3.9 | 0.475 |
| AST U/L | 34 [24, 53] | 30 [23, 43] | 0.201 |
| ALT U/L | 20 [13, 28] | 21 [14, 29] | 0.869 |
| Creatinine mg/dL | 1.1±0.8 | 1.1±0.7 | 0.425 |
| Low Molecular Weight Heparin | 56 (74) | 109 (73) | 0.986 |
| Glucocorticoids | 53 (70) | 86 (7) | 0.351 |

**Table 2. Clinical characteristics between deceased and survivors.**

| Table n.2 | Deceased | Survivors | p |
|---|---|---|---|
| Population of the study | 63 | 162 | - |
| Females n (%) | 35 (55) | 83 (51) | 0.560 |
| Age years (median [IQR]) | 82±7 | 81±7 | 0.376 |
| Clinical characteristics | Deceased | Survivors | p |
| Smokers (%) | 14 (22) | 18 (11) | 0.04 |
| COPD (%) | 12 (19) | 26 (16) | 0.394 |
| Diabetes (%) | 19 (30) | 36 (22) | 0.223 |
| Hypertension (%) | 41 (65) | 106 (65) | 0.810 |
| CAD (%) | 12 (19) | 28 (17) | 0.792 |
| Dementia (%) | 31 (49) | 44 (27) | 0.002 |
| Stroke (%) | 13 (20) | 10 (10) | 0.03 |
| Tumors (%) | 9 (14) | 15 (9) | 0.393 |
| Dyslipidemia (%) | 6 (9) | 24 (15) | 0.246 |
| Serum Albumin g/dl | 30.9±4.9 | 33.5±4.8 | <0.001 |
| D-DIMER ng/ml (median [IQR]) | 2422±1729 | 1942±1467 | 0.04 |
| P/F ratio | 217±91 | 271±98 | <0.001 |
| Creatinine mg/dL | 1.3±0.8 | 1.0±0.7 | 0.01 |
| SpO2 (median [IQR]) | 93.1±4.7 | 94.2±4.4 | 0.106 |
| AST U/L | 36 [27, 41] | 30 [22, 42] | 0.069 |
| ALT U/L | 21 [15, 29] | 20 [14, 29] | 0.967 |
| CRP mg/L | 27 [6, 41] | 11 [3, 15] | 0.122 |
| Low Molecular Weight Heparin | 40 (63) | 125 (77) | 0.517 |
| Glucocorticoids | 51 (80) | 88 (54) | 0 |

## 72. LACK OF A ROLE FOR ANGIOTENSIN RECEPTOR BLOCKERS (ARBS) AND ACE INHIBITORS ON OUTCOME OR LONG-TERM SEQUELAE IN COVID-19 UNVACCINATED PATIENTS

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**Introduction:** Coronavirus disease 2019 (COVID-19) pandemic represented and still represents a major clinical problem worldwide. Many studies are actively being carried out to better understand prognostic factors of outcome as well as optimal treatment. One "hot" topic remains the possible role of anti-hypertensive drugs on outcome of SARS-CoV-2 infection.
Namely, ACE2 receptor is highly expressed on the surface of cardiac and pulmonary cells, and it is used by coronaviruses, such as SARS-CoV and SARS-CoV-2, to enter host cells; specifically, the interaction between the "spike" protein of coronaviruses and ACE2 has been identified as a key factor for the virus transmission.
This makes the role of ACE-inhibitors and Angiotensin Receptor Blockers (ARBs) drugs extremely controversial and their role – if any – is still to be elucidated. Moreover, it is still unclear whether these drugs may have any impact on SARS-CoV-2 sequelae.
**Patients and Methods:** In this retrospective study, we analysed a group of 244 hypertensive unvaccinated patients admitted to our Medicine ward for moderate to severe COVID-19 pneumonia during pandemic. Patients were divided in two groups according to hypertensive treatment: ACE-inhibitors (n. 134) or ARBs (n. 110).
To avoid potential biases, in a preliminary analysis we considered a further group of 153 hypertensive patients treated with anti-hypertensive drugs other than ARBs and ACE-inhibitors: apart from a lower number of subjects with heart disease (as expected), we did not find any significant difference. Overall mortality was not significantly different as well.

The groups considered where homogeneous for age, sex, number and type of main comorbidities, number of medications taken (beyond anti-hypertensives). Their condition at admission were not significantly different (blood pressure, heart rate, temperature, biochemical and respiratory parameters), nor the treatment administered during hospital staying (oxygen, steroids, antibiotics, tocilizumab, remdesivir, low-molecular weight heparin and anti-coagulants). Number and type of complication (mainly atypical bacterial pneumonia, sepsis, pulmonary embolism) were not statistically different between groups.
For this reason, we focused our further analysis on patients treated with ACE-I or ARBs
Of these patients, a group of 46 (20 treated with ACE-I and 26 treated with ARBs) came to a follow-up visit after a mean of 260 days.
They were evaluated through a quality-of-life phone interview, standard laboratory tests, chest x-ray and/or chest computed tomography, spirometry with evaluation of the Diffusing capacity of the Lungs for Carbon Monoxide (DLCO).
**Results:** A total of 20 of 110 (18%) patients under treatment with ARBs and 23 of 134 (17%) died during hospitalization (p=0.8, NS). Overall mortality during the same period of hypertensive patients not treated with ARB or ACE-inhibitor
At admission we found only a significantly higher CRP in ARBs group, compared with the ACE-inhibitors group, but difference faded during hospitalization and at discharge, biochemical, radiological and respiratory data were not significantly different between surviving patients of the two groups.
Interestingly, as shown in the table, when the follow-up group was evaluated, we did not find any significant difference in terms of number of non-specific radiological alterations (i.e. ground-glass opacities, irregular linear/reticular opacities), lung fibrosis, spirometry data, DLCO diffusion, persisting effort dyspnoea.
Biochemical data were, once more, not different in the two groups.
**Conclusions:** In our study, we could not detect any difference in outcome nor in complication type or number in the two groups of hypertensive patients which were different only for ongoing anti-hypertensive treatment (ACE-inhibitor vs ARBs) at the time of hospital admission.
These results seem to support the idea that ACE-inhibitors and ARBs do not play a significant role in onset, evolution and outcome of moderate to severe COVID-19 pneumonia (as well as other anti-hypertensive drugs that do not have any interaction with ACE-receptor or its expression).
Although the number of follow-up patients is small, we did not find any difference in sequelae in both groups. Larger studies are needed to confirm these findings, but these preliminary data furthermore strengthen the hypothesis that no harm comes from ARBs or ACE-inhibitors even in long term follow up. Other mechanisms are probably involved in the development of long term sequelae of COVID-19.

| Demographic data | ACE-I | ARBs | Significance |
|---|---|---|---|
| Total number | 134 | 110 | |
| Male/Females | 85/49 | 68/42 | |
| Age | 74±12 | 73±11 | NS |
| Deaths | 23 | 20 | NS |
| Weight (kg) | 80±18 | 78±17 | NS |
| Hearth disease % | 51% | 42% | NS |
| Type 2 diabetes % | 38% | 34% | NS |
| COPD/Athsma % | 7% | 12% | NS |
| Neoplasm | 5% | 5% | NS |
| Mean comorbidities (beyond hypertension) | 2.0±0.4 | 1.9±0.3 | NS |
| Mean medications (beyond anti-hypertensives) | 2.3±0.3 | 2.1±0.3 | NS |

| Parameters at admission | ACE-I | ARBs | Significance |
|---|---|---|---|
| Temperature | 37.3±1.0 | 37.3±0.8 | NS |
| Systolic blood pressure | 136±21 | 137±25 | NS |
| Diastolic blood pressure | 77±13 | 78±14 | NS |
| Mean blood pressure | 97±14 | 97±16 | NS |
| Heart rate | 83±15 | 86±16 | NS |
| $FiO_2$% | 33±19% | 34±20% | NS |

| Biochemistry at admission | ACE-I | ARBs | Significance |
|---|---|---|---|
| WBC (10^3/µl) | 6.8±3.2 | 6.8±3.0 | NS |
| Neutrophils (10^3/µl) | 5.1±3.0 | 5.0±2.3 | NS |
| Lymphocytes (10^3/µl) | 1.2±0.9 | 1.1±0.9 | NS |
| Monocytes (10^3/µl) | 0.5±0.3 | 0.5±0.3 | NS |
| Hb (g/dl) | 13.1±1.8 | 12.7±1.8 | NS |
| Haematocrit (%) | 38±5 | 36±5 | NS |
| Platelets (10^3/µl) | 217±89 | 218±85 | NS |
| CRP (mg/L) | 79±69 | 104±83 | p<0.05 |
| D-Dimer (ng/ml) | 1363±2107 | 779±1133 | NS |
| Ferritin (µg/L) | 890±977 | 976±1292 | NS |
| Creatinine (mg/dl) | 1.1±0.6 | 1.2±0.7 | NS |

| Alterations at follow-up | ACE-I | ARBs | Significance |
|---|---|---|---|
| Radiologic alterations (%) | 70% | 75% | NS |
| FEV1/FVC % | 79±9% | 79±4% | NS |
| DLCO alteration | 45% | 38% | NS |
| DLCO % (of predicted) | 81±18 | 87±15 | NS |
| Pulmonary fibrosis (%) | 22% | 25% | NS |

| Quality of life at follow-up | ACE-I | ARBs | Significance |
|---|---|---|---|
| Persisting Fever | 0% | 0% | NS |
| Effort dyspnea | 70% | 52% | NS |
| Fatigue | 65% | 62% | NS |
| Anorexia | 25% | 15% | NS |
| Insomnia | 35% | 31% | NS |
| Anxiety | 50% | 46% | NS |

## 73. THE ROLE OF INFLAMMATION AND RISK FACTORS IN THE PROGNOSIS OF GERIATRIC SUBJECTS HOSPITALIZED FOR SARS-COV2. THE EXPERIENCE OF INTERNAL MEDICINE

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**Background:** Several evidence have shown that SARS-Cov-2 infection has been sustained by a high systemic inflammatory status with severe cytokine storms, which contributed to severity of disease, morbidity, and mortality in hospitalized patients. We aimed to evaluate the outcome of COVID-19 hospitalized patients according to clinical and inflammatory profile.
**Methods:** The study enrolled 595 older (>65 yrs) patients (F: M=266: 329, BMI=27.4 Kg/mt2 ± 5 SD) hospitalized for Sars-Cov2 at the Internal Medicine of Bari (Clinica Medica "A. Murri", and Medicina Interna Ospedaliera "N. Pende") from September 2020 to May 2021. The following parameters were assessed: white blood cells, plates, ferritin, transaminases, LDH, CPK, CRP, fribinogen, D-dimers, presepsin, serum amyloid (SAA), procalcitonin (PCT), interleukin 6 (IL-6). The following features were assessed: lenght of hospitalization, BMI, comorbidities (obesity, smoke, diabetes mellitus, cardiovascular diseases, neoplasia, liver disease, COPD), days of COVID-19 positivity, COVID-19 severity scoring (0-5) during hospitalization, and symptoms (fever, cough, dyspnea, chest pain, asthenia, ageusia/anosmia, diarrhea).
**Results:** The lenght of hospitalization was 14 days ± 11 SD and it was positively correlated with the COVID-19 severity scoring. According to BMI (27.4 Kg/mt2 ± 5 SD; F 27±6 vs. M 28±4, p=NS) there was a positively correlation with the length of hospitalization (N= 595; R=0,01; p<0,01). According to symptoms, 14% was asymptomatic; fever was reported by 63% of subjects (F 42% vs M 58%, p<0,0001); cough by 36% (F 40% vs M 60%, p<0,001); dyspnea by 45% (F 43% vs M 57%, p=0,002); chest pain by 45% (F 54% vs M 46%, P=NS); asthenia by 27% (F 46% vs M 54%, P=NS); ageusia/anosmia by 6% (F 56% vs M 44%, P=NS); diarrhea by 9% (F 60% vs M 40%, P=NS). According to comorbidity, 26% of subjects didn't have comorbidities; smoke was reported by 18% (F 16% vs M 84%, p<0,001); diabetes mellitus by 20% (F 37% vs M 63%, p=0,0001); cardiovascular pathology by 62% (F 47% vs M 53%, P=NS); neoplasia by 11% (F 50% vs M 50%, P=NS); hepatopathy 4% (F 39% vs M 61%, P=NS); COPD 10% (F 36% vs M 64%, p=0,002). According to bioumoral exams, CRP was 69 ± 62 mg/dL (F 72 ± 63 vs M 68 ± 62, P=NS; r=0,29, p<0,001); D-dimers 2968 µg/mL ± 19544 (F 3548 ± 28918 vs M 2402 ± 5656, P=NS; r=0,04, p=NS); presepsin 674 pg/ml ± 800 (F 660 ± 778 vs M 680 ± 802, P=NS; r=0,04, p=NS); SAA was 366 mg/L ± 440 (F 371 ± 469 vs M 363 ± 407, P=NS; N=178, r=0,12, p=NS); PCT 0,7 ± 5,5 (F 0,4 ± 2 vs M 0,6 ± 5,1, P=NS; N=457, r=0,12, p<0,01) and IL-6 was 45 ± 81 (F 42 ± 58 vs M 45 ± 72, P=NS; N=518, r=0,15, p<0,0004). According the COVID-19 severity scoring there was a positively correlation with PCT (N=457, r=0,12, p<0,01), IL-6 (N=518, r=0,15, p<0,0004). According to the length of hospitalization there was a positively correlation with inflammation indexes ((WBC, r=0,20, p=0,01; LDH, r=0,17, p=0,0001; CRP, r=0,19, p<0,001; fibrinogen, r=0,16, p<0,001; SAA, r=0,30; p<0,001, IL-6, r=0,18, p<0,001). Finally, patients who died during hospitalization showed greater values of SAA and IL-6 than those survived (740,6 ± 544,8 vs. 399,5 ± 480,4, p=0,02; 98,8 ± 163 vs. 43 ± 65,8, p<0,0001, respectively).
**Conclusion:** Based on the study results, several inflammatory biomarkers might represent sensitive indicators in evaluating the severity and prognosis of COVID-19. A complete approach considering clinical profile and inflammatory status might be useful in driving clinical decisions tailored to hospitalized COVID-19 patients.

## 74. LONG-LASTING FEVER AND HYPER INFLAMMATION IN FRAGILE PATIENTS WITH SARS-COV-2 INFECTION WHO UNDERWENT EARLY ANTIVIRAL TREATMENT: A CASE SERIES

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**Background:** During the COVID-19 pandemic, evidence has shown that some particular conditions (i.e. hematologic/oncologic or cardiovascular (CV) diseases, obesity, immunodeficiencies, immunosuppressive therapies, Chronic Obstructive Pulmonary Disease (COPD), kidney or liver failure) increase the risk of developing severe SARS-CoV-2-related pneumonia. In this scenario, the administration of early antiviral therapy has demonstrated to improve the outcome of fragile patients [1, 2, 3], reducing the risk of hospitalization and death from COVID-19. Indeed, most of the fragile patients who were visited in the Mild-to-Moderate COVID-19 outpatient clinic of San Raffaele University Hospital (MMCO) [4] and received early antiviral therapy, had a favourable course of the infection. However, some patients did not particularly benefit from this therapeutic approach, and developed major inflammatory state and interstitial pneumonia.
**Aim of the Case Series:** The aim of the present case series was to analyze the clinical features and outcomes of a cohort of patients attending the MMCO from January 2022 to April 2022, who underwent early antiviral therapy for SARS-CoV-2.
**Case Description:** Data from 156 patients (87 males, 69 females) were

analyzed. In particular, 98 patients received the anti-viral agent Remdesivir, 33 Nirmatrelvir/Ritonavir and 25 Molnupiravir.
The main indications for therapy in our study population were: primary or acquired immunodeficiency (n=70, 44.9%); active hematologic disease (n=44, 28.2%), Body Mass Index >30 kg/m2 (n=16, 10.2%), CV diseases (history of coronaropathy, Ischaemic myocardial infarction, heart failure, congenital cardiomyopathies; n=12, 7.7%), solid tumors (n=9, 5.8%), severe COPD (n=4, 2,6%) or chronic kidney failure (1 patient, 0.64%). Of note, most of these patients had multiple underlying conditions, which put them further at risk of developing a severe form of COVID-19.
In this scenario, 11/156 (7.05%, mean age 65 ± 13) patients developed a severe inflammatory state and interstitial pneumonia, and all of them had been treated with Remdesivir or Molnupiravir (8 and 3 patients, respectively).
Within these patients, 4 had Chronic Lymphocytic Leukemia (CLL) and were in current therapy with BK-inhibitors (3 with Ibrutinib, 1 with Acalabrutinib) for their hematological disease. Four patients had Non-Hodgkin Lymphoma (NHL, 3 with Follicular Lymphomas, 1 with Mantle Cell Lymphoma) and were in current treatment with CD-20 inhibitors (Rituximab). The last 3 patients, who were suffering from autoimmune diseases, were also being treated with CD-20 inhibitors, or had received at least one dose of Rituximab during the past year.
All of these patients had persistent fever at the onset (soon after contracting the infection or after an initial reduction in symptoms, with a variable response to NSAIDs or paracetamol) and required steroid therapy (dexamethasone up to 6-8 mg, with some cases requiring a following administration of prednisone up to 75 mg). Moreover, all of them showed signs of interstitial pneumonia, with evidence of an increasing Lung Ultrasond Score (LUS) [5] or with the typical "ground glass" pattern at the thoracic CT scan. 9 patients required hospitalization, and 5 worsened to acute respiratory failure. One of the hospitalized patients deceased in spite of intensive care support.
**Conclusion:** Our data suggest that patients suffering from a hematological/autoimmune disease (in particular patients affected by CLL or follicular and mantle NHL exhibiting B-cell suppression because of the treatment with BK-inhibitors or CD-20 inhibitors) are less likely to benefit from early antiviral therapy than individuals with other underlying conditions or with the same disease but treated with different therapies.
New England Journal of Medicine
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## 75. COVID19 AND SNEAKY BLEEDINGS IN ANTICOAGULATED PATIENTS: A CASE SERIES

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**BACKGROUND:** SARS-CoV2 infection is associated with a hypercoagulable state in hospitalized patients and high rates of venous thromboembolism (VTE) have been reported. Prophylactic anticoagulation is normally recommended during infection, while intermediate or treatment-intensity regimen is restricted to highly suspicion or evidence of VTE. Bleeding is a growing concern in anticoagulated COVID19 patients. Spontaneous rectus sheath hematomas (RSHs), oblique muscle hematoma (IMH) and retroperitoneal hematomas (RPHs) are often overlooked cause of abdominal pain and potentially life-threatening bleedings. In literature, 18 COVID19 anticoagulated patients with RPH/RSH are described.
**Methods:** Herein, we describe a case series of five COVID19 patients suffering from spontaneous RSH/IMH/RPH in an Internal Medicine University Department between 5th october 2021 to 20th april 2022.
**Case Series:** 5 patients out of 468 COVID19 patients hospitalized in a non-intensive care setting suffered from RSH/IMH/RPH during anticoagulant treatment. All patient had confirmation of SARS-CoV2 infection with Polymerase Chain Reaction test and had evidence of Pneumonia at Chest X-ray. Four patients were vaccinated against SARS-CoV2. No patient had alteration in clot time or history of major bleeding.
**Case 1:** An 81-years-old woman was admitted to the hospital due to abdominal pain. She had been recently diagnosed with metastatic pulmonary cancer and VTE in treatment with intermediate-anticoagulant treatment. Her lab test showed Hemoglobin (Hb) 80 g/L. A contrast enhanced CT scan (CECT) showed RSH. Urgent embolization was performed and red blood cell (RBC) transfusion administered. She required low dose O2 supplementation. Anticoagulant was initially stopped. When she ameliorated, anticoagulant was gradually reintroduced with no further complications. She was discharged after 25 days.
**Case 2:** A 62-years-old, not vaccinated male was admitted to the hospital due to respiratory failure and required mechanical ventilation in ICU. Hb was 140 g/L at lab test. Due to evidence of VTE, intermediate anticoagulant treatment was started. He was then transferred to our department. After seven days of admission, he presented sudden onset of flank pain. Urgent lab tests showed Hb 118 g/l. CECT showed a left IMH with no evidence of active bleeding. He was treated conservatively. Anticoagulant was stopped and caval filter placed. He was discharged after 22 days.
**Case 3:** A 59-years-old, woman was admitted to the hospital due to respiratory failure. Her past medical history included sarcoidosis in steroid treatment and severe chronic kidney disease (CKD). She required O2 supplementation and prophylaxis with heparin was started. The initial laboratory test showed Hb 104 g/l. After 8 days since admission, she complained of sudden onset of abdominal pain. Urgent test showed Hb 64 g/l and RBC transfusion was administered. CECT showed vast left RSH and embolization was performed. The next day new embolization was performed due to right RSH. She experienced cardiovascular instability and acute kidney injury. Thus, she underwent ultrafiltration in ICU and then transferred to Surgery department for abdominal collection drainage. The patient is still admitted after 36 days.
**Case 4:** A 78-years-old, women was admitted to the hospital due to respiratory failure. Her past medical history included multiple myeloma and mild CKD. She presented with Hb 74 g/l and Platlet count of 51000/mm3. RBC transfusion was needed and Hb rise to 97 g/l. Due to evidence of VTE, intermediate anticoagulation was started because of thrombocytopenia. After 6 days of admission, she presented left leg impotency. Hip X-ray was negative. The day after the patient developed hypotension and urgent test showed Hb 74 g/l and platlet count 37000 mm3. CECT showed a vast left RPH with multiple bleeding spots. No invasive treatment could be undertaken due to patient's comorbidity. RBC and platlet transfusion were administred. In the next hours, the patient developed abdominal pain and died because of hypovolemic shock.
**Case 5:** A 93-years-old man was admitted to the hospital due to respiratory failure due to acute heart failure. His past medical history included Chronic Myeloid Leukemia in active treatment, ischemic cardiomyopathy in treatment with aspirin. Lab test showed Hb 122 g/l and creatinine 2,6 mg/dl. He tested positive for SARS-COV2 infection and transferred to our department. When he ameliorated, prophylaxis with heparin was introduced. He complained of hip and flank pain. X-ray and groin ultrasound were negative. During hospitalization, Hb slowly dropped to 99 g/l. The CECT showed a RSH without spot of active bleeding. He was managed conservatively. He was discharged after 19 days.
**Conclusion:** All patient presented with moderate/severe COVID19 infection and treated with prophylactic or intermediate anticoagulant treatment, which are generally considered safe. Spontaneous RPH/RSH/IMH should be considered in the differential of abdominal/flank pain in anticoagulated COVID19 patients and as a life-threatening complication which lengthen the hospital stay.

## 76. ANTI-SARS-COV-2 MONOCLONAL ANTIBODIES USE: OUR EXPERIENCE

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**Introduction:** Anti-SARS-CoV-2 monoclonal antibodies (mAbs) that target the spike protein have been shown to have clinical benefits in treating SARS-CoV-2 infection. The effectiveness of the different anti SARS-CoV-2 mAb therapies varies dramatically depending on the circulating variant, and the role of each anti-SARS-CoV-2 mAb in the treatment of COVID-19 remains fluid. Treatment with anti-SARS-CoV-2 mAbs should be started as soon as possible after SARS-CoV-2 infection is confirmed by an antigen test or a nucleic acid amplification test and within 7 days of symptom onset and should be administered in a setting where severe hypersensitivity reactions, such as anaphylaxis, can be managed. Treatment with anti-SARS-CoV-2 mAbs should be considered for patients with mild to moderate COVID-19 who are hospitalized for a reason other than COVID-19 if they otherwise meet the Emergency Use Authorization (EUA) criteria for outpatient treatment. In this paper we analyze the Anti-SARS-CoV-2 mAbs use

in our clinical practice.
**Methods:** This single-center retrospective study was conducted between March 22, 2021 and January 22, 2022 at a Internal Medicine COVID ward in adult patients with COVID-19 in Pordenone Hospital. Data on patient demographics, clinical characteristics, and outcomes were collected from health records of the hospital. Data on safety outcomes (adverse events [AEs], serious adverse events [SAEs], and suspected drug-related hypersensitivity reactions) were extracted from the medical records. Inclusion criteria were hospitalized and outpatients with SARS-CoV-2 infection as confirmed by reverse-transcription polymerase chain reaction assay and meet the Anti-SARS-CoV-2 mAbs Emergency Use Authorization (EUA) criteria.
**Results:** A total of 133 patients received anti-SARS-CoV-2 mAbs and were included for the analysis. The median (range) age was 59 (17-98) years, with the majority being male (n=79; 60,1%). We used BAMLANIVIMAB+ETESEVIMAB in 22 patients (median age was 65 years, male n=13; 59%), CASIRIVIMAB E IMDEVIMAB in 97 patients (median age was 66 years, male n=59; 60%), SOTROVIMAB in 13 patients (median age was 66 years, male n=7; 53%). Most patients had ≥1 comorbidity, including diabetes mellitus (28%), hypertension (50%), chronic heart disease CHD (13%), chronic kidney disease CKD (8%), obesity (33%), and chronic respiratory disease (asthma/chronic obstructive pulmonary disease [COPD]; n=10, 8%). Among the 133 patients, none had AE or SAEs after drug administration. Of the 77 hospitalized patients, 59 (76%) were discharged, and 8 (10%) died. The median (interquartile range [IQR]) LOHS was 12 (2-33) days. Ten patients required mechanical ventilation and transferred to intensive care unit. Outpatiens group was younger than hospitalized patients. In 26 hospitalized patients we also used remdesivir. 47 hospitalized patients had completed the sars-CoV-2 vaccination course and only seven had a protective antibody titer.
**Discussion and Conclusion:** The advantage of monoclonal antibodies is that they are a very specific therapy, with good success rates, as it is specially built around the virus, but with efficacy only in the very early stages of the disease. But the disadvantage of monoclonal antibodies, which does not make them a treatment and prevention tool for Covid-19 that can be pursued and feasible on a large scale, is represented by high cost and limited time duration. The use of bamlanivimab plus etesevimab and casirivimab plus imdevimab has paused in Italy because the Omicron VOC has markedly reduced in vitro susceptibility to these mAbs, therefore, this regimen is not expected to provide clinical benefit for patients with Omicron infection. Sotrovimab retains in vitro activity against the Omicron BA.1 and BA.1.1 subvariants, but it has substantially decreased in vitro activity against Omicron BA.2 and is not expected to provide clinical benefit for patients with Omicron BA.2 infection. To define the utility of specific mAbs in the future, ongoing of the types and proportions of circulating SARS-CoV-2 variants, as well as studies on the susceptibility of different variants to available anti-SARS-CoV-2 mAbs, will be important.

## 77. ACUTE EMBOLISMS IN MULTIPLE ARTERIAL DISTRICTS FOLLOWING AD26.COV2-S VACCINE

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A 74-year-old Caucasian man presented abdominal pain, vomit, loss of appetite, constipation, and polyuria, appearing 15 days before hospitalization. He also complained mild hypoesthesia and paresthesia in the right foot and right-side brachialgia.
The medical, surgical, or family history was negative for relevant diseases or risk factors (including alcohol or cigarette use), except the presence of treated arterial hypertension. Thirty days prior to hospital admission, the patient was vaccinated with the adenoviral vector vaccine Ad26.COV2-S.
The patient had not previously been exposed to heparin nor reported any previous positive COVID-19 molecular test, and on admission he tested negative to rhino-pharyngeal swab for SARS-CoV-2.
In ED, the patient was stable (temperature 36.8°C, blood pressure 160/90 mmHg, pulse rate 112 beats/minute, oxygen saturation of 96% on room air). Cardiovascular system examination noticed a systolic murmur (intensity 2/6). Crackling sounds were reported at lung auscultation. No alteration in the physical examination of the abdomen was observed. The results of blood tests were normal except for a specific mild elevation of amylase, lipase, creatinine, and PCR levels. Chest x-ray was normal, while direct abdominal x-ray displayed constipation, few air-fluid levels and rectal fecaloma.
A subsequent contrast-enhanced abdominal CT showed mesenteric panniculitis and diverticulosis for which he started therapy with Metronidazole 500 mg three times daily, Ceftriaxone 2 g once daily and Enoxaparin 4000 UI once daily.
On day 2 of hospital stay, the patient presented sudden pain in the right arm, with the disappearance of the right radial pulse. Arterial Doppler ultrasound displayed acute subclavian artery occlusion without lesion or alteration in the whole supra-aortic arterial district. Therefore, the patient had successful Fogarty arterial embolectomy. Enoxaparin 4000UI was increased twice a day.
From day 3 to day 5 of hospital stay, the patient presented paresthesia of the right leg and progressive reduction of the right leg pulse. Arterial Doppler ultrasound showed superficial right femoral artery occlusion. The patient had another successfully Fogarty arterial embolectomy. The Echocardiography and prolonged (72 hours) Holter ECG resulted normal allowing to exclude cardiac sources of embolization.
On day 9 of hospital stay, the persisting anorexia and nausea, leading the patient to significant weight loss led us to order a new contrast-enhanced total body CT that showed coeliac artery occlusion with splenic infarction, and mesenteric panniculitis. Blood test [homocysteine, lupus anti-coagulant antibodies, beta-2 glycoprotein antibodies, ANA, ANCA, IgG4, CA 125, CA 19.9, CEA, PSA total and free, NSE] gastric and colon endoscopy were negative making unlikely the presence of autoimmune disease, vasculitis, or primary coagulation disorders.
Suspecting an unusual form of Vaccine-induced immune thrombotic thrombocytopenia (VITT) (absence of thrombocytopenia and negative PF4-Antibody), the patient underwent treatment with intravenous immunoglobulin (0.4 g/Kg/die), Methylprednisolone 80 mg once daily (1 mg/kg/die) and Fondaparinux 7.5 mg once daily.
During the last two weeks of hospitalization arterial thrombosis did not recurr and he started physical/motor rehabilitation to prevent loss of motor function; glucocorticoids were also tapered. On day 29 the patient felt better and was discharged at home. The therapy-specific response and the clinical manifestation suggested an unusual presentation of VITT, confirmed after the hospital discharge performing a different anti-PF4 antibody assay (ASSE- RACHROM HPIA IgG; absorbance at 405 nm, 0.063 e 1.478 for negative or positive case, respectively) on the blood sample drown prior to any treatment indicated for VITT; the assay was frankly positive.
**Conclusions:** An increase in vigilance regarding extremely rare side effects associated with COVID-19 vaccination is needed. VITT is a serious complication of vaccination that is not possible to predict or prevent and that can occur also in the absence of thrombocytopenia. When patients, among 5-30 days post-vaccination, begin to manifest sustained headache, neurologic symptoms/signs, abdominal pain, dyspnea, or limb pain/swelling, reduced platelet count or D-dimer elevation, antibody to PF4 must be measured, and imaging for thrombosis performed. Reporting unusual adverse events of the vaccinations is crucial to help clinicians better understand the long-term outcomes.

## 78. FIB-4 AND IN-HOSPITAL MORTALITY

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**Background:** Cumulating evidence suggests that severe Sars-CoV-2 infection is associated with multi-organ involvement including hepatic impairment. Increased values of FIB-4 score appear to be associated with poor clinical outcomes. The aim of our study is to analyze clinical features associated with adverse outcomes using artificial intelligence for data collection. In particular we evaluated FIB-4 as a predictor of mortality. FIB-4 is a scoring system derived from routine blood tests, including AST, ALT, platelet count, and age and it has been validated to predict advanced fibrosis in liver diseases.
**Methods:** A retrospective study including all consecutive in-hospital patients with confirmed COVID-19 (at least one positive RT-PCR SARS-CoV-2 test from nasopharyngeal swab) was performed. All clinical and laboratory data were collected at admission through the "Gemelli Generator" an artificial intelligence system of our tertiary hospital. Date of discharge or death were recorded. Kaplan-Meier survival analysis was adopted to plot the overall survival probability.
Univariate analysis and Cox regression model were used to identify predictors of in-hospital mortality. A subgroup analysis was performed among

patients for whom a FIB-4 could be calculated.
**Results:** 2563 patients were included (median age: 68 years, IQR 54.00 – 80.00). Fever and dyspnea were reported in the majority of them (68.2% and 55%, respectively). The most common comorbidities were: hypertension (37.4%), active cancer (29.3%), diabetes (16.4%) and heart failure (15,6%).
During the hospitalization, 453 patients (17.7%) died. Patients who did not survive had a higher median age (81y [IQR: 72-87] vs 64y [IQR: 52-77], p < 0.01), were more likely male (60 %, p=0.03).
The median length of stay (LOS) was 12 days [IQR: 7-21 days].
Fib4 was calculated only on 226 patients as the routine testing of our emergency department does not include AST, which is one of the essential parameters to calculate Fib4.
Subgroup analysis revealed that increased values of FIB-4 score are associated with higher mortality. Moreover through the ROC analysis we also found a cut-off of 2.53 over which patients have a significantly higher risk of death. This was confirmed at multivariate Cox regression: patients with FIB-4 values greater than 2.53 had a risk of dying five times higher than those who had values lower than this threshold (HR: 5.077, 95% CI 2.526 - 10.206, p=<.001).
**Conclusions:** We argue in favour of calculating that FIB-4 for all COVID patients at the time of hospitalization, in order to an early identification of these fragile patients who might require a more intensive monitoring and therapies.

## 79. ENDOTHELIAL DYSFUNCTION AND INCREASED OXIDATIVE STRESS IN PATIENTS WITH COVID-19 PNEUMONIA

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**Background:** Previous studies have tried to elucidate the pathogenesis of Sars-COV-2. Great interest has focused on vascular endothelium and its changes as a potential underlying mechanism of the "cytokine storm" and hypercoagulability of this disease. Some studies hypothesized that oxidative stress and endothelial dysfunction, could be responsible of the altered endothelium homeostasis in patients with COVID-19. However, it is unclear the role of NADPH oxidase and endothelial function in patients with COVID-19 and and the comparison with patients affected by community acquired pneumonia (CAP).
**Objective:** To analyse endothelial function and NADPH-oxidase-2 activation in patients with COVID-19 pneumonia and CAP. Furthermore we want to analyze the role of LPS in this setting.
**Study Design:** In this cross-sectional study, we enrolled 60 consecutive patients, 20 with COVID-19 infection and SARS-CoV2-related pneumonia, 20 hospitalized patients with CAP and 20 hospitalized patients without acute infections and matched for sex, age, and comorbidities. In all subjects we performed flow mediated dilation (FMD) to assess endothelial dysfunction and collected blood samples to analyse markers of oxidative stress (Serum sNOX2-dp detection, H2O2 production, Nitrite/Nitrate Serum and Platelet Level Measurement). Finally, we assessed LPS and zonulin serum levels, in order to investigate a potential pathogenesis.
**Results:** Compared with controls, Covid patients had significant higher values of LPS, sNOX-2-dp, H2O2, and zonulin; conversely FMD dilatation, HBA and NO were significantly lower in patients with Covid compared to controls (Table). Moreover, Covid patients had significantly higher levels of LPS, sNOx-2-dp, H2O2 than patients with CAP (Table). Simple linear regression analysis showed that FMD inversely correlated with serum with sNOX2 (Rs= -0,423; p<0.001), H2O2 (Rs=-0,428; p<0.001); conversely FMD was directly correlated with NO bioavailability (Rs=0.294; p<0.023) and HBA (Rs=0.411; p<0.001). A multiple linear regression analysis, including the variables linearly associated with the dependent variable, was performed to define the independent predictors of FMD; LPS resulted as the only predictor of FMD.
**Conclusion:** This study shows that patients with COVID-19 infection have endothelial dysfunction, and increased oxidative stress. Low-grade endotoxemia could be involved as an underling mechanism.

| | Patients with COVID-19 | P | Patients with CAP | P | Controls |
|---|---|---|---|---|---|
| N. | 20 | - | 20 | - | 20 |
| Age | 69.8±17.8 | 0.841 | 70.9±15.7 | **<0.001** | 74.3±5.4 |
| Male/Female (no/yes) | 14/6 | 0.507 | 12/8 | 0.723 | 15/5 |
| SAH (no/yes) | 7/13 | 0.599 | 4/11 | 0.144 | 3/17 |
| Diabetes (no/yes) | 15/5 | 0.727 | 12/3 | 1.000 | 15/5 |
| Liver disease (no/yes) | 19/1 | 0.883 | 14/1 | 0.311 | 20/0 |
| Kidney failure (no/yes) | 14/6 | 0.503 | 12/3 | **0.037** | 19/1 |
| AF (no/yes) | 17/3 | 0.016 | 7/8 | 0.429 | 15/5 |
| CVD (no/yes) | 16/4 | 0.372 | 10/5 | 0.667 | 12/2 |
| Previous stroke (no/yes) | 19/1 | 0.833 | 14/1 | 0.396 | 14/0 |
| Neoplasm (no/yes) | 17/3 | - | - | 0.129 | 14/0 |
| Dyslipidemia (no/yes) | 14/6 | 0.833 | 10/5 | 0.256 | 17/3 |
| Encephalopathy (no/yes) | 17/3 | 0.117 | 15/0 | 0.129 | 14/0 |
| Creatinine (mg/dL) | 1.2±0.7 | 0.829 | 1.0±0.2 | 0.024 | 0.9±0.2 |
| CRP (mg/L) | 5.5±5.1 | 0.886 | 5.8±6.1 | **<0.001** | 1.0±0.7 |
| hs-cTn (ng/mL) | 0.035±0.045 | 0.335 | 0.052±0.064 | - | - |
| Statin (no/yes) | 16/4 | 1.000 | 12/3 | 0.288 | 13/7 |
| Antiplatelet (no/yes) | 16/4 | 0.372 | 10/5 | 0.667 | 17/3 |
| Anticoagulant (no/yes) | 10/10 | 0.557 | 9/6 | 0.197 | 14/6 |
| FMD dilatation (%) | 2.8±3.1 | 1.000 | 3.5 | **0.001** | 6.1±2.5 |
| sNOX-2-dp (pg/ml) | 47.9±6.7 | **0.001** | 32.1±16.8 | **<0.001** | 10.5±13.3 |
| H2O2 (µM) | 54.5±8.6 | **<0.001** | 30.8±7.6 | **<0.001** | 9.3±3.3 |
| NO (µM) | 29.6±9.2 | 0.180 | 24.5±7.6 | **<0.001** | 51.9±8.2 |
| HBA | 16.7±5.5 | **<0.001** | 31±9.7 | **<0.001** | 52.3±10.6 |
| LPS | 52.9±11.4 | **0.02** | 45.7±6.1 | **<0.001** | 18.2±5.1 |
| Zonulin (ng/mL) | 3.3±0.5 | 1.000 | 3.2±0.4 | **<0.001** | 1.6±0.5 |

## 80. SARS-COV-2 INFECTION IN A WOMAN AFFECTED BY GLANZMANN THROMBASTHENIA AND ATRIAL FIBRILLATION: BALANCING BLEEDING AND THROMBOTIC RISKS

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Glanzmann thrombasthenia (GT) is a rare autosomal recessive platelet disorder, characterized by an impaired platelet function due to a quantitative and/or qualitative defect of the αIIbβ3 integrin. Despite normal platelet count and morphology, patients with GT show a reduction or absence of clot retraction and prolonged bleeding time. The main clinical manifestation of GT is represented by mucocutaneous bleeding.
The current worldwide pandemic of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is also associated with a hypercoagulability status leading to increased incidence of thromboembolic events (VTE). Notwithstanding, haemorrhagic manifestations have been reported. This leads to a complex pharmacological management and consequently more caution is needed in the intensive use of anticoagulant treatment in COVID-19.
We report here a rare case of a 79-years old female with GT who developed bleeding manifestations and anemization after SARS-CoV-2 infection. GT was diagnosed at the age of 31 and she also had history of arterial hypertension, permanent atrial fibrillation (AF), diverticular disease of both descending and sigmoid colon. She was not vaccinated against COVID-19.
On February 9, 2022 she was admitted to the Internal Medicine Unit of the Messina University Hospital because of increasing fatigue and shortness of breath, orthopnea and ecchymosis on the trunk. After 7 days, she had a positive result of the molecular detection of SARS-CoV-2 and consequently she was referred to our COVID-19- Internal Medicine Unit. On February 16, 2022 her laboratory examinations showed a hemoglobin (Hb) concentration level of 8.4 gr/dL, with normal count of both platelet and conventional coagulation parameters; factors VII, VIII, IX and XII were within normal limit.
Given the patient's high thromboembolic risk (permanent AF, obesity, immobility, increased D-dimer, SARS-CoV2 infection), despite the underlying hemopathology, thromboembolic prophylaxis with low molecular weight heparin (enoxaparin 4000 IU/day) was started but then suspended after 48 hours because of onset of melena. During the hospitalization she experienced multiple bleeding events (i.e. rectorrhagia, melena and two events of macroscopic hematuria), as well as new onset of ecchymosis on the upper and lower limbs. On March 2, 2022 a complete blood count revealed a drop in hemoglobin levels to 6.8 g/dl, consequently she totally recei-

ved 2 units of packed red blood cells and 1 platelet pool. On March 03, 2022 she underwent both colonoscopy and esophagogastroduodenoscopy; the first showed diverticulosis of sigma and ascending colon, a small polyp of ascending colon and first-degree internal hemorrhoids; the esophagogastroduodenoscopy showed a sliding hiatal hernia, petechial erosive gastritis and a small gastric polyp. Due to the concomitant presence of hypertensive heart disease, we chose to manage patient's gastrointestinal bleedings with an intravenous administration of the antifibrinolytic agent (tranexamic acid) instead of desmopressin. Successfully, gastrointestinal bleedings stopped and hematuria gradually disappeared, thus improving hemoglobin count with a significant reduction of blood transfusions. On day 23, patient underwent another molecular diagnostic test for SARS-CoV-2, which resulted negative; hence, she was admitted to the Internal Medicine Unit for the subsequent management and then discharge, without any evidence of venous thromboembolic complications.
We described here a rare case of SARS-CoV-2 infection in a GT patient with a complex management of the imbalance between hemorrhagic and thrombotic risk. We hypothesize that GT-related bleeding diathesis may have led to a reduced risk of venous thromboembolic complications associated with SARS-CoV-2 infection.
**References:** [1] Botero JP, Lee K, Branchford BR, Bray PF, Freson K, Lambert MP, Luo M, Mohan S, Ross JE, Bergmeier W, Di Paola J; ClinGen Platelet Disorder Variant Curation Expert Panel. Glanzmann thrombasthenia: genetic basis and clinical correlates. Haematologica. 2020 Apr;105(4): 888-894. doi: 10.3324/haematol.2018.214239. PMID: 32139434; PMCID: PMC7109743. [2] Lorini FL, Di Matteo M, Gritti P, Grazioli L, Benigni A, Zacchetti L, Bianchi I, Fabretti F, Longhi L. Coagulopathy and COVID-19. Eur Heart J Suppl. 2021 Oct 8;23(Suppl E): E95-E98. doi: 10.1093/eurheartj/suab100. PMID: 34650364; PMCID: PMC8503535. [3] Al-Samkari H, Karp Leaf RS, Dzik WH, Carlson JCT, Fogerty AE, Waheed A, Goodarzi K, Bendapudi PK, Bornikova L, Gupta S, Leaf DE, Kuter DJ, Rosovsky RP. COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. Blood. 2020 Jul 23;136(4): 489-500. doi: 10.1182/blood.2020006520. PMID: 32492712; PMCID: PMC7378457. [4] Sattler L, Feugeas O, Hager C, Grunebaum L, Desprez D. COVID-19 in a pediatric patient with Glanzmann thrombasthenia. Pediatr Blood Cancer. 2020 Oct;67(10): e28662. doi: 10.1002/pbc.28662. PMID: 32798297; PMCID: PMC7460953.

## 81. NAFLD IS ASSOCIATED TO POST-COVID SYNDROME

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**Background:** Post-Acute COVID syndrome (PACS) is an increasingly widespread emerging nosological entity, affecting millions of people all over the world.
The association between non-alcoholic fatty liver disease (NAFLD) and PACS has never been explored so far. The aim of our study is to assess the prevalence of steatosis in a cohort of patients previously hospitalized for COVID-19 and with PACS.
**Methods:** We enrolled consecutive patients attending the post-acute outpatient service for individuals after recovery from COVID-19 of our tertiary Hospital.
Patients were considered suffering of PACS in case of persistence of symptoms (present or not at the onset of the infection) after 4 weeks of infection, with a permanent, relapsing / remitting or progressive improvement course or/and in case irreversible tissue damage after 12 weeks that could trigger different degrees of permanent dysfunction and associated symptomatology. The diagnosis of steatosis was performed according to ultrasound criteria or non-invasive fibrosis scores. Data was collected during in a single multispecialistic assessment visit at 121-day (SD ± 89.2) from hospital discharge. We recorded symptoms or sequelae of COVID-19 acute infection and laboratory tests.
**Results:** Of 2092 patients, 301 were excluded due to lack of data or due to active cancer or other liver disease than NAFLD. Of the remaining, 1395 had PACS and 396 showed no long-term symptoms or sequelae related to Sars-Cov-2 infection.
Mean age was comparable between two groups (54.6 years; SD ± 16.2 vs 54.6 SD ± 13.9 p=0.961). Women were more frequently affected by PACS (51.4%, p<0,001). Patients in the PACS group were more frequently overweight (BMI: 26.7 SD ± 4.9 vs 25.4 SD ± 4.0, p<0.001), obese (21.4% vs 9.3%, p<0,001), more likely to be affected by hypertension (45.4% vs 39.4%, p=0.032) and hypertrigliceredemia (19.9% vs 14.1%, p<0.001). Metabolic syndrome was more frequent in patients without PACS (83.6% vs 75.4%, p<0.001). There were no significant differences regarding the other major comorbidities.
Concerning main laboratory findings there were no significant differences except for triglycerides, as mentioned above, and albumin was slightly lower in the PACS group (42.5 SD 3.1 vs 43.1 SD 3.2, p=0.002).
Remarkably, patients with PACS were more likely affected by steatosis (49.3% vs 27.3%, p<0.001).
Univariate analysis was performed and showed higher rates of PACS in patients with NAFLD (odds ratio [OR] 2.60, CI, 2.04-3.33, p<0.001). Logistic regression analysis identified the presence of NAFLD and hypertrigliceredemia as independent predictors of PACS (OR: 2.27, CI, 1.69–3.08, p <0.001 and OR: 1.42, CI, 1.01-2.02, p=0.050, respectively). Conversely, male sex was shown to be protective against the onset of PACS (OR 0.43, CI, 0.33-0.55, p<0,001).
**Conclusions:** Our results clearly show that the presence of NAFLD represents an independent risk factor for the onset of PACS in a selected population of patients previously hospitalized for COVID-19.
Moreover, NAFLD was highly prevalent in our study cohort (44.4%), which suggests a wide prevalence in the general population, likely to be underdiagnosed, with potential serious consequences for affected patients and public health.

## 82. PERICARDITIS AFTER COVID-19 INFECTION: A CASE SERIES

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**Background:** Pericarditis and myocarditis are caused in many cases by viral infections. Among the various viruses, also COVID-19 can be related to these diseases. Pericarditis develop after clinical recovery from infection, usually with mild course, in the setting of the long-COVID, a condition in which certain symptoms persist after resolution of COVID-19 infection.
Aim of our study was to identify the clinical profile of pericarditis occurred after COVID-19 infection in our Institute.
Setting. We present a case series of patients who developed pericarditis after COVID-19 infection in the Department of Internal Medicine at Fatebenefratelli Hospital in Milan, followed from December 1, 2021 to April 15, 2022.
**Methods:** We analyzed 11 cases of patients suffering from pericarditis after infection with COVID-19 over a five-month time window.
**Results:** Eleven individuals, of which 7 were women and 4 were males, had COVID-19 infection related pericarditis, with a median age of 44 years.
Chest pain was reported in all cases, whereas pericardial effusion (in one case larger than 10 mm) was evidenced in 3 subjects. Nine patients experienced tachycardia, whereas ten subjects reported asthenia.
An increase in indices of inflammation (CRP) was documented in six patients, usually mild.
With regard to therapy, nine patients were treated with NSAIDs, ten with colchicine, while in six cases was required treatment with low-dose steroids.
**Discussion:** COVID-19 infection acts as a trigger inducing a non-typical form of pericarditis, often occurring after virological recovery. In our patients the clinical course was characterized by less typical chest pain, normal indices of inflammation and little instrumental alterations. These forms didn't require hospitalization. However, tachycardia and marked asthenia were common symptoms referred by the patients, with considerable functional limitation, similar to what sometimes occurs in the so-called "long-COVID," when some complaints persist after resolution of the infection.
These forms of pericarditis were treated with NSAIDs at appropriate dosage and low dose colchicine. Low dose oral steroid therapy (5 mg prednisone) was useful in the presence of marked asthenia or systemic symptoms, while beta-blockers or ivabradine were used in the presence of tachycardia.
**Conclusions:** COVID-19 infection may induce insidious pericarditis, often occurring after virological recovery, but with good prognosis, with no need of hospitalization. Clinical course is often mild, with less typical chest pain and low indices of inflammation, and modest instrumental abnormalities, even if patients often develop tachycardia and weakness, which impact on their quality of life.
Keywords: pericarditis; COVID-19 infection.

### 83. A CASE OF ANEMIA IN COVID-19

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**Case Report:** a 57-year-old woman was admitted to our COVID-19 Unit for anaemia and fever, with a positive SARS-CoV2 nasal swab.
Her past medical history included a B-cell lymphoma of the marginal zone, appendicectomy and tonsillectomy.
The patient reported a single dose of anti-SARS-CoV2 vaccine administered six months earlier, after which a post-vaccination hemolytic crisis had occurred.
At admission, she presented with fever, dry cough, tiredness, dark urine and mild jaundice. A chest X-ray excluded signs of pneumonia.
Laboratory tests showed severe macrocytic anaemia (Hb 6.8 g/dl, MCV 100 fl), normal WBC (5 migl/mmc), PLTs 500 migl/mmc, mildly raised CRP, hyperbilirubinemia (5 mg/dl), mainly of the indirect type and suppressed haptoglobin, in keeping with a haemolytic crisis. Blood cultures collected from two different sites and urine culture revealed no bacterial growth. A Coombs direct test was positive, presence of cold agglutinins was detected.
Previous blood tests carried out during a similar haemolytic crisis in the occurrence of a respiratory infection, had showed a positive polyvalent direct Coombs test, presence of cold agglutinins (titre 1: 1024), while a bone marrow biopsy had showed a marginal B cell lymphoma with erythropoietic hyperplasia suggestive of autoimmune hemolysis.
In the suspicion of an exacerbation of Cold Agglutinin Syndrome (CAS) secondary to COVID 19 infection, the case was discussed with the Haematology specialist, and steroid treatment with methylprednisolone 1 mg/Kg was started; during the first days of her in hospital stay, on the basis of Hb values, two units of pre-heated concentrated erythrocytes were transfused after steroid bolus i.v. injection.
Anti-SARS-CoV2 IgG test was negative, while SARS-CoV2 typing showed Omicron variant; according to the internal protocol used at the time, the use of anti spike 2 monoclonal antibodies was discussed with the patient, who refused it.
During hospitalization there were two febrile episodes with a concomitant drop in Hb values and worsening of hemolysis indices; also, for increase in productive cough with yellow sputum, in the suspicion of bacterial over-infection we started an empirical antibiotic treatment, with improvement of the clinical scenario.
The need to switch to rituximab treatment was re-discussed with the haematologist, but we decided to postpone such treatment, considering the reached clinical stability and the ongoing infection.
After 24 days the patient was discharged with Hb values stably above 8 g/dl and decreasing hemolytic indices, absence of fever or other symptoms. She was kept on tapering doses of steroids and a follow-up visit at the Hematology clinic was planned.
**Discussion:** Cold agglutinin syndrome (CAS) is a rare disorder accounting for 25–30% of autoimmune haemolytic anaemias, which has been associated with infection, autoimmune disorders and lymphoid malignancies. The exact pathogenesis behind infectious causes of CAS remains undetermined. However, it is clear that it includes complement system activation associated with inflammation and upregulation of cytokines. Among patients with SARS-CoV-2 infection (also known as COVID-19), pneumonia, respiratory failure and acute respiratory distress syndrome are frequent severe manifestations. Other, less common complications include autoimmune disease such as Guillain Barre Syndrome, immune thrombocytopenia, Kawasaki disease, antiphospholipid syndrome and autoimmune hemolytic anemia (AIHA). Although the pathophysiology behind severe COVID-19 still needs to be fully elucidated, there is evidence that supports a role for hyperinflammatory syndrome, associated with massive release of cytokines. Also, the molecular similarity between the virus and certain human proteins could play a crucial role in the autoimmune phenomena.
For instance, a significant similarity between the SARS-CoV-2 spike (S) glycoprotein, and some molecules of the human proteome has been described, including the ankyrin-1 protein present on the red blood cell membrane.
We hypothesize SARS-CoV-2 infection in our patient could have triggered the cold-agglutinin associated haemolysis either by hyperactivation of complement or mechanism of molecular mimicry, in which antibodies produced against the virus reacts against erythrocytes by a cross reactivity mechanism.
COVID-19 may be an independent risk factor for development of CAS, particularly in those patients with known predisposing conditions such as certain malignancies as lymphomas.
There is no evidence-based therapy for secondary CAS in COVID-19 patients, and treatments are mainly based on previous case reports and clinical experiences. Previous reports have documented the successful use of corticosteroids, rituximab, and red cell transfusions. The treatment of our patient was successful with a combination of transfusions and corticosteroids. Since association between COVID-19 and CAS is a recent finding, further research is required to obtain established evidence-based treatments for the disorder.

## ECOGRAFIA

### 84. LUNG ULTRASOUND IN CORONARY CARE UNIT, AN IMPORTANT DIAGNOSTIC TOOL FOR CONCOMITANT PNEUMONIA

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**Background:** In the setting of coronary care unit (CCU), early detection of pneumonia is of paramount importance to prevent severe complication in patient affected by acute coronary syndrome or acute heart failure. The present study was designed aiming to evaluate diagnostic accuracy of lung ultrasound (LUS) in detection of pneumonia and compared with chest x-ray (CXR).
**Method:** We enrolled 83 consecutive patients admitted to CCU of Federico II University Hospital. Each patient underwent CXR and bedside LUS on admission. Skilled clinicians, blinded to CXR results and clinical history, performed LUS. The final diagnosis (pneumonia vs no-pneumonia) was established by another clinician reviewing clinical and laboratory data independent of LUS results and possibly prescribing chest contrast-enhanced CT (n=24). We used 2 × 2 contingency tables to analyze sensitivity, specificity, of the lung ultrasound and chest x-ray for the diagnosis of acute pneumonia. ROC curve were used to evaluated overall diagnostic accuracy of LUS and chest radiography and compare with de Longis Method.
**Results:** Mean age was 70±12 years old, 64% males. Pneumonia was clinically diagnosis in 17 (21%) patients. LUS was positive for pneumonia in 15 patients (sensitivity 88% specificity 77%). Chest radiography was positive in 5 patients (sensitivity 36% specificity 94%). Using CT scan as referee LUS exhibit 100% of sensibility and a specificity of 72%. In ROC curve analysis accuracy of Lung Ultrasound were 0.82 (0.69-0.94) while accuracy of chest radiography were 0.65 (0.47-0.83), $p<0.05$.
**Conclusion:** Based on the findings of the present study, accuracy of LUS in detection of pneumonia was significantly higher than chest x-ray, with comparable sensibility compare to CT scan. Therefore, considering characteristics such as safety, low cost, being portable, and being available, ultrasonography seems to be a reasonable tool for screening and diagnosis of patients with pneumonia in the setting of CCU.

### 85. QUANTIFICATION OF HEPATIC STEATOSIS WITH A NOVEL ATTENUATION IMAGING (ATI) ULTRASOUND TECHNIQUE (QAI): PRELIMINARY FINDINGS ON FEASIBILITY, REPRODUCIBILITY AND DIAGNOSTIC ACCURACY

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**Purpose:** In recent years various ultrasound (US) techniques, such as attenuation imaging (ATI), have been developed to quantitively assess the hepatic fat content. The aim of the study was to assess technical feasibility and reproducibility (both intra- and inter-observer) of ATI with QAI (Esaote) in healthy volunteers and in patients with suspected steatosis. The secondary aim was to evaluate the correlation of QAI with hepatic steatosis assessed by standard US and to assess diagnostic accuracy for steatosis quantification.
**Methods:** This prospective study included two different study groups, composed of healthy volunteers (group 1,n=25) and patients with suspected hepatic steatosis (group 2,n=61); among them 28 patients underwent also liver biopsy. In group 1 two operators performed both US and two sessions of ATI respectively. Intra-class correlation coefficients (ICCs) were used

to assess the intra-observer and inter-observer reproducibility in group 1. In group 2, QAI values were correlated with the degree of hepatic steatosis using Spearman rank correlation analysis. Temptative cut-off values for steatosis were calculated with ROC analysis as compared to liver histology.
**Results:** For the intra-observer reproducibility of ATI, the ICC was 0.932 (95%CI, 0.854-0.969); inter-observer reproducibility showed an ICC of 0.902 (95%CI, 0.793-0.955). QAI measurements showed a significant correlation with the visual grade of hepatic steatosis (rho 0.860;p<0.001). ATI enabled the identification of mild steatosis ($S^3$1) with an AUC of 0.97 with an optimal cut-off of 0.60 dB/cm/MHz.
**Conclusion:** ATI imaging with QAI showed high intra- and inter-observer reproducibility in healthy volunteers. Correlation between QAI and hepatic steatosis assessed by standard US is very good. Our study identifies for the first time normal values of QAI in healthy volunteers and preliminary cut-off thresholds for steatosis staging in NALFD patients.

## 86. ASCENDING AORTA PROFILE CHANGES IN RELATION TO TYPE OF NORMALIZATION FOR BODY SIZE IN HYPERTENSIVE PATIENT: THE CAMPANIA SALUTE NETWORK

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**Background:** In hypertensive patients dilatation of the sinus of Valsalva (SoV) is associated with increased cardiovascular risk but less is known about the remodeling of ascending aorta (AscAo).
**Methods:** 1634 hypertensive patients > 18 years old with available data on AscAo were included. AscAo was measured at end-diastole with leading edge to leading edge method. Pearson correlation analysis was used to asses main correlates of AscAo and AscAo indexed for body surface area (AscAo/BSA) and height (AscAo/HT). Multivariable regression models were built to assess possible determinants of AscAo, AscAo/BSA and AscAo/HT.
**Results:** AscAo measured 33±4.3 mm, AscAo/BSA was 17.6±2.7 mm/m2 and AscAo/HT 19.7±2.6 mm/m. Correlation with age, eGFR, systolic BP and HR were similar in the 3 aortic measurements. Male gender was associated with grater AscAo and smaller AscAo/BSA and AscAo/HT. Obesity was associate grater aortic dimension using AscAo and AscAo/HT while was associated with lower AscAo/BSA. Diabetes and triglycerides level were associated with greater AscAo and AscAo/HT, not with AscAo/BSA. In multivariable regression, both AscAo and AscAo/HT were independently associated with older age, lower systolic BP and higher diastolic BP, lower heart rate and presence of obesity; AscAo/BSA was greater in women and smaller with obesity (Table).
**Conclusions:** Our study demonstrated that age and sex influence AscAo dimension but the correlation of sex varies differently according to the normalization for BSA or HT. Diabetes, obesity and triglycerides level are associated with increased AscAo and AscAo/HT as expected but using indexation of BSA lead to an unexpected inverse correlation.

## 87. LONG-TERM ULTRASOUND FOLLOW-UP IN PATIENTS WITH FOCAL NODULAR LIVER HYPERPLASIA: IS IT REQUIRED? MONOCENTRIC STUDY RESULTS

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**Introduction:** Focal nodular hyperplasia (FNH) is the second most frequent benign tumor of the liver. It is the result of focal aberrant vascularization of liver parenchyma which determine hyperplasia of hepatocytes and nodular regeneration, as a focal cirrhosis. Many risk factors have been linked to FNH, particularly hormone-related factors such as the use of oral contraceptive pills (OCPs) and pregnancy, but recent evidence suggests that there is no correlation between these risk factors and the development or progression of FNH. Regarding FNH management, current international recommendations do not clearly define the role of clinical and instrumental long-term follow-up, and there is a scarcity of evidence on the natural history of FNH. The aim of this study was to investigate the dimensional evaluation of FNH nodules in a long-term ultrasound follow-up and the relationship between measurements and clinical parameters.
**Materials and Methods:** In our monocentric retrospective study, 54 consecutive patients with established diagnosis of FNH were enrolled. The diagnosis was made with non-invasive methods (magnetic resonance imaging with hepatospecific contrast, multiphasic computed tomography, contrast-enhanced ultrasound) in 52/54 patients and only two cases required liver biopsy to confirm the presence of FNH. Patients with an ultrasound follow-up of at least 24 months were included in the final analysis. Each FNH nodule was defined as enlarging or diminishing if the main diameter variation was more than or equal to 5 millimeters (mm) from the first measurement; the nodule stability was established if the variation difference was less than 5 mm. The demographic, clinical and biological information of all patients was obtained from their medical records.
**Results:** A total of 24 patients with FNH and ultrasound follow-up longer than 24-months were included in the final analysis. They were mostly female (21 female vs 3 male) and the mean age was 43 years. The 76% of the female population had taken OCPs for a variable length of time (mean 79 months) and the 67% had been pregnant. Three patients have been continuing the treatment with OCPs even after the diagnosis of FNH. In these patients, 40 FNH nodules were identified at baseline and followed with periodic ultrasound. At the baseline, the median diameter was 35 mm (12 - 98 mm). The median follow-up was 47 months, ranging from 26 to 77 months. At the end of the long follow-up, 4 nodules resulted as increased, with a mean increment of 11 mm (6 – 20 mm) and a growth rate of 0.2 mm/month, 24 nodules significantly decreased (mean 12 mm) and the remaining 12 nodules did not show significant changes. There was no significant association between the growth or reduction of FNH nodules and clinical factors such obesity, pregnancy, or OCPs, and the nodule growth was asymptomatic.
**Conclusions:** This study demonstrated how most of the FNH nodules remain stable or decrease over time; the growth occurs in about 10% of cases and is clinically negligible. These results do not support the utility of prolonged ultrasound follow-up in patients with FNH.

## 88. SCREENING FOR ABDOMINAL AORTIC ANEURYSM DURING TRANSTHORACIC ECHOCARDIOGRAPHY

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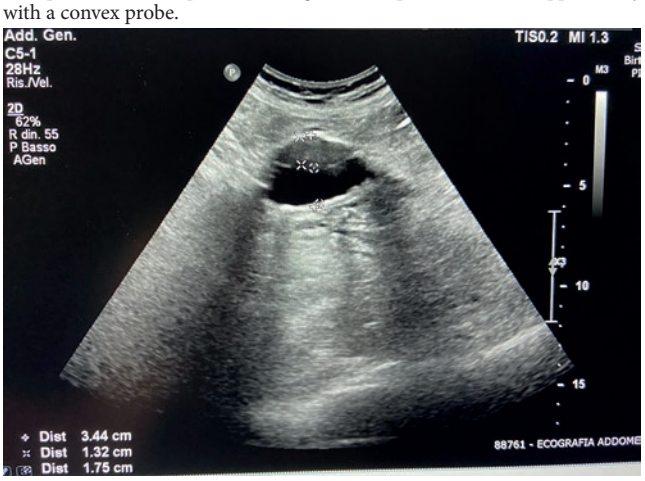
A 67-year-old pensioner living in Sardinia, was admitted to the cardiac surgery department for an elective coronary artery bypass operation. The operation was successful with a regular post-operative hospitalization and the patient began the regular course of the cardiac rehabilitation facility.
During one of the follow-up echocardiographic examinations, a suspected abdominal aortic aneurysm (AAA) was incidentally found, which had probably never been detected before due to its location outside the usual echocardiographic sections.
The patient was referred to the ultrasound laboratory and a complete abdominal ultrasound exam with colordoppler was performed, using a proper convex probe. The study revealed an aneurysmal dilatation of the abdominal aorta with suprarenal collar extending for about 5 cm down to the iliac bifurcation (as we shall see later, it should be borne in mind that at the study with the sector probe the suspicion had been subrenal AAA) with involvement of the origin of the inferior mesenteric artery. The maximum calibre was 3.4 cm and there was parietal thrombotic deposition with a pervious lumen of 1.7 cm. A pseudoaneurysm of the right external iliac artery measuring 5 x 3.5 cm was found as an additional finding.
Abdominal aortic aneurysm is a disease with a significant and increasing prevalence due to increased risk factors; in selected populations of at-risk individuals the prevalence may be as high as 12%. It is often an insidious disease that gives no symptoms except in the case of major complications such as rupture and embolisation, and physical examination does not usually allow a diagnosis to be made.
The diagnosis is usually made during acute events or incidentally during imaging examinations such as abdominal CT or ultrasounds, which have a sensitivity of almost 100%.
Considering these epidemiological data, the high mortality rate, the existence of a method with high sensitivity and specificity and low cost and invasiveness such as ultrasound, it is evident how important it is to encourage ultrasound screening methods.
The routine transthoracic echocardiographic examination consists of four basic windows (parasternal, apical, subcostal, suprasternal and their variants) which exclude the abdominal aorta from the study. Adding a few seconds study of the abdominal aorta to the echocardiographic examination would significantly increase early diagnosis of AAA at no cost, also because of the high prevalence of risk factors in the population of patients under-

going this examination.
However, the study of the abdominal aorta with a sector probe has limitations, mainly related to the portion of the vessel that can be viewed, which is limited to the proximal 13 +/- 4.6 cm. This limitation rarely makes it easy to assess whether the collar of an aneurysm is suprarenal or subrenal and usually excludes the study of the iliac bifurcation from the examination.
Both these limitations became evident in the present clinical case, that however represents an emblematic case in which the screening strategy mentioned above could have saved che patient's life.
In conclusion, it would be desirable to add a fifth projection to the basic echocardiographic examination to study the abdominal aorta, and then refer patients with suspicious findings to a complete echocolordoppler study with a convex probe.




## 89. DIFFERENTIAL DIAGNOSIS OF AN INTRACARDIAC MASS IS NOT ALWAYS EASY: WHEN THE ANAMNESIS IS MISLEADING

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A 71-year-old woman performed a follow-up visit. She performed an echocardiogram control that showed a rounded, pedunculated plus image (diameter 0.7 [1] 0.7 cm) adhering to the free margin of the non-coronary aortic cusp, mobile and floating in the aortic vascular side. Her past medical history included: drainage surgery for abscess in the right parotid four months earlier, due to which she began and continued empirical broad-spectrum antibiotic therapy and a NSTEMI treated by PCI with implantation of two medicated stents in the anterior descending coronary artery. After suspicion of thrombotic formation, the antibiotic was withdrawn, maximum-dose anticoagulant therapy was initiated and blood cultures were performed. Blood cultures were negative and a month later she underwent a transesophageal echocardiogram which showed no change in the size of the mass and was not conclusive to the diagnosis. It could be a vegetation for the recent diagnosis of parotid abscess and for non-optimal antibiotic therapy in a possible suspicion of endocarditis; It could appear to be a tumor considering the echocardiographic characteristics, the laboratory tests and the non-response to the beginning of the anticoagulant therapy; It could be a thrombus due to the suspicion that during the catheterization there was an insult to the valve flap that predisposed to a state of hypercoagulability, and that it could be rich in fibrin since it did not respond to the anticoagulant. Instead this mass does not appear to be a vegetation because the valve is healthy and there are no other signs of endocarditis; it should not be a tumor because there was no mass in the recent checks and it didn't grow in two months of follow up, and it does not appear to be a thrombus because the diameter has not changed after one month of anticoagulation therapy. Due to the risk of embolization and to have a diagnosis of certainty the patient performed a surgery to remove the mass. The surgical technique used was a lateral mini thoracotomy with mass removal and aortic valve replacement with sutureless valve. The extracted mass had a gelatinous consistency, extensive fibro-myxoid degeneration of the connective tissue and fields of chronic inflammation, such as a fibroelastoma. Histological examination then confirmed the diagnosis of papillary fibroelastoma of the aortic valve with associated signs of previous endocarditis.

## 90. A CASE OF PULMONARY ADENOCARCINOMA SUSPECTED WITH LUNG ULTRASOUND

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In the last years lung ultrasound has become relevant role for the evaluation of pulmonary and pleural disease expecially in the internal department. Chest ultrasound helps in the assesment, differentiation and follow up of pleural effusion, empyema, pneumothorax and pleural thickenings. We describe a 62-year old patient that was admitted to hospital for dyspnoea and bone pains. The classical instrumental examination such as chest x-ray and pulmonary CT scan were not essential, while the execution of a pulmonary ultrasound was determinant.
The patient referred to our hospital with a history of progressive dyspnoea over four months and complaining of bone pain. For this reason he had performed a bone scan which showed the presence of bone lesions probably of a repetitive nature.
The patient had only hypertension. He had not a significant familiar history. There was no other significant past medical history nether a recent history of infections. His occupation was metalworker.
At the time of admission vital signs were good. The general physical examination was negative except for a pain in his right leg that prevented him from walking independently. Laboratory studies revealed hemoglobin 12,8 g, white blood cells 914000/mm3 with normal differential count, blood urea nitrogen 39 mg/dL, creatinine 0,78 mg/dL, serum albumin 4,2 g/dL, cholesterol 131 mg/dL. Liver function tests were normal. CRP was 51,8 mg/l, sideremia was 26 mcg/dl. Tumor markers were: CEA 96,6 ng/ml, CA 19.9: 357,0 U/ml, CA 125: 146 U/ml.
A chest ultrasound was done that showed consolidation at the base of the left lung with a mild pleural effusion. This seemed to be an exudate because it was echoic, complex and septated. The amount of effusion it was minimal and estimated around 100 cc. A chest X-ray that was normal and a pulmonary TC that reported: on the left there is minimal mammellon thickening of some segments of the pleura with apico-parieto-basal effusion flap. No focal alterations in the pulmonary parenchyma are seen. Mediastinal lymphadenomegalies are not evident.
It was also performed a real-time ultrasound-guided thoracentesis to obtain pleural fluid that showed a citrine yellow fluid. This was analyzed and the result was: total protein 4,9 g/dl, LDH 389 U/l. To cytological examination: morphological and immunophenotipic picture indicative of epitheliomorphic malignant neoplasm of glandular origin. Then was made a biopsy on the right femur and the result was: bone localization of adenocarcinoma. A PET was finally made. This reported an intense and pathological increase in glucose metabolism in the right femur, at the level of the left shoulder blade, on the sixt right rib, on the left eighth rib and the left iliac wing. The patient was then sent to oncologist.
Thoracic ultrasound has a significant complementary role to traditional examinations in diagnosis of pulmonary cancer. Diagnosticate these tumors is difficult because it is a challenge to obtain adequate malignant cellular material to perform a cytological diagnosis. This case highlights how lung ultrasound con be fundamental in these conditions both to support the diagnostic suspicion and to guide procedures such as thoracentesis. The diagnostic specificity and sensitivity of ultrasound for pleural effusion is higher compared to that of chest X-ray and allows identifying the pleural fluid characteristics that differentiate complicated and uncomplicated effusions and homogeneous and heterogeneous effusions. In addition, the routine implementation of pulmonary ultrasound in the ICU decreases the number of chest X-rays, with a reduction in medical costs and radiation exposure, without affecting the clinical results. It's a simple, practical and accurate procedure without significant patient's risk.
This case highlights how torax ultrasound is irreplaceable in study and management of pulmonary disease. In fact in this case ultrasound examination has allowed an early suspicion of neoplastic lung that otherwise other traditional radiographic methods would have made it more difficult with diagnostic delay. We therefore believe to underline the importance of thoracic ultrasound in the daily practice of the internist in the evaluation of lung disease.

### 91. ULNAR ARTERY THROMBOSIS AFTER PERCUTANEOUS THROMBIN INJECTION OF A PSEUDOANEURYSM WITH A CONCOMITANT RADIAL ARTERY OCCLUSION: THREE COMPLICATIONS AFTER PERCUTANEOUS CORONARY INTERVENTION

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A 78-year-old woman was referred to the emergency room for chest pain and ECG evidence of a ST-elevation myocardial infarction (STEMI). She underwent to percutaneous coronary intervention (PCI) of the right coronary artery from the right ulnar artery via a 6 F guiding sheath, as a result of cannulation failure of the ipsilateral radial artery. She reported a successful transradial PCI years before. After removal of the hemostatic device, a painful pulsatile mass in the distal forearm has been found. Colordoppler ultrasonography (CDUS) revealed a complete occlusion of the right radial artery and the presence of a 15 x 35 mm pseudoaneurysm with a 'yin-yang' sign, adjacent to the punctured ulnar artery. Because of the suboptimal perfusion of the hand, percutaneous embolization with thrombin was considered the safer treatment option. After 24 hours, CDUS revealed the complete thrombosis and exclusion of the pseudoaneurysm, moreover, a segmental thrombotic occlusion of the ulnar artery was found. The patient didn't present signs of digital ischemia.
Microinvasive endovascular procedures are an everyday occurrence and are liable of systemic and local complications, including arterial occlusion and pseudoaneurysm. In contrast to femoral and brachial approach, puncture of the radial artery is often preferred because assure haemostasis even in presence of anticoagulant and antiplatelet therapy, provides greater comfort for patients, allows early ambulation and fewer complications. A recent meta-analysis shows a 65% to 80% rate reduction of radial approach complications including major haemorrhages over the transfemoral route. However, there are cases where radial route is not feasible, so transulnar approach has been studied as alternative forearm access for percutaneous endovascular procedures. Possible indications may be unfavourable conditions, such as steno-occlusion of the artery, anatomical variants, tortuosities, aberrant origin, hypoplasia and vasospasm. Transulnar approach has been proposed as suitable alternative arm choice, even in patients with previous radial puncture complications, after unsuccessful attempts to ipsilateral radial cannulation, in patients with prior or future radial artery harvesting for CABG and in those where the integrity of the deep palmar arch was not assessed by an inverse Allen's test.
Pseudoaneurysm is an infrequent non-haemorrhagic complication that can arise after arterial puncture and is responsible for prolonged hospitalization, life-threatening events, so requires subsequent treatment. Typically, a trauma of the vessel wall can follow a breach through the tunica media and a collection of blood in the adjacent tissues, surrounded by the tunica adventitia or by a thrombotic layer and soft tissues. Complications are critical ischemia in the distal vascular territory from thromboembolisation, rupture or over-infection. Treatment involves the replacement of the pressure bandage, ultrasound-guided compression, ultrasound-guided percutaneous thrombin injection and open surgical repair.
Prevalence of pseudoaneurysm ranges from 0.05% to 6%, with higher rate after prolonged therapeutic interventions, larger sheath sizes and the use of antiplatelet and/or anticoagulant therapy. Several studies shows that success and complication rates related to transulnar approach are similar to those found in transradial. Ultrasound-guided percutaneous thrombin injection (UGPTI) is an effective technic for treatment of pseudoaneurysms, that ensures rates of obliterations around 93% to 100% of cases, with a low rate of complications. UGPTI is the preferred choose of treatment in absence of absolute contraindications (i.e. allergy to bovine-derived products, PSA with rupture, skin necrosis, infection or arterio-venous fistula), because eliminates the risk of wound-related complications and can be performed under anticoagulation therapy. However, expert opinion is not to treat pseudoaneurysm larger than 5 cm with a neck larger than 1 cm and in case of multiple unsuccessful attempts, in order to avoid potential complications. A CDUS after 24 hours is necessary to check patency of the native artery. Although few cases have been reported in literature, the native arterial thrombosis is a feared adverse event that can result in limb threatening ischemia. Some authors suggest to use a low rate of administration of small volume of thrombin, to avoid extravasation and/or embolization.
In conclusion, transulnar approach ensures many potential advantages and minimizes transfemoral use. Pseudoaneurysm is an infrequent but harmful adverse event that can be early recognized by a systematic vascular follow-up and successfully treated. Ultrasound-guided percutaneous thrombin injection represents the safer choose of treatment for most cases, although its related complications are underestimated.

### 92. RITIRATO

## EMATOLOGIA

### 93. ISOLATED AND ACQUIRED DEFICIENCY OF IDIOPATHIC FACTOR VII: CASE REPORT

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**Introduction:** Factor VII (FVII or proconvertin) is a vitamin K-dependent glycoprotein that plays an essential role in triggering the blood coagulation cascade. It is synthesized in the liver and the gene (F7 of 12.8 Kb) maps to the long arm of chromosome 13 at position 13q34. 1 It circulates in the plasma in the form of a single chain of 406 amino acids with a molecular weight of about 48 KD; it is present in low concentrations (0.5 mcg / ml) and its half-life is very short (3-4 hours). Factor VII exists mainly in an inactive form, only 1% circulates in the blood in an active form (FVIIa). Unactivated FVII possesses low procoagulant activity, which increases only after its activation. The FVII is converted into FVIIa through the cleavage of Arg 152-Ile 153 generating a molecule with two chains joined by disulfide bonds with marked serine-protease activity. Cleavage can be caused by FXa, FIXa, FXIIa and thrombin. Furthermore, in order to carry out its procoagulant activity, FVIIa must interact and form a complex with tissue factor (TF), a plasma membrane glycoprotein constitutively expressed by subendothelial cells and following direct injury by endothelial cells and macrophages. Furthermore, the TF itself greatly increases the activation speed of the FVII. The FVIIa / TF complex, therefore, can be considered the main initiator of coagulation in vivo. This complex in the presence of calcium ions and phospholipids activates FX and FIX, which in the presence of FVIIIa, calcium ions and phospholipids activates FX. The common pathway starts from FXa (activated by the intrinsic or extrinsic pathway) and is characterized by the formation of a complex consisting of the FXa itself, FVa, phospholipids and calcium ions. This complex acts on the prothrombin substrate causing thrombin formation. This is followed by the transformation of fibrinogen into fibrin, the formation of the fibrin clot and its stabilization by FXIIIa.
**Case Report:** The Authors presented the case report of an 80-year-old woman, who came to our observation for severe anemia, treated with ACO for AF, PMK carrier, hypertensive. Upon physical examination, she presented with extensive hematoma of the limbs and trunk. At the entrance the Hb values were 7 g for which blood transfusion is performed. She undergoes CT TB with contrast medium which highlights gross bleeding in FID in the pudendal area (Photo 4) for which she undergoes angiography with embolization of a branch of the upper and lower epigastric and lower. The search for neoplastic markers is negative. Thrombophilic screening is negative. The EGDS is negative. Colonoscopy shows sigmoid diverticula. The search for ANA, ENA, anti-native DNA, Rheuma test, Waaler Rose, AMA, ASMA, circulating immune complexes, C3-4 assay, APCA, p-ANCA and c-ANCA shows values within the limits. The ACO is suspended. Factor VII (35% with VN 70-140%) and factor VIII c (253% with VN 70-140) are measured. The search for factor VII inhibiting factors is negative. During hospitalization, the relationship between CHADS2VASC2 (= 4) and HAS-BLED (= 2) is constantly evaluated. The peripheral smear does not show immature shapes. Therapy with cortisone is undertaken and there is an increase in the values of factor VII.
**DISCUSSION:** Congenital defect of factor VII is a rare bleeding disorder due to a genetic abnormality of chromosome 13. It is transmitted in an autosomal recessive manner (the parents are healthy carriers of the mutation, while each child of the couple has a 25% chance of to be ill). 4 The M: F ratio is 1: 1. Its incidence is about 1 case per 500,000 people. More than 130 mutations have been identified to date and associated with a decrease in plasma FVII levels. Generally the defect is quantitative. This means that there are mutations in the DNA gene sites that involve the blocking of the normal biosynthesis process of this protein, the presence of very low levels in the bloodstream and, consequently, the onset of the typical symptoms of this disease. In the remaining 20% of cases, however, these are variants that present a qualitative defect in the synthesis of FVII. FVII levels lower than normal (between 70 and 140%) characterize this deficit, which is usually

symptomatic only for values below 30%. A concentration of FVII> 10-25% is sufficient to guarantee haemostasis safe. Subjects with FVII <10%, are considered homozygous, while those with FVII equal to 50% are heterozygous. Only homozygotes or compound heterozygotes (with two different mutations) develop the hemorrhagic syndrome; heterozygotes are asymptomatic. The bleeding tendency among affected individuals is remarkably variable, ranging from absolutely asymptomatic patients to patients with life-threatening bleeding. They range from mild forms, with susceptibility to epistaxis and bruising, to more severe forms, with hemarthrosis in children as soon as they begin to walk, to potentially fatal forms, with severe intracranial hemorrhages and intestinal hemorrhages in the first weeks of life.
**CONCLUSIONS:** The authors presented the case report of an 80-year-old woman with isolated and acquired, idiopathic deficiency of coagulation factor VII.

## 94. A RARE THROMBOCYTOPENIA: A CASE REPORT

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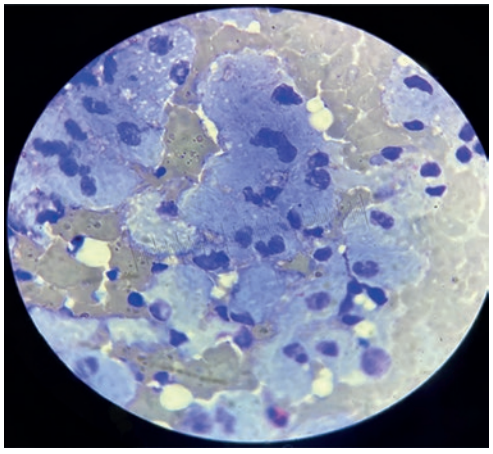
A 55-years old woman, in eradication therapy for Helicobacter pylori with Bismuth citrate and gastroprotector, was admitted to our department because of the onset of dark discharge from anal region for about two days. There weren't significant pathologies in her clinical history.
In the emergency room she performed Ecofocus with evidence of splenomegaly with the presence of hyperechoic nodularities. Blood data showed thrombocytopenia (92.000). She performed the dermatological consultation which diagnosed perianal dermatitis with de-epithelialization, probably from contact. Abdominal Ultrasound revealed an enlarged spleen (188 x 59 mm) with multiple focal roundish hyperechoic lesions, a hepatomegaly (178 mm) in the absence of alterations in the echostructure., findings that were confirmed by Total body CT. On suspicion of lymphoproliferative disease, first morphological examination on medullary agospirate was performed and showed the presence of numerous voluminous cells with sometimes foamy or "onion-shell" cytoplasm and intense basophilia of probable macrophage derivation, then karyotype on bone marrow cells, showing no alterations. Tandem mass spectrometry from dried blood spot conducted to distinguish between Gaucher and Niemann-Pick A/B disease showed a low beta-Glucocerebrosidase activity, while the acid Sphingomyelinase activity was above the cut-off value. MOC revealed osteoporosis of the spine and osteopenia of the femur and MRI showed an alteration of the signal involving the spongiosa of the bone structures of the pelvis and both femurs.



The diagnosis of Gaucher's disease was confirmed also by genetic test, in which she resulted heterozygous for two mutations [604 C] and [1226AG] and was treated with Eliglustat. This case report demonstrated that a modest often neglected thrombocytopenia could hide a pathology that would not be so rare if it was considered in the differential diagnosis of thrombocytopenia.

## 95. INCREASED RISK OF NEW ONSET OF ARTERIAL HYPERTENSION IN PATIENTS WITH MULTIPLE MYELOMA TREATED WITH CARLFIZOMIB

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**Introduction:** Several new drugs are used nowadays to treat multiple myeloma (MM). Some drugs are loaded with an increased risk of developing cardiovascular diseases. Carfilzomib (K), a proteasome inhibitor, is well recognized to cause cardiovascular side effects. Also, arterial hypertension is a main factor leading to LV dysfunction. Purpose is to evaluate if patients who underwent the carfilzomib treatment may present an increased incidence of arterial hypertension.
**Methods:** We evaluated 34 patients (group K, 20M, 14F, aged 65.87±5.98) treated with carfilzomib: 25 patients were given 56 mg/m2 (group 1, 14M, 9F, aged 67.30±5.98) while 9 27 mg/m2 (group 2, 6M, 3F, aged 63.00±5.39). As controls, we recruited 34 patients (16M, 18F, aged 69.80±9.13) who underwent in the same period the MM treatment without carfilzomib. Hypertension was identified as new onset of disease or worsening of disease (need double the dose used, add a new drug, or no pressure control in at least 3 drugs treatments).
**Results:** At baseline, the controls presented an increased arterial hypertension rate (76.47% vs group K 47.06%, p=0.07). There was no difference in any other CVD risk factor. There was no difference in LV mass, volumes and ejection fraction. The group K experienced an increased incidence of arterial hypertension compared to controls (controls 0% vs group K 41.17 %, p=0.001). This result was not related to the drug dose. Finally, there was no difference in mortality between the two groups also by analysing the CV death.
**Conclusions:** Carfilzomib is a potent and effective drug in MM. Its cardiovascular toxicity relates to a vascular and endothelial damage leading to a new onset of arterial hypertension. This observation may be useful in preventing evolution of the CV dysfunction in survivors and long survivors MM patients. Also, it may be important for studies of vascular damage in arterial hypertension pathophysiology.

## 96. EVALUATION OF ERYTHROCYTOSIS IN PATIENTS WITH TIBETAN EGLN1C127S MUTATION LIVING AT A SEA LEVEL

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**Background:** Absolute erythrocytosis is characterized by persistently raised Haemoglobin (Hb) and hematocrit (Ht) levels. Some congenital erythrocytosis (CE) are caused by mutations in a variety of genes, including those involved in the Oxygen-sensing pathway (OSP) (VHL, HIF2a, PHD2) and erythropoietin-receptor (EPO-R) gene. We recently focused our attention on patients with PHD2 mutations, having encountered a number of them affected by erythrocytosis. The EGLN1C127S is considered a polymorphism being very common in Tibetan individuals: in these subjects it facilitates adaptation to high altitude and therefore it is not associated with a phenotype of erythrocytosis. Our aim was to study if there is erythrocytosis in PHD2 patients people living at sea altitude like our patients.
**Methods:** We have chosen 12 patients with a PHD2 mutation previously studied with the Sanger method and we reevaluated them again with NGS panel specific for genes involved in erythrocytosis: JAK2, EGLN1 (PHD2), EPOR, FTL, FTH, ASXL1, HFE, HFE2, TFR2, HAMP, SLC40A1, SLC11A2, VHL, BPMG, EPAS1 (HIF-2α). We then collected their hemoglobin and hematocrit at diagnosis, treatment for erythrocytosis and presence of other relatives with erythrocytotic phenotype. We arbitrarily used phlebotomies to maintain Ht under 50%, or antiplatelet agents to prevent thrombotic complications.
**Results:** The main data of our patients are summarized in the table. The median basal Hb and Ht levels of both patients with Tibetan or other mutations are similar. Two third of patients (66%) needed phlebotomies and 2 patients antiplatelet agents: 6 (85.7%) patients with Tibetan mutation and 4 (80%) of the others with different mutations needed treatment. Three patients had associated mutations: 1 EPO-R A99V, 1 VHL P25L and 1 EPAS1 T766P genes. All of them underwent phlebotomies.
**Summary and Conclusion:** This research shows how most patients with PHD2 mutated erythrocytosis needed a treatment regardless of the muta-

tion. Therefore, we can conclude that EGLN1C127S genotype is associated in our patients with a phenotype of erythrocytosis and necessity of treatment, given the fact that they live at sea level. While the Tibetan mutation facilitates adaptation to chronic reduced oxigen pressure which decreases erythrocytes production in subjects living at high altitude, at the normoxia condition occurring at the sea level the normal process is altered and the erythropoietin gene is activated through not degraded HIF-2 alpha by PHD2. Congenital erythrocytoses are very rare conditions, and those due to PHD2 mutations are only a small part of them. Our study shows an intriguing aspect that needs larger and collaborative researches.

| Sex/ Age | PHD2 mutations | Hb (g/L) | Ht (%) | Treatment | Family History |
|---|---|---|---|---|---|
| M/58 | I269T | 183 | 55.6 | Phlebotomies | No |
| M/64 | Q157H | 170 | 51 | Phlebotomies | Yes |
| M/56 | Q157R | 172 | 49 | Phlebotomies | No |
| M/64 | Q157R | 170 | 51 | None | Unknown |
| M/22 | Q157R | 170 | 53 | Phlebotomies | No |
| F/60 | C127S | 162 | 49.5 | Aspirin | Yes |
| M/30 | C127S | 172 | 51 | None | No |
| M/59 | C127S+R370G | 196 | 53.8 | Phlebotomies | Yes |
| M/62 | C127S | 178 | 50.9 | Phlebotomies | No |
| M/60 | C127S | 188 | 53.1 | Clopidogrel | Unknown |
| M/42 | C127S | 148 | 45.8 | Phlebotomies | Yes |
| M/26 | C127S | 173 | 49.8 | Phlebotomies | Yes |

## 97. THE UNCOMMON FIRST MANIFESTATION OF JAK2 MUTATION: A RARE CASE OF BUDD-CHIARI SYNDROME IN A HEALTHY YOUNG WOMAN

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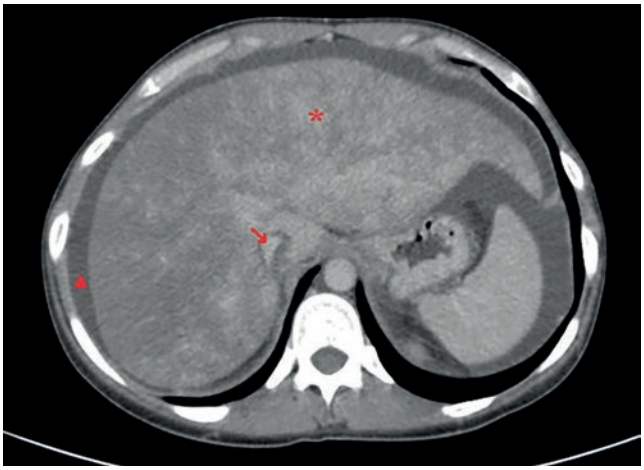
Budd-Chiari syndrome (BCS) is a rare vascular disorder characterized by hepatic venous outflow obstruction. It is classified as primary (caused by thrombosis) and secondary (benign or malignant tumors, cysts, etc. causing ab-estrinseco obstruction or invasion of hepatic flow), depending on the exact nature of the hepatic venous outflow obstruction. Myeloproliferative neoplasms (MPNs) are known risk factors for venous and arterial thrombosis, including splanchnic vein thrombosis as BCS. Janus kinase 2 (JAK2) V617F mutation is detected in more than half of the patients with MPNs. Among BCS patients without known pre-existing MPNs, the presence of JAK2 V617F mutation is associated with subsequent development of overt MPNs as reported in a few cases in scientific literature. In fact, MPN can develop before, simultaneously (in this case BCS is the MPN's initial symptom) or, more rarely, after BCS. Sometimes, peripheral blood evidence of MPNs may not be present in BCS patients because of portal hypertension and its sequelae (splenomegaly, hemodilution, and iron deficiency). However, the study of bone marrow is the key to identifying an occult MPN, by showing the myeloproliferative alterations.
We present a case of a healthy 32-year-old woman admitted to the Internal Medicine ward of the University of L'Aquila with mild abdominal pain in the previous 3 months, nausea, vomiting, and fever (38°C). All data were collected during the hospitalization. BCS was diagnosed with Ultrasound (US) and Computed Tomography (CT). At the admission, the patient showed elevated transaminases (AST 232 IU/L; ALT 484 IU/L), hyperbilirubinemia (total 2.19 mg/dl; direct 0.82 mg/dl), and elevated INR (3.12). She wasn't taking any medication. Count cell in peripheral blood was normal as also hemoglobin, erythropoietin, and serum iron values. The Child-Pugh score was B8.
The patient underwent a US examination that showed hepatomegaly, heterogeneous echotexture, no focal lesions, and ascites, without splenomegaly. Subsequently, a contrast-enhanced computed tomography (CECT) showed suprahepatic vein thrombosis, left hepatic lobe hypertrophy, inhomogeneous liver parenchyma, heterogeneous enhancement, inability to identify hepatic veins, and partially collapsed inferior vena cava. Gastroscopy for gastro-oesophageal varices check didn't show any alteration. The blood test ruled out major and minor viral hepatitis, autoimmune hepatitis (ANA, AMA, ASMA, LKM, ANCA), genetic liver disease (ceruloplasmin, ferritin, and alpha-1-antitrypsin), and prothrombotic conditions (Protein C, Protein S, fibrinogen, antithrombin III, homocysteine, anti-cardiolipin antibodies, LAC, anti-β2glycoprotein antibodies, factor V Leiden mutation, factor II mutation, MTHFR C677T mutation). Upon suspicion of thrombosis due to myeloproliferative disease, JAK2 mutation was tested and JAK2-V617F was found to be positive, in the absence of peripheral cytosis in the blood count and with any alterations in peripheral blood smear. Therefore, a hematological consultation indicated osteomedullary biopsy, which was found to be normal. According to WHO 2016 diagnostic criteria for MPNs, diagnosis of MPNs was excluded. Anticoagulant therapy with low molecular weight heparin (Enoxaparin 4000 IU/bid) was introduced and subsequentially substituted with a vitamin K antagonist (with an INR target between 2 and 3). It was also administered diuretic therapy including furosemide and canrenone achieving a gradual reduction of ascites and reduction of transaminases. At the hospital discharge, the patient was addressed to hematological follow-up and periodic check-ups to monitor liver function.
BCS may be the first manifestation of JAK2 mutation without peripheral blood or bone marrow abnormalities. Although it is extremely rare for BCS the presence of JAK2-V617F mutation without other myeloproliferative diagnostic criteria, it is anecdotally reported that these patients may develop an overt MPN in later years. Therefore, it is important to provide these patients with hematological follow-up.



Contrast-enhanced - computed tomography

## 98. IRON DEFICIENCY IN INTERNAL MEDICINE; A MONOCENTRIC OBSERVATIONAL STUDY

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**Background:** In a non-selected cohort of internal medicine patients, a monocentric observational study previously demonstrated high prevalence of anaemia, its impact on important clinical outcomes and the lack of attention of clinicians in its diagnosis and treatment. It is known that iron deficiency can have prognostic influence as an independent factor in several diseases. Most available data refer to acute heart failure, whereas we have still insufficient evidence concerning the remainder of hospitalized patients in internal medicine wards.
**Objectives:** To evaluate differences in prevalence, therapeutic strategies, and outcomes in subgroups of anaemic and non-anaemic patients found to have iron deficiency (ID).
**Methods:** We collected data on complete blood count and iron profile in 417 patients hospitalized in First Clinical Medicine of Padua University Hospital from Dec. 2017 to Apr. 2018 (189 F, 228 M, median age 77 years). The presence of anaemia was identified by WHO criteria (Hb < 120 g/L in females and < 130 g/dL in males). ID was defined by the presence of ferritin < 30 ug/L and/or transferrin saturation < 16% with C-reactive protein (CRP) < 5 mg/L. In the presence of an inflammatory state (CRP > 5 mg/L), absolute ID was identified when ferritin was below 100 ug/L or between 100-300 ug/L in association with transferrin saturation < 20% and/or, when available, soluble transferrin receptor (sTfR) > 1.76 mg/dL.
**Results:** In our cohort, 270 patients (64.7%) had anaemia while 147 (35.2%) had normal haemoglobin level. ID was present in 122 patients (29.5%) and in 69 of them (56,5%) was associated with manifest anaemia. Iron deficiency anaemia (IDA) occurred in 28 cases as an isolated diagnosis, in 4 associated with B12 or folate deficiencies and in 37 chronic diseases (17 chronic kidney disease and 20 other diseases). In the remaining 53 patients, ID was not associated with anaemia (43.4%): ID prevalence was significantly higher (p=0.024) among non-anaemic (36%) compared to anaemic patients (25.5%).

During hospitalization, intravenous iron (ferric carboxymaltose, FCM) was administered in 37 (53.6%) IDA patients but only in 1 (1,8%) of not-anaemic ID, being the treatment prevalence significantly lower in non-anaemic patients with ID (p<0.001).
Duration of hospital stay and in-hospital mortality were not different comparing IDA and ID without anaemia. Re-hospitalization in 30 days was significantly more frequent in IDA compared with ID without anaemia (p=0.022).
**Discussion:** In our study, we observed a high prevalence of ID in hospitalized patients both with and without manifest anaemia. Unfortunately, we did not register the main diagnosis of each patient, but our results suggest the possible association of ID not only with heart failure but also with many other diseases.
Only half IDA patients received iron supplementation in spite of their manifest anaemia, while ID alone is ignored by the clinicians, despite a growing body of evidence pointing to ID as an independent negative prognostic factor for other diseases of interest for internal medicine.
Interestingly, IDA patients had a higher re-hospitalization rate compared to ID without anaemia in spite of a better therapeutic approach for anaemia. This could underline the need of an appropriate follow-up in these patients after discharging to improve the iron stores and correct the etiologic factors that sustain the iron deficiency when opportune. In non-anaemic patients with ID, we observed longer hospital stays compared to other non-anaemic patients, pointing to a prognostic significance of ID even in an unselected internal medicine population.

| | Pats. with ID | IDA | ID without anaemia | p |
|---|---|---|---|---|
| Number (%) | 122 | 69 (56.5) | 53 (43.5) | / |
| Treated pats (%) | 38 (31.1) | 37 (53.6) | 1 (1.8) | 0.001 |
| Median Hospital stays (days, range) | 8 (1-43) | 8 (2-43) | 8 (1-21) | NS |
| 30-day re-hospitalization (%) | 28 (22.9) | 23 (33.3) | 5 (9.4) | 0.022 |
| In-hospital mortality (%) | 4 (3.2) | 3 (4.3) | 1 (1.8) | NS |

## 99. NAVIGATING THROMBOPOIESIS AND ERYTHROPOIESIS IN PATIENTS WITH SEVERE COVID-19: HUMAN MEGAKARYOCYTES AND ERYTHROID PROGENITORS ARE INFECTED BY SARS-COV-2

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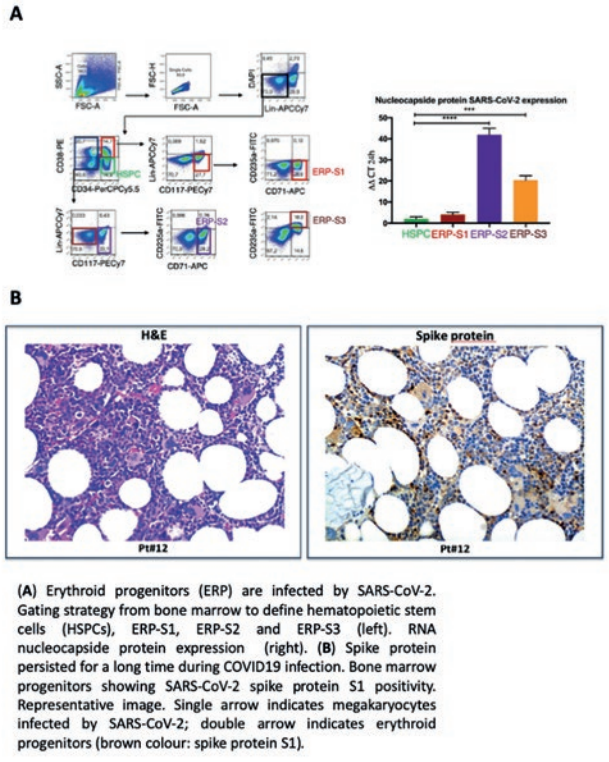
Gravity and mortality in SARS-CoV-2 infected subjects are associated with an aberrant decrease of thrombocytes, red cells, and blood cell count abnormalities and with an enhanced number of erythroid precursors in the circulation. Moreover, hypoxia and coagulopathy imbalance are present. It has been suggested that COVID-19 also involves the bone marrow (BM) while exhibiting a blood cells tropism. Our aim was to investigate the interaction between the virus and the BM precursors, namely megakaryocytes and erythroid progenitors amid the COVID-19 disease, to elucidate a potential role in disrupting the physiological thrombopoiesis and erythropoiesis. An extensive in silico interrogation of publicly available datasets prompted us to import RNAseq data and analysis of ACE2, CD13 and TMPRSS2 and expression from GSE144024, GSE118537 and The Human Cell Atlas BM Single-Cell Interactive Web Portal. A sample of 20 consecutive cytopenic patients (10 pts during infection and 10 pts after about ten days from swab negativization) who were being treated for SARS-CoV-2 severe infections were analyzed. Five subjects with benign anemia were used as controls. BM trephine biopsies from patients with thrombocytopenia, anemia or bilinear cytopenia were obtained and the sections were incubated with SARS-CoV-2 spike protein S1 antibody (MA5-36247) in immunohistochemistry, rabbit monoclonal, isotype: IgG, at a concentration of 0.2 µg/mL, with a heat-mediated antigen revelation with citrate buffer at pH 6. All subjects treated for severe SARS-CoV-2 infection displayed a rapid and profound decrease in platelets count and hemoglobin following admission [51.0 (127.0; 2.0)/mm3 and 1.4 g/dL (0.8; 2.1), respectively]. Specifically, monitoring of platelet count, hemoglobin levels and nucleated red blood cells during the first 28 days post hospitalization showed an increased RDW, MCV and the appearance of circulating erythroid progenitors. In silico interrogation pinpointed the expression of ACE2, CD13 and TMPRSS2 on megakaryocytes and erythroid progenitors. BM staining confirmed the presence of SARS-CoV-2 Spike protein in erythroid and megakaryocytes. Finally, the persistence of the SARS-CoV-2 Spike protein was detected in marrow precursors and also in patients who recovered from infection (Figure). We showed that subjects with severe COVID-19 infection suffered from thrombocytopenia, anemia or bi-linear cytopenia and had increased RDW, MCV and erythroid precursors in peripheral blood, suggesting a direct or indirect detrimental effect of SARS-CoV-2 on thrombo- and erythropoiesis. The detection of SARS-CoV-2 Spike protein in BM precursors and its persistence after infection recovery indicate that the virus is capable of damaging marrow precursors also after the systemic clearance. Finally, the presence of Spike protein on BM precursors may suggest humoral/cellular autoimmune attack against these cells in patients seroconverted after COVID-19 and paves the way for studies on vaccine-induced cytopenias.




**(A)** Erythroid progenitors (ERP) are infected by SARS-CoV-2. Gating strategy from bone marrow to define hematopoietic stem cells (HSPCs), ERP-S1, ERP-S2 and ERP-S3 (left). RNA nucleocapside protein expression (right). **(B)** Spike protein persisted for a long time during COVID19 infection. Bone marrow progenitors showing SARS-CoV-2 spike protein S1 positivity. Representative image. Single arrow indicates megakaryocytes infected by SARS-CoV-2; double arrow indicates erythroid progenitors (brown colour: spike protein S1).

## 100. PROGNOSTIC VALUE OF IMMUNE CELLS IN THE MULTIPLE MYELOMA BONE MARROW MICROENVIRONMENT: A META-ANALYSIS WITH IN SILICO AND IN VITRO VALIDATION

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**Introduction:** During multiple myeloma (MM) immunoediting, the immune cells can be effective in eliminating the initiating tumor MM cells (MMPCs) in the elimination phase or at least, in the equilibrium phase, which can prompt functional dormancy at early stages. However, malignant MMPCs can take advantage of immune dysfunction and permissive immune microenvironment to escape immune elimination, proliferate and generate active MM.
**Methods:** We performed a systematic literature research on Pubmed, Scopus and Web Of Science databases from inception to 5th August 2021 considering cohort or case-control studies published in English language which explored the impact of bone marrow immune cells on overall survival of adult patients suffering from multiple myeloma. Studies which dealt with peripheral blood immune cells were discarded.
The hazard ratio (HR) for overall survival (OS) was chosen as the main outcome. The second aim of this study was to evaluate the local immune cell anti-MM immunity using a supervised transcriptomic approach. In order to do that, we generated a discovery dataset, from GSE47552, GSE6477, GSE19784, GSE2658, GSE15695; GSE9782; we also interrogated a validation dataset from GSE4204, GSE2658, GSE136324, GSE15695, GSE57317 and GSE2658. As an extra validation dataset, we interrogated the CoMMpass database. As target genes we used a supervised approach with selected genes known to be representative of key immune mechanisms and cancer microenvironment. To determine whether there was at least one gene in a gene-set with an association with OS we did a ridge regression analysis. If these groups had at least one gene that was associated with OS, they were also interrogated in the validation dataset. If the validation dataset confirmed the results, they were all interrogated for an individual gene analysis. Secondly, by applying a Cox regression for each individual gene for each individual dataset, and a meta analysis performed. The genes that kept the statistical significance after multiple testing in the discovery data were applied to the validation data, in which the same analysis was performed and the selected genes significant after multiple testing were included into a multivariable model corrected for ISS in the CoMMpass dataset.
**Results:** 5021 articles were found with the literature research, which became 3713 after duplicates removal. After title and abstract screening, 178 articles underwent full-text examination. Of these, 10 were included in the meta-analysis. Figure 1 shows the results of the meta-analysis.CD4 T cells were the ones with the highest point estimate on OS, tough with a low precision. This result was not considered significant by the authors because of a poor phenotypical characterization. The same is true for the result of the CD8 T cells. Among the B cells compartment, the only ones with a significant impact on OS were memory B cells. In the innate immunity cells compartment, neutrophils and mast cells were associated to a protective effect on OS. On the other hand, NKT cells and macrophages, in particular the M2 subtype, were associated to increased mortality risk. Finally, the increased expression of various proteins involved in immune checkpoint had a significant impact on OS: VISTA and CD40 had a protective effect, and CD200 and PDL1 increased the mortality risk. Gal-9 was found to be a risk factor for mortality only in PDL1-high patients.
The in silico interrogation of the discovery and validation cohorts showed CD40 (HR 0.35; P<.0001), VISTA (HR 0.4; P<.001), TIM3 (HR 2.2; P<.05); ITGB1 (HR 1.9; P=.001), and FABP5 (HR 2.8; P<.001). However, when we investigated those gene expression within the CoMMpass dataset, only VISTA, FABP5 and ITGB1 remained significant with HR 0.75 (P<.005), 14.42 (P<.001), 4.71 (P<.05), respectively. Subsequently, we functionally validated the downstream pathways related to cytoskeleton rearrangement, proliferation, epithelial- mesenchymal transition, and dissemination in vitro (figure 2).
**Conclusions:** Supervised transcriptomic analysis reveals VISTA, FABP5 and ITGB1 as independent prognostic factor in MM; thus, we propose this immune basket as a promising tool in MM clustering for theragnostic purposes in MM. Our study has clear limitation due to the lack of a statistically powered wet validation. Currently, we have reached the end of patient recruitment for a new randomized myeloma trial and once survival data are available, we will validate the immune basket in this large cohort, and at the same time, further delineate which cell type within the TME will contribute the most. Due to the meta-analysis, it is tempting to speculate on a pivotal role played by the M2 macrophages.

## 101. TEAM AND TIME: THE IMPORTANCE OF A MULTIDISCIPLINARY APPROACH TO PLASMA CELL LEUKEMIA

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**Background:** Plasma cell leukemia (PCL) is a rare aggressive hematological malignancy, which can be defined either as primary when the leukemic phase presents at diagnosis or secondary when it develops from preexisting multiple myeloma. The diagnostic criteria have been matter of debate: even though the Kyle criteria have been revised by the WHO and the International Myeloma Working Group, emerging data are highlighting that even much lower plasma cell counts are associated with progression free survival.
Case presentation: A 59-year-old Caucasian man presented to the Emergency Department complaining of a 10-day history of worsening low back pain, with no response to common painkillers. Remarkable data of his medical history included: chronic HCV hepatitis, HIV infection on Dolutegravir/Lamivudine, known monoclonal gammopathy of undetermined significance (MGUS) (IgG kappa 3.8 g/L) with no further follow-up in the past 6 years. During a routine outpatient visit, the results of a complete blood count revealed leukocytosis (WBC 42.760/mm3, L 66%, N 5%), Hb 12.3 g/dl, and thrombocytopenia (PLTS 97000/mm3), the latter confirmed also on sodium citrate count, no renal impairment. Given worsening back pain, the patient had still not undergone more detailed workup when he presented to the ED. The physical examination revealed no palpable lymph nodes, slightly enlarged spleen. Due to new onset atrial fibrillation, flecainide was administered, with timely restoration of sinus rhythm. Anticoagulation with enoxaparin was started. MRI of the dorsal and lumbar spine showed D9 collapse with swollen surrounding tissues, possibly consistent with spinal abscess or osteolytic lesion.
He was admitted to the Internal Medicine Unit. Mild anemia, hypercalcaemia (12 mg/dl), mild hypoalbuminemia (28 g/l), increased serum β-2 microglobulin (6.1 g/L) and rapidly worsening renal impairment (eGFR 22 ml/min) were detected. Quantiferon Plus, blood culture (including Mycobacterium), Brucella serology, HIV and HCV RNA were negative. At first the peripheral blood smear seemed to identify atypical medium/small size lymphocytes; however, immunophenotyping analysis highlighted 78% cluster of CD38+/CD138+/CD56+ plasma cells, with some plasmablasts and binucleated/vacuolated cells. Serum protein electrophoresis and immunofixation confirmed an IgG monoclonal component (2.8 g/l); a significant alteration of the serum-free light-chain ratio was found (lambda–kappa ratio < 0.01, with lambda chains 4349 mg/l). Nephrotic syndrome was detected (24hours urine protein over 3.5 g), with positive Bence Jones at 24hours urine protein electrophoresis and immunofixation and metabolic alkalosis. Cast nephropathy as well as light chain deposition disease and amyloidosis were considered in the differential diagnosis. The bone marrow aspiration and biopsy confirmed a very rich plasma cell infiltrate (95%) with the following immunophenotype CD138+/CD20+/Cyclin D1+/CD56+/Mum1+/CD5-/CD3-. Fluorescent in-situ hybridisation cytogenetics revealed t(4: 14) and deletion of the variable region of the IGHG1 gene. Congo red stain of the bone marrow biopsy did not show amyloid deposition. Troponin was 15 ng/l and NT-proBNP 1107 ng/l. 24hours Holter ECG confirmed stable sinus rhythm. Cardiac transthoracic ultrasound as well as cardiac MR were not consistent with cardiac amyloidosis. Abdominal ultrasound showed mild splenomegaly (12,3 cm) and reduced renal corticomedullary differentiation. Lower limb electromyography and motor evoked potentials revealed mild degree sensory motor polyneuropathy with possible demyelination.
After accurate multidisciplinary risk-benefit evaluation, interpretation of already available data and also considering the thrombocytopenia-related bleeding risk, no renal or vertebral biopsy was performed. Whole body low dose computed tomography without contrast revealed osteolytic lesions involving D4, D8, D9 and the skull.
The patient was treated with intensive fluid replacement together with low-dose diuretics, glucocorticoids at low dose at first and dexamethasone 40 mg afterwards, together with proton pump inhibitors. Pain relief therapy was optimized. Induction therapy with VDT-PACE (bortezomib,

dexamethasone, thalidomide, doxorubicin, cyclophosphamide and etoposide) without cisplatin, due to renal impairment, was administered. After improvement of kidney function, intravenous zoledronate was also added. A profound decrease of serum free-light-chains has been achieved, together with improvement of renal function. The patient is waiting for autologous hematopoietic cell transplantation.
**Conclusion:** When dealing with a patient with monoclonal gammopathy, awareness of the multiple clinical conditions which may present with this feature is warranted and the differential diagnoses to be considered include both plasma cell disorders (e.g. multiple myeloma, MGUS, monoclonal gammopathy of renal significance, AL amyloidosis) and B cell lymphoproliferative disorders (e.g. chronic lymphocytic leukemia). PLC is a systemic condition with a potentially ominous prognosis, so that timely diagnosis and treatment are of paramount importance.

## 102. UNCOMMON ORGAN DAMAGE IN A PATIENT WITH HYPEREOSINOPHILIC SYNDROME

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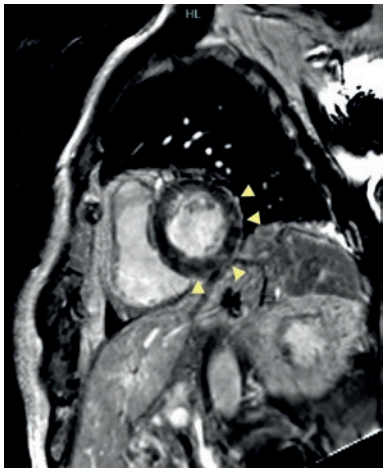
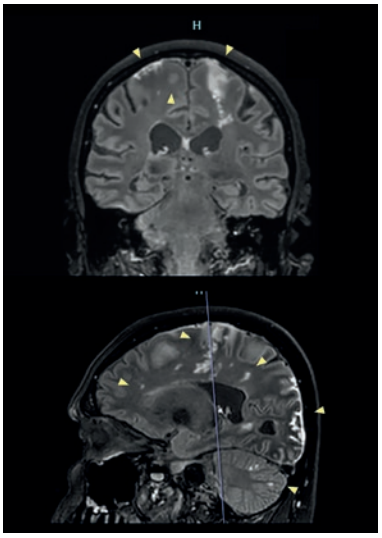
**Background:** Hypereosinophilia (HE) is defined as an absolute eosinophil count (AEC) greater than 1.5 x10^9/L in the peripheral blood on two examinations at least one month apart and/or pathologic confirmation of tissue HE (on a bone marrow section or tissue biopsy). HE can be secondary, clonal or idiopathic. Hypereosinophilic syndrome (HES) is defined by the association of HE with evidence of eosinophil-mediated organ dysfunction, when no other cause can explain such damage.
**Case Report:** We report the case of a 62-year-old man who presented to the emergency room of our institution with diarrhea and altered mental status. Ten days before, he had been discharged from another hospital with a diagnosis of gastroenteritis and the indication to take metronidazole. The patient was admitted to our internal medicine department for further evaluation. His past medical history was relevant for type 1 diabetes and stage 3 chronic kidney disease. He complained of diarrhea, confusion and fatigue, which appeared a few days after consuming raw fish. His vital signs were normal, his neurological examination showed paralysis of his right arm, weakness of lower extremities, dysmetria and leg myoclonus. His blood exams revealed an AEC of 8.0 x10^9/L, anemia (Hb 11.6 g/dl) and increased liver cytolytic and cholestatic enzymes. Consequently he underwent an extensive series of exams to determine the magnitude of the damage and the cause of HE.
ECG showed myocardial overload in the lateral leads, cardiac enzymes were extremely elevated (troponin T 1723 ng/L, proBNP 22920 ng/L). A transthoracic echocardiogram demonstrated apical hypokinesis but preserved ejection fraction. These findings led to the execution of a cardiac magnetic resonance imaging (MRI) which revealed multiple small intramyocardial areas of edema and fibrosis with a patchy distribution of the septum and the lateral wall on late enhancement sequences, consistent with myocarditis (figure 1).
Moreover, considering the neurological deficits, the patient underwent a non-enhanced head CT scan, with no abnormal findings. Subsequently a head MRI was performed, which showed hyperintense areas in the cortical and subcortical matter of the cerebellar hemispheres, bilateral fronto-parietal and occipital lobes on T2 and FLAIR-weighted sequences, suggestive of ischemic vasculitic lesions (figure 2).
A presumptive diagnosis of HES was made. At this point, multiple specialists were involved in the management of the patient. Blood and fecal samples were collected to demonstrate secondary causes. A bone marrow biopsy and lumbar puncture were done to rule out clonal eosinophilia and an ongoing infection of the central nervous system (CNS) respectively. After the latter procedure revealed no CNS infection, the patient was started on methylprednisolone (1 mg/kg). The following day the AEC was zero, but the patient required an adjustment of his insulin regimen.
Cultures and parasitic search on stool were unrevealing as were an autoantibody screening and a helminthic serology panel, except for the Western blot IgG of Toxocara canis, which was slightly positive. The test was repeated, meanwhile the patient underwent a prophylactic course of albendazole. However, the second exam was negative. Bone marrow biopsy showed slight hypocellularity with eosinophilic expansion, without blasts or lymphoid infiltration. Blood cytogenetic analysis was negative for BCR-ABL1 fusion, JAK2, PDGFRA, PDGFRB and FGFR1 mutation. Finally, a whole body PET-CT showed diffuse uptake of the vertebrae, ribs and small bowel, which was not considered specific.
By the time the results of the tests became available, the patient's right arm had recovered most of its motion and myocardial necrosis enzymes returned to baseline. Repeated echocardiography and brain MRI were stable. We began glucocorticoid tapering and observed stability of the AEC and he was discharged. Follow-up on an outpatient basis is still ongoing.
**Discussion:** HES is a rare disease caused by different pathogenic mechanisms. Organ involvement is varied, with skin, lung and gastrointestinal tract being the most frequently targeted. Although brain and cardiac damage is uncommon, its morbidity and mortality are elevated. Therefore, the involvement of these organs should be ruled out and the approach to this kind of patients should always be multidisciplinary. The diagnostic algorithm is complex, but finding the underlying cause of HE can lead to specific treatment. Even when in front of an idiopathic HES, clinicians must recognize severe forms of the disease (life-threatening complications, extremely elevated AEC, signs of leukostasis) such as in this case and begin treatment immediately. The diagnostic evaluation should never defer treatment.




## 103. IDIOPATHIC HYPEREOSINOPHILIC SYNDROME

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A 29-year-old male was admitted to the hospital with few days history of abdominal pain associated with nausea, vomiting, diarrhea and fever (t max 38°). No history of cutaneous symptoms, asthma or atopy was reported. At the admission he was conscious, apyretic and with normal vital parameters. The physical examination was normal except for mild abdominal discomfort on right-middle abdominal side during deep palpation. Complete skin examination excluded rash, ulcers or eczema. Initial investigation showed white blood cell count of 12,69 x 10 3/uL with absolute eosinophil count of 5960/uL (47% of the total WBC). Coagulation times were

mildly prolonged (the prothrombin time-international normalized ratio was respectively 68% and 1.31). Acute phase reactants were negative. He performed abdominal CT which documented gallbladder distension with biliary sludge and peritoneal fluid in the dependent regions in association with mild pleural and pericardial fluids. The patient was admitted to the Internal Medical Care department for in-depth diagnostic analysis. On the evaluation of the hyperosinophilia (HE), we conducted the peripheral blood smear which showed various eosinophil without aberrant morphology or dysplastic form. Secondly, we performed stool examination for parasite, Widal test and serologic test for Cytomegalovirus, Adenovirus, Coxackiae-virus and Epstein-Barr virus which were all negative. Antibody screen was also done with ANA, ENA screen, ANCAs, anticardiolipin immunoglobulin M and G and viral hepatitis profile were all negative. We performed also antismooth muscle autoantibodies (SMA) which were mildly elevated, 1: 320. High levels of IgE were also noted (1793 kU/L). IgA, IgM and IgG were within normal ranges. Therefore, we measured IgG4 in the preserved serum which were marked highly, 414 mg/dL (normal range 4.8 to 105 mg/dL and constituted 28% of the total IgG (normal value <7%). Therefore, he performed total body CT with contrast which excluded malignant lymphadenopathy and other expansive masses. Based on these results, Hypereosinophilic Syndrome (HES) remained as the most likely diagnosis. To categorize HES, we performed bone marrow aspiration which demonstrated increased eosinophils and eosinophil precursors and molecular studies (research for rearrangement of FGFR1 and PDGFRB fusion genes, BCR-ABL1, JAK2 V617F, KIT D816V, and clonal T cell receptor) which were all negative. Collectively, these findings pointed to a diagnosis of Idiopathic HES. Prednisolone was started at 60 mg/day with immediate clinical benefits and reduction of peripheral eosinophils. In consideration to his abdominal pain, we performed endoscopy evaluation in both the upper and the lower gastrointestinal tract which documented eosinophilic gastroenteritis and eosinophilic colitis (biopsies taken from stomach, terminal ileum and ascending colon showed > 70 eosinophils per high-power field). In relation to SMA-positivity, we performed also Colangio RM which revealed normal aspect of biliary tree and resolution of the peritoneal, pleural and pericardial effusions. At the discharge, the patient was apyretic, asymptomatic and with a dramatic reduction of eosinophil (40 cell/uL) after a trial of steroid therapy, continuously tapered in the out-patient setting. Interestingly, he had a younger brother who performed for laboratory test which showed HE and negative molecular studies. Both performed molecular genetic testing, which are underway. Here we presented a peculiar case of Hypereosinophilic Syndrome. HES is defined by the association of HE (defined as absolute eosinophil count > 1,5 x103 cells/uL) with eosinophil-mediated organ damage and/or dysfunction, when other potential causes have been excluded. Despite careful evaluation of HE, none of the test showed a positive result. It is important to underline that as many as 75 percent of cases of presumed HES remains undefined. In these situations, the terms "idiopathic HES" and "HES of unknown etiology" are used to distinguish these patients from those in earlier analysis. A genome-wide study may be needed to understand the "idiopathic" cases that would ultimately lead to better patient care. Our patients had an idiopathic HES with gastrointestinal involvement. He also had abnormal coagulation tests in absence of clinical manifestation of coagulopathy, well-known associated to HES. Glucocorticoids effectively suppressed HE and corrected both laboratory anomalies and disease complications. Furthermore, according to his high value of IgG4, our patient's case is likely to be an example of IgG4 related disease (IgG4RD). Interestingly, he had also positivity to SMA autoantibodies. HE has been often associated with IgG4RD and with some autoimmune diseases (such as IBD). Both conditions are related with immunodysregulation and responds well to glucocorticoids. The etiology of the HE in such cases is unknown and its impact on disease complication and clinical manifestation remains inconclusive. Further researches into causal relationship between HE and IgG4 are required.

## 104. HYPERCALCEMIA AND DIFFUSE LARGE B-CELL LYMPHOMA: AN EMERGING ASSOCIATION

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**Introduction:** Hypercalcemia is a common metabolic abnormality seen in our patients. Depending on the serum calcium levels, hypercalcemia is categorized either as mild when levels are between 10 to 12 mg/dl, moderate when levels are between 12 to 14 mg/dl or severe when levels are more than 14 mg/dl. We present a rare unsuccessful case of severe hypercalcemia caused by Non-Hodgkin Lymphoma. Case report: A 82-year old Caucasian male was admitted to our Hospital for asthenia and constipation with onset two weeks prior. His wife reported a recent onset of intercurrent delirium too. His past medical history included: appendicectomy, hypertension, chronic gastritis, osteoarthritis and previous urinary tract infections. Home therapy was: acetylsalicylic acid 100 mg/day, metoprolol 100 mg/day and ramipril 5 mg/day. He did not drink alcohol. On physical examination, abdominal and respiratory examination were negative for pathological findings while neurological examination revelead space time disorientation without focal neurological signs. Blood pressure was 190/80 mmHg, heart rate was 100 bpm in absence of fever. Electrocardiogram showed sinus tachycardia (heart rate equal to 110) with aspecific alterations on repolarization. A brain CT, chest and abdomen X-ray were negative. Biochemical studies were planned. Serum biochemical tests showed severe hypercalcemia (20.7 mg/d), WBC 11230/mmc (N 79%) Hb 14.1 g/dl MCV 77 fL PLT 318000/mmc, acute kidney injury (creatinin 2.6 mg/dl) without dysionemia, no signs of infection (PCR 2.3 mg/dl PCT 0.03 microg/L), total proteins 7.4 g/dl (alb 58%, gamma 12%), ALT 26 U/L, LDH 405 U/L, no alteration of tumor markers, INR 0.9, PTH suppressed, TSH 0.18 mUI/L, vitamin D 7 microg/L, ACE normal, immunofixation and urine test negative. The nasopharyngeal swab was negative for SARS-CoV-2 real-time polymerase chain reaction. Intravenous hydration (SF 2000 ml ev die), furosemide (20 mg bid), steroid (prednisone 20 mg tid) and one dose of zoledronic acid 4 mg were started. Serum calcium levels decresead to 18 mg/dl but state of consciousness got worse. A lumbar puncture was performed and the analysis of liquor was negative. EEG showed aspecific brain suffering. Although medical therapy for hypercalcemia, we did not observe normalization of calcemia and we decided to start dyalisis requiring thorax and abdomen CT. Radiologist described bilateral bronchopneumonia, mediastinal lymphadenopathy (26x17 mm), bilateral axillary lymphadenopathy (33x15 mm), a space-occupying lesion at left renal pelvis (7.5x6.5x25 cm) long psoas muscle, bilateral adrenal nodules suspected for metastasis, no bone lesions. FNAB under CT guide of mass highlighted Non-Hodgkin Lymphoma as diffuse large cell lymphoma B (CD20+, CD3-, Bcl2+, Bcl6, CD30-, CD10-, CD68/PGM1-, MUM1+, EBV-, CD5-, cMyc+, CD21-, CD23-, Ki-67: 90%). Later, serum calcium returned normal but clinical situation deteriorated with fever, dyspnea, hypotension and coma in multiorgan failure. Patient was intubated, broad spectrum antibiotic treatment and noradrenalin iv were initiated without benefit and the patient died. Discussion: The causes of hypercalcemia can be divided into various categories: hyperparathyroidism, vitamin D-related causes, malignancy, medications, other endocrine disorders, genetic disorders, granulomatous diseases and miscellaneous causes. No specific physical examination findings indicate hypercalcemia. However, patients can present with a wide spectrum of symptoms. Depending on the acuity and severity, patients can either be asymptomatic or can have involvement of multiple organ system such as gastrointesinal tract, musculoskeletal system, cardiovascular system, renal involvement and central nervous system or psychiatric disturbances. In particular, in a case of an acute confusional state without fever, metabolic alterations as hypercalcemia should always be considered in the differential diagnosis of change in consciousness or in behaviour. The initial evaluation of hypercalcemia mandates a through history and physical as it can prompt the clinician to the underlying cause and pathology. Medication history, dietary history, family history and evidence of prior diseases need to be reviewed.
**Conclusions:** Severe hypercalcemia can be life threating. Hypercalcemia in NHL is emerging and according data literature, it was found mainly at diagnosis in higher-risk patients and those with diffuse large B lymphoma stage III/IV disease and elevated LDH. As seen in our case, it is associated with poor progression-free survival, overall survival and could be a biomarker of the underlying biological aggressiveness of diffuse large B-cell lymphoma. A rapid work up including laboratory testing and imaging is necessary to reach differential diagnoses of hypercalcemia. Aggressive intravenous rehydration is the mainstay of management in severe hypercalcemia and antiresorptive agents such as biphosphonates frequently can alleviate the clinical manifestations of hypercalcemic disorder. Dialysis is generally reserved for those with severe persistent hypercalcemia complicated with kidney failure.

## 105. STAT1 GAIN-OF-FUNCTION VARIANT UNCOVERS A STAT1 DYSREGULATION AS A FEATURE OF APLASTIC ANEMIA IN A PATIENT WITH AN INBORN ERROR OF IMMUNITY

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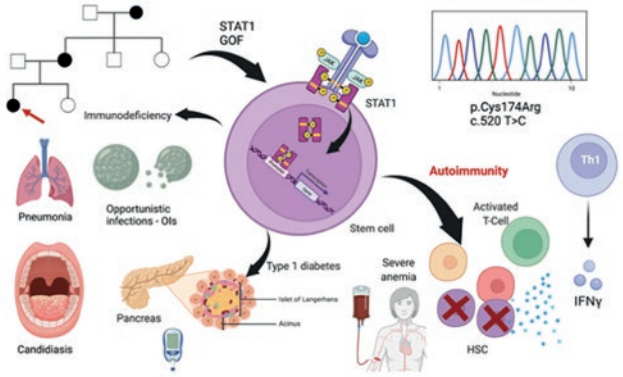
Case presentation and aplastic anemia diagnosis
A 32-year-old female presented with 3 weeks of pallor, weakness, cough and dyspnea. On ex- amination, she was pale but well appearing with a body mass index of 19.5. She had painful oral ulcers and CMC on the soft palate/ recurrent infections/DM1. Her peripheral blood laboratory values were notable for pancytopenia with a hemoglobin level of 7.6 g/dL (reference range 12–16 g/dL) without signs of hemolysis, a white blood cell count nadir of 3700 cells/mcL (reference range 4,500–11,000 cells/mcL), an absolute neutrophil count nadir of 2,100 cells/mcL (reference range 1,800–7,700 cells/mcL), and a platelet count of 12100/mcL (reference range 140,000–430,000 platelets/mcL). She was urgently transfused red blood cells, and a bone marrow biopsy demonstrated normocellularity for age (70% cellularity) with a myeloid and megakaryocytopoiesis predominance, but absent erythroid precursors. An extensive infectious and rheumatologic workup was unrevealing. Testing for paroxysmal nocturnal hemoglobinuria, Fanconi anemia, and telomere shortening diseases were all negative. Bone marrow panel mutational testing, karyotypic analysis, and T cell receptor spectrotyping were normal. Bone marrow flow cytometry demonstrated that CD3+ T cells were 99% of bone marrow cells, and the CD4: CD8 ratio was 0.5 (absent b lymphocytes, increased T lymphocytes, higher CD8+ than CD4+). Though her platelet count remained relatively preserved, criteria of peripheral neutrophils <500/mL, reticulocytes <2%, and bone marrow hypo-cellularity confirmed a diagnosis of severe aplastic anemia.
Her medical history was notable for recurrent severe oral and esophageal candidiasis since childhood, for which she had taken prednisone 10 mg daily on an as-needed basis during flares for years. She also suffered from oral mucocutaneous candidiasis (CMC), type 1 diabetes (DM1) opportunistic infections and recurrent pneumonia since childhood. CMC caused her main discomfort, and nystatin, the oral suspension was prescribed and specific endocrinologic therapy.
The patient and her family were of Caucasian descent. Her family history was remarkable in that her mother, also suffered from DM1 since early childhood. Her grandmother was diagnosed with autoimmune thyroiditis. The construction of a pedigree suggested an autosomal-dominant pattern of inheritance for the phenotype of DM1 severe oral and esophageal candidiasis.
Identification of a pathogenic STAT1 gain-of-function variant
Given the autosomal-dominant inheritance pattern of the patient's DM1, recurrent infections aphthous lesions and unclear etiology of her aplastic anemia, whole-exome sequencing of the patient was performed. A heterozygous variant (p.520T>C, p.Cys174Arg) in the coiled-coil domain of STAT1 was identified in the patient and was confirmed by Sanger sequencing
Rigorous criteria have been established to determine the causality of a genotype for a given phenotype in single-patient studies [1]. The p.Cys174Arg variant identified in our patient has been classified as pathogenic because it is (1) absent from large population databases, (2) has been identified in more than 10 individuals from multiple families with chronic mucocutaneous candidiasis/recurrent infections DM1, and (3) has been shown in vitro to have GOF activity [1]. Thus, p.Cys174Arg was taken to be causal for the patient's oral inborn error of immunity. An extensive workup of the patient's aplastic anemia ruled out toxin-mediated, hematologic, rheumatologic, and infectious etiologies. Given that aplastic anemia has been associated with STAT1 GOF, the patient's p.Cys174Arg variant was deemed to be causal for the patient's aplastic anemia as well, though it is impossible to exclude the possibility that aplastic anemia developed coincidentally in the setting of our patient's STAT1 GOF mutation.
This led us to query whether a similar pattern of STAT1 hyperactivation might be present in other cases of idiopathic aplastic anemia which were not associated with a congenital STAT1 GOF variant. Indeed, the majority (7 out of eleven) of idiopathic aplastic anemia cases displayed increased STAT1 activity by phospho-STAT1 staining of bone marrow core sections. These findings raise the clinical question of whether patients with idiopathic aplastic anemia who display STAT1 hyperactivation may benefit from JAK inhibitor therapy, a question that should be addressed in the context of a randomized trial. This case demonstrates how the careful study of patients with rare inborn errors of immunity can lead to pathophysiologic insights and to potential therapies which may be more broadly applicable to the extended spectrum of aplastic anemia and inborn errors of immunity [2,3] (Figure).
References: - 1.Liu, L., et al. J. Exp. Med. 2011, 208, 1635–1648, doi: 10.1084/jem.20110958. - 2. Solimando, A.G., et al. Encyclopedia of Infection and Immunity; Elsevier, 2022; pp. 798–818 ISBN 978-0-323-90303-5. - 3. O'Shea, J.J., et al. Annu. Rev. Med. 2015, 66, 311–328, doi: 10.1146/annurev-med-051113-024537.




Family pedigree and graphical abstract. The phenotype of severe oral ulcers or type 1 diabetes is denoted by shaded symbols (males, squares; females, circles, patient: red arrow). STAT1 gain-of-function seems to be related to immunodeficiency, immune dysfunction, diabetes mellitus and, ultimately, aplastic anemia. Aplastic anemia in the setting of a GOF STAT1 variant. We identified JAK/STAT activation also in other aplastic anemia cases, suggesting the possibility that JAK inhibitors could have efficacy in patients with idiopathic aplastic anemia. HSC: hematopoietic stem cell.

## 106. THE MANAGEMENT OF HEMATOLOGICAL ELDERLY PATIENTS IN AN INTERNAL MEDICINE DEPARTMENT: THE CLINICA SAN CARLO EXPERIENCE

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**Introduction:** The epidemiological landscape of hematological patients has changed in the recent years, mainly due to comorbidities e.g. infective disease, in an increasingly elderly and frail population. In addition, the internal medicine specialist has to deal with hematological conditions in diagnosis, treatment and complication management. Because of the complexities present in these patient populations, the internal medicine specialist may be the preferred one for a multidisciplinary approach.
**Aim:** The aim of this study is to describe the experience in an outpatient setting with patients affected by hematological conditions that are managed by hematologists and geriatricians, and subsequently followed at the Internal medicine department of Clinica Polispecialistica San Carlo-Paderno Dugnano.
**Material and Methods:** Clinical characteristics of 123 patients followed from 2020 to 2022 were retrospectively collected. Patients were followed at our Day ward, and hospitalized in our Internal medicine ward, whenever necessary. Descriptive statistics was performed.
**Results:** The median age at diagnosis was 77 years (range 40-93), and the majority were male (72/123, 58%). Forty patients/123 (32%) were affected by lymphoproliferative disorders, 24/123 (20%) by myeloproliferative neoplasms, 21/123 (17%) by multiple myeloma, 23/123 (19%) by Myelodysplastic syndromes, 4/123 (3%) by acute leukemia, and 11/123 (9%) by other hematologic diseases.
Among these, 81/123 (63%) were treated with chemo- or immuno-therapy, whereas 42/123 (34%) with supportive treatment. No differences in median age between these two groups were found.
Here we report data by disease
-Lymphoproliferative disorder: 40 patients (23 pts male/17 female); 34 alive with a median age of 77.8 yo
-Myeloproliferative neoplasm: 24 patients (16 male/8 female); 23 alive with a median age of 75 yo
-Multiple myeloma: 21 patients (11 male/10 female); 15 alive, median age 77 yo
-Myelodysplastic syndrome: 23 patients (14 male/9 female); 15 alive, median age 84 yo
-Acute leukemia: 4 patients (2 male/2 female); median age 74 yo at diagnosis
-Other conditions: 11 patients (hypogammaglobulinemia, hemolytic anemia, idiopathic aplastic anemia)
A total of 35 (28%) patients were admitted at our Internal medicine ward for acute illness. The mean age was 79 years. Twenty-one (17%) were admitted for acute complication related to hematological disease (i.e. severe

infections, neutropenia or severe anemia), whereas 14/123 (11%) were admitted for a non-related acute illness (e.g heart failure, COPD). A total of 23 patients died. Out of them, 10 died during hospitalization.
**Conclusions:** The activity of our Day ward in this complex setting with patients with hematological diseases is necessary and strictly complementary to the hospital activity. This approach responds to the new emerging needs of the this elderly onco-hematological population and furthermore this management allows:

## 107. TOO BLOOD CAN KILL YOU

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A 56-year-old man, born in Sri Lanka, was admitted to the emergency room due to dyspnea and dry cough worsened in the last 5 days; dizziness was also reported.In the past eight years the patient suffered from two strokes with no lasting damage (2014, 2018) and one minor stroke (2019); since then the patient underwent dual-antiplatelets therapy. He also suffered from hypertension and dyslipidemia. He was an active mild smoker. At the physical examination the patient was alert and oriented, severely dyspnoic. Blood oxygen saturation was 90%. Arterial blood pressure 180/100 mmHg, heart rate 66 bpm. He showed bilateral conjunctival hyperaemia. Since the condition of respiratory failure combined hypoxemia and hypercapnia (Emogas analysis: pH 7.33, pO2 44.3 mmHg, pCO2 68.5 mmHg, hco3- 32.7 mmol/L, P/F 210 mmHg) the patient was treated with oxygen therapy (Venturi Mask 40%) and afterwards, because of clinical worsening, with non-invasive. Unacknowledged chronic obstructive pulmonary disease (COPD) with cardiac failure was the preliminary hypothesis for the underlying condition. Loop diuretics, nitrate and steroids were administered with progressive resolution of the respiratory and cardiac failure.On the account of the previous strokes occurred during young age and considering high blood cells count with hemoglobin 18 g/dL and hematocrit 55%, serum erythropoietin levels were investigated and revealed lower then normal. JAK2 V617F mutation was then researched, resulting positive. Bone marrow biopsy was performed with the histological examination being compatible with a prodromal state of polycythemia vera ("masked-PV").A JAK2-mutated myeloproliferative disease compatible with polycythemia vera was then diagnosed.The patient was treated with therapeutic bloodletting and the HCT target was setted at 45% with decreasing of the arterious pressure values and regression of the hyperviscosity-related dizziness. According to these results and considering the previous strokes as a consequence of the myeloproliferative disease we studied the status of the arterious blood flow with echocolordoppler of the supra-aortic vessels with no evidence of pathology. So, single-antiplatelet therapy was confirmed.
Polycythemia vera is a rare pathology, considered a type of blood cancer that causes the bone marrow to overproduce red blood cells. These cells cause blood hyperviscosity and increase the risk of blood clots and thromboembolism, both arterial and venous. Polycythemia vera can be either symptomatic or asymptomatic, main symptoms include: hepato/splenomegaly, sweating, ischaemic events (even in uncommon sites), headache, dizziness, conjunctival hyperaemia, double vision and shortness of breath. Thicker the blood is, most serious the symptoms are, so it could also become a life-threatening pathology. Treatment for low-risk patients is based on antiplatelet therapy and periodic phlebotomy; Hydroxycarbamide can be administered to lower the red blood cells count. For high-risk patients treatment is based on Ruxolitinib (a JAK-inhibitor) and Ropeginterferon alfa-2b-njft (a particular form of interferon alpha). Proper diagnose and treatment are fundamental: life expectancy is about 2 years without therapy, otherwise patients who receive a correct treatment have an average survival of at least 20 years.

## 108. DIAGNOSTIC CHALLENGE IN INTERNAL MEDICINE: THINK RARE. UN UNPREDICTED CASE OF INTRAVASCULAR LYMPHOMA

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**Background:** Intravascular large B-cell lymphoma (IVLBCL) is a rare, clinically aggressive, subtype of Diffuse Large cell B-cell lymphoma (DLBCL), characterized by a typical neoplastic lymphocyte proliferation within the lumen of small blood vessel. It may occur without extracellular tumor masses, parenchymal invasion or observable circulating lymphoma cells in the blood. IVLBCL usually affects elderly individuals and presents with various clinical symptoms, mainly caused by the occlusion of small vessel. Constitutional B syntoms (fever of unknown origin, night sweat and weith loss) are seen in the majority of patients. Affected individuals often present elevated serum lactate dehydrogenase (LDH), beta-2-microglobulin, C-reactive protein, serum monoclonal protein and may have alterated hepatic or renal functions and unexplained hypoxemia. Rapid deterioration in performance status (PS) is very frequent, particularly due to the highly heterogeneous neurological symptoms related to involvement of the central and peripheral nervous systems. The most frequent manifestations include sensory and motor deficits, neuropathies, paresthesia, dysarthria, dysphagia, altered conscious state up to dementia. Cutaneous involvement may be present at diagnosis in 40% of patients and displays a wide range of lesions, including painful erythematous and desquamated plaques up to cellulitis. Regarding the immunophenotype, IVLBCL cells display the features of mature peripheral B cells with strong CD20 expression, a marker critical for the current therapeutic implications. However, the few reports avaible reveal that the immonophenotype is strongly heterogeneous as well. Analyzing the few series, it was notet that the immunophenotype of IVLBCL may in some cases overlap with DLBCL not otherwise specified. As mentioned above, the vast majority of IVLBCL literature is represented by single or small series case reports, that often only partially overlap. Furthemore, IVLBCL diagnosis still remain a diagnostic challange because no pathognomonic signs and symptoms exist. A skilled clinician may suspect the disease based on personal experience and clinical observation. In any case, definitive diagnosis needs to be confirmed by histopathological examination. Regarding the treatment, the poor prognosis of the disease substantially has improved by immunochemotherapy, in particular by rituximab for the high CD20 cellular expression. Despite improved outcome, a significant proportion of patients relapse and a Chinese monocentric study has demonstrated an overall survaval less than 2 years even after chemoterapy treatment.
Case presentation: A 85-year-old Italian man was admitted to Emergency Department for recurring fever in the last two week, weight loss (7 kg in 3 months), arthalgias and diffuse pain especially in the lower limb. He was subsequently admitted to our Department in order to complete patient evaluation. His past medical history included rheumatoid arthritis under methotrexate therapy. At admission, he presented high LDH values (5045 U/L) then increased up to 7100 U/L, D-dimer 23755 mcg/ifEU (in the absence of imaging evidence of pulmunary embolism), severe leukopenia (white cells 870/mmc) with neutropenia, mild thrombocytopenia, severe anemia, elevated beta-2-microglobulin, high troponine values without EKG and clinical signs of acute ischemical events. A cardiologic evaluation did not reveal ventricular akinisias and showed a normal ejection fraction with no sign of infective endocarditis vegetations. His renal function was in the normal range. Tests for general autoimmunity were negative. Protein electrophoresis demonstrated a monoclonal gammopathy IgMk (0.1 g/dl) associated with a moderate increase of lamda light chain (200 mg/l). During the hospital stay, he continued to present intermitten fever. Steroid treatment was started, achieving a progressive defervescence and improving of pancytopenia. The abdomen and chest CT scan was negative for nodal tumor mass, but an interstizial lung disease was present for which oxygen therapy has became necessary. In the meantime, he developed swelling and erythema at right upper limb suspected for cellulitis that required broad-spectrum antibiotics. During the hospitalization he rapidly worsen, devoloping dysfagia, weakness and neuropatic pain due to axonal polyneuropathy confirmed by an electromyography. Evaluating the complicated diagnostic workup and patient clinical manifestations, the suspicion of an intravascular lymphoma was raised. A bone marrow biopsy (BMB) was then performed. It reported growth of large cells CD20+ within the vessel lumen and marrow sinusoids in overlap with DLBCL, with no immature precursor cells. An FDG-PET/TC showed lung and surrenal increased FDG-uptake, consistent with published case series. Given the clinical status and the BMB, the diagnosis of IVLBCL was made. The patient died soon after dicharge from the hospital.
**Conclusion:** This case report highlights the importance of meticulously investigating the etiology of patient's clinical conditions in Internal Medicin setting, even when common investigation yield negative results, taking into account the possibility of rare disorders.

## 109. TO CRY WOLF OR NOT TO CRY WOLF?

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A 69-year-old patient from Senegal presented to the emergency department reporting chest pain on exertion for two weeks, marked asthenia, headache and melena.
Examination at the admission revealed a fatigued African male who was afebrile, mildly tachycardic (sinus rhythm 110 beats per minute), hypertensive (BP 160/90 mmHg), with preserved ambient-air oxygen saturation and conjunctival pallor. There was no evidence of hepatosplenomegaly, peripheral edema, nor rash. Neurological examination was unremarkable as well as cardiopulmonary examination. Digital rectal examination revealed normal stools.
The patient complained of persistent oppressive chest pain, and an EKG showed severe ST-segment elevation in V3-V4. High sensitive-Troponin I was dosed showing rising values on serial assessments (from negative up to 1.5 ng/ml) and an echocardiography was performed showing severe reduction of ejection fraction (30%) and akinesia of the whole cardiac apex. Meanwhile, blood gas analysis reported a mixed alkalosis and haemoglobin (Hb) 5.6 g/dl. All clinical data suggested an ST-elevation myocardial infarction (STEMI), worsened by severe anemia. Transfusion therapy was administered and Hb values were restored. Given the recent history of melena, it was decided to perform an esophagogastroduodenoscopy first, and then to proceed with a coronary angiography. In fact, in the case of a critical coronary occlusion, a stent would be deployed, and double antiplatelet therapy would be necessary at least for one month, but it would be unfeasible in the case of active bleeding. The gastroscopy excluded hemorrhagic lesions and coronagraphy was performed a few hours after hospital admission excluding coronary occlusions, revealing a case of myocardial infarction with non-obstructive coronary artery disease (MINOCA). EKG and echocardiography progressively improved with restoration of normal left ventricular ejection fraction and segmental kinesis. All of the evidence gathered led to the interpretation of the cardiologic presentation as Takotsubo disease.
Meanwhile, complete blood tests confirmed severe anemia and showed macrocytosis and signs of hemolysis (Hb 5.7 g/dl, MCV 112 fl, LDH > 2000 U/L, consumed haptoglobin, increased indirect bilirubin, negative direct and indirect Coombs test) with elements suggestive of intravascular hemolysis (8 out of 100 schistocytes per field in peripheral smear, hemoglobinuria on urine examination), associated with initial thrombocytopenia.Given the presence of a Coombs negative hemolytic anemia, with schistocytes on peripheral smear, microangiopathic hemolytic anemia was suspected. The absence of kidney impairment led to the exclusion of a hemolytic uremic syndrome. Considering the myocardial damage, typical manifestation of thrombotic thrombocytopenic purpura (TTP), a sample for the determination of ADAMTS13 activity was sent. In order to decide whether to immediately start plasma exchange and steroids, pre-test probability of severe TTP was predicted with PLASMIC score that resulted 5, meaning low-intermediate probability. No empiric therapy was started and ADAMTS13 dosage turned out normal. Once the patient's condition had been stabilized, further investigation of the causes of the hemolytic anemia was warranted. Considering the patient's geographical area of origin, in order to exclude prevalent haemoglobinopathies an Hb electrophoresis and an HbA2 assay were performed, which were found to be normal. Severe malaria was excluded performing plasmodium research, HIV and HCV infection were excluded on serologies. Then, red cell membrane disorders such as spherocytosis and elliptocytosis were ruled out with peripheral blood smear. Parossistic nocturnal hemoglobinuria clone research turned out negative too. The patient denied alcohol abuse and an abdominal ultrasound excluded liver cirrhosis or splenomegaly. The only remarkable finding was a severe vitamin B12 deficiency. Intramuscular supplementation of vitamin B12 was started, leading to delayed but complete resolution of hemolysis and normalization of Hb values and platelet count.
Indeed, the cause of this hemolytic anemia was a vitamin B12 deficiency-induced pseudothrombotic microangiopathy: this is a rare condition that resembles clinical features of TTP with polysymptomatic presentation (megaloblastic anemia and hypersegmented neutrophils, hemolysis, thrombotic microangiopathy and neurologic manifestations), highlighting the B12 vitamin's role in essential physiological cellular functions. Despite the benign course of this condition, the exclusion of other rapidly evolving diseases is often challenging.
In conclusion, it is pivotal to rapidly exclude other microangiopathies with a severe prognosis and at the same time to avoid unnecessary and potentially dangerous treatments. Similarly, it was important to quickly rule out a coronary occlusion, although severe anemia was the cause of myocardial infarction in this case.

## 110. A CASE OF HEMOLYTIC-UREMIC SYNDROME TRIGGERED BY AN UNEXPECTED INFECTION

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A 61-year-old formerly healthy man from Albania, arrived at the Emergency Department of a Hospital near Verona on the 21st of April 2022, complaining of abdominal pain, nausea, vomiting, fatigue and fever (body temperature 39°C). He also reported dark urine. He appeared asthenic and markedly icteric, neither purpura nor skin petechiae were documented.
He had a history of hypertension under treatment with an unspecified drug. He reported a recent infection (7 days before) diagnosed as a virosis, with acute hepatitis following the contact with a grandson suffering from gastroenteritis. He has been working as a warehouse worker in a food industry.
The lab tests found anemia with thrombocytopenia (Hb 9.5 g/dL, PLTs 126.000/uL), his WBC was 20.000/uL, haptoglobin undetectable, LDH beyond the maximum dosable value (>2000 U/L), total bilirubin 13 mg/dL, creatinine >3 mg/dL as for acute renal failure with hemoglobinuria on urinalysis. Coombs test resulted negative. He received the transfusion of 2 packed RBC, he was given aggressive IV hydration with crystalloids and he started therapy with ceftriaxone 2 g/day and methylprednisolone 40 mg/day. Despite the treatment performed, he remained anuric and began to get confused.
He was then transferred to the Intensive Care Unit of the Policlinico of Verona with the initial suspicion of Microangiopathic hemolytic anemia (MAHA). In ICU he performed: chest X-rays (parenchymal thickening of the left retrocardiac region), abdominal ultrasound (spleen with the major axis of 14.5 cm and homogeneous echo structure, renal cortical hyperechogenicity, empty bladder), ECG (no signs of ischemia), ecocardiography (left ventricle of normal size with normal overall contractile efficiency). The lab tests confirmed severe anemia and thrombocytopenia (Hb 5.9 g/dl, PLTs 95.000/uL), his WBC was 19.400/uL, PCR 71 mg/L, PCT 3.25 ng/mL, creatinine 5.3 mg/dL with an eGFR 10 ml/min. There was a significant increase in hemolysis/cytolysis indices with a total bilirubin of 7.66 mg/dL and a decrease of haptoglobin. Coagulation indices (PT INR 1.31, aPTT 0.68). Peripheral blood smear showed anisopoikilocytosis, microspherocytes and poor schistocytes. The PLASMIC score was 4 defining a low risk for TTP, confirmed by ADAMTS13 activity of 65%. A complement essay revealed low levels of C3 (0.64 g/L) and C4 (0.03 g/L). Total complement activity (CH50) could not be measured because of the unavailability of the test. Moreover, G6PD was normal and the search for a PNH clone was negative.
The picture was suggestive of hemolytic-uremic syndrome (HUS). Given the rapid evolution of the condition, he was started on plasmapheresis (PEX) and Eculizumab (C5 inhibitor), along with the best supportive care (broad-spectrum antibiotics, blood transfusions, CRRT). Blood cultures and urine cultures were negative as well as the urinary antigen of Legionella and Pneumococcus, HBV DNA, HCV RNA, HIV RNA, and the serology of treponema pallidum. The PCR on the stool revealed the presence of an Enteropathogenic E. Coli - EPEC. He continued PEX and Eculizumab on weekly basis plus a recall after PEX cycles. From day 4 of treatment, hemoglobin concentration and platelets began to rise. At the same time, we appreciated a decrease in hemolysis indices. Given the therapy with Eculizumab, we extended antibiotic and antimycotic prophylaxis and performed vaccination for meningococcus. The immunoassays were negative for ANA, ENA, and ANCA. NGS genomic analysis for 15 genes associated with TMA/HUS was also performed but is still ongoing.
Here we described a case of hemolytic-uremic syndrome (HUS), following sepsis from EPEC infection, which resolved due to the rapid treatment with Eculizumab and PEX. HUS is a life-threatening disease that presents with hemolytic anemia, thrombocytopenia, and acute renal impairment following the damage of the vascular endothelium. HUS comprises a typical form (STEC-HUS associated with Shiga toxin-producing E. Coli enteric infection or Pneumococcal associated HUS) and an atypical form (aHUS, associated with uncontrolled activation of the alternative complement pathway). Eculizumab is a monoclonal antibody that is approved for aHUS since it is able to bind the complement protein C5 and inhibit the alternative complement pathway. However, there are some reports of its off-label use in patients with STEC-HUS and acquired infectious-induced HUS with multiorgan dysfunction, in which it is demonstrated an increase in complement activation products (C3b, C3c, C3d, FactorB2, C5b-9).

In this case, the patient was affected by EPEC infection, a very rare cause of HUS. The improvement of thrombocytopenia, hemolytic anemia and renal dysfunction, thanks to the treatment with Eculizumab and PEX quickly undertaken, suggests the hypothesis of an acquired HUS, in the context of impaired complement activation secondary to EPEC infection.

## EMOSTASI E TROMBOSI

### 111. LOW DOSE RIVAROXABAN IN PATIENTS WITH CARDIOVASCULAR DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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**Background:** Low dose rivaroxaban 2,5 mg twice daily (LDR) has been approved as secondary prevention in patients with coronary artery disease (CAD) and peripheral artery disease (PAD).
**Aim:** To assess the efficacy and safety of LDR in patients with CAD and/or PAD in RCTs.
**Methods:** Systematic review and meta-analysis of randomized controlled trials (RCTs) including CAD and/ or PAD patients treated with LDR. Efficacy endpoints were cardiovascular events (CVEs), myocardial infarction, stroke, all-cause and cardiovascular death. Any, major and fatal bleeding, and intracranial haemorrhage (ICH) were safety endpoints. Number needed to treat (NNT) and number needed to harm (NNH) were calculated for LDR+ASA vs ASA treatment.
**Results:** 7 RCTs were included with 45,836 patients: 34,276 with CAD and 11,560 with PAD. Overall, 4,247 CVEs and 3,082 bleedings were registered. LDR in association with either any antiplatelet drug or ASA alone reduced the risk of CVEs (Hazard Ratio [HR] 0.86, 95% Confidence Interval [95%CI] 0.78-0.94) and ischemic stroke (HR 0.68, 95%CI 0.55-0.84). LDR + ASA increased the risk of major bleeding (HR 1.71, 95%CI 1.38-2.11) but no excess of fatal bleeding or ICH was found. The NNT to prevent one CVE for LDR was 63 (43-103) and the NNH to cause a major bleeding was 107 (77-193).
**Conclusion:** LDR reduces CVEs and ischemic stroke in patients with CAD/PAD. There was an increased risk of major bleeding but no excess of fatal or ICH was found. LDR seems to have a favourable net clinical benefit compared to ASA treatment alone.

### 112. PREDICTION OF EARLY MAJOR BLEEDING IN ACUTE PULMONARY EMBOLISM PATIENTS: EXTERNAL VALIDATION OF PE-SARD

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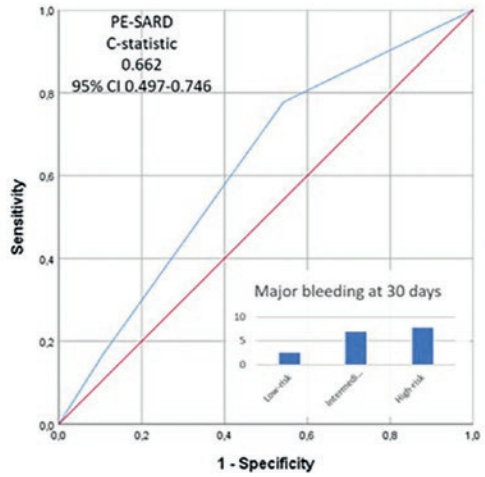
**Background:** In the acute phase of pulmonary embolism (PE), anticoagulant treatment is necessary to reduce mortality. The most worrying consequence is the occurrence of major bleeding. Recently, the PE-Sard score (Syncope, Anemia, Renal Dysfunction) was derived and internally validated to predict major bleeding events in patients with acute PE.
**Methods:** From an observational cohort including consecutive patients with acute PE, we performed a preliminary post hoc analysis. We validated the proposed PE-SARD model, regardless of the severity of PE and the anticoagulant treatment.
**Results:** Overall, 376 patients were admitted with acute pulmonary embolism in our hospital. Of those, 12 were excluded due to the lack of baseline data. 364 patients were included in the analysis and followed for 30 days after PE diagnosis. The mean age was 69.7 (±15.7) and 51.6% were female. During the follow-up period, 18 major bleedings occurred (5%), of those, 2 were fatal (0.6%). Among the PE-SARD items, only anemia resulted as a major bleeding predictor (p=0.004).43.9% of patients were classified as at the low risk (160 patients), 43.9% as at intermediate risk (160 patients), and 10.4% (39 patients). Observed bleeding rates increased with the risk group, from 2.5% in the low-risk group to 7.7% in the high-risk group. C-statistic (AUC) was 0.622 (95% CI 0.497-0.746).
**Conclusions:** In a real-life cohort of patients with acute PE, the predictive value of the PE-SARD bleeding risk score is fairly good in identifying patients at intermediate and high risk of bleeding in the acute phase of PE. The role of the PE-SARD score should be assessed in management studies.




### 113. VALIDATION OF PLASMIC SCORE IN A COHORT OF PATIENTS WITH SUSPECTED THROMBOTIC MICROANGIOPATHY IN AN ACADEMIC MEDICAL CENTER

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**Background:** The PLASMIC score is a rapid and inexpensive clinical assessment tool for predicting severe ADAMTS13 deficiency (< 10% activity) in patients with suspected thrombotic thrombocytopenic purpura (TTP). The score includes 7 parameters: absence of active cancer, absence of stem-cell transplant or organ transplant, platelet count < 30 × 109/L, hemolysis, mean corpuscular volume <90 fl, International Normalized Ratio < 1.5, and serum creatinine < 2 mg/dL.
**Materials and Methods:** In this retrospective study we evaluated a cohort of 59 patients with suspected thrombotic microangiopathy referred to the Hemostasis and Thrombosis Center of the "Federico II" University of Naples, Italy, for measurement of ADAMTS13 activity. For all patients relevant clinical and laboratory information were collected.
**Results:** The PLASMIC score was calculated in 52 of the 59 patients included in the study. In the high-risk group (PLASMIC score 6-7) 12 out of 20 patients (60%) had ADAMTS13 <10%. Interestingly, 6 of 6 patients (100%) with PLASMIC score 7 had ADAMTS13 <5%. In the intermediate risk group (score 5) only 1 case out of 17 (5.9%) had ADAMTS 13 <10%. In the low-risk group (score 0-4), no severe ADAMTS13 deficiency was observed in any patient. The collected data allowed to calculate the sensitivity and specificity of PLASMIC score in TTP, reaching 92% (95% CI 0.80-0.98) and 79% (95% CI 0.66-0.89) respectively. The PLASMIC score showed good discrimination between patients with and without severe ADAMTS13 deficiency with an AUC of 0.92 (confidence interval 0.82 - 1.0, p <0.001).
**Discussion:** In our cohort, a high-risk PLASMIC score successfully predicted patients with severe ADAMTS13 deficiency, proving useful for the clinician to quickly define the best therapeutic approach, especially for clinicians not used to diagnosis and treatment of TMA.

### 114. SINGLE NUCLEOTIDE POLYMORPHISMS (SNPS) OF PRO-INFLAMMATORY/ANTI-INFLAMMATORY AND THROMBOTIC/FIBRINOLYTIC GENES IN PATIENTS WITH ACUTE ISCHEMIC STROKE IN RELATION TO TOAST SUBTYPE: A PROSPECTIVE STUDY OF THE RELATIONSHIP BETWEEN THROMBO-INFLAMMATORY GENETIC AND ACUTE PHASE CYTOKINE SERUM LEVELS PATHWAYS AND MID-TERM STROKE PROGNOSIS

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**Background:** The genetic basis of complex diseases like ischemic stroke probably consists of several predisposing risk factors, such as genes involved in inflammation and thrombotic pathways.
Thrombo-inflammation, a process referring to the complex interplay between both thrombotic and inflammatory pathways, has become increasingly recognized as an important contributor to stroke pathogenesis and post-stroke neuronal and functional damage and its related prognosis in terms of death and recurrence rates
**Aims:** On this basis the aim of our study was to evaluate the role of SNPs (single nucleotide polymorphisms) of some pro-inflammatory/anti-inflammatory and coagulation/fibrinolytic genes and of the serum levels of some markers of thrombo-inflammatory activation in the acute phase and the prognosis of in patients with acute ischemic stroke at a two years follow-up.
**Methods:** The study sample consisted of adult patients who were hospitalized in the enrollment centers (Internal Medicine Department at the University of Palermo, Stroke Unit Civico Hospital of Palermo, Emergency Unit Giglio Hospital, Cefalù Palermo, Stroke Unit Villa Sofia Hospital Palermo, Stroke Unit San Camillo Hospital, Internal Medicine Department, University of Bari) between November 2009 and January 2016, and who met inclusion criteria. The cases were patients admitted with a diagnosis of acute ischemic stroke, and age-matched (± 3 years) control subjects: patients admitted to our Internal Medicine Department for any cause other than acute cardiovascular and cerebrovascular events and for routine checkup examinations in the same period. Patients underwent follow-up visits every six months for three years after discharge. Death and stroke recurrence rates were analyzed and we also evaluated other vascular event rates.
Molecular analysis of alleles at the -308 nucleotide (-308G/A) of TNF-α gene, -1082/-819 haplotypes of IL-10 gene, IL-1RN exon 2 VNR polymorphism, alleles at the -174 nucleotide (-174G/C) of IL-6 gene, PAI-1675 5G/4G polymorphism, alleles at the -7351 nucleotide (-7351C/T) of tPA gene, PTGS2 (prostaglandin Synthase) rs 5275, PTGS2 (prostaglandin Synthase) rs20417,PTGS2 - rs689466, MMP-9 (matrix metalloproteinase-9) rs17576, MMP-9 (matrix metalloproteinase-9) rs3918242 was undertaken in both patient groups. Serum Levels ad admission of TNF-alfa, IL-6, IL-1beta, IL-10 and TPA and PAI1 were evaluated.
**Results:** We analyzed 421 subjects with acute ischemic stroke and 198 control subjects enrolled between 2009 and 2019 in seven enrollment centers. We reported higher serum levels of IL-6, IL-1 beta and TNF-alfa in subjects with ischemic stroke in comparison with control subjects; Subjects with cardioembolic strokes showed significantly higher serum levels of IL-6, IL-1 beta and TNF-alfa in comparison to atherosclerotic strokes and in particular in comparison to lacunar strokes. We observed a significantly higher frequency of IL-10 1082 AA genotype in stroke patients with a significant risk trend. We also reported a higher frequency in stroke subjects with a significant risk trend of the TPA 7351-CT genotype and of IL-1RN-VNTR 86 bp 2/2 genotype. Moreover, we observed a significant relationship with TOAST subtype only with regard to CC TPA genotype and 1/1 IL-1 VNTR 86 bp and PTGS2- rs689466 CT and CC alleles (prostaglandin Synthase) rs 5275, and lacunar strokes and of MMP-9- rs3918242 CT alleles with cardioembolic strokes We observed a significant relationship between death and stroke recurrence and serum levels at admission of TNF-alfa, IL-6 and IL-1 beta and the CC. We also reported a better prognosis in subject with and PTGS2- rs689466 CT and CC alleles (prostaglandin Synthase) rs 5275 and a worse prognosis in subject with MMP-9- rs3918242 CT alleles.
**Conclusions:** Ischemic stroke is a common multifactor disease, which is affected by a number of genetic mutations and environmental factors. Our findings showing a relationship between pro-inflammatory/anti-inflammatory and thrombotic/fibrinolytic genes SNPs and ischemic stroke and its prognosis may contribute to delineate a possible stroke risk profile in subjects with cerebrovascular risk factors.

## 115. A UNIQUE CASE OF LEMIERRE'S SYNDROME AND CEREBRAL VEIN THROMBOSIS IN A CARRIER OF PROTHROMBIN GENE G20210A MUTATION

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We describe here a case of a woman admitted to our Internal Medicine Unit for multifocal pneumonia. Chest CT detected multiple areas interpreted as septic emboli. Moreover, a left internal jugular thrombosis was incidentally reported. These findings confirmed the diagnosis of a Lemierre's Syndrome. A CT-angiography showed the left internal jugular thrombosis extension to cerebral sinuses. ENT consultation reveled a left medium otitis. Anticoagulation with Fondaparinux was associated to antibiotic therapy and after 2 weeks the neurologic symptoms totally remitted. The genetic thrombofilic panel showed a heterozygosis for prothrombin gene G20210A mutation and the patient was discharged with Rivaroxaban for home continuation of anticoagulant therapy for at least 6 months. The prevalence of inherited thrombophilias in Lemierre's Syndrome is unknown and to our knowledge, this article is the first to identify a prothrombin gene G20210A mutation in a patient with Lemierre's Syndrome with thrombosis extension into the cerebral venous system. Exploring patients for underlying thrombophilia could help us to better understand whether thrombophilias may favorite retrograde thrombotic extension of the process to cerebral venous system.

## 116. PROGNOSTIC ROLE OF DIFFERENT FINDINGS AT ECHOCARDIOGRAPHY IN ACUTE PULMONARY EMBOLISM. A CRITICAL REVIEW AND META-ANALYSIS

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**Background:** Different definitions and different parameters of right ventricle dysfunction (RVD) at echocardiography have been used to predict mortality in patients with acute pulmonary embolism (PE). We aimed at assessing the individual role of these definitions and parameters of RVD in a meta-analysis.
**Methods:** A systematic search was performed in MEDLINE and EMBASE from inception to October 2021 for studies i) including patients with confirmed acute PE; ii) reporting on RV assessment at echocardiography at early phase; iii) reporting on short-term death. The primary study outcome was death occurring in-hospital or at 30 days.
**Results:** RVD defined as a combination of findings at echocardiography was associated with an increased risk of death in all comers with PE (20 studies, 6018 patients RR 2.17, 95% CI 1.48-3.20, I2 24%), and in hemodynamically stable patients (11 studies, 3274 patients, RR 2.91 95% CI 1.59-5.32, I2 6%). Abnormal TAPSE at echocardiography was associated with increased risk for short-term death in all comers with acute PE (10 studies, 4095 patients; RR 2.29 CI 1.45-3.59, I2=49%). The association was confirmed for different cut-off values of TAPSE (≤15mm or any cut-off value >15mm). Abnormal RV/LV ratio at echocardiography was not associated with increased risk for short-term death in all comers with acute PE (ten studies; 4019 patients; 1.61, 95% CI 1.90-2.39, I246%). In hemodynamically stable patients, TAPSE (6 studies, 3240 patients; RR 2.29 CI 0.97-5.44) and increased RV/LV ratio (6 studies, 2173 patients; RR 1.11 CI 95% 0.91-1.35) did not reach a significant association.
**Conclusion:** RVD as a combination of findings and an abnormal TAPSE are associated with all-cause death in-hospital or at 30 days in patients with acute PE. These results can inform future studies and clinicians dealing with the management of patients with acute PE.

## 117. EVALUATION OF PLATELET FUNCTION IN PATIENTS WITH ACQUIRED HEMOPHILIA A: A CASE SERIES

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**Background:** Acquired hemophilia A (AHA) is a rare autoimmune disorder caused by autoantibodies that inhibit the coagulant activity of factor

VIII (FVIII). The bleeding pattern in AHA is different from that observed in inherited hemophilia. Bleeding episodes are spontaneous and present as huge subcutaneous hematomas (>80%), severe muscle bleeding (>40%), gastrointestinal and intracerebral bleeding (> 20%), all being much more frequent than hemarthroses at variance with inherited hemophilia. It is a common and still somewhat unexplained observation that the bleeding tendency of patients with AHA is more severe than that of patients with inherited hemophilia. Platelet functions disorders (PFDs) are a group of heterogeneous diseases that can be acquired or congenital and are mainly characterized by mucosal and cutaneous bleeding. The acquired forms may be associated with medications, procedures and frequently with underlying medical conditions and hematological diseases. Previously we described a patient with AHA and delta storage pool deficiency. Objective The aim of the study is to explore if the concomitant presence of an acquired PFD may play a mechanistic role in the hemorrhagic manifestations of patients with AHA, with the hypothesis that a platelet dysfunction contributes to explain the severe muco-cutaneous bleeding tendency in AHA. We elected to carry out in these patients a broad panel of platelet function tests with the primary aim to evaluate at the time of diagnosis the presence and prevalence of a platelet dysfunction. Methods We enrolled consecutive patients referred to the Angelo Bianchi Bonomi Centre with a diagnosis of AHA. Data regarding clinical characteristics of patients, especially bleeding symptoms were collected. FVIII: C levels and FVIII inhibitor titer were measured by the one-stage method and the Bethesda assay, respectively, using HemosIL Synthasil on ACL Top analyzer (Werfen, Bedford, MA).Platelet count and function testing at the time of diagnosis and before starting any therapy were analyzed. Light transmission aggregometry was used to evaluate whether or not in AHA patients there is an abnormality of platelet function. Aggregation and ATP secretion were carried out in citrated PRP by means of a lumi-aggregometer (Chronolog, Mascia Brunelli, Milano Italy). The aggregation and secretion responses to several agonists were analyzed. The intraplatelet δ-granule content, i.e., adenine nucleotides (ADP e ATP) and serotonin (5HT) was be measured respectively by using a luminometric method using luciferin-luciferase and by fluorometric detection using o-phthalaldehyde (OPT). Results Here we present preliminary data on three patients.
Patient1 was a 50-yr-old woman. She was referred to our centre for a one month history of diffuse ecchymoses and recent spontaneous hematoma of leg. She had a history of autoimmune diseases: Sjögren syndrome, type 1 diabetes mellitus and . Factor VIII activity (FVIII: C) was <1 UI/dL and the anti-FVIII inhibitor was 47 Bethesda units (BU). Activated prothrombin complex concentrate (APCC) was administrated for one week and immunosuppression with oral prednisone (1 mg/kg/day) was started. Platelet aggregation and secretion were normal. Intraplatelets nucleotides were normal. Intraplatelet serotonin was lower than the normal range due to the use of serotonin uptake inhibitors.
Patient2 was a 64-yr-old male patient. He had no relevant medical history except for psoriasis and he had a bleeding history in the last five months with haematomas of calf, pectoral muscle and left arm and with left knee haemartrosis. He was admitted to our Internal Medicine unit for hematuria and left knee hemartosis. FVIII: C was <1 UI/dL and the anti-FVIII inhibitor was 200 BU. He was treated with recombinant activated factor VII (rFVIIa) at a dose of 90 mcg/Kg every 4 hours twice and prednisone (1 mg/kg/day) was started. He was transfused with one unit of red cells during hospitalization. Platelet aggregation and secretion were normal. Serotonin concentration was normal.
Patient3 was a 77-yr-old woman with a history of hypertension and chronic bronchitis. She referred spontaneous cutaneus hematoma and ecchymosis in the last twenty days. FVIII: C was 2 UI/dL and the anti-FVIII inhibitor was 9 BU. She was treated with prednisone 1 mg/Kg/day and cyclophosphamide 2 mg/Kg/day was added. A mild defect of platelet secretion was present only after ADP stimulation (normal nucleotides and serotonin)
**Conclusions:** In our case series we described three patients with AHA with heterogeneous characteristics and we found only in one of them a mild alteration of platelet function. Further studies are necessary to clarify the mechanism that could contribute to the different hemorragic diathesis between acquired and congenital hemophilia.

## 118. HIGH PLASMA LEVELS OF ACTIVATED FACTOR VII-ANTITHROMBIN COMPLEX INDICATE INCREASED TISSUE FACTOR EXPRESSION/ACTIVATION IN PATIENTS WITH COVID-19

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**Background:** The infection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causal agent of coronavirus disease 2019 (COVID-19), is associated with coagulation abnormalities, in which endothelial injury/dysfunction may be a key pathogenic mechanism. Endothelial dysfunction triggers tissue factor (TF) expression. Activated factor VII-antithrombin (FVIIa-AT) complex is a potential biomarker of prothrombotic diathesis reflecting FVIIa-TF interaction.
**Aims:** To evaluate FVIIa-AT plasma levels in subjects with COVID-19 pneumonia.
**Methods:** FVIIa-AT plasma levels were assessed in 40 subjects (30 males and 10 females; 64.8 ± 12.3 years) admitted for COVID-19 pneumonia during the first pandemic wave in Italy (April 2020). FVIIa-AT data were compared with those of two sex- and age-matched groups of subjects without COVID-19, with or without laboratory signs of systemic inflammation. The concentration of FVIIa-AT was measured by ELISA on frozen citrate plasma samples. Data of coagulant activities of factor II (FII: c), factor V (FV: c), and factor VIII (FVIII: c) were available in a subgroup of subjects.
**Results:** COVID-19 patients had significantly higher FVIIa-AT levels than no COVID-19 subjects (Table 1), either with or without inflammation (P=0.013 and P=0.017 by ANOVA with Tukey post-hoc comparison, respectively). No difference in FVIIa-AT levels was observed between no COVID-19 subjects with or without inflammation (P=0.995). The association between COVID-19 and FVIIa-AT levels in the whole study sample remained significant by linear regression analysis adjusted for sex, age, C reactive protein, estimated glomerular filtration rate, fibrinogen, prothrombin time, and activated partial thromboplastin time (B coefficient 0.322 with standard error 0135, P=0.019). In sub-analysis COVID-19 patients showed also lower FII: c, FV: c, and FVIII: c levels (Table 1).
**Conclusions:** Our results indicate that SARS-CoV2 infection, at least during the first pandemic wave, was characterized by increased FVIIa-AT levels, thereby suggesting an increased FVIIa-TF interaction, which may be consistent with increased TF expression/activation due to SARS-CoV2 -induced endotheliopathy.

| | No COVID-19 No inflammation (n =40) | No COVID-19 inflammation (n = 40) | COVID-19 (n = 40) | P * |
|---|---|---|---|---|
| Female sex (%) | 25.0 | 25.0 | 25.0 | NS |
| Age (years) | 60.6 ± 11.5 | 60.9 ± 12.1 | 64.8 ± 12.3 | NS |
| BMI (kg/m2) | 26.5 ± 3.5 | 27.0 ± 3.9 | 26.8 ± 4.4 | NS |
| CRP (mg/L) | 0.9 (0.7 - 1.2) | 51.6 (44.0 – 60.4) | 71.5 (54.4 – 93.8) | <0.001 |
| eGFR (mL/min) # | 73.9 (67.9 – 80.4) | 71.8 (60.9 – 80.6) | 70.8 (63.6 – 78.8) | NS |
| PT | 0.98 (0.97 – 1.00) | 0.97 (0.95 – 1.00) | 1.10 (1.07 – 1.14) | <0.001 |
| aPTT | 0.97 (0.94 – 1.01) | 1.03 (0.98 – 1.08) | 1.01 (0.97 – 1.06) | NS |
| Fibrinogen (g/L) | 3.16 (2.95 – 3.37) | 5.33 (4.67 – 6.07) | 6.19 (5.48 – 7.00) | <0.001 |
| FVIIa-AT (pmol/L) | 80.7 (71.3 – 91.3) | 80.0 (70.3– 91.0) | 107.1 (89.8 – 127.8) | 0.006 |
| FII:c ^ | 120.0 ± 24.5 | 118.4 ± 24.2 | 82.9 ± 19.7 | <0.001 |
| FV:c ^ | 140.7 ± 52.2 | 142.2 ± 25.3 | 99.8 ± 23.3 | <0.001 |
| FVIII:c ^ | 148.9 ± 60.7 | 200.9 ± 66.6 | 65.2 ± 21.9 | <0.001 |

**Table 1:** Clinical and laboratory characteristics of the 3 study groups: i) no COVID-19 subjects without inflammation, ii) no COVID-19 subjects with inflammation, and iii) COVID-19 subjects.
CRP: C reactive protein; eGFR: estimated Glomerular Filtration Rate; PT: Prothrombin Time; aPTT: activated Partial Thromboplastin Time; NS: not significant
[1]: by ANOVA or c2-test, when indicated
#: eGFR was calculated by means of Modification of Diet in Renal Disease (MDRD) equation
^: Data of FII: c were available for 40 subjects in COVID-19 group, 25 subjects in no COVID-19 and no inflammation group, and in 9 subjects in no COVID-19 and inflammation group

## 119. HEMORRHAGE AND THROMBOSIS: HOW TO MANAGE A PATIENT WITH BOTH RISKS?

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**Objective:** Our aim is to examine the therapeutical approach in a patient with both hemorragic and trombotic events.
**Case Description:** A 84 years old woman acceded the ER because of an episode of rectal bleeding. She had multiple comorbidities: arterial hypertension, atrial fibrillation in treatment with anticoagulant therapy (DOAC), diabetes type 2 in treatment with oral hypoglicemic drugs, mitral stenosis, cronic heart failure, cronic sideropenic anemia, cronic renal failure, COPD and a previous ischemic stroke in the right occipital lobe. At the ER the patient performed routine tests that showed severe anemia (Hb 6.0 g/dl), therefore she was admitted to the short-stay observation unit (SOU), where she underwent two blood trasfusions. First of all, our colleagues suspended the anticoagulant (Apixaban 2,5 mg x2/day) in order to perform an esophagogastroduodenoscopy (EGD), which resulted negative for active bleeding. The patient was then discharged from SOU planning to perform a colonoscopy after a few days. The following day the patient was again brought to the ER because of pain and paresthesia of the right upper limb, so an angio-CT scan was performed and showed a thrombotic occlusion of the humeral artery in its third proximal tract and the presence of pulmonitis in the right lung with massive pleural effusion, therefore she was admitted to the Vascular Surgery Unit. The surgeons started a medical treatment with low dose heparin (4000 UI/day), taking into consideration her comorbidities and the non-critical stage of the thrombosis, thanks to the collateral circulation. During the first days of the hospitalization, the patient developed an acute respiratory failure which was explained by the finding of pulmonitis and massive pleural effusion though a pulmonary CT scan. Our colleagues discussed the case with cardiologists and pneumologists, who recognized the clinical presentation as a exacerbation of the known cronic heart failure and the presence of severe pulmonary hypertension secundary to COPD. The patient was then admitted to our internal medicine unit to proceed the diagnostic-therapeutic process. We started oxygen therapy and we switched the previous antibiotic therapy (Ceftriaxone 2g/day EV and Clarithromicin 500 mg x2/day per OS) to Piperacillin/Tazobactam according to the GFR. During the hospitalization the patient had a recurrence of ischemic stroke in the right occipital lobe, probably a cardioembolic stroke (CHAD-VASC score 9), followed by a sudden drop in the binocular vision, which was confirmed by a brain CT scan performed at 24 hours after the onset of symptoms. Therefore, we started an antiplatelet therapy with cardioaspirin in association with heparin, according the recommendation of Stroke Unit specialists. The following brain CT scan showed two new hyperintense areas of dubious meaning, for which we performed more CT scans the following days to rule out potential hemorrages that were never confirmed. Consequently, we continued the antithrombotic and prophylactic anticoagulant treatment, because of the patient's considerably high thrombotic risk and a partial posterior middle cerebral artery's occlusion. Considering the patient renal failure (GFR 20 ml/min), we continued the treatment with heparin in a prophylactic dosage despite the patient's atrial fibrillation and we considered a possible treatment with the closure of the left auricle. Unfortunately the echocardiogram revealed a large thrombus in the atrium that prevented us to perform the procedure, so we increased the heparin dosage to obtain an anticoagulant effect and we planned another echo in a month. Sadly the patient couldn't perform the procedure for the onset of a cardiocirculatory arrest and death.
**Results:** The heparin treatment tailored on the renal function in association with the antithrombotic one, despite the high bleeding risk (recent GI bleeding and ischemic stroke with hemorragic conversion), was thought to be the most fitting approach to this case.
**Conclusions:** The complexity of frail elderly patients often involves assessing thrombotic and hemorrhagic risk. Often the patient evaluation is carried out with a multidisciplinary team whose each member can contribute to the most appropriate decision. Unfortunately, despite everything, the risks are sometimes so high that they inevitably lead to therapeutic failure due to the complexity and intrinsic fragility of the specific case.

## 120. REAL WORLD DATA ON CAPLACIZUMAB: OUR ONGOING EXPERIENCE

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Acquired thrombotic thrombocytopenic purpura (aTTP) is a rare life-threatening condition. Recently, Caplacizumab was approved for the treatment of acute episode of aTTP added to plasma exchange (PEX) and immunosuppressors at least for 30 days after withdrawal of daily PEX. Caplacizumab inhibits platelet adhesion to von Willebrand factor (VWF) multimers preventing microvascular thrombosis. We report our experience with Caplacizumab (collected data September 2020-December 2021) in ten patients admitted in our Internal Medicine Department, diagnosed with aTTP. Patients' cohort baseline characteristics were reported in Tab.1. Neurologic symptoms occurred in all patients (focals, transient ischemic attack, drowsiness). The patients were submitted to daily PEX as administered steroids and Caplacizumab. Median time to platelet count normalization (4 days), duration of PEX (8 days), and hospital stay (13 days) were comparable with RCT data, with complete neurological symptoms remission in all patients, in absence of hemorrhagic adverse events or death. Immunosuppressive therapy in aTTP aims at controlling the underlying autoimmune disease, but requires time to take effect, leading patients to thrombotic complications and death. Caplacizumab treatment prevents disease exacerbations, death and long-term sequelae, irrespective of the type of initial immunosuppression used, allowing time for immunosuppressive therapy to take effect, reducing length of hospitalization.

| | |
|---|---|
| Age, mean (range), y | 51 (30-82) |
| Female sex, % (n/total) | 60 (6/10) |
| Platelets, initial, median (range), ×109/L | 18 (15-22) |
| LDH, initial, median (range), U/L | 525 (380-698) |
| ADAMTS13 activity below 10%, % (n/total) | 100 (10/10) |
| Glasgow Coma Scale, % (n/total) | |
| < 13 | 20 (2/10) |
| 13-15 | 80 (8/10) |

## 121. A RARE ANATOMICAL ABNORMALITY UNDERLYING MASSIVE SPLENIC THROMBOSIS

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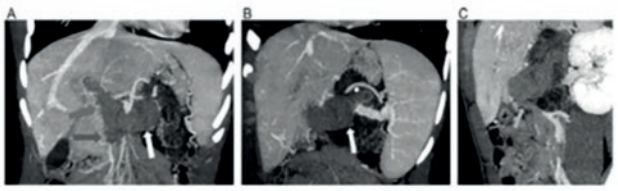
Splenic vein aneurysm, firstly described in 1953, can be acquired or congenital. Congenital aneurysms etiology still remains partly unknown and typically arise from aberrant development of the vitelline veins during the embryonic period or from an inherent weakness in the vessel wall. This pathologic entity may be asymptomatic or can lead to severe conditions such as colicky abdominal pain, jaundice due to compression "ab extrinseco" of adjacent biliary tract, and digestive bleeding secondary to portal hypertension. Diagnosis of an aneurysm of the portal venous system is carried out with high accuracy with contrast enhanced CT (ce-CT) by finding a dilatation of more than 2 cm in diameter. In conclusion, we would pay attention in case of massive spleno-portal thrombosis, in absence of acquired or congenital thrombofilic conditions, in which accurate CT-scan can reveal rare vascular portal aneurism, leading to severe complications ad thrombosis, requiring "sine die" anticoagulation. In figure 1 contrast-enhanced portal phase CT scan: the coronal MIP images depict a large venous aneurysm with a superimposed massive thrombosis involving the portal vein, the superior mesenteric vein, the splenic vein and the inferior mesenteric vein. Enlarged spleen is also observed.




## 122. WHEN CAUSE CAN ALSO BE THE CURE. HEMOPHILIA A AND INHIBITORS

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**Background:** Hemophilia A is an inherited blood clotting disorder that occurs when clotting factor VIII is either absent or not present in sufficient amounts. People with hemophilia may experience excessive bleeding or bruising in the joints, muscles, or soft tissue. While there is no cure for hemophilia A, there are several effective treatment options available. One common treatment is called factor replacement therapy, which is an injectable treatment that helps replace the clotting factor VIII (fVIII). Prevention and treatment of bleeds with fVIII replacement products have greatly improved the quality of care for patients with hemophilia A. However, development of neutralizing antibodies, or inhibitors, against infused factor remains a challenging complication of hemophilia treatment. Approximately ~30% of patients with severe hemophilia A will develop inhibitors, in addition to 5% of patients with mild and moderate hemophilia A. Inhibitors significantly increase the cost of care, intensify the financial and psychosocial stressors on patients and their families, and have a negative effect on disease morbidity and mortality by making bleeding episodes more difficult to treat. Bypassing agents (BPAs) are the primary treatment modalities currently available for patients with inhibitors. Traditionally, the use of BPAs during ITI has been reserved for patients with inhibitor titers higher than 10 BU/mL and persistent bleeding symptoms despite high doses of fVIII replacement. Recombinant FVIIa is often chosen as the first-line BPA for patients with hemophilia A and B with inhibitors before the start of ITI because of the potential risk for anamnesis and allergic reaction with aPCC resulting from small amounts of fVIII and the presence of fIX, respectively. Patients with low titer and low responding inhibitors (<5 Bethesda units BU/mL) can often continue receiving factor replacement therapy, albeit at higher doses, for prophylaxis and treatment of bleeds. CASE HISTORY Male, 46yo, entered ER for severe anemia (Hb 4gr/dl) due to gingival haemorrhage, secondary to tooth extraction. Patient did not practice antihemorrhagic prophylaxis before and after the dental procedure. Test performed showed a picture compatible with his diagnosis of moderate Hemophilia A (aPTT ratio 3.2, FVIII 4.5%). In our department, blood transfusion is administered with antihemorrhagic prophylaxis (rFVIII 3000IU bid) and antifibrinolytics, also performing local haemostasis of the bleeding site. Following days, however, in absence of clinical and laboratoristic improvement (constantly reduced circulating FVIII levels even after supplementation, continuous need for transfusion support) we requested inhibitor dosage, which was confirmed to be present. Considering low inhibitor titer (4.1 BU/ml n.v, <0.5), we decided to continue higher dose replacement therapy, antifibrinolytics and blood transfusions, obtaining in a few days normalization of Hb values and optimal bleeding control with a gradual reduction in the level of inhibitor, which was eradicated after about 3 months. DISCUSSION Inhibitors remain a challenging complication of treatment in patients with hemophilia. Several questions remain regarding the optimal therapeutic approach in poor-risk patients. Nonetheless, there are several novel therapies in development or active clinical trials that may potentially lessen the burden of disease and reduce bleeding risk in patients with hemophilia with or without inhibitors.

## 123. ROLE OF RESIDUAL PULMONARY VASCULAR OBSTRUCTION ON THE RISK OF LONG-TERM RECURRENCE OF VENOUS THROMBOEMBOLISM AFTER A FIRST EPISODE OF PULMONARY EMBOLISM: A COHORT STUDY

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**Background:** Residual vascular pulmonary obstruction (RVPO) after pulmonary embolism (PE) has been associated with recurrent venous thromboembolism (VTE) after 2-3 year follow-up. However, there is no standardized definition of RPVO and its predictive role on recurrent VTE requires confirmation. Our aim was to determine whether RPVO is associated with recurrent VTE after 10 years.
**Methods:** Between 2004 and 2008 consecutive patients were evaluated 6 to 12 months after objectively diagnosed PE at the Thrombosis Center of the teaching hospital of Varese, Italy and underwent lung perfusion scan to detect RPVO, as part of a previously published study. In 2019 patient electronic clinical records were searched or, if missing, patients were contacted by telephone, to detected objectively diagnosed recurrent VTE.
**Results:** 112 patients were included in the study. At the time of PE diagnosis, the mean age was 62.5 years (DS 16.3), 58% of patients were females. PE was unprovoked in 62 patients (55.4%) and deep vein thrombosis (DVT) was diagnosed in 72 patients (64.3%). Follow-up lung perfusion scan, was performed after a mean of 12.9 months (SD 10.4) and showed no reperfusion in 21 patients (19%), partial reperfusion in 25 (22%) and complete reperfusion in 66 (59%). Older age and unprovoked PE were more frequent in patients with RPVO as compared to those without. During a mean follow-up of 117.1 months (SD 59.6), 31 patients (27.7%) were diagnosed with recurrent VTE (23 PE, 8 isolated DVT). Recurrent VTE occurred in 26.1% of patients with RPVO as compared to 28.8% without RPVO (p=ns). Mortality was significantly associated with RVPO (46% vs 21%; p=0.007).
**Conclusions:** In this study, during 10-year follow-up, RPVO was not associated with recurrent VTE, while it was associated with mortality. Larger studies are needed to confirm the predictive role of RPVO, by using a standardized definition.

## 124. ACUTE UNILATERAL RENAL INFARCTION IN THE SETTING OF AN INHERITED THROMBOPHILIA

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Renal infarction is rare with an incidence rate of 0.007% (1, 2). Its most common etiologies are cardioembolic disease (55.7%), renal artery injury (7.5%), hypercoagulable state (6.6%), and idiopathic (30.1%).
We present a case of renal infarction in a 50-year-old male without any other pathological medical history and no history of hypertension.
He attended the emergency room for a sudden, continuous pain the abdominal region and in particular in the right flank. Laboratory tests showed high LDH levels with normal renal function, electrolytes, PCR and PCT. Chest and abdominal X-rays were unremarkable. An urgent abdominal contrast-enhanced computed tomography revealed oatchy hypodense wedge-shaped area in the lower pole of the left kidney consistent with a renal infarction ("gross infarction of the superior-external region of the left kidney with integrity of the lower III. Extensive eccentric thrombosis is documented for an 8 mm tract of the intermediate portion of the ipsilateral renal artery with regular opacification of the downstream portions that can be seen"). Transthoracic echocardiogram showed no thrombus neither shunt defect like atrial septal defect (ASD) - a transthoracic echocardiogram was performed with agitated saline at rest and after valsalva maneuver to rule out this condition. Basal laboratory tests showed a normal coagulation levels.He was found to be heterozygous for the prothrombin G20210A gene mutation (also known as variant c.[1]97G>A) and homozygous for polymorphism C667T in MTHFR gene, with normal omocystein level (10.7 mcmol/l). He tested also positive for cardiolipin antibody IgM, while cardiolipin antibody IgG and Lupus Anticoagulant (LAC) were negative. Anti-Beta-2-Glycoprotein IgM are also positive (40 U/mL), while IgG are negative. It is planned to repeat this tests at 12 weeks. The remaining thrombophilia study was otherwise normal (negative for Factor V Leiden mutation, Antithrombin III activity, Protein C, and S activity and ANA).
Prothrombin gene mutation is the second most common inherited thrombophilia with a prevalence of approximately 2% (3); this mutation is associated to a 30% increase in baseline prothrombin levels that predisposes to thrombotic events. Its role in arterial thrombosis is unclear, with a slight risk of AMI or stroke occurrence. An increased risk exists in patients aged< 55 years and female patients, with a more significant effect if concomitant coagulation disorders (4). A 2017 meta-analysis reported a slightly increased risk of stroke in children and young adults with the prothrombin gene mutation (5).
Patient received a medical treatment (not surgery or interventistic indication) with heparin with decoagulant dosage. He had a favorable course, with disappearance of pain and gradual decrease in LDH. One month later, patient underwent to a new CT that confirmed renal infarction and showed the resolution of thrombosis ("The presence of a large hypodense parenchymal area as from infarct outcomes localized on the antero-external side is confirmed in the renal parenchyma of the left to the middle third, interesting also the upper renal pole. The remaining lung parenchyma appears properly opacified… Both renal arteries appear patent, the eccentric thrombosis of the intermediate portion of the left renal artery which appears tortuous is almost resolved, minimal thickening of the contextual wall remains").
In conclusion, the coexistence of different thrombophilic disorders, together with the positivity of anticardiolipin antibodies (although the latter must be confirmed at 12 weeks), could justify the ischemic event in our patient. In particular, the site of the thrombotic event could be somehow related to the particular thrombotic mechanism typical of the syndrome of phospholipid

antibodies with tropism for the renal parenchyma (6,7).

## EMOSTASI E TROMBOSI

### 125. CATHETER-RELATED RIGHT ATRIAL THROMBOSIS IN CANCER PATIENTS: A RETROSPECTIVE ANALYSIS

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**Background and Aims**: Literature data on catheter-related right atrial thrombosis (CRAT) are scarce and based only on case reports or case series1-2. Data mostly concern dialysis patients while reports on oncological patients are poor2. In this study we investigated characteristics of cancer patients with CRAT to provide a better characterisation and to improve the knowledge of this disease.
**Methods:** We retrospectively analysed data of 21 consecutive cancer outpatients with CRAT that referred to our Internal Medicine and Thromboembolic Pathology Unit over a period of 3 years. Of these patients we collected epidemiological and clinical data and evaluated the efficacy (resolution of the thrombotic process and recurrences) and safety (bleedings) of the different anticoagulant treatments used.
**Results:** In our study, the median age was 57 years. There were 4 (19%) males and 17 (81%) females. All patients had active neoplasia: 8 (38%) ovarian, 5 (24%) uterine, 5 (24%) colorectal, and 3 (14%) breast cancer. Of them, 15 (71%) were metastatic. In 5 (24%) cases, thrombosis was present at other sites, in addiotion to the right atrium, i.e., pulmonary embolism (PE) and deep veins of the upper limbs. In 2 cases, the diagnosis of CRAT was made by echocardiography, while in the other 19 cases by CT-angiography, with further confirmation by echocardiography in 15 patients. The median follow-up was 10 months. Nineteen (90%) patients received anticoagulant treatment for 3-6 months: 17 with low molecular weight heparin ad 2 with direct oral anticoagulants (DOACs). After completion of the treatment period, 9 (43%) patients extended treatment with low dose anticoagulation. In 12 (57%) patients there was complete resolution of CRAT, in 5 (24%) a partial resolution, and in 3 (14%) the thrombus remained stable. Data are not available in 1 (5%) patient. No major bleedings occurred, nor clinically televant non major bleedings. There were only 4 minor bleedings: 2 epistaxis and 2 genital bleedings. One pulmonary embolism occurred during anticoagulant treatment.
**Conclusions:** With the increase of patients with central venous catheters, CRAT is becoming less uncommon than previously thought. Early treatment may lead to complete thrombosis resolution in more than half of patients. Anticoagulants are safe with low risk of bleeding. The risk of recurrences is similar to that display by thrombosis in usual sites in cancer patients3-4.

### 126. PRESCRIPTION APPROPRIATENESS OF ANTITHROMBOTIC DRUGS FOR PROPHYLAXIS OF VENOUS THROMBOEMBOLISM IN HOSPITALIZED MULTIMORBID OLDER PATIENTS: THE REPOSI STUDY

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**Background:** Venous thromboembolism (VTE) is an important cause of morbidity and mortality in acutely elderly patients hospitalized in Internal Medicine Unit.1 International guidelines such as "the 2012 American College of Chest Physicians (ACCP)" and subsequently "the 2018 American Society of Hematology (ASH) guidelines" recommend the pharmacological prophylaxis in hospitalized medical patients at high risk of VTE. In order to stratify patients in relation to their VTE and bleeding risks and thus to select those more likely to benefit from pharmacological prophylaxis, two validated risk assessment models (RAM) have been suggested: the Padua prediction score (PPS) and the IMPROVE bleeding risk score. 2
**Objective:** The aims of this study were to assess, in a large sample of multimorbid older patients admitted from 2012 to 2019 to more than 100 Italian internal medicine and geriatric wards, the prevalence of prescription of antithrombotic drugs for prophylaxis; the appropriateness of prescription or non-prescription by assessing patient's VTE and bleeding risks and the in-hospital mortality rate in appropriately versus not appropriately prescribed cases.
**Methods:** Data were obtained from the REgistro POliterapie Società Italiana Medicina Interna (REPOSI). Patients participating in REPOSI between 2012 and 2019 were included in this study.
We identified patients on thromboprophylaxis (TP) among those prescribed, at admission and/or during hospital stay, subcutaneous low molecular weight heparin, unfractioned heparin, fondaparinux or direct-acting oral anticoagulants given at the low dosages recommended for TP. The risk of developing VTE and major bleeding complications was evaluated using the PPS and IMPROVE scores, respectively. According to clinical guidelines, antithrombotic drugs were considered appropriately prescribed when patients had both a high VTE risk and a low bleeding risk (PPS≥ 4 and IMPROVE<7), but were considered not appropriately prescribed in cases at low VTE risk and high bleeding risk (PPS<4 and IMPROVE≥7), as well as in those both at low VTE and bleeding risks (PPS<4 and IMPROVE<7).
**Results:** From 2012 to 2019, among 5705 older patients admitted to internal medicine and geriatric wards 2102 were prescribed and 3603 non-prescribed antithrombotic drugs. Overall, 1,233 (25.5%) patients were prescribed a drug for TP at admission and/or during the hospital stay, and thus prevalence varied over time from 27% in 2012 to 23% in 2019. The most frequently prescribed drug was enoxaparin (n=909, 73.7%).
A total of 375 patients were not assessable for being at low or high risk according to the PPS or IMPROVE scores. Thus, 4461 patients, 1138 prescribed drugs for TP and 3323 non-prescribed, were ultimately considered. Among them, 1052 cases (23.6%, 95% CI 22.3-24.8) were at high VTE risk according to the PPS (≥ 4) and 549 (12.3%, 95% CI 11.3-13.3) at high bleeding risk according to the IMPROVE score (≥ 7). The most common VTE and bleeding risk factors were advanced age (≥70 years for PPS, and ≥85 years for IMPROVE), male sex and moderate renal failure.
3136 patients (70.3%) were appropriately prescribed or non-prescribed with antithrombotic prophylaxis according to their thrombotic and bleeding risk. Among those prescribed, 360 (31.7%) were appropriately prescribed owing to their high VTE risk. Among those non-prescribed, 2776 (83.5%) were appropriately non-prescribed owing to their low VTE risk or both high VTE and bleeding risks. Thus, 709 patients (62.3%) were inappropriately prescribed because at both low VTE and bleeding risks.
The prevalence of patients inappropriately prescribed or not-prescribed decreased overtime, from 32.0% in 2012 to 25.8% in 2019. The choice of prescribing or not prescribing drugs for TP was considered always appropriate for patients at both high VTE and bleeding risk (PPS≥4 and IMPROVE ≥7). Among the 221 patients appropriately prescribed or non-prescribed, 130 (58.8%) had a PPS between 4 and 5 and an IMPROVE score between 7 and 8.5.
**Conclusions:** This study shows a high rate of prescription appropriateness of antithrombotic drugs for TP. Since the appropriateness of prescription or non-prescription was associated with a lower in-hospital mortality, the use of risk prognostic scores is strongly advised in order to safely manage these drugs in their complex older multimorbid and hospitalized population.
**References:** 1) Engbers MJ, van Hylckama Vlieg A, Rosendaal FR. Venous thrombosis in the elderly: incidence, risk factors and risk groups. J Thromb Haemost. 2010 Oct;8(10): 2105-12. - 2) Kahn SR, Lim W, Dunn AS, Cushman M, Dentali F, Akl EA, Cook DJ, Balekian AA, Klein RC, Le H, Schulman S, Murad MH. Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl): e195S-e226S.

### 127. A RARE CAUSE OF MESENTERIC THROMBOSIS

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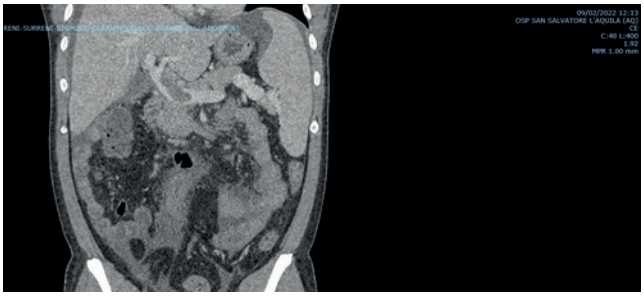
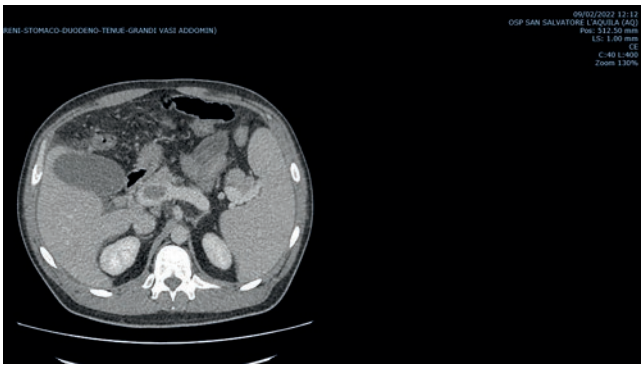
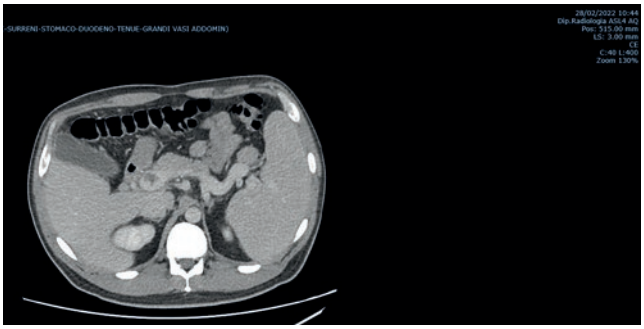
Mr. E.C., 40 years old, with a history of steatohepatitis and weak ANA positivity, came to Our Observation for the onset of asthenia and fever with chills, for which he took antibiotic therapy but, given the onset of widespread and worsening abdominal pain associated with constipation, he went to the Emergency Room where hematochemical examinations showed hypertransaminasemia, increase in gamma GT, INR, PCR, lymphomonocytic and basophilic leukocytosis, hyperbilirubinemia (with prevalent indirect component), posi-

tive evidence for IgG and IgM of the VCA of the Epstein Barr virus.
A direct RX of the abdomen was negative for pathological distensions of the intestinal loops and for free air with extraintestinal distribution while reporting sporadic hydroaerial levels in hypochondrium-right flank.
An ultrasound of the abdomen completed with CT examination showed a widespread thickening-imbibition of the mesenterial adipose tissue at the mesenteric root and in the peri-cephalo-pancreatic site with loss of normal acinar lobing, enlarged spleen with bipolar diameter of 20 cm, pericardial fluid film 8 mm thick, areas of parenchymal thickening "frosted glass" in the subpleural site in the lateral segment of the LIS. A surgical evaluation excluded the presence of surgical urgencies in progress.
Blood cultures were performed, which were negative, while the search for EBV DNA and CMV DNA showed acute infection in progress.
An urgent abdomen CT scan with administration of contrast medium documenting the presence of thrombosis of the mesenteric veins with extensive involvement of the distal branches and the spleno-mesenteric confluence up to the proximal portion of the portal vein, aspects of parietal edema and delayed vascularization of the ileal loops, CT signs of ischemia with concomitance of small aerial coefficients. (Figures 1 and 2).

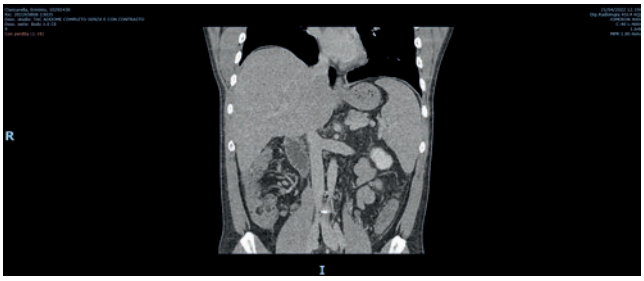


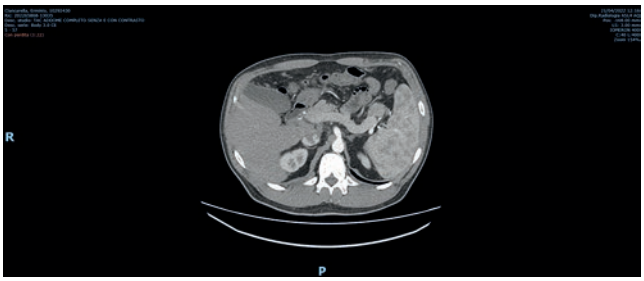


Anticoagulant therapy with enoxaparin and antibiotic therapy with meropenem and metronidazole were set.
A surgical evaluation and then interventional radiology did not consider intervening.
A cholangio-MRI showed no parenchymal alterations and an EGDS was normal.
The study of pro-trombotic prophyl, autoimmune structure and the main known haematological mutations gave inconclusive results positivity for ANA, heterozygous MTHFR, IgM type beta2 glycoprotein antibodies, antiplatelet antibodies and doubtful dsDNA.
A further CT scan of the upper and lower abdomen with mdc appreciated a discrete reduction of the endoluminal defect of a thrombotic nature, partial rehabilitation of the same; reduction of the fine thickening of the mesenterial adipose tissue in the mesogastric site. (figure 3).



Mr. E.C. was discharged to the home with subcutaneous anticoagulant therapy and subjected to weekly hematological checks.
The last CT scan of the abdomen with mdc performed at the third month of therapy, showed complete resolution of the endoluminal defect affecting the portal vein, and substantial reduction also of the thrombosis of the mesenteric vein with residual thrombosis of the pre-confluence tract. Also reduced the size of the spleen (16 cm). (figures 4 and 5)





Portal vein thrombosis is a common complication of liver cirrhosis or neoplasms, but is rarely related to an EBV or CMV infection, especially in immunocompetent individuals.
Clinically it presents with abdominal pain, sometimes fever, vomiting, dyspepsia.
It is estimated that between 2 and 9% of patients admitted for portal thrombosis have a CMV infection
The pathogenetic mechanism seems to be linked to the production of antiospholipid antibodies, anticardiolipin or the viral peptide TIFI, similar to human beta2 glycoprotein.
A second possible mechanism could be given by the immune response against viral envelope phospholipids, such as phosphatidylserine.
Finally, the engraftment of the virus on endothelial cells would represent a motive that leads to both venous and arterial thrombosis (lysis of tissue factor, inhibition of antithrombin III and fibrinolysis),
The portal phase of the CT scan of the abdomen represents the gold standard for diagnosis.
Therapy consists of anticoagulant treatment and support for pain therapy in the early stages. The choice to perform an endovascular thrombectomy depends on the age of the subject and the extent of the thrombus as well as the presence of intestinal ischemia in progress.

## 128. SENSITIVITY AND SPECIFICITY OF DIAGNOSTIC TESTS FOR THROMBOSIS WITH THROMBOCYTOPENIA SYNDROME – A SYSTEMATIC REVIEW OF CASE REPORTS AND CASE SERIE S

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**Background:** Diagnostic accuracy measures of the diagnostic tests for Thrombosis with Thrombocytopenia Syndrome (TTS) are lacking.
**Aims:** To estimate sensitivity and specificity of Platelet Factor 4 (PF4) Enzyme-linked Immunosorbent Assays (ELISAs), Platelet Activation Assays (PAAs) and PF4-enhanced PAAs (PF4-PAAs).
**Methods:** A systematic search of the literature was performed by 2 researchers with a pre-defined research string. We evaluated for inclusion (i) observational studies on TTS providing results of the performed laboratory diagnostic tests, (ii) studies investigating the prevalence of anti-PF4

antibodies in vaccinees with an adenoviral vector vaccine with no signs or symptoms of TTS, and (iii) laboratory studies investigating novel diagnostic tests and/or comparing different available diagnostic tests written in English and published from January 1st 2020 until August 17th 2021. Patients were considered affected by TTS according to guidelines definition or to authors' judgement. This study was unfunded.
**Results:** Fifty-seven studies describing diagnostic test results of 508 TTS patients and 691 vaccinees with adenoviral vector vaccines without signs or symptoms of TTS were included in the analysis (Figure 1). All studies were case reports and case series. The summary sensitivity estimates of PF4-ELISAs, PAAs and PF4-PAAs were 94.5% (95%CI, 92.4-96.1%), 65.1% (95%CI, 55.2-74.1%), and 96.7% (95%CI, 90.6-99.3%), respectively (Table 1, Panel A). Summary estimates of specificity were 95.5% (95%CI 93.7-96.9%) for PF4-ELISAs and 100% (95%CI, 92.9-100.0%) for PF4-PAAs; data for specificity estimation of PAAs were scarce (Table 1, Panel 2). Our research is limited by a likely overestimation of test sensitivity and by the absence of primary cross-sectional diagnostic accuracy studies.

| Test | Negative tests/total tests (n) | Test Specificity (95% CI) |
|---|---|---|
| **IgG-specific ELISAs** | | |
| Lifecodes PF4 IgG | 486/492 | 98.78% (97.36-99.55%) |
| Zymutest HIA IgG | 37/41 | 90.24% (76.87-97.28%) |
| | **Unspecified ELISAs** | |
| | 137/158 | 86.71% (80.40-91.58%) |
| **All ELISAs** | | |
| | 660/691 | 95.51% (93.69-96.93%) |
| **Platelet Activation Assays** | | |
| HIMEA | 6/6 | 100.00% (54.07-100.00%) |
| **PF4-Platelet Activation Assays** | | |
| HIPA | 30/30 | 100.00% (88.43-100.00%) |
| PIFPA | 20/20 | 100.00% (83.16-100.00%) |
| Total | 50/50 | 100.00% (92.89-100.00%) |

**Table 1, Panel A.**
Abbreviations: CI, Confidence Intervals; IgG, immunoglobulin G; ELISA, enzyme-linked immunosorbent assay; PF4, Platelet Factor 4; HIPA, heparin-induced platelet activation; SRA, serotonin release assay; HIMEA, heparin-induced multiple electrode aggregometry; HIT, heparin-induced thrombocytopenia; PAT, platelet aggregation test; LTA, light transmission aggregometry; PIFPA, PF4-induced flow cytometry-based platelet activation.
95% Confidence Intervals were calculated using the exact method.
Tests that were performed less than 5 times were excluded from this analysis.
Sensitivity analysis was based on PF4-ELISA results from studies describing at least 10 VITT patients.

| Test | Negative tests/total tests (n) | Test Specificity (95% CI) |
|---|---|---|
| **IgG-specific ELISAs** | | |
| Lifecodes PF4 IgG | 486/492 | 98.78% (97.36-99.55%) |
| Zymutest HIA IgG | 37/41 | 90.24% (76.87-97.28%) |
| | **Unspecified ELISAs** | |
| | 137/158 | 86.71% (80.40-91.58%) |
| **All ELISAs** | | |
| | 660/691 | 95.51% (93.69-96.93%) |
| **Platelet Activation Assays** | | |
| HIMEA | 6/6 | 100.00% (54.07-100.00%) |
| **PF4-Platelet Activation Assays** | | |
| HIPA | 30/30 | 100.00% (88.43-100.00%) |
| PIFPA | 20/20 | 100.00% (83.16-100.00%) |
| Total | 50/50 | 100.00% (92.89-100.00%) |

**Table 1, Panel B.**
Abbreviations: CI, Confidence Intervals; IgG, immunoglobulin G; ELISA, enzyme-linked immunosorbent assay; PF4, Platelet Factor 4; HIMEA, heparin-induced multiple electrode aggregometry; HIPA, heparin-induced platelet activation; PIFPA, PF4-induced flow cytometry-based platelet activation.
95% Confidence Intervals were calculated using the exact method.
Tests that were performed less than 5 times were excluded from this analysis.
**Conclusions:** Our results may suggest that due to their high sensitivity and specificity PF4-ELISAs constitute appropriate first-level tests when suspecting TTS, and a positive PF4-ELISA confirms TTS diagnosis. PF4-PAAs, highly sensitive and specific tests limited by their low availability and technical complexity, can be used as confirmatory tests in selected cases.
Uploaded File(s) Table and Figures Figure 1 Flow-chart of study selection.
Abbreviations: PF4, Platelet Factor 4; ELISA, enzyme-linked immunosorbent assay; TTS, Thrombosis with Thrombocytopenia Syndrome; PAA, Platelet Activation Assay.

## 129. GASTRIC PNEUMATOSIS: A CASE OF WATCHFUL WAITING

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Gastric pneumatosis is a rather rare radiological finding, even more so if it is also associated with portal pneumatosis and gastro-lienal vessels. From the review of the literature carried out by Schattner and Glick it appears that the main causes of gastric pneumatosis are gastric ischaemia /infarction both local and systemic hypoperfusion (sepsis, hypovolemia, etc.), gastric intramural infection and gastric mucosal disruption both spontaneous and iatrogenic. Gastric pneumatosis can be also a consequence of extension (dissection) of supra-diaphragmatic air (such as secondary to pneumomediastinum) or idiopathic, even if in rare cases.
The clinical case that came to our observation concerns a 48-year-old man hospitalized in our department for diagnostic-therapeutic classification of atypical arterial thrombosis of the celiac tripod, upper and lower mesenteric and thrombosis of the renal arteries, of probable paraneoplastic origin from adrenal carcinoma.
The patient, who came to our observation after an access to the emergency room for intense abdominal pain, was stabilized and, following a new episode of epigastralgia, underwent urgent exploratory laparotomy with cholecystectomy and left adrenalectomy for a suspected lesion then to be an adrenal carcinoma, sarcomatoid variety, on histological examination. Subsequently, abdominal aortography was performed via the left femoral route and treatment of the stenosis of the superior mesenteric artery with a medicated STENT implant, with gradual clinical recovery. Once the patient was stabilized again and a prudential partial enteral feeding was reintroduced, an episode of vomiting and epigastralgia led to the urgent carrying out of a chest and abdomen CT angiography with finding of "portal pneumatosis and of the wall of fundus and of the great gastric curvature which appear thin and hypovascularized, persistence of ostial thrombosis of the celiac tripod with reduced patency of the hepatic and splenic artery and compensatory hypertrophy of the left gastric artery. Pneumatosis also appreciated in the gastro-lienal vessels with evidence of multiple splenic infarcts. " The parameters found were the following: PA 150/90 mmHg, FC: 86 bpm, SpO2: 98% in ambient air. On blood chemistry tests: WBC: 15X103/Ul, Na+: 133 mmol/L, K+: 3,2 mmol/L, PCR: 7,1 mg/L, AST 85 U/L. The nasogastric tube was then positioned with total parenteral nutrition, antibiotic therapy and, as a precaution, the oral pharmacological therapies were switched to intravenous therapies. After three days, in gradual clinical improvement, CT re-evaluation was carried out and the previously reported pneumatosis of the portal and of the fundus wall and of the great gastric curvature, previously reported, was no longer appreciable with reabsorption also of the pneumatosis of the gastro-lienal vessels. On the other hand, the stenosis of the inferior mesenteric artery and the celiac tripod remained unchanged, revascularized just downstream, immediately upstream of the origin of the hepatic artery and splenic artery which showed regular caliber, with reduction of vicarial hypertrophy of the left gastric artery. Therefore, in our patient there was a case of pneumatosis on an ischemic basis with self-resolution of the same and is therefore an example of how gastric pneumatosis is a condition that can be treated conservatively with a prognosis that however depends on the etiology and the speed of recognition and timely treatment.

## 130. NO EVIDENCE OF INCREASED RATE OF THROMBOTIC RECURRENCES IN PATIENTS WITH HISTORY OF VENOUS THROMBOEMBOLISM AFTER VACCINATION FOR COVID-19

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Patients who have suffered from thrombotic events in the past, are widely concerned whether they are at increased risk for a new thrombotic event after COVID-19 vaccination. This report provides physicians with substantiated evidence to address this concern. We analyzed the records of patients with history of VTE treated at our Outpatient Clinic who were vaccinated against COVID-19 in 2021. Inclusion criteria were age ≥ 18 years and at least one episode of VTE prior to vaccine administration. We analysed all the data regarding the characteristics of the previous VTE episode (including the date of thrombosis, the site of thrombosis, and the type and duration of anticoagulation treatment they received) and information about the COVID-19 vaccine (including the type of vaccine, the number of doses, and the date of each dose, and the presence of risk factors for thrombosis at the time of vaccination). We identified 242 subjects with fully available data. There were 72 males and 170 females, with a mean age of 63.8 ± 14.3 years. History of VTE consisted of previous DVT of the lower limbs in 143 patients (59.1%), DVT of the upper extremities (catheter-related) in 41 patients (16.9%), splanchnic DVT in 5 patients (2.0%), and CVST in 1 patient (0.4%). History of PE, either isolated or associated with DVT, was present in 103 patients (42.6%). Regarding the presence of risk factors at the time of vaccination, 155 patients (64.0%) had previous or current cancer, 99 patients (40.9%) were on active chemotherapy. There were 15 patients (6.2%) with thrombophilic conditions and 5 patients with antiphospholipid syndrome (APS), one of whom also had protein S deficiency. Regarding anticoagulation at the time of vaccination, 35 patients (15.5%) were on full anticoagulant treatment because of a recent thrombotic event, 163 patients (67.4%) were on a low-dose anticoagulant treatment for the prevention of VTE recurrence, and 5 patients (2.1%) were on full anticoagulant treatment because they had APS. Finally, there were 39 patients (16.1%) who were not on anticoagulant treatment at the time of vaccination. Of these, 36 had no indications to extended anticoagulation after completion of therapeutic regimen for acute VTE, 1 had suspended treatment after the removal of a central venous catheter (CVC), and 2 had suspended treatment for chemotherapy-induced thrombocytopenia. In the course of 2021, this cohort of patients received a total of 550 doses of COVID-19 vaccine, distributed as follows: Comirnaty 463 doses (84.2%), Moderna 72 doses (13.1%), Vaxzevria 12 doses (2.2%), Janssen 3 doses (0.5%). The number of first, second, and third (booster) doses were 242 (44.0%), 231 (42.0%), and 77 (14.0%), respectively. We found 1 early (within 30 days after vaccination) and 4 late (beyond 30 days after vaccination) thrombotic recurrences on a total of 550 doses of vaccine (recurrence rate was 0.2% and 0.7%, respectively). The mean time elapsed between the last dose of vaccine and the thrombotic recurrence was 105.5 days. The results of our analysis indicate that the rate of thrombotic recurrence is low among subjects with history of VTE who have received vaccination against COVID-19. It is 0.2% when considering only early events (within 30 days from vaccination), which are those with a higher likelihood of being associated with vaccine administration. The only early recurrence occurred in a patient at very high risk of thrombosis. Indeed, she was an elderly woman with active cancer who developed an upper limb DVT where a CVC was present and used for chemotherapy. In this type of patients, it is estimated that rate of thrombotic recurrence is greater than 5% per year, and more than 30% over 5 years. Therefore, it is more likely that this thrombotic event is due to the intrinsic thrombotic risk of the patient, rather than to the vaccine. The same considerations can be made for the late recurrent events observed in our cohort, which always occurred in subjects affected by active cancer and many days after vaccination.In our cohort, the percentage of patients with active cancer was higher than usually reported in VTE epidemiological studies. However, regarding the objective of the current study, this cannot be considered a limitation, but instead a factor that strengthens the concept that COVID- 19 vaccination does not increase the risk of recurrence, even in subjects at high risk of thrombosis. Same considerations can be made about thrombophilic conditions. It is also worth mentioning that in our cohort there were 84 doses of COVID-19 vaccine that were administered to patients who were not on anticoagulant treatment, because of completion of a therapeutic regimen for acute VTE and had no indication to extended anticoagulation, as they were considered at low risk of recurrence. None of them experienced a new thrombotic event after COVID-19 vaccine. In conclusion, our analysis – although limited by the small sample size – shows that patients with history of VTE do not have increased rate of thrombotic recurrence after COVID-19 vaccination. These data may support physicians in dealing with patients who have vaccine hesitancy because of a previous history of VTE.

## 131. CIRCULATING MIRNAS RELEASE PREDICTS SUBOPTIMAL RESPONSE TO ASPIRIN IN PATIENTS AT HIGH CARDIOVASCULAR RISK WITH AND WITHOUT TYPE 2 DIABETES MELLITUS

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**Background:** The recovery rate of platelet COX-1 activity during the 12 to 24h dosing interval of aspirin administration, in aspirin-treated subjects, is characterized by substantial interindividual variability. Circulating myeloid-related protein (MRP)-8/14 is an inflammatory protein associated with residual thromboxane (TX)-dependent platelet activation in aspirin-treated patients with acute coronary syndrome.
**Aims:** To identify any circulating miRNAs associated with a suboptimal ASA response in patients at high cardiovascular (CV) risk.
**Methods:** Two-hundred high CV risk patients (100 with type 2 diabetes mellitus (T2DM)) in chronic treatment with ASA (100 mg/day), for cardiovascular prevention, were enrolled. Blood sampling was performed at 10 (T10) and 24 hours (T24) after a witnessed ASA administration. Patients were stratified in tertiles according to serum TXB2 slope. First vs. third tertile were compared. Circulating miRNAs custom array cards were applied to assay the expression levels of 14 miRNAs in plasma. We also measured plasma myeloid-related protein (MRP)-8/14 as an inflammatory index and predictor of cardiovascular events.

FIG.1

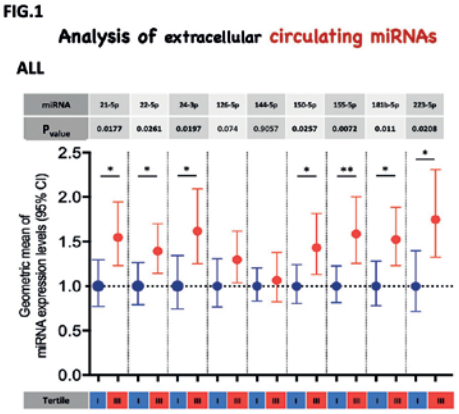
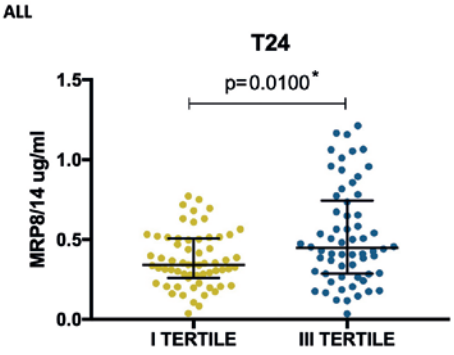



FIG.2



**Results:** miRNA-21-5p (p=.017), 22-5p (p=.026), 24-3p (p=.020), 150-5p (p=.026), 155-5p (p=.007), 181b-5p (p=.011), 223-5p (p=.021) were significantly lower in first vs. third tertiles at 24 hours after ASA administration in all patients (FIG.1). MRP-8/14 were higher in third vs. first sTXB2 slope tertile in all patients (FIG.2). MRP-8/14 was directly correlated with miRNA-21-5p (rho=.279, p=.008), 22-5p (rho=.264, p=.012), 24-3p (rho=.239, p=.023), 150-5p (rho=.236, p=.025), 155-5p (rho=.270, p=.011), 181b-5p (rho=.240, p=.023) and 223-5p (rho=.244, p=.030) in all patients (data not shown).
**Conclusions:** MRP 8/14 may contribute to circulating miRNA release and response variability to ASA. Vice versa, shorter duration of aspirin effect at 24 hours in third sTXB2 slope tertile patients translates into higher degree of TX-dependent platelet activation, possibly promoting the release of both circulating MRP8/14 and miRNAs. Reduced levels of circulating miRNAs may be a potential biomarker for predicting response to ASA treatment in high-risk cardiovascular patients.

## 132. LOW DOSE RIVAROXABAN TO PREVENT RECURRENCES OF VENOUS THROMBOEMBOLISM IN CANCER PATIENTS: A REAL-LIFE EXPERIENCE

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**Background and Aims**: Patients with active cancer are a high-risk population for venous thromboembolism (VTE) and its recurrences, with a significant burden in terms of morbidity, mortality, and quality of life. For this reason, international guidelines suggest long-term anticoagulation for secondary prophylaxis (beyond 6 months) rather than short-term treatment alone (3-6 months). However, this is a conditional recommendation, with low certainty in the evidence of effects. Similarly, it is not clear which type nor dose of anticoagulant should be administered to patients with active cancer and VTE requiring extended anticoagulation. Guidelines suggest to use direct oral anticoagulants (DOACs) or low-molecular weight heparin (LMWH), but also this recommendation has low certainty in the evidence of effects.
The present study provides real-life data on the extended use of rivaroxaban 10 mg to prevent recurrence of VTE in cancer patients, after completion of a full anticoagulation regimen of at least 6 months for the treatment of acute VTE.
**Methods:** This is a prospective observational study performed at the "Section of Internal Medicine and Thromboembolic Diseases" of the A. Gemelli University Hospital of Rome, Italy.
Patients with active cancer who received rivaroxaban 10 mg for the secondary prevention of VTE were enrolled. All patients had previously completed a cycle of at least six months of full-dose anticoagulation for the treatment of a VTE qualifying event.
For VTE qualifying event, we intended either deep vein thrombosis (DVT) of the lower limbs (both proximal and distal), pulmonary embolism (PE), or DVT in unusual sites, including splanchnic/abdominal veins, cerebral veins, jugular veins, and deep veins of the upper limbs, either in the presence or the absence of a central venous catheter (CVC).
The primary efficacy endpoint was any type of objectively verified recurrent VTE. Primary safety endpoints were major bleedings or clinically relevant non-major bleedings (CRNMB), defined according to the criteria of the International Society of Thrombosis and Haemostasis (ISTH).
**Results:** Our study included 106 patients. The median age was 60 (IQR 50 - 69) and the male/female ratio was 6/100. Cancer types were distributed as follows: breast cancer in 31 patients (29.2%), ovarian cancer in 43 patients (40.6%), cervical cancer in 7 patients (6.6%), endometrial cancer in 17 patients (16.0%), colorectal cancer in 5 patients (4.7%), gastric cancer in 1 patient (0.9%), lung cancer in 1 patient (0.9%), prostate cancer in 1 patient (0.9%), cholangiocarcinoma in 1 patient (0.9%), ampullary carcinoma in 1 patient (0.9%), tonsil carcinoma in 1 patient (0.9%), haematologic neoplasm in 1 patient (0.9%). There were 4 patients (3.8%) with multiple synchronous cancers.
A total of 81 patients (76.4%) had metastatic cancer. Of these, 6 patients (5.7%) had brain metastases.
All patients had previously presented a qualifying VTE event, which had undergone full anticoagulant therapy for at least 6 months. About the qualifying VTE events, pulmonary embolism (PE) occurred in 39 patients (36,8%), of whom 15 isolated PE without deep vein thrombosis (DVT) (14.1%), proximal deep vein thrombosis (DVT) of the lower limbs in 28 patients (26.4%), distal DVT of the lower limbs in 13 patients (12.3%), central venous catheter (CVC)-related thrombosis of the upper limbs in 45 patients (42.5%), venous thrombosis of the upper limbs not associated with a CVC in 3 patients (2.8%), CVC-related atrial thrombosis in 1 patient (0.9%), and splanchnic vein thrombosis in 1 patient (0.9%). The most frequent comorbidities were hypertension (47.2%), overweight and obesity (25.5% and 22.6%, respectively), chronic kidney disease (24.7%), diabetes (9.4%), and dyslipidaemia (19.8%).
Upon completion of a therapeutic regimen of full anticoagulation for at least 6 months, all patients were treated with rivaroxaban 10 mg once daily. They were followed-up for a median time of 333 days (IQR 156-484).
We observed 4 VTE recurrences, with a recurrence rate of 3.8%. In terms of safety, we observed no major bleedings (0.0%) and 3 CRNMB (2.8%).
Interestingly, the 4 recurrences that we observed were proximal DVTs of the lower limbs in patients whose qualifying previous event was a proximal DVT of the lower limbs. In two patients, the VTE recurrence developed in the presence of extrinsic vascular compression.
**Conclusion:** The present study suggests that extended therapy with rivaroxaban 10 mg may be considered as a therapeutic strategy and could be safely administered to patients with active cancer to prevent recurrences of VTE. Large-scale studies are needed to confirm these data.

## 133. REDUCED PLATELET GLYCOPROTEIN IBA SHEDDING ACCELERATES THROMBOPOIESIS AND COX-1 RECOVERY: IMPLICATIONS FOR ASPIRIN DOSING REGIMEN

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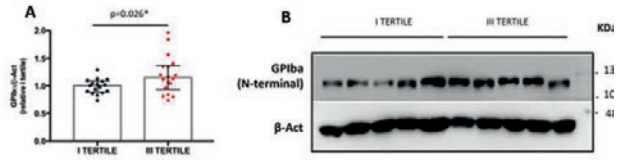
Cardiovascular prevention with low-dose aspirin can be less effective in patients with a faster recovery of platelet cyclooxygenase (COX)-1 activity during the 24-hour dosing interval. We previously showed that incomplete suppression of TXA2 over 24 hours can be rescued by a twice daily aspirin regimen.
Here we show that reduced platelet glycoprotein (GP)Ibα shedding characterizes patients with accelerated COX-1 recovery and may contribute to higher thrombopoietin production and higher rates of newly-formed platelets, escaping aspirin inhibition over 24 hours.
Two-hundred aspirin-treated patients with high cardiovascular risk (100 with type 2 diabetes mellitus) were stratified according to the kinetics of platelet COX-1 activity recovery during the 10-24h dosing interval. Whole proteome analysis showed that platelets from patients with accelerated COX-1 recovery were enriched in proteins involved in cell survival, inhibition of apoptosis and cellular protrusion formation. In agreement, we documented increased plasma thrombopoietin, megakaryocyte maturation and proplatelet formation, and conversely increased platelet galactose and reduced phosphatidylserine exposure and ADAM17 activation, translating into diminished GPIbα cleavage and glycocalicin release. Treatment of HepG2 cells with recombinant glycocalicin led to a dose-dependent reduction in liver thrombopoietin mRNA, suggesting that reduced GPIbα ectodomain shedding may unleash thrombopoiesis. A cluster of clinical markers, including younger age, non-alcoholic fatty liver disease, visceral obesity and higher thrombopoietin/glycocalicin ratio, predicted with significant accuracy the likelihood of faster COX-1 recovery and suboptimal

aspirin response.Circulating thrombopoietin/ glycocalicin ratio, reflecting a dysregulation of platelet lifespan and production, may provide a simple tool to identify patients amenable to more frequent aspirin daily dosing.




## 134. CLINICAL HISTORY OF PATIENTS WITH LEFT VENTRICULAR THROMBOSIS RECEIVING VITAMIN K ANTAGONISTS

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**Background:** Left ventricular thrombosis (LVT) represent a potential life-threatening condition being responsible for a high risk of stroke and systemic embolism. The optimal antithrombotic strategy to achieve thrombus resolution and avoid cardioembolic events has not yet been established and international guidelines weekly recommend anticoagulant therapy with vitamin k antagonist (VKA) for at least three months. The aims of our study is to evaluate the effectiveness and safety of anticoagulant therapy in patients with LVT receiving VKA.
**Methods:** All consecutive patients referring to our antithrombotic center for LVT development were retrospectively included from January 2013 through January 2021 if they received anticoagulant therapy with VKA - International Normalized Ratio target range between 2 and 3 - for at least three months and data on clinically relevant baseline characteristics and outcomes were available. Exclusion criteria comprehended anticoagulant therapy different from VKA, treatment duration shorter than three months, and unavailability of relevant data. The primary effectiveness outcome included on-treatment thrombus resolution while secondary effectiveness outcomes on-treatment acute ischemic stroke, acute peripheral embolism, and acute myocardial infarction during 12-months follow-up. The safety outcomes comprehended on-treatment major and clinically relevant non-major bleedings as defined by the International Society of Thrombosis and Haemostasis (ISTH) criteria.
Continuous variables were expressed as median and interquartile ranges and categorical variables were expressed as counts and percentages. Follow-up time was calculated from LVT diagnosis up to outcomes development or 12-months follow-up, whichever came first. The frequency of thrombus resolution was expressed as cumulative incidence with 95% confidence intervals (CIs) while the frequency of other outcomes was descriptively reported. RStudio (version 3.6.3, R Core Development Team, Vienna, Austria) was used for the analysis.
**Results:** A total of 21 patients were included in the analysis. Median age was 73 year and 90.5% of patients were male. A total of 95.2% of patients had acute myocardial infarction as risk factor for LVT development while 4.8% of patients had primitive dilated myocardiopathy. No patients had primitive hypertrophic cardiomyopathy as underlying risk factor for LVT. A reduced ejection fraction and atrial fibrillation was present in 52.4% and 19% of included patients, respectively. All patients received warfarin with a median time in therapeutic range (TTR) of 59% and 52.4% of patients received concomitant dual antiplatelet therapy.
During a median follow up of 7 months, 11 patients had complete resolution of LVT while 10 did not with a 3-months and 12-months cumulative incidences (Figure) of thrombus resolution of 42.9% (95% CI, 21.3% to 62.9%) and 57.1% (95% CI, 32.8% to 75.5%), respectively. Between patients with thrombus resolution and thrombus persistence, no significative difference was noted about underlying cardiomyopathy, comorbidities, and treatment characteristics (Table). While no patients developed on-treatment acute ischemic stroke, acute peripheral embolism, and acute myocardial infarction, two patients (9.5%) developed an on-treatment major gastrointestinal bleeding (one in the upper and one in the lower gastrointestinal tract) and one patient (4.8%) developed an on-treatment genitourinary clinically relevant non-major bleeding. All bleeding events occurred within the first three months of therapy.
**Conclusion:** Despite suboptimal TTR values, the cumulative incidence of thrombus resolution during the three recommended months of VKA therapy was roughly 40% and rose to roughly 60% if anticoagulant therapy lasted for 12 months. AVK therapy, however, protected patients against cardioembolic events and is associated with an acceptably low rate of major and clinically relevant non-major bleeding.

| Variables | Overall population N = 21 | Thrombus persistence N = 10 | Thrombus resolution N = 11 | p-value |
|---|---|---|---|---|
| Male sex, n (%) | 19 (90.5) | 8 (80.0) | 11 (100.0) | 0.415 |
| Median age (IQR) | 73.50 [63.75, 79.75] | 72.00 [61.00, 76.00] | 75.00 [66.00, 80.50] | 0.470 |
| ***Risk factors*** | | | | |
| Acute myocardial infarction, n (%) | 20 (95.2) | 10 (100.0) | 10 (90.9) | 1.000 |
| Primitive dilated cardiomyopathy, n (%) | 1 (4.8) | 0 | 1 (9.1) | 1.000 |
| Reduced ejection fraction, n (%) | 11 (52.4) | 5 (50.0) | 6 (54.5) | 1.000 |
| ***Comorbidities*** | | | | |
| Smoking history, n (%) | | | | 0.276 |
| No | 7 (33.3) | 5 (50.0) | 2 (18.2) | |
| Actual | 2 (9.5) | 1 (10.0) | 1 (9.1) | |
| Former | 12 (57.1) | 4 (40.0) | 8 (72.7) | |
| Diabetes mellitus, n (%) | 5 (23.8) | 2 (20.0) | 3 (27.3) | 1.000 |
| Atrial fibrillation, n (%) | 4 (19.0) | 2 (20.0) | 2 (18.2) | 1.000 |
| Prior Acute ischemic stroke, n (%) | 4 (19.0) | 2 (20.0) | 2 (18.2) | 1.000 |
| Peripheral arterial disease, n (%) | 0 | 0 | 0 | NA |
| ***Treatment characteristics*** | | | | |
| Median TTR [IQR] | 59.00 [51.00, 70.00] | 56.00 [47.25, 63.75] | 59.00 [57.00, 75.50] | 0.245 |
| Concomitant dual antiplatelet therapy, n (%) | 11 (52.4) | 5 (50.0) | 6 (54.5) | 1.000 |

**Table:** Baseline patients' characteristics

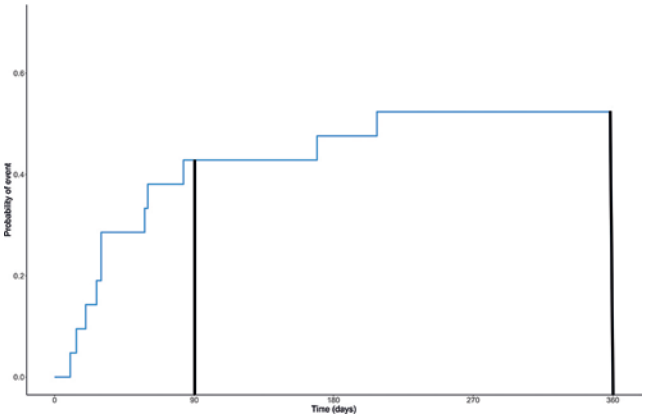


**Figure:** Cumulative incidence of thrombus resolution in patients receiving vitamin K antagonists

## 135. EFFECTS OF GASTROINTESTINAL RESECTION AND OSTOMY SURGERY ON THE PLASMA CONCENTRATION OF APIXABAN: AN OBSERVATIONAL PROSPECTIVE STUDY

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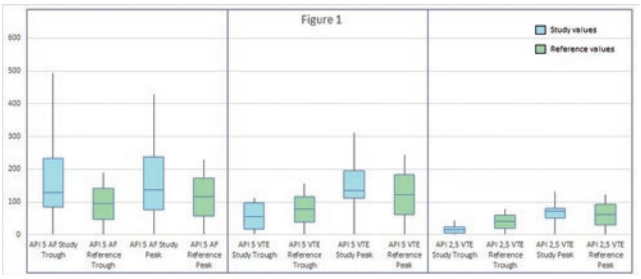
**Background:** Patients who underwent gastrointestinal resection or ostomy surgery may have altered absorption of orally administered drugs. This could be an important clinical problem in subjects taking direct oral anticoagulants (DOACs), for whom an evaluation of effective anticoagulation is not warranted. In this study, we evaluated whether therapeutic plasmatic concentrations of Apixaban can be found in this category of patients.
**Methods:** We designed an observational prospective study and included patients with medical history of gastrointestinal resection or ostomy surgery who were on oral anticoagulation with Apixaban for the treatment or prophylaxis of venous thromboembolism (VTE) and/or for the prevention of cardioembolic stroke due to nonvalvular atrial fibrillation (NVAF). We measured the peak and the trough (2-3 and 12 hours after drug intake respectively) plasma concentrations of Apixaban using a chromatographic

assay and compared the levels obtained with the expected levels, as established by the European Medicines Agency. We included in the study patients who had undergone gastric, small and/or large intestine resection up to the descending colon and/or ostomy surgery. We excluded resection of sigmoid colon and/or rectum due to the poor absorption properties of these bowel tracts.

**Results:** 26 patients were enrolled, of whom 12 (46%) were taking Apixaban 5 mg BID for the treatment of VTE, 4 (15%) were taking Apixaban 5 mg BID for the prevention of cardioembolism in NVAF, and 10 (39%) were taking Apixaban 2.5 mg BID for the prevention of VTE recurrence. The mean age was 65 ± 11.7 years, the mean BMI was 24.8 ± 9.6, and the mean creatinine clearance was 78.9 ± 32.9 ml/min (according to Cockroft–Gault). Regarding surgical interventions, 10 (39%) patients had undergone ileostomy, 4 (15%) subtotal gastrectomy, 5 (19%) small bowel resection (mainly ileum), and 7 (27%) colon resection. Two patients had undergone both gastric resection and small bowel resection, while 2 others both ileostomy and colectomy.

The peak and trough plasma concentrations of patients on Apixaban 5 mg BID for VTE treatment were respectively 174.4 ± 92.1 ng/mL and 72.25 ± 41.3 ng/mL, on Apixaban 2.5 mg BID for VTE secondary prevention was 107.3 ± 38.8 ng/mL and 50.4 ± 14.2 ng/mL, and on Apixaban 5 mg BID for NVAF was 304.7 ± 183.1 ng/mL and 238.0 ± 213.3 ng/mL [Fig.1]. We observed that 2/26 (8%) patients, both receiving Apixaban 5 mg BID for the treatment of VTE, were below the trough reference range. 1/26 (4%) patient, on therapy with Apixaban 5 mg BID for the treatment of VTE, was below the peak reference range.

**Conclusions:** These results show that almost all patients (92% for trough and 96% for peak plasma concentrations, respectively) who had undergone resections of the gastrointestinal tract, during Apixaban therapy achieved plasma drug concentrations within the reference range. Despite the limitations of our study, undoubtedly due to the small sample size and variety of surgeries, these results are encouraging for further studies.




## 136. ENDOTHELIAL DYSFUNCTION AND OXIDATIVE STRESS IN CHILDREN EXPOSED TO PASSIVE SMOKING OF HEAT-NOT-BURN CIGARETTES AND TRADITIONAL COMBUSTION CIGARETTES

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**Background:** Tobacco habit represents the leading preventable cause of morbility and mortality worldwide. Heat-not-burn cigarettes are considered as an alternative to traditional combustion cigarettes due to the lack of combustion and the absence of combustion-related specific toxicants. Altough effects of heat-not-burn cigarettes ar still not known, we assist to a widespread use in the last years. There are no evidence on their effects in cronic passive exposition in children.

**Objectives:** This study has the purpose to study possible negative outcome to passive exposition to IQOS smoking in children age. In details we decided to analyze oxidative stress and endothelial function in children exposed to passive smoking of heat-not-burn cigarettes compared to traditional combustion cigarettes. To evaluate the possible damage passive smoking-induced we analize markers of oxidative stress like soluble peptide NOX2, sieric isoprostanes, H2O2 and bioavaibility of NO as an antioxidant markes. to quantify the grade of exposition to passive smoking of childern, serum cotinine levels were also measured. Furthermore it was evaluated the flow-mediated dilation (FMD) as a marker of endothelial disfunction.

**Methods:** We recruited 60 children and divided in three groups: the first one, with 20 children, were exposed to passive smoking of heat-not-burn cigarettes; the second one is composed of 20 exposed to traditional combustion cigarettes and the last of 20 children were controls, so not exposed to passive smoke. Children included in the study were between 2 and 18 years old and in apparent good health state; they were excluded if they had one of the caractheristic listed below: obesity or severe underweigh; chronic inflammatory disease; diabetes mellitus, cardiopulmonary diseases; severe nephropathy; liver disease; neuromuscolar disease; vitamine assumption.

A cross-sectional study was performed to compare endothelial function by FMD, blood levels of isoprostanes, serum activity of soluble NOX2-dp (sNOX2-dp), and nitric oxide bioavailability in these three groups of children. Serum cotinine levels were assessed to measure exposure to passive smoking.

Continous variables were expressed as medium and standard devation. The categorical variables were expressed as percentage. Statistical analisis of data were obtain using the software SPSS. To evaluate if variables has a normal distribution a Kolmogorov-Smirnov test was executed. The analisys of differences among groups was obtained with the Kruskal-Wallis test for data which didn't have a normal distribution or with ANOVA. Differences between percentages were analized by the chi-square test. The Spearman correlation has been used for bivariate analysis. The statistically significance was considered for P-value <0,05.

**Results:** Compared with healthy controls, children exposed to passive smoking had significantly higher sNOX2-dp and isoprostanes levels, lower FMD and reduced NO bioavailability. No significant difference for serum sNOX2, isoprostanes, NO bioavailability and FMD was observed between children exposed to passive smoking of heat-not-burn cigarettes vs traditional combustion cigarettes.

Bivariate analysis showed that FMD was correlated with sNOX2 (R: -0.420, p=0.001), serum isoprostanes (R: -0.273, p=0.03), and cotinine (R: -0.292, p=0.02). Furthermore, sNOX2 correlated with NO bioavailability (R: -0.373, p=0.003), serum isoprostanes (R: 0.424, p=0.001) and cotinine (R: 0.441, p=0.001).

Below the table shows our results:

| VARIABLES | GROUP | N. | MEAN | DS | P |
|---|---|---|---|---|---|
| Age(years) | Controls | 20 | 8,95 | 3,05 | 0,068 |
| | Passive smoking by Traditional Tobacco Cigarette (TTC) | 20 | 9,10 | 3,15 | |
| | Passive smoking by heat-not-burn cigarettes (HNBC) | 20 | 11,37 | 4,35 | |
| NO(mM) | Controls | 20 | 60,45 | 11,04 | 0,000 |
| | Passive smoking by TTC | 20 | 47,05 | 9,92 | |
| | Passive smoking by HNBC | 20 | 50,09 | 7,73 | |
| 8-iso-PGF2a(pmol/L) | Controls | 20 | 141,35 | 20,83 | 0,001 |
| | Passive smoking by TTC | 20 | 178,25 | 48,96 | |
| | Passive smoking by HNBC | 20 | 182,55 | 33,23 | |
| NOX2(pg/mL) | Controls | 20 | 16,95 | 8,30 | 0,001 |
| | Passive smoking by TTC | 20 | 25,90 | 5,66 | |
| | Passive smoking by HNBC | 20 | 24,88 | 6,89 | |
| H2O2(mM) | Controls | 20 | 22,15 | 5,44 | 0,000 |
| | Passive smoking by TTCT | 20 | 32,10 | 6,66 | |
| | Passive smoking by HNBC | 20 | 29,25 | 6,61 | |
| Cotinine(ng/mL) | Controls | 20 | 1,26 | 1,15 | 0,000 |
| | Passive smoking by TTC | 20 | 36,59 | 9,42 | |
| | Passive smoking by HNBC | 20 | 34,49 | 5,97 | |
| FMD(%) | Controls | 20 | 7,51 | 2,22 | 0,017 |
| | Passive smoking by TTC | 20 | 5,05 | 2,49 | |
| | Passive smoking by HNBC | 20 | 5,00 | 4,10 | |

Multivariable linear regression analysis showed that sNOX2 (standardized coefficient β: -0.169; SE: 0.048; p=0.01) emerged as the only independent predictive variable associated with FMD (R2: 0.44). Furthermore, flow-mediated dilation (standardized coefficient β: -0.318; SE: 0.290; p=0.009) and serum cotinine (standardized coefficient β: 0.349; SE: 0.053; p=0.004) were independently associated with sNOX2-dp levels. Of note, sNOX2-dp serum levels were significantly higher in children with allergic rhinitis exposed to smoke, as compared with unexposed children with allergic rhinitis.

**Conclusions:** Children exposed to passive smoking of heat-not-burn cigarettes have endothelial dysfunction and increased oxidative stress as those exposed to traditional combustion cigarettes. Future studies are strongly warranted to confirm these data.

## ENDOCRINOLOGIA

### 137. ANALYSIS OF MIRNA EXPRESSION FROM THE ADIPOSE TISSUE SURROUNDING THE ADRENAL NEOPLASIA

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**Introduction:** Primary aldosteronism (PA), is characterized by several metabolic changes as insulin resistance, metabolic syndrome, and adipose tissue (AT) inflammation. Mi(cro)RNAs (miRNAs) are a class of noncoding small RNA molecules representing critical regulators in several cellular process associated with adipose tissue dysfunction.
**Aim:** aim of this study was to evaluate the expression of some miRNAs in visceral and subcutaneous AT in patients undergoing adrenalectomy for aldosterone-secreting adrenal adenoma (APA), respect samples of AT obtained in patients undergoing adrenalectomy for non-functioning adrenal mass (NFA).
**Methods:** Quantitative expression of selected miRNA using PCR real time was analyzed in surrounding adrenal neoplasia, peri-renal and subcutaneous AT samples of 16 adrenalectomized patients (11 patients with APA and 5 patients with NFA).
**Results:** Real-time PCR cycles for miRNA 132, miRNA 143 and miRNA 221 in fat surrounding adrenal neoplasia and in peri-renal AT were significantly higher in APA than in NFA patients. Unlike NFA patients, miRNA 132, miRNA 143, miRNA 221 and miRNA 26b were less expressed in surrounding adrenal neoplasia AT compared to subcutaneous AT in APA patients.
**Conclusion:** This study, conducted on tissue expression of miRNAs, highlights the possible pathophysiological role of some miRNAs in determining the metabolic alterations in PA patients.

### 138. SHORT TERM EFFECTS OF DIFFERENT DOSES OF CHOLECALCIFEROL ON CIRCULATING LEVELS OF 24,25(OH)2D

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**Background:** There are no data in the literature examining the short-term effect of different doses of cholecalciferol on 24,25(OH)2D, the inactive metabolite of vitamin D.
**Purpose:** Assess the short-term effects of two different doses of cholecalciferol on 24,25 (OH)2D levels in adult subjects with vitamin D <30 ng/ml.
**Methods:** 27 subjects with 25(OH)D <30 ng/ml were randomized, in three groups of 9 subjects each, to receive a single oral dose of: 25,000 IU of cholecalciferol, 600,000 IU of cholecalciferol, or placebo. 25(OH)D, 1,25(OH)2D, 24,25(OH)2D and ionized calcium were measured at baseline and after 72 hours. 1,25(OH)2D/25(OH)D ratio, 1,25(OH)2D/24,25(OH)2D ratio and 24,25(OH)2D/25(OH)D ratio have been calculated
**Results:** There were no differences in the anthropometric and biochemical parameters at baseline between the three groups. After 72 hours, significant absolute increases in 25(OH)D and 1,25(OH)D levels were found in every group except controls. In the 600,000 IU, 25(OH)D increased from 16.55±13.07 to 58.61±29.40 ng/ml ($p<0.05$), while in the 25.000 IU group from 12.24±8.82 to 19.86±11.26 ng/ml ($p<0.05$). In the group supplemented with 600,000 IU a significant increase in ionized calcium (1.24±0.03 vs 1.28±0.16 mmol/l, $p<0.05$) was observed; a decrease in 1,25(OH)-2D/25(OH)D ratio (0.003±0.001 vs 0.001±0.001, $p<0.05$) and 1,25(OH)-2D/24,25(OH)2D ratio (0.13±0.10 vs 0.06±0.06, $p<0.05$) after 72 hours were observed. Changes in mean values of 24,25(OH)2D/25 (OH)D ratio were not statistically significant.
**Conclusion:** An oral supplementation of 600,000 IU of cholecalciferol after 72 hours is able to significantly increase 25(OH)D and 1,25(OH)2D with a small increase in ionized calcium. The finding that the 24,25(OH)-2D/25(OH)D ratio does not change suggests that after acute huge administration of vitamin D, the CYP 24A1 enzyme is actively involved in the catabolism of vitamin D also in adult subjects with vitamin D <30 ng/ml.

### 139. COVID-19 OUTBREAK AND DE-ESCALATION OF THYROID CANCER DIAGNOSIS AND TREATMENT

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**Background:** The COVID-19 outbreak in Italy forced the health system to cancel all non-urgent outpatient activities, to avoid further spreading of the disease inside the healthcare facilities. At our institution, for cancer patients the hospital allowed treatments and consultations: the medical team, however, identified patients whose procedures could be postponed. Even after May 2020, the capacity for non-urgent thyroid surgeries was reduced. These events enhanced our efforts to reduce overdiagnosis and overtreatment of non-threatening thyroid cancers, as was already suggested by current practice guidelines. The aim of this analysis was to describe the features of patients submitted to thyroid surgery with a final diagnosis of cancer before and after the Italian lockdown.
**Methods:** Single-center, subgroup analysis of a prospective observational study (NCT04031339), approved by the institutional review board. The records on all patients being followed up at our center were analyzed. The cohort was split in two groups: the first one, before the COVID-19 lockdown (March 2019-February 2020, group A) – used as a control, and the second one during and after the lockdown (March 2020-February 2021, group B). The early response to treatment was assessed 6 to 12 months after initial treatment, according to the American Thyroid Association (ATA) guidelines.
**Results:** Group A consisted of 58 patients, while group B of 38 patients, due to a reduction of the number of thyroid surgeries. There were no difference in age (group A: 48 years, interquartile range 36-61; group B: 52 years, 33-61; $p=0.9$), gender distributions (females 74.1% and 65.8%, respectively), and known risk factors (i.e., family history of thyroid cancer, previous neck irradiation). Also, the histotype distribution was similar in the two cohorts ($p=0.46$). However, in the cohort of patients submitted to surgery after COVID-19 outbreak, the median tumor size was higher: 14 mm (IQR 10-25 mm) vs 9 mm (IQR 6-20 mm; $p=0.01$), and the rate of microcarcinomas was lower (12 [31.6%] vs 33 [56.9%], $p=0.02$). Furthermore, the ATA risk stratification distribution was different ($p=0.036$), with less low-risk and more high-risk cancers (19.4% vs 5.5%). This is consistent with a reduction in overtreatment of low-risk diseases. However, the early outcomes (evaluated according to the ATA response to treatment) were not affected ($p=0.73$), as the vast majority of patients had no evidence of persistent disease after treatment (A, 51.7% and B, 57.9%).
**Conclusions:** The "forced" reduction of thyroid surgeries due to COVID-19 outbreak improved the adherence to international practice guidelines, with decreased overtreatment: the short-term outcomes were not negatively impacted.

### 140. CHARACTERIZATION OF EXTRACELLULAR VESICLES IN OSTEOPOROTIC PATIENTS COMPARED TO OSTEOPENIC AND HEALTHY CONTROLS

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**Background:** Extracellular Vesicles (EVs) are increasingly recognized to play a pivotal role in cell-to-cell communication. They are released by many cells, including cancer cells, immune cells, platelets, mesenchymal stem cells, osteoclasts and osteoblasts and could be mediators of a range of pathological conditions. However, their involvement in bone diseases has not been well understood.
**Purpose:** The aim of this study was to characterize the circulating EVs of osteoporotic postmenopausal women (OP) compared to both osteopenic (OPN) and healthy controls (CN) and to investigate their effects on bone cells.
**Methods:** 102 postmenopausal women (age range 50–85 years) were enrolled for the study. They underwent a lumbar and femoral DEXA scan. Bone serum markers were analyzed by ELISA assays. EVs were isolated from plasma of OP, OPN and CN by ultracentrifugation and were analysed by transmission electron microscopy (TEM) and Fluorescence Activated Cell Sorting (FACS). To investigate the content of EVs, MiRNome and proteomic analyses were performed. To study the effect of EVs on bone remodeling, bone cells (osteoclasts, osteoblasts and mesenchymal stem cells) were treated and evaluated for differentiation and activity.
**Results:** Patients were classified into the three groups based on DEXA results. No differences were revealed on serum markers between the groups. FACS analysis showed a significant increase of EVs in OP patients (EV number: CN: 4955±6590; OPN: 5938±7193; OP: 17168±13043[1]#. [1]p=0.0143 vs. CN; #p=0.0248 vs. OPN) compared to both OPN and CN. The number of EVs was found to be negatively associated with the lumbar spine T-score (Beta=-0.36, p=0.049) and femoral neck T-score (Beta=-0.37, p=0.043). Interestingly, FACS analysis revealed an increase of RANKL+ EVs in OP patients (RANKL+ EV number: CN: 2110±1357; OPN: 2303±1942; OP: 6307±3609[1]#. [1]p=0.004 vs. CN; #p=0.009 vs. OPN) compared to both CN and OPN. Moreover, RANKL+ EVs were positively associated with the serum RANKL (Beta=0.64, p=0.03).
Since EVs act as cell-cell communication vectors and are able to transfer miRNAs, miRNAs content was characterized. NGS analysis highlighted an increase of miR-1246 and a reduction of miR-1224-5p in osteoporotic women compared to OPN and CN. Gene Ontology pathways revealed that the modulated EVs-miRNAs in OP are related to osteoclast differentiation, Interleukin-13 production and regulation of the canonical WNT pathway.
The protein profile of EVs, identified by Mass Spectrometry, highlighted that the differentially expressed protein in OP were related to blood coagulation, gonadropin-releasing hormone receptor, inflammation mediated by chemokine and cytokine signaling, and plasminogen activade cascade pathways. In particular, Von Willebrand factor was completely absent in OP-EVs.
To investigate the role of EVs in the etiopathogenesis of osteoporosis, bone cells were treated with EVs. OP-EVs were the only particles able to induce the osteoclast formation from Healthy Donor (HD) Peripheral Blood Mononuclear Cells (PBMC). Furthermore, gene expression analysis of mature HD-osteoclast treated with EVs revealed that OPN-EVs could support osteoclast differentiation and function. During osteoblast differentiation, OP-EVs reduced the ability of MSC to differentiate into mature osteoblasts, while induced an increase of OSTERIX and RANKL expression in mature osteoblasts.
**Conclusion:** Our study characterized for the first time the EVs from osteoporotic postmenopausal women compared to control and osteopenic subjects. We evaluated EVs cargo and their action on bone cells, with the long-term aim to use extracellular vesicles as new diagnostic and prognostic tools for osteoporosis.

## 141. PRIMARY HYPERPARATHYROIDISM: AN ATYPICAL PRESENTATION OF PARATHYROID HYPERPLASIA WITH BROWN TUMORS AND HYPERCALCEMIC CRISIS

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**Introduction:** Primary hyperparathyroidism consists of excessive release of parathyroid hormone (PTH) from one or more parathyroid glands and it is the most common cause of hypercalcemia. In about 80-85% of cases is caused by a single parathyroid adenoma, less frequently by hyperplasia and rarely by a carcinoma. Affected patients are usually asymptomatic or could have non-specific symptoms like fatigue, anorexia, constipation, depression. Complications of hypercalcemia include resorptive bone disease mediated by PTH, nephrolithiasis or neprhocalcinosis and Central Nervous System dysfunction in severe cases. Brown tumor is a rare benign, focal, lytic bone lesion occurring approximately 5% of patients with primary hyperparathyroidism. We present a case of parathyroid hyperplasia complicated with hypercalcemic crisis and osteoclastoma.
**Case Report:** A 52-year-old man was admitted to the Emergency Department because of persistent hip and leg pain for about a month. In his medical history he had recent finding of arterial hypertension and mild chronic kidney disease, previous right uretherolitihiasis in 2011 and nephromicrolithiasis since 2019. The x-ray performed at the Emergency Department showed osteolysis of the left distal femur and proximal tibia. Moreover, the blood tests detected severe hypercalcemia (total serum calcium 16.4 mg/dl, 2.35 mmol/l ionized calcium), hypomagnesemia (1.4 mg/dl), hypophosphatemia (1.4 mg/dl) and mild worsening of kidney function (serum creatinine 1.5 mg/dl compared to his baseline value of 1.3 mg/dl). The patient was then admitted to our Internal Medicine Unit for the necessary investigations and treatment.During hospitalization, the patient presented no other signs or symptoms referable to hypercalcemia, except for constipation. At the blood tests markedly high PTH values (1040 ng/l) were detected as well as high bone turnover markers like serum telopeptide of type I collagen, bone-specific ALP isoenzyme and type D hypovitaminosis. Furthermore, in agreement with the orthopedics colleagues, the patient underwent surgical biopsy of the femoral and tibial osteolytic lesion and the histological examination diagnosed brown tumor, a resorptive bone disease due accumulation and activation of osteoclasts and fibrous tissue deposition in response to PTH. In order to evaluate parathyroids, an ultrasound of the neck was performed, showing multi-lobed enlarged left parathyroid (5.6 mL volume). A neck CT scan confirmed the parathyroid finding and described mandibular and zygomatic hypodense formations with fine sclerotic margins and clavicular hyperdense formation with sign of cortical interruption of not univocal interpretation. Parathyroid scintigraphy showed a hyperfunctioning parathyroid formation in the middle third of the left thyroid lobe. The patient was surgically evaluated and became a candidate for parathyroidectomy. As part of the monitoring of hypercalcemia complications, an abdominal ultrasound and Bone Mineral Density assessment were performed: the former depicted the already known bilateral kidney microcalcolosis and the latter showed osteoporosis with a lumbar and femoral T score respectively of -2.7 and –4.0. Moreover, an ECG showed a short QTc (325 msec) as in early repolarization.Hypercalcemia was treated with large volume of intravenous fluids and a first Zolendronate infusions, with only small biochemical response, so that administration of a calcimimetic therapy with Cinacalcet was necessary. Nevertheless, serum calcium values still remained stable around 13 mg/dl so another Zolendronate infusion was necessary, reaching a maximum drop of serum calcium down to 12.3 mg/dl (ionized calcium 1.62 mmol/l). After that, the patient underwent left upper parathyroidectomy and hemithyroidectomy and during the surgical intervention a biopsy of both parathyroid and the voluminous mandibular exophytic formation was performed. Interestingly, histology revealed chief cell parathyroid hyperplasia and brown tumor in the mandibular formation. Right after surgery, serum calcium e PTH values substantially decreased until normalization in few days and the patient was then discharged.
**Conclusion:** Severe manifestations of primary hyperparathyroidism are more frequently associated with parathyroid carcinomas but also benign lesions like hyperplasia can cause a hypercalcemic crisis, so that a periodic monitoring of calcium levels should be suggested also in these cases. In addition, along with correction of calcium values, a careful evaluation of primary hyperparathyroidism complications is important, as in our patient who developed a severe bone disease with multiple brown tumors and a marked osteoporosis associated with high risk of fractures. Finally, Chief cell parathyroid hyperplasia is the most common histotype and it is usually associated with other endocrine disorders, so that the patient after discharge was recommended to undergo genetic testing for familiar form of primary hyperparathyroidism, but results are still ongoing.

## 142. MYXEDEMA COMA, A LIFE-THREATENING CONDITION

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**Introduction:** Myxedema coma is a severe complication of hypothyroidism. It is a rare but true medical emergency and can result in profound hemodynamic instability and airway compromise. Common symptoms include mental and physical slowness, hypothermia, macroglossia, hoarse voice and weight gain. Treatment should be begun at the earliest. Results of the total serum thyroxine and free thyroxine index tests confirm the diagnosis. In some cases, adrenal insufficiency may coexist, so along with thyroid hormones replacement, hydrocortisone should be administered. Moreover, therapy focuses on critical care measures to treat complications.
**Case Report:** a 75-year-old woman was admitted to the emergency department (ER) mental and physical slowness lasted almost 1 week. In the past medical history, she had a stroke 10 years ago without neurogical sequalae, obesity, dislipidemia and untreated hypertension.
At the ER, the patient presented a Glasgow Coma Scale of 9. She was hypothermic, with low respiratory rate, bradycardic, with lower and upper limbs and periorbital swelling. Blood tests showed microcytic anemia (Hb 5.4 g/dL, MCV 65.3 fl), with normal white cells count and only slightly increased in CRP (0.60 mg/dL),but rise in CPK 1759 U/L and creatinine 1.52 mg/dL. A brain CT-scan excluded ischemic or hemorrhagic events. Flumazenil was administrated to exclude a benzodiazepines intoxication without benefits. A chest-X Ray showed cardiomegaly and bilateral pleural effusion. To better investigate her symptoms, a total body CT-scan with contrast was performed. It detected a pericardial effusion, a mild perihepatic effusion and a diffused imbibition of subcutaneous tissues. The patient underwent a transthoracic echocardiogram which described an atrial compression by the pericardial effusion (thickening 1.3 cm), fortunately without cardiac tamponade. Therefore, a pericardiocentesis was performed and drained 1200cc of transudate liquid.
Based on an endocrinologist consultancy, TSH-reflex and FT4 tests were performed that showed low value, respectively 115 mIU/L and 0.4 ng/L, so a therapy with levothyroxine (T4) and liothyronine (T3) intravenously and hydrocortisone was started in the suspect of myxedema coma. Because of the persistent neurological state, rise in lactate (4.5 mEq/L), hypothermia (body temperature 34.5°), and bradycardia the patient was transferred to the intensive care unit (ICU).
During the period in ICU, she was treated first with isoprenaline, then with dopamine reaching normal cardiac frequency. Furosemide and albumina were furthermore administrated. A new echocardiogram showed ejection fraction 55% and a stable pericardial effusion. The patient also experienced severe respiratory failure requiring oxygen supplementation with High Flow Nasal Cannula (HFNC) 50L/min FiO2 35%. Finally, blood transfusions were prescribed, with rise in Hb levels up to 7.3 g/dl.
After two days at ICU because of clinical stabilization she was then transferred to our ward, where infusion of intravenous therapy with levothyroxine and liothyronine were continued, with a slight increase in FT4 (2.1 ng/L) and decrease in TSH (25.7 mIU/L) and improvement of cognitive status, swelling and respiratory failure, with progressive wean from oxygen.
The anti-thyreoperoxidase and anti-thyroglobulin antibodies turned out positive and an ultrasound showed an enlarged thyroid with non-homogeneous structure so that a final diagnosis of myxedema coma consequent to autoimmune thyroiditis was made.
As the patient clinically improved and given the normalization thyroid function, therapy with liothyronine and hydrocortisone were stopped and substituted with oral cortone acetate and levothyroxine was reduced and switched to oral administration. Moreover, following the successful treatment with intravenous furosemide and canreonate, also an important reduction in peripheral edema was observed.
Unexpectedly, despite normalization of thyroid function the patient experienced several episodes of palpitations and the ECG showed a junctional rhythm with chaotic atrial rate, associated with inverted T waves in anterolateral and inferior leads. A new echocardiogram depicted a mildly reduced systolic function due to diffused hypokinesia and inferior akinesia, a moderate left atrium dilatation and a pericardial effusion 1 cm in thickness. A following 24 hours recording ECG revealed an atrial fibrillation. A cardiologist was then consulted and diagnosed a possible recent ischemic event, without indication to coronarography. He further prescribed new oral anticoagulants (NOAC) therapy.
After 18 days she was discharged in stable condition and was then referred to an endocrinologist for her follow-up.
**Conclusion:** Myxedema coma is a life-threatening condition. It has an insidious onset with many symptoms common to neurological problems which is why it should be taken into account for a correct differential diagnosis. Although thyroid hormone therapy is critical to survival, adjunctive measures, such as ventilation, warming, fluids and corticosteroids, may be essential for survival.

## 143. RITIRATO

## 144. AN UNUSUAL CASE OF SEVERE THYROTOXIC MYOPATHY WITH DYSPHAGIA AT THE ONSET OF GRAVES' DISEASE

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Thyroid disorders are a recognized cause of endocrine myopathies, caused by both a lack and excess of thyroid hormones (1). Muscle weakness occurs in 60 to 80 percent of patients with untreated hyperthyroidism, but it is rarely clinically relevant or accompanied by muscle atrophy. Bulbar muscle involvement is an extremely rare manifestation in thyrotoxicosis and only a few cases are reported in literature. (2)
Here we present a case of severe thyrotoxic myopathy with subacute onset, with involvement of bulbar muscles and respiratory failure. A 80 years old man was evaluated in our emergency department (ED) with progressive onset of tachycardia, excessive sweating, generalized weakness, dysphagia and dysarthria for almost one month. He worked as a newsagent in the city of Milan, a former smoker of 20 pack/years and his medical record reported chronic obstructive pulmonary disease (COPD), a solitary pulmonary nodule stable at follow-up and rheumatic polymyalgia. The patient had a previous CT finding of heterogeneous thyroid gland with a normal function and unchanged at follow-up. His blood pressure was 135/70, the pulse rate 125 beats per minute, the respiratory rate 24 breaths per minute, and the oxygen saturation 94% at rest in room air. The physical examination was relevant for cachexia and edema of the lower limbs. His complete blood count showed a normocytic anemia with kidney and liver functions within normal limits. TSH was undetectable and fT4 was over 77 ng/L. Our endocrinologist consultant advised him to begin a therapy with high dose thiamazole (30mg/die for ten days) associated with propranolole and systemic steroids. However, in the following days the patient developed confusion, exertional dyspnea and worsening generalized weakness, leading him to hospitalization for treatment and further investigations. To investigate the etiology of dysphagia and dysarthria, a neck NMR with gadolinium and a fibroendoscopy were performed, excluding organic alterations of the vocal cords and of the swallowing structures. A nasogastric tube was inserted to allow for adequate nutrition and hydration. Single-fiber electromyography showed evidence of chronic myopathy, excluding myositis and myasthenia gravis. Autoimmune tests revealed positivity of anti-TSH receptor autoantibodies (7.44 KIU/L), anti-thyroperoxydase antibodies (46 KIU/L) and anti-thyroglobulin antibodies (537 KIU/L), while the rest of the autoimmune screening was negative. Thyroid ultrasonography showed the presence of three nodules (two TIRADS 3 and one TIRADS 4) and fine needle aspiration biopsy of the latter showed a TIR 4 cytologic result. Based on the results shown above, a diagnosis of Graves' disease complicated by thyrotoxic myopathy was made. Despite a proper biochemical response after two-weeks of antithyroid treatment (initial reduction of fT4 to 32.2 ng/L), the patient developed acute hypercapnic respiratory failure due to both aspiration pneumonia and to pump failure. Antimicrobial therapy (piperacilline/tazobactam) obtained infection control, but persistent pump failure led to increasing need for oxygen support up to high flow nasal cannula. Motor physiotherapy was started with gradual improvement, while percutaneous endoscopic gastrostomy was performed as a bridge to adequate logopedic rehabilitation. The patient was eventually deferred to a specialistic rehabilitation center. After three months from dismission the patient is recovering and currently is in follow up at our endocrinologic clinic.
Thyrotoxic myopathy has two main presentations, acute and chronic, the latter being by far the most common and usually taking several weeks to

months to develop after the onset of hyperthyroidism. Chronic thyrotoxic myopathy is usually characterized by proximal muscle involvement, with symmetrical limb weakness without muscle paralysis and sensory disturbance (3). Thyrotoxic myopathy can be easily misdiagnosed if there is not an already established diagnose of hyperthyroidism, with patients often referred to departments of neurology or rheumatology. Myopathy with important muscle atrophy is an uncommon presentation. Weakness usually regresses within 4 months of treatment, while atrophy takes significantly longer, depending on the degree of severity. As stated above, dysphagia and bulbar muscle deficits have rarely been reported in literature (2). The cornerstone of the treatment is the administration of antithyroid agents, given that the reversal of the thyrotoxic muscular dysfunction is to restore the euthyroid state. Prompt recognition of hyperthyroidism-related bulbar palsy is essential to avoid serious complications like aspiration pneumonia and thyroid storm.

**References:** - 1. Duyff RF, van den Bosch J, Laman DM, van Loon BJ, Linssen WH. J Neurol Neurosurg Psychiatry. 2000 Jun;68(6): 750–5. - 2. Chiu W-Y, Yang C-C, Huang I-C, Huang T-S. Dysphagia. 2004;19(2): 120–4. - 3. Alshekhlee A, Kaminski HJ, Ruff RL. 2002 Feb;20(1): 35–58, v–vi.


## 145. RITIRATO

## 146. A RARE CASE OF REFRACTORY HYPOGLYCEMIA

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A 79-year-old man was admitted to our Internal Medicine Unit for recurrent hypoglycemic episodes associated with symptoms such as night sweats, fatigue and palpitations. Patient has a history of type I refractory celiac disease, GERD, hyperemic-erosive gastropathy and duodenopathy, previous moderate-grade dysplastic polyp mucosectomy,colon diverticula, arterial hypertension, dyslipidemia, previous prostatectomy for adenocarcinom, recent hospitalizations to Geriatric Unit for profuse diarrhea with subsequent diagnosis of celiac disease; during that hospital stay he practiced corticosteroid therapy at low doses (6 mg / day) and antibiotic therapy with ertapenem.During hospitalization, infusion therapy with glucose solution and potassium chloride was set up with partial control of glycemic values. With the improvement of the glycemic profile it was performed by weaning therapy with subsequent episodes of severe hypoglycemia. In the suspicion of an insulinoma, a series of diagnostic tests were performed including the assay of the C-peptide and insulinemia performed in the fasting state and in hypoglycemia which showed an increase in the value of insulinemia. (C peptide: 3,29 ng/ml,v.n. 0,81-3,85, insulinemia: 48,1 mcU / ml, v.n. 3-25). Subsequently, the patient performed instrumental checks such as: contrast enhanced CT abdomen which showed exclusively in the liver, areas of enhancement compatible with transient hepatic attenuation Difference (THAD), upper abdomen MRI and ultrasound endoscopy that did not show changes in the pancreas, selective arteriography with intra-arterial injection of calcium gluconate with C-peptide and insulin samples on various arterial districts (splenic artery, proper hepatic artery, gastro-duodenal artery, common hepatic artery) at the time 0-30'-60'-120 ', which showed a plateau trend during all stages. The examination also revealed two peripheral areas of hypervascularization in the right hepatic lobe and one in the left lobe, compatible with the clinical suspicion of insulinoma. To better characterize this radiology evidence, the patient performed Gallium-PET which did not reveal areas of hypercaptation compatible with the clinical suspicion. Considering the high levels of fasting insulin, the literature describes the autoimmune etiology as rare causes of refractory hypoglycemia, therefore fasting anti-insulin antibodies (AAI) were performed, with values 7 times above the normal range (175 IU / ml, v.n. 0-20). Therefore, he practiced corticosteroid therapy at a dosage of 1 mg / kg / day with progressive good glycemic compensation, without the need for infusion therapy for 24 hours. In the scientific literature, rare cases of an autoimmune form of relapsing hypoglycemia have been identified in the world, called Hirata Syndrome 6, characterized by high levels of circulating insulin, positivity of anti-insulin antibodies (AAI) and the absence of pancreatic alterations. Hypoglycemia usually occurs in post-prandial phase, but can also occur in the fasted state 3.The cases reported in the world are about 380 with a significant prevalence in the Japanese population. It can occur in patients with other autoimmune (LES, rheumatoid arthritis, ANA positivity) or haematological diseases (generally monoclonal gammopathies or multiple myeloma 4), secondly to exposure to drugs containing a sulfhydryl group 4 (such as imipenem, captopril, isoniazid, penicillins etc. 2) or the use of alpha-lipoic acid products. It would seem that exposure to drugs containing thiol groups causes a decrease in the disulfhydryl bridges that bind the A and B chains of insulin, making it more immunogenic and promoting the production of specific antibodies. In addition to corticosteroid therapy, immunosuppressive drugs such as aziatoprine or plasmaferesis can be used 5. This pathology undergoes a spontaneous remission after about 1-3 months (82% of cases 3).The clinical case described opens up a broad reflection on the importance of recognizing rare diseases even in internal medicine departments, this appears fundamental in those complex patients where it is not possible to arrive at a clear clinical diagnosis and who risk waiting for years in the hospitals to get an certain diagnosis.

Bibliography
1.Uchigata Y, Hirata Y, Iwamoto Y (2009) Drug-induced insuline autoimmune syndrome. Diabetes Res Clin Pract 83: e19–e202.Lupsa BC, Chong AY, Cochran EK et al (2009) Autoimmune forms of hypoglycemia. Medicine 88: 141–1533.Uchigata Y, Eguchl Y, Takayama-Hasuml S, Omori Y (1994) Insulin autoimmune syndrome (Hirata disease): clinical features and epidemiology in Japan. Diabetes Res Clin Pract 22: 89–944.Lupsa BC, Chong AY, Cochran EK et al (2009) Autoimmune forms of hypoglycemia. Medicine 88: 141–1535. Uchigata Y, Hirata Y (1999) Insuline autoimmune syndrome (IAS,Hirata disease). Ann med Intern 150: 245–2536.Gullo D, Evans JL, Sortino G, Golfine ID, Vigneri R. Insulin autoimmune syndrome (Hirata disease) in European Caucasians taking α-lipoic acid.

# EPATOLOGIA

## 147. HEART RATE VARIABILITY AS A MEASURE OF THE SYMPATHO-VAGAL BALANCE IN PATIENTS WITH CIRRHOSIS AND PORTAL HYPERTENSION

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**Background and Aims**: Activation of the autonomic nervous system (ANS) in patients with cirrhosis and portal hypertension is linked to an hyperdynamic circulation leading to reduction in mean arterial pressure. Heart rate variability (HRV) is a clinically validated non-invasive method to assess the sympatho-vagal balance. To investigate the correlation between the time-domain HRV parameters, a measure of ANS deregulation, and their correlation to the stage of liver disease and of portal hypertension, we studied a cohort of patients with cirrhosis, taking into account the possible role of treatments.

**Patients and Methods:** In this prospective, observational cohort study, 157 outpatients with a clinical diagnosis of non-alcoholic cirrhosis of mixed etiology (HCV, HBV, NASH) were assessed consecutively by abdominal ultrasound and by upper GI endoscopy to search for esophagogastric varices (EVs). 24-hour ECG Holter monitoring with HRV measurement according to time domain analysis were performed in all patients. Three HRV time-domain parameters (standard deviation of the NN intervals, SDNN; root mean square successive difference of NN intervals, RMSSD;-standard deviation of averages of NN intervals, SDANN) were considered. Sixteen patients with large EVs underwent measurements of the hepatic venous pressure gradient (HVPG) at baseline and after 45-day therapy on carvedilol, and the HRV parameters were assessed at the same time points.

**Results:** The stage of liver dysfunction, as expressed by Child Pugh class (CP) or by MELD score (MS), was directly related to RMSSD and inversely

related to SDANN. Presence of ascites was inversely related to SDANN and to SDNN, while the presence of porto systemic encephalopathy (PSE) was directly related to RMSSD and inversely related to SDNN 24h. Treatment with spironolactone or furosemide was directly related with RMSSD and inversely related with SDANN and SDNN, while treatment with carvedilol had an inverse relation with SDANN. Presence and size of EVs had an inverse relation to SDANN and SDNN. Upon multivariate analysis associations between SDANN and CP class, varices dimensions and ascites were all confirmed.
Subjects undergoing EVs ligation presented an inverse relation with SDANN and SDNN. In the subgroup of patients undergoing HVPG measurement, formed by 11 responders and 5 non-responders to carvedilol, the pressure gradient was not related only to heart rate and other HRV parameters.
**Conclusion:** The time-domain HRV parameters, when measured in patients with cirrhosis at different stage of disease, confirm the presence of ANS alteration, and their correlation to the stage of liver disease and to portal hypertension suggesting a role of the ANS in the vicious circle leading to hepatic decompensation. The role of HRV in predicting tolerability of non-cardioselective beta-blockers used in preventing portal hypertensive bleeding needs further assessment.

## 148. DETERMINANTS OF CLINICAL COMPLEXITY IN HOSPITALISED CIRRHOTIC PATIENTS

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**Background:** Liver cirrhosis may be an example of clinical complexity (CC) due to its various clinical manifestations and due to its frequent association with other multiple chronic conditions (MCC). Additionally, socioeconomic factors (e.g., educational level, marital and employment status), though poorly described, may have a significant impact in these patients. Finally, there are no data regarding the prevalence of comorbidity (i.e., additional conditions in reference to an index disease) and multimorbidity (i.e., co-occurrence of multiple diseases in which no one holds priority) in patients with liver cirrhosis. On these bases, we sought to determine the rate of co- and multimorbidity depending on the aetiology of cirrhosis and to highlight potential clinical and sociodemographic differences between the groups.
**Methods:** We have prospectively analysed sociodemographic and clinical characteristics of patients with liver cirrhosis, according to the International Classification of Diseases (ICD) 9 codes, admitted to our internal medicine ward in 2017-2019; then we divided patients according to the aetiology of cirrhosis, namely alcoholic, infectious, and non-alcoholic fatty liver disease (NAFLD) related. Patients without liver cirrhosis were used as control group. The prevalence and risk factors for co-multimorbidity were assessed.
**Results:** Overall, 1451 patients were enrolled. Of these, 187 (median age 78 years, IQR 66-84; 88 females) had liver cirrhosis. Patients with cirrhosis displayed higher Cumulative Illness Rating Scale (CIRS) comorbidity (p=0.003) and severity (p<0.001) indexes, and lower educational level (p=0.002) compared to the whole cohort. Patients with alcohol cirrhosis were significantly younger than patients with cirrhosis of other aetiologies (p<0.001) and more commonly males. Comorbidity was more prevalent in patients with alcohol cirrhosis, and multimorbidity was more prevalent in infectious and NAFLD cirrhosis (p=0.015). In a multivariable model for factors associated with multimorbidity, a CIRS comorbidity index >3 (OR 2.81, p=0.024) and admission related to cirrhosis (OR 0.19, p=0.002) were the only significant associations.
**Conclusions:** We observed that patients with liver cirrhosis had a higher disease burden and a lower educational level. The different patterns of co- and multimorbidity might translate into different pathways of care.

## 149. LIVER TRANSPLANTATION FOR HEPATOCELLULAR CARCINOMA: OUTCOME AND PROGNOSTIC FACTORS FOR RECURRENCE

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**Background and Aim:** Hepatocellular carcinoma (HCC) accounts for approximately 75% of primary liver cancers1 and is the fourth leading cause of death from malignancy worldwide. The 5-year survival rate is around 10 – 15%2, often due to late diagnosis with detection of advanced neoplastic disease. Liver transplant (LT) is now universally recognized as a curative treatment in some patients3-4. The post-transplant recurrence rate of HCC is very wide, between 5 and 30%, due also to different listing policies. The aim of our study was to evaluate the recurrence rate of HCC after LT in Verona and to identify the main risk factors for recurrence.
**Methods:** 230 patients (84% male, mean age 59 years) with HCC transplanted between February 2007 and December 2020 were followed until recurrence or death. Etiology of cirrhosis was viral in 57%, alcoholic in 29.6% and metabolic (NAFLD) in 12.6%. 69% of patients had undergone pre-transplant treatments (PEI, RFA, TACE, TARE, resection). The majority of patients had MELD scores ≤19, while 4.8% had scores ≥30. Milan criteria were applied for listing. Etiology, biochemical data, pre-transplant treatments, and histological evaluation of the native liver were collected.
**Results:** The mean follow-up was 47±39 months, with 77.4% survival. After LT, 9.1% of patients had HCC recurrence, and 22.6% died. Average survival of patients without HCC recurrence was 48.6±39.4 months, with recurrence was 23±25.1 months. Among those who had HCC recurrence, 57% of patients had recurrence within the first 12 months after transplantation; 19% at 12-24 months, 19% at 24-36 months, 5% at 36-60 months. In 66.6% of patients with relapsed HCC, the tumor started with extrahepatic localizations (lynphonodes, lungs). TACE and RFA were the most frequently performed treatments (respectively 76% and 49% of patients). 26% of patients had undergone resection, 7,8% PEI and only 1.3% TARE. In the multivariate analysis, factors that predicted HCC relapse were: extranodal microvascular invasion (p< 0,001), size of the largest nodule (p< 0.005) and number of pre-transplant local-regional treatments (p< 0,04). Patients with higher pre-LT MELD and diabetes had a worse outcome (p = 0.028) and poorer survival (p = 0.021).
**Conclusions:** In our 13 years experience, recurrence of HCC after transplantation was low (9.1%). Number of pre-transplant treatments, size of nodules and microvascular invasion were the only predictors of recurrence of HCC after transplantation.

## 150. THE IMMUNOLOGICAL MICROENVIRONMENT OF HEPATOCELLULAR CARCINOMA IN PATIENTS WITH DIFFERENT CIRRHOSIS ETIOLOGY: AN OBSERVATIONAL STUDY

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**Introduction:** Hepatocellular carcinoma (HCC) is the second leading cause of cancer-related death. Most cases (90%) of HCC arise in the setting of a chronically liver disease. The advanced stages of HCC are amendable only to systemic treatment. Systemic management has been revolutionized by immune-based therapies. However, a recent meta-analysis of three randomized phase III clinical trials that tested inhibitors of PD-L1 or PD1 in more than 1,600 patients with advanced HCC revealed that immune therapy did not improve survival in patients with non-viral HCC.
**Aim:** The aim of the study is to identify differences in immunological microenvironment of patients with HCC according to etiopathogenesis of hepatic cirrhosis that could identify different pattern of response to immunotherapy.

**Materials and Methods:** We prospectively analyzed 50 leukocyte subpopulations using flow cytometric technique in a cohort of 111 consecutive HCC cirrhotic patients with different stages and etiopathogenesis. The Mann-Whitney U test was used to evaluate differences between populations of patients with HCC.
**Results:** We divided HCC patients with cirrhosis into three principal sub population according to etiology of liver disease: alcoholic, viral (HCV/HBV) and NAFLD/NASH. We found significant differences in leukocyte subpopulation between alcoholic and viral etiology and the rest of population. In particular, in subpopulation of alcoholic etiology there were increased levels of PMN ($p<0.01$), monocytes ($p<0.01$) and NKT cells CD57+RA-(4-8-) ($p=0.011$), while in viral etiology subpopulation there were increased levels of T cells CD57-RA+(4-8-) ($p=0.007$) and T cell CD3+(4-8-) ($p=0.009$). No difference in metabolic population.
**Conclusions:** These data suggest that liver disease with different etiopathogenesis there are different immunological microenvironment. Innate and innate-like cells are the principal regulators of immune response in alcoholic HCC. Adaptive immune system is predominant in viral etiology, instead. This could suggest that differences in cancer-mediated immune escape could explain the different response to immunotherapy and may be helpful in identification of responder patients of new HCC therapy.

## 151. A CHALLENGING CASE OF METHOTREXATE-INDUCED LIVER INJURY

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**Introduction:** We describe the case of a 78-year-old man with signs of portal hypertension who was admitted to our Internal Medicine ward.
**Case Report:** In November 2021 a 78-year-old man developed hyporexia, nausea, and abdominal distension. His previous medical history was significant for sero-negative arthritis and Horton's arteritis treated with methotrexate, cholecystectomy, type II diabetes mellitus, chronic kidney disease, and no history alcohol abuse. He underwent an abdominal ultrasound with evidence of splenomegaly (splenic length was 13.3 cm) and liver alteration with an uneven echo structure, lumpy profiles, irregular margins, and significant ascitic effusion. Subsequently, he underwent a CT scan that confirmed the liver structural alterations with ascitic decompensation and patency of the hepatic and portal veins. In December 2021 he underwent large-volume paracentesis with the finding of elevated white blood cell count in ascitic fluid and suspicion of spontaneous bacterial peritonitis. Thus, he was admitted to our Internal Medicine ward. At blood tests, we found increased inflammatory biomarkers, impaired renal function, and reduced hepatic synthesis with normal liver enzymes. To investigate the aetiology of the ascitic effusion, he underwent the following tests: autoantibody screening with positive ANA with titer 1/160 (ASMA, AMA, LKM, ENA, ANCA, anti-dsDNA, C3, C4 resulted negative), anti-Schistosoma antibodies, tumor markers (CA19.9, CEA and alpha-fetoprotein) and serology for hepatotropic viruses (HCV and HBV) that were all negative. We performed an echocardiography that excluded the cardiogenic etiology of portal hypertension. The administration of methotrexate was suspended due to the possible toxic etiology of the liver disease, and clinical improvement was observed. After his discharge, in February 2022, he underwent transjugular liver biopsy that showed chronic hepatitis with mild activity with a probable toxic/pharmacological etiology, compatible with damage caused by methotrexate. He also underwent hepatic veins catheterization and hepatic manometry with a normal hepatic venous pressure gradient (HVPG). Esophagogastroduodenoscopy showed esophageal varices. Therefore, we hypothesized a diagnosis of non-cirrhotic portal hypertension. Low-dose steroid therapy was introduced to control the autoimmune and hepatological diseases.
**Conclusion:** Portal hypertension (PHT) is a clinical syndrome defined by a portal venous pressure gradient between the portal vein (PV) and inferior vena cava exceeding 5 mmHg. Cirrhotic PHT is associated with an elevated HVPG predominantly due to raised sinusoidal resistance, while in the non-cirrhotic PHT (NCPH), HVPG is normal or only mildly elevated. The diseases leading to NCPH are primarily vascular and classified anatomically based on site of resistance to blood flow, as prehepatic, hepatic (further subdivided into pre-sinusoidal, sinusoidal, and post-sinusoidal), and post-hepatic. Although schistosomiasis is the most common cause of NCPH worldwide, a wide spectrum of systemic diseases and medications can lead to the development of NCPH. Methotrexate is a cause of drug-induced hepatic (sinusoidal) NCPH. No single test is sufficient to diagnose NCPH, which is challenging and mainly a diagnosis of exclusion. The proposed diagnostic criteria for NCPH are: 1) presence of unequivocal signs of portal hypertension, 2) absence of cirrhosis, advanced fibrosis, or other causes of chronic liver diseases, and 3) absence of thrombosis of the hepatic veins or of the portal vein at imaging. From a pathophysiological point of view, there are different suggested mechanisms leading to the development of hypertension in the portal system by increased vascular resistance (sinusoidal compression, sinusoidal occlusion/infiltration, vascular remodeling) or increased flow through arterio-portal shunts. The management of NCPH is based on removing the potential cause and preventing and treating PHT complications. Patients are typically managed in the same manner as those with portal hypertension due to cirrhosis. Our patient was referred to the hepatology clinic to monitor blood tests and optimize the treatment of portal hypertension.

## 152. THE IMPACT OF BACTERIAL INFECTIONS ON CIRRHOSIS COMPLICATIONS IN A COHORT OF CIRRHOTIC PATIANTS IN A TERTIARY CARE CENTER

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**Introduction:** Bacterial infections represent a major cause of morbidity and mortality in patients with liver cirrhosis. Moreover, infections sustained by multi-drug resistant organisms (MDROs) are dangerously increasing globally in the last few years. Our aim was to assess the incidence of bacterial infectious events in a cohort of cirrhotic patients, the incidence of MDROs and the association with hepatic complications in a center in which an antibiotic stewardship program was introduced during the follow-up.
**Methods:** A retrospective analysis on prospectively collected data from January 2017 to December 2020 has been conducted on 229 consecutive cirrhotic patients, followed in our Liver Unit as inpatients or outpatients.
**Results:** 72 patients (31.4%) developed at least one bacterial infection during the study period (median follow-up 4.3 y). 101 bacterial infections were recorded, 31.7% occurred in patients with a previous infection during the study period. Sepsis was the most frequent infection (25%), followed by pneumonia (20%), spontaneous bacterial peritonitis (18%), urinary tract infections (12%). Patients with at least one infection in each year of observation were older ($66.2\pm13$ y, $p < .016$), with higher MELD and Child-Pugh scores at the enrolment ($p < .001$). 15 cases (14.8%) among all infections were sustained by MDROs. No significant differences between patients with MDROs vs non-MDROs infections were detected, with the exception of gender and chronic obstructive pulmonary disease. 16 patients were found to be MDROs carriers on rectal swabs. Liver complications such as ascites ($p < .001$), hepatorenal syndrome ($p <.001$) and hepatic encephalopathy ($p <.001$), occurred more frequently in infected than in non-infected patients.
**Conclusions:** Our study confirms the epidemiological burden of bacterial infections in cirrhotic patients and the strong interconnection between infections and the development of liver complications. Therefore, cirrhotic patients require closer clinical surveillance, including a routine rectal swab to identify colonized patients and avoid the horizontal spread of MDROs and to promote a rational approach to empirical antibiotic therapy according to the stewardship programs.

## 153. ROLE OF LIVER STIFFNESS IN PORTO-SINUSOIDAL VASCULAR LIVER DISEASE ASSOCIATED WITH AMYLOIDOSIS

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In autopsy series, 56–95% of patients with amyloidosis had extracellular deposition of amyloid fibrils in the liver, and rare cases associated with Non-Cirrhotic Portal Hypertension have been described. Portal Hypertension is probably due to massive perisinusoidal amyloid deposits which involve increased resistance to blood flow. Recently, in a multicenter retrospective study (Elkrief L. et al. Hepatology 2021;74: 364), Liver Stiffness Measurement (LSM) has been proposed to differentiate between liver cir-

rhosis and Porto-Sinusoidal Vascular Liver Disease (PSVD), and a cut off < 10 kPa strongly suggests PSVD in patients with signs of portal hypertension. In this cohort of 155 patients with PSVD, no case of amyloidosis has been reported.
Recently we observed two cases (cases 1 and 2) of amyloidosis associated with Non-Cirrhotic Portal Hypertension. All patients underwent liver biopsy that confirmed amyloidosis by Congo red staining and excluded liver cirrhosis. Both patients showed esophageal varices and ascites and fulfilled Vascular Liver Disease Interest Group criteria for PSVD diagnosis. Surprisingly, LSM values were extremely high (136 and 69 Kpa, respectively) not in agreement with the observations of Elkrief and coll. We observed another case (case 3) of histologically confirmed hepatic amyloidosis, not associated with portal hypertension, nor with cirrhosis, with also high value of LSM (47 kPa).
**Conclusion:** Porto-Sinusoidal Vascular Liver Disease associated with amyloidosis seems associated with elevated values of LSM and seems to represent a peculiar elastographic phenotype among the forms of PSVD, possibly due to infiltrative pathogenesis. Observations on larger case series are needed to confirm this hypothesis.

| Patient number | LSM (IQR) kPa | Age (Years) | Liver Histology | Presence of a cause of Cirrhosis | Extrahepatic Condition associated with PSVD | Specific* signs of Portal Hypertension | Nonspecific* Signs of Portal Hypertension |
|---|---|---|---|---|---|---|---|
| 1 | 136 | 60 | Massive deposition of eosinophilic amorphous material Congo red +<br><br>Atrophic hepatocytes with no signs of cirrhosis.<br><br>Moderate perisinusoidal fibrosis | None | Multiple Myeloma | F1 esophageal varices without red marks | Splenomegaly (15 cm)<br><br>Ascites |
| 2 | 75 | 69 | Deposition of amorphous eosinophilic material, Congo Red +<br><br>Marked atrophy of hepatocytes with no signs of cirrosis | None | Systemic scleroderma | F2 esophageal varices without red marks<br><br>Congestive gastropathy<br><br>Recanalization of the umbilical and spleno-renal shunt | Thrombocytopenia (138 x 10^9)<br><br>Splenomegaly (19.6 cm)<br><br>Moderate ascites |
| 3 | 68.5 | 47 | Deposition of positive Congo red amyloid material<br><br>No sign of cirrhosis | None | None | None | None |

* According to Vascular Liver Disease Interest Group (VALDIG) criteria for Porto-Sinusoidal Vascular Liver Disease (PSVD) diagnosis.
LSM=Liver Stiffness Measurement

## 154. LIVER STIFFNESS RELATES TO AN INCREASED RISK FOR ATHEROSCLEROTIC CARDIOVASCULAR DISEASE IN PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE

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**Aim:** non-alcoholic fatty liver disease (NAFLD) is one of the end-target organ damage of lipid metabolism alterations. There are no clear data about the connection between steatohepatitis and heart involvement. However, many risk factors overlap in both diseases. Therefore, a possible connection between the two organs may be plausible.
Our purpose was to evaluate the risk of cardiovascular disease in NAFLD.
**Methods:** We studied 41 patients (26 male, mean age 58.71±13.56 SD) who presented NAFLD detected FLI score and by ultrasound compared to 88 controll patients who were NAFLD negative (55M, mean aged 57.39± 9.91 SD). We evaluated liver stiffness as fibrosis marker measured by share wave technology. To evaluate the cardiovascular risk we calculated for each patient the Atherosclerosis Cardiovascular disease score (ASCVD-10-yr).
**Results:** in NAFLD group, arterial essential hypertension was found in 58% (n.=24) and diabetes in 34% (n.=14); no differences in control group. However, patients with NAFLD had an increased liver fibrosis (median metavir class 1 [IQR 1-3], p<0.05), and an increased cardiovascular risk compared to controls (ASCVD-10-yr 17.21 ± 17.99% vs 7.93 ± 7.68, p<0.05). The Metavir class was directly correlated to ASCVD-10-yr (Spearman r 0.37, p<0.01). The same direct correlation was found between ASCVD-10-yr and absolute liver stiffness values evaluated as kPa (Pearson r 0.39, p<0.05).
**Conclusions:** Our data suggest that NAFLD may be associated to a reduced life-expectancy also due to cardiovascular disease. These data suggest to evaluate the cardiovascular disease in the course of liver steatosis. Thus, a comprehensive evaluation may be useful in order to optimize the tailored therapy for these patients. Further prospective studies are needed to confirm our data.

## 155. PREVALENCE OF PORTAL VEIN THROMBOSIS IN NON-ALCOHOLIC FATTY LIVER DISEASE: A META-ANALYSIS OF OBSERVATIONAL STUDIES

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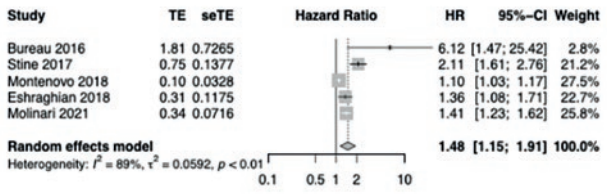
**Introduction:** Portal vein thrombosis (PVT) is a common complication of cirrhosis because of significant modification in the hemostatic balance, especially in decompensated stage. Furthermore, patients with non-alcoholic fatty liver disease (NAFLD) seem to be at higher risk of PVT development than patients with cirrhosis due to other causes. Nevertheless, definitive data in favor of an increased rate of PVT in NAFLD are missing. This meta-analysis attempted to estimate the prevalence of PVT in patients with NAFLD.
**Methods:** We systematically searched PubMed, Scopus and Web of Science databases from the inception date to April 20th 2022 using predefined keywords to identify observational cohort studies. Meta-analysis was performed using random-effects modelling.
**Results:** We included five articles published over the past 10-year period and reported a total of 177080 patients from five different countries. NAFLD patients were 23931 (13,5%) and PVT incidence in this population was 8.2% (n=1971). Meta-analysis demonstrated a significant positive association between NAFLD and PVT (OR 1.48, 100% CI 1.15-1.91 p < 0,01). The between-study heterogeneity was substantial (I2 = 89%).
**Conclusions:** This meta-analysis suggests that NAFLD-cirrhosis is associated with an increased risk of developing PVT. Further research is required to understand the complex link between NAFLD and PVT development.




## 156. AVATROMBOPAG BEFORE PROCEDURES IN PATIENTS WITH LIVER CIRRHOSIS AND SEVERE THROMBOCYTOPENIA: FIRST LESSONS FROM REAL-PRACTICE

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**Introduction:** Severe thrombocitopenia (platelet count <50 x 10^9/L) occurs in 5-10% of patients with liver cirrhosis and has been associated with post-procedure bleeding after invasive procedures, like liver biopsy. Platelet transfusion is considered the standard treatment, but has major limitations such as short lifespan, limited availaibility and potential adverse effects. In 2021 avatrombopag, a second generation, orally bioavailable, small molecule thrombopoietin receptor agonist, was approved in Italy for adult patients with chronic liver disease and thrombocytopenia who are scheduled to undergo an invasive procedure, avoiding the need of platelet transfusions. In our report we describe the experience with avatrombopag in two clinical practice setting not included in the pivotal trials.
**Patient 1:** A 70-year-old man with an history of liver cirrhosis related to hepatitis C virus infection, Child-A stage, associated with esophageal varices at high risk of bleeding and early-stage hepatocellular carcinoma. His platelet count was 33 x 10 ^9/L. He started avatrombopag 60 mg daily for 5 days and platelet count rise up with a peak of 102 x 10 ^9/L at day 12. He underwent endoscopic band ligation at day 13, with no complications. At day 17, he underwent transarterial embolization of hepatocellular carcinoma when his platelet count was still 63 x 10 ^9/L, with no complications. No platelet transfusions were required before or after the procedures and duplex ultrasound excluded portal vein thrombosis or portal flow reversal.
**Patient 2:** A 65-year-old man with an history of alcoholic cirrhosis, Child-B

stage, complicated by partial chronic vein thrombosis, underwent diagnostic workup before waiting list registration for liver transplantation. Colonoscopy showed a lateral spreading tumor in the sigmoid colon of 1.2 cm diameter. His platelet count was 36 x 10^9/L. He started avatrombopag 60 mg daily for 5 days and platelet count rise up with a peak of 80 x 10 ^9/L at day 13. Endoscopic removal of lateral spreading tumor occurred on day 14 without bleeding complications or needed rescue platelet transfusions. Computed tomografy scan performed after avatrombopag treatment showed no progression of portal vein thrombosis.
**Discussion and Conclusions:** The first case undeline the possibility of carrying out a second invasive procedure within the same course of treatment with avatrombopag. In this case, the effect on the platelet count was particularly pronounced (up to three times basal values) and allowed to cross the procedural window (days 10–13) tested in pivotal trials.
In the second case we described a safe use of avatrombopag in a patient with pre-existing portal vein thrombosis, a population that was excluded from registrative trials. Since eltrombopag, a first generation thrombopoietin receptor agonist, was halted because of an increased incidence of portal vein thrombosis in ELEVATE trials, safety data on this patients setting are urgently needed for second generation thrombopoietin receptor agonists.
In conclusion, we need more real practice data about the use of avatrombopag in patients with cirrhosis and thrombocytopenia in clinical settings not investigated in registrative trials.

## 157. BACTERIAL INFECTIONS AS A PREDISPOSING FACTOR FOR THE DEVELOPMENT OF PORTAL VEIN THROMBOSIS IN CIRRHOTIC PATIENTS: A PROSPECTIVE STUDY

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**Background and Aims**: Non-malignant portal vein thrombosis (PVT) is one of the complications of liver cirrhosis. The predisposing factors for PVT in cirrhotic patients are not entirely clear. The aim of this study was to identify possible clinical risk factors related to the development of PVT in patients with liver cirrhosis.
**Method:** We data of 229 in our Liver Unit in Verona, enrolled from 2017 to 2020 with an median follow-up of 3.3 years. PVT was determined by ultrasound, computer tomography and/or magnetic resonance imaging. Malignant PVT was considered an exclusion criteria.
**Results:** Of the 229 patients with liver cirrhosis 26 (11%) developed non-malignant PVT. 17 (65%) were male, with a mean age of 67.3 ± 12.3 y. In patients with non-neoplastic PVT compared to the remaining population, we observed that the prevalence of bacterial infections (sepsis, pneumonia, urinary tract infections, cholangitis, gastroenteritis, bacteriaemia, spontaneous bacterial peritonitis) that required hospitalization was significantly higher (50% vs 27.2%; p = 0.017). In the multivariate logistic regression analysis, when adjusted for age, sex, type 2 diabetes mellitus and chronic kidney disease, PVT was significantly and independently associated with bacterial infections (OR 2.72 [95% CI 1,12 to 6.57; p = 0.026]) and (HCC) (OR 2.87 [95% CI 1.11 to 7.41; p = 0.029].
**Conclusion:** Our study showed that bacterial infections requiring hospitalization in patients with liver cirrhosis could be a predisposing factor for the development of PVT. Further studies will be needed to confirm this evidence.

## 158. NEUROLOGICAL STATE DETERIORATION IN A CIRRHOTIC PATIENT: BEYOND HEPATIC ENCEPHALOPATHY, HYPERCALCEMIA AS A RARE MANIFESTATION OF HEPATOCELLULAR CARCINOMA

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**Introduction:** Hypercalcemia is a common clinical problem with symptoms ranging from an asymptomatic presentation to coma in severe cases. In more than 90% of cases, it is sustained by primary hyperparathyroidism and paraneoplastic syndromes, the latter often associated with squamous cell carcinoma, multiple myeloma, renal, bladder, breast, or ovarian carcinomas; conversely, hepatocellular carcinoma (HCC) presents with hypercalcemia in only prevalence 4-8% of cases. Hepatic encephalopathy (EE) is a very frequent complication of cirrhosis, especially in presence of decompensation, HCC or infection.We present a tricky case of a cirrhotic patient affected by HCC and presenting with neurological state deterioration consequent to paraneoplastic severe hypercalcemia secondary to HCC.
**Case Report:** A 60-year-old man was admitted to the Emergency Department for deterioration of the cognitive status, polyuria and hyporexia that occurred over the last 3-weeks.In his recent medical history, he had a focal recurrence of Hepatocellular Carcinoma (treated by 4 sessions of radiofrequency) and a finding of multiple focal micronodular alterations of lung parenchyma at a CT scan performed as HCC follow-up. In his past medical history, he underwent surgical resection for a parathyroid adenoma in 2009. In the emergency department, the general examination was unremarkable, whereas the neurological one excluded any focal defects but showed a status of confusion, impairment of cognition and drowsiness, configuring a state of encephalopathy. Blood exams showed increased inflammatory markers (CRP 5.12 mg/dL; WB count 28.2 10e9/L). A brain CT scan excluded an acute neurological event leading to the suspect of a portosystemic encephalopathy caused by an infection; therefore, Ceftriaxone and cathartic therapy were initiated. In our ward the antibiotic course was completed, however urine and blood cultures were negative, and the patient did never experience fever. In addition, the neurological status did not improve despite the cathartic therapy. On the contrary, over the days the patient's mental status worsened, with severe impairment in consciousness, and blood tests highlighted the presence of severe hypercalcemia (corrected serum calcium 14.8 mg/dL). Intravenous hydration and diuretic therapy were promptly started; however, because of both biochemical and clinical lack of improvement, an urgent dialytic therapy was initiated, with only partial response (corrected serum calcium dropped to 13.1 mg/dL). Subsequently, the patient was administered intravenous bisphosphonate, with progressive improvement in cognitive status till complete recovery, accompanied by a reduction in calcium levels until normalization. To investigate the etiology of hypercalcemia, blood tests were performed and showed PTH values at the lower limits of normality (7.4 ng/L), 25- OH-vitamin D in a normal range (48 ng/L), low levels of 1,25-OH vitamin D (16.9 µg/L), and normal values of calcitonin and TSH (0.8 mIU/L). Given the severity of hypercalcemia and the oncologic history of the patient, in the suspect of paraneoplastic disease, a PET-FDG was requested, with hyper fixation at the site of HCC, diffuse uptake in various skeletal areas and in the multiple pulmonary foci bilaterally. In addition, Total-body bone scintigraphy depicted a picture compatible with metabolic-bone pathology, excluding the presence of lytic lesions. An endocrinological evaluation concluded for a hypercalcemia consequent to paraneoplastic production of PTHrp by HCC, a rare event described in literature, even though its determination was not assessed because not routinary tested at the local laboratory. Indeed, as suggested by all blood tests and imaging studies performed, other causes of hypercalcemia as recurrence of primary hyperparathyroidism, skeletal lytic lesions, macrophage 1-Alpha-Hydroxylase activation in the setting of granulomatous or infectious pathology were excluded, the latter characterized by high 1,25-OH vitamin levels and low PTH. Given the concomitance of the known hepatic neoplasm and the diffuse pulmonary uptake at the PET scan, the pulmonary lesions were classified as metastasis from Hepatocellular Carcinoma, with no indication to further invasive investigations by both pneumologists and surgeons.After 18 days of hospitalization, the patient was discharged with complete recovery of his mental status and normalization of serum calcium levels. He was referred to the hepatology and endocrinology clinics to continue the diagnostic and therapeutic course for the HCC and to evaluate the necessity of a new bisphosphonate administration according to calcium monitoring.
**Conclusions:** Despite very rarely, hypercalcemia could present in patients with Hepatocellular Carcinoma, so that in cirrhotic patients with this neoplastic complication a deterioration in the neurologic state should not be quickly classified as EE, but a suspect of alternative causes should be considered. Anamnesis and clinical presentation are crucial to rise the suspicion of paraneoplastic hypercalcemia; however, blood tests finally drive the diagnosis.

## 159. CURMUMIN-ASSOCIATED ACUTE CHOLESTATIC HEPATITIS IN ABCB4 MUTATION

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**Rationale:** intrahepatic cholestasis can have several etiologies and the differential diagnosis is often difficult. Drug-induced liver injury (DILI) is a recognized cause of cholestatic hepatitis. In rare cases, cholestasis may be due to genetic factors; in particular, variants of Multi-Drug Resistance glycoprotein-3 (MDR3, codified by ATP-binding cassette subfamily B member 4, ABCB4, gene) are associated with many biliary disorders: from Familial Intrahepatic Cholestasis type-3 (PFIC-3) and intrahepatic cholestasis of pregnancy (ICP) to DILI and even adult biliary cirrhosis and intrahepatic cholangiocarcinoma. In severe forms, patients at risk for developing progressive liver disease may need to be referred to liver transplant.
The established trend of growth in assumption of herbal dietary supplements (HDS) by the general population underlines the necessity of timely suspicion and early recognition of their complications. Specifically, turmeric-derived substances, such as curcumin, are among the most consumed. Several case reports have already described cases of DILI induced by these substances.
In this case report, we describe a case of severe cholestatic hepatitis caused by turmeric-derived products, in a woman carrying a mutation in the ABCB4 gene.
**Clinical presentation and diagnosis:** a 46 year-old woman presented to our emergency department with chief complaints of pruritus and jaundice associated with urine and stool dyschromia. She denied alcohol abuse and referred no current use of medications. Her past medical history was significant for Gilbert's syndrome and past episodes of ICP treated with ursodeoxycholic acid (UDCA). No clinical (e.g. ascites, encephalopathy) or other biochemical (e.g. prolonged coagulation times) signs of liver failure were present.
Her blood tests showed severe acute hepatitis with predominantly direct hyperbilirubinemia. Serological and antigenic tests for viral and autoimmune hepatitis were negative. Abdomen ultrasonography (US) and magnetic resonance cholangiopancreatography (MRCP) only revealed a mild degree of liver steatosis, and clearly excluded extrahepatic cholestasis. There were no clinical, biochemical, genomic or radiologic stigmata of hemochromatosis or Wilson's disease. After a more thorough history investigation, the patient reported the recent consumption of a ketogenic diet and the use of turmeric-derived HDS, which had been discontinued upon hospital admission. Liver biopsy was performed to test the plausibility of our hypothesis of curcumin-induced DILI. The histopathologic exam revealed acute hepatitis with cholestasis, compatible with DILI, and the research for predisposing genetic factors showed a homozygous mutation in the ABCB4 gene, along with a heterozygous mutation in the tight junction protein 2 (TJP2) gene.
**Conclusions and considerations:** Both genetic factors and curcumin liver toxicity contributed to cause severe cholestasis in this patient. Accordingly, we observed signs of clinical and biochemical regression after drug withdrawal, although only after several weeks. ABCB4 mutations can predispose to different forms of cholestasis, with several environmental factors potentially acting as triggering events. In our patient, curcumin exposure might have played such a role. As mentioned above, turmeric-derived HDS have already been reported as potential causes of DILI. Differently from other reports in which liver injury rapidly decreased after curcumin withdrawal, in this case, the severity of jaundice and the long latency of reversion are probably due to the genetic predisposition. Further studies are needed to investigate potential toxicities of HDS, especially in light of their increasing popularity.
In conclusions, identifying the genetic background of recurrent cholestatic episodes can be determinant in setting appropriate follow-up measures, aimed at preventing severe potential complications such as liver failure and malignancies.

## 160. PREDICTORS OF EARLY HOSPITAL READMISSION IN PATIENTS WITH DECOMPENSATED CIRRHOSIS DISCHARGED AFTER AN ACUTE DECOMPENSATION

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**Background and Aims**: Patients with decompensated cirrhosis are at high risk of emergent hospitalizations leading to a very economic and social burden. For patients with cirrhosis who survive their hospitalization, the period after discharge is at high risk of readmission due to the development of a new complication or a suboptimal management during the previous hospitalization. This study aimed to determine the incidence of readmission up to 1 year after discharge from an index hospitalization and to identify predictors of liver-related early readmission (within 30 days).
**Method:** We performed a post-hoc analysis in a prospectively collected cohort of patients admitted to hospital for acute decompensation (AD) complicated or not by acute-on-chronic-liver-failure (ACLF). After discharge, patients were prospectively followed until death, liver transplantation or up to a maximum of 1 year for recording any emergent hospitalization and related cause. Laboratory and clinical data at admission and discharge of the index hospitalization and the occurrence of nosocomial bacterial infection and ACLF were also collected.
**Results:** Three-hundred twenty-nine patients were included in the analysis. The median age of the patients was 63 years. Nineteen percent of patients had ACLF at admission and a further 9% developed nosocomial ACLF during index hospitalization. The median MELD score was 15 and about 50% of patients where in Child-Pugh class B. The median length of the index hospitalization was 11 days. Of the 329 patients, 182 patients were hospitalized during the 1-year follow-up (26% once, 15% twice, 10% three times and 6% four or more times, leading to a total of 369 readmissions). The most frequent causes of readmission liver-related were hepatic encephalopathy (36%), ascites (22%) and bacterial infection (21%). No differences were detected in the frequency of causes responsible for re-admissions occurring within 30 days or thereafter except for bleeding which are more common beyond 30th day (14% vs 3%, p=0.02). Cumulative incidence of all-cause readmission was 19% at 30 days, 36% at 90 days and 56% at 1 year. Fifty-four patients were readmitted for emergent liver-related causes within 30 days after discharge. During the follow up, 113 patients (34%) died and 28 (9%) received a liver graft. Early readmission was associated to a higher 1-year mortality (47 vs 32%, p=0.04). Data collected both at admission (MELD-Na score, diabetes), during hospitalization (development of ACLF, days spent in hospital) and at discharge (hemoglobin (Hb) value, MELD-Na score) were significantly associated with early readmission. Multivariable competing risk regression analysis showed that Hb lower than 8.75 mg/dL (sHR 2.38 [95%CI 1.22-4.64], p=0.011), MELD-Na>16 at discharge (sHR 2.25 [95%CI 1.27-3.99], p=0.005), and diabetes (sHR 1.74 [95%CI 1.02-2.99], p=0.044) were independent predictors of early readmission. Cumulative incidence of early readmission was 8% (95% CI 4-14) in patients without risk factors, 16% (95% CI 11-22) in those presenting one risk factor and 35% (95% CI 23-47) in those presenting 2 or more risk factors (p<0.001). Considering patients with MELD-Na> 16 at discharge, the presence of Hb <8.75 g/dl doubles the risk of early re-hospitalization (42% vs 21%, p=0.031).
**Conclusion:** Simple and inexpensive clinical (diabetes) and laboratory (Hb and MELD-Na) parameters easily available in both referral and spoke centres are valuable predictors of early re-hospitalization. In particular Hb<8.75 g/dl emerged as a new independent risk factor for liver-related early readmission. Although the present study cannot reveal the pathophysiological link between low Hb levels and the risk of early readmission, it can be hypothesized that Hb may be a surrogate marker of disease severity and the role of systemic inflammation which characterizes advanced cirrhosis may be predominant. These findings can help physicians in identifying a subgroup of patients who are at high risk of early readmission and therefore deserve a close surveillance after discharge by inclusion in transitional care models with the objective of improving their management and quality of life and saving healthcare resources.

## 161. COMPARISON OF METABOLIC ALTERATIONS, HEPATIC AND CARDIOVASCULAR DAMAGE BETWEEN HIV PATIENTS WITH STEATOSIS AND PRIMARY NAFLD: ROLE OF LOW VISCERAL ADIPOSITY

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**Introduction:** People living with HIV show a high prevalence of hepatic steatosis (HS), along with frequent metabolic comorbidities, due to HIV chronic inflammation itself and long-lasting exposure to antiretroviral therapy (ART), which is also responsible for aging of HIV patients. In addition, because of the onset of these comorbidities, patients with HIV are also expose to high cardiovascular (CV) risk. However, if presentation of HS in this category of patients is different from that of primary non-alcoholic fatty liver disease (NAFLD) is unknown. Aim: to evaluate prevalence of HS, metabolic alterations, liver and CV damage in people living with HIV and to compare them with those observed in primary NAFLD subjects.
**Material and Methods:** 42 HIV mono-infected patients (mean age 46+12 ys, male 81%; 90% with viral suppression) were enrolled. The cohort of HIV patients underwent hepatic ultrasound (US) and those with evidence of HS were compared to a sex and age matched NAFLD control group (1: 2). For HIV patients, information about duration of disease, type of ART, HIV viral load and lymphocytes CD4+ count was collected. For all enrolled subjects, anthropometric parameters (BMI, waist circumference-WC) and prevalence of metabolic comorbidities were assessed. Bioimpedance (BIA) was performed to quantify sarcopenia (SMI ≤10.75 /6.75 kg/m2 male/females) and fat mass. All patients underwent transaminases determination and Fibroscan to detect advanced fibrosis (LSM>8.9/7.2kPa M/XL probe). CV risk was assessed by ESC guidelines and CV damage was evaluated by carotid ultrasound (plaques, arterial stiffness by radiofrequency as pulse wave velocity-pWv) and heart ultrasound (systolic and diastolic function and epicardial adipose tissue - EAT). Genotyping for PNPLA3 was determined by Taqman assay.
**Results:** In HIV patients hepatic steatosis was found in 30 (71%) subjects and advanced fibrosis in 7 (17%), however neither duration of disease or type of ART or HIV viral load and CD4+ count were associated to higher prevalence of HS or advanced fibrosis. The Thirty HIV patients presenting HS were compared with 60 primary NAFLD patients. HIV patients with HS presented lower BMI (27.1+4 vs 29.1+4.3 kg/m2, p=0.04), WC (98+9 vs 103.1+10.3 cm, p=0.03) and trunk fat mass (9.8 +3.3 vs 12.4 + 4.7 kg, p=0.02) compared to primary NAFLD. Nevertheless, the prevalence of metabolic alterations (type 2 diabetes 13% vs 13%, p=1.0; hypertension 47% vs 42%, p=0.82; dyslipidemia 83% vs 85%, p=1.0) and sarcopenia (40% vs 52%, p=0.81) was not significantly different between HIV patients with HS and NAFLD. In addition, no difference in liver damage was observed between groups, being the prevalence of increased transaminases (17% vs 20%, p=0.78) and advanced fibrosis (17% vs 12%, p=0.53) superimposable in the two groups. Similarly, people living with HIV with HS and primary NAFLD patients showed the same prevalence of high CV risk according to ESC Guidelines (84% vs 83%, p=0.86), carotid plaques (39% vs 28%, p=0.33), increased EAT (20% vs 17%, p=0.77), systolic (6% vs 5%, p=1.0) and diastolic dysfunction (7% vs 6%, p=1.0), as well as similar pWv values (7.4+2 vs 6.9+1.4 m/s, p=0.18). Finally, PNPLA3 distribution was not significantly different between groups (p=0.16).
**Conclusions:** Hepatic steatosis and fibrosis are highly prevalent in the setting of HIV infection. Interestingly, even though HIV patients with HS present lower BMI and lower visceral adiposity than NAFLD patients, the two groups show similar prevalence of metabolic alterations, together with hepatic and cardiovascular damage. Therefore, screening and follow up for hepatic steatosis in HIV patients is mandatory independently of their body weight, as the increased risk of metabolic, liver and CV complications.

## 162. SUBOPTIMAL ACCURACY AND FEASIBILITY OF THE 2021 EASL GUIDELINES FOR NON-INVASIVE RISK STRATIFICATION FOR SEVERE LIVER DISEASE IN SUBJECTS WITH METABOLIC RISK FACTORS AT THE GENERAL POPULATION LEVEL

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**Background:** The European Association for the Study of the Liver (EASL) has recently released the updated guidelines for the non-invasive evaluation of liver disease severity and prognosis[1]. According to EASL recommendations, individuals with metabolic risk factors or significant alcohol consumption, but free from already diagnosed liver diseases, should be screened at the primary care level applying a two-step approach: first, the FIB4 (a non-invasive score, calculated with a formula including age, aspartate aminotransferase [AST], alanine aminotransferase [ALT] and platelets); subjects with high probability of advanced liver fibrosis based on a FIB4≥1.3 should be then investigated with the determination of liver stiffness (LS) by Transient Elastography (TE), and – when positive (LS≥8KPa)- referred to the hepatologic clinic for further investigations and closer monitoring. We aimed at verifying the accuracy and feasibility of this approach at the general population level.
**Methods:** We exploited data from two large population-based cohorts: the UK biobank (UKBB, total N 502,507) and the 2017-2018 National Health and Nutrition Examination Survey (NHANES17-18, total N 9,254). In both cohorts, subjects with already diagnosed liver disease or active cancer at baseline were excluded. Thereafter, we selected subjects with any of: obesity, diabetes mellitus, significant alcohol consumption (>30/20 g/day for men/women), or metabolic syndrome[2]. A longitudinal analysis was conducted in the UKBB toward the incidence of severe liver disease during a 3 years' follow-up (3ySLD, defined as occurrence of cirrhosis, decompensated liver disease, hepatocellular carcinoma, and/or liver transplantation), whereas a cross-sectional analysis was carried out in the NHANES17-18 towards the identification of subjects with LS≥8KPa. The accuracy (with 95% confidence intervals [CI]) of the EASL first-step screening through FIB4, along with the rate of unnecessary TE consequently performed, and the true positive rate of subjects with 3ySLD or LS≥8KPa, was reported. All analyses were carried out with R statistics.
**Results:** We analyzed 262,707 (women 49%, median age 56.9, 3ySLD 197[0.07%]) and 3,368 (women 50%, median age 50.2, LS≥8KPa 387 [11%]) individuals from the UKBB and the NHANES17-18, respectively (Table 1, panel A). By applying the EASL first-step screening through FIB4, 157/197(80%) subjects experiencing 3ySLD in the UKBB, and 143/387(37%) subjects with LS≥8KPa in the NHANES17-18 are detected, with an overall accuracy of 0.572 (95%CI 0.570-0.573) and 0.698 (95%CI 0.682- 0.713), respectively (Table 1, panel B). This would lead to the execution of an un-necessary TE in 112,378 (43% of the UKBB population) and 773 subjects (23% of the NHANES17-18 population).
**Conclusions:** Differently from what observed at the tertiary care level[3], the EASL algorithm with first-step screening by FIB4 in the general population of dysmetabolic individuals showed suboptimal accuracies towards the identification of those experiencing 3ySLD or with LS≥8KPa, with execution of a huge and unfeasible number of unnecessary TE. Given the costs and limited availability of TE at primary/secondary care level, alternative strategies are eagerly awaited to improve the cost-efficacy of screening campaigns for the early referral of subject with significant liver fibrosis.
**References:** 1. European Association for the Study of the Liver (2021) J Hepatol 75: 659–689. 2. Eslam M, et al (2020) J Hepatol 73: 202–209. 3. Boursier J, et al (2022) J Hepatol 76: 1013–1020.
**Table 1.** Clinical characteristics of the study cohorts (Panel A) and the accuracy of EASL approach.

| PANEL A | UK Biobank | | | NHANES 2017-18 | | |
|---|---|---|---|---|---|---|
| N | 262,707 | | | 3,368 | | |
| *Demographics* | | | | | | |
| Age (years) | 56.9 (7.9) | | | 50.2 (17.2) | | |
| Sex (female) | 128,584 (49%) | | | 1,693 (50%) | | |
| *Metabolic profile* | | | | | | |
| Waist circumference (cm) | 94.0 (12.4) | | | 103.6 (15.6) | | |
| Hip circumference (cm) | 105.5 (8.9) | | | 109.2 (14.2) | | |
| BMI (Kg/m2) | 28.8 (4.5) | | | 31.1 (7) | | |
| Obesity | 81,362 (31%) | | | 1,605 (48%) | | |
| Diabetes mellitus | 16,144 (6%) | | | 713 (21%) | | |
| Hypertension | 92,652 (35%) | | | 1,311 (39%) | | |
| Dyslipidaemia | 66,374 (25%) | | | 1,347 (40%) | | |
| *Non-invasive indices* | | | | | | |
| FIB4 | | | | | | |
| *Low(<1.3)* | 150,172 (57.2%) | | | 2,452 (72.8%) | | |
| *Interm(1.3-2.67)* | 107,100 (40.7%) | | | 833 (24.7%) | | |
| *High(>2.67)* | 5,435 (2.1%) | | | 83 (2.5%) | | |
| Transient Elastography | | | | | | |
| *LS (kPa)* | - | | | 5.0 (4.1-6.3) | | |
| *LS ³ 8 KPa* | - | | | 387 (11%) | | |
| *Follow-up* | | | | | | |
| Severe Liver Disease - 3 years | 197 (0.07%) | | | - | | |
| **PANEL B** | | FIB4 | | | FIB4 | |
| | *Outcome* | <1.3 | ≥1.3 | *Outcome* | <1.3 | ≥1.3 |
| | *No 3ySLD* | 150,132 | 112,378 | *LS<8KPa* | 2,208 | 773 |
| | *3ySLD* | 40 | 157 | *LS≥8KPa* | 244 | 143 |
| Accuracy (95%CI) | 0.572 (0.570-0.573) | | | 0.698 (0.682- 0.713) | | |
| Undue Transient Elastography | 112,378 | | | 773 | | |
| True Positive Rate | 157/197 (80%) | | | 143/387 (37%) | | |

Continuous variables shown as mean (standard deviation) or median (interquartile range), if normally or not-normally distributed, respectively.

## 163. A CLINICAL CASE OF ACUTE FULMINANT HEPATITIS COMPLICATED BY DISSEMINATED INTRAVASCULAR COAGULATION

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**Objective:** evaluate the therapeutic approach and the differential diagnosis in a patient with acute liver failure.
**Case Description:** An 83-year-old man acceded the ER because of persistence jaundice for few weeks, associated with mild itching and hyperchromic urine in the past few days. In anamnesis: right and left-sided colon adenocarcinoma treated 2 years before with surgery and chemotherapy with Capecitabin, hypercholesterolemia in treatment with Rosuvastatin. Privately, he performed an abdomen ultrasound that showed hepatopathy, ascites and splenomegaly. Routine blood tests showed mixed jaundice (bilirubin tot 25 mg/dl, 50% direct and 50% indirect), elevated levels of markers of liver necrosis (GOT 556 U/L, GPT 225 U/L, GGT 162 U/L), amylase and lipase (178 U/L, 93 U/L). On suspicion of cancer recurrence, the he was admitted to our Internal Medicine Unit to prosecute the diagnostic process.
We started infusion of fluids, treatment with Dexamethasone and Pantoprazole and we suspended the statin considering the RUCAM score (=4), assuming a possible iatrogenic hepatitis. We carried out other blood analysis that showed increased levels of erythrocyte sedimentation rate, procalcitonin and c-reactive protein, hypoalbuminemia (1.7 g/dl) and a severely altered INR (5.18). Therefore, we adjusted the therapy with potassium correction, Piperacillin/Tazobactam tailored on the renal function, Furosemide, Canrenone and Phytomenadione according to INR levels.
We performed a total body CT scan to rule out the presence of an occult tumour. It revealed a likely etheroplastic lesion on the left mammarian gland worthy of a detailed imaging with mammography and a thickening of the gallbladder wall, with no focal lesions in other organs. Considering the persistence of acute liver failure, we carried out more exams for a differential diagnosis between acute autoimmune hepatitis, alcoholic hepatitis, acute infectious hepatitis and peritoneal carcinomatosis. We excluded viral hepatitis because of the negativity of the tests for minor and major hepatotropic viruses, instead tests for autoantibodies showed a positivity for ANA 1: 160 with reduced C3 and C4 and an increase in gamma globulin and IgG, placing a strong suspect for an autoimmune hepatitis. To confirm it, we scheduled a biopsy investigation the following day, but the patient tested positive to Covid-19, because of a Covid-19 cluster in our unit, so we had to postpone the procedure. Furthermore, given the patient poor clinical condition, we started parenteral nutrition.
Considering the severe liver disease, in the suspicion of DIC and consumption coagulopathy, the coagulation profile and the dosage of coagulation factors were immediately carried out, leading to reveal an overall deficiency of plasma factors, antithrombin and fibrinogen, due to the deficient hepatic synthesis and/or consumption, needing transfusion of fresh frozen plasma and fibrinogen. We performed also the direct and indirect Coombs tests, tested positive, and a peripheral blood smear which showed a true thrombocytopenia. Moreover, the blood chemistry tests found reduced levels of haptoglobin, Antithrombin III, Clauss fibrinogen (at first in range) and increased levels of D-dimer.
Before performing the liver biopsy, we administered to the patient Prothrombin Complex and Fibrinogen. The abdomen ultrasound revealed a picture of chronic liver disease with cirrhotic evolution, portal hypertension with moderate to severe ascites, chronic pancreatopathy, thickening of the gallbladder walls (as occurs in congestive cholecystopathy) with biliary sludge and splenomegaly. We took some samples of the serous-hematic ascitic fluid to check the presence of neoplastic cells, because of the suspect of peritoneal carcinomatosis, and for chemical and physical investigations. A few hours after the biopsy the patient experienced an episode of hypotension and we performed a urgent abdominal CT scan in suspected haemorrhagic shock. The scan showed an acute hemoperitoneum, probably caused by the biopsy, therefore we requested two units of packed red blood cells from the blood transfusion centre. Considering the severity of the clinical picture, we required surgical and resuscitation consultations, which did not suggest urgent surgical treatment and/or hospitalization in intensive care. At the end of the imaging test, the patient went into cardiorespiratory arrest resulting in the patient's death.
**Results:** The histopathological image analysis showed a picture of autoimmune hepatitis in its acute phase, characterized by aggregates of hepatocytes with ballooning degeneration, cholestasis, unicellular necrosis, fibrotic areas with ductular proliferation, stagnation of bile and lymphocytic inflammatory infiltrate with numerous granulocytes affecting the ductal epithelium. Finally, scattered plasma cells were found in the portal and lobular areas.
**Conclusions:** It may be hard to confirm the diagnosis of autoimmune hepatitis in patients with DIC and/or consumption coagulopathy, because of the need to perform biopsy procedures which can lead to significant bleeding, worsening the patient's clinical course and facing life-threatening conditions.

## 164. RITIRATO

## 165. LESSONS FROM THE WAITING LIST: PITFALLS OF NUTRITIONAL ASSESSMENT IN ADVANCED LIVER DISEASE

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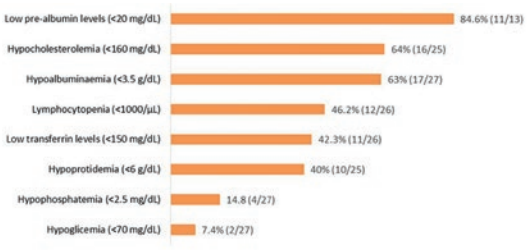
**Introduction:** From the end of 2019 the Clinical Nutrition and the Liver Transplant Unit of Niguarda Hospital (Milan) have shared a project for ameliorating the nutritional management of potential candidates for liver transplant. This study aims to assess the most critical aspects of nutritional evaluation in patients with advanced liver disease.
**Methods:** We retrospectively collected data on clinical, laboratory and instrumental evaluations. All patients underwent screening for malnutrition with MUST score and assessment according to GLIM criteria; resting energy expenditure was measured by indirect calorimetry when feasible; muscle mass was estimated with bioimpedence analysis or with anthropometric measures (mid-arm muscular area); biochemical markers of nutritional status and micronutrients' blood levels were assessed. Results were described as percentages and medians (interquartile range).
**Results:** We included 27 patients. Median age was 60.0 years (56.0-63.8). Female patients were 51.9%. Median Charlson comorbidity index was 5 (4-6). The most common associated conditions were arterial hypertension (33.3%), diabetes mellitus (25.9%), severe chronic kidney failure (11.1%), thyroid dysfunction (11.1%), peptic ulcer (7.4%), and ulcerative colitis (7.4%). Eighty-nine percent of patients had liver cirrhosis due to alcoholic (37%), viral (33.3%) or metabolic (14.8%) causes; mixed aetiologies were present in 22.2%. The majority of patients were in Child-Pugh class B (66.7%) and C (25.9%), with median MELD score of 15 (12.5-18) and MELD-Na of 16 (13-19). Forty-eight percent of patients were hospitalized at the time of the first nutritional visit. Median body mass index was 21.8 Kg/m2 (10.4-24.3). In comparison with the usual weight, 72% of patients showed some degree of weight loss; among them, median relative 6-month weight loss was 5.1% (1.9-7.1%). MUST score was 0 in 55.6% of patients, 1 in 29.6%, 2 or more in 29.6%. A proportion of patients reported reduced food intake due to hyporexia (30.8%) or nausea (7.4%). GLIM criteria for malnutrition were satisfied in 66.7% of cases. Triceps skinfold thickness and arm muscular area were below the 5th percentile in 44.4% and 52.6% of patients, respectively. Handgrip strength was below the 10th percentile in 63.2%. EGWSOP criteria for low muscle strength were satisfied in 47.4% of cases. Appendicular skeletal muscle mass was not measurable with the available bioimpedence analysis instrument; total fat free mass was low in 59% of patients. Resting energy expenditure measured by indirect calorimetry resulted lower than predicted in 23.1% of patients, higher in 23.1% and comparable in 53.8% (highest differences: +21% and –17%). Figure 1 shows prevalence of biochemical malnutrition markers. Regarding micronutrients, zinc deficiency was documented in 87.5% of patients; vitamin D, A, B6, folate, B1, E, C, and B12 deficiencies were present in 64%, 50%, 31.6%, 23.8%, 15.8%, 7.1%, 6.7%, and 0% of patients, respectively.
**Discussion:** In patients with advanced liver disease, malnutrition may result from poor food intake due to anorexia, ascites and psycho-social problems, malabsorption, metabolic disturbances, and higher energy consumption due to a pro-inflammatory state (Johnson et al., 2013). BMI and MUST score might underestimate malnutrition risk because of fluid overload in patients with ascites or oedema. In our study, GLIM criteria demonstrated a higher prevalence of malnutrition than expected with screening tools (MUST score). Biochemical malnutrition markers are poorly reliable in patients with advanced liver disease, being affected by hepatic synthesis (serum proteins, transferrin, albumin, pre-albumin), or altered by therapies or disease complications (lymphocytes, albumin) (Zhang et al., 2017); this is particularly relevant in hospitalized patients. With these limitations, we detected a high occurrence of low levels of pre-albumin, cholesterol and albumin. Besides common deficiencies (vitamin D, B1, folates),

we documented a high prevalence of vitamin A, B6 and zinc deficiencies; the latter might be responsible for taste alteration and hyporexia. Vitamin B12 levels were likely affected by hepatic cytolysis. Moreover, we highlighted the low accuracy of energy expenditure predictive equations in advanced liver disease, with almost half of the patients being either hypermetabolic or hypometabolic. Due to retrospective analysis limitations, we were not able to assess appendicular skeletal muscle mass or physical performance in order to fulfil sarcopenia diagnostic criteria; however, handgrip strength test suggests a prevalence of sarcopenia up to 47.4% in our study.
**Conclusions:** The peculiar features of advanced liver disease should encourage the choice of appropriated nutritional assessment tools. GLIM criteria could help identifying malnourished patients and suggest the need for indirect calorimetry measurement of energy expenditure, sarcopenia evaluation and thorough laboratory screening for micronutrient deficiencies (e.g. zinc, vitamin A).




## 166. RIBOCICLIB AS A POSSIBLE CAUSE OF DILI-INDUCED AIH: A CASE REPORT

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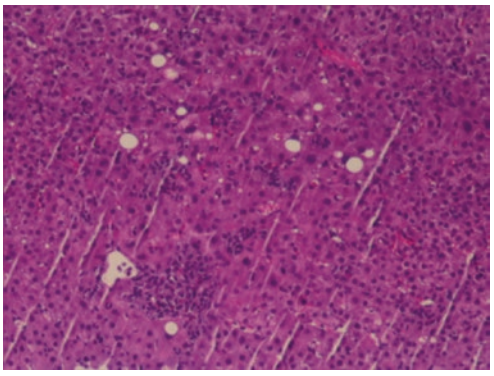
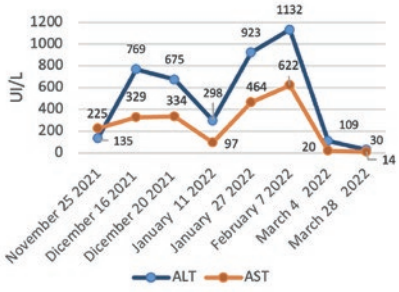
**Introduction:** We would like to present the case of a female patient affected by breast cancer who developed acute hepatitis while being treated with Ribociclib.
Ribociclib is an antineoplastic drug which makes part of cyclin dependent kinase 4 and 6 inhibitors class. It is used in combination with aromatase inhibitors (such as Letrozole) in the treatment of metastatic or locally advanced breast cancer. Liver toxicities were common adverse effect in clinical trials. The liver injury commonly presented with serum ALT elevation, followed by symptoms and jaundice. Immunoallergic and autoimmune features were not present, although liver histology sometimes showed autoimmune hepatitis-like features.
**Case:** A 55-year-old woman affected by breast cancer with lymph nodes and mediastinal metastases was referred by her oncologist to our Hepatological Centre in February 2022. The patient weighed 70 kg, was 164 cm tall and had a BMI of kg / m2. Her oncological history began in August 2021 with diagnosis of infiltrating ductal carcinoma of left breast with lymph node metastases. No liver lesions was identified on level I and II imaging exam. In September the patient started treatment with first-line therapy according to combination Ribociclib 600 mg/day plus Letrozole 2.5 mg/day. Therapy was suspended in November due to increased ALT value (four times the upper limit). Consequently, she started therapy with glutathione 600 mg/day and acetylcysteine 600 mg/day. In December a further increase in serum transaminase and bilirubin levels occurred, and patient started oral steroid therapy with prednisone 12.5 mg/day for 14 days and subsequent 5 mg/day for a further 5 days. Steroid therapy was gradually suspended starting from January 2022 because of partial reduction in transaminases and bilirubin serum levels. On January 27, the patient experienced a biochemical relapse and was then referred to our liver center. On February 7, she presented asymptomatic and serology for major and minor hepatotropic viruses resulted negative. Immunoglobulin dosage was normal as well as protein electrophoresis. First level (anti-nuclear, anti-smooth muscle, anti-liver kidney microsome anti-mitochondrial) and second level autoimmunity assay (anti-M2/nPDC, anti-M2/ OGDC-E2, anti-M2/BCOADC-E2, anti-gp210, anti -sp100, anti-LKM1, anti-LC1, anti-SLA, anti-f-Actin) resulted negative. Abdominal ultrasound documented a mild grade steatosis with no focal lesions. No pathological issues of gallbladder, biliary tract and hepatic vascularization. Liver stiffness, measured by Shear Wave Elastosonography, was 5.4 kPa. Temporary suspension of steroid therapy was then indicated, and liver biopsy performed on 15 of February 2022. The histological examination showed severe lobular inflammatory activity with marked Kupfferian CD68 + histoid activation, PAS diastase + and moderate expansion of the portal spaces with mixed inflammatory infiltrate also including some eosinophils and rare plasma cells CD138 + (Fig.2). Focally mild notes of ductular neoformation and rare foci of hepatocytic biliary metaplasia CK7 +. Mild fibrosis. Staining with Perls for hemosiderin was negative. In February 15 re-test of first level immunity assay was done and two autoantibodies resulted positive: ANA (titre 1: 160 with finely dotted pattern) and SMA antibody (titre 1: 40). Then the patient reintroduced corticosteroid therapy adjusting prednisone dose to 50 mg / day starting from February 24. At blood tests performed on March 4 we documented AST 20/35, ALT 109/35 and total Bilirubin 1,02. Prednisone therapy was continued at dosage of 50 mg / day for a further 3 weeks. On March 28 we documented AST 14/35, ALT 30/35, total bilirubin 1,56. Hence, she started steroids tapering with maintenance of the clinical response (Tab. 1).
**Discussion:** This clinical case could be suggestive of a DILI-induced AIH. Although histological examination does not have all typical features of acute autoimmune hepatitis (interface hepatitis, lymphocytic / lymphoplasmacytic infiltrates in portal tracts and extending into the lobule, emperipolesis, and hepatic rosette formation) and electrophoretic examination with immunoglobulin assay was negative, the mentioned characteristic may have been impaired by early starting of steroid therapy before the patient was referred to our liver center. Simplified AIH Score and Revised Original AHI Score resulted were indicative of possible AIH. In favor of the hypothesis of an autoimmune form of hepatitis we considered two aspects: 1- Evidence of autoantibodies ANA and SMA (performed two time by the same laboratory), resulted negative in January 2022 and positive in February 2022. The DILI scenario could have caused cells necrosis and release of antigens recognized by the immune system as non-self-antigen.This evidence does not contrast with well-known pathogenesis of hepatic damage induced by certain drugs (such as nitrofurantoin and minocycline) with formation of neoantigens recognized by the immune system.






## 167. THE LINK BETWEEN SYMPATHO-VAGAL BALANCE AND INFLAMMATION IN CIRRHOSIS: THE ROLE OF OSTEOPONTIN, IL-22, IL-6, IL-17, IL-1RA AS BIOMOLECULAR MARKERS OF PORTAL HYPERTENSION SEVERITY

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**Background and Aims**: The cytokinic "mileu" of the cirrhotic patient is intimately linked to the anatomopathological alterations and therefore to the expression of the disease at a clinical and molecular level. The autonomic nervous system (ANS) is linked to an hyperdynamic circulation and represent a therapeutic target with betablockers in patients with cirrhosis and portal hypertension.
Several lines of evidence have revealed that decreased Heart rate variability (HRV), a clinically validated non-invasivemethod to assess the sympatho-vagal balance, holds prognostic information and can predict survival of patients independent of the severity of liver disease. Notably, several studies have highlighted the crucial role that systemic inflammation elicits in conferring the reduction in patients' HRV.
To investigate the correlation between the time-domain HRV parameters, serum cytokines concentrations and degree of portal hypertension, we studied a cohort of patients with cirrhosis, accounting for etiology and treatments.
**Patients and Methods:** In this cross-sectional, observational cohort study, 107 outpatients with a clinical diagnosis of non-alcoholic cirrhosis of mixed etiology (HCV, HBV, NASH) were assessed consecutively by abdominal ultrasound and by upper GI endoscopy to search for esophagogastric varices (EVs). 24-hour ECG Holter monitoring with HRV measurement (standard deviation of the NN intervals, SDNN; root mean square successive difference of NN intervals, RMSSD; standard deviation of averages of NN intervals, SDANN) was performed and serum concentrations of osteopontin, IL-22, IL-6, IL-1Ra, IL-17 were obtained for dosage in all patients.
**Results:** The present study showed that IL-6, OPN, IL-22, and IL-1Ra concentrations in cirrhotic patients are largely associated to disease severity expressed by Child-Pugh and MELD score, to portal hypertension's indirect signs and to some of its complications, as well as to the 24-hour HRV parameters that best represent the activity of the sympathetic nervous system in the total sympatho-vagal balance. IL-6 together with OPN, IL-1Ra and IL-22 was shown to be significantly associated with the diagnosis of PSE. A significant increase in systemic concentrations of OPN in patient with HCC was also encountered. Finally, a reduction of SDANN and SDNN values, which better express the sympatho-vagal balance, was associated with an increase in serum levels of IL-6, OPN, IL-1Ra and IL-22. Moreover, OPN was also associated with an increase in RMSSD
**Conclusions:** This study lays the foundations for new researches that intend to investigate the ability of some cytokines such as IL-6, IL1-Ra and OPN to identify a part of the population at high risk for portal-hypertension complications. Finally, for the first time, this study underlines the interaction between the alteration of the ANS and the activation of inflammatory pathways that characterize portal hypertension in chronic liver diseases. Deepening the knowledge of this interaction could provide insights into the mechanisms that influence patient responsiveness to beta-blocker therapy in the future

## 168. PPIS INTAKE IS ASSOCIATED TO HEPATIC DECOMPENSATION IN FEMALE WITH LIVER CIRRHOSIS

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**Introduction and Aims:** The real effect of Proton Pump Inhibitors (PPIs) on cirrhotic patients remains controversial. It is well established, in fact, that the commonly described side-effects of PPI in the general populations such as alterations in the intestinal microbiome, anemia and encephalopathy as well as a greater susceptibility to infections, are also commonly observed in patients with liver cirrhosis. The aim of this study is to evaluate the outcome of patients with cirrhosis who underwent PPIs treatment for at least 60 months. Subsequently, we analyse the impact of the considered variables on the onset of liver decompensation in this cohort of patients.
**Methods:** We have retrospectively evaluated all cirrhotic patients attending the Liver Unit of Messina University Hospital between January 1st to December 31st 2021, who had at least a 10 years follow-up. Exclusions criteria were: liver transplantation, diagnosis of HCC and/or portal vein thrombosis within six months before enrolling into the study. For each patients we recorded in our database, demographics, laboratory parameters, presence of diabetes, arterial hypertension, liver etiology with medications at the time of diagnosis; in particular, we focused our attention on the start date of PPI therapy and its duration, we also stratified patients on the basis of PPI intake in two groups: group a) continuous intake of PPI for at least 5 years, and group b) continuous intake of PPI for at least 1 year. We considered "no PPIs intake" (group C) patients who claiming to use PPIs only occasionally.
**Results:** Two hundred fifty-four cirrhotic patients [149 males (58,7%) and 104 females (41,3%), median age 71 years (range 33-92)] were enrolled in the study. Child–Pugh class score was: A in 153/254 (60,3%), B in 71/254 (28%) and C in 13/254 (5,2%) patients. Diagnosis of liver cirrhosis was HBV and/or HCV related in 129 (50,8%) cases, alcohol-related in 51(20,1%) cases, dysmetabolic disease in 48 (18,9%) cases and other etiologies in 26 (10,2%) cases. Overall, 132 out of 254 (51,9%) patients have undergone PPIs treatment, in particular 67/132 (50,7%) were included in group A (PPIs intake for more than 5 years) and 65/132 (49,3%) were included in group B (PPIs intake for more than 1 year). Among the 254 patients evaluated, 108 (42,5%) had hepatic decompensation at the time of evaluation or had a previous decompensation event (78 and 30 patients, respectively). In 68 out of 108 (62,9%) patients with liver decompensation was recorded PPIs intake. In particular 59/108 patients were in group A, 9/108 in group B and 41 in group C (p<0,001). Multivariate logistic regression showed that hepatic decompensation was associated to PPIs (p=0,003), female gender (p=0,01), and from duration of PPI intake (p=0,03)
**Conclusion:** In our series of cirrhotic patients liver decompensation was correlated to PPIs treatment, female gender and duration of PPI treatment.

## 169. RITIRATO

## 170. LIVER FRAILTY INDEX PREDICTS POOR OUTCOMES IN PATIENTS HOSPITALIZED FOR ACUTE DECOMPENSATION OF CIRRHOSIS

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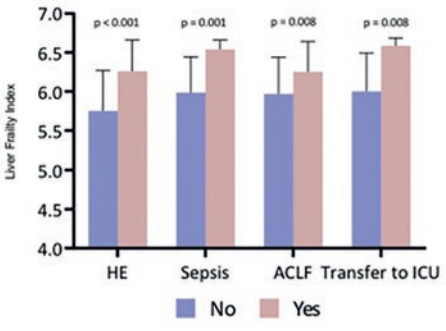
**Background and Aims**: Physical frailty is highly prevalent in patients with end stage liver disease and has been associated with poor outcomes. Liver Frailty Index (LFI) is a standardized tool to assess frailty in patients with cirrhosis on liver transplant waiting list. However there is a paucity of data on the prognostic value of LFI in patients hospitalized for acute decompensation (AD) of cirrhosis. We evaluated LFI in patients hospitalized for AD and the association of LFI with complications occurred during hospitalization and 90-day survival.
**Patients and Methods:** We enrolled 117 consecutive patients admitted for AD of cirrhosis from 2019 to 2021. LFI was performed at the time of hospital admission. Occurrence of complications (hepatic encephalopathy [HE], sepsis, organ failures, ACLF) during hospitalization was recorded. Patients were followed up until death, liver transplant or 90 days.




**Results:** mean age and MELD-Na were 64 + 10 and 20 + 7, respectively. The majority of patients were male (71%) and had and alcohol-related cirrhosis (56%). Median LFI was 6.1 (IQR 5.0 – 6.5). LFI showed a weak, but significant, correlation with age (r=0.202; p=0.029), MELD-Na (r=0.292; p=0.001)

and parameters of systemic inflammation such as C-Reactive Protein (r=0.235; p=0.014) and white blood cell (WBC) count (r=0.207; p=0.025). LFI was significantly higher in patients developing hepatic encephalopathy, sepsis, renal failure, circulatory failure, respiratory failure and ACLF than in those who did not (Figure 1). Patients transferred to the ICU had significantly higher LFI than those who did not (Figure 1). LFI was significantly higher in patients who died than in those who survived during hospitalization (median=6.5 [IQR=6.0-6.7] vs 6.0 [IQR 4.8-6.5]; p=0.006) and at 90 days (6.45, IQR 6-6.64 vs 5.87, IQR 4.81-6.37; p=0.001). In multivariate analysis LFI was an independent risk factor of 90-day mortality (HR=1.88, 95% CI 1.07-3.32; p=0.028), as well as MELD-Na (HR=1.11, 95% CI 1.04-1.18; p=0.01) and WBC (HR=1.08, 95% CI 1.00-1.17, p=0.046).
**Conclusions:** In patients with cirrhosis hospitalized for AD, LFI identifies patients at higher risk of worse outcomes and can be used for the assessment of frailty in these patients.

## 171. INCREASED LIVER STIFFNESS IN SUBJECTS WITH NON-ALCOHOLIC FATTY LIVER IS INDEPENDENT FROM FIBROSIS

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**Background:** Fat accumulation can alter the mechanical phenotype of the liver. Increased liver stiffness, however, is also linked with fibrosis, potentially increasing disease severity from steatosis to steatohepatitis, and ultimately cirrhosis. It is still unclear if fat accumulation per se increases liver stiffness independently from fibrosis.
**Methods:** A total of 60 consecutive outpatients underwent Acoustic Radiation Force Impulse shear wave elastography of the liver (ARFI, liver stiffness), APRI and FIB-4 calculation. Ultrasonography (US) served to grade steatosis: absent/mild (normal liver echogenicity or isolate finding of liver echogenicity brighter than the renal cortex), moderate (additional presence of portal margin blurring), or severe (additional presence of diaphragmatic attenuation).
**Results:** Absent/mild (controls), moderate or severe steatosis was found in 40, 11 and 9 subjects, respectively. Subgroups were comparable for age and gender ratio. The body mass index (BMI, Kg/m2) was significantly higher in moderate (32.4±1.4) or severe (34.3±1.4) steatosis, than in controls (26.7±0.7). Liver stiffness increased from 1.32±0.04m/s in controls to 1.52±0.08m/s and 1.58±0.09m/s in moderate and severe liver steatosis, respectively (P=0.01 ANOVA). Overall, ARFI showed a normal or mild (i.e., F1-F2) grade of fibrosis in 93% of subjects. The absence of severe fibrosis was confirmed by APRI (<0.7 in all subgroups) and FIB-4 values (<0.45 in all subgroups).
**Conclusions:** The combined use of liver US and ARFI can reliably detect early alterations of the viscoelastic properties of liver tissue in subjects with NAFLD, in the absence of advanced fibrosis. In these subjects, increased liver stiffness seems to mainly depend on the extent of fat accumulation. This evidence might lead to primary and secondary prevention measures, able to avoid a possible progression towards more severe liver diseases

## 172. CHARACTERIZATION OF SARCOPENIA WITH ULTRASOUND-BASED MEASUREMENTS IN PATIENTS WITH ADVANCED CHRONIC LIVER DISEASE

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**Introduction:** Sarcopenia is a very common complication of cirrhosis affecting patients with compensated and decompensated disease. It has a multifactorial aetiology and can identify patients with a worst prognosis even in the context of hepatocellular carcinoma. It is mainly diagnosed in the clinical setting using operational definitions based on low muscle mass and, to date, there is not a gold standard for the diagnosis in patients with chronic liver disease. Currently, the most validated tools are the psoas and lumbar vertebral body cross-sectional imaging assessments by computed tomography (CT) or magnetic resonance imaging (MR). Notably, muscle ultrasound-based measurement has recently achieved great attention in the evaluation of sarcopenia because of its easier feasibility; however, only a few studies evaluating this approach have been reported. Here, in a cohort of patients with chronic liver disease evaluated by CT or MR imaging during follow-up for hepatocellular carcinoma, we aimed to validate ultrasound-derived measurements for the assessment of sarcopenia.
**Materials and Methods:** Consecutive adult outpatients attending the Hepato-Oncology Unit of the Campus Bio-Medico Hospital from June 2020 to June 2021 were included in the study. CT or MR scans were imported and analysed by one single radiologist (E.F.), with a dedicated software (Osirix), and the L3-skeletal mass index cm2/m2 was calculated. Ultrasound was performed by one single operator (P.G.) to obtain muscle thickness and derived indices according to different already described techniques: evaluation of quadriceps muscle according to Tandon et al; evaluation of psoas muscle according to Hari et al. and Kobayashi et al; evaluation of diaphragmatic excursion and thickness according to Soldati et al.. Receiver operating characteristic (ROC) curve analysis was performed to assess the diagnostic accuracy of each technique with respect to sarcopenia as determined by CT and/or MR analyses.
**Results:** As reported in Table 1, 51 patients were included. The average age was 74 years (±7.07), with a prevalence of male gender (70.6%). Mean BMI was 27.4 kg/m2. The most common etiology of cirrhosis was metabolic, i.e., non-alcoholic steatohepatitis (41.2%), and more than half of the patients (68%) had a preserved liver function (68% Child A). Most patients (48%) were in follow-up after a complete response to surgical or locoregional treatments for HCC.

| | | |
|---|---|---|
| Average age (mean; SD) | 74 (±7,07) | |
| Sex [n (%)] | F= 15 (29,4) | |
| | M= 36 (70,6) | |
| Aetiology [n (%)] | Metabolic | 14 (27,5) |
| | Viral | 15 (29,4) |
| | Alcoholic | 11 (21,6) |
| | Alcoholic/Metabolic | 7 (13,7) |
| | Other causes | 4 (7,8) |
| Diabetes mellitus [n (%)] | Yes=28 (54,9) | |
| | No= 23 (45,1) | |
| HCC [n (%)] | Complete treatment response 21 (41,2) | |
| | Active HCC 30 (58,8) | |
| Child-Pugh [n (%)] | A= 35 (68,6) | |
| | B= 15 (29,4) | |
| | C= 1 (2) | |

**Table 1:** Characteristics of the study population.

| ULTRASOUND INDICES | Odd Ratio (OR) (95%CI) | p value |
|---|---|---|
| *Average compression index* | 7.84 (0.44, 174.65) | 0.171 |
| *Average feather index* | 13.64 (1.25, 196.17) | 0.04 |
| *IleoPsoas-index* | 1.01 (1, 1.02) | 0.01 |
| *US-PTHR* | 1.06 (0.97, 1.19) | 0.256 |
| *US-PMI* | 1.25 (0.95, 1.94) | 0.219 |
| Diaphragmatic excursion | 0.98 (0.94, 1.02) | 0.384 |
| Diaphragmatic thickness inspirium | 0.99 (0.95, 1.02) | 0.443 |
| Diaphragmatic thickness espirium | 0.99 (0.94, 1.04) | 0.605 |

**Table 2:** As shown in Table 2, logistic regression analysis identified the Average feather index and the IleoPsoas-index as significantly associated (p 0.04) with a Low muscle mass expressed with CT/MR.

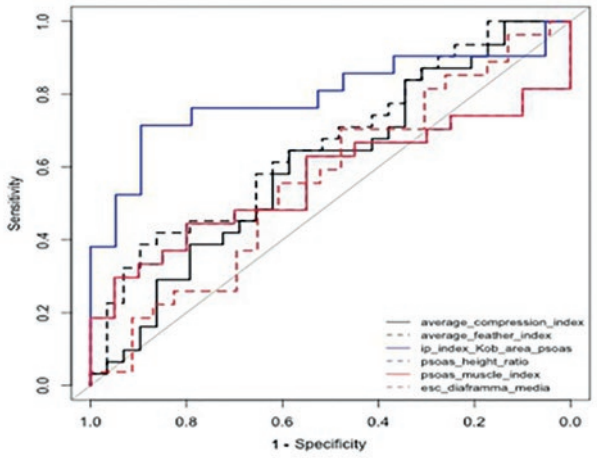


**Table 3:** Moreover, the IleoPsoas Index was the only one showing an adequate discriminative ability, with an AUROC of 0.79 (0.65-094) (Table 3,

Figure 1).

| ULTRASOUND INDICES | Discriminative ability (AUROC) |
|---|---|
| *Average compression index* | 0.61 (0.46-0.75) |
| *Average feather index* | 0.66 (0.52-0.8) |
| *IP-index* | 0.79 (0.65-0.94) |
| *US*-PTHR | 0.57 (0.4-0.73) |
| *US*-PMI | 0.57 (0.4-0.73) |
| Diaphragmatic excursion | 0.56 (0.4-0.73) |
| Diaphragmatic thickness inspirium | 0.56 (0.41-0.72) |
| Diaphragmatic thickness espirium | 0.56 (0.4-0.71) |

**Conclusions:** Our preliminary results show, for the first time, a statistically significant association between some ultrasound-based techniques and a reduced muscle mass defined with the TC\MRI scan. Indeed, our analysis showed a better discriminative ability of the IP-index. If these results will be confirmed in larger and external series, muscle ultrasound-based measurements would represent a feasible and cheap tool for assessing sarcopenia at least in patients with chronic liver disease.

## 173. OCCASIONALLY DIAGNOSED NON-CIRRHOTIC PORTAL HYPERTENSION: A CASE REPORT

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**Background:** The etiology of an occasionally diagnosed NCPH (Non-Cirrhotic Portal Hypertension) could be hard to find out. Massive acute upper gastrointestinal bleeding is usually the first manifestation of NCPH, leading to hospitalization. Differential diagnosis with other types of liver cirrhosis is challenging and it is based on the clinical manifestations, laboratory findings and liver histology.
**Case Description:** A 76-year-old man was admitted to our department of Internal Medicine with a new diagnosis of non-cirrhotic portal hypertension. The patient suffered from arterial hypertension and type 2 diabetes. He denied alcohol or drugs intake. Formerly, he was an employee of a petrochemical industry. He has a brother who suffers from NASH and manifested bleeding varices. The patient attended the Emergency department two days before for upper gastrointestinal bleeding. An Esophagogastroduodenoscopy (EGD) was performed, showing bleeding F3 grade esophageal varices. A contrast abdominal CT scan revealed ascites, portal hypertension with a dilatation of the portal vein and the presence of esophageal and gastric collateral circulation. There was no evident cause of portal hypertension, neither pre-hepatic nor post-hepatic. The CT scan did not show liver abnormalities. There were no signs of portal or splenic vein thrombosis, no occlusion or thrombosis of the hepatic veins (Budd-Chiari syndrome), no inferior cava occlusion or obstruction of the right ventricle filling. A ligation of the esophageal varices was performed. The patient required several blood transfusions due to severe anemia. The cause of portal hypertension remained unclear. During hospitalization we performed several exams. The liver ultrasonography showed: 1) no clear signs of cirrhosis; 2) ascites; 3) a dilatation of either portal vein (1,8 cm max) or splenic vein (1.1 cm max); 4) splenomegaly (bipolar diameter 19,9 cm, section area 122 cm2). Laboratory tests showed leucopenia. There were no serological signs of cirrhosis or liver damage. The patient was also tested for hepatotropic viruses (HAV, HBV, HCV, HSV, VZV, EBV, CMV), all negative for acute or chronic infection. Autoimmune tests were also performed: AMA, ASMA, LKM1, ENA, ASCA IgA/IgG, antiDNA, MPOS, PR3S were all negative. The ANA test was positive, with a title 1: 160 and a granular pattern. Alpha1-antitrypsin deficiency was excluded. A liver biopsy was performed. The histology showed a preserved acinar architecture with enlarged portal spaces and marked lymphocytic infiltrate, interface hepatitis and prominent fibrosis of portal spaces, with fibrotic septa. There was no evidence of necrosis or iron deposits. Based on the results of the histology, on the clinical and laboratory findings and on the patient's history, we concluded that the possible causes for such microscopic fibrosis could have been either autoimmune hepatitis (AIH) or hepatoportal sclerosis (HS).
**Conclusions:** Hepatoportal sclerosis (HS) is an idiopathic NCPH, characterized by splenomegaly, upper gastrointestinal bleeding, hypersplenism and portal hypertension. The disease is more prevalent in Asia. It would not appear to be linked to either age or sex. Often, the first manifestation of HS is an active gastrointestinal bleeding and splenomegaly, whereas laboratory tests can be associated with pancytopenia and alteration of liver function indices. The course is usually benign and rarely evolves into cirrhosis. If a correct follow-up and prevention of bleeding complications from gastric and esophageal varices are performed, the patients live in good general conditions. However, particularly aggressive forms can lead to cirrhosis with ascites, hepatic encephalopathy, jaundice, with a high risk of thrombosis of the portal vein. The etiology is unknown, often falling into the macro-group of "non-cirrhotic portal hypertension". It has been hypothesized a link with the exposure to toxics (arsenic or vinyl chloride) or drugs (vitamin A and 6-mercaptopurine) but also with autoimmune diseases, infections and coagulations defects; a genetic cause is also possible.
In our case, however, the histology was compatible with an AIH pattern (marked lymphocytic infiltrate with evidence of chronic active hepatitis and interface hepatitis); furthermore, based on the Comprehensive Diagnostic Scoring System of the International Autoimmune Hepatitis Group, the diagnosis of AIH was "probable".
Nevertheless, the presence of a serious portal hypertension leading to bleeding varices without overt histological features of cirrhosis led us to believe uncertain an AIH diagnosis. Moreover, the clinical manifestations, in particular the late onset of the disease with massive upper gastrointestinal bleeding, the laboratory findings, the exposition to toxics due the patient's employment history, all support the hypothesis of a HS. Finally, we cannot exclude an overlapping between AIH and HS, as it is described in literature (Abe K. et al., Hepatology Res., 2013), emphasizing that the etiology of HS could be also based on a possible autoimmune mechanism.

## 174. RITIRATO

## 175. HIGH RATE OF LATE REFERRAL AND DIAGNOSIS OF LIVER CIRRHOSIS DURING A FOUR-YEAR PERIOD IN A SECOND LEVEL MEDICAL CENTER. THE EXPERIENCE OF FONDAZIONE POLICLINICO GEMELLI

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**Background:** In Italy the overall prevalence of liver cirrhosis is estimated to be 0.3% and about 20,000 patients die each year because of cirrhosis related complications. Most patients remain asymptomatic until the onset of decompensation, characterized by the occurrence of portal hypertension related symptoms (ascites, hepatic encephalopathy, bleeding from gastrointestinal tract) often associated with hematochemical signs of liver function failure with or without concurrent hepatocellular carcinoma. Delay in cirrhosis diagnosis impacts not only on the individual health status, as cirrhosis transition from the compensated to the decompensated stage is associated with decreased survival, but also on the public health, as the total disease cost encompasses direct costs (medical costs) and indirect costs (due to reduced quality of life and lost productivity).
**Aim:** Analyzing data from a second level Center in order to assess the real life burden of cirrhosis diagnosis delay.
**Materials and Methods:** We collected and analyzed data from the Liver Disease Outpatient Center of Fondazione Policlinico Gemelli University Clinic from January 2018 to December 2021, focusing on the newly diagnosed cirrhosis cases. For each year, we investigated the etiology of liver disease and the number of adult patients who had a new diagnosis of cirrhosis in the decompensated phase (DP) or in the compensated phase (CP).
**Results:** We observed a total of 191 new diagnoses of cirrhosis due to non alcoholic fatty liver disease (NAFLD) in 29.3% of the cases, alcoholic liver disease (ALD) in 29.3%, hepatitis C virus (HCV) in 18.8%, hepatitis B virus (HBV) in 7.3%, primary biliary cholangitis (PBC) in 3.7%, and autoimmune hepatitis (AIH) in 1.6% (figure 1); other causes and cryptogenic disease were detected in the remaining 10% of patients. The patients were male in 60.7% of the cases, the mean age was 57.9 years and the cirrhosis diagnosis was made in DP in 68.8% of the cases and CP in 31.4%. No significant differences were found across the years as the rate of decompensated disease at diagnosis was 67%, 61%, 77%, and 64% in the years 2018, 2019, 2020, and 2021, respectively (figure 2). Among the patients diagnosed in DP, the most frequent symptom was ascites (47.4%) followed by bleeding (15.3%), and by encephalopathy (10.9%). Hepatocellular carcinoma was concurrently diagnosed in 37/130 patients in DP (28%). According to the etiology of liver disease, the rate of patients diagnosed in DP was 81% in NAFLD cases, 63%

in ALD cases, 62% in HCV cases, and 50% in HBV cases with a statistically significant difference between NAFLD and HBV ($p < 0.05$) but not between NAFLD and ALD or HCV.
**Conclusions:** Our study shows that in a second level referral Center the diagnosis of cirrhosis is made in the DP in about two-thirds of the cases and that NAFLD, ALD and HCV are the most frequent etiologies. We think that, in spite of the availability of effective non-invasive screening tools, there is a delay in the recognition of cirrhosis in CP in at risk patients with subsequent negative impact on patients' referral and prognosis. Urgent interventions are needed to increase the patients' awareness of chronic liver disease and the screening capacity of territorial medical services.

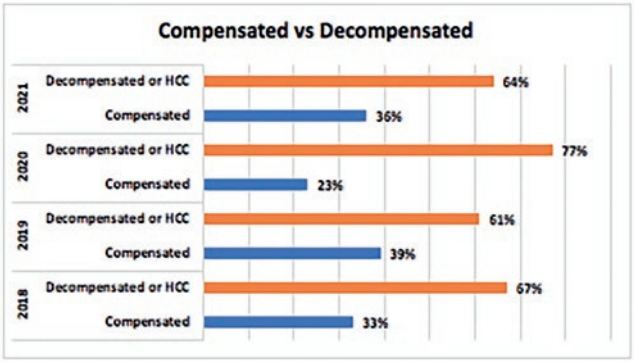


**Figure 1**

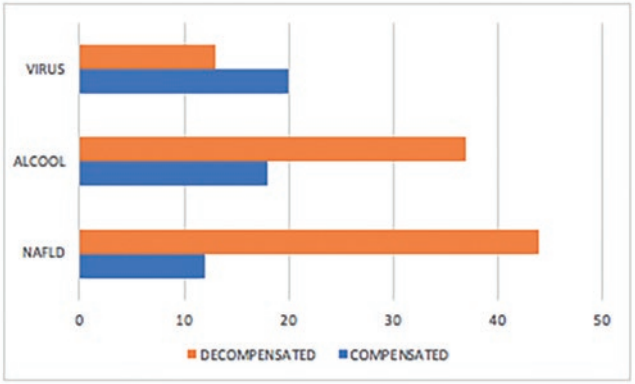


**Figure 2**

## 176. CLINICAL AND PROGNOSTIC CHARACTERIZATION OF THE PATTERNS OF DECOMPENSATION OF LIVER CIRRHOSIS

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**Background and Aims**: The clinical course of liver cirrhosis is characterized by two phases, compensated and decompensated cirrhosis, the latter characterized by the onset of complications (ascites, variceal bleeding, hepatic encephalopathy) and a worse prognosis. Recently, Acute Decompensation (AD), i.e. the development of complications that require hospitalization, has been characterized. However, complications of cirrhosis do not necessarily require hospitalization and can develop progressively. This type of decompensation has recently been defined as Non Acute Decompensation (NAD). At present time, there is no information regarding the incidence and prognostic impact of NAD. The aim of the study was therefore the evaluation of the incidence of NAD and AD in a group of outpatients with liver cirrhosis and the prognostic impact of these two decompensation patterns.
**Patients and Methods:** 749 outpatients with cirrhosis were enrolled and consequently followed up until death, liver transplantation or the end of the study (August 2021). Clinical and biochemical data were collected, as well as the development of complications during follow up, which were considered as AD if they resulted in hospitalization or NAD if they were managed at outpatient clinic.
**Results:** 379 patients (50.6%) did not develop any decompensation, 163 patients (21.8%) had NAD as first decompensation and 207 (27.6%) had AD. During follow up, 216 patients (28.8%) died and 145 (19.4%) were transplanted. Survival at 10 years was significantly higher in patients who did not develop decompensations (79.6%) than in patients who developed NAD or AD (33.7% and 21.3%, respectively; $p<0.001$, Fig.A). Eighty-three patients with NAD (50.9%) subsequently developed AD. There was no significant difference in 10-year survival between patients who developed AD after NAD and those who only had AD, while both of these groups showed shorter survival than patients who had only NAD. In multivariate analysis, age (HR 1.05, $p<0.001$), MELD (HR 1.10, $p<0.001$), varices at inclusion (HR 1.48, $p=0.03$), albumin (HR 0.94, $p<0.001$), MAP (HR 0.98, $p=0.006$), effective etiological treatment (HR 0.38, $p<0.001$) and NAD (HR 2.65, $p<0.001$) or AD (HR 3.51, $p<0.001$) were independent predictors of mortality.
**Conclusions:** In more than 20% of patients with cirrhosis the first decompensation is a NAD, which often precedes AD and is associated with a decreased survival. Patients who develop NAD must be monitored closely to prevent any development of AD.

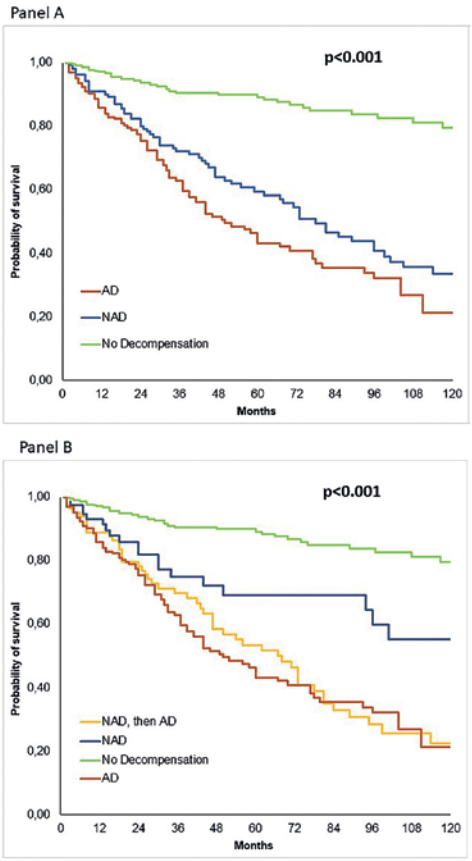


**Figure:** 120-month survival in patients according to the pattern of decompensation

## 177. ETIOLOGICAL CURE PREVENTS FURTHER DECOMPENSATION AND MORTALITY IN CIRRHOTIC PATIENTS WITH ASCITES AS THE SINGLE FIRST DECOMPENSATING EVENT

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**Background and Aims**: Etiologic treatment reduces the risk of decompensation and mortality in compensated cirrhosis. However, in the setting of decompensated cirrhosis the impact of etiologic treatment is less predi-

ctable, in particular in patients with ascites, who remain at high risk of developing further decompensating events and death. The aim of the study was to evaluate the impact of etiological treatment in decompensated patients with cirrhosis and ascites as the single index decompensating event. The endpoints were the occurrence of further decompensation (i.e. refractory ascites, spontaneous bacterial peritonitis [SBP], hepatorenal syndrome [HRS-AKI], variceal bleeding [VB] and hepatic encephalopathy [HE]) and mortality.
**Methods:** Cirrhotic patients with ascites as single first decompensation event at the University Hospital of Padova or the Vienna General Hospital between 2003-2021 were included and followed until death, liver transplantation or September 2021. The etiology was considered as "cured" in case of removal of the primary etiological factor (e.g. HCV: virological cure, HBV: virological suppression, ALD: alcohol abstinence) and as "controlled" in case of partial removal of etiologic factor (e.g. HBV: partial suppression of HBV-DNA, ALD: mostly abstinent but with drinking episodes).
**Results:** We included 622 patients (mean age: 57±11 years, male 68%, mean MELD 15±6), the most common etiology were ALD(59%) and HCV(23%). Etiology was "cured" in 146 patients (24%), "controlled" in 170 (27%) and uncontrolled in 306 (49%). During a median follow up of 33months, 350 patients (56%) developed further decompensation (33%refractory ascites, 29% HE, 17% SBP, 13% HRS-AKI, 9% VB). The incidence of further decompensation at 5 years was significantly lower in patients with "cured" vs "controlled" vs uncontrolled etiology (38% vs 64% vs 72%, respectively; p<0.001; Fig.1A). In multivariable analysis (adjusted for age, varices, etiology, Child Pugh class, creatinine and sodium), "cured" (aHR=0.52; p<0.001) and "controlled" etiology (aHR=0.60; p<0.001) were both independently associated with a lower risk of further decompensation. Considering response to etiological treatment as time-dependent covariates, 5-year cumulative incidence of survival was significantly higher in patients with cured vs controlled vs uncontrolled etiology (83% vs 58% vs40%, respectively; p<0.001; Fig.1B). In multivariable analysis, etiological cure (aHR=0.35, p<0.001) and controlled etiology (aHR=0.61, p=0.003) were independently associated with lower mortality.
**Conclusions:** In cirrhotic patients with ascites as single first decompensating event, the cure or control of etiology of liver disease reduces the risk of further decompensations and mortality.

## 178. A PECULIAR CASE OF IRON OVERLOAD OR HYPERFERRRITINEMIA?

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**Introduction:** Iron absorption occurs in the duodenum with basolateral iron transporter Ferroportin-1 (FPN1). Hepcidin, produced in the liver in response to circulating iron levels, binds to FPN1 on macrophages, intestinal absorptive cells, and other tissues, after which FPN1 is internalized and degraded; this results in reduced iron release from the cells, diminished transfer of iron across the enterocyte, and reduced iron mobilization from the macrophages.
There are 4 main types of hereditary hemochromatosis (HH). Type 1 is the most frequent inherited form of iron overload, due to a mutation of HFE gene. Type 2, is associated with mutations in the HJV gene or the hepatic antimicrobial protein gene, leading to hepcidin deficiency. Type 3 is associated with mutations in the transferrin receptor 2 gene, also leading to hepcidin deficiency.
Type 4, also known as ferroportin disease (FD) disease, is the only autosomal dominant form of hemochromatosis due to mutations in the FPN1 gene leading to a diminished exporting function of FPN1. FD is characterised by intracellular iron retention with low levels of plasma iron and normal or low levels of transferrin-iron saturation but elevated Ferritin levels. The spleen is the most affected organ, because of high FPN1 activity at the level of macrophages. This form of haemochromatosis is characterised for lower tolerance to phlebotomies and for development of anemia (1), because of inability of macrophage to release iron necessary to production of red cells.
Treatment of HH is iron depletion. In the classic form patients have iron overload (transferrin-iron saturation > 45% and ferritin > 300 ng/mL in men and >200 ng/mL in women). Usually the initial phase of phlebotomy therapy is done with weekly removal of 450-500 mL of blood. It is important to check the hemoglobin level before and during treatment to ensure it is above 11 g/dL. Once iron depletion is reached (ferritin level 50–100 ng/mL) maintenance is continued with phlebotomies generally 3-4 times a year(1). In FD non-aggressive phlebotomy regimen is recommended, with careful monitoring of transferrin saturation and hemoglobin due to the risk of anemia (2).
**Case Report:** A 41 years old woman was referred to our hepatology clinic because of suspected iron overload in thalassemic trait. Apart from that, she had no relevant medical history.
At presentation, physical examination was unremarkable. Blood tests showed haemoglobin of 10.2 g/dL, with mean corpuscular volume of 66 fl, normal platelet and white cells count, normal transaminases and C-reactive protein, bilirubin of 1.4mg/dL, severe hyperferritinemia (2044 ng/mL) with transferrin-iron saturation of 40%. Abdominal ultrasound showed only mild splenomegaly, and a transient elastography (Fibroscan) ruled out steatosis (controlled attenuation parameter 200 dB/m) but showed mild fibrosis (liver stiffness measurement of 8 kPa). Because of high ferritin levels the patient was investigated for HFE genetic mutations, and turned out heterozygous only for alleles H63D, so hereditary haemochromatosis type 1 was excluded. In order to assess if ferritin could represent a real iron overload, the patient was further investigated by a T2-weighted MRI that excluded cardiac iron overload but showed moderate hepatic iron overload. A hepatic biopsy was therefore performed in order to stage liver damage and to direct measure the amount of hepatic iron. Liver histology showed diffuse siderosis associated with iron stores in Kupffer cells and reticuloendothelial cells, suggestive for hemochromatosis.
The patient was investigated for non-HFE genetic polymorphism, and was found heterozygous for ferroportin gene, thus being diagnosed with type 4 hereditary haemochromatosis.
Due to the thalassemic trait and the type of hemochromatosis, a course of small volume phlebotomies was started; however, the rate of phlebotomies had to be reduced due to worsening of anemia, and the patient could not reach a significant iron depletion. The clinical situation was discussed collegially with the hematologist, who excluded the possibility of iron binding therapy (deferasirox is only approved for treatment in transfusion-dependent patients with thalassemia).
The patient therefore continued small phlebotomies with increased interval between sessions. From 2019 the patient was treated with 34 phlebotomies of 250 cc, at the last blood exams her ferritin was 1097ng/ml.
**Conclusion:** This case stresses on some points that need to be discussed: firstly, the importance to consider non-HFE mutation in subjects with hyperferritinemia and low or normal TS, once common causes of secondary hyperferritinemia have been ruled out iron overload; secondly, the difficulty of treating patients with type 4 hemochromatosis who are more likely to develop anemia during phlebotomies especially if the thalassemic trait coexist.
**References:** (1)Kowdley KV. Brown KE et al. ACG Clinical Guideline: Hereditary Hemochromatosis. Am J Gastroenterol 2019; 114: 1202–1218. (2) Pietrangelo A Ferroportin disease pathogenesis, diagnosis and treatment. Haematologica 2017 102: 1972-1984

## 179. SPUR CELLS ANAEMIA IN LIVER CIRRHOSIS: A COHORT STUDY

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**Background and Aims**: Chronic anaemia in advanced liver disease is a frequent finding that need to be carefully evaluated. Several factors can contribute to the pathogenesis, including bleeding, malnutrition, bone-marrow diseases, haemolysis. The aim was to explore the clinical impact of spur cells anaemia, a rare form of non-immune haemolytic anaemia in which red blood cells are spiky-like and that is typically associated with end-stage cirrhosis with poor outcome in absence of etiological therapy, focusing on prevalence, clinical presentation, associated factors and possible prognostic implications.
**Methods:** 119 consecutive patients (73.9% males) with different cirrhosis aetiologies (43.7% alcoholic, 35.7% HBV/HCV, 10.1% autoimmune, 10.9% metabolic) referring to our Liver Unit were enrolled. Inclusion criteria were consistent with a diagnosis of liver cirrhosis of any aetiology, disease severity and hepatocellular carcinoma. Patients with bone marrow diseases or nutrients deficiencies (iron, folates, vitamin B12) were excluded. A complete blood biochemical panel was recorded together with Child-Pugh score (CPS) and MELD score. In all patients a blood smear was collected in order

to assess red blood cells morphology and quantify spur cells (achantocytes and echinocytes). For each patient clinical, endoscopic, imaging data and 1-year liver-related mortality were obtained. A cut-off of 5% of spur cell was considered as a threshold for clinical significance.
**Results:** 11 out of 119 patients (9.2%) had more than 5% of spur cells in blood smear, 7 out of 11 had alcoholic cirrhosis and 2 out of 11 had evidence of haemolysis; 33.6% (40/119) had more than 1%. In patients with more than 5% of spur cells, haemoglobin (9.7 [9.0-11.1] vs 11.7 [10.2-13.5] p=0.006) was lower compared with the other sub-group, while CPS (9.0 [8.0-11] vs 7.0 [5.5-9.0], p=0.002), MELD (18 [14-20] vs 12 [8-16], p=0.001), prothrombin time (1.5 [1.2-1.7] vs 1.2 [1.1-1.5], p=0.014), creatinine (1.3 [1.0-1.4] vs 0.8 [0.7-1.2], p=0.023) and unconjugated bilirubin (1.2 [0.7-1.3] vs 0.6 [0.3-1.0], p=0.045) were higher; no differences were shown in ferritin, folates, B12 vitamin, albumin and total bilirubin. Patients with more spur cells were more frequently decompensated (ascites: 100% vs 55.1%, p=0.002; hepatic encephalopathy 63.6% vs 20.8%, p=0.008). One-year liver-related mortality was significantly higher in these patients compared with subjects with lower spur cells (77.2% vs 22.2%, p=0.001). Similar results were shown when considering patients with more than 1% of spur cells.
**Discussion:** Our results are consistent with a relatively high prevalence of spur cells in blood smear of outpatient cirrhotics. Despite not always associated with clinically overt haemolytic anaemia, the presence of spur red cells is associated with a more severe disease and worse outcome, underlining the role of blood smear in patients with advanced-liver disease to better stratify prognosis and eventually prioritize patients for liver transplant. Future larger studies are needed.

## 180. CHLORPROMAZINE-INDUCED HEPATOTOXICITY AND CHOLESTATIC JAUNDICE

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Phenothiazine-induced jaundice is classified as a form of cholestatic hepatocanalicular hepatotoxicity and as an acute liver disease. Phenothiazine-induced cholestatic jaundice occurs relatively infrequently and is usually self-limited. Occasionally cholestatic jaundice may progress to chronic liver disease. The mechanism of hepatotoxicity is not completely understood but may involve a combination of physiochemical, immune, and direct toxic effects. The pattern of serum enzyme elevations is typically cholestatic or mixed. Autoantibody formation is rare. The onset of jaundice usually occurs during the first one to four weeks of therapy. In most cases, discontinuation of the offending drug is the only treatment required. Ursodeoxycholic acid and methylprednisolone can be efficient. Jaundice usually resolves without sequelae two to eight weeks later. Whenever possible, reinstitution of neuroleptic therapy should be delayed until the reaction has resolved. Selection of a nonphenothiazine neuroleptic agent may be preferred.
We reporte a case of 82 year old caucasian woman presenting to the emergency department (ER) for jaundice with acholic feces. Her personal history was notable for Moderate Major Neurocognitive Disorder in Major Depression for whom she had been starting theraphy with Chlorpromazine since a month. ER blood tests showed AST 272, ALT 306, GGT 526, alkaline phosphatase 483, total bilirubin 16,9, direct 9, PCR 1.53, LDH 304, pancreatic amylase 40.
Total body CT resulted normal. Autoimmune and infective patterns turned negatives. No indications was given to liver biopsy in consideration of the patient's age and comorbidities. Therefore, an iatrogenic origin of the haepatic disease was supposed and chlorpromazine was replaced by benzodiazepines. Ursodeoxycholic acid (450 mg tid) and methylprednisolone (20 mg tid) was also given, decreasing it progressively during the hospitalization. The jaundice and serum aminotransferase reduced in four weeks (total bilirubin 2,8, direct 1,2; GGT 255; alcaline phosphatase 111; AST 74; ALT 144). The cholestatic hepatitis and jaundice caused by chlorpromazine have been marked by short incubation period (1-4 weeks). Patient had benefit from ursodeoxycholic acid (12-15 mg/kg/day) and corticosteroids therapy

## 181. CURCUMA AND LIVER: FRIENDS OR FOES?

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**Introduction:** Drug-induced liver injury is a common condition, which sometimes is responsible for acute liver failure and consequently urgent liver transplant. Recently, several cases of acute non-infectious cholestatic hepatitis appeared in Italy following consumption of Curcuma longa-containing dietary supplements. Herein, we described our clinical experience of an acute drug induced hepatitis associated with Curcuma use.
**Case Report:** A 66-year old Italian female was admitted to our Hospital for asthenia, itching and jaundice with onset one week prior. Her past medical history included: appendicectomy and osteoarthritis. The woman was housewife, she had no children and she lived with her housband. Personal history was negative for alcohol intake, smoke and risk factors for leptospirosis infection as well as for food poisoning. She reported curcume use as chondroprotector from one month for joint pain, she denied consumption of other drugs/herbal remedies/dietary supplements. On physical examination, the patient was jaundiced in absence of hepatic encephalopathy or ascites, no signs of chronic liver failure were found and no additional signs were detected in other organs and systems. BMI was 23, blood pressure was 120/80 mmHg, heart rate was 100 bpm, O2 Sat was 98%. Serum biochemical tests showed WBC 5210/mmc Hb 14.1 g/dl MCV 77 fL PLT 216000/mmc, ALT 3033 U/L AST 1999 U/L, creatinine 0.9 mg/dl, ALP 128 U/L GGT 184 U/L total bilirubin 20 mg/dl (direct 18 mg/dl), no signs of infection (PCR <0.3 mg/dl PCT 0.14 microg/L), total proteins 5.4 g/dl (alb 61%, gamma 18%), no alteration of tumor markers, INR 1.08, ammonium 51 micromol/L, TSH 2.55 mUI/L, IgA 193 mg/dl IgG 1210 mg/dl IgM 64 mg/dl, ferritin 4274 microg/L, iron 280 microg/dl, % transferrin saturation 93%. Additional blood markers of autoimmunity (AMA, ASMA, LKM, ANA, ENA, SLA, ANCA, native DNA) as well as of antigen and/or antibody profiles of the most important hepatotropic viruses (HAV, HBV, HCV, HDV, HEV, HSV-1, HSV-2, CMV, EBV), of HIV as well as toxoplasma were negative. Major genetic mutations for hemochromatosis (C282Y and H63D) were not detected. The nasopharyngeal swab was negative for SARS-CoV-2 real-time polymerase chain reaction. Thorax and abdomen CT revealed hepatomegaly without lesions, inflammation of gallbladder without stones, regular spleen, small lymphadenopathy in the hepatic hilum, no suggestive features for cirrhosis or portal hypertension. Liver biopsy showed acute portal/periportal hepatitis. The inflammatory infiltrate was mainly mononuclear with lymphocytes and prominent presence of eosinophils. Treatment with steroid (prednisone 60 mg die) was started with rapid clinical improvement and normalization of LFTs. Later, therapy was gradually reduced and discontinued without rebound of transaminases.
**Discussion:** Turmeric is a well-known spice with medicinal and cuisines use. It is obtained from a plant growing in the far Eastern countries and has long been claimed to be a good remedy for joint health and also to protect against the toxic effects of hepatotoxic drugs, such as acetominophen or alcohol. However, data literature explained that excessive doses of tumeric or long term intake can induce oxidative stress, inflammation and risk of liver injury. Most patients still consider herbal remedies as healthy and secure. When questioning patients with adverse reactions it is always essential to specifically ask them about the consumption of this kind of herbal remedies and also vitamins or other supplements which are not completely devoid of risks but can be falsely perceived as good by the patients. So, clinicians should do not forget to collect an accurate medication history and dietary history.
**Conclusions:** DILI is a well described condition and it is a diagnosis of exclusion. In these clinical situations, it is necessary check for potential counfounding factors such as pre-existing liver disease, presence of liver metastases, viral infections, and rule out underlying autoimmune hepatitis. Liver biopsy can be considered as it can provide information supporting the diagnosis/prognosis or it can suggest an alternative diagnosis (as AIH). Prognosis of DILI is generally good, even if only 10% have ALF with coagulopathy and encephalopathy. When DILI is suspected, liver injury may resolve promptly on cessation of the causal medication and steroid can be used in selected cases.

## 182. ADHERENCE TO SURVEILLANCE FOR HEPATOCELLULAR CARCINOMA (HCC) IN HEPATITIS C VIRUS (HCV) CIRRHOTIC PATIENTS DURING THE COVID19 PANDEMIC

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**Background:** and Aim: Hepatocellular carcinoma (HCC) represents a

major complication in HCV cirrhotic patients, who need a surveillance with upper abdomen ultrasound, performed every 6 months, although treated and cured with direct antiviral agent (DAA).
The aim of this study is to evaluate the adherence to this follow-up and to propose to patients a parallel follow-up through the GALAD score, a combined demographic and biochemical test including alfa-fetoprotein (AFP), alfa-fetoprotein-L3 (AFP-L3) and des-carboxy-prothrombin (DCP).
**Patients:** 375 cirrhotic patients treated in our clinic with DAA between 2013 and 2021.
**Results:** Out of 375 patients, 158 (42.1%) have been enrolled to underwent the GALAD score; of the other 217, 87 (23.2%) were lost at the follow-up, 35 (9.3%) refused informed consent, 23 (6.1%) developed HCC before the study, 72 (19.2%) deceased; of which 19 patients (26%) for HCC. Refusal causes was: residence in a nursing home (5 patients), lack of interest (12 patients), other medical conditions (13 patients), difficulties in reaching the hospital (4 patients) and language barriers (1 patient). About 193 alive patients, 75 patients (39%) performed a regular follow-up (every 6 months), 53 (27%) performed an irregular follow-up (over 6 months), 65 (34%) did not performed any follow up; of them 6 (9%) for forgetfulness, 9 (14%) have not performed any follow-up for lack of interest, 14 patients (21%) missed the regular follow-up because of the COVID-19 pandemic, 7 (11%) because they reside in nursing home or suffer from other diseases and 3 (5%) did not know they had to do it. Of the remaining 26 (40%) the reason of the lack of follow-up is not known.
**Conclusions:** Only 39% of HCV cirrhotic patients underwent to HCC screening according to international guidelines. Probably a faster and more accessible screening method, such as the GALAD score, could increase adherence of the patients to HCC surveillance.

## 183. RITIRATO

## 184. AUTOIMMUNE HEPATITIS AFTER SARS-COV2 VACCINATION: A MULTICENTER OBSERVATIONAL STUDY

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**Background and Objectives:** Autoimmune hepatitis (AIH) is a severe liver disease that arises in genetically predisposed individuals. Diagnosis of AIH is made clinically applying diagnostic scores; however, the heterotopic disease phenotype often makes a rapid determination of disease challenging. AIHs have been reported in association with SARSCoV2 infection and recently has been related with SARS-CoV-2 vaccines as a potential trigger as well. Liver histology depicts inflammatory portal infiltrate with interface hepatitis, lobular and centrilobular inflammation with centrilobular necrosis, in absence of fibrosis and steatosis. Apparently, no specific antibodies pattern is shown in this kind of hepatitis. A good response to medical treatment with steroids is found in most of cases. The aim of this study is to investigate if exist a possibile relationship between SARSCOV2 vaccination and the development of AIH.
**Methods:** Cases of AIHs of undefined diagnosis from different hospitals among Lombardy region (Pavia Hospital, Policlinico San Marco Hospital and IRCCS San Raffaele Hospital) were studied from March 2022 so far. In all patients other causes of increasing liver enzymes were excluded and liver biopsy was performed. The vaccines studied were Pfizer mRNABNT162b2 (Comirnaty), Moderna mRNA -1273 vaccine (Spikevax) and Astrazeneca AZD1222 (ChAdOx1) (Vaxzevria) as first, second or booster dose. We collected the following biochemical and anthropometric parameters: age, sex, body-mass index (BMI), habits, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), bilirubin, albumin, prothrombin time (PT), antinuclear antibodies (ANA), anti-smooth muscle antibodies (ASMA) and perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA). Finally, we studied the lag time between the vaccine injection and the development of hepatitis and the response to medical treatment.
**Results:** 8 patients were studied. Median age was 59 years, men were 3, no one had a history of autoimmune disorders. Seven patient have been submitted to mRNA vaccine (Comirnaty, Spikevax) and 1 to viral vector vaccine (Vaxzevria). The median lag time between injection and development of AIH was 24 days, 3 patients developed hepatitis after second dose of Pfizer vaccine, respectively 28, 50 and 14 days after the injection; 2 patients developed AIH after Moderna vaccine booster dose 24 days after the inoculation, one female patient developed hepatitis after 11 days from the first dose of Vaxzevria vaccine. The main symptoms of presentation were jaundice and asthenia. All of them showed a considerable increase of liver enzymes (ALT median 780 U/L, AST median 733 U/L, GGT median 229 U/L), PT value was in range in all the cases, while bilirubin levels were found increased in 5 cases (median 2.31 mg/dl). Seven patients had ANA pattern positivity, while one patient had ASMA and another one had p-ANCA potivity, both of them were female. Five patients were taking chronic therapy for hypertension mostly with ACE inhibitors/ diuretics and beta-adrenergic blocking agents, one patient was receiving treatment with flunarazine and duloxet for chronic hadeache, while another male patient was taking inhibitor of type 1 alpha-adrenergic receptor therapy and vitamin D supplementation. All out patients was treated with glucocorticoids (7 with prednisone and 1 with budesonide) and 7 of them also with azathioprine. Good response to medical treatment was registered in all cases.
**Conclusions:** our data suggest that, although on a small cohort, doesn't exist a relationship between SARSCOV2 vaccination and the development of AIH with none of the vaccines examined. Moreover hepatitis that occurs after SARS-COV2 vaccination has a good response to medical treatment.

## 185. A MISLEADING CASE OF HEPATITIS

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**Introduction:** Hepatitis A is an inflammation of the liver caused by hepatitis A virus (HAV). The infection is transmitted via the fecal-oral route, through direct person-to-person contact or ingestion of contaminated food/water. HAV shows impressive survival ability as it is resistant to freezing and inactivation by moderate heating or chemical/physical agents. The incubation period is usually 14-28 days, but it can take up to 50 days for symptoms to occur. Clinical course is strongly associated with age: children often have asymptomatic infections, while the severity of disease increases in older ages groups. Acute liver injury induced by HAV infection is usually self-limited and supportive care is often sufficient for treatment. Nevertheless, acute liver failure can occur with a reported incidence of 0.015-0.5% and may require life-saving liver transplantation. We present a case illustrating how challenging the diagnosis of Hepatitis A can be.
**Case Report:** A 54-year-old woman was admitted to Emergency Department complaining of fever, malaise, abdominal pain, nausea and vomiting in the previous week. One day before, jaundice had also occurred. In anamnesis: dermatomyositis treated with methotrexate and prednisone, no chronic alcohol abuse. The patient was hemodynamically and neurologically stable. Laboratory tests documented an impaired liver function (AST 3560 U/L, ALT 6200 U/L, total bilirubin 12.5 mg/dL, direct bilirubin 9.8 mg/dL, PT ratio 6, glycemia 33 mg/dL). Contrast-enhanced CT-scan of the abdomen showed hepatic steatosis and signs of inflamed gallbladder, without biliary tract dilatation. The patient was diagnosed with acute liver failure and transferred to the ICU of our hospital in order to ensure a prompt transplantation listing in case of further worsening of liver function. She was treated with glucose infusion, plasma transfusion, lactulose, albumin and vitamin K supplementation. Methotrexate therapy was suspended due to its potential hepatotoxicity, while prednisone was continued. Hepatic cytolysis and functional markers progressively improved: in two days transaminases were more than halved, albumin normalized and PT shortened. On the other hand, biochemical markers of cholestasis started developing an incremental trend. Given this biochemical improvement, the patient didn't undergo a liver transplant and was transferred to our intermediate care unit. Lab tests showed:
The patient had already denied contact with other cases of Hepatitis A, travel to endemic areas and previous consumption of shellfish or raw vegetables/fruits. When repeatedly asked, she only remembered having eaten mushrooms on Christmas time (about 50 days before symptom onset). The hepatologist consultant declared that anti-HAV IgM positivity was not reliable and could be the result of a cross-reactivity in a patient with medical history of immunological disorders. For epidemiologic and anamnestic reasons, the most likely diagnosis seemed to be an autoimmune hepatitis, but the clinical course was not typical because of the discrepant trends of hepatocellular damage and cholestasis markers. As symptoms regressed in 10 days with only supportive measures, we decided not to perform a liver biopsy. Meanwhile, blood and fecal samples previously collected were sent

to Pavia's Policlinic, where HAV-RNA testing is performed. In a couple of weeks molecular analysis detected HAV-RNA in stool and blood specimens (respectively over 4 and 2 million copies/mL). The diagnosis of HAV-induced acute liver injury was finally confirmed. After 1 month of hospitalization, total serum bilirubin started decreasing (peak level of 23 mg/dL reached 25 days after symptom onset), so the patient was dismissed. Follow-up outpatient visits were scheduled in the Liver Unit of our hospital; 3 weeks after discharge the patient was in good shape with preserved synthetic liver function (PT 1.04, CHE 6700 U/L, albumin 4 g/dL) but still altered cholestatic markers (total bilirubin 2.5 mg/dL, direct bilirubin 2.2 mg/dL, ALP 161 U/L, GGT 88 U/L).
**Conclusions:** Even if Italy is considered an area with very low endemicity, HAV infection should be considered in the differential diagnosis of acute liver injury. HAV-IgM positivity is usually the gold standard for hepatitis A diagnosis, but serologic tests are often misleading because of the known risk of false results. Detection of HAV-RNA in blood or stool samples may be used as an alternative diagnostic method in cases of acute hepatitis of unknown etiology. Furthermover, discrepancies between biochemical markers may be suggestive.

## 186. NON-ALCOHOLIC STEATOHEPATITIS (NASH) INCIDENCE IN A LARGE COHORT OF TYPE 2 DIABETES MELLITUS (T2D) PATIENTS: AN UNICENTRIC OBSERVATIONAL STUDY

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**Abstract:** The current European guidelines recommend screening for non-alcoholic steatohepatitis (NASH) in high-risk individuals: age >50 years, type 2 diabetes mellitus (T2D) and metabolic syndrome. Growing evidence suggests non-alcoholic fatty liver disease (NAFLD) often coexists with T2D, mainly because both diseases share common metabolic risk factors. Furthermore, NAFLD is associated with increased risk of complications of T2D and, similarly, T2D increases the risk of NASH, cirrhosis and hepatocellular carcinoma (HCC). The aim of the study is to select reliable clinical and laboratory parameters for the screening of diabetic patients with NASH who could develop further liver-related events.
**Methods:** We conducted an observational retrospective study on a cohort of 191 adult patients followed by the Diabetology Unity of our Center (IRCCS San Raffaele Hospital) from January 2017 to December 2021. All the patients were affected by T2D with a body mass index (BMI) ≥ 25 kg/m2 and elevation of transaminases or documented steatosis by abdomen ultrasound (US). We evaluated the association between biochemical data (ALT), anthropometric data (BMI), duration of T2D, specific T2D therapy (insulin therapy, oral hypoglycemic agents and diet) and evidence of NAFLD.
**Results:** Patients characteristics are presented in Table 1. Patients had a median age of 64 years (27-92) and men represented the 77.5% of the cohort. Median duration of T2D was 10 years (1-40). Furthermore, the BMI median value was 29 kg/m2 (25-75): 49.2% of the patients were obese (BMI ≥25) and 50.8% were overweight (BMI between 25 and 29.9). We also studied the trend over time of ALT (n.v. 0-40 U/L) and we observed a median value of 56 (41-435). Finally, the use of insulin therapy was used by 42 (21.99%) of the patients, while the remaining 149 (78.01%) were treated with oral hypoglycemic agents (alone or in combination) or with diet alone.
**Conclusions:** Strong and healthy collaboration between hepatologists and diabetologists is essential for this typology of patient, especially in view of new emerging and promising therapeutic options for NAFLD treatment. It is also important to raise awareness of NAFLD screening in scientific diabetological community, because a good glycemic control reduces the risk of hepatopathies and, vice versa, a good management of liver diseases decreases the possibility of developing T2D complications.

| Variable | Value |
|---|---|
| Age (yrs)* | 64 (56-72.5) |
| Sex° | • M 77.5<br>• F 22.5 |
| BMI (kg/m2)* | 29 (25.8-32.3) |
| T2DM duration (yrs)* | 10 (5-16) |
| ALT (U/L)* | 56 (47-79) |
| T2D Therapy° | • Insulin therapy: 21.99<br>• Oral hypoglycemic agents/diet: 78.01 |

**Table 1:** Data with [1] are median (IQR) or ° number (%)

## 187. N-ACETYLCYSTEINE ADMINISTRATION AND CIRCULATING OXIDATIVE STRESS MARKERS IN AMIODARONE-INDUCED ACUTE LIVER INJURY: A CASE REPORT

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Amiodarone is a powerful class III antiarrhythmic drug used to revert atrial and ventricular tachyarrhythmias. Even though this compound is the most frequently prescribed in the United States and Europe, it can potentially present with several side effects, including hepatic toxicity. When orally administered for long periods, it may cause micro- and macrovesicular steatosis that progresses to steatohepatitis. Intravenous (IV) amiodarone-induced liver injury is infrequent but may induce severe hepatic enzyme elevation. The mechanisms of liver damage induced by amiodarone are not completely clarified; however, oxidative stress might play a significant role.
Here, we describe the case of a 74-year-old man presenting with atrial fibrillation with rapid ventricular response associated with supraventricular paroxysmal tachycardia, for which IV amiodarone was administrated. After 16 hours from the first administration of 900 mg IV amiodarone, laboratory tests showed very high levels of both aspartate aminotransferase (AST) and alanine aminotransferase (ALT), which were representative of extensive hepatic necrosis (5057 U/L and 2442 U/L, respectively). After ruling out other possible causes of liver damage, the Naranjo Adverse Drug Reaction Probability Scale and the Roussel Uclaf Causality Assessment Method (RUCAM) were applied, both resulting in definite adverse drug reaction. Thus, IV amiodarone was promptly stopped, followed by infusion of 300 mg/Kg N-acetylcysteine (NAC) according to the United States Food and Drug Administration approved acetaminophen toxicity protocol. After 24 hours from amiodarone discontinuation and NAC administration, both serum AST and ALT quickly decreased (827 U/L and 1575 U/L, respectively) until normalization after 24 days. Serum samples were collected to evaluate hydroxynonenal (HNE)- and malondialdehyde (MDA)-protein adducts – considered as circulating markers of oxidative stress – on the day of IV amiodarone administration, 24 hours later, and 24 days later. Of interest, both HNE- and MDA-protein adducts raised immediately 24 hours after IV amiodarone administration; a consistent decrease was observed after 24 days, simultaneously with AST and ALT normalization.
Differently from chronic oral administration, acute IV amiodarone toxicity is relatively rare. However, several case reports have been described. IV amiodarone is frequently administered to seriously compromised patients for acute arrythmias, so that it can be challenging to distinguish DILI from other acute causes of hepatitis. Moreover, as is the case in this report, liver histology is frequently not performed. Even though the pathophysiology of IV amiodarone-induced liver injury is unknown, previous experiments from our laboratory evidenced the impact of mitochondrial oxidative stress and respiratory chain dysfunction as key mechanisms of amiodarone hepatotoxicity and showed that NAC specifically counteracts these harmful effects. Showing a striking improvement in serum aminotransferase levels immediately following NAC administration, this case report is consistent with a pathogenetic role of oxidative stress in IV amiodarone-induced hepatic damage. Circulating levels of HNE- and MDA-protein adducts from this patient strongly support this hypothesis. Further studies are warranted to explain the possible protective role of NAC in amiodarone-induced acute liver failure.

## 188. CHOLESTASIS IN A PATIENT WITH HODGKIN'S LYMPHOMA

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We present the case of a 34-year-old woman, who first complained of worsening pain in her lower back at the end of 2021. She was prescribed non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids by her general practitioner, with partial benefit. After five months, the pain spread to the hips and she experienced weight loss, together with an increase in C-reactive protein (7.3 mg/dl). On suspicion of sacroiliitis, she was admitted to an orthopedic clinic. During the stay, a magnetic resonance imaging (MRI) showed infiltrations of the iliac bones and adjacent muscles and

vertebrae. Therefore a whole body contrast-enhanced CT was performed and revealed supra- and infra-diaphragmatic lymphadenopathies together with hypodense areas within the spleen. A whole body FDG-PET showed intense radionuclide uptake of lymph nodes, spleen and bones, consistent with aggressive lymphatic disease. A biopsy was performed on the right iliac bone. While awaiting results, the patient suddenly developed an increase in liver cytolytic and cholestatic enzymes (ALT 274 U/l, AST 517 U/l, GGT 317 U/l, ALP 520 U/l, direct bilirubin 3.1 mg/dl). She stopped taking a selective cyclo-oxygenase 2 inhibitor and underwent an abdominal ultrasound (US), with no abnormal findings. Major hepatic viral serology was negative, as was an autoantibody screening (rheumatic factor, ANA, ENA, ACPA, AMA, ASMA, LKM). In the following days vomit, epigastric pain and fever appeared and a new US was performed, which revealed thickening of gallbladder walls. She was started on protonic pump inhibitor, intravenous rehydration and ceftriaxone on suspicion of acalculous cholecystitis. Despite a decrease in liver cytolytic and cholestatic enzymes, bilirubin level increased.
For this reason, at the end of June, the patient was transferred to our hospital. We performed a new biopsy, this time on an inguinal lymph node. The histological result was consistent with a diagnosis of Hodgkin's lymphoma (HL, classic variant). She was started on methylprednisolone on 1st of July and underwent the first cycle of chemotherapy (ABVD combination) one week later. Two weeks after admission, liver tests reached a peak (AST 412 U/l, ALT 713 U/l, GGT 529 U/l, ALP 823 U/l, total bilirubin 19.5 mg/dl, direct bilirubin 18.2 mg/dl). Having excluded other causes of hepatitis, cholecystitis and cholangitis, vanishing bile ducts syndrome (VBDS) was suspected as a paraneoplastic manifestation and a liver biopsy was performed. The histologic section showed focal lymphoid infiltration of portal spaces, widespread ductopenia of interlobular biliary ducts in 75% of portal spaces and degenerative modifications of the rare residual ducts, which lead to confirming the diagnosis of VBDS. The patient started ursodeoxycholic acid and continued glucocorticoid therapy. Liver tests improved rapidly (AST 80 UI/l, ALT 384 UI/l, GGT 354 UI/l, ALP 573 UI/l, total bilirubin 14.3 mg/dl, direct bilirubin 12.8 mg/dl). The patient was discharged shortly after and continued chemotherapy in our oncology day unit, with complete remission after 6 cycles.
**Discussion:** VBDS is a rare cholestatic disease that may eventually lead to bile duct destruction with disappearance of intrahepatic bile ducts. It can be associated with several conditions such as adverse drug reactions, infectious diseases, autoimmune diseases and malignancies. The disease can be severe with cirrhosis or acute liver failure as possible consequences. The diagnosis can be suspected in patients presenting with signs and symptoms of cholestasis and liver biochemical abnormalities. However, the diagnosis can only be established through liver biopsy, which should show a loss of interlobular bile duct in more than 50% of portal areas (with a specimen containing at least 10 portal tracts), after excluding other conditions. In the case of our patient, both HL and the COX-2 inhibitor may have led to VBDS, with worsening of liver function due to the administration of chemotherapy.
**Conclusion:** Liver involvement in HL may be due to a plethora of causes ranging from biliary duct obstruction by lymph nodes enlargement to hepatic infiltration, including chemotherapy complications and viral diseases. Though VBDS is rare, it should be suspected when cholestatic abnormalities on blood exams are found, in the absence of common conditions associated with cholestasis. Liver impairment caused by VBDS confers a poor prognosis and limits chemotherapy. Therefore a better understanding of its pathogenesis is needed to improve the treatment of patients with Hodgkin's lymphoma and VBDS.

## 189. INTERLEUKIN-6 AS A NEW MARKER FOR ADVANCED SARCOPENIC HCC PATIENTS WITH DIFFERENT CIRRHOTIC AETIOLOGY

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**Background:** Hepatocellular carcinoma (HCC) is a major cause of liver cancer-related death worldwide. It usually occurs in cirrhosis with different etiopathogeneses. Sarcopenia is present in almost one third of patients with HCC and is a strong and independent risk factor for mortality. Interleukin-6 (IL-6) is a proinflammatory cytokine that increases considerably in pathological settings such as trauma, inflammation and neoplasia. Based on pre-clinical data in HCC, IL-6 signaling leads to tumor progression or local recurrence. Aim of the study was to clarify if the levels of IL-6 are associated with sarcopenia and HCC progression.
**Methods:** 111 consecutive HCC cirrhotic patients (with different stages and etiopathogeneses) were enrolled and compared with 36 cirrhotic patients without HCC. Patients were subdivided according to Child Pugh (CP) class and BCLC classes to establish the severity of HCC disease ("advanced HCC" was considered HCC with portal invasion and extrahepatic spread). The major anthropometric and biochemical parameters, particularly serum IL-6, were collected. The degree of sarcopenia was also evaluated using CT dedicated software. Sarcopenia cut-off values derived from cirrhotic patients on the liver transplant list and based on clinical outcomes were: 50 cm2/m2 for men and 39 cm2/m2 for women.
**Results:** IL-6 levels were different between advanced and non-advanced HCC (p = 0.01), they were increased in advanced HCC (OR 4.58 CI: 1.19-17.55; p < 0.001). IL-6 levels were different also between different etiologies of cirrhosis (p< 0.001); in particular, no differences were evident in viral and metabolic HCC, low levels were present in alcoholic HCC and increased levels in autoimmune HCC or in combination of different aetiologies. In linear regression IL-6 was correlated with AFP (p < 0,001, r = 0.57). IL-6 was correlated with sarcopenia (p = 0.051, Figure 1) especially in advanced HCC patients (p= 0.04, Figure 2). However, IL-6 did not correlate with sarcopenia grading (p = 0.108). In no-HCC CP-C patients, IL 6 did not correlate with sarcopenia.
**Conclusions:** These data suggest that IL-6 has a close relation with advanced HCC. Different IL-6 levels in different ethiologies of cirrhosis are related to different inflammatory settings. Therefore, IL-6 could be a new marker to detect advanced HCC and a possible future drug target considering the different cirrhotic etiopathogeneses. Eventually, IL-6 seems to be a predictor of sarcopenia in advanced HCC patients, but it can't predict the severity of sarcopenia and it isn't influenced by severity of cirrhosis.

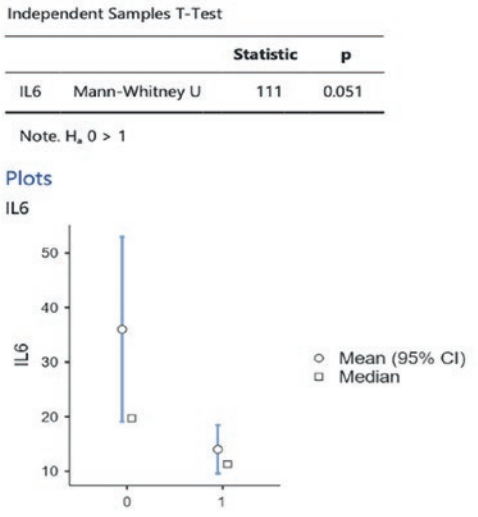


**Figure 1:**

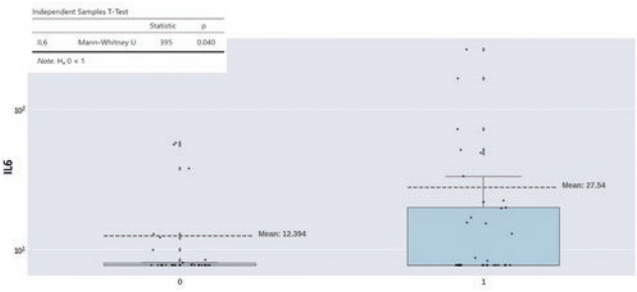

**Figure 2**

## 190. DISSECTING NAFLD INTO MORE ACCURATE CLASSIFICATIONS: PREVALENCE OF TOXICANT-ASSOCIATED FATTY LIVER DISEASE

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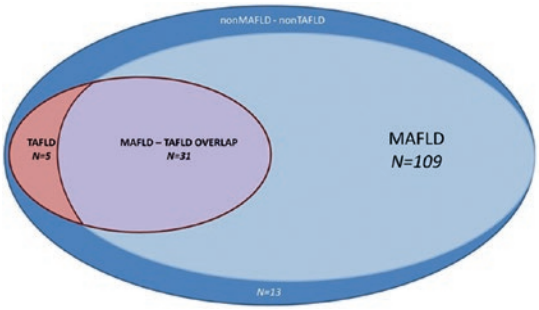
**Background and Aims**: Non-alcoholic fatty liver disease (NAFLD) encompasses different conditions characterized by hepatic steatosis without significant alcohol consumption. Most patients have features of metabolic syndrome. Consequently, a novel classification of metabolic dysfunction associated fatty liver disease (MAFLD) has been proposed for these cases. Environmental toxicants are another cause of hepatic steatosis and steatohepatitis,and a novel clinical entity called toxicant-associated fatty liver disease (TAFLD) was coined in 2010. Toxicants not only induce steatosis/steatohepatitis in lean subjects, but also contribute to liver damage impacting on the same metabolic pathways of MAFLD (Sen, J Hepatol 2021). Given the increase in NAFLD-associated cirrhosis and HCC, the prevalence of TAFLD should be evaluated to enact effective preventive measures. We hereby report the preliminary results of a dedicated study funded by the Italian Ministry of Health.
**Method:** consecutive NAFLD patients were administered a questionnaire to obtain a detailed anamnesis of occupational and environmental exposures. This information was integrated with clinical data obtained as part of normal clinical practice Questionnaires were evaluated by specialists in occupational medicine. Based on the reported data, the probability of TAFLD was classified as highly likely/likely, possible, and unlikely. Diagnosis of NAFLD and MAFLD was made according to the existing criteria.
**Results:** We enrolled 158 patients, mostly males (n=90, 56.9%), with a median age of 65 years. Positive criteria for TAFLD (highly likely or likely) were found in 36 (22.8%) NAFLD patients. Amongst them, 31 also satisfied MAFLD criteria while 5 patients had no signs of metabolic dysfunction (Figure). The most frequently found professional exposures were amongst farmers, steelworkers, mechanics, textile and petrochemical workers. The median body mass index and prevalence of diabetes and dyslipidemia were not significantly different between patients with and without TAFLD.
**Conclusions:** TAFLD is a not uncommon cause of NAFLD, especially amongst lean patients. Significant professional exposures to chemicals involved in TAFLD were also found amongst patients who satisfied the MAFLD criteria. Since the pathogenic mechanisms of liver damage are similar in both conditions, further studies are warranted to verify the opportunity of preventive and therapeutic measures for highly exposed workers.




## 191. TOLERABILITY OF FIRST LINE SYSTEMIC THERAPY IN ELDERLY PATIENTS WITH HEPATOCELLULAR CARCINOMA

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Liver cancer is the fourth leading cause of cancer death globally, with hepatocellular carcinoma (HCC) representing 90% of primary cancer. The average age of HCC development is 70 with aging being a known risk factor. Population in Italy is older than in other countries with expected increasing incidence of HCC. Most studies support the concept that, in general, all available treatments for primary cancer can also be recommended for elderly patients, keeping comorbidities into account in choosing process3.
Given these principles we studied patients' overall survival (OS), time to progression (TTP) represented as therapy duration and adverse events (AE) secondary to two different first line systemic therapy agents (sorafenib and lenvatinib).
Our population was composed by 103 patients affected by HCC, afferent to the hepatological clinic of A.O.U. Maggiore della Carità (Novara). Median age at diagnosis of HCC was 72 [27-88] with a median age at systemic therapy start equal to 73 [27-88]. Patients older than 65 years represented the 79.2% of our population, over 70 were the 59,4%, while patients older than 80 years were 19,6% of the total. Patients were predominantly men (79,6% male vs 20,4% female) and the majority of them suffered from chirrosis (85,4%). The most common etiology was viral (55,7%). Alpha-fetoprotein (AFP) values had a median of 50,9 [1-61962] before starting therapy. There was no statistically significant difference (p=0,08) in number of patients treated with the two systemic therapies: 21 patients were treated with lenvatinib, with a median age of 76 years at the start of therapy, while 82 patients were treated with sorafenib with median age of 72,5 years. Median systemic therapy duration was 4,7 months in sorafenib-patients (SP) and 10 months in lenvatinib-patients (LP) (p=0,003). OS was 15,8 months in SP and 26,4 months in LP (p=0,04). No difference in systemic therapy duration was observed considering age ≥80 years (p=0,63). Patients older than 80 years showed reduced OS as might be expected for age. Most reported AE were fatigue, anorexia and diarrhea with no statistically significant difference in terms of prevalence between patients older than 80 and younger ones. Regarding diarrhea and anorexia, no patients over 80 had a Common Terminology Criteria for Adverse Events (CTCAE) grade greater than 1. Patients over 80 did not require dose reduction any more than younger patients.
Our study demonstrates how elderly patients could be treated safetly with the same intensity as younger patients. Adverse events didn't represent a crucial factor for discontinuing therapy in elderly patients. It is essential to know how to manage adverse events in a timely and precise way, educating the patient to recognize them as such and to report them to the attending physician. Knowing that the epidemiology of HCC will increasingly affect elderly patients, the choice of treatment based on the characteristics of the subject will be decisive but age alone should not represent a limitation at the beginning of systemic therapy.

## 192. VALIDATION OF THE PROGNOSTIC ROLE OF A NEW DISTINCT ASSESSMENT OF LIVER FUNCTION IN NON SURGICAL HCC PATIENTS

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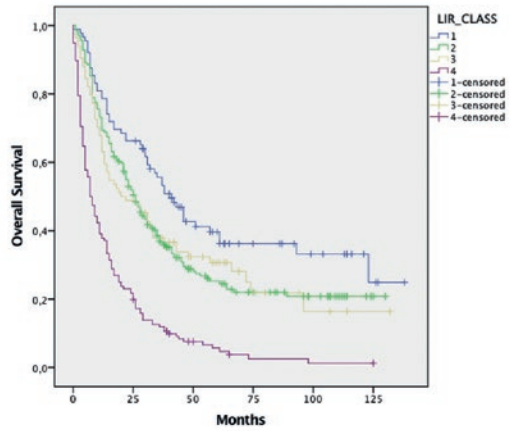
**Background and Aims**: While the role of distinct HCC tumor burdens is quite consolidated, new insights about the impact of more granular assessment of liver function in the prognosis of HCC patients are emerging.
A very recent review published in Journal of Hepatology described the prognostic relevance of liver functional reserve across the various non-surgical HCC treatments. Based on their experience, the authors proposed a new staging algorithm combining liver functional reserve and tumor bulk separating patients even within the Child-Pugh A and B classes. The present study aims to validate the prognostic role of such system.
**Method:** We retrospectively evaluated all patients with HCC who were not surgically treated in two large Italian centers between 2010 and 2021. A Kaplan-Meier survival analysis was carried out classifying patients according to the new classification proposed by D'avola, Piscaglia et al. which identifies four different subclasses considering the liver functional reserve:
**Results:** A total of 538 patients were analyzed. Median overall survival was 41 months in LIR 1 (89 pts), 26 months in LIR 2 (209 pts), 20 months jn LIR 3 (84 pts) and 16 months in LIR 4 (156 pts).
Interestingly, LIR 1 median OS was significantly higher than LIR 2 subgroup ($p<0.05$), despite both including only CPT class A patients. LIR 2 OS which instead was closer to that of LIR 3 subgroup suggesting an important prognostic role for ALBI grade and past episodes of hepatic decompensation even for patients within the Child-Pugh A class. Additionally within the CPT B/C classes, a current decompensation must be kept separated from CPT B7 patients.
**Conclusion:** This new classification based on more granular assessment

of liver functional reserve confirms its significant prognostic impact with significant differences even within the same Child-Pugh class.




**Figure**

## 193. IMMUNE CHECKPOINT INHIBITORS' LIVER TOXICITY DURING MELANOMA THERAPY: A CASE SERIES

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**Background:** Immune checkpoint inhibitors (ICIs) are the first-line treatment option for advanced (stage III-IV) melanoma. Hepatic toxicity is rare but clinically significant ranging from abnormal liver function tests to immune-related adverse events (irAEs). Here we report three cases of patients with metastatic melanoma who developed adverse liver events.
**Methods:** To report a case series of 3 female patients, with metastatic melanoma treated with ICIs therapy with different type of liver injury. Screening for other causes of liver disease was negative in all cases

| | CASE 1 | CASE 2 | CASE 3 |
|---|---|---|---|
| Age | 53 | 65 | 65 |
| Gender | Female | Female | Female |
| **Diagnosis** | Stage IIIc nodular melanoma | Metastatic cutaneous melanoma | Metastatic vulvar melanoma |
| Immunotherapy | Pembrolizumab | Nivolumab | Nivolumab |
| Syntomps | Nausea, Epigastric pain, | No obvious signs or symptoms indicating liver injury | Vomiting and Diarrhea |
| Comorbidites | Autoimmune thyroiditis | Undifferentiated connectivitis | Unspecified rheumatologic disease. |
| AST(UI/L) | 1439/34 | 1328/34 | Normal range |
| ALT(UI/L) | 1568/49 | 1426/49 | Normal range |
| Alkaline phosph(U/L) | 180/40 | 399/150 | 117/104 |
| Gamma GT(U/L) | 188/116 | 716/73 | 45/40 |
| Bilirubin (mg/dl) | 1.4/1.2 | 4.1 | Normal Range |
| Auto-antibodies | none | ANA + 1:160 ; AMA + 1:40(anti-M2/BCOADC-E2, anti GP210) | ANA 1:160 |
| RUCAM score | 9 points | 2 points | / |
| Original score for AIH | / | 6 points | / |
| Therapy | Metilprednisolone 60 mg/die and weekly tapering | Prednisone 30 mg/die | UCDA 300 mg x 3 |
| Clinical Course | Normalization of liver enzymes and cholestatic indices | Relapse at Prednisone 10 mg/die | Normalization Of Cholestatic indices |
| Second line Therapy | / | Re-induction of Prednisone 25 mg/die +UCDA 300 mg x 3 /die+ Azatioprin 50 mg | / |
| Diagnosis | DILI | AIH/CPB*induced | Sclerosing Cholangitis **induced |
| Outcome | Complete resolution | Complete resolution | Complete resolution |

*Liver Biopsy was performed, suggestive for AIH.
** RM was performed, it was suggestive for nivolumab-related sclerosing cholangitis

**Results:** #1 A patient with stage IIIc nodular melanoma was referred to us for suspicion of DILI after the last administration of Pembrolizumab in August 2022. Laboratory test showed cytonecrosis AST 1439 IU/L (v.n 0-34 IU/dL), ALT 1568 IU/dL (v.n 0-49 IU/Dl), and cholestasis ALP 188 IU/L (v.n 0-116 IU/dL), GGT 180 IU/L (v.n 0-40 IU/L). We applied the RUCAM causality assessment scored 9 (high probability of DILI). She was successfully treated with steroids therapy with a progressive improvement of liver tests.
#2 A patient affected by metastatic cutaneous melanoma who developed DILI after a course of Nivolumab was in August 2022. She showed a cholestatic pattern (AST1184 IU/L, ALT1106 IU/dL, ALP 690 IU/L, GGT 348 IU/L) and ANA 1: 160 (+), AMA 1: 40(+). A liver biopsy confirmed an Overlap AIH/PBC. She was successfully treated with steroids, Azathioprine, and UCDA.
#3 A patient with metastatic vulvar melanoma was referred after course of Nivolumab in May 2022. She had ANA + (1: 160), ALP 117 UI/L and normal GGT, AST and ALT. MRI showed biliary tract alteration suggestive for ICIs-induced sclerosing cholangitis.She was successfully treated with UCDA.
**Conclusion:** According to EASL Clinical Practice Guidelines, in all the cases, immunotherapy was discontinued and the treatment driven by liver manifestation lead to the complete resolution of the liver toxicity.
Immunotherapy has radically improvement the survival of metastatic melanoma, but it could be related to irAEs. Therefore, DILI should be kept in mind in subjects treated by ICIs and liver function should be monitored during the therapy course.

## 194. PORTAL HYPERTENSION DUE TO INFILTRATING METASTATIC MELANOMA IN THE LIVER: A CASE REPORT

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Melanoma is an aggressive malignancy that originates from melanocytes; it can arise in different sites, the most common is the skin. At diagnosis, 84% patients with melanoma will have early-stage disease and 4% will present with metastases. Metastases may involve any organ with different prognosis depending on the site; the most unfavorable prognosis concerns localization in the liver, bones and brain. Hepatic metastases from melanoma may present in up to 33% of cases with a sinusoidal growth pattern, which represent a challenge diagnosis and could lead to portal hypertension regardless of the presence of pre-existing cirrhosis.
Herein we present the case of a woman aged 74, sent for a first hepatologic evaluation due to liver enlargment and increase of liver function tests by the treating oncologists. The patient had no previous history of liver diseases. She has been suffered from diabetes mellitus type 2, hypertension, overweight, osteopenia, previous breast cancer dating back to 2013, treated with surgery, radiotherapy and hormone therapy, in follow up at the oncology unit. An abdominal ultrasound showed an enlarged liver without focal lesions. Serovirological markers for HBV, HCV, HIV, CMV and EBV were negative. During physical examination, the liver was found to be increased in size, about 5 cm from the costal arch, of increased consistency. On the abdominal wall, in the umbilical region, was evident a nevus with irregular margins and inhomogenous appearance, waiting for a surgical excision. The hepatologist prescribed liver elastometry evaluation with Fibroscan and upper abdomen CT with triphasic study of the liver. The latter was negative for focal hepatic lesions but showed splenomegaly and osteolytic lesions of a vertebra and two ribs. Liver stiffness resulted compatible with advanced chronic liver disease: liver stiffness (LS) 75 kPa, interquartile (IQR) 0 kPa and success rate (SR) 100% (10/10 shots). A subsequent esophagogastroduodenoscopy (EGD) showed hypertensive gastropathy and F1 esophageal varices. In order to study the liver disorder a hepatic biopsy was planned. On the same day the patient underwent the abdominal nevus excision. The histological examination of the skin lesion was compatible with epithelioid and spindle cell melanoma, with superficial diffusion, infiltrating the superficial and deep dermis. The hepatic biopsy revealed massive hepitelioid melanoma infiltration (HMB45 +, S100 +, V600E +); no signs of fibrosis were reported. After collegial discussion, it was proposed to start first-line therapy with a combination of dabrafenib and trametinib. Three months after starting immunotherapy, the patient was reevaluated with liver elastometry. The new values resulted: LS 21.7 kPa, IQR 6.4 kPa (29%), CAP 235 dB/m (IQR 43 dB/m). Six month after, a total body CT scan showed reduction of bone lesions.
This case report shows how hepatic melanoma metastasis could be involved in development of clinically significant non-cirrhotic portal hypertension that could lead to further complications other than the malignancy itself. Immunotherapy previously showed great beneficial effects in metastatic melanoma with high rates of response. The reduction of LS in this patient could be explained by the great efficacy of the therapy, as seen in other body

parts but more data are needed to confirm this hypothesis. Melanoma infiltration of the liver should raise suspicion of a vascular disease of the liver.
Epidemiologia clinica

## 195. BACTERIAL COLONIZATION AND HOSPITALIZATION OUTCOMES: COHORT STUDY

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*Medicina Interna, Università Campus bio-medico di Roma*

**Background:** Healthcare-associated infections (HCAIs) represent a major risk to patient safety, and a critical challenge for scientific community. Active surveillance is a mainstay of the control of HCAIs. The main aim of our study was to estimate any differences in length of hospital stay and in-hospital mortality, according to the presence or absence of multidrug resistant organisms in rectal and nasal surveillance swabs. A secondary objective was to evaluate any difference in survival rates according to the positivity of surveillance swabs, as well as the presence of at least one positive culture test during hospitalization.
**Methods:** We analyzed the retrospective data of 530 patients consecutively admitted to any of the Departments of the Campus Bio-Medico University, Rome between January 1st 2019, and December 31th 2019, without exclusion criteria. On admission, nasal and rectal surveillance swabs were collected. Data on length of hospital stay and in-hospital mortality were recorded. According to a standardized protocol, participants' data on demographics, lifestyle habits, functional ability, inserted devices, need of surgery, and setting of discharge were analyzed. Comorbidity was quantified using the Charlson Comorbidity Score Index.
**Results:** A positive surveillance swab was found in 72 (14%) patients. Specifically, 68 (13%) patients tested positive for rectal surveillance swabs, while 17 patients (3%) had positive nasopharyngeal surveillance swabs; 13 (2%) patients tested positive for both rectal and nasal swabs. Positive surveillance swabs were significantly associated with increased mortality (HR=2.18; IC 95%=1.02-4.65; P=.044) in Cox model, after adjusting. Also, according to linear regression, positivity of surveillance swabs was significantly associated with prolonged hospital stay (B=7.38; 95% CI=.42-14.34; P=.038). We found that prevalence of cognitive decline, functional disability, cancer and need for caregiver was higher in deceased patients as compared with survivors. Also, deceased patients experienced a longer length of hospital stay, with a more prevalent use of total parenteral nutrition, insertion of bladder catheter, and CVC, as compared with controls.
**Conclusions:** The positivity of surveillance swabs is associated with increased risk of in-hospital mortality, as well as prolonged hospitalization. Protracted antibiotic therapies, unavoidably used in patients with higher degrees of clinical complexity and frailty, facilitate the alteration of the normal bacterial flora with ensuing development of infections by multidrug-resistant pathogens. Furthermore, patients with positive surveillance swabs, as well as those having positive surveillance swabs and isogerm infections, are at higher risk of death; conversely, the positivity of at least a single cultural test during hospitalization doesn't seem to be associated with increased mortality.
Therefore active surveillance is a mainstay of the control of HCAIs, nasal and rectal screening on admission are recommended for active surveillance of asymptomatic carriers, in order to reduce the spread of multidrug resistant organisms. Overall, the results of this study indicate that patients with multidrug resistant organisms are characterised by greater clinical complexity and frailty.

## 196. BEDSPACING DUE TO PATIENTS' OVERFLOW IN INTERNAL MEDICINE WARDS: THE EXPERIENCE OF CUNEO HOSPITAL

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**Background:** When demand of hospitalization exceeds capacity of medical or surgical divisions, patients are relocated in different specialities' wards, that is, bedspacing. Care for bedspaced patients is provided by physician from home wards and nurses from the bedspaced ward. In this difficult situation, care for patients could be affected by eventual gaps in communication between members of two different teams; moreover, the team of the accepting Unit could lack specifical skills to manage acute medical patients2. In two large cohort studies, bedspacing, a common response to Emergency Department crowding, was significantly associated with care inefficiency, adverse events, increased length of stay and excess in mortality 1,3. In our study we report the burden of bedspacing in Internal Medicine Department of Cuneo Hospital, Italy, over a period of 5 months, and evaluate the possible effects of this impending situation.
**Methods:** We performed an observational study of bed occupation and distribution. Physicians of Internal Medicine Unit of Cuneo Hospital filled in a daily report of hospitalization, discharges, count of occupied beds (in and outside our ward) and other movements. Then we collected all the reports in a database. The period in analysis was September, October, November, part of December 2021, March, and part of April 2022, for 143 days in total. The Covid-19 outbreak of winter 2021/2022 was excluded to avoid biases due to the reorganization of the whole Hospital during pandemic.
**Results:** On average, the bedplaces available for Internal Medicine wards in our hospital were 46,7 (SD 0,7). We had a mean of 51,9 (SD 4,7) patients per day in charge of internal medicine physicians. Therefore, the mean percentage of occupation of our bedplaces was 111% (SD 10.3), with a maximum of 137% on 15 of December 2021 (Fig.1). Remarkably, the percentage of bed occupation was over 100% on about 9 out of 10 days (Fig.2). We analysed the rate of patient hospitalization and discharge, in relation with an ideal discharge rate of 1 patient in every 10 occupied beds. Delta between theoretical and effective discharging rates was 4,6 on average (SD 5,3), and, despite fluctuations due to differences between weekdays and weekends, we didn't reach the target only 22% of time (Fig.3).

| Variable | N | Mean | Std. Dev. | Min | Pctl. 25 | Pctl. 75 | Max |
|---|---|---|---|---|---|---|---|
| RICOVERI | 143 | 4.9 | 2.3 | 1 | 3 | 6 | 12 |
| TRASF.IN | 143 | 0.8 | 0.9 | 0 | 0 | 1 | 3 |
| DIMISSIONI | 143 | 4.3 | 2.4 | 0 | 3 | 6 | 10 |
| TRASF.OUT | 143 | 0.6 | 0.8 | 0 | 0 | 1 | 3 |
| DECESSI | 143 | 0.3 | 0.5 | 0 | 0 | 0 | 2 |
| TOT.IN | 147 | 5.6 | 2.5 | 0 | 4 | 7 | 12 |
| TOT.OUT | 147 | 5.1 | 2.8 | 0 | 3 | 7 | 13 |
| APPOGGI | 142 | 6.6 | 4.2 | 0 | 3 | 10 | 18 |
| Tot.posti.disponibili | 147 | 46.7 | 0.7 | 44 | 47 | 47 | 47 |
| Posti.occupati | 147 | 51.9 | 4.7 | 37 | 49 | 55 | 64 |
| X..occupazione | 147 | 111.1 | 10.3 | 79 | 104 | 117 | 137 |
| tasso.uscite.teoriche | 147 | 5.2 | 0.5 | 3.7 | 4.9 | 5.5 | 6.4 |
| tasso.uscite.reali | 147 | 9.8 | 5.3 | 0 | 6 | 13.2 | 24.5 |
| delta.uscite | 147 | 4.6 | 5.3 | -6 | 1 | 8 | 19.2 |



**Conclusion:** Nowadays more and more attention is given to patient's outcomes and satisfaction as a goal for health facilities. Good results on performance can't be obtained merely by cutting resources. Some authors argue that cost reduction without regard to the real outcomes achieved leads to false "savings" in the short period, but on other hand it could limit effective care3. In our experience, despite a good discharge rate, the amount of bedplaces in Internal Medicine wards didn't match the needs of patients crowding in the Emergency Department, as the elevated percentage of bed occupancy showed. We believe that an excessively quick turnover and the oversaturation of bedplaces could mine quality of care, in regards risk management and, ultimately, patients' morbidity and mortality.
**References:** 1. Kohn R et al. Influence of bedspacing on outcomes of hospitalised medicine service patients: a retrospective cohort study. BMJ Qual

Saf. 2021 - 2. Bai AD et al. Mortality of hospitalised internal medicine patients bedspaced to non-internal medicine inpatient units: retrospective cohort study. BMJ Qual Saf. 2018 - 3. Bogler O et al. Quality of care and outcomes in internal medicine patients bedspaced to noninternal medicine units. Medicine (Baltimore). 2021

## 197. THE INFLUENCE OF THE PANDEMIC ON THE HOSPITALIZATION ACTIVITY IN THE EMILIA-ROMAGNA REGION: HAS HEALTH CARE BEEN ADEQUATE?

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**Background:** The SARS-CoV-2 infection, due to its high contagiousness and the severity of clinical manifestations, let to the need a deep reorganization of the hospital facilities in order to manage a growing demand of assistance. As a consequence, it was necessary to apply new operative protocols for Covid disease. Other non-urgent health care activities have been rescheduled or suspended and a campaign to disincentive access to hospital has been implemented.
A review of the data collected during the first pandemic year from 20 different countries in the world, showed an overall 37% reduction in healthcare benefit. The most significant peak was recorded for the outpatient visits (-42%) and the nadir for hospital admissions (-28%) (1). In Italy, we estimated a reduction in planned and emergency hospital admissions of about -49.9% and 24% respectively, with significant differences from region to region (2).
**Aim of the study:** We wanted to analyzed all discharges from regional healthcare structures during 2020 and 2021 comparing them with 2019 to evaluate the health care activity reduction, the economic cost of this reduction and the subsequent expected recovery.
**Methods:** We used the data of the Emilia-Romagna region database evaluating all discharges (either COVID-free and COVID-related) from public and private health structures. Data were classified by medical or surgical DRG (Diagnosis Related Group) and MDC (Major Diagnostic Category).
**Results:** The data showed a reduction in discharges of about 17% in 2020 compared to 2019. There was a concomitant reduction in economic income of 12.2%, in particular for the planned healthcare activity, compared to the urgent one (-23.8% vs -10.5%) with a secondary reduction of earnings (-18% vs -5.9%). We found about the same reduction in the planned medical and surgical health activity, nevertheless the economic differences were significant (planned surgical activity -20.4% vs planned medical activity -11.8%). In 2021 healthcare activity showed a slight increase (+6.0%), especially for planned surgical activity (surgical activity +13.1%, planned surgical activity + 15.2%). On the contrary the planned medical activity showed an additional reduction compared with 2020 (-1.8%). This recovery of the activity during 2021 was not enough to achieve the pre-pandemic results (-12%), with a lesser reduction for the planned activity compared with the urgent one (-17% planned vs -7.3% urgent) that presented an important reduction also in economic income despite the positive economic performance of the urgent activity (-9.0% vs +2.7%).
**Conclusions:** Our results confirm the pandemic reduction in Emilia-Romagna's hospital discharges (-17%) but it appears to be slightly lower than the national average (-28%). In the 2021, discharges have increased, but activity is still far from pre-pandemic levels. Probably, the absence of an efficient recovery should be caused by an inadequate territorial reorganization of the healthcare system during 2020 and 2021 which resulted in the inability to handle both COVID-related and COVID-free patients to the detriment of the latter.
The financial loss was huge (310 million in 2020 and 88 million in 2021 with respect to 2019) but even more important were the loss of healthcare services, admissions, early diagnosis and quality of life and welfare. As a consequence it would be necessary a complete reorganization of the resources of the sanitary system to be more efficient during the next emergency conditions in order not to be unprepared and to preserve the public health.

## 198. HOSPITAL-ACQUIRED ANEMIA IN INTERNAL MEDICINE PATIENTS: LEARNING FROM THE "LESS IS MORE" PERSPECTIVE

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**Background:** Hospital-acquired anemia (HAA) is defined as a new-onset anemia in hospitalized patients who had normal hemoglobin level at admission. It is estimated that more than 50% of hospitalized patients develop a HAA before discharge and that, in most cases, anemia is either moderate or severe. However, most studies published on this topic have been conducted in intensive care unit patients with limited applicability to less acute settings, such as internal medicine wards. The few available and old studies, that have focused on internal medicine patients, had limited sample sizes and did not adequately control for the role of potential causes of blood loss during hospitalization. Therefore, the magnitude, severity and impact on the clinical course of HAA in an internal medicine setting are largely unknown. Our aim was to estimate the prevalence and severity of HAA and the impact of blood loss for laboratory tests on changes in hemoglobin (Hb) levels in hospitalized internal medicine patients.
**Methods:** We conducted a retrospective study and analyzed data from clinical records of 342 patients admitted to the Liver Unit, Institute of Internal Medicine, of the University of Foggia between October 2021 and February 2022. All included patients had one hemoglobin value tested on admission and within 72 hours before discharge
The exclusion criteria were:
Anemia was defined as Hb<12 g/dl in women and <13 g/dl in men.
Total phlebotomy volume per patient was calculated based on the number and type of blood tubes collected during hospitalization. Complete blood count was obtained using a 3 ml tube; electrolytes, renal and liver profiles were studied using 5 ml tubes, whereas 8 ml was the volume calculated per each bottle for blood cultures. Over 15 random days during our study, we calculated for each type of specimen tube (except for bottles for blood cultures) the height to which each tube was filled. The mean of the height was used to obtain the volume of blood collected in each tube.
**Results:** A total of 129 patients (35,6%) were included in the our final analysis. In our study population, the mean of fill volumes of blood tubes was 68% with a standard deviation (SD) of 27%. Median value of phlebotomy during hospitalization was 46 ml (IQR 30-72 ml) whereas the median length of hospital stay was 9 days (IQR 5-13 days) . The median value of hemoglobin reduction was -0,56 g/dl (p<0,001) and the maximum value of drop in hemoglobin value was -2,6 g/dl. All patients who experienced a phlebotomy >85 ml had a hemoglobin reduction >0,6 g/dl. 20,9% of patients developed anemia during the hospital stay (7% moderate and 13,9% mild). No cases of severe anemia were observed. In our study population, for every milliliter of blood drawn a drop in Hb value of -0.011 g/dl was observed. Univariate and multivariate logistic regression analysis showed that only the volume of blood drawn during the hospital stay (p=0,016) and the Hb value on admission (p=0,001) were statistically associated with the development of anemia, whereas gender, age, and chronic diseases such as diabetes, history of cancer, or heart failure were not.
**Conclusions:** Strategies such as elimination of unnecessary laboratory tests and the use of smaller tubes for blood collection are needed to reduce the volume of iatrogenic blood loss and to avoid blood wastage occurring during hospitalization in internal medicine patients. We intentionally excluded patients with anemia at hospital admission to investigate only the potential role of the medical care practices in the development of anemia. More data are needed to study the impact of hospitalization on the temporal trend of Hb levels in patients with anemia on admission and the role of concurrent chronic diseases in developing anemia during the hospital stay.
**References:** 1. Shander A, Corwin HL (2020) A Narrative Review on Hospital-Acquired Anemia: Keeping Blood where It Belongs. Transfus Med Rev 34 (3): 195-199. - 2. Makam AN, Nguyen OK, Clark C, Halm EA (2017) Incidence, Predictors, and Outcomes of Hospital-Acquired Anemia. J Hosp Med 12 (5): 317-322. - 3. Thavendiranathan P, Bagai A, Ebidia A, Detsky AS, Choudhry NK (2005) Do blood tests cause anemia in hospitalized patients? The effect of diagnostic phlebotomy on hemoglobin and hematocrit levels. J Gen Intern Med 20 (6): 520-524.

## ESERCIZIO FISICO E SPORT

### 199. EFFECTS OF MEDITERRANEAN DIET COMBINED WITH CROSSFIT TRAINING ON TRAINED ADULTS' PERFORMANCE AND BODY COMPOSITION

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CrossFit is a discipline increasingly practiced in recent years. Specific nutritional approaches are usually required to improve performance and body composition in high-intensity training regimens, notwithstanding, to date there are no targeted nutritional recommendations for CrossFit athletes. The Mediterranean Diet (MD) is a diet approach that contains a well-designed proportion of macronutrients, using only available/seasonal food of the Mediterranean area whose health benefits are well demonstrated. No studies have evaluated this dietary strategy to date among CrossFit athletes and practitioners; for this reason, we aimed at testing the effects of an 8-weeks MD approach on CrossFit athletes' performance and body composition.
A longitudinal experimental study was adopted to investigate the effects of an individualized MD-based food plan for CrossFit athletes on training-related variables such as explosive strength, muscular endurance, anaerobic power/capacity and body composition.
Participants were assigned to two groups: a diet group (DG) in which participants performed a CrossFit training plus a MD-based food plan which was accurately individualized during the 8 weeks; a control group (CG) in which participants partook in the CrossFit training avoiding any modification of their diet habits. Participants were tested before (T0) and after 8 weeks of training period (T1). In this study, it was chosen not to allow supplements or integration of any kind (proteins, amino acids, creatine, etc.). Individual food plans were drafted by an experienced dietician who supervised the participants during the entire duration of the study.
The study took place in a gym equipped specifically for CrossFit training, in which all subjects continued to follow their regular CrossFit training program without any variation. Each training was structured as a classic workout with a specific warm-up phase (10 minutes), a 1-hour central phase, and a cool-down phase (10 minutes). During the warm-up specific exercises to prepare the body for the central phase exercises were applied. The central phase was then structured into two parts: 1-Strength Training of a specific exercise (e.g. Front Squat, Push Press, Pull-Up, Bench Press, Snatch, Deadlift); 2-Workout of the Day (WOD) which was characterized by a circuit training composed of a specific succession of CrossFit exercises to target metabolic response (e.g. burpees, box jump, jump squat, thruster, push-up, pull-up and chin-up). Coll-down was administered at the end of the central phase, in which static stretching exercises were performed. The CrossFit training was carried out under the supervision of a qualified CrossFit coach.
After 8 weeks of intervention, no significant difference was noted in participants' body composition, however improvements in power output, explosive strength of lower limbs and CrossFit performance were observed in the DG. After 8 weeks of MD and CrossFit training, max speed was significantly increased only in the diet group (T0: 787.28 ± 106.5, T1: 835.43 ± 128.9; p=0.043). The DG showed also significant variations after 8 weeks on Squat Jump (SJ) performance. Jump height increased significantly in DG (T0 - 26.96 ± 5.6 cm, T1 - 29.61 ± 5.6 cm; p=0.035). Consistently, also jump fly time during SJ showed a significant increase in the DG group (T0 - 0.47 ± 0.05, T1 - 0.49 ± 0.06; p=0.033). The main improvement was observed in the CrossFit specific performance: the DG group showed significant improvements during the push-up test to exhaustion, the chin-up test to exhaustion and during the Fran (a characteristic CrossFit training consisting of 3 rounds respectively of 21-15-9 repetitions of thrusters and pull-ups). The push-up number increased from 36.10 ± 15.3 repetitions to 38.90 ± 15.5 repetitions at the end of the 8-weeks (p=0.001). However, also the control group showed a significant improvement during this test (T0 - 31.25 ± 15.4, T1 - 34.50 ± 17.2; p=0.034). Regarding the Chin-up test to exhaustion, only DG showed a significant improvement (T0 - 11.70 ± 5.6, T1 - 13.60 ± 6.2; p=0.008). Similar results were noted when considering the Fran test. The time to complete the test at T1 (365.20 ± 166.7 s) was shorter when compared to T0 (476.30 ± 330.1 s) for DG (p=0.002).
Our results, the first in literature to the best of our knowledge, suggest that a MD approach seems to be a useful strategy to improve fitness levels in CrossFit athletes in terms of specific strength and endurance, anaerobic capacity, and jump ability, and maintaining overall body composition.

## FARMACOLOGIA CLINICA

### 200. PRESCRIPTION APPROPRIATENESS OF DRUGS FOR PEPTIC ULCER AND GASTRO-ESOPHAGEAL REFLUX DISEASE: BASELINE ASSESSMENT IN THE LAPTOP-PPI CLUSTER RANDOMIZED TRIAL

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**Background:** Drugs for peptic ulcer and gastro-esophageal reflux disease (GERD) are among the most widely prescribed, frequently without appropriate indications. This represents an important issue, as it leads to unnecessary costs and risk of adverse events.
**Aim:** To assess the prescription appropriateness of drugs for GERD, in the frame of the "Evaluation of the effectiveness of a Low-cost informative intervention to improve the Appropriate PrescripTiOn of Proton PumP Inhibitors in older people in primary care: a cluster-randomized controlled study" (LAPTOP-PPI) (Clinicaltrial.gov: NCT04637750)
**Methods:** The appropriateness of drug prescription was assessed on data collected in administrative databases, by integrating information on concomitant medications, outpatient medical and laboratory procedures and hospital discharge diagnoses, according to the reimbursement criteria provided by the Italian Medicine Agency. We analyzed data of community-dwelling people aged 65 years and over, living in the areas of Bergamo (Northern Italy) and Caserta (Southern Italy), from July 1 to December 31, 2019.
**Results:** Among 380,218 patients, 175,342 (46.1%) received at least one prescription of drugs for GERD. All in all, we found that only 41.2% of patients received appropriate prescriptions.
**Conclusion:** Given the potential risk of adverse drug reactions, especially in older people, more educational interventions should be prompted for physicians, in order to improve the quality of prescription of drugs for GERD and, in turn, avoid unfavorable health outcomes and unnecessary costs.

### 201. SEVERE HYPOMAGNESEMIA RELATED TO PROLONGED INTAKE OF PROTON PUMP INHIBITORS

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The association between the use of proton pump inhibitors (PPIs) and the development of hypomagnesemia has been known for years. A review of some meta-analyses concluded that hypomagnesemia is a possible but rare side effect of PPIs intake (1,2) and that further studies are needed to define its incidence.
**Case Report:** 70-year-old woman, hospitalized for the persistence of nausea and vomiting with evidence at blood test of hypokalemia and hypocalcemia. In the medical history there was arterial hypertension and esophageal reflux. Medications included an association of Losartan/HCT and pantoprazole. The first tests performed at the admission showed an increase in the values of urea (78 mg / dl) and creatinine (2.09 mg / dl), associated with hypokalemia (2.9 mmol / L) and hypocalcemia (5.9 mg /dl corrected value on albumin). The patient continued to occasionally have nausea and some episodes of food vomiting in the absence of clinical signs referable to abdominal pain syndrome (Murphy sign and Blumberg absent). Further analyses showed marked increases in ESR (120), PCR (6.38 mg/dl) and fibrinogen (998 mg/dl). The ABG showed metabolic alkalosis (associated with dehydration). Culture tests for enteric pathogens were negative.
Fluid therapy was started since the admission. After some days of treatment with infusion therapy, a transition to oral supplementation was started and values of potassium and calcium remained stable. Gastrointestinal symptoms resolved within a few days. And the values of ESR and PCR gradually normalized.
A larger evaluation of electrolytes showed very low values of magnesemia (<0.7 mg / dl) corrected with infusion therapy and the intake of hydro-

chlorothiazide was suspended. The study of urinary electrolytes did not show significant data and the progressive normalization of the blood levels of sodium and potassium did not lead to an increase in magnesemia. The patient was discharged in good general condition with normal blood test except for magnesium blood levels which remained low and required oral supplement but with poor increase. A re-evaluation of the clinical case posed the suspicion of a possible side effect of one of the drugs she was taking. We conducted a literature search on PUBMED and we decided to stop Pantoprazole with subsequent rapid increase of Magnesium values.
**Discussion:** The clinical elements available at the admission were compatible with a gastroenteritis, started a few weeks earlier and complicated by dehydration and electrolytic alterations. The chronic inflammatory condition (at the entrance high values of ESR and PCR) led to the development of anemia (no signs of intestinal blood loss, both EGDS and colonoscopy were negative). The ev therapy has led to a normalization of blood values with the exception of magnesium which remains below the reference values and the oral dose has been increased without an obvious benefit. The evaluation of a possible rare side effect of a medication cannot be underestimated in daily clinical practice. Although the incidence of hypomagnesemia in the prolonged use of PPIs is not clear an initial careful evaluation of possible pharmacological side effects seems unavoidable in case of unclear laboratory or clinical elements.
**Conclusion:** "When you hear hoof beats, look for horses, not zebras" is a medical proverb that was created as a methodological warning referring the statistic evaluation of the onset of a symptom and the subsequent diagnostic evaluation. This clinical case highlights how it is often necessary to carefully evaluate the possibility of a rare pharmacological side effect. Shall we think of zebras sometimes ?
**References:** 1. Epstein M, McGrath S, Law F. Proton-pump inhibitors and hypomagnesemic hypoparathyroidism. N Edwards J With 2006;355: 1834–6. - 2. Srinutta et al. Proton pump inhibitors and hypomagnesemia A meta-analysis of observational studies Medicine (2019) 98: 44

## 202. DOACS: NEW OPPORTUNITIES FOR NEW CHALLENGES

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**Background:** Direct oral anticoagulants (DOACs)have changed medical practice significatively
**Case History:** SD, 40yo, affected by cryptogenic hepatitis, atrial fibrillation (AF), entered Emergency Room with hemiparesis and dysarthria, NIHSS 3. Onset was 90 minutes before, stroke team administered systemic thrombolysis (IV alteplase, 0,9mg/Kg bw, 10% bolus initially, remaining dose over 1 hour). Immediately patient's symptoms resolved and plain cranial CT scan detected after alteplase infusion, showed absence of hemorrhage. On day 3, low molecular weight heparin (100IU/kg bw twice daily) was started, followed by oral anticoagulation, in view of discharge. AF in the setting of bioprosthetic valve is still considered nonvalvular and DOACs are recommended over warfarin therapy. We decided to start dabigatran over others DOACs, because his clearance predominantly occurs via renal excretion unchanged drug, the pharmacokinetic profile is unaffected by mild-to-moderate hepatic impairment and last, but not least, idarucizumab reverses its anticoagulants effects within minutes.
**Discussion:** Dabigatran representing an important therapeutic option, in order to balance hemorrhagic and thromboembolic risk, by means of availability of a specific antagonist with an immediate, complete and sustained reversal of anticoagulation, with high safety profile, in absence of thromboembolic complications within 30days in real-world experience.
**References:** (1) 2021 Guideline for the Prevention of Stroke in Patients with Stroke and Transient Ischemic Attack - (2) Haastrup s et al, Real-world experience with reversal of dabigatran by idarucizumab Thrombosis Research, vol 197, jan 2021.179-18

## 203. A RARE BUT SEVERE SIDE EFFECT: DAPTOMYCIN-INDUCED EOSINOPHILIC PNEUMONIA

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A 65-year-old patient came to our emergency room (ER) with sudden onset of retrosternal pain and dyspnea at rest. The medical examinations showed severe aortic insufficiency secondary to Streptococcus Anginosus endocarditis. The patient underwent heart valve replacement surgery and started targeted antibiotic therapy with Ceftriaxone. The postoperative course was complicated by Staphylococcus Epidermidis multidrug-resistant (MDR) sepsis, so antibiotic therapy with Daptomycin was started (1g/die). Therefore, the patient was transferred to a rehabilitation hospital with the indication to continue the eradicating antibiotic therapy.
A few days later the patient returned to our ER for respiratory failure. Blood tests showed leukocytosis (WBC 20.000/mcl) with neutrophilia and eosinophilia (E 1630/mcl) and an increase of inflammatory markers (PCR 300 mg/L). Chest computed tomography (CT) showed extensive bilateral interstitial pneumonia. Therefore, the patient was hospitalized and started continuous positive airway pressure (CPAP) ventilation. Due to the progressive worsening of respiratory exchanges, the patient was transferred to intensive care unit and started non-invasive ventilation (NIV). The patient underwent a bronchoalveolar lavage (BAL) with no evidence of microorganisms; the leukocyte characterization was not performed due to the unsuitability of the material. Because of the clinical picture, Daptomycin therapy was suspended and antibiotic therapy with Ceftobiprole and Azithromycin was then introduced. Steroid therapy was also introduced in the suspicion of daptomycin-induced eosinophilic pneumonia. Thanks to the therapeutic measures, there was a rapid clinical and laboratory improvement. At discharge the patient was in good general condition, asymptomatic and eupnoic; the inflammatory markers were decreasing, as was eosinophilia.
Daptomycin is a lipopeptide antibiotic with an antimicrobial activity against Gram-positive pathogens, including methicillin-resistant Staphylococcus aureus (MRSA) or vancomycin-resistant enterococci (VRE). Daptomycin-induced eosinophilic pneumonia is a rare adverse effect of Daptomycin use, that can result in severe respiratory failure. The exact pathophysiological mechanism of the lung toxicity remains unknown. It is hypothesized that Daptomycin binds to pulmonary surfactant, resulting in high concentrations of the drug and causing epithelial injury and inflammation. The frequency of this side effect appears to increase in patients receiving this drug for a prolonged time or taking a total dose greater than 10 g (for example in the treatment of osteomyelitis, endocarditis and bacteremia), reaching 3-4.6%. Other demonstrated risk factors are male sex, old age (over 70 years) and a high Charlson Comorbidity Index (CCI). The finding of elevated BAL eosinophil count (greater than 25%) in a patient currently or recently treated with Daptomycin is the diagnostic gold standard. Other signs and symptoms are fever, hypoxia, dyspnea and crackles on lung auscultation. Chest x-rays may show pulmonary infiltrates or organized pneumonia. In the acute form, that is clinically more serious, the onset of symptoms occurs approximately 2-4 weeks after the start of Daptomycin therapy, while in the chronic form the clinical picture is milder and can occur even months later. The treatment involves the use of high-dose corticosteroids with slow tapering, even though the exact duration and dosage have not yet been defined by the guidelines.
We report this case with the aim of highlighting how Daptomycin-induced eosinophilic pneumonia is a rare but severe side effect of Daptomycin use, which must be promptly recognized by clinicians to act correctly.

## 204. A CASE OF STAPHYLOCOCCAL ADENITIS IN FOLLICULITIS IN A PATIENT TAKING GALCANEZUMAB

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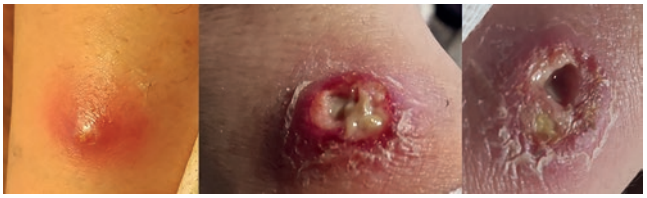
**Introduction:** Galcanezumab is a humanized monoclonal antibody blocking the calcitonin gene-related peptide (CGRP) pathway by targeting the CGRP. It is used for migraine and cluster headache prevention. In addition to its role in mediating migraine attacks, CGRP is widely expressed throughout the body and in general has an antiinflammatory/immunoregulatory role. Thus, inhibitory CGRP may potentiate a pro-inflammatory state, with potential clinical implications. We describe a case report of a patient who delveloped a staphylococcal adenitis while undergoing Galcanezumab.
**Case Report:** A 55 years-old female, with a medical history of severe migraine treated with Galcanezumab and, for a few years in the distant past, periodic skin infections with a tendency to abscess, presented to the

Emergency Department with left inguinal lymphadenopathies and onset in the right forearm of an initially pustular injury and subsequent cratering (Fig.1), one week after the Galcanezumab injection. During the hospitalization in Internal Medicine was started immunological and infectious screening; she was subjected to an inconclusive dermatological evaluation for neutrophilic dermatosis and to a gynecological one that did not show ongoing specific pathology. An abdominal and thoracic computer tomography (CT) scan observed only inguinal adenopathies with a reactive character. The patient underwent an excisional biopsy of the inguinal lymph node, with lymphocyte typing, microbiological and cultural examination for Mycobacteria and common germs, resulting in a positivity for Staphylococcus aureus methicillin susceptible. Blood and biopsy samples for serology and molecular research of Leishmania were negative. All microbiological and serological tests were negative too and the histology showed no lymphoproliferative disease and/or neoplastic disease. The patient was treated with Doxycycline 100 mg and Mupirocin for 10 days, with remission of the disease. We suppose that these manifestations were induced by Galcanezumab.

**Discussion:** There is no documented evidence of any staphylococcal infections with this medication. Per the literature, the presence of Staphyloccocus stimulates sensory neural tissue to release CGRP that can act on adjacent cells, including Langerhans' cells, macrophages and tissue mast cells. After binding, CGRP activates cyclic AMP/protein kinase A signalling, which in turn inhibits NF-κB and ICER signalling. As a result, CGRP negatively regulates the production of several cytokines (including IL-12, IFN-γ, TNFα, and IL-23), and increases IL-1 and MHC class II expression with effects on dendritic cells, B cells, T cells, and macrophages. Overall, CGRP influences differentiation of CD4 T cells away from the Th1 and Th17 pathways [1,2].The disruption of this cascade could lead to a decrease in the innate immune response to infection, thus leading to its proliferation (Fig.2). Long-term anti-CGRP effects on human physiology are not yet understood due to the relatively novelty of this medication. We review the literature to support that CGRP is involved in staphylococcal immunity, and its antagonism incurs susceptibility to infection.

**Conclusion:** This case report provides potential molecular mechanisms and side-effects of CGRP inhibition and warrants vigilance in clinical practice.

**References:** [1] Jason C. Ray et al. Inflammatory complications of CGRP monoclonal antibodies: a case series. The Journal of Headache and Pain. 2021[2] Daria Agustiniak et al. Mammalian Neuropeptide as Modulators of Microbial Infections: Their Dual Role in Defense versus Virulence and Pathogenesis. International Journal of Molecular Sciences. 2021



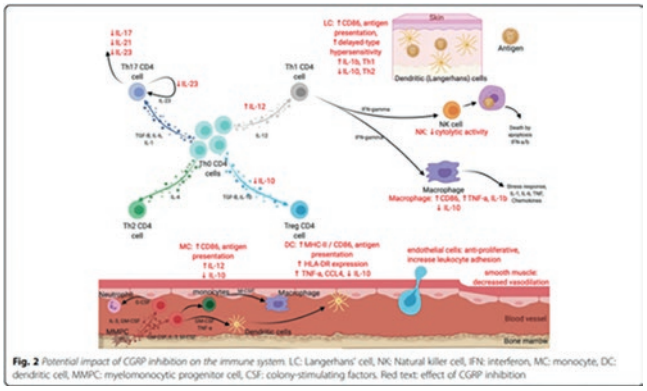



**Fig. 2** *Potential impact of CGRP inhibition on the immune system. LC: Langerhans' cell, NK: Natural killer cell, IFN: interferon, MC: monocyte, DC: dendritic cell, MMPC: myelomonocytic progenitor cell, CSF: colony-stimulating factors. Red text: effect of CGRP inhibition*

## 205. CEFEPIME-INDUCED NEUROTOXICITY (CIN)

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G.L.M, a 68-year-old female patient, was admitted to our Emergency department for fever, cough and worsening of mild exertional dyspnea. Her medical history included a liver transplant for hepatocellular carcinoma in HCV-related cirrhosis and subsequent surgical and systemic treatments for an intestinal carcinoma and breast cancer. Other comorbidities were chronic kidney disease and type 2 diabetes.

The chest x-ray showed an accentuation of broncovascular pattern without consolidation, and chest CT-scan performed later demonstrated multiple peripheral consolidations localized at inferior and superior pulmonary lobe, associated with ground-glass areas and alveolar-interstitial edema. Despite extensive microbiological investigations, including bronchoalveolar lavage, search for all potential etiological agents were negative, in particular fungi, galactomannan, Aspergillus-DNA, M. tuberculosis, CMV-DNA, PJ-DNA, SARS-CoV-2, Legionella-DNA, Virus and Bacteria PCR panel. Despite an empiric treatment with piperacillina/tazobactam, clinical picture further deteriorated, with persisting fever and worsening of dyspnea and oxygenation, which compelled a shift of antimicrobial treatment to Cefepime (2 g every 12 hours, as for reduced glomerular filtration rate). However, after three days the patient was found with altered mental status, confusion, upper extremity myoclonus, weakness and stereotyped speech. Head CT was negative for acute events and ammonia levels were not increased. An electroencephalogram was performed and showed a dysrhythmic and slow pattern with slow/paroxysmal irregular aberrations in all the leads, consistent with drug toxicity. Therefore, a diagnosis of Cefepime-induced neurotoxicity (CIN) was made, which was probably correlated to the reduced glomerular filtration rate, despite the appropriate dosage correction. Antibiotic therapy was promptly interrupted and hydration with Ringer Lactate was started with full regression of neurologic symptoms in 48 hours and normalization of brain electrical activity. The dosage of Cefepime at 24 hours from the event was 18.1 mg/dL, which was consistent with CIN diagnosis.

**Discussion:** Cefepime is a fourth-generation cephalosporin antibiotic and represent a mainstay in treatment of healthcare-associated infections including pneumonia, urinary tract infections, skin and soft tissue infections, and others1. The primary risk factor for cefepime neurotoxicity is renal dysfunction, which necessitates careful dosage adjustment. The pathophysiology of cefepime neurotoxicity is thought to be related to inhibition of GABA-A receptors or possibly inhibition of GABA release, consistent with development of seizures, global encephalopathy and myoclonus2. Approximately 10% of serum cefepime crosses the blood brain barrier (BBB). However, renal impairment, decreased protein binding, and increased organic acid accumulation can increase BBB transfer up to 45%. Despite being a frequent adverse event, in particular in ICU patients, the clinical picture of cefepime toxicity often overlaps with underlying critical illnesses, and diagnosis may be tricky. Notwithstanding, in every patient undergoing cefepime treatment, depressed consciousness, disorientation, aphasia, tremor, and myoclonus should lead to further investigation of potential toxicity. Although the target serum trough concentrations of cefepime are not well established/have not been established, the neurotoxic threshold may be around 20 mg/dl. Moreover, the association with electroencephalogram may further increase clinical suspicion, in particular in patients with risk factors for toxicity (renal dysfunction, hypoalbuminemia).

In conclusion, cefepime-induced neurotoxicity should be suspected when new onset of acute neurological deficits occurs in patients with risk factors for CIN. To prevent CIN, dose adjustment according to renal function is essential in patients with kidney failure, and then, careful monitoring of renal function and neurological status is required. However, CIN may also occur in patients with normal renal function and adjusted dose based on renal function. A diagnosis of CIN can be made after excluding other causes of altered mental status, supported by generalized periodic discharge (GPD) on EEG or increased serum levels of cefepime. Early recognition of this condition is crucial, as CIN is often reversible after prompt discontinuation of cefepime.

**References:** 1.Bazan JA, Martin SI, Kaye KM. Newer beta-lactam antibiotics: doripenem, ceftobiprole, ceftaroline, and cefepime. Infect Dis Clin North Am. 2009;23(4): 983-996, ix. doi: 10.1016/j.idc.2009.06.007- 2 Sugimoto M, Uchida I, Mashimo T, et al. Evidence for the involvement of GABAA receptor blockade in convulsions induced by cephalosporins. Neuropharmacology. 2003;45(3): 304-314. doi: 10.1016/S0028-3908(03)00188-6

## 206. URIDINE AND PYRUVATE (URIPYR®) REDUCE IMMUNE CELL DYSFUNCTIONS DURING TREATMENT WITH MITOTOXIC ANTIBIOTICS: A PILOT STUDY

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**Introduction:** Antibiotics are natural or synthetical substances whose role is to kill bacteria and/or prevent their reproduction. Many studies performed over the last 20 years reported that molecules inhibiting protein synthesis and the structure and function of DNA (i.e. quinolones) are not selective for bacterial structures and they can also damage human cells. In particular, these antibiotics can target even the human mitochondria whose disruption inhibits cellular proliferation and differentiation. Immune cells of mammalians require an efficient mitochondrial activity for their complex function and their fast division rate, and so they can be considered a possible "sensible" population for this antimicrobic-linked bioenergetic dysfunction. In this study, we tested for the first time this hypothesis and we demonstrated that oral supplementation with pyruvate and uridine can reduce the mitotoxic side effects caused by antibiotics.

**Materials and Methods:** Fifty-five subjects were enrolled in Urology, Andrology, and Kidney Transplantation Unit of University of Bari between July 2017 and December 2019. The population underwent a complete blood count, urine analysis, and a urine and/or semen culture (according to the clinical judgment) at baseline (defined as "time zero" T0), before starting any antimicrobic treatment. Then, participants were randomly allocated to the group "Antibiotic treatment plus Uripyr®"(Uripyr group) or "Antibiotic treatment without Uripyr®" (control group). Research personnel who isolated blood cells from the serum of patients was blinded to drug allocation. Patients of the experimental group assumed three sachets of the pharmaceutical preparation called Uripyr and each of them contains 150 mg of uridine and 2 g of pyruvate; the total amount of metabolic components was ingested only one time and at least within an hour from antibiotic assumption. Finally, at the end of the antibiotic assumption, each patient repeated the same tests of the baseline (defined as TEND values).

We evaluated the differential value between the count at the end of treatment (TEND) and one of the baseline (T0) of white blood cells and different subpopulations of leukocytes. In a subgroup of patients of both the experimental groups, peripheral blood mononuclear cells (PBMCs) were freshly isolated from the venous bloodstream at TEND. In this ex vivo experimental setting, PBMCs were cultured in autologous serum, thus avoiding the possibility that exogenous supplementation of essential microelements and metabolites with laboratory culture media could represent an "artificial enrichment" for these cells as well as maintaining blood cells in their specific physiological environment. PBMCs underwent a cytofluorimetric analysis and the percentage of dividing cells from each population was calculated as a delta of the mean percentages of TransAct® stimulated versus unstimulated cells (antibiotic treatment +/- Uripyr®).

**Results and Discussion:** We firstly analyzed in vivo effect of oral supplementation with Uripyr® during antibiotic therapy comparing the differential blood cell count in 48 patients (23 subjects in the control group and 25 in experimental one) between the end of the antibiotic treatment (TEND) and the baseline (T0). Our data showed no significant difference in the total White Blood Cells (WBCs); a similar trend was found for monocytes (t=-0.87, df=45.79) and neutrophils (t=0.70, df=43). By contrast, a 3.4-fold significant difference was found in the lymphocytes population, showing a delta value of 0.34 [0.45] in the Uripyr® group versus 0.10 [0.52] in the control group ($p<0.05$). Cytofluorimetric analysis of CD3+ cells gated from total PBMCs showed a 3.7-fold increase in the percentage of dividing cells in the Uripyr® group (39.71±4.93) as compared to the control group (10.84±2.77).

The theory elaborated in this study is based on the metabolic variations of mitochondria function caused by antibiotic-mediated protein synthesis inhibition. In fact, the inhibition of mitochondrial oxidative phosphorylation (OXPHOS) leads to the shift of cell metabolism towards the glycolytic pathway, whose final product is lactate (which is released into the blood) from pyruvate. Moreover, a reduction of OXPHOS causes a subsequent impairment of dihydroorotate dehydrogenase (DHODH), the most important enzyme of uridine biosynthesis pathway; the "stalled" DHOH reaction diminished uridine pool and consequently decreased the rate of cell division, a process that need a great amount of purines and pyrimidines for DNA synthesis.

In conclusion, the administration of uridine refills the pool of the organism and guarantees a proper division rate. Similarly, the administration of pyruvate caused an increase of inner cellular pyruvate which restarts biochemical reactions of glycolysis. Thanks to this bioenergetic and biosynthetic by-pass, the main mitochondrial activities are reverted and restored.

## GASTROENTEROLOGIA

### 207. CORRELATION BETWEEN INTESTINAL PNEUMATOSIS AND MESENTERIC ISCHEMIA: THE "PNEUMES" STUDY. COMPARATIVE ANALYSIS WITH COCHRAN Q TEST IN 30 PATIENTS WITH INTESTINAL ISCHEMIA. FIVE-YEAR EXPERIENCE (2017-2021)

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**Introduction:** The authors presented the study "PNEUMES", an acrostic deriving from "PNEUmatosis MEsenteric iSchemia" which enrolled 30 patients hospitalized in the period January 2017 - December 2021 with a diagnosis of mesenteric ischemia. In the light of the experience in the literature, the association between the tomographic finding of intestinal ischemia and the presence of pneumatosis has been documented. All patients underwent CT angiography of the abdomen with contrast medium. Therefore, a database with Microsoft Access © called "PNEUMES" was created. The database contained the following fields: 1) patient number, 2) Intestinal pneumatosis, 3) Mesenteric ischemia. All patients were analyzed, during recruitment, according to the aforementioned 3 fields, collected from time to time in masks created in "structure view" and "data sheet view" mode as allowed by the program.

**Purpose of the Work:** The "PNEUMES" study has the following objectives: 1) verify any relationships existing between the values of Intestinal Pneumatosis and Mesenteric Ischemia in the 30 patients enrolled in the "PNEUMES" study during the five-year period January 2017 - December 2021; 2) verify the statistical significance found by applying the Cochran parametric Q test as a comparative analysis test for continuous variables to establish whether the relationships of the variables considered are due to chance.

**Material and Method:** For the calculation of $\chi 2$ the following formula is applied: $\chi 2 = (k\text{-}1)\ [(k\ x)\ \text{-}y2]\ /\ (k\ y)\ \text{-}z$. With "k" the 3 variables considered are indicated, with "x" indicates the total of the squares of the 3 variables considered. "Y" indicates the total number of clinical conditions. "Y2" indicates the square of the total clinical conditions. "Z" indicates the total of the squares of the clinical conditions. The relative value (VR) of the $\chi 2$ obtained is 60 with Degrees of Freedom (GL) = 2. The critical value (VC) of $\chi 2$ for $p = 0.001$ is 13.816.

**Analysis of the Results:** The Cochran Q test applied to the 30 patients involved in the "PNEUMES" study, shows how the clinical situation "PI" (Pneumatosis with mesenteric ischemia) highlighted in all patients is not attributable to chance but assumes a high statistical significance since the relative value (VR) of the $\chi 2$ obtained is 60 with Degrees of Freedom (GL) = 2 and the critical value (VC) of $\chi 2$ for $p = 0.001$ is 13.816. The differences are therefore highly significant with $p < 0.001$.

**Discussion:** The data obtained in the 30 patients enrolled in the "PNEUMES" study show a highly significant association between intestinal pneumatosis and mesenteric ischemia. Intestinal Pneumatosis (PI) is defined as the "presence of gas inside the intestinal wall" and can be recognized with ultrasound, radiography, endoscopy and abdominal CT. The wide diffusion of the latter (which is the most sensitive method) now allows PI to be identified early. The pathogenesis of this sign is uncertain. From a morphological point of view it is classified into two types: 1) cystic or bubble-like (if it mainly consists of air bubbles in the intestinal wall); 2) linear or band-like (when the air forms continuous bands in the intestinal wall). In bubble-like, intestinal infarction is present in 70% of cases, compared with an incidence of 90% in the presence of band-like morphology. The first, therefore, can be asymptomatic and benign, while in the presence of linear appearance the suspicion of intestinal infarction must be high. From the etiological point of view it is possible to distinguish two forms of PI: primary (15%) and secondary (85%). Primary PI (also known as Cystic Intestinal Pneumatosis) is a benign idiopathic condition characterized by the presence of multiple air-containing cysts in the thickness of the intestinal wall (particularly in the submucosa or subserosa of the colon). It is a usually asymptomatic form and the diagnosis of which is occasional (sometimes, if the cyst protrudes into the intestinal lumen it can be confused with a neoformation). The most frequent secondary PI is, on the other hand, to various patholo-

gies. The majority of the cases described concern cases of intestinal ischemia or necrosis (e.g. necrotizing enteritis, intestinal volvulus ischemia), but there are other non-ischemic variants (e.g. trauma, GI ulcers, inflammation, mechanical obstructions, infections, autoimmune diseases, chemotherapies, chronic lung diseases, transplant patients, immunodeficiency). The pathophysiological mechanism is uncertain. The sources of intramural gas can be in the intestinal lumen, due to bacterial production, pulmonary. Pneumatosis would form due to the interaction of various factors including the integrity of the intestinal mucosa, intraluminal pressure, bacterial flora and the amount of gas endoluminal.
**Conclusions:** The "PNUMES" study showed that in the group of 30 patients with intestinal pneumatosis and mesenteric ischemia there is a highly significant correlation

## 208. EOSINOPHILIC ESOPHAGITIS: A CASE REPORT ONSET WITH SEVERE ANAEMIA!

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**Introduction:** Eosinophilic esophagitis (EE) is an inflammatory condition of the esophagus characterized by eosinophilic infiltration. It is more common in childhood and rare in adulhood: estimates indicate 1 subject in 10.000 people with a prevalence of 4-5 people out of 10.000 and it is more frequent in men that in women with a ratio of 3: 1. The symptomatology of EE is represented by dysphagia and it is often misdiagnosed as gastroesophageal reflux, so endoscopic biopsy is required to distinguish between the two conditions. The cause of the disease is probably an immune response to antigens in patients with genetic susceptibility: food and environmental antigens can also be triggers. The most effective treatment in adults is based on steroids, proton pump inhibitors (PPI), leukotriens and hypoallergenic diet.
**Case Report:** A 53-year-old white man no-smoker with a personal history of atopy, allergic rhinitis, dermatitis and occasional diarrhea and asthma, was admitted to our Department for increasing dysphagia, heartburn, chest pain and epigastric abdominal pain sudden onset of severe asthenia. He appeared very asthenic and his skin and mucous membranes were deeply pale, his hair and nails were normal, and he had no peripheral lymphadenopathy, edema or skin lesions. His respiratory rate was 18 breaths per minute and he had a mild vesicular murmur with scattered wheezing in both lung fields, while his heartbeats were rhythmic and without alterations. His blood pressure was 98/55 mm Hg and his body temperature was 35.7°C. His abdomen was soft and depressible to touch and without pain. There were no signs of visceromegaly. The rest of the physical examination found no alterations. The fundi of his eyes were normal. Laboratory data confirmed the severe iron-less microcytic anaemia clinically suspected showing a hemoglobin level of 5.1 g/dL, a hematocrit level of 17.1% a mean corpuscular volume of 66.9 fL a platelet count of 521,000/mm3, while the white blood cell differential included 82% N, 5% L, 5% M, 6% E, and 2% B, ferritin and iron levels were respectively of 2.3 ng/mL and 11 mcg/dL. Due to severe and symptomatic anaemia he was immediately treated on blood transfusions of 4 Units of packed red blood cells obtaining the rapid amelioration of the clinical picture. After the transfusion, his hemoglobin level was 12 g/dL. Esophagogastroduodenoscopy found focal stenosis, superficial punctate papules with evident inflammation, and circumferential rings (feline esophagus) with abundant punctate exudates and histological study showed inflammation with numerous intraepithelial eosinophils with extensive granulation plus microabcesses on the surface. The intraepithelial eosinophils were most numerous in the upper half of the epithelium. The histological study of the stomach and duodenum was normal. The diagnosis of EE was made. Luckily, our patient, discharged in stable clinical conditions and treated on steroids orally for eight weeks, and progressively decreased over six months, montelukast and PPI combined with hypoallergenic diet, got better in a few months.
**Discussion:** The pathophysiology of EE includes atopy, eotaxin-3, and interleukins. Some foods and aeroallergens are indicated in atopy while eotaxin-3 implies a genetic component and interleukins are mediators of inflammation while the role of gastroesophageal reflux is controversial. The presence of eosinophils in the esophagus is pathological and prone to chronicity, but the cause of eosinophilic infiltration of the esophagus is currently ignored. Manifestations vary greatly from patient to patient according to their ages. Some patients' symptoms are constant while other patients' symptoms appear intermittently or seasonally. Dysphagia and food impaction occur more frequently in adults, as well as symptoms of gastroesophageal reflux, chest pain and abdominal pain. In 50% to 80% of both adult and pediatric patients, one or more of the following atopic conditions occur: asthma, sinusitis, dermal lesions, food allergies and/or eczema. Complications include esophageal structural abnormalities, Boerhaave syndrome and nutritional deficiencies. The diagnosis is confirmed with endoscopy and biopsy when there are more than 15 eosinophils observed per field. The most common endoscopic findings are esophageal grooves, esophageal rings, whitish granulations, esophageal strictures, whitish plaques associated with eosinophilic microabscesses, and areas of high density of eosinophil infiltrate. Treatment of EE is controversial, but the combination hypoallergenic diet, proton pump inhibitors, leukotrienes and steroids a significantly improve symptoms and histological findingsMore recently, therapies that act against specific substances identified within the inflammatory cascade as mepolizumab, a humanized monoclonal antibody that blocks IL-5, have been proposed.

## 209. DIAGNOSTIC DELAY IN COELIAC DISEASE: AN ITALIAN MULTICENTRE STUDY

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**Background:** and aim: Coeliac disease (CeD) is an immune-mediated disorder occurring in genetically susceptible individuals after gluten ingestion and causing various degrees of villous atrophy. CeD may lead to severe complications if not promptly recognised. There are few recent data regarding diagnostic delay and its predisposing factors in CeD. The aim of our study was to investigate the overall, the patient-dependent, and the physician-dependent diagnostic delays.
**Material and Methods:** Data regarding CeD patients diagnosed between 2011-2021 were retrospectively collected at eighteen Italian CeD outpatient clinics. Overall diagnostic delay was estimated as the time lapse occurring between the appearance of the first likely symptoms, laboratory alterations, and other clues indicative of CeD and the final diagnosis. Patient-dependent and physician-dependent delays were also assessed. Several clinical and sociodemographic factors were collected. Multivariable regression models for factors affecting delay were fitted.
**Results:** Overall, 2679 patients with CeD (median age 35 years, IQR 23-45; M: F ratio=1: 3) were included. The median overall diagnostic delay was 8 months (IQR 5-14), while patient- and physician-dependent delays were 3 (IQR 2-6) and 4 (IQR 2-6) months, respectively. Regarding factors affecting delay, there were no variables associated with patient-dependent delay, while

age at CeD diagnosis >35 years (coefficient 0.202, p=0.03) and a previous misdiagnosis (1.112, p=0.005) were significantly associated with a greater physician-dependent delay. The previous assessment by >2 specialist physicians (0.390, p=0.02) and a previous misdiagnosis (0.621, p=0.003) were associated with greater overall delay. Finally, a family history of CeD was associated with lower overall (-0.314, p=0.025) and physician-dependent (-0.348, p=0.012) diagnostic delay. Socioeconomic factors, including income, level of education, and marital status did not affect the diagnostic delay.
**Conclusion:** Although CeD diagnostic delay has decreased compared to previously published studies, we identified some physician-dependent factors that still hamper CeD timely diagnosis.

## 210. THE INCIDENCE OF THROMBOEMBOLIC EVENTS IN PATIENTS WITH CHRONIC INFLAMMATORY BOWEL DISEASE IN SARS COV2 INFECTION'S ERA IN THE COURT OF PATIENTS OF "S.ANNA" HOSPITAL, FERRARA

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It is now known that patients with chronic inflammatory bowel diseases are characterized by an increased incidence, about three times higher than the general population, of thromboembolic events involving all parts of the body, both arterial and venous. A new factor has been added to this series of increasingly consolidated data: infection with SARS CoV2. Many respiratory viruses, prior to the current Coronavirus 2019 (COVID 19), had been associated with an increase in thrombotic and thromboembolic events, with evidence of activation of procoagulation systems and the development of thrombosis. It is well established that the development of thrombosis, more frequently venous, is an integral part of the pathophysiology of COVID19 pneumonia. It is also important to underline that neither chronic inflammatory bowel diseases nor related therapies seem to be a risk factor for COVID19; on the other hand, it is interesting to evaluate potential interactions between the immune response related to SARS-CoV-2 infection and the dysregulated immunity associated with IBD.
The goal of our study is therefore to evaluate the incidence of a complication, such as thromboembolic events, common to both patients with chronic inflammatory bowel disease and those with SARS CoV2 related infection.
This observational study evaluated the hospital discharge forms of all patients admitted to the medical department of the Sant'Anna Hospital in Ferrara, in the period from 2017 to 2021. The diagnoses are classified using the ICD system. During the observation period, 162 patients, 72 males (44.4%) and 90 females (56.6%), suffering from chronic inflammatory bowel diseases (Chron's disease and ulcerative colitis), were hospitalized and analyzed in the study. The mean age of the patients was 64.6 ± 17.5 years. There were only 4 cases of SARS CoV2 related infection out of all patients (2.5%), of which 3 with evident manifestation of SARS CoV2 related pneumonia and one with only positive nasopharyngeal swab performed at the entrance. The main comorbidities reported were: chronic renal failure (9.9%), arterial hypertension (9.3%), diabetes (8%), ischemic heart disease (5.6%), atrial fibrillation (5.6%), decline cognitive (3.1%), COPD (2.5%), neoplasms (2.5%), arteriopathy (1.9%), obesity (0.6%), haematological tumors (0.6%). None of the patients with chronic inflammatory bowel disease admitted for SARS CoV2 related infection presented a clinical course complicated by deep vein thrombosis or by confirmed pulmonary embolism. 8 patients died, none of whom were SARS CoV2 positive. Only 1.9% of hospitalized patients required further intensification of care with transfer to intensive care, without a statistically significant difference between the ages (p= 0.683).
Our study certainly has several limitations. The first is certainly represented by the fact that it watches a very limited period of time. Of the years analyzed, only two were affected by the COVID19 pandemic. SARS CoV2 related infection is a pathology yet to be discovered and potential complications could develop in future years. Furthermore, it is certainly useful to continue with the analysis of the data in future years to actually verify an increase in the incidence of thromboembolic events in this category of patients over a longer period of observation. Another limitation is the number of patients. Ours is a small cohort. The analysis of data from a larger group of patients could, in fact, highlight greater and more evident associations. Finally, the use of the database generated by ICD classification certainly allows you to approach a large number of information but on the other hand it may not be complete with all the complications of hospitalization of the patient. In this case, the analysis of medical records could fill some gaps and increase the incidence of real cases of venous thromboembolism.

## 211. THE ROLE OF THYMIC STROMAL LYMPHOPOIETIN PATHWAY IN HUMAN AUTOIMMUNE GASTRITIS

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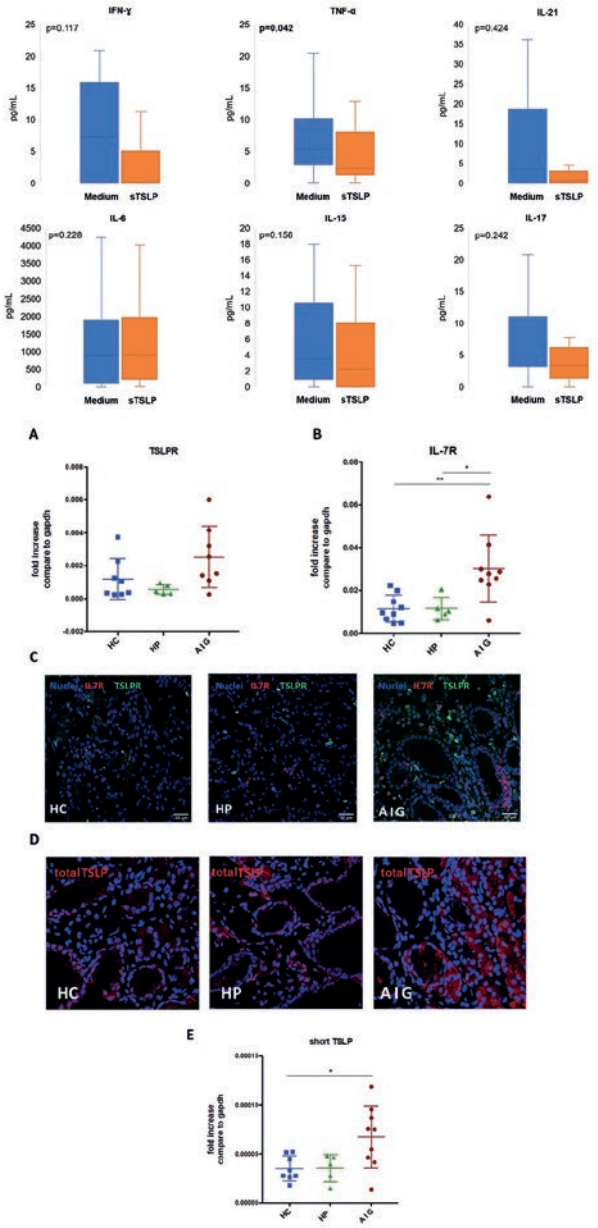
**Background and Aims**: Autoimmune gastritis (AIG) is an immune-mediated disorder affecting the oxyntic mucosa, leading to progressive mucosal atrophy. The pathogenic mechanisms underlying AIG are complex and yet to be clearly defined. Previous experimental models suggested a potential role of thymic stromal lymphopoietin (TSLP), an epithelium-derived anti-inflammatory cytokine involved in T cell maturation, and its receptor (TSLPR) in counteracting the inflammatory process. We therefore conducted an ex vivo study to assess the TSLP pathway role in human AIG.



**Methods:** Eighteen AIG patients (median age 59 years, 12 females), and ten age and sex-matched healthy controls (HC) and H. pylori-infected patients (HP) were enrolled. Perendoscopic gastric corpus biopsy specimens were placed on iron grids in the central well of an organ culture dish and placed in a tight chamber with 95% O2/5% CO2 at 37°C. Biopsies were cultured for 24 hours in serum-free HL-1 medium (Cambrex Bio Science, Milan, Italy), added with antibiotics, with or without 10 ng/mL short TSLP. After 24-hour culture, supernatants and tissues were used to assess the cytokine production in AIG. Total RNA was extracted from biopsies by using the Direct-zol RNA Miniprep Kit (Zymo Research, Irvine, CA, USA). TSLPR and IL-7R primers were provided by Qiagen (QuantiTect Primer Assays). Finally, four 5-µm-cryostat sections were fixed in cold acetone or in para-formaldehyde 4%. Primary antibodies were incubated overnight at 4°C, namely anti-total TSLP (#ab47943, Abcam) and anti-TSLPR (#743961, BD Biosciences). Slides were visualized under a Leica TCS SP8 laser scanning confocal microscope.
**Results:** Short TSLP significantly reduced TNF-α, while it had no significant effect on the other tested cytokines. No difference was found among the three groups with regards to TSLPR levels, while IL-7R was significantly more expressed in AIG compared to HC and HP. At immunofluorescence, both IL-7R and TSLPR were more expressed in AIG compared to HC and HP. Total TSLP expression, assessed by immunofluorescence, was also more evident in AIG compared to HC and HP. Short TSLP transcripts were significantly increased in AIG compared to HC. All results are summarised in the Figure.
**Conclusions:** In this ex vivo study, TSLP and TSLPR levels appear to be significantly higher in AIG than in control groups, suggesting a pathogenic role for this pathway. It can be assumed that the lamina propria over-expression of TSLP could function as a compensatory -although ineffective- anti-inflammatory mechanism.

## 212. PATHOGENIC ROLE OF GASTRIC VASCULAR BARRIER IN H. PYLORI AND AUTOIMMUNE GASTRITIS

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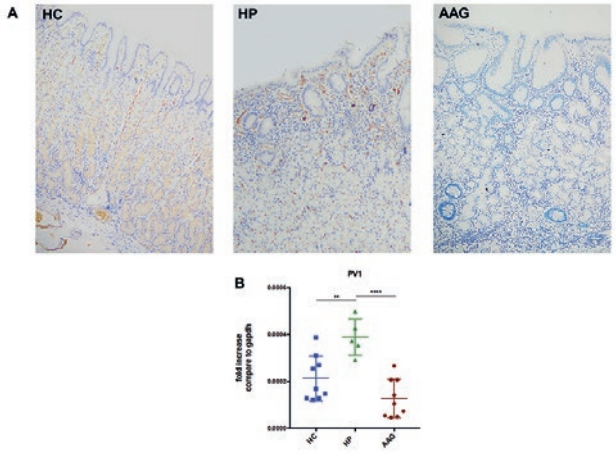
**Background and Aims:** The impairment of the gut vascular barrier, an anatomical structure capable of controlling the systemic dissemination of resident bacteria, has been shown to underlie inflammatory bowel disorders. Instead, nothing is known to date about the gastric vascular barrier, that may play a role in maintaining the local immunological homeostasis. We sought to evaluate the expression of plasmalemma vesicle-associated protein-1 (PV1), a marker of vascular barrier damage, in the stomach of healthy individuals (HC) compared to different types of gastritis, including autoimmune gastritis (AAG) and active H. pylori gastritis (HP).
**Methods:** We enrolled five HP patients (median age 54 years, 3 females) and sex- and age-matched patients with AAG (n=9), as well as HC (n=9). Perendoscopic gastric corpus biopsies were collected. Total RNA was extracted from human biopsies by using the Direct-zol RNA Miniprep Kit (Zymo Research, Irvine, CA, USA). RNA was reverse transcribed with oligo(dT) and ImProm-II™ Reverse Transcriptase (Promega, Milan, Italy). cDNA expression was detected by Rotor-Gene Q 2Plex (Qiagen, Valencia, CA, USA). PV1 primers (genome wide bioinformatically validated primers sets) were provided by Qiagen (QuantiTect Primer Assays). Real-time PCR reactions were carried out using the Fast Sybr Green PCR kit (QuantiStudio 7 Flex R real Time PCR, Applied Biosystems, Thermo Fisher). Results are expressed as 'fold induction' in reference to the expression of the housekeeping gene. Also, three-millimeter-thick paraffin sections were used for immunohistochemistry by Dako Omnis automatic platform (Agilent, Santa Clara, CA, USA). An anti-plasmalemma vesicle-associated protein-1 (PV1)/PLVAP antibody (clone 174/2; LSBio, Seattle, WA, USA) was used to visualize the gastric vascular barrier.
**Results:** The immunohistochemical expression of PV1 resulted almost absent in the gastric corpus of patients with AAG, mildly expressed in HC, and over-expressed in HP. Also, significantly higher levels of PV1 transcripts were found in HP in comparison to both AAG and HP. PV1 transcript levels were reduced in AAG in comparison to HC, although the difference did not reach a statistical significance. The results are summarised in the Figure.
**Conclusions:** Compared to HC, gastric vascular barrier was disrupted in HP and appeared to be less permeable in AAG. It can be assumed that the impairment of the vascular barrier could play a pathogenic role in gastric diseases, just as in the gut. Larger studies are needed to confirm this assumption.




## 213. CLINICAL AND HISTOPATHOLOGICAL FEATURES OF AN ITALIAN MONOCENTRIC SERIES OF SMALL BOWEL T-CELL LYMPHOMAS

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**Background:** and Aim: The gastrointestinal (GI) tract is the most common extra-nodal site of occurrence of non-Hodgkin lymphomas. Most GI lymphomas are of B-cell lineage, while T cell lymphomas account for up to 15% of all cases, in particular enteropathy-associated T-cell lymphoma (EATL), which is associated with coeliac disease (CD), and monomorphic epitheliotropic T-cell lymphoma (MEITL, former EATL type II). The aim of our study is to depict the clinical-pathological profile of a series of patients affected by small bowel T-cell lymphomas (SBTCL).
**Material and Methods:** We retrospectively collected data of patients affected by SBTCL diagnosed at out centre in 2001-2021, from 226 total cases of gastrointestinal lymphoma. For each patient we retrieved clinical and histopathological data. We performed univariate survival analyses for clinical and pathological features. To calculate the overall survival (OS) we considered the time between the initial diagnosis and the death or last follow-up.
**Results:** We identified 28 patients with SBTCL (median age 59 years; 16 males). Among the cases of SBTCL, we found 17 EATL, 5 MEITL, 3 indolent T-cell lymphoproliferative disorder of GI tract and 3 intestinal T-cell lymphoma-not otherwise specified (NOS). More than 70% of patients presented with B-symptoms; other systemic presentation symptoms were diarrhoea and GI complications (perforation, haemorrhage, fistula or obstruction). MEITL did not show a significant difference in clinical presentation. Clinical stage according to Lugano was I or II in 40% of cases and IV (disseminated) in 36%. CD was diagnosed in around 70% of the cases. Serum LDH was slightly elevated in 25/28, and serum β2-microglobulin was elevated in all patients. Two patients died before receiving any treatment. Twenty-two patients were treated with either CHOP or CHOEP schemes. Only 10.7% are still alive at last follow-up EATL alone showed an overall survival of 7 months.
**Conclusions:** SBTCL are a group of rare and very aggressive extra-nodal lymphomas. Similarly to other western series, EATL was the most frequent diagnosis, generally involving the distal small intestine and being associated to CD. The presence of intestinal perforation, B-symptoms or a history of CD prior to EATL diagnosis increases the prognostic efficacy of the International Prognostic Index score.

## 214. A STRANGE CASE OF GASTROENTERITIS AND MALABSORPTION SYNDROME IN A YOUNG BOY WITH RECENT SARS COV2 INFECTION

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A 17-year-old young man was admitted to our clinic for various episodes of persistent vomiting, epigastric pain, diarrhea and syncopal episodes.
The patient had a clinical history of Mediterranean anemia and bilateral astragal arthrodesis for flat feet.
He had a recent paucisymptomatic SARS CoV2 infection.
Since then, he has been apparently in good health, with no history of recurrent respiratory tract infections or family history for inflammatory bowel disease and he reported regular intestinal transit.
Bioumoral exams showed a slight microcytic hypochromic anemia, an increase of inflammatory indices (WBC 26620/mmc, CRP 2 mg/dl) a slight persistent hypereosinophilia (1140/mmc, 10% of the granulocytes), a slight increase of pancreatic enzymes and indices of severe malnutrition, likely due to malabsorption. In particular he presented severe hypoalbuminemia, B12, D vitamin and folic acid deficiency, hypophosphatemia, hypoproteinemia with severe hypogammaglobulinemia (IgG 312 mg/dl, IgM 31 mg/dl), very low levels of total cholesterol and pseudocholinesterase.
Nephrotic syndrome was ruled out (absence of proteinuria and albuminuria).
Serological and molecular tests for acute viral infection (including CMV, EBV, HIV, HSV 1/2, VZV, HHV-6, HHV-7 HHV-8, Adenovirus), bacterial diseases (including measles, mumps and rubella) and parasite infection (including Strongyloides Stercolaris, Toxocara Canis, Schistosoma Mansoni, Entamoeba Hystolitica, Leishmania Infantum, Trypanozoma Cruzii) were negative. A complete microbiological screening on stools ruled out the most relevant bacterial, viral and protozoan infections, included T. Whipplei.
Autoimmune diseases and hematologic disorders were excluded in particular ANA reflex, APCA, ANCA and anti IF antibodies were all negative, while lymphocyte typing tests were normal. Celiac disease was ruled out (only DQ2 positivity) and RAST test (allergen- specific IgE) were negative.
Different radiologic and endoscopic investigations were performed: chest X-ray was negative for parenchymal and pleural lesions; chest-abdomen CT scans were negative for neoplastic lesions or linfoproliferative disorders; MR enterography did not detect inflammatory bowel disease; colonscopy was macroscopically and histologically normal while gastroduodenoscopy revealed a severe diffuse gastritis with erythema and mucosal erosions. The histological examination showed greater than or equal to 35-40 eosinophils per high-power field (HPF) especially in the duodenum and gastric areas. Celiac disease, H. Pylori infection, Whipple and IgG4 disease were all ruled out.
Based on bioumoral, radiological, endoscopic and histological examinations eosinophilic gastroduodenitis was finally considered the most likely diagnosis.
Eosinophilic gastroenteritis (EGE) is a digestive disorder in children and adults characterised by eosinophilic infiltration in the stomach and intestine. The underlying molecular mechanisms predisposing to this disease are unknown but hypersensitivity response seems to play a major role in its pathogenesis. Symptoms and clinical presentations vary, depending on the site and layer of the gastrointestinal wall infiltrated by eosinophils. The diagnosis cornerstone remains the histological examination of gastric and duodenal specimens for evidence of eosinophilic infiltration (>20 per HPF), in correlation with and by exclusion of other disorders associated with eosinophilic infiltration.1 Management options include both dietary and pharmacological approach, with corticosteroids being the mainstream of therapy and highly effective. Some patients have no recurrences, while a few experience recurrent symptoms during or immediately after corticosteroids interruption.2 Alternative therapies are mast-cell stabilizers, leukotriene antagonist, antihistamines, immunomodulators and biological agents.3
The patient was initially given a high dose of endovenous PPI, parenteral nutrition and protein, vitamins and electrolytes supplement and, due in view of the severe hypogammaglobulinemia, intravenous immunoglobulins were administered. Once the EGE diagnosis was established, a steroid therapy was started (first intravenous, then oral administration): the patient showed a prompt clinical and biochemical improvement and complete symptom relief.
**References:** 1.Sunkara T, et al. "Eosinophilic gastroenteritis: diagnosis and clinical perspectives." Clinical and experimental gastroenterology 12 (2019) 2.Oh HE, et al. "Eosinophilic gastroenteritis: a review." Journal of gastroenterology 43.10 (2008). - 3.Stone KD, et al. "Immunomodulatory therapy of eosinophil-associated gastrointestinal diseases." Clinical & Experimental Allergy 38.12 (2008)

## 215. THE ROLE OF FECAL TRANSPLANTATION IN MUCOSAL HEALING OF MURINE MODELS AFFECTED BY DSS-INDUCED ULCERATIVE COLITIS

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Fecal microbiota transplantation (FMT) is a technique that has been proven effective for the treatment of relapsing C. difficile infections, however, its effectiveness has yet to be assessed in the treatment of inflammatory bowel diseases (IBDs).
Our study aims to evaluate the impact that FMT has on the microbiota composition and mucosal integrity of murine models. We used mice that were pre-conditioned for a week with a mix of antibiotics to deplete most of the intestinal microbiota, then a 7-day DSS treatment was carried out to induce the colitis and, during those days, two microbiota infusions were performed, the mice were sacrificed at the end of seven days of recovery. The FMTs were performed with samples coming from either patients with active disease or remission patients.
Previous studies have shown that the composition of the microbiota is not affected by the DSS treatment, however, the relative abundance seems to differ to be influenced by the composition of the samples' microbiota. Our study confirmed that some families, such as Firmicutes, are more represented during IBDs and others, such as Bacteroidetes, are more represented during the remission phase. Moreover, the quantification of immunological markers on the colonic mucosa, such as INFg, TNFa, and IL-17, revealed an impact on the expression of these cytokines depending on the FMT samples. Further studies are indeed required, however, our study suggests how the composition of the FMT samples can induce an anti-inflammatory setting on a mucosal level and induce the proliferation of those bacterial families associated with remission.

## 216. THE SOLUTE CARRIER LC22A4/OCTN1 AS A NOVEL IBD DETERMINANT AT THE MICROBE-HOST INTERFACE

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**Background:** The putative Ergothioneine Transporter, SLC22A4/OCTN1, is expressed in the intestine and in monocytes/macrophages, and its widely represented missense variant L503F (0.4 Minor Allele Frequency in Caucasians) has been found to be associated with Crohn's disease, sporadic colorectal cancer in early age and ulcerative colitis (UC) patients. The leucine-to-phenylalanine substitution at amino acid 503 affects OCTN1 capacity to transport ergothioneine, acetylcholine and likely other substrates of endogenous or microbial origin; however, whether this defect contributes to inflammatory bowel disease (IBD) pathogenesis, and the mechanistic underpinnings, remain elusive.
**Methods:** In order to gain mechanistic insight on the role of SLC22A4 in IBD, we first analyzed primary monocytes from healthy donors and UC patients of varying OCTN1 genotypes. Then we stably knocked-down or overexpressed OCTN1 and its disease-associated variant in the monocytic cell line THP-1. Finally, we compared wild type and OCTN1 knockout C57BL/6 mice in a chemical colitis paradigm in vivo.
**Results:** Primary adherent monocytes from healthy donors homozygous for the IBD-associated allele (TT) displayed a significant enhancement of interleukin 1 beta (IL-1β) response to peptidoglycan (PGN) compared to the other genotypes. Likewise, cells from UC patients bearing the 503F

variant released more IL-1β in response to live bacteria and displayed reduced expression of autophagy markers (e.g. p62, LC3), compared to patients negative for the variant.
In agreement with these findings, OCTN1-deficient THP-1 macrophages secreted reduced amounts of IL-1β when challenged in vitro with PGN or live bacteria. Most relevant, THP1 cells engineered to overexpress the 503F variant of OCTN1 displayed a much stronger IL-1β response to muramyl dipeptide and PGN challenge, compared to cells transduced with the "wild type" transporter. Also consistent with a role for OCTN1 variants in inflammatory cascades relevant to IBD, in vivo studies revealed a milder DSS-induced colitis in OCTN1 knockout mice compared to wild type animals, both at the peak of disease severity and at the end of the recovery period.
**Conclusion:** Collectively our initial evidence supports the view that OCTN1 may have a causative role in IBD via deranged bacterial sensing and cytokine production, with 503F likely behaving as a gain-of-function variant. Thus, targeting OCTN1 variant may provide unprecedented opportunities for the personalized treatment of IBD patients and a better understanding of disease pathogenesis.

## 217. STOPPING NUCLEO(S)TIDE ANALOGUE (NA) TREATMENT IN NON-CIRRHOTIC PATIENTS WITH CHRONIC HEPATITIS B: SERUM HBSAG AND DDPCR HBV-DNA AS PREDICTIVE PARAMETERS OF HBSAG LOSS

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**Background:** The suspension of nucleo(s)tide analogue (NA) treatment in selected patients with non-cirrhotic Chronic Hepatitis B (CHB) often leads to virus-induced flares, resulting on some occasions in life-threatening liver failure.
**Objectives:** to determine predictive parameters of off-NAs response at the end of treatment, and their association with HBsAg loss or HBsAg < 100 IU/ml, ensuring a safe NAs discontinuation.
**Materials and Methods:** 38 non-cirrhotic CHB patients, with complete virological suppression after 4 years of NAs, were prospectively monitored after stopping treatment for a median (IQR) time of 16 (10-19) months. Highly sensitive droplet digital PCR (ddPCR) was used to quantify serum HBV-DNA of plasma samples collected at suspension date (baseline, BL). HBsAg was quantified by the ARCHITECT HBsAg assay at BL, every 2 weeks from suspension in the first month, then by every month until the sixth month, subsequently every 3 months.
**Results:** At BL, 28 (73.7%) patients had detectable serum HBV-DNA (median [IQR] 5 [2-11] IU/mL), while 10 (26.3%) were completely negative to HBV-DNA. After NA discontinuation, 7 (18.4%) achieved HBsAg < 100 IU/mL (median [IQR]: 43 [35-53]IU/ml) and 8 (21.1%) lost HBsAg at last follow-up.
Patients achieving HBsAg loss had lower HBsAg levels at BL (140 [70-480] IU/ml with vs 1162 [439-3135] without HBsAg loss, p=0.014).
The negativity to HBV-DNA by ddPCR at BL strongly correlated with the achievement of HBsAg < 100 IU/mL or HBsAg loss after NA suspension (70% [7/10] with vs 28.6% [8/28] without negative BL HBV-DNA; OR [95%CI]: 5.8 [1.3-23.6], p=0.03).The combination of HBsAg < 500IU/mL + negativity HBV-DNA by ddPCR at BL was the best predictor for achieving HBsAg < 100 IU/mL or HBsAg loss (85.7% with vs 27.6% without this combination; OR [95% CI]: 15.8 (1.6-152.2; p=0.008; PPV=86%; NPV=72%).
**Conclusions:** Measuring residual HBV replicative activity by highly sensitive assays at the end of NA treatment, provides an added value in identifying patients more prone to achieve HBV functional cure.

## 218. EMERGING ROLE OF IL-33/ST2 AND GUT MICROBIOTA AXIS IN THE INFLAMMATORY PROCESS OF ULCERATIVE COLITIS PATIENTS WITH ILEAL POUCH-ANAL ANASTOMOSIS.

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**Background and Aims**: It is now well-established that IL-33/ST2 axis and gut microbiota are important factors in the pathogenesis of IBD with a potential reciprocal influence. Recent evidence has shown that IL-33/ST2 axis controls the mucosal healing process during intestinal inflammation. Restorative proctocolectomy with ileal pouch-anal anastomosis is a surgical procedure in patients with ulcerative colitis (UC) refractory to medical therapies. Pouchitis, the most common complication, is the inflammation of the pouch with a controversial etiology.
In this scenario, we aimed to explore the potential combined involvement of the IL-33/ST2 axis and gut microbiota in the inflammatory process of pouchitis.
**Materials and Methods:** 23 ulcerative colitis patients with ileal pouch-anal anastomosis were enrolled. After clinical, endoscopic and histological assessment (based respectively on Pouchitis Disease Activity Index and Pouchitis Histological Score) 13 showed pouchitis and 10 a normal pouch. Mucosal samples were collected from the afferent ileal loop and from the pouch and processed for cytokines assessment, histological evaluation and gut microbiota analyses. Multiplex analysis for inflammatory and regulatory cytokines was performed. ELISA and western blot were run to assess IL-33/ST2 protein levels and to evaluate protein isoforms, respectively. IHC was done to evaluate mucosal IL-33/ST2 expression and localization. Microbiota was analyzed by 16S ribosomal RNA gene amplicon pyrosequencing. Pouchitis Disease Activity Index and Pouchitis Histological Score were calculated, and CRP and fecal calprotectin were obtained for each patient. Multivariate analyses were run to generate transcriptional interaction networks and identify biomarkers for patients with inflamed pouches.
**Results:** Between the two categories of patients, IL-1Ra, IL-6, IL-8, IL-17, IP-10, MCP-1, MIP-1a, MIP-1b resulted increased in mucosal samples obtained from the inflamed pouch vs. those obtained from normal pouch. No differences were registered between samples obtained from the afferent ileal loop. In patients with pouchitis, IL-7 resulted reduced in the inflamed pouch vs. samples obtained from the afferent ileal loop. In patients with normal pouch, no differences were recorded between the pouch and the afferent ileal loop. In patients with pouchitis, IL-33 and ST2 protein levels were significantly reduced in the pouch vs. the afferent ileal loop and resulted overall decreased vs. samples obtained from patients with normal pouch indicating a potential IL-33/ST2-mediated defective healing process. Full-length, bioactive IL33 (31 kDa), ST2L (76 kDa) and sST2 (52 kDa) were expressed in all experimental groups; the cleaved, less active form of IL33 (24 kDa) was increased in only patients with pouchitis. IHC confirmed these observations. In particular, IL-33 and ST2 staining was less intense within the inflamed and ulcerated mucosa of pouchitis patients compared to normal pouch, and in close proximity to areas of re-epithelialization. Microbiota analysis showed an overall decreased biodiversity in patients with pouchitis vs. patients with normal pouch (both at pouch and afferent ileal loop level). Among phyla, lower levels of Verrucomicrobia and increased abundance of Actinobacteria were recorded in inflamed pouch vs normal pouch. Among genera, in patients with pouchitis the afferent ileal loop and the pouch showed significantly decreased levels of Akkermansia muciniphila and augmented abundance of Collinsella vs. samples obtained from patients with normal pouch. In patients with pouchitis, multivariate analyses evidenced a significant inverse correlation between Collinsella e Collinsella aereofaciens abundance and ST2 levels.
**Conclusions:** In patients with pouchitis vs patients with normal pouch divergent inflammatory molecular pathways and microbial populations distinctly characterize the pouch and the afferent ileal loop. Overall, our results suggest a potential role for IL-33/ST2 and gut microbiota axis in driving the gut mucosal wound healing in patients with ileal pouch-anal anastomosis. Further studies are underway to determine mechanisms of action that support these findings.

## 219. IF THE EYES ARE THE MIRROR OF THE SOUL, IS THE UMBILICUS A MIRROR FOR INNER PROBLEMS? A CASE REPORT

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A 63 years old man affected by non-insulin dependent diabetes mellitus and hepatic cirrhosis associated to both compound heterozygotic hemochromatosis (C282Y/H631; diagnosis in 2004, treated with salassotherapy every 15 days until 2015) and alcohol assumption (2 alcoholic units/day for 20 years) was admitted to our Hospital with iron-deficiency anemia, weight loss of about 15 kg in the last six months due to ingravescent inappetence, asthenia and the appearance of fever (up to 39°C with no other signs or symptoms). For about a month, he noticed the appearance of a painless umbilical extroversion (the navel was formerly normal) associated with intense local itching and purulent exudate, needing regular medical dressings.
Blood tests confirmed severe anemia (haemoglobin 5.6 g/dl, MCV 80.5 fl, ferritin 18 ng/mL), INR 1.36, total bilirubin 1.8 mg/dL, direct 0.9 mg/dL, hypoalbuminemia 2.8 g/dL, normal liver function, gamma-glutamyl-transferase and alkaline phosphatase; alpha-fetoprotein <1,3 ng/dl, Ca 19-9 162 UI/ml (normal value <37). A transfusion of red blood cells was performed with slight benefit on the general malaise. Concerning the liver disease, the Child-Pugh score was B8 due to the presence of moderate ascites.
The thoraco-abdominal computed-tomography (CT) scan pointed out a thickening in the gastric fundus, multiple abdominal lymphadenopathies and a large number of metastases in the peritoneum and anterior abdominal wall: particularly, in the sub-umbilical area, a solid formation of 5 cm was described, with ulcerations due to umbilical vein recanalizazion related to liver disease.
Endoscopic exams were performed: the colonoscopy showed severe hemorrhoidal congestion; the esophagogastroduodenoscopy documented an ulcerated and bleeding neoformation of the gastric fundus (diameter 35 mm). Histology demonstrated the presence of an adenocarcinoma of the gastric fundus. The subcutaneous periumbilical extroversion was a metastatic lesion.
Due to the advanced stage of the neoplasia and the patient's comorbidities, it was not possible to apply a radical treatment. Chemotherapy with 5-fluorouracil, folinic acid and oxaliplatin was started.
**Conclusions:** Sister Mary Joseph's nodule is an umbilical or paraumbilical nodule representing a rare physical sign, sometimes the only "red flag" suggesting the presence of an advanced stage malignancy in a patient with aspecific symptoms, mainly in the abdomen or pelvis, sometimes also in the thoracic district [1].
The mechanism determining the umbilical metastatic implantation is unknown: apart from the possible hematogenous dissemination or direct transperitoneal diffusion, other suggested hypotheses are lymphatic spread through the embryonic residues alongside the falciform ligament, obliterated umbilical vein or median umbilical ligament or blood spread [2].
An accurate differential diagnosis (umbilical hernia, endometriosis localizations, pyoderma gangrenosum, keloids, omphalitis, primary umbilical neoplasia, metastases) is necessary in order to prevent diagnostic delay and grant an appropriate therapeutic path to these patients, despite the frequently unfavourable prognosis.
**References:**[1] Tso S, Brockley J, Recica H, Ilchyshyn A. Sister Mary Joseph's nodule: an unusual but important physical finding characteristic of widespread internal malignancy. Br J Gen Pract. 2013 Oct;63(615): 551-2. doi: 10.3399/bjgp13X673900. PMID: 24152477; PMCID: PMC3782795 - [2] Omura T, Tamura Y, Kodera R, Oba K, Toyoshima K, Chiba Y, Matsuda Y, Uegaki S, Kuroiwa K, Araki A. Pancreatic cancer manifesting as Sister Mary Joseph nodule during follow up of a patient with type 2 diabetes mellitus: A case report. Geriatr Gerontol Int. 2019 Apr;19(4): 363-364. doi: 10.1111/ggi.13602. PMID: 30932308

## 220. PROTON PUMP INHIBITORS APPROPRIATENESS IN CLINICAL PRACTICE: AN UPDATE IN INTERNAL MEDICINE

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**Introduction:** Proton-Pump Inhibitors (PPI) are among the most widely used drugs in clinical practice, and, in specific conditions, chronic therapy is required. Thus, as for every other drug, prescriptive appropriateness is of primary importance even in relation to potential adverse effects.
**Objective:** To assess the prescriptive appropriateness of PPI in patients admitted to a department of Internal Medicine.
Design: Observational "cross-sectional" study.
**Methods:** The discharge records of all patients admitted to the Internal Medicine Department of "A. Manzoni" Hospital of Lecco from 01/01/2022 to 31/03/2022 have been evaluated. The parameters assessed were age, sex, comorbidity and PPI therapy, already in use at the entrance or prescribed at discharge. Prescriptive appropriateness has been assessed according to Gastroenterology Guidelines (UEG, BSG, ASGE).
**Results:** 347 patients were admitted during the study period (51.9% men, mean age 74.6 ±15.3 years). At the admission, 173 patients (49.8%) were in treatment with Proton-Pump Inhibitors. Therapy was in use in 87 (38.4%; 95% IC = 31.9-44.5) of 228 patients without proper indication (overuse), while it was not assumed in 33 (27.7%; 95% IC = 19.7-35.8) of 119 patients in which it was indicated (underuse). At the discharge, PPI therapy was prescribed in 228 (65.7%) patients. In detail, the therapy was in use in 97 (52.2%; 95% IC = 45-59.3) of 186 patients without proper indication (overuse), while it was not assumed in 30 (18.6%; 95% IC = 12.6-24.6) of the 161 patients in which it was indicated (underuse). (Table 1).
Overall, PPI prescription was inappropriate in 120 (34.6%; 95% IC = 29.6-39.6) and 127 (36.6%; 95% IC = 31.6-41.7) of the 247 patients, admitted and discharged, respectively, with no statistically significant difference (P = NS). At discharge there was a significant increase in "overuse" prescriptions compared to entry (52.2% vs 38.2%; P<0.005).
Patients treated with PPI had a higher average age and a higher number of comorbidities; this was most noticeable for patients with cerebral and cardiovascular diseases (Tables 2 and 3).
Pantoprazole was the most widely used PPI (Figure 1) both at entry and discharge.

**Table 1.** PPI therapy appropriateness

| | Admission | | Discharge | |
|---|---|---|---|---|
| | Prescribed | Not Prescribed | Prescribed | Not prescribed |
| Indication | 86 | 33 | 131 | 30 |
| Not indication | 87 | 141 | 97 | 89 |

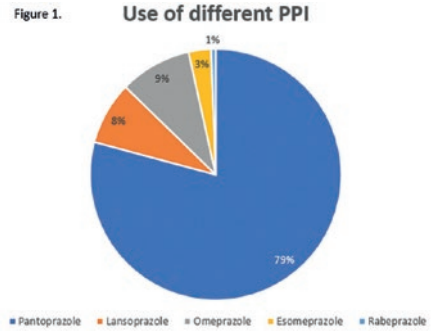
**Table 2.** Number, age, sex, comorbidities in patient with and without PPI therapy. Admission.

| | In PPI therapy | Not in PPI therapy |
|---|---|---|
| Number of patient (%) | 173 (49.9%) | 174 (50.1%) |
| Male sex (%) | 87 (50.3%) | 93 (53.4%) |
| Mean age (±DS) | 79.1 (±10.86) | 70.1 (±17.4) |
| Cardiovascular comorbidity | 151 | 107 |
| Gastroenterological comorbidity | 58 | 33 |
| Neurological comorbidity | 74 | 29 |
| Pneumological comorbidity | 77 | 27 |
| Renal comorbidity | 57 | 16 |
| Pathologies /N Pts | 2.23 | 1.40 |

**Table 3.** Number, age, sex, comorbidities in patient with and without PPI therapy. Discharge.

| | In PPI therapy | Not in PPI therapy |
|---|---|---|
| Number of patient (%) | 228 (65.6%) | 119 (34.4%) |
| Male sex (%) | 113 (49.6%) | 67 (56.3%) |
| Mean age (±DS) | 76.9 (±13.5) | 70.0 (±17.3) |
| Cardiovascular comorbidity | 182 | 76 |
| Gastroenterological comorbidity | 68 | 23 |
| Neurological comorbidity | 74 | 29 |
| Pneumological comorbidity | 77 | 27 |
| Renal comorbidity | 57 | 16 |
| Pathologies /N Pts | 2.01 | 1.44 |

Figure 1.



**Conclusions:** The data collected shows that, at admission, in one-third of patients receiving PPI treatment the prescription is inappropriate. After hospitalization, this value remains unchanged. Hospitalization, moreover, favors an improper use of Proton-Pump Inhibitors, mostly in prescriptive excess and in patients with cardiovascular diseases. These preliminary data indicate the need for training courses to improve adherence to the Guidelines between General Practitioners and Hospital Doctors.

## 221. THINKING OUTSIDE THE BOX: AN UNUSUAL CAUSE OF CHRONIC DIARRHEA

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**Introduction:** Olmesartan is an angiotensin II receptor blocker (ARB) commonly used to treat hypertension. Rubio-Tapia et al. described a sprue-like enteropathy linked to olmesartan for the first time in 2012, with intestinal villous atrophy as the most common histological finding. Clinical presentation of olmesartan-related enteropathy is various and unspecific. Chronic non-bloody diarrhea is the most common symptom, with onset from the start of treatment varying from few months to many years. Several cases of lymphocytic colitis (LC) related with olmesartan have been reported in recent years, however, ARB is not specifically mentioned as a cause of microscopic colitis (MC) in European guidelines for MC.
**Case Presentation:** We hereby report a case of a 63-year-old man who was referred to our tertiary care centre because of a two-month history of watery non-bloody diarrhea with a bowel frequency of 7 to 10 times per day. Diarrhea was associated with weight loss of 10 kg over the past two months, severe electrolyte abnormalities and dehydration, which led to metabolic acidosis and acute renal failure requiring hospitalization and hemodialysis. His past medical history was unremarkable, except for hypertension treated with olmesartan for a year and a half. He smoked half a pack of cigarettes per day and reported occasional alcohol consumption.
From the onset of symptoms, the patient underwent three different hospitalizations. Laboratory tests revealed a slight increase in C-reactive protein levels and white blood cell count within the range of normality with preserved leukocyte formula. Stool culture for Salmonella spp, Shigella spp, Campylobacter spp, and Vibrio cholera, parasitological stool examinations and Clostridium difficile toxins were negative. Celiac disease serology (anti-endomysial antibodies and anti-tissue transglutaminase IgG and IgA) was negative, serum thyroid-stimulating hormone (TSH) and adrenocorticotropic hormone (ACTH) were normal, as well as vasoactive intestinal peptide (VIP). Chromogranin A (119 ng/ml, range 19.4 – 98.1 ng/ml) and ASCA IgA (14 AU/ml, normal < 12 AU/ml) were slightly non-specifically increased. There were laboratory signs of malabsorption (low level of vitamin D, total proteins, and albumin). Autoimmune screening and immunoglobulin G (IgG) were normal.
Furthermore, in the suspicion of paraneoplastic symptoms, a total body CT scan was performed, with negative response for inflammatory bowel disease or intra-abdominal abnormalities.
An upper and lower endoscopy were performed with biopsies. The upper endoscopy showed hyperemic gastritis and bulbar micro-nodular duodenopathy with redness of the mucosa. Colonoscopy documented the absence of organic lesions or inflammation in all its tracts. The histological examination revealed non-specific findings in all the districts examined: < 20 intraepithelial lymphocytes per 100 surface epithelial cells in the colonic tissue and 25 intraepithelial lymphocytes per 100 surface epithelial cells in the duodenal tract with only slightly dysmorphic villi.
In the absence of a clear etiology of diarrhea, olmesartan was discontinued and after 10 days the symptoms improved, with normalization of gastrointestinal function.
**Conclusion:** This clinical case showed an unusual presentation of ARB-related enteropathy, with histological inflammatory changes in the duodenum and colon that did not fulfill the diagnostic criteria. This suggests that olmesartan enteropathy may present itself with different endoscopic and histological findings in addition to those classically defined. Despite the frequent use of olmesartan in clinical practice, olmesartan-related enteropathy is a not completely understood and underestimated cause of diarrhea. It should always be considered in the differential diagnosis of chronic diarrhea.

## 222. TOWARDS A PERSONALIZED APPROACH IN ULCERATIVE COLITIS: ROLE OF OCTN1 IN PREDICTING INDIVIDUAL RESPONSE TO THERAPY

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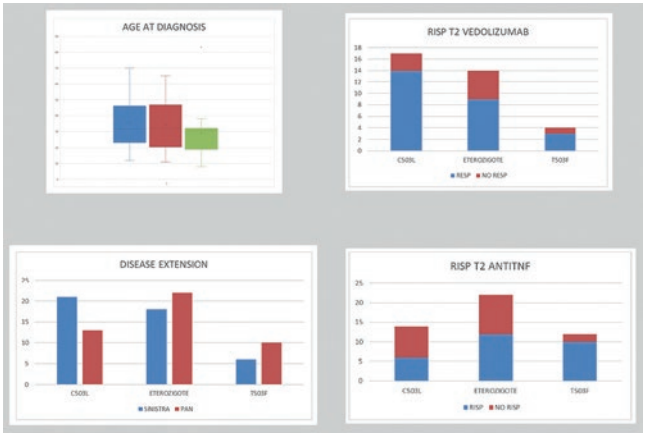
**Background:** Ulcerative colitis is a chronic invalidating disease, whose therapeutic strategies include amino-salicylates, steroids, probiotics, immune-modulators, biologics, fecal microbiota transplantation and surgery. Though, in clinical practice, there are no evidence available about elements that could predict response to each of the above-mentioned therapies. Our group thinks that OCTN1, an organic cation transporter directly involved in innate immunity, with its variants (C503L homozygous, heterozygous or T503F), could have a role in predicting individual response to biologic therapies (antiTNFa and vedolizumab).
**Methods:** In this prospective and retrospective study, we enrolled a cohort of 90 patients with active ulcerative colitis (50 in treatment with antiTNF agents and 40 with vedolizumab), determining their OCTN1 genotype and evaluating their clinical response to therapy, calculated with clinical Mayo score, after six weeks (T1) and six months (T2).
**Results:** Left colitis at diagnosis was more frequent in C503L patients (61.7%% left colitis vs 38.3% pancolitis) than patients than in patients with T503F (32.5% left colitis vs 62.5% pancolitis). At the same way, the average age at diagnosis was sensibly lower in patients with T503F genotype (35.5 years C503L vs 33.3 years heterozygous vs 28.9 years T503F).
We used clinical response at T2 (6 months) as a primary outcome of our study. Among patients under antiTNFa therapy, patients with C503L genotype were divided into 8 no responders and 6 responders (43% responders vs 57% no responders), whilst patients with T503F genotype were divided into 10 responders and 2 no responder (80% responders vs 20% no responders). On the contrary, patients under vedolizumab therapy showed different trend: patients with C503L genotype were divided into 15 responders and 4 no responders (78.9% responders vs 21.1% no responders)., whilst patients with T503F genotype were 3 responder and 1 no responder.
**Conclusions:** Patients with T503F genotype present an overall worse course of disease, with higher rate of pancolitis and younger age at diagnosis.
Furthermore, the presence of the mutation (allele T) could have a role in increasing the response rate to antiTNFa.




## 223. HELICOBACTER PYLORI AND SARS-COV-2 ASSOCIATION: A COINCIDENCE OR A PATHOGENETIC CORRELATION?

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**Introduction:** Covid-19 can be associated with viral, bacterial, and fungal

co-infections. While the correlation between Covid-19 and other bacterial respiratory infections such as S. pneumoniae or S. aureus is well known, the correlation between Covid-19 and non-respiratory bacteria is unexplored. The following considerations led us to investigate a possible correlation btw HP and SARS- CoV2: SARS-CoV-2 binds ACE-2 receptors to enter cells, which are widely expressed in the GI tract. In addition, HP is known to induce changes in the structure of the microvilli of the GI epithelium, e.g. by increasing the expression of ACE-2 receptors.
Added to this is the fact that Covid-19 pandemic overshadowed the diagnosis and therapy of numerous other diseases, including HP gastric infection: the limited availability of breath tests (BT) due to organisational restrictions in public structures (applied in order to contain the spread of the virus) had led to under-diagnosis and therefore non-treatment of the infection.
**Aims of the Study:** This study aims to investigate, by C13 Urea BT the prevalence of HP infection and the DOB (delta over baseline), which is a reliable indicator of bacterial load, in pre-pandemic period (April '17-March '20) and during Covid-19 pandemic (April '20-March '22) to evaluate whether SARS-CoV-2 and HP infection association is only due to chance or whether represents a pathogenetic correlation and, in this latter case, to determine how much one influences the other.
**Materials and Methods:** This is a retrospective preliminary study on 1532 randomized patients reffered to private Internal Medicine ambulatories who reported digestive symptoms (epigastralgia, hearth burn, nausea, GE reflux, abdominal pain, meteorism, diarrhoea; clinical signs of small intestine bacterial overgrowth and lactose malabsorption were also found in most patients): 825 referring to pre-pandemic period, 707 referring to pandemic period.
**Results:** Only 490 patients underwent C13 Urea BT for the diagnosis of HP gastric infection: 229 and 261 respectively during pre-pandemic and pandemic period. In pre-pandemic period 54 patients tested positive for HP infection (23,58%), while in pandemic period 87 (33,33%) resulted positive with a DOB of 40.4 ± 17.5, significantly higher when compared to the mean value found in pre-pandemic period: 17.4 ± 16.5. We then carried out a subgroup analysis: of the 707 patients evaluated in the pandemic period, 32 (4,53%) reported in anamnesis a previous infection with Sars- Cov2. Among the 87 HP positive patients diagnosed in the pandemic period, only 4 (4,59%) reported a previous Sars-Cov2 infection at the time of the 13C - UBT execution. However, it should be noted that this is a retrospective study and that information about a previous Sars-CoV-2 infection was often absent from the patients' medical records, allowing us to deduce, on the basis of epidemiological data relating to global prevalence of Covid-19, that there is a marked underestimation.
**Discussion:** Neglecting the search for HP infection represented a risk condition for diseases (e.g. peptic ulcer disease, gastritis, stomach cancer), especially considering the remarkable elevation of the bacterial load.
The finding of an increased prevalence and of a significantly higher than average bacterial load in patients diagnosed with HP infection during the pandemic period suggests that there is some association between HP and Sars-Cov2 infection: if on the one hand we can hypothesise that the morphological changes in the GI epithelium induced by HP (increased expression of ACE-2 receptors) may favour the rooting of the Sars-Cov2, so as to elicit the GI effects of Covid, in particular abdominal pain and diarrhoea [Balamtekin N et al., J Pediatr Gastroenterol Nutr, 2019], on the other hand, we can assume that SARS-Cov-2 infection, whether current or previous, could somehow favour the replication of HP. There are several hypotheses that could explain this data:
- Sars-CoV-2 infection may alter the immune system of patients;
- the limited availability of BT during the pandemia delayed the diagnosis of HP infection;
- Sars- CoV-2 binds to ACE-2 receptors and may cause a damage to GI cells leading to morphological changes, that may promote colonisation and replication of the HP. In this regard, it is recalled that there are no data in literature about the morphological ultrastructural changes of GI cells in Covid 19, while HP adhesion mechanism is deeply known.
**Conclusions:** We recommend to the General Practitioner not to neglect the symptoms that may point to a HP infection, despite the considerable difficulties encountered in this period to access BT.
-Both Sars-Cov-2 and HP infection may influence each other. GI morphological and functional alterations due to Sars-Cov-2 infection, which can promote HP colonization and replication, need further investigation. For this reason we suggest performing ultra-structural electron microscopy studies, as has been done in our previous studies on the adhesion mechanisms of HP [Gasbarrini G et al., Eur. Rev. Med. Pharmacol., 2018].

## 224. RADIOMICS COULD PREDICT SURGERY AT 10 YEARS IN CROHN'S DISEASE

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**Background and Aim:** Predicting clinical outcomes represents a major challenge in Crohn's disease (CD). Radiomics provides a method to extract quantitative features from medical images and may successfully predict clinical course, however its application in CD is still scarce. The aim of this pilot study is to evaluate the use of radiomics to predict the need for surgery at 10 years in a cohort of CD patients.
**Methods:** We retrospectively selected a cohort of CD patients with available CT scan enterographies and a 10-year follow up. Typical lesions of CD were segmented in each CT scan. An open-source R library (Moddicom) was used to extract radiomic features from each segmented lesion.
A logistic regression model based on selected radiomic features was developed to predict 10-year surgery. The model was evaluated by computing the area under the curve (AUC) of the receiver operating characteristic curve, sensitivity, specificity, positive and negative predictive values (PPV, NPV).
**Results:** We enrolled 30 patients, with 44 CT scans and 93 lesions. We extracted 217 radiomic features from each lesion.
The developed model was based on two radiomic features (intensity variance and normalized grey-level non-uniformity from the grey-level run length matrix) and presented an AUC (95% CI) of 0.83 (0.73-0.91) in predicting 10-year surgery. Sensitivity, specificity, PPV and NPV of the radiomic model were equal to 0.72, 0.90, 0.79, 0.86, respectively.
**Conclusion:** Radiomics could be a helpful tool to identify patients with high risk for surgery and needing a stricter monitoring or therapy intensification.

## 225. THE ILLUSIONIST - INFLAMMATORY BOWEL DISEASE VERSION

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A 19-year-old male was admitted to our unit with abdominal pain, fever and diarrhoea started two days earlier.
Past medical history included appendicectomy, orchiectomy, episodes of rectal bleeding from congested haemorrhoids. In the last months he had been complaining of perianal discomfort; he also had a positive faecal occult blood test. His family history was significant for inflammatory bowel disease (father with ulcerative colitis). As pharmacological treatment, he reported the intermittent use of anabolic steroids for muscle growth purpose.
At admission, the patient was febrile, and the abdominal examination showed a mild diffuse abdominal tenderness, normal bowel sounds and no hepatosplenomegaly. At rectal examination presence of liquid stool without blood.
Laboratory tests revealed mildly increased inflammatory markers (WBC 14.5 migl/mmc, neutrophils 85%, CRP 5.2 mg/d) without anemia (Hb 14.5g/dl).
A plain abdominal radiography displayed minimal bowel dilatation with no gas-fluid levels, excluding bowel obstruction, while a CT scan exposed signs of intestinal inflammation: concentric thickness of the walls of the caecum, colon (to the hepatic flexure), ileum (6-7 cm of the terminal loop) and of the ileo-caecal valve, with some enlarged perivisceral lymph nodes. The patient was therefore started on i.v. fluids and oral mesalazine (4800 mg/day).

To exclude infectious causes, on day one samples for blood cultures, CMV DNA level, stool cultures for Salmonella spp, Shigella, C. Difficile, and Campylobacter spp were collected.
Also, blood tests for coeliac disease screening (Anti-gliadin Ig, Anti-tTG Ig) were carried out.
For persistent high fever and the clinical suspicion of an IBD at its first onset, supported by the family history and the radiological findings of an involvement of the last ileal tract, the patient was started on i.v. steroids (methylprednisolone 60 mg), with rapid defervescence.
To provide the gold-standard test for IBD diagnosis, on day three the patient underwent a colonoscopy: the endoscopic findings were highly indicative of an ileo-colon inflammatory disease, displaying a widely hyperaemic ileum with micro-erosions and a cobblestone-like mucosal. All samples collected through colonoscopy were reviewed by the histopathologist and IBD specialist, unveiling an active inflammation process, both in colon and ileum samples, with cryptic abscesses and focal cryptitis in the colon.
Such histological changes were considered consistent with the presence of Crohn's disease.
After the resolution of all symptoms, the patient was discharged with oral mesalazine, with the plan of a bowel MRI to study the whole bowel tract and a visit at the IBD clinic as an outpatient.
Two days later the bowel MRI was performed, and it did not confirm the presence of pathological thickness related to IBD, neither in the small or large intestine.
A few days later, the results of the stool cultures collected at admission revealed the presence of an infection from Campylobacter jejuni.
Since the symptoms had resolved, no antibiotic was administered; however, at this point we wondered if the C. jejuni infection was the main and sole origin of the symptoms and bowel manifestations that had led to hospital admission or rather a concurring factor in the onset of an IBD, hypothesis that we were not able to exclude with certainty at this stage. We therefore kept the patient on oral mesalazine for the following 30 days.
Four months after discharge, and after a 3 months-period off any anti-inflammatory drug (mesalazine or steroids), the patient underwent another colonoscopy which, in line with the previous bowel MRI, showed a normal colon with no sign of inflammation, also at the histological level.
Therefore, the hypothesis of an IBD-like presentation of enterocolitis by C. jejeuni was confirmed. At 12 months from discharge the patient is well, with no relapsing symptoms.
**Discussion:** this case adds to the list of the few described cases of enterocolitis by C. jejeuni mimicking an inflammatory bowel disease.
It is known that GI tract infections may present echoing the typical symptoms and/or signs of an IBD, often self-limiting; however, it still is unclear whether such infections may lead to the onset of an IBD in predisposed individuals or act as risk factor for recurrences.
Early differential diagnosis in such cases is of crucial importance, particularly because corticosteroids may worsen the clinical state of patients with an ongoing infection. Our patient improved very rapidly during hospitalization without antibiotic treatment, supporting a self-limiting course of the infection; corticosteroids were administered for only 2 days, without any worsening in symptomatology.
In conclusion, the differential diagnosis amid new onset IBD and infective enterocolitis can be challenging, especially in patients with predisposition to IBD, and imaging and endoscopy techniques are often unable to discern among the two. It is therefore vital to collect information about familial and past medical history and possible exposure to infection, and to promptly run a stool test looking for the most common pathogens involved.

## 226. A RARE COMPLICATION OF A COMMON PROCEDURE

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**Introduction:** . We report the case of a female adult patient who was admitted to our Internal Medicine ward in February 2022 complaining pharyngodynia and dry cough.
**Case Report: .** A 78-year-old woman presented to our Emergency Department with a 5-day history of fever, dry cough and sore throat. She had a recent diagnosis of intrahepatic cholangiocarcinoma causing biliary tract compression, for which Endoscopic Retrograde Cholangiopancreatography (ERCP) with stenting had been performed approximately 1 month before hospitalization. Her past medical history was remarkable for chronic hepatitis C infection, autoimmune hypotiroidism and isteroannessectomy. On admission to our ward, the patient was alert and comfortable at rest, febrile, her vital signs were stable. Her oxygen saturation was 97% breathing room air, her respiratory rate was 20 breaths per minute. Examination of the chest, heart, and abdomen was normal. She complained of pharyngodynia and painful swallowing, associated with a foreign body sensation that caused mild solid food dysphagia. Laboratory tests showed high inflammation markers, and a cholestatic pattern with moderately increased gamma-glutamyltransferase, alkaline phosphatase, and bilirubin. Blood cultures were negative. The chest X-ray showed a bilateral pleural effusion and left lobar pneumonia. We started empiric antibiotic therapy with piperacilline/tazobactam with a prompt clinical and biochemical response (i.e., resolution of fever and decrease of inflammation markers). Nevertheless, pharyngodynia and dry cough did not improve, even after bronchodilator therapy and low dose steroid. During the first days of hospitalization, the patient experienced an acute episode of severe respiratory distress associated with hypoxemia, dyspnea with tirage, wheezing, and stridor. Oxygen therapy was promptly started and the patient was treated with high dose steroid, nebulized bronchodilators, and intravenous magnesium with clinical improvement. Fibroscopy displayed mild pharyngeal edema, probably due to the recent endoscopic procedure. The CT scan of neck and chest surprisingly showed a large retroesophageal cervical abscess of 17x28x95 mm. No foreign body ingestion was observed. esophagogastroduodenoscopy did not detect any fistulas.
Even if the patient had achieved clinical stability and resolution of fever, in the context of an abscess lesion, exclusive reliance on antibiotic therapy would have been burdened with a high risk of therapeutical failure. Moreover, since the patient presented with symptoms of space-occuping lesion, surgical drainage by right cervicotomy was performed. Abscess culture and search for cancer cells were negative. The drains were removed after 3 days, and antibiotic therapy was then discontinued. The following CT scan confirmed the complete resolution of the fluid collection.
**Conclusion:** Deep neck space infections are a rare but serious complication of endoscopic procedures and carry great morbidity and mortality1. They usually occur days to months after the procedure and their clinical presentation may be subtle 2. A correct and prompt identification of cervical abscess is crucial, given the need for emergent operative intervention and the complications associated with a diagnostic delay, such as cervical osteomyelitis3. This case report emphasizes the importance for clinicians to always consider this potentially life-threatening condition, especially shortly after endoscopic procedures.
**References:** 1.Almuqamam M, Gonzalez FJ, Kondamudi NP. Deep Neck Infections. [Updated 2021 Dec 26]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https: //www.ncbi.nlm.nih.gov/books/NBK513262/ - 2 Rajdev K, Shahidi S, Goh S, et alRetropharyngeal phlegmon and cervical osteomyelitis after upper gastrointestinal endoscopy: a rare consequence of a routine procedureBMJ Case Reports CP 2022;15: e247977. - 3 Bonaddio, Vincenzo et al. "Vague neck pain following a gastrointestinal procedure: a rare case presentation of vertebral osteomyelitis and cervical epidural abscess." Spinal cord series and cases vol. 6,1 40. 13 May. 2020, doi: 10.1038/s41394-020-0290-9

## 227. EFFECTIVENESS AND SAFETY OF SWITCHING FROM INTRAVENOUS TO SUBCUTANEOUS VEDOLIZUMAB FORMULATION IN INFLAMMATORY BOWEL DISEASE PATIENTS IN CLINICAL REMISSION

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**Background and Aims**: Recently, subcutaneous vedolizumab (scVDZ) formulation has been approved for the treatment of Inflammatory Bowel Disease (IBD). In the randomized controlled trials for Crohn Disease (CD) and ulcerative colitis (UC), scVDZ formulation was comparable to intravenous (ivVDZ) one in terms of efficacy and safety. The aim of our study was to evaluate the safety and the effectiveness of switching IBD patients (pts) in clinical remission from ivVDZ to scVDZ in a real-life setting.

**Methods:** In this prospective cohort study, we collected data on consecutive IBD pts in steroid-free clinical remission who switched from ivVDZ to scVDZ from September 2021 to April 2022 at our IBD-Unit center. Demographic characteristics, baseline and 12-weeks follow-up clinical activity and C-reactive protein (CRP) levels, and adverse events (AEs) were recorded. Clinical IBD activity was evaluated with Harvey Bradshaw Index (HBI) for CD, and Partial Mayo Score (PMS) for UC. The primary outcome of the study was to evaluate steroid-free clinical remission plus biochemical remission (CRP <5 mg/l) at week 12.
**Results:** 94 pts (42 CD, 52 UC, median age 52 years [IQR 42-67.2]) switched from ivVDZ to scVDZ-maintenance therapy. Median duration of disease was 11.5 years [IQR 7-18.2] and median duration of ivVDZ treatment was 36.5 months [IQR 16-52.2]; hence, 51/94 pts (54.2%) were anti-Tumor Necrosis Factor alfa (anti-TNFα) exposed. Most of pts (94.7%) were on every 8-weeks maintenance therapy. At baseline, 46 (85.2%) UC pts and 36 (85.7%) CD pts had normal CRP levels. 78/94 (82.9%) pts (35 CD, 43 UC) reached the 12-weeks follow up visit. Of 66/78 pts (84.6%) with normal CRP values at baseline, 58/66 (87.9%) pts maintained clinical steroid-free remission and normal CRP values at 12-weeks follow up. Eleven AEs were recorded: 3 SARS-COV2 infections, 1 dental abscess, 4 mild injection site reactions, 1 diffuse urticarial reaction, and 1 new onset of arthralgia. 8 pts (10.3%) discontinued scVDZ: 3 pts for AEs, 3 for disease flare and 2 for pts'preference.
**Conclusions:** switching from ivVDZ to scVDZ can be considered a reasonably safe and effective treatment in maintaining remission in IBD pts at 12 weeks. Thus, recent availability of scVDZ can possibly permit an improvement of the quality of life of the pts and an abatement of the health care costs due to less frequent accesses to outpatient department for intravenous infusions. However, larger real life studies with longer follow up to confirm the long term efficacy, tolerability and safety to scVDZ are needed.

## 228. ROLE OF ENDOSCOPIC BALLOON DILATATION ASSOCIATED WITH BIOLOGIC THERAPY IN CROHN'S DISEASE STRICTURES MANAGEMENT: A III LEVEL CENTER EXPERIENCE FROM ITALY

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**Introduction:** Intestinal strictures frequently occur in Crohn's disease history as consequence of local transmural inflammation and fibrogenesis, de novo or after surgery. In Crohn's disease patients, strictures can develop in small bowel, colon and along the anorectal segment. Endoscopic balloon dilatation (EBD) is a safe technique to treat ileal stricture and delay surgery in those cases, however safety and efficacy of EBD combined with biologic therapy have been poorly evaluated.
**Aims and ethods:** Aim of the study was to assess, in a real-life experience, safety of EBD combined with biologic therapy for treatment of ileal, colonic, anastomotic and anal strictures of Crohn's disease. We conducted a retrospective study including all Crohn's disease patients who underwent successful EBD for evidence of bowel strictures from January 2018 until March 2021 at our tertiary IBD center. Clinical or endoscopic strictures recurrence, needs of re-EBD or surgery in those patients were evaluated in a follow-up of one year.
**Results:** A total of 46 patients underwent EBD during considered period. Of those, two patients were excluded due to lack of follow-up. Remaining 44 patients were included in study population: 18 (41%) were female, mean age was of 48 (19-77) years; 36 (81%) patients had a stricturing disease at diagnosis. Thirty-one patients of all (70%) were in active treatment with biologic therapy at the moment of EBD. Seventeen patients (39%) underwent EBD for de novo ileal stricture, 17 (39%) for anastomotic stricture, 4 (9%) for colonic stricture and 6 (13%) for anal stricture. At EBD, 31 patients (70%) had evidence of moderate or severe endoscopic disease activity and ulcerative lesions were documented at stricture site in 30 patients. EBD was performed with 12-15 or 15-18 mm dilation balloon and 24% patients received concomitant submucosal steroids injection. Technical success was reported in 96% of procedures and no adverse events were registered. Twelve patients (29%) underwent multisession EBD and 35 patients (83%) underwent biologic therapy after endoscopic procedure, 52% with anti-TNFα, 19% with ustekinumab and 10% with vedolizumab. Though endoscopic stricture recurrence was documented in 14 patients (33%): 4 patients (24%) with ileal stricture, 5 patients (29%) with anastomotic stricture, 3 patients (75%) in colonic stricture and 2 patients (33%) with anal stricture. Within a year from EBD, re-EBD was performed in 10 patients (24%) and 3 patients (7%) underwent surgery due to intestinal stenosis.
**Conclusion:** Our real-life data suggest a good safety profile of EBD combined with biologic therapy for the treatment intestinal stricture in Crohn's disease patients. EBD combined with biologic therapy could be effective in reducing needs of surgery in short term. Further controlled studies are needed to investigate long term safety and efficacy of EBD combined with different biologic therapies.

**Table 1.** *Study population characteristics*

| | N 44 |
|---|---|
| **Gender, n (%)** | |
| female | 18 (41) |
| **Age,** mean (range) | 48(17-77) |
| **Montreal A, n (%)** | |
| - A1 | 5 (11) |
| - A2 | 28 (64) |
| - A3 | 11 (25) |
| **Montreal B, n (%)** | |
| - B1 | 1 (2) |
| - B2 | 36 (81) |
| - B3 | 7 (17) |
| **Montreal L, n (%)** | |
| - L1 | 10 (23) |
| - L2 | 3 (7) |
| - L3 | 30 (68) |
| - L1+L4 | 1 (2) |
| **Stricture site, n(%)** | |
| Ileum | 17 (39) |
| Ileo-colonic Anastomosis | 17 (39) |
| Colon | 4 (9) |
| Anorectal | 6 (13) |
| **Concomitant biologic therapy, n (%)** | |
| infliximab | 7 (16) |
| adalimumab | 17 (39) |
| vedolizumab | 1 (2) |
| ustekinumab | 5 (11) |
| upadacitinb | 1 (2) |

## 229. HISTOLOGICAL FEATURES OF JOINT INFLAMMATION IN INFLAMMATORY BOWEL DISEASE PATIENTS WITH PERIPHERAL ARTHRITIS

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**Background and Aims:** Up to 50% of patients with Inflammatory Bowel Disease (IBD) experience at least one extraintestinal manifestation during their life among whom musculoskeletal manifestations (arthralgia and arthritis) are the most common. This study aims to explore the role of synovial histological assessment in the therapeutic management of IBD patients with clinical signs of peripheral articular involvement.
**Methods:** A retrospective study enrolling consecutive IBD patients receiving TNFa inhibitor, with concomitant joint involvement was performed from April 2015 to October 2020. At baseline, each patient underwent synovial-tissue (ST) biopsy for the semiquantitative assessment of synovitis degree through H&E-based Krenn score (KSS) by trained pathologist, blinded to clinical characteristics. Clinical IBD activity was evaluated with Harvey Bradshaw Index for Crohn's disease (CD), and Partial mayo Score for Ulcerative colitis (UC). Based on ST findings, 4 different therapeutic interventions were done: 1. addition of a conventional disease modifying antirheumatic drug (DMARD); 2. switch to another anti-TNFα; 3. swap to other biological class or 4. addition of a second biological drug. Patients were followed in an outpatients clinical setting to record treatment response within 12 months.
**Results:** 46 IBD patients (31 CD; 15 UC) with median age of 46 years [IQR 35-53 years] and a median of disease duration of 8 years [IQR 4-16 years] were included. At enrollment all patients showed clinical signs of peripheral arthritis. Overall, 31 patients (67%) had at least histologically proven low-grade synovitis (Jh+), defined as a KSS≥2. IBD patients were stratified based on baseline ST (Jh) and IBD activity (B+/B-) as follows: B-Jh+ (22 patients), B+Jh+ (9 patients) and B-Jh- (15 patients) respectively. The rate of B-Jh+ patients under anti-TNFα and paradoxical arthritis was 82%. Considering the whole cohort, 12(54%) IBD patients added a DMARD among whom 33% achieved joint remission at 12 months while one patient swapped to other biological class, resulting in joint remission. In the B+Jh+ group, 4(44%) patients maintained the baseline therapy, resulting in no joint remission while one patient added a second biological drug, achieving joint remission. In the B-Jh- group, 7(46%) patients added a cDMARD of whom 39% achieved articular remission; conversely, 4 (27%) patients did not modify the baseline therapy of whom 75% achieved joint remission. Finally, the persistence on the therapeutic strategy was 60% at the median follow-up of 42.5 months (IQR 23.5-57.2).
**Conclusions:** The semiquantative evaluation of synovial inflammation is a useful tool which might help physicians to better address therapeutic intervention, especially for IBD patients with mild/remission bowel activity or paradoxically developed arthritis.

## 230. LONG-TERM EVOLUTION OF CELIAC DISEASE-ASSOCIATED METABOLIC BONE DISEASE AND RISK OF FRACTURE: RESULTS FROM A 10-YEAR FOLLOW-UP

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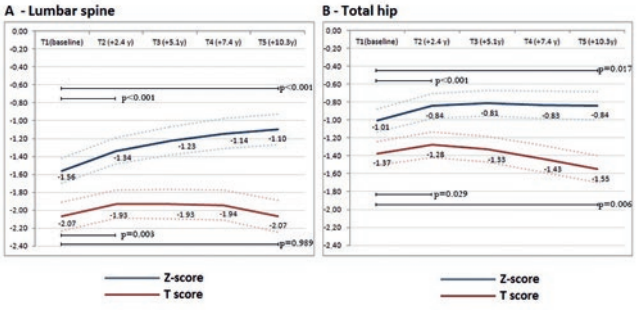
**Background and Aims**. Metabolic bone disease is frequent in celiac disease (CD) and can improve after a gluten-free diet. Most of the current guidelines for CD call for a dual-energy X-ray absorptiometry (DEXA) to be performed at the diagnosis and repeated every 2-3 years in case of low bone mineral density on index measurement. Still, the long-term evolution of DEXA values and the risk of fractures in CD patients remain unknown. Thus, the current guidelines are still calling for an optimized management of metabolic bone disease.
**Methods:** We explored our database of CD patients to identify patients who had: 1) abnormal values at the index DEXA (performed <12 months after CD diagnosis); 2) subsequent DEXAs performed every 2-3 years; 3) a total follow-up length of at least 10 years after the index measurement. Longitudinal evolution of DEXA scores and predictive indexes (FRAX and DeFRA), as well as the prevalence of osteoporotic fractures, are reported.
**Results:** Amongst 107 eligible patients (median age 43 years, females 82.2%) the index measurement showed osteoporosis in 26.2% at the lumbar spine and 5.6% at the total hip. Z-scores improved at both sites at the first follow-up, continuing to increase at the lumbar spine and remaining stable at the total hip (Figure). T-scores had similar changes at the first follow-up, then slightly declined after a median observation time of 7.5 years. Changes were particularly evident for patients with osteoporosis, while osteopenic subjects had more stable DEXA scores. Twelve patients (11.2%) had fractures at the spine (n=8), hip (n=2) and wrist (n=2) during the 10-year follow-up. All fractured patients had either osteoporosis at index measurement or other risk factors for fractures. Both FRAX and DeFRA scores were able to capture high-risk patients in our population.




**Conclusions:** Our data suggest that a strict follow-up could be recommended only in patients with osteoporosis or elevated risk of fracture according to FRAX or DEFRA. On the contrary, patients with osteopenia and no additional risk of fracture had very stable DEXA values over time and could repeat DEXA scans after a longer time (reducing the costs and stresses of the follow-up and allowing a better allocation of resources).

## 231. EX-VIVO OVER-PRODUCTION OF NICOTINAMIDE PHOSPHORIBOSYLTRANSFERASE IN AUTOIMMUNE ATROPHIC GASTRITIS AND UNTREATED COELIAC DISEASE

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**Background:** The nicotinamide phosphoribosyltransferase (NAMPT) is a biosynthetic enzyme involved in the metabolism of nicotinamide. NAMPT seems also to play a role as a pro-inflammatory cytokine in inflammatory bowel disease and its neutralization ameliorates experimental colitis. Instead, nothing is known to date about the role of NAMPT in other gastrointestinal disorders, such as autoimmune atrophic gastritis (AAG) and coeliac disease (CD), which are characterized by an activation of several inflammatory pathways in the gastric and duodenal mucosa, respectively. Our aim was to explore the pathogenic role of NAMPT in AAG and CD.
**Methods:** We collected perendoscopic gastric biopsies from 10 patients with AAG and duodenal biopsies from 10 patients with untreated CD and 10 CD patients following a strict gluten-free diet for at least 12 months. In addition, perendoscopic gastric and duodenal biopsies were collected from 10 healthy controls (i.e., patients with no gastrointestinal alterations). The biopsies were processed for RT-PCR to assess the mRNA expression of NAMPT in all groups. Furthermore, biopsies from healthy subjects were ex-vivo stimulated with NAMPT (500 ng/mL) and the expression of a panel of cytokines, namely tumor necrosis factor (TNF)-alpha, interferon (IFN)-gamma, transforming growth factor (TGF)-beta, interleukin (IL)-6, IL-8, IL-15, IL-17A, IL-33, was assessed at baseline and after NAMPT stimulation by RT-PCR.
**Results:** We found a NAMPT mRNA over-production in gastric biopsies from patients with AAG compared to healthy controls. An increased NAMPT production was found also in duodenal biopsies from patients with untreated CD, compared to both treated CD and healthy controls. Remarkably, patients with treated CD displayed roughly the same NAMPT mRNA expression of healthy controls (p not significant). The exposure of human biopsies from healthy patients to NAMPT led to an increase in the mRNA expression of IL-6, IL-8, IFN-gamma and TGF-beta.
**Conclusions:** Our findings confirm a NAMPT pro-inflammatory effect and suggest that this cytokine might sustain the pathogenic pathway of AAG and CD, representing a potential future therapeutic target.

## 232. REAL LIFE VS TRIAL ACCESS TO BIOLOGIC THERAPY DIFFERENCES: A 2019-2020 EXPERIENCE IN AN ITALIAN TERTIARY IBD CENTER

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**Background:** Inflammatory Bowel Diseases (IBD) are multifactorial diseases that afflict the gastrointestinal tract and include Ulcerative Colitis (UC) and Crohn's Disease (CD).
Up to 50% of IBD patients show a primary or secondary non-response to standard biological therapy. Therefore, Randomized Clinical Trials (RCTs) represent a significant therapeutic opportunity for them. However, not all patients can be enrolled in RCTs due to their stringent inclusion criteria.
**Aimf of the Study:** This study aims to describe the clinical characteristics and outcomes of "trial patients" vs. "real-life" and evaluate the presence of predictive factors which may affect the effectiveness of the different approaches: clinical practice or clinical research.
**Methods:** We prospectively selected all patients who started biological therapy from August 2019 to August 2020. We divided patients into four sub-groups: (1) "real-life" patients, (2) "real-life suitable for trial", patients who respected all the inclusion and exclusion criteria of RCTs but were treated with standard of care, (3) "trial" patients, and (4) "screening failure" at trials, patients who did not respect the eligibility criteria for RCTs.
Real-life patients were treated with standard biological therapy.
Trial patients were treated with drugs from phase 2b and 3 studies actively recruiting in our center.
Clinical response to treatment at six months follow-up was defined as the reduction of at least 3 points of Harvey-Bradshaw index (HBI) in CD and of Mayo Partial-score in UC patients (PMS). HBI score less than 5 and PMS less than 2 defined the clinical remission.
**Results:** We enrolled 141 patients: 75 with Ulcerative Colitis (UC) and 66 with Crohn's Disease (CD). "Real life" patients included 39 UC and 40 CD, "real-life suitable for trial" 6 UC and 14 CD, "trial patients" 28 UC and 10 CD, and "screening failure for trial" 2UC and 2 CD.
According to the existing inclusion and exclusion criteria, the study showed that only 45% of UC patients and 36% of CD patients were suitable for enrollment in an RCT, however only 15% of CD patients were finally enrolled in RCTs.
Patients were mainly excluded from a clinical trial for neoplastic comorbidities, chronic infectious diseases (TBC and EBV), or concomitant topic therapy.
Another primary reason for exclusion in CD patients was a low CDAI (<220) at the beginning of therapy. At the same time, UC patients were also excluded due to the limited extension of the disease (Montreal E1). Instead, patients suitable for trial were not included, mainly due to a smolder disease or for the absence of disease complications.
Data evidenced a longer persistence of biological therapy at six months follow up in "real life" (77.5%) and "suitable for trial" (93%) CD patients compared to "trial" CD patients (30%). UC patients did not show the same trend. Both "trial" UC and CD patients showed more extraintestinal manifestations of disease, especially the articular ones, thus resulting in a more severe self-perception of disease. Besides, they failed more lines of standard therapies compared to "real-life" patients. Clinical remission at six months follow up was reached by 54% of "real life" UC patients, 67% "suitable" UC, and 25% "trial" UC, while in CD patients, only "real life suitable" patients showed an increased rate of remission at six months (78%) compared to the other groups.
**Conclusions:** This study highlights some substantial differences between clinical practice and clinical research, particularly regarding the criteria to get access to biological therapies in CD. In fact, in clinical practice, patients with severe endoscopic or radiologic disease are candidates for biological therapies even without severe clinical symptoms, whereas these patients are generally excluded in clinical trials, for example, due to the limiting criteria of CDAI score in CD. In UC, clinical practice and research are more similar. However, globally "trial patients" have more complex diseases that significantly impact their clinical status. In addition to the use of clinical scores (HBI or CDAI) to assess the response to therapy in RCTs, these differences could cover the actual effectiveness of a new drug compared to the theoretical efficacy derived from registration RCTs.

## GERONTOLOGIA E GERIATRIA

### 233. AGING UNDERLIES HETEROGENEITY BETWEEN COMORBIDITY AND MULTIMORBIDITY FRAMEWORKS

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**Background:** Although of potential interest in clinical practice, studies exploring differences between comorbidity (i.e., the co-existence of additional diseases with reference to an index condition) and multimorbidity (i.e., the presence of multiple diseases in which no one holds priority) are lacking.
**Objectives:** We sought to evaluate the prevalence of patients with two or more multiple chronic conditions (MCC), categorising them into comorbidity or multimorbidity, and correlating them with other sociodemographic and clinical patients' characteristics.
**Methods:** This was a single-center, prospective, observational study conducted in an academic, internal medicine ward from Northern Italy, in which patients were enrolled in 2017-2019 (the follow-up is still ongoing). We compared the three categories no MCC, comorbidity, and multimorbidity, with regard to the Cumulative Illness Rating Scale (CIRS) comorbidity index, age, gender, polytherapy, 30-day readmission, in-hospital and 30-day mortalities. A multivariable analysis for factors associated with in-hospital mortality, 30-day mortality, and 30-day readmission was fitted.
**Results:** Overall, 1394 consecutive patients (median age 80 years, IQR 69–86; F: M ratio 1.16: 1) were included. Of these, 1341 (96.2%; median age 78 years, IQR 65–84; F: M ratio 1.17: 1) had MCC. Fifty-three patients (3.8%) had no MCC, 286 (20.5%) had comorbidity, and 1055 (75.7%) had multimorbidity, showing a statistically significant ($p<0.001$) increasing age trend (median age 38 years vs 71 vs 82, respectively) and increasing mean CIRS comorbidity index (1.53±0.95 vs 2.97±1.43 vs 4.09±1.70, respectively). The CIRS comorbidity index was always higher in multimorbid patients, but only in the subgroups 75–84 years and≥85 years was a significant ($p<0.001$) difference (1.24 and 1.36, respectively) noticed. At multivariable analysis, age was always independently associated with in-hospital mortality ($p=0.002$), 30-day mortality ($p<0.001$), and 30-day readmission ($p=0.037$), while comorbidity and multimorbidity were not.
**Conclusions:** We herein found that age determines the most important differences between comorbid and multimorbid patients, as well as major outcomes, in a hospital, internal medicine, setting.

### 234. RATE AND RISK FACTORS OF IN-HOSPITAL AND EARLY POST-DISCHARGE MORTALITY IN PATIENTS ADMITTED TO AN INTERNAL MEDICINE WARD

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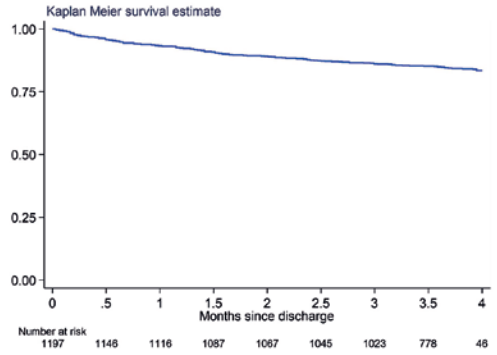
**Background:** Mortality rate is frequently evaluated through in-hospital mortality, without considering early post-discharge mortality. We sought to quantify in-hospital and early post-discharge (4-month) mortality rates and to assess their determinants in hospitalized patients.
**Methods:** This was a monocentric, prospective, cohort study conducted in a tertiary referral, academic ward from Northern Italy. Specifically, consecutive adult patients admitted to an internal medicine ward were prospectively enrolled in 2017-2019 and followed-up for four months after discharge. A prognosis of <24 hours was the only exclusion criterion. The rates of in-hospital and 4-month post-discharge mortality and their possible associated sociodemographic and clinical (e.g., Cumulative Illness Rating Scale [CIRS], body mass index [BMI], polypharmacy, Barthel Index) factors were assessed.

**Results:** Overall, 1451 consecutive patients (median age 80 years, IQR 69-86; female sex 53%) were included. Of these, 93 patients (6.4%) died during hospital stay, while 4-month post-discharge mortality was 15.9% (191/1200). Age (as a continuous variable) and high dependency (Barthel

Index ≥60) were significantly (p<0.01) associated with greater risk for both in-hospital (odds ratio 1.04 and 2.15, respectively) and 4-month (hazard ratio 1.04 and 1.65, respectively) mortality, while malnutrition (BMI<18.5) and length of stay were significantly (p<0.01) associated with greater risk of 4-month mortality (hazard ratio 2.13 and 1.59, respectively). CIRS and polypharmacy did not show any association with mortality. The Kaplan Meier curve (Figure) of the post-discharge mortality showed a constantly decreasing slope.




**Conclusions:** Older age, malnutrition, dependency, and length of stay are negative prognostic factors for early mortality in patients admitted to internal medicine wards. Interventions addressing dependency and malnutrition, when feasible, could potentially decrease early post-discharge mortality.

## 235. RESILIENCE IS ASSOCIATED WITH FRAILTY, DEPENDENCY, AND OLDER AGE IN HOSPITALISED PATIENTS

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**Background:** Although resilience may potentially influence several health outcomes, little is known regarding its significance and its relationship with frailty and other important patients' characteristics. We sought to assess resilience and its relationship with frailty and other clinical and sociodemographic data in a cohort of hospitalised patients.
**Methods:** In 2017-2019, we consecutively and prospectively enrolled patients in our academic, tertiary referral, hospital in Northern Italy, in an internal medicine ward. We selected all patients who filled in the 25-item Connor-Davidson resilience scale (CD-RISC). Mean resilience was evaluated according to baseline demographic (i.e., age, sex, marital and socioeconomic status) and clinical (i.e., Cumulative Illness Rating Scale [CIRS], Edmonton Frail Scale [EFS], Barthel index, Short Blessed test, length of stay [LOS]) data, and a multivariable analysis for assessing factors affecting resilience was fitted.
**Results:** A total of 143 patients (median age 64 years±18.7, 74 females) were included. Resilience was significantly lower in frail (p=0.010), elderly (p=0.021), dependent (p=0.032), and more clinically (p=0.028) and cognitively compromised patients (p=0.028), and in those with a low educational status (p=0.032). No relation between resilience and LOS was noticed (p=0.597). Frail patients (EFS>5) were significantly older (p<0.001), had a greater disease burden as measured by CIRS comorbidity (p<0.001) and severity indexes (p<0.001), were more dependent (p<0.001), more cognitively impaired (p<0.001), and displayed a lower educational level (p=0.011) compared to non-frail patients. At multivariable analysis, frailty (p=0.022) and dependency (p=0.031; according to the Barthel index) were associated with lower resilience in the age groups 18-64 and ≥65 years, respectively.
**Conclusion:** Low resilience was associated with frailty and dependency with an age-dependent fashion. Studies assessing the impact of this finding on important health outcomes are needed.

## 236. A TRIVIAL BACK PAIN

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*Dipartimento di Medinina, Università degli studi di Napoli Federico II*

R.A. 84-year-old male was admitted to our ward in February 2022 for disabling lower back pain and recent deterioration of his general state and consciousness, such as to make the patient no longer self-sufficient.
History: insulin-dependent type 2 diabetes mellitus with peripheral neuropathy, interstitial COPD, chronic cerebral vasculopathy, ischemic stroke in December 2021, chronic cystitis with multiple bladder diverticula and prostate adenoma.
In August 2021 he was hospitalized in another facility for hematuria and uro-sepsis and, again, in September for worsening of cognitive status.
At admission, the physical examination showed: widely reduced MV with bilateral basal crackles and poor spatial-temporal orientation, with a GCS of 13/15, while the EGA showed pO2 = 53 mmHg with SpO2 in AA: 92%.
On the first day, feverish peak at 38 ° C, for which blood cultures were performed and therapy with Sulfamethoxazole + Trimethoprim was started.
On the third day of hospitalization, a pleural effusion was found and, therefore, thoracentesis was performed with the withdrawal of 250 cc of serum-blood fluid from which samples were obtained for cytological, bacteriological and chemical-physical analysis.
Due to the onset of dyspnea and reduction in saturation, the patient was in a Venturi mask up to an FiO2 of 31% with a moderate clinical response (SpO2 at 93%).
In addition to antibiotic therapy, IV corticosteroids, meropenem and enoxaparin prophylaxis were introduced.
The evacuative thoracentesis was then repeated, on the seventh day, with the withdrawal of 1200 cc of serum-haematic liquid with improvement of the respiratory panel.
Further instrumental examinations were performed: chest CT showed thickening of the lower lobes with a ground-glass appearance and transthoracic echocardiography suspected vegetation on the native mitral valve, for which transesophageal echocardiography was performed and it onfirmed the diagnosis and estimated the size of the vegetation to about 2 cm.
Culture tests on pleural fluid and blood culture were positive for E. Fecalis and antibiotic therapy was modified by introducing tazobactam / sulfametazole and vancomycin.
Subsequently, the clinical examination showed an improvement in the inflammation indices and the patient's performance status; however, lower back pain and lack of spatial-temporal orientation persisted with significant short-term memory impairment.
An extension of the imaging exams was then proceeded to study the spine and skull.
The CT examination of the spine revealed a plausible picture of spondylo-discitis at the level of L4-L5, subsequently confirmed by MRI.
The same MRI, at the brain level, showed, in addition, findings of various focal lesions diffused bilaterally, of which the two larger ones of 27x17 mm and 20x10 mm, respectively in the lower frontal seat on the right and occipital on the left, not present in the previous examination performed in December 2021 and compatible with the diagnosis of infectious secondarisms.
The final diagnosis was E. fecalis mitral valve endocarditis with cerebral, bone and pulmonary dissemination.
After multidisciplinary evaluation, surgical indication was placed, however the family members decided on a conservative approach.
What seems interesting to underline, in conclusion, is how the presence of extremely common symptoms in the elderly patient like "spatio-temporal disorientation and lumbar pain", especially in ones with comorbidities that R.A. presents, has proved to be a key element in defining the future quality of life of our patient, although it may prove misleading to a first clinical approach due to the tendency to bring them back to simple senility or to the natural history of basic pathologies.

## 237. AGE-ASSOCIATED MODIFICATIONS IN BLOOD COUNTS. THE FINDINGS FROM AN OUTPATIENT POPULATION OF NORTHERN ITALY

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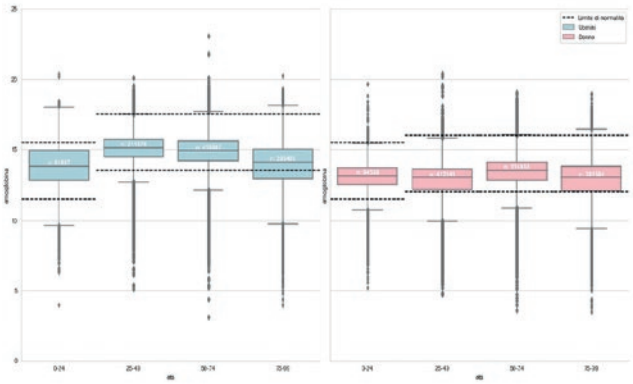
**Introduction:** . Blood counts are widely used in routine laboratory investigation as markers of disease conditions. Older subjects often present a reduction in red blood cell count, hematocrit and hemoglobin levels. Whether this must be considered a manifestation of overt disease condition

(anemia), deserving an adequate clinical approach, or otherwise represent a physiological change associated with aging, is a matter of debate.
**Aim:** The objective of the present study was to investigate the association between changes of blood count parameters and aging, in a large population of outpatients undergoing clinical biochemistry evaluation.
**Methods:** We examined all blood count examinations collected by laboratories external to hospitals in the province of Modena, Italy, in the period between January 2010 and March 2020. This included hemoglobin, red blood cells, white blood cells, platelets and mean corpuscular value. Analyses of hospitalized patients were excluded from the study. Data were stored in a Vertica Sequel Server and have been analyzed by means of the platform Anaconda 3, Python 3.7 and related statistical and graphical packages.
**Results:** Modena's resident database at the end of February 2020 was composed by 45,831,269 different analyses of the investigated parameters. Among these, hemoglobin data, without errors about gender, age and personal code were 4,007,945. The distribution of both hemoglobin and red cell count shows that older persons (age 75 and over), both males and females, are largely under the lower limit (respectively, 41.6% and 29.6% over 552,938 exams). In order to minimize selection biases, we divided the data by year, and took the average value per person per year; the trend was similar (32.8% of men and 22.2% of women below the normal boundaries). Finally, in order to exclude patients with organ disease, we limited our observation to subjects with normal values of serum glucose, creatinine and ALT, again considering a single value per year per patient. In this set, composed by 920,012 analyses, 19% of older male subjects were still below normal values (see Figure).
**Conclusions:** In the studied population of outpatients a relevant proportion of older subjects, especially of male gender, showed hemoglobin levels below the lower limit of the normal range. The exclusion of in-hospital analyses and of patients with altered liver or kidney tests and hyperglycemia appear to exclude, at least, some of the most common systemic or organ diseases.
These findings suggest extreme caution in the interpretation of blood counts in old age, and might ultimately support a re-definition of the normal laboratory values in this population.



## 238. CLOSTRIDIUM DIFFICILE ENTERITIS IN THE FERRARA'S COHORT

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Clostridium difficile enteritis is certainly one of the most common causes of infectious colitis and typically has nosocomial origin, although community-acquired cases are on the rise. Commonly associated risk factors include age, hospitalization and its duration and the use of drugs such as proton pump inhibitors and antibiotics (especially cephalosporins, penicillins, clindamycin and fluoroquinolones).
This observational study evaluated the hospital discharge forms of all patients admitted to the medical and surgical department of the Sant'Anna Archispedale in Ferrara, in the period from 2017 to 2021. The diagnoses are classified using the ICD system. During the observation period, 168 patients, 63 males (37.7%) and 104 females (62.3%), affected by Clostridium difficile enteritis were analyzed in the study. The mean age of the patients was 82.2 ± 9.7 years. The main comorbidities of the patients analyzed were: bed rest (9%), malnutrition (1.2%), arterial hypertension (18%), atrial fibrillation (10.8%), cachexia (4.2%), sarcopenia (15, 6%), ischemic heart disease (6%), dementia (23.4%), diabetes (13.8%), chronic renal failure (16.2%), chronic lung disease (8.4%), rheumatic disease (1, 8%), mild and severe liver disease (4.8%), leukemia (0.6%), lymphoma (0.6%) and cancer (1.2%). For a better and more objective evaluation of the patients we therefore calculated and used the Charlson comorbidity index, with an average value of 5.1 ± 1.6. There was no correlation between the Charlson Index score and death in patients admitted to Clostridium difficile infection (p 0.819). The main pathologies contributing to hospital admission were: anemia (21.6%), urinary tract infection (16.2%), (13.2%), heart failure (12%), pneumonia (9, 6%), sepsis (9%), septic shock (2.4%), pulmonary embolism (3.6%), respiratory failure (1.2%), DVT (1.2%). The mean length of hospitalization was 14.3 ± 8.7 days. 26 patients died during the hospital stay (15.6%). Only in 1.2% (2 patients) it was necessary to request an intensification of treatment. As might be expected, the longer hospital stay was correlated with higher mortality (p 0.026).

## 239. THE IMPORTANCE OF INTERNAL MEDICINE IN PATIENTS WITH MULTIPLE COMORBIDITIES

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77-year-old woman entered in Emergency Room for dyspnea and asthenia. In remote pathological history: hypertension, chronic heart failure, diabetes, obesity and COPD. In home therapy: Delapril + Indapamide, Metformina, Umeclidino Bromuro+ Vilanterolo, Omeprazolo. In the emergency medicine unit the patient was stabilized and then transferred to the internal medicine department. At the entrance to the ward, the patient was in fair clinical conditions, haemodynamically stable, alert and dyspnoic. Vital signs were: heart rate 140 bpm, blood pressure 110/70 mmhg, oxygen saturation 98%, blood sugar 295 mg/dl. The objective examination found edema of the lower limbs, vesicular murmur abolished in the bilateral basal site and systolic murmur 4/6 in the aortic focus. For this reason we performed an echocardiography that showed: an ejection fraction of 37%, tricuspid and sclerocalcific aortic valve with reduced systolic opening of the cusps that determines severe grade aortic stenosis (Valvular area 0.5 cmq, jet speed 5 m/s, average gradient 55 mmhg); left atrium dilated, moderate mitral regurgitation (vena contracta 4 mm); TAPSE 20 mm; medium-grade tricuspid regurgitation with PAPS 65 mmHg. Vena cava of increased dimensions little collapsible. Chest Ultrasound ed Rx showed bilateral basal pleural effusion and a thickening area in the middle lobe. At this point there were three connected problems to solve: severe aortic stenosis, acute heart failure and exacerbation of COPD. We set therapy with Methylprednisolone, Insulin, Clexane, Clarithromycin, Furosemide, Bromide Umeclidin + Vilanterol, Potassium Camphorate, Verapamil and oxygen therapy. In addition, Heart and Thorax Angio-CT was performed and the patient applied to TAVI. With drug therapy the exacerbation of COPD was resolved, the heart rate was reduced but heart failure did not improve, blood pressure was reduced and pulmonary congestion increased too. At this point we could not increase the diuretic to not lower the pressure further and not reduce the preload since in a severe aortic stenosis it is important to ensure good cardiac output, too much fluid could not be administered to avoid acute pulmonary edema, and norepinephrine and dobutamine were also contraindicated. The only solution was to remove the triggering cause of acute heart failure, so the patient was successfully applied and subjected to TAVI with a good improvement in symptoms and resolution of acute heart failure in the following days. At discharge, the patient had solved all the problems and was discharged with a therapy that optimized her chronic pathologies: the therapy of heart failure was optimized with the addition of Sacubitril/Valsartan, Empaglifozin and Aldactone and the addition of Empaglifozin for heart failure also improved diabetes therapy which, on the basis of the glycated hemoglobin values, could show that it was not well controlled. The case of this patient highlights the importance of multidisciplinary vision in patients with numerous comorbidities, and how we can't and shouldn't manage one organ or one pathology at a time but we have to solve all the problems at once because the various systems, especially the pulmonary and cardiological, are always related to each other.

## 240. TECHNOLOGY AS A TOOL FOR MANAGING CHRONICITY: PROPOSAL OF A MANAGEMENT MODEL FOR HOSPITAL-COMMUNITY PATHWAYS

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**Background:** In recent years, burden of complex patients in Internal Medicine Wards (IMW) is increased. To improve chronic patients management both during the acute and stable phase of disease, randomized wireless monitoring studies (WMS) are ongoing in Castelli Hospital IMW.
**Material and Methods:** A portable wireless system allowing continuous, real-time vital sign monitoring and creation of a personalized alert system for each patient via a portable device was used both for inpatients and after discharge in polipathologic, frail patients admitted in IMW.
**Results:** Up to now WMS of inpatients (LIMS study) recruted 145 patients, outpatients recruted in Greenline Study were 126. During 2021 the total number of people discharged from IMW were 737. Out of these 130 were transferred to territorial structures (17%), in 80% long-term care-Hospice and 105 dead (14%) which represent 31% of the hospitalized. 30-day hospitalization rate was 12%. Activity data confirms the evidence from the LIMS study that end-stage disease represents more than 30% of the sample admitted in IMW and the majority of re-hospitalized patients are in the terminal stage of the disease.
**Conclusions:** WMS combined with activity data analysis suggests the need for a model of patient management that envisages the increase in field structures offering patients subacute care (antibiotic treatments, blood transfusions, infusion support and pain therapy) for the timely management of chronic patients in the terminal phase, for which treatment in IMW should be guaranteed only for acute phase mangement.

## 241. KREBS CYCLE DERIVATIVES, DIMETHYL FUMARATE, DIMETHYL MALONATE AND ITACONATE, CONTROL LPS-INDUCED RESPONSE IN MICROGLIA BY PECULIAR CELLULAR BIOENERGETICS REWIRING

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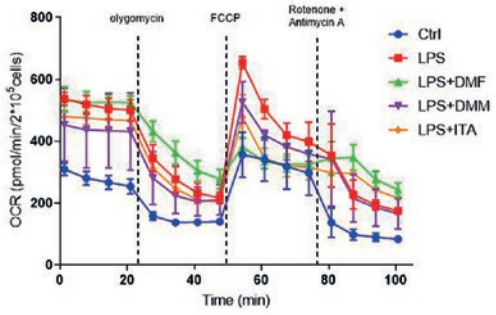
Metabolic reprogramming is a driving force of pro-inflammatory activation and differentiation in macrophages, where Krebs cycle (KC) intermediates seem to play a crucial role as signaling molecules. However, no current translational applications are available. Microglia, macrophage-like resident cells of central nervous system, are significantly involved in the pathogenesis of almost all neurodegenerative disorders. Here, we analysed the bioenergetic profile of LPS-activated human microglia cells (HMC3) and its modulation by treatment with KC derivatives, namely dimethyl-fumarate (DMF), dimethyl-malonate (DMM), and itaconate (ITA). To do this, oxygen consumption rate (OCR) and extracellular acidification rate (ECAR) were measured by Seahorse XFe96 Extracellular Flux Analyzer (Agilent technologies, Santa Clara, CA), to quantify mitochondrial respiration and glycolysis, respectively. Moreover, mitochondrial function and cytokine expression were assessed. The experimented three molecules reduced the cytokine expression (i.e. IL-1beta, TNF-alpha, IL-6) in LPS-primed microglia, with slight differences. Upon LPS activation microglia metabolism shifted towards an energetic phenotype requiring high levels of glycolysis and mitochondrial respiration, which were significantly inhibited by KC metabolites exposition. In particular, DMF was the least efficient to reduce glycolysis, although provoked the most significative reduction of maximal and spare respiratory capacity.




Moreover, DMF inhibited the respiratory-chain complex-I enzymatic activity, while DMM abolished the complex-II activity and boosted the complex-I. ITA significantly reduced both complex-I and complex-II activity and was the most efficient molecule to improve oxidative stress. Interestingly, IL-1β expression was proportional to the maximal respiratory capacity, hence DMF was the most efficient to downregulate IL-1β. In conclusion, metabolic rewiring occurring in activated microglia implies high glycolysis, and high mitochondrial respiration with consequent proton leak and oxidative stress. DMF, DMM and ITA controlled LPS-induced metabolic adaptation by acting in a different way, although exhibiting similar anti-inflammatory properties.

## 242. VITAMIN D STATUS IS ASSOCIATED WITH WORKING MEMORY AND ANXIETY IN OSTEOPOROTIC POSTMENOPAUSAL WOMEN

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Working memory (WM) and anxiety play a crucial role for the accurate execution of several daily activities. It is known that postmenopausal osteoporosis may be accompanied by cognitive and psychological disturbances. On the other hand, vitamin D levels have been previously associated with cognitive and psychological conditions, in addition to fracture risk in older adults.
The purpose of this cross-sectional study was to explore the associations between 25(OH)D level with both verbal WM, as expression of executive functioning, and anxiety in postmenopausal osteoporotic women.
Patients with severe neurocognitive and psychiatric disorder (according to the DSM-5 criteria), as well as patients with pathological conditions, which might interfere with cognitive performances, were previously excluded. Verbal WM was assessed by the Digit Span Test, with both the backward (DSB) and the forward tasks. Anxiety was assessed through the administration of Hamilton Anxiety Scale (HAM-A). 25(OH)D level was determined by high-performance liquid chromatography.
Sixty women (mean age 66 ± 7.99 years) were included in the study. Correlation analysis revealed that 25(OH)D level was positively associated with DSB score ($r= 0.423$; $p<0.001$), and negatively correlated with HAM-A score ($-0.295$; $p<0.05$). Furthermore, according to the Italian normative data, participants who showed an insufficient DSB score (N= 35) exhibited significantly lower levels of 25(OH)D (mean 34.29 ± 10.73 nmol/l), compared to participants (N= 25) who had a DSB within the normal range (mean 44.24 ± 16.6 nmol/l) ($p=0.008$).
Osteoporotic postmenopausal women with impaired verbal WM showed lower 25(OH)D concentration, compared to women with verbal normal performances. Moreover a poor vitamin D status was associated with higher anxiety symptoms. Further longitudinal studies should be carried out to deeply comprehend the positive impact of higher 25(OH)D levels on cognitive functioning and anxiety in postmenopausal osteoporotic women.

## 243. INTRODUCING SUSTAINABILITY IN MEDICINE: THE SIM STUDY

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**Introduction:** The clinical profile of patients hospitalized in Internal Medicine wards mirrors demographic and epidemiological trends in general population. In this setting, subjects of advanced age with multiple clinical comorbidities are most frequently represented. Such patients frequently need continuous assistance for their activities of daily living (ADL) due to loss of autonomy. As current strategies for healthcare resources allocation and organization had not been tailored to the current epidemiological landscape, available infrastructural and personnel resources might easily be overwhelmed by excessive workload. This can lead to prolonged hospitalizations, which might constitute a fertile soil for nosocomial infections and increase in-hospital mortality. Identifying potential clinical and organizational factors affecting survival is crucial to promote practice changes and

improve patient management; however, tools to assess care complexity and sustainability are currently limited. To address this issue, we performed a prospective "ward-wide" observational study in the General Internal Medicine Department of one of the largest metropolitan hospitals in Milan, and we hereby present the results of preliminary analyses.

**Materials and Methods:** The SIM (Sostenibilità in Medicina) study involved all adult patients hospitalized in the General Medicine and Advanced Care Department at San Raffaele Hospital, Milan between March 2016 and March 2017. Data collection was performed daily and included socio-demographic information, chronic comorbidities, reasons for admission and outcomes. Care intensity was estimated through the Nine Equivalents of Manpower Score (NEMS), while patient complexity was measured through the Cumulative Illness Rating Scale (CIRS), including its severity (CIRS-SI) and morbidity (CIRS-CI) sub-scores. Data regarding variations in healthcare personnel were also collected daily. Predictors of nosocomial infection, length of hospital stay and in-hospital death were estimated through logistic, linear and Cox regression analyses, respectively. Data are expressed as median (interquartile range, IQR).

**Results:** We enrolled 1075 patients (59% men and 42% women) with a median age of 74 (62 – 82) years; 432 patients (40%) were dependent in at least one ADL at hospital admission. Throughout the study, the median NEMS, CIRS-SI and CIRS-CI scores were 18 (15 – 18), 0.7 (0.4 – 0.7) and 3 (2 – 5) respectively. The physician/patient and nurse/patient ratio were 0.12 (0.09 – 0.14) and 0.14 (0.14 – 0.16), respectively. A total of 106 patients (10%) were transferred to our Internal Medicine ward from intensive care units (ICUs) or nursing home facilities, 35 (3%) from surgical Units. Most frequent comorbidities were infectious diseases (68%), followed by heart (53%), pulmonary (49%) and neurologic diseases (41%). Univariable regression analysis (Table 1) identified age, ADL/instrumental ADL dependency, CIRS severity score, worst general mean NEMS, admission from ICUs or from health care related facilities, worst physician patient ratio and nurse patient ratio as most significant predictors of nosocomial infections. ADL/IADL dependency, infective or neurologic disease at hospital admission, being admitted from ICU or from health care related facilities or from surgical units, CIRS severity score, the worst physician/patient ratio, the worst nurse/patient ratio were among the predictors of length of hospital stay. Age, ADL/IADL dependency, being admitted from ICU or from health care related facilities, oxygen and vasoactive therapy during hospital stay, invasive procedures, NEMS score, CIRS severity score, physicians/patient ratio were the most significant predictors of in-hospital mortality.

**Table 1: univariate regression analysis for the major study outcomes**

| **Nosocomial infections** | | | |
|---|---|---|---|
| | OR | 95% C.I. | p |
| Age | 1.03 | 1.01 - 1.04 | **< 0.001** |
| ADL/IADL dependency | 2.01 | 1.37 - 2.95 | **< 0.001** |
| Admitted from ICU or from health care related facilities | 2.28 | 1.34 - 3.87 | **0.002** |
| CIRS total score | 1.1 | 1.06 - 1.14 | **< 0.001** |
| CIRS severity score | 3.32 | 2.03 - 5.45 | **< 0.001** |
| CIRS comorbidity score | 1.26 | 1.14 - 1.39 | **< 0.001** |
| General mean length of hospital stay of all patients in the Ward | 1.08 | 1.04 - 1.13 | **< 0.001** |
| Worst Physician/patient ratio | 5.27 $e^{-9}$ | 1.05 $e^{-16}$ – 0.26 | **0.04** |
| Worst nurse/patient ratio | 0.005 | 0.0 - 0.75 | **0.04** |
| Worst general mean NEMS | 1.51 | 1.23 - 1.85 | **< 0.001** |
| **Length of hospital stay** | | | |
| | B | 95% C.I. | p |
| ADL/IADL dependency | 5.81 | 3.92 - 7.71 | **< 0.001** |
| Neurological disease (including dementia) | 4.22 | 2.31 - 6.12 | **< 0.001** |
| Infectious disease at hospital admission | 3.97 | 1.96 - 5.99 | **< 0.001** |
| Admitted from ICU or from health care related facilities | 15.58 | 12.55 - 18.61 | **< 0.001** |
| Admitted from surgical units | 13.99 | 8.73 - 19.24 | **< 0.001** |
| CIRS total score | 0.03 | 0.13 - 0.48 | **0.001** |
| CIRS severity score | 3.78 | 1.39 - 6.17 | **0.002** |
| CIRS comorbidity score | 0.72 | 0.24 - 1.19 | **0.003** |
| Worst Physician/patient ratio | -125.05 | -166.64 - -83.47 | **< 0.001** |
| Worst nurse/patient ratio | -80.69 | -109.64 - -51.75 | **< 0.001** |
| **In-hospital deaths** | | | |
| | HR | 95% C.I. | p |
| Age | 1.04 | 1.02 - 1.06 | **< 0.001** |
| ADL/IADL dependency | 2.63 | 1.73 - 4.01 | **< 0.001** |
| Admitted from ICU or from health care related facilities | 0.54 | 0.31 - 0.94 | **0.03** |
| Oxygen during hospital stay | 1.46 | 1.01 - 2.12 | **0.046** |
| One vasoactive drug | 5.04 | 2.2 - 11.55 | **< 0.001** |
| Invasive procedures performed in the unit | 3.62 | 1.33 - 9.84 | **0.012** |
| Invasive procedures performed outside the unit | 0.30 | 0.09 - 0.93 | **0.04** |
| NEMS score | 1.04 | 1.003 - 1.08 | **0.03** |
| CIRS total score | 1.08 | 1.04 - 1.11 | **< 0.001** |
| CIRS severity score | 2.79 | 1.82 - 4.29 | **< 0.001** |
| CIRS comorbidity score | 1.17 | 1.07 - 1.27 | **< 0.001** |
| Physicians/patient ratio | 0.00031 | 0.000008 - 0.01 | **< 0.001** |

**Conclusion:** Patients hospitalized in Internal Medicine departments are charged with a high burdern of comorbidities, which, in turn affect hospitalization length, occurrence of complications and survival. Context variables such as the clinical complexity of co-hospitalized patients and the size of healthcare personnel, contribute to individual patient outcomes, supporting the need for a sustainable model of care with adequate resources. The complexity of the patients in term of comorbidities and dependency in the activity of daily living should guide the allocation of the healthcare personnel in the Internal Medicine Wards. In spite of the initial increase of the healthcare expenditure for the employment of more personnel this would reduce nosocomial infections, length of hospital stay and in-hospital mortality.

## 244. A PRESERVED ENDOTHELIAL FUNCTION IS A CHARACTERISTIC OF HEALTHY CENTENARIANS

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**Background and Aim:** Aging is a global challenging issue for public health. Therefore, it is of interest to study models of successful aging as in the case of centenarians. This is in fact a special population that was able to escape or survive to age related diseases as cardiovascular diseases, cancer, or diabetes. Endothelial function has a critical role in atherosclerosis and aging. Endothelial dysfunction is the essential requisite for atherosclerosis and is the result of an imbalance between oxidant and antioxidant factors that consist of genetic, nutritional and environmental factors. Therefore, healthy aging is expected to be associated with a good endothelial function, especially in centenarians and ultra-centenarians. However, up till now no study has investigated endothelial function in centenarians. We investigated for the first time the endothelial function measured as flow-mediated dilation (FMD) of the brachial artery, that is the gold-standard test for measuring endothelial function in vivo in humans, in a group of healthy centenarians living in the Madonie, a district in the Palermo's area with high prevalence of centenarians.

Table

| | Centenarians | Controls | P |
|---|---|---|---|
| Males/females | 4/7 | 25/72 | |
| Age (years) | 100.5 ± 0.5 (100 - 105) | 40.7 ± 13.8 (18 - 67) | < 0.001 |
| Body weight (kg) | 60.6 ± 10.3 (43.0 - 74.7) | 81.0 ± 20.6 (42 - 145) | < 0.005 |
| BMI (kg/m2) | 27.5 ± 4.8 (17.9 – 32.7) | 27.8 ± 8.0 (22.2 – 57.7) | 0.90 |
| Waist circumference (cm) | 104.1 ± 6.9 (93.0 – 113.0) | 98.1 ± 19.1 (65.0 – 153.0) | 0.31 |
| FMD (%) | 12.1 ± 4.3 (8.0 – 21.7) | 8.6 ± 5.3 (1.2 – 28.9) | < 0.05 |
| ABI (average) | 1.03 ± 0.27 (0.80 – 1.65) | 1.11 ± 0.17 (0.70 – 1.65) | 0.17 |
| Blood concentrations of (mg/dl): | (n=7) | | |
| glucose | 81 ± 7 (73 - 91) | 92.0 ± 12.2 (55 - 119) | < 0.05 |
| cholesterol | 181 ± 51 (124 - 222) | 195 ± 42 (118 - 355) | 0.38 |
| HDL-cholesterol | 54 ± 23 (38 - 70) | 54 ± 19 (26 - 116) | 1.00 |
| triglycerides | 118 ± 48 (72 - 168) | 109 ± 58 (38 - 303) | 0.69 |
| uric acid | 6.2 ± 1.5 (3.8 – 8.0) | 4.9 ± 1.3 (2.5 – 8.1) | < 0.05 |
| creatinine | 1.4 ± 0.8 (0.8 – 3.0) | 0.9 ± 0.2 (0.3 – 1.7) | < 0.001 |

**Selection of Participants:** The centenarians (age >99 years) living in the municipalities of the Madonie area were contacted (their care-givers) through the municipal administrations. Fifty centenarians were identified, 28 gave consent to be evaluated at their respective residences where between 19th and 30th July 2021 a team of researchers consisting of doctors and dieticians conducted all the evaluations. The project was approved by the Palermo 1 ethics committee and is part of the ABCD project (Nutrition, Cardiovascular Wellness and Diabetes; ISRCTN15840340). The FMD test could be performed in 11 (7 females and 4 males) healthy centenarians and this subgroup was compared to a healthy younger control group obtained from the ABCD cohort.
**Methods:** The FMD of the brachial artery was measured with a high-resolution ultrasound linear probe (10 MHz, Cx50 Philips; US). A sphygmomanometer was cuffed at 220–250 mmHg 2 cm below the antecubital fossa for 300 s to occlude the artery and establish reactive hyperemia. A real-time computed video-analysis of B-mode ultrasound images (FMD Studio; Institute of Physiology CNR; Pisa, Italy) recorded the brachial artery diameter variations. The mean of the measures obtained during the first minute set the baseline vessel size. The FMD was calculated as the maximum percentage increase of brachial artery diameter over baseline. All the FMD tests were performed by the same operator. The intra-observer coefficient of variation for FMD is 2.9% in our laboratory. Also, biochemical data and the ankle-brachial index (ABI) were obtained.
**Results:** The results are reported in Table. This results demonstrate that the endothelial function of the healthy centenarians is significantly better than that of the control group. The ABI was similar in both groups thus suggesting a comparable peripheral artery condition despite higher serum creatinine and uric acid concentrations.
**Comments and Conclusion:** There are very few studies on centenarians, most have investigated small series which often also include not true centenarians (age> 90 years). This study shows that a preserved, or even better, endothelial function is characteristic of healthy centenarians. This is the first time that the FMD is measured in centenarians and despite the small sample of centenarians our study probably contributes to confirm the importance of the relationship between endothelial function, health, and aging.

## 245. IMPACT OF THE COVID-19 PANDEMIC ON THE COGNITIVE, FUNCTIONAL AND PSYCHOLOGICAL STATUS OF FRAIL OLDER OUTPATIENTS

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**Background:** Older adults mostly suffered from the consequences of the COVID-19 pandemic. The cost of confinement was paid in terms of social isolation, distance from relatives and friends, lack of social support, and limited access to the healthcare system, resulting in a negative impact on health, especially for subjects with comorbidities and frailty.
**Objectives:** The purpose of the study was to investigate the consequences of one-year living during the COVID-19 pandemic on cognitive performances, functional status, and quality of life among frail outpatients.
**Method:** The present study involved a cohort of older outpatients. Those outpatients who have undergone a first follow-up evaluation between April and May 2020 were contacted between April and May 2021, and were asked to voluntarily participate in a second telephone-based evaluation. Cognitive performances (through Mini Mental State Examination - MMSE), functional autonomy in basic and instrumental daily activities, physical and mental components of quality of life (SF-12 PCS and SF-12 MCS, respectively) were evaluated, and compared to previous evaluations.
**Results:** 71 outpatients (mean age of 80.69 years) completed the present follow-up evaluation (t2). Patients reported at t2 significantly lower cognitive performances (mean MMSE 19.37; p<0.001), lower physical quality of life (mean score 31.69; p<0.001), and lower mental quality of life (mean score 38.79; p<0.001) compared to both pre-pandemic baseline (t0) and the first follow-up (t1). Moreover, patients at t2 showed a significantly reduced autonomy in basic daily activities (mean score 3.8; p= 0.004), and a significantly reduced autonomy in managing telephone (p= 0.012) and medications (p= 0.035), compared to baseline.
**Conclusions:** The COVID-19 pandemic has been a prolonged stressor over time, which has markedly affected health-related quality of life of frail outpatients, and has denoted a stressor that has exacerbated patients' cognitive and functional vulnerability.

## 246. DIET CHARACTERISTICS AND NUTRITIONAL STATE OF HEALTHY CENTENARIANS

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**Background and Aim:** Aging is a global challenging issue for public health. Therefore, it is of interest to study models of successful aging as in the case of centenarians. This is in fact a special population that was able to escape or survive to age related diseases as cardiovascular diseases, cancer, or diabetes. It is clearly established that healthy eating patterns and a good body composition are associated with good health and are expected to be associated with longevity, especially in healthy centenarians. However, up till now few studies investigated food habits in small sample of centenarians, and no study is available concerning body composition in this special population, at least to our knowledge. The aim of this study was to investigate the nutritional characteristics of a group of healthy centenarians living in the Madonie, a district in the Palermo's area with high prevalence of centenarians.
**Selection of Participants:** The centenarians (age >99 years) living in the municipalities of the Madonie area were contacted (their care-givers) through the municipal administrations. Of the 50 centenarians, 28 gave consent to be evaluated at their respective residences where between 19 and 30 July 2021 a team of researchers consisting of doctors and dieticians conducted all the evaluations. The project was approved by the Palermo 1 ethics committee and is part of the ABCD project (Nutrition, Cardiovascular Wellness and Diabetes; ISRCTN15840340). They were compared to younger control groups obtained from the ABCD cohort divided as young elderly (age: 65-74 years), elderly + very old people (75-99 years).
**Methods:** Dietary habits were investigated using a food frequency questionnaire (FFQ) validated for Italian adults living in Sicily (J Food Sci Nutr. 2015;66: 426-38.). Body composition was investigated using bioimpedance analysis (BIA 101; Akern, Italy).

Table

| | young elderlypeople (65-74 years) n=198 | elderly + very old people (75-99 years) n=40 | Centenarians (≥ 100 years) n=28 | ANOVA P* | ANCOVA P** |
|---|---|---|---|---|---|
| Body weight (kg) | 76.0±14.4 | 74.1±13.7 | 54.6±12.5 a,b | <0.001 | <0.001 |
| BMI (kg/m2) | 29.5±5.1 | 29.5±3.6 | 25.7±5.6 a,b | <0.001 | <0.05 |
| Body circumferences: | | | | | |
| waist (cm) | 100.8±11.7 | 103.3±10.0 | 100.1±7.8 | 0.43 | <0.05 |
| hip (cm) | 105.7±9.3 | 103.9±7.0 | 101.3±9.1 | 0.05 | 0.05 |
| Body composition: | | | | | |
| Massa grassa (%) | 29.1±9.3 | 29.2±8.2 | 28.7 ± 10.9c | <0.05 | <0.001 |
| Massa magra (kg) | 53.8±10.4 | 52.7±11.9 | 38.7 ± 4.9a, b | <0.001 | <0.001 |
| Energy intake: | | | | | |
| kcal/24h | 1356±303 | 1292±261 | 1027±222a, e | <0.001 | <0.001 |
| kcal/kg-BW·24h | 18.3±5.0 | 18.0±5.0 | 19.5±5.2 | 0.49 | 0.67 |
| Carbohydrates: | | | | | |
| g/24h | 169±50 | 168±46 | 125±33a, e | <0.001 | <0.005 |
| % EI | 48.3±7.5 | 53.0±20.3c | 47.1±5.5 | <0.05 | 0.31 |
| Lipids: | | | | | |
| g/24h | 44±11 | 41±8 | 36±7d | <0.01 | 0.05 |
| % EI | 30.2±5.5 | 29.7±5.2 | 33.1±4.2c, f | <0.05 | 0.22 |
| Proteins: | | | | | |
| g/24h | 66±15 | 63±15 | 49±13a, e | <0.001 | <0.001 |
| % EI | 20.4±3.8 | 19.9±2.2 | 19.5±2.8 | 0.48 | 0.22 |
| Glycemic load | 97.5±31.4 | 91.8±26.2 | 69.8±22.0a, f | <0.001 | <0.05 |

**Results and Comments:**The demographic, anthropometric and dietary characteristics of the studied groups are shown in the Table. Interestingly, the nutritional status assessed on the basis of different measurements (body weight and circumferences, body composition) progressively deteriorates from the condition of young elderly to that of centenarian. This fact might be considered as a marker of aging, potentially affecting the duration of life. The diet was varied and balanced, typical products of the Madonita area were referred to be habitually consumed as cereals and derivates, fruit and vegetables, legumes, meat, eggs, fish and dairy products. In general, the

centenarians exhibited a higher consumption of lipids than the younger groups, probably because consuming more energy dense foods facilitates as the chewing and the introduction of an adequate quantity of calories. Very simple dishes were consumed, made with local foods as vegetable soups, pasta in broth, omelettes, mashed potatoes, homogenized meat or fish, fresh or cooked fruit, soft cheeses, mozzarella, yogurt, extra virgin olive oil, and in some instances also small amounts of local red wine consumed at lunch or dinner. Desserts, as ice cream in the summer or pastries on Sundays were consumed from time to time. Some centenarians also eat homemade pizza once a week. Interestingly, almost all centenarians referred that they don't eat pork or cured meats.
In conclusion, this cohort of centenarians still exhibited an adequate nutritional state for their age, with maintenance of appetite with actual dietary habits that roughly consist of typical foods of the Mediterranean diet.
ean±SD; [1]ANOVA c2; [2]ANCOVA: sex as covariate. Tukey's test: aP< 0.001 vs young elderly people; bP< 0.001 vs elederly+very old people; cP< 0.05 vs young elderly people; dP< 0.01 vs young elderly people; eP< 0.01 vs elederly+very old people; fP< 0.05 vs elederly+very old people.

## MALATTIE CARDIOVASCOLARI

### 247. PEARSON'S TEST AND THE "CAPNO-TEC" STUDY: CORRELATIVE ANALYSIS IN 20 PATIENTS WITH CHRONIC VENOUS THROMBOEMBOLISM. FIVE-YEAR EXPERIENCE (2017-2021)

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**Introduction:** "CAPNO-TEC" study, acrostic from "chronic venous CAPNO-Thromboembolism" reports 20 patients, from 48 and 88 years old, affected with chronic venous thromboembolism (central pulmonary embolism) admitted to the unit "High Intensity Internal Medicine" from January 2017 to December 2021. We calculated the following chronic criteria: 1) all the patients showed pulmonary embolism > 12 months proved by angio TC; 2) all the patients suffered from post-thromboembolic pulmonary hypertension proved by echocardiogram; 3) all the patients suffered from chronic venous occlusion with particular evidence of nearest recanalization that was already reported in the previous embolic episode; 4) all the patients had pCO2 values at the entry > 35mmHg. We measured pCO28 in all the patients at the entry (FiO2 21%) with arterial sample. As a consequence, we created a database with Microsoft Access© called "CAPNO-TEC". This database included the following fields: 1) number of patient, 2) pCO2 values at the entry with FiO2 21%, 3) chronic clinical aspects. A comparative analysis was carried out for nominal variables with the Cochran's Q test. The aim was to check if there is a significant relationship between pCO2 values at the entry and the chronic embolism.
**Purpose of the Experiment:** Our research has two main goals: first of all, to check any differences in pCO2 values at the entry in 20 patients affected with chronic pulmonary embolism. Moreover, to check its statistical importance by applying the Cochran's Q test in order to determine if the differences are due to chance.
**Methodology:** In order to apply the Cochran's Q test, we created Table 2. This includes pCO2 values at the entry with FiO2 21% in those patients enlisted in this case, with distinguishing values > 35mmHg, values between 35 and 45mmHg and values > 46mmHg. To calculate $\chi 2$ we apply the following formula: $\chi 2 = (k-1)[(k\,x)-y2]/(k\,y)-z=28,9$. "K" refers to 3 variables, "X" refers to the total sum of squares of the 3 variables. "Y" stands for the total of the chosen scores. "$Y^2$" is the square of the total chosen scores. "Z" means the sum of the squares of the chosen scores. The $\chi 2$ relative value (VR) is 28,9 with Degree of Freedom (GL) =2. The $\chi 2$ critical value (VC) per p=0,001 is 13,816.
**Results:** By applying the Cochran's Q test to the pCO2 values in 20 patients, the results demonstrate how pCO2 values with FiO2 21% at the entry in those patients affected with chronic pulmonary embolism are not at all due to chance. They have indeed a significant importance because the $\chi 2$ obtained relative value (VR) is 20,95 with Degrees of Freedom (GL)=2, and the $\chi 2$ critical value (VC) per p=0,001 is 13,816. The differences in choice are consequently strongly significant with p<0,001.
**Discussion:** The results show how comparing pCO2 values with FiO2 21% at the entry between 36 and 45 mmHg in patients with chronic pulmonary embolism is much more common than pCO2 pathognomic values <35mmHg due to central acute pulmonary embolism. As a matter of fact, the direct consequences of the acute pulmonary embolism are: the increase in death area, bronchoconstriction connected with platelets and mastocytes, flow redistribution in the healthy alveolar capillary unit, relaxation of the alveolar capillary unit with the excitation of J receptors, tachypnea, hyperventilation, hypocapnia. In the chronic embolism, the opening of vascular shunts is vital, with flow deflection from pulmonary area to the systemic circulation, jumping over the alveolar capillary exchange.
**Conclusions:** "CAPNO-TEC" study points out the correlation between pCO2 values in the arterial emogas analysis from 36 to 45mmHg and the chronicization of illness due to the opening of vascular shunts in 20 patients with venous thromboembolism. This correlation represents a significant concordance

### 248. DIFFERENCE IN INTERPRETATION OF COMPUTED TOMOGRAPHY PULMONARY ANGIOGRAPHY DIAGNOSIS OF SUBSEGMENTAL THROMBOSIS IN PATIENTS WITH SUSPECTED PULMONARY EMBOLISM: "SUMMARY" STUDY

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**Introduction:** The introduction of computed tomography pulmonary angiography (CTPA) as a diagnostic modality to diagnose pulmonary embolism (PE) has led to a significant increase in the incidence of PE diagnosis. Multidetector CTPA has improved the sensitivity for diagnosis of PE, allowing better visualization of segmental and subsegmental pulmonary arteries. Concomitantly, the proportion of patients with suspected PE in whom isolated subsegmental pulmonary embolism (SSPE) is reported has increased. The management of PE isolated to the subsegmental pulmonary arteries (single or multiple vessels) without a concomitant deep vein thrombosis (DVT) is controversial among thrombosis experts and clinical equipoise exists regarding the use of anticoagulant therapy in the management of those isolated SSPE. Given how important it is for clinicians to have an accurate diagnosis in order to decide on the risk-benefit ratio of anticoagulant therapy to treat SSPE, we sought to determine the proportion of agreement between radiologists on the diagnosis of isolated SSPE in patients presenting with suspected PE, We conducted a retrospective cohort study (SUMMARY Study), acrostic for SUbsegMental pulMonARY embolism) of consecutive patients with suspected isolate SSPE who underwent CTPA at the Rome St. John Hospital between January 2014 and December 2021. Computed tomography pulmonary angiography was performed using 64-detectors CT device. SSPE was defined as any number of pulmonary artery filling defects isolated to the subsegmental pulmonary arteries detected on CTPA. The CTPA images of all patients with an index diagnosis of SSPE were reviewed by an experienced thoracic radiologist. The examiner was blinded to the diagnosis and original filling defect location. Disagreements were reviewed by a second experienced thoracic radiologist.
**Methods:** Over the study period, 343 CTPAs were carried out for SSPE at the St. John Hospital. 175 (51%) patients had a diagnosis of isolated SSPE. The median age was 69 (range 37–95) and 60% were female. Twenty-two per cent had a prior history of VTE. Twenty-five per cent of patients had cancer.
**Results:** The reviewing radiologists (first and second) agreed with the initial diagnosis of isolated SSPE in 73% (128/175) of the cases. A total of 66% (56/112) of the included CTPA examinations without any evidence of PE index diagnosis of SSPE were re-interpreted by the thoracic radiologists to be with evidence of PE index diagnosis of SSPE. There are significant differences (X2 = 1324,91 con GL = 1 e VC 10,82 per p=0,001) in the interpretations of a diagnosis of isolated SSPE among radiologists. This uncertainty around the diagnosis could potentially lead to inappropriate use of anticoagulation and related complications (major bleeding episodes or recurrent VTE). The diagnosis of isolated SSPE on CTPA should be reviewed by an experienced thoracic radiologist before physicians make any clinical decision on anticoagulant therapy.
**Discussion:** Our results are consistent with previously published literature. A very good interobserver agreement was reported for the diagnosis of massive PE using CTPA (overall j = 0.82; 95%CI, 0.68–0.95). However, the concordance was lower with regard to segmental and subsegmental PE (j = 0.47; 95% CI, 0.16–0.84). Similarly, another interobserver agreement study reported a j of 0.38 (95% CI: 0.0 – 0.89) for SSPE among radiologists

with varied levels of experience. The clinical importance of an SSPE diagnosis is unknown. The increased incidence of SSPE with CTPA seems to be associated with a lower severity of illness in the CTPA era. A completed randomized controlled trial comparing the utility of CTPA with ventilation/perfusion scanning for the management of patients with suspected PE has shown that CTPA resulted in a significantly greater number of VTE diagnoses than did ventilation/perfusion scans; hence, more patients diagnosed by CTPA were treated with anticoagulants.
**Conclusions:** Our results indicate that significant differences (p<0,001) exist in the interpretations of a diagnosis of isolated SSPE on CTPA among radiologists. Given the clinical equipoise that exists around the management of single and multiple isolated SSPE, CTPA examinations with isolated SSPE diagnosis should be reviewed by an experienced thoracic radiologist to ensure proper risk-benefit ratio assessment and clinical management of patient care.

## 249. ATYPICAL ANTIPSYCHOTICS AND VENOUS THROMBOEMBOLISM: UP-REGULATION OF 5HT2A RECEPTORS. CASES REPORT

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**Introduction:** In the light of the numerous studies available in the literature, we have analyzed the relationship between the intake of oral antipsychotics and the onset of venous thromboembolism in 30 patients enrolled between January 2019 and December 2021 and admitted to the "Medicine High Intensity Internal Care ". The clinical picture of onset was characterized in all patients by severe respiratory insufficiency (arterial blood gas value of pO2 <60 mmHg) possibly associated with chest pain, confusional state, hemodynamic instability (PAS <90 mmHg) according to the American College of Chest Physicians Evidence -Based Clinical Practice Guidelines. All patients had undergone oral therapy for <30 days for schizoaffective disorder with so-called "atypical" antipsychotics: 14 patients with risperidone and 16 patients with olanzepine. In table 1 we have reported the main individual characteristics at the entrance.
**Purpose of the Work:** Our cases report has the following objectives: 1) verify the relationship between atypical antipsychotics and venous thromboembolism; 2) to analyze the pathogenetic mechanism of thrombogenesis in patients undergoing treatment with atypical antipsychotics.
**Cases Report:** The 30 patients enrolled with venous thromboembolism were aged between 58 and 78 years; 18 were female, 12 were male; among the risk factors in 12 patients we found obesity, in 18 patients with arterial hypertension, in 14 patients with COPD; 16 patients took olanzepine at a dosage between 10 and 15 mg / day, 14 patients took risperidone at a dose of 3 mg / day. All patients underwent: thoraco-abdominal-pelvic CT with contrast medium; pulmonary angiography with loco-regional fibrinolysis according to the protocol provided by the UKEP Study (2000 IU / Kg / h for 24 hours + sodium heparin) modified by us to 1000 IU / Kg / h for 48-72 hours up to angiographic demonstration of thrombus resolution after serial angiographic checks every 24 hours and after serial fibrinogen checks every 6 hours, in association with sodium heparin, in a peripheral vein, initially at a dose of 18 U / kg / h or 1,300 U / h, then adjusting the infusion rate based on PTT values serialized every 6 hours, as required by the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines; pre-discharge echocardiography with pulmonary arterial pressure (PAP) measurement; venous echocolordoppler lower limbs and possible elastic compression bandage; search for thrombophilic and neoplastic markers that were negative in all 30 patients.
**Discussion:** As emerges from our cases report, there is a relationship between the intake of so-called atypical antipsychotics (olanzepine and risperidone) and the appearance of venous thromboembolism within the first month of therapy. These drugs are used in schizoaffective disorders due to the serotonergic hypothesis underlying the treatment as antagonists of the serotonin receptors and high affinity for 5-HT2 receptors.
**Conclusions:** Our experience has shown how the use of atypical antipsychotics is associated with venous thromboembolism in accordance with the numerous experiences reported. The hypothesis of Van Oekelen, with which we agree, it seems, from the examination of the literature, the most accredited. In fact, the acute blockade of the 5-HT2A and 5-HT2C receptors involves, above all at the beginning of therapy, due to the effect of the receptor modulation, an up-regulation of the same responsible, as can be seen from table 2, of vasoconstriction in the lungs. and platelet hyperaggregability, primum movens towards venous thromboembolism. This makes it plausible that our 30 patients developed venous thromboembolism in the first month of therapy.

## 250. CENTRAL INDIRECT ECHOCARDIOGRAPHIC SIGNS OF PULMONARY EMBOLISM: COCHRAN'S Q TEST AND THE "SINCE" STUDY. COMPARATIVE ANALYSIS WITH COCHRAN Q TEST IN 20 PATIENTS WITH VENOUS THROMBOEMBOLISM. THREE YEAR EXPERIENCE (2019-2021)

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**Introduction:** "SINCE" study, acrostic of "Signs echocardIographic iNdirect Central of pulmonary Embolism" enrolled 20 patients, between 48 and 82 years old, with venous thromboembolism (central pulmonary embolism) hospitalized in the two-year period 2019-2021. The results obtained from the case history showed a severe respiratory failure in all patients (arterial blood gas analysis value pO2<60 mmHg), associated with chest pain, confused state of mind, hemodynamic instability (PAS<90 mmHg). In the 20 patients, we examined echocardiographic values at the entrance, both direct and indirect, of the overload of the right ventricle according to Kurzyna criteria. As a consequence we carried out a comparative analysis for nominal variables with the Cochran's Q test to check if there is a significant relationship between A conditions (RV overload criteria), B (60-60 SIGN), C (Mc Connell Sign).
**Purpose of the Experiment:** "SINCE" study has the following goals: to test any association with A conditions (RV overload criteria), B (60-60 SIGN), C (Mc Connell Sign) in 20 patients enrolled in SINCE study. Moreover, to check its statistical importance by applying the Cochran's Q test in order to determine if the differences are due to chance.
**Materials and Methods:** To calculate $\chi 2$ we apply the following formula: $\chi 2 = (k-1)[(k\ x)\text{-}y2]/(k\ y)\text{-}z=28,9$. "K" refers to 3 variables, "X" refers to the total sum of squares of the 3 variables. "Y" stands for the total of the chosen scores. "$Y^2$" is the square of the total chosen scores. "Z" means the sum of the squares of the chosen scores. The $\chi 2$ relative value (VR) is 28,9 with Degree of Freedom (GL) =2. The $\chi 2$ critical value (VC) per p=0,001 is 13,816.
**Results:** By applying the Cochran's Q test, the results demonstrate how A, B, C conditions are not at all due to chance. They have indeed a significant importance because the $\chi 2$ obtained relative value (VR) is 20,95 with Degrees of Freedom (GL)=2, and the $\chi 2$ critical value (VC) per p=0,001 is 13,816. The differences in choice are consequently strongly significant with p<0,001.
**Discussion:** The results obtained show how the significant association in SINCE study, reveals the coexistence, according to Kurzyna criteria, of A conditions (RV overload criteria) + B conditions (60-60 SIGN) + C conditions (Mc Connell Sign). This means that the case report begins with right ventricular distress. From the literature we survey the following experiences that come out. Pech connects PEI with the survival of patients with pulmonary embolism. Miller focused on a scoring system based on the number of obstructive vascular segment during pulmonary angiography. Fava explains the effectiveness of mechanical fragmentation linked to pulmonary intra arterial thrombolysis with urochinasi. Nakazawa looked into the risk of distal embolization with pulmonary hypertension after loco-regional lysis combination with thromboembolism fragmentation. Kursyna and Toosi considered indirect central echocardiographic criteria in order to assess the ventricular overload in those patients affected with severe pulmonary embolism. Casazza studied Mc Conell's signs, concerning those patients with acute right ventricular failure, a particular marker for pulmonary embolism.
**Conclusions:** "SINCE" study showed how in 20 patients affected with venous thromboembolism (central pulmonary embolism), the most significant association is linked to the coexistence of A conditions (RV overloaded criteria) + B conditions (60-60 SIGN) + C conditions (Mc Connell Sign). This correlation is very significant according to the Cochran's Q test, in 20 patients with central pulmonary embolism. Among all the similar case reports in literature, "SINCE" study reveals data that complete those provided from Kurzyna, Toosi, Casazza.

## 251. COCHRAN TEST AND THE "ANGIOTC SCORE" STUDY: COMPARATIVE ANALYSIS IN 20 RADIOLOGISTS. BIENNIAL EXPERIENCE (2020-2021)

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**Purpose of the Experiment:** "AngioTC SCORE" study reports 20 radiologists who were given Miller, Mastora and Qanadli scores, in order to assess the severity of the angiotomographic clinical picture in those patients with venous thromboembolism hospitalized in the period 2020– 2021. This study has the following aims: to verify the differences in the choice of given scores, as well as to determine the meaning of statistical significance by using the Cochran's Q test in the comparative analysis.
**Procedures Used:** To calculate $x^2$ we apply the following formula: $\chi 2 = (k-1)[(k\,x)-y2]/(k\,y)-z=28,9$. "K" refers to 3 variables, "x" refers to the total sum of squares of the 3 variables. "Y" stands for the total of the chosen scores. "$Y^2$" is the square of the total chosen scores.. "Z" means the sum of the squares of the chosen scores. The $x^2$ relative value (VR) we obtained is 28,9 with Degree of Freedom (GL) = 2. $X^2$ critical value (VC) for p=0,001 is 13,816.
**Results:** The Cochran's Q test shows how the Qanadli choice is so significant because the $x^2$ relative value (VR) we obtained is 28,9 with Degree of Freedom (GL) = 2 and $x^2$ critical value (VC) for p=0,001 is 13,816. The differences in the choice are really important with p<0,001.
**Conclusions:** "AngioTC Score" study reveals how the choice of Qanadli score, assessed with the Cochran's Q test, is based on statistical criteria of high importance.

## 252. KLIPPEL-TRENAUNAY SYNDROME: CASE REPORT

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**Introduction:** Klippel-Trenaunay syndrome (KTS) is an unusually seen congenital vascular disorder, mostly occurring sporadically and characterized by a triad of presentations: (1) capillary malformations, manifesting as a "port wine stain", (2) vascular anomalies, mostly varicose veins and (3) bone and/or soft tissue hypertrophy of usually one lower extremity. We present a case of a 56-year-old patient with fully symptomatic KTS, after incident pulmonary thromboembolism in the past and with severe phlebolymphedema, effectively treated with decongestive lymphatic therapy (DLT).
**Case Report:** 56-year-old men were admitted to the High Intensity Internal Medicine ward due to the right lower limb edema. The patient was complaining about increasing discomfort, heaviness, swelling, ulceration and increasing lymphorrhoea within the right lower extremity. Lymphedema had appeared in the patient at the age of 30 and gradually increased. Medical history of the patient was also relevant for arterial hypertension, deep vein thrombosis of the right lower limb and the pulmonary thromboembolism diagnosed 8 years earlier. The patient has been on chronic anticoagulation (acenocumarol) as secondary prophylaxis of deep vein thrombosis. During physical examination, the following abnormalities within the right lower extremity were found: hypertrophy of the limb, large flat cutaneous capillary malformation (port wine stain) extending to the abdominal skin, severe phlebolymphedema, numerous varicose veins and skin lesions secondary to venous and lymphatic insufficiency, including hyperpigmentation, thickening and keratosis of swollen skin and minor ulceration on the calf. Lymphoscintigraphy revealed numerous lymphatic malformations and cutaneous lymph stasis within the right lower extremity. Doppler ultrasound of the lower limbs showed the insufficiency of the right saphenous vein, numerous varicose veins and an arteriovenous fistula located on the medial side of the right knee joint. Computed tomography angiography (angio-CT) confirmed the presence of the arteriovenous fistula: it revealed a small arterial vessel with a diameter of approximately 0.2 cm, originating from the right femoral artery, approximately 15.0 cm above the right knee joint, and supplying the right saphenous vein, approximately 2.5 cm below the right knee joint and causing it to widen to a diameter of about 1.0 cm in the whole further course. During the next hospitalization, the patient underwent arteriography with embolization of the arteriovenous fistula with histoacryl glue with a good clinical effect. Arteriography also showed numerous micro-arteriovenous fistulas within the right lower extremity. The treatment of phlebolymphedema consisted of decongestive lymphatic therapy (DLT), involving the following components: multilayer short-stretch compression bandages, manual lymphatic drainage (MLD), sequential intermittent pneumatic compression (SIPC), skin care, and decongestive exercises. It resulted in significant edema reduction, improvement of the skin condition of the lower limb. The patient requires regular follow-up visits.
**Discussion:** KTS affects men and women in all ethnic groups equally. The aetiology of the syndrome remains unknown and many theories have been proposed. It is generally accepted that KTS is a congenital disorder, in which blood and lymph vessels do not properly form during intrauterine development. KTS is postulated to be the result of sporadic mutations, including chromosomal translocations such as: t(5;11) (q13.3;p15.1) or t(8;14) (q22.3;q13), supernumerary ringed chromosome 18, mutations in the PIK3CA gene, and somatic mutations in RASA 1 gene. Typically, the syndrome affects unilaterally, however, the involvement of all 4 extremities have also been reported. In the study of 252 patients with KTS, port wine stain was found in 98%, varicose veins or venous malformations in 72% and limb hypertrophy in 67%. Asymmetric enlargement of the affected extremity can include long bones elongation, soft tissue hypertrophy and, less commonly, muscular hypertrophy, accompanied by increasing skin thickness and vascular tissue. The diagnosis of Klippel-Trenaunay syndrome is primarily clinical, based on an interview, past history, current patient's complaints and physical examination. Imaging tests, including Duplex ultrasonography, magnetic resonance imaging (MRI), computed tomography (CT), lymphoscintigraphy, standard radiography are useful to confirm the diagnosis and evaluate the severity of the disease and its complications. The decongestive lymphatic therapy (DLT) is the primary complex treatment for lymphedema with the purpose of preventing dermatolymphangitis, elephanthiasis and ulcerations. The DLT includes four components: (1) compression therapy with use of short-stretch multilayer compression bandaging, compression sleeves, garments, and sequential intermittent pneumatic compression (SIPC), (2) manual lymph drainage (MLD), (3) skin and nail care, and (4) decongestive exercises. Surgery should be considered in patients refractory to conservative care.
**Conclusion:** The authors presented a KTS case report

## 253. POST-THROMBOTIC SYNDROME: CASE REPORT

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**Introduction:** The Authors present a case report of post-thrombophletic syndrome in a 38-year-old woman who came to our observation for persistent turgor in the left lower limb as a result of deep vein thrombosis treated 8 months previously at another hospital. Post-thrombotic syndrome (PTS) is the most frequent complication after an episode of deep vein thrombosis (DVT). This pathology has a chronic course and is often disabling, affecting the quality of life.
**Case Report:** We describe the case report of a 38 year old woman who came to our observation for persistent left thigh turgor for 8 months after diagnosis of deep vein thrombosis of the left iliac-femoral axis treated at hospital with LMWH imbricated to ACO until optimization of the therapeutic range of INR. From the anamnestic collection of previous digestive haemorrhage. The following tests are carried out during the hospitalization: 1) ECG: sinus rhythm 2) Blood tests: within the limits 3) Search for secondary thrombophilia markers: negative 4) Search for primary thrombophilia markers: negative 5) Trans-thoracic echocardiogram: LV within the limits, Chinese preserved, FE 67%, 1st degree diastolic dysfunction, right sections within the normal range, pericardium free 6) Venous Doppler ultrasound of the lower limbs: non-occluding segmental thrombosis of the left external iliac vein with proximal tense rhizomelic edema 7) chest-abdomen CT with contrast medium: absence of opacification defects of the pulmonary arteries; subocclusive thrombus of the left external iliac when passing through the femoral vein 8) MRI abdominal angiography: stenotic ribbon-like appearance of the left external iliac vein and left common; the stenosis originates in the inguinal ring and ends at the entrance to the VCI with collateral venous circulation 9) Phlebography of the left lower limb: examination performed via the left transfemoral route with guided echo access: sub-oc-

clusion of the left external iliac cranial to the inguinal ligament is documented, recanalization is performed by positioning a dedicated metal stent type Cook Zilver vein 14x60 mm, it dilates the stent and its correct positioning with good internal flow and complete recanalization of the left iliac axis is verified. The patient is discharged for treatment with ACO with a therapeutic range of INR. On discharge, detumescence of the left thigh is observed.
**Discussion:** A more recent review of the literature suggests an incidence of PTS of 1-1.5% which in 20-50% of patients manifests itself within two years of the thrombotic event despite the use of adequate anticoagulant therapy. This syndrome has an important clinical weight also in children since it occurs in more than 15-25% after an episode of deep vein thrombosis. Although most of the data refers to a syndrome of the lower limbs it is important to emphasize that in the 15- 25% is observed in the upper limbs with significant repercussions on the quality of life.
**Conclusions:** The authors presented a case of post-thrombotic syndrome treated with PTA + venous stent.

## 254. MONDOR SUPERFICIAL VEIN THROMBOSIS: CASE REPORT

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**Introduction:** Mondor's disease (MM) is a rare disease that generally affects women of adult-senile age, characterized by superficial thrombophlebitis of the thoraco-epigastric veins and / or their confluents. Rare cases localized in atypical sites (upper limbs, abdomen, groin and penis) have been reported. The most common symptoms are represented by tension and pain in the chest wall and by the presence of a linear or serpiginous subcutaneous cordoniform swelling, painful on palpation, which corresponds to the affected vessel, often associated with redness, edema or retraction of the overlying skin. The etiopathogenesis of the disease is unknown. MM can be idiopathic or secondary to local traumatic factors, surgical procedures, bandages, or the use of constricting clothing and infections. MM can be associated with breast cancer. It has generally self-limiting evolution and a favorable prognosis, usually requiring only symptomatic treatment. Surgery is necessary in the rare cases in which it is associated with a neoplastic pathology and in case of severe local pain or skin retraction.
**Case Report:** The Authors present the case of a 21 year old woman which comes to our observation for appeared a few days ago in the abdominal area after a slight blunt trauma of a hard, painful cord and painful. She denies fever. Migraine is reported in the medical history. She is not on estrogen progestins. She carries an umbilical piercing and tattoo.
• The search for thrombophilic markers is negative.
• Abdominal ultrasound does not show changes or lymphadenomegaly.
• Blood tests: ESR, CRP, leukocytes increased.
• ANA and ENA are within limits.
• Skin swab in the piercing site (hyperemic skin) shows positivity for staphylococcus aureus.
• The ecocolordoppler show TVS in Mondor
• Brain MRI does not show alterations and the study of the venous sinuses does not show thrombosis The patient undergoes treatment with LMWH and oral antibiotic therapy (tetracyclines) for 2 weeks with complete remission of the symptoms.
**Discussion:** Mondor disease is a rare benign breast condition characterized by thrombophlebitis of the subcutaneous veins of the breast and anterior chest wall. It can also occur in the dorsal veins of the penis.Although Mondor disease is rarely reported in the literature, this is likely in part due to a lack of awareness of the entity. It tends to dominate in women between 30-60 years. Incidence rates of 0.5-0.8% have been reported, however, it reflects only the symptomatic population. Patients usually present with a painful breast (cord-like) mass. There may be overlying skin erythema. It may be accentuated when the ipsilateral arm is raised. The pathogenesis includes the formation of venous thrombosis with total or partial occlusion and vascular recanalization causing fibromuscular hyperplasia of the vessel wall and infiltration plus fibrosis of surrounding subcutaneous cellular tissue. The thrombotic vessel can adhere to the superjacent skin causing retraction and formation of characteristic cordiform grooves secondary to local fibroblastic proliferation. The vessels most commonly involved are the thoraco-epigastric, lateral thoracic vein, and superior epigastric veins. In most patients, the condition is idiopathic 4. Recognized associations include:
Most commonly affects the thoraco-epigastric and/or lateral thoracic veins towards the upper outer quadrant. The upper inner quadrants of the breasts are almost never involved. Typically, Mondor disease appears as superficially located tubular beaded density corresponding to a palpable rope-like mass. Mammography can be normal in a significant proportion of cases. On ultrasound, Mondor disease appears as a tubular anechoic or isoechoic structure with multiple areas of narrowing, giving a beaded appearance. Sometimes low-level internal echoes may be present representing clot. The surrounding soft tissues may be hyperechoic due to the associated inflammatory response. No flow is present on color or spectral Doppler studies and in some situations, an abrupt cut off with the normal vessel may be seen. It is a benign self-limiting condition, and the natural history is for the thrombosed vein to recanalize and for clinical symptoms to resolve gradually (~ 6 weeks).
**Conclusion:** The Authors presented a Mondor's syndrome case report

## 255. PARADOXICAL EMBOLISM: CASE REPORT

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**Introduction:** Paradoxical embolism is characterized by passage of a thrombus from the venous system to the arterial one, a phenomenon that commonly happens due to a defect in the septum septal. Documented for the first time from Cohnheim in 1877, the patency of the oval foramen represents a congenital anomaly which, according to recent studies, may have an important role in etiopathogenesis of arterial embolisms, particularly of stroke ischemic juveniles.
**Case Report:** A 71-year-old woman, with no significant cardiological record, came to our symptomatic center for dyspnoea from exertion for some days, which has become progressively increasing and forearm pain and left hand with functional impotence and cold thermotact from 4 hours. The physical examination showed the absence of pulmonary stasis, absence of jugular turgor, no signs of phlebitis in the lower limbs, values of arterial blood pressure 130/70 mmHg on the right and not detectable on the left, left humeral, ulnar and radial left wrists. Blood tests showed a mild neutrophilic leukocytosis, increased erythrocyte sedimentation rate and C-reactive protein, high values of D-dimer (1.26 microgr./ml); blood gas analysis showed hypoxemia (pO2 60 mmHg) and hypocapnia (pCO2 19 mmHg), with reduction of oxygen saturation in ambient air (85%), with normal pH. The ECG showed sinus tachycardia (110 b / min), without signs of right overload. The computerized chest tomography with contrast medium has documented the presence of a partial thrombosis of both main branches of the pulmonary artery and their lobar and segmental branches. The arterial Doppler echo confirmed the presence of a acute thrombosis of the omeral artery axis distal left, which required a Fogarty thrombectomy treatment, with extraction of thrombotic formation about 2.5 x 1 cm, with a subsequent one restoration of excellent downstream flow. For the unusual contemporary presence of pulmonary and arterial embolism, in doubt of paradoxical embolism, the patient was subjected to transesophageal echocardiography, which showed slight dilation of the right sections with conserved contractility (then confirmed echocardiogram data transthoracico) and excluding formations endocavitary thrombotic, showing a patency of the oval foramen, with a thinned septum primum, widely redundant, not completely welded to septum secundum, with the presence of a tunneling of the caliber of 2 mm after Valsalva maneuver; after microbubble injection and Valsalva maneuver a right-left paradoxical shunt of marked entity (> 30 microbubbles). Primary and secondary thrombophilic screening shows negativity of oncological markings and shows deficiency of protein C and S (50%). The patient undergoes treatment with loco-regional urokinase in the left humeral area with right transfemoral access, systemic sodium heparin after aPTT and fibrinogen monitoring. Subsequently aVK is introduced to discharge after optimization of the therapeutic range of INR. Unfortunately, as a periprocedural complication we note the formation of pseudoaneurysm with fissure of 1.8 mm that is excluded by surgical suture.
**Discussion:** The paradoxical embolism is a clinical event whose incidence It is relatively low, less than 2% of all emboli systemic arteries; this despite this condition can cause very serious consequences, with an incidence of early mortality reported in some series up to 21%. The paradoxical embolism must always be suspected in case of evidence of concomitant arterial embolism and venous. The definition of paradoxical embolism requires

documentation of the so-called triad, characterized from the patency of the oval foramen, from the finding of embolism arterial system in the absence of thrombotic foci in the left cardiac sections and in the first section of the aorta, and from the documentation of a venous thrombosis or a pulmonary embolism5. In the case described they are satisfied all the elements of the triad. At the base of embolism paradox is the increase in pressure in the sections cardiac signs secondary to pulmonary embolism, who is able to determine a right-to-left shunt through the patent oval foramen. The therapeutic options, in case of finding of thrombus in transit in the right or trapped cardiac sections in oval foramen, include anticoagulation, hrombolysis and surgical embolectomy. Each of these options has advantages and disadvantages and treatment of choice is not clear. If on the one hand the therapies anticoagulant and thrombolytic are more readily available and have a better cost-effectiveness ratio, on the other they can fragment the thrombus and provoke indirectly further embolization. The embolectomy Surgical has the dvantage of removing it entirely the thrombus even when it is trapped in the foramen oval, also allows the surgical closure of the patency by applying a "patch", eliminating further risks of paradoxical embolism.
**Conclusions:** In the case presented, the patient is considered to be elevated risk of recurrence, given the anatomical characteristics of the interatrial septum, the extent of the right-to-left shuntand the documented alterations of the blood coagulation profile.

## 256. ORMOND SYNDROME: CASE REPORT

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**Introduction:** Idiopathic retroperitoneal fibrosis is a rare disease. Symptoms include constitutional symptoms and abdominal/flank pain. Causes of retroperitoneal fibrosis include non-infectious and infectious etiologies. Of the infectious etiologies, tuberculous and syphilitic aortitis is an important differential as it is associated with a high mortality rate. We present a case of a 68-year-old man with a retroperitoneal periaortic mass. The diagnosis was amended to idiopathic retroperitoneal fibrosis. He was successfully treated with prednisone.
**Case Report:** A 68-year-old man with a known infrarenal abdominal aortic aneurysm and significant smoking history, presented with a 4-month history of dry cough, lethargy, night sweats and 6 kg weight loss. He was pyrexial on admission. Physical examination was unremarkable. Laboratory tests demonstrated an elevated C-reactive protein (42 mg/L), creatinine of 152 µmol/L (baseline 80), QuantiFERON-TB Gold, HIV and Treponema Test were negative while ASMA antibodies levels and serum immunoglobulin G4 (IgG4) were elevated at 2.6 g/L (range 0.03–2.01). Whole body computed tomography showed a retroperitoneal mass extending around the infrarenal abdominal aorta, obstructing the right ureter with hydronephrosis, lymphadenopathy adjacent to the mass and a number of lung granulomas. Core biopsy of the mass demonstrated a mixed inflammatory infiltrate comprising macrophages, plasma cells, lymphocytes, neutrophils and a small number of eosinophils, with no evidence of lymphoma, IgG or sclerosing disease. He was started therapy on 60 mg of prednisone (dosed at 1 mg/kg/day). A ureteric stent was inserted to relieve the left renal tract obstruction. Treatment led to a resolution of his constitutional symptoms, reduction in C-reactive protein and creatinine, and size of the para-aortic mass on imaging at 6 weeks. The diagnosis was thought to be more in keeping with idiopathic retroperitoneal fibrosis (IRPF), also known as Ormond's disease.
**Discussion:** Causes of retroperitoneal periaortic masses include infection (eg Histoplasmosis, Tubercolosis aortitis), malignancy (eg lymphoma), sarcoidosis, previous radiotherapy and previous surgery. IRPF is a rare disease, tending to affect males in their fifth decade. The adventitia of the abdominal aorta, iliac arteries and, less commonly, the thoracic aorta can be involved. Symptoms include fevers, weight loss, and pain in the flank, back or abdomen. Ureteral involvement due to ureteral deviation or obstruction is a common complication. C-reactive protein and erythrocyte sedimentation rate is usually elevated and can be used to monitor disease activity. Pathologically, the inflammatory infiltrate consists of lymphocytes, plasma cells and macrophages. First-line therapy is glucocorticoid, dosed at 0.75–1 mg/kg/day with gradual tapering to 5–7.5 mg/ day over 6–9 months. Response is rapid with remission rates of 75–95% after glucocorticoid therapy.2 Cyclophosphamide, mycophenolate mofetil and methotrexate have been used effectively as well. Relapse is common and occurs in up to 72%, therefore monitoring with laboratory markers and imaging is required. Tubercolosis aortitis should also be considered as a differential diagnosis as it carries a mortality rate of up to 50%. It is often difficult to diagnose due to possible inconclusive culture, histology and blood markers. Treatment is with oral antituberculous drugs for 6 months although surgery may sometimes be required.
**Conclusion:** IRPF presents with constitutional symptoms and is a rare cause of retroperitoneal fibrosis. Tubercolosis aortitis should also be considered in the presence of high-risk features, such as immigration/travel from an tuberculosis endemic area, immunosuppression etc as it is associated with significant morbidity and mortality. Both IRPF and Tubercolosis aortitis can be effectively treated.

## 257. CORRELATION BNP-TROPONIN-TAPSE-MILLER SCORE-PEINDEX. "BROSEND" STUDY: CORRELATIVE ANALYSIS IN 30 PATIENTS WITH VENOUS THROMBOEMBOLISM. THREE YEAR EXPERIENCE (2019-2021)

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**Introduction:** The "BROSEND" study, an acrostic deriving from "BRain natriuretic peptide-trOponina-tapSe-millEr score-pulmonary embolism iNDex", enrolled 30 patients, aged between 48 and 82, with venous thromboembolism (central pulmonary embolism) hospitalized in the three-year period January 2019-December 2021. The onset clinical picture was characterized in all patients by severe respiratory failure (arterial blood gas pO2 <60 mmHg) associated with syncope, chest pain, confusional state, hemodynamic instability (PAS <90 mmHg) according to the European Society of Cardiology (2019 Edition). All patients underwent: thoraco-abdominal-pelvic CT with contrast medium; pulmonary angiography with loco-regional fibrinolysis according to the protocol provided by the UKEP Study associated with mechanical thrombectomy; pre-lysis echocardiography; venous echocolordoppler lower limbs and possible elastocompression; search for thrombophilic and neoplastic markers. In all patients, the pre-lysis values of BNP (VN <200 pg / ml), RV Diameter (VN <30 mm in diastole), the Pulmonary Embolism Index (PEI) were measured, the PESIndex values, the Miller Score values. Therefore, a database with Microsoft Access © called "BROSEND" was created. A correlative analysis was performed to verify if there is a significant relationship between the pre-lysis BNP values and those of the pre-lysis PEIndex, pre-lysis PESIndex, pre-lysis RV diameter, Miller Score pre-lysis.
**Purpose of the Work:** The "BROSEND" study has the following objectives: 1) verify any relationships existing between the pre-lysis BNP values and the PESIndex, PEIndex, RV diameter, and Miller Score pre-lysis values; 2) verify the statistical significance found by applying the Student's "t" test as a correlative analysis test to establish whether the relationships of the variables considered are due to chance.
**Material and Method:** The test calculates the relative value (VR) of the t index to be associated with the difference found according to the following formula: t = (M1-M2) / √DS12 / N1 + DS22 / N2. Therefore, the value of "t" obtained with Degrees of Freedom (GL) = 29 is 14.45. Since the Critical Value (VC) of "t" 3.659 with GL = 29 for p = 0.001, the Relative Value (VR) of "t" equal to 15.01 expresses an absolute positive agreement of the covariation between the values of the four variables considered compared to the BNP: RV DIAMETER: Student's "t" test applied to 30 patients shows a highly significant correlation (p <0.001) of the two variables examined and, therefore, not attributable to chance. In fact, the value of "t" obtained is 21.56 and the VC (critical value) of "t" for p = 0.001 is 3.659 with GL = 29. MILLERS SCORE: Student's "t" test applied to 30 patients shows a highly significant correlation (p <0.001) of the two variables examined and, therefore, not attributable to chance. In fact, the value of "t" obtained is 7.86 and the VC (critical value) of "t" for p = 0.001 is 3.659 with GL = 29. PESIndex: Student's "t" test applied to 30 patients shows a highly significant correlation (p <0.001) of the two variables examined and, therefore, not attributable to chance. In fact, the value of "t" obtained is 5.58 and the VC (critical value) of "t" for p = 0.001 is 3.659 with GL = 29. PEIndex: Student's "t" test applied to 30 patients shows a highly significant correlation (p <0.001) of the two variables examined and, therefore, not attributable to chance. In fact, the value of "t" obtained is 4.76 and the VC (critical value) of "t" for p = 0.001 is 3.659 with GL = 29. The chi-squared test, therefore, was used to analyze the relationship between categorical variables. The BNP parameter appears to be strongly correlated with the other variables in a significant way.

**Analysis of Results:** Student's "t" test applied to 30 patients shows a highly significant correlation ($p < 0.001$) of the variables examined (values of BNP with those of PESIndex, PEIndex, RV diameter, Miller Score pre-lysis) and, therefore, not attributable to chance. In fact, the value of "t" obtained is 21.56 (RV diameter), 7.86 (MILLER SCORE), 5.58 (PESIndex), 4.76 (PEIndex) with VC (critical value) of "t" for $p = 0.001$ it is 3.659 with GL = 29.
**Discussion:** The data obtained suggest that the correlation of the pre-lysis BNP values with those of the PEIndex, PESIndex, RV diameter, Miller Score pre-lysis study expresses a highly significant difference whose clinical significance lies in the overload of the right cardiac sections, in the presence of high blood pressure regimes attributable to the pulmonary embolic picture, assessed with the PEIndex, BNP, PESIndex, RV diameter, Miller Score pre-lysis which results in a sudden reduction in blood flow to the left heart sections, right ventricular distress with a discrepancy in the supply of O2 to the coronary arteries.
**Conclusions:** The "BROSEND" study showed that in the group of 30 patients with venous thromboembolism (central pulmonary embolism) there is a highly significant correlation between the variables considered: pre-lysis BNP and PEIndex, PESIndex, RV diameter, Miller Score pre- lysis

## 258. CORRELATION BETWEEN ATRIAL CARDIOMYOPATHY AND PREDICTIVE BIOMARKERS OF CRYPTOGENIC STROKE IN PRIMARY AND SECONDARY PROPHYLAXIS: POTENTIAL ROLE OF ENDOTHELIAL PROGENITOR CELL (EPCS) DYSFUNCTION

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Recent advances support the concept that pre-persistent Atrial Fibrillation (AF) and paradoxical embolism do not explain the wholeness of embolic strokes, suggesting the recently postulated hypothesis of a broad Atrial Cardiomyopathy (AC). Despite its worldwide distribution, pathogenic mechanisms underlying AC are still largely unknown. Folate cycle disorders are a dysmetabolism only partly explained by methylene tetrahydrofolate reductase (MTHFR)-inherited defects [1]. On a translational basis, folates dysmetabolism could hinder both endothelial and circulating endothelial progenitor cell (EPCs) functioning, therefore providing one-shot explanation to both atrial stasis and endothelial dysfunction, in the context of the Virchow Triade [2]. If such cardiac-bone marrow (BM) networking would be verified, a fundamental pathogenic mechanism of AC and subsequent AF would be unraveled.
Here, we aim to study whether: i) AF patients would show dysfunctional EPCs and ii). atrial fibrosis (AFib – intended as a relative percentage of low voltage area in the context of left atrial endocavitary voltage mapping) would relate to folate cycle disorders (intended as both: MTHFR C677T inherited mutations and BM function disorders, here referring to erythropoiesis diversions).
We studied 59 patients admitted to the Cardiology Unit of the General Hospital "F.Miulli", with preserved EF, subjected to AF ablation and 30 hypertensive patients (as controls), enrolled by the Unit of Internal Medicine and Clinical Oncology, University of Bari Aldo Moro Medical School. AFib was quantified by bipolar peak-to-peak voltage at each acquired point, measured and defined through the relative percentage of low-voltage areas (<0,5 mV) with respect to the wholeness of the picked voltage points. Blood count cell was evaluated at the admission. MTHFR C677T genotypes were elucidated by real-time PCR. Serum folates were measured by a commercial laboratory test. EPCs isolation and characterization were performed by Ficoll-Hypaque gradient and following flow cytometry analysis for cell surface antigens: CD45, CD34, CD133, Vascular Endothelial Growth Factor Receptor2 (VEGFR2) and KDR (Kinase Insert Domain Receptor). EPCs functional wound healing assay was performed to determine the number of EPCs migrated into the "wound", measuring the percentage of relative wound closure compared with matched-controls. In the AF group, number and migration capacity of EPCs was significantly reduced with respect to controls. The AFib percentage significantly differed between C677T MTHFR homozigosis patients (n=15) with respect to non-C677T MTHFR homozygosis patients (n=44). Once univariate analysis was performed, subsequent multivariate analysis highlighted highest fit once merged RBC, RDW-SD and folates values were inputed: goodness of fit was proper, modelling good. Either RBC, RDW-SD and folates coefficient reached significance in AF patients compared to controls.
From data obtained so far, our findings support the hypothesis that genetically determined folates dysmetabolism (MTHFR dysfunction) promotes AFib via a complex cardiac-BM networking involving circulating EPCs and unraveled by erythropoiesis diversions, thereby contributing to AC development.
**References:** 1. Sgarra L, Bortone AS, Potenza MA, Nacci C, De Salvia MA, Acquaviva T, De Cillis E, Ciccone MM, Grimaldi M, Montagnani M. Endothelial Dysfunction May Link Interatrial Septal Abnormalities and MTHFR-Inherited Defects to Cryptogenic Stroke Predisposition. Biomolecules. 2020 Jun 4;10(6): 861. doi: 10.3390/biom10060861. PMID: 32512924; PMCID: PMC7355772. -2. Kukumberg M, Zaw AM, Wong DHC, Toh CM, Chan BPL, Seet RCS, Wong PTH, Yim EKF. Characterization and Functional Assessment of Endothelial Progenitor Cells in Ischemic Stroke Patients. Stem Cell Rev Rep. 2021 Jun;17(3): 952-967. doi: 10.1007/s12015-020-10064-z. Epub 2020 Nov 10. PMID: 33170433; PMCID: PMC7653671.

## 259. DOLICOARTHERIOPATHIES AND MINOR STROKE

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**Introduction:** We describe a clinical case of a 68 year old woman, sent for our outpatient evaluation at the vascular diagnostics clinic, to complete with an echocolor doppler of the TSA and transcranial doppler(TCD) all investigations carried out up to them aimed at verifying the possible causes of transient ischemic attack or minor stroke. Past medical history of arterial hypertension in therapy, previous virus Sars Cov 2 infection in April 2022,nothing else to report.
**Clinic History:** The last 22.02, the patient, showed up at the Emergency Room of our Hospital for assessment regarding strenght reduction with falling obiects, loss of sensitivity togheter with writing difficulties and deficit of grip on the right hand.
Physical examination, specialistic visits, clinical laboratory and instrumental results: The cardiopulmonary, abdominal and vascular examination were normal. Neurological examination confirmed patient with hypoastenia, dysesthesia, agraphy, dispraxia, tactile and painful sensitivity reduced in the right hand and other test were negative.The neurological examination concludes with a possible minor stroke of indetermined genesis. Cardiological evalutation was negative and the echocardiogramm showed waving of the atrial septum without shunts. Twenty four hour blood pressure monitoring showed a blood pressure homeostasis not garanted by the therapy in place. Blood chemestry tests including coagulation, chest x-ray and electrocardiogram were normal.The brain CT scan showed: hypodensity of the white matter of both emipspheres.
**Clinical Course:** The echocolor TSA did not show stenosis and but the presence of acute kinking of the Internal carotid (IC) especially the one on the left with possible reduction of cerebral flow in relation of sudden rotations of the neck. The TCD with the bubble test resulted normal excluding the presence of patent foramen ovale. Cardiac ECG Holter was negative.Magnetic Resonance (RM) and RM Angiography of the brain showed results of vascular suffering, with a recently onset ischemic area with Willis Polygon in the standard.The patient underwent the therapeutic protocol with antiplatelet and antilipidemic therapy, according to the indication of the European Guidelines; antihypertensive therapy was modulated. At the 30 day outpatient check up of the patient considering the complete regression of the neurological symptoms, quoad vitam continuation of antiplatelet and antilipidemic therapy were recommended, with control of blood pressure values with blood pressure diary and 24 hour blood pressure monitoring to be repeated.
**Discussion and Conclusion:** The clinical picture in question (minor stroke), considering the negativity in the instrumental and haematochemical findings is to be traced back to kinking of the internal carotid which in the parts of greatest curvature create a shearing stress of the wall with platelet hyperaggregation and cerebral microemobolism(1). The reduction of the tone and of the trophism of the mastoid sternocleid muscle toghether with arterial hypertension not controlled by therapy in place can create kinking and coiling over time of the IC artery.(2).Arterial hypertension, especially if not controlled by the therapy in place,can increase the parietal tension of the vessels and favor the development of morhological variations of the IC(3).Not only kinking with acute angles (angles less than 90%) but also those with atherosclerotic plaques not ste-

nosing, should be reserved for the evaluation and possible surgical treatment(4,5). Severe kinking can cause cerebral hypoperfusion with important cognitive dysfunction(6). Based on the clinical picture and the basis of the tests performed,a diagnosis of TIA attribuible to carotid kinking can be formulated. A good control of blood pressure are always to be guaranteed in patient with kinking and coiling to avoid the onset of transitory ischemic attack(7).

**References:** 1)Sacco S.,Totaro R.et al.Morphological variations of the internal carotid artery: prevalence, characteristics and association with cerebrovascular disease. Int.J.Angiol.16(2): 59-61,2007 - 2)Ovchinnikov N.,Rao R.et al.: Unilateral congenital elongation of the cervical part of the internal carotid artery with kinking and looping. Two case reports and review of the literature.Head & Face Medicine 3: 29: 1-14, 2007 - 3) Mumoli N.,Cei M.Asyntomatic Carotid Kinking. Circulation Journal 72: 682-683, 2008 - 4)Ballotta E.,Thiene G.,Baracchini C.,et al.Surgical vs medical treatment for isolated internal carotid artery elongation with coiling or kinking in symptomatic patients: a prospective randomized clinical study. J.Vasc.Surg.42: 838-846, 2005 - 5)Yu J.,Qu L., Xu B.,et al.Current Understanding of Dolichoarteriopathies of the internal Carotid Artery. Review. Int.J.Med.Sci.14(8): 772-784, 2017- 6)Amel A., Naida T.,et al.Kinking of bilateral Internal Carotid Arteries as cause of Cognitive Dysfucntion. Med. Arch.74(1): 58-60,2020 - 7)Togay-Isikay C., KimJ.,et al.Carotid artery tortuosity, kinking, coiling: stroke risk factor,marker or curiosity?. Acta Neurol. Belg.105: 68-72,2005

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## 260. RITIRATO

## 261. CORONARY CT AND NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD). IS CORONARY CT USEFUL TO PREVENT THE ONSET OF MAJOR CARDIOVASCULAR EVENTS IN NAFLD ASYMPTOMATIC PATIENTS?

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**Background and Aims**: The natural history of non-alcoholic fatty liver disease (NAFLD) is variable and patients may progress from simple hepatic steatosis (HS) to steatohepatitis up to end-stage liver disease. Growing evidence indicates that the presence of NAFLD increases cardiovascular (CV) morbidity and mortality.
Among non-invasive procedures, computed tomography (CT) is routinely used to detect and characterize liver steatosis. NAFLD is associated with increased coronary calcifications.
The aim of this study is to evaluate the correlation between the degree of NAFLD and coronary calcification using coronary CT, in terms of prognostic stratification of asymptomatic NAFLD patients at risk of developing coronary heart disease (CHD).
**Methods:** A retrospective cohort of 270 patients (181 males and 89 females), who underwent coronary CT in the period between 2017 and 2021, was enrolled. Images were acquired by prospective cardio-synchronous technique; pre-contrastographic scan performed for Calcium Score (CS), was extended to the upper abdomen for assessment of liver density. CS (using Agatston score), hepatic steatosis (in terms of density in HU) and degree of fibrosis (using FIB-4 score) were evaluated.
**Results:** Data on 270 patients were analyzed. On coronary CT images, the association between the Agatston score and the grading of hepatic steatosis was significant (p 0.03). The CS also showed a close correlation with the degree of fibrosis as assessed by the FIB-4 score (p 0.0091), higher in males (p 0.003) than in females. Age was also strongly associated with CS ($p < 0.001$).
**Conclusions:** Our study suggest that should be considered the opportunity to perform coronary CT to patients with high NAFLD fibrosis score in order to prevent the onset of major cardiovascular events in NAFLD asymptomatic patients.

## 262. ASSOCIATION OF PROPROTEIN CONVERTASE SUBTILISIN/KEXIN TYPE 9 (PCSK9) LEVELS WITH ABNORMALLY HIGH ANKLE-BRACHIAL INDEX IN ATRIAL FIBRILLATION PATIENTS

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**Background:** High ankle-brachial index (ABI) has been associated with increased risk of worse outcomes in the general population. Few data on atrial fibrillation (AF) do exist. Experimental data suggest that proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) contribute to vascular calcification but clinical data on this association are lacking.
**Methods:** We analysed data from 579 patients included in the prospective ATHERO-AF study. An ABI ≥ 1.4 was considered as high. Patients with an ABI <0.9 were excluded. PCSK9 levels were measured coincidentally with ABI measurement. We used an optimized cut-off of PCSK9 >1150 pg/ml obtained from ROC curve analysis. All-cause mortality according to the ABI value was also analysed.
**Results:** 110 (19.9%) had an ABI ≥1.4. The mean age was 72.1 years and 42.1% of patients were women. Patients with ABI ≥1.4 were older, more frequently male and diabetic. Multivariable logistic regression analysis showed an association between ABI ≥1.4 and serum levels of PCSK9 >1150 pg/ml (Odds Ratio 1.835, 95%CI 1.133-2.970, p=0.014). During a median follow up of 41 months, 112 deaths occurred. At multivariable Cox regression analysis, ABI ≥1.4 was associated with an increased risk of mortality (Hazard Ratio 1.676, 95%CI 1.073-2.617, p=0.023).
**Discussion:**. In AF patients, PCSK9 levels relate to an abnormally high ABI, which is in turn associated with an increased mortality risk. This is the first clinical evidence of an association between PCSK9 and vascular calcification in AF patients.

## 263. SEPTIC OR CARDIOGENIC SHOCK: SOMETIMES A CHALLENGING DIFFERENTIAL DIAGNOSIS. A CASE REPORT

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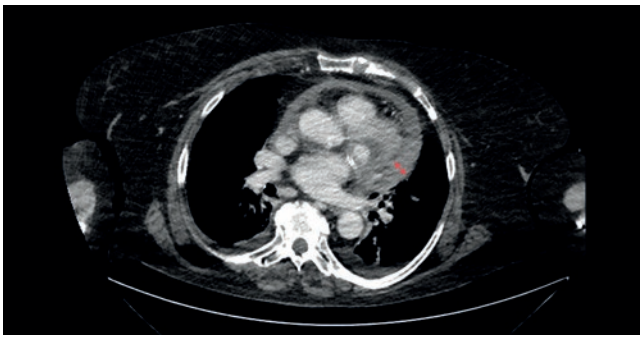
Pseudoaneurysm of the mitral-aortic intervalvular fibrosa (PaMAIVF) is a rare, potentially life threatening, complication of infective endocarditis. We described a case of a 79 y/o woman affected by infective endocarditis which was complicated with a PaMAIVF and its rupture into the pericardium with consequent cardiac tamponade.



## 264. CAROTID PLAQUE OFFSETS THE SEX DIFFERENCE IN CARDIOVASCULAR RISK IN YOUNG TO MIDDLE AGE HYPERTENSIVE PATIENTS: THE CAMPANIA SALUTE NETWORK

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**Background:** Although women have in general lower risk for cardiovascular disease, presence of left ventricular hypertrophy (LVH) in hypertension offsets the female sex-protection in cardiovascular risk. The aim of the present study is to assess whether presence of carotid artery plaque (CP) has a similar impact on the sex difference in risk for future cardiovascular events.
**Methods:** we studied 5209 women and men <65 years old with hyperten-

sion and free from prevalent cardiovascular disease enrolled in the prospective Campania Salute Network registry were followed over a mean of 5.9 years. Subjects were grouped according to the absence or the presence of CP identified by Doppler ultrasound (intima-media thickness>15mm). Main outcome was major cardiovascular events (MACE; combined acute coronary syndromes, stroke, hospitalization for heart failure and incident atrial fibrillation).
**Results:** Among patients without CP (n = 3139), women were older, with higher systolic BP, cholesterol level and prevalent LVH but lower triglycerides and eGFR, compared to men (all p<0.001). Among patients with CP (n=2070), women were older, taking higher number of antihypertensive drug, with higher cholesterol level and prevalent LVH but lower triglycerides and eGFR compared to men (all p<0.001). In Cox regression analysis adjusting for cardiovascular risk factors, LVH and antihypertensive treatment during follow up women without CP had lower hazard rate (HR=0.41) for MACE (n=107) than men (95% confidence interval [CI] 0.39–0.89, p=0.01). In contrast, among patients with CP, women had similar HR for MACE (n=132) as men (HR 0.79 [95% CI 0.54–1.14], p=0.203).
**Conclusion:** This study demonstrates that presence of carotid organ damage in hypertension contributes to offset the female sex-protection in cardiovascular risk. Thus, expanding previous finding, young to middle-age women and men with hypertension and carotid organ damage have comparable cardiovascular risk.

## 265. PERIPHERAL ARTERY DISEASE IN THE EMERGENCY DEPARTMENT FOR ELDERLY AND PATIENTS ≥80 YEARS: A RETROSPECTIVE ANALYSIS OF THE CLINICAL OUTCOMES

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**Background:** This study was aimed at investigating the role of increasing age in the clinical outcome of patients acutely hospitalized for peripheral artery disease (PAD), with particular regard to the differences in clinical outcomes between older adults aged 65-79 years and patients ≥ 80 years old.
**Methods:** The study enrolled all the patients ≥ 65 years old consecutively admitted to our emergency department (ED) from January 2015 to December 2021, who were evaluated in ED for PAD-related conditions and subsequently were admitted to a ward. Patients were divided into two groups based on age. The group ≥ 80 years old was compared to the younger aged 65-79 years with respect to the occurrence of Major Adverse Limb Events (MALE), Major Adverse Cardiovascular Events (MACE), and all-cause in-hospital death. The Odds for each endpoint were adjusted for baseline covariates including sex, clinical presentation, clinical history and comorbidities, and the severity of PAD based on Rutherford's classification at ED admission. The adjusted odds were calculated by logistic regression analysis models including the age group as a factor. A two-sided p<0.05 was considered significant in all the analyses.
**Results:** Overall 1337 patients were enrolled, 789 in the 65-79 years group and 548 in the ≥ 80 years group. None of the patients considered had a PAD disease graded below 3 according to Rutherford's classification, while most of the patients considered had a grade 6 disease (697, 52.1%). Overall we recorded 637 MALE (47.6%). The events did not significantly differ between the patients aged ≥ 80 years compared to the younger group (249/548 vs 388/789, adjusted odds 0.77 [0.59 – 1.02], p=0.070). Similarly, we recorded 112 MACE (8.4%). The adjusted odds of MACE for older patients were 1.18 [0.79 – 1.77], p=0.411. The all-cause in-hospital death occurred in 129 patients (9.6%). The adjusted odds for all-cause in-hospital death were increased for patients ≥ 80 years (OR 1.91 [1.32 – 2.78], p=0.001).
**Conclusions:** The clinical outcome of patients urgently admitted for PAD is similar in patients aged ≥ 80 years compared to elderly aged 65-79 years old. However, although the adjusted odds for cumulative cardiovascular and limb events (MACE and MALE) are similar, the older patients experience a lower odds for amputation and a higher odds for both cardiovascular and all-cause death. These findings and the clinical peculiarities of PAD disease in older adults should be taken in account for the best treatment of this condition.

## 266. SERUM HIGH MOBILITY GROUP BOX-1 LEVELS CORRELATE WITH MAJOR CARDIOVASCULAR EVENTS IN DIABETIC PATIENTS AFTER ENDOVASCULAR REVASCULARIZATION: A PROSPECTIVE COHORT STUDY

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**Background:** Peripheral arterial disease (PAD) and type 2 diabetes mellitus (T2DM) are clinical conditions characterized by elevated serum inflammatory biomarkers and worsening vascular calcification. In addition, T2DM patients with PAD are at increased risk of major adverse cardiovascular events (MACE) and major adverse limb events (MALE). High mobility group box-1 (HMGB-1), a nuclear protein that also acts as an inflammatory mediator, is associated with lower extremity PAD in patients with T2DM.
**Objectives:** The aim of this study was to evaluate the relationship between baseline serum levels of HMGB-1, MACE and MALE occurrence after endovascular revascularization in T2DM patients with PAD and chronic limb-threatening ischemia (CLTI).
**Methods:** We conducted a prospective, nonrandomized study of 201 T2DM patients with PAD and CLTI requiring lower extremity endovascular revascularization. Serum HMGB-1 levels were measured prior to endovascular intervention and event outcomes were assessed during 12-month follow-up.
**Results:** During follow-up, 81 MACE and 93 MALE occurred. Serum HMGB-1 levels were higher in patients who subsequently developed MACE and MALE. Specifically, 7.46 ng/mL vs 4.88 ng/mL (p < 0.000) for MACE and 7.17 ng/mL vs 4.8 ng/mL (p < 0.000) for MALE. After adjusting for traditional atherosclerotic risk factors, the association between HMGB-1 serum level and vascular outcomes remained significant in multivariate analysis. In our receiver operating characteristic (ROC) curve analysis, serum HMGB-1 levels were good predictors of MACE incidence (area under the curve [AUC] = 0.80) and MALE incidence (AUC = 0.77).
**Conclusions:** This study demonstrates that serum HMGB-1 levels are associated with the incidence of MACE and MALE after endovascular revascularization in diabetic populations with PAD and CLTI.

## 267. UNUSUAL CAUSE OF LONG QT IN A YOUNG MAN

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Several conditions may be responsible for long QT syndrome, among which electrolyte disturbances play a major role, particularly hypopotassemia and hypomagnesemia. Although the causes can be countless, it is good practice to always perform an accurate anamnesis, a thorough physical examination and targeted laboratory tests. Gitelman Syndrome is one of the rare disorders that could manifest with these electrolyte alterations. It is a hereditary tubulopathy which impairs the kidney's ability to reabsorb salt resulting in hypokalemia, hypomagnesemia, metabolic alkalosis and increased urinary potassium excretion. It can be completely asymptomatic or associated with asthenia, muscle weakness, cramps, gastrointestinal symptoms such as abdominal pain, nausea and vomiting. There have also been reported, although rare, events of ventricular tachyarrhythmia or sudden cardiac death caused by the prolongation of the QT interval.
We report the case of an 18-year-old man who presented asthenia, without prior medical history or a family history of syncopal and cardiological events. An ECG recorded at the age of 12 for the preparticipation to sportive activity, showed an elongation of the QT tract. A Holter recording revealed a further increase in QT frequency-dependent. A genetic study could not identify any known gene related to congenital cardiac Long QT syndrome. Considering the electrocardiographic picture, a beta-blocking treatment was administered and sports activity was not recommended.
About six years thereafter, the patient was hospitalized due to a car accident. Hyposodiemia, hypomagnesemia, hypolcemia, hypopotassemia and hypocloremia were detected. All the biochemical alterations were resistant

to first attempts of correction and the patient was sent to our center for an overall evaluation and further investigation. The blood test detected the presence of marked hypopotassemia (Potassium 1.8 mmol/l) accompanied by hypomagnesemia (Magnesium 1.2 mg/dl) and hypochloremia (Chloride 86 mmol/l). Sodiemia was 141 mmol/l. Hyperreninemia was diagnosed (Renin 21.7 ng/ml/h). Phosphatemia and aldosteronemia were within the normal range (Phosphorus 4 mg/dl and Aldosterone 138 pg/ml).
Blood gas analysis showed a metabolic alkalosis (Ph 7,47, pCO2 52 mmHg, PaO2 96 mmHg, HCO3- 47.7 mmol/l, BE 22.6 mmol/l, Calcemia 0.97 mmol/l). The 24-hours urine measurements showed a reduction in Calciuria (15 mg/24 h) and Magnesuria (53 mg/24 h). Echocardiogram was carried out, which was within the normal limits for the age as well as the values of FSH, LH, Cortisol, Progesterone 17-OH.
Dynamic ECG and stress test did not reveal any threatening ventricular arrhythmias. The tests suggested the diagnosis of Gitelman Syndrome.
Anti aldestorenic therapy (Canrenone 200 mg/die) was prescribed together with a specific diet. Canrenone was discontinued for gynecomastia and amiloride with potassium and magnesium integration were prescribed. As a result of the recommended therapy the patient had an increase of the Potassemia to 3.5 meq and a reduction of the QT. The patient also experienced a significant reduction in asthenia.
This case report opens the door to understanding the role of the prevention, early diagnosis and knowledge of potential trigger factors to avoid fatal events in patients with Gitelman syndrome. Gitelman syndrome patients present several electrolyte abnormalities such as hypokalemia and hypomagnesemia, conditions that prolong the duration of the action potential of cardiomyocytes and consequently increase the risk for development of ventricular arrhythmia such as torsades de point and ventricular fibrillation. There is no cure for Gitelman syndrome. Actually, the purpose of treatment is to improve symptoms, to normalize electrolytes plasma levels and to prevent the onset of factors and events that could be fatal. The therapy recommended is composed by potassium sparing diuretics, high salt diet with oral potassium and magnesium supplements. Aldosterone antagonists, ACE Inhibitors and cyclooxygenase inhibitors have utilized. Furthermore, it is suggested the administration of magnesium (4-6 times/day to avoid diarrhea) and the combination of amiloride (5-10 mg/1.73 m2/day) with KCl (1-3 mmol/kg/day divided in 3-4 doses).
It is essential to find out what is necessary for these patients like periodic electrocardiograms and biochemical exams associated with the avoidance of drugs that could prolong QT interval and the exercise withdrawal. Malnutrition and diarrhea are particularly dangerous in these patients.
This case report illustrates the importance of long QT syndrome differential diagnoses, including Gitelman syndrome. Actually, sudden cardiac arrest has been reported occasionally, however as the occurrence of severe electrolyte imbalances the probability of cardiac involvement is still high.
In conclusion, patients with Gitelman syndrome should be referred for further investigations and should be informed about the risks and factors that could lead to dangerous situations.

## 268. EFFECTS OF TREATMENT WITH MODERATE/HIGH DOSES OF INTRAVENOUS FUROSEMIDE PLUS SMALL-VOLUME HYPERTONIC SALINE SOLUTION (HSS) AND AN ACUTE SALINE LOAD ON MARKERS OF ATRIAL STRETCHING, FIBROSIS AND INFLAMMATION IN SUBJECTS WITH ACUTE DECOMPENSATED HEART FAILURE WITH REDUCED EJECTION FRACTION (HFREF)

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**Background:** Preliminary studies reported the safety and tolerability of treatment with an intravenous (i.v.) combination of hypertonic saline solution (HSS) and high-dose furosemide in subjects with congestive heart failure. Markers of inflammation, fibrosis and atrial stretching, such as inflammatory cytokines, suppression of tumorigenicity 2 (sST2), galectin-3 and natriuretic peptides, are overexpressed in patients with heart failure. Differentially expressed miRNA patterns are associated with various pathophysiological mechanisms of heart failure, such as hypertrophy, cardiac remodelling, hypoxia and myocyte apoptosis. Few studies have examined the effects of intravenous diuretic treatment on markers of congestive heart failure.
**Aims:** We sought to compare the effects of furosemide + HSS treatment in patients with acute decompensated heart failure in comparison to i.v. furosemide alone and the response in a compensated state after an acute saline load with regard to serum levels of heart failure biomarkers and miRNAs.
**Results:** We enrolled 141 patients with acute decompensated heart failure with reduced ejection fraction admitted to our Internal Medicine ward from March 2017 to November 2019. Seventy-three patients were randomized to treatment with i.v. high-dose furosemide plus HSS, whereas 68 patients were randomized to i.v. high-dose furosemide alone. Patients treated with i.v. furosemide plus HSS compared to controls treated with i.v. furosemide alone showed a comparable degree of reduction in the serum levels of IL-6, sST2, and NT-proBNP in the "between-group" analysis. Nevertheless, patients treated with high-dose furosemide + HSS showed significantly higher absolute and percentage delta values of IL-6, sST2 and NT-proBNP than patients treated with furosemide alone. Furthermore, after the acute saline load, patients treated with i.v. furosemide + HSS in comparison to subjects treated with furosemide alone showed a significantly lower increase in the serum concentrations of IL-6, sST2, hs-TnT, galectin-3 and NT-proBNP and an increase in expression of Mir150-5p, Mir-365, Mir-181b and Mir-125a-5p.
**Discussion:** Our findings concerning a comparable degree of reduction in the serum levels of three cardinal biomarkers indicate that a reduction in serum heart failure markers is not linked to a higher degree of congestion relief with a more rapid achievement of a clinical compensation state. Nevertheless, our findings of higher delta values after treatment with i.v. furosemide plus HSS, and an increase in miRNA expression with myocyte protective functions seem to indicate a possible higher efficacy through modulation of the stretching and fibrosis mechanisms.

## 269. NOVEL PROTEIN-TRUNCATING VARIANT IN THE APOB GENE PROTECTS FROM CORONARY ARTERY DISEASE: RESULTS FROM A PILOT-ANALYSIS OF TARGETED NEXT-GENERATION SEQUENCING OF GENES REGULATING CHOLESTEROL HOMEOSTASIS WITHIN A CARDIOVASCULAR COHORT

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**Background:** Genetic testing is still rarely used for the diagnosis of dyslipidemia, even though Familial Hypercholesterolemia (FH) is considered the most common genetic cause of coronary artery disease (CAD).
**Objective:** To perform a pilot-analysis of targeted Next Generation Sequencing (NGS) of FH related genes in patients selected within a cohort of subjects with or without angiographically-demonstrated CAD.
**Methods:** NGS of LDLR, APOB, PCSK9, HMGCR, and APOE genes was performed in 24 subjects not taking lipid-lowering drugs, presenting very high (≥190 mg/dL, n=18) or very low (≤60 mg/dL, n=6) LDL-cholesterol plasma levels.
**Results:** Within the group with hypercholesterolemia, 6 subjects (33.3%) had 7 rare variants predicted to be potentially pathogenic. Five variants were in LDLR gene: 2 nonsense, c.274C>T (rs774467219) and c.126C>A (rs751317621), 2 missense, c.662A>G (rs373822756) and c.1735G>T (rs875989929), and 1 in a splice region, c.2312- 3C>A (rs875989942). Two APOB missense variants, c.5741A>G (rs1801699) and c.3337G>C (rs12713844) were found. All subjects carrying LDLR variants had CAD. Among subjects with low LDL-cholesterol we found a novel rare mutation in APOB gene, c.6943G>T, determining a truncating variant with premature stop codon after the ApoB-48, thus allowing chylomicron synthesis but reducing VLDL secretion and then LDL levels. The heterozygous carrier of APOB c.6943G>T, despite a very high-risk profile encompassing all the traditional risk factors except for dyslipidemia, had normal coronary arteries by angiography and did not report any major adverse cardiovascular event during a 20-year long follow-up.
**Conclusions:** Our data support the use of targeted NGS in well-characterized clinical settings. APOB genetic variants reducing ApoB production may improve cardiovascular outcomes.

## 270. MULTIPLE ABDOMINAL ANEURYSMS

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A 35-year-old young man with no risk factors presented to the emergency department with abdominal pain and a lypothimic episode, and a CT scan revealed intra-abdominal hemorrhage from a ruptured aneurysm of the hepatic artery treated with a stent implant. Subsequent CT controls revealed a leak in the prosthesis requiring reconnection, as well as several other aneurysms and dissections of visceral arteries, including but not limited to the splenic artery, the superior mesenteric artery near the origin, the right common iliac artery, and the bilateral external iliac arteries, extended to the left common femoral artery. The first goal was to determine the breadth and depth of arterial involvement in the visceral region and to assess disease progression and extension that may require urgent treatment. This assessment was performed with an abdominal CT angiography (CTA) integrated with lower limbs' arterial Doppler ultrasound to evaluate hemodynamic relevance of iliac and femoral abnormalities in distal vessels, and our studies showed no disease progression. In addition, we performed coronary CTA and ruled out aneurysms in this district.
History, clinical presentation, and radiographic findings suggested Segmental Arterial Mediolysis (SAM), but more common causes of aneurysmal disease had to be excluded. Transthoracic echocardiography was performed to assess the presence of endocarditis and possible fungal origin of the disease. Only some minor valve abnormalities were found and the examination also reconfirmed that the explorable portion of the aorta was free of aneurysm abnormalities. To rule out an active inflammatory process in the arterial wall due to vasculitis or local microbial infection, we requested a 18-fluorodeoxyglucose PET-CT scan, which did not document any abnormal accumulation of radiotracer in the walls of large vessels, so locations of high metabolic activity, such as inflammatory processes and local inflammatory processes, were excluded.
Following a multidisciplinary discussion of the case by our hospital's "Vascular Team", the Medical Genetics Unit was involved, and several histological samplings were performed during surgery and endovascular intervention as we turned our attention to congenital connective tissue abnormalities.
Selective embolization of the common hepatic artery pseudoaneurysm and replacement of the abdominal aorta and iliac arteries distal to the renal artery were performed to prevent the spread of the aneurysm phenomenon. After the surgical intervention, the vascular surgeon reported that the aneurysm and the wear of the arterial wall in the restricted area. Samples have been collected and genetic analysis has not documented any noteworthy alterations.
SAM is a non-inflammatory non-atherosclerotic arteriopathy causing the lysis of the outer portion of arterial smooth-muscles resulting in aneurysms and dissection, particularly in middle-caliber splanchnic vessels. The correct evaluation of the burden of disease and the exclusion of infectious and inflammatory causes are paramount for the correct management of the disease and step-by-step approach should be practiced.

## 271. TLRS ACTIVATORS IN HEART FAILURE

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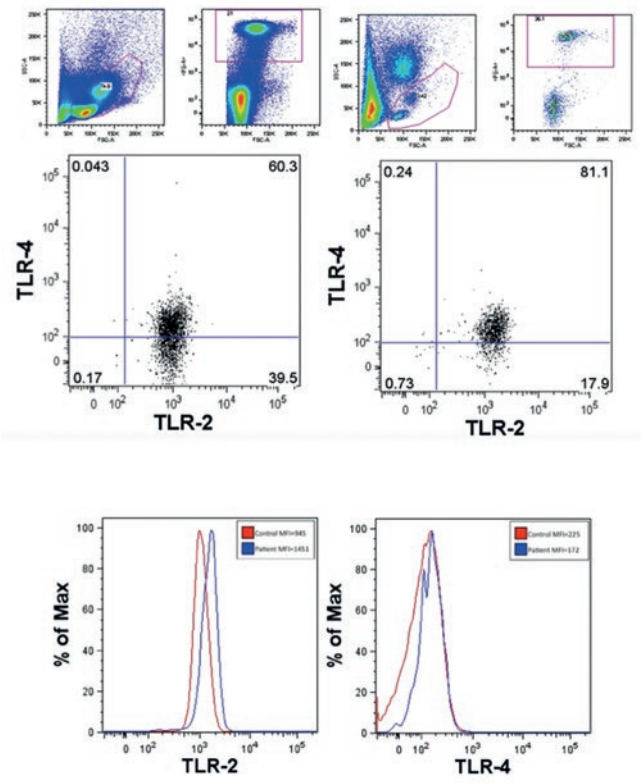
**Introduction:** Heart failure (HF) is a complex clinical syndrome, characterized by impairment of both the cardiac structure and function leading to left ventricle filling or ejection abnormalities. Recently, according to the value of echocardiographic left ventricular ejection fraction (EF), HF guidelines have identified three main forms of HF including: HF-rEF (EF ≤40%), HFpEF (EF ≥50%), and an intermediate form with an EF ranging from 41 to 49%. It is well established that HF patients show increased levels of pro-inflammatory cytokines, associated. This inflammatory status is maintained by other mechanisms such as immune system activation. Recent evidence demonstrated a role for TLR4 in the progression of chronic HF. TLRs recognize specific ligands, termed damage-associated molecular patterns (DAMPs) and pathogen- associated molecular patterns (PAMPs). Activation of the innate immune system contributes to the inflammatory milieu in HF. Pattern-recognition receptors (PRRs) such as TLRs play a crucial role in the innate immune system. Lipopolysaccharide (LPS, endotoxin) is a glycolipid that is embedded in the outer membrane of Gram negative bacteria and plays a crucial role in maintaining the structural integrity of the organism and is one of the most important activators of TLRs. Usually, increased activity of LPS reflect a parallel increase in zonulin levels; zonulin is a protein involved in the increased intestinal permeability, particularly expressed in all chronic conditions characterized by an inflammatory status, as HF is supposed to be. Thus, in this study we measured LPS activity and zonulin levels in both HFrEF and HFpEF patients compared with a control group, in order to search for a possible difference between groups able to explain the different expression of pro-inflammatory parameters between HF groups previously detected. Thus, this study is aimed to investigate possible differences in LPS activity (evaluated through both endotoxin activity assay [EAA] and limulus amebocyte lysate [LAL] levels) and zonulin levels between HF patients (both HFrEF and HFpEF) and a control group.
**Methods:** In this study we enrolled 60 consecutive Caucasian outpatients, 41 males and 19 females with a mean age of 72.7+11.0, divided into 3 groups: HFrEF (N=20), HFpEF (N=20), controls (N=20). We measured endotoxin activity in both a semi-quantitative (through the Endotoxin Activity Assay, EAA, which measures the biological response of the neutrophilis in a patient's blood to an immunological complex of endotoxin and exogenous antibody as a measure of the endotoxin activity in the patient) and quantitative way (through Limulus Amebocyte Lysate, LAL). The assay reacts specifically with the Lipid A moiety of LPS of Gram-negative bacteria and does not cross-react with cell wall constituents of Gram-positive bacteria and other microorganisms.




**Results:** HF patients (both HFrEF and HFpEF) showed significantly higher expression of both TLR-2 and TLR-4 (Fig. 1), IL-1, IL-6, IL-8, respect to controls. When considering possible activators of TLRs we found a significantly higher LPS activation (EAA) and zonulin levels (with an increase of about 10-fold) in controls rather than in HF patients, while no differences in LAL levels were found among groups. No significant differences between HFrEF and HFpEF groups were found. Since zonulin values are influenced by renal function, we performed a linear regression analysis to test the relationship between eGFR and different covariates. In the whole study population, eGFR resulted significantly related to both zonulin (r=0.402, P=0.001) and EAA (r=0.291, P=0.024). The same relationship was seen in the HFrEF

group for both zonulin (r 0.014, P 0.954) and EAA (r 0.640, P 0.002).
**Conclusion:** The most important finding emerging by our study is that HF patients, both those with HFrEF and those with HFpEF, have a significant higher expression of both TLR2 and TLR4 that, in turn, induce the gene transcription of pro-inflammatory cytokines.
The real novelty of this study is the fact that, beyond TLRs expression, we also investigated the activity of specific PAMPs able to activate TLRs; in particular, we investigated LPS levels, with both a direct (LAL) and indirect (EAA) method. Conditions showing an enhanced inflammatory burden are also characterized by an increased intestinal permeability, demonstrated by an increase in zonulin levels that, in such conditions, may be considered as an inflammatory marker. High levels of zonulin have been associated with increased intestinal permeability due to zonulin capacity to disrupt tight junctions. Several studies have demonstrated a direct relationship between zonulin and e-GFR, highlighting the fact that in patients with chronic kidney disease, despite the presence of a systemic inflammatory status, zonulin levels are not increased; a possible explanation could be found in the increased renal permeability to zonulin in this setting of patients.

## 272. A COMPLEX CASE OF MYOPATHY

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A 78-year-old woman presented to the emergency department with dyspnea and chest pain, and a recent echocardiogram showed a severe pericardial effusion. Home treatment included beta-blockers for atrial fibrillation, antihypertensive drugs, and rosuvastatin in combination with ezetimibe.
On admission, the patient presented with tachycardia, but pulse oximetry showed good peripheral oxygen saturation. Because the inferior vena cava was dilated but collapsible, bedside ultrasonography confirmed a peripheral effusion without hemodynamic effects. Abdominal and chest ultrasonography and chest CT scan were performed for possible embolic causes of paraneoplastic effusion and dyspnea. All tests were negative except for bilateral cystic pleural effusions that the thoracic surgeon judged not worth draining.
Medical therapy was started with ibuprofen 600 mg tid and colchicine 0.5 mg/day.
The patient was then transferred to our ward where a follow-up echocardiogram was performed three days later, and initial signs of right cardiac section tamponade were found. Echo-guided evacuative pericardiocentesis was performed the following day, and 500cc of fluid were collected. Draining tube was left inside the pericardium, in aspiration, for the following 72 hours. Post-procedural echoscopy demonstrated persistence of highly organized, moderately sized, effusion with reduced hemodynamic impact. Following imaging showed a gradual but constant regression of the condition. Without ulterior complication we discharged the patient at home to continue follow-up in an ambulatory setting.
During follow-up period the patient reported worsening weakness in lower limbs and difficulty in ambulation. We performed blood analyses and elevated CPK and myoglobin were found. After rosuvastatin and colchicine discontinuation, electromyography (EMG) was performed to show that myopathic recruitment patterns in the quadriceps correlate with spontaneous activity characterized by myotonic discharges and fibrillation potentials. MRI of the spinal cord and lower extremity muscles was also performed to confirm pre-existing disc hernias that were not considered warranting special treatment, and showed early muscle atrophy and steatosis in the proximal muscles of the pelvis and legs. A muscle biopsy was performed to assess the possibility of drug-related myopathy, without complications. Histological examination of the collected specimen by the pathologist nearly confirmed our diagnosis.
Our patient was admitted to intensive care rehabilitation after completing the diagnostic process to restore lost muscle function.
Neuromyopathy is a rare but known complication of colchicine therapy. The pathogenic mechanism is unclear, but it is speculated that drug effects on the cytoskeleton, especially on microtubules, affect peripheral axonal transport and lysosome transport in muscle cells. There are both acute and chronic forms of neuromuscular toxicity, with acute being associated with drug overdose, while chronic manifestations usually occur with long-term low-dose treatment, but can occur if myotoxicity is present when incidental factors such as concomitant treatment with CYP3A4-inhibiting drugs or other molecules (i.e. statins and ezetimibe, etc.), can produce acute myopathy even at low doses. Proximal muscle weakness in the lower extremities is typical. CPK levels are almost always elevated, and EMG usually records myopathic changes and axonal neuropathy. When the drug is stopped promptly, complete resolution is observed in a few weeks.

## 273. CARDIAC SYMPATHETIC INNERVATION AND MORTALITY RISK SCORES IN PATIENTS SUFFERING FROM HEART FAILURE WITH REDUCED EJECTION FRACTION

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**Introduction:** Cardiac Sympathetic Nervous System (SNS) derangement represents a key feature of chronic Heart Failure with reduced Ejection Fraction (HFrEF) and exerts a crucial role in the onset, progression and prognosis of this syndrome. Critical clinical implications derive from these pathophysiological mechanisms, as chronic systolic dysfunction is burdened with high arrhythmic mortality risk. Accordingly, international societies guidelines recommend therapy with Implantable Cardioverter Defibrillator (ICD) for primary and secondary prevention of Sudden Cardiac Death (SCD) in well-selected patients. Nevertheless, the proportion of those who actually benefit from this treatment, which is not free from complications such as infections and inappropriate shocks, is low, and, importantly, several reports indicate the rate of non-arrhythmic deaths to significantly negatively impact on devices utility. Tools to ameliorate risk stratification and increase the accuracy of the selection of candidates for ICD therapy have been developed. 123I-meta-IodineBenzylGuanidine (123I-mIBG) scintigraphy has emerged as effective non-invasive imaging method to assess cardiac adrenergic innervation, with independent role in predicting HF decompensation, major arrhythmic events, cardiac mortality and even appropriate ICD intervention. Similarly, several clinical risk scores and models have been proposed to identify patients with HF at the highest risk of all-cause mortality, for whom the net clinical benefit of device positioning would presumably be lower. Nevertheless, the association between the two classes of tools, one suggestive of major arrhythmic risk, the other of all-causes mortality, has not yet been adequately investigated.
**Objective:** Therefore, the aim of the present manuscript is to test the relationship between the main risk scores for predicting mortality and cardiac sympathetic innervation, assessed through myocardial 123I-mIBG imaging, in a population of HFrEF patients.
**Methods:** Patients with HFrEF underwent clinical examination, transthoracic echocardiography and cardiac 123I-mIBG scintigraphy. Eight risk stratification models were identified, through literature research, as applicable to the study population: AAACC, FADES, MADIT, MADIT-ICD non-arrhythmic mortality score, PACE, Parkash, SHOCKED and Sjoblom.
**Results:** Overall population consisted of 269 patients suffering from HFrEF. As reported in table 1 very weak negative correlation for early H/M only emerged with FADES ($r = -0.12$, $p = 0.047$) and SHOCKED ($r = -0.15$, $p = 0.018$) scores. Late H/M showed significant negative correlation with all the predicting models, although generally weak, ranging from -0.15 ($p = 0.013$) for PACE to -0.32 ($p < 0.001$) for FADES. Similar results were obtained for the washout rate, whose stronger positive relationship emerged with FADES score ($r = 0.17$, $p = 0.004$), and other significance tresholds reached with lower coefficients for MADIT, MADIT-ICD non-arrhythmic mortality score and Sjoblom.
All the scores showed poor discrimination for cardiac denervation, defined as late H/M <1.6, with areas under the curve (AUC) ranging from 0.546 for Parkash to a maximum of 0.621 for FADES (figure 1).
**Conclusion:** A weak association emerged among eight mortality risk scores and cardiac 123I-mIBG parameters. This study suggests the need to integrate in clinical practice tools indicative of both arrhythmic and general mortality risks, when evaluating patients affected by HFrEF eligible for device implantation.
**References:** Goldenberg I et al. Risk Stratification for Primary Implantation of a Cardioverter-Defibrillator in Patients With Ischemic Left Ventricular Dysfunction. J Am Coll Cardiol 2008;51: 288–96.Nevzorov R et al. Deve-

loping a risk score to predict mortality in the first year after implantable cardioverter defibrillator implantation: Data from the Israeli ICD Registry. J Cardiovasc Electrophysiol 2018;29: 1540–7.Van Rees JB et al. Clinical prediction model for death prior to appropriate therapy in primary prevention implantable cardioverter defibrillator patients with ischaemic heart disease: the FADES risk score. Heart 2012;98: 872–7.Younis A et al. Predicted benefit of an implantable cardioverter-defibrillator: the MADIT-ICD benefit score. Eur Heart J 2021;42: 1676–84.Kramer DB et al. Development and validation of a risk score to predict early mortality in recipients of implantable cardioverter-defibrillators. Hear Rhythm 2012;9: 42–6.Parkash R et al. Predicting early mortality after implantable defibrillator implantation: a clinical risk score for optimal patient selection. Am Heart J 2006;151: 397–403.Bilchick KC et al. Prediction of mortality in clinical practice for medicare patients undergoing defibrillator implantation for primary prevention of sudden cardiac death. J Am Coll Cardiol 2012;60: 1647–55.Sjöblom J et al. Clinical risk profile score predicts all cause mortality but not implantable cardioverter defibrillator intervention rate in a large unselected cohort of patients with congestive heart failure. Ann Noninvasive Electrocardiol 2017;22

| *Mortality Risk Scores* | *Early H/M* | *Late H/M* | *Washout Rate* |
|---|---|---|---|
| **AAACC** | -0.075 | -0.170* | 0.027 |
| sig. | 0.244 | 0.008 | 0.676 |
| **FADES** | -0.120* | -0.319* | 0.174* |
| sig. | 0.047 | <0.001 | 0.004 |
| **MADIT** | -0.011 | -0.176* | 0.141* |
| sig. | 0.852 | 0.003 | 0.020 |
| **MADIT-ICD-NA** | -0.024 | -0.194* | 0.169* |
| sig. | 0.695 | 0.001 | 0.005 |
| **PACE** | -0.099 | -0.151* | 0.033 |
| sig. | 0.105 | 0.012 | 0.580 |
| **Parkash** | -0.073 | -0.152* | 0.078 |
| sig. | 0.231 | 0.012 | 0.199 |
| **SHOCKED** | -0.155* | -0.286* | 0.101 |
| sig. | 0.010 | <0.001 | 0.097 |
| **Sjoblom** | -0.082 | -0.219* | 0.124* |
| sig. | 0.177 | <0.001 | 0.041 |

Table 1. The relationship between cardiac $^{123}$I-mIBG imaging parameters and ICD predicting mortality scores.

The p value correspond to Pearson's Correlation coefficient.

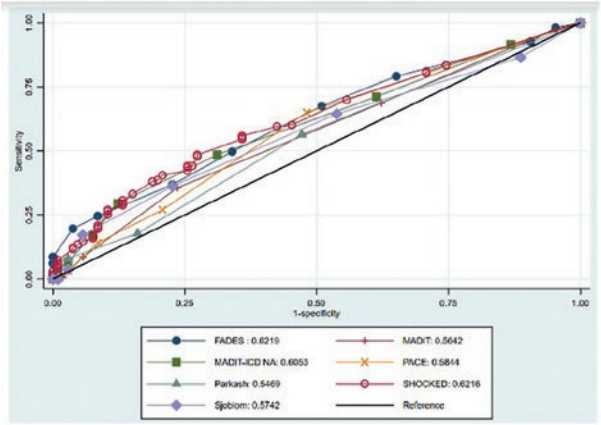


**Figure 1.** ROC curves of mortality risk scores for impaired cardiac innervation

## 274. ONE-HOUR POSTLOAD GLYCAEMIA AND SUBCLINICAL LEFT ATRIAL DAMAGE

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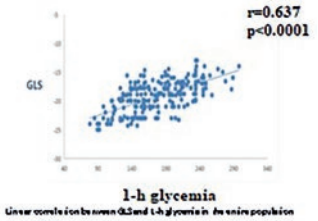
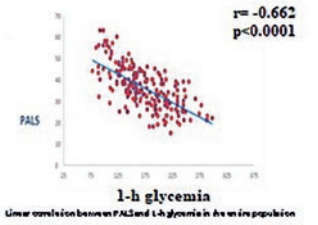
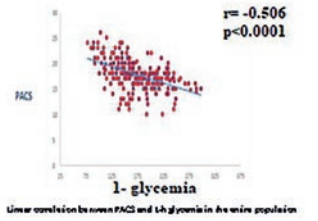
Recent studies demonstrated that normoglucose-tolerant subjects (NGT) with one-hour (1-h) post load plasma glucose value >155 mg/dl during oral glucose tolerance test (OGTT) (NGT≥155), present an higher risk of developing type 2 Diabetes Mellitus (T2DM) than NGT<155 mg/dl, because they have a worse cardio-metabolic profile, with subclinical myocardial damage. Atrial morphological and functional alterations, closely related to diastolic dysfunction, are important predictors of atrial fibrillation, cardiovascular (CV) events, and mortality in the entire population and in diabetic patients. However, in literature there are no association studies between early left atrial dysfunction and patients different glycometabolic phenotypes. The aim of our study was to evaluate atrial and subclinical myocardial damage, assessed with speckle tracking echocardiography, in NGT≥155 mg/dl patients, comparing to NGT<155 mg/dl subjects, impaired glucose tolerance (IGT) and T2DM newly diagnosed patients.




We enrolled 229 Caucasian patients (117 male and 112 female, mean age 58.7±10.7) afferent to CATAMERI study. Main exclusion criteria were CV and respiratory diseases, cancers, drugs influencing glucose metabolism, alcohol and smoking abuse. All subjects underwent anthropometrical and hemodynamic parameters evaluation, blood chemistry analysis, OGTT, advanced color-Doppler echocardiography with evaluation of main atrial and ventricular parameters: ejection fraction (EF), global longitudinal strain (GLS), left atrial volume index (LAVI), atrial reservoir (PALS) and atrial pump (PACS), atrial ejection fraction (aEF), LAVI/PALS and LAVI/E/e'. Plasma glucose was measured by the glucose oxidation method and plasma insulin concentration was determined by a chemiluminescence-based assay. Insulin sensitivity was estimated using HOMA-IR. Echocardiographic recordings were performed using an E-95 Pro ultrasound system (GE Technologies). ANOVA test was used to test the differences between groups. According to plasma glucose's value during OGTT, subjects were divided into four groups: NGT<155 mg/dl (n=77), NGT>155 mg/dl (n=57), IGT (n=57) and TDM2 (n=38). There were no significant differences among groups regarding age, sex, body mass index, triglycerides, total and LDL cholesterol. As expected, NGT <155 mg/dl patients presented better metabolic profile than the others groups; HOMA-IR and high-sensitivity C-reactive protein (hs-CRP) showed a significant increase (p<0.0001) from the first to fourth group. Concerning echocardiographic parameters, NGT>155 had worse ventricular function valuated by GLS than NGT<155, but similar to IGT (p<0.0001), higher LAVI and lower PACS than NGT<155 mg/dl. Furthermore, NGT<155 presented higher PALS values compared to other groups (p<0.0001), while IGT and NGT>155 patients presented similar values. However, T2DM showed lower values of PALS (p<0.0001) and EF (p=0.013), compared to other study groups. NGT<155 subjects exhibited lower derived parameters LAVI/PALS and LAVI/E/E' than the other groups (p<0.0001). Stepwise multiple regression analysis demonstrated that 1h-glycaemia was the major predictor of PALS variability, explaining 43.8% of its variation; HDL-cholesterol added an additional 4.5% in NGT<155 mg/dl and 7.5% in NGT> 155 mg/dl patients, respectively; uric acid added about 6% only in IGT. Our study demonstrated for the first time that

subjects with 1-h post load glycaemia >155 mg/dl present subclinical atrial dysfunction. These results may be clinically relevant because highlighted that atrial myopathy occurs early in pre-diabetes stage regardless of fibrotic and morphological alterations of the ventricular myocardium. Fibrotic remodelling and atrial compliance's reduction can determine arrhythmias such as atrial fibrillation, so atrial strain could be used to predict the risk of atrial fibrillation development, thus allowing to consider a better therapeutic strategy in this patients' setting.

## 275. SERUM ENDOCAN LEVELS AS PREDICTIVE BIOMARKER OF CARDIOVASCULAR RISK IN PATIENTS WITH DIFFERENT GLYCOMETABOLIC PHENOTYPES

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The presence of cardiovascular disease (CVD) such as, hypertension, coronary artery disease and atherosclerosis is the leading cause of disability and mortality in patients with type 2 diabetes (T2DM) and the occurrence of CVD is closely related to endothelial dysfunction. Endocan is a soluble proteoglycan mainly secreted by endothelial cells and is considered to play a key role in vascular disease, endothelium-dependent pathological disorders and organ-specific inflammation. The over expression of endocan can accelerate endothelial dysfunction and it is promoted by inflammation, oxidative stress and cell adhesion. Therefore, endocan is currently considered to be a meaningful biomarker of CVD. Endocan is overexpressed in T2DM patients, especially in patients with worst blood glucose regulation. Many studies demonstrated that in normoglucose-tolerant subjects (NGT), 1-h post load plasma glucose value ≥155 mg/dl (NGT≥155), during oral glucose tolerance test (OGTT), identifies an increased risk for T2DM and a worse cardio-metabolic risk profile. The aim of this study was to investigate serum endocan levels and a possible association between subclinical myocardial damage, oxidative stress and platelet activity, in NGT≥155 patients, comparing them to NGT<155, impaired glucose tolerance (IGT) and T2DM newly diagnosed patients. We enrolled 110 Caucasian patients (mean age 61.6±10.5) afferent to CATAMERI study. Main exclusion criteria were secondary hypertension, clinical evidence of CV complications, endocrinological and malignant disease, alcohol or smoking abuse. All subjects underwent anthropometrical and clinical evaluation and OGTT. Plasma glucose was measured by the glucose oxidation method and plasma insulin concentration was determined by a chemiluminescence-based assay. Insulin sensitivity was evaluated using the Matsuda index (Matsuda/ISI). Renal function was tested by estimated glomerular filtration rate (e-GFR) with CKD-Epi formula. The serum values of endocan, markers of oxidative stress (8-isoprostane and NOX-2) and platelets activity were assessed with ELISA sandwich. Echocardiographic recordings were perfomed using an E-95 Pro ultrasound system. ANOVA test was used to test the differences between groups. A linear correlation analysis was performed to compare values of endocan with different covariates. Variables reaching statistical significance were inserted in a stepwise multivariate linear regression model. According to plasma glucose value during OGTT, subjects were divided into 4 groups: NGT<155 (n=33), NGT≥155 (n=26), IGT (n=30) and T2DM (n=21). There were no significant differences among groups regarding age, systolic blood pressure (SBP), total, HDL and LDL cholesterol. There were significant differences, among the four groups, for fasting plasma glucose (FPG) (p<0.0001), 1-h post load (p<0.0001), and 2-h post load plasma glucose levels (p<0.0001), fasting insulin (p<0.0001), 1-h insulin (p=0.002) and 2-h insulin values (p<0.0001) during OGTT. Moreover, from the first to the fourth group, there was a significant increase in triglyceride (TG) (p<0.0001), high sensitivity C reactive protein (hs-CRP) (p<0.0001), 8-isoprostane (p<0.0001), Nox-2 (p<0.0001), HbA1c (p=0.006) as well as a reduction in e-GFR. Interestingly, a significant increase of endocan levels was observed from the first to fourth group (p<0.0001); post-hoc analysis by Bonferroni test showed that NGT≥155 subjects had significantly higher serum endocan levels compared to NGT<155 (p<0.0001), by contrast no differences were observed in the comparison with IGT group. Moreover there was an increase of sP-selectin (p<0.0001), from the first to the fourth group, indicating an increase in platelet activity with the worsening of the metabolic status. The linear correlation analysis showed that endocan was significantly and directly correlated with, 1-h glycemia (r=0.676, p<0.0001), hs-CRP (r=0.508, p<0.0001), sP-selectin (r=0.533, p<0.0001), Nox-2 (r=0.488, p<0.0001), 8-isoprostane (r=0.475, p<0.0001), triglyceride (r=0.311, p=0.001), HbA1C (r=0.261, p=0.007) and inversely correlated with Matsuda/ISI (r= -0.590, p<0.0001) and e-GFR (r= -0.292, p=0.002). GLS was significantly and directly correlated with endocan (r=0.581, p<0.0001). From stepwise multivariate linear regression model, Matsuda/ISI was the major predictor of endocan, justifying 37% (p<0.0001) of variation; sP-selectin and hs-CRP added another 8.7% and 5.4% respectively. This is the first study that has estimated the serum endocan levels in NGT≥155 patients and its correlation with subclinical myocardial damage, oxidative stress and platelet activity in patients with different glycometabolic phenotypes. Results of our study may demonstrate that NGT≥155 present early endothelial dysfunction, as indicated by high endocan levels and its expression in cardiomyocytes may explaining subclinical myocardial damage. These results suggest that endocan may be an early biomarker of endothelial dysfunction and a predictor of appearance and progression of CVD in NGT≥155 subjects.

## 276. ORAL ANTICOAGULANT THERAPY AND DECLINE OF KIDNEY FUNCTION IN ELDERLY PATIENTS WITH NON-VALVULAR ATRIAL FIBRILLATION: REAL WORLD EVIDENCE DATA

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Non Valvular Atrial fibrillation (NVAF), the most frequent cardiac arrhythmia found in clinical practice, is an independent predictor of cardiovascular mortality and morbidity. This arrhythmia has a strong impact on the patient's quality of life; hospitalization is frequent both for the acute management of the arrhythmia and for possible complications such as stroke or worsening of a previous heart failure; it is associated with twice death rate in comparison with the healthy population. Over the next few decades, we will see a major increase in the prevalence of NVAF; the older age groups will be more affected reaching a prevalence of 4.8% between 70 and 79 years and 8.8% between 80 and 89 years. The incidence and prevalence increase in proportion to age and comorbidity burden especially in elderly patients in whom oral anticoagulant therapy (OAT) is difficult to manage, and it is often underused for limitations of efficacy and safety presented by vitamin K antagonists (AVK), however non-vitamin k antagonist oral anticoagulats (NOAC) are effective as AVKs with better safety profile. NOAC ensuring a lower incidence of major bleeding, limited pharmacological interactions and better therapeutic compliance of frail and older patients. NOAC do not require monitoring of the INR and they should be use at fixed doses that are established according to renal function, clinical conditions and the risk of individual bleeding; these features make them particularly manageable in more complex patients. NVAF and Chronic Kidney Disease (CKD) are mutually connected and often coexist in the elderly patient. NVAF is a risk factor for the progression of CKD, the prevalence and incidence of AF increase with decrease in renal function, CKD also increases the risk of bleeding and thromboembolism, making risk stratification and treatment very difficult. All available NOAC are partially eliminated by the kidneys therefore, renal function inevitably influences our therapeutic strategies. The aim of this work was to evaluate, in a large elderly population of NVAF patients with important comorbidities, the difference on renal function decline between AVK and NOAC users. We enrolled 411 Caucasian patients aged ≥ 70 years, affected by NVAF with important comorbidities, 135 patients receiving VKA and 276 receiving NOAC. All subjects underwent a medical history and physical examination at baseline; all were suffering from paroxysmal, persistent or permanent NVAF, documented electrocardiographically. Patients underwent clinical-instrumental and laboratory evaluation for a follow-up of 6.9 ± 2.5 years. Patients with severe hepatic (Child-Pugh C) or renal impairment (eGFR <15 ml/min/1.73 m2) were excluded from this study. Rapid decline in renal function was defined as annual loss ≥5 mL/min/1.73 m2 of eGFR. Data were expressed as mean and standard deviation or as median and interquartile range (IQR) when appropriate. At baseline the mean age of the population was 76.4 + - 5.8 years, the prevalence of arterial hypertension (AH) was 89.8%, type 2 dia-

betes mellitus (T2DM) 39.9%, COPD 39.6%, heart failure (HF) 25.5%, and chronic ischemic heart disease 38.4%. Baseline eGFR was 62.9 (49.1-80.3) mL/min/1.73m2, haemoglobin (Hb) 13.5 (12.7-14.1) g/dL, systolic blood pressure (SBP) 136 (122-148) and diastolic blood pressure (DBP) 76 (70-87) mmHg. Two groups were comparable for sex, smoking and T2DM prevalence. The NOAC group had a higher prevalence of HF (p=0.0028), COPD (p=0.0017), AH (p=0.0004). Whole population showed a ΔeGFR between follow-up and baseline of -13.2 ml/min/1.73 m2 (IQR -28.3/-6.8) with ΔeGFR/year -1.96ml/min/1.73m2 (IQR-3.4/-1.24). During an average follow-up of 6.9 ± 2.5 years there were statistically significantly differences between VKA and NOAC in eGFR (p<0.001), creatinine (p<0.0001), blood glucose (p<0.0001), SBP (p<0.0001), HB (p<0.0001), number of renal events/year 35/135 (25.9%) in AVK group vs 36/276 (13.0%) in NOAC group, (p=0.001). In NOAC group, a linear correlation analysis was performed between eGFR and different covariates expressed as Δ variation between baseline and follow-up. ΔeGFR was significantly directly correlated with ΔHb (r=0.142, p=0.044), and inversely with ΔDBP (r=-0.230, p<0.0001), ΔSBD (r=-0.221, p<0.0001) and ΔBMI (r=-0.139, p=0.029). From stepwise model, ΔHb was the main predictor of ΔeGFR, accounting for 18.0% of its variation, while ΔDBP, ΔSBP and ΔBMI added 5.3%, 3.6% and 2.0% respectively for a total of 28.9%. The present study confirms a better safety profile of NOAC compared to AVKs on the decline of renal function in elderly and multimorbid population, even though patients receiving NOAC were older and showed a greater burden of comorbidities that negatively affect renal function such as arterial hypertension, COPD, heart failure; and at baseline a significantly lower eGFR value than the AVK group.

## 277. COFFEE CONSUMPTION RELATES TO A REDUCTION OF VASCULAR AND HEART DAMAGE IN WELL-CONTROLLED HYPERTENSIVES

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**Introduction:** Nutritional interventions that could prevent hypertension-related organ damage are far from being fully defined. Coffee is one of the most used beverages all over the world. Many studies have tried to define the optimal amount of coffee in order to understand whether coffee has a role in cardiovascular prevention. Thus, we evaluated heart and vascular damage in well controlled hypertensives according to coffee consumption.
**Methods:** We evaluated 316 patients (150F, 166M, aged 62.22±10.76) with essential hypertension. All patients were checked for organ damage screening. The number of coffee cups per day was asked during the visit. The median coffee consumption was 2 cups per day.
**Results:** patients were subdivided into three groups according to tertiles of cups consumed: Group 1, 0-1 cups 112 patients (57F, 55M; 64.21±10.91), Group 2, 2 cups, 101 patients (53F; 48 M; 61.95±10.10), Group 3, >2 cups, 103 patients (40F; 63M; 60.32±10.95). No differences were seen in weight and BMI, nor in blood pressure (both systolic and diastolic). Group 1 had an increased left ventricular mass compared to the other two groups (p= 0.0008 and p=0.019 respectively). Similarly, Group 1 had a significant reduction in E/e' ratio (p=0.042 and p=0.019, respectively). No significance was found between Group 2 and 3 for left ventricular mass and diastolic function. Group 3 had an increased intima-media thickness (p=0.004 and p=0.005 vs Group 1 and 2, respectively). Prevalence of carotid stenosis was lower in Group 3 (p=0.011 and p=0.039, respectively) and was comparable in Group 1 and 2.
**Conclusion:** Coffee consumption may have a role in prevention of heart remodelling. Consumption of at least 2 cups of coffee per day reduces left ventricular mass and diastolic dysfunction.

## 278. CENTRAL SLEEP APNEA SYNDROME RESOLUTION AFTER MITRACLIP®: A CASE REPORT

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Sleep breathing disorders (SBD) are alterations of normal breathing occuring during sleep and include central sleep apnea syndrome (CSA), Cheyne-Stokes respiration (CSR) and obstructive sleep apnoea syndrome (OSAS). The association between SBD and heart failure (HF) is widely reported in literature with a prevalence reaching 75% in heart failure with reduced ejection fraction (HFrEF). In particular, CSA prevalence ranges between 25% and 40% in HFrEF and it is related to increased mortality and adverse prognosis through different mechanisms still not well understood. First, contrasting apnoic and hypopnoic events generates an inspiratory effort, which modifies intrathoracic pressure and haemodynamics, resulting in an augmented myocardial oxygen request, alterations of cardiac chambers volumes and reduced cardiac output. Concurrently, intermittent hypoxia combined with repeated arousals, causes sympathetic nervous system hyperactivation, further worsening haemodynamics. Even without sufficient evidencies on prevalence and association of SBD with HF and valvulopathies, data about the impact of surgical correction of mitral valve disease on SBD, in particular on CSA, are encouraging and corroborate our suggestion to screen SBD patients with HF and valvulopathies. Case report. We present a case of 75 years-old man admitted to our department complaing of ingravescent dyspnea (NYHA II-III). He had a history of dilated cardiomyopathy (DCM), PM-ICD implanted after an AMI (treated with PTCA and stents on anterior interventricular artery and left coronary), COPD, nocturnal respiratory failure secondary to OSAS on CPAP and O2 therapy at 2 L/min. Our first approach involved: chest X-rays (negative), arterial EGA (normal blood gas) and ecocardiography. Ecocardiography highligted a reduction of EF from 42% to 33% Simpson, worsened mitral valve insufficiency (from moderate to severe), left atrial enlargement and increased PAPS (from 40 to 55 mmHg), when compared to the last one. So we decided to optimize medical treatments for HFrEF and record a new cardiorespiratory polygraphy exam (PG) in basal condition. Nocturnal respiratory failure was confirmed: TC90 60,1%; ODI >3% 88/h; average SpO2 89%. Severe CSA with CSR was diagnosed with a number of apnoic/hypopnoic events (AHI) of 87,8/h. According to AASM guidelines, ventilation mode has been changed to BILEVEL PSV (IPAP min-max 13-18 cmH2O, EPAP 7 cmH2O) keeping O2 therapy at 2L/min. After one week, AHI was 12/h and TC90 4.5%. Due to functional mechanism of mitral insufficiency, we requested a cardiological consult to evaluate the need of a percutaneous treatment of the underlying mitral insufficiency (MitraClip®). After one month, the patient underwent MitraClip®, with notable reduction of symptoms (NYHA I-II). Three months later even echocardiographic parameters improved. One year later, the patient was hospitalized for COPD exacerbation and treated with antibiotic therapy. After the resolution of the acute state, we recorded a nocturnal oximetry on NIV and O2 therapy at 2L/min, demonstrating not only the persistance but also a further improvement of previously achieved benefits (TC90 from 60.1% to 1.4%, ODI> 3% from 88/h to 18.6/h, SpO2 average from 89% to 94%). After three months, the patient (as his symptoms further regressed) autonomously chose to lower O2 therapy to 1.5 L/min and to interrupt NIV. A new PG in O2 therapy at 1.5 L/min was recorded, showing a reduction in AHI (9.2/h), stable value for TC90, ODI and average SpO2 %. Arterial EGA in O2 therapy at 1,5 L/min: pH 7.42, PCO2 38 mmHg, PO2 81.5 mmHg, SpO2 97%. Clinical and instrumental evolution led us to discharge the patient prescribing only O2 therapy at 1.5 L/min, deeming NIV no longer necessary. CSA can develop through two different mechanisms: an increased sensitivity of the chemoreceptor centers (controller gain) and an increased circulatory time (feedback delay). These two phenomena can occur in HF, stroke, opiates use and brainstem diseases and can be exacerbated by overload volume, as in the case of our patient. Finally, in HF and valvulopathies, lung vascular congestion triggers the juxtacapillary receptors (J receptors), increasing hyperventilation and worsening apneas. Therefore, to reduce apnoic/hypopnoic episodes, it is crucial to normalize the circulatory time by improving cardiac output and reducing volume overload, through medical and when feasible, percutaneous or surgical therapies. Oxygen therapy, in conditions of normal circulatory time, can contribute to reduce central apneas by decreasing chemoreceptor centers sensitivity. This clinical case documents the need of a multidisciplinary approach to patients with HF and respiratory diseases and highlights the usefulness of PG in patients with mitral insufficiency elegible for MitraClip®. The presence of CSR and the severity of CSA could suggest the need for early treatment of even moderate and/or paucisymptomatic mitral insufficiency.

## 279. REDUCTION IN EJECTION AND PRE-EJECTION PERIODS ARE PREDICTIVE OF MORTALITY IN AL AND ATTR HEART AMYLOIDOSIS

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**Background:** Amyloidosis is a systemic disease caused by fibrillary misfolded protein deposition in several organs including the heart. Cardiac deposition is the leading cause of death in these patients1. Echocardiography is the imaging technique mostly used to study cardiac amyloidosis. Many studies tried to identify earlier markers to stratify the mortality risk2. Heart stiffness is the main issue leading the heart dysfunction. However, few data are available on the possible role of connection between heart and possible vessels alterations.
**Purpose:** Aim of this study was to evaluate heart stiffness using Ventricular–arterial coupling (VAC) for relationship between heart and vessel tree.
**Methods:** We studied 58 patients (22 F and 36 M, aged 67.14± 12.49) with AL or ATTR amyloidosis and heart involvement. They were 42 AL and 16 ATTR patients. All patients were evaluated before treatment with a complete history, physical exam, serum markers of disease, and echocardiogram. The abdominal fat biopsy to confirm amyloid deposition was performed before treatment. Among all patients, 18 died with a mean OS of 12 months [IQR 1-24 months].
**Results:** At baseline, VAC was increased in died patients (alive 1.53 ± 0.43 vs died 2.06 ± 1.73, p=0.09) but was ineffective to predict the risk of mortality (ROC analysis AUC 0.54, p=0.57). By analysing ejection and pre-ejection periods we found that they were both increased in alive patients (p=0.0016 and p=0.0072, respectively). Moreover, these periods were effective in prediction of the death risk (ejection time AUC 0.81, cut-off 239 msec, sensitivity 61.54% and specificity 88.24%; pre-ejection time AUC 0.75, cut-off 82 msec, sensitivity 84.62% and specificity 58.82%) (Fig. 2). No difference in VAC, ejection time or pre-ejection time were found comparing AL to ATTR, nor both parameters had a predictive role.
**Conclusion:** Amyloidosis induces an increase in heart stiffness and reduces heart contractility. This causes a reduction of peripheral blood flow and a worsening in heart failure. We demonstrated that this mechanism affects the capacity to pump blood in vessels due the reduction in time for loading during the systole. These results may predict the mortality with a significant sensitivity and specificity, regardless of the type of amyloidosis.
**References:** 1. Dittrich T, Dittrich T, Kimmich C, Kimmich C, Hegenbart U, Hegenbart U, Schönland SO, Schönland SO. Prognosis and Staging of AL Amyloidosis. Acta Haematol 2020: 388–399. - 2. Cicco S, Solimando AG, Buono R, Susca N, Inglese G, Melaccio A, Prete M, Ria R, Racanelli V, Vacca A. Right Heart Changes Impact on Clinical Phenotype of Amyloid Cardiac Involvement: A Single Centre Study. Life 2020;10: 247.

## 280. EFFECTS OF SACUBITRIL-VALSARTAN ON CLINICAL, ECHOCARDIOGRAPHIC, AND POLYGRAPHIC PARAMETERS IN PATIENTS AFFECTED BY HEART FAILURE WITH REDUCED EJECTION FRACTION AND SLEEP APNEA

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Heart failure with reduced ejection fraction (HFrEF) is a clinical condition frequently diagnosed in clinical practice. In patients affected by HFrEF, sleep apnea (SA) can be detected among the most frequent comorbidities. Sacubitril–valsartan (sac/val) association has been proven to be effective in reducing disease progression and all-cause mortality in HFrEF patients. Sac/val treatment can potentially attenuate SA development via several pathophysiologic mechanisms, including improvement of global hemodynamics, reduction of extracellular fluid overload, and decrease of sympathetic neural activity. The objective of our work was to evaluate the effects of a 6-month therapy with sac/val on hemodynamic and metabolic parameters hemodynamic and metabolic parameters, as well as on the occurrence of apnea/hypopnea and oxygen saturation in patients with HFrEF and SA, already in treatment with CPAP.The study population consisted of 132 consecutive outpatients with mean age of 67.0 ± 9.8 years, 107 men and 25 women, enrolled from March 2018 to January 2020, referring to both the Chronic Heart Failure Unit of the Geriatrics Division, located at the "Mater Domini" University Hospital of Catanzaro, Italy, and the Internal Medicine Unit—Center for the Prevention, Diagnosis, and Management of Cardiovascular Disease, located at the University Hospital of Messina, Italy. The study included outpatients complaining of HFrEF and eligible for treatment with sac/val, because of symptom persistence despite an optimized therapy. They were recruited according to the indications of the previous European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of acute and chronic HF, which have been later updated, after the completion of our study. The eligibility criteria included: written informed consent; age > 18 years; left ventricular ejection fraction (LVEF) < 35%; NYHA class II–III; persistence of symptoms despite an optimized treatment with stable doses of ACE-Is or ARBs for at least 4 weeks; presence of SA under treatment with CPAP since at least 3 months. SA diagnosis was performed according to the current guidelines. Echocardiographic recordings were performed using an E-95 Pro ultrasound system (GE Technologies). No patient took drugs or other substances that could interfere with sleep. The exclusion criteria included: severe renal dysfunction (estimated glomerular filtrate-eGFR <30 mL/min/1.73 m2), severe hepatic impairment (Child-Pugh Class C), history of angioedema or side effects induced by ACE inhibitors or ARBs, pregnancy or breastfeeding, systolic blood pressure (SBP) < 100 mmHg, serum potassium levels > 5.4mmol/L, current treatment with sac/val, chronic obstructive pulmonary disease (COPD) and relevant valvular heart diseases (VHD), resynchronization therapy within 3 months before the enrolment. After 6 months, sac/val induced statistically significant changes in clinical, hemodynamic, biohumoral, in particular NT-proBNP (from 1840 (886.0–3,378) to 970.0 (571.3–2,870) pg/ml; p<0.0001), estimated glomerular filtration rate (eGFR) (from 67.2 ± 19.2 to 96.4 ± 31.0 ml/min/1.73 m2; p<0.0001); and uric acid (from 6.7 ± 0.8 to 5.9 ± 1.0; p<0.0001), and echocardiographic parameters. In particular, cardiac index (CI) (from 1675.6 ± 199.9 to 1856.6 ± 212.9 ml/min/1.73 m2; p <0.0001), left atrial volume index (LAVi) (from 49.8 ± 13.7 to 46.1 ± 12.0; p=0.001) and left ventricular end-diastolic volumes (LVEDV/BSA) (from 89.6 ± 9.8 87.8 ± 8.4 ml/m2; p<0.0001), global longitudinal strain (GLS) improved (from −7.9 ± 1.7 to −9.0 ± 1.4 %; p <0.0001) and tricuspid annular plane excursion (TAPSE) (from 16.3 ± 1.1 to 17.1 ± 1.7 mm; p <0.0001). Moreover, polysomnography, carried out during a temporary CPAP interruption, revealed a significant reduction in global apnea-hypopnea index (AHI) value (from 26.5 ± 10.4 to 21.7 ± 8.3 AHI; p < 0.0001), oxygen desaturation index (ODI) (from 18.0 ± 3.7 to 13.5 ± 4.9 %; p < 0.0001), Mean SpO2 (from 91.3 ± 1.9 to 92.0 ± 2.0%; p<0.0001) and percentage time of saturation below 90% (TC90) (from 14.1 ± 4.5 to 6.8 ± 3.9%; p<0.0001). The changes in Patients with HFrEF and SA of CI, estimated glomerular filtration rate (eGFR), NT-proBNP, and tricuspid annular plane excursion (TAPSE) contributed to 23.6, 7.6, 7.3, and 4.8% of AHI variability, respectively, and the whole model accounted for a 43.3% of AHI variation. Our results suggest that treatment with sac/val is able to significantly improve the cardiorespiratory performance of patients with HFrEF and SA, integrating the positive impact of CPAP. Thus, both CPAP and sac/val therapy may synergistically contribute to lower the risks of both cardiac and pulmonary complications in HFrEF patients with SA.

## 281. EFFECT OF SACUBITRIL/VALSARTAN ON ENDOTHELIAL DYSFUNCTION AND ARTERIAL STIFFNESS IN PATIENTS WITH CHRONIC HEART FAILURE

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Heart failure (HF) is associated to endothelial dysfunction, a pathological condition characterized by imbalance between the production of vaso-

constrictor and vasodilator factors, increase in the production of cytokines, down-regulation of eNOS, platelets activation and increased oxidative stress. Furthermore, endothelial dysfunction promotes the increase of arterial stiffness, augmenting myocardial damage. Sacubitril/Valsartan (sac/val) is used in the treatment of HF reduced ejection fraction (HFrEF) and has been proven effective in reducing cardiovascular (CV) disease progression and all-cause mortality in HFrEF patients. The aim of the study was to evaluate the effect of sac/val on endothelial dysfunction and arterial stiffness in patients with HFrEF, at baseline and after 6 months of treatment. Moreover, we evaluated the effects of sac/val on oxidative stress levels and platelets activation. We enrolled 100 Caucasian patients (mean age 70.1±7.1), suffering from HFrEF. Inclusion criteria were EF<35, functional class NYHA II or III. All clinical evaluation and laboratory tests were performed at baseline and after 6 months of treatment. The serum values of the markers of oxidative stress (8-isoprostane, NOX-2) and platelets activation (Sp-selectin, GPVI) were assessed with ELISA sandwich. Endothelial function was estimated with the measurement of the reactive hyperemia index (RHI); arterial stiffness (AS) was evaluated with the measurement of carotid-femoral pulse wave velocity (PWV), augmentation pressure (AP) and augmentation index (AI). Continuous variables were expressed as mean ± standard deviation (SD) (normally distributed data) or as median and interquartile range (IQR) (non-normally distributed data). For all continuous variables, comparisons between baseline (T0) and post-treatment values (T6) were performed using paired Student's t test. All variables which deviate from the normal distribution were log-transformed (ln) before to be introduced into paired Student's t test. A linear regression analysis was performed to assess the relationship between variation in arterial stiffness (PWV) and endothelial function (RHI) indices, expressed as Δ of variation between baseline and follow-up (ΔT0–6) and the variation of metabolic, inflammatory, oxidative stress and platelets activation covariates that significantly improved after the treatment (expressed as ΔT0–6). Of the 100 outpatients evaluated, 80.85% were males, 21.28% active smokers. NYHA class II was represented in 39.13% and NYHA class III in 60.87% of patients. The mean dose of sac/val was 180.5±110 mg without serious adverse events. At 6 months, data showed a significant improvement in in hemodynamic and clinical parameters such as heart rate (HR) (p<0.0001), NT-ProBNP (p<0.0001), fasting plasma glucose (FPG) (p<0.0001). Furthermore, there was a significant reduction in oxidative stress biomarkers such as 8-isoprostane (p<0.0001), Nox-2 (p<0.0001), and platelets activity biomarkers such as sP-selectin (p<0.0001) and GPVI (p<0.0001). Regarding the inflammatory profile, there was a statistically significant reduction in c-reactive protein (CRP) (p<0.0001), IL-6 (p<0.0001) and TNF-α (p<0.0001), indicating an improvement in the inflammatory state, after 6 months treatment with sac/val. Moreover, we observed a significant improvement in arterial stiffness parameters such as PWV (p<0.0001), AI (p<0.0001), AP (p<0.0001) and in endothelial function indices such as RHI (p<0.0001). The linear correlation analysis showed that ΔPWV was directly correlated with ΔHOMA (p=0.037), ΔIL-6 (p=0.034), ΔTNF-α (p=0.001), Δ8-isoprostane (p=0.016), ΔNox-2 (p=0.01), ΔGP6 (p=0.018), ΔSp-selectin (p=0.023); ΔRHI was inversely correlated with ΔHOMA (p=0.003), ΔIL-6 (p=0.004), ΔTNF-α (p=0.023), ΔCRP (p=0.011), Δ8-isoprostane (p=0.012), ΔNox-2 (p=0.01), ΔGP6 (p=0.014), ΔSp-selectin (p=0.015). From stepwise multivariate linear regression model, ΔTNF-α was the stronger predictor of ΔPWV, justifying 48.5% of its variation and ΔSp-selectin was the major predictor of ΔRHI explaining 23.2% of its variation. In conclusion, results obtained from our study demonstrated that 6 month treatment with sac/val, in patients with HFrEF, improved endothelial dysfunction and arterial stiffness, due to reduced levels of oxidative stress, platelet activation and inflammation, without adverse effects.

## 282. A TRICKY CASE OF ACUTE DYSPNEA: LOOK AT THE THYROID

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**Introduction:** Hyperthyroidism is an endocrinological disorder characterized by overproduction of thyroidal hormones and could presents also with cardiac manifestations as tachycardia, atrial fibrillation, arterial hypertension and heart failure. Over last years, evidence is accumulating on the onset of transient pulmonary hypertension in patients with hyperthyroidism. We report a case of acute and progressively invalidating dyspnea caused by pulmonary hypertension in active Basedow disease.
**Case Presentation:** A 57-year-old woman was admitted to our ward of Internal Medicine for subacute onset exertional dyspnea and orthopnea. The patient also complained in the previous two weeks asthenia, hyporexia and progressive weight loss (about 6 kg). In her past medical history, she has a recently diagnosed paroxystic atrial fibrillation in treatment with flecainide and edoxaban, arterial hypertension and mild anaemia secondary to hemorrhoidal disease.
At the emergency department physical examination and the vital parameters were normal, except for mild tachypnea (respiratory rate 24 acts/minute). The 12-lead ECG showed sinus rhythm, the arterial blood gas analysis was normal, and the chest X-rays revealed only a mild bilateral pleural effusion. Blood exams showed mild normocytic anaemia (10.9 gr/dL) with normal platelet and white cells count, along with electrolytes and liver and kidney function. Conversely, an increase of D-dimer levels was found (1165 μg/L), so a thorax CT scan with contrast was performed, excluding pulmonary embolism. After these diagnostic tests the patient was admitted to our ward. During the hospitalization the patient continued to experience invalidating subjective dyspnea with normal respiratory parameters and normal blood gas exchanges. Moreover, spirometry with diffusing capacity of the lung for carbon monoxide (DLCO) test was performed, with normal findings. Autoimmunity excluded presence of autoimmune disease that could cause lung involvement. Serial ECG performed during hospitalization always showed sinus rhythm and a transthoracic echocardiography described normal systolic and diastolic function in absence of significative valvular abnormalities with a mild increase of pulmonary artery systolic pressure (44 mmHg).
Because of the onset of emotional lability with crying spells and limbs and neck tremor made us think about a possible psychiatric component of dyspnea, so an empiric treatment with benzodiazepines was started, however with only partial improvement of the dyspnea and emotional status.
In the end, given the recent onset paroxystic atrial fibrillation and the symptoms suggestive for hyperthyroidism (as weight lost, tremor, asthenia and emotional lability), thyroid function was tested showing low TSH levels (< 0.005 mIU/L) with increased fT3 levels (6.2 ng/L) and normal fT4 levels (14.9 ng/L). Moreover, thyroid ultrasonography was performed, showing an organ with increased volume, dysomogeneous parenchyma and accentuation of vascular texture as for thyroiditis. Then, the match of positivity of anti-thyroglobulin and anti-TSH receptor autoantibodies lead us to the diagnosis of clinical hyperthyroidism in Basedow disease.
Finally, a diagnosis of mild pulmonary hypertension secondary to high cardiac output due to hyperthyroidism was driven and treatment with methimazole was promptly started with progressive reduction in thyroidal hormones and a mild improvement of symptoms. Therefore, after 24 days of hospitalization the patient was discharged with indication to outpatient follow-up with endocrinologist and cardiologist.
During the next three months the patient responded well to the therapy with a reduction of fT3 and TSH levels, improvement of symptoms (including dyspnea) and at a transthoracic echocardiography of control made after two months from the discharge was found an improvement of pulmonary artery systolic pressure (37 mmHg) with normal right ventricular outflow tract acceleration time (120 msec) and normal function of the right chambers of the heart.
**Conclusions:** Pulmonary hypertension is a clinical condition with a wide spectrum of aetiologies, mainly cardiac and pulmonary ones, but hyperthyroidism should be taken in mind. Indeed, if on the one hand patients with pulmonary hypertension have a bad prognosis, on the other hand, forms secondary to hyperthyroidism frequently are mild and transient and they respond well to endocrinological therapy. Our case points out on the need of a careful evaluation of associated symptoms of dyspnea, as anxiety, cardiac arrhythmia and weight loss in our patient could have raised the suspect of hyperthyroidism since the very beginning.

## 283. A COMPLEX CASE OF STROKE

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A 56 years old Caucasian man was taken to the emergency department (ED) after his relatives found him conscious on the floor of his home, but reported difficulty speaking and walking and weakness in his left upper extremity. On admission, arterial pressure was elevated 190/85 mmHg, other parameters were normal and within normal ranges, and aphasia and left-sided weakness were found on examination. An urgent brain CT scan was performed and intracranial hemorrhage was excluded, no edema or other changes in lipid density in the left nucleus basal region were reported. After testing negative for SARS-CoV-2, the patient was transferred to our ward in a stable condition.
After a thorough reconstruction of his clinical history, silent on major triggers and previous cerebrovascular events in the previous few days, we assessed major cardiovascular risk factors. The patient had chronic arterial hypertension, type 2 diabetes, and hypercholesterolemia. The patient also self-reported active smoking habit with a cumulative pack/year score of sixty.
During hospitalization, the patient experienced several rapid increases in blood pressure, up to 200/100 mmHg. Medications were gradually increased after each attack, with early involvement of a cardiologist to manage the condition. During an acute attack, no significant changes in neurological or general status occurred.
As the patient's clinical condition was better controlled, the entity and origin of ischemia were investigated. The cause of cardiac embolism was assessed by electrocardiography and Holter ECG monitoring, no apparent arrhythmias were reported, and echocardiography revealed the presence of chronic hypertensive changes with left ventricular hypertrophy, but no cases of intracardiac thrombosis or other possible embolism. Carotid Doppler ultrasound examination showed only 45-50% stenosis at the outlet of both internal carotid arteries.
A MRI with vascular-TOF sequence was therefore performed and the exam found the nearest ischemic area to the right of the left cingulum and corpus callosum, the latter change was not detected by the CT scan performed in the ED. Due to atypical localization, scan unrecognizable and radiological follow-up were recommended. Intracranial blood vessels did not change.
On the same day as the MRI, the patient experienced a brief deterioration in language function that resolved spontaneously four hours later. An electroencephalogram was performed, showing stimulatory changes in the mid-posterior right region, occasionally shifting to the left counterpart. No overt seizures or borderline posterior waves were reported.
Following this event and concomitant optimization of antihypertensive and statin therapy, the patient was subsequently transferred to an intensive rehabilitation center in good clinical condition.
Corpus callosum strokes are rare, occurring in 2.9% to 8%, half of which involve the slum. Strokes isolated in this area are rare and require further investigation. This area is located at the junction of the anterior and posterior branches of the cerebral arteries, and alterations in one or both of these vasculatures may lead to infarction. There are rarer causes such as hypoxia and vasospasm.
In the era of the COVID-19 pandemic, a group of callous stroke patients, usually those who tested positive for SARS-CoV-2 on presentation, have been reported.
In our patient, a fully vaccinated healthy individual, undiagnosed/asymptomatic infection in the days prior to the onset of neurological symptoms cannot be completely ruled out, nor can it be confirmed, but we recommend that a complete medical history should be taken to determine possible evaluation correlation
**Reference:** Sparr SA, Bieri PL. Infarction of the Splenium of the Corpus Callosum in the Age of COVID-19: A Snapshot in Time. Stroke. 2020 Sep;51(9): e223-e226. doi: 10.1161/STROKEAHA.120.030434. Epub 2020 Jul 20. PMID: 32684144; PMCID: PMC7386678.

## 284. IMPACT OF HORMONAL-ANABOLIC DEFICIENCIES IN IDIOPATHIC PULMONARY ARTERIAL HYPERTENSION

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**Background:** Anabolic Deficiencies play a pivotal role in left-sided heart failure. Little is known about their impact on idiopathic pulmonary arterial hypertension (iPAH). Therefore, the aim of this study was to assess the impact of multiple hormone-metabolic deficiencies on clinical features and outcomes in idiopathic pulmonary arterial hypertension.
**Methods:** In this single-centre, retrospective study we assessed hormone deficiency in idiopathic pulmonary hypertension. Patients were divided into two groups: 1) no hormone deficits or with a single deficit (MHDS-) and 2) concomitant hormone deficits (≥2, MHDS+ deficits). Clinical status, Lung Hemodynamics, six-minute walking distance, time to clinical worsening (TTCW) and survival were evaluated between the two groups.
**Results:** According to the previously defined cut-offs, 1 patient presented no deficit (3.3%), 16 patients a single deficit (53.3%), 5 patients 2 deficits (16.7%), 6 patients had 3 deficits (20.0%), 1 patient had 4 deficits (3.3%) and finally, 1 patient had 5 deficits (3.3%) Table 1 shows the differences in the main clinical parameters examined between MHDS- and MHDS+ deficits). MHDS+ showed reduced exercise capacity as shown by a more impaired six-minute walking distance (456.91 ± 70.35 vs 380.12±66.11 m, p: 0.012), increased pulmonary vascular resistance (PRV) (7.08 ± 2.99 vs 12.62±3.26 WU, p: 0.001) and reduced right ventricle ejection fraction (37.30 ± 10.07 vs 26.76±16.05, p: 0.05). Although a small positive trend, no differences were recorded regarding TTCW.
**Conclusions:** Multiple hormonal deficits are very common in iPAH and in particular, characterize a subgroup of patients with worse exercise capacity, pulmonary hemodynamics, right ventricular size and function, generating the hypothesis about the potential role of hormonal replacement therapy. These data should be confirmed by larger studies.

| Parameter | MHDS- | MHDS+ | p value |
|---|---|---|---|
| BMI (Kg/mq) | 26.62 ± 5.02 | 26.26 ± 6.58 | ns |
| WHO (I,II,III,IV) | 10,6,1 | 2,9,2 | 0.03 |
| 6MWD (m) | 456.91 ± 70.35 | 380.12 ± 66.11 | 0.012 |
| sPAP (mmHg) | 64.95 ± 22.73 | 80.62 ± 17.11 | ns |
| mPAP (mmHg) | 40.77 ± 12.81 | 57.37 ± 9.33 | 0.001 |
| dPAP (mmHg) | 25.09 ± 8.47 | 40.62 ± 4.77 | 0.0001 |
| Cardiac Index (l/mq) | 2.59 ± 0.465 | 2.14 ± 0.64 | 0.04 |
| wedge (mmHg) | 9.00 ± 3.51 | 11.62 ± 2.72 | ns |
| PVR (Woods Units) | 7.07 ± 2.99 | 12.62 ± 3.26 | 0.001 |
| PAC (ml/mmHg) | 1.81 ± 0.72 | 1.37 ± 0.84 | ns |
| RV-EDV (ml) | 172.01 ± 48.77 | 214.53 ± 51.95 | ns |
| RV-ESV (ml) | 93.7 ± 48.91 | 153.25 ± 51.34 | 0.01 |
| RV-EF (%) | 37.30 ± 10.07 | 26.76 ± 16.05 | 0.05 |
| RV-massa (g) | 80.28 ± 20.75 | 100.31 ± 18.23 | 0.03 |

MHDS= multiple metabolic hormone syndrome, BMI: body mass index; 6MWD: six-minute walk distance test, PAP: pulmonary pressure, s: systolic, d: diastolic, m: mean, PAC: pulmonary artery compliance, RV: right ventricle, EDV: telediastolic volume, EDS: telesystolic volume, EF: ejection fraction, ns: not significant

## 285. CARDIOVASCULAR BIOMARKERS IN DIABETIC PATIENTS UNDERGOING ENDOVASCULAR REVASCULARIZATION FOR CHRONIC LIMB THREATENING ISCHEMIA (CLTI)

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**Background:** Peripheral artery disease (PAD) is one of the most relevant complications of diabetes and chronic limb threatening ischemia (CLTI) is its most dangerous manifestation. Without revascularization, CLTI often causes limb loss. In the last years, lower limb endovascular revascularization (LER) became the primary approach of revascularization in patients with CLTI, depending on atherosclerotic lesions distribution. However, neither LER nor open surgical revascularization ensure long-term success. In clinical practice, different clinical outcomes after LER in patients with similar comorbidities undergoing the same procedure (in terms of revascularization technique and localization of the disease) cause unsolved issues. The progression of atherosclerosis is characterized by an inflammatory reaction orchestrated by several molecules belonging to different families of inflammatory mediators, such as cytokines, chemokines, adhesion molecules, and proteolytic enzymes. However, no definitive molecular associations have been described that could explain the difference in outcomes after LER in diabetic patients with CLTI.
**Methods:** We evaluated the relationship between the levels of a panel of

biomarkers associated with diabetic atherosclerosis and the outcomes after LER in diabetic patients with CLTI.
**Results:** A total of 88 diabetic patients with CLTI undergoing an angioplasty procedure were enrolled. The levels of a panel of biomarkers-interleukin-6 (IL-6) and 1 (IL-1), C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), high-mobility group box-1 (HMGB-1), osteoprotegerin (OPG), sortilin and omentin-1-were measured, and major adverse limb events (MALE) and major adverse cardiovascular events (MACE) were assessed at 3, 6, and 12 months after the procedure. There was a linear association for each cytokine at baseline and incident MALE and MACE. Receiver operating characteristics models were constructed using clinical and laboratory risk factors, and the inclusion of cytokines significantly improved the prediction of incident events.
**Conclusions:** We demonstrated that elevated IL-6, IL-1, CRP, TNF-α, HMGB-1, OPG and sortilin levels and low omentin-1 levels at baseline correlate with worse vascular outcomes in diabetic patients with CLTI undergoing an endovascular procedure. Assessment of the inflammatory state with this panel of biomarkers may support physicians to identify a subset of patients more susceptible to the procedure failure and to develop cardiovascular adverse events after LER.

## 286. EFFECT OF CONTINUOUS POSITIVE AIRWAY PRESSURE TREATMENT ON GLYCEMIC AND LIPID PROFILES IN PATIENTS WITH OBSTRUCTIVE SLEEP APNEA: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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**Background and Aim:** Continuous Positive Airway Pressure (CPAP) is the main therapy for obstructive sleep apnea (OSA). Nevertheless, uncertainty remains about the effectiveness of CPAP in improving OSA-related metabolic dysregulation. This meta-analysis of randomized controlled trials (RCTs) aimed to investigate whether CPAP treatment, as compared to other control therapies, could improve glucose metabolism and/or lipid metabolism in OSA patients.
**Methods:** Relevant articles were searched in three different databases (MEDLINE, EMBASE and Web of Science) from inception to 6stFeb 2022 through specific search terms and selection criteria.
**Results:** From a total of 5,962 articles, 32 RCTs were included. CPAP treatment significantly decreased fasting plasma glucose (FPG) levels (standardized difference in means [SDM]=-0.11 [95%CI, -0.17- -0.33], p=0.004) and improved insulin sensitivity reducing both fasting plasma insulin (SDM=-0.17 [95%CI, -0.28- -0,05], p=0,005) and HOMA-IR (SDM=-0.19 [95%CI, -0.29- -0,08], p=0,001). In subgroup analysis, prediabetic and type 2 diabetic patients as well as those that demonstrated either a higher CPAP usage (≥4/h per night) or an apnoea-hypopnea index≥30 events/h at baseline showed the greatest response to CPAP. Regarding lipid metabolism, CPAP was associated with a significant reduction of both total cholesterol (TC; SDM=-0.19 [95%CI, -0.28- -0,1], p=<0.0001) and LDL-cholesterol (SDM=-0.11 [95%CI, -0.2- -0,01], p=<0.03) levels. In sensitivity analysis, favorable metabolic effects were present in patients that exhibited a greater adherence to CPAP (≥4/h per night), in those that presented more severe nocturnal oxygen desaturations (minimum SatO2 <77%) and an apnoea-hypopnea index≥30 events/h at baseline. CPAP treatment did not affect glycated haemoglobin, triglycerides, and HDL-cholesterol levels.
**Conclusion:** CPAP treatment, even if with low effect size, improves insulin sensitivity and reduces FPG, TC and LDL-cholesterol levels in OSA patients. Both prediabetic and type 2 diabetic patients and those that exhibited a greater CPAP usage as well as higher number of apnoeic events or oxygen desaturations at baseline may benefit the most from CPAP.

## 287. ASSOCIATION BETWEEN SERUM URIC ACID LEVEL AND PERIPHERAL ARTERIAL DISEASE IN DIABETIC PATIENTS WITH CORONARY ARTERY DISEASE

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**Background:** Peripheral artery disease (PAD) is one of the most relevant complications of diabetes. Elevated serum uric acid (SUA) has been addressed as a possible cardiovascular risk factor since 1879. Several studies have investigated the association between elevated SUA and cardiovascular disease, including coronary artery disease (CAD), stroke, heart failure, arterial hypertension and atrial fibrillation. Evidence available also suggests an association between elevated SUA and traditional cardiovascular risk factors, such as metabolic syndrome, diabetes, obesity, non-alcoholic fatty liver disease and chronic kidney disease. Although the causality in the relationship between SUA and cardiovascular disease remains unproven, SUA may participate in the pathophysiology potentiating the deleterious effects of cardiovascular risk factors on vascular tissue. However, the independent role of SUA in the development of PAD in diabetic patients is still unsettled.
**Methods:** In this cross-sectional study, we analyzed SUA levels in diabetic patients with CAD, with and without PAD. None of the patients were on hyperuricemia treatment.
**Results:** A total of 106 diabetic patients with CAD were enrolled, with (n = 72) and without (n = 34) PAD. The mean age of both populations was 70 years. We found that SUA levels were significantly higher in diabetic patients with CAD and PAD than in diabetic patients with CAD without PAD (6.1 mg/dL vs 4.9 mg/dL, P < 0.002). The association of SUA levels with PAD remained after adjusting for major risk factors in a multivariate analysis.
**Conclusions:** This result suggests that SUA level may be a safe and easy to measure biomarker of PAD in diabetic patients with story of CAD. Therefore, SUA may support physicians in screening diabetic patients with CAD to identify patients more susceptible to develop PAD.

## 288. EPIDEMIOLOGY OF NEW-ONSET ATRIAL FIBRILLATION IN HOSPITALIZED COMMUNITY-ACQUIRED PNEUMONIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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**Background:** Community-acquired pneumonia (CAP) is the commonest lower respiratory tract infection, often complicated by cardiovascular events, including cardiac arrhythmias. New-onset Atrial Fibrillation (noAF) has been associated with increased mortality in CAP patients, especially in critically ill ones; however, the epidemiology of noAF in patients with CAP is still unclear.
**Aim:**To estimate the pooled prevalence of noAF and its impact on adverse outcomes in patients with CAP, through a systematic review and meta-analysis of the literature.
**Methods:** MEDLINE and EMBASE were systematically searched from inception to 27th January 2022. All studies reporting the prevalence of noAF in CAP patients were included. The pooled prevalence of noAF, 95% Confidence Intervals (CI), and 95% Prediction Intervals (PI), were computed using generalized linear mixed models. The inconsistency index (I2) was calculated to measure heterogeneity. Subgroup analyses according to the study design and the geographical location were also performed. A protocol for this study was registered on PROSPERO (CRD42022307422).
**Results:** Among 7,655 records retrieved, 10 studies were finally included, with a total of 280,589 CAP patients. Pooled prevalence of noAF in CAP patients was 7.6% (95% CI 6.4-9.0%, 95% PI 4.3-13.1%, I2=95%, Figure 1). Subgroup analyses showed no significant differences according to geographical location or study design. Patients with noAF had a higher risk of mortality among the studies included in the systematic review.
**Conclusions:** NoAF is commonly found in CAP patients and may impact both short and long-term prognosis. No significant subgroup differences

were observed according to geographical location or study design.

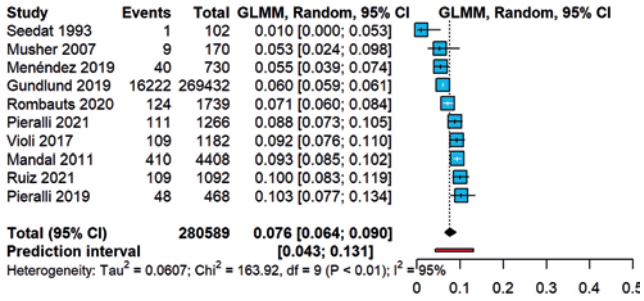


**Figure 1.**
Legend: CAP: Community-acquired pneumonia; CI: Confidence Interval; GLMM: Generalized Linear Mixed Model; I2: Inconsistency Index; noAF: new-onset Atrial Fibrillation

## 289. A CHALLENGING CASE OF CRYPTOGENIC STROKE IN A MIDDLE-AGE WOMAN

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A 47-year-old woman was admitted in emergency room with acute neurological syndrome characterized by mental confusion, drowsiness and blurry vision. Her past medical history was significant for beta-thalassemia minor, Hashimoto's thyroiditis and abnormal uterine bleeding; moreover no cardiovascular risk factors were reported. On admission she was apyretic, eupnoic, with blood pressure 120/80 mmHg, heart rate 65 bpm, 14 points at Glasgow Coma Scale because of impairment of verbal response. Inspection revealed paleness of skin and mucosae, whereas lung, abdomen and cardiac examination resulted regular. Neurological evaluation showed mainly a physiological picture: no abnormalities of cranial nerves, preserved muscle strength and stretch reflexes, negative cerebellar tests, intact somatosensory system. EKG exhibited sinus rhythm with normal intervals and waves. Arterial blood gas test detected hypoglycemia (60 mg/dl) and severe anemia (Hb 6.0 g/dl), so 500 cc 10% dextrose solution was given and 2 bags of red blood cells were required. Laboratory studies highlighted: WBC 5120/µL, RBC 3.38 106/mm3, Hb 5.8 g/dL, HCT 20%, MCV 60 µm3, MCH 17.2 pg, CRP 0.08 mg/dl, D-dimer 2053 µg/L, normal liver and kidney function, negative cardiac biomarkers. Due to the persisting symptoms CT brain was carried out, which showed bilateral symmetrical thalamo-capsular hypodensity. This area also presented signal restriction in DW-MRI sequences and hyperintensity on FLAIR series, consistent with an ischemic injury caused by the occlusion of artery of Percheron (AOP). Afterwards the patient was transferred to the department of Internal Medicine to investigate the etiology of the stroke. First, we excluded two main subtypes of stroke (large artery atherosclerosis and cardioembolism) through a basic cardiovascular work-up based on carotid US, transthoracic echocardiography and Holter monitor – no evidence of significant stenosis of a major brain artery, no potential cardiac source of embolism, absence of supraventricular arrhythmias. Moreover, normal values of thrombofilia panel (antithrombin III deficiency, protein C and protein S deficiency, factor V Leiden mutation, activated protein C resistance, prothrombin mutation, antiphospholipid Ab) and ANCAs led us to rule out less common causes of stroke such as both acquired and inherited trombophilia or vasculitis. At this point we reconsidered all the diagnostic elements available, focusing especially on the elevation of D-dimer and an abnormal waving of the atrial septum on echo. Therefore, in the suspicion of a paradoxical embolism, a contrast echocardiography was performed, which demonstrated the presence of patent foramen ovale (PFO). This finding was confirmed at transesophageal echocardiography (TEE), associated with severe right-to-left shunt and atrial septal aneurysm. Finally, the patient was discharged with a diagnosis of "PFO related stroke by occlusion of AOP", with direction for continuing antiplatelet therapy (ASA 100 mg QD) and for subsequent percutaneous closure of PFO. During hospitalization anemia was also investigated: a value of 1.6 at reticulocyte production index, reduction of transferrin saturation (12%) and the history of uterine bleeding suggested an iron deficiency anemia with mild hyperproliferation; transvaginal US didn't notice organic diseases, so we recommended iron supplementation and gynecological follow-up. Hypoglycemia described at the beginning was attributed to reactive hypoglicemia. Stroke is a major cause of death and disability. Determining the cause of stroke is essential for proper management, however the identification of the etiology may result challenging. In our case stroke presented with atypical clinical features: confounding signs (anemia, hypoglycemia), absence of cardiovascular risk factors, non-specific neurologic symptoms, bilaterality of infarcted areas. Only the demonstration of AOP involvement and PFO detection led us to integrate all elements in an unified perspective. AOP is a rare anatomical variant of thalamic vascularization characterized by a perforating artery that arises from posterior cerebral artery, supplying the paramedian thalamus and rostral midbrain on both sides. It is estimated that AOP infarction accounts for 0.1-2% of all ischemic stroke. The clinical picture is very varied both for the symptomatology and for the severity, up to coma. PFO is a communication between the atria at the level of the fossa ovalis, that usually closes after birth but can remain pervious in about 25% of cases. PFO may allow the passage of emboli from the venous system to the cerebral arteries (paradoxical embolism), for this reason it should be looked for in adults with cryptogenic stroke. In case of suspicion of PFO it is necessary to perform a contrast echocardiography that shows right-to-left shunt and its severity. TEE is the gold standard to define the anatomy of PFO. In adults until 60 years at high-risk (severe shunt and/or interatrial septal aneurysm) transcatheter PFO closure is indicated, to be associated with antiplatelet therapy.

## 290. RIGHT HEART PULMONARY CIRCULATION UNIT RESPONSE TO EXERCISE IN PATIENTS WITH CONTROLLED SYSTEMIC ARTERIAL HYPERTENSION: INSIGHTS FROM THE RIGHT HEART INTERNATIONAL NETWORK (RIGHT-NET)

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**Background:** Systemic arterial hypertension (HTN) is the main risk factor for the devel- opment of heart failure with preserved ejection fraction (HFpEF). The aim of the study was was to assess the trends in PASP, E/E' and TAPSE during exercise Doppler echocardiography (EDE) in hypertensive (HTN) patients vs. healthy subjects stratified by age.
**Methods:** EDE was performed in 155 hypertensive patients and in 145 healthy subjects (mean age 62 ± 12.0 vs. 54 ± 14.9 years respectively, $p < 0.0001$). EDE was undertaken on a semi-recumbent cycle ergometer with load increasing by 25 watts every 2 min. Left ventricular (LV) and right ventricular (RV) dimensions, func- tion and hemodynamics were evaluated.
**Results:** Echo-Doppler parameters of LV and RV function were lower, both at rest and at peak exercise in hypertensives, while pulmonary hemodyna-

mics were higher as compared to healthy subjects. The entire cohort was then divided into tertiles of age: at rest, no significant differences were recorded for each age group between hypertensives and normotensives except for E/E' that was higher in hypertensives. At peak exercise, hypertensives had higher pulmonary artery systolic pressure (PASP) and E/E' but lower tricuspid annular plane systolic excursion (TAPSE) as age increased, compared to normotensives. Differences in E/E' and TAPSE between the 2 groups at peak exercise were explained by the interaction between HTN and age even after adjustment for baseline values ($p < 0.001$ for E/E', $p = 0.011$ for TAPSE). At peak exercise, the oldest group of hypertensive patients had a mean E/E' of 13.0, suggesting a significant increase in LV diastolic pressure combined with increased PASP.
**Conclusion:** Age and HTN have a synergic negative effect on E/E' and TAPSE at peak exercise in hypertensive subjects.

## 291. INSULIN-LIKE GROWTH FACTOR-1 (IGF-1) AS PREDICTOR OF CARDIOVASCULAR MORTALITY IN HEART FAILURE PATIENTS: DATA FROM THE T.O.S.CA. REGISTRY

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**Introduction:** Data from the "Trattamento Ormonale nello Scompenso CArdiaco" (T.O.S.CA) registry showed that heart failure (HF) represents a complex clinical syndrome with diferent hormonal alterations. Renal failure represents a frequent complication in HF. We evaluated the relationship between renal function and insuline-like growth factor-1 (IGF-1) defciency and its impact on cardiovascular mortality (CVM) in patients enrolled in the T.O.S.CA. registry.
**Methods:** At the enrolment, all subjects underwent chemistry examinations, including circulating hormones and cardiovascular functional tests. COX regression analysis was used to evaluate factors related to CVM during the follow-up period in all populations, in high-risk patients and in the young-adult population. Also, we evaluate the efects of renal function on the CVM.
**Results:** 337 patients (41 deceased) were analyzed. CVM was related to severe renal dysfunction (HR stages IV–V=4.86), high-risk conditions (HR 2.25), serum IGF-1 (HR 0.42), and HF etiology (HR 5.85 and HR 1.63 for valvular and ischemic etiology, respectively). In high-risk patients, CVM was related to IGF-1 levels, severe renal dysfunction and valvular etiology, whereas in young patients CMV was related to the high-risk pattern and serum IGF-1 levels.
**Conclusion:** Our study showed the clinical and prognostic utility of the IGF-1 assay in patients with HF.

## 292. THE C2HEST AND MC2HEST SCORES TO PREDICT NEW ONSET ATRIAL FIBRILLATION AFTER ACUTE CORONARY SYNDROME: A REPORT FROM THE MULTICENTER REALE-ACS REGISTRY

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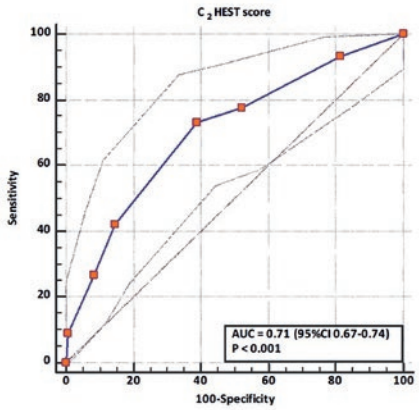
**Aim:** New onset atrial fibrillation (NOAF) is associated with worse clinical outcomes after acute coronary syndrome (ACS). Identification of patients at risk of NOAF remains challenging, and various clinical scores of varying complexities have been proposed to predict incident AF. We tested the value of the simple C2HEST score for predicting NOAF in patients with ACS.
**Methods:** We studied patients from the prospective ongoing multicenter REALE-ACS registry of patients with ACS. NOAF was the primary endpoint of the study. The C2HEST score was calculated as coronary artery disease or chronic obstructive pulmonary disease (1 point each), hypertension (1 point), elderly (age ≥75 years, 2 points), systolic heart failure (2 points), thyroid disease (1 point). We also tested the mC2HEST score.




**Results:** We enrolled 555 patients (mean age 65.6±13.3 years; 22.9% women), of which 45 (8.1%) developed NOAF. Patients with NOAF were older ($p<0.001$) and had more prevalent hypertension ($p=0.012$), COPD ($p<0.001$) and hyperthyroidism ($p=0.018$). Patients with NOAF were more frequently admitted with STEMI ($p<0.001$), cardiogenic shock ($p=0.008$), Killip class ≥2 ($p<0.001$) and had higher mean GRACE score ($p<0.001$). Patients with NOAF had a higher C2HEST score compared with those without (4.2±1.7 vs 3.0±1.5, $p<0.001$). A C2HEST score >3 was associated with NOAF occurrence (odds ratio 4.33, 95% confidence interval 2.19-8.59, $p<0.001$). ROC curve analysis showed good accuracy of the C2HEST score (AUC 0.71, 95%CI 0.67-0.74, Figure 1) and mC2HEST score in predicting NOAF (AUC 0.69, 95%CI 065-0.73).
**Conclusion:** The simple C2HEST score may be a useful tool to identify patients at higher risk of developing NOAF after presentation with ACS.

## 293. CASE REPORT ON CARDIOTOXICITY DUE TO MEK-I AND BRAF-I

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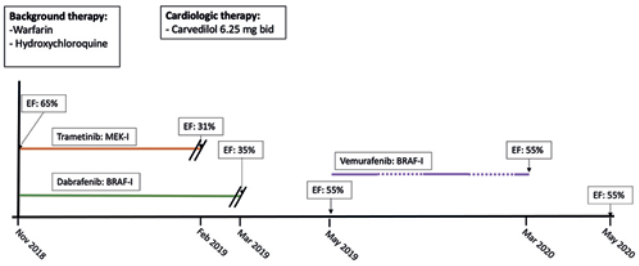
**Background:** Novel antineoplastic therapies have drastically improved cancer patients' survival. In particular, the use of target therapy (MEK and B-RAF inhibitors) and immune-checkpoint inhibitors (ICI) was associated with a significant improvement in melanoma patients' survival. Nevertheless, these drugs present different cardiovascular (CV) side effects, which may be even fatal and might compromise the completion of oncological treatments.
**Case Report:** L.T., 41 y.o., woman. Smoker (13 pack/year). No family history of CV diseases. Personal history of systemic erythematous lupus treated with hydroxychloroquine, and antiphospholipid syndrome, diagnosed after an episode of pulmonary thromboembolisms in 2007, in treatment with warfarin. No personal history of other CV diseases.
In October 2018 she was diagnosed with BRAF-mutated malignant melanoma with subcutaneous metastasis in the submammary area (stage IV) and she was started on oral MEK-I and BRAF-I (Trametinib and Dabrafenib). Before starting the oncological treatments, she underwent cardiological assessment.
EKG: normal sinus rhythm.
Echocardiography: normal left ventricle ejection fraction (LVEF) 65%, normal cardiac chambers dimensions.
In February 2019 she was admitted to our Cardio-Oncology out-patients clinic lamenting shortness of breath. At clinical evaluation she presented progressive exertional dyspnea (NYHA III).
Normal vital signs, BP: 120/80 mmHg; SpO2: 98%.
EKG: normal sinus rhythm with non-specific ST-T repolarization abnormalities. QTc 474 msec.
Echocardiography: Enlarged and hypokinetic left ventricle, with moderate reduction of ejection fraction (LVEF 31%). Mild left atrial enlargement.
Blood withdrawal: normal thyroid, kidney, and liver function. NTproBNP 730 ng/L.
Myocardial perfusion SPECT: not significant for reversible stress induced ischemia.
She is diagnosed with cardiotoxicity due to MEK-I and BRAF-I. In accordance with her oncologists, MEK-I (Trametinib) is suspended (continuing treatment with BRAF-I, Dabrafenib) and she is prescribed with Carvedilol 6.25 mg bid.
At 4 weeks follow-up visit, she's in stable clinical conditions, lamenting significant decrease in exercise tolerance (NYHA III).
Vital signs: BP: 120/70 mmHg, HR: 65 bpm.
EKG: normal sinus rhythm, with non-specific ST-T repolarization abnormalities. QTc 468 msec.
Echocardiography: Enlarged and hypokinetic left ventricle, with moderate reduction of ejection fraction (LVEF 35%). Mild left atrial enlargement.
Dabrafenib is then suspended.
At follow-up visit in May 2019 the patient is significantly ameliorated. She presents no dyspnea (NYHA I).
Vital signs: BP120/70 mmHg. HR: 65 bpm.
EKG: normal sinus rhythm, with non-specific ST-T repolarization abnormalities. QTc 470 msec.
Echocardiography: Normal cardiac chambers dimensions. Improvement of ejection fraction (LVEF 55%).
Blood withdrawal: NTproBNP 102 ng/l.
In accordance with her oncologists, the patient starts antineoplastic treatment with Vemurafenib (BRAF-I), which is less frequently associated with CV side effects. During the following year, the patient temporary suspends different times treatment with Vemurafenib, due to gastro-intestinal side effects. Nevertheless, she presents no other CV side effect. In May 2020 the patient dies due to oncologic diseases progression.
**Conclusions:** The present case report rises interesting challenging regarding the management of melanoma patients eligible for oncological treatment. In a smaller percentage of cases compared to classic antineoplastic agents, target therapy with MEK-I and BRAF-I might be associated with LVEF impairment. This toxicity is usually reversible after target therapy suspension, as shown in this case report.
Among risk factor for the development of cardiotoxicity associated with MEK-I and BRAF-I, our patient was an active smoker, but the role played by autoimmune diseases is not clear in this subset of patients. Doubtless, the presence and the clinical manifestations of her underlying autoimmune diseases played an important role in the choice of the oncologic protocol to use. In particular, in this case, the use of immune-checkpoint inhibitors was not recommended due to the higher risk of systemic adverse events, leaving the target therapy as the only feasible choice.
Moreover, this case report highlights the need for appropriate diagnostic flow-charts to identify patients at higher risk of developing CV events associated with oncologic treatments and to early diagnose any manifestation of such events. Furthermore, the appropriate clinical management of CV events risen during oncological protocols and how to coordinate antineoplastic treatments with CV care is yet to be cleared.




## 294. IMPACT OF A CARDIO-ONCOLOGY UNIT ON PREVENTION OF CARDIOVASCULAR EVENTS IN CANCER PATIENTS

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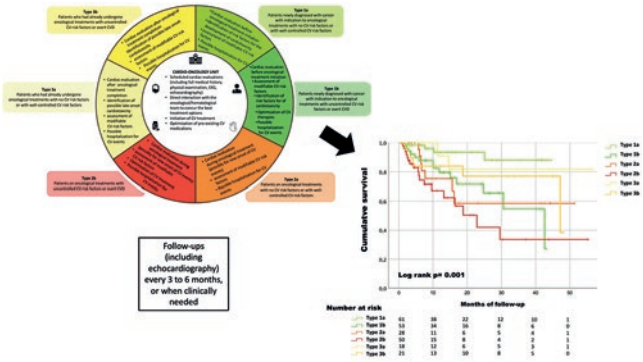
**Aims:** As the world population grows older, the co-existence of cancer and cardiovascular comorbidities becomes more common, complicating management of these patients. Here, we describe the impact of a large cardio-oncology unit in Southern Italy, characterizing different types of patients and discussing challenges in therapeutic management of cardiovascular complications.
**Methods and Results:** We enrolled 231 consecutive patients referred to our cardio-oncology unit from January 2015 to February 2020. Three different types were identified, according to their chemotherapeutic statuses at first visit. Type 1 included patients naïve for oncological treatments, Type 2 patients already being treated with oncological treatments, and Type 3 patients who had already completed cancer treatments. Each type was also divided in subgroup a (patients with no cardiovascular risk factors or well-controlled cardiovascular risk factors at the time of the first cardiological assessment) and subgroup b (patients with uncontrolled cardiovascular risk factors or over cardiovascular diseases at the time of the first cardiological assessment). Figure 1 summarizes the major findings of the study.
Clinical outcomes were defined as: cardiovascular events during antineoplastic treatments, temporary suspension or change in oncological treatments due to cardiovascular complications, cancer treatment permanent withdrawal, death for all causes. Also, cardiovascular treatment optimization and the prescription of new cardiovascular drugs were analyzed.
Type 2 patients presented the highest incidence of cardiovascular events (46.2% vs. 12.3% in Type 1 and 17.9% in Type 3) and withdrawals from oncological treatments (5.1% vs. none in Type 1) during the observation period. Type 2 patients presented significantly worse 48 months of survival (32.1% vs. 16.7% in Type 1 and 17.9% in Type 3), and this is more evident when in the three groups we focus on patients with uncontrolled cardiovascular risk factors or overt cardiovascular disease at the first cardiological assessment (Figure 2 summarizes clinical outcomes according to the 6 types). Nevertheless, patients in subgroups b for each type showed the greatest benefit from our cardiovascular assessments, as witnessed by a small, but significant improvement in ejection fraction during follow-up (Type 2b: from 50 [20; 67] to 55 [35; 65]; P = 0.04).

**Conclusions:** Patients who start oncological protocols without an accurate baseline cardiovascular evaluation are at major risk of developing cardiac complications due to antineoplastic treatments.




| Clinical indication | All (n =231) | Type 1a (n=61) | Type 1b (n=53) | Type 2a (n=28) | Type 2b (n=50) | Type 3a (n=18) | Type 3b (n=21) | p-value |
|---|---|---|---|---|---|---|---|---|
| CV events during follow-up, n (%) | 57 (24.7) | 6 (9.8) | 8 (15.1) | 4 (14.3) | 32 (64.0) | 2 (11.1) | 5 (23.8) | 0.012 |
| Cancer treatment modification or temporary suspension, n (%) | 21 (9.1) | 2 (3.3) | 1 (1.9) | 2 (7.1) | 16 (32.0) | 0 (0) | 0 (0) | <0.01 |
| Cancer treatment withdrawal, n (%) | 4 (1.7) | 0 (0) | 0 (0) | 0 (0) | 4 (8.0) | 0 (0) | 0 (0) | 0.012 |
| Death for all causes, n (%) | 51 (22.1) | 4 (6.6) | 15 (28.3) | 7 (25.0) | 18 (36.0) | 2 (11.1) | 5 (23.8) | <0.01 |

## 295. CARDIOVASCULAR EVENTS IN CHILDREN TREATED FOR HIGH RISK MEDULLOBLASTOMA

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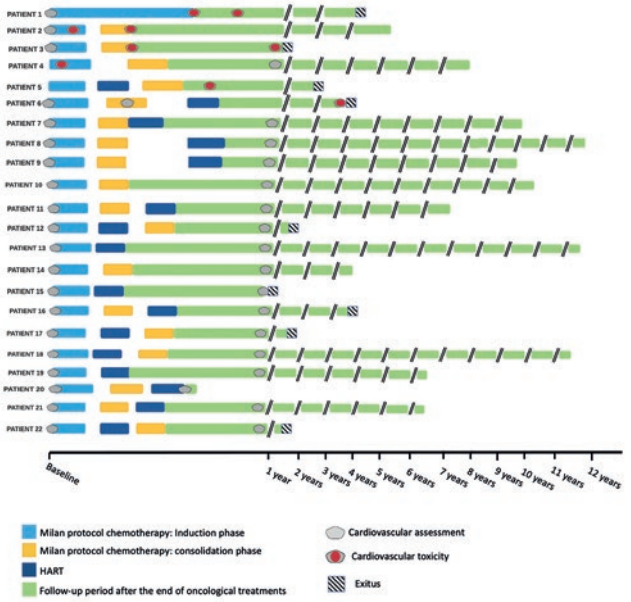
**Background:** Medulloblastoma is among the most frequent pediatric malignancies. Children with high-risk medulloblastoma are treated with chemotherapeutic protocols, including high dose drugs, which may affect heart function.Purpose: In the current work, we aim at assessing cardiovascular events (CVE) in children undergoing oncological treatment for medulloblastoma or primitive neuroectodermal tumors (PNET).
**Methods:** We retrospectively collected data from children with high-risk medulloblastoma/PNET eligible for chemotherapeutic treatment. Patients underwent cardiac examination, including ECG, echocardiography and serum biomarkers, before antineoplastic treatment initiation and then when clinically needed. CVE occurrence was defined, according to the 2016 ESC Consensus paper, by reduction of left ventricular ejection fraction (LVEF) >10% with a final LVEF<50%, by the presence of new-nosed cardiac arrhythmias and new-onset arterial hypertension.
**Results:** 22 children meet the inclusion criteria. All patients received Milan HART protocol for high-risk brain malignancies as first line treatment, (except for 1 patient who received Milan HART as second line therapy) including vincristine, high dose (HD)-methotrexate, HD-etoposide, HD-cyclophosphamide and carboplatin, followed by, if necessary, radiation therapy directed to the brain. Patients who do not achieve complete remission before radiation treatment are then administered with HD chemotherapy with thiotepa followed by hematopoietic stem cell transplantation. Four patients also received second line treatment, while four patients also received maintenance therapy. Six patients developed CVE (CVE group); 16 patients had no CVE (NO-CVE group). In the CVE group, 3 patients presented acute CVE during chemotherapy (2 patients with LV dysfunction, 1 patient with arterial hypertension), while 3 patients presented chronic CVE after chemotherapy completion (2 patients with LV dysfunction, 1 patient with ectopic atrial tachycardia). After a 51 months median follow-up, 9 patients died: 4 from the CVE group (in 2 cases heart failure-related deaths) and 5 from the NO-CVE group (progression of disease). Figure 1 summarizes the timeline for each patient.
**Conclusion:** A relevant percentage of children treated for medulloblastoma/PNET develops CVE (27% incidence in the present cohort: ). In particular, LV dysfunction due to chemotherapy is among the most common manifestations of CVE (18%), and it may represent a cause of death (9% mortality according to our population). Hence, in these patients, strict cardiac surveillance is essential.




## 296. CORR ELATION BETWEEN FAMILIAL HYPERCOLESTEROLEMIA GENOTYPE AND RESPONSE TO LIPID- LOWERING THERAPY

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**Background:** Familial hypercholesterolemia (FH) is the most frequent Mendelian disorder among genetic diseases and is characterized by the plasma accumulation of cholesterol in the form of LDL. The early genetic diagnosis of FH is essential in the fight against atherosclerosis also thanks to biotechnological drugs with monoclonal antibodies.
**Aim:** The aim of the study was to evaluate the efficacy of therapy with PCSK9i drugs, both in terms of overall reduction of the lipid profile and in terms of reaching the LDLc target, in a population of patients with a clinical phenotype suggestive of familial hypercholesterolemia (FH), confirmed by genetic testing.
In particular, we stratified patients on the base of genotype to study the correlation with the great phenotypic variability (both in terms of the severity of plasma LDLc levels and the prevalence of major cardiovascular events related to atherosclerosis) and with the response to therapy.
**Methods:** The subjects involved in the study (195 subjects, divided into three groups: Group I = patients with confirmed FH, Group II = patients negative to the genetic test and Group III = patients with high cardiovascular risk) were evaluated with clinical and laboratory parameters and the lipid profile was analyzed at baseline and 1 month after the introduction of lipid-lowering therapy (with Statins, Ezetimibe and PCSK9i alone or in various combinations). Furthermore, within the population affected by genetically confirmed FH (90 patients), the molecular profile of the various "major candidate genes" implicated in the disease (LDLR, APOB, PCSK9, LDLRAP1, LIPA) was examined and the correlation was analyzed between the different mutations found and the changes in the lipid profile before and after treatment.
**Results:** In the analyzed population (patients with FH + patients with high CV risk), the PCSK9i biotechnological drugs show good efficacy. Patients with confirmed FH appear to be more responsive to Alirocumab than to Evolocumab (54% vs 44% reduction in LDLc), while those at high risk appear to be more responsive to Evolocumab compared to Alirocumab (67% vs 52% reduction in LDLc). The most responsive patients to PCSK9i drug therapy are those carrying mutations on the PCSK9 gene (overall reduction of LDLc, after treatment, by 64%), as expected based on the intrinsic mechanism of the molecule. Patients less responsive to PCSK9i drugs are those carrying mutations on the LDLRAP1 gene (overall LDLc reduction, after treatment, by 30%); in only one case this mutation was present as a single one, whereas in most cases it was associated with other genes' mutations

(double heterozygosity in 12 out of 13 patients with mutation of LDLR). Patients with mutations on the other genes (LDLR, APOB, LIPA), on the whole, are on average responsive to treatment with PCSK9i (LDL reduction of about 40-50%).
**Conclusions:** The efficacy of PCSK9i drugs could be conditioned by the each individual's "genetic pedigree"; therefore, in daily clinical practice, therapeutic choices should also converge towards "tailored therapy" interventions, related to the mean expected response to the different treatments we could choose.

## 297. IMPACT OF SLCO1B1 AND ABCB1 POLYMORPHISMS ON THE RISK OF ADVERSE STATIN REACTIONS

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**Aim** Statins are the gold standard in reducing cardiovascular risk through lowering LDL cholesterols. However, 7 to 29% of statin-treated patients experience myopathy. The SLCO1B1 and ABCB1 gene are responsible for hepatic reabsorption and biliary and renal elimination of statins, respectively. The aim of the study was to evaluate the presence of a correlation between heterozygous rs 4149056 SLCO1B1 or homozygous rs 2032582 ABCB1 mutations and adverse events in patients treated with (rosuva, prava, atorva/simva) statins.
**Methods:** We monitored through clinical and laboratory parameters two statin metabolism's regulatory genes (SLCO1B1,ABCB1) in patients under statin therapy.
**Results:** SLCO1B1 gene: in patients treated with atorvastatin / simvastatin, 7 out of 8 patients experienced adverse events such as to discontinue therapy; in those treated with rosuvastatin, 50% in a group of 10 patients required a change of therapy while for pravastatin, only 1 out of 5 patients experienced side effects.ABCB1 gene: there was a marked intolerance towards atorvastatin / simvastatin (6 out of 6 patients discontinued therapy), while for pravastatin 2 out of 3 patients discontinued therapy and, about rosuvastatin, only 1 out of 6 had to discontinue therapy
**Conclusions:**Despite the small sample size, the SLCO1B1 mutation appears to be strongly associated with an increased probability of adverse reactions from statins in drugs metabolized by cytochrome CYP450 3A4 (simvastatin and atorvastatin). Instead, rosuvastatin minimizes the risk of adverse effects in patients with the ABCB1 polymorphism.Although metabolism of pravastatin is not influenced by cytochromes, a greater number of adverse events have been observed in patients carrying the ABCB1 mutation.The genotyping of the polymorphisms rs 4149056 SLCO1B1 and rs 2032582 ABCB1, could help to improve the therapeutic management of the statins in future increasing the safety of the administration, and allowing to implement more and more a "tailored therapy".

## 298. MARANTIC AORTIC ENDOCARDITIS IN AN ELDERY PATIENT WITH SUSPECTED CARDIAC AMYLOIDOSIS: A RARE ANTE-MORTEM EXCLUSION DIAGNOSIS

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Marantic endocarditis (also known as non-bacterial thrombotic endocarditis, Libman-Sacks endocarditis or verrucous endocarditis) is a rare form of non-infectious endocarditis involving the deposition of sterile platelet thrombi mostly on the aortic and mitral valves, usually in patients with an hypercoagulable state due to advanced malignancies or autoimmune conditions. It is often a post mortem finding, since most patients are asymptomatic until they develop clinical manifestations of systemic embolization.
We describe the case of an 81-year-old caucasian man presenting to the ER with delirium and transient aphasia. Medical history included permanent atrial fibrillation on DOAC treatment, diabetes mellitus type 2, a previous ischaemic stroke and recurrent transient ischaemic attacks of suspected cardio-embolic origin. A recent trans-thoracic echocardiography aroused suspicion of cardiac amyloidosis, not further explored according to patient's will.
CT brain scan was performed showing multiple areas of focal hypodensity consistent with ischaemic cardioembolic lesions. No pathological findings emerged from EEG and carotid-vertebral Doppler ultrasound.
Transthoracic echocardiography revealed little mobile structures attached to the aortic valve leaflets confirmed as endocardial vegetations at the transesophageal echocardiography. Blood coltures were performed, resulting negative, prior to administration of broad-spectrum antibiotics. Additional blood tests for culture-negative microorganisms (Bartonella sp, Coxiella burnetii, Legionella spp, Streptococcus and Mycoplasma pneumoniae and Brucella) also resulted negative. White cells count, C-reactive protein and procalcitonin were normal and no significant peripheral stigmata of infective endocarditis were found. Total body CT scan excluded neoplastic diseases and tumor markers were negative. Therefore an exclusion diagnosis of marantic endocarditis was performed, supposedly connected to the folding protein disorder. Anticoagulation therapy has been modified shifting to VKA. The patient refused further diagnostic investigations to confirm the suspected amyloidosis Marantic endocarditis should always be considered in patients with advanced malignancies or autoimmune conditions who present with embolic phenomena, once the infective etiologies have been ruled out. Trans-esophageal echocardiography is a mandatory diagnostic test, having greater sensitivity and specificity than trans-thoracic echocardiography. Here we present a peculiar case of marantic endocarditis without a clear undelying condition, except for the suspected amyloidosis.

## 299. CHEST PAIN OF CARDIAC ORIGIN: NOT JUST ISCHEMIA! A CASE OF MYOPERICARDITIS IN A YOUNG MAN

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**Case Report:** A 25-year-old Caucasian man was admitted in the emergency room with retrosternal chest pain that recurred 12 hours after the first episode. He described the pain as an oppressive feeling, of moderate intensity, lasting about 30 minutes, without irradiation, unchanged with decubitus and not associated with meals. Neither remarkable diseases nor cardiovascular risk factors were found upon past medical history. He received the second dose of mRNA-1273 SARS-CoV-2 vaccine 3 weeks earlier. On admission the patient appeared in substantial discomfort, apyretic, with normal vital signs except for a mild tachypnea; he didn't complain of cough or dyspnea. On cardiovascular examination we detected pure tones, no heart murmurs or pericardial rubbing, and normosphigmic arterial pulses; likewise lung and abdomen examination resulted regular. EKG revealed sinus rhythm at 90 bpm with PR-segment depression in lead II and concave ST elevation in both precordial (V4-V6) and limb (II) leads, with reciprocal changes in aVR. Nasopharingeal swab for the detection of SARS-CoV-2 using RT-PCR test came back negative. Chest X-ray didn't report any pathological signs. Transthoracic echocardiography showed left ventricle of normal size and wall thickness, regular segmentary and global contractility, functional valves and absence of pericardial effusion. Laboratory studies highlighted: WBC 12800/µL (72.1% neutrophils), Hb 14.0 g/dl, PLT 225.000/µL, D-dimer 314 ng/mL, normal liver and kidney function, CRP 1.37 mg/dl and marked increase of cardiac biomarkers (high-sensitivity cardiac troponin T 924 ng/L – threshold value 14 ng/L, myoglobin 192 ng/ml). Transferred to the cardiology department, the patient underwent coronary CT angiography to exclude coronary stenosis. In the clinical suspicion of myocarditis cardiac MRI was performed, which revealed edema of the middle-apical myocardium along the left ventricle free wall associated with late gadolinium enhancement (LGE), to be referred to post-inflammatory fibrosis, and hyperemia of the contiguous pericardial serosa. The collected evidence – EKG changes, elevation of cardiac biomarkers, radiological signs of myocardial and pericardial inflammation – led us to diagnosis of myopericarditis. At this point an anti-inflammatory therapy based on ibuprofene 600 mg TID and colchicine 1 mg QD was set up, with the addition of pantoprazole 40 mg QD and bisoprolol 1.25 mg QD. During hospitalization the patient experienced early symptomatic recovery, there was also a progressive reduction of cardiac biomarkers and evolution of EKG through the typical pattern described in pericarditis. Our diagnostic work-up continued with the search of etiology of myopericarditis through further investigations: abdomen US didn't notice any abnormalities, autoimmune tests (rheumatoid factor, ACPA, ANCAs, ANAs, ENAs, C3-C4) and tumor markers were negative, serology and molecular biology tests for viral pathogens failed, QuantiFERON®-TB Gold excluded tubercolosis infection. Ruled out most of the recognized causes of myocarditis and pericarditis, we assumed that the disease could be related with COVID-19 mRNA vaccination on the basis of the temporal link between the two events. 10 days after admis-

sion the patient was discharged with a diagnosis of "acute myopericarditis likely due to COVID-19 mRNA vaccination" and with indication to abstain from competitive sport for 3 months and to a cardiological follow-up with an MRI reassesment at 6 months. Concerning about home treatment, we prescribed continuation of ibuprofene for 3 months and prednisone 25 mg QD with tapering schedule.
**Discussion:** Acute chest pain is one of the most common and challenging symptoms for which patients approach to the emergency departments. It can be caused by an extensive variety of disorders ranging from life-threatening syndromes (primarily ACS) to conditions that are relatively harmless. Myopericarditis is a pericarditis with elevation of cardiac biomarkers, as a result of extension of the inflammatory process to myocardium, in absence of left ventricular dysfunction. It shares common etiologic agents with pericarditis, either infectious (mainly cardiotropic viruses) or noninfectious. Compared with simple pericarditis, patients with myocardial involvement have peculiar epidemiological (younger, male predominance) and clinical features (lower recurrence rate, increased risk of LV dysfunction at 1-year). Vaccine-associated myocarditis is a well recognised adverse event of mRNA-based SARS-CoV-2 vaccine, with estimated absolute rate of 1-2 cases per 100.000 individuals. The highest incidence is observed in men aged 16 to 29 years after the second dose of mRNA-1273. Although the onset of symptoms is commonly few days after vaccination, the time limit described in literature to identify an association with vaccine is 30 days. The mechanisms underlying this type of myocarditis are not clear, in the same way specific treatment is still unknown. His clinical course is generally mild but it can sometimes lead to myocardial damage, as illustrated by our case.

## 300. PERICARDITIS AFTER SARS-COV-2 VACCINATION: EXPERIENCE AT PERIODIC RESEARCH FEVER CENTER OF FONDAZIONE POLICLINICO A. GEMELLI

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**Introduction:** Messenger RNA (mRNA) vaccines against Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) are effective and safe. Pericarditis may rarely be associated with vaccination but more frequently may be manifestations of SARS-CoV-2 infection. The only two studies available on the incidence of pericarditis in post-vaccine mRNA for SARS-CoV-2, reveal an incidence between 1.8 and 3 cases per 100,000 vaccinated subjects, mean age of 59 years and higher prevalence for the male sex. Episodes more frequently occurred after the second dose. There are also no unambiguous guidelines on the safety of completing the vaccination course for these patients, so this decision is therefore left to the doctor. In fact, the risk of recurrence of pericarditis after administration of the dose following the one that caused the first event is not known.
**Aim:** Data analysis of Periodic Research Fever Center and Rare Diseases at Policlinico A. Gemelli to describe our experience in the management of Pericarditis after Vaccination for COVID-19.
**Materials and Methods:** We analyzed the confirmed cases of pericarditis afferent in the last year to the Center for Rare Diseases and Periodic Fevers and specifically the cases of pericarditis secondary to SARS-CoV-2 vaccination.
**Results:** In the last year, 41 patients with a confirmed diagnosis of pericarditis were referred to the Center for Rare Diseases and Periodic Fevers: 11 post-vaccination SARS-CoV-2 pericarditis and 3 post-SARS-CoV-2 infection; 23 cases were idiopathic forms and 9/23 in recurrent form; finally 4 patients had other causes (Dressler's syndrome, autoimmune diseases, etc). Among the 11 post-vaccine SARS-CoV-2 pericarditis patients, 6 were female and 4 male, the mean age was 38.6 years. 2/11 patients had a family history of idiopathic pericarditis: the father in one case, in the other the sister. In all cases, pericarditis was diagnosed by the presence of at least 2/4 criteria according to the ESC guidelines. In 9/11 the presence of pericardial effusion was recognized. In 8/11, pericarditis resulted from the second dose of vaccine, in 2/11 it occurred after the first dose. The mean time to onset after vaccine administration was 69 days. All patients were treated with NSAIDs and colchicine. In 7/11 cases there was a good response to medical therapy. In 4/11, however, pericarditis was incessant, probably due to inappropriate tapering of anti-inflammatory therapy and in 1/4 it was even necessary to use the recombinant interleukin-1 receptor antagonist anakinra to resolve symptoms and to avoid a second pericardiocentesis. Regarding the completion of the vaccination course for SARS-CoV-2: none of the patients with post-vaccination SARS-CoV-2 pericarditis completed the vaccination course. 1/3 with post-SARS-COv-2 infection pericarditis completed the vaccination course without complications. Instead, the majority of patients with idiopathic pericarditis completed the vaccination course without recurrence.
**Conclusions:** Post-vaccination SARS-CoV-2 pericarditis is a rare but not uncommon condition. Among thepatients referred in the last year for pericarditis to the Center for Periodic Fevers and Rare Diseases, post-vaccination SARS-CoV-2 pericarditis represented 26.8% of the total. The vaccine acts like the virus as a trigger for pericarditis but, from our experience, post-vaccination SARS-CoV-2 pericarditis has a better prognosis than virus-activated disease. The most frequent phenotype of post-vaccination SARS-CoV-2 pericarditis is characterized by an acute onset of pericarditis a few days after vaccination. However, the sub-acute onset phenotype is not rare, characterized by more or less typical chest pain and mild instrumental alterations that make diagnosis and therefore therapeutic management more difficult. As for the possibility of completing the vaccination course, there are no clear indications and therefore observational studies are needed in this regard. Often the vaccination is not completed due to poor compliance of the patient or the reluctance of the doctor for the risk of relapse. As with idiopathic forms, we believe that even for pericarditis secondary to the vaccine, the administration of a new dose of the vaccine is associated with a low risk of reactivation of the pericarditis.
**References:** 1. Barda N, Dagan N, Ben-Shlomo Y, Kepten E, Waxman J, Ohana R, Hernán MA, Lipsitch M, Kohane I, Netzer D, Reis BY, Balicer RD. Safety of the BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Setting. N Engl J Med. 2021 Sep 16;385(12): 1078-1090. doi: 10.1056/NEJMoa2110475. Epub 2021 Aug 25. PMID: 34432976; PMCID: PMC8427535. - 2. Diaz GA, Parsons GT, Gering SK, Meier AR, Hutchinson IV, Robicsek A. Myocarditis and Pericarditis After Vaccination for COVID-19. JAMA. 2021 Sep 28;326(12): 1210-1212. doi: 10.1001/jama.2021.13443. PMID: 34347001; PMCID: PMC8340007. - 3. Perna F, Verecchia E, Pinnacchio G, Gerardino L, Brucato A, Manna R. Rapid resolution of severe pericardial effusion using anakinra in a patient with COVID-19 vaccine-related acute pericarditis relapse: a case report. Eur Heart J Case Rep. 2022 Mar 18;6(4): ytac123. doi: 10.1093/ehjcr/ytac123. PMID: 35445166; PMCID: PMC8992233.

## 301. INNOMINATE ARTERY STEAL SYNDROME: A CASE REPORT OF INNOMINATE ARTERY OCCLUSION

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A 74-year-old man presented at Emergency Department for a three days history of melena. During the hospitalization at the Department of Internal Medicine and Gastroenterology, he had a non-ST segment elevation myocardial infarction. After optimization of medical treatment, he had been evaluated to elective coronary artery bypass surgery.
In his medical history he reported a coronary and peripheral arterial disease, type 2 diabetes mellitus, hypertension, dyslipidaemia, and an history of twenty years of smoking stopped ten years ago. When questioned on eventual neurological disturbances in his past, he referred a single episode of transient loss of vision ten years ago that not required medical intervention. On physical examination neither alterations of neurological sings nor peripheral pulses were noticed, exception for a weakened right radial pulse. Laboratory examination showed normal value of LDL cholesterol (41 mg/dL) and triglyceride (168 mg/dL).
He was referred to the Angiology Unit of our Hospital for a pre-surgical evaluation of epiaortic vessels.
Doppler ultrasound (DUS) revealed a reversal of blood flow in the right vertebral artery (VA); a mid-systolic deceleration of blood flow (bi-directional) in the right common carotid artery (CCA) and internal carotid artery (ICA); an anterograde blood flow in external carotid artery (ECA). No evidence of plaques determining stenosis or occlusion were found. Contralaterally, an atherosclerotic plaque involving the bulb of internal carotid and occluding 50% of the lumen was found; the spectral analysis didn't show alteration in blood flow direction in CCA, ICA, ECA, VA.
In the suspicion of a steno-occlusive disease involving the innominate artery, a computed tomographic imaging with CT angiography of head and neck was made, that showed an 18 mm long complete occlusion of the vessel. Circle of Willis resulted intact.
A diagnosis of innominate artery steal syndrome was made and the patient was referred to a vascular surgery follow-up.

Innominate artery steal syndrome is a rare clinical entity due to a sever stenosis or occlusion of the brachiocephalic trunk that may cause cerebrovascular symptoms, upper-limb ischemia or stroke.
The brachiocephalic trunk (BT), also referred as brachiocephalic artery or innominate artery, is one of the three great vessels that arises from the aortic arch to supply blood to the head, neck, and upper extremities. Specifically, it is a short vessel, only about 4 to 5 centimetres in length, that bifurcates into the right carotid artery, that goes on upper to the head and neck (cephalic branch), and into the right subclavian artery, that goes down to the arm (brachium branch).
One of the most significant clinical entities involving the BT is the steno-occlusive disease, mostly due to atherosclerotic lesions. This condition leads to the establishment of a compensatory perfusion pattern through the reversal of blood flow in ipsilateral vertebral and carotid arteries. These hemodynamic changes imply that the blood is stolen from vertebrobasilar branches two times: one time by the right subclavian artery to supply circulation of the arm, and then the flow restored in subclavian artery is stolen again from the right carotid artery to support circulation of the brain.
This condition is known in literature since 1965 with the name of both innominate steal phenomenon and double subclavian-carotid steal syndrome. The name reminds to the subclavian steal syndrome, described in the early years of 1960, in which the retrograde vertebrobasilar blood flow is due to steno-occlusive prevertebral lesion of subclavian artery.
Despite similarities, steno-occlusive disease involving the BT is a more rare and severe condition. It is essential to recognize this type of lesion because the double steal phenomenon puts patients at risk of developing neurological symptoms of both vertebrobasilar and hemispheric district, as well as upper limb ischemia.

## 302. RITIRATO

## 303. PROGNOSTIC ROLE OF TRANSTHORACIC ECHOCARDIOGRAPHY FOR THE PREDICTION OF INTRAHOSPITAL DEATH IN PATIENTS WITH PULMONARY EMBOLISM. A MONOCENTRIC RETROSPECTIVE STUDY

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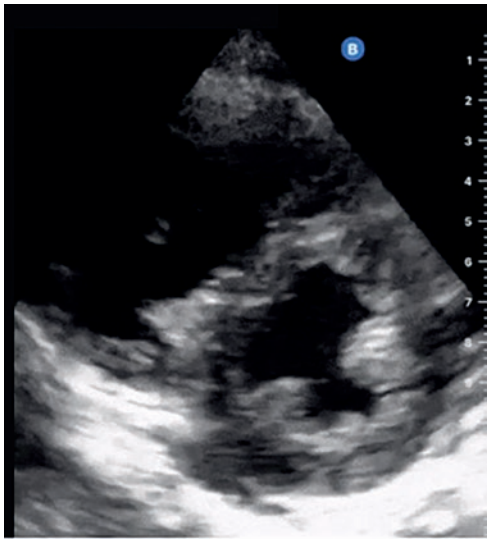
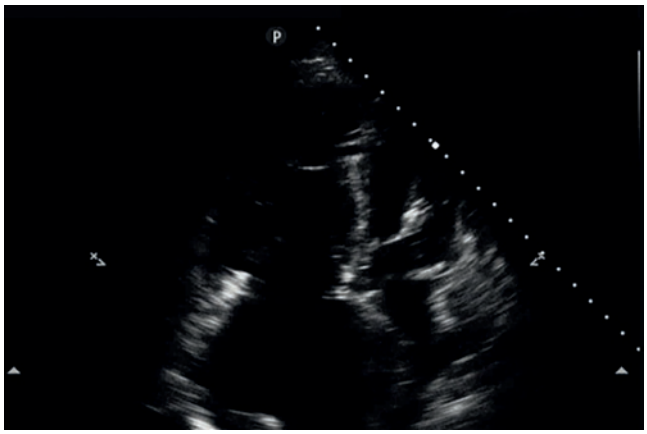
**Introduction:** Pulmonary embolism (PE) is the third leading cause of cardiovascular death after myocardial infarction and stroke; it is defined as the embolization of thrombotic material in the pulmonary arterial circulation. The latest ESC guidelines about PE recommend evaluation of right ventricular overload (RVx) signs by transthoracic echocardiography (ETT) for short-term prognostic stratification. The aim of the study is to evaluate which of the signs of right ventricular dysfunction is the most predictor of in-hospital mortality.
**Materials and Methods:** Monocentric retrospective study conducted at the Sant'Anna Hospital in Ferrara, which enrolled adult patients admitted to the Emergency Department (ED) between 1/1/2018 and 5/31/2021 with a final diagnosis of PE and underwent a TTE in the ED or during the subsequent hospital admission. performed. Past medical records, vital signs, laboratory and instrumental data were recorded and the ESC risk class was calculated (presence of hemodynamic instability, right ventricle (RV) dysfunction at ETT, Troponin increase and PESI class).
**Results:** 227 patients aged 21 to 95 years (mean age 71 years) were included, 10% of whom died in hospital. The ETT was performed on average 2.28 (SD 3) days from entering the PS. The reduction in TAPSE (OR 1.10; p = 0.031), Vdx / Vsn ratio> 1 (OR 4.19; p = 0.049), size and collapse of the vena cava in mm (respectively OR 1, 22; p = 0.023 and OR 1.22; p = 0.014), troponin positivity (OR 5.46; p = 0.013) and ESC risk class (OR 8.23; p <0.001). The finding of D-Shape (OR 3.30; p = 0.1), left ventricle VSx ejection fraction (LVEF) reduction (OR 0.95; p = 0.12) and increased estimated systolic pulmonary arterial pressure (eSPAP) (OR 1.02; p = 0.372) were not predictors of in-hospital mortality. In multivariate analysis, none of the echocardiographic elements proved to be an independent predictor of mortality, unlike troponin.
**Discussion:** Acute RV dysfunction plays a role in predicting mortality, however, only increased troponin values have been shown to be an independent predictor. Troponin is a more sensitive marker of early RV dysfunction than ultrasonography. Furthermore, the dubious prognostic ability of the RV dysfunction may be secondary to the timing of execution of the TTE and the role of the dysfunction preceding the onset of PE, which is not known.
**Conclusions:** In conclusion, while echocardiography is useful in the early identification of patients with severe hemodynamic impact from PE, troponin remains the main marker of cardiac damage of fundamental prognostic value. It may be useful, in the future, to explore the sensitivity of TTE performed at admission on ED.




## 304. RITIRATO

## 305. THE ORAL MICROBIOME: A NEW PERSPECTIVE FOR CARDIOVASCULAR RISK PREDICTION

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**Background:** Dysbiosis of gut and oral microbiota contributes to individual susceptibility to atherosclerotic cardiovascular disease (ASCVD) through low-grade chronic inflammation. Particularly high oral Porphyromonas gingivalis (Pg) and lower Fusobacterium nucleatum (Fn) concentrations have been associated with clinical and experimental atherosclerosis. We assessed oral Pg and Fn abundance in very high-risk patients with previous ASCVD, with or without heterozygous familial hypercholesterolemia (HeFH), and in healthy control subjects.
**Methods:** In this cross-sectional study, we quantified oral Pg and Fn abundance by qPCR and assess oral health status in three group of patients: 40

patients with previous ASCVD (10 with genetically proven HeFH and 30 without FH), 26 subjects with HeFH in primary prevention and 31 healthy controls.
**Results:** Patients with previous ASCVD showed higher Pg (1101.3 vs 192.4, p=0.03), but similar Fn abundance, compared to controls. Even higher concentrations of Pg has been shown in HeFH patients with ASCVD than non-HeFH patients and controls (1770.6 vs 758.4 vs 192.4, respectively; p=0.048). No differences were found in Pg and Fn abundance in HeFH subjects in primary prevention, compared to controls. In all patients examinated, BMI was correlated positively with Pg abundance and negatively with Fn abundance.
**Conclusions:** Very high-risk patients with previous ASCVD, with or without FH, are characterized by higher oral Pg abundance. These data suggest a potential relationship between Pg concentration and CV events. Future studies will assess the predictive value of Pg abundance measurement in ASCVD risk stratification.

### 306. NEUTROPHILS IN IDIOPATHIC PERICARDITIS: IMPLICATIONS AND CORRELATIONS WITH ACUTE DISEASE AND RISK OF RECURRENCES

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**Background:**Elevation of white blood cell (WBC) count is common in acute pericarditis, but it is not known whether this elevation is sustained by an increase in lymphocyte or neutrophil count.
Aim of our study was to evaluate absolute numbers and percentages of neutrophils and lymphocytes, then calculate the neutrophil-to-lymphocite ratio (the so called NLR), obtained by dividing the number of absolute neutrophils by the number of absolute lymphocytes, during acute attack of idiopathic pericarditis.
**Setting:** Observational study.
**Methods:** 63 patients affected by idiopathic recurrent pericarditis were observed over a 12 months period (30 females, mean age 42 years). We measured relative and absolute values of neutrophils and lymphocytes during the first attack of acute idiopathic pericarditis (referred as the "index attack") and the neutrophil to lymphocyte ratio (NLR).
**Results:** Relative and absolute values of neutrophils and NLR positively correlated with C-reactive protein elevation (p = 0.01 for relative neutrophil count, p = 0.04 for absolute neutrophil count, p = 0.008 for NLR), moderate or severe pericardial effusion (p = 0.16 for relative values, p = 0.36 for absolute values, p= 0.25 for NLR), pleural effusion (p = 0.04 for relative neutrophil count, p = 0.27 for absolute neutrophil count, p = 0.06 for NRL), and recurrences during the follow up (p = 0.007 for relative neutrophil count, p = 0.571 for absolute neutrophil count, p = 0.004 for NLR), while lymphocytes values had in general a negative correlation. Troponin elevation (9 patients) was not associated with increased absolute or relative neutrophil counts.
**Conclusions:** Acute attacks of pericarditis are associated with neutrophil count elevation; this is in agreement with a pathogenetic role of IL-1, leading to a chemotactic recruitment of neutrophils, generating neutrophilia. Neutrophil and lymphocyte count and NLR may be considered relevant biomarkers during acute attack of idiopathic pericarditis.
Keywords: acute idiopathic pericarditis; recurrent pericarditis; inflammasome; IL-1; pericardial effusion; neutrophil-to-lymphocite ratio.

### 307. SAFETY OF INTRAVENOUS THROMBOLYSIS IN PATIENTS WITH ACUTE ISCHEMIC STROKE AND INCIDENTAL INTRACRANIAL ANEURYSMS: A RETROSPECTIVE STUDY

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**Aim:** Unruptured intracranial aneurysms (UIAs) represent a relative contraindication for intravenous thrombolysis (IVT) in acute ischemic stroke (AIS). However, presently few data on the risk of UIA rupture secondary to IVT are reported. Our retrospective study aimed to assess whether IVT for AIS is associated with UIA rupture and intracranial hemorrhages (ICHs) in patients with unruptured UIAs.
**Methods:** We conducted a retrospective, single-center, observational study and included patients admitted to the Perugia Stroke Unit from January 2019 to December 2021. Patient inclusion criteria were an AIS, regardless of its location and treatment with IVT. The group of cases consisted of patients with UIAs at the time of the AIS, while the controls had no UIAs.
**Results:** A total of 238 patients were collected. The median age was 76 yy (IQR 17), and 102 patients (42,9%) were females. 133/223 patients received IVT alone: 119/133 did not have any UIA, while 14/133 had a concomitant UIA. Among patients treated with IVT, 52/192 patients with no history of UIAs experienced ICHs, while 1/19 patients with UIAs experienced any ICH (OR 0.15, CI 95% 0.02-1.15, p=0.070). No significant differences in patient comorbidities were observed between the two groups. Admission NIHSS was lower in patients with UIA than in patients with no UIA (9.70±0.94 vs. 12.79±0.43, p=0.016).
**Conclusion:** One patient with UIAs experienced ICH after IVT, which appears to be safe in patients with AIS and concomitant UIAs, including the larger ones (≥10 mm).

## MALATTIE INFETTIVE

### 308. AMEBIASIS: CASE REPORT

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**Introduction:** The Authors presented the case report of a 41-year-old patient, of Bengali nationality, living in Italy for years, who came to our observation for serotin fever for about 10 days resistant to antibiotic therapy. The anamnestic collection shows chronic inflammatory bowel disease, asthmatic bronchitis, smoking habit, chronic pancreatitis. The last trip to Bangladesh dates back to 18 months earlier, when he took water directly from the local water supply at his family's home as planned in Bangladesh.
**Case Report:** During the hospital stay the patient is subjected to the following tests: 1) CT Skull with contrast medium: does not show areas with enhancement of pathological significance; 2) Chest CT scan with contrast medium: shows atelectatic phenomena in the middle lobe with mediastinal lymphadenopathy (max 12 mm diameter); 3) CT scan of the abdomen with contrast medium: in the right hepatic lobe there is a voluminous polylobed formation (11x9.3x7 cm) with fluid content and thin walls that show impregnation after contrast medium, as in an abscess focus; 4) MRI of the facial mass with contrast medium showing the presence of solid tissue of 23x23x13 mm that occupies part of the posterior portion of the middle and upper right nasal choana up to the posterior homolateral ethmoidal cells, adhering to the nasal septum and the middle horn; after contrast medium, marked and homogeneous enhancement of the tissue occurs; 5) Echo-guided abdominal drainage: under ultrasound guidance and fluoroscopy, a drainage of 16 Fr is placed inside the liver abscess, 250 cc of purulent-corpuscular, chocolate-colored material are aspirated; 4 days later, the drainage of the liver abscess is checked and by administering water-soluble contrast medium, the collection is cleared and percutaneous drainage is removed; 6) EGDS: absence of lesions and biopsies show signs of chronic inflammation; 7) ILEOCOLONSCOPY: The ileum, covered for 20 cm, shows small erosions and biopsies do not show active phenomena; fibrin-bottom erosions are present in the cecum and biopsies show chronic lymphoplasmacellular infiltrate; in the colorectal absence of findings; the histological examination of mucosal fragments of the large intestine shows acute and chronic inflammation of the lamina propria with a finding of granulation tissue in the context of which microorganisms compatible with Ameba Histolytica are found; 8) FIBROBRONCOSCOPY: viscous and stringy secretions are present in the middle lobe and negative bronchial washing is performed for neoplastic cells; 9) Seriated ECGs: show sinus rhythm 10) Blood tests: SGOT, SGPT, ALP, GB and PCR values show regression trends at discharge; lymphocyte typing is within limits; Negative HIV test; ANA, ENA, native antiDNA within limits; urine sterile culture; EGA within the limits; search for negative neoplastic markers; HAV, HBV, HCV negative; electrophoretic protidogram shows hypoalbuminemia (35.9%, NV 55.8-66.1%), hyperalpha 1 (10.7%, NV 2.9-4.9%), hyperalpha 2 (17.5%, N 7, 1-11.8), hyperbetes 2

(7.8%, VN 3.2-6.5%), hypergamma (21.7%, VN 11.1-18.8); Direct negative BK; negative parasitological examination of stool; Entamoeba Histolytica IgG present evaluated by ELISA method. Therapy is started with intravenous metronidazole at a dose of 750 mg every 8 hours for 10 days and subsequently with oral paromomycin at a dose of 200 mg every 8 hours for 7 days.
**Discussion:** The pathogenic action exerted by E. histolytica is a consequence of three basic properties of trophozoites: adhesiveness to tissues, cytolytic and proteolytic powers of the parasite, ability to evade the body's immune defenses. The trophozoites overcome the mucus layer that covers the intestinal wall, adhere to the epithelium and mucin through a lectin (adhesin). Contact with the extracellular matrix induces in the trophozoites, through structures called "amebapores", the release of proteolytic enzymes capable of degrading collagen, laminin, matrix macromolecules and local secretory IgA. Cytotoxicity is mediated by phospholipases, hemolysins and the parasite microfilaments. The parasites penetrate between the separated epithelial cells, erode the lamina propria and spread (amoeboid movements) in a lateral direction causing extensive necrotic events (flask ulcers). The bottom of the ulcer is covered with necrotic residues, the margins are undermined. Amoebas can "metastasize" (via blood or contiguity) to other organs and cause extra-intestinal amoebiasis (hepatic, pulmonary, cerebral). The liver abscess is present in> 50% of cases without prodromes or positive history for intestinal form (as in our patient's case) with septic-type fever, right hypochondrium pain, hepatomegaly, neutrophilic leukocytosis. Tissue amoebicides such as metronidazole, other nitroimidazoles (tinidazole), dihydroemetine hydrochloride in severe forms and contact amoebicides such as paromomycin, diloxanide furoate, iodoquinolone are used for therapy.
**Conclusions:** The authors presented the case report of a 41-year-old Bengali patient with entamoeba histolytica liver abscess.

## 309. GIANT SOLITARY HYDATID CYST OF SPLEEN: CASE REPORT.

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**Introduction:** Hydatid disease (Echinococcosis) is a zoonotic infection caused by the larval form of parasites of tapeworm, Echinococcus granulosus. Humans are the accidental intermediate host in the development cycle of hydatid disease. It is an endemic disease in the sheep and cattle raising countries Middle East, North Africa, New Zealand, Australia, and South America.
**Case Presentation:** A 63 years male patient farmer by occupation presented to our internal and emergency ward with a mass in the left upper quadrant of the abdomen. There was left hypochondriac dull aching pain which did not shift or radiate. Patient complained of malaise with nausea, vomiting and weight loss since one year. Also there was intermittent fever every fifteen days since last six months. Physical examination showed an asymmetric abdomen and a growing lump with smooth surface in left hypochondriac, epigastric and umbilical region. There was no lymphadenopathy. Routine laboratory investigation CBC, coagulation profile, biochemistry, renal function test, liver function test and electrolytes revealed no abnormalities. Plain radiograph of the abdomen revealed a well-defined, rounded soft-tissue opacity with calcified margins in the left hypochondrium. Chest radiograph was normal. Abdominal ultrasonography showed round, well defined, cystic lesion of size 165 × 140 mm over pancreas which moving left kidney and spleen. Abdominal CT scan shows large homogenous cystic lesion in spleen measuring 20 × 22 cm loculated cyst with many septa, originating from the spleen. The cyst in the spleen appeared to fill the left quadrant of the abdominal cavity, displacing the intestines to the right, most likely suggestive of hydatid cyst. There were no cysts in other abdominal viscera. A CT scan of his chest did not show any cysts. Surgical exploration revealed a hydatid cyst occupying whole splenic parenchyma only thin rim of splenic tissue was present in inferior surface. The mass measuring approximately 250 × 200 mm was attached to left diaphragm. The cyst was resected en-bloc with the spleen. Histopathological examination showed the classic laminated cyst wall encircling many scolices with a double layer of hooklets; which is consistent with Echinococcus granulosus infection thus confirmed the diagnosis of splenic hydatid cyst. On cut section there was hydatid sand and fluid around 3.9 litres.
**Discussion:** Hydatid disease is a major health problem worldwide, mainly in sheep- and cattle-raising areas of the world. Hydatid disease of spleen is a rare clinical condition as even in the endemic region the frequency is reported to be 0.5–4% of abdominal hydatid diseases. The most common sites of hydatid disease are the liver (60–70%), which acts as a first filter and the lungs (10–40%), which acts as second filter. Primary infestation of spleen through the arterial route. Splenic hydatid disease may also arise with retrograde spread of parasites via the portal and splenic veins bypassing the lung and liver. The hydatid cyst consists of three layers. The presentation of splenic hydatid disease can vary greatly. Splenic hydatid cysts are usually asymptomatic, solitary slowgrowing and incidentally diagnosed. Severe anaphylactic reactions due to rupture of the cyst are also reported leading to fever, pruritus, dyspnoea, stridor and oedema of the face. Pre-operative diagnosis may be difficult due to the similarity of the presenting symptoms and the radiological findings to those of other more commonly encountered lesions of the spleen. The Casoni skin test is sensitive but not specific. Radiological diagnosis by plain X-Ray, Ultrasonography (USG), CT and MRI can also be used to diagnose hydatidosis. Serological tests are highly sensitive and specific for Echinococcosis. The standard treatment is splenectomy as complete resection removes all parasitic and pericystic tissues. Antihelminthic drug therapy using Benzimidazole chemotherapy drugs with Albendazole 10–15 mg/kg/day for one month or Mebendazole 40–50 m/kg/day for 3–6 months, in addition to Praziquantel 40 mg/kg/wk for 2 weeks pre and postoperative to reduce the chance of anaphylactic shock and decrease the tension in the cyst wall are used. We performed total splenectomy.
**Conclusion:** The splenic hydatid cyst may become a challenging surgical problem. Computerised tomography scan is the most sensitive investigation for diagnosis. The anatomical relations of splenic hydatid cyst should be demonstrated before surgery on account of varied presentations. Although the management must be individualized for each patient, a surgical resection is the best curative procedure.

## 310. NEUROCYSTICERCOSIS: CASE REPORT

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**Introduction:** It starts with intestinal infection, often asymptomatic, due to the adult form of taenia solium cestode. The cerebral localization in the larval level may cause neurocisticercosis with appearance of convulsions.
**Case Report:** We describe a case history of a 34-year-old woman with habitual syncope-like episodes in the last 6 months lasting a few minutes. She was compelled to go to the emergency ward for the frequency of the very last episodes. Thanks to the anamnestic examination, we found out that the woman, coming from Madagascar, has been living in Italy since 8 months in order to find a job. Since she lives in Italy, she suffers from habitual syncope-like episodes. The body temperature is 36,6C, the arterial pressure 110/70mmHg, the cardiac frequency 74/m RS. The patient is conscious, without any focal deficits or signs of meningism. Laboratory tests: hemochrome reveals microcytemia, normal electrolytes. All the hepatic, pancreatic and renal fuctions are normal. Muscle and myocardial enzymes are all negative. The arterial emogas analysis is within the limits. Coagulation, electrophoretic protidogram, urine analysis with urine culture are all within the limits. Search for neoplastic markers is within the limits. Parasitological test is always negative. Search for markers of hepatitis, TORCH complex, HIV, treponema is negative. Rachicentesis is carried out, which shows clear liquor. The bacterial culture test is negative. ECG: within the limits. Chest x-rays 2p: there are no pleuroparenchymal alterations. Abdominal ultrasound: there are no alterations in endo-abdominal organs. Muscular ultrasound and subcutaneous flat tissues: there are no cystic lumps. Electroencephalogram: it reveals graphic bi-hemispheric irritating anomalies. Cranial CT without mdc: it displays some bi-hemispherical cyst formation, with prefrontal oedema in the right side. Encephalon RM: sequences have been carried out on three orthogonal levels with SE, FSE, DWI, GR and FLAIR technique taken on T2 and T1. These last ones before and after giving paramagnetic mdc ev. We notice small nodular areas in ubiquitous distribution, particularly with variable dimensions from point form to about 10 mm. The greatest one is located in the frontal right subcortical region and seems to be surrounded by vasogenic oedema. Some of these have on the inside a small eccentric formation with high signal intensity in all the sequences. We notice that after mdc there is a strengthening of cercine in most of them. Whereas others have homogenic strengthening. One of these lesions seems

to have a meningeal form. Intra-cranial ANGIO RM: TOF 3D sequence is performed with VR reconstruction. Good representation of Willis polygon and main ramifications. No aneurysmatic formation. Consequently, antiparasitarial treatment is used for neuro cysticercosis with Albendazole 15mg/kg/die (es. 800mg) PO to be taken with meals for 1 month in cycle. Antiepileptic drug has to be taken with Levetiracetam 500mg, 1 tablet cpx2/die in the first week, and then gradually increasing the dosage. Moreover it must be taken Prednisone 60mg/die over 1 month in order to reduce oedema caused by the bigger lesions, to associate with H2 PO antagonists.
**Discussions:** It is noticeable that the syncope-like episodes reported by the woman are equivalent to epilepsy as you can see from the electroencephalogram, TC and encephalon RMN images for neuro cysticercosis. Once the patient began the antiepileptic treatment, she did not suffer anymore from critical episodes. In order to prevent any frequent convulsive crisis, it is necessary to take antiepileptic treatment, to suspend in case of radiological resolution of the lesions.
**Conclusions:** We analysed the case report of a 34-year-old woman suffering from habitual syncope-like episodes, which come from epilepsy.

## 311. BOTULISM: COOKING AND CLINICAL RECOGNITION ALONE DO CHANGE LIVES

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**Introduction:** Botulism is a rare but potentially fatal neuroparalytic syndrome resulting from the action of a neurotoxin elaborated by a gram-positive, rod-shaped, spore-forming, obligate anaerobic bacteria: Clostridium botulinum. We here present a classical case of foodborne botulism promptly recognized and treated avoiding, in such manner, life-threatening neurological and respiratory outcomes.
**Case Presentation:** A 49-year-old man was admitted at our Emergency Department (ED) for dysphagia, diplopia, and postural instability. He reported assumption three days before, of a rotten pre-packaged soup followed by the onset of gastrointestinal symptoms characterized by nausea and vomiting.
At clinical examination he was alert, oriented, with pupils poorly responsive, convergent strabismus was present with diplopia, dysphagia for liquids, mild hypoxemia (SO2 90%), and postural instability. ECG and blood tests were normal except for an increase in transaminases (AST 114U/L, AST 98U/L). In the hypothesis of an ischemic insult a cerebral angiography was carried out, excluding brain abnormalities and hemorrhages. In the clinical suspicion of foodborne botulism, the antitoxin was administered after collecting serological and microbiological samples.
He was therefore admitted to our Sub-Intensive Emergency Medicine ward to continue multiparametric monitoring, given the further worsening of dysphagia and limitation in eye movements, mainly in bilateral abduction with diplopia.
The result of the serological tests confirmed botulism, for which the official notification was made to the Higher Institute of Health.
During hospitalization rehydration therapy and oxygen at low doses were given with benefit. Blood tests resulted always normal and progressive clinical improvement was observed with a reduction in the dysphagia, ophthalmoplegia, balance in walking, and maintenance of good oxyhemoglobin saturation values in ambient air, allowing a subsequent relocation in the Neurology department.
**Discussion and Conclusion:** Clostridium botulinum is ubiquitous and easily isolated from the surfaces of vegetables, fruits, and seafood, and exist in soil and marine sediment worldwide. Several forms of botulism exist with foodborne botulism representing 25% of all cases. It is caused by ingestion of food contaminated with preformed botulinum toxin; the toxin is resistant to degradation by gastric acidity, though Clostridium botulinum spores can be destroyed by heating. Botulinum neurotoxin can target multiple tissues including motor and sensory neurons and can block the cholinergic neuromuscular innervation of striated and smooth muscles as well as the cholinergic innervation of the tear, salivary, and sweat glands. The onset and evolution of symptoms in foodborne botulism are highly variable. Symptoms usually begin within 12 to 36 hours after ingestion of the preformed toxin with prodromal gastrointestinal symptoms (i.e. nausea, vomiting, abdominal pain and diarrhea) prior to the development of the classical acute onset of bilateral cranial neuropathies (diplopia, nystagmus, ptosis, dysphagia, dysarthria, and facial weakness) associated with symmetric descending weakness.
Other key features include absence of fever, maintenance of alertness, and lack of sensory deficits other than blurred vision.
A careful history and physical examination are essential to the diagnosis of botulism, which can be made based on the clinical findings alone. The diagnosis of botulism is confirmed by identification of toxin and/or isolation of Clostridium botulinum in serum, stool, vomitus, or food sources with detection requiring from 1 to 4 days. Hence, the decision to administer antitoxin should be based on the presumptive clinical diagnosis of botulism and not be delayed while awiating results of confirmatory diagnostic studies in order to avoid secondary paralysis responsible for respiratory failure (primary cause of death). Antitoxin acts by binding to circulating neurotoxins preventing paralysis avoiding interactions with the neuromuscolar junction. Prompt recognition is thus mandatory since antitoxin cannot reverse paralysis, once established.
Our case wants to reinforce on one hand, how proper food handling and management (boiling foods for at least 10 minutes before consumption will render food safe) can be sufficient and effective, and on the other, how the antitoxin administration early in the course of disease, is critical and life saving.

## 312. A PARTIQULAR CASE OF FUO

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**Introduction:** Q fever is a zoonosis caused by Coxiella burnetii, an obligate gram-negative intracellular bacterium. The C. burnetii infects various hosts, including humans, ruminants, pets, birds, ticks. The infection can be acquired by inhalation of aerosolized bacteria or skin contact, while the direct exposure to a ruminant is not needed for the infection. In humans, acute C. burnetii infection is often asymptomatic or mistaken for a flu-like illness or atypical pneumonia. In rare cases, C. burnetii can involve cardiovascular system, musculoskeletal system, lymphonodes.
**Case Presentation:** A 55-year-old woman came to our attention for fever with shivering for about a week (T max 39.8°C), poorly responsive to paracetamol, and with mild headache. The patient had history of recurrent febrile episodes in the last two months, she was not responsive to multiple lines of antibiotic therapies performed at home. The patient also reported a recent onset of a dry cough. Her past medical history (April 2021) included aortic valve and ascending aorta replacement with a mechanical valved conduit for aortic bicuspidia. The patient was also affected by rheumatoid arthritis in previous therapy with Upadacitinib currently interrupted for fever episodes. She also reported a recent trip to Zanzibar and denied insect bites, weight loss, diarrhea, itchiness and contact with animals. On admission, the patient was alert and oriented, vital signs were normal. On physical examination, spleen was palpable two fingers below the costal margin, and a 4/6 systolic murmur was hearable at the aortic focus, while the remaining systemic examination was normal. Laboratory data showed a chronic inflammation anemia, a normal WBC count, ESR 60 mm/h (normal< 38 mm/h), CRP 8.4 mg/dl (normal< 0.6 mg/dl), PCT 0.65 ng/ml (normal<0.05 ng/ml), IL-10 11.2 pg/ml (normal<9.10 pg/ml), polyclonal hypergammaglobulinemia, with normal hepato-renal function. A chest X-ray showed only a moderate increase of the broncho-interstitial texture, and a nasopharyngeal swab for Sars-Cov2 and urine culture resulted negative. Due to a recent trip to Zanzibar, we ruled out the suspicion of malaria by blood smear examination. In the following days, the patient had fever (T max 39°C), for which, in the suspicion of endocarditis, blood cultures and a transesophageal echocardiography resulted negative for bacterial proliferation. Empiric therapy with multiple antibiotic lines (piperacillin-tazobactam, teicoplanin, vancomycin, rifampicin and gentamicin, meropenem) was sequentially started without any clinical improvement. The chest-abdomen CT scan did not show any infectious foci or neoplastic mass-nodules. So we explained the mild metabolic activity visualized by PET-CT cardiac tissue scans as a reaction to the recent cardiac surgery. In the suspicion of infectious diseases characterized by negative culture tests, we performed serology tests for C. burnetii, Bartonella, Brucella and Leishmania, finding both positive anti-C. burnetii

IgM (phase I 1: 256, phase II 1: 64) and IgG (phase I and phase II 1: 128) antibodies, suggesting active infection in progress. Therefore, doxycycline 100 mg/die was administered to the patient with rapid clinical improvement and gradual normalization of inflammation indices. The therapy was maintained for two weeks, and the patient remained stably apyretic after its suspension.

**Discussion and Conclusion:** Due to the high risk of endocarditic localization of C. burnetii in a patient with aortic valve prosthesis, we have investigated all the possible diagnostic criteria of Q fever endocarditis (pic.1). The diagnosis of Q fever endocarditis is not immediate, since C. burnetii does not grow on the routine laboratory blood culture, its vegetations are very small on echocardiography, PCR exam is not available in any hospital departments, a biopsy sampling is not always indicated. Furthermore, 18F-FDG PET/CT imaging may be helpful in diagnosing of endocarditis, but the cardiac imaging must be interpreted in the clinical context. For these reasons, diagnosis in common clinical practice is based on serology. In this case, due to the low antibody titers, the absence of patent endocarditic vegetations and the low metabolic activity at cardiac PET imaging in patients with valve prosthesis (considered as a reactive inflammatory response to the recent cardiac surgery), the diagnostic criteria of Coxiella endocarditis were not fulfilled, so we opted for a "simple" diagnosis of Q fever, treated with doxycycline for two weeks. It is unclear where the case patient was infected, but with a depth anamnesis the patient has recalled that a few months earlier she had been in the countryside and she had touched a little sheep. Fever of unknown origin, combined with negative blood cultures and unexplained splenomegaly should suggest Q fever in the differential diagnosis flowchart, also in absence of clear exposure to risk factors.

**A. Definite criterion**
Positive culture, PCR, or immunochemistry of a cardiac valve.
**B. Major criteria**
Microbiology: positive culture or PCR of the blood or an emboli or serology with IgGI antibodies ≥6400
Evidence of endocardial involvement:
Echocardiogram positive for IE: oscillating intra-cardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation; or abscess; or new partial dehiscence of prosthetic valve; or new valvular regurgitation (worsening or changing of pre-existing murmur not sufficient).
Pet-scan showing a specific valve fixation and mycotic aneurism.
**C. Minor criteria**
Predisposing heart condition (know or found on echography)
Fever, temperature > 38 °C
Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm (see at Pet-scan), intracranial hemorrhage, conjunctival hemorrhages, and Janeway's lesions.
Immunologic phenomena: glomerulonephritis, Osler's nodes, Roths spots, or rheumatoid factor.
Serological evidence: IgGI antibodies ≥800 <6400
*Diagnosis definite*
1) 1A criterion
2) 2B criteria
3) 1B criterion, and 3C criteria (including 1 microbiology evidence, and cardiac predisposition)
*Diagnosis possible*
1) 1B criterion, 2C criteria (including 1 microbiology evidence, and cardiac predisposition)
2) 3C criteria (including positive serology, and cardiac predisposition)

## 313. A CASE OF VARICELLA ZOSTER VIRUS ENCEPHALITIS

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A 89-year-old man came to the attention of our Emergency Department (ED) with worsening of general conditions for five days, alternation between clarity and mental confusion, and a brief loss of consciousness, without convulsive seizures. He had been found on the ground two times. Three days earlier he had been diagnosed with herpes zoster with impetiginization in the right half of his face, including the eye, without signs of keratitis. He had no fever or other organ symptoms.
His pathological history included arterial hypertension, dyslipidemia and previous colorectal cancer.
His current home therapy included enalapril and atorvastatin; besides, he had been taking valaciclovir and amoxicillin clavulanate for three days.
In the ED, he was alert, with floating orientation and no motor or sensory deficits. Vital signs were normal. His mucous membranes were dehydrated. Arterial blood gas test showed ph 7,38, pCO2 34, pO2 77,5, lactate 1,1, Na 132. Blood exam revealed WBC 10.200, high PCR, creatinine and CPK. SARS-CoV-2 nasopharyngeal swab was negative. CUS, chest and cardiac ultrasound were normal. Head CT scan and chest radiograph didn't reveal any abnormalities. Electroencephalogram showed diffuse slowing with no epileptiform potentials. We performed lumbar puncture, which demonstrated clear liquid leaking. Meanwhile, in the suspicion of herpes zoster encephalitis, we started empirical therapy with intravenous acyclovir (by dose adjustment for kidney disease) and ceftriaxone, aside from administering intravenous hydration. Cerebrospinal fluid (CSF) analysis revealed elevated proteins, presence of lactate and white blood cells (with a prevalence of lymphocytes). CSF microscopic examination for common germs was negative. CSF virus testing detected the presence of Varicella Zoster Virus. We therefore diagnosed Varicella Zoster Virus encephalitis.
The patient was first admitted to the Infectious Disease Unit and then transferred to an Internal Medicine Unit, where he continued antiviral and antibiotic intravenous therapy.
At the time of hospital discharge, he was fairly oriented.
In adults, Varicella Zoster Virus infection most commonly presents as shingles. One of the potential complications of this infection is involvement of the central nervous system causing encephalitis. Risk factors for this complication are immunosuppression and extreme age. It is associated with increased risk of mortality and morbidity. VZV encephalitis is treated with intravenous acyclovir.

## 314. A NEGLECTED DISEASE: HYPERINFECTION SYNDROME DUE TO STRONGYLOIDES STERCORALIS

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**Introduction:** Strongyloides is a parasite endemic in tropics and subtropics. In its life cycle, it travels from skin to lungs and then to gastrointestinal tract of the host. Strongyloidiasis may present with cutaneous, pulmonary or gastrointestinal symptoms but it is often asymptomatic, presenting only with hypereosinophilia. Immunosuppressed patients are at high risk of developing hyperinfection syndrome (HS), a life-threatening complication characterized by systemic sepsis and multiorgan failure sustained by Strongyloides larval proliferation.
**Case Report:** A 37-year-old Nigerian man was admitted to our ward because of chronic watery diarrhea, weight loss and anasarca. He denied fever.
His past medical history was mute. He has been living in Italy for four years with no travels to Africa since then. He currently lived with his family in a community for refugees in Milano.
At the emergency department blood tests showed high inflammatory markers (CRP 23 mg/dL, leucocytes 20000/uL, procalcitonin 74 ug/L) so that in the suspicion of sepsis sustained by gastrointestinal infection, empiric antibiotic therapy with piperacillin/tazobactam was started.
In our ward, the patient appeared severely malnourished and he referred anorexia in the months before. Blood tests showed albumin 0.8 g/dL, pseudocholinesterase 500 UI/L and normocytic anemia (hemoglobin 6.5 g/dL). Nephrotic syndrome was excluded by a normal 24-hour proteinuria.
To investigate the infectious picture, urine and blood cultures were performed, the latter being positive for Methicillin-sensitive Staphylococcus Aureus, thus antibiotic therapy was simplified by switching to oxacillin. Serology for Entamoeba histolytica and Schistosoma were negative. Stool cultures resulted positive for Salmonella of group C1 but finally fecal search for parasites identified Strongyloides stercoralis rhabditoid larvae. This parasite was also detected in histological examination of duodenal biopsy taken during the upper endoscopy performed to rule out intestinal malabsorption disease, as Celiac disorder (which was excluded also by serologic tests). Blood tests showed elevated IgE without hypereosinophilia, as is typical in HS. Therapy with oral ivermectin 200 mcg/ kg/day was started, with improvement in general condition and, because of Salmonella coinfection and considering the risk of Gram- and anaerobic bacterial translocation, endovenous therapy with cefotaxime and metronidazole was added. Therefore, a diagnosis of malabsorption consequent to Strongyloidiasis was driven so that albumin supplementation, parenteral nutritional support and free diet were set up. Moreover, because of multifactorial anemia, the patient underwent red blood cells transfusions and was supplemented with folic acid and vitamin B12 with rise in hemoglobin values up to 8.5 g/dL. The patient refused to undergo colonoscopy.
In order to assess a systemic involvement of the infection, thorax and abdomen CT scan was required and showed thickening of loops of small intestine, ascites and reticulo-interstitial micronodulations at lung apexes and multiple pseudonodulations. These lesions could be suggestive of mycotic lesions, but because of negativity of Galactomannan and BetaD-Glucan, they were classified as pulmonary localization of Strongyloides. Conversely, brain CT scan with contrast did not highlight any infectious

foci. Because of a rise in cholestasis indexes, serology for all hepatotropic viruses were performed and resulted negative, while only hepatomegaly was detected at abdomen ultrasound. According to the normalization of cholestasis indices in response to ivermectin and exclusion of other causes, these alterations were defined as Strongyloides hepatic involvement in line with literature.
Since a disseminated Strongyloidiasis was evident and because of the typical onset of this condition in immunodepressed subjects, the patient was tested for HIV and HTLV1-2 (mostly associated with strongyloidiasis) but serology was negative. A positive quantiferon-TB was found, but search for mycobacterium tuberculosis by CRP, microscopic and culture on sputum, urine and feces excluded an active disease. Similarly, ANA, ENA and complement dosage ruled out an autoimmune disease. Lastly, serum protein electrophoresis showed only oligoclonal increase of gamma-globulins, compatible with infection.
The patient is currently hospitalized in our ward, continuing his treatment with ivermectin and albumin supplementation with improvement in both clinical and biochemical parameters.
In conclusion, a clear cause of immunodepression has not been identified in our patient, but HS could rise also in malnourished patients, as in our case, in which poor sanitary conditions and poor quality of food intake may have favored strongyloidiasis. In case of chronic diarrhea with malabsorption, mostly in patients from risk areas, parasitosis should be considered. Strongyloidiasis may manifest clinically even long after the first exposure, furthermore may persist and cause recurrence of disease after initial successful treatment, so a follow up is essential to prevent complications.

## 315. CYTOMEGALOVIRUS-RELATED GASTROENTERITIS DESPITE PROPHYLAXIS IN A PATIENT AFFECT BY ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

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**Introduction:** Cytomegalovirus (CMV) is a double-stranded DNA virus belonging to the Herpesviridae family that affects many primates, including humans. Infections generally proceed asymptomatically, but in patients with compromised immune system can cause serious complications such as esophagitis, pneumonia, hepatitis, retinitis, encephalitis, etc., especially if associated with HIV infection. Once contracted, it remains in a latent form and can reactivate after weakening of the immune system. In Italy, 70-80% of the adult population is positive for anti-CMV antibodies.
**Case Report:** M.S., a 41-year-old man, accessed in March 2022 to the Emergency Department of the Tor Vergata Polyclinic for persistent hyperpyrexia for about 7 days, unresponsive to antibiotic therapy, associated with shaking, shivering, asthenia and diarrhoea. He also reported an episode of hyperpyrexia and diarrhea manifested by his child a few days earlier.
In medical history, acute lymphoblastic leukaemia (ALL) was reported in 2018, successfully treated with allogeneic transplantation and complicated by acute GVHD responsive to immunosuppressive therapy. In December 2021 ALL relapsed and currently is in molecular remission with tyrosine kinase inhibitors. Contextually, a reactivation of CMV infection was observed despite valacyclovir prophylaxis and was successfully treated with valgancyclovir.
At hospitalization, blood tests showed a relative lymphocytosis and a slight increase in C-reactive protein. Excluding the first hypothesis of hematological disorder in remission and SARS-CoV-2 infection given the current epidemiological needs, in order to investigate the aetiology of the fever, rheumatological and infectious disease panels were performed to detect autoantibodies or most common bacteria, viruses (influenza, HIV, CMV, EBV, HBV, HCV) and parasites (Leishmania spp, Toxoplasma gondii) on urine, blood and stool speciments. The patient was also subjected to total body CT, which showed no infectious foci or effusions. The only positivity was found for CMV on stools. In agreement with the infectious and haematological colleagues, the symptoms were attributed to a reactivation of CMV with gastrointestinal involvement despite valacyclovir prophylaxis prolonged after the previous reactivation event. Valgancyclovir antiviral treatment was set up with gradual remission of signs and symptoms. The negativization of CMV on stool was achieved one week after starting antiviral therapy.
**Conclusion:** Although the incidence has decreased in recent decades thanks to vaccines and new drugs such as immunoglobulins, the reactivation of the Cytomegalovirus represents one of the most common and feared infectious complications in patients with solid or allogeneic hematopoietic stem cells transplantation. Immunosuppressive therapies, post-transplant GVHD, infusion of donor cells depleted of T lymphocytes, advanced age, pre-transplant seropositivity of the recipient (40-80%) and seropositivity of the donor in seronegative host (30% of risk of primary infection) are the main predisposing factors for Cytomegalovirus reactivation.
To achieve a complete remission of symptoms, a reduction of hospitalization time and a lower risk of developing serious complications, an early diagnosis, followed by appropriate therapy and prophylaxis is essential.

## 316. EFFICACY OF DALBAVANCIN IN THE TREATMENT OF MRSA MULTIFOCAL OSTEOMYELITIS AND PYOMYOSITIS

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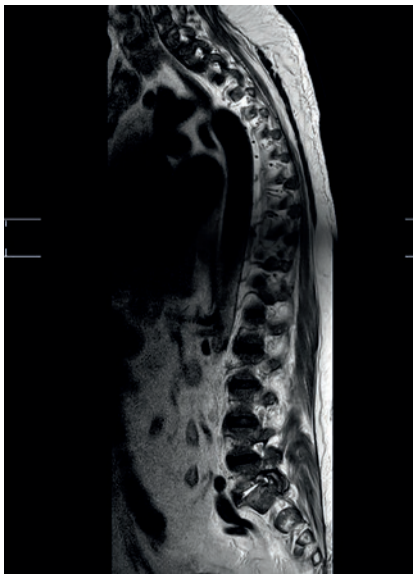
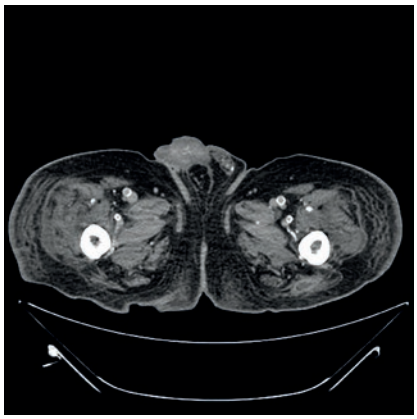
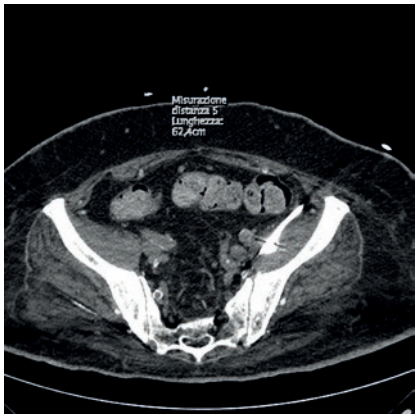
Staphylococcus aureus is the most frequent pathogen of hematogenous osteomyelitis and muscular abscesses. Adult hematogenous osteomyelitis accounts for approximately 20% of osteomyelitis cases; it most commonly involves the vertebral bones and less frequently involves the long bones of the skeleton. Pyomyositis is a purulent skeletal muscle infection that arises from hematogenous dissemination and is usually accompanied by abscess formation.
**Case Report:** A 68 year-old-man presented with progressive painful edema on the right arm (site of previous peripheral venous access) associated with intermittent fever. In medical history diabetes mellitus, arterial hypertension and ischemic heart disease; previous month hospitalization for pneumonia Sars-CoV2 related.His vital signs on admission revealed a temperature of 38.7°C, heart rate of 90 beats/min and blood pressure of 90/70 mmHg. His right arm was warm and there were no skin or soft tissue lesions. He was subjected to haematochemical tests, blood cultures and urineculture. On the 2nd day, he developed septic shock caused by gram-positive cocci that were detected from the 2 sets of blood cultures. Hematological investigations confirmed an elevated C reactive protein and procalcitonin, and an acute kidney injury. He underwent a CT scan of the chest and abdomen revealed normal lungs and pleura, with no hilar or mediastinal lymphadenopathy. There was evidence of intra-abdominal fluid suffusion of the subcutaneous tissue and destruction of D7-D8 and L5-S2 as for discitis, as confirmed by column MRI (Fig.1) Due to hypotension and severe metabolic acidosis he was transferred to the Intensive Care Unit with diagnosis of "septic shock". He was subjected to echocolordoppler of the right upper arm, which documented a suspicious of abscess, and an incision and drainage was performed: culture examination isolation of MRSA. To find positive blood cultures for S. Aureus MRSA, therapy was initially initiated with linezolid 600 mg/day, vancomycin 2 g/day and piperacillin/tazobactam 9 mg/day for 2 weeks, changed with tigecycline 100 mg/day, linezolid 600 mg/day and rifampicin 600 mg/day (for three week) and subsequently vancomycin 2 g/day and levofloxacin 750 mg/day.After about 2 months of hospitalization in the intensive care unit he was transferred to our ward and after two weeks of antibiotic treatment, due to the persistence of fever and increased inflammation indices, a control MRI lumbar and sacral spine with contrast showed increased bone edema of D7-D8 and L5-S2 and areas of altered signal with colliquative aspects and predominantly peripheral enhancement in the context of the explored tract of the iliopsoas muscle bilaterally and the gluteal musculature bilaterally (Fig.2). He underwent a CT-guided drainage of the abscess at the ileo-psoas muscle level and because of the therapeutic failure, antibiotic therapy with dalbavancin was started (1 g/week for two weeks, followed 500 mg/day for a total 7 weeks) (Fig.3). After about 8 weeks of treatment, the patient underwent column MRI which documented a clear reduction in volume of the abscesses and resolution of the acute picture of spondylodiscitis. The patient was transferred to a rehabilitation clinic because of Critical Illness miopathy and neuropathy; follow-up after one year showed no residue from the osteomyelitis.
**Conclusion:** Multifocal osteomyelitis is usually caused by hematogenous dissemination of the pathogen from a main infection source, which is not necessarily close to the osteomyelitis lesions. The common predisposing factors for hematogenous osteomyelitis and pyomyositis are immunodeficiency, diabetes mellitus, and intravenous drug abuse. Vancomycin, teicoplanin, daptomycin, and linezolid have limitations due to toxicity and drug resistance. Dalbavancin is a new semisynthetic lipoglycopeptidewith in vitro activity against susceptible and multidrug-resistant bacteria such as MRSA, methicillin-resistant and vancomycin-resistant enterococci. Dalbavancin is a lipoglycopeptide with a very prolonged half-life enabling treatment with a single intravenous administration that has been approved to treat complicated skin and soft-tissue infections. Fig. 1








## 317. AMINO ACIDS, SEPSIS &... MACHINE LEARNING

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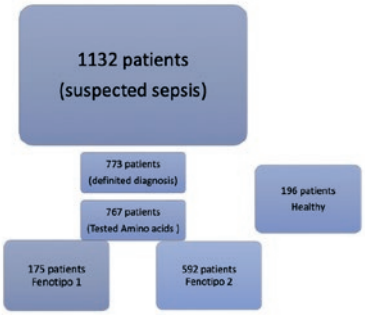
**Background:** In 2015, Longxiang Sù et al. demonstrated that changes in concentrations of amino acids and other macronutrients are associated with a different outcome in the septic patient.
At the same time, an increasing number of research groups in different ways have identified a high mortality cluster among septic patients. This subgroup has been classified in various ways: immunocompromised, afebrile, atypical. Unfortunately, it is still not possible to give an unambiguous definition of 'immunocompromised'.

**Aim of the Study:** With our study we want to assess whether changes in amino acid concentrations can predict immune capacity in septic patients, in the absence of the clinical characteristics commonly used in medical hospitalisation.
**Materials and Methods:** Population
We performed a secondary analysis of a multicentre prospective study of 1132 undifferentiated patients with suspected sepsis who met at least 2 SIRS criteria at the time of admission to the emergency department, were over 18 years of age, were not pregnant and were mentally and physically fit to sign the informed consent.
From the latter cohort, we extracted a group of 767 patients diagnosed with sepsis who underwent amino acids analysis, then we divided them according to body temperature and leukocyte count into:
- Phenotype 1: septic patients with at least 2 SIRS criteria.
- Phenotype 2: Patients who had a body temperature measured at the tympanum ≤ 37.8° and/or a white blood cell count ≤ 12000 on admission to the ward. (Figure 1)

**Figure 1**




**Outcomes:** Demographic characteristics and outcome
Phenotype 2 patients had a higher age than Phenotype 1 patients (82 Vs 80 years p=0.002), lower inflammatory indices (PCR [96.1 Vs 134.5 mg/100ml p=0.010, Procalcitonin [0.493 Vs 1.057 µg/L p=0.001], higher Charlson index (2 vs 3 p=0.001) and higher 30-day mortality (24.2% Vs 16.6% p=0.039). (Table 1)

| | Fenotipo 1 (175) | Fenotipo 2 (592) | p | *unOR* |
|---|---|---|---|---|
| Age | 80(73.25-86.75) | 82(75.75-88) | 0.002 | 1.017(1.005-1.030) |
| Charlson Index | 2(1-4) | 3(2-5) | 0.001 | 1.134(1.047-1.22) |
| Steroid | 15(8.6%) | 64(10.8%) | 0.479 | 0.773(0.429-1.394) |
| Immunosuppressor D. | 8(4.6%) | 18(3%) | 0.342 | 1.528(0.653-3.576) |
| Antimicrobial at home | 51(29.1%) | 195(32.9%) | 0.358 | 0.837(0.579-1.21) |
| SOFA | 3 (2-4) | 3 (2-5) | 0.261 | 1.06(0.978-1.150) |
| CRP | 134.5(64.97-213.2) | 96.1(33.95-185.27) | 0.010 | 0.998(0.997-1) |
| Lactate | 16.15(12.15-27.87) | 14.35(9.9-22.22) | 0.445 | 1.002(0.990-1.014) |
| PCT (IQR) | 1.057(0.331-12.89) | 0.493(0.184-3.247) | 0.001 | 0.992(0.986-0.997) |
| Lenght of hospital stay | 10(7-16.25 ) | 10(7-17) | 0.672 | 1.003(0.987-1.020) |
| Mortality at 30 days | 29(16.6%) | 143(24.2%) | 0.039 | 1.603(1.032-2.491) |

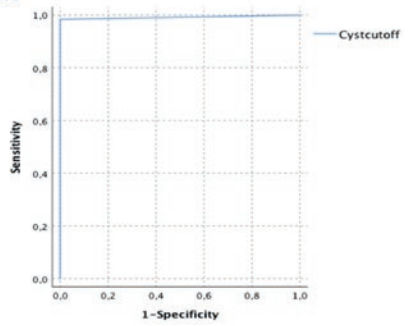
**Table 1**

**Clinical and Laboratory Manifestations:** On univariate analysis between healthy and septic patients, the serum concentration of most of the amino acids tested was higher in healthy patients. The only amino acid with an inverse trend was Phenylalanine. On ROC analysis, with a cysteine cut-off of 226 nmol/ml we obtain an AUROC of 0.99 with a specificity of 99% and a sensitivity of 98%. (Table 2-Figure 2)

| | Infetti (767) | Sani (196) | p |
|---|---|---|---|
| ALA | 247(192-321) | 319(285.25-374.75) | <0.001 |
| GLY | 130(103-162) | 208(179-239) | <0.001 |
| LEU | 116(91-143) | 117(106-135) | 0.081 |
| PHE | 82(70-101) | 50(55-63) | <0.001 |
| GLU | 399(313-499) | 483(437-538) | <0.001 |
| AC.GLU | 135(96-201) | 162.5(121.25-200.75) | 0.001 |
| OXO5 | 102(76-134) | 149(123.25-172) | <0.001 |
| TYR | 55(45-68) | 62(56-71.75) | <0.001 |
| THR | 68(54-86) | 115(104-126) | <0.001 |
| SER | 66(55-82) | 96(86-108) | <0.001 |
| PRO | 136(104-174) | 173(147.25-213) | <0.001 |
| CYS | 68(39-106) | 323(294-353) | <0.001 |
| MET | 17(12-22) | 23(21-25) | <0.001 |

**Table 2**

Figure 2




Phenylalanine also showed an inverse trend (83 Vs 81.5 nmol/ml) to the remaining amino acids in the univariate analysis between Phenotype 1 and Phenotype 2. (Table 3) At logistic regression between all independent variables were statistically significant: Glutamine (p>0.001), Glutamic Acid (p=0.001), Procalcitonin (p=0.003), Charlson index (p=0.014). (Table 4)
In the decision tree the variables found to be positive are:
1) Procalcitonin at concentrations above 6.850 ng/ml, it shows a discrete association with phenotype 2, identifying 62.3% of patients; at concentrations between 0.164 ng/ml and 6.850 ng/ml, Proline appears as the new discriminating variable, while at concentrations below 0.164 ng/ml Glutamine.
2) Glutamine when present at concentrations above 431 nmol/ml, in the group with procalcitonin below 0.164 ng/ml (89 patients), it succeeded in identifying 58% of the phenotype 2 patients. In the group with procalcitonin between 0.164 ng/ml and 6.850 ng/ml (454 patients), Proline concentrations above 110 nmol/ml identified 54% of the Phenotype 2 population, concentrations below 110 nmol/ml only 22%.
3) Proline in concentration lower than 110 nmol/ml (144 patients), age above 80 years identifies 39% of the patients; if higher than 110 nmol/ml (310 patients) a Glutaminemia higher than 469 nmol/ml identifies 30% of the population with Phenotype 2, the group with concentration lower than 364 nmol/ml differs little identifying the Phenotype 2 for 29%.

| | Fenotipo 1 (175) | Fenotipo 2 (592) | *p* | *unOR* |
|---|---|---|---|---|
| ALA | 241(193.25-320.5) | 250(190-336.25) | 0.366 | 1.001(0.999-1.002) |
| GLY | 119.5(97-147.75) | 130(104-164) | 0.001 | 1.009(1.004-1.013) |
| LEU | 112.5(91.25-134) | 119(91-149) | 0.451 | 1.003(0.999-1.007) |
| PHE | 83(70.25-113.5) | 81.5 (69.75-99) | 0.006 | 0.996(0.992-1) |
| AC.GLU | 119(82-180) | 140.50(99-213.25) | 0.001 | 1.003(1.001-1.005) |
| GLU | 374.5(300.5-450) | 409.5(322.5-515.2) | 0.001 | 1.002(1.001-1.004) |
| OXO5 | 89.5(67.25-122) | 103(79-138) | 0.001 | 1.008(1.004-1.012) |
| TYR | 52.5(41.5-64) | 55.5(46-69.25) | 0.075 | 1.011(1.002-1.020) |
| THR | 60.5(48-75.75) | 70(54-86) | 0.001 | 1.012(1.005-1.019) |
| SER | 62(49.25-78.75) | 67.5(55.75-84) | 0.001 | 1.014(1.006-1.023) |
| PRO | 102.5(89.5-178) | 135.5(107-183) | 0.001 | 1.005(1.002-1.008) |
| CYS | 60.5(38-97.25) | 73(41-113) | 0.052 | 1.003(1-1.007) |
| MET | 14.5(10.25-18.75) | 17(12-22) | 0.108 | 1.013(0.977-1.030) |
| PHE/TYR | 1.65(1.333-2.075 | 1.457(1.209-1.752) | 0.001 | 1.568(1.250-1.966) |
| GLUT/ACGLUT | 0.313(0.203-0.526) | 0.3171(0.207-0.547) | 0.608 | 1.010(0.978-1.044) |

Table 3

| | B | S.E. | Wald | gl | Sign. | Exp(B) | 95% C.I.per EXP(B) Inferiore | Superiore |
|---|---|---|---|---|---|---|---|---|
| Charlson Index | 0,109 | 0,044 | 5,994 | 1 | 0,014 | 1,115 | 1,022 | 1,216 |
| Procalcitonin | -0,012 | 0,004 | 9,128 | 1 | 0,003 | 0,988 | 0,981 | 0,996 |
| GLU | 0,003 | 0,001 | 15,727 | 1 | 0,000 | 1,003 | 1,002 | 1,004 |
| AC.GLU | 0,004 | 0,001 | 11,832 | 1 | 0,001 | 1,004 | 1,002 | 1,006 |
| k | -0,768 | 0,410 | 3,518 | 1 | 0,061 | 0,464 | | |

Table 4

Overall, the decision tree was able to correctly place 64% of patients with phenotype 2. (Figure 3)

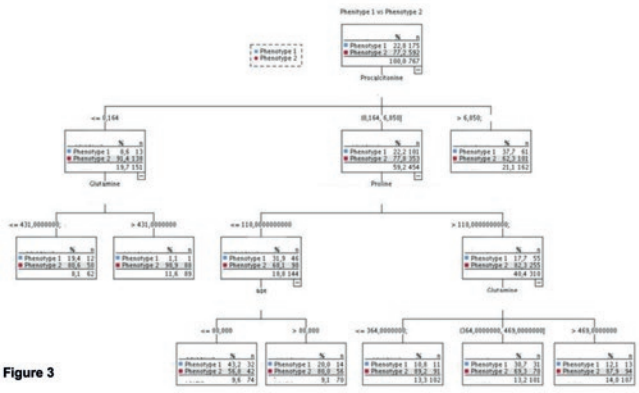
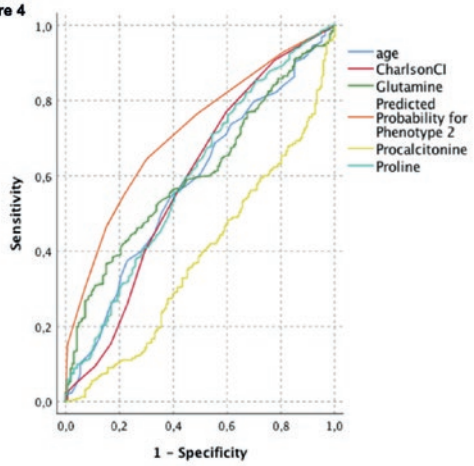


Figure 3

On ROC curve analysis, the decision tree had an AUC of 0.719, clearly outperforming the individual constituent variables (Figure 4-Table 6).
**Discussion:** Comparing two groups of septic patients, Phenotype 1 (175 patients) and Phenotype 2 (592 patients), we found that Phenotype 2 showed a reduced tendency to inflammation with lower PCR and Procalcitonin values, and also exhibited a higher Charlson index and a higher tendency for 30-day mortality.
Next, we identified amino acid concentrations useful in discriminating between the two phenotypes. We started a preliminary analysis to assess whether our population was in line with those used in large multicentre studies; we then compared the same concentrations between the two groups. The concentration of amino acids was different when comparing phenotype 1 and phenotype 2. For this reason, we decided to carry out the calculation of a decision tree based on all the independent variables identified previously. Integration of the obtained variables to the clinical diagnostic procedure of the septic patient could help the clinician in the evaluation of doubtful cases.

Figure 4




| | z | Sign. ( 2 tails) | Difference ROC | CI 95% | |
|---|---|---|---|---|---|
| PredictedProbability Ph2- Age | 4,759 | 0,000 | 0,135 | 0,080 | 0,191 |
| PredictedProbability Ph2 - Procalcitonine | 8,514 | 0,000 | 0,332 | 0,256 | 0,408 |
| PredictedProbability Ph2 - Charlso Ind | 3,985 | 0,000 | 0,127 | 0,065 | 0,189 |
| PredictedProbability Ph2 - Glutamine | 3,926 | 0,000 | 0,110 | 0,055 | 0,165 |
| PredictedProbability Ph2 - Proline | 4,412 | 0,000 | 0,118 | 0,066 | 0,171 |

Table 6

## 318. EMERGING IN-HOSPITAL PREVALENCE OF CANDIDA INFECTIONS AND ANTIMICROBIAL RESISTANCE IN AN INTERNAL MEDICINE WARD. A PROSPECTIVE STUDY

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**Background:** In-hospital infections are frequent, delay discharges and increase health costs, also due to a progressive increase of antibiotic resistance. The real burden of infections and antimicrobial resistance in acute, general hospital settings is still unclear.
**Methods:** Enrolled were all patients admitted (all causes) from December 10, 2021 to March 30, 2022 in a division of Internal Medicine. Patients with clinical and/or instrumental evidence of bacterial infection were examined to characterize microbes and antimicrobial resistance.
**Results:** Entered the survey 152 consecutive patients. In-hospital infection prevalence in the examined period was 19% (on average, 1.4 cases of infections per day). The infection prevalence increased with age, being the lowest in subjects with <30 years (0.7%), and the highest in those with >70 years (9.9%). Blood culture was positive in 65.5% of infected patients. Urinary tract was the most common site of infection, followed by skin

(mainly pressure ulcers). The majority of cultures (72.4%) were positive for Candida. Candida albicans was the main responsible species for Candida infections (41.1% of positive cultures). However, non-albicans Candida species (i.e., C. glabrata, Krusei, tropicalis, lusitaniae, parapsilosis) were also frequent (31% of positive cultures). The most frequent bacteria were Klebsiella pneumoniae (34.4%), and Pseudomonas Aeruginosa (31%). All patients with a positive culture received antimicrobial and/or antifungal therapy. A total of 61 antimicrobial resistances was detected, with the most frequent among beta lactam (42.6% of total resistances), oxazolidinone (19.7%) and antifungal drugs (16%).
**Conclusions:** The prevalence of in-hospital infections in an acute hospital setting is relevant, in particular in elderly. Candida colonization/infection also due to non-albicans species represents a growing threat, probably due to immune depression, increasing antimicrobial resistance and extensive antimicrobial use. This last finding represents an under-recognized, emerging challenge, with relevant implications in terms of in-hospital management and primary prevention measures

## 319. A STRANGE CASE OF "DELIRIUM"

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**Objective:** The aim of our case report is to show, through our personal clinical experience, the issues concerning undetected diseases of the CNS hidden behind states of impared consciousness, for istance the encephalitis. We experienced that the association between corticosteroids and antiviral drugs could lead to a better outcome in the patient with acute infection from Herpes Zoster virus, in spite of the lack of a general consent about the use of corticosteroids as a preventive treatment. Treatment with Aciclovir is the current standard therapy for Herpes Zoster virus infection. However, over the years the tissue damage caused by the inflammatory response became more and more relevant than the damage related to the direct injury caused by the viral replication. These evidences strenghten the purpose of the use of corticosteroids in the treatment for viral encephalitis, since it has been proved a worse outcome in patients who haven't received this treatment.
**Case Description:** Based on a patient who was admitted to our Internal medicine unit, we went through all related data and we put together a multidisciplinary team made of internists, neurologists and infectiologists to develop a common strategy to approach our clinical case, taking advantage of the expertise of each part of the team. Our 84 years old female patient, affected by multiple comorbidities (arterial hypertension, extranoadal arrhythmia, carotid atheromatosis, colon diverticulosis, ostheoporosis with multiple vertebral collapses, arthosis, enuresis, hypoacusis, partially dependent on her ADL and unable to walk without assistance), was brought to the ER because of the onset of weakness of the inferior limbs, impaired consciousness, hypertension and vomit, preceded by episodes of dizziness the week before. In the ER she underwent brain CT scan (negative for acute ischaemic events) and a neurological examination though which a diagnosis of hypoactive delirium was made.
The patient was then admitted to our ward. During the following hours after the admission, we assisted to a rapid worsening of the clinical status of the patient, regarding a worsening of the impaired consciousness and onset of lethargy, flaccid paralysis of the lower limbs and the right upper limb and myoclonic seizures of the left upper limb and the left half of the face. We performed a brain MRI with contrast scans that showed a highly non specific supra and subtentorial pachymeningeal enhancement, therefore the patient underwent rachicentesis: the analysis of the cerebrospinal fluid revealed a high replication of the HZ virus (265.000 copies/ml); the clinical suspicion was confirmed by the appearance, a few days after the procedure, of vesicular lesions at the site of the lumbar punture. Comprehensive analyses were performed on CSF and serum for differential diagnosis: cytochemical analysis of the CSF (clear, colorless, protein 200 mg/dl), culture of the CSF, PCR for neurotropic viruses (EBV, HZV, HSV1, HSV2, CMV), research of Listeria, Brucella, Leptospira, Anaplasma, Coxiella, Bartonella, Rickettsia and Leishmania, oligoclonal bands and IgG4, complete screening for autoimmunity (ANA, ASMA, AMA, Anti LKM, C-ANCA, P-ANCA, ENA) and dosage of the angiotensin converting enzyme (ACE). We also performed an EEG resulted in signs of widespread brain suffering also with irritative features for which an antiepileptic therapy was introduced. In agreement with the other specialists, we decided to begin a corticosteroid therapy with Dexamethasone 8 mg x2/day in association with the standard antiviral treatment with Acyclovir EV 10 mg/kg every 8 hours and antibiotic coverage with continous infusion of Meropenem 6g, with gradual clinical improvement. At the end of the third week of therapy, we performed a brain MRI that showed a reduction of the pre-existing diffuse pachymeningeal dural enanchement, therefore we interrupted the treatment according also the opinion of the infectiologists.
We carried out a second EEG that confirmed the presence of an irritative pattern, which is why we increased the dose of Levetiracetam to 1500 mg x2/day.
**Results:** Although the patient has arrived to our department in critical clinical conditions, the early use of viral therapy in association with corticosteroid and antiepileptic therapy proved to have a good therapeutic efficacy: the patient in fact showed a slow but progressive improvement in general clinical conditions, switching from the soporous and non-contactable level of consciousness to a waking state, with understanding of simple orders and resumption of verbal communication. The patient was still dysphagic, so she underwent Percutaneous Endoscopic Gastrostomy (PEG) and it was prescribed a riabilitation program for the immobilization syndrome.
**Conclusions:** although there is still no consensus within the scientific community, in our experience corticosteroid treatment in combination with antiretroviral therapy has shown a remarkable improvement in the patient outcome.

## 320. LATENT TUBERCOLOSIS INFECTION SCREENING: TIME TO TAKE A STEP FORWARD

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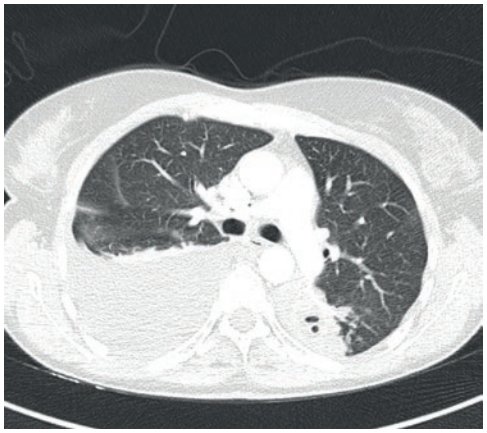
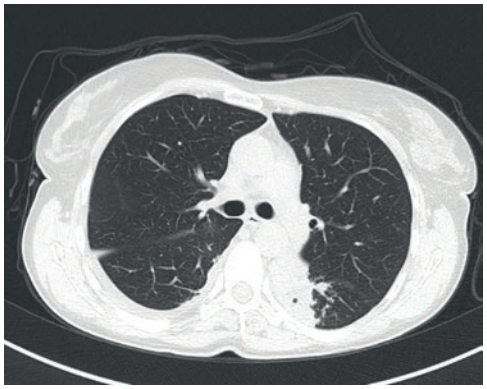
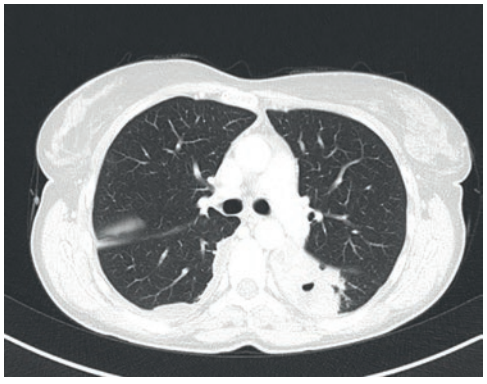
We report a case of 46-years-old immunocompromised woman who presented at our emergency department complaining of persisting cough, fever and thoracalgia. Her past history was positive for neuromyelitis optica spectrum disorder (NMOSD), treated with multiple immunosuppressors (high-dose corticosteroid, then rituximab and finally tocilizumab and plasmaferesis). Before starting rituximab, she had a complete screening tests for TBC (quantiferon), HCV, HBV, EBV (sierology), with negative results.
After a positive nasopharyngeal swab for SARS-CoV-2, she first consulted her general practitioner who suggested to take azithromycin and eventually amoxicillin/clavulanic acid bid, due to recurrence of fever and cough. A few weeks later she presented to our Emergency Department with increasing chest pain and fever. The nasopharyngeal swab was still positive, and the lung ultrasound showed lower bilateral B lines and right basal pleural effusion associated with lung consolidation. A chest CT scan with contrast confirmed the presence of right pleural effusion and consolidation in the mid-basal segment of the LID and in the apical segment of the LIS with necrotic components, compatible with an inflammatory focus (figure 1). Clinical signs and collateral diagnostics were suggestive of bilateral pneumonia, with mixed bacterial and viral genesis, so the patient was admitted to the Department of Internal Medicine at High Intensity Care of our Hospital. During hospitalization she was treated with piperacillin/tazobactam and linezolid associated with low-flow oxygen and monoclonal antibodies (casirivimab/imdevimab) obtaining the regression of symptoms and the decrease of inflammatory markers (CRP 22,66 mg/dl -> 1,8 mg/dl). To investigate the etiology of pneumonia, multiple analyses were performed, including a nasal swab for MRSA, microbiological investigations on BAL and pleural fluid (standard culture for bacteria and fungi; multiplex respiratory viruses; culture, direct microscopic examination and DNA search for mycobacteria; CMV-DNA; PJP-DNA) and on peripheral blood (BDG, Galactomannan Ag, CMV-DNA assay, blood cultures). All the analyses resulted negative, except for pleural fluid culture for BK, still ongoing at the time of discharge. After 11 days of hospitalization, given the negative result of TNF and the improvement of consolidation at the CT scan control (figure 2), the patient was discharged with indication to complete the antibiotic therapy for 10 days more.
A few days after the end of the antibiotic treatment, she returned to the ER because of fever. The CT scan with contrast showed an improvement of the right pulmonary consolidation; the left one was still present (figure 3). She was then admitted to our Unit of Internal Medicine. Diagnostic tests were repeated in order to identify the etiological agent (urinary Ag, nasal swab for respiratory viruses, blood cultures, Galactomannan Ag, BDG, CMV/EBV-DNA, quantiferon) but they were all negative; sputum culture was not performed due to unproductive cough. Given the persistence of high-grade fever (higher than 39°C) in an immunocompromised patient, we initially restarted the previous antibiotic therapy, with an initial clinical and biochemical response (CRP 13 mg/dl -> 4 mg/dl). Since the etiological agent was not found, it was decided to proceed with CT-guided biopsy of the right

lung lesion for microbiological and histological investigations (including direct microscopic examination, gene amplification and culture examination for BK). After the procedure, the patient developed blood-streaked sputum that was collected and analyzed. The analyses run on lung tissue and sputum allowed to identify Mycobacterium tuberculosis as the etiological agent of pneumonia: the empirical antibiotic therapy was replaced with antitubercular drugs. Meanwhile, also the pleural fluid culture that was performed during the previous hospitalization, gave a positive result for BK. After antitubercolar therapy was started, in a few days the symptoms almost disappeared and a reduction of the lung consolidation was appreciated on radiological examinations performed after one month. To correlate clinical and laboratory findings to our case, we conduced a careful interview and we found that the patient's father had tuberculosis when she was a child.
We decided to describe this case to show that quantiferon test, performed as screening for tubercolosis before starting immunosuppressive therapy, might be misleading especially in immunocompromised patient because of immune system anergy, as reported in the literature (1) (2). Therefore, a new test called quantiferonTB Gold Plus has been recently developed to detect a higher percentage of latent TB in immunocompromised patients, but its efficacy is still debated and more studies are necessary (3) (4). In conclusion, in case of TB suspicion, microbiological investigations (culture first, but also gene amplification and direct microscopic examination) are still the gold standard to diagnose tuberculosis.







## 321. NOT ALL THAT GLITTERS (AT PET) IS LYMPHOMA

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Abdominal pain and bowel discomfort are common symptoms in general population. Given that a wide range of etiologies may cause these symptoms, thus an accurate patient's medical history, physical examination and differential diagnosis are fundamental to find out the causes.
A 65-year-old Italian woman with a past medical history significant for chronic hydrocephalus, Addison's disease, osteoporosis, depression, was referred to out outpatient clinic because of abdominal pain. The pain was prevalently nocturnal, responsive to ketoprofen. About three months before, the patient had a 7-days fever, associated with chills and night sweats.
At physical examination, the abdomen was soft, a non-tender but painful mass was palpable in the hypogastrium. No other significant signs were found. Abdominal US-scan revealed the presence of a mesogastric hypoechoeic dyshomogeneous roud mass, with internal calcifications, surrounded by thickened bowel loops. The patient was admitted to our inpatient unit for further examination.
Lab tests showed mild anemia (HGB 10.8 g/dl, n.v. 12-14 g/dl) and elevated inflammatory indices (VES 42 mm, n.v. 2.0-15.0 mm; CRP 2.39 mg/dl, n.v. 0.30 mg/dl) with a trend to leukopenia (4840/mm3 n.v. 4300-10.800). Other lab tests were normal.
Colonscopy and gynecological examination with pelvic endocavitary US scan were negative.
Due to iodinated contrast agent allergy, patient underwent abdominal CE-MRI-scan completed with CT-scans documenting in the hypogastrium the presence of voluminous multilobular lymphadenopathies (45 mm of diameter) with calcific nucleus surrounding the mesenteric vessels and infiltrating the mesenteric fat. A subsequent PET-CT revealed the presence of diffuse and pathological accumulation of the radio-tracer (max SUV 13.6) in correspondence with the lymphatic nodules seen on MRI.
These results led to the need for diagnostic evaluation of abdominal lymphadenopathies of unknown origin.
Serology for EBV and CMV were consistent with previous infection, while HBV and HCV antibodies were negative. Quantiferon-TB test resulted positive, in absence of pulmonary lesions; Wright test for brucellosis was positive (1/400). Thus, Patient was scheduled for surgical excision of the neoformation.
Histological result described a fibro-hyaline nodule with calcifications and lymphoplasmacellular and granulocyte infiltrate associated with purulent necrosis.
These findings, coupled with the high title for Brucella antibodies and Quantiferon excluded malignancies (i.e. lymphoma) and oriented toward a chronic infectious disease. With this regard, real-time polymerase chain reaction (PCR) to attest Brucella DNA or mycobacteria was required. Unfortunately, these procedures were not possible after paraffin fixation.
By re-evaluating clinical history, Patient confirmed a recent consumption of unpasteurized milk.
Clinical, microbiological and histological data were consistent with mesenteric lymphadenopathies due to Brucella infection, and treatment with rifampin 600 mg daily and doxycycline 100 mg twice a day for 6 weeks was prescribed. Rifampin was subsequently continued for a total of 4 months in order to treat also latent tuberculosis. After 4 weeks of treatment, patient's symptoms completely resolved, blood exams and abdominal US-scan were normal. Six months after ending treatment Wright serology was negative.
Brucellosis is a common zoonosis affecting half a million people annually. The most common mode of infection is by consuming unpasteurized milk or milk products. Four species have been reported to cause human disease: Brucella melitensis (being the most common cause), Brucella abortus, Brucella suis and Brucella canis.
Brucellosis has a wide spectrum of clinical manifestations from asymptomatic presentation to a multiorgan involvement and can mimic any disease, making the diagnosis difficult.
The most common symptoms are fever, night sweats, chills, headaches, and joint pain but it can be affected any other organs.
Lymphadenopathies are found in 10-20% of the cases of brucellosis, cervical lymphnodes being the most common site of involvement.

This case leads us to conclude that, even if rare, it is necessary to consider brucellosis as a possible cause of abdominal pain.

## 322. A CHALLENGING CASE OF VISCERAL LEISHMANIASIS

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Leishmaniasis is a severe infectious disease given by a group of protozoan parasites of the genus Leishmania that could cause multiple clinical pictures, from cutaneous manifestations to disseminated visceral infection. The immunoinflammatory response plays a major role in pathogenesis, since healing is associated with activation of macrophages that kill intracellular amastigotes, while persistent infection, associated to visceral dissemination, is characterized by an ineffective immune response [1].
The clinical phenotype is mainly driven by the leishmania biologic characteristics and, ultimately, also by the host immune status. The disease is endemic in focal areas in the tropics, subtropics, and southern Europe, transmitted by the bite of female phlebotomine sandflies. Sandflies regurgitate the parasite's flagellated promastigote stage into the host's skin; promastigotes bind to receptors on macrophages, are phagocytized, and transformed within phagolysosomes into non flagellated amastigotes, which replicate and infect additional macrophages. Amastigotes ingested by sandflies transform back into infective promastigotes. Depending on the host's innate and acquired immune status, systemic and visceral Leishmaniasis can be characterized by irregular fever, weight loss, enlargement of the spleen and liver, anaemia [2]. Recently, few cases/year of visceral leishmaniasis have been recorded in the Taranto area, caused to the presence of probable reservoir in the rats.
We present a 42 years-old man with long-lasting type 1 autoimmune hepatitis and autoimmune cholangitis in immunosuppressive treatment. In May 2017 the patient started to experience low-grade unresponsive to empiric antibiotic therapy. The patient developed severe anemia and progressive multilineage cytopenia along with raised inflammation markers too. FDG-PET pointed out an increased glucose uptake in the liver, spleen, and the whole bone marrow. Consequently, a bone marrow biopsy was performed, with the evidence of Leishmania infantum amastigotes inside macrophages, confirmed with serological positivity to anti-Leishmania antibody.
Immunosuppressive therapy was interrupted and treatment with amphotericin B was started at 4 mg/kg/die at day 1 to day 5, followed by single infusion at days 10, 17, 24, 31, 38. The bone marrow smear after treatment still evidenced few Leishmania amastigotes; unconventionally, two further doses of amphotericin B on days 45 and 52 were employed, in consideration of patient's immunosuppressed status, with infection resolution. In real-life, as represented by this case the additional administration of two doses of amphotericin B compared to the guidelines, offered an additional curative opportunity in patient in long-term immunosuppressive treatment.
**References:** 1. Torres-Guerrero, E.; Quintanilla-Cedillo, M.R.; Ruiz-Esmenjaud, J.; Arenas, R. Leishmaniasis: A Review. F1000Res 2017, 6, 750, doi: 10.12688/f1000research.11120.1. - 2. van Griensven, J.; Carrillo, E.; López-Vélez, R.; Lynen, L.; Moreno, J. Leishmaniasis in Immunosuppressed Individuals. Clin. Microbiol. Infect. 2014, 20, 286–299, doi: 10.1111/1469-0691.12556.

## 323. A RARE COMPLICATION OF THE RARE RETROPHARYNGEAL ABSCESS

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The retropharyngeal abscess is a potentially life-threatening diagnosis that can be frequently observed in children while being seldom observed in adults. In this latter case, the most common etiology is trauma. Risk factors are poor oral hygiene, diabetes, immunocompromise, and low socioeconomic status. The lack of a specific symptomatology makes the retropharyngeal abscess hard to be diagnosed.
A 69-year-old woman affected by diabetes, hypertension and liver cirrhosis was hospitalized for refractory ascites and hyperglycemia without fever. The visual inspection of neck showed a hard and painful swelling with not well-defined margins that extended posteriorly and inferiorly and with the typical ultrasound characteristics of abscess. CT showed a large abscess cast extending from the retro pharynx along the chest wall to the thoracoabdominal junction. The abscess was subjected to drainage with MSSA isolation that was also found in the ascitic fluid and treated with a targeted antibiotic therapy. The complete remediation of the abscess of the patient was not possible due to the worsening of the conditions. The patient died of septic shock.
The patient was affected by retropharyngeal abscess that is very rare in adults. In addition, she developed a rare complication, namely the abscess cast in the chest wall. None of the red flags that typically apply in the case of retropharyngeal abscess (e.g., fever, odynophagia) was observed. The drainage collection was only possible in the laterocervical region and, unfortunately, the patient died of septic shock.

## 324. DIAGNOSTIC CHALLENGE OF A MYSTERIOUS MYCOBACTERIUM

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23-year-old man, originally from Burkina Faso, moved to Italy for 3 years, had been in the emergency room for fever and abdominal pain for about 15 days. A year earlier he reported an episode of pneumonia treated and resolved with antibiotic therapy. He was being transferred to our internal medicine department for further diagnostic work. On physical examination the abdomen was tense, batracian, sore and painful with reduced peristalsis. We screened for hepatitis B and C viruses and for HIV, without any positive results; the blood tests revealed polyclonal hypergammaglobulinemia and non-specific rise in inflammation indices, nothing else of significant importance. We performed bedside abdominal ultrasound which showed the presence of abundant ascitic effusion; for this reason we performed paracentesis by sending a biological sample for chemical, cultural, microscopic, cytological examination and PCR study for the search for mycobacteria. During the procedure, three liters of turbid liquid with the presence of fibrin were drained, the microscopic examination, PCR and culture were negative, the cytological examination showed the presence of red blood cells, small and medium-sized lymphocytes, some histiocytes and neutrophilic granulocytes on a serous background with albumin serum-ascites gradient lower than 1.1, compatible with a reactive effusion pattern. To search for a possible infectious agent, blood cultures and sputum studies were also performed, both negative; quantiferon, on the other hand, was positive. We carried out a gastroenterological consultation that raised the suspicion of tuberculous infection and suggested the execution of a CT scan with contrast of the chest, abdomen and neck. We performed the required CT and again highlighted the presence of abundant ascitic effusion, multiple solid tokens on the peritoneum, increased volume of both abdominal and mediastinal lymph nodes, with the presence of mediastinal lymph nodes with central necrosis and parietal ehnancement. We decided to perform exploratory laparoscopy with possible biopsy for the study of peritoneal solid tokens reported on CT. The histological examination described the presence of a parietal peritoneum site of chronic flammable inflammation with the formation of non-confluent epithelioid granulomas, partly necrotizing and with infiltrate of neutrophilic granulocytes; the Warthin-Starry and PAS-Green histochemical stains were negative. On the biological material collected we also performed the search for bacterial DNA with the Anyplex MTB / NTM Real Time detection Kit which is able to identify the presence of Mycobacterium tubercolosis, M. avium, M. kansasii, M. fortuitum and M. chelonei; however, this examination was negative. In consideration of the whole clinical case, the possibility that there was an infection by a Mycobacterium not analyzed by our kit and the condition of the patient who con-

tinued to have fever, abdominal pain and ascitic effusion, we still decided to start therapy ex adjuvantibus for Tuberculosis with HRZE scheme (isoniazid, rifampicin, pyrazinamide, ethambutol). After a week of treatment, we observed a clear improvement in the patient's clinical conditions and a reduction in inflammation indices (from an initial PCR value of 15.56 mg / dl to a current value of 1.80 mg / dl). 15 days after the start of ex adjuvantibus therapy, we discharged the patient in good clinical condition, without ascites and with normal inflammation indices, giving him an appointment in infectious disease clinic for follow-up.

## 325. DIAGNOSTIC CHALLENGES: STRANGE PRESENTATION FOR A COMMON DISEASE. A CASE OF FEVER WITH SPLENIC INVOLVEMENT OF UNKNOWN NATURE IN A PERIPHERAL T-CELL LYMPHOMA TREATED WITH ALEMTUZUMAB

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**Introduction:** Fever is often challenging in patients with oncohematological disease, because of broad differential diagnosis between typical or opportunistic infection and disease progression. Frequently an invasive approach to reach definitive diagnosis is not feasible.
**Case Presentation:** A 78 year-old woman was admitted to our unit because of fever and cough. She had a history of peripheral T-Cell lymphoma, recently treated with alemtuzumab with clinical remission and T cell normalization on blood count.
Physical examination demonstrated fever up to 39°C, tachycardia and light abdominal tenderness. Blood exams revealed elevation of C-reactive-protein and left shift leukocytosis; chest-X-ray was unremarkable.
Abdominal US revealed two echo-poor heterogeneous splenic lesions.
A splenic abscess was suspected and piperacillin/tazobactam was initiated.
**Differential Diagnosis:** All microbiological tests were negative, including blood, urine and stool culture, CMV and EBV DNA, beta-D-glucan, galattomannan and Cryptococcal antigen on serum, PCR for candida. A negative Interferon-Gamma Release Assay (IGRA) for Tuberculosis was reported in the patient history and was not repeated also considering the lack of sensitivity in the setting of alemtuzumab induced T-Cell depletion.
Total body CT-scan, abdominal MRI and FDG-PET were performed to better characterize the splenic lesions and exclude other possible septic foci but were not conclusive on the nature of the lesions and were negative for other localizations. Transthoracic and transesophageal echography were negative for endocarditis.
Considering the severe immunodepression of the patient and the worsening condition of fever and abdominal pain, empiric antimicrobial therapy was gradually upgraded to daptomycin, meropenem and caspofungin, without any benefit.
Main differential diagnosis included hematological disease progression and an atypical infection.
A definite diagnosis could only be made by splenectomy, but the surgical risk was very high, so we decided to defer it after a marrow evaluation for lymphoma relapse.
The bone-marrow biopsy excluded relapse and demonstrated the presence of alcohol acid fast bacilli, with positive PCR for M. Tuberculosis.
Four-drug therapy was started, with complete remission of symptoms.
**Discussion and Conclusion:** Alemtuzumab facilitates opportunistic infections, including tuberculosis and a negative IGRA does not rule out mycobacterial etiology. Splenic involvement is a rare presentation of mycobacterial infection and diagnosis is mainly postoperative. Nevertheless, the surgical risk of splenectomy is often too high, especially in immunocompromised patients.
In the setting of hematological patients with unresponsive fever tuberculosis must be always considered in the differential diagnosis. Bone-marrow biopsy could be crucial for the diagnosis, especially if there is splenic involvement, both to evaluate a possible disease progression and to search for pathogens targeting the reticuloendothelial system.

## 326. A WOMAN WITH MULTIPLE BRAIN LESIONS: A DIAGNOSTIC CHALLENGE

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**Case Presentation:** A 58-year-old Caucasian woman, with a history of Hashimoto's thyroiditis, arterial hypertension, previous herpes zoster infection, presented to our Emergency Department due to fever, syncopal episode, and consequent acute confusional state. Two months before, the patient referred the onset of progressive lower strength of the left upper and lower limbs associated with low back pain. Also, an unvoluntary body weight loss of 5% in the previous 6 months was reported. In the Emergency Department, the patient was hemodynamically stable, awake, and oriented, no altered speech and/or memory loss were present. Moderate weakness of upper and lower limb was present associated with weakness of the lower two-thirds of the face with preservation of the upper third. The brain CT scan without contrast showed bilateral multiple focal areas of hypodensity, the largest located in right temporal region (5.3 cm X 5.5 cm) with vasogenic oedema with mild effacement of neighboring sulci and lateral ventricle temporal horn. The brain MRI with gadolinium confirmed the presence of multiple focal enhancing lesions with highly suspicion of metastatic disease. To investigate the possible presence of a primary tumor, the patient was admitted to our Internal Medicine Division. We ruled out the presence of lung, breast, melanoma, and kidney cancer. In fact, the examinations performed (including a TB-CT scan) were negative for the presence of cancer disease.
Therefore, we focused on the possibility of a primary brain cancer and/or brain infectious disease. Considering possible opportunistic infections (the patient had previous herpes zoster infections, mucosal candidiasis, both oral and esophageal) and mild lymphopenia, we performed a serologic HIV test resulted positive with a CD4 cell count < 200cells/microL with evidence of acquired immunodeficiency syndrome (AIDS), C3 stage.
In this light, the anti-retroviral therapy was started, and we tested anti-Toxoplasma Gondii antibodies (IgG) which resulted positive. At this stage, with this clinical picture the anti-toxoplasma treatment was initiated. The efficacy of the treatments was evaluated at 14 days by cerebral-MRI which showed a significant reduction of the multiple lesions with clinical improvement, that allowed us to confirm the diagnosis of cerebral toxoplasmosis.
**Conclusions:** This clinical case shows the diagnostic work-up of an adult patient presenting with multiple brain lesions. Although the initial suspicion of cerebral metastases, we also considered other possible causes of brain lesions in association with clinical and laboratory signs of immunodepression, finally diagnosing a cerebral opportunistic infection.

## 327. DALBAVANCIN FOR THE TREATMENT OF OSTEOMYELITIS IN ADULT PATIENT

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**Abstract:** Dalbavancin is a semi-synthetic lipoglycopeptide antibiotic for intravenous administration, with strong activity against Gram-positive cocci, a favorable safety profile, a long half-life and high concentration in bone which makes it an alternative for treatment of osteoarticular infections such as osteomyelitis and spondylodiscitis. Due to its long half-life (372 hours), its dosage is 1,500 mg administered as a single infusion or 1,000 mg followed by 500 mg one week later. This pharmacokinetic characteristic opens new doors in terms of management of patients.
**Introduction:** Spondylodiscitis is a spinal infection affecting primarily the intervertebral disk and the adjacent vertebral bodies. The clinical presentation is often insidious and the delayed diagnosis causes disabling outcomes. The initial onset usually involves inflammatory back pain, though the disease may course with fever, asthenia and neurological deficit. These are the most severe complications. Diagnosis is based on clinical, radiological, laboratory, microbiological and histopathological data. Magnetic resonance imaging is the technique of choice for the diagnosis of spondylodiscitis. The

aim of the treatment is to eliminate the focus of infection with antibiotic therapy, restore spinal functionality, and reduce pain.
**Case Report:** A 43-years old woman was admitted to hospital complaining of disabling back pain, occasionally treated with NSAID. Her past medical history was not significant. Lower back pain, that caused functional limitation of movements, started two weeks after an invasive dental procedure. On the suggestion of her doctor, she made a lumbosacral magnetic resonance. MRI revealed spondylodiscitis with an important involvement of L3 and of its adjacent soft tissues and left psoas muscle. Lasegue maneuver was positive to the left; Wesserman maneuver was positive bilaterally. At the blood count: White blood cells: 8,64 x 103/uL with 85 % neutrophils and CRP was 25 mg/l (n.v. 0-5). During the hospitalization a biopsy under TC guide was performed with a transpedicular introducer and two samples of the lesion were picked up in the left paravertebral area at the level of L3. The culture of the bone biopsy was positive for Staphylococcus epidermidis. So we started infusion of Dalbavancin (1500 mg). A further intravenous infusion of Dalbavancin 1500 mg was subsequently administered eight days later. The infusions were well tolerated without any adverse events. The patient was discharged with clinical improvement of the symptoms. 30 days later, the patient underwent one other infusion of dalbavancin at the same dosage (1500 mg). After two months, at the follow-up, the lumbo-sacral magnetic resonance showed improvements of findings compared to that carried out before hospital admission.
**Discussion:** The most common Gram-positive pathogen associated with osteomyelitis are staphilococci, and typical treatment durations for this infection are recommended to be at least 4 weeks. There is scientific evidence that the treatment of osteomyelitis for 4 weeks at a dose between 1000 and 1500 mg has an excellent safety and tolerability profile.The concentrations of dalbavancin in bone are expected to be relevant to treatment of osteomyelitis. The bone concentrations are expected to be free and available for antimicrobial activity. These pharmacokinetic results indicate that agents with good penetration profiles would have a potential utilization in such infections.
**Conclusion:** Dalbavancin is a therapeutic option that has demonstrated an excellent safety profile. Its use represents a cost-effective solution for the treatment of those patients with spondylodiscitis who would need hospitalization. It also has the advantage of reducing the duration of hospitalization. Further real-life studies with a larger sample size are therefore needed to better assess the safety profile of the dalbavancin, especially to investigate the true incidence of rare adverse events.

## 328. MEROPENEM-VABORBACTAM AS SALVAGE THERAPY IN ACUTE PYELONEPHRITIS CAUSED BY PSEUDOMONAS AERUGINOSA XDR IN IMMUNOCOMPROMISED HOST

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Pseudomonas aeruginosa is an opportunistic aerobic Gram-negative bacterial pathogen associated with a variety of genitourinary, pulmonary and abdominal infections in hospitalized patients often in association with significant morbidity. We report a case of a 64 year old female affected by acute pyelonephritis. The infection had previously been treated with several courses of antibiotics and resolved after initiation of meropenem-vaborbactam. The past several years have brought several new treatment options including meropenem vaborbactam, a beta-lactam/beta-lactamase inhibitor combination antibiotic with in vitro activity against Gram negative bacteria such as Enterobacterales (>99,9% susceptible) and Pseudomonas aeruginosa isolates (89,5% susceptible). This bacterium is an opportunistic pathogen usually acquired in hospital so it causes nosocomial infections especially in intensive care units. It affects severely immunocompromised hosts.
Vaborbactam is a boronic acid, non-β-lactam β-lactamase inhibitor with no antibacterial activity. More specifically, vaborbactam inhibits various class A carbapenemases, class A ESBLs, and class C cephalosporinases. By inhibiting β-lactamase it, he allows meropenem to act against gram negative bacteria by interfering with wall synthesis. Compared to meropenem monotherapy it is more effective against resistant gram negative bacteria. Furthermore it has shown an excellent tolerability profile and no safety concerns.
We present a case of a 64 year old female with a history of previous non Hodgkin lymphoma, hygammaglobulinemia, recent hospital admission for removal of cerebral meningioma followed by a stop in intensive care unit. The patient presented a history of repeated hospitalizations for febrile symptoms, in the last of which she presented at blood count neutrophilic leukocytosis, increase in ves and crp and a positive urineculture for Pseudomonas aeruginosa and Enterococcus faecalis. At the time of admission the patient presented a fever of 39 accompanied by chills, dysuria, suvrapubic pain, nausea and vomiting. During previous hospitalizations the patient had been treated with different antibiotic regimens based on: amoxicillin/clavulanate (875/125 mg q12h per os for five days), ciprofloxacin (500 mg q24h per os for five days), piperacillin/tazobactam (4,5 g q12h ev for five days) plus amikacin (500 mg q24h ev for five days). All of these therapies were set on the basis of the antibiogram. Despite the repeated treatments carried out, neither the clinical nor the microbiological picture was resolved. At the time of admission the patient was in poor general conditions. On physical examination, the patient was found to be febrile with oral temperature 38.5°C, heart rate 93 bpm, and blood pressure 117/65 mm Hg. Chest and cardiac auscultation did not reveal any abnormality. Urinalysis showed the presence of leukocyte esterase and nitrite. Urineculture showed positivity for Pseudomonas aeruginosa resistant to amoxicillin/clavulanate, amikacin, ciprofloxacin, piperacillin/tazobactam. The germ had an intermediate resistance to meropenem.
The bacterium that was previously sensitive to different classes of antibiotic had acquired an extensive-drug resistance. At blood count there was neutrophilic leukocytosis, there was also present an increase in ves, crp. Chemistry panel and liver enzyme levels were normal. Plasma immunoglobulin dosage showed a quantitative deficit of IgG (5,3g/l nv 7-16). Renal US showed calyceal estasia and slight thickening of the urothelium. On the basis of the information of the urinoculture it was decided to set up therapy with meropenem-vaborbactam at a dosage of 2g q8h/die. Evolution was rapidly favorable, with apyrexia reached at day 2 and with a notable improvement in general clinical conditions. The treatment was continued for fifteen days and concluded in the absence of any complications. It was also noted the normalization of the previous alterations in the blood count and the negativization of the inflammatory index.
Urine culture was repeated one week after the end of therapy and it was negative.
This case report highlights the importance of using new drugs in some clinical contests especially in immunocompromised patients with histories of multiple hospitalizations especially in intensive settings. In this patient in a state of sepsis, the use of this drug proved to be crucial in the resolution of the clinical context. In the era of antibiotic resistance it is important to learn how to use these new drugs by minimizing their use in empirical therapies and using them instead in a targeted manner so as to preserve their effectiveness as much as possible. The optimization of the use of antibiotics aims to improve the patient's care pathway and therefore also the treatment outcome by ensuring a therapy that meets the criteria of efficacy and minimization of adverse effects including that of the onset of antimicrobial resistance.

## 329. PULMONARY INVOLVEMENT IN EBV INFECTION IN AN IMMUNOCOMPETENT PATIENT: A CASE REPORT

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Mononucleosis is a worldwide herpersvirus infection caused by Epstein Barr Virus (EBV). Typically, patients present with fever, pharyngitis and lymphadenopathy; splenomegaly is usually founded on physical examination. Although there are few reports describing severe clinical manifestations of the EBV infection in immunocompetent patients, pulmonary involvement appears to be rare (8%).
We describe a case of 34 years old male patient arrived in March 2022 at our Emergency Department complaining a one-week history of fever (40°C), headache and dyspnoea. He had no past or chronic conditions except for monoclonal gammopathy of undetermined significance. Physical examination revealed splenomegaly (confirmed by abdomen ultrasound), laterocervical adenopathy and maculopapular rash (which may followed the administration of penicillin at home few days before recovery). Chest auscultation showed decreased breath sound on left side. A thorax X-ray showed a left lower consolidation. Lung ultrasound was performed later using an ultrasound scanner (MyLab ™ X6, Esaote, Genova, Italy) with a 3.5 MHZ convex probe in transversal scan and each emitorax is systematically divided into six regions: it documented bilateral B-lines, minimal bilateral pleural effusion and a small subpleural consolidation at right pulmonary

apex.
Initial laboratory values were as follows: haemoglobin 12.9 g/dl, platelet count 144/mm3, white cell count 8/mm3 (with 32% segmented neutrophils, 56.5% lymphocytes, 9.5% monocytes), C-reactive Protein 50.3 mg/l (normal <6 mg/l), erythrocyte sedimentation rate 39 mm/h (normal <35 mm/h), alanine aminotransferase 224 U/l (normal 10-65 U/l), aspartate aminotransferase 329 U/l (normal 5-40 U/l), alkaline phosphatase 141 U/l (normal 30-120 U/l), gamma-glutamyl transpeptidase 179 U/l (normal 10-80 U/l), lactate dehydrogenase 463 U/l (normal 87-241 U/l) and prothrombin time ratio 1.37 (normal 0.85-1.15). The remainder of the chemistry profile was unremarkable. Group A Streptococcus, Legionella pneumophila, Mycoplasma pneumoniae, Bordetella pertussis and respiratory virus (included SARS-CoV-2) were excluded. Blood cultures, hepatitis B, C, HIV and Cytomegalovirus serologies were negative, while EBV VCA- IgM antibodies were positive (121 U/ml). Serum EBV DNA quantification confirmed this result. The patient was then recovery and treated with acetaminophen for fever: he did not require oxygen administration and he was discharged after a week.
Pulmonary involvement was considered an EBV-related complication, after excluding of other causative agents: studies show the presence of interstitial infiltrates in 3-5 % of cases, while pleural effusion has rarely been reported in association with mononucleosis.
EBV pneumonia is a rare condition, however it's one of the three most common cause of severe viral community acquired pneumonia (CAP), along with influenza and adenovirus. EBV pneumonia should be considered in patients with atypical lymphocytes and mildly elevated serum transaminases.
The pathophysiology of lung involvement in patients affected with infectious mononucleosis is still unclear and it could be related to mononuclear infiltrations in the perivascular and peribronchial tissues.
However, symptomatic pneumonia and hypoxemia are very uncommon and radiographic and sonography findings often appear to be clinically insignificant: for this reason, it is possible that pulmonary involvement is more common in infectious mononucleosis than previously reported. Further systematic studies are needed to establish the real incidence of pulmonary involvement in EBV infection: lung sonography could be helpful to detect pleural effusion and consolidation in patients asymptomatic for hypoxemia.

## 330. POTENTIAL LIGHTS AND SHADOWS OF IMMUNOSUPPRESSIVE THERAPY

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Several autoimmune diseases are currently treated by immunosuppressive medications, often prescribed in association to minimize the side effects of each individual drug. Benefits clearly exceed harms of immunosuppressive therapy. However, serious and potential life-threatening side effects occasionally occur.
Here we report a case of an opportunistic infection (neuro-toxoplasmosis) complicated with adrenal insufficiency.
A 53-years-old woman was admitted to our Ward because of low grade fever (37.5 – 37.8 °C) started one week before. She was affected by seronegative myasthenia gravis treated with immunosuppressors (prednisone 25 mg/die since 2009 and cyclophosphamide 50 mg bid since 2010) and pyridostigmine – and allergic asthma. Because of a recent worsening of O2 pressures she benefitted of continuous home oxygen therapy.
At the admission the physical and neurological exam did not show any alteration. The SARS-Cov2 assay was negative. Her arterial gas analysis confirmed respiratory failure with hipoxemia and normocapnia. While chest radiography at the admission was normal, in the second day a lung CT scan showed areas of consolidation consistent with bilateral pneumonia and at the blood teste we observed a pancytopenia affecting more the B line in the lymphocytes (total lymphocytes: 123/mcL; CD4: 25/mcL; CD8: 57/mcL; ratio CD4/CD8: 0.440; CD19: 0; NK: 33/mcL) and reduced IgG production (298 mg/dL, nr 650 – 1600) associated with anemia (Hb 10.5 g/dL), thrombocytopenia (137 000/mL). We set a broad spectrum antibacterial therapy (meropenem) and oxygen therapy (4 L/min in simple mask) and we stopped the cyclophosphamide and reduced the dosage of prednisone. We also added, as suggested by guidelines, prophylactic therapy with trimethoprim-sulfamethoxazole and acyclovir.
The coltural test failed to isolate germs in the blood and identified Candida lusitania and Enterococcus faecalis in the urine. Multiplex PCR panel failed to identify any germ on the bronchial aspirate sample so we started therapy with fluconazole.
On day the third, the patient presented focal neurological deficits (paresis of the upper left arm). Brain CT showed an area of ipodensity in the right frontal cortico-subcortical area in a context of diffuse leukoencephalopathy suggesting a possible opportunistic infection of the CNS (central nervous system). This suspicion was confirmed by a brain MRI soon after performed. Analysis of the cerebrospinal fluid revealed: increased proteins, decreased glucose, normal WBC count; positive PCR for Toxoplasma gondii.
In agreement with the Infettivologist, a specific treatment with sulfadoxine/pyrimethamine (stopping trimethoprim-sulfamethoxazole) was initiated.
On day the ninth in spite of the specific chemotherapy, the patient presented hemodynamic instability with fever (38.9°C), arterial hypotension and tachycardia. The differential diagnosis included worsening of septic status and an acute adrenal insufficiency, triggered by the systemic infection (in addition to reduction corticosteroid therapy). We immediately started fluide therapy and i.v. corticotherapy (methylprednisolone 40 mg) resulted in a temporary improvement.
Ten days after the toxoplasmosis diagnosis, no change in neurological signs was observable and a control brain MRI showed an abscessual organization of the already known cerebral lesions.
The day after the realization of this MRI the patient died of sudden (cardiac?) death.
This complex clinical case was marked by the development of an opportunistic infection of the central nervous system which, despite specific therapy, is known to have poor prognosis. We remember the necessity, in all patients treated with immunosuppressive drugs, to be correctly followed-up (e.g. regular execution of blood counts and lymphocyte subpopulations, drug dose adjusting or tapering strategies) in order to prevent infectious and non-infectious complications. Early infection can be detected by PCR assays, which can be performed in different samples according to clinical suspicion (bronchial aspirate, cerebrospinal fluid, etc).

## 331. EFFICACY AND SAFETY OF THE NOVEL CEPHALOSPORINS CEFTAROLINE AND CEFTOBIPROLE IN A TERTIARY CARE SETTING

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Efficacy and safety of the novel cephalosporins Ceftaroline and Ceftobiprole in a tertiary care setting
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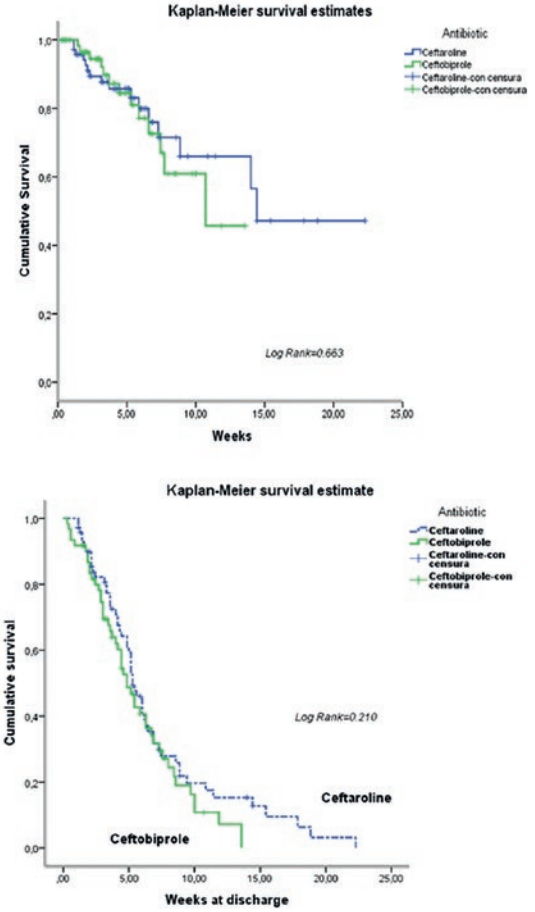
**Background:** Gram-positive bacteria show increasing rates of resistance to antimicrobials and cause significant morbidity, mortality and health care costs. New and more effective treatment options are needed. Two recently approved cephalosporins, Ceftaroline and Ceftobiprole, have shown potent activity against resistant Gram-positive cocci, a good tolerability, time-dependent bactericidal activity and coverage of methicillin-resistant Staphylococcus aureus and penicillin-resistant Streptococcus pneumoniae. Approved indications include pneumonia and acute bacterial skin and skin structure infections (ABSSSI) for Ceftaroline, but several studies suggested efficacy and safety of Ceftaroline and Ceftobiprole in other infection settings. In this study we describe clinical results with the use of Ceftaroline and Ceftobiprole in our Hospital real life practice.
**Methods:** Single center, observational, retrospective clinical study of patients treated with Ceftaroline or Ceftobiprole in clinical practice at the Monaldi Hospital, Naples, Italy, between October 2016 and August 2021. Data retrieval was approved by our Institution Ethics Committee. All patients treated with Ceftaroline or Ceftobiprole, alone or in combination with other antimicrobials, were included. There were no exclusion criteria. The following variables were collected and analyzed: demographic, clinical and hemato-chemical data, comorbidities (CCI), severity of disease, type and characteristics of infection, indications, doses and duration of Ceftaroline/Ceftobiprole administration, outcomes of treatment and length of hospitalization, adverse events. Safety assessment was also done. Continuous variables were compared using the Mann-Whitney U test, whereas categorical variables were compared using Pearson's chi-square test. Analysis of variance for repeated measures was performed using the Bonferroni post-hoc test. Multivariable Cox's regression analyses were used to identify predictors of hospital mortality. Survival curves were obtained using the

Kaplan-Meier estimate. A two-sided probability p-value <0.05 was considered statistically significant.




**Results:** 138 patients were included, of whom 75 were treated with Ceftaroline and 63 with Ceftobiprole. Most patients received Ceftaroline at the dose of 600 mg every 12h and Ceftobiprole at the dose of 500 mg every 8h, with dose adjustments according to renal function. No differences were observed between the two treatment groups in terms of demographic and anthropometric features, biochemical parameters of inflammation, liver and renal function or preferential use in hospital wards with different intensity of care. In culture-positive infection episodes, Staphylococcus aureus was the most commonly isolated pathogen. Patients treated with Ceftobiprole had a higher CCI (p<0.001) and a higher prevalence of multiple site infections (p<0.01). Moreover, Ceftobiprole was more often used in empirical treatment regimens (p< 0.004). In contrast, Ceftaroline was more frequently used in patients with health care related infections (p = 0.014). Most patients stopped antibiotics due to completion of therapy in both groups. Ceftaroline and Ceftobiprole were largely used in combination with other antibiotics, most frequently daptomycin, piperacillin/tazobactam and meropenem. Ceftobiprole was used more often as the first-line antimicrobial (in 23/63 (36%) patients compared with 16/75 (21%) for Ceftaroline [p= 0.058]). No significant differences between Ceftaroline and Ceftobiprole groups were observed in terms of hospital mortality (p = 0.663; Figure 1), and length of hospital stay (p= 0.210; Figure 2). Significant CRP reduction from baseline to the end of treatment was noted in both groups while an improvement of blood glucose and renal functional parameters were seen in the Ceftaroline group. The only factor significantly associated with the outcome at univariate and multivariate Cox's regression analysis was S. aureus infection. Treatment with Ceftaroline and Ceftobiprole was generally very well tolerated.
**Discussion:** In a tertiary care center, use of both Ceftaroline and Ceftobiprole in patients with significant comorbidities was associated with a favorable outcome in most cases, with a limited burden of adverse events.

## 332. A CASE OF POTT DISEASE

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**Introduction:** Tuberculous spondylitis, or Pott disease, is the most common form of skeletal tuberculosis (TB); it usually affects vertebral bodies of lower thoracic and upper lumbar region. During primary M.Tuberculosis infection, bacillemia may spread in bone tissue; in subclinical disease small sites of infection are confined by local immune processes. Reactivation of infection with progression to clinically apparent disease may occur when local immune defences fail, like in malnutrition, old age, HIV infection, alcohol intake, organ transplantation, chemotherapy, CKD etc. Disease begins with inflammation of the anterior ligament and it could spread to the adjacent vertebral body with risk of spinal cord compression and paraplegia. A paravertebral cold abscess may also be present. The most common symptom is local pain, sometimes in association with muscle spasm and rigidity; fever and weight loss are less prevalent. With advanced disease, collapse of vertebral bodies results in kyphosis. There are not typical radiologic findings of tuberculous spondylitis. CT scan, myelography, and mainly MRI are valuable in demonstrating soft tissue extension and compression on nervous structures. Diagnosis of musculoskeletal TB is established by microscopy and culture of infected sample obtained by needle aspiration or biopsy of the lesion. Differential diagnosis includes cancer and other infections (e.g. S.aureus osteomyelitis or brucellosis). Treatment of musculoskeletal TB consists of the same antimicrobial therapy as that for pulmonary TB with isoniazid (INH), rifampin (RIF), pyrazinamide (PZA) and ethambutol (EMB) as first-line drugs. Longer therapeutic course should be preferred for musculoskeletal TB because of poor drug penetration into osseous tissue. 6 to 9-month regimens containing RIF are at least as effective as 18-month treatment without RIF. Chemotherapy is efficacious in skeletal TB, but severe cases may require surgery like in presence of an abscess. Drug-induced hepatitis (DILI) is the most frequent serious adverse reaction to the first-line drugs, particularly in presence of prior advanced liver disease, liver transplant, or hepatitis C infection. For patients with marginal hepatic reserve DILI may be severe, even life-threatening. Regimens with fewer potentially hepatotoxic agents are selected in patients with advanced liver disease or whose serum ALT is >3 times the upper limit of normal at baseline. Alternative regimens to use in patients with hepatic disease can include: treatment without PZA (often it causes DILI), treatment without INH and PZA in case of advanced liver disease, or regimens with poor hepatotoxicity for patients with severe and unstable liver disease, like fluoroquinolones and cycloserine. During antituberculous treatment patients need clinical monitoring, measuring serum aminotransferases and total bilirubin concentration every 1–4 weeks for the first months of therapy. Treatment must be discontinued if total bilirubin is >3 mg/dl or serum transaminases are more than five times the upper limit of normal, even if asymptomatic patient. Once liver function tests return to baseline (or fall to less than twice normal) it should resume antituberculous regimen composed of liver sparing drugs or first line agents in stepwise manner.
**Case Report:** A 58-years-old female patient presented to Emergency Department because of severe anemia discovered during an orthopaedic consultation for the removal of leg plaster. She had history of HBV and alcohol associated cirrhosis, thrombocytopenia, F2 esophageal varices, psoriasis and an adjustment disorder. She was admitted to Internal Medicine Department. Because of presence of melena she underwent gastroscopy with evidence of congestive gastropathy. During the hospitalization she developed persistent fever despite antibiotic therapy, pancytopenia, mild increase of serum C reactive protein (16 mg/L [n.v. 0-5mg/L]), serum procalcitonin was <0.5 ng/ml. Chest and abdomen CT scan, transesophageal echocardiography and culture tests were negative. PET and MRI showed suspicion of D11 vertebral osteomyelitis, so she underwent biopsy of the lesion that demonstrated granulomatous inflammation and necrosis typical of tuberculosis disease. Ziehl-Neelsen stain was negative, interferon-gamma release assay was positive. She had Child C cirrhosis, normal serum aminotransferases concentration, pseudocholinesterase was 2640 U/L (n.v 4900-12000 U/L), total bilirubin 1.4 mg/dl (n.v 0.3-1.2 mg/dl), INR 1.5 (n.v 0.8-1.2). So she was moved to the Infectious Disease Department where she started antitubercular medications, at first INH 150 mg twice daily plus EMB 400 mg three times daily and levofloxacin 750 mg/daily. After a week in absence of hepatotoxicity signs, it was added RIF 300 mg twice daily. The next liver function tests were unchanged, she had neither other fever episodes either neurological symptoms.
**Conclusion:** Diagnosis of Pott disease is frequently delayed because of its subacute course especially in regions where the incidence of TB is relatively low. Late diagnosis is the main factor in determining the outcome of disease.

## 333. FEVER, SUBCUTANEOUS NODULES, AND PULMONARY PROCESS. A CASE OF DISSEMINATED NOCARDIOSIS

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**Introduction:** Nocardiosis is an infection caused by Nocardia, an aerobic gram-positive actinomycetes with acid-fast filamentous branching rods. Global prevalence is unknown. Annually, around 90–130 cases, with male prevalent, are reported in Italy. It affects immunocompromised and immunocompetent patients by ingestion, inhalation, or cutaneous inoculation of particles founded in soil, water environment or dust. Risk factors are immunosuppressive or autoimmune diseases, malignancy, infections (HIV, TB), DM, alcoholism, COPD. N.farcinica is more virulent, with tendency to CNS dissemination and to relapse or progress despite appropriate therapy. Nocardiosis is a localized or disseminated disease, who involves mainly lung, CNS and skin, but also bone, joints, heart, kidney, adrenal gland, liver etc. Primary infection affects most commonly lung (nodular or interstitial pattern) and non-intact skin (ulcerations, cellulitis, nodules, abscess, lymphangitis, mycetoma), while bacteremia and CNS infection (abscess or meningitis) are consequence of dissemination. Symptoms vary from fever to night sweats, fatigue, anorexia and weight loss, associated or not with neurologic or pulmonary disorders. Definitive diagnosis is made by isolation, speciation and antimicrobial susceptibility test of organism from a clinical specimen. Differential diagnosis is made by fungal (Aspergillus), parasitic (Toxoplasma, Leishmania), mycobacterial and other bacterial infection (K.Pneumoniae, P.Aeruginosa), but also by neoplasms of lung, skin and CNS. Antibiotic therapy against N.farcinica consists with TMP-SMX, amikacin, imipenem. Oral or monotherapy is advised in localized disease. In case of cerebral and multiorgan dissemination is better to associate iv therapy with TMP-SMX (15 mg/kg/day), imipenem (500 mg q.i.d) and amikacin (7,5 mg/kg/day) for 3 to 6 weeks, then switched to oral therapy if clinical improvement (TMP-SMX plus minocycline or amoxicillin-clavulanate). Duration of therapy is variable: 3-6 months for immunocompetent patient, 6-12 months for immunocompromised patient or with serious pulmonary infection, at least one year in case of CNS dissemination. It depends on clinical and radiologic follow up every 1-3-6-12 months, monitoring drug toxicity. Mortality rate is up to 50% in immunocompromised patients with disseminated infections and about 10% in immunocompetent patients with pulmonary lesions, in course of appropriate therapy.
**Case Report:** A 75-year-old male was admitted to Internal Medicine Department for recurrent fever, unintentional weight loss, hemoptysis, and new-onset painful subcutaneous nodules. He was former smoking with history of hypertension, dyslipidemia, atheromasias, peptic ulcer, diverticulosis, BPH. His therapy was rosuvastatin, clopidogrel, losartan/HCT, amlodipine. At physical examination resulted subcutaneous nodules of back and right leg and systolic heart murmur. Laboratory tests showed neutrophil leukocytosis, hypokalemia. Chest X-ray and Thoraco-Abdominal CT scan discovered excavated pulmonary, muscular, renal, and adrenal gland lesions. Differential diagnosis was made between neoplasm, infection, or inflammation state. BAL displayed atypical filamentous Gram-positive bacilli. Lung and subcutaneous nodule biopsies showed acute suppurative inflammation process. HIV, fungal infections and M.Tuberculosis screening resulted negative; autoimmune screening panel was normal; urine and saliva sample were negative while N.farcinica was isolated from hemoculture and subcutaneous nodule swab. TTE excluded infective endocarditis, but brain CT scan showed abscessed lesions compatible with cerebral disseminated nocardiosis. It was prescribed iv empiric therapy with cefazolin plus amikacin for 7 days. Based on antibiogram, it was switched to TMP-SMX plus imipenem/cilastatinfor 6 weeks, with progressive tests negativization and clinical improvement. He was dismissed at home with indication to CT scan follow up after 2 weeks of oral monotherapy with TMP-SMX. However, this exam showed new-onset brain, lung and subcutaneous nodules, so he was readmitted to our department to perform iv association therapy with TMP-SMX, imipenem and amikacin for 4 weeks. Another TTE and TEE showed a lesion suspicious for endocarditis, so PET was performed, with result of active metabolism of gluteus subcutaneous nodule and resolution of other localizations. Brain CT scan demonstrated reduction of cerebral lesions, so he was dismissed at home with indication to prolong oral therapy with TMP-SMX and to perform brain CT scan and PET at 30-45 days, with consecutive ambulatory management follow up.
**Conclusion:** Nocardiosis should be suspected in patient with brain, soft tissue or cutaneous lesions and pulmonary process. Empiric antibiotic therapy should be prescribed as soon as possible because of dissemination risk. Diagnosis is made late due to the need for invasive examination and slow bacterial growth. It is important to determine antimicrobial susceptibility test to tailor the regimen and prevent antimicrobial resistance, but also because N.farcinica is able to relapse or progress despite appropriate therapy.

## 334. A MAZE OF MISDIAGNOSES

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**Case Report:** A 75-year-old man presented to the Emergency Department because of profound asthenia with a progressive reduction of functional autonomy and bed confinement in the last few days. No fever, cough, dyspnea nor blood losses were reported, but the patient referred a weight loss of about 10 kg in the previous month.
His medical history was notable for hypertension, dual antiplatelet therapy in chronic ischemic heart disease, recurrent urinary tract infections (he had recently ended a course of levofloxacin), a recent diagnosis of giant cell arteritis and rheumatic polymyalgia for which he was under treatment with prednisone 20 mg per die.
On admission, the patient was alert and oriented. His physical examination was unremarkable. Lab tests showed leukocytosis (16300/mL) with neutrophilia, increased reactive-C-protein serum levels (13.4 mg/dL) and elevated creatinine (1.8 mg/dL). Urine chemical-physical examination was suggestive for urinary tract infection, so urine samples for cultural analysis were collected and empiric antibiotic therapy with ceftriaxone was initiated. The patient was then admitted to our unit, where he only reported muscular and joint pain responsive to NSAID and consistent with exacerbation of his rheumatic disorder. Creatinine levels rapidly improved with intravenous fluid therapy, inflammation markers progressively reduced and urine culture tests resulted negative, so antibiotic therapy was suspended after 7 days. On suspicion of a paraneoplastic syndrome in a patient with recent weight loss, reduction of his performance status and recent diagnosis of rheumatic polymyalgia, we decided to perform a total body CT. Thoracic and Abdomen CT-scans resulted negative, while head CT-scan revealed millimetric focal brain lesions suggestive for melanoma metastasis, according to the radiologist. The patient was then inspected by the dermatologist consultant, who detected three small melanocytic nevi worthy of further investigations. After 8 days of hospitalization, the patient was dismissed in order to pursue the diagnostic work-up in an outpatient setting.
He quickly underwent contrast-enhanced brain MRI, which didn't confirm the CT-scan hypothesis but raised the suspicion of amyloid angiopathy in presence of diffuse hemosiderin deposition. A FDG PET/CT was carried out, with evidence of a single, focal increased metabolic uptake within the large bowel (suggestive for a colonic adenoma).
Just 5 days later, the patient was readmitted to our hospital for the occurrence of vomiting and worsening mental confusion. Brain CT-scan showed a subtle cortical and subcortical hypodensity in the right temporoparietal region and cerebral CT angiography demonstrated the occlusion of the M2 segment of right middle cerebral artery. Thrombolytic therapy was excluded (NIHSS 6, almost 24 hours from last time the patient had been seen normal, high bleeding risk). In the following days left-sided motor and sensory deficits occurred, so repeated brain CT-scans were performed and documented a sharp dermarcation of the right ischemic injury with no hemorrhagic transformation. In order to rule out a cardioembolic origin of the ischemic event, in absence of atrial fibrillation on continuous EKG monitoring, an echocardiographic approach was implemented: both transthoracic (TTE) and transesophageal (TEE) examination revealed the presence of valve vegetations associated with both aortic and mitral moderate-to-severe regurgitation. Multiple blood cultures were performed and resulted positive for Streptococcus gallolyticus, so antibiotic therapy with ampicillin was initiated. Another brain MRI confirmed multiple ischemic lesions, while abdominal CT-scans excluded other embolic complications. TEE was repeated 7 days after the previous one and showed persistent vegetations (up to 20 mm) with occurrence of one aortic valve cusp perforation, so an early surgical intervention was indicated. Almost 20 days after the ischemic event, neu-

rological improvements were documented and the patient was transferred to another center with surgical facilities. He was also given the indication to perform a colonoscopy because of the previous PET evidence and the detection of Streptococcus gallolyticus on blood samples (strongly related to the presence of gastrointestinal neoplasia).
**Conclusions:** Our patient was misdiagnosed several times and it took more than 1 month to reach the final diagnosis of infective endocarditis. This clinical entity is really difficult to be suspected and diagnosed. TTE is frequently inadequate to make a definitive diagnosis, and TEE is often mandatory. Embolic events are frequent life-threatening complications and the presence of valve vegetations should always be ruled out in case of stroke. Moreover, the isolation of the microorganism involved is really important, not only to administer a targeted antibiotic therapy, but also to identify potentially associated conditions and address further diagnostic investigations.

## 335. PITFALLS IN PROCALCITONIN DAILY USE: CASE REPORT AND REVIEW

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**Case Report:** A 69 years-old woman with stage 4 non-small cell lung cancer (NSCLC) was transferred to our ward from the Intensive Care Unit (ICU) of the hospital. She had been admitted to the ICU because of severe SARS-CoV-2 related pneumonia. There, she was treated with invasive ventilation and vasopressors, and her stay had been complicated by a non-ST elevation myocardial infarction and by lower limb critical ischemia, for which she underwent urgent surgical revascularization via a femuro-femural extra-anatomical bypass. She also underwent a cycle of antibiotic therapy with ceftriaxone for suspected pulmonary bacterial super-infection, with isolation of S. pneumoniae on broncho-alveolar lavage. Also, E. faecium was isolated on urine culture.
Upon admission in our ward she did not complain of any symptoms, was afebrile, hemodynamically stable and eupnoeic in nasal cannula 2L/min. Her cardiac and abdominal physical exam were normal; at lung auscultation diffuse ronchi were present; on her left foot, necrotic toes were noted.
Her blood cell count was notable for mild leucocytosis (10.22 x 10^9/L), a C reactive protein of 51.4 mg/L (reference range <5 mg/L) and procalcitonin levels of >50 ng/mL (reference range <0.5 ng/mL).
Empiric antibiotic treatment was started with meropenem and vancomycin, later switched to linezolid, according to the antibiogram on urine culture. After 7 days of treatment the patient remained afebrile, without urinary symptoms, but with very elevated levels of procalcitonin (above the upper measurable limit).
We then decided to dose calcitonin blood levels, in the hypothesis of ectopic PCT production by the NSCLC. The hormone blood levels came out very high (1950 pg/mL, reference range <10 pg/mL), thus confirming our suspicion of paraneoplastic syndrome. A CT scan of the neck executed during the hospitalization had not shown any abnormality in the thyroid parenchyma. Therefore, in the absence of any clinical signs of infection, antibiotic therapy was stopped. The patient has been discharged after a week, with no further complications.
**Discussion:** Procalcitonin is a widely used marker of bacterial infection. It can help clinicians to diagnose bacterial infections and to decide when to stop antibiotic therapy. However, there are some caveats when interpreting this test's results.
The example above illustrates one scenario, that of paraneoplastic syndrome, reported not only for NSCLC but also for small cell lung cancer and medullary thyroid cancer. Other non-infectious causes of PCT elevation include severe physiological stress, chronic kidney disease, immunomodulatory agents and Kawasaki disease.
Even though PCT is more specific for bacterial infection compared to other inflammatory markers (i.e., white blood cell count, erythrocyte sedimentation rate and C-reactive protein), false positives still occur, potentially leading to misdiagnosis of sepsis; conversely, low PCT levels may be found in the early course or in localized forms of infection.
Therefore, physicians should be familiar with the interpretation of this common blood test to improve patient care.

## 336. CAP HOSPITALIZATIONS CHANGES IN PANDEMIC PERIOD: A RETROSPECTIVE STUDY IN TWO AREAS OF ABRUZZO REGION

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Community-Acquired Pneumonia (CAP) represents one of the first causes of hospitalization and death in the elderly all over the world, and heavily weights on public health system. Since the beginning of the COVID-19 pandemic, everybody's behavior was forced to change, as of the result of a global lockdown strategy and the obligation of using personal protection equipment (PPE). We aimed to evaluate how the containment measures adopted to fight SARS-CoV-2 infection have influenced the spread of CAP in two different Local Health Boards (LHBs) of central Italy.
We considered two main periods of observation, before and after the national start of lockdown, in two Abruzzo's LHBs.
We analyzed 19,558 hospital discharge records of various pneumopathy causes, including COVID-19. We observed a significant decrease in bacterial and viral CAP hospitalizations in the pandemic period. The most important reduction was related to the first phase of pandemic. We highlighted the great economic advantage resulting from this condition through Diagnosis Related Group (DRG) values.
The enactment of social distancing measures to contain COVID-19 spread brought down admissions for bacterial and viral pneumonia. Our study emphasizes that, in closed spaces as well as at specific time of the year, costs for hospitalizations due to CAPs could be drastically reduced by mask wearing and social distancing.

# MALATTIE RARE

## 337. CARDIOVASCULAR RISK IN PATIENTS WITH TAKAYASU ARTERITIS DIRECTLY CORRELATES WITH DIASTOLIC DYSFUNCTION AND INFLAMMATORY CELL INFILTRATION IN THE VESSEL WALL: A CLINICAL, EX VIVO AND IN VITRO ANALYSIS

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Takayasu arteritis (TAK) is a chronic granulomatous vasculitis that increases vascular stiffness and arterial resistance. Most often the insidious and nonspecific early clinical symptoms may cause this vasculitis to be overlooked until its later stages, although in other cases all symptoms are synchronous and disease progression faster1.
Abnormal immune response is a crucial factor in the pathogenesis of TAK. Regulatory T lymphocytes (Tregs) are central mediators of peripheral tolerance2. Recent evidence suggests that Tregs can differentiate into T helper (Th)1, Th2 or Th17 cells, leading to a shift from an immunosuppressive function to a role in the pathogenesis of autoimmune diseases3. The potential role of Tregs and their associated cytokine secretion in TAK patients is under active investigation to expand the horizon toward more effective therapies.
In TAK disease, first-line treatment generally consists of high-dose steroids, and second-line agents include immunosuppressants4. Although these traditional agents can effectively promote TAK remission, relapses remain common when prednisone is discontinued4. Current treatment options, including new biologic therapies, focus on agents able to modify the disease pathophysiology in TAK patients5. The administration of anti-tumor necrosis factor-alpha (TNFα) agents, such as infliximab, appears to be a valuable and safe alternative to standard therapy6. By blocking TNFα-induced

activation of inflammatory signals, infliximab leads to long-term clinical improvement with significant benefits on patients' quality of life.
On these bases, we aimed to investigate which vascular and cardiac ultrasonography parameters might be predictive of increased cardiovascular risk in TAK patients, with respect to atherosclerotic patients (controls). We also investigated the potential role and importance of new markers (frequency of Treg and Th17 cells) in TAK-refractory patients treated with infliximab.
Clinical, instrumental and biochemical data in patients with active TAK were compared with age- and sex-matched atherosclerotic patients. In a subpopulation of TAK patients, Treg/Th17 cells were measured before (T0) and after 18 months (T18) of infliximab treatment. Echocardiogram, supra-aortic Doppler ultrasound, and lymphocytogram were carried out in all patients. Histological and immunohistochemical analysis were performed to correlate the vessel wall patho-morphology with clinical and laboratory results.
According to our findings, TAK patients displayed increased aortic valve dysfunction and diastolic dysfunction with respect to patients with atherosclerotic disease. When mild-to-moderate and moderate-to-severe aortic regurgitation were observed in TAK patients, the most severe conditions correlated with the highest serum levels of uric acid. A significant increase in aortic stiffness was also associated with peripheral T lymphocyte levels. Histological analysis revealed an increase in CD3+CD4+, and CD8+ cell infiltration in samples from TAK patients compared with controls. To evaluate neutrophilic vessel wall infiltration, CD15+ immune cells were stained and found significantly higher in TAK-derived vessels than in samples from controls, suggesting an association with inflammation-related vascular damage. The flow cytometric analysis showed that the mean percentage of Tregs was significantly reduced in TAK patients vs control. Interestingly, in patients treated with infliximab, this value significantly increased at T18 compared to T0. Concomitantly, the frequency of CD3+CD4+IL-17+ cells behaved in the opposite way: the higher number of Th17 cells observed in TAK patients at T0 compared to controls significantly decreased at T18 compared to T0. These observations strengthen the clinical efficacy of infliximab in TAK patients, supporting the idea that biologic therapy may achieve a better control of TAK progression and help to stabilize the Treg/Th17 score toward values similar to those found in atherosclerotic patients. Overall, supporting the specific pathogenetic mechanisms of vessel damage in TAK patients, our data suggest that the increased risk of atherosclerotic cardiovascular disease (ASCVD) correlates directly with the degree of inflammatory cell infiltration in the vessel wall. Importantly, by restoring the normal frequency of Tregs/Th17 in TAK patients, infliximab therapy might help to reduce the cardiovascular risk in TAK patients.
**References:** - 1. Vanoli M et al. Arthritis Care Res. 2005. doi: 10.1002/art.20922. - 2. Dominguez-Villar M et al. Nat. Immunol. 2018. doi: 10.1038/s41590-018-0120-4. - 3. Gao N et al. Clin. Exp. Rheumatol. 2020. - 4. Wen D et al. Int. Rev. Immunol. 2012. doi: 10.3109/08830185.2012.740105.- 5. Clifford A et al. Curr. Opin. Rheumatol. 2014. doi: 10.1097/BOR.0000000000000004. - 6. Goujon, C et al. Ann. Dermatol. Venereol. 2019. doi: 10.1016/j.annder.2019.04.013.

## 338. RITIRATO

## 339. VEXAS SYNDROME: A PROTOTYPE FOR HEMATO-INFLAMMATORY DISEASES? A CASE REPORT

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**Background:** VEXAS (Vacuoles, E1 enzyme, X-linked, Autoinflammatory, Somatic) syndrome is a rare adult disease, first reported in 2020 (1, 2), caused by somatic mutations in hematopoietic progenitor cells in the X-linked gene UBA1, resulting in decreased ubiquitylation, impaired hematopoiesis and systemic inflammation.
**Case Presentation:** A 62-year-old male had a diagnosis of relapsing polychondritis (RP) on the basis of fever, weight loss and non-productive cough with pulmonary infiltrates, associated with nasal and laryngotracheal chondritis, costochondral and costovertebral arthritis, episcleritis, urticarial papules and aortitis. The transbronchial biopsy showed inflammatory lymphocytic infiltrates and signs of organizing pneumonia. An oral steroid treatment was started and any attempts to reduce steroid dose resulted in the appearance of infectious complications. In parallel with the onset of RP, a macrocytic anemia developed with normal laboratory tests and bone marrow biopsy (BMB). A DNMT3A mutated gene, predisposing to clonal hematopoiesis, was reported and mild thrombocytopenia developed.
Three years later the patient was admitted to the Internal Medicine ward because of the acute onset of fever for 4 days associated with headache, left hemisome hypoesthesia, bilateral hearing loss, chest wall pain and conjunctivitis. At laboratory neutrophilic leukocytosis, macrocytic anemia, thrombocytopenia and increased PCR, with slightly modified PCT but normal lactates and increased Serum Amyloid A (SAA) protein (day 1) were present. The absence of alterations at chest X-ray, abdominal ultrasound, brain CT and EEG, with negative blood and urine cultures, suggested a systemic reactivation of RP. Treatment with intravenous methylprednisone, ampicillin, meropenem and acyclovir was administered, with clinical improvement (day 8). Steroid therapy was stepped down, antibiotic therapy was discontinued and infection prophylaxis was started. The patient underwent weekly administration of erythropoietin and red blood cell transfusions. A BMB was repeated, showing trilinear maturation disorder, consistent with myelodysplastic syndrome. We suspected VEXAS syndrome and the somatic mutation in UBA1 (M41T) was found.
On day 21st, after the reduction of 10 mg/day of methylprednisone, fever, dyspnea and arterial oxygen desaturation relapsed, with negative chest X-ray, increased PCR, SAA and hematological worsening; steroid dosage increase improved clinical and laboratory changes. On day 32nd the patient developed pneumonia with septic shock, with neutrophilic dermatitis and worsening of anemia and thrombocytopenia. Empirical antibiotic therapy, fluid challenge, norepinephrine, oxygen therapy and red blood cell transfusions were given. Steroid therapy was maintained for 10 days and then given orally. After discharge a slow steroid decalage was carried out, with persistence of normal inflammatory markers, improvement of anemia and thrombocytopenia and without relapse of systemic symptoms. Six months after discharge the patient complained a right popliteal deep vein thrombosis.
**Discussion:** VEXAS syndrome is characterized by difficulty in treating RP with myelodisplastic syndrome. RP is a systemic autoimmune disease characterized by recurrent episodes of inflammation of cartilaginous and proteoglycan-rich tissues; in our patient the diagnosis was made on the basis of nasal chondritis, costochondral inflammatory non-erosive polyarthritis with typical chest wall pain and ocular inflammation. During hospitalization neurological symptoms, probably linked to nervous system vasculitis, and sensorineural hearing loss developed. In RP in VEXAS inflammatory pulmonary infiltrates and deep vein thrombosis may occur (3). A good clinical response to steroid with refractoriness to drugs other than glucocorticoids, typical of VEXAS, was observed in this patient. Studies, aimed to find effective steroid-sparing drugs, especially azacitidine and JAK inhibitors (4), are ongoing.
**Conclusions:** VEXAS syndrome is a rare severe hemato-inflammatory disease with a genetic link (1). A diagnosis should be considered in patients with treatment-refractory inflammatory disease (especially RP, Sweet syndrome and polyarteritis nodosa) associated with progressive hematologic alterations. Further studies are needed to identify the syndrome's pathogenesis, in order to design appropriate therapeutic strategies.
KEYWORDS: VEXAS, hemato-inflammatory diseases
REFERENCES: (1) Peter C. Grayson et al., VEXAS syndrome. (2) D.B.Beck et al., Somatic mutations in UBA1 and severe adult-onset autoinflammatory disease. (3) Ferrada et al., Somatic mutations in UBA1 define a distinct subset of relapsing polychondritis patients with VEXAS. (4) Bourbon et al., Therapeutic options in VEXAS syndrome: insights from a retrospective series.

## 340. IGG4 RELATED FIBROSIS: A RED FLAG IN CANCER DIAGNOSIS?

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**Introduction:** IgG4-related disease (IgG4 RD) is a rare fibro-inflammatory disorder characterized by a lymphoplasmacytic infiltrate and various degrees of fibrosis affecting several organs and systems. In 70% of cases, these findings correspond to an elevation of serum IgG4 subclasses. The clinical presentation is heterogeneous and the most common manifestations are sialoadenitis or dacrioadenitis, autoimmune pancreatitis type 1 (AIP-1),

pseudotumor orbitae, retroperitoneal fibrosis with aortitis, nephritis. Early immunosuppressive treatment with steroids, methotrexate, azathioprine or rituximab is essential to avoid the irreversible evolution. A close relationship between IgG4 disease and the development of malignant neoplasms has been observed, raising the suspicion of a possible paraneoplastic syndrome.
**Case Report:** A 60-year-old man was admitted to the emergency department after the onset of low back pain and oliguria. Blood tests showed increase in creatinine, BUN and serum electrolytes, suggesting a picture of acute renal failure. An abdominal CT scan revealed a solid hypo-dense tissue of 80 x 65 mm attached to L4-L5 and surrounding the sub-renal abdominal aorta, the common iliac arteries and veins and the ureters causing hydronephrosis. After confirmation of ureteral stenosis, pyelovescical stents were placed to treat the acute event. In the suspicion of a lymphoproliferative disorder, PET CT TB was performed showing an increased glucose uptake in the mass visualized on CT (SUV 4) with inhomogeneous radiopharmaceuticals distribution. Even if the retroperitoneal localization and radiological features raised the suspicion of retroperitoneal fibrosis, to further exclude the neoplastic nature an exploratory laparotomy with biopsy was performed. The histological examination showed fibrosis with lymphoplasmacytic infiltrate and numerous lymphoid follicles with germinal centres. The dosage of serum IgG4 subclasses demonstrated an increase in these subclasses (1.8 vs 1.4 g/L) leading to diagnosis of IgG4-related retroperitoneal fibrosis. The patient began treatment with prednisone at low-medium dose (0.3 mg/kg per day) because of difficult to control arterial hypertension. A rapid improvement in creatinine values and normalization of IgG4 titre were observed after which a gradual tapering of steroid was started. At the follow-up CT with mdc, performed still during steroid therapy, the fibrotic mass appeared unchanged but a new lesion, measuring 20 mm diameter, was detected at right kidney. The lesion was surgically removed and the histological finding showed a T1 clear cell renal carcinoma. After oncological consultation, it was decided to suspend immunosuppressive therapy and to continue close monitoring of the retroperitoneal fibrous mass. A CT scan with mdc, performed 3 months after surgery, showed a major reduction of the retroperitoneal mass, which was halved in size (20 x 45 mm), and the absence of radiopharmaceutical uptake at PET despite the suspension of steroid therapy.
**Conclusion:** The rapid regression of the mass, after removal of the renal neoplasm, suggests a close relationship between the onset of kidney cancer and IgG4 disease. Rare cases of paraneoplastic fibrosis are described in literature and in most of them the development of cancer occurred within one year after the diagnosis of IgG4 disease. Regression of fibrosis was also observed in these patients solely after surgical removal of the cancer lesion. Autoimmune pancreatitis represents the most studied form of IgG4-related disease of paraneoplastic nature and it is most frequently associated with gastric, pulmonary and prostatic neoplasia. Several cases of IGG4-related sialoadenitis associated with solid tumors have also been described.
To date, no case of IgG4-related retroperitoneal fibrosis has been associated with the development of kidney cancer although the findings are clearly correlated in the presented case. However the underlying pathogenic mechanism is still uncertain and requires further studies. A careful follow-up to detect early development of neoplasms is essential for patients affected with IgG4-related disease.

## 341. IS COVID-19 ALL THAT GLITTERS?

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An 18-year-old girl was admitted to the Emergency Department (ED) of our hospital for history of intermittent fever, fatigue and tachycardia for 1 month. These symptoms started after severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) infection. She reported no past medical or surgical history and allergies. Drug assumption was denied. She had refused COVID-19 vaccine for her own choice.
The patient reports that during the time of COVID-19 she had fever, mild exertional dyspnea, "brain fog", tachycardia and loss of appetite. At that time the general practitioner (GP) recommended antimicrobial (Clarithromycin 250 mg BID) and corticosteroid (Prednisone 25 mg QD) therapy for 6 days with transient clinical benefit. After swab test negativity, the fever relapsed in an intermittent pattern reaching 39°C. According to GP's recommendation, blood tests were performed showing elevated C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) with no leukocytosis. Because of the 1-month persistent symptoms since SARS-CoV2 infection, the patient was admitted to the ED of our hospital and then transferred to our Internal Medicine Department with the diagnosis of "fever and fatigue in a recent SARS-CoV2 infection".
On admission, she reported severe fatigue and weight loss in the last 2 months (>5% of the body weight). The molecular swab test for SARS-CoV2 was negative. Physical examination showed tachycardia (HR 110 bpm), normal conjunctiva, no skin rash, no superficial lymphadenopathy and no joint redness or swelling. Sinus tachycardia (HR 120 bpm) was recorded by the electrocardiogram without other findings. Thus, routine laboratory tests and temperature curve was performed. Blood tests showed elevated CRP/ESR, hyperfibrinogenemia, prolonged activated partial thromboplastin time (aPTT) and international normalized ratio (INR). The temperature curve recorded daily fever in the evening (peak 38.5 °C) without any signs or symptoms.
Supported by the clinical and laboratory findings, the differential diagnosis for Fever of Unknown Origin (FUO) was started following a recently available flowchart (Haidar and Singh, NEJM 2022). According to this algorithm, we could rule out:
In the current historical context, the diagnostic work-up could have found a possible conclusion in the diagnosis of multisystemic inflammatory syndrome of childhood (MIS-C). MIS-C is a newly defined condition in children and adolescents associated with SARS-CoV2 infection. In our patient, the persistent fever, the "brain fog", the elevated CRP/ESR and the prolonged aPTT/INR, associated with the recent SARS-CoV2 infection supported the MIS-C hypothesis but didn't fully meet the CDC and WHO criteria for the diagnosis.
For this reason, it was mandatory to continue the diagnostic workup to rule out other FUO's possible etiologies. According to the flow chart, CT scan of the chest and the abdomen were the next steps. This decision was carefully weighed, evaluating risks and benefits in consideration of the patient's young age. We decided to perform the CT scan that showed extensive wall thickening of the aortic arch, the abdominal aorta and its main branches. PET-CT was then performed and showed abnormal metabolic activity of the aortic arch, the ascending and descending thoracic aorta, and the abdominal aorta. These findings were suggestive of large-vessels arteritis. According to the EULAR/PRINTO/PRES for childhood-Takayasu Arteritis, the diagnosis of Takayasu arteritis was made. On rheumatologist's recommendation, corticosteroid therapy at high dose was administered. The patient reported clinical benefits, moreover, the near normalization of the inflammatory markers after 7-days therapy was observed. She was then discharged home with further medical management.
**Notable Conclusions:** considering the pandemic period, the clinical presentation of our patient could have been attributed to a COVID-19 complication in the emergent nosography entity called MIS-C. In this case, we think that was fundamental not to have underestimated the young patient's illness, in a period where there is the risk to associate everything with COVID-19. However, are we sure that SARS-CoV2 is totally innocent? The link between viral infections and vasculitis has been already described in literature and we cannot exclude it in the examined case in consideration of the temporal coincidence. However, in this case, the correlation between the infection and the autoimmune disease is not easy to evaluate. In conclusion, it is mandatory to suspect that not all that glitters is COVID-19.

## 342. HEMOCHROMATOSIS AND GAUCHER DISEASE: "AN UNLIKELY BUT NOT IMPOSSIBLE IRON PACT"

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Gaucher disease (GD) is an autosomal recessive, lysosomal storage disease characterized by deficiency of the enzyme glucocerebrosidase (GBA). Three pathological clinical variants are recognized: type 1 with prevalent visceral involvement, type 2 characterized by severe neurological involvememnt often fatal in the first years of life and type 3 with a variable neurological and visceral impairment. Type GD 1 represents the most frequent form with an estimated prevalence of 1 / 50,000 in the general population. The clinical presentation is characterized by asthenia, growth retardation or delayed puberty. Splenomegaly was present in about 90% of cases and could be complicated by splenic infarcts, hepatomegaly and in rare cases hepatic fibrosis and cirrhosis. Thrombocytopenia, anemia, and leukopenia are other common signs. GD was the first genetic disease for which enzyme replacement therapy (ERT) was developed and today it can also be treated with other innovative therapeutic approaches such as substrate reduction therapy (SRT).

Hyperferritinemia (HF) is one of the most common metabolic alterations in GD. The exact pathophysiology of HF in GD is still debated and ferritin levels, generally decreasing during treatment, have been proposed as biomarker of disease activity. Hereditary hemochromatosis (HH) is characterized by an excessive absorption and subsequentially elevated serum levels of iron and overload in various organs, such as liver, heart, pancreas and gonads.
In December 2020, ES, male, 56 yrs old, attended the annual follow-up visit for GD at our Center for Adult Lysosomal Storage Disease. The patient was affected by GD type 1 diagnosed at age 45 due to the family history and findings of thrombocytopenia and splenomegaly. At diagnosis, the GBA activity measured on leukocytes resulted low and the molecular analysis showed a double pathologic heterozygosity (R170C; 589-12C> G). Two sisters out eight siblings (five sisters and three brothers) were affected by GD1. At follow-up, the patient presented splenomegaly, hepatomegaly and bone pain localized to the right leg. Ferritin (666 ng / ml), hemoglobin (17.2 mg / dl), hematocrit (52.2%), serum chitotriosidase values increased compared to the previous evaluation.
At this follow-up visit, the patient reported a significant worsening of short-term memory and the skin was a marked bronze hue. Despite ERT, an increase in ferritin and transferrin saturation levels (> 50%) were observed. To exclude the clinical suspicion of HH, a genetic test was carried out for the mutation of the HFE gene, which showed homozygosity for H63D mutation. Subsequently abdominal magnetic resonance imaging (MRI) quantified the hepatic iron with evidence of accumulation. The patient then began a cycle of bloodletting aimed at reducing the martial overload. Currently at the last check the ferritin value stands at 382 ng/ml with a signinificat reduction in transferrin saturation.
**Discussion:** This case report showed the coexistence fo GD type and homozygous mutation for hemochromatosis in HFE gene in the same patient. ES presented the typical manifestations of the GD such as splenomegaly, thrombocytopenia and bone involvement (evidence of bone infarction). HF in GD is frequently found. The cause is not yet defined, however a state of chronic low-grade inflammation can lead to high levels of ferritin and an increase in hepcidin transcription with consequent entrapment of ferritin in macrophages. As reported in the literature, ferritin levels tend to normalize with ERT and therefore ferritin levels were considered among the disease markers of response to the treatment. However ferritin levels can be elevated in many others conditions such as hereditary hemochromatosis, inflammatory liver disease, cancer, autoimmune disease and obesity. Our patient presented a typical bronzed skin color which correlated to a persistence of high levels of ferritin and high transferrin saturation values, despite ERT. These observation led as to investigate further to find alternative causes of HF.
**Conclusion:** Although hyperferritinemia is common in GD patients, when it does not respond adequately to treatment, it is associated with high transferrin saturation and / or radiological evidence of iron overload, hemochromatosis should be excluded.

## 343. RITIRATO

## 344. POPEYE, THE SAILOR MAN

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A 65-yo multimorbid woman with type II diabetes, hypertension and chronic kidney disease was admitted to hospital due to general asthenia, worsening lower back pains and progressive bilateral lower limb weakness that had left the patient bed bound in the preceding weeks. The initial blood tests showed elevated CRP (C-Reactive Protein), a worsening renal function and normal CPK (28U/L). In the Emergency Room a lower back X-ray revealed spondiloarthrosis and the consulting neurologist suggested a brain CT scan to further study the hyposthenia. The patient therefore initiated an empiric antibiotic therapy and was admitted to our Internal Medicine ward. There the patient's hospitalization was complicated by sepsis with positive blood cultures, mainly caused by lower limb diabetic ulcers; the latter were then revealed to be the source of an osteomyelitis of the first and third metatarsal bones of the right foot, diagnosed through a PET scan. Since contrast uptake was also localized at D6-D9, the patient underwent a spinal MRI which showed significant paraspinal muscle involvement, especially in the lumbar tract, and compatible with diffuse myositis. After excluding central and peripheral causes, the patient received a muscle biopsy: a myophosphorylase deficiency was found associated with the presence of glycogen granules in the cytoplasm of the muscle cells; this resulted compatible with McArdle's Disease. The neurologist suggested a carbohydrate-rich diet and a carnitine supplement. After having resolved the infective state, the patient was discharged at a neurorehabilitative facility. At follow-up, one year later, the patient had a normal lifestyle, had started walking and gently exercising again.
**Discussion:** McArdle's Disease, also known as glycogen storage disease (GSD) type 5, is caused by myophosphorylase deficiency and is inherited recessively. It is the most frequent GSD in Europe and is phenotypically characterized by muscle weakness, muscle contractures, myoglobinuria and rhabdomyolysis (Gandhi S., 2021). This condition severely impairs physical activity which is dependent on anaerobic glycolysis (Scalco R., 2014) and the heterogeneity of manifestations seem to be due to disease-modifying genes such as ACE and alfa-actinin-3 (Quinlivan R., 2014).
More than 90% of patients undergo genetic testing and a muscle biopsy at some stage of the diagnostic work-up, the latter being the gold standard since all affected patients display an absent myophosphorylase activity (Gandhi S., 2021) such as was revealed in our patient.
Differently from our case, the median age at diagnosis is thirty years old despite the fact patients start identifying symptoms during childhood. However, a diagnostic delay is common and in Europe the oldest case diagnosed was in a 79-year-old patient (Scalco L., 2020). Approximately 82% of patients identify the 'second wind' phenomenon that corresponds to the metabolic shift to fatty acid oxidation that takes place approximately 10 minutes after the start of prolonged physical activity and that allows affected people to continue exercising after having overcome initial painful muscle cramps (Scalco R., 2014). Despite this, the absence of this phenomenon does not exclude the disease, similarly to our case. Likewise, the absence of rhabdomyolysis like in our case, does not exclude the disease, even if baseline serum CPK is frequently elevated (Scalco L., 2020).
The comorbidities most frequently related to the disease are chronic kidney disease, hypothyroidism and type II diabetes; for the latter many studies demonstrated an impaired insulin action in patients with this GSD (Gandhi S., 2021).
Paraspinal muscle involvement, particularly in the thoracic and lumbar tracts, is frequently associated to the disease and is denoted by fat replacement which can be easily diagnosed through MRI. Like in our patient, it worsens over time, is particularly serious in the elderly and causes proximal fixed muscle weakness (Velasco-Alvarez R., 2022).
No curative therapy has been found; a carbohydrate-rich diet reduces work effort and heart rate during exercise in a statistically significant way. Moreover, aerobic training improves cardiovascular fitness, disease-related symptoms and quality of life without adverse effects (Quinlivan R., 2014).
**Conclusion:** McArdle's Disease is a neuromuscular disorder that equally affects males and females of all ages and needs to be suspected whenever muscle weakness and exercise intolerance are the predominating symptoms. Despite no cure has been found lifestyle changes help mitigate the condition.

## 345. OXIDATIVE STRESS BIOMARKERS IN FABRY DISEASE: IS THERE A ROOM FOR THEM?

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**Background:** Fabry disease (FD) is an X-linked lysosomal storage disorder, caused by deficient activity of the alpha-galactosidase A enzyme leading to progressive and multisystemic accumulation of globotriaosylceramide. Recent data point toward oxidative stress signalling which could play an important role in both pathophysiology and disease progression. In recent years, several findings reported that the accumulation of Lyso-Gb3 is not the only mechanism underlying the progression in FD. Some authors have hypothesized that oxidative stress has a key role in the progression of organ damage in FD; moreover, some data highlighted the role of oxidative stress in FD pathophysiology. These aspects are supported by the observation that FD patients present high lipid and protein oxidative damage, decre-

ased antioxidant defenses and increased inflammatory biomarkers and cytokines.
**Aims:** The aim of our multicenter project was to evaluate the role of oxidative stress in FD. In particular, we have evaluated (i) if oxidative stress occurs in blood; (ii) if there is an association between oxidative stress biomarkers and FD clinical manifestations and\or a difference between classic and late onset FD; (iii) if oxidative stress parameters over time are related with Lyso-Gb3 and disease appearance or progression, in a subgroup of eight treatment-naïve subjects/patients with normal Lyso-Gb3 levels, in order to see if selected oxidative stress biomarkers could represent early markers of disease progression.
**Methods:** The patients group consisted of 60 Caucasian genetically proven FD subjects from Italy recruited from seven Italian centers with expertise in FD and 77 healthy controls. Diagnosis and phenotype classification was performed according to international recommendations We have examined oxidative stress biomarkers [Advanced Oxidation Protein Products (AOPP), Ferric Reducing Antioxidant Power (FRAP), thiolic groups] in blood samples from patients and controls.
**Results:** AOPP levels were higher in patients than in controls ($p < 0.00001$) and patients presented decreased levels of antioxidant defenses (FRAP and thiols) with respect to controls ($p < 0.00001$). In a small group of 8 treatment-naïve subjects with FD-related mutations, we found altered levels of oxidative stress parameters and incipient signs of organ damage despite normal lyso-Gb3 levels.
**Conclusions:** In this study, we observe a significant imbalance of the oxidative stress status in FD patients in different disease stage, including those cases in which Lyso-Gb3 was normal and\or organ damage was not yet manifested. Oxidative stress occurs in FD in both treated and naïve patients, highlighting the need of further research in oxidative stress-targeted therapies. Furthermore, we found that oxidative stress biomarkers may represent early markers of disease in treatment-naïve patients with a potential role in helping interpretation of FD-related mutations and time to treatment decision.
Keywords: Fabry disease, Biomarkers, lysoGb3, Oxidative stress

## 346. CHRONIC INTESTINAL PSEUDO-OBSTRUCTION (CIPO): A RARE CAUSE OF FUNCTIONAL INTESTINAL OCCLUSION

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C.K., a 24-year-old female patient, was admitted to our Emergency Department for progressive decay of cognitive performance and abdominal distension. Her medical history included previous episodes of intestinal occlusion (in one case complicated with septic shock) with loss of weight, mental retardation since birth and major thalassaemia.
The abdominal CT-scan showed marked overdistension without mechanical obstruction and a subsequent colonoscopy was carried out in order to reduce the overdistension of the bowel.
A nasogastric tube and a rectal probe were placed and intravenous hydration was started. For persistent fever with high CRP, broad-spectrum empirical antibiotic therapy (piperacillin/tazobactam, vancomycin) was added, in the hypothesis of infection from abdominal source. The gastroenterologist suggested metronidazole and prucaloprid as a prokinetic. Further diagnostic exams were required to identify the cause of functional intestinal occlusion (total-IgA, anti-transglutaminase Ab, ANA, ENA, anti-Hu-Yo-Ri Ab, coprocultures and faecal calprotectin) and all resulted negative. A rectal swab resulted positive for Klebsiella pneumoniae "New Delhi", as a gut colonizator. The case was interpreted as CIPO, a rare syndrome characterized by signs and symptoms of a mechanical obstruction of the bowel in the absence of an obstructive anatomic lesion, and the presence of dilation of the bowel on imaging.
Given the persistence of intestinal sub-occlusion with severe abdominal distension despite medical treatment, other prokinetics (subcutaneous neostigmine and subsequently pyridostigmine by nasogastric tube) were administered, with benefit on bowel movements but not on abdominal distension. Given the persistent apyrexia and CRP reduction, antibiotic therapy was discontinued on the 12th day with immediate recurrence of fever, the day after. Antibiotics were witheld for 24 hours in order to identify the causative agent to set up targeted therapy, but a fast and dramatic clinical deterioration occurred, leading to overt septic shock with severe desaturation and hypotension. After oro-tracheal intubation and intravenous vasopressor-support, the patient was transferred to ICU and treated with Ceftazidime/Avibactam and then with meropenem/vaborbactam against Klebsiella pneumoniae MDR. After proper stabilization, total colectomy was performed and the histological examination showed neuronal dysplasia type B related to neuromuscular gastrointestinal disease.
CIPO is a severe digestive syndrome characterized by derangement of gut propulsive motility which resembles mechanical obstruction, in the absence of any obstructive process. Although uncommon in clinical practice, this syndrome represents one of the main causes of intestinal failure and is characterized by high morbidity and mortality. Even if the acute phases can be hardly differentiated by mechanical occlusions and the inter-crisis digestive symptoms can mimic other severe functional digestive syndromes, CIPO should be recognized based on the typical combination of clinical features, natural course and radiological signs. The diagnostic suspicion should be then confirmed by more accurate examinations, in order to distinguish idiopathic or secondary forms and to identify the underlying pathophysiological mechanisms. Most cases are sporadic, even though familial forms with either dominant or recessive autosomal inheritance have been described. Based on histological features intestinal pseudo-obstruction can be classified into three main categories: neuropathies, mesenchymopathies, and myopathies, according on the predominant involvement of enteric neurones, interstitial cells of Cajal or smooth muscle cells, respectively. Treatment of intestinal pseudo-obstruction involves nutritional, pharmacological and surgical therapies, but it is often unsatisfactory and the long-term outcome is generally poor in the majority of cases.
In conclusion, intestinal occlusion is not uncommon in Internal Medicine Wards and once mechanical obstruction is excluded, differential diagnosis among functional disorders should include CIPO, especially in young adults. Acute exacerbations of CIPO are challenging and septic shock of GI origin remains one of the main causes of death among these patients. Despite the choice of appropriate antibiotics is of primary importance, in critically ill patient antibiotics wash-out should be carefully considered, given the high risk of destabilization and evolution in septic shock.

## 347. THE HEALTH STATUS OF A COHORT OF FAMILIAL MEDITERRANEAN FEVER PATIENTS ASSESSED BY TELEMEDICINE

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**Background:** Long-term follow-up in rare diseases is critical for adequate clinical management. The pandemic represents a risk period, due to difficult routine workup in referral centers. We therefore aimed to verify the usefulness of telemedicine in a group of patients with Familial Mediterranean Fever (FMF), and to depict an overview of the health status in these subjects.
**Methods:** FMF patients followed at Clinica Medica "A. Murri", Policlinico of Bari (Italy) were contacted by phone, video-calls and social networks during a 4-months period (March-July 2021). A specific questionnaire was used, and answers were recorded and analyzed.
**Results:** A total of 51 (20 males) out of 60 patients followed by our FMF outpatient clinic was successfully contacted. Overall, the mean age of symptom onset was 21.1±2.5 years. The mean age of diagnosis was 31.1±2.6 years, with a diagnostic delay of about 10 years. The majority of subjects (57.4%) were on colchicine, which caused mild side effects (mainly diarrhea) in a low number of cases (7/29). The average interval since the last visit was high (46,4±8,2 months). However, the number of FMF attacks since the last visit remained low (0-1) in the majority of patients (74%). The 50% of subjects reported a trigger event preceding the last attack (mainly physical effort, stress, exposure to cold, infections). The 82% of subjects reported as "stable" the health status since last visit. However, a progression towards a more severe clinical course was reported by 9% of subjects, requiring an urgent reassessment.
**Conclusions:** Telemedicine can be a useful tool in the management of FMF. In the majority of the examined subjects the health status was stable, despite the lack of recent visits. However, telemedicine can efficiently select patients reporting a worsening of the health status, who need an urgent reassessment.

## 348. SYSTEMIC SARCOIDOSIS - CASE REPORT

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Sarcoidosis is an inflammatory disease characterized by the presence of noncaseous granulomas in one or more organs or tissues. The patient may

be asymptomatic or present with cough, dyspnea from exertion, while respiratory failure or organ failure is rare. The diagnostic hypothesis is suspected for lung involvement and confirmed with X-ray and / or CT examination, biopsy and the exclusion of other granulomatous diseases. First-line therapy is based on the use of cortisone. Prognosis is usually good but can be poor in advanced disease. The authors present a clinical case of systemic sarcoidosis.
**Case Report:** 69-year-old male, former smoker of a few cigarettes a day for 10 years. Comorbidities: diabetes mellitus, ischemic heart disease (PTCA + 1 DES on IVA for unstable angina), arterial hypertension, hypercholesterolemia. Comes to our observation for asthenia, dyspnoea from exertion, diffuse arthralgias and severe weight loss (about 10 kg over the last two months). No peripheral edema. The chest x-ray showed thickened and badly decomposable ili. Abdomen echo: presence of celiac adenopathy of 16 mm, probably reactive; routine blood tests, dosage of thyroid hormones and negative tumor markers, while the search for occult blood in the faeces was positive. For this reason he performed EGDscopy which detected cardial incontinence and petechial gastropathy and colonoscopy reported negative. For the persistence of the symptoms and the continuous weight loss, chest and abdomen CT examinations with contrast medium were prescribed which showed gross lymphadenomegaly spread to all the ilo-mediastinal stations, with variable dimensions, in the epiaortic area, of 32x30 mm and 31x23 subcarinal... The tdm picture orientates in the first hypothesis for a thoracic lymphomatous localization. In the light of the CT examination the following tests are carried out: Ab search for EBV, Mycoplasma pneumoniae, Chlamydya Pneumonia, Quantiferon TB negative. After a multidisciplinary meeting it was decided to perform a global body tomoscintigraphic examination (PET) to resolve the diagnostic doubt. The PET examination revealed: .. presence of numerous pathological hyperaccumulations, of adenopathic significance, located in the bilateral supraclavicular, retro and right paratracheal site, at the aortic reflection, at the aorto-pulmonary window, in the anterior mediastinal, pre and subcarinal site, inferior paraesophageal right, retrocardiac, to the right anterior costo-diaphragmatic cavity, in celiac and suprarenal precaval. The PET study is indicative of a disease with high metabolic activity in the supra and subdiaphragmatic lymph node; accumulation in the skeletal area suspected due to localization of metabolically active disease. At this point it was decided to perform a bone medullary biopsy with diagnosis: hematopoietic marrow with a prevalence of granulopoiesis. No evidence of replacement disease. Given the negativity of the osteomedullary biopsy due to haematological disease, a lymph node biopsy was performed in the left subclavicular area which showed: a picture of non-necrotizing giganto-cellular granulomatous lymphadenitis similar to sarcoidosis. In the light of the outcome of the biopsy of the lymph node in the left subclavicular site, a diagnosis of sarcoidosis was made and therapy with prednisone 25mg / day was established. The control PET after about one year showed: ... high uptake of the glucose metabolism tracer due to adenopathies in the right supraclavicular, thoracic and abdominal area; high uptake increased by extension of the medial portion of the left clavicle... focal area of high accumulation in correspondence of the 9th right rib... The chest and abdomen CT examination with contrast medium revealed: . some of which have a globular appearance, the largest of which in the Barety loggia with a short axis of 14 mm and some subcentimetric lymph nodes are found in the hepatic hilum, at the cardio-phrenic recess on the right, in the celiac, paracaval, inter-orthocaval, iliac and bilateral inguinal. Since PET and CT still showed signs of disease, it was recommended to continue therapy and re-evaluate after six months. After about six months the clinical picture had improved considerably so it was recommended to decrease the dosage of prednisone to 10mg / day for one month and then to 5mg / day for another month. The control PET showed the disappearance of the abnormal hyperaccumulations of the tracer of adenopathic relevance in the thoracic and abdominal area and in the bilateral lung area, in the medial section of the left clavicle and in the IX right rib. The PET picture confirmed the remission of the sarcoidotic disease.
**Discussion and Conclusions:** the clinical case describes a rare pathology which is systemic sarcoidosis and outlines how the authors followed a step-by-step diagnostic path for a correct differential diagnosis with other pathologies characterized by volumetric increase of the lymph node stations (haematological, oncological, infectious etc..) and it can be paradigmatic of how the internist always follows a methodology based on an articulated clinical reasoning and the rational use of diagnostic methods.

## 349. A RARE CASE OF INTRAMUSCULAR ABSCESS IN A PATIENT WITH HEREDITARY HAEMORRHAGIC TELANGIECTASIA

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**Background:** Hereditary Haemorrhagic Telangiectasia (HHT) is a rare inherited disease, transmitted with an autosomal dominant pattern with incomplete penetrance (97%). This Syndrome is a disorder of angiogenesis characterized by mucocutaneous telangiectases and visceral arteriovenous malformations that may potentially affect any body district, particularly liver, lung, brain and skin. AVMs are usually asymptomatic but can lead to complications that produce highly variable manifestations, such as brain abscesses, strokes, haemorrhagic rupture.
**Case Report:** A 22-year-old male patient, previously diagnosed with HHT, came to our observation for clinical and diagnostic evaluation after being hospitalized for left hip pain, fever and asthenia for several days. As his maternal family was already followed at our Rare Diseases Centre, this patient had been subjected to genetic testing in 2020, resulting carrier of the familial HHT-causing mutation in the ENG gene (c. 1098_1120del23bp). His medical history was silent, except for mild epistaxis. He smoked 1 pack/die. No alcohol habits was reported. No allergic diathesis was referred. In ER, laboratory tests showed an increase in the main inflammatory markers such as CRP, fibrinogen, ESR and White blood cells count, mainly neutrophils. Investigation of his left hip pain with abdominal CT disclosed the presence of a large abscess (47mm x 61mm x 11cm) in iliopsoas muscle, which compressed the ureter, resulting in left kidney hydronephrosis. He had been hospitalized at Urology Department where a stent was inserted into the ureter. Moreover, the muscular abscess was drained and antibiotic therapy with Teicoplanin and Meropenem was set up. Few days later, he was transferred to our Department for clinical-instrumental screening for HHT. No cutaneous telangiectases were detected at the physical examination, whereas digital clubbing was evident. Oxygen saturation at the entrance was 87%. Chest CT revealed numerous pulmonary AVMs at both sides, the largest of which was located in the lower lobe of right lung (maximum size of diameter of feeding artery of 3.5 mm). Upon embolization procedure of the two largest vascular malformations by the interventional radiologist, Oxygen saturation rose to 94%. Further PAVMs will be treated in a second step. Brain MRI evidenced multiple AVMs located in supratentorial region of both hemispheres, right cerebellum, left pons, pituitary gland and medulla, which were recommended for stereotaxic radiation therapy by the neurosurgeon's evaluation. Rhinoscopy displayed multiple telangiectases in both nasal mucous cavities.
**Conclusions:** We presented the case of a young male with family Background and for Hereditary Haemorrhagic Telangiectasia who had never performed screening procedures for poor compliance, despite knowing to be carrier of the familial disease-causing mutation. He presented with intramuscular abscess, presumably secondary to pulmonary-AVM-driven paradoxical shunt-effect. According to our knowledge, there are few similar cases of pulmonary-AVM-driven abscess in sites other than brain, reported in literature, and no cases have been previously reported in iliopsoas muscle. The case further demonstrates the extreme importance of performing timely screening procedures and periodical follow up, since the delay to accept screening left this patient to exposure of serious complication risk. The importance of early treatment of Pulmonary AVMs (that may manifest with brain abscesses, strokes, transient ischemic attacks, signs of chronic hypoxaemia and haemorrhagic rupture) and AVMs of the central nervous system (that can be haemorrhagic or, rarely, produce signs of slow compression) is well-known. This case proves that complications related to the HHT pathology may occur even in less studied districts.

## 350. EFFICACY OF VAGAL NEUROMODULATION IN CYCLIC VOMITING SYNDROME: A CASE REPORT

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We reported a case of a 20 years old female who presented to our outpatient clinic for cyclic vomiting episodes. The patient had a history of cycling vomiting syndrome (CVS) since the age of 12, when she had the first attack approximately 7 days after the papilloma virus vaccine. From that moment, she had CVS attacks characterized by 3 days of nausea, vomiting, severe

dehydration with the need of IV hydration every 2 months. The attacks only required supportive therapies (anti-emetic, hydration) and resolved on their own.
The patient was evaluated in our clinic in order to exclude the presence of a dysautonomia, often associated with CVS. A previous echocardiography, EEG, brain imaging through nuclear magnetic resonance and computed tomography were negative.
We performed 7 days ECG Monitoring which revealed a severe heart rate (HR) increase from sleep to wake phase in the morning (ΔHR=70 bpm). The 24-h Holter ECG monitoring also highlighted a progressive reduction of the ΔHR in the days preceding the vomiting episode.
In order to exclude the presence of dysautonomia, we performed a head up tilt test (HUTT) to evaluate the dynamic autonomic response. The HUTT revealed an exaggerated HR response during orthostatism (ΔHR=35) in the absence of orthostatic hypotension, suggesting a diagnosis of Postural Orthostatic Tachycardia Syndrome (POTS).
Considering the CVS and the POTS, possibly linked to an important autonomic dysfunction, we decided to start a 3 months treatment with transauricular vagal nerve stimulation (t-VNS). T-VNS is a non-invasive approach able to target the autonomic nervous system (ANS) by activating the afferent fibres of the auricular branch of vagus nerve. T-VNS has been approved for the treatment of refractory epilepsy, migraine and chronic pain.
After 3 months of t-VNS (non-consecutive 4 hours per day), the patient reported no CVS attacks (only one episode of mild nausea without vomiting). The 24-h Holter ECG revealed a decreased ΔHR from sleep to wake (ΔHR=40 bpm).
In conclusion, t-VNS could be considered an effective treatment for autonomic dysfunction present in CVS and POTS, with beneficial effects on the cardiovascular autonomic control and on the CVS attacks. These favourable outcomes could be due to the neuromodulatory effect of t-VNS, which activates afferent vagal fibres and, through an action of the main nuclei in brainstem (nucleus of tractus solitarius, nucleus ambiguus), is able to reduce the sympathetic hyperactivation and to prevent the vagal rebound that leads to the vomiting episodes.

## 351. A QUESTIONABLE DIAGNOSIS OF EXTRAPULMONARY TUBERCOLOSIS

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**Background:** Granulomatous diseases is a heterogenous group of disorders with different etiologies, pathogenesis, and variable natural histories. They are all characterized by granulomas as inflammatory response to a tissue insult, which could depend on infections of intracellular pathogens like Mycobacterium tuberculosis (MT), but also could be due to hypersensitivity reactions or other disturbances of immunity system. A meticulous differential diagnosis is paramount for their identification and for a correct therapeutical management.
Case presentation: A 63-year-old man with a diagnosis of extrapulmonary tuberculosis presented with fever, weight loss, thoracalgia, diffuse lymphadenopathy and a massive pleural effusion. He had already undergone two hospitalizations for the same clinical picture. He was investigated through extensive laboratory and radiologic examination for possible autoimmune, infectious, hematologic, and neoplastic conditions, all resulted negative. Even though MT had never been isolated and tuberculin skin test resulted negative, a lymph node biopsy showed a granulomatous necrotizing lymphadenitis suspicious for tuberculosis, hence anti-tubercular therapy was started ex juvantibus.
However, when the patient came to our attention, total-body CT and PET scans showed a progression of new disseminated nodular consolidations, despite strict adherence to five months of traditional anti-tubercular regimen.
We repeated microscopic and cultural search for MT and other micro-organism, which again resulted negative on urine, stool, blood, pleural fluid, and spinal lesion biopsy. Without any element that supported the diagnosis of MT infection, except for the granulomatous lymphadenitis found on the biopsy previously performed, we started considering alternative diagnosis for necrotizing granulomatosis. These include multidrug-resistant tuberculosis, Wegener granulomatosis, Churg Strauss syndrome, necrobiotic nodules of rheumatoid arthritis, lymphomatoid granulomatosis and Necrotizing Sarcoid Granulomatosis (NSG). Having already rejected other autoimmune, hematological, and neoplastic disorders, NGS resulted the most consistent hypothesis.
The histological specimens were re-examined by an expert, who made the diagnosis of atypical presentation of sarcoidosis. Steroid therapy was initiated, achieving symptoms improvement and inflammatory indexes decline, and the patient was referred to a highly specialized center for follow-up of sarcoidosis and its therapy management.
**Conclusion:** Sarcoidosis is a rare condition that can be challenging to diagnose, due to its variability in clinical presentation, often mimicking alternative conditions like disseminated tuberculosis. Being a diagnosis of exclusion, a high degree of suspicion and an experienced lab in anatomical pathology are essential for its identification, which should always be the conclusion of a multi-disciplinary work-up.

## 352. UNCOMMON MANIFESTATIONS OF A RARE DISEASE

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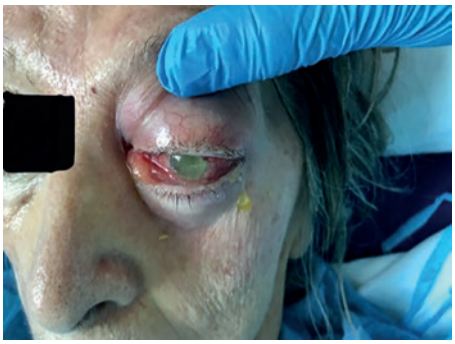
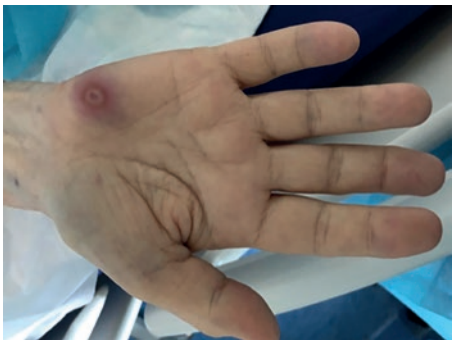
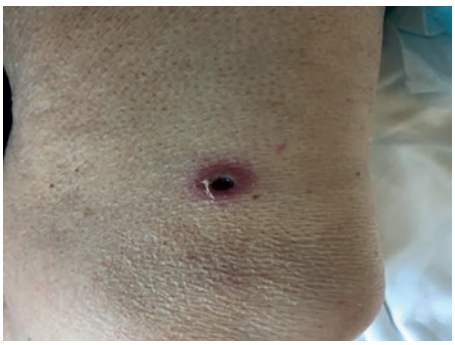
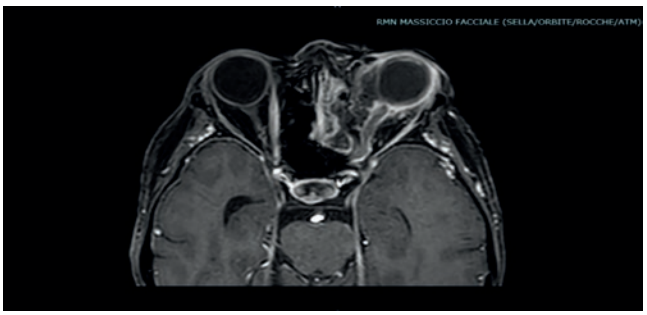
**Introduction:** Sweet syndrome, also known as acute febrile neutrophilic dermatosis, is a condition that causes fever, neutrophilia, and erythematous skin plaques, while extracutaneous manifestations are uncommon. Neuro-Sweet disease is a rare entity associated with neurological involvement and several ocular manifestations, including ocular movement disorders, episcleritis and conjunctivitis. We report a patient with orbital inflammation, aseptic meningoencephalitis and skin rash in the setting of neutropenic myelodysplastic syndrome. Biopsy of the skin lesion confirmed the diagnosis of Sweet syndrome. This is a rare case of neuro-Sweet syndrome causing orbital inflammation mimicking orbital cellulitis and an aseptic meningoencephalitis.
**Case Report:** A 75-year-old female presented with fever, painful eyelid swelling, limited ocular movement and erythematous skin lesions in the limbs and trunk, occurred after taking levofloxacin some days before. She had a history of myelodisplastic syndrome (in therapy with azacytidine and a recent bone marrow examination showing a blast percentage inferior to 10%). Systemic physical examination revealed left eye proptosis conditioning reduced eyelid opening and painful erythematous papillary skin lesions. Blood tests showed elevated C-reactive protein, severe neutropenia (neutrophils were 500/mm3) and anemia (Hb 5,9 g/dL) requiring transfusional support. Renal, hepatic and clotting function was normal and SARS-CoV-2 molecular nasopharyngeal swab was negative. Computed Tomography (CT) scan showed edema of the left retrobulbar tissue resulting in homolateral ocular proptosis. The patient was hospitalized in our Service of Internal Medicine. Given the state of immunosuppression, in the suspicion of retro-orbital abscess, she was treated with broad-spectrum antibiotic treatment (PIP-TZB and Vancomycin), without an evident reduction of orbital swelling, despite subsequent apyrexia and reduction in inflammatory markers. Contrast-enhanced magnetic resonance (MRI) of the head showed orbital cellulitis in pre and post-septal region with peribulbar exudates and abscess-like lesion, which required a left orbital decompression surgery with drainage of periorbital material. Interestingly, all microbiological examinations on collected samples were negative. A second MRI after seven days showed an increased size of peribulbar exudates and abscess-like lesion, associated with evidence of diffuse leptomeningeal and pachymeningeal enhancement compatible with meningoencephalitis. The patient underwent a lumbar puncture: cerebrospinal fluid (CSF) glucose was normal (63 mg/dL), proteins were elevated (72 mg/dL), red blood cell count and white blood cell count were normal (respectively: 3/ μL and < 1/μL). CSF cultures and cytology were negative for infectious or leukemic localization. Meanwhile, biopsy of skin lesions was performed. The sample was negative for leukemic dermal infiltration or infectious disease but histologic examination demonstrated a perivascular and interstitial dense neutrophilic infiltrate with numerous histiocytes, which is the hallmark of Sweet syndrome. MRI images were reviewed and confirmed the potential non-infective inflammatory involvement of orbital and CNS structures. Given these associated neurologic and dermatologic findings, we confirmed the diagnosis of Sweet syndrome with associated orbital inflammation and meningoencephalitis. Therefore, a systemic steroid therapy was started (Prednisone 0,5 mg/kg), which lead to a progressive reduction of skin lesions and rapid improvement of ocular motility. However, due to extreme fragility and severe comorbidi-

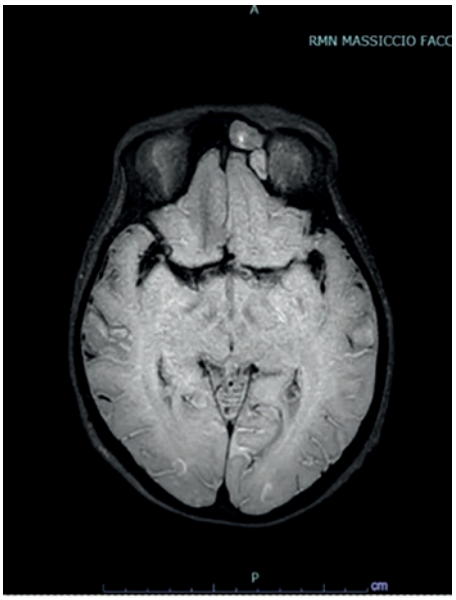
ties, despite a rapid resolution of Sweet syndrome infiltrates, she passed away few weeks later.
**Discussion:** Sweet syndrome is an inflammatory disorder that causes fever, neutrophilia, and erythematous skin plaques, with skin biopsies demonstrating dermal infiltration with neutrophils in the absence of vasculitis. Infiltration can also occur in other organs, including the eyes, lungs, liver, kidneys, gastrointestinal tract and CNS. Sweet syndrome can be idiopathic, associated with upper respiratory tract or gastrointestinal infection, inflammatory bowel disease, pregnancy, malignancy, or drug-induced. Most common medications are G-CSF derivates, but also fluoroquinolones are involved. We reported in this case levofloxacin administration shortly before symptoms onset, which could represent a potential trigger of a drug-induced form.

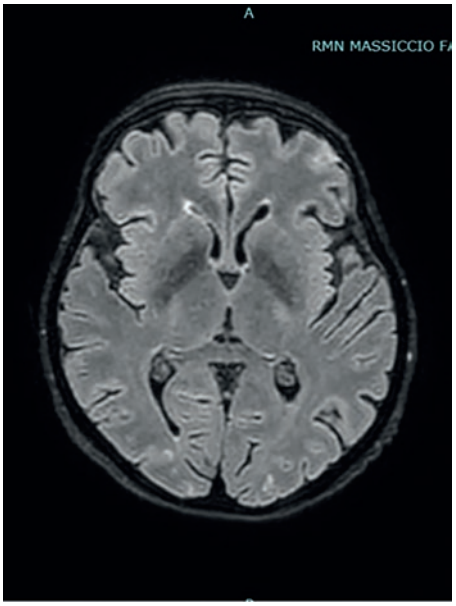









**Conclusion:** Although the most common ocular manifestations that occur in approximately one third of patients with Sweet syndrome are conjunctivitis or episcleritis, there have also been three other reports of orbital involvement1. Our patient had myelodysplastic syndrome but low neutrophils count (</= 500/mm3) does not represent an exclusion criteria for the disease. Moreover, there is a suggestion that Sweet syndrome secondary to myelodysplastic syndrome can cause more atypical manifestations compared to other forms of this rare syndrome.
**References:** 1. Taravati P. Neuro-Sweet Disease Causing Orbital Inflammation. Neuroophthalmology. 2015

## 353. COMMON VARIABLE IMMUNODEFICIENCY AS A MODEL FOR UNDERSTANDING THE ROLE OF B CELLS IN ATHEROSCLEROTIC CARDIOVASCULAR DISEASE

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**Background:** and AIM: Although the immune system is involved in vascular disorders, the actual role of B cells in atherosclerotic cardiovascular

disease (ASCVD) remains unclear. Inflammatory conditions like Rheumatoid Arthritis and Systemic Lupus Erythematosus present an accelerated atherosclerotic process, that is somehow limited by appropriate treatment, including B cell depleting therapies. Common Variable Immunodeficiency (CVID) is a rare primary immunodeficiency of adulthood, characterised by impaired B cell function and antibody response. Thus, it may represent a pathological condition suitable for studying the role of B cells in ASCVD. The cardiovascular risk profile of patients affected by this rare disease is unexplored and it is unclear whether CVID patients are protected from atherogenesis or instead at higher risk due to an infection-driven chronic inflammation. We investigated the prevalence of cardiovascular risk factors and the presence of subclinical ASCVD in CVID patients.
**Methods:** We enrolled 123 CVID patients divided into 2 groups according to the clinical phenotype: patients presenting only the infectious features of the disease ("infection only) and patients with a complicated clinical phenotype (presenting autoimmunity and/or polyclonal lymphoproliferation and/or enteropathy). Clinical and biochemical data were collected. Vascular structural and functional investigation was performed, evaluating the presence of atherosclerotic plaques, arterial elastic properties, intima media thickness (IMT) and endothelial function.
**Results:** We enrolled 55 males (44,2 %) and 67 females (55,8 %) with an age range between 22 and 82 and a mean age of 50.9 ± 14,4 years. Mean BMI was 25.4 (± 5.1) and mean Waist circumference was 95,9 (±13,2) for males and 93,5 (±15,2) for females. No differences in age, sex, BMI and waist circumference were detected between infection only and complicated patients. Patients with complicated clinical phenotype showed increased inflammatory markers like CRP (6.0 ± 4.3 vs 3.6 ± 1.2 mg/L) and more often required steroidal (30.6% vs 11.6%, p=0.017) and immunosuppressive treatment (23.5% vs 0%, p<0.001). Surprisingly, they presented lower total cholesterol (182 ± 36 vs 204 ± 41mg/dl, p=0.009) and LDL cholesterol (112 ± 33 vs 129 ± 42mg/dl, p=0.04), as well as lower blood glucose (89 ± 14 vs 98 ± 17mg/dl, p=0.011) and glycosylated haemoglobin levels (33 ± 4 vs 38 ± 6mmol/mol, p<0.001) as compared to uncomplicated cohort. Patients with complicated phenotype also presented higher levels of CD21lo B cells (10.8%, IC95% 3.6-18.0 vs 6.8%, IC95% 4.2-9.4), significantly increased levels of large granular lymphocytes (26.0%, IC95% 19.5-32.5 vs 14.4%, IC95% 10.9-17.8; p<0,001) and significantly reduced levels of switched memory B cells (4.0%, IC95% 1.8-6.2 vs 7.8%, IC95% 5.5-10.0; p=0,043) in the peripheral blood. Flow mediated dilation (FMD) and IMT were not different between groups in a sub-cohort of 45 patients.
**Conclusions:** Our data suggest that clinical phenotypes of CVID may be associated with different cardiovascular risk profiles, and that this might be based on the different underlying immunological features. Further studies are ongoing, including vascular follow-up with FMD and IMT measurements, in order to confirm our findings and dissect the possible physiopathological basis of these findings.

## 354. NEPHROTIC SYNDROME ASSOCIATED WITH CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY: A CASE REPORT

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Chronic inflammatory demyelinating polyradiculoneuropathy (CIPD) have been reported to occur in association with membranous glomerulonephritis or focal sclerosing glomerulonephritis. We report a case of the combination of CIPD with FSGN in a patient with peripheral edema and a history of weakness of lower limbs. Both conditions have an autoimmune aetiology but much still remains to be clarified.
CIPD is a clinical entity characterized by progressive or relapsing muscle weakness with loss of sensation, absence or decrease of tendon reflexes. The course can be recurrent, chronic progressive or monophasic. The disease is due to an immune reaction that causes segmental demyelination. In some cases there is also cranial nerve dysfunction. The diagnosis is based on the clinical picture, electrophysiological sign, a two-month history of progressive demyelinating neuropathy. The need for cerebrospinal fluid examination and nerve biopsy depends on the grade of certainly of the clinical diagnosis. In the presence of clinical signs present for at least two months and of three criteria present on the electroneurogram the diagnosis is confirmed. Therapy depends on the severity of the clinical presentation.
A 58 years old man presented with a 3 month history of lower limb edema, symmetrical weakness of lower limbs associated with paraesthesia and mild upper limb weakness. In this period he had also a paralyze of facial muscles at the right side of the face. For this reason his doctor prescribed a short course of steroid therapy after which the symptoms of the face had completely disappeared. There was no other significant past medical history nether a recent history of infections. Perhaps he had not a significant family history. Vital signs were normal. On physical examination it was revealed bylateral pitting edema below his knees. The rest of general examination was normal. Neurological examination showed several anomalies: strength deficit in the four limbs, impairment of all modalities of peripheral sensation in all limbs. The tendon reflexes were all absent. Babinski test was negative. Laboratory studies revealed hemoglobin 13,5 g, white blood cells 11500/mm3 with normal differential count, blood urea nitrogen 22 mg/dL, creatinine 0,8 mg/dL, serum albumin 3,7 g/dL, cholesterol 180 mg/dL. Liver function tests were normal. CRP, complement factors, rheumatoid factor and thyroid function were normal. ANA was negative. Hepatitis B, hepatitis C, syphilis and human immunodeficiency viruses serologies were negative. Immunoelectrophoresis was normal. No blood or casts were present in urine and 24-h urine protein excretion was 3.2 g/day; so a diagnosis of nephrotic syndrome was made.The tests carried out were: a chest X-ray and an abdominal ultrasound that revealed no anomaly, an echocardiography that revealed a normal biventricular function and a bilateral leg vein ultrasound that was normal except for the presence of edema. Nerve conduction studies were performed. The sensory nerve conduction velocity revealed absence of sensory nerve action potential in all four limbs. The motor nerve conduction study showed prolonged distal latencies over all tested nerve. Absence or prolonged latencies of F wave were noted over all tested nerves. Bilateral H reflex was absent. The diagnosis of CIPD was thus performed without proceeding either to examination of the CSF or to biopsy of the affected nerves. The patient was treated with prednisone at a dosage of 1 mg/kg/day for the first week and then 50 mg/die and ramipril 10 mg/die. He progressively reported increased motor strength and the bilateral lower leg edema disappeared. At three months follow up protein excretion was 1 g/day. He repeated the proteinuria other times and the values were always around 500 mg/day and the dosage of steroid was gradually tapered.
The association of CIPD with glomerulonephritis is rarely reported in literature. The question of these association are due to some common or different etiology remains unanswered. However, in both pathologies there are autoimmune mechanisms that can occur at the level of the glomeruli or the axons of the nerves. Probably the target is an antigen that the glomerular basement membrane shares with the myelin of the axons. One of these antigens recently mentioned in the literature is contactin 1. However in most cases the main targeted antigen remains to be defined.
A greater recognition of renal involvement in CIPD may be important for many reasons. The renal involvement probably requires a more specific therapy. Furthermore, the presence of renal involvement has a different prognostic value from the cases in which this involvement does not exist.
In conclusion the combination of GN with CIPD may be underestimated. Careful scrutiny of the urinalysis results in future cases may yield evidence of a more common association of renal abnormalities in patient with CIPD. However large studies are necessary to understand the pathogenesis of the renal damage and the real association between the two pathologies.

## 355. HISTIOCYTOID SWEET SYNDROME ASSOCIATED WITH ULCERATIVE COLITIS: A CASE REPORT

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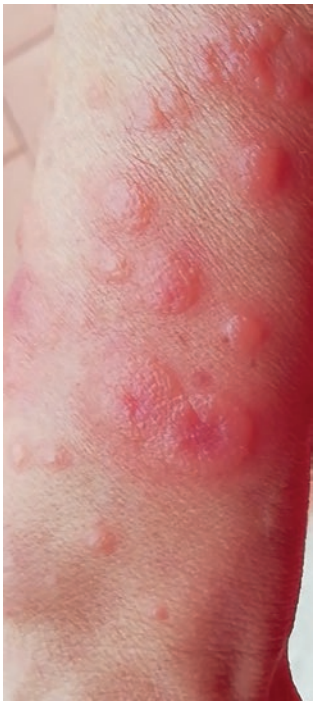
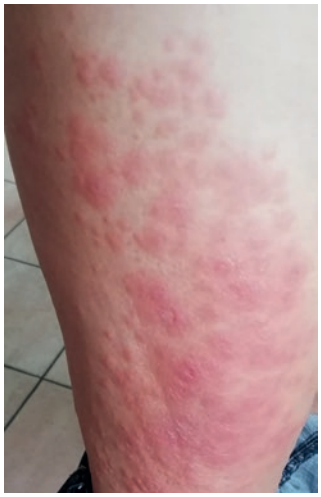
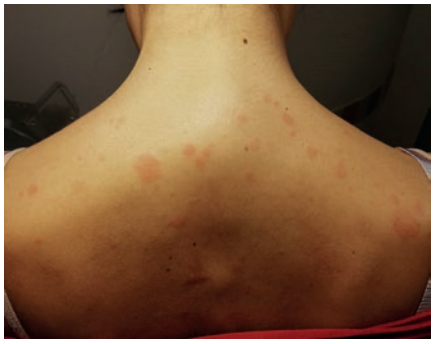
We report the case of a 55-year-old female with distal ulcerative colitis (UC), diagnosed in 2016. The patient's medical history is otherwise unremarkable, and she takes no chronic medications except for mesalamine for maintenance of UC remission.After a stressful life event, in March 2021 the patient experienced a severe disease flare, confirmed endoscopically and histologically, which required hospitalization and intravenous steroid treatment. Due to the subsequent development of steroid-resistance, biological treatment with anti-TNF (infliximab) was initiated in September 2021.After the second administration of infliximab, the patient presented two self-limiting febrile episodes (39°C). Concurrently, intensely pruriginous, erythematous plaques appeared on the extensor surfaces of the upper limbs (Image n°1), and papules appeared on the thighs (Image n°2). In the following days, these lesions merged into infiltrating plaques with vesiculobullous elements. The lesions appeared also on the patient's back (Image n°3), were hard to the touch, and were non-painful.Laboratory exams revealed anemia (Hb 10.6 g/dL), relative lymphocytosis and monocytosis, hypoalbuminemia and elevated inflammatory markers; findings compatible in part with active ulce-

rative colitis.







As the clinical picture was suspect for inflammatory bowel disease (IBD)-related Sweet syndrome (SS), with onset after the initiation of infliximab, treatment was suspended and the patient was started on intravenous steroids. Cutaneous biopsy was performed, confirming histiocytoid-variant Sweet syndrome (dermal edema with subdermal dense inflammatory infiltrate with a prevalence of histiocytes and sparse lymphocytes, neutrophils and eosinophils; histiocyte intracytoplasmic cellular debris, absence of vasculitis).The patient's UC-related symptoms are currently poorly controlled with corticosteroids, and the cutaneous lesions recently reappeared on the upper limbs after steroid tapering, even after anti-TNF suspension. A multidisciplinary gastroenterologic and dermatologic evaluation will establish the subsequent treatment strategy, which will likely involve either biologic treatment with ustekinumab or immunosuppressive therapy with azathioprine, to treat both conditions.A systematic review found 95 cases of IBD-related Sweet syndrome. In 64% of cases, Sweet syndrome was detected after IBD, and 76% had active IBD at the time of SS diagnosis. Fifteen patients were on anti-TNF treatment at diagnosis; histiocytoid Sweet syndrome was present in 5.6% of cases. While most patients (90%) responded to corticosteroids, 14.8% improved with anti-TNF treatment.In conclusion, this case represents a rare extraintestinal manifestation of inflammatory bowel disease, in which treatment options are uncertain and based only on case report like this.

## 356. BULLOUS PEMFIGOID PROBABLY INDUCED BY VILDAGLIPTIN IN A COMPLEX MULTI-MORBID PATIENT

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**Introduction:** Bullous pemphigoid (BP) is a rare skin disease associated with significant morbidity and mortality. It's the most frequent autoimmune blistering disease, characterized by the presence of tense bullae caused by autoantibodies against the hemidesmosomal elements BP antigen 1 (BP230) and BP antigen 2 (BP180), that play essential roles in maintaining firm adhesion between the epidermis and the dermis. Several used drugs (NSAIDs, antibiotics, ACE-I) may contribute to the development of BP. It is unclear the mechanism by which they can provoke BP. They may operate as haptens that stimulate an altered antibody response. Vildagliptin is a member of a class of oral antidiabetic agents known as dipeptidyl peptidase-4 (DPP-4) inhibitors (also known as gliptins). They are glucose lowering agents approved for use in diabetes type 2, as monotherapy or in combination with other oral antidiabetic agents or with insulin. Gliptins inhibit the enzymatic activity of DPP-4 (which is ubiquitously expressed on the surface of a great variety of cells), blocking therefore the degradation of the incretin hormones GIP and GLP-1. Clinical case: A 68-year-old man from Brazil presented to the emergency department with a pruritic tense bullous eruption extended throughout the body which started about four weeks earlier. His past medical history included rheumatic heart disease which required aortic and mitral mechanical valve replacement, HFpEF, AFib, pulmonary hypertension, type 2 diabetes, chronic kidney failure, anaemia, MCI, hypothyroidism and BPH. His home medications included daily vildagliptin, recently introduced, metformin, furosemide, warfarin, sacubitril/valsartan, levothyroxine, sertraline and doxazosin. Examination revealed numerous flaccid bullae and blisters on inflammatory skin affecting the face, neck, trunk and the extremities, including the palmoplantar areas. Some bullae were also haemorrhagic. No mucosal involvement was present and the Nikolsky sign was positive. Laboratory findings showed high inflammation indexes (CRP 79 mg/L), anaemia (Hb 99,6 g/L) and leukocytosis (11,500 cells/μL) with peripheral eosinophilia (8%), low serum albumin level (28,9 g/L), decompensated diabetes mellitus (HbA1c 8,9%) and NTproBNP 1384 pg/mL. Metabolic panel and urinalysis were non-significant, liver function tests were within normal ranges and serum creatinine level was highlighted mild acute renal failure. Vildagliptin was immediately discontinued, switching to insulin. A punch biopsy was performed on a blister on the right forearm. In the meantime, waiting for the histological results, a dermatological consultation advised the start of high-dose intravenous corticosteroids (prednisone-equivalent of 1 mg/kg daily) with potent topical corticosteroid, topical gentamicin, eosin and skin bandage until clinical response on the reduction of new bullae formation. Such therapy was continued for 10-15 days, subsequently the corticosteroid was gradually tapered and then switched to oral methylprednisolone in a few weeks. Doxycycline was started as steroid sparing agent. Blood sugar levels were carefully monitored. Antihistamines drugs were prescribed for itching. Pain control was achieved with oral morphine. Albumin and red blood cell transfusions were also necessary. His hospital stay was complicated by the secondary infection of the skin lesions, treated with broad-spectrum antibiotic therapy and acutely decompensated heart failure. The clinical diagnosis of BP was confirmed by histologic analysis and by immunological tests positive for anti-BP180

antibodies (10,54 U/mL, r.r. < 9 U/mL) and for anti-BP 230 (12,08 U/mL, r.r < 9 U/mL). Due to technical problems, it was not possible to complete DIF on biopsy. The patient was discharged with oral methylprednisolone, doxycycline, alendronate and cholecalciferol weekly and indications to daily cutaneous medications. Antidiabetic insulin therapy was continued and was prescribed canagliflozin plus metformin. Control visit one month after the discharge highlighted only skin scars of the pathology without new bullae. The case was reported to the Pharmacovigilance Unit of the Region.
**Conclusions:** We presented a case of a man who developed BP most likely due to vildagliptin. The Naranjo algorithm for adverse drug reaction revealed a "probably" association between vildagliptin use and BP. The particularly serious skin manifestations made the case very challenging due to the concomitant clinical worsening for the state of systemic infection and a labile cardiac compensation. Cases of BP in people on gliptins have been confirmed by several studies. It is extremely important to be aware of vildagliptin induced BP as a rare complication in at risk populations because this medication, and other DPP4-I, are widely used for the treatment of diabetes mellitus. It is more even important now with the recent introduction of Nota 100 by AIFA, that extends prescribability of such drugs directly to general practitioners and all specialists of the SSN.

### 357. KINSBOURNE SYNDROME IN AN ADULT PATIENT: NEW NAME, OLD FRIEND?

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**Case Report:** A 44-year-old woman was admitted to our Unit with fever and pain on the right side of the lower back.
Her past medical history included: diagnosis of Kinsbourne syndrome (or Opsoclonus-Myoclonus syndrome) at the age of 18 months, with recurrent episodes of exacerbation treated with cycles of steroid therapy and apparently resolved by the age of 8 years old (no brain tumour was found at the time) with long-term mild intellectual disability (IQ 49) as neurological sequelae; recurrent urinary tract infections, kidney stone disease treated by extracorporeal shock wave lithotripsy (ESWL); two regular pregnancies.
In the last few months before admission, after a flu-like episode, she had developed apathy and irritability associated with dizziness. To investigate the cause of such symptoms, she had undergone a neurological examination (NPS test) that showed a deficit of executive functions with altered praxic-constructive elaboration processes, and a brain MRI, that was normal.
At admission in our ward, the patient was febrile, with otherwise normal vital parameters. She also seemed slowed in psychological and physical activity.
Laboratory tests showed increased inflammatory markers (WBC 23.03 migl./mmc, Neuthophils 81%, CRP 17.1 mg/dl), without other significant serum biochemical changes.
For signs and symptoms of urinary infection, a broad-spectrum antibiotic treatment with piperacillin/tazobactam was started after collection of samples for blood and urine culture test. These tests later confirmed a sepsis from E.coli of urinary origin, susceptible to the ongoing antibiotic treatment.
Because of suspicion of pyelonephritis, the patient underwent an abdominal CT scan, with the evidence of hypodense areas on the right kidney that confirmed the hypothesis.
After the first days of hospitalization, for persistent apraxia of speech, a full neurological examination was carried out, with evidence of ataxia, tremor/tremulousness, balance impairment with dizziness and episodic opsoclonus.
In order to better study the case and exclude metabolic, infectious or degenerative neurologic aetiologies, the following tests were performed: EEG, which did not show any electric abnormality; brain CT and MRI, which did not show alterations; lumbar puncture and subsequent liquor culture and molecular tests, which were negative; a chemical-physical test of liquor, which was normal; and onconeural markers on liquor, which were negative; in order to exclude a paraneoplastic neurologic syndrome, chest and abdomen contrast CT scan were requested and resulted negative for lesions attributable to neoplasms. A specific test on liquor, with IgG quantification and electrofocusing, was performed, showing increased IgG with a 'Mirror pattern'.
After five days of antibiotic treatment, in the suspicion of an inflammatory/autoimmune neurological syndrome, after discussion with the Neurologist specialist, a steroid treatment with methylprednisolone 500 mg iv for 5 days, then prednisone 50 mg orally, was administered with gradual improvement of the neurological symptoms.
At the end of the diagnostic process, and considering the past medical history, a suspicion of possible opsoclonus-myoclonus syndrome with infectious aetiologic trigger was formulated. In order to complete the diagnostic process and for the follow-up, the patient was referred to an italian centre specialised in Neuroimmunology and Neuroinflammation.
**Discussion:** Opsoclonus-myoclonus syndrome in adults is a rare, heterogeneous disorder which can present with the clinical features of opsoclonus, myoclonus, ataxia, and behavioral and sleep disturbances. The pathophysiology is thought to be immunological, in the context of paraneoplastic or infectious aetiologies. Several autoantibodies have been identified against a variety of antigens, but no clear diagnostic immunological marker has yet been identified. In such cases, immunomodulatory therapy is the treatment of choice, even if the response is sometimes incomplete. In our patient, steroid treatment, started after the systemic infection had been controlled, was efficient at obtaining a gradual improvement of the neurological symptoms, which are completely resolved five months after discharge, even after steroid treatment was gradually tapered until suspension.
The OMS literature describes mainly case series with childhood onset that occurs between the first year of life and three years of age; otherwise, there are small case series regarding affected adults. Therefore, further research, from larger case series, are needed to better understand the underlying mechanisms and develop preventative strategies and optimal treatment approaches.

## MEDICINA D'URGENZA

### 358. D-DIMER VALUES IN 30 PATIENTS WITH SEPTIC SHOCK AND CID: INTEREST STUDY

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**Introduction:** The Authors presented the "INTEREST" study, an acrostic deriving from "dissemINaTEd intRavascular coagulation in sEpsis Shock paTients" which enrolled 30 patients, in the period 2018-2021. The presentation was characterized by haemodynamic shock, IRA, rhabdomyolysis, multi-organ failure, consumptive coagulopathy, cardiorespiratory insufficiency, metabolic acidosis with hyperlactataemia, sepsis with q_SOFA 3. Blood cultures reveal positive Staphylococcus Aureus in 7 patients. positivity for Candida Krusei, in 4 patients positivity for Escherichia Coli. The DIC score was applied to evaluate the CID.
**Purpose of the Work:** The "INTEREST" study has the following objectives: 1) verify any relationships existing between the DIC Score values in the 30 patients enrolled in the "INTEREST" study during the period January 2018 - December 2021; 2) verify the statistical significance found by applying the Cochran1,2,3,4,5 parametric test Q as a comparative analysis test for continuous variables to establish whether the relationships of the variables considered are due to chance.
**Material and Method:** The 30 patients enrolled with cancer and venous thromboembolism were examined according to the fields of the database created with Microsoft Access © called "INTEREST". We compare the DIC Score values in the 30 patients enrolled. For the application of the Cochran Q test. The "Subjects" column shows the patients who participated in the study. The central column shows the 3 variables k "N", "DICS <5", "DICS> 5" which correspond to the patient classes respectively "N" (No DIC), "DICS <5" (DIC Score <5), "DICS> 5" (DIC Score> 5) involved in the "INTEREST" study. The "Subjects" column shows the patients who participated in the study. The central column shows the variables "N", "DICS <5", "DICS> 5" which correspond to the clinical classes they belong to: N (No DIC), DICS <5 (DIC Score <5), DICS> 5 (DIC Score> 5). In column "Y" the number of clinical situations. In column "Y2" the square of the values of "Y". The total of the conditions for the No CID, the DICS <5, the DICS> 5 is indicated in the "Totals" row. The square of the totals of the clinical conditions is indicated in the "Totals2" row. The total number of clinical conditions is indicated with the abbreviation "Y = 30". The acronym "Z = 30" indicates the square of the total clinical conditions. The acronym "Y2 = 900" indicates the square of the total clinical conditions. The sum of the squared totals is indicated with the following formula: X = xN2 + xR2 + xD2 = 900 + 0 + 0 = 900. For the calculation of $\chi 2$ the following formula is applied: $\chi 2 = (k-1)\ [(k\ x)\ -y2]\ /\ (k\ y)\ -z = 20.95$. With "k" the 3 variables considered are indicated, with "x" indicates the total of the squares of the 3 variables considered. "Y" indicates the total number of clinical conditions. "Y2" indicates the square of the

total clinical conditions. "Z" indicates the total of the squares of the clinical conditions. The relative value (VR) of the $\chi 2$ obtained is 60 with Degrees of Freedom (GL) = 2. The critical value (VC) of $\chi 2$ for p = 0.001 is 13.816.
**Analysis of Results:** The Cochran Q test applied to the 30 patients involved in the "INTEREST" study, shows how the clinical situation "DICS> 5" (DIC Score> 5) highlighted in all patients not is attributable to chance but assumes a high statistical significance since the relative value (VR) of the $\chi 2$ obtained is 60 with Degrees of Freedom (GL) = 2 and the critical value (VC) of $\chi 2$ for p = 0.001 is 13.816. The differences in choice are therefore highly significant with p <0.001.
**Discussion:** In all patients, while reaching a score according to the DIC Score System that is consistent for CID, we observed D-Dimer values always between 1 and 5 microgr./ml and no higher. The explanation could depend on the fact that all the patients enrolled in the "INTEREST" study presented a sepsis due to Staphylococcus Aureus which is a producer of Coagulase which in turn activates the thrombin system, unbalancing the Thrombin-Plasmin balance in favor of thrombin. This results in a reduction in plasmin with a reduction in D-Dimer levels, as is observed in leukemic patients.
**Conclusions:** The "INTEREST" study demonstrates how in the 30 patients enrolled with CID and sepsis the DIC Score values are always greater than 5 with D-Dimer values between 1 and 5 microgr./ml as for thrombin hyperactivation to the detriment of plasmin activation. It seems that this trend is attributable to coagulase-producing Staphylococcus Aureus sepsis which unbalances the coagulation cascade in favor of thrombin activation (low D-Dimer values). This association is not attributable to chance but achieves a high statistical significance documented with the Cochran Q Test.

## 359. STEVEN-JOHNSON SYNDROME: CASE REPORT

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**Introduction:** Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are well-known severe cutaneous adverse reactions (SCAR). First reported in 1922, these reactions were initially thought to be infectious in nature, however, the concept has changed over the years. SJS–TEN refers to SCAR associated with widespread epidermal detachment and mucocutaneous involvement. Incidence of SJS and TEN is estimated to be 1.0–6.0 per million and 0.4–1.2 per million, respectively. Over 100 medications have been implicated in SJS and TEN, most frequently sulfonamide antibiotics, followed by nonsteroidal anti-inflammatory drugs and antigout drugs, particularly allopurinol. Risk of developing these SCAR after drug exposure appears to be greatest during the first few weeks of treatment initiation. These SCAR are characterised by fever, rash, and mucosal blisters. Diagnosis depends on the total body surface area involvement of detached/detachable skin lesions: <10%, 10–30%, and >30% represent SJS, SJS–TEN overlap, and TEN, respectively. Both SJS and TEN can occur at any age, but appear to be more prevalent in adults, especially in older adults over 65 years. SJS–TEN overlap is slightly predominant in females compared with males (3: 2). The dihydroxy bile acid ursodeoxycholic acid (UDCA) is used for the treatment of chronic cholestatic liver disorders. It is normally present in human bile at a low concentration of almost 3% of total bile acids. Cutaneous complications are rare, though there have been reports of generalised rash, fixed drug eruptions, and lichen planus secondary to this drug. The present report describes a suspected case of UDCA-induced SJS–TEN overlap.
**Case Report:** A 84-year-old female, who was normotensive and euglycaemic, was admitted with whole-body maculopapular rash with oromucocutaneous erosions and skin desquamation. The patient had a history of arterial hypertension, and was symptom-free before the development of the rashes. No other viral infections were reported during this 1-year time frame. Ten days prior to the presenting features, she was commenced on UDCA 300 mg twice daily (bid), along with a fixed-dose combination of omeprazole and domperidone once daily (qd), by a local physician owing to deranged liver function tests. On the seventh day of consumption of these medications, she presented with a rash, appearing first on the face and then slowly progressing all over the body. The rash was pruritic in nature and was followed by blister formation. The blisters were confined to the facial region, particularly involving the oromucocutaneous region. The blisters were followed by denudation of the skin. The patient was afebrile with no urinary abnormalities, and there were no genital lesions. She also described watery discharge from her eyes and had difficulty in opening her eyes and mouth. The patient was admitted, with prompt cessation of all ongoing medications. She had a history of previous treatment with omeprazole and domperidone on multiple occasions, without any adverse event. However, skin biopsy and histopathology of the involved area was not performed, due to its unavailability in the rural setting of this case. Prognosis was assessed using SCORe of Toxic Epidermal Necrosis (SCORTEN) criteria, which conferred a score of 2 for the index case. The patient was managed with a short course of steroid therapy with qd dosing of dexamethasone for 3 days, intravenous fluid (normal saline) 8 hourly, cyclosporine 100 mg bid, chlorhexidine mouthwash, calaminol lotion, hydroxyzine 25 mg qd, moxifloxacin eye drops, and methylcellulose eye drops. The patient responded to this regimen and was discharged within 3 weeks.
**Discussion:** Approximately 45% of adverse drug reactions are manifested in the skin, with the majority being mild. However, drug-induced SCAR are not rare and are potentially life threatening. These hypersensitivity reactions, including SJS and TEN, are primarily recognised as a dysregulation of cellular immunity caused by a release of various cytotoxic signals, including granulysin, perforin/granzyme B, and Fas/Fas ligands, which are activated by cytotoxic T lymphocytes and natural killer cells. These SCAR differ from classical allergies as there is no classic sensitisation. As evidenced in the literature, mortality rates of SJS, SJS–TEN overlap, and TEN are 5–10%, 30%, and 50%, respectively. Mostly, the lesions initially involve the trunk and upper torso, which spread distally to involve the limbs, followed by skin exfoliation. SJS is characterised by involvement of <10% body surface area, SJS–TEN overlap signifies 10%–30% involvement and the most severe form of the spectrum, and TEN is characterised by involvement of >30% body surface area. Mucosal inflammation (oral, ocular, and genitourinary) is nearly universal. Pseudo-Nikolsky and Asboe-Hansen signs can be elicited in most cases.
**Conclusion:** Keeping in mind the significant morbidity and mortality associated with these SCAR, it would have been extremely beneficial if the culprit drug could be prevented. Proper elucidation of drug allergy history is imperative.

## 360. EFFICACY AND SAFETY OF REPERFUSION TREATMENTS IN MIDDLE-OLD AND OLDEST-OLD STROKE PATIENTS

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**Introduction:** Intravenous thrombolysis (IT) and mechanical thrombectomy (MT) have significantly changed the clinical outcome of acute ischaemic stroke (AIS). Concerns about possible complications often reduce the use of these treatment options for older patients, preferentially managed with antiplatelet therapy (AT). Aim of this study was to evaluate, in a population of middle-old (75-84 years) and oldest-old (≥ 85 years) subjects, the efficacy and safety of different treatments for AIS (IT, IT + MT, MT or AT), mortality and incidence of serious complications.
**Patients and Methods:** All patients aged over 75 years admitted for AIS in two Stroke Units were enrolled. The physician in each case considered all treatment options and chose the best approach. NIHSS and modified Rankin Scale (mRS) were obtained and differences between admission and discharge scores, defined as delta(NIHSS) and delta(mRS), were calculated. The relationship between delta(NIHSS), delta(mRS) and type of procedure was analysed with a GLM/Multivariate model. Differences in mortality and incidence of serious complications were analysed with the chi-square test.
**Results:** A total of 273 patients, mean age 84.07 (± 5.47) years, were included. The delta(NIHSS) was significantly lower in patients treated with AT than in those treated with IT and MT ($p < 0.009$ and $p < 0.005$, respectively). Haemorrhagic infarction occurrence was significantly lower ($p < 0.0001$) among patients treated with AT (10.6%) or IT (16.7%) compared to MT (34.9%) or MT + IT (37.0%). No significant difference was observed for in-hospital mortality. Age did not significantly influence the outcome.
**Conclusions:** Our results suggest that IT and AT are effective and relatively safe approaches in middle-aged and older patients.

## 361. THE ROLE OF BIOMARKERS IN THE PREDICTION OF SHORT-TIME EVENTS IN ACUTE HEART FAILURE IN A LARGE POPULATION OF ELDERLY PATIENTS

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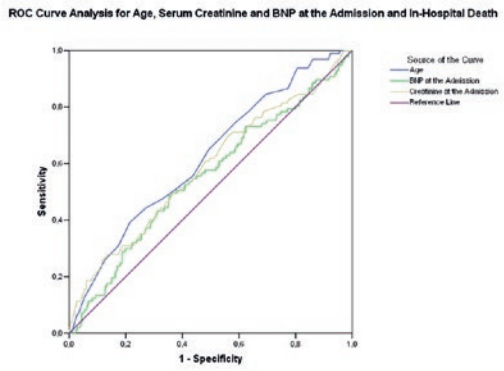
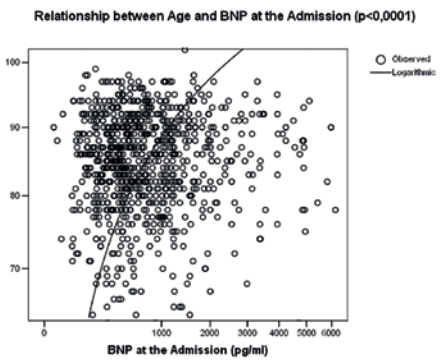
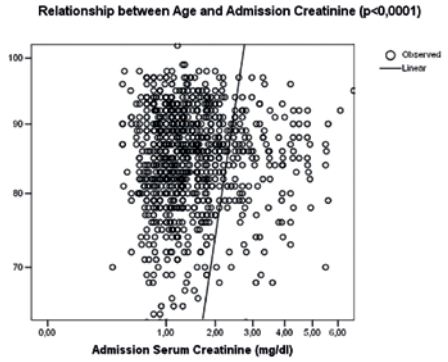
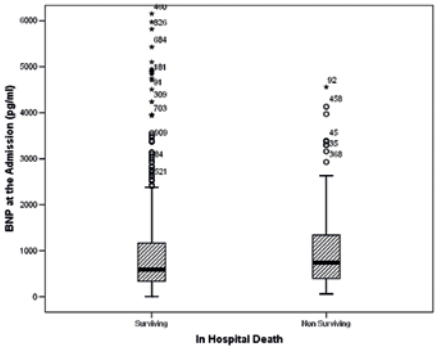
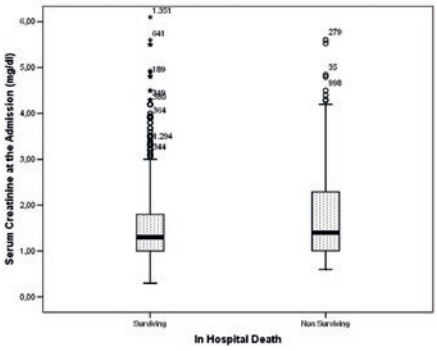
**Background and Aims**: Patients affected by acute heart failure (AHF) are old, often comorbid, with a high short-term mortality that should be assessed by prognostic scores, as EHMRG. Natriuretic peptides (NPs) and serum creatinine are commonly used biomarkers to evaluate AHF prognosis, often included in validated predictive scores. However, the role of NPs, particularly BNP, is less defined in particular groups of subjects, as elderly patients, since several factors, including age, can modify their serum levels. Moreover, chronic kidney failure is common in older ages. With this work, we aimed to assess the role of two commonly used biomarkers in the prognostic assessment of elderly patients with AHF.
**Materials and Methods:** we conducted a large, single-center, retrospective study considering AHF subjects admitted to an Internal Medicine Department (INRCA-IRCCS, Osimo-Ancona) from the Emergency Department in the timeframe between 01/01/2015 and 31/12/2020. We considered age, sex, admission BNP (aBNP, defined as BNP collected within 24 hours from the Internal Medicine admission), admission creatinine (aCr, defined as creatinine collected within 24 hours from Internal Medicine admission), length of admission and in-hospital death. We excluded patients affected by acute coronary syndromes, acute valvular failure, cardiac tamponade, constrictive pericarditis and end-stage renal disease. Association between variables was evaluated with Pearson's bivariate test and with multiple regression analysis choosing the best-fitting trendline according to r2. Accuracy in predicting in-hospital death was assessed with ROC curve analysis. Differences between variables were calculated with t-test for continuous variables or chi-squared test for binary variables.




**Results:** from a sample of 1512 patients, we obtained a final cohort of 1364 subjects, aged 86,2 (±6,02) years, of which 724 (53,1%) were males. Age (p<0,0001), aCr (p=0,0001), longer admission (p=0,0001) were significantly associated with in-hospital death at Pearson's test. ROC analysis confirmed that aBNP did not significantly predict the short-term outcome (AUC: 0,55;95%CI: 0,49-0,62;p=0,095), while aCr (AUC: 0,58;95%CI: 0,52-0,65;p=0,008) and age (AUC: 0,62;95%CI: 0,56-0,68;0=0,0001) resulted significant (Figure 1). We also observed that age had a significant logarithmic association with aCr (r2=0,698; p<0,0001) and aBNP (r2=0,969; p<0,0001) (Figures 2 and 3). We did not find any statistically significant difference in serum aBNP (p=0,818) and aCr (p=0,083) levels between surviving and non-surviving patients (Figures 4 and 5).
**Conclusions:** aBNP and aCr, albeit included in several prognostic algorithms, seem inaccurate assessing elderly subjects' AHF short-term prognosis. Age alone seems to perform better and is associated to both aBNP and aCr: this could explain the reduced biomarkers' role in the prognostic assessment of AHF in elderly subjects. Nowadays, short-term prognosis for AHF should be assessed with validated, multidimensional scores as EHMRG, MEESSI or OHFRS.

## 362. ACCURACY OF CHADS2 AND CHA2DS2-VASC IN PREDICTING STROKE/TIA IN CRITICALLY ILL PATIENTS WITH NON-VALVULAR ATRIAL FIBRILLATION: A PILOT STUDY FROM THE AFICILL 2.0 COHORT

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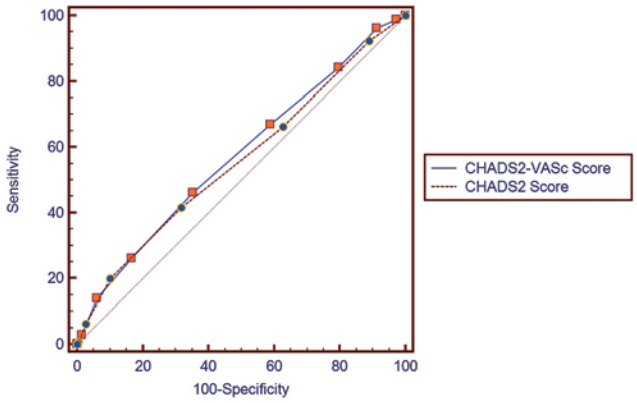
**Introduction:** non-valvular atrial fibrillation (NVAF) is the most common arrhythmia among adult subjects, often burdened by a high stroke risk. Among critically ill patients, NVAF is associated with a markedly raised stroke/TIA and major bleeding risk, due to the interactions between critical illness itself and patients' characteristics. Despite the importance of this issue and the difficulties in the antithrombotic management of these patients, the stratification of cardioembolic risk is still currently performed with CHADS2 and CHA2DS2-VASc scores. We have already observed that these scores were not helpful to stratify stroke risk in the original AFICILL 1.0 cohort [1]. With this paper, we aimed to (i) assess the prevalence of stroke/TIA in a larger cohort of critically ill patients and (ii) evaluate the capacity of CHADS2 and CHA2DS2-VASc score to assess stroke/TIA risk in a larger cohort to validate the observations of our first studies [1, 2].
**Materials and Methods:** We retrospectively enrolled all the consecutive patients from 02/01/2002 to 02/02/2011 admitted to our Subintensive Medicine unit for a critical illness and affected by NVAF. For each patient we calculated CHADS2 and CHA2DS2-VASc scores and the occurrence of stroke/TIA during admission. We assessed the accuracy of each score with ROC curve analysis, comparing their performance with the DeLong method. We performed the analysis with SPSS 13.0 for Windows Systems.
**Results:** we obtained a cohort of 3372 consecutive, critically ill patients. Baseline characteristics are synthesised in Table 1. We observed 336 (9,96%) stroke/TIA events. ROC curve analysis showed that both CHADS2 (AUC: 0,558; 95%CI: 0,542-0,575; p<0,0001) and CHA2DS2-VASc (AUC: 0,573;95%CI: 0,557-0.590; p<0,0001) had a very poor performance in predicting stroke/TIA, and that the scores' performances did not significantly differ (difference between areas: 0,015; p=0,07), as shown in Figure 1.
**Conclusions:** with this preliminary study conducted in a larger cohort, we confirm the high prevalence of stroke/TIA among critically ill subjects and corroborate the observations performed on the original AFICILL 1.0 studies, underlining the poor performance of the classical approach to predict stroke/TIA in critically ill patients affected by NVAF [1]. Newer methods based on topological data analysis and machine learning could be helpful, by improving the quality of prediction, to optimize anticoagulant treatment in this subset of patients, as we already shown with our recent experiments performed in the AFICILL 1.0 cohort [2].
**References:** [1] Falsetti L, Proietti M, Zaccone V, et al. Impact of atrial fibrillation in critically ill patients admitted to a stepdown unit. Eur J Clin Invest. 2020 Nov;50(11): e13317. doi: 10.1111/eci.13317. Epub 2020 Jun 29. PMID: 32535903. - [2] Falsetti L, Rucco M, Proietti M et al. Risk prediction of clinical adverse outcomes with machine learning in a cohort of critically ill patients with atrial fibrillation. Sci Rep. 2021 Sep 23;11(1): 18925. doi: 10.1038/s41598-021-97218-2.

| Variable | Value |
|---|---|
| Age (mean ±SD), years<br>• < 65 years<br>• 65-74<br>• ≥ 75 years | 78,4 ±9,78<br>• 263 (7,8%)<br>• 765 (22,7%)<br>• 2344 (69,5%) |
| Chronic Heart Failure (n, %) | 1220 (36,2%) |
| Hypertension (n, %) | 1704 (50,5%) |
| Type 2 Diabetes Mellitus (n, %) | 664 (19,7%) |
| Previous stroke/TIA (n, %) | 546 (14,7%) |
| Female Sex (n, %) | 1695 (45,7%) |
| Vascular disease (n, %) | 1460 (43,3%) |
| | |
| CHA2DS-VASc (median, [IQR]) | 4 [2] |
| CHADS2 (median, [IQR]) | 2 [2] |

**Table 1:** Baseline characteristics of the sample




## 363. NEUTROPHIL-TO-LYMPHOCYTE RATIO AS A PREDICTOR OF ATRIAL FIBRILLATION IN ACUTE ISCHEMIC STROKE

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**Background:** Neuroinflammation is one of the main determinants of the final damage in acute ischemic stroke (AIS). Neutrophil-to-Lymphocyte Ratio (NLR) is a marker of systemic inflammation related to poor outcomes in AIS and a higher risk of non-valvular atrial fibrillation (NVAF). However, little is known about the association between NLR and NVAF in AIS.
**Methods:** We enrolled patients admitted for AIS to the Emergency Department, then to the Stroke Unit of the Ospedali Riuniti Ancona in the timeframe 01/01/2019-31/12/2019. We collected sex, age, AIS features, and white blood cells count on admission for each patient. We evaluated the occurrence of new-onset NVAF, the presence of pre-existing NVAF, and the presence of any type of NVAF.
**Results:** We evaluated 153 subjects (mean age 70.7 ±11.8 years; 53% males), of whom 23 (15.0%) had pre-existing NVAF, and 21 (13.7%) had new-onset NVAF. Patients affected by any form of NVAF had a significantly higher NLR than patients without NVAF (p = 0.001, Figure 1). Patients with new-onset NVAF had a mean NLR of 8.0 ±7.1, significantly higher than the cohort without NVAF, which was 4.7 ±4.1 (p = 0.003, Figure 2).
**Conclusions:** Inflammation plays a key role in NVAF development and maintenance. Therefore, NLR could reflect a higher level of systemic inflammation, a predisposing factor also for NVAF insurgence. More extensive studies are needed to clarify the relationship between AF and NLR as a biomarker of suspected cardioembolic stroke.

## 364. INCIDENCE AND TYPE OF MAJOR BLEEDINGS AFFECTING THE CRITICALLY-ILL PATIENT WITH NON-VALVULAR ATRIAL FIBRILLATION: A PILOT ANALYSIS OF THE AFICILL 2.0 COHORT

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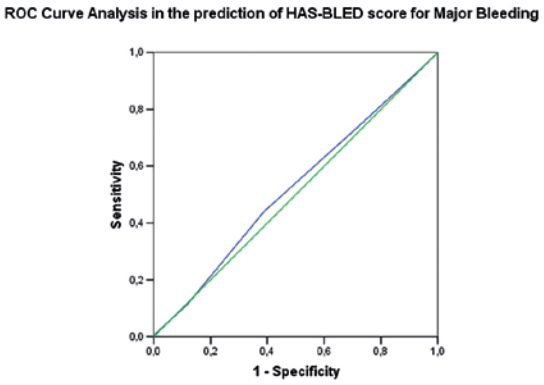
**Introduction:** non-valvular atrial fibrillation (NVAF) is the most common arrhythmia among adult, especially elderly subjects. NVAF is burdened

by a high stroke risk, which can be counterbalanced by anticoagulation. Among critically ill patients, NVAF is associated to both a markedly raised stroke/TIA and a major bleeding risk: despite the importance of this issue, antithrombotic management of these patients is still hard, since the stratification of haemorragic and cardioembolic risk is still currently performed scores which are not validated for this type of patients. We have already observed that CHA2DS2-VASc, CHADS2 and HAS-BLED scores were not helpful to stratify stroke risk in the original AFICILL 1.0 cohort [1]. With this paper, we aimed to (i) assess prevalence and characteristics of major bleeding and (ii) to evaluate the reliability of HAS-BLED score to assess bleeding risk in a larger cohort of critically ill subjects affected by NVAF to validate the observations of our first studies [1, 2].
**Materials and Methods:** We retrospectively enrolled all the consecutive patients from 02/01/2002 to 02/02/2011 admitted to our Subintensive Medicine unit for a critical illness and affected by NVAF. For each patient we calculated HAS-BLED score and observed the occurrence of major bleeding (defined according to the ISTH definition) during the admission. We assessed the accuracy of this score with ROC curve analysis. We performed the analysis with SPSS 13.0 for Windows Systems.
**Results:** we obtained a cohort of 3457 consecutive, critically ill patients (age 78,4 ±9,78 years, 45,7% females). We observed 449 (13,0%) in-hospital deaths or ICU transfers, 336 (9,90%) stroke/TIA and 393 (11,4%) major bleedings. Major bleedings were represented by intracranial (152 patients, 4,4%), gastrointestinal (137 patients, 4,0%), intramuscular or retroperitoneal (37 patients, 1,0%), genitourinary (17 patients, 0,5%) and other (50 patients, 1,4%) bleeding. Median HAS-BLED was 2 [2]. ROC curve analysis showed that HAS-BLED score (AUC: 0,521; 95%CI: 0,490-0,551; p=0,184) was not accurate in predicting major bleeding in this clinical setting, as shown in Figure 1.




**Conclusions:** with this preliminary study conducted in a larger cohort, we confirm the high level of therapeutic failure, defined by mortality or ICU transfer, a higher prevalence of stroke/TIA and a very high risk of major bleeding in this cohort of critically ill subjects affected by NVAF. These preliminary observations corroborate the original AFICILL 1.0 studies, underlining the poor performance of the classical approaches to stratify the cardioembolic and the haemorragic risk among critically ill patients affected by NVAF [1]. Newer methods based on topological data analysis and machine learning could improve the quality of prediction and optimize anticoagulant treatment in this subset of patients, as we already shown with our recent experiments performed in the AFICILL 1.0 cohort [2].
**References:** [1] Falsetti L, Proietti M, Zaccone V, et al. Impact of atrial fibrillation in critically ill patients admitted to a stepdown unit. Eur J Clin Invest. 2020 Nov;50(11): e13317. doi: 10.1111/eci.13317. Epub 2020 Jun 29. PMID: 32535903. - [2] Falsetti L, Rucco M, Proietti M et al. Risk prediction of clinical adverse outcomes with machine learning in a cohort of critically ill patients with atrial fibrillation. Sci Rep. 2021 Sep 23;11(1): 18925. doi: 10.1038/s41598-021-97218-2.

## 365. PROGNOSTIC VALUE OF DEEP VEIN THROMBOSIS IN PATIENTS WITH PULMONARY EMBOLISM: MONOCENTRIC RETROSPECTIVE STUDY

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**Introduction:** Pulmonary Embolism (PE) is the third most common cause of cardiovascular disease after myocardial infarction and stroke. It is characterized by an acute obstruction of part of the pulmonary arterial circulation caused by embolization of thrombotic material mainly involving deep veins of the lower limb.
The objective of this study is to analyze the localization of deep vein thrombosis (DVT) detectable in patients with PE and determine its prognostic value.
**Materials and Methods:** Retrospective, monocentric, observational study conducted at the Arcispedale St.Anna, Cona, Ferrara, which included patients older than 18 years admitted to the Emergency Department (ED) with a final diagnosis of PE in the period 2018-2021. Each included patient had to have doppler ultrasound (DUS) available in the clinical record. Anamnestic, vital, laboratory and instrumental data were also analyzed.
**Results:** We evaluated 477 patients, 43.2% male, average age 71.5 years old (yo), with intrahospital mortality of 4.6%. DVT was found in 72.3% of patients: 36.6% with unilateral femoral, 37.6% monolateral popliteal, 3% bilateral femoral or popliteal thrombosis. A distal thrombosis was identified in 43.5% of patients. Thrombotic involvement of the iliac-caval axis, found in 7.6% of cases, has proven to be an independent predictor of mortality. Patients >80 yo had more often a previous DVT. Furthermore, patients >80 yo and those with history of cancer had a more frequent involvement of the proximal bilateral veins of the lower limb. Patients with a previous DVT had more often a newly diagnosed bilateral popliteal DVT. Also, 74% of patients with recent immobilization showed DVT, more frequently localized in the proximal and bilateral venous system.
**Discussion:** Our study showed that DVT is detectable in about 75% of patients with PE, a finding indicating that the lack of DVT cannot exclude the diagnosis of PE. Prothrombotic factors were more frequently associated with proximal lower limb DVT. The presence of proximal or distal thrombosis, mono or bilateral, does not influence intrahospital mortality. Recent ESC Guidelines on acute PE do not consider thrombosis and extension as essential determinants of intrahospital mortality stratification (ESC classes and HESTIA criteria). However, the finding of iliac thrombosis resulted to be an independent predictive factor that places the patient at high risk of short-term mortality.
**Conclusion:** Our data indicated that DVT alone cannot be considered a prognostic factor for intrahospital mortality in patients with PE. However, iliac-caval involvement could be an important factor in risk stratification.

## 366. INTRA-HOSPITAL MORTALITY IN PULMONARY EMBOLISM: DERIVATION AND VALIDATION OF THE PLATELETS, AGE, TROPONIN, HEART RATE, OXIMETER, AND SYSTOLIC BLOOD PRESSURE (PATHOS) SCORE. A RETROSPECTIVE, MULTICENTER STUDY

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**Objectives:** Pulmonary Embolism (PE) is defined as the migration of blood clots (as well as fat or gasses) to the pulmonary arteries leading to signs and symptoms related to a variable abrupt increase in pulmonary artery pressure, right ventricular dysfunction, and circulatory impact. According to the ESC 2020 guidelines on PE, prognosis relies on the PESI and ESC class risk for short-term mortality. However, PESI is a complex score with a debated validity and ESC classification depends on echocardiography, a technique not widely available in any emergency department (ED). The objective of this study is to develop and validate a new prognostic score for in-hospital mortality (IHM) for patients with PE.
**Methods:** This is a retrospective, multicenter cohort study conducted in the

EDs of two third-level university hospitals in Italy (derivation and validation cohort). Patients aged >18 years with a contrast-enhanced computed tomography confirmed PE were included. Clinical variables according to 4 prognostic scores (GENEVA, RIETE, PESI, sPESI, and Shock Index [SI]) and laboratory tests were evaluated blindly to IHM. The new prognostic score accuracy was compared with PESI, sPESI, and SI in both ED and global populations.
**Results:** In this study 1358 patients were included in our study, 586 in the derivation cohort and 772 in the validation cohort, 44.2% male, with a median age of 69.88 years, and with 10.6% of IHM. Platelets, Age, Troponin, Heart rate, Oxygenation, and Systolic blood pressure were identified as independent predictors and included in the PATHOS score. PATHOS score showed significantly higher accuracy than PESI, sPESI, and SI in the derivation, validation, and global cohort. A PATHOS score >2 was the best single cut-off with 61% sensitivity, 82% specificity, 3.32 +LR, and 94% NPV for IHM.
**Conclusion:** PATHOS is a simple and effective prognostic score for the prediction of IHM in patients with PE in the emergency setting.

## 367. HEMOLYTIC CRYSIS AND FAVISM DIAGNOSIS IN AN UNAWARE ADULT PATIENT IN EMERGENCY SETTING

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**Introduction:** Glucose-6-phosphate dehydrogenase (G6PD) deficiency is one of the most common human enzyme defect, usually diagnosed in pediatric age. Although patients are often asymptomatic, they can manifest acute hemolysis, consequent to acute red blood cell (RBC) oxidative stress triggered by agents such as drugs, infections or the ingestion of fava beans.
**Case Presentation:** A 46-year-old male patient from Morocco, with history of allergic rhinitis, bronchial extrinsic asthma and recently diagnosed hypertension, presented to our Emergency Department with abdominal and thoracic pain, jaundice and hyperchromic urine since the last 12 hours. The patient reported having experienced a similar episode two years before, associated with lighter symptomatology and followed by spontaneous resolution. At clinical presentation he had a 15 Glasgow Coma Scale (GCS), blood pressure was 160/110 mmHg, heart rate 110 bpm, SpO2 95%, body temperature 36.9°C. At physical examination skin and scleral jaundice was evident, without itching. The abdomen was treatable but painful on deep palpation of the lower right quadrants, with negative Murphy and Blumberg signs. The heart sounds were valid and normo- frequent. The electrocardiogram did not show any sign of acute myocardial ischemia and troponin was within the normal range. Blood chemistry showed indirect hyperbilirubinemia (total bilirubin 16.35 mg/dL [0,2-1,1], direct bilirubin 1.5 mg/dL [0,2-0,8]), anemia (Hb 9.8 g/dL [13,2-17,3]), CPK 474 mg/dL [30-150], preserved renal function (creatinine 0.95 mg/dL [0,73-1,18]) and increased inflammation indices (CRP 10 mg/dL [<0,5], WBC 21690/mmc [4,00-10,00], with 75.8% neutrophils, procalcitonin 2.11 ng/mL [0,00 - 0,50]). Blood cultures were performed. Abdominal ultrasound showed dilated gallbladder, with slightly thickened walls containing hypoechoic sludge in the body and infundibulum. CT scan of the abdomen with contrast medium (MC) showed undamaged gallbladder without any evidence of parenchymal organ damage. Chest X-ray revealed a faint opacity in the left midfield, interpreted as a possible fibrotic outcome. Nasal swab for SARS COV2 was negative. As the results of imaging and blood analysis, we excluded surgical emergencies, such as acute cholecystitis, biliary colic or cancer, focusing our attention on potential hemolytic causes. With a deeper anamnesis, the patient answered to our specific question: he had fava beans for lunch the day before. He was therefore admitted in the Internal Medicine Department. Coombs test was within normal limits. Blood chemistry tests showed increasing of hemolysis indices and progressive worsening of anemia (LDH 2101 mU/mL [80-300]; haptoglobin 9 mg/dL [50-150]; total bilirubin 17,0 mg/dL [1,3-1], Hb 6,9 g/dL [14-18]), so that the patient was treated with blood transfusion (2 concentrated RBC units). The enzymatic assay confirmed the presence of G6PD deficiency.
**DISCUSSION:** Based on the initial symptoms and the age of the patient, firstly surgical etiology was suspected but then excluded by laboratory and imaging findings. Given the combination of anemia and hemolysis, with decreased haptoglobin, and increased indirect bilirubin and LDH levels, we ruled out the main causes of hemolysis, such as trauma (imaging was negative), infections (microbiological cultures were negative), or immuno-mediated hemolysis (Coombs test was negative). The family and patient's history did not show anything clinically relevant. As the patient reported a similar episode (although less intense) few years before, we supposed a previous triggering hemolysis event. Given the patient's Country of origin (North Africa), we suspected fava beans ingestion in an adult with unknown favism. This hypothesis was then confirmed by patient's recent history and the specific enzymatic assay. According to the literature, in the same person, favism attacks show a striking variability from one exposure to another. This could be the reason why the patient had a similar but milder previous episode, most likely triggered by fava beans ingestion.
**Conclusion:** Considering that favism-related hemolytic crisis is more frequent in the pediatric age than in the adult one, finding a first episode in a 46-years-old patient can be considered a rarity. Indeed, it appears that the patient was not previously been exposed to other major triggering hemolytic agents. Even in a fast and dynamic environment of an Emergency Department, this case demonstrates the importance of collecting an accurate medical history integrated with the signs and symptoms of the semeiotic examination.

## 368. SUCCESSFUL TREATMENT OF A VERY SIMILAR KOUNIS SYNDROME TYPE 1

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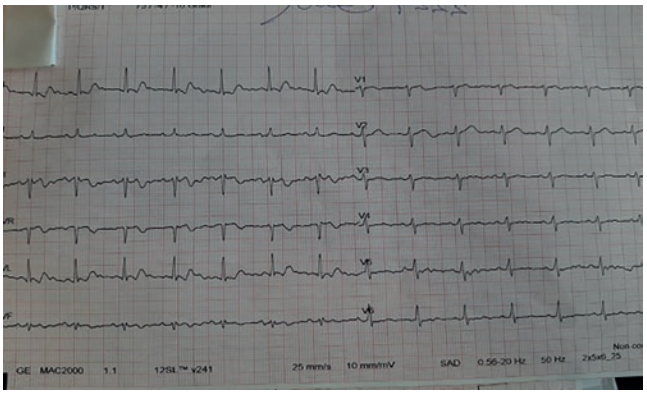
**Introduction:** Kounis syndrome is defined as a hypersensitivity coronary disorder caused by the activation of mast cells. It is a rare condition, and its reported incidence in emergency departments is 0.0194% of all admissions and 3.4% of allergy patient admissions. The diagnosis of Kounis syndrome is mainly based on clinical manifestations. Due to a lack of awareness, Kounis syndrome is thought to be frequently missed or under-diagnosed. It is critical to identify Kounis syndrome because the treatment of Kounis syndrome is different from that of classic acute coronary syndrome. Triggers are increasingly being reported: Antibiotics (27.4%) and insect bites (23.4%) are the most common. Here we report a case of Kounis syndrome induced by Amoxicillin/Clavulanic acid.
**Case Description:** A 72 y.o. a woman presented to the emergency department (E.D.) of Presidio Ospedale Luigi Sacco, ASST Fatebenefratelli Sacco, Milan on February 14th 2022 with tongue oedema and urticarial rash on both arms after taking Amoxicillin/Clavulanic acid the night before because of gingivitis.
She reported hypertension, hypothyroidism and dyslipidemia; furthermore she had a similar episode 8 months before with a negative allergologic follow-up.
She was hemodynamically stable with a GCS of 15; her vital signs at the arrival (at 2 pm) were as follows: BP 145/90 mmHg, a regular pulse of 90 bpm, TC 36 °C and a spO2 of 96%. Chlorphenamine 10 mg and Methylprednisolone 60 mg were administered.
At 3.30 pm urticaria was slowly improving but epigastric pain, nausea and a single episode of bilious vomit were reported; a pantoprazole 40 mg iv bolus was given. The ECG showed a sinus rhythm of 90 bpm with diffuse ST segment-T wave abnormalities more pronounced in I and aVL.
At 6 pm the epigastric pain was resolved but the rash was rapidly worsening with extension to lower limbs and eyelids; BP was 105/50 mmHg. Hydrocortisone 500 mg and 500 ml of crystalloids were IV administered with a reduction of the urticarial rash.
The blood tests showed the following: WBC 11.590/mm3, Hb 15.6 g/dl, PLTs 160.000/mm3, PCR 43 mg/L, no abnormalities of the renal function, electrolytes, coagulation and other laboratory tests; the chest X-Ray was also within limits. A first TnT sample showed a significant elevation (79 ng/L); a 3 hour third blood draw showed no significant variation (64 ng/L).
The patient underwent continuous monitoring and spent the night with stable vital signs.
At 10 am a complete cardiological evaluation was made: The echocardiography showed normal regional movement and preserved EF (55%) with hypertrophic LV and moderate aortic insufficiency. The suspicion was of cardiac injury due to the allergic reaction. The execution of a coronary-CT and the administration of bisoprolol 1.25 mg was suggested.
The patient was then admitted to the internal medicine ward for further testing. During the continuous monitoring, the patient experienced other episodes of anginous pain without ECG modifications, TnT elevations and

with stable vital signs. An echocardiography was repeated that confirmed previous results. The coronary-CT showed an anatomical variant of both origin and route of the right coronary artery with right dominance. There was only one coronary ostium at the right coronary sinus that gave way to 3 branches: Two of these vessels were scarcely evaluable for the degree of stenosis.
The indication for a coronarography was made: no significant obstruction was found; no interventional practices were made.
She was discharged 14 days after her ED admission with the prescription of bisoprolol 1.25mg and an allergologic follow-up.
**Discussion:** We described a successful treatment of a patient suffering from acute myocardial injury likely to be connected with a hypersensibility reaction to Amoxicillin / Clavulanic acid. Clinical suspicion derived from the connection between the myocardial necrosis enzymes, ECG dynamic alterations and the clinical presentation of the patient. Diagnosis was made after excluding significant coronary stenosis at coronarography.
We can hypothesize that this presentation could be linked to Kounis Syndrome.
There are three types of presentations: in type 1 there is no evidence of underlying coronary illnesses, both considering ischemic and non ischemic ones, and the anaphylactic trigger leads to an arterial spasm and myocardial hypoperfusion. Type 2 is just like type 1 with the addition of coronary spasm in asymptomatic cardiovascular illness or plaque rupture; and type 3 considers coronary and stent thrombosis. Considering these reasons Kounis Type 2 and 3 had been ruled out.
The treatment was essentially based on the administration of steroids and anti-H1 medications. It must be noted that even if there are no further diagnostic tests available to clear the etiology, a limit of this case report is that considering the latest ESC Guidelines on MINOCA, performing a cardiac MRI could have excluded myocardial necrosis caused by a myocarditis.




## 369. PROGNOSTIC ROLE OF PULMONARY ANGIO-CT IN PREDICTION OF INTRA-HOSPITAL DEATH IN PATIENTS WITH PULMONARY EMBOLISM. MONOCENTRIC RETROSPECTIVE STUDY

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**Introduction:** Pulmonary embolism (PE), i.e. the mobilization of thrombotic material into the pulmonary arterial circulation, is one of the most frequent causes of cardiovascular death in daily practice. In this study, we evaluated the predictive role of the localization of PE at computed tomography pulmonary angiogram (CTPA), on intrahospital mortality (IHM).
**Materials and Methods:** Monocentric retrospective study conducted at the St. Anna Hospital, Ferrara, which enrolled adult patients admitted to the Emergency Department (ED) between 1/1/2018 and 31/5/2021 with PE demonstrated by CTPA. Past medical records, vital signs, laboratory and instrumental data were collected, and where available, the ESC risk class was calculated (presence of haemodynamic instability, right ventricular [RV] dysfunction on echocardiography, elevated troponin I, and PESI class III-V or sPESI ≥1).
**Results:** N= 446 patients with an average age of 73 years were included; 8.7% died in hospital; 268 patients were classified according to ESC. We observed a statistically significant association between thrombus site and ESC class: patients at higher risk of IHM had more frequently a concomitant involvement of the right and left pulmonary arteries (72.4%); patients at intermediate-high risk showed more frequently bilateral lobar PE (53.3%), while patients at low-intermediate risk had minimal bilateral segmental PE (25%). Considering the location of the thrombus at CTPA, only the concomitant localization of both arteries showed predictive value of IHM. However, evaluating localization of the thrombus, tachycardia, hypotension, desaturation and increased troponin values at multivariate regression analysis, CTPA data showed no independent predictive value.
**Discussion:** PE causes cardio-circulatory dysfunction due to acute increase in pulmonary arterial pressure and right-to-left pulmonary shunt, resulting in overload and hypoxic damage to the right ventricle. This causes right ventricular hypocontractility with a reduction in the left ventricle preload and systolic output, and cardiocirculatory shock due to obstructive shock. A 30-50% occlusion of the pulmonary arterial tree is estimated to be required for initiation of this cascade. In our study embolization to large caliber arterial segments correlate with unfavorable risk classes. The hemodynamic impact is highly variable depending on the location of the embolism. Based on careful evaluation of the variables, the localization of the thrombus on CT lost its predictive value of IHM compared to the clinical-laboratory data, which predict the patient's hemodynamic response.
**Conclusions:** Based on our data, the therapeutic strategy of patients with PE should be dictated by clinical features and existing scores rather than radiological imaging.

## 370. TRALI AND TAKOTSUBO: A CASE OF IMBRICATED RARE DISEASES

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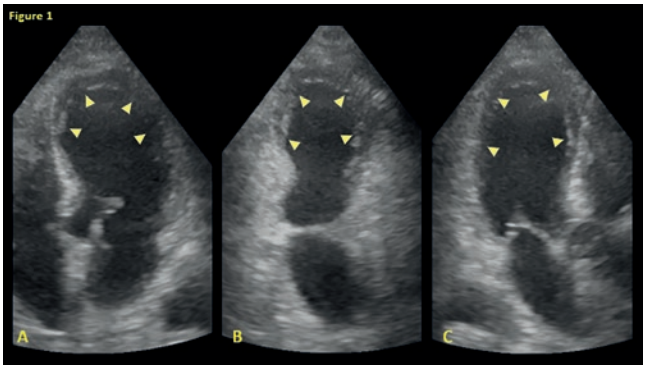
A 78 years-old man was admitted to the emergency department (ED) for pneumonia. He was affected by Chronic lymphocytic leukemia and a related immunosuppression state caused by depletion of gamma globulins, causing recurrent bronchial infections resulting in bronchiectasis. Because of that, he was treated with monthly infusions of immunoglobulins (IVIG). His medical history includes chronic coronary syndrome treated with angioplasty with normal left ventricular function with ejection fraction (EF) ~60%, chronic anemia and thrombocytopenia.
At admission to ED patient had respiratory failure; sputum and blood cultures were collected before antimicrobic treatment was started and he was admitted to our unit. Detected bacteria were susceptible to therapy and we recorded improvement in patient clinical condition with rapid oxygen weaning.
We planned to administrate the patient's IVIG treatment before discharge. Within one hour of IVIG's administration, he complained of back pain and shivering, transfusion was immediately discontinued. On clinical assessment he presented wet lung rales, desaturation and respiratory distress. Anaphylaxis and bronchospasm were ruled out and a chest x-ray showed the new onset of bilateral upper and lower lobe pulmonary infiltrates. We suspected transfusion related acute lung injury (TRALI). Non-invasive respiratory support with continuous positive airway pressure (CPAP) was started and patient was treated with intravenous corticosteroids. Blood gas revealed elevated lactate and ECG showed no new significant alterations. After few hours patient presented low blood pressure, diaphoresis and complained of acute chest pain. CPAP was discontinued, ECG showed no significant differences. Bedside transthoracic echocardiography (TTE) was performed, showing a severe reduction of left ventricular EF (~20%) with diffuse balloon akinesia of all mid-apical segments and hyperkinesia of basal segments. Blood tests showed elevated troponin T and proBNP. We suspected takotsubo cardiomyopathy (TTC) as a consequence of acute respiratory failure. Given the patient's critical condition urgent angiography was not performed considering: typical apical ballooning at the TTE, onset and timing of symptoms, anemia and thrombocytopenia with elevated bleeding risk in context of chronic antiaggregation treatment, generalized risks of procedure. We started oxygen administration with Venturi mask to

avoid PEEP and reduction of venous return; dopamine at inotropic dosage was started to support cardiac output. With such treatment we observed an improvement in blood pressure, cardiac contractility and respiratory symptoms. Dopamine and oxygen support were suspended after five and seven days, respectively. TTE was performed on a daily basis, showing complete amelioration of global wall motion, no residual abnormalities and increase in EF from 20% to 67%; the typical apical ballooning aspect gradually disappeared (Fig.1).
Our report shows the succession of two infrequent conditions with elevated life-threatening risk, that could have been lethal if not promptly diagnosed. TRALI is a complication of blood product transfusion characterized by new acute respiratory distress within six hours of transfusion; this case shows a TRALI type II. Prospective studies of TRALI in diverse multicenter populations reported an incidence rate of 0.0008% to 0.001% of transfused patients. All blood components can cause it, but red blood cell transfusion is associated with the highest risk. In our case, patient presented other risk factors: white individual, other medical illness in the prior six months, active infection and hematologic malignancy. TRALI is a rare complication and diagnosis can be missed. It represents the primary cause of transfusion-related fatalities and mortality is significant (41-67%); clinically meaningful cases are rare and surviving patients generally recover completely.
TTC is a great imitator of acute myocardial infarction, without evidence of complicated coronary artery disease and its prevalence has been reported to be 1-3% of all patients presenting with clinical manifestation of acute coronary syndrome. Emotional or physical stress are triggers for the onset of TTC which pathophysiology remains unknown. Some authors suggest avoiding catecholamine since stress cardiomyopathy may be precipitated. In our case, considering cardiogenic shock without left ventricular outflow tract obstruction, inotropic therapy was considered a valuable option to sustain cardiac output. We suspected TTC according to Mayo Clinic criteria, even if angiography was not performed for reasons before mentioned.
Our case highlights the role of Point of Care Ultrasonography as a useful tool for early diagnosis, for addressing therapy in acute events and monitoring the evolution of pathological states.




## 371. DIAGNOSTIC AND PROGNOSTIC VALUE OF HMBG1 IN A SEPTIC PATIENT COHORT

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Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection: it is a significant burden for health care system in terms of morbidity, mortality, and economic cost. Latest study estimated 48.9 million cases and 11 million deaths all over the world per year, and in US it is the most common cause of in-hospital deaths and costs more than US$ 24 billion annually. Nowadays, there is no gold-standard laboratory test able to determine its diagnosis; our research aim is to detect a molecule correlated to septic process in order to ameliorate a prompt recognition, guiding physicians to an adequate, and rapid medical treatment. In this contest, there is ongoing research for such kind of molecules, among them we decide to evaluate High mobility group box-1 (HMGB1), which is a damage associated molecular pattern (DAMP) both secrete actively and released passively during an inflammatory response determined by tissue damage.
The aim of our study is to evaluate the difference of HMGB1 concentration between critically ill patient arrived at the Emergency Department (ED), and make a comparison in terms of diagnostic and prognostic correlated with its plasmatic concentration.
We had conducted our experimental analysis collecting data within a single-center, prospective, observational study. All patients had been recruited after admission in our emergency department for suspected infection defined as quick-SOFA (qSOFA) score ≥ 2. Our analysis had been made on clinical data and biological samples obtained at the time of initial ED evaluation (T0) and after 24 hours (T1), clinical evaluation follow-up was performed at day 7 and at day 30 after hospital discharge. Plasma citrated sample had been collected, aliquoted and stocked at minus 80 degrees Celsius, and analyzed through "Enzyme-Linked Immuno-Sorbent Assay" (ELISA) HMGB1 concentration [ng/mL]. At the end of the study, collected data had been used to classify patient in two different groups, defined as non-septic and septic patients, first ones had no criteria for sepsis or septic shock diagnosis, second ones matched criteria proposed by Sepsis-3 conference. In this last group patients were divided in septic and septic shock. Our evaluation and diagnosis were reviewed by our working group clinical experts.
In this study we collected samples from 117 patients, all affering to ED. Comparison was made on non-septic and septic patients (septic and septic shock) median HMGB1 plasmatic concentration [ng/mL], at T0 (4,08; IQR 1,65 – 7.51 vs 1,93; IQR 1,27 – 3,78; p = 0,021) and T1 (2,51; IQR 1,76 – 4,53 vs 1,38; IQR 1,05 – 2,12; p = 0,015) a significant difference was found. We compared, then, median HMGB1 plasmatic concentration between three different groups: non septic, septic and septic shock, its value progressively grows with statistical significance: at T0 respectively were 1,93 (IQR 1,27 – 3,78) vs 3,63 (IQR 1,52 – 6,61) vs 6,39 (IQR 3,32 – 9,29) (p < 0,001), while at T1 1,38 (IQR 1,05 – 2,12) vs 2,35 (IQR 1,62 – 3,76) vs 3,38 (IQR 2,02 – 6,25) (p = 0,006).
HMGB1 plasmatic concentrations at T0 (6,63 ng/dL vs 3.75 ng/dL; p = 0.035) and even a T1 (3,57 ng/dL vs 2.36 ng/dL; p = 0,017), showed significative difference comparing them with fatality and survival rate at day 7.
We performed a multivariate analysis, that pointed out as independent predictor of mortality HMGB1 plasmatic concentration (HR 1,06; IC 95% 1,04 – 1,09; p < 0,00019), in association with PaO2/FiO2 reduction, Red blood cells Distribution Width- coefficient of variation (RDW-CV) and q-SOFA of 3 (HR 1,06; IC 95% 1,04 – 1,09; p = 0,0104).
Data collected in our study revealed potential diagnostic role in plasmatic HMGB1 concentration analysis, its value is higher in septic patient than in non-septic. Therefore, in our data is evident how, even at ED access, higher concentrations are independently correlated with augmented risk of death. These data could be of potential aid for emergency physicians in guiding their decision when treating critically ill patients and also stratifying them by risk of worsening.

# METABOLISMO, DIABETE E NUTRIZIONE CLINICA

## 372. CONTROLLING NUTRITIONAL STATUS (CONUT) AS PREDICTOR OF HOSPITAL LENGTH OF STAY (LOS) AND MORTALITY IN AN INTERNAL MEDICINE UNIT

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**Background:** COntrolling NUTritional status (CONUT) is a simple score based on the values of serum albumin, total lymphocyte count, and total cholesterol, useful to investigate nutritional status in several clinical contexts. To date, a prognostic value on hospital length of stay (LOS), hospital mortality, and admission, has not yet been evaluated in patients admitted to an Internal Medicine Department. We aimed to demonstrate an association between the CONUT score at admission and LOS, in-hospital mortality, and 30-days hospital readmission in an internal medicine unit of an Italian Tertiary Care center.
**Methods:** CONUT score was calculated at admission in a total of 203 patients admitted to the Internal Medicine and Gastroenterology Department at Fondazione Policlinico A. Gemelli IRCCS, Rome.
Patients were divided into four groups: normal CONUT (0-1), mild-high CONUT (2-4), moderately high CONUT (5-8), and severely high CONUT (9-12) according to previous literature.
Also, we divided patients into two more nominal groups: low CONUT score (if CONUT ≤3) and high CONUT score (if CONUT >3). LOS, hospital mortality, and readmission were retrieved from clinical files. Statistical analyses were carried out using STATA software. Continuous data are expressed in mean +- SD, categorical ones in absolute number (and percentage). Differences among groups were analyzed with unpaired t-test or with Chi-squared when appropriate. Uni- and Multi-variate Cox Regressions were constructed to analyze LOS. A $p < 0.05$ was set as statistically significant.
**Results:** In a total of 203 patients, a normal CONUT score was found in 44 patients (21.7%), mild-high CONUT patients were 66 (32.5%), moderately-high CONUT patients were 68 (33.5%), while a severely high CONUT was found in 25 patients (12.3%). A CONUT score >3 was found in 118 patients (58.1%), while 85 patients had a CONUT ≤3. In-hospital mortality was 4.4% (9 patients), while 30 days readmission rate was 6.4% (13 patients). Mean LOS in those with CONUT≤3 was 6.52±4.46 days, while in CONUT >3 group was 9.47±6.26 days (p-value 0.0003). There was also a significant stratification of LOS among CONUT classes: in normal CONUT patients LOS was 6.36±5.23 days, in mildly-high patients was 7.03±4.38 days, in those moderately high 9.57±5.22 days, while extremely-high patients had 11.12±8.76 days (p-value 0.0004). In-hospital mortality in the low CONUT group was 1.18%, while in the high CONUT group was 6.78% (p-value 0.05). Logistic regression confirmed significant in-hospital mortality in patients with higher CONUT levels (p-value 0.001).
On the other hand, there was no significant association between CONUT levels or CONUT>3 and 30-days hospital readmissions.
**Conclusions:** A higher CONUT score at admission is associated with a longer LOS and higher mortality in our internal medicine unit. CONUT score could be a useful tool to identify highly complex and frailty patients at admission to medical care units in order to pay specific clinical and nutritional attention.

## 373. ALTERED GLUCOSE TOLERANCE CONDITIONS ARE ASSOCIATED WITH AN ACTIVATION OF ER STRESS RELATED RESPONSES IN THE GUT

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Preclinical evidence indicates that high glucose levels may affect intestinal expression of tight-junction (TJ) proteins, thus leading to a disruption of intestinal epithelial integrity. Activation of endoplasmic reticulum (ER) stress plays an important role in cellular damage associated to glucotoxicity, and it has been reported to affect intestinal barrier integrity in animal studies. However, whether subjects with dysglycemic conditions have an activation of ER stress related responses in the colon has not been explored. In this study, we aimed to evaluate whether subjects with prediabetes or T2DM exhibit an activation of ER stress along with a disruption of mucosal integrity in the gut. We studied 38 Caucasian adults who underwent a complete clinical characterization including OGTT, and colonoscopy with collection of colonic mucosa biopsies. Study participants were classified as having normal glucose tolerance (NGT, n=15), prediabetes (n=11) and T2DM (n=12) in accordance to the current American Diabetes Association criteria. Colonic levels of the ER stress activation markers Bip, Inositol-requiring enzyme 1 (IRE-1), C/EBP homologous protein (CHOP), and phosphorylation levels of eukaryotic initiation factor 2 (eIF2α) and c-Jun N-terminal kinases (JNK) were assessed by Western blot (WB). Expression of TJ proteins was assessed by RT-PCR and WB. Activation of pro-inflammatory pathway was evaluated by measuring nuclear factor kB (NF-kB) activity by a specific ELISA kit, and mRNA levels of the pro-inflammatory cytokines IL-1β, TNF-α and IL-6 by RT-PCR. Subjects with prediabetes and T2DM displayed progressively increased levels of the ER stress markers Bip, IRE-1α, phosphorylated eIF2α and CHOP in the colonic mucosa as compared to those with NGT ($P<0.05$). Moreover, we found a 1.5- and 2-fold increase in phosphorylation levels of the stress kinase JNK in subjects with prediabetes and T2DM as compared to NGT group ($P<0.05$). The intestinal up-regulation of ER stress found in subjects with altered glucose tolerance was paralleled by an altered intestinal mucosa integrity. We found that subjects with prediabetes and T2DM have significantly reduced expression levels of the TJ protein zonulin (ZO)-1, claudin-1 and occludin in the colonic mucosa (-30% and -50% respectively, $P<0.05$), coupled with increased circulating levels of ZO-1, a surrogate indicator of increased intestinal permeability (+15% and +20% in prediabetes and T2DM, respectively). Additionally, we found an up-regulation of the pro-inflammatory NF-kB activity along with increased levels of IL-1β, TNF-α and IL-6 in colonic mucosa of subjects with prediabetes and T2DM as compared to those with NGT. In conclusion, our results demonstrate that both prediabetes and T2DM are linked to an activation of ER stress along with a compromised intestinal barrier integrity, and inflammation in the colonic mucosa.

## 374. DOWN-REGULATED FXR SIGNALING IN THE GUT IN SUBJECTS WITH PREDIABETES AND TYPE 2 DIABETES

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Bile acids have recently emerged to be involved in the regulation of glucose, lipid and energy homeostasis, by targeting farnesoid X receptor (FXR). Treatment with obeticholic acid (OCA), a FXR selective agonist, has been found to improve glucose metabolism in subjects with type 2 diabetes (T2DM) with mechanisms not completely elucidated. In the gut, FXR is mainly expressed in the ileum and promotes transcription of fibroblast growth factor-19 (FGF-19), a hormone with positive effects on energetic and glucose homeostasis. Additionally, preclinical evidence suggests that FXR preserves intestinal barrier integrity by promoting expression of intestinal tight-junction (TJ) proteins. Altered gut permeability has been associated with cardiometabolic disorders. Herein, we examined whether subjects with prediabetes or type 2 diabetes have reduced ileal FXR abundance along with a downregulation of FGF-19 and TJ expression, and whether treatment with OCA is able to restore intestinal FXR/FGF19/TJ integriy axis. The study population includes 32 subjects subdivided on the basis of their glucose tolerance in: normal glucose tolerance (NGT) (n=12), prediabetes (n=10) and T2DM (n=10). All subjects underwent to a colonoscopy with terminal ileum endoscopy and collection of ileum mucosa biopsies. Intestinal levels of FXR, FGF-19 and TJ proteins were assessed by western blot and RT-PCR. Serum levels of FGF-19 were evaluated by ELISA assay. To investigate the effect of OCA treatment, ileal mucosa specimens collected from subjects with T2DM were cultured in absence or presence of OCA. Ileal protein levels of FXR were progressively reduced in individuals with prediabetes (-15%, $P=0.01$) and T2DM (-25%, $P=0.01$) as compared to those with NGT. The reduced ileal FXR abundance observed in subjects with dysglycemic conditions was paralleled by a reduction in ileal levels of FGF-19 mRNA with subjects with prediabetes exhibiting a 25% reduction, and those with T2DM a 50% reduction (both $P<0.05$). These changes were accompanied by a similar reduction in serum FGF-19 concentration (-25% and -45% for individuals with prediabetes and for those with T2DM, respectively, $P<0.05$) as compared to NGT group. Additionally, we observed a progressive decrease in ileal mRNA and protein levels of the TJ zonulin (ZO)-1, claudin-1 and occludin in subjects with prediabetes and T2DM ($P<0.05$). Next, in order to explore whether FXR stimulation by OCA treatment may revert dysglycemic related aberrations in ileal FXR/FGF-19/TJ integrity axis, we performed intestinal organ culture experiments. Ileal mucosa specimens collected from subjects with T2DM were cultured in presence or absence of OCA (20 μM) for 6 hours. We found that OCA treatment resulted in an up-regulation of FGF-19 mRNA by 10-fold and in a 6-fold increased TJ protein ZO-1 and occludin expression ($P<0.01$). In conclusion, our findings demonstrate that a dowregulation of FXR/FGF-19/TJ axis occurs in subjects with prediabe-

tes and type 2 diabetes conditions, indicating intestinal FXR signaling as a novel target in prevention and/or treatment of T2DM.

## 375. IMPAIRMENT IN MUSCLE STRENGTH AND ITS DETERMINANTS IN PRIMARY HYPERPARATHYROIDISM: A STUDY IN POSTMENOPAUSAL WOMEN

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**Purpose:** Neuromuscular manifestations may be seen in patients with primary hyperparathyroidism (PHPT) even in the absence of symptoms of the disease. Mechanisms associated with impaired muscle function are not completely understood and include hypercalcemia, hypophosphatemia, elevated parathyroid hormone (PTH) levels, and hypovitaminosis D. The role of proteins mediating the interplay between bone and muscle homeostasis is unknown. The study aimed at assessing muscle strength and its main determinants in postmenopausal women with PHPT.
**Methods:** We studied 48 postmenopausal women with asymptomatic PHPT and 38 healthy age-matched postmenopausal women (Table 1). Maximal voluntary contraction (MVC, Newton, N) was measured using a hand held dynamometer (Kayser Italia srl, Livorno, Italy). Areal BMD (aBMD) was measured at the lumbar spine, total hip, femoral neck, and nondominant distal one-third radius in all subjects by dual X-ray absorptiometry (DXA) (Hologic, Waltham, MA). Serum 25-hydroxyvitamin D [25(OH)D], ionized calcium (Ca++), phosphorus (P), PTH, and myostatin were measured in both groups.
**Results:** Patients with PHPT had significant lower MVC values compared to healthy women ($p<0.001$, Table 1). As expected, serum Ca++ and PTH levels were higher and P lower in PHPT compared to controls (Table 1). There was a significant positive association between MVC and total hip and one-third radius aBMD ($R=0.320$ and 0.370, $p<0.05$) and negative association with Ca++ ($R=-0.340$, $p<0.05$) in the PHPT group; MVC was positively associated with one-third radius aBMD ($R=0.360$, $p<0.05$) and negatively with age, BMI and myostatin ($R=-0.390$, -0.340 and -0.450, $p<0.05$) in the group of healthy women. The linear model using BMI, Ca++, P, 25(OH) D, PTH, myostatin, and aBMD as covariates showed that one-third radius aBMD had significant positive effect on MVC in PHPT patients ($p<0.02$) and in healthy subjects ($p<0.001$). Additionally, serum PTH and myostatin negatively impacted MVC in healthy subjects ($p<0.03$ and $p<0.01$).
**Conclusions:** Muscle strength is significantly impaired in postmenopausal women with asymptomatic PHPT. Some of the mechanisms influencing muscle function in PHPT are similar to those observed in healthy subjects and related with a regional-specific influence of aBMD on the skeletal muscle. Contrary to what observed in healthy women, hypercalcemia seems to be the main determinant of muscle strength impairment in PHPT, while no role is played by myostatin.

**Table 1. Mean ± SD values of all the parameters in both groups**

| Characteristics | PHPT (n=48) | Healthy subjects (n=38) | p value |
|---|---|---|---|
| Age, years | 60.8 ± 5.6 | 58.6 ± 5.9 | NS |
| Height, cm | 159 ± 7.6 | 157.4 ± 5.8 | NS |
| Weight, kg | 65 ± 14.3 | 62.3 ± 8.7 | NS |
| BMI, kg/m$^2$ | 25.6 ± 5.5 | 25.2 ± 3.5 | NS |
| Time since menopause, years | 12.2 ± 7.3 | 9.6 ± 5.8 | NS |
| Serum ionized calcium, mmol/L (nr 1.17-1.33) | 1.42 ± 0.08 | 1.25 ± 0.04 | <0.0001 |
| Serum phosphorus, mg/dl. (nr 2.5-4.5) | 2.8 ± 0.4 | 4 ± 0.4 | <0.03 |
| Serum PTH, pg/mL (nr 15.5 – 65.5) | 90.7 ± 51 | 40 ± 12.8 | <0.0001 |
| Serum 25(OH)D, ng/mL | 22 ± 9.4 | 21 ± 11.7 | NS |
| Serum myostatin, ng/mL | 61.7 ± 43.6 | 49 ± 14.2 | NS |
| *L1-L4 aBMD, g/m$^2$* T-score | 0.794 ± 0.169 -2.2 ± 1.2 | 0.877 ± 0.123 -1.6 ± 1.2 | <0.03 |
| *Femoral Neck aBMD, g/m$^2$* T-score | 0.650 ± 0.104 -1.9 ± 0.9 | 0.692 ± 0.100 -1.4 ± 1 | 0.05 |
| *Total Hip aBMD, g/m$^2$* T-score | 0.741 ± 0.111 -1.6 ± 0.8 | 0.828 ± 0.103 -1 ± 0.8 | <0.01 |
| *One-third Radius aBMD, g/m$^2$* T-score | 0.559 ± 0.705 -2.3 ± 1.2 | 0.632 ± 0.626 -1 ± 1 | <0.0001 |
| MVC, Newton | 183.5 ± 61.3 | 234 ± 56.3 | <0.001 |

## 376. PROINSULIN INSULIN IN SITU LOCALIZATION DEFECTS ARE ASSOCIATED TO UPR RESPONSE AND LOSS OF BETA CELL PHENOTYPE IN ISLETS OF TYPE 2 DIABETIC AND GLUCOSE INTOLERANT LIVING DONORS

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**Background and Aims**: Our preliminary results showed that in pancreatic islets of impaired glucose tolerant (IGT) and type 2 diabetic (T2D) patients, proinsulin (PI) intracellular localization was altered. Moreover, the insulin-proinsulin (PI-INS) colocalization coefficient as well as PI levels and PI/INS ratio gradually increased from NGT to IGT and T2D pancreatic islets and were related to the loss of glucose tolerance and impaired β-cell function. The molecular mechanisms driving such alterations are not fully characterized neither their occurrence were correlated with patients' metabolic profile. To fill in this gap, we investigated the correlation between altered PI expression and localization, and phenotypic/functional changes of β-cells during metabolic stress in extensively clinical characterized IGT and T2D individuals, compared to NGT.
**Materials and Methods:** We analyzed microdissected pancreatic islets of n=4 NGT, n=7 IGT and n=4 T2D patients subjected to partial pancreatectomy (PP) and metabolically profiled. We evaluated the expression of ER stress genes and β-cell mature phenotype-related genes. Given the high heterogeneity among pancreatic islets we also performed an individual islets analysis on two frozen serial pancreatic sections for each donor. We analyzed n=88 individual islets from n=3 NGT, n=3 IGT and n=3 T2D patients. On the first section we performed an INS-PI double immunofluorescence staining in order to evaluate the in-situ expression levels of INS and PI. After image analysis we mapped individual islets in the whole section. Subsequently, on the second serial section, we microdissected the same single islets previously mapped for gene expression analysis.
**Results:** We observed that PDIA1 (Protein Disulfide Isomerase-1), GRP78 (Glucose Regulated Protein-78) and XBP1 (Splicing X-Box Binding Protein-1) genes, involved in unfolded protein response (UPR) were significantly upregulated in pancreatic islets of IGT and T2D patients vs NGT ($p<0.05$) and were positively correlated with in-situ PI/INS ratio ($r=0.6$; $p=0.01$) and PI-INS colocalization ($r=0.5$, $p<0.05$), with in-vivo measurements of glucose intolerance ($r=0.6$-$0.8$; $p<0.001$) and β cell functional reduction ($r=-0.6$; $p=0.04$). Individual islets phenotyping approach revealed a progressively increased heterogeneity from NGT to IGT and T2D patients. Of note, in-situ PI/INS ratio and PI-INS colocalization were positively correlated with the expression of UPR genes ($r=0.3$; $p<0.01$) and negatively with those associated to β cell identity ($r=-0.2$; $p<0.01$).
**Conclusion:** Our data demonstrated that β-cells PI localization alterations reflected metabolic and molecular defects in IGT and T2D patients. Furthermore, individual islet phenotyping analysis, even though revealing a high heterogeneity among pancreatic islets, uncovered the association of PI-INS intracellular localization alterations with increased ER stress and loss of β-cell phenotype during T2D metabolic alterations.

## 377. MEDITERRANEAN DIET AND METABOLIC SYNDROME: RELATIONSHIP BETWEEN ADHERENCE TO A MEDITERRANEAN DIET AND NUMBER OF DIAGNOSTIC CRITERIA OF METABOLIC SYNDROME

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**Background:** Both prospective studies and clinical trials indicate the association between adherence to the Mediterranean diet and a lower risk of developing the metabolic syndrome
Few studies have analyzed the association between adherence to a Mediterranean type diet, the presence of metabolic syndrome and the possible relationship with the severity of the syndrome

**Aims:** To evaluate the association between adherence to the Mediterranean diet, as assessed by the calculation of the Mediterranean Diet Score (MDS), and the diagnosis of metabolic syndrome and its severity in terms of an increasing number of diagnostic criteria.
**Methods:** This is a retrospective study in a cohort of patients from the urban area of Palermo, Italy. The information relating to patients' dietary habits was collected using a special semi-quantitative food frequency questionnaire (FFQs). In addition, the adherence to a Mediterranean Diet type was evaluated using the Mediterranean Diet Score (MDS).
**Results:** Adherence's degree to the Mediterranean diet, as assessed by the Mediterranean diet score, was significantly higher in control patients without metabolic syndrome than in patients with metabolic syndrome.
At the Spearman's correlation analysis, some negative correlations were observed between MDS and BMI, heart failure, intake of drugs such as statins, insulin, sulfonylureas, calcium channel blockers, sartans and antiplatelet. Crucially, we also observed a significant negative correlation between adherence to the Mediterranean diet and metabolic syndrome that was highly significant in all patients' groups at the increasing presence of diagnostic criteria from 3 to 4 to 5 criteria. In addition, we observed a highly significant inverse relationship between mean MDS and the increasing number of diagnostic criteria. In particular, patients with 5 criteria compared to patients with 3 and 4 criteria showed the lowest MDS mean value as an expression to the lowest adherence to a Mediterranean Diet style.
**Discussion:** Thus, the higher cardiometabolic risk profile of patients with Metabolic Syndrome is linked to the lower adherence to a Mediterranean Diet style. It is mediated by the higher frequency of the cardiometabolic risk factors in subjects with low adherence to the Mediterranean Diet. A growing body of evidence strongly supports the assumption that adhering to a Mediterranean diet may reduce the risk of cardiometabolic diseases.

## 378. TIMELY DETECTION OF NON-ALCOHOLIC FATTY LIVER DISEASE IN TYPE 2 DIABETES MELLITUS PATIENTS

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**Background:** Non-alcoholic fatty liver disease (NAFLD) is a major source of liver disease, including liver cirrhosis and hepatocarcinoma. Despite several studies showing a strong association between NAFLD and type 2 diabetes mellitus (T2DM), protocols for the identification of T2DM patients who have concurrent liver damage are not routinely applied. The aim of this study was to evaluate the presence of NAFLD and the severity of the liver fibrosis in patients with T2DM, using not invasive methods.
**Methods:** After the exclusion of patients with history of liver disease or positive for hepatitis B (HBV) and/or C (HCV) viruses and of those who did not agree to participate, 205 out of 382 consecutive T2DM subjects without known history of liver disease, consecutively attending a second-level metabolic disease clinic from January 1th 2021 to March 30th 2021, were enrolled into the study. Laboratory parameters, including transaminases and gamma glutamyl transferases (GGT) levels were measured, and FIB-4 score was calculated in all the patients. All participants underwent fibroscan examination for controlled attenuation-parameter (CAP) and liver stiffness evaluation. HBV and HCV serum markers were also available for all participants.
**Results:** 205 consecutive T2DM subjects [144 males (70%) and 61 females (30%), median age 64 years (range 40-84), median BMI 29,6 kg/m2 (range 20,4-49,6)] entered the study. Overall, T2DM patients had a diabetes duration of 11 years, and they were on fair/good glucose control (HbA1c 7.4%). One hundred and twelve (54,6%) subjects had hypertransaminasemia (AST and/or ALT ≥ 40 UI and GGT ≥ 50UI).
Median liver stiffness was 8.4 kPa (range 4,1-32,2), with a median CAP value of 302 (range 103-400). In particular, 32 subjects (15.6%) had a liver stiffness value > 10,1 Kpa (severe fibrosis), 114 subjects (55.6%) had CAP values >290 dB/m (severe steatosis), and FIB-4 score was >2 in 38 T2DM subjects (18,5%), with 15 of them (7,3%) having a FIB-4 score >2.67. When stratifying study subjects according to the presence of hypertransaminasemia, those with hypertransaminasemia had higher values of liver stiffness (p=0.004), FIB-4 score (p=0.005) and triglycerides (p=0.01).
At logistic regression analysis, liver stiffness (cut-off 10,1 kPa) was influenced by BMI (p=0.016) and transaminases values (p=0.023), and FIB-4 score value > 2 was associated with male gender (p=0.015) and GGT value >50 (p=0.001). Overall, 49 (23,9 %) T2DM patients without known liver disease had a clinically meaningful liver harm, with either FIB-4 score >2 and/or fibroscan > 10 kPa, and were therefore addressed to the liver outpatient clinic.
**Conclusion:** T2DM is associated to a high risk of liver fibrosis and steatosis, especially in the presence of obesity, hypertransaminasemia, and male gender. Liver stiffness evaluation, CAP values and FIB4 score should be routinely performed in clinical practice for the timely diagnosis of NAFLD/NASH in T2DM outpatients with no history of liver disease, in order to undertake appropriate follow-up and therapeutic strategies and improve patients' outcomes.

## 379. INVESTIGATING THE PRESENCE OF PROGLUCAGON-DERIVED PEPTIDES IN HUMAN PANCREAS

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**Background and Aims**: Emerging evidence suggest production of GLP-1 in pancreatic islets. Prohormone convertase 1/3 (PC1/3), the enzyme responsible for GLP-1 cleavage from the proglucagon precursor, has been detected in rodent glucagon-producing cells, especially under β-cell stress conditions. However, only few α-cells are thought to produce GLP-1 in non-stressed conditions. Here, we evaluate whether fully processed active GLP-1 and N-terminally extended GLP-1 can be detected in biopsies obtained at partial pancreatectomy. The patients were carefully characterized regarding glucose tolerance: normal (NGT), impaired glucose tolerance (IGT), diabetes (DM)).
**Materials and Methods:** We enrolled n=33 individuals with no known history of type 2 diabetes (18F/15M, age 66.2±9.29 yrs., BMI 25.1±4.74 kg/m2) scheduled for partial pancreatectomy periampullary tumors. To detect differences in the glucose tolerance and insulin secretion among subjects enrolled we performed a preoperative 75 gr OGTT and subjects were classified into n=9 NGT, n=14 IGT and n=10 T2D. Pancreas biopsies were collected during surgery. In extracts of frozen specimens of pancreatic tissue we measured chromogranin A (CgA), GLP-1 1-36, GLP-1 7-36, GIP, glucagon, insulin, c-peptide. Tissue proglucagon-derived peptides levels were also adjusted for CgA and expressed as percentage of CgA levels. Tissue measurements were correlated with patients' clinical parameters.
**Results:** In the entire cohort, extractable levels of intact GLP-1 was 10 times lower compared to GLP-1 1-36 levels (mean levels of pancreatic GLP-1 1-36: 8.14 ± 1.41 pmol/g vs. mean levels of intact GLP-1: 0.81 ± 0.13 pmol/g). Further, CgA levels correlated to levels of GLP-1 1-36 (r=0.47, p=0.02) and intact GLP-1 (r=0.41, p=0.02), indicating that the expression of proglucagon-derived peptides is directly linked to the amount of endocrine tissue available in the biopsies. When subjects were classified according glucose tolerance and proglucagon-derived peptides levels adjusted for CgA, we observed similar levels of glucagon, while GLP-1 1-36 and intact GLP1 (p<0.01) levels were increased in T2D subjects compared to IGT and NGT. Moreover, we observed that intact GLP-1 tissue levels were positively correlated to in-vivo 2h glucose levels during OGTT (r=0.5, p=0.01).
**Conclusion:** Our data revealed that GLP-1 detected in human pancreas primarily consist of biological inactive GLP-1 1-36, while expression of intact GLP-1 is very low. We furthermore demonstrated that levels of intact GLP-1 were significantly increased in subjects with increased 2-h glucose levels. Our findings suggest that poor glucose metabolism is linked to increased islet levels of GLP-1, but the functional implication of this is still uncertain.

## 380. QUANTITATIVE PROTEOMIC ANALYSIS ON HUMAN ISLETS: NEW MARKERS OF CELLULAR AND METABOLIC DYSFUNCTION

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**Background:** The pathogenesis of type 2 diabetes is characterized by a progressive β-cell dysfunction resulting in both quantitative and qualitative loss of insulin secretion. However, the molecular mechanisms underlying this progressive functional loss are still unknown. The aim of the study is to highlight changes in the proteome of pancreatic islets that can anticipate and eventually predict diabetes' onset.
**Methods:** High performance liquid chromatography mass spectrometry (HPLC-MS) analysis was applied to islets isolated by laser capture microdissection (LCM) from human samples of both diabetic and no diabetic subjects, underwent to duodeno-cefalopancreatectomy for extra-pancreatic and low grading tumors. The subjects were classified on the basis of glucose tolerance assessed by an OGTT before surgery in normal tolerant (NGT, n: 7), glucose intolerant (IGT, n: 5) and diabetic subjects (T2DM, n: 2). Qualitative and quantitative analyses were performed to detect differential protein expression among the 3 study groups.
**Results:** Sixty-seven proteins were found to be differentially regulated in diabetic subjects compared to NGT, with 29 upregulated and 38 downregulated proteins, while 95 proteins were differentially expressed in IGT compared to NGT with 49 upregulated and 46 downregulated. These proteins are mainly involved in cellular and metabolic processes. In particular IGT and DM, compared to NGT, showed a lower expression of proteins involved in cell proliferation such as PURA and NAP1L1, as well as proteins involved in the insulin cleavage process, like ERO1B. While other proteins involved in endoplasmic reticulum stress, CASP14, ERP27 and PDIA3, resulted upregulated in both IGT and DM compared to NGT.
**Conclusions:** Our data suggest that metabolic and cellular processes of islet cells are already dysregulated in patients with impaired glucose tolerance, highlighting some proteins as potential early markers of beta-cell dysfunction and novel therapeutic targets to slow the progression to type 2 diabetes.

## 381. EFFECT OF SEMAGLUTIDE ON GLOBAL LONGITUDINAL STRAIN AND GLOBAL MYOCARDIAL WORK EFFICIENCY IN PATIENTS WITH UNCONTROLLED TYPE 2 DIABETES MELLITUS AND OBESITY

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Type 2 Diabetes mellitus (T2DM) has a prevalence of 422 million adults; patients with T2DM have a two-to three-fold increased risk of cardiovascular disease (CVD), which accounts for approximately 80% of mortality causes. Glucagon-like peptide-1 receptor agonists (GLP1-RAs) are peptide molecules that exert their action through potentiation of insulin secretion, suppression of glucagon release, delayed gastric emptying, and weight loss. Cardiovascular outcome trials (CVOTs) demonstrated that GLP1-RAs have effectively reduced CV risk in T2DM patients, so their use is recommended by guidelines. In particular, in SUSTAIN-6 trial, semaglutide, a long acting GLP1-RA with once weekly subcutaneous administration, showed a significant reduction of major adverse cardiovascular events. The objective of our work was to evaluate the effect of Semaglutide administration in a cohort of uncontrolled diabetic patients (within 5 years from diagnosis) on oxidative stress validated markers (8-isoprostane and NOX-2), platelet activation indicators (Sp-Selectin) and subclinical myocardial damage evaluated by measurement of deformation and efficiency parameters, obtained by speckle tracking echocardiography (STE).mWe performed a retrospective analysis enrolling patients who met the following inclusion criteria: diagnosis of T2DM within 5 years, uncontrolled T2DM, obesity. Exclusion criteria were as follows: previous cardiovascular events, atrial fibrillation, Heart Failure, severe chronic kidney disease, liver failure with Child-Pugh class C. All clinical evaluation, echocardiographic and laboratory tests were performed at baseline and after 6 months of treatment. The serum values of oxidative stress markers (8-isoprostane, NOX-2) and platelets activation indicators (Sp-selectin) were assessed with ELISA sandwich. Echocardiographic recordings were performed by a single operator not aware of blood chemistry analysis results and therapy. Continuous variables were expressed as mean ± standard deviation (SD) (normally distributed data). For all continuous variables, comparisons between baseline (T0) and post-treatment values (T6) were performed using paired Student's t test. A linear regression analysis was performed to assess the relationship between variation in Global Longitudinal Strain (GLS), GLS endo-epi ratio, and global myocardial work efficiency (GWE), expressed as Δ of variation between baseline and follow-up (ΔT0–6) and the variation of metabolic, inflammatory, oxidative stress and platelets activation parameters that significantly improved after the treatment (expressed as ΔT0–6). We enrolled 70 Caucasian patients (mean age 65.5±8.2) with T2DM and obesity, 85.7% with hypertension, 14.2% with chronic obstructive pulmonary disease (COPD), 57.1% with sleep apnea syndrome, 18.5% chronic kidney disease, and 41.4% with dyslipidemia. All patients were in treatment statins and metformin, 42.8% with insulin, 24.2% with diuretics, 37.1% with ACE inhibitors, and 48.5% with angiotensin receptor antagonists. The mean dose of Semaglutide was 0.59±0.29 mg/week without serious adverse events. At 6 months, data showed significant improvement in hemodynamic and clinical parameters such as systolic and diastolic blood pressure, heart rate ($p<0.004$), NT-ProBNP ($p<0.0001$), fasting plasma glucose, insulinemia, HOMA, IGF-1, HbA1c and BMI ($p<0.0001$). Lipid profile and renal function also showed a improvement ($p<0.0001$). There was a significant reduction in biomarkers of oxidative stress such as 8-isoprostane, Nox-2 and uric acid ($p<0.0001$), biomarkers of platelet activity such as Sp-Selectin ($p<0.0001$). and high-sensitivity C-reactive protein (hs-CRP) profile ($p<0.0001$). We observed a significant improvement in left ventricular myocardial deformation parameters such as GLS ($p<0.0001$), GLS endo/epi ($p<0.0001$) and GWE ($p<0.0001$). The linear correlation analysis showed that ΔGLS endo-epi was inversely correlated with ΔHOMA ($p=0.001$), Δuric acid ($p=0.012$), ΔNox-2 ($p=0.016$), ΔSp-selectin ($p=0.010$); ΔGLS was inversely correlated with ΔHOMA ($p=0.011$), Δuric acid ($p=0.025$) and ΔSp-selectin ($p<0.0001$); ΔGWE was inversely correlated with ΔHOMA ($p=0.011$), Δuric acid ($p=0.025$) and ΔSp-selectin ($p<0.0001$). From stepwise multivariate linear regression model, ΔSp-selectin, ΔHOMA, Δuric acid and Δ NOX-2 justifying respectively 18.1%, 7.2%, 5.6% and 5.3% of ΔGLS endo-epi; ΔSp-selectin, Δuric acid and ΔHOMA justifying 27.8%, 4.4% and 5.6% of ΔGLS respectively. Instead ΔNOX-2, Δhs-CRP and ΔBMI justifying 22.3%, 15.6% and 4.0 % of ΔGWE respectively, for total of 41.9%. Results of our study demonstrated that 6 month treatment with Semaglutide, in patients with uncontrolled T2DM and obesity, improved GLS, GLS endo-epi ratio and GWE. It's plausible that this improvement may be justified by the reduction of inflammatory, oxidative stress and platelet activation parameters together with favorable matbolic changes; thus promoting the protection of the cardiac microcirculation with improving in myocardial contractility.

## 382. THE POTENTIAL IMPACT OF MODIFICATION IN REIMBURSEMENT CRITERIA FOR VITAMIN D PRESCRIPTION ON PATIENTS WITH SKELETAL FRAGILITY

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**Introduction:** Vitamin D (VD) deficiency is a common condition - especially in patients with osteoporosis - associated with increased risk of fragility fractures and with reduced effectiveness of several anti-resorptive drugs, thus leading many national and international guidelines to recommend VD supplementation as add-on treatment for osteoporosis. The Italian Medicines Agency (AIFA) Notes are regulatory documents that define the therapeutic indications for which a certain drug can be reimbursed by the Italian National Health Service (INHS). In October 2019 AIFA (through the regulatory recommendation "Note 96"), with the aim to reduce the possible risk of inappropriate use of VD for the clinical management of condition different from skeletal fragility, decided to limit the reimbursement criteria for VD supplements (cholecalciferol and calcifediol) to "prevention and treatment

of VD deficiency in adult subjects", outside the indication for osteoporosis. In the following months AIFA reported a 30% reduction in the use of VD supplements in Italy, but no data are available to evaluate if this reduction could have affected VD prescriptions even in patients with skeletal fragility.
**Methods:** Administrative databases of 5 Local Health Units, covering approximately 2.6 million subjects were retrospectively analysed. Inclusion criteria were age ≥ 50 years and at least one of the following: a) prescription of osteoporotic treatment from 2011 to 2020 or b) previous femoral/vertebral fractures. Exclusion criteria were renal disease, cancer and death during the follow-up period. Among patients included, the prevalence of VD supplementation prescription was evaluated in Period 1 (March-June 2019) and the interruption of VD, defined as the absence of prescription for VD supplementation was analysed in the following four months (Period 2, July-October 2019); similarly, among patients prescribed with VD during Period 2, the interruption rate was evaluated during Period 3 (November 2019-February 2020), i.e., following the introduction of Note 96. To limit seasonal variation bias, a further analysis was performed to compare the interruption rate of Period 3 in the previous year (Period 3b, November 2018-February 2019) among patient prescribed VD during the same months of Period 2 (Period 2b, July-October 2018).
**Results:** A total of 94,505 patients (aged 69.4 years) were included, and 47,866 patients during Period 1 and 45,736 during Period 2 were identified with evidence of VD prescriptions; the cohort of Period 2 mainly included all patients from Period 1 that were still on treatment plus incident patients. Among patients with evidence of VD prescriptions in Period 1, the proportion of interruption during Period 2 (i.e. interruption pre-Note 96) was 23.4%. An increased interruption rate was observed post-Note 96, with 37.6% of VD users in Period 2 discontinuing their supplementation during Period 3 ($p<0.001$); VD supplementation interruption was more evident in patients without vertebral or femoral fractures than in those with fractures (37.8% vs 32.9%) and in patients aged > 90 years (47.2%). To avoid the potential bias due to seasonal variation, a subsequent analysis was performed to compare the interruption rate of VD considering the same months of Period 2 and 3 from the previous year. Among patients with VD prescription identified in Period 2b, 19.2% discontinued supplementation during Period 3b, thus confirming a trend of high rate of interruption after the application of Note 96. To identify potential risk factors associated with VD interruption, a logistic regression analysis was performed; rheumatoid arthritis, dyslipidemia and previous fracture were associated with a lower risk of VD interruption while stroke increased the risk of VD interruption.
**Conclusions:** This study highlights how the restriction of reimbursement criteria for VD prescription for indications outside the osteoporosis setting affected even patients with skeletal fragility, thus leading to potential risk of reduced effect of osteoporotic treatment and increased risk of negative outcomes.

## 383. TYPE 1 DIABETES FAMILY SCREENING AND CLINICAL TRIALS AT THE SAN RAFFAELE INSTITUTE: A 33-YEAR EXPERIENCE

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Type 1 diabetes (T1D) is the most prevalent chronic disease of infancy and adolescence, thus representing a major challenge for public health. Currently, there is neither a cure nor a prevention for T1D, with exogenous insulin as the only available treatment for patient survival. Conversely, the disease is predictable. T1D is characterized by a long preclinical period, marked by the presence of circulating autoantibodies to pancreatic islet cells. Autoantibody screening programs to identify individuals at risk within families started at the San Raffaele Institute in late 1980s, with many thousands people screened since. T1D associated autoantibodies include the autoantigen-specific anti-GAD (GADA), anti-insulin (IAA), anti- tyrosine phosphatase-like IA2 (IA2A) and anti-Zinc Transporter-8 (ZnT8A) and the historical islet cell antibodies (ICA) measured by immunofluorescence on pancreas sections. Current evidence indicates a risk near to 100% of developing overt T1D in people with ≥2 autoantibodies, around 5-10% in those positive for a single autoantibody and negligible in autoantibody-negative. Additional assessment of β-cell function by Oral Glucose Tolerance Test (OGTT) in ≥2 autoantibody-positive individuals enables staging of the asymptomatic phase prior to clinical onset: stage 1 normal glucose tolerance, Stage 2 dysglycemia, Stage 3 overt hyperglycemia and clinical T1D. The aim of screening programs is to identify people in their early phase of T1D in order to reduce the risk of progression to diabetic keto acidosis (DKA), a potentially fatal complication of T1D at clinical onset. Moreover, individuals identified as at risk are eligible to disease modifying intervention trials aimed at preventing or slowing their progression to clinical T1D. Screening programs at our Institution were conducted in first or second degree relatives of T1D probands over three era. In 1989-2003 the San Raffaele academic Family Study screened nearly 2000 relatives, with 8.7% positive for at least 1 autoantibody and 2.0% positive for ≥2 autoantibodies. In 2004-2020 the JDRF/TrialNet San Raffaele International Center (funded by JDRF and part of the NIDDK/TrialNet Consortium) screened 4072 relatives, 3.0% positive for at least 1 autoantibody and 1.7% positive for ≥2 autoantibodies. Participants who were autoantibody negative and less than 18 years of age were invited to be re-screened annually, with a further 5147 blood samples collected. Since 2021, the FID-INNODIA San Raffaele Center (funded by Fondazione Italiana Diabete and part of the EU INNODIA Consortium) screened 301 relatives, with 4.6% positive for at least 1 autoantibody and 2.6% positive for ≥2 autoantibodies.
Eligible Stage 1 and Stage 2 individuals were invited to participate in the following prevention trials, available at the time (in brackets the sponsor and the number of subjects enrolled at our center): gluten-free diet, (Academic, n=17), oral insulin (TrialNet, n=13); immune effects of oral insulin (TrialNet, n=4); anti-CD3 Teplizumab (TrialNet, n=0); Abatacept (TrialNet, n=1). Currently ongoing: Hydroxychloroquine (TrialNet, n=1). In Stage 3 new onset T1D patients, several trials were performed with the aim of preserving β-cell function: Mycophenolate Mofetil-Daclizumab (TrialNet, n=8); anti-CD3 Otelixizumab (DEFEND-1, Tolerx/GSK, n=5), Albiglutide (GSK, n=3); MITO islet cell transplantation (Academic, n=6); Ladaraxin (Dompé, n=9). Currently ongoing: IMPACT Imotopes (INNODIA-Imcyse, n=10), anti-CD40 Iscalimab (INNODIA-Novartis, n=1), Verapamil (INNODIA, n=0) and anti-thymocyte globulin ATG (INNODIA, n=0). Unfortunately, despite all these efforts, prevention of T1D remains elusive, but research is more and more appreciated as the fundamental tool to fight this devastating disease. At Public Health level, moving screening programs from T1D families to the general population is considered by a growing number of developed Countries as the next strategic step to respond to the disease burden. At our Center, in addition to intervention trials, taking advantage of the access to biological samples from people at different stages of T1D, important functional and mechanistic studies on disease pathogenesis were performed: among these, the novel observation of the T1D associated mild neutropenia and related NETosis and platelet-neutrophil aggregates and of exocrine pancreas functional impairment.

## 384. EFFECTS OF 26-WEEK TREATMENT WITH EMPAGLIFLOZIN VERSUS GLIMEPIRIDE ON CARDIOVASCULAR ORGAN DAMAGE IN PATIENTS WITH TYPE 2 DIABETES: THE RANDOMIZED, OPEN-LABEL, ACTIVE-CONTROLLED CROSSOVER FIORE TRIAL

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**Aim:** Cardiovascular outcome trials indicate that the treatment with sodium-glucose co-transporter 2 (SGLT2) inhibitors is associated with a reduction in cardiovascular morbidity and mortality. So far, the potential beneficial effects of SGLT2 inhibitors on vascular function have led to conflicting results. Although some prior studies have shown a reduction in arterial stiffness induced by the treatment with SGLT2 inhibitors, a recent meta-analysis failed to show significant effects on arterial stiffness in patients treated with SGLT2 inhibitors. To further investigate the potential mechanism of SGLT2 inhibitors on vascular organ damage, we performed an analysis from the FIORE study, a head-to-head trial that compared the cardiovascular effects of empagliflozin versus glimepiride in patients with type 2 diabetes.
**Materials and Methods:** We performed a 26-week, randomized, open-label, cross-over, active-comparator study to determine the effects of empagliflozin 10 mg versus glimepiride 2 mg daily on arterial stiffness assessed by both carotid–femoral pulse wave velocity (PWV) and Pulse Pressure (PP), and on subclinical carotid atherosclerosis assessed by ultrasound measurement of carotid intima–media thickness (IMT) in 23 patients with type 2 diabetes

without history of cardiovascular disease receiving a stable dose of metformin. We also measured cardiovascular parameters, including systolic and diastolic blood pressure and resting heart rate.
**Results:** As compared with glimepiride, treatment with empagliflozin resulted in a greater reduction from baseline to 26 weeks in PWV (adjusted difference -1.62 m/sec, (-2.15, -1.09), P<0.0001) and PP (adjusted difference -5.88 mm/Hg, (-11.3, -4.26) P=0.03). Moreover, as compared with patients treated with glimepiride, those treated with empagliflozin exhibited a greater decrease in systolic blood pressure (adjusted difference -11.94 (-17.5, -6.36); P<0.0001), diastolic blood pressure (adjusted difference -5.33 (-9.08, -1.57); P=0.007), and resting heart rate (adjusted difference -9.55 (-13.79, -5.3); P<0.0001). Conversely, no differences between the two groups were observed in change from baseline to 26 weeks in IMT.
**Conclusions:** These data suggest that the short-term beneficial cardiovascular effects of SGLT2 inhibitors may involve a reduction in arterial stiffness, but not a regression of vascular atherosclerosis.

## 385. METABOLIC SYNDROME IS ASSOCIATED WITH IMPAIRED MYOCARDIAL GLUCOSE METABOLIC RATE IN INDIVIDUALS WITH TYPE 2 DIABETES: A CARDIAC DYNAMIC 18F-FDG-PET STUDY

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Metabolic syndrome (MetS) is a condition characterized by a clustering of metabolic abnormalities associated with an increased risk of type 2 diabetes (T2DM) and cardiovascular disease (CVD).
An impaired insulin-stimulated myocardial glucose metabolic rate (MrGlu) has been shown to be a risk factor for the development of CVD in patients with T2DM. Whether cardiac insulin resistance occurs in subjects with MetS remains uncertain. To investigate this issue, we evaluated myocardial MrGlu in three groups: a group of non-diabetic individuals without MetS (n=10), a group of T2DM individuals with MetS (n=19), and a group of T2DM without MetS (n=6). Myocardial glucose metabolic rate was evaluated using dynamic cardiac 18F-FDG PET combined with euglycemic hyperinsulinemic clamp, which allows to assess peripheral insulin sensitivity normalized for lean body mass (MFFM) and to standardize metabolic and hormonal conditions during PET. The 18F-FDG PET imaging procedure started 60 minutes after the insulin infusion. The insulin-glucose infusion continued throughout the PET imaging sequence, maintaining euglycemia by continuous adjustment of the glucose infusion rate according to the glucose levels of the arterialized blood samples collected every 5 min. The estimation of myocardial MRGlu was performed using a Patlak compartmental modelling, a widely diffuse technique provided by a graphical tool specific for cardiac images analysis (PCARD) in PMOD Software platform.
After adjusting for age and gender, T2DM MetS individuals exhibited a significant reduction in myocardial MrGlu (10.5±9.04 mmol/min/100g) as compared with both control subjects (32.9±9.7 mmol/min/100g; P<0.0001) and T2DM subjects without MetS (25.15±4.92 mmol/min/100g; P=0.01).
Moreover, myocardial MRGlu progressively decreased in parallel with the increase of the number of MetS components.
Univariate correlations showed that MrGlu was positively correlated with insulin-stimulated glucose disposal (r= 0.488, P=0.003), and negatively correlated with the presence of MetS (r= -0.743, P<0.0001) and with its individual components.
Our data suggest that metabolic syndrome can aggravate myocardial insulin resistance in individuals with type 2 diabetes.

## 386. EVALUATION OF THE PREVALENCE OF THE MOST COMMON PSYCHIATRIC DISORDER IN PATIENTS WITH TYPE 2 DIABETES USING THE PATIENT HEALTH QUESTIONNAIRE (PHQ): THE DIA2PSI STUDY.

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**Aim:** Common Psychiatric Disorder (CPD) are associated with the development of overweight and obesity, the strongest risk factors for the onset and subsistence of Type 2 Diabetes (T2D). T2D cause widespread early development of atherosclerosis and is considered an equivalent of cardiovascular disease (CVD). This study evaluates the prevalence of the CPD in a sample of T2D patients' numerically representative of the Italian population. There are currently no similar studies in Italy.
**Methods:** This is a monocentric cross-sectional study carried out at the Fondazione Policlinico Universitario Agostino Gemelli IRCCS (FPUAG). The sample size was determined in 184; T2D patients, aged 18 to 85 were screened for CPD using the PHQ. The study protocol was approved by the IRB and Ethics Committee of the FPUAG. The expected prevalence was estimated from previous international studies carried out in T2D patients.
**Results:** Patients presents T2D from an average of 12 years, 64% are men, mean age is 66±11 years, mean HbA1c 7.13%±1,63%, mean BMI 28±5 kg/m$^2$, 40% have a history of CVD, 27% shows Chronic Kidney Disease (CKD), 76% suffer from hypertension.The 43% of the sample tested positive for one or more mental disorders, 25% for depression. These values correspond to the prevalence of CPD described in similar international studies.
**Conclusions:** The prevalence of CPD and depression in the general Italian population is 7.3% and 3% respectively. The higher prevalence of CPD in T2D patients results in poor adherence to prescriptions of lifestyle changes and therapy thus these patients are less likely to achieve the weight loss necessary for T2D remission. Lack of adherence to lifestyle changes and therapies leads to the development of atherosclerosis and CVD. An integrated psychiatric-diabetic therapy is required in these subjects in the early years of the T2D development, aiming at the remission of the psychiatric and diabetic conditions in order to prevent the development of CVD.

## 387. CONTROLLING NUTRITIONAL STATUS (CONUT) SCORE AS A POTENTIAL PROGNOSTIC INDICATOR OF IN-HOSPITAL MORTALITY, INFECTION AND LENGTH OF STAY IN INTERNAL MEDICINE DEPARTMENT

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**Background:** Malnutrition is currently considered a predictor of adverse clinical outcomes in several clinical settings; however, current guidelines do not recommend a specific diagnostic tool to assess nutritional status. Previous studies suggested controlling nutritional status (CONUT) score as a nutritional scoring system to identify undernourished subjects among hospitalized patients. The score is derived from the values of serum albumin, total cholesterol, and lymphocyte counts. CONUT score has been identified as a potential indicator of adverse outcomes in several diseases, such as chronic heart failure and cancers; however, the role of CONUT score in predicting in-hospital mortality in adult patients hospitalized in Internal Medicine Department has not been established. The aim of this study was to investigate the prognostic role of the CONUT score on in-hospital mortality, risk of sepsis, and length of stay in adult inpatients in an Internal Medicine Department.
**Methods:** This is a retrospective cohort study analyzing data from 369 patients, aged ≥14 years old, hospitalized in the Internal Medicine Department of Garibaldi-Nesima Hospital in Catania, during the months of September, October and November in the years 2019, 2020 and 2021. We con-

sidered patients hospitalized in these months, before and after the outbreak of the pandemic, in order to look for a relationship between the intercourse of COVID-19 pandemic and in-hospital outcomes' variations. Indeed, the emergence of the COVID-19 pandemic in early 2020 determined a decline in patients seeking emergency care for serious medical conditions.
The patients were divided into 4 groups on the basis of CONUT score. We defined a CONUT score of 0–1 as normal, 2–4 as mild, 5–8 as moderate high, and 9–12 as marked high according to the previous reports. Comparisons among 4 groups were performed using the chi-square test for categorical variables and 1-way ANOVA for continuous variables. We used a multivariable logistic regression model including the low and high CONUT score as continuous variables to estimate the incremental impact of malnutrition on in-hospital mortality, risk of sepsis and length of in-hospital stay. The model was adjusted for age, sex, chronic heart failure, diabetes mellitus, chronic kidney disease, solid tumors, hemoglobin levels, previous stroke or TIA and COPD.
**Results:** Patients in the high CONUT score group were older, were more often male, and were more likely to have diabetes mellitus, chronic heart failure, previous stroke, chronic liver disease, renal dysfunction, malignancy, low systolic blood pressure at presentation, anemia and high CRP levels (>1.0 mg/dL) than those in the low CONUT score groups (table 1 and 2). In-hospital all-cause mortality was higher in group 4 and 3 patients compared with group 2 and 1 (15.3% vs 13.4% vs 3.6% vs 2.2%, p<0.009; table 2). Moreover, it emerged that a severe and moderates rate of malnutrition (groups 4 and 3) is linked with a longer length of hospital stay (13.10 ± 8.12 vs 12.45 ± 7.88 vs 11.09 ± 7.11 vs 9.48 ± 6.22, p< 0.013 table 2). As regard the distribution of sepsis occurring during hospitalization, a higher prevalence emerged in groups 4 and 3 (table 2). The excess risk of high CONUT score relative to low CONUT score for in-hospital all-cause death remained significant after adjusting for confounders such as age, sex, chronic heart failure, diabetes mellitus, chronic kidney disease, solid tumors, hemoglobin levels, previous stroke or TIA, COPD (HR: 3.39, 95% CI: 1.17- 9.75, p<0.02). In addition, the excess risk for sepsis and pneumonia of a high CONUT score versus a low CONUT score remains significant after multiple adjustments (HR: 2.73, 95% CI: 1.50- 4.97, p< 0.001) (HR: 3.56, 95% CI: 1.71-7.40, p< 0.0007). Finally, the excess risk of higher CONUT score relative to low CONUT score for a longer length of hospital stay remained significant after adjustment (HR: 0.99, 95% CI: 0.98-1.012, p< 0.061).
**Conclusions:** The results of this study demonstrated that a high CONUT score is associated with an increased risk of in-hospital mortality and short-term complications such as sepsis and longer hospital stays. Therefore, the CONUT score may be used as a potential prognostic tool for adverse events occurring during hospitalization in Internal Medicine Departments.

**Table 1** – Clinical and biochemical characteristics of the patients according to CONUT Score.

| | CONUT Score | | | |
|---|---|---|---|---|
| | Normal (0-1) *N=45* | Mild High (2-4) N=110 | Moderate High (5-8) N=149 | Marked High (9-12) N=65 |
| **Age (years)** | 56.6± 21.1 | 64.6± 19.7* | 69.1± 16.1*# | 72.3± 9.7*# |
| **Sex (M%)** | 40% | 52.7% | 61% | 73.8% |
| **Systolic Pressure (mmHg)** | 125.3± 18.8 | 126.2± 17.6 | 126.5± 20.5 | 123.2± 20.4 |
| **Diastolic Pressure (mmHg)** | 70.3± 10.9 | 74.0± 12.3 | 71.6± 9.7 | 69.2± 10.5# |
| **Glycemia (mg/dL)** | 95.9± 36.4 | 112.6± 56.6 | 110.1± 47.7 | 112.7± 57.2 |
| **Serum Creatinine (mg/dL)** | 0.7± 0.3 | 1.3± 1.8* | 1.3± 1.3* | 1.1± 1.2 |
| **eGFR (ml/min/1.74 $m^2$)** | 94.7± 27.5 | 78.8± 33.7* | 70.7± 34.4*# | 73.8± 29.1* |
| **Total cholesterol (mg/dL)** | 189.4± 35.9 | 164.4± 48.5* | 137.2± 40.2*# | 102.4± 26.3*#@ |
| **HDL cholesterol (mg/dL)** | 46.5± 13.7 | 37.5± 14.6* | 31.6± 13.6*# | 21.2± 9.1*#@ |
| **Triglycerides (mg/dL)** | 134.7± 56.7 | 128.9± 65.1 | 130.2± 62.4 | 103.4± 44.5 |
| **LDL Cholesterol (mg/dL)** | 115.8± 34.7 | 100.2± 43.8* | 80.6± 35.3*# | 60.3± 23.6*#@ |
| **Total Proteins (g/dL)** | 6.8± 0.5 | 7.1± 6.8 | 5.8± 0.6# | 5.3± 0.7# |
| **Albumin (g/dL)** | 4.5± 4.0 | 3.5± 0.4* | 2.9± 0.4*# | 2.4± 0.3*#@ |
| **GOT (U/L)** | 34.0± 33.4 | 48.9± 109.1 | 41.6± 70.9 | 36.5± 29.2 |
| **GPT (U/L)** | 40.5± 65.5 | 44.4± 92.9 | 35.6± 56.4 | 26.2± 41.4 |
| **Hs-CRP (mg/dL)** | 2.4± 3.4 | 6.1± 8.8 | 8.1± 8.1* | 16.9± 22.2*#@ |
| **WBC ($10^3$/ µL)** | 9.6± 6.2 | 8.9± 4.6 | 11.0± 14.7 | 8.0± 5.9 |
| **RBC ($10^6$/ µL)** | 4.4± 0.5 | 3.9± 0.8 | 6.5± 30.1 | 3.5± 0.8 |
| **Hemoglobin (g/dL)** | 13.3± 4.6 | 11.4± 2.2* | 10.4± 1.8*# | 9.7± 1.8*#@ |
| **Hematocrit (%)** | 38.7± 9.5 | 34.3± 6.2* | 31.4± 5.6*# | 30.4± 8.1*# |
| **PLT ($10^3$/µL)** | 85.6± 6.9 | 87.9± 10.2 | 85.7± 12.8 | 87.1± 12.9 |
| **INR** | 1.9± 4.4 | 2.1± 5.2 | 1.6± 4.0 | 1.3± 0.2 |

**Table 2** – Medical history and comorbidities of the patients according to CONUT Score.

| | CONUT Score | | | |
|---|---|---|---|---|
| | Normal (0-2) *n=45* | Mild High (3-4) n=110 | Moderate High (5-8) n=149 | Marked High (9-12) n=65 |
| **Deaths (%)** | 2.2 | 3.6 | 13.4 | 15.3 |
| **Days of in-hospital stay** | 9.4± 6.2 | 11± 7.1 | 12.4± 7.8* | 13.1± 8.1* |
| **Sepsis (%)** | 6.97 | 18 | 31.6*# | 38.3*# |
| **Blood Trasfusion (%)** | 8.8 | 16.3 | 18.8 | 29.7*# |
| **Diabetes Mellitus (%)** | 17.7 | 27.2 | 34.2 * | 45.1 *# |
| **Hypertension (%)** | 48.8 | 67.2%* | 61% | 44.2%#@ |
| **Chronic Heart Failure (%)** | 13.3 | 23.6 | 24.8 | 26.2 |
| **Previous Stroke (%)** | 6 | 13.5 | 10 | 12.2 |
| **Chronic Kidney Failure (%)** | 2.2 | 19.09 * | 24.1* | 8.3* |
| **Neoplasm (%)** | 18.1 | 14.8 | 30.5# | 39.1*# |
| **COPD (%)** | 6.7 | 17.2 | 24.1* | 25* |
| **Chronic Liver Disease (%)** | 6.6 | 7.2 | 11.4 | 26.2*#@ |

## 388. SGLT1 FUNCTIONAL POLYMORPHISMS ARE ASSOCIATED WITH 1H-OGTT GLUCOSE LEVELS

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**Background:** The sodium/glucose co-transporter 1 (SGLT-1) is primarily responsible for the intestinal uptake of glucose and galactose, through an active transport driven by the Na+/K+ ATPase. Homozygous mutation of the gene encoding SGLT1 (SLC5A1) are the cause of glucose/galactose malabsorption, a condition characterized by severe life-threatening neonatal watery diarrhea and dehydration. It has recently been shown that carriers of a haplotype with 3 missense mutations (N51S rs17683011, A411T rs17683430, and H615Q rs33954001) of SLC5A1 exhibit lower 2-hour glucose levels during OGTT and a lower risk of impaired glucose tolerance. Subjects with normal fasting and 2h-OGTT (normotolerant, NGT) glucose but with 1h-OGTT ≥155 mg/dL (NGT-1h-high) have a worse cardio-metabolic risk profile and higher incidence of diabetes type 2 compared to the NGT population with blood glucose at 1h <155 mg/dl (NGT-1h-low). In this study, we investigated the possibility that the N51S/A411T/H615Q haplotype of SGLT1 was associated with 1h-OGTT glycemic pattern in NGT subjects, and we assessed the functional significance of these variants in vitro.
**Methods:** 800 well-characterized adult NGT subjects were subjected to a 75g OGTT and stratified accordingly into two groups: NGT 1h-high or NGT 1h-low. Site specific mutagenesis was performed in order to introduce the three variants into a cellular model of human intestinal epithelium (CACO2 cells). The functional effects exerted by the variants on glucose uptake, intracellular and extracellular glucose content were evaluated by commercial kits.
**Results:** The frequency of the rare allele of each SNP was higher (P<0.05) in NGT-1h-low subjects (1.515% rs17683011, 9.139% rs17683430, 3.926% rs33954001) than in NGT-1h-high subjects (0.549%, 1.315%, 1,515%, respectively). When the 3 SNPs were collectively analyzed in a genetic risk score, it was observed that carriers of rare alleles had a dose-dependent lower risk of showing 1h-OGTT glucose levels ≥155 mg/dL (OR 0.419, CI95% 0.217-0.810, P< 0.01). When CACO2 cells were evaluated, the mutant proteins were present in the cells at comparable levels to wild-type, while sugar transport was significantly reduced (%reduction = ~30% rs17683011, ~25% rs17683430, ~35% rs3395400). It remains to be defined whether the simultaneous presence of more than one variant generates a more dramatic reduction in the transport of glucose.
**Conclusion:** These data suggest that the genetic variants of SGLT-1 may have a role in the determination of early post-prandial pattern of glucose levels. Future research on this topic might drive the development of novel therapeutic approaches targeting intestinal glucose uptake with the intent of preventing the formation of a dysglycemic milieu, and long-term cardio-metabolic protection.

## 389. CATHEPSIN K AS AN EARLY MARKER OF CARDIOVASCULAR ORGAN DAMAGE IN TYPE 2 DIABETES

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**Background:** Several clinical evidences reported the involvement of a particular class of cysteine proteases, cathepsins B, C, K, L and S, and their endogenous inhibitor, cystatin C, in the pathogenesis of cardiovascular diseases (CVD). In particular, high Cathepsin K (CatK) concentrations have been found in atherosclerotic lesions. Furthermore, clinical studies showed that CatK ablation in a murine model ameliorated diabetes-induced hyperglycemia, alterations in energy metabolism, and cardiovascular structural/functional abnormalities. However, the involvement of CatK in cardiovascular complications associated with diabetes and the potential molecular mechanisms involved have not been elucidated yet.
**Methods:** To address this issue, we analyzed the potential role of serum CatK levels in a cohort of 536 well-characterized individuals participating in the CATAMERI study, of which 134 were normo-glucose tolerant, 134 were pre-diabetic, 268 had type 2 diabetes, with 30% prevalence of CVD. We evaluated the clinical utility of physiological CatK in assessing subclinical cardiovascular organ damage by measuring carotid artery intima-media thickness (c-IMT) via high resolution B-mode ultrasound, and left ventricular mass index (LVMI) calculated using the Devereux equation for LVM and normalized by body surface area.
**Results:** Our exploratory analysis performed on 103 non-diabetic individuals showed that CatK is significantly increased when HbA1c values (beta = 0.296, p = 0.031), 2h-post load glucose (beta = 0.197, p = 0.046), and TYG index (beta = 0.225, p = 0.023) are raised, as well as when glucose tolerance worsens (beta = 0.19, p = 0.027).The correlation analysis between CatK and c-IMT in our cohort confirmed the existence of a positive association (r = 0.365, p = 0.0001) which remained significant also after correction for age, sex and BMI (r = 0.307, p = 0.002). We observed also a significant association (r = 0.404, p = 0.0001) between CatK and LVMI after correction for age, sex and BMI (r = 0.358, p = 0.0001).
**Conclusion:** For the first time, we have highlighted the role of CatK as marker of CVD risk. Our evaluation of c-IMT and LVMI strongly suggests that measuring serum CatK levels could be a useful and inexpensive instrument for the precocious identification of patients with higher cardiovascular risk. Finally, our data support the hypothesis that the assessment of CatK as part of the initial work-up might help unravel the presence of subclinical organ damage in subjects at increased risk of cardiovascular complications.

## 390. EFFECT OF BEMPEDOIC ACID ON ENDOTHELIAL FUNCTION

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**Background:** Bempedoic acid is an oral, small-molecule cholesterol synthesis inhibitor in development for the treatment of hyperlipidemia. It acts upstream of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase to inhibit cholesterol biosynthesis and increase LDL receptor expression, it activates Adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK) and inhibits ATP-citrate lyase (ACL), resulting in lower LDL cholesterol and atherosclerosis in pre-clinical models.AMPK is also an upstream activator of endothelial NO synthase (eNOS), which is phosphorylated on Ser1177 in endothelial cells by several stimuli including metformin, adiponectin and leptin. However, it remains unknown whether bempedoic acid promotes endothelial function through eNOS activation, and the molecular mechanisms involved in this pathway.
**Methods:** We have characterized the effects of bempedoic acid in HAECs cells (human aortic endothelial cells) by evaluating the phosphorylation of AMPK at Thr172, AMPK substrate ACC at Ser79, and eNOS at Ser1177. The cells were exposed to increasing concentrations of bempedoic acid (10, 25, 50 and 100 μM) for 24 hours. We treated HAECs with AICAR 2mM for 24 hours, to obtain a visual positive control, and we pre-treated the cells for 1 h with Compound C (40 μM) as a negative control. We will use small inhibitory RNA (siRNA) to evaluate if the down-regulation of AMPK regulatory subunit β1 or β2 impairs bempedoic acid-induced eNOS phosphorylation in HAECs. Moreover, we will analyze eNOS activity, by assessing the intracellular formation of L-[14C]citrulline from L-[14C]arginine, and measure intracellular cGMP.
**Results:**Our preliminary data show that bempedoic acid treatment significantly increased AMPK (Thr172) and ACC (Ser79) phosphorylation levels in a dose-dependent manner, with maximal effect occurring at 100μM (P<0.05). HAECs exposed for 24 hours to bempedoic acid showed a dose-dependent increase of eNOS (Ser1177) phosphorylation (100μM, P<0.001).
**Conclusion:** The results of this project support the hypothesis of that bempedoic acid exerts beneficial actions on the endothelial system and will help shed new light on the molecular mechanisms involved and lay the basis for future development of therapeutic and preventive strategies for reducing the burden of cardiovascular risk.

## 391. OVERWEIGHT AND OBESITY ARE PREVALENT AMONG KIDNEY TRANSPLANT RECIPIENTS, AND ADHERENCE TO MEDITERRANEAN DIET IS LOW, REGARDLESS OF WEIGHT STATUS

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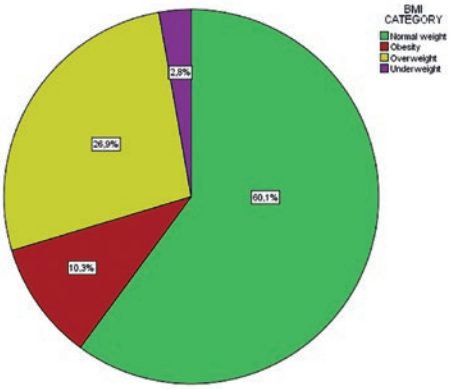
**Background:** Approximately 2,000 kidney transplants (KTs) are performed every year in Italy. Weight gain is common after a KT. Overweight/obesity (OW/OB) is an independent risk factor for poor renal outcomes, including survival of a kidney graft. There are no recent data on the prevalence of OW/OB among KT recipients (KTRs) in Italy, and it is not known whether adherence to the Mediterranean Diet (MD), which may favourably impact both body weight and kidney outcomes, is associated with a healthier weight in KTRs. We sought to estimate the prevalence of OW/OB among adult KTRs in Italy, and to investigate their adherence to the MD.
**Methods:** We conducted an anonymous, online survey using Google Forms. The survey was advertised through social media platforms by the main national associations of patients with polycystic kidney disease or on renal replacement therapy. We collected self-reported height and weight to compute body mass index (BMI), age, sex, year of transplant, smoking habit, level of education. Adherence to MD was assessed using the MEDI-LITE questionnaire. Adherence to MD was considered inadequate if the score on the MEDI-LITE questionnaire (range 0-18) was ≤ 9 (median), and adequate if it was > 9 We also asked about weight changes after KT, and whether a physician had provided recommendations about the participant's weight. The protocol was approved by the Ethics Committee of IRCCS San Raffaele Roma.




**Results:** A total of 253 kidney transplant recipients participated in the survey. Median (25th;75th percentile) age was 56.0 (47.5; 62.0) years, 56.1% were male, median KT duration was 6.0 (3.0; 13.0) years. Prior to KT, 73.4% had undergone hemodialysis or peritoneal dialysis. Median BMI was 23.9 (21.6; 26.5) kg/m2. Overall, 47.4% of KTRs reported having gained weight following KT. At the time of the survey, 94 (37.2%) participants had OB (10.3%) or OW (26.9%). We found no significant differences in terms of age, sex distribution, level of education, or smoking between KTRs with

or without OW/OB. Sixty-three (71.3%) KTRs with OW/OB reported that their physician had recommended weight loss, whereas 21.3% reported that their physician had never addressed their weight, and 6.4%reported that their physician said their weight was correct. One KTR with OW/OB (1.1%) was advised to gain weight. Overall, 55.3% had inadequate adherence to MD. There was no significant difference in the adherence to MD between KTRs with or without OW/OB (43.4% vs. 46.8%, respectively; p=0.598).
**Conclusions** The prevalence of OW/OB among KTRs participating in this survey was high, and similar to that of the Italian general population. Adherence to MD was low, independent of OW/OB status. Strikingly, despite the well-known association between OW/OB and adverse renal outcomes, nearly 30% of KTRs with OW/OB reported not having received counselling about weight loss. Strategies are needed to prevent/manage weight gain in KTRs, and to increase awareness about OW/OB among physicians involved in the follow-up of KTRs.

## 392. COAGULATION IMBALANCE IS ASSOCIATED WITH HEPATIC FIBROSIS AND VASCULAR COMPLICATIONS IN PATIENTS WITH TYPE2 DIABETES AND NAFLD

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**Introduction:** Non-alcoholic fatty liver disease (NAFLD) and type 2 diabetes mellitus (T2DM) are characterized by a pro-coagulant state and vascular complications.
**Aim:** to evaluate in patients with T2DM and NAFLD if alterations in coagulation are associated with hepatic fibrosis and vascular complications.
**Matherials, Methods and Results:** 96 patients with T2DM and NAFLD (mean age 65 ±7 years, 66% male) and a matched control group of 156 healthy individuals were enrolled. For all subjects, determination of serum pro- (factor II-FII, factor VIII-FVIII) and anti-coagulant factors (protein C-PC, antithrombin-AT) and test of thrombin generation (ETP ratio, FVIII/PC) were obtained. In the T2DM cohort, significant liver fibrosis (>F2) was diagnosed by Fibroscan (LSM>7.0/6.2 kPa, M/XL probe) and microvascular (retinopathy, nephropathy and neuropathy) and macrovascular complications (carotid plaques and history of cardiovascular (CV) events) were assessed. Compared to the control group, patients with T2DM and NAFLD presented a pro-coagulant imbalance (ETP ratio 0.64±0.09 vs 0.59±0.18, p=0.02; FVIII/PC 1.2±0.3 vs 1.02±0.3, p=0.03). Hepatic fibrosis was present in 14% of patients, microvascular complications in 30% (retinopathy in 8%, nephropathy in 23%, neuropathy in 4%), plaques in 73% and CV events in 24%. In the T2DM/NAFLD cohort indexes of procoagulant imbalance were independently associated with LSM>7.0/6.2 kPa (M/XL probe) (multivariate analysis corrected for age, sex, T2DM duration, HbA1c, overweight, hypertension; AT: OR 0.89; CI 95% 0.80-0.98) and with microvascular complications (multivariate analysis corrected for age, sex, smoking, T2DM duration, HbA1c, overweight, hypertension, use of statins, uric acid; AT: OR 0.93; CI 95% 0.88-0.98; FVIII/PC ratio: OR 8.0; CI 95% 1.00-65.8).
**Conclusions:** In patients with T2DM and NAFLD a pro-coagulant imbalance was confirmed and associated with hepatic and vascular complications, speculating on a possible common pathogenetic pattern. Further studies are necessary to define the clinical application of coagulation alterations, however a careful evaluation of hepatic complications in diabetics is recommended.

## 393. REDUCED HIGH-DENSITY LIPOPROTEIN (HDL) IS AN INDIPENDENT DETERMINANT OF ALTERED BONE MICROARCHITECTURE IN WOMEN WITH TYPE 2 DIABETES

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**Background and Aims**: Osteoporosis and type 2 diabetes mellitus (T2DM) are chronic conditions with increasing prevalence worldwide. T2DM is associated with an increased fracture risk, but the exact mechanisms leading to bone structure alterations are still not fully understood. In the absence of fragility fractures, osteoporosis is usually diagnosed through bone mineral density (BMD) measurement by dual-energy x-ray absorptiometry (DXA). However, in patients with T2DM, BMD is often normal to increased, making it an unreliable parameter to assess fracture risk; conversely, evidence points towards a role of the trabecular bone score (TBS), a BMD-independent texture parameter of the spine DXA image, in fracture risk prediction in presence of T2DM. The aim of our study was to assess clinical predictors of bone alterations in a population of women with diabetes, compared to a control group.
**Materials and Methods:** This study included 71 consecutive T2DM women (mean age 63.6±9.5 years, diabetes' duration 7.8±5.6 years), in good glycaemic control (HbA1c<7.5%), treated with metformin in monotherapy. Main exclusion criteria were: treatments known to significantly influence bone metabolism, other causes of bone disease and secondary osteoporosis. A cohort of 27 healthy, age-comparable women was selected as a control group. All participants underwent complete clinical examination, routine biochemistry and DXA scan for BMD and TBS assessment.
**Results:** Patients with T2DM had significantly lower TBS than non-diabetic women (1.19±0.1 vs 1.24±0.1; p<0.05) and this association persisted statistically significant after adjustment for age, smoking, physical activity and menopausal status (p= 0.02), despite higher BMD in all the districts investigated. When dividing the study population according to validated TBS cut-offs, T2DM patients were more represented in the degraded (TBS≤1.2) and partially degraded (1.2<TBS≤1.35) bone category (43.9% vs 42.9%, 50% vs 33.3%) and less represented in the normal bone category (TBS>1.35; 6.1% vs 23.8%, p=0.04) compared to controls. In T2DM patients, TBS positively correlated with HDL levels(p=0.003), intense/moderate physical activity (p=0.048) and insulin sensitivity (p=0.03), whereas negative association was observed with body mass index (BMI) (p=0.04), transaminases (AST and GGT: p<0.001) and metabolic syndrome (p=0.003). Lower HDL represented the main predictor of altered bone architecture regardless of age, physical activity, glycaemic control and statin use (p= 0.009).
**Conclusion:** In T2DM women the prevalence of bone alterations was significantly higher than in non-diabetic ones, and was easily assessable by the DXA-derived TBS, also in presence of normal BMD. In women with T2DM, low HDL predicted the presence of degraded bone structure, likely for the loss of the pleiotropic anti-inflammatory effects of this lipoprotein on bone microenvironment.

## 394. CANCER-ASSOCIATED ANOREXIA: MODULATION OF AUTONOMIC NERVOUS SYSTEM ACTIVITY ASSESSED BY THE ANALYSIS OF HEART RATE VARIABILITY

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**Introduction:** Autonomic nervous system is involved in the regulation of body weight modulating energy expenditure. We assessed changes in autonomic nervous activity evaluated by heart rate variability (HRV), according to the presence of anorexia (symptom directly related to alterations in energy control) in a cohort of cancer patients compared to healthy subjects.
**Methods:** Anorexia was assessed by the Functional Assessment of Anorexia-Cachexia Therapy (FAACT) questionnaire. HRV was analyzing by the 24-hour EKG the domains of low frequencies (LF, index of the sympathetic modulation) and high frequencies (HF, index of the parasympathetic modulation). The standard deviation of normal-to-normal RR intervals (SDNN) (ms) and the square root of the mean of the sum of the squares of differences between adjacent NN intervals (RMSSD) represented markers of sympathetic and parasympathetic system, respectively.
**Results:** We enrolled a total of 29 cancer patients and 23 controls. Among cancer patients, anorexia accounted for 12/29 (41.4%), according to FAACT≤ 30. Anorexic patients presented with lower food intake (%) compared to non-anorexic (p<0.001). Cancer patients presented with lower LF with respect to controls (p=0.034), as well lower SDNN (p=0.004) and RMSSD (p<0.0001) In addition, LF were lower in anorexic vs controls (p=0.024), whereas no differences were present between anorexic vs non-anorexic, as well as between non-anorexic vs controls. The SDNN was

decreased in anorexic patients vs non-anorexic (p=0.018) and vs controls (p<0.0001). The SDNN significantly correlated with body weight loss (R=-0.421; p=0.029), C-reactive protein serum levels (R=-0.465; p=0.013) and percent of food intake (R=0.460; p=0.012).
**Conclusions:** Our data suggest a dysregulation of autonomic activity in cancer patients presenting with impaired appetite and body weight loss.

## 395. GLIM-DIAGNOSED MALNUTRITION PREDICTS HOSPITALIZATION RISK IN SYSTEMIC SCLEROSIS

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**Rationale:** Malnutrition is a well-known risk factor for morbidity and mortality in many clinical settings, to date, only few studies assessed the role of malnutrition on systemic sclerosis (SSc) patients' outcomes. The aim of the study was to evaluate the role of malnutrition as a predictive risk factor for mortality and/or hospitalization in SSc patients during a 4-year follow-up.
**Methods:** One hundred and one adult patients with diagnosis of SSc admitted to our Scleroderma Unit were included in the study. Biochemical analyses, disease activity index (DAI), disease severity scale (DSS) and anthropometric data were recorded at enrollment. Malnutrition was assessed by the Global Leadership Initiative on Malnutrition (GLIM) criteria.
**Results:** Malnutrition according to GLIM criteria was found in 22 patients (21.8%). During a 4-year follow-up, 7 (6.9%) patients died, 4 of which (57.1%) were malnourished. Moreover, 19 (18.8%) patients were hospitalized for all causes, 11 of which (57.9%) were malnourished. Kaplan-Meier analysis showed a hospitalization-free survival significantly [41 months (±12) vs 46 months (±8), p=0.001] shorter in malnourished patients than in non-malnourished SSc patients. In multivariate analysis, malnutrition [HR=3.363 (95% CI=1.249-9.057), p=0.016] and interstitial lung disease [HR=0.188 (95% CI=0.040-0.884), p=0.034] were predictive risk factors for hospitalization. Kaplan-Meier curves showed that overall survival was significantly shorter in malnourished than in non-malnourished patients [46 months (±8)Vs 47 months (±3), p=0.019]. However, in multivariate analysis, only cardiac disease was a predictive risk factor for death in SSc patients [HR=0.102 (95% CI=0.018-0.571), p=0.009].
**Conclusions:** Malnutrition according to GLIM criteria represents a predictive risk factor for hospitalization in SSc patients.

## 396. PHASE ANGLE, NUTRITIONAL STATUS AND MORTALITY IN SYSTEMIC SCLEROSIS

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**Rationale:** Systemic sclerosis (SSc) is a rare autoimmune disease characterized by microvascular damage, immune dysregulation and fibrosis of the skin and internal organs. Among complications, changes in nutritional status have a negative impact on quality of life and predispose to malnutrition.
The aim of the study was to examine whether bioelectrical impedance analysis (BIA) derived-phase angle (PhA) was parameter of nutritional status and marker of mortality in SSc patients.
**Methods:** Consecutive adult patients with diagnosis of SSc admitted to our Scleroderma Unit were included in the study. Biochemical analyses, disease activity index (DAI), disease severity scale (DSS), anthropometric data and BIA assessment were recorded at enrollment. Malnutrition Universal Screening Tool (MUST), Global Leadership Initiative on Malnutrition (GLIM) were performed to assess nutritional status.
**Results:** One hundred and four consecutive SSc patients [(88 female; median age 55 years (IQR 45.5 years – 66 years)] were enrolled. The median values of PhA were significantly lower in SSc patients than in healthy controls [(4.51° (IQR 4° - 5°) vs 5.4° (IQR 5° - 5.7°), p<0.0001]. In SSc patients with high malnutrition risk according to MUST, the mean values of PhA were significantly lower than SSc patients with low malnutrition risk [4° (IQR 3.7° - 4.4°) vs 4.6° (IQR 4.2° - 5.1°), p=0.004]. SSc patients with malnutrition according to GLIM criteria showed significantly lower PhA with respect to SSc patients without malnutrition [3.8° (IQR 3.5° - 4.3°) vs 4.6° (IQR 4.2° - 5.1°), p<0.0001]. Kaplan–Meier curves demonstrated that overall survival was significantly shorter [34.57 months (±13.35) Vs 48 months (±0), p=0.001) in SSc patients with PhA < 3.75°. In multivariate analysis, only PhA is a predictive factor for death [HR=0.283 (95% CI=0.083-0.965), p=0.044].
**Conclusions:** In SSc patients lower PhA values are associated with increased malnutrition risk at MUST, malnutrition at GLIM and increased mortality.

## 397. AN UNUSUAL PRESENTATION OF MALNUTRITION

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**Case Presentation:** A 74-year-old woman presented to the emergency department with flaccid paraparesis and hypo-anaesthesia of the lower limbs, urinary and fecal retention for about a month and the appearance, in the last week, of significant bilateral columnar edema.
Her past medical history was characterized by osteoporosis complicated by vertebral fractures, paroxysmal atrial fibrillation, previous bilateral K. pneumoniae pneumonia and pulmonary interstitial disease due to amiodarone (December 2021). On admission, the patient was alert and oriented.
Vital signs revealed a pressure of 135/80 mmHg, pulse 95/minute, oxygen saturation of 97%. The physical examination found flaccid paraparesis, mild hypoesthesia of the lower limbs and exuding bilateral columnar edema.
Laboratory data showed a white blood count of 7940/mL with preserved leukocyte formula, hemoglobin of 11 g/dL, platelets of 224000/ml, creatinine 0.18 mg/dl, total protein 3.8 g/dl, albumin 2.2 g/dl, serum protein picture: hypogammaglobulinemia with IgG 264 mg/dl, IgA 104 mg/dl, IgM 32 mg/dl; ferritin 92 ng/ml, folic acid 30 ng/ml, vitamin D 6.1 ng/ml, vitamin C 6.9 mg/l, vitamin A 18 mcg/dl, vitamin E 11.62 mcg/dl, vitamin B1 28 ng/ml, vitamin B2 210 ng/ml, vitamin B6 11 ng/ml, vitamin B12 100 ng/ml (reference value 200-950). Negative fecal H. pylori and fecal elastase research.
**Discussion and Conclusion:** For the diagnostic study of neurological symptoms, MRI of the spinal cord was performed with evidence of signal alteration affecting the posterior portion of the entire dorsal spinal cord, interpreted as myelopathy due to vitamin B12 deficiency for which vitamin supplementation was started. The EGDS was also performed with biopsy, negative for alterations compatible with atrophic gastritis, and antibodies to gastric parietal cells resulted negative. Neoplastic markers, celiac disease antibodies, anti-ganglioside antibodies, screening for lue and HBV-HCV-HIV serology were also negative.
To investigate the aetiology of the edema, an echocardiography was performed which excluded the cardiogenic origin, a nephrotic syndrome was excluded by evaluating the 24-hour proteinuria found within the limits, a chest-abdomen CT was performed which excluded its paraneoplastic origin, showing the presence of modest pleural and abdominal effusion, and haematochemical tests were taken with evidence of hypogammaglobulinemia and hypoalbuminemia. We then proceeded to intravenous supplementation of immunoglobulins and albumin, well tolerated by the patient, and a personalized diet with vitamin supplements was set, in particular with vitamin B12 and vitamin D weekly. During the hospitalization there was a progressive improvement of the edema, a resumption of fecal continence, an improvement of laboratory tests, with restoration of normal values of albumin, immunoglobulins and vitamins and an evident improvement of the neurological picture on an MRI control.
The initial clinical picture was therefore interpreted as secondary to significant chronic malnutrition prior to hospitalization, with a possible component of malabsorption; in particular, the vitamin B12 deficiency was secondary to malnutrition linked to the patient's depression due to the death of her husband a few months earlier.
This case indicates that conducting a thorough medical history in patients is essential to obtain a correct diagnosis.

## 398. ADHERENCE TO MEDITERRANEAN DIET MAY REDUCE FRACTURE RISK BY PRESERVING MUSCLE HEALTH

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The Mediterranean diet has been associated with favorable cardiovascular, oncologic, neurodegenerative, and mortality outcomes. However, little evi-

dence exists regarding its effects on musculoskeletal health. The aim of the study was to investigate the association between adherence to the Mediterranean diet and some surrogates of muscle and bone health in a setting of postmenopausal women evaluated for osteoporosis.
Postmenopausal women referred to the outpatient clinic for bone and mineral metabolism disorders of the Department of Clinical and Experimental Medicine of the University Hospital of Messina were consecutively recruited. The 10-year probability of fracture was calculated using the fracture risk assessment tool (FRAX). In addition, instrumental investigations including measurements of bone mineral density (BMD) at the lumbar spine and femur and radiography of the spine to check for vertral fractures were performed. The likelihood of sarcopenia was estimated by administering the SARC-F questionnaire that explores strength, assistance in walking, getting up from a chair, climbing stairs, and falls. Muscle performance was measured by hand grip strength using a Jamar dynamometer. Adherence to the Mediterranean diet was calculated using the validated Medi-Lite questionnaire proposed by Sofi.
Ninety-six women with a median age of 66 years (64 to 70 years) were recruited. The median BMD T-score values were -2.5 SD (-2.7 to -2.2 SD) at the lumbar spine and -2.2 SD (-2.3 to -2.1 SD) at the femoral neck. The 10-yr probability of major osteoporotic fractures was 13% (11 to 17%). Greater adherence to the Mediterranean diet was associated with lower likelihood of sarcopenia, as suggested by lower score on the SARC-F questionnaire ($r = -0.24$; $p = 0.017$). Participants' age was associated with SARC-F score ($r = 0.407$; $p < 0.001$), and lower SARC-F score was also associated with lower hand grip strength ($r = -0.221$; $p = 0.036$) and higher 10-yr probability of major osteoporotic fracture and hip fracture ($r = 0.440$; $p < 0.001$ and $r = 0.413$; $p < 0.001$, respectively).
These data support an association between greater adherence to the Mediterranean diet and more favourable indices of muscle health. Because sarcopenia is frequently accompanied by higher risk of fractures, it is likely to hypothesize that the Mediterranean diet, preserving muscle function, may contribute to reduce fracture risk in postmenopausal women.

## 399. WINE NOT?

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A 65-year-old woman was admitted to the emergency room due to bilateral leg weakness and loss of balance determining fall.Repetitive myoclonus in upper and lower limbs and ataxia were noticed; these symptoms had progressed over a period of three months but worsened in the last three weeks. Her history includes generalized anxiety disorder and stage IV lung adenocarcinoma treated from 2020 with a combined immune and chemo-therapy regimen (cisplatinum plus pembrolizumab). No other relevant anamnestic data were reported. Initially, the patient did not report significant dietary misbehavior, alcohol abuse and denied any illicit drug use. After few days of hospitalization, the patient developed fever with confabulation, progressive cognitive impairment with delirium, nystagmus, auditory/visual hallucinations, as well as a worsening of ataxia and myoclonus. There were no significant findings in her laboratory analysis except for increased levels of c-reactive protein and γ-glutamyltransferase. Thiamine replacement therapy was empirically prescripted in case of encephalitis, in differential diagnosis with platimun toxicity and metastatic menigeal or brain tumor. Blood cultures were collected and an antimicrobical therapy was started without clinical benefits. In the following few days neurological symptoms presented even without fever, with no responsive delirium and generalized myoclonus. Neurological clinical examination was not conclusive due to the poor compliance; In order to improve neurological status and myoclonus, diazepam was administered and her conditions drastically improved. Electroenchephalogram (EEG) showed general slow activity without spikes suggestive for seizures. Furthermore, additional history was obtained asking her husband and moderate alcohol consumption (wine and beer, 6 alcohol unit per day) was reported; thiamine replacement and diazepam doses were thus increased. In the light of her recently reported excess alcohol use and no alternate diagnosis available, Wernicke encephalopathy was postulated as a possible source of her ongoing neurological symptoms. In a few days general conditions improved, there was a restitutio ad integrum of the neurological status and myoclonus also disappeared. EEG dramatically improved, so the patient was discharged at home in good conditions.
Wernicke encephalopathy is an acute neurological disorder usually characterized as a clinical triad of acute mental confusion, ataxia, and ophthalmoparesis; even delirium, mental confusion, amnesia, ataxia and/or myoclonus can be observed; it results from vitamin B1 (thiamine) deficiency, especially caused by alcohol abuse, but even in starving, hyperemesis, unbalanced diet, bariatric surgery, malignancy and anorexia nervosa. Thiamine and benzodiazepines administration leads to a quick improvement. A delay or lack of treatment may lead to irreversible dementia, Korskoff disease (delineated a chronic amnestic syndrome affecting memory out of proportion to other cognitive deficits) or even death. Our patient history of cancer with ongoing immuno-chemotherapy were at first hypothesized as the main diagnostics routes; this case shows that even small and unpredictable details of personal history are crucial in finding the right path to follow.

## 400. METFORMIN: SWING THE BALANCE? A CASE OF LACTIC ACIDOSIS

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Patient (pt) of 74aa arrives in Emergency Room for diarrhea and epigastralgia for a few days, nausea and vomiting from the previous day, contraction of diuresis for about 12h and episodes of hypoglycemia. APR: Grade I obesity, hypertension in unspecified therapy and T2DM in therapy with metformin of unknown dosage.At triage: BP 105 / 40mmHg, HR 90bpm, SpO2 97% in AA, DTX 152mg / dl, T °C 36.5. Pt is agitated, tachypnoic and uncooperative; ECG and Arterial Blood Gas (ABG) are also performed. In light of the latter, the patient is re-evaluated in code red: pH 6.789, pCO2 16.7 mmHg, pO2 138.8 mmHg, K + 6.1 meq / L, Cl- 94meq / L, gluc 161mg / dl, lac 19mmol / L, HCO3- 5.0 mmol / L, Anion Gap (AG) 44.1meq / L, Base Excess (BE) -32.2mmol/L.Given the history, the clinic and the ABG, lactic metabolic acidosis with attempted respiratory compensation, with increased AG, is suspected. The patient's hyperventilation and tachypnea in this case are not a sign of respiratory distress, but reflect the attempt of respiratory compensation to acidosis.Hematochemical tests are taken and medical infusion therapy with physiological solution, calcium gluconate and HCO3 - 8.4% is stardet; however, the ABG repeated after 1 hour is unchanged. The patient is monitored to assess hemodynamic stability and a second bottle of HCO3- 8.4% is infused.Given the age of the patient, the labile hemodynamic compensation and the lack of response to the therapy practiced, the resuscitator is alerted who admits the patient to Intensive Care Unit (ICU). In laboratory tests: Cr 10.96 mg / dl, eGFR 4.93 ml / min, BUN 157 mg / ml, K + 6.35 mmol / L, LDH 324U / L, troponins 366,700pg/mL and CRP 87.88mg / L.In ICU the patient is intubated. In patients with Metformin Associated Lactic Acidosis (MALA), intubation is rarely necessary; otherwise, must be maintained a ventilation that does not affect respiratory compensation, checking the patient with frequent ABG until the patient is hemodynamic stabilized.Medical infusion therapy with ringer acetate, bicarbonate, calcium gluconate and insulin is continued and hemodialysis is performed from CVC (approximately 70h), associating prophylactic therapy with LMWH 6000UI/day.During hospitalization, we perform blood culture from CVC due to an increase in inflammation indices, which was positive for S. epidermidis sensitive to beta-lactams that the patient is already receiving as therapy for a pneumonia found on the chest x-ray.After a week, the patient was transferred to the Department of Medicine, extubated, with spontaneous and valid diuresis. There was a progressive improvement of the clinical and laboratory picture, of the renal function and reduction of the inflammation indices. At discharge: HbA1c 68 mmol/mol (8.4%), glycaemia 174 mg / dl, Cr 2.85 mg / dl, Az 88 mg / dl, eGFR 28.51 ml / min, normal electrolytes, mild hypertransaminase and hyperparathyroidism, probably secondary at severe renal failure.The clinical case presented is a type B lactic acidosis, i.e. with systemic tissue normoperfusion in which the cause of acidosis lies in alterations of cellular metabolism induced by toxic agents (e.g. metformin). Biguanides can cause lactic acidosis either for an overdose or for the presence of precipitating factors that can cause a worsening of renal function, with consequent reduction of clearance (eg diarrhea, vomiting, dehydration). MALA is characterized by a blood lactate concentration greater than 5mmol/L and arterial pH less than 7.35 in association with metformin exposure. Factors involved in the development of MALA include: vomiting, diarrhea, acute kidney damage, high doses or accumulation of metformin and concomitant acute disease states. While nausea is a common adverse effect of metformin, out-of-the-ordinary vomiting and diarrhea are a clear first sign of MALA. In these cases, metformin therapy should be discontinued and patient should receive urgent

medical attention.Furthermore, it should be considered that metformin is a highly ionized water-soluble drug, which is absorbed, distributed and excreted by organic cation transporters; although the effect of an acidotic episode on its pharmacokinetics is unknown, studies suggest that acidosis may alter drug absorption, distribution and elimination.Hemodialysis is an effective treatment for hemodynamically unstable patients with MALA. Medical therapy includes the use of sodium bicarbonate in case of severe metabolic acidosis, evaluating the risks such as a shift to the right of the hemoglobin dissociation curve, excessive sodium intake, rebound metabolic alkalosis, electrolyte alterations (K+ and Ca++), decreased myocardial contractility, increased CO2 production and reflex vasodilation after bolus administration. Bicarbonate therapy should be start in case of severe acidemia (pH <7.1), or pH <7.2 in case of acute renal failure, in order to restore pH> 7.1 or> 7.3 in patients with AKI.With regard to prognosis, some parameters indicating poor outcome such as advanced age, arterial pH below 7.35, and the need for mechanical ventilation and vasopressors should be considered.

## MISCELLANEA

### 401. HOW IMPORTANT IS A GOOD AND CORRECT DISEASE COMMUNICATION?

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The patient, a young woman, aged 44, had a clinical history of hormone-responsive infiltrating breast cancer, known for 12 years, multi-metastatic and multi-treated with surgery (right mastectomy, lymphadenectomy and hepatic metastasectomy), hormone therapy and multiple lines of chemotherapy; the check-ups performed just before entering our hospital showed disease progression and bone marrow infiltration with pancytopenia. The patient, although still in active treatment until recently, had already begun to receive oncological home care for palliative therapy and titration of analgesic therapy. Given the worsening of the general conditions, the onset of confusion and the appearance of general malaise, despite the therapy already administered at home by palliative colleagues, she was conducted in the emergency room, where she was treated with sedative therapy (midazolam and fentanest in pump) and admitted to the medical department. Blood chemistry tests performed at admission confirmed severe microcytic anemia (Hb 6.6 g / dL), severe thrombocytopenia (PLT 4,000 / mcl) and neutropenia (N 1,410 / mcl) with an increase in inflammation indices. During our short hospitalization, we continued palliative support and accompanying therapy without carrying out blood component transfusions, despite the family required and expected a much more aggressive and almost "curative" therapeutic attitude. As the general clinical conditions and the long history of disease could predict, we observed rapid clinical worsening with death occurring on the second day of hospitalization. This clinical case is certainly important for various aspects, first of all the young age of the patient, and wants to be voluntarily "provocative". It is a condition that we encounter more and more often, with the increase in the incidence of neoplastic diseases. Often doctors, especially in internal medicine wards, are faced with conditions of terminality of patients with neoplastic or degenerative pathology. Humanly and professionally, it is difficult to manage the right approach both towards the patient, especially if young, and towards family members. A right management should start with a fair communication of disease by the early stages. The colleagues who manage the disease in all its phases (oncologists, palliativists, family doctors) have an important role both in managing the disease "physically", but also in preparing people psychologically to the possible exitus. Often there isn't preparation for the management of terminal conditions and communication with patient and family members. It should arise from a collaboration between hospital and local services. Furthermore, the intimacy of death should be respected. In these situations, what better care can this type of patient receive in the hospital? What benefit can they have from it? One thing is sure. Hoping for a miracle, he loses the comforts of his home and the last moments with his family.

### 402. SSSS IN AN ADULT WITH OBESITY AND TYPE 2 DIABETES BUT NO OBVIOUS IMMUNOLOGICAL DEFIENCY: A CASE REPORT

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La sindrome da cute scottata da Stafilococco (malattia di Ritter) è una patologia grave causata da una esotossina epidermolitica prodotta da alcuni ceppi di Stafilococco aureo, che colpisce neonati e bambini o, più raramente, adulti con compromissione del sistema immunitario.
A settembre, una donna di 58 anni è giunta all'attenzione del Pronto Soccorso del nostro Policlinico per la comparsa di un eritema pruriginoso con bolle flaccide desquamanti, con risparmio delle mucose, interessante il 70-80% della sua superficie corporea. La paziente ha riferito esposizione solare, senza adeguata protezione, e consumo di crostacei il giorno precedente alla comparsa delle lesioni. Inoltre, ha riferito assunzione di elevate dosi di FANS e paracetamolo, nei giorni precedenti, per trattare un dolore persistente a livello del piede destro.
In anamnesi, diabete di tipo 2 in terapia con analoghi del GLP1 e insulina complicato da retinopatia diabetica e piede di Charcot, obesità di classe II (BMI 35 kg/m2), ipertensione arteriosa in terapia con ACE inibitore, calcio-antagonista, beta-bloccante e diuretici, dislipidemia in terapia con statina, stenosi carotidea bilaterale non significativa, pregresso TIA e pregressa encefalite erpetica.
In quinta giornata, si è assistito a un aggravamento del quadro clinico per comparsa di febbre (TC 39°C), ipotensione (PA 95/50 mmHg), desaturazione ossiemoglobinica (SpO2 in aria ambiente 74%) con segni elettrocardiografici di sottoslivellamento ST e rialzo degli indici di miocardiocitonecrosi. L'episodio sarebbe stato successivamente inquadrato come angina da discrepanza e trattato con angioplastica (PTCA) e stenting medicato della arteria coronarica destra e discendente anteriore.
Dalle emocolture raccolte da vena periferica, è stato isolato uno Stafilococco aureo MSSA, per cui, in associazione con la clinica cutanea, è stata posta diagnosi di sindrome da cute scottata da Stafilococco.
La nostra paziente non presentava alcuna causa franca di immunodepressione che potesse far sospettare in prima istanza una patologia infettiva grave, gli unici fattori associabili a depressione del sistema immunitario erano il diabete mellito e l'obesità.
Diversi studi in letteratura suggeriscono l'associazione tra diabete, obesità e un aumentato rischio di infezione, sebbene i meccanismi patogenici alla base di tale associazione non siano stati ad oggi completamente compresi. Verosimilmente lo stato sub-infiammatorio cronico che caratterizza entrambe le condizioni, per l'aumentata produzione di radicali liberi, la glicosilazione proteica e la produzione di fattori pro-infiammatori, è in grado di interferire con l'efficacia della risposta immunitaria adattativa e innata.
La paziente è stata trattata con oxacillina per 10 giorni, con completa regressione delle lesioni cutanee e della sepsi.
Il nostro caso sottolinea l'importanza di considerare i pazienti affetti da obesità e diabete mellito, soprattutto se mal controllato, come pazienti estremamente fragili, non solo per l'aumentato rischio di eventi cardiovascolari, ma anche per lo stato di immuno-depressione.

### 403. MEDIASTINAL SYNDROME REVEALED HEART LOCALIZATION OF A PRIMARY MEDIASTINAL B-CELL LYMPHOMA: A CASE REPORT

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**Background:** Primary mediastinal B-cell lymphoma (PMBCL) is an aggressive lymphoma that represents 2-3% of non –Hodgkin lymphoma cases and typically affects young adult Caucasian women. Diagnosis can be difficult and often need a multidisciplinary approach.
**Case:** a 75-year old female, with history of hypertension, came to emergency room for severe dyspnoea. She displayed also neck and left arm oedema. Blue swelling of face and trunk were seen. Heart point of care ultrasound (PoCUS) was inconclusive, describing only a hypoechoic dilation of right atrium while the other three heart chambers were reduced in dimensions. Chest CT revealed a huge mediastinal mass next to a thrombosis of superior cava vein and right atrium (7 cm diameter), and a diffuse subsegmental pulmonary embolism. Arm and neck lymph nodes were also enlarged. Low molecular weight heparin was given twice a day. Due to the respiratory failure a high-flow nasal cannula oxygen treatment was perfor-

med. PET revealed FDG uptake in antero-superior mediastinum, but there was the same uptake in heart right atrium without a connection with the above described one. Therefore, this was no more considered as thrombus but as a mass. The micro-bubble test revealed right to left shunt. She refused heart MRI. She was not suitable for an open-surgery biopsy, thus she was scheduled for a CT guided one, in order to obtain a pathological diagnosis for a suspected right atrium sarcoma. Due to the high risk, we performed the less invasive as possible way to obtain a histological sample. Thus, and intravascular biopsy of atrial mass by femoral vein was done. The patient did not present any sequelae after this procedure and she continued anticoagulation. The subsequent histological analysis revealed a PMBCL with a primary localization in the right atrium. Unfortunately, a sepsis by multiple resistant Pseudomonas aeruginosa and Aspergillus spp. arose, and the patient died three weeks after biopsy.
**Conclusion:** A PMBCL is a rare and aggressive lymphoma. Like in our patient, mediastinal syndrome is often associated to the disease. However, intracardiac localization is a rarer event. In large case series, less than 1% of intracardiac masses were lymphomas. In our patient, the open-surgery was not suitable for multiple comorbidities. However, intravascular approach was less aggressive but effective to obtain enough tissue for diagnosis. Unfortunately, the immune suppression related to PMBCL and opportunistic infections drove a lethal sepsis.

## 404. A STRANGE CASE OF FEVER AND LYMPHADENOPATHY

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A 23-year-old female patient, with an otherwise normal remote medical history, on March 2021 presented an erythematous pharyngo-tonsillitis firstly treated with anti-inflammatories. Cephalosporin antibiotic therapy (Cefixima 400 mg/day for 5 days) was then introduced when laterocervical swelling, swallowing difficulties and asthenia emerged. Corticosteroid therapy (Betamethasone 3 mg/day for 7 days) was introduced later on by her general practitioner, due to her worsening conditions, with a clinical improvement readily regressed after treatment conclusion. Febrile angina (evening fever ≤ 37.5°C), laterocervical lymphadenopathy, asthenia, diffuse muscle pain and sometimes an irritative cough were the main recurring symptoms while alternating unsuccessful antibiotic therapies, with corticosteroid therapy, leading to a temporary relief. All the performed screening for infectious and autoimmune disease tested negative. By contrast c-reactive protein (1.35mg/dl), Erythrocyte Sedimentation Rate (ESR) 21mmH (0-15) and LDH 202U/L(100-190) were increased. Chest X-ray documented an accentuation of bronchus-vascular texture and pulmonary hilus calcifications. Four months after the onset, due to the persistence of the symptoms, the patient came to our attention for further investigation. The clinical examination highlighted: several increased bilateral laterocervical lymph nodes, with benign clinical characteristics. We repeated all serological infectious and autoimmune tests (antibodies anti-CMV, TOXO, Widal-Wright and Weil-Felix serodiagnosis, EBV DNA and Parvovirus B19 DNA, beta D glucan, urine culture, blood culture, lymphocyte typing and measurement of IgG, IgA, IgM, C3, C4, beta2microglobulin, LDH, ANA and ENA), confirming once again patient's negativity. The only findings were a throat swab was positive for Staphylococcus aureus and an increased value of anti EBV-VCA IgG suggesting a previous infection. The blood count was normal with negative inflammatory indices (WBC 6360/ul with preserved formula, PCR 0.74 ng/l (<3), ESR 12 mm/h) as well as routine biochemistry and SPEP. The echocardiography documented: remodeled mitral flaps with preserved coaptation point in the AV plane, hyperechoic aspect of the papillary muscles (postero-medial>antero-lateral); slight detachment of the epipericardial junction (anterolateral wall), thickened pericardial sheets (infero-lateral and antero-lateral walls). We required ultrasound of the abdomen and of the lymph node stations. The latter revealed numerous lymph node stations located bilaterally in the latero-cervical area with: elongated morphology, barely recognizable hilum, and increased vascularization and size. (Maximum size of 3 cm). A complementary PET/CT TB reported: moderate glucose hypermetabolism affecting small bilateral laterocervical lymph nodes (SUV max 2.3) which according to the morphology, intensity of uptake and coexistence of artifacts (active brown adipose tissue), suggested a reactive-inflammatory pathology and glucose hypermetabolism in the left adnexal region (SUV max 4.1) assuming physiological significance. To further corroborate our hypothesis, we performed a lymph node biopsy removing 3 lymph nodes in the left laterocervical region (largest one measuring 2x1.5x0.8 cm). The histological examination described the presence of chronic granulomatous lymphadenitis, non-necrotizing epithelioid granulomas with giant cells (foreign body and Langhans), furthermore two lymph nodes presented histiocytosis of the sinuses. ACE and Quantiferon sampling were requested testing negative. In absence of therapy, the patient continued to present evening fever, with a tendency to spontaneous resolution, confusion, widespread muscle pain, irritative cough and laterocervical lymph adenomegaly. Infectious, autoimmune and oncohematologic causes ruled out, the combination of histological examination characterized by non-necrotizing granulomatosis, the coexistence of irritative cough and low-grade fever, the clinical response to corticosteroid therapy and the evidence of pericarditis outcomes oriented us towards a diagnosis of sarcoidosis. Relative to this diagnostic orientation, the PET aspect of the left ovary, first considered as physiological could then can acquire a different meaning as a rare manifestation of the disease. Considering the young age, the absence of imaging evident pulmonary involvement and the need for prolonged steroid therapy, it was necessary to consider sending the patient to a reference center for sarcoidosis for diagnostic confirmation. A later pulmonary assessment with spirometry and chest x-ray, a repetition of routine blood chemistry and dosage of ACE, all of which in the normal range furthertly reinforced our diagnosis of lung-sparing sarcoidosis. So the patient started a treatment with Deltacortene 40 mg/day with a gradual down-titration, which is still in progress. The clinical response was immediate and lasting.

## 405. ISCHEMIC STROKE AND ANATOMIC VARIANTS OF INTRA AND EXTRACRANIAL BRAIN-FEEDING ARTERIAL SYSTEMS

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**Background:** The circle of Willis, as an anastomotic polygon at the base of the brain, forms an important collateral network to maintain adequate cerebral perfusion. Changes in the normal morphology of the polygon of Willis may condition the appearance and severity of symptoms of cerebrovascular diseases such as aneurysms, infarctions and other vascular disorders.
**Clinical Presentation and Neuroradiologic Findings:** Mrs C. L., a 88-year-old woman with arterial hypertension, hypertensive cardiopathy, chronic atrial fibrillation and glaucoma, was admittted to the emergency room after developing sudden mild speech disturbace. A Computed Tomographic Angiography showed the interruption of the enhancement at the level of the M2-M3 and M4 (distal) branches of the left Middle Cerebral Artery (MCA) and a defined area of ischemic penumbra correspondig with the left temporal-parietal-occipital carrefour. Besides, CT Angiography incidentally revealed some interesting morphological anomalies concerning both the extracranial and the intracranial arterial circulation. 1. The left Vertebral Artery (VA) took origin from the arch of aorta instead from the left Subclavian Artery (SA), entered into the transverse foramen of the fifth cervical vertebra (C5), was thinner than the contralateral and exhibited a kinking trajectory. 2. The left Posterior Cerebral Artery (PCA) came from the left Internal Carotid Artery (ICA), not from the ipsilateral Basilar Artery (BA), thus representing the so-called Fetal Posterior Cerebral Artery (FPCA).
**Discussion:** The neurovascular anomalies documented at neuroradiology are noteworthy and deserve some remarks. 1. Variations in the origin and in the course of VAs are well-known and may be unilateral or bilateral. The VA usually originates from the SA, wich itself derives from the brachiocephalic trunk on the right side and from the aortic arch on the left side. In approximately 5% of cases the left VA originates directly from the aortic arch. In rare cases the VA stems from the common carotid artery, inferior thyroidal artery, brachiocephalic trunk or from other arteries. In contrast with the ICA, the VAs show considerable differences between the right and the left side, with the frequent finding of a "dominant" left side artery (80% of cases). If the left VA originates from the arch of aorta, it is more likely to enter the transverse foramina of the cervical vertebrae at a level higher than C6 (even in C2). All these conditions are considered simply anatomical variants without clinical value because usually they do not impair brain perfusion, a part from the unilateral or bilateral hypoplasia/dysplasia of the VA. 2. In "normal" circle of Willis (describred by Thomas Willis in 1664) the ICA bifurcates, at the medial end of the Sylvian fissure, into anterior and middle cerebral arteries. The two anterior cerebral arteries (ACAs) are joined, at

the anterior end of the longitudinal fissure, by the anterior communicating artery (AComA). The BA bifurcates, at the ponto-mesencephalic junction, into two PCAs, which are in turn connected to the ipsilateral ICAs by the Posterior Communicating Arteries (PComA). Owing to the lack of a valvular system, blood flow through this circle can follow the direction of need. However, this configuration, with a completely developed polygon of Willis, is found in less than 30% of population because are frequently encountered a wide range of variations from normal anatomy like anomalies of origin and course, hypoplasia, hyperplasia, accessory vessels (duplications/triplications), absent vessels and so on. In the fetal-type posterior circle of Willis there is an embryonic derivation of the PCA from the ICA (unilateralllly or bilaterally) rather than from the BA, due to persistent embryological circulation. This variant can be classified into two subtypes. Complete: the PCA originates completely from the ICA. The P1 segment is absent and only the ICA supplies the occipital lobes. This variant is found unilaterally in 4-26% of individuals and bilaterally in 2-4%. Hypolastic BA may be associated with bilateral complete FPCA. Partial: the P1 segment is still present but it is very small, thus most of blood supply to the occipital lobes originates from the ICA. This variant is found unilaterally in 11-29% and bilaterally in 1-9%. CONCLUSION. Fetal origin of the PCA is not uncommon but whether patients with this anomaly have a higher risk of ischemic stroke in the territory of the PCA is not known. Some Authors suggest a negative influence of FPCA variant on the cerebral collateral circulation, in particular on the growth of leptomeningeal vessels after an ischemic stimulus when primary collaterals are insufficient. The leptomeningeal vessels develope between the anterior (ACA), middle (MCA) and posterior cerebral arteries (PCA) and represent an important connection between the ICA and the vertebrobasilar territories. The FPCA could make leptomeningeal vessels impossible to develop since both the MCA and the PCA are joined to the ICA rather than to the vertebrobasilar circulation. To date the subject is somewhat controversial.

## 406. SEIZURES AS A RARE MANIFESTATION OF A CRITICAL MEDICAL CONDITION

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Chronic use of opioids is known to lead to tolerance to their effects and to a distressing withdrawal syndrome (OWS) when they are discontinued, or dosage is reduced.
OWS can begin soon after opioid discontinuation, its symptoms are often severe, and may motivate patients to restart opioids or prevent from attempting to stop them at all. We report a case of complicated OWS presenting mainly with alteration in gastro-intestinal function and seizures.
An obese 59 years old man was admitted to our Ward because of a severe hypercapnic respiratory failure with ground glass opacities in the lung CT.
His past medical history consisted of Crohn's disease since 2009 complicated with an episode of bowel obstruction in 2017. He also had a personal history of substances abuse (alcohol, opioids) recovered in community and since then in substitutive therapy with buprenorphine/naloxone. This therapy was not confirmed at admission because of the severe respiratory failure and since the patient declared not to use this medication regularly. We set a broad spectrum antibacterial therapy (piperacillin-tazobactam and levofloxacin) and continuous diuretic infusion with furosemide.
Few hours later a sudden worsening of the respiratory failure required transferring the patient to the Intensive Care Unit, coming back to our unit 3 days later. At this point he started to complain abdominal pain and diarrhoea, with an increase in pancreatic function enzymes (amylase up to 919 U/L – nr 30 -118; lipase 1138 U/L – nr 12 - 53). Neither abdomen imaging nor faeces cultural test identified a possible explanation for those symptoms. We then ascribed these alterations to a iatrogenic event and temporally suspended therapy with piperacillin-tazobactam.
During the following day he showed a sudden alteration in personality and features of delirium, together with severe headache and muscular cramps. Above all, he started to present repeated generalized tonic-clonic seizures which only partially responded to diazepam i.v. A brain CT scan excluded any acute CNS lesions and an EEG failed to identify epileptiform activity. Nonetheless, the same day the patient had two additional episodes of seizures with the same clinical features described above.
After this last episode, the patient admitted to have already experimented episodes diagnosed as epilepy during one of the previous hospital admission for bowel obstruction. He later stopped the treatment for epilepsy without further episodes. This anamnestic information allowed us to consider that we were dealing with a possible manifestation of opioid withdrawal. As a matter of fact, the whole clinical features quickly and completely resolved after restarting buprenorphine/naloxone, which the patient was used to take for 15 years. Few days later we also performed a brain MRI, which confirmed the absence of structural causes of seizures.
Seizures are known to be caused by both neurological diseases and acute medical illnesses, such as metabolic disturbances but also withdrawal states (alcohol, benzodiazepines) or opioid overdose, but they are not described as a typical presentation of OWS. It generally includes aches/pain, muscle spasms, tremor, abdominal cramps, nausea, diarrhea, anxiety, irritability, pupillary dilatation. Withdrawal with buprenorphine, a long acting opioid, is described to be less severe than withdrawal from short-acting opioids, but in this case it was the trigger of a potentially life-threatening complication (seizures resistant to diazepam treatment). There are only few reports available on complicated opioid withdrawal with seizures, showing as it has to be considered a valid entity that requires further research evaluation.

## 407. KEY ASPECTS OF PRIMARY CARE MEDICINE IN DIFFERENT EU AND NON-EU COUNTRIES: A REPORT

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**Introduction:** . Lately, Primary Care (PC) is under great scrutiny, especially in Italy where the health crisis caused by the pandemic highlighted the weaknesses of that portion of the healthcare infrastructure that was neglected for too long. On such premises, attempts are made to reorganize and evolve PC. Actually, experts of the field know that many publications from health authorities such as the World Health Organization and the European Union were fostering changes in healthcare organization long before the recent events, as a more silent, yet not less alarming, pandemic was developing: that of an ageing-multicomorbid population. Our institution is playing a key role in the area of Milan in pursuing such reorganization, by opening its doors to collaborations with the local General Practitioners. To better guide our steps, we therefore designed a survey to gather data about key aspects of PC in other EU and non-EU countries. We learnt of fundamental differences, generalized flaws and grasped some new concepts for our future works.
**Materials and Methods: .** We conducted an online survey using a questionnaire that included 11 open questions investigating four domains: - Contracts and payments- Logistics (office location, nurse availability)- Relationship with hospitals (data sharing, ease of specialist consultation)- Patient trustPhysicians working in different EU and non-EU countries were identified through personal academic and non-academic connections and asked to participate in the survey between September 2021 and October 2021. The questionnaire was sent to potential participants by e-mail along with a cover letter describing the objective of the study. Participation was voluntary and there were no incentives to participate. Participants were contacted if further explanations or clarifications were needed.
**Results and Discussion:** Table 1 reports a summary of the gathered answers. Each country has a peculiar organization of its primary care, but most NHS hire GPs directly, which are paid via a flat-rate scheme and work in consortia where a solid array of tests and services can be dispensed with the aid of skilled nurses. Much needs to be done in terms of integration of PC with hospitals, in most countries. Few examples of alternatives to ER for direct evaluation of patients in a hospital setting exist, and few countries have solid data linkage systems and specialist consult availability for GPs. However, trust in GPs is declining and this will surely represent a huge problem in patients management. Indeed, trust in GPs is an essential foundation to support efforts in restructuring and strengthening PC in our NHS; these efforts are much needed, as the COVID19 pandemic is teaching us, or we may risk to see the end of the family doctor. Our survey of physicians provides an overview of PC in 16 EU and non-EU countries, which serves as source to guide evaluation and re-structuring of our NHS with a focus on its two main components, primary and hospital care. Furthermore, it may allow to identify concepts to improve the interface between primary and hospital care.
**Future Perspectives:** A key aspect highlighted by our work is a widespread lack of a proper integration between GPs and hospitals. Increasing this integration is the focus of the PRIME project (PRIMary care-hospital Embed-

ding) that we are designing as a consortium merging medical teams of three big Milanese hospitals with the experiences of GPs representing the PC of the city. We aim at offering to GPs a way to fast-track their patients to hospital resources, but not to the ER, when such cases require advanced, but not critical, care. Building on evidence acquired during the pandemic, we think that this approach may represent a turning point in healthcare organization by: i. Increasing the support received by GPs from local hospitals; ii. Reducing inappropriate admissions to the ER and healthcare costs; iii. Increasing the overall quality of care offered to patients in terms of experience and outcome.

## 408. EVALUATION OF SEVERE MATERNAL OUTCOMES AND SURGICAL SITE INFECTIONS (SSI) IN THE MATERNITY HOSPITAL OF PORT SUDAN (SUDAN): A RETROSPECTIVE STUDY

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**Background:** Perinatal and post-surgical complications leading to increased morbidity and mortality constitute a major issue in low-income Countries such as Sudan, which contributes with other ten Countries to for 65% of global maternal deaths according to a recent World Health Organization (WHO) estimate. Port Sudan Maternity Hospital is the main governmental hospital of the Red Sea State in Sudan, receiving up to 900 outpatients and hosting more than 400 deliveries per month. Until March, 2nd 2022, it encompassed a 47-bed ward (commonly occupied by more than one patient), a 6-bed Intensive Care Unit (ICU) and a Labour and Delivery Room with an Operating Theatre (OT) for emergencies caesarean sections. The elective gynaecological and obstetric surgery was performed by the medical staff in a facility nearby. The hygienic conditions and resources were very poor. There were frequent cleaning materials and medical drug shortages. Starting from March, 2nd 2022 a new compound, donated by AISPO (an Italian non-governmental organization), has become operational and specialised personnel reached Port Sudan with the purpose of giving technical assistance and encourage strategies for infection prevention and control. Little is known about factors affecting poor hospitalisation outcomes and potential areas of cost-effective amelioration in settings such as those of Port Sudan
**Aim of the Study:** We therefore set up an observational study with the aim of assessing health assistance quality in the biggest public gynaecological hospital of the capital of Red Sea State, before opening a new surgical and obstetric area. The evaluation of the rate of surgical site infection (SSI) and severe maternal outcomes, such as ICU admission and death, can be considered indicators to quantify the impact of recent organisational changes and drive additional improvements in the next future for Port Sudan Hospital and other similar settings.
**Methods:** We analysed all clinical files of patients admitted from February, 1st 2022 to March, 15th 2022. We collected demographic data (age, parity, gestational age) and clinical information including antenatal care; blood cell count; comorbidities; viral screening for HIV, HBV and HCV; antibiotic therapy received before and after surgery. We also collected data on infections, ICU admissions or death occurring within within 42 days from admission or delivery.
**Results:**. A total of 395 women were admitted during the study timeframe, but three patient files were excluded after analysis because of lack of clinical information. Among these 392 subjects, 284 were admitted after delivery, 41 underwent gynaecological surgery and 67 were admitted for other clinical issues related to pregnancy. Post-surgery wound infection rate was 3.2% in patients undergoing caesarean section and 4.9% in patients undergoing gynaecological surgery, in line with previous reports from low- to high-income countries. There was a 3.1% admission rate, with a higher frequency of ICU admission in patients undergoing gynaecological surgery (7.3%) and caesarean section or receiving episiotomy (3.9%) compared to admissions for clinical reasons (1.5%). We recorded two deaths. One patient died after surgery and another one was admitted for fever in her first trimester and died after one week from admission. Therefore, while the overall and delivery-related mortality rates were 0.5% and 0.4%, the mortality rate of women admitted for clinical issues was 1.5%, which is higher than expected in higher-income Countries.
**Conclusions:** SSI are major causes of maternal morbidity and mortality. The baseline rate of SSI at Maternity Hospital of Port Sudan is similar to that expected in other clinical settings, but post-surgical mortality rates are still higher compared with high-income countries. To identify the critical aspects causing infective and life-threatening complications may help to introduce specific prevention strategies to adopt and reduce these events. Further analysis is ongoing to compare these data with the status after the new compound became operational.

## 409. SEX-SPECIFIC IMMUNE RESPONSE TO THE ORAL MICROBIOME IN INDIVIDUALS WITH PERIODONTITIS AND HEALTHY CONTROLS

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**Background and Aim:** Recent evidence suggests that sex-based differences in immune responses exist that are are, at least in part, shaped by sex-specific host-microbial interactions and that can impact on the individual susceptibility to a variety of diseases. We examined whether a sex-based dimorphism in the humoral immune response to the periodontal microbiota (outcome) existed in a propensity score matched (PSM) cohort (population) of adult men (exposed) and women (control).
**Methods:** One-to-one PSM was applied to male and female adult individuals (≥40 years) enrolled in the National Health and Nutrition Examination Survey (NHANES) III to obtain exact matches for age, race/ethnicity, periodontitis diagnosis and severity, hypertension history, diabetes, smoking habits, body mass index, and income between sexes. Participants underwent determination of serum antibodies to 21 periodontal microorganisms, as well as periodontal and biochemical evaluations. Antibody titers were log-normalized; non-parametric and machine learning (ML) approaches were applied to test whether specific antibodies could predict sex and if a sex-specific immunological phenotype could discriminate between healthy and periodontitis individuals.
**Results:** A total of 2724 exactly matched female and male participants (n. 1362/group) was included in the study (mean age: 57±12 years; 54.8% non-Hispanic Whites; 41.8% overweight; 55.9% smokers; 25.8% with periodontitis; 23% with moderately severe periodontitis; 31.3% with diagnosed hypertension). In terms of Socranski complexes, antibodies to the orange complex were more abundant in men, while antibodies to the blue complex were more abundant in women. Sex-based differences by periodontal health status were observed in terms to antibody titers to P.gingivalis, T.denticola, A.naeslundii, P.nigrescens, P.intermedia, C.ochracea, which differed between men and women only in healthy individuals, and T.forsythia and V.parvula, which differed based on sex only in individuals with periodontitis. These differences were driven by higher titers in men than in women, except for antibodies to A.naeslundii, where the opposite occurred. In ML, antibody titers to periodontal bacteria predicted sex with a sensitivity of 53% and a specificity of 65% (AUC-ROC: 0.645).
**Conclusions:** The humoral immune response to periodontal microbiota appears to be sex-specific, with different features in health and periodontal disease states. Elevated antibody titers to A.naeslundii have been previously inversely associated with systolic blood pressure and with all-cause and cardiovascular mortality. Our observation of higher antibody titers to A.naeslundii in women compared with in men is intriguing in this sense, as women are typically protected against hypertension and cardiovascular diseases by sex hormones. Future investigations are needed to clarify the clinical meaning of our findings, and whether a sexual dimorphism in the immune response carries prognostic implications.

## 410. RITIRATO

## 411. KLOTHO IN HEALTHY SUBJECTS: AN UPGRADED UPDATE

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**Background and Aim:** Alpha-Klotho is a type I, single-pass transmembrane protein expressed in the kidney, parathyroid glands, and choroid plexus. It acts as a coreceptor for fibroblast growth factor-23. The extracellular domain of Klotho can be cleaved by membrane proteases (ADAM10-17) and be released as soluble form (soluble Klotho, sKl) into the blood, urine and cerebrospinal fluid, acting as a paracrine and endocrine mediator. Low sKl concentrations are related to increased risk of significant cardiovascular disease, vascular calcification, and progressive chronic kidney disease. Serum/plasma sKl concentration is measured by a solid-phase sandwich ELISA kit and countless ELISA tests are currently available on the market. Defining the best concentration range of sKl in healthy subjects remains an unmet need for researchers. A large amount of data concerning Klotho was obtained over the last twenty years; in 2021 we systematically reviewed the literature aiming to identify reference sKl concentrations in healthy subjects and to define the standard values. In the last year, new studies have been published in which more than a thousand healthy subjects were enrolled; an update on the previously published data was deemed necessary.
**Methods:** In January 2022, an updated literature search was performed using two electronic databases: Pubmed and Embase. Full text articles published between March 2021 and January 2022, written in English and that were eligible for inclusion, were recorded on a new database that was already comprised of the articles previously selected, the latter published within February 2021. A total of 40 new articles were found;36 from Pubmed and only four from Embase that met the inclusion criteria and didn't overlap with the Pubmed research. 23 abstracts were excluded either because the results were not specifically related to sKl in healthy adult subjects, or the sKl concentration was not determined in serum/plasma, or finally because the ELISA kit manufacturer was not reported. Of the remaining 17 articles, only six reported the concentration of sKl as mean ± SD and were expressed in pg/ml; these were included in the final analysis. For each study, the number of subjects enrolled, the ELISA kit manufacturer, the mean age and the average sKl concentration were reported. Pooling together last year's results we examined a total of 31 abstracts.
**Results:** In this systematic review 10,823 healthy subjects were tested (5,331 males and 5,317 females). Four studies (169 subjects) lacked to report the sex distribution. 22 studies measured sKl in serum/plasma from Caucasian healthy subjects, 23 studies tested sKl in Asian subjects' serum. 25 laboratories used the Immuno-Biological Laboratories (IBL; #27998) ELISA kit, whilst four used each different ELISA kits (Cusabio Biotech, China; CloudClone, USA/USCN Business, China; Eastbiofarm, China; Elabscience, China). The weighted averages of serum/plasma Klotho were calculated: the weighted average of IBL's kit was 805.56 pg/ml; pooling together the remaining four kits, we obtained a weighted average sKl concentration of 1731.49 pg/ml. The overall weighted average was 834.64 pg/ml. Focusing on the most used kit (IBL; #27998), we measured the weighted average of sKl separately in the serum and in the plasma. The Serum sKl had a weighted average equal to was 806.94 pg/ml; the plasma sKl weighted average corresponded to was instead 783.4pg/ml instead. No significant difference (p=0.4) was found.
**Conclusions:** Knowing the average concentration of the Klotho protein in healthy subjects is important to allow an adequate comparison during pathological states and to define the potential role of the Klotho protein as an early marker of disease.

## 412. ACUTE KIDNEY INJURY AND HYPERTENSION ASSOCIATED WITH ANDROGENIC STEROIDS AND HYPERPROTEIC SUPPLEMENTS IN YOUNG BODYBUILDERS

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**Background:** The increasing use of anabolic steroids and supplements among bodybuilders is a known fact.Less known are the side effects of these molecules. In this regard, cases of acute renal failure and chronic kidney disease with different histopathological profiles have also been reported. Severe hypertension with cardiovascular disease, retinal disease and hypertensive encephalopathy were observed in relation to nephropathy.
**Case Description:** 36 years old male, testosterone and aromatase inhibitors abuser bodybuilder showed scotoma and arterious hypertension (210/120 mmHg) and fourth degree retinopathy after COT evaluation. Lab tests reported a rise in serum creatinine (2.36 mg/dl), hypercolestherolemia and proteinuria.Echocardiography test revealed concentric ventricular hypertrophy and supra-aortic doppler ultrasonography showed a diffused and accentuated thickening of the vessel walls. Further secondary hypertension causes were excluded in differential diagnosis. Kidney biopsy showed IgA nephropathy correlated with glomerulosclerosis and nephroangiosclerosis.
**Conclusions:** In young patients with renal injury of no clear etiology in the anamnestic evaluation, the use of anabolic steroids should always be considered, given the increasingly frequent use. Further studies could evaluate whether the duration of use of these substances is related to the severity and irreversibility of kidney damage.

## 413. A NEW STRATEGY FOR INTERNAL MEDICINE: FROM INPATIENT TO OUTPATIENT AND AMBULATORY CARE

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**Background and Aims**: The current growing demand in healthcare, as a result of increased life expectancy and chronic diseases, over-burden most healthcare systems worldwide. The mismatch between rising costs and limited resources has been exacerbated by the coronavirus disease 2019 (COVID-19) pandemic over the past two years. Furthermore, hospitalization in itself, is responsible of significant morbidity, mortality and resource utilization due to hospital-acquired complications such as pressure injuries, falls, infections, adverse drug reactions, venous thromboembolism, unplanned surgery and intensive care unit admissions, especially in elderly patients.
The aim of this paper is to propose an innovative model to reduce the congestion of emergency departments rather than merely increase the number of beds and to provide a more appropriate use of staff and cost-effective delivery through the implementation of hospital ambulatory management strategies.
In this new setting, Internal Medicine specialists, due to their high skills, have a central role in order to manage a heterogeneous spectrum of clinical scenarios ranging from ageing and multidisciplinary chronic illness to complex and rare diseases.
**Methods:** In order to relieve the pressure on hospital bed availability during COVID-19 pandemic, we have implemented an alternative to inpatient care, based on a Day Hospital regimen (hospital-based outpatient conventionally designed to require inpatient admission, which does not involve an overnight stay or multi-day stay in hospital). The DH staff consists of an Internist with proven experience, three internal medicine residents and a qualified nurse. Between January and March 2022 the number of Day Hospital/Day service patients was one hundred and twenty-three, of which, twenty-five percent was selected by emergency physicians to be referred to our outpatient care.
Sixty-five percent of the patients selected by emergency physicians, was affected by multiple chronic diseases with variably coexisting gastroenterological (39%), cardiological (19%), haematological (16%), endocrinological (13%), neurological (6,5%) and oncological (5%) pathologies. The reported average waiting time between the discharge from emergency ward and DH admission was seven days, the average number of outpatient accesses was three for each patient and the overall average number of provided medical performances was five (nearly two for every access). All patients have been subjected to clinical examination, blood tests and electrocardiogram. In the same setting, abdominal ultrasound was performed in eight clinical cases, of which, three required a second level imaging examination. In addition, infusion therapy (32%) and endoscopic examinations (10%) were performed with an average wait list of six days (taking into account the wholeness of provided performances). Few patients (19%) required a multidisciplinary

approach, including an extra specialist consultation and only 6% required hospital admission with a short length of hospitalization. Seventy-five percent of the total number was entirely managed by the Internal medicine physician.
**Conclusions:** The classical concept of hospital care has great limitations. Hospitals overcrowding has been worryingly and rapidly magnified by the rapid increase in beds demand caused by COVID-19 pandemic. The implementation of hospital ambulatory alternatives to inpatient care allows to optimize patient flow, relieve pressure on hospital bed availability and prevent unnecessary inpatient admissions. Participants are generally satisfied with this model, nevertheless, an implemented outpatient flow has to be supported by a parallel expansion of collateral services, primarily radiological performances with a short wait-list. Additionally, further evaluations are mandatory to determine optimal patient eligibility criteria for every condition (including social factors) because in this framework, some services will and must continue to be delivered in hospitals to ensure safety, quality and efficacy.
In conclusion, avoidance of hospitalization maybe regarded as an auspicious quality improvement process of which proficient Internal Medicine specialists seem to be the best potential coordinators.

## 414. A NEW SOFTWARE TO SIMULATE CLINICAL CASES: THE FIRST EXPERIENCES

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**Introduction:** Before the pandemic period, the practical activities have become progressively difficult and frustrating for the increasing number of medical students but a finite and fixed number of spaces in the hospitals. During the Covid-19 pandemic, medicine teachers and tutors were asked to found solutions to force remote teaching: training and internships suffered mostly for the lock-down.
We therefore developed an easy usable informatic platform dedicated to clinical cases discussion and focusing on learning and reinforcing clinical methodology and critical thinking in medicine.
**Materials and Methods:**
We created a completely "in house" software platform aimed to discuss clinical cases more interactively. Real or constructed ad hoc cases or cases from the literaturecan be inserted in the platform.
The teacher declares sex, age and patient's ethnic origin but the software changes the patient's name each time to make difficult to the student to identify the case if previously used.
The teacher tags each case with pathology, presentation and comorbidities but also with medical and surgical specializations involved as well most relevant signs and symptoms to more easily navigate the archive. Thereafter, the teacher uploads historic data, physical examination with pictures when useful, laboratory results, pathologic photos, static or dynamic imaging diagnostic tests, or any other material that could be useful for the discussion.
The students can access the platform both in presence or remotely using a code or a QR-code and the case is provided through a brief presentation defining the setting (surgery, ward or emergency room), the role of the student in the simulation and the cause that brings the patient to the medical attention.
The case discussion occurs orally between teacher and students which ask the tutor the data they think useful for the diagnosis. It is significant that this way of discussing gives the tutor the opportunity to evaluate the critical capacity and the diagnostic and therapeutic methodology.
When used in class setting the software allows the interaction with polls.
This platform can be used for exams, training, internships or lectures, face to face or remotely, for a single student or for the entire class.
**Results:** The platform has been experimentally used in 2020-21 for 24 frontal lessons of Medical Clinic of the 5th course year, in 20 lessons in 2021-22 and in 6 access sections for medical students, and in 7 year- round assessments of specialty doctors.
A survey shows that 96% of students think the platform is a useful instrument, 86% thinks the software is easy to use and 75% of them consider the software adequate for assessment.
At present we have performed 2 courses for medical doctors and 14 tutors are now active.
**Conclusions:** The first experiences with this software showed that it can be used both for frontal lessons and exams. The practical experience during training is irreplaceable, however, the software seems a possible instrument in emergency conditions that request forced remote teaching but can also be used in class lessons.

## 415. ANTIBIOTIC CONSUMPTION IN AN INTERNAL MEDICINE WARD OVER A 5- YEARS PERIOD

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**Introduction:** Antimicrobial resistance, driven by sub-ottimal prescriptions, is a major concern in public health. Antibiotic surveillance sistems are an essential requirement for antibiotic control strategies.
**Objective:** we assessed the antibiotic consumption in an Internal Medicine ward of a medium-size teaching hospital over a 5-years period (2017-2021).
**Methods:** data from pharmacy records are presented as defined daily dose divided by patients days an expressed as 100 bed-days (DBD). Antibiotic consuption and patients days for Covid-19 sections were not considered.
**Results:** in the study period, 6546 patients were admited, with a total of 2908587 bed-days. The avarage lenght of stay increased from 13.5 days in 2016 to 17.2 days in 2021; in the same period the avarage weight of DRGs raised from 1.15 to 1.23. We documented an overall antibiotic consuption of 56.6 DBD, with the most prescribed therapy being third-generation cephalosporins (15.7 DBD, 27.0%), combinations of penicillins (13.6 DBD, 24.1%), macrolides (6.2 DBD, 11.0%) and fluoroquinolones (5.1 DBD, 11.0%). Considering single years, the antibiotic consumption varied from 50.4 DBD in 2017 to 53.5 DBD in 2021 with a maximum of 61.6 DBD in 2020. When comparing 2021 and 2017 data, we observed an increase in cosumption of combinations of penicillins (from 10.7 to 14.4 DBD, +31.0%), third-generation cephalosporins (from 11.6 to 13.0 DBD, +20.3%), linezolid and daptomycin (from 0 to 2.4 DBD) and carbapenems (from 3.5 to 5.6 DBD, +58.8%); on the contrary, in the same period, there was a reduction in the usa of macrolides (from 7.2 to 2.8 DBD, -61.5%), fluoroquinolones (from 6.8 to 2.6 DBD, -61.0%), imidazole derivatives (from 5.5 to 2.3 DBD, -57.2%) and beta-lactamase resistant penicillins (from 1.2 to 0.3 DBD, -73.4%).
**Conclusions:** Our findings suggest an higher antibiotic consuption then described for similar experiences in litterature, with an increase over the study period. The observed reduction in 2021, in the absence of stewardship programs, is probably related to patients characteristcs and lenght of stay during coronavirus epidemy. Special concerns stem from the trend of consuption of carbapenems, as well as linezolid and daptomycin. This work will provide a stimuls to review our antibiotic prescribing policies.

## 416. INTRODUCING A NOVEL HOSPITAL-TO-HOME CARE PROGRAMME IN CHRONIC/COMPLEX/FRAIL PATIENTS: THE PRO-CCF STUDY

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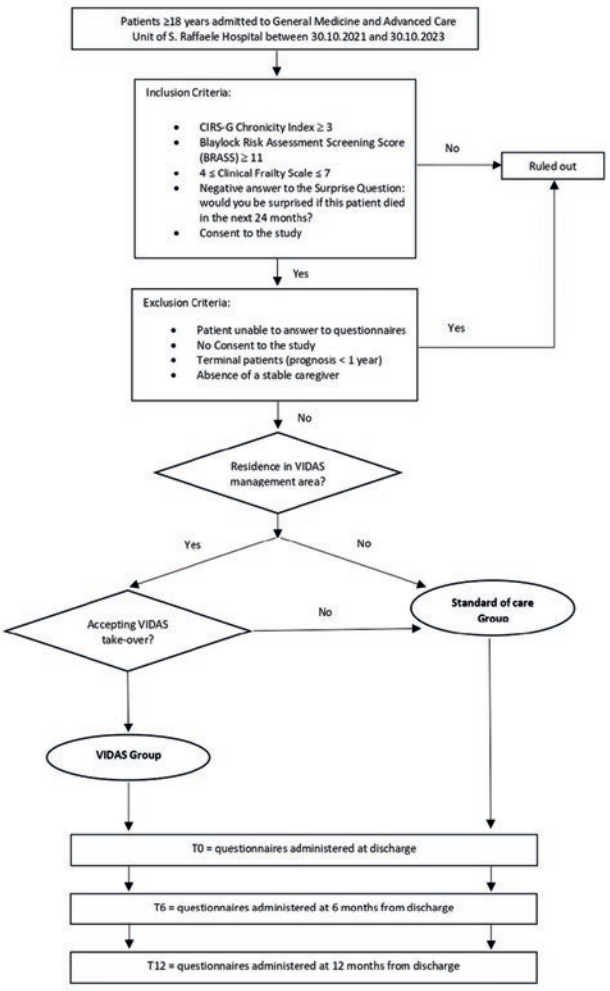
**Background:** New organizational models are needed for the management for chronic, complex and frail patients (CCF) due to increasing prevalence of chronic diseases. Identifying frailty determinants before hospital discharge is crucial for continuity of patient care in the community. VIDAS is a non-profit organzation aiming at providing free assistance to patients with chronic diseases and short-medium term prognoses through dedicated socio-medical équipes specialized in pain therapy and palliative care. San Raffaele Hospital and VIDAS have recently set up a collaborative project for the post-discharge home care of CCF patients treated in the Unit of General Medicine and Advanced Care and in need for enhanced home assistance. The efficacy of such measures is unknown. Measuring the potential effect of a comprehensive programme to potentiate post-discharge patient home care might be of potential interest for a broad range of in- and outpatient Internal Medicine settings. To address this issue, an observational case-control study (PRO-CCF) has recently been set at out Institution and is currently ongoing.

**Objectives:** The primary aim of the study is to assess the effectiveness of a new model of post-discharge management in terms of perceived quality of care. Secondary measures of improvement include survival, reduction of readmission and quality of life for the patient and the caregiver. Preliminary analyses were focused on sample definition and monitoring of patient characteristics during the early phases of enrolment.
**Methods:** The study has been designed as a monocentric, observational prospective protocol based on the collection of clinical data from patient history, hospitalization and post-discharge follow up, along with dedicated questionnaires administered at discharge (T0) and after six (T6) and 12 months (T12; Figure 1) focused on patient quality of life and post-hospital quality of care. These encompass the Physician- and Patient-reported assessment of chronic illness care (ACIC and PACIC, respectively) scores to assess assistance quality, the Euro Quality five dimensions five levelsscore (EQ-5D-5L) for quality of life, the modified caregiver strain index (MCSI) for caregivers' quality of life, a Clinical Frailty Scale for frailty, the mini nutritional assessment scale (MNA), the blaylock risk assessment screening score (BRASS) for the need for continuity of care after discharge, thecumulative illness rating scales (CIRS, including the severity, CIRS-SI, and comorbidity, CIRS-CI, subscores) to assess patient's comorbidities and the strength, assistance in walking, rising from sitting position, climbing stairs, and falls (SARC-F) index for nutritional state. The Karnofsky's Scale is used to quantitate patient Performance Status. Patients are divided into a study group (taken over by VIDAS Association) and a control group (referred back to the caregiver, which is currently the standard of care. Caregivers' data will be also be collected anonymously.The primary endpoints will be measured as differences in aggregate PACIC scores between the test and the control group. Feasibility preliminary analyses have been performed to estimate a suitable sample size for the study. Basic clinical descriptors of patients enrolled within the first six months of the study were also analysed. Interim comparative analyses between the two study groups will be performed once 50% of the predicted patients per group will be recruited.




**Results:** Taking the NCT00121940 trial (Boyd C, 2009) as reference, we have estimated an effect size of 0.391 by the use of enriched models of post-discharge care towards the aggregate PACIC score. By setting the target statistical power to 80% and alpha error probability to 0.05, we have calculated the need for approximately 200 patients to achieve a reliable measurement of the primary endpoint. After six months from the beginning of the study, 15 patients have been recruited (ten women, five men) with a median (interquartile range, IQR) age of 81 years (IQR 71-85). The main diagnosis at discharge was respiratory failure due to exacerbation of COPD, bronchitis or pneumonia, followed by congestive heart failure. Patients' caregiver are patients' children in 40% of cases, patients' spouse in 33% of cases and a home assistant in 13% of cases, suggessiting that familiar support is prominent in comparison to external caregivers. The median (IQR) BRASS score was 18 (14-20), consistent with medium risk requiring post-discharge assistance planning, but with reduced probability of subsequent institutionalisation. The median (IQR) CIRS-SI and CIRS-CI were 2 (2-3) and 4 (3-5).
**Conclusion:** PRO-CCF is an ongoing study aiming to define the potential role of a comprehensive home care assistance programme in ameliorating patient quality of life. Patients enrolled so far are loaded with a significant burden of comorbidities and should therefore be indicative of the effects of such measures in the post-discharge management of CCF patients. Evidence from this study will also potentially disclose novel hints for improved CCF patient care in a multitude of in- and outpatient Internal Medicine settings

## 417. RECURRENT SKIN ISCHEMIC LESIONS: UNCOVERING THE SKIN

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We describe a peculiar case of a woman admitted to our Internal Medicine ward because of a right-side ischemic stroke and abdominal and thigh necrotic ulcers.
A 53 years-old obese woman presented to the Emergency Department of our institution in December 2021 because of hemiplegia, dysarthria, and deviation of oral rhyme. A computed tomography (CT) scan showed an acute right-side ischemic stroke. She was out of the time window for thrombolysis, and a thrombectomy was not performed because of her poor performance status. Then, she was admitted to our internal medicine ward.
In her medical history, she reported hypothyroidism and severe obesity (grade III). In June 2021, she had an acute myocardial infarction (STEMI) and was re-hospitalized two times, one because of acute pulmonary edema and, one month later, because of acute kidney injury due to acute diarrhea caused by ticagrelor. In September 2021, she was admitted to another internal medicine ward because of abdominal ulcers and panniculitis that required prolonged antibiotic therapy. She was then discharged to a sub-acute hospital to continue the antimicrobial therapy with meropenem. Her home treatment was acetylsalicylic acid, clopidogrel, bisoprolol, furosemide, levothyroxine, calcium carbonate.
At admission, she had left hemiplegia and hypoesthesia. Moreover, the physical examination showed extremely painful abdominal open ulcers with subcutaneous palpable nodules and two painful necrotic eschars on her thighs with subcutaneous palpable nodules.
We performed multiple microbiology cultures from curettage tissue, isolating P. aeruginosa, P. mirabilis and K. pneumoniae carbapenemase-producing (subtype New Delhi Metallo beta-lactamase). Together with the infectious disease specialist, we decided not to treat the colonization of the ulcers in the absence of clinical symptoms of infection and elevation of indices of inflammation. We performed escharotomy of the thigh's ulcers and began daily medication with topical disinfectant.
To investigate the etiology of constantly infected ulcers, we decided to perform a skin biopsy of one of the abdominal ones, which showed necrosis of dermis-hypodermis and arterioles with marked fibro-intimal proliferation obliterating the lumen and characterized by calcific degeneration. These findings were consistent with cutaneous calciphylaxis, confirmed by the dermatologist in light of the clinical manifestations. Being renal failure the major risk factor for this disease, serum creatinine was checked and resulted within normal range.

To investigate the etiology of the ischemic stroke, we performed echocardiography that showed contractile dysfunction, complete apex akinesia, and intracavitary thrombosis. We promptly started anticoagulant therapy with enoxaparin and continued with aspirin-only antiaggregant therapy.
Meanwhile, the patient developed a bacteriemia from C. striatum and E. faecalis, probably starting from the colonized ulcers, and vancomycin was initiated with clinical benefit. However, during the following days the patient developed an insidious but rapid neurological deterioration, first with diplopia, then with altered mental status. Thus, we performed a brain CT scan, which showed a new ischemic event, not confirmed by the magnetic resonance imaging.
The patient became more and more unresponsive to external stimuli and developed candidemia from C. tropicalis. In the suspicion of central nervous system infection, we started a broad-spectrum antibiotic, antiviral and antimycotic therapy, and performed a spinal tap, which was inconclusive.
The patient entered a coma during the following days and died a few days later.
**Conclusion:** Calciphylaxis, also known as calcific uremic arteriolopathy, is a rare condition often associated with end-stage renal disease, called uremic-calciphylaxis. Rarely calciphylaxis develops in the absence of renal failure, as in the case of our patient. Of note, only a few cases are described in the literature. Obesity, female sex, diabetes mellitus, vitamin K antagonists treatment, and hypercalcemia are potential risk factors [1]. In our patient, obesity and female sex were the only risk factors identified.
Calciphylaxis is characterized by calcium deposits in the arterioles, which reduce the blood vessel diameter and facilitate the thrombotic process, leading to necrosis of the irrorated tissues (adipose and dermis). Clinically, cutaneous manifestations begin with areas of erythema/livedo of the skin, which evolve into necrotic eschars and then into open ulcers. Typically, lesions are extremely painful and represent an entrance door for bacteria and fungi. Calciphylaxis has an extremely high level of mortality, higher in uremic-calciphylaxis (1-year mortality: 45-80%) than in non-uremic one (1-year mortality: 25-45%). The presence of ulcerated lesions appears to reduce the 6-moths survival rate to 20%.
There is no specific treatment. Although not supported by strong evidence, sodium thiosulfate is often used in uremic-calciphylaxis. Supportive therapy with regular topical medications for ulcers and antalgic therapy are the pillars of the management of these patients.

## 418. INTERIM ANALYSIS OF THE AI-ECHOS CLINICAL TRIAL FOR VOICE-MEDIATED EARLY DETECTION OF SARS-COV-2 CASES: A 12-MONTH REPORT OF RECORDINGS

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**Introduction:** The SARS-CoV-2 pandemic led to widespread healthcare crisis even in most advanced contexts, following its emergence in December 2019. After two years of close fight with the virus, early recognition of positive cases is still an unwon challenge. Infection detection at its earliest stage would allow prompt interruption of viral spread through isolation of those asymptomatic or pre-symptomatic cases, still untackled by current measures and responsible for fueling COVID-19 outbursts, as the Omicron variant recently showed.
Early diagnosis also allows for timely patient candidature for therapy: current molecules targeting viral load find therapeutic opportunity only at the very initial phase of infection (1).
Artificial intelligence (AI), through machine learning (ML) algorithms, is a fast-developing widely-applied technology, shown capable of augmenting human diagnostic performance (2,3).
Among the most common symptoms of COVID-19 are cough, sneezes, shortness of breath, sore throat, and runny nose (4). Based on the assumption that virus-induced inflammation - even at stages preceding symptom development - significantly and specifically modifies usual sounds produced through the upper airways (voice, breath and cough) and upon recent advances in sound analysis algorithms, we applied an AI-based sound-driven SARS-CoV-2 screening tool originally trained on a British dataset (5) to an Italian cohort of outpatient cases and controls, in an innovative clinical trial (6, NCT05115097). We hereby report an interim analysis after a 12-month run, from April 2021 to March 2022.
**Methods:** We collected vocal sounds from Sars-CoV-2 positive outpatients - all confirmed by molecular nasal swab determination - referring to the Mild-to-Moderate COVID-19 unit (MMCO) at San Raffaele Hospital from April 2021 to March 2022. We also collected sounds from negative-tested healthcare personnel to serve as negative controls recorded in the same rooms, with the same background noises and same native language. Recordings were obtained through a smartphone app: patients were asked - following an interactive guide - to sequentially cough, breathe and speak (reading a fixed sentence) in front of the smartphone and answer a multiple-choice survey assessing their current signs and symptoms.
Recordings were repeated at follow-up visits and in some cases the last recording was actually collected when the rtPCR naso-pharyngeal swab of the subject had turned negative, therefore providing a case-specific negative control sample and allowing for disease evolution studies.
Signals were analyzed to extract a set of predetermined features that are used to classify sounds either as COVID-19 positivity or negativity via machine learning classifiers, exploiting a pretrained deep learning model (4).
Our primary outcome is to determine the algorithm accuracy in detecting SARS-CoV-2 infected patients in terms of sensitivity, sensibility, and ROC-AUC. The algorithm also provides, for each prediction, an estimation of the confidence of the prediction itself, thereby enabling disease evolution studies (as the patient recovers from the infection, the confidence of the prediction made by the algorithm of the recording to belong to a positive subject declines).
**Results:** 105 patients were enrolled in the reference time period. Overall, 170 recording sessions were performed, producing a total of 510 samples for algorithm fine tuning and testing. Exact algorithm accuracy will be tested by the collaborators in Cambridge as soon as they receive the first batch of recordings in the form of data transferred after the approval of the Data Transfer Agreement, currently pending at the Ethic Committee of San Raffaele Hospital. Preliminary analysis suggests that being English the native language of the subjects on which the algorithm was originally trained, the performance on samples from Italian subjects declines considerably. However, such AI platforms are designed so that fine tuning can be performed on specific data trains, if properly sized, to increase overall performance.
**Conclusions:** Great advances in shortening bench-to-bedside time have been one of the cornerstones of the battle against COVID-19, as vaccine availability and antiviral targeted therapy, brought to market at unprecedented speed, changed the course and history of such devastating contagious disease. Technological revolutions, as the case of mRNA strands as main vaccine constituents, have laid the grounds for leaps in both pharmacologic development and efficacy. Another ally on our side, not yet fully exploited, is the adjunct value of AI-based tools in the trained hands of clinicians.
Distinguishing with accuracy a positive case from a negative one simply having a subject vocally interact with a digital app on a mobile phone could mean extraordinary potential in terms of diagnostic efficiency, epidemiological analysis, outburst preparedness, healthcare burden and costs reduction. To our knowledge, ours is the first application in the clinical context of an AI algorithm for sound-driven disease diagnosis.

## 419. A REAL-WORLD SNAPSHOT OF END-OF-LIFE MANAGEMENT IN INTERNAL MEDICINE WARDS IN PIEDMONT-LIGURIA-AOSTA VALLEY: PILOT RESULTS FROM THE EOLO SURVEY

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**Background:** Patient care at the end of life is a daily issue for the internist. It

is clinically relevant and has social, ethical, and psychological implications. SARS-COV 2 pandemic highlighted that there is a lack of and a demand for training on end-of-life (EOL) management by medical specialists and residents in Internal Medicine. There is also a lack of evidence and guidelines on this issue, which is likely to result in heterogeneity in end-of-life management between Internal Medicine departments and between different internists.
Under the auspices of the Italian Society of Internal Medicine (SIMI), a team of internists from hospitals in Liguria and Piedmont was set up, with the participation of fellow psychologists, to study the issue and create proposals to improve the quality of patient care at the end of life.
The meetings and reflections that followed led to the creation of a survey on EOL opinions (EOLO) concerning end-of-life management in Internal Medicine wards.
**Objectives:** We want to conduct a pilot survey exploring clinical practice and expertise in palliative medicine and capturing unmet needs for implementing training and organizational gap.
In the interests of research and improving knowledge, our aim was to generate and administer a questionnaire describing EOL in internal medicine wards and being a source of reflection and enrichment for those who complete it.
We believe that the results of our survey and their dissemination could be the starting point to develop a targeted undergraduate and postgraduate training course on one of the most complex topics of internal medicine.
**Methods:** We have created an easy-to-use questionnaire consisting of 25 closed-ended questions, which assesses the following domains:
- epidemiological domain: what is the perceived size of the problem of EOL;
- pharmacological domain: which drugs are preferred in the choice of analgesic therapy in clinical practice;
- psychological domain: personal satisfaction of medical staff in proper EOL management, and how doctors handle communication with the patients;
- practical domain: the extent to which standardized quoad vitam prognosis assessment systems are used;
- training domain: what undergraduate and postgraduate education there is on EOL care, and how it can be improved.

The questionnaire will be presented for the first time at the SIMI congress of Piedmont-Liguria-Aosta Valley and subsequently to all internal medicine departments of the interregional section.
**Results:** Results will be presented at the national congress of the Italian Society of Internal Medicine in October 2022 in Rome.
**Perspectives:** If the epidemiological relevance of the problem emerges, as we expect, dedicated multidomain training courses could be designed. The questionnaire could also be extended to other professionals, such as nurses, who highly involved in palliative care management. It would be relevant to involve general practitioners, who are likely to manage many EOL situations at home, to understand what proportion of patients are treated at home and what makes out-of-hospital palliative care management critical. Finally, the questionnaire could be extended to the whole country to offer a more comprehensive landscape of EOL in internal medicine wards.

## 420. A TRICKY CASE OF JAUNDICE AND ABDOMINAL PAIN IN EMERGENCY DEPARTMENT

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A 36-year-old female presented to the Emergency Department complaining of fatigue, abdominal pain, headache and dyspnea, which were worsening since several weeks. The abdominal pain was described as diffuse, continuous, worsened after meals, with no specific irradiation and not related to recumbency. She also referred chronic constipation, as well as some episodes of vomiting. She described her headache as post-prandial, bifrontal and gravative, not clearly related to vomiting. She denied any recent modification in everyday habits, as well as use of any lassative medication.
In her previous medical history there were autoimmune thyroiditis, isolated anti-cardiolipine antibodies positivity and factor V Leiden heterozygous positivity. About one year earlier, the patient was diagnosed with nervous anorexia causing malnutrition, in regular follow-up. She was not taking any medications and reported no allergies.
The patient told us that she already underwent an abdominal ultrasonography about one month earlier to investigate for such abdominal discomfort, which reported a minimal peri-hepatic and peri-splenic ascites (too thin to allow paracentesis). The other findings were normal: in particular, the examination ruled out any pancreatic nodule, gallbladder stones, and dilation of biliary tract. She also had blood exam done, showing a mild leukopenia (as already known), elevation of bilirubin (mostly indirect), normal thyroid function, marked vitamin D deficiency and a PTH elevation.
Physical examination revealed a marked sarcopenia, cutaneous jaundice and dehydrated skin.
Cardiac and pulmonary examination were negative. The abdomen was distended, with no ascites but markedly meteoric. Hyperperistalsis was appreciable, but no signs of acute peritoneal irritation were found.
Although the patient complained with persistent headache, the neurologic examination resulted normal; however, due to the strength of symptom and her history of pro-thrombotic state, we performed a brain CT-scan, which resulted negative.
The patient also underwent chest X-ray, with normal findings, as well as abdominal first-level ultrasonography, that we performed in the emergency department as point-of-care ultrasound. We could confirm the absence of focal lesions involving liver and pancreas; the biliary tract appeared not dilated and the gallbladder was normal. We did not find, at that moment, any ascites. Both small bowel and colon appeared markedly meteoric, with some tracts of dilated intestinal loops but no signs of occlusion.
Blood examination was also performed, with no relevant differences and confirmation of slight indirect bilirubin elevation. Emogasanalysis was also normal.
Despite all the negative results of the multiple analysis, the broad spectrum of symptoms was tricky, although no relevant signs of potential severe condition emerged.
Suddenly, by reviewing all the clinical history and a further physical examination, we noticed that her jaundice did not involve the sclera, it was hyper-represented on palms of the hands and tended to be more as a "yellowish" tone. So, we asked the patient further for her specific dietary habits, and we found out that her diet was mostly based on carrots and pumpkins, which she regularly consumed on a daily basis.
This information, together with the peculiarity of jaundice features, led us to argue that this condition was probably related to beta-carotene excess (carotenosis), although we could not confirm the diagnosis by carotene blood measurement. So, our patient was discharged with indication to modifying her diet and continuing with strict nutritional follow-up, and, to our knowledge, the condition has gradually improved.
In literature is reported that this condition, although benign, is related to chronic abdominal discomfort, constipation and fatigue; it may also explain headache as well as vitamin D deficiency, because of the impairment in the absorption of lipophilic vitamins due to beta-carotene accumulation.
This case, in our opinion, is worth to be known as it could be easily misdiagnosed as other-cause jaundice, especially in an emergency setting, leading to perform repeated unnecessary instrumental investigations.
Another message that is fundamental to keep in mind, no matter the clinical setting, is the importance of being able to carry on a proper interview, as it could really play the difference in the diagnostic process in some cases, by guiding the patient through the right questions.

## 421. A CASE OF CONCOMITANT ONSET OF DERMATOMYOSITIS AND C3-RELATED GLOMERULOPATHY IN A YOUNG MAN: THE OFF-LABEL ROLE OF RITUXIMAB

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Dermatomyositis is a connective tissue disease of not fully known etiology, in which exogenous factors are able to trigger a lymphocyte-mediated (auto)immune response in genetically predisposed subjects. This mechanism causes damage to the skin and the skeletal muscle. In the reported case, this pathological condition occurred concomitantly with C3-related glomerulonephritis, without evidence of serum hypocomplementemia. This glomerulonephritis has been defined as an entity that includes a group of kidney diseases caused by alteration of the complement activation control with a deposit of C3 in the glomeruli, which cause inflammation of varying degrees.
The patient, a 21-years-old boy, who had been diagnosed with type 1 diabetes mellitus for about 7 years, being treated with continuous subcutaneous insulin infusion (C.S.I.I.), comes to our observation following the onset of joint pain in wrists and ankles, which worsened with movement,

myalgia in the quadriceps, associated with worsening asthenia, low back pain, erythematous rash in the upper limbs and edema. The onset of dysuria with "Coca-cola" colored urine, serotine fever, with peaks up to 38.5 °C and diarrhea progressively occurred. At an initial external medical evaluation, the patient was advised to perform blood chemistry tests, which showed an increase in transaminases and lactate dehydrogenase (LDH) and an electroneurography, which was negative. At admission to our Internal Medicine Unit, the patient complained of difficulty in autonomously reaching an upright position, asthenia at minimal physical exertion and pitting edema that could be at the lower limbs. During the hospitalization, he was subjected to laboratory evaluation, which showed an increase in the indexes of myonecrosis. Alongside these, a reduction in immunoglobulin G (IgG) due to urinary loss was recorded, together with a proteinuria up to 300 mg/dL. Due to the rise in myocardiospecific enzymes also, a cardiological evaluation was necessary, aimed to exclude the cardiac involvement of this damage: electrocardiogram and echocardiogram were found to be normal. The neurological evaluation, performed in the suspicion of a neuromuscular disease, was oriented towards an inflammatory myopathy on a dysimmune basis. For this reason, in-depth studies with electromyographic, electroneurographic examination (these two studies showed evidence of primitive muscle suffering, with signs of denervation), magnetic resonance imaging (MRI) of the thigh muscles (these findings were not specific for any diagnosis but allowed to support the hypothesis of a dermatomyositis) and capillaroscopy (non-diagnostic alterations of a specific pattern) were performed. Meanwhile, the patient started steroid therapy with intravenous Methylprednisolone 80 mg daily. Upon completion of the diagnostic process, due to dysuria, "Coca-cola"-colored urine and proteinuria, a nephrological evaluation was necessary, which, following the execution of renal ultrasound, showed normal morphovolumetry of the kidneys, indicated a renal biopsy, performed without periprocedural complications. The picture, observed at immunofluorescence, optical microscopy and electron microscopy, proved compatible with a glomerulonephritis with dominant deposits of C3, with minimal glomerular lesions. In the light of the instrumental tests carried out, a neurological re-evaluation recommended a modification of the steroid therapy, replacing Methylprednisolone 80 mg iv with oral administration of Prednisone 100 mg daily. Furthermore, on joint neurological and nephrological indications, the indication was given to off-label administration of i.v. Rituximab 1 g. A first infusion was carried out during hospitalization in our Internal Medicine Unit, under close medical monitoring; the second infusion, on the other hand, was scheduled 15 days after the first one.
During the hospitalization, the steroid therapy, undertaken in the first instance, had allowed an improvement in the clinical picture, with a reduction in edema and effusion, also thanks to Amiloride/hydrochlorothiazide, and in myalgias, despite the improvement of the laboratory indices did not occur so quickly. Over the weeks, the patient was able to recover part of his walking ability, with residual difficulty in assuming an upright position from that sitting, and his asthenia was reduced to minimal physical effort. The indices of myonecrosis remained altered, even if in reduction compared to the admission to the ward, with fluctuations that did not allow to reach the resolution of the pathological picture. By virtue of this deadlock, an innovative approach was opted for, which allowed the desired results to be achieved. Although rituximab has been used several times in the case of C3-related glomerulonephritis, with evidence of good therapeutic results, this monoclonal antibody appears to be off-label in the treatment of dermatomyositis. In our case, there was evidence of not only clinical, but also laboratory response, to biological treatment.

## NEFROLOGIA

### 422. URINARY URODILATIN LEVELS IN PATIENTS WITH RENAL SALT WASTING SYNDROME AS A POSSIBLE NEW DIAGNOSTIC MARKER. A CASE-CONTROL STUDY

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Renal Salt Wasting Syndrome (RSW) is a clinical syndrome with laboratory characteristics completely overlapping with the syndrome of inappropriate ADH secretion (SIADH). The fundamental difference between the two syndromes lies in the extracellular volume (ECV), reduced in RSW and normal or slightly increased in SIADH. The difficulties in the differential diagnosis of this syndrome and in understanding the precise pathogenetic mechanism have contributed some authors to question the very existence of RSW. Considering the characteristics of RSW, natriuretic peptides were investigated to explain its onset such as ANP and BNP, with unsatisfactory results. However, no studies have yet investigated the possible role of urodilatin, a peptide belonging to the natriuretic peptide family, which seems to have a crucial role in regulating blood sodium and urinary sodium even more than ANP. We performed a retrospective observational study, the patients were divided into 3 groups: a group of patients without hyponatremia and two groups of patients with hyponatremia, one consisting of patients with RSW and the other consisting of patients with hyponatremia from other causes. Patients with RSW display significantly higher mean urodilatin levels than both patients with (median 5.46 vs 0.57 ng/mL, p=0.006) or without hyponatremia (median 5.46 vs 0.27 ng/mL, p<0.001) (Figure 1). Statistically significant higher mean levels of urodilatin were also observed when patients with RSW were compared with the other two groups of patients considered together (5.46 vs 0.32 ng/mL, MW test p<0.001). Conversely, proANP levels were not statistically different among the 3 subgroups (overall KS test p=0.266) or between patients with RSW and patients with/without hyponatremia (4.9 vs 9.7 nM, MW test p=0.122). Diagnostics performances of mean urodilatin levels for RSW diagnosis were evaluated by ROC curve (Figure 2). Area under the curve (AUC) was 0.94 (95%CI 0.86-1.00). Best cut-off for mean urodilatin levels, according to Youden's index, was 2.87 ng/mL. At this cut-off sensitivity, specificity, positive predictive value and negative predictive value were, respectively, 1.00, 0.88, 0.60 and 1.00. In conclusion, this pilot study has shown interesting results regarding the dosage of urinary urodilatin in patients with RSW, with potentially clarifying implications of practical utility both regarding the pathogenesis of this syndrome and regarding its diagnostic criteria and therefore on the clinical management of patients. We hope that further future studies can continue to shed light on this interesting topic.

### 423. A CASE OF ACUTE KIDNEY INJURY AFTER INTRAVENOUS IMMUNOGLOBULIN ADMINISTRATION IN A KIDNEY TRANSPLANT PATIENT

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Intravenous immunoglobulins (IVIG) are being used increasingly in a range of immune-mediated and autoimmune diseases and they are usually considered a quite safe and effective treatment. Although this therapy is well tolerated, adverse events may occur. Most of them are mild and can be treated by infusion withdrawal or by reducing the infusion rate.
Renal impairment after IVIG administration is a rare adverse effect. In particular, renal failure occurs mostly when using sucrose-containing products with a higher osmotic effect. Indeed, the incidence of this event has progressively declined when reducing the use of sucrose-containing products. Isolated cases of renal failure due to hemolytic reactions are also reported.
We describe a case of Acute Kidney Injury following IVIG infusion in a kidney transplanted patient.
Our patient was a 54 year old man affected by Adult Polycystic Kidney Disease with chronic kidney disease and the need of dialytic treatment. After two years of hemodialysis, at the age of 52, the patient received a standard kidney transplant. Six months after the kidney transplant a BK polyomavirus infection was documented with a high urinary viral load (> 2500000 copies/ml) and an increasing plasma viral load (maximum of 6590 copies/ml). Because of a progressive deterioration in renal function, we decided to perform a graft biopsy. The histological exam documented a BKV nephropathy with nuclear immunohistochemical SV40 positivity in 1% of tubular cells with no tubular atrophy.
Because of the histological evidence of BKV nephropathy with an already minimized immunosuppressive therapy we decided to treat the patient with IVIG with total dose of 2 g/Kg for 4 days, according to our center protocol for BKV nephropathy treatment.
After the first infusion we documented an oliguric Acute Kidney Injury (AKI) with creatinine rising up to 9 mg/dl in the following days. At urinalysis glycosuria (1000 mg/dl) and proteinuria (30 mg/dl) appeared.
We started iv. furosemide with increasing dosage up to 1 g/24 hrs and IVIG treatment was suspended. Moreover. because of a further deterioration of

renal function the patient needed a hemodialytic session.
Two days after the last IVIG infusion, diuresis started progressively to recover together with creatinine levels which started to decrease. Renal function recovered completely in 20 days.
According to reported cases of renal toxicity after IVIG infusion we hypothesized a tubular damage due to osmotic injury of excipients.

## 424. IMPACT OF CARDIOVASCULAR RISK FACTORS ON OUTCOME OF KIDNEY TRANSPLANT RECIPIENTS

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Kidney transplantation is the treatment of first choice in patients with end-stage renale disease (ESRD) and it is associated with a better outcome than dialysis tratment. In end-stage disease, the poor residual renal function is no longer sufficient to keep under control the clinical manifestations of the disease, therefore, the need to start a replacement renal treatment is evident. The mortality and morbidity of patients on treatments are significantly increased compared to the general population, but are significantly reduced after kidney transplantation. However, the risk of mortality and morbidity in transplanted patients remains higher than in the general population due to an increased incidence of cardiovascular (CV) events. Some risks' factors of mortality and morbidity are shared with the general population -"traditional"- and others are peculiar to the kidney transplant population -"non-traditional"- and are directly related to graft function.
We performed a retrospective observational study to identify the impact of traditional and non-traditional CV risks factors on the outcome of the transplanted patient, in terms of development of CV events, loss of graft function (LOF) and mortality. A total of 284 patients undergoing kidney transplantation at the Transplant Medicine Unit of San Raffaele Hospital in the period between 2012 and 2019 were included in the study. During the observation period 24 patients (8.5%) developed at least one CV event, which was represented by an acute myocardial infarction in 13 (54.2%) of these cases. Loss of graft function affected 42 patients (14.8%). During the follow-up period 22 (7.8%) patients died, 9 (40.9%) of them following a CV event, confirming CV events as the major cause of mortality in transplanted patients.
Among traditional CV risks' factors, the presence before transplant of hypertension (PAH), diabetes mellitus (DM), previous CV events and active smoking showed, in univariate Cox regression, a predictive role in the occurrence of new CV events. The role of tobacco habit was also being confirmed by multivariate analysis. A pre-transplantation positive history of CV events was also discovered to be a predictor of mortality in univariate Cox regression.
The presence at transplant of an FE < 55% was associated with an increased risk of developing CV, LOF and mortality in the observation period. At the time of transplantation, in univariate Cox regression, also age >60 years was significantly associated with mortality.
In the post-transplant period, the presence of PAH, dyslipidaemia, DM, active smoking and suboptimal organ function (GFR CKD-EPI < 45ml/min/1.73mq) were significantly associated with CV events. On multivariate analysis, only the presence of hypertension confirmed the predictive role of increased cardiovascular risk.
Active smoking and post-transplantation dyslipidaemia, DM and suboptimal organ function (GFR CKD-EPI < 45ml/min/1.73mq) were also linked to LOF and mortality in the follow-up period.
Active smoking and suboptimal organ function (GFR CKD-EPI < 45ml/min/1.73mq) exitus predictive roles were confirmed on multivariate analysis.
In conclusion, the pre-transplant identification of patients potentially exposed to an adverse CV outcome and the subsequent control of the risk factors associated with it are essential to ensure better outcome of the patient and the transplanted organ. In addition, the need to ensure adequate organ function in the long term through correct donor selection and careful management of immunosuppressive therapy in the post-transplant period is essential.

## 425. SARCOPENIA AND CHRONIC KIDNEY DISEASE IN THE ELDERLY: THE FRAS-NET STUDY

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**Background:** The aging of the population parallels a reduction in kidney and muscle function. Sarcopenia is a progressive loss of strength, muscle mass and function, and is associated with an increased risk of physical disability, impaired quality of life and increased overall mortality. Chronic kidney disease (CKD) is characterized by the slow and progressive reduction in function and structure of the kidneys, which usually becomes irreversible. Risk factors for CKD include older age, cardiovascular diseases, and obesity. CKD in the elderly accelerates muscle wasting resulting in sarcopenia.
**Objective:** The main goal of the study was to assess the relationship between CKD and sarcopenia in aged people. Besides, body composition in relation to sarcopenia and CKD was also evaluated.
**Materials and Methods:** The present study ("FRAS-NET") is a transversal observational clinical study recruiting non-hospitalized elderly patients (over 65 years). Inclusion criteria were: Mini-Mental-State-Examination score grater or equal to 18, capacity of walking more than 500 meters in self-government, stable health condition with life expectancy of more than six months. Sarcopenia was assessed through the Short Physical Performance Battery test (SPPB) that evaluates strength, balance and walking, and through bio-impedance balance (BIA) to measure global fat, skeletal muscle and visceral fat mass. Sarcopenia was defined as a reduction in muscle mass of ≥25% of total body mass. Patients with sarcopenia (after adjustment for sex and age) and at least one altered parameter between the SPPB test (score less than or equal to 8) and a reduced walking speed (less than 1 m/s) were defined as being sarcopenic with loss of function. CKD was defined as a glomerular filtration rate (eGFR) of less than 60 ml/min/1.73 m2, an albumin-creatinine ration equal or greater than 30 mg/g, and evidence of renal injury.
**Results:** A total of 1250 subjects were enrolled (39,76% males and 67% aged <75 years). CKD was present in 21,3% of patients while 44% had sarcopenia. Of these, 68% had preserved muscle function and 32% loss of function. Increasing age was associated with a decrease in kidney function. No significant difference was detected in the prevalence of sarcopenia between males and females, while the percentage of sarcopenic subjects increased with age. We found a significant increase in the prevalence of CKD in subjects with sarcopenia with loss of function (40%) compared with those with sarcopenia with no loss of function (18%, p <0.001). The rate of sarcopenia progressively increased in subjects with advanced stages of CKD (p <0.001). Results of physical tests showed a reduction in performance in all fields (strength, balance and walking) with worsening stages of CKD (p<0.001). The rate of sarcopenia with loss of function progressively increased from 8,6% in subjects with stage 1 CKD to 52,4% in those with stage 4-5 CKD (p<0.001). In addition, in our cohort, 70% of patients were overweight or obese. We found a tendency of progressive BMI increase with worsening CKD. Interestingly, 30% of overweight or obese subjects were sarcopenic. The percentage of visceral fat significantly increased in patients with sarcopenia (14%) compared with those without sarcopenia (9%, p<0.001). Similarly, subjects with CKD had higher visceral fat mass compared with those with no renal disease (p<0.001).
**Conclusions:** Our results indicate that sarcopenia, body composition and CKD are inter-connected. Specifically, patients with CKD were more prone to develop visceral obesity and sarcopenia. It is known that obesity is a major contributing factor to CKD, and several studies pointed to a beneficial effect of weight loss on albuminuria and kidney function. Although the exact mechanisms underlying the association between body composition and CKD are still not completely clear, the loss of muscle mass in patients with CKD may be attributed to an unbalance between protein synthesis, muscle catabolism and myogenesis. Sarcopenia exposes subjects with CKD to a deterioration of both physical and mental functions as well as to an increase in cardiovascular risk. The identification of such subjects could allow setting treatment plans to improve patient health and prevent complications.

## 426. RAPIDLY PROGRESSIVE ACUTE RENAL FAILURE FOLLOWING THE OXFORD-ASTRA ZENECA COVID19 VACCINE: IS IT A COINCIDENCE OR AN ASSOCIATION?

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**Case Presentation:** In September 2021, a 68-year-old woman was admitted to our emergency department (ED) referring fatigue and progressive dyspnea from about one week. She also had bilateral chlamydial eye infection, treated with oral minocycline for about 2 weeks. In anamnesis she reported arterial hypertension, diabetes mellitus II and post-surgical hypothyroidism.
At ED, her blood pressure was 170/70 mmHg, peripheral oxygen saturation was 97% in ambient air and heart rate was 73 bpm; thoracic auscultation documented the presence of cracklings in the basal site bilaterally, accompanied by evident edema of the lower extremities. Blood chemistry tests showed increased creatinine value (1.9 mg/dl), suggesting acute kidney injury (AKI). A chest X-ray evidenced bilateral hilar congestion. Further, transthoracic echocardiography showed normal left ventricle endocavitary size and increased parietal thicknesses, good global systolic performance, normal values of regional left ventricular endocardial motion and ejection fraction of 60%. The patient was then admitted to our Internal Medicine ward for further diagnostic evaluations.
After an accurate anamnesis, we discovered that her clinical history was dated back to June 2021, when she complained progressive asthenia, eye infection and finally dyspnea about 3 weeks after receiving the second dose of inactivated SARS CoV2 vaccine (Oxford–Astra Zeneca, AZD1222).In the next few days after admission, her blood pressure was constantly high and serum creatinine progressively increased up to 3.2 mg/dl. The urine test showed hematuria and non-nephrotic range proteinuria (1740 mg/24h). Moreover, despite intravenous diuretic therapy, sloping edema and periorbital edemas persisted, outlining a nephritic syndrome. The patient was then subjected to Color Doppler ultrasound of the kidneys that showed increased kidney size, normal cortico-medullary differentiation and absence of renal artery stenosis.
Based on these findings we hypothesized a rapidly progressive glomerulonephritis (GN); for this reason, we tested autoantibody panel and decided to perform a renal biopsy. Bioptic report described "twenty-five glomeruli, seven out them presenting global sclerosis, six out of them presenting fibro/epithelial crescents; focal necrosis of the convolute capillary of the glomerulus and modest mesangial expansion due to increase in the cellular component and fundamental substance, moderate interstitial fibrosis and diffuse inflammatory infiltrate predominantly lymphoplasmacellular, tubular atrophy", finally formulating diagnosis of pauci-immune GN. Then, we started immunosuppressive induction therapy with intravenous methylprednisolone 500 mg/day for 3 days followed by oral prednisone 0.5 mg/kg/die. Moreover, we improved intravenous diuretic and oral antihypertensive therapy, observing clinic benefit. Serum pANCA antibodies were found, thus confirming our first diagnostic hypothesis. After discharge, the patient underwent four weekly rituximab infusions (375 mg/m2). Last laboratory findings showed improvement in renal function (serum creatinine 1.4 mg/dl) and reduction in proteinuria (800 mg/24h), blood pressure values had progressively became normal.
**Conclusion:** Pauci-immune GN is one of the most common causes of rapidly progressing GN (RPGN). It is characterized by the pathognomonic clinical signs of RPGN (AKI, hematuria, hypertension), which result in renal failure within a few days or weeks. Typical clinical signs of systemic vasculitis (arthralgia, fever, seizures, mononeuritis and lung involvement) may be associated. From the histological point of view, pauci-immune GN is characterized by focal necrotizing and crescenting GN, with mild or absent glomerular staining for immunoglobulin and complement under the fluorescence microscope. The etiology remains unknown, it seems to be associated with genetic predisposition and exposure to environmental triggers such as toxics, drugs or infections. Our patient had no risk factor nor she was exposed to particular triggers which could have justified such clinical manifestations, except for the AZD1222 vaccination around 3 weeks before the onset of symptoms. Only one similar clinical report had been recently described in literature. Thus, although minimal lesion glomerulopathy is the most reported in association with vaccinations, we evidenced a temporal association between pauci-immune GN and AZD1222 vaccine. However, further investigations are needed to estabilish a pathophysiological link between vasculitis and inactivated SARS CoV2 vaccine.

## 427. CHA2DS2-VASC SCORE AS PREDICTOR OF MORTALITY AND LENGTH OF STAY IN CKD PATIENTS HOSPITALIZED IN INTERNAL MEDICINE DEPARTMENT

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**Rationale:** The CHA2DS2-VASc score was mainly used to stratify risk of stroke in patients with atrial fibrillation. However, high CHA2DS2-VASc score was also associated with adverse clinical outcomes in different settings other than atrial fibrillation, such as hemodialysis. We aimed at evaluating association between CHA2DS2-VASc score and clinical outcomes (in-hospital mortality and length of stay) in patients hospitalized in internal medicine department according to the presence/absence of chronic kidney disease (CKD).
**Methods:** We conducted a retrospective analysis of 983 patients admitted consecutively between December 2009 and December 2012 in internal medicine department. Clinical data was extracted from electronic clinical records and CHA2DS2-VASc score were calculated. The primary outcome was a composite of all cause mortality and length of stay > 10 days.
**Results:** We collected data on 983 inpatients with a mean age of 66.9 years ± 16.4 (males 42.4 %). CKD was present in 215/983 (21.9%) patients (stage 3, 16.1%; stage 4, 3.7%; stage 5, 2.1%). The most prevalent comorbidity was hypertension (50.1%), followed by type II mellitus diabetes (22.1%). History of cancer was present in 177 (18.0%) participants. Patients with CKD presented with an increased CHA2DS2-VASc score with respect to non CKD patients (3.9 ± 1.8 vs 2.3 ± 1.6, respectively)($p<0.001$). No significant differences were observed in CKD patients according to the stage of the disease in CHA2DS2-VASc score. The area under the curve (AUC) of receiver operating characteristic (ROC) curve to evaluate association of CHA2DS2-VASc and primary outcome was 0.631. Adding the presence/absence of infectious diseases during hospitalization and positive cancer history to the model determined an increase in AUC (0.667 and 0.663, respectively). Patients with CHA2DS2-VASc score ranging from 2 to 4 and from 5 to 9 presented an increased length of stay with respect to patients with CHA2DS2-VASc score 0-1. Also, patients with higher CHA2DS2-VASc died earlier during the hospitalization with respect to those with CHA2DS2-VASc score 0-1. In a Multivariate Cox regression analysis, adding the presence/absence of infectious diseases during hospitalization and positive cancer history to CHA2DS2-VASc score showed that CHA2DS2-VASc score was independently associated with the occurrence of the primary outcome (OR 1.349; 95% CI, 1.248 to 1.462).
**Conclusions:** Incrementally higher CHA2DS2-VASc score is associated with increased in-hospital mortality and length of stay in patients hospitalized in internal medicine regardless of presence/absence of CKD.

## 428. STOP THE FLOW

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**Case Report:** A 63-years-old man with a history of hypertension and dyslipidemia presented in the ER with abdominal pain, oliguria, and vomit. In 2011 he underwent left nephrectomy due to a Clear Cell Carcinoma; in 2019 a tumoral lesion in the right ectopic kidney was found and it was subjected to thermoablation; multiple pancreatic metastasis were identified in follow up.
The patient was febrile (38°C) and appeared suffering, with tense and painful abdomen and fever. Blood tests showed neutrophilic leukocytosis, high levels of C-reactive protein (CRP 365,9 mg/L; normal value < 5 mg/L) and acute kidney failure (creatinine 7,71 mg/dL). Electrolytes and hepatic enzymes were within the normal range. The abdomen X-Ray showed coprostasis, no air-fluid levels.
The patient was submitted to abdominal CT scan, with no contrast-enhancement, which revealed an ectopic, polylobed and extra-rotated right kidney located in the right pelvis and pyelocaliceal ectasia; fluid collection was extended from bladder to the right peri-renal space.
Due to anuria and acute kidney failure, he underwent hemodialysis twice. Urinary catheter was placed and the following day a right ureteral stent was positioned. Fourty-eight hours later, the CT scan still evidenced right renal hydronephrosis. An empiric antibiotic therapy with Tazobactam/Piperacillin was started, after urine and blood samples collection. Few hours later edema and erythema appeared on limbs and face; Tazobactam/Piperacillin was suspended and replaced by Trimethoprim/Sulfamethoxazole.
Ten days later, abdomen CT scan was repeated, and it showed mild pyelic ectasia and a significant reduction of liquid collection in the right para-colic

and perirenal space. The following urological evaluation suggested removal of urinary catheter and scheduled ureteral stent removal one month later. Urine and blood cultures were negative. Spontaneous diuresis was restored. Antibiotic therapy was stopped after ten day; complete clinical resolution, great reduction of CRP reduction (6,8 mg/l) and restoration of normal creatinine levels (1,20 mg/dl). The patient was discharged alive and in good health status.
**Conclusions:** Considering abdominal fluid collection, and acute renal failure, clinical presentation, and markedly elevated CRP, urinoma and renal cyst rupture were the most likely causes. They are both rare and usually self-limiting events. The diagnosis between renal cyst rupture and urinoma is clinic.
A urinoma is an encapsulated collection of extravasated urine in the retroperitoneum or in the perirenal space, as the result of a breach of the integrity of the pelvis, calices or the ureter. As urine extravasates, it can cause lipolysis of the surrounding fat with resultant encapsulation of urine, forming a urinoma. Urinomas are more often due to urinary obstruction secondary to calculus, abdominal trauma or surgery. They may be also caused by retroperitoneal fibrosis or cancer of the renal pelvis, ureter or bladder. Urine leakage is usually directly demonstrated on contrast-enhance studies on the excretory phase (CT or MRI). Small urinomas are usually treated conservatively. Percutaneous drainage is recommended in case of persistent or symptomatic urinomas.Our patient had a renal cancer history with an ectopic kidney and no evidence of renal cysts. No previous instrumental examinations were available. Moreover, no contrast-enhanced study was possible due to severe renal failure. After empiric antibiotic therapy and ureteral stent placing, our patient had a complete clinical and chemical recovery and was discharged with a diagnosis of obstructive renal failure due to urinoma.

## ONCOLOGIA

### 429. RISK OF BLEEDING AND THROMBOTIC EVENTS IN PATIENTS WITH ATRIAL FIBRILLATION AND CANCER: A SYSTEMATIC REVIEW AND META-ANALYSIS

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**Background:** Atrial fibrillation (AF) and cancer are frequently coexisting in elderly patients. Pooled metanalytic data on the impact of cancer on outcomes in AF patients are lacking. To investigate the impact of cancer in patients with AF, particularly in relation to bleeding and ischemic events.
**Methods:** We performed a systematic review and meta-regression analysis of clinical studies retrieved from Medline (PubMed) and Cochrane (CENTRAL) databases according to PRISMA guidelines. Safety endpoints included any, major, gastrointestinal (GI) bleeding and intracranial haemorrhage (ICH). Efficacy endpoints included myocardial infarction (MI), ischemic stroke/systemic embolism (IS/SE), cardiovascular (CV) and all-cause death.
**Results:** 15 studies were included in the metanalysis: 4 prospective, 3 randomized clinical trials and 8 retrospective studies with 2,868,010 AF patients, of whom 479,571 (16.7%) had cancer. The pooled HR for cancer was 1.43 (95% confidence interval [95%CI] 1.42-1.44) for any bleeding, 1.27 (95%CI 1.26-1.29) for major bleeding, 1.17 (95%CI 1.14-1.19) for GI bleeding, and 1.07 (95%CI 1.04-1.11) for ICH. The risk of major bleeding increased with the proportion of breast cancer. Cancer increased the risk of all-cause death (HR 2.00, 95%CI 1.99-2.02) whereas no association with MI (HR 0.97, 95%CI 0.94-1.01) and CV death (HR 1.01, 95%CI 0.99-1.03) was found. Patients with AF and cancer were less likely to suffer from IS/SE (HR 0.91, 95%CI 0.89-0.94).
**Conclusion:** The presence of cancer modifies the clinical history of AF patients, mainly increasing the risk of bleeding. Further analyses according to the type and stage of cancer is necessary to better stratify bleeding risk in these patients.

### 430. UNEXPECTED DIAGNOSIS: A CASE OF ADRENOCORTICAL CARCINOMA WITH VERTEBRAL BONE METASTASIS, A VERY UNCOMMON SITE

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**Background:** Adrenocortical carcinoma (ACC) is a rare aggressive tumor with a poor prognosis. In a quarter of cases it is associated with metastases at the time of diagnosis. Typical sites of metastasis are lung, liver, and lymph nodes and only rarely may ACC present with bone metastasis without hepatic and lung metastases.
**Case Report:** A 62-year-old Caucasian man with a history of smoking and metabolic syndrome (body mass index 27 Kg/m2, arterial hypertension and type 2 diabetes) was admitted to our hospital on the grounds of neck pain lasting for about three weeks and headache. His blood tests showed hypokalemia (K 2.7 mEq L) and spine CT scans a suspected cancer-associated osteolysis of C3 vertebral body. An Aspen-type cervical brace was placed and analgesic therapy started. All blood cancer markers were within the normal range. High-resolution chest computed tomography (CT) and brain CT scans were negative for secondary lesions. Abdominal ultrasonography (US) identified a large mass in the right adrenal gland, 13cm x 8 cm in size, featuring a hyperechoic periphery and hypoechoic center, where multiple areas of necrosis were appreciated. Contrast-enhanced US showed early vascularization of the lesion with a rapid wash-out in the periphery and a slower wash-out in the center, compatible with adrenal malignancy. Needle biopsy revealed histological and immunohistochemical features consistent with primary adrenal cortical carcinoma. A PET scan confirmed the primary tumor in the right adrenal gland and metastasis to the C3 vertebra. The patient was therefore referred to the oncology team and began palliative radiotherapy pending the evaluation for the eligibility to chemotherapy regimens with mitotane.
**Discussion:** Adrenal carcinoma is a rare cancer that has a peak incidence between the fourth and fifth decade of life. Women are generally affected more often than men. Smoking has been suggested as a risk factor to develop this cancer. According to the European network for the study of the adrenal tumors staging system, an ACC with distant metastases is considered a stage IV1. Among the few cases of metastatic ACC published in the literature, the sites most frequently reported are the liver and the lung and, very rarely, the bone. Medical literature supports the notion that more than 80% of bone metastases in men are caused by prostate and lung cancers whereas other cancers are less frequently represented. Moreover, metastases are preferentially located in the thoracic spine (71%), in the lumbar region (61%) and only rarely do they affect the neck backbone2.
In conclusion, based on our literature review, the present case is a unique and atypical case of bone metastasis in a patient with adrenocortical carcinoma. This case highlights the importance of considering this uncommon cancer type in the differential diagnosis of those patients presenting with bone metastasis, after ruling out other common primary cancer types.
**References:** 1 Fassnacht, European Journal of Endocrinology (2018)2 Amelot, Surgical Oncology (2019)

### 431. KAPOSI SARCOMA: CASE REPORT WITH ATYPICAL SECONDARY INVOLVEMENT OF THE ILIOPSOAS MUSCLE

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**Background:** Kaposi Sarcoma (KS) is a vascular neoplasm etiologically associated with Human Herpes Virus 8 (HHV8). In the classic form, the disease is usually limited to the skin, but in the epidemic or AIDS-related form, visceral involvement may occur. In the latter form, optimal antiretroviral therapy (ART) is required to increase CD4+ lymphocytes, the value of which correlates with survival. In case of advanced disease, it may be necessary to add chemotherapy, such as pegylated liposomal doxorubicin.
**Case Report:** A 39-year old man was admitted to our Hospital for anemia, fever and right groin pain. He reported a minor trauma to his right lower limb following an accidental fall about 2 weeks before hospital admission.

The patient's history revealed a ten-years history of HIV infection, although the ART (Dolutegravir/ Lamivudine and Doravirine) was started just 2 years before. In 2020, a diagnosis of KS was made, involving skin, lungs and gastrointestinal system. Consequently, the patient was given 9 cycles of chemotherapy with pegylated liposomal doxorubicin with subsequent partial radiologic remission of KS, HHV8-DNA negativity and stable CD4 values (>500 mm3). At the time of hospital admission, laboratory tests showed anemia (Hb: 7.8 g/dL), increased inflammatory indexes (CRP 172.3 mg/L and PCT 0.51 ng/mL) and altered coagulation parameters, with an isolated increase in aPTT (64 sec). A CT angiography of the abdomen/lower limbs was performed, which documented the presence of a mass in the right iliopsoas muscle, suspected for hematoma or abscess, without evidence of active bleeding. Therefore, serial blood cultures resulted negative, and the PICC line was removed. Then empirical broad-spectrum antibiotic therapy was started. Meanwhile, the mixing test did not show any correction in the aPTT value after 2 hours. Therefore the diagnosis of acquired haemophilia was excluded, even because factor VIII levels were in the normal range and no serum clotting factors inhibitors were detected. Moreover, the Lupus Anticoagulant (LAC) Ratio Test resulted positive after the addition of Russell's viper serum. However, the clinical criteria (absence of current and past arterial and venous thrombosis), and the complete assay of the specific autoimmune panel ruled out an antiphospholipid antibody syndrome. At this point, in the suspicion of atypical location of KS, perhaps complicated by bleeding, he underwent (18)F-FDG PET/CT with evidence of FDG uptake with high SUV at the level of the documented mass in the iliopsoas muscle. To corroborate the diagnostic suspicion, CT-guided biopsy was performed. The histologic pattern confirmed the neoplastic nature of the lesion and showed the positivity for HHV8-DNA.
**Conclusions:** Muscle localization of KS is very rare and only few cases have been reported in literature, especially occurring in AIDS-related KS. Our case appears to be even more rare, because the clinical and laboratory parameters supported a diagnosis of muscle hematoma in the context of a coagulation disorder. Clinical, radiological and histological findings identified the neoplastic nature of the lesion.

## 432. AN UNCONVENTIONAL CASE OF FOOT SWELLING IN A RECENTLY OPERATED ONCOLOGICAL PATIENT

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A 49-year-old Filipino woman was admitted to the Internal Medicine Department for fever (38°C) without chills, abdominal pain, mucous diarrhoea and discomfort walking due to an atraumatic right foot arthralgia. The symptoms started few weeks before and worsened in the last days.
Three months before, she was diagnosed with serous ovarian carcinoma disseminated to the peritoneum (FIGO classification IIIC) and underwent bilateral oophorectomy and hysterectomy in the Philippines. After surgery, she came back to Italy in an acceptable general status, waiting for a first oncological evaluation to eventually start chemotherapy. In her past medical history, a year before, she also had presented latero-cervical lymphadenopathy with histological examination consistent with non-necrotizing granulomatous lymphadenitis. In that occasion, she had first been treated with empiric tuberculosis four-drug regimen treatment, since tuberculous lymphadenitis could not be excluded (positive QuantiFERON TB-Gold test in the context of a close contact with an affected family member but negative cultures and negative bacilloscopy). Eventually, she received corticosteroids under the suspicion of sarcoidosis.
On admission, she was not taking any medication and denied use of antibiotics or other drugs at home. Her general status was compromised as she was feverish, malnourished and dehydrated. Remaining vital signs were normal. Pathological findings at physical examination were abdominal tenderness and pain with positive Blumberg sign in the lower quadrants and swelling on the right foot, that was normally perfused but painful at compression. Blood tests showed leucocytosis with increased inflammatory markers (C reactive protein), while biochemical parameters were normal. Under the suspicion of infectious enterocolitis, she was started on 4/0.5 g i.v. piperacillin-tazobactam qid. Stool culture and parasites test, rectal swab, Clostridium difficile toxin stool test, blood and urine cultures, tubercular bacilloscopy in stools and blood samples (BK) and Sars-Cov2 molecular test were all negatives. Total-body CT scan confirmed the known peritoneal carcinomatosis and abdominal lymphadenopathies secondary to ovarian carcinoma dissemination and excluded infectious foci, other secondary neoplastic involvement and sub-acute abdominal complications. Diarrhoea improved with antibiotics but elevation of inflammatory markers persisted and the patient remained feverish (T >38°C). The antibiotic spectrum was therefore expanded by adding empiric i.v. vancomycin.Additional investigations were performed for the swollen right foot. X-rays ruled out fractures. MRI showed complete necrosis of the first cuneiform bone, surrounded by markedly vascularized solid tissue and peripheral soft tissue oedema. These findings were consistent with osteomyelitis and rose the suspicion of local tubercular dissemination. However, the perilesional mass surrounding necrosis had an expansive and irregular appearance, suggesting bone metastasis with superimposed inflammation. Bone metastases from ovarian cancer are rare (1-4% according to previous studies). However, the higher the pathological stage of ovarian cancer the higher the risk of bone metastasis. Pelvis and vertebral bone are the most common localizations, while no cases of extra-axial metastasis so far described to our knowledge. We therefore decided to perform a bone biopsy along with microbiological analyses. BK search through polymerase chain reaction and cultures on biopsy specimens was negative. Histological analysis was consistent with metastatic localization of serous ovarian carcinoma. The tumour stage was re-classified to Figo IV. Chemotherapy with Carboplatin and Paclitaxel was started with no need for tuberculosis treatment. To the best our knowledge this is the first reported case of an unusual extra-axial skeletal involvement by ovarian carcinoma.

## 433. RECURRENT EFFUSIONS: THE IMPORTANCE OF RETHINK DIAGNOSIS

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**Background:** In pericardial disease, is very important to clarify the kind of involvement of pericardium. Inflammatory recurrent pericarditis doesn't develop constrictive forms usually: then a similar clinical history could raise suspicions and hypothesis of another origin, like malignancy. But when recurrencies happen in inflammatory pericarditis, we are not obliged to think about neoplastic origin, but also about starting of a wrong therapy during the first episode (e.g. steroid). This introduction already suggests to be ready to changes in our patients' clinical history and that in pericardial diseases we could have in front different ways to follow.
Another consideration is that pericarditis or pericardial effusion in a patient with a malignancy doesn't mean that pericardium is in all cases embedded by neoplastic disease: pericarditis could also be a reaction to cytokines production. So understanding the possibile origin is important also to drive the next therapeutic process and make the best choice for our patient.
**Methods and Results:** We report the case of a middle-age men, hospitalized in our Unit of Papa Giovanni XXIII Hospital in Bergamo during July and August of 2021. He had a history of three previous hospitalizations, started in February 2021, for recurrent pericarditis with pericardial and pleural effusion: he underwent to two pericardiocentesis and one thoracentesis. All of microbiological and cytological exams for malignant neoplastic cells turned out to be negative: in his blood exams never appeared high PCR. Since the first episode he started a steroid therapy, with a overdose of colchicine, and he had recurrencies after each steroid reduction.
He was hospitalized for the fourth time in our Unit after a steroid reduction with dyspnoea, failure to effort, pericardial effusion not in need of pericardiocentesis and pleural bilateral effusion, more on right side. The aim of hospitalization was the execution of last exams, before starting INN-Anakinra. To role out neoplastic origin of these recurrent effusions, we made a total-body CT (negative) and a right thoracentesis, with collection of whole pleural effusion, that underwent to cytological examination for malignant neoplastic cells after centrifugation. The exam revealed positive.
Then pericardial and pleural effusions were considered expressions from a malignancy of unknow origin: the patient underwent to total-body PET, positive only on a bowel lump, that was biopsied. The result was not diagnostic for a malignancy. No more findings were available to study the malignant origin.
After a clinical improvement with thoracentesis, dyspnoea started again associated with a chest constrictive pain. With heart MR was diagnosed a constrictive pericarditis, therefore we decided to submit the patient to pericardiectomy to treat symptoms no more responsive to maximal therapy. During the surgery, pericardium revealed completely embedded by neoplastic disease and difficult to removal: biopsy reported a bowel adenocarcinoma.

Unfortunately the patient died few days after the surgery in Intensive Care Unit with a diagnosis of neoplastic constrictive pericarditis from malignancy of unknow origin, considered with a poor prognosis.
**Conclusions:** according to us, this case report underlines three points:
This case underlines the trouble in pericardiectomy, a surgery burdened by high mortality. Especially in patients with neoplastic pericardial effusion, prognosis must be evaluated since if less than six months, may not be the best choice.

## 434. CASE REPORT: MAHA AND PRES AS PARANEOPLASTIC SYNDROMES IN METASTASIZED RING CELL CARCINOMA FROM UNKNOW PRIMITIVITY

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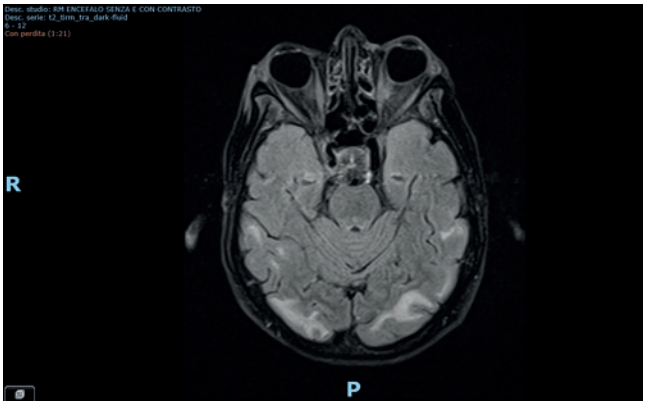
**Background:** Microangiopatic hemolytic anemia (MAHA) is a rare hematological disorder which can appear in different diseases such as thrombocytipenic purpura (TTP, Moschowitz's disease), hemolytic uremicsyndrome (HUS), malignant hypertension and vasculitis. MAHA can also occur as a paraneoplastic syndrome in different solid tumor. It is definedas a severe hemolytic anemia with a negative Coombs test and schistocytes in the peripheral blood smear.
**Case Report:** An 82-year-old woman was admittedto our Internal Medicine Department in November 2021, with complaints of inappetence and hyporexia, nausea, fatigue and some episodes of vomiting in the previous days, without diarrhea. She also reported a loss of weight of around 7 kg. Her past medical history revealed, among other less relevant conditions, mild chronic renal failure, arterial hypertension with some hypertensive crisisand osteoporosis.
On admission she was afebrile and eupneic, her blood pressure was 154/61 mmHg and there were no relevant signs on physical examination, with soft and not tender abdomen. The laboratory tests at baseline revealed: plasma creatinine: 1,47 mg/dL (0.66-1.09 mg/dL), e-GFR: 33 mL/min/1.73 m2 (>90 mL/min/1.73 m2), urea: 184 mg/dL (17-43 mg/dL), plasma albumin: 3.45 g/dL (3.5-5.2 g/dL), LDH: 2046 U/L (0-247 U/L), alkaline phosphatase 874 U/l (< 180 U/l), C-reactive protein: 19,5 mg/L (< 4 mg/L), fibrinogen and INR were in range, hemoglobin: 9.1 g/dL (11-16 g/dL), platelet: 176x103/µL (100-400 103/µL) which rapidly dropped to 81x103/µL, with appearance of schistocytes on the peripheral blood film. Direct Coombs test was negative. Levels of complements C3 and C4 were within the normal range. ADAMTS 13 (Von Willebrand factor cleaving protease) was determined as 38% (> 10%) effectively excluding thrombotic thrombocytopenic purpura (TTP). An autoimmune screen consisting of anti-nuclear antibody, anti-phospholipid antibody and lupus anticoagulant was negative. Genetic analysis of complement proteingenes was not carried out. We started the patient on eculizumab considering the hypothesis of atypical Hemolytic Uremic Syndrome (aHUS), while waiting for the C5b-9 deposits test results. Only one dose could be administered, for the patient passed away after only 5 days. Nevertheless, no improvement was observed, nor clinically nor by lab results (e.g. the platelets count remained approximately around 30 x103/µL). Endothelial resting and activated cells C5b-9 deposits were analyzed, obtaining non-specific results for aHUS.




During her stay, a few days after the admission, an hypertensive crisis occurred, followed by neurological symptoms such as confusion, drowsiness and sopor. Brain CAT and MRI imaging, performed during the episode, revealed bilateral symmetrical hyperintensities of the cerebral hemispheres on the occipital lobes at the T2 scans. This was defined as a "posterior reversible encephalopathy syndrome (PRES)". The blood pressure was kept under control by antihypertensive therapy administered both IV and per os, obtaining an ensuing neurological amelioration.
Total body CT scan was then performed showing some nodules of the left adrenal gland (max 24 x 18 mm), described as probable multiple adenoma, and an enlargement of the whole right adrenal gland. Unfortunately, we couldn't be able to perform gastrointestinal endoscopy, due to the patient's clinical aggravation. The autopsy revealed an adrenal gland localization of poorly differentiated adenocarcinoma, with appearances of signet ring carcinoma, plausibly originating from the gastrointestinal tract. Nevertheless, no primary tumor was found, configuring a "carcinoma of unknown primitivity syndrome (CUP)".

## 435. FIBROBLASTS-DERIVED EXTRACELLULAR VESICLES ENHANCE BONE MARROW ANGIOGENESIS IN PATIENTS WITH MULTIPLE MYELOMA

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**Background:** Multiple myeloma (MM) onset and progression closely depend on bone marrow (BM) microenvironment that plays an essential role in promoting plasma cell proliferation, angiogenesis, invasion, and metastasis. The complex interplay between tumor cells and BM microenvironment involves cell-to-cell interactions, cytokines, growth factors, and extracellular vesicles (EVs). Here, we explored the role of EVs released by BM fibroblasts of MM patients (FB-EVs) on angiogenesis.
**Method:** FB-EVs were purified from cell culture media of FBs cultured for 72 hours. Uptake of FB-EVs by endothelial cells purified from MM patients (MMECs) was measured by flow cytometry. The angiogenic effect of FB-EVs on MMECs was analyzed at 6h and 24h using functional angiogenic assays (Matrigel® assay, migration, chemotaxis). The cytokine cargo of FB-EVs was analyzed Human angiogenesis array. Finally, we studied the pathways involved in FB-EVs-induced angiogenesis carrying out using the Human phospho-kinase array.
**Results:** Flow cytometric analysis of MMECs co-cultured with Bodipy TR ceramide-labelled FB-EVs demonstrated that EVs uptake started at 12 hours of co-culture and it was virtually negative at 6 hours. By contrast, Matrigel® angiogenesis assay showed that MMECs co-cultured with FB-EVs formed branching points, anastomosing tubes with capillary-like structures after 6 hours of incubation. Furthermore, co-cultured MMECs increased their migration in response to stimuli. Finally, FACS analysis of MMECs co-cultured with FB-EVs for 6 hours pointed out an upregulation of p-VEGFR2, p-cMET and p-Tie/TEK2 as sign of increased activated phenotype. Cytokine array of FB-EVs cargo demonstrated that it contains pro-angiogenic factors (angiopoietin 1, VEGF, HGF and IGFBP-2) that activated specific receptors expressed on MMECs. Next, analysis of angiogenesis-related functions of MMECs co-cultured with FB-EVs for 24 hours showed that EVs uptake increased MMECs abilities to migrate spontaneously and in response to stimuli and to form meshwork of capillary-like structures on Matrigel®. The effect of FB-EVs at 6 and 24 hours on intracellular signaling of MMECs was analyzed by using a phospho-kinase array that evaluates the phosphorylation status of 43 kinases. At 6 hours, pro-angiogenic cytokines released by FB-EVs activated mTORC2 pathway, by contrast at 24 hours FB-EVs uptake activated mTORC1/2, β-catenin, c-Jun, PYK2, CREB, RSK1/2 that improve the transcription of pro-angiogenic cytokines.
**Conclusions:** Overall results indicate an early/late pro-angiogenic effect of FB-EVs. At 6 hours, in absence of EVs uptake, FB-EVs interact with MMECs receptors triggering angiogenesis via cytokines release. At 24 hours, EVs uptake exacerbates MMECs angiogenic abilities by sustaining the expression of pro-angiogenic cytokines.

## 436. EVALUATION OF SKELETAL MUSCLE MICRORNAS AND SMALL NON-CODING RNAS IN PATIENTS WITH GASTROINTESTINAL CANCER

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**Introduction:** MicroRNAs and small non-coding (snc) RNAs are considered pivotal molecules in cell-to-cell and inter-tissue communication and possibly playing a role in muscle wasting during cancer. In this light, we aimed to assess miRNAs expression and other sncRNAs in skeletal muscle from gastrointestinal (GI) cancer patients and controls.
**Methods:** We considered GI cancer patients and controls undergoing surgery for tumor resection and for non-malignant diseases. We collected specimens of rectus muscle during first phases of surgery. We performed Next Generation Sequencing on RNA extracted from skeletal muscle of all the participants for the miRNAome sequencing.
**Results:** We enrolled 25 cancer patients and 15 controls. Using a minimum read cut-off of 20 normalized counts, we identified 373 miRNAs and 190 piRNAs, accounting for 72% and 19% of raw reads, respectively. 66 miRNAs (10 upregulated and 56 downregulated) resulted as differently expressed in cancer group compared to controls. Among the downregulated miRNAs, 10 had log2 (fold change) <-2, with miR-223 and miR-15b being represented by both 3p and 5p mature sequences. 24 miRNAs, 6 piRNAs and 4 snoRNAs resulted differently expressed (mainly downregulated) in male cancer patients compared to controls. Network analysis revealed miR-106b-5p, miR-15b-5p and miR-106a-5p as central interactors with mRNAs related to ubiquitin ligase/transferase activities. As for the validated targets, some genes were targeted by different miRNAs, being SMAD2, YOD1 and TRAF3IP2 the mRNAs with most validated interactions with downregulated miRNAs in CP.
**Conclusions:** In gastrointestinal cancer patients, myomiRs and other types of sncRNAs were profiled and alterations were documented with mechanisms, biological implications and gender differences to be further elucidated. The data obtained shed new light on the pathogenic mechanisms of cancer-associated cachexia.

## 437. ANALYSIS OF GENE EXPRESSION IN PERIPHERAL BLOOD MONONUCLEAR CELLS (PBMCS) OF LUNG CANCER PATIENTS WITH OR WITHOUT ANOREXIA

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**Introduction:** The pathophysiology of cancer anorexia is complex and still unclear. We aimed at assessing gene expression of PBMCs in a cohort of lung cancer patients according to presence/absence of anorexia.
**Methods:** Gene expression was assessed by genome-wide transcriptomic profiling analyses in patients with a new diagnosis of lung cancer and controls (non-cancer, non-anorexic). Anorexia was assessed according to a Functional Assessment of Anorexia/Cachexia Therapy (FAACT) score≤30. We validated the differentially expressed genes (DEGs) by quantitative Real-Time PCR, in particular, Adam8, Smad4, Clu and Ccr4 mRNA levels were measured.
**Results:** RNA-seq analysis was performed on PBMC of 20 lung cancer patients (10 anorexic and 10 non-anorexic) and in 10 healthy controls. We observed a total of 983 DEGs (843 up-regulated; 140 down-regulated) in anorexic cancer with respect to controls. The DEGs were mainly represented within the immune regulatory pathways, such as inflammation signaling, chemokine- and cytokine-mediated inflammation signaling, TGF-beta signaling and interleukin signaling pathways. The Adam8, Smad4, Clu and Ccr4 expression levels were in line with the trend of RNA-seq analysis. Adam8 mRNA levels were decreased in cancer vs controls ($p<0.001$) and in anorexic vs controls ($p=0.001$). Smad4 mRNA levels were lower in cancer vs controls ($p=0.003$), as well as in those with anorexia vs controls ($p=0.009$). Also, we observed increased Ccr4 expression in cancer patients with anorexia vs non-anorexia ($p=0.011$) and a similar trend for CLU ($p=0.057$).
**Conclusions:** According to RNA-seq data, the major pathways involved in anorexia where those mediating inflammation, TGF-beta, chemokine and cytokine pathways. We found changes of several genes associated with poor appetite in lung cancer patients that may play a crucial role for the development of anorexia.

## 438. THOSE STRANGE LESIONS

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**Background:** Paraneoplastic syndromes are characterized by symptoms or signs that result from damage to tissues distant from the site of the neoplasm due to complex interactions between the body's immune system and the malignant neoplasm. Cholangiocarcinoma (CCA) is an aggressive epithelial neoplasm of the hepatobiliary tree and is associated with several paraneoplastic syndromes. These syndromes can present as dermatological, neurological, renal, hematological or multisystemic manifestations. Clinical suspicion and timely recognition of these syndromes can lead to an early diagnosis of neoplasms such as cholangiocarcinoma which, at the time of diagnosis, in most cases is not candidate to surgery for the advanced stage of the disease.
**Case Report:** A 63-year-old woman came to our attention, sent by her own doctor, for glycometabolic decompensation (Glycemia 322 mg / dl, HbA1c 11.2%, Triglycerides: 212 mg / dl, GGT: 75 U / l (<40). Pathological History: Diabetes mellitus type 2, arterial hypertension, anxiety-depressive syndrome. During the medical examination, the patient reported elevated blood glucose values that were not controllable with insulin therapy, metformin and Sglt-2 inhibitor. The physical examination revealed the presence of diffuse erythematous itchy lesions, also present in the scalp. These injuries over time seemed to be at first as bullous lesions, then underwent ulceration, peripheral desquamation and finally disappeared without scarring. The patient reported sudden appearance of these skin lesions about 5 months earlier, not associated with the introduction of new drugs or foods or associated with the appearance of new symptoms, and she also reported that she had already undergone a dermatological examination for this reason which diagnosed: " adverse drug reaction "and prescribed local therapy with steroid without benefit. Our first intent was to exclude that these lesions could be associated with neoplastic or systemic pathologies, it was therefore decided to hospitalize the patient for a diagnostic-therapeutic study. Blood chemistry tests were included within the norm, except for a slight increase in GGT (60UI / l) and pancreatic amylase (61IU / l). It was therefore decided to perform an ultrasound of the complete abdomen which documented: " bulky lesion at the level of the hepatic hilum with irregular margins". Because of this finding, a total body CT scan was performed which highlighted "voluminous hepatic expansive formation, involving segments I, II, IV, VII and VIII, with dimensions of about 11 cm in maximum diameter, the same determines ectasia of the intrahepatic biliary tract intralesional and is characterized by intense and inhomogeneous contrast enhancement in the arterial phase with a progressive tendency to isodensity in the subsequent contrastrographic phases. There are 3 nodular formations with similar characteristics affecting the VI and VIII segments. Centrimetric expanded on the right adrenal and two areas of bone reworking of the lithic type on the left iliac wing. Presence of numerous sub- and peri-centimetric short-axis lymph node formations in the hepatic hilar, interporto-caval, inter-aortic, along the small gastric curvature and in the left para-aortic site and in the mesenteric fan. For these reasons, an ultrasound-guided percutaneous liver biopsy was performed at the hilum level. The histological examination revealed: "Sclerosing ductal tubular carcinoma. Morphological and immunophenotypic findings referable to biliary tract adenocarcinoma. Immunohistochemical tests gave results: CK7 +, CK20-, CK19 +. "
**Conclusions:** It is fundamental in daily medical practice to make a reasoning that does not exclude rare manifestations of a disease, by thoroughly evaluating of medical history and correlating it with the clinical picture. Paraneoplastic syndromes can present with skin, neurological, renal, haematological or multisystemic manifestations, clinical suspicion and early recognition of these syndromes can lead to an early diagnosis which remains essential in the treatment of neoplastic pathologies.

## 439. MYELOMA CELLS REGULATE MIRNA TRANSFER FROM FIBROBLAST-DERIVED EXOSOMES BY EXPRESSION OF LNCRNAS

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**Background:** Multiple myeloma (MM) progression strongly depends on the cross-talk between MM cells and bone marrow (BM) stromal cells, including fibroblasts (FBs). Expression of non-coding RNAs (ncRNA), i.e. microRNAs (miRs) and long non coding RNAs (lncRNAs), contributes to disease progression modulating gene expression via the lncRNA-miRs-mRNA axis (López-Urrutia E et al, Front Oncol, 2019). We previously demonstrated that tumor cells modify the BM microenvironment by reprogramming FBs behavior through the expression of an aberrant miR profile (Frassanito MA et al, J Pathol 2019). Since exosomes (EXOs) are considered a new mechanism of cell-to-cell communication within tumor microenvironment, we analyzed the role of FB-derived EXOs (FB-EXOs) in affecting miRNAs profile of MM cells. Finally, as the lncRNAs/miRNAs axis represents an important hallmark of tumor development and progression, we investigated the role of lncRNAs in the regulation of miRNAs profile of MM cells.
**Methods:** EXOs were purified from culture media of FBs harvested from BM aspirates of newly diagnosed MM patients (n=15). U266 cells were co-cultured with MM FB-EXOs to assess the effect of exosomal miRs on miRNAs profile of recipient MM cells. Transient inhibition of lncRNA was performed with lnc·siRNA targeting lncRNAs HOTAIR, MALAT and TOB1-AS1.
**Results:** RT-qPCR analysis of FBs-EXOs miRNA cargo revealed the expression of miR-23b, miR-27b, miR-125b, miR-214, and miR-5100. Analysis of miRNAs expression in recipient MM cells co-cultured with FBs-EXOs revealed a selective transfer of miR-214-3p and -5100 but not of miR-23b-3p, miR-27b-3p, miR-125b-5p miRs. Selective overexpression was not dependent on the content of these miRs in FB-EXOs, in that RT-qPCR revealed comparable expression of miR-23b, miR-27b, miR-125b, miR-214, and miR-5100, but it was related to lncRNA expression by MM cells. Accordingly, RT-qPCR studies showed that U266 cells as well as CD138+ express lncHOTAIR, TOB1-AS1, and MALAT1. Transient transfection of U266 cells with HOTAIR·siRNA, TOB1-AS1·siRNA, MALAT1·siRNA enhanced the expression of miR-23b, miR-27b and miR-125b, indicating that these lncRNAs are sponges for miR-23b, miR-27b and miR-125b. Finally, similar results were obtained in U266 cells co-cultured with MM FB-EXOs.
**Conclusions:** Overall, these data show that recipient MM cells do not behave as a passive container where EXOs empty their cargo. On the contrary, they select and neutralize exosomal miRs that could be dangerous for cell survival.

## 440. AN EXTREMELY RARE CAUSE OF PERICARDIAL EFFUSION

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**Introduction:** We present a case of primary cardiac angiosarcoma diagnosed after recurrent pericardial effusions. The diagnostic workup of persistent pericardial effusion should consider alternative etiologies, such as malignancy. Primary cardiac angiosarcoma are extremely rare and can be misdiagnosed during the early course of the disease. The diagnosis is challenging, the imaging characteristics of primary cardiac angiosarcoma are not well understood because most of the current knowledge is mainly based on case series.
**Case Report:** A 49-year-old male with no past medical history, except for familiarity with Marfan syndrome, was admitted to Emergency Department for worsening dyspnea and foot oedema. He was hemodynamically stable, Electrocardiogram (ECG) showed electrical alternans and transthoracic echocardiogram documented abundant pericardial effusion with swinging heart effect and right ventricular narrowing. He underwent Computed Tomography (CT) angiography to exclude aortic dissection. A pericardiocentesis was performed and 2000 ml of serohematic fluids were drained. Laboratory tests documented a 13.240/ml white blood cell, C reactive protein 37 mg/dl and pericardial fluid cytology was negative. During recovery, the patient showed rapid clinical improvement and pericardial effusion gradually diminished; Positron Emission Tomography showed a non-specific increased 16-fluorodeoxyglucose uptake of the right atrium interpreted as inflammatory. He was discharged on NSAIDs and colchicine and referred to our clinic. One month after, he relapsed with chest pain and pericardial effusion, he underwent a second pericardiocentesis. Computed Tomography was not diagnostic while Magnetic Resonance Imaging (MRI) documented an extra cavitary area with clear borders between right atrium and right ventricle which rises aortic root suspected of malignancy. A pericardiectomy was performed and histopathology from the pericardial biopsy was consistent with an epithelioid angiosarcoma. Whole body CT was negative for distant metastases. The patient's hospital course was complicated by methicillin sensitive staphylococcus aureus's sepsis and liver damage; therefore, chemotherapy was not undertaken. He was transferred to Intensive Care Unit and passed away for infective complications 4 months after symptoms onset.
**Discussion:** Primary cardiac neoplasms are rare, with a prevalence ranging from 0.001 to 0.03% in autopsy series (1). Primary cardiac angiosarcoma accounts for approximately 30% of those cases. Cardiac angiosarcomas have male preponderance (3: 2), especially in the age group of 20-50 years and have right atrial predilection (2). Clinical manifestations are not specific and depend on their infiltration into the myocardium and adjacent structures as well as the extent of metastases (3). Biopsy with histopathological analysis is the gold standard test and noninvasive imaging can improve the early detection of cardiac neoplasms. Our case report highlights diagnostic difficulties and limits in imaging, MRI identified suspected cardiac malignancy while CT was negative. An aggressive diagnostic work up should be considered in young patients with pericardial effusion, especially when presenting with tamponade with hemorrhagic pericardial effusion. The prognosis of primary cardiac angiosarcoma is poor because of aggressive disease invading critical structures and limited treatment options providing durable disease control. According to case series (4,5), the median overall survival ranges from several days to several months.
**References:** 1. Silverman NA: Primary cardiac tumors. Ann Surg. 1980, 191: 127-38 - 2. Kurian KC, Weisshaar D, Parekh H, Berry GJ, Reitz B: Primary cardiac angiosarcoma: case report and review of the literature. Cardiovasc Pathol. 2006, 15: 110-2. - 3 6. Patel, S.D.; Peterson, A.; Bartczak, A.; Lee, S.; Chojnowski, S.; Gajewski, P.; Loukas, M. Primary cardiac angiosarcoma—A review. Med. Sci. Monit. 2014, 20, 103–109 - 4. Yu, J.F.; Cui, H.; Ji, G.M.; Li, S.Q.; Huang, Y.; Wang, R.N.; Xiaop, W.F. Clinical and imaging manifestations of primary cardiac angiosarcoma. BMC Med. Imaging 2019, 19, 16. - 5. Rao, J.N.; Gowda, G.D.; Anand, R.; Desai, N.B. Angiosarcoma of the right atrium and right ventricle. J. Card. Surg. 2017, 32, 807–808.

# PNEUMOLOGIA

## 441. COMPETITIVE INTERACTION BETWEEN SMOKING AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE FOR EXPLAINING RENAL FUNCTION REDUCTION IN HYPERTENSIVE PATIENTS

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**Introduction:** Chronic kidney disease (CKD) is a clinical condition characterized by a progressive reduction of renal function until end-stage kidney disease. Over the last years the prevalence of CKD is growing worldwide in the general population. In addition, CKD is a strong and independent risk factor for cardiovascular (CV) and end-stage renal diseases (ESRD). In particular, CKD is associated with both increased CV and all-cause mortality. Clinically relevant, CKD rising prevalence reflects the increase of established CV risk factors such as age, diabetes, hypertension, and obesity. Similarly, cigarette smoking is one of the most important modifiable risk factors for atherosclerotic diseases and other chronic clinical conditions, such as hypertension, chronic obstructive pulmonary disease, cancer, etc. In addition, COPD, that is the third leading cause of death in developed Countries, is often associated with other chronic comorbidities that negatively impact on patients' outcomes. Interestingly, in this context, some data demonstrated that COPD represents, per se, a risk factor for renal function impairment.To our knowledge, few and conflicting data are available regarding the association between CKD and COPD smoking singly, while no data exist about the possible interaction between smoking and COPD on renal function. Thus, the aim of present study was to test the combined effect of both smoking and COPD on renal function decline.

**Methods:** We conducted an observational retrospective cohort study that included 1,728 Caucasian hypertensive outpatients referred to the University Hospital of Catanzaro (1,046 M and 682 F, mean age 61.4±12.0 years). Patients were stratified by smoking status (current smokers/former-never smokers) and presence/absence of COPD.
Unpaired Student's t-test was used to test differences between clinical and biological data, and the chi-square test for categorical variables. To test the mutual effect modification by smoking and COPD between these two risk factors and e-GFR, we performed linear regression models of increasing complexity. Finally, we performed a multiple linear regression model adjusted for a series of potential confounders to confirm the effect modification by smoking of the COPD-e-GFR link. The same analysis was carried out to investigate the effect modification by COPD on the smoking-e-GFR link.
**Results:** Smokers were significantly younger than non-smokers, and showed significantly higher values of SBP (143±16 vs 141±18 mmHg) and hs-CRP (4.1±3.5 vs 3.9±3.2 mg/L), while total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides were significantly lower in the smokers group rather than in the non-smokers one (183±26 vs 186±35 mg/dl, 50±13 vs 51±15 mg/dl, 108±25 vs 109±34 mg/dl, 129±58 vs 130±76 mg/dl, respectively). When considering the study population stratified according to the presence/absence of COPD, patients with COPD were older than non-COPD subjects and showed significantly higher values of BMI (27±4 vs 27±3 Kg/m2), SBP (146±17 vs 142±17 mmHg), hs-CRP (5.1±3.4 vs 3.6±3.3 mg/L). On the contrary, COPD patients showed lower values of DBP (84±11 vs 85±11 mmHg), and HDL-cholesterol (48±13 vs 51±14 mg/dl). No differences between groups were found with regards to fasting plasma glucose, total and LDL-cholesterol, and triglycerides.
Of note, smokers displayed e-GFR values which were significantly lower than those in non-smokers (90±24 vs 121±35 ml/min/1.73 m2), and this difference was also true when comparing e-GFR values between patients with and without COPD (81±17 vs 109±32 ml/min/1.73 m2). Interestingly, smoking and COPD were directly and significantly interrelated (point bi-serial correlation = 0.20, P<0.0001).
Smoking significantly modified the effect of COPD on e-GFR and, given the mutualistic nature of the effect modification, also COPD significantly modified the effect of smoking on e-GFR On crude analysis (Figure 2 panel A) among no smokers, e-GFR was 35 ml/min/1.73 m2 lower (95% CI: 30-41 ml/min/1.73 m2) in patients with COPD than in those without. The same analysis carried out to investigate the effect modification by COPD on the smoking-e-GFR link provided similar results on both crude (Figure 3 – panel A) and adjusted (Figure 3 – panel B) linear regression analyses. Tthese results indicate a competitive interaction between smoking and COPD in the pathway conductive to renal damage in the study population.
**Conclusion:** In this study, conducted in a wide population of well characterized hypertensive patients, we demonstrated for the first time that smoking and COPD competitively interact in the appearance of renal function decline. In particular, we demonstrated that smoking significantly modified the effect of COPD on e-GFR and, vice versa, COPD modified the effect of smoking on e-GFR.

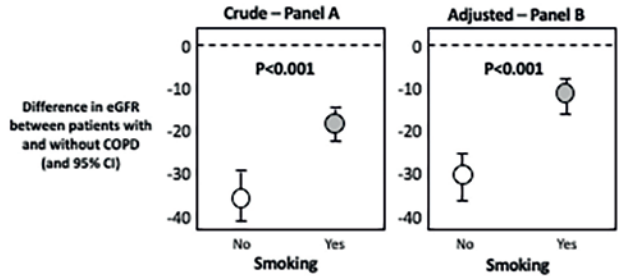


**Figure 2**

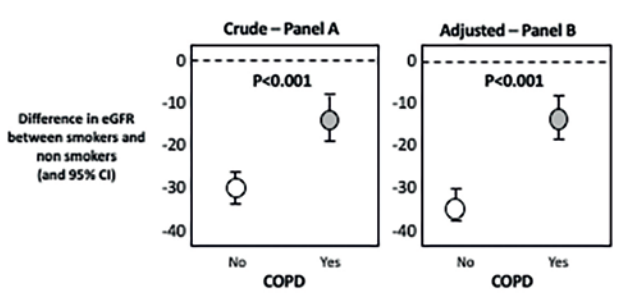


**Figure 3**

## 442. REAL-LIFE RAPIDITY OF HIGH FLOW THROUGH NASAL CANNULA (HFNC) EFFECTS ON RIGHT HEART DYSFUNCTION IN PATIENTS WITH RESPIRATORY FAILURE AND INTERSTITIAL LUNG DISEASES

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High Flow through Nasal Cannula (HFNC) delivers heated and humidified air–oxygen mixture to the patient, with an inspiratory fraction of oxygen (FiO2) ranging from 21 to 100% and a flow up to 60 L/min through a large bore nasal cannula. It is well-known that pulmonary hypertension in interstitial lung diseases (ILDs) is mainly determined by hypoxia-induced vasoconstriction and remodeling. However, the effects of HFNC on right heart dysfunction have not yet been well evaluated. The primary outcome of this study was to assess the effectiveness of HFNC in subjects with hypoxemic respiratory failure and ILDs. We enrolled 10 patients hospitalized at the "Magna Græcia" University Hospital of Catanzaro (Italy) and treated with HFNC. Echocardiographic evaluation was performed at the time of admission (baseline) and at discharge from the ward (mean length of stay 11.80 ± 4.077 days). Systolic pulmonary artery pressure (sPAP) levels decreased from baseline (72.20 ± 17.70 mmHg) at discharge (55.20 ± 15.68 mmHg; p<0.001). In the same period right atrium area (RAA) declined from 28.20 ± 10.52 cm2 to 23.50 ± 8.031 cm2 (p<0.05) and tricuspid annular plane systolic excursion (TAPSE) increased from 18.20 ± 3.882 mm to 20.90 ± 3.843 mm (p<0.05). These effects were associated with inferior vena cava (IVC) diameter reduction from baseline (24.70 ± 6.395 mm) at discharge (19.80 ± 3.120 mm; p<0.05). Moreover, right ventricular outflow tract (RVOT) changed from 3.60 ± 0.804 cm to 3.44 ± 0.739 cm, but this variation was not statistically significant (p=0.423). Within a real-life context, these data highlight the very rapid and effective therapeutic action of HFNC on right heart echocardiographic parameters, assessed in patients complaining of respiratory failure associated with ILDs and pulmonary hypertension.

## 443. REAL-LIFE DATA IN THE MANAGEMENT OF THE ASTHMATIC PATIENT: ANALYSIS OF A SURVEY IN GENERAL MEDICINE

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According to the GINA guidelines, asthma affects about 300 million people in the world, that is, one in 20. In Europe there are about 30 million asthmatics, the prevalence in Italy is 4-6%. The WHO estimates that asthma is still responsible for around 250,000 deaths a year. In the management of asthma, the cornerstones are the control of symptoms and the reduction of future risks. Despite the improvement of therapeutic strategies in the control of asthma disease, in recent years there has been an increase in cases of uncontrolled asthma. For this reason, it is essential to know the real-life data of patient management In the light of the aforementioned data, we wanted to conduct a survey that involved the research group SIMG of Messina, to outline the management of the asthmatic subject. The aim of the research is to: a) know the prevalence in our population of subjects with asthma, b) know the behavior of the GP in the management of these patients and evaluate, through some parameters, the control or not of the disease and recognize severe asthma (use of questionnaires, spirometry, eosinophilia, drug therapy; adherence; assessment of disease control, access to PS, systemic cortisone therapy, use of biological drugs).
**Materials and Methods:** The survey involved the population belonging to the general medicine studies of the SIMG research group (13 doctors contributed for a population of about 17,000 subjects). The survey was structured in ten questions: number assisted, number of asthmatic subjects, evaluation of disease control, use of questionnaires (ACT, ACQ), use of spirometry, control of eosinophilia, access to PS in the last twelve months, use of oral or systemic cortisones in the last year, use of ICS or ICS / LABA, periods of use of ICS or ICS / LABA, use of biological drugs.
**Results and Conclusions:** The study found the prevalence of 3.9% of asthmatic subjects. The GP's doctors answered for 54% that the disease is controlled in 50% of cases, only 39% administer questionnaires in 30-50% of the subjects, 50% use spirometry in 50-70% of the subjects. asthmatics and 47% state that the control of eosinophilia is rarely carried out. 38% of doctors

report that patients have used PS in the last year for at least 1-5 times, 23% respond that patients use CSO from 3 to 5 times in the last year. 70% of doctors respond that 50-70% of these subjects use ICS or ICS / LABA and 61% say that the therapy is carried out for six months a year. And finally, 46% of doctors replied that they are in charge of 1 to 3 subjects who use biological drugs. These data underline once again how the asthmatic patient does not achieve good control of the disease (50%) and drug adherence is not sufficient, and many patients still resort to oral or systemic cortisone therapy and access the PS, doctors use little. questionnaires, spirometry, and eosinophil counting. From the aforementioned data and from the fact that 46% of doctors are in charge of subjects undergoing therapy with biologics, it is evident that many patients suffer from severe asthma.

## 444. A "NODULAR" DYSPNEA: A CASE REPORT

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**Introdution:** A 49-year old male whit a twenty days history of dyspnea and asthenia. Drug, environmental or food allergies were excluded. No cough or fever. For this reason the general practitioner had recommended aereosol therapy with little benefit.
**Materials and Methods:** At visit, the patient's vital signs were as follows: blood pressure 115/60 mmHg, pulse rate 72 bpm, rhythmic, body temperature 36.6°C, respiratory rate 18 beaths for minute and oxygen saturation was 98% without oxygen. Full blood counts, chemistry panel, autoimmunity panel, total serum IgE, complement levels, interferon-gamma release assays for latent tubercolosis were all within normal range (except for an MGUS IgGK and a reduction in T helper lymphocytes). Chest-TC shows an interstitial pattern of predominantly nodular type, localized mainly to the upper and middle pulmonary fields in the peribronchovascular site, with involvement also of the subpleural parenchyma in the dorsal and schissuro-periscissural site, tendency to thickening and reduction of the bronchial caliber and ileo-mediastinal adenopathies (some with calcific deposits). Spirometry showed a medium-sized obstructive ventilatory deficiency (DLCO in the norm), bronchoscopy shows a picture of intense mucosal hyperemia, PET/CT confirms a disease with high metabolic activity in the pulmonary and lymph node sites. A lymph node biopsy was then performed in mediastinoscopy. Lymph node biopsy showed the presence of granulomas with un necrotized epithelioid cells (non-caseous granuloma). We then diagnosed Sarcoidosis with bilateral adenomegalyas and parenchymal involvement (stage II). The patient then started systemic corticosteroid therapy (deltacortene 25 mg/day for 20 days then to scale) and inhalation (beclomethasone/formoterol 100 mcg/6 mcg 2 puff/day), with considerable clinical improvement, and was sent to pulmonologist specialists for management.
**Discussion and Results:** Sarcoidosis is a multisystemic granulomatous disease that affects individuals worldwide. The lungs are most commonly involved but any organ can be involved. It has variable manifestations and clinical course. Diagnosis of sarcoidosis is based on clinicopathologic findings and the exclusion of other causes of granulomatous disease. Its hallmark is the formation of granulomas in affected organs. The evolution and severity of sarcoidosis are highly variable. Mortality is estimated at between 0.5– 5%. In most benign cases (spontaneous resolution within 24–36 months), no treatment is required but a regular follow-up until recovery is necessary. In more serious cases, a medical treatment has to be prescribed either initially or at some point during follow-up according to clinical manifestations and their evolution. Immunosuppressive therapy is the cornerstone of the management of sarcoidosis and is indicated when there is evidence of symptomatic or progressive disease or when critical organs (ocular, cardiac, nervous system) are involved..
**Conclusions:** This case represents an uncommon cause of dysnea. In the case described, the introduction of GC obtaining almost complete resolution of asthenia and dyspnea.

## 445. FINDING AN EXCAVATED LUNG LESION: DON'T FORGET ACTINOMYCOSIS, A CASE REPORT OF A RARE DIAGNOSIS

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**Introduction:** Actinomycosis is a chronic bacterial infection, caused by the Actinomyces, a commensal of the digestive and genital tract. The most common presentation involves the cervicofacial region, but other anatomical sites in the abdomen, thorax and central nervous system may be involved. Differential diagnosis includes neoplasia and tuberculosis. With the appropriate course of antibiotic treatment, the prognosis is good in most cases.
**Methods and Results:** A 57-year-old man, a former smoker, with a family history of lung cancer and no occupational and environmental risk factors, performed screening tests in December 2021. A tiny non-calcific nodularity on the right inferior lobe and small hilar lymph node calcifications on the right chest were found at thorax CT scan. At the end of December, he reported serotonin fever, night sweats, cough and poor brownish and smelly expectoration. Ten days after the symptoms persisted. He went to the Emergency Room and performed a new chest CT scan that showed an excavated lung lesion at the right superior lobe (about 5 x 4 cm) compatible with inflammatory infiltrate. In suspicion of tuberculosis disease, he performed bronchial bronchoscopy with bronchial lavage. Culture examination for common germs and fungi on bronchial lavage, culture on sputum and urine for Kock Bacillum and pneumonia serology were all negative. After these tests he came to our clinic in mid-January without having practiced any therapy yet. On physical examination, the patient presented eupneic at rest, without signs of peripheral cyanosis, diffusely weakened vesicular murmur without added noises, SpO2 96%, HR 98 bpm, Modified British Medical Research Council Questionnaire (mMRC) = 1. Therapy with ceftriaxone and levofloxacin, N-acetylcysteine, pantoprazole, paracetamol as needed, and aerosol therapy with salbutamol and ipratropium bromide was the treatment setted up. After 7 days a new chest x-ray showed an expansive formation with excavated core and a maximum diameter of 3 cm in the right sub-apical area. At the following outpatient check-up on January 27, 2022, the patient reported apyrexial for about 48 hours with persistence of cough and mucus sputum, sometimes streaked with blood, profound asthenia and pain in the medial area of the right foot. On physical examination, the patient did not show significant changes. Due to the new symptoms, he replaced ceftriaxone and levofloxacin with cefditoren and metronidazole for 7 days and continued the rest of the ongoing therapy, adding beclomethasone to the aerosol therapy. On January 11, he performed a new chest CT which described a reduction in the size of the nodular infiltrate at the right inferior lobe, no longer excavated, but with central necrotic-colliquative hypodensity. The patient reported improvement in general and respiratory clinical conditions. Cytological examination on bronchial lavage, negative for the search for neoplastic cells, described an inclusion of mucus, red blood cells and rare colonies of actinomycetes. Kock Bacillum on bronchial lavage was negative while the QuantiFERON test was positive. Due to the diagnosis of actinomycosis amoxicillin/clavulanic acid were started. The patient reported clinical improvement and a new thorax CT scan was scheduled two months after the start of the treatment, showing a significant reduction of the lesion (1,8 x 1,9 cm).
**Conclusion:** Actinomycosis is a rare chronic bacterial infection, slowly progressive. Prognosis correlates directly with early diagnosis and is more favorable in the cervico-facial form. It progressively worses in thoracic, abdominal and generalized forms, especially if the central nervous system is affected. Moreover, the clinical manifestations and imaging features of pulmonary actinomycosis are nonspecific; therefore it could easily be misdiagnosed and confused with other chronic suppurative lung diseases and with malignancy. It is always necessary to evaluate every differential diagnosis also if there aren't manifested risk factors (dental abscesses, bronchiectasis, pulmonary emphysema, alcohol abuse) or common presentations of the disease. Most patients with actinomycosis respond to antibiotics, but the response is usually slow due to the marked hardening of the tissue and the relatively avascular nature of the lesions. Therefore, treatment should be continued for at least 8 weeks and occasionally for ≥ 1 year until signs and symptoms subside. Surgery may be necessary to drain abscesses and remove fistulas.

## 446. DYSPNEA OF UNKNOWN ORIGIN OR RECURRENT SPONTANEOUS PNEUMOTHORAX IN A MIDDLE-AGED WOMAN: LYMPHANGIOLEIOMIOMATOSIS, THE RARE DISEASE WE MUST NECESSARILY THINK ABOUT

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Lymphangioleiomyomatosis (LAM) is a rare neoplastic disease characterized by proliferation of immature smooth muscle cells. It affects almost

exclusively women, mainly in child-bearing age, and occurs sporadically (S-LAM) or as part of Tuberous Sclerosis (TSC-LAM). Pulmonary LAM is the most common form and its clinical manifestations include breathlessness on exertion, recurrent spontaneous pneumothorax, chylothorax and hemoptysis. Pneumothorax occurs frequently (70%) and definitive management with pleurodesis is recommended as the risk of recurrence is high. The most frequent pulmonary function abnormalities are airflow obstruction and decreased lung diffusion capacity. Extrapulmonary manifestations include renal angiomyolipomas and lymphangioleiomyomas that are found primarily in the abdomen, retroperitoneum and pelvis. The disease is diagnosed histologically and/or using typical high-resolution computed tomography (HRCT), whose remarkable feature is the presence of diffuse thin-walled cysts in the lung. Even the presence of elevated serum levels of a vascular endothelial growth factor-D (VEFG-D) has good diagnostic specificity. Mammalian target of rapamycin (mTOR) inhibitors are possible treatment options, but the gold standard remains lung transplantation with a mean transplant-free survival >20 years from the time of diagnosis.
We report the case of a 33-year-old Chinese woman non smoker presenting to the ER for cough and breathlessness on exertion. Her personal history was notable for mild airflow obstruction and decreased lung diffusion capacity, as shown by a recent spirometry. In the ER she was hemodynamically stable and blood tests were normal. Chest X-ray showed right spontaneous pneumothorax and a chest tube was placed. In the next days she experienced recurrent chest pain and dyspnea and a chest radiography revealed a contralateral spontaneous pneumothorax. Thus a chest HRCT was performed showing the presence of diffuse thin-walled cysts in both lungs suggestive for LAM. The patient was examinated for clinical features of Tuberous Sclerosis Complex and an abdominal CT resulted in normal. She underwent right apical pleurectomy, bullectomy and pleurodesis; the histopathological examination confirmed the diagnosis of LAM and she was put on the lung transplant waiting list.
When faced with dyspnea of unknown origin or recurrent spontaneous pneumothorax in a middle-aged woman, in particular non smoker, LAM should be considered. A prompt diagnosis is crucial and it is based on the evidence of diffuse thin-walled cysts in the lung highlighted on chest HRCT. Biopsy may be required when a diagnosis cannot be made noninvasively.

## 447. ECHOCARDIOGRAPHIC EVALUATION OF THE CARDIAC CHAMBERS IN THE ASTHMATIC PATIENT: THE BADA (BLOOD PRESSURE LEVELS, CLINICAL FEATURES AND MARKERS OF SUBCLINICAL CARDIOVASCULAR DAMAGE OF ASTHMA PATIENTS) STUDY ECO

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The BADA Study is a study started a few years ago with the main objective of defining the blood pressure profile, the cardiovascular risk profile and the markers of subclinical and clinical vascular and cardiac damage in asthmatic patients. Very few studies in literature have assessed the echocardiography of otherwise healthy asthmatic patients, i.e. in the absence of concomitant heart disease. We wanted to design a study aimed at ascertaining in a sample of asthmatic patients the prevalence of alterations in the morphology and/or function of the cardiac chambers, assessed by performing a trans-thoracic echocardiogram and comparing the results obtained with those of a control group without chronic respiratory diseases.
The data collected on 86 patients with bronchial asthma, referred to the dedicated outpatient unit of the UOC of Pneumology (Director Prof. N. Scichilone) and to the outpatient unit of Internal Medicine with Stroke Care (Director Prof. A. Pinto / Prof. A. Tuttolomondo) of the AOUP "P. Giaccone" of the University of Palermo were analyzed.
Exclusion criteria:
- Coexistence of Chronic Obstructive Pulmonary Disease (COPD);
- Coexistence of Obstructive Sleep Apnea Syndrome (OSAS)
- Active smoking status
- History of chronic ischemic heart disease, valvulopathy, or other structural heart disease with or without secondary impairment of left ventricular ejection fraction.
- History in the six months preceding the study of any acute myocardial, endocardial or pericardial pathology capable of transiently or permanently compromising cardiac structure and/or function
A control group of 100 patients was created, referred to the U.O.C. of Internal Medicine with Stroke Care of the University of Palermo for outpatient visits of various nature, not affected by acute or chronic respiratory or cardiological disease; the subjects enrolled in this group have in particular denied clinical history of bronchial asthma or active use of steroid therapy for any reason and have not presented spirometric evidence of respiratory flow limitation.
The Ecocardiographic parameters evaluated were the following:
LV EDD: TELEDIASTOLIC DIAMETER OF THE LEFT VENTRICLE;
LVESD: TELESYSTOLIC DIAMETER OF THE LEFT VENTRICLE;
IVS: INTERVENTRICULAR SEPTUM;
LV-RWT: RELATIVE WALL THICKNESS OF THE LEFT VENTRICLE;
LAVI: LEFT ATRIUM VOLUME INDEXED/SUP. BODY;
LVMI: LEFT VENTRICULAR MASS INDEXED/SUP. CORPORAL;
LV hypertrophy: left ventricular hypertrophy;
LV EF: LEFT VENTRICULAR EJECTION FRACTION;
(E/A)m ratio: MITRICAL E/A RATIO;
E/e': E/e' RATIO;
LV TEI INDEX: LEFT VENTRICULAR TEI INDEX;
RA Vol: RIGHT ARIUM VOLUME INDEXED
TAPSE: SYSTOLIC EXCURSION OF THE TRICUSPID ANNULUS;
RVEF: RIGHT VENTRICULAR EJECTION FRACTION;
RV TEI INDEX: RIGHT VENTRICULAR TEI INDEX.
**Results:** The percentage of hypertensive asthmatics was significantly higher than controls: 57.5% (50 pts) vs 35.0% (35 pts) (p: 0.013), confirming previous similar results of the BADA Study.
Cardiac structure and function in asthmatics and controls was significantly different in both left and right sections:
-the telediastolic diameter of the left ventricle (50.14 vs 66.51 mm; p: 0.01);
-the thickness of the interventricular septum (11.33 vs 7.57 mm; p: 0.01);
-the relative wall thickness of the left ventricle (0.37 vs 0.31; p: 0.045);
-the volume of the left atrium indexed by body surface area (40.2 vs 32.3 mL/m2; p: 0.001);
-left ventricular mass indexed by body surface area (99.5 vs 89.2 g/m2; p: 0.01);
-the percentage of subjects who exceeded the threshold for the definition of left ventricular hypertrophy (48.8% of asthmatics vs 12% of controls; p<0.0001);
-left ventricular diastolic function estimated by mitral E/A ratio (1.03 vs 1.46; p: 0.03);
-right atrial volume indexed by body surface area (32.7 vs 26.4 mL/m2; p: 0.01);
-right ventricular systolic function measured by ejection fraction (42.9% vs 50.5%; p: 0.05) and global right ventricular function assessed by TEI Index (0.56 vs 0.62; p: 0.04).
A Multivariate regression analysis that evaluated the presence and strength of correlation between asthma and some of the main factors related to it (severe asthma, duration of asthma, FEV1%, average daily dosage of inhaled corticosteroids, average daily dosage of short-acting beta-agonists) with four of the echocardiographic alterations that we showed to be associated with asthma and that we considered emblematic for the independent association between asthma and myocardial involvement (indexed left ventricular mass, presence of left ventricular hypertrophy, right atrial volume, right ventricular TEI index) showed that asthma, severe asthma, and FEV1% levels were independently correlated with all echocardiographic parameters examined. All results of multivariate analysis are adjusted for essential hypertension, Diabetes, Body Mass Index, Creatinine Clearance.
In conclusion Our study shows that an in-depth cardiovascular study in asthmatic patients allows to identify a cardiovascular involvement that is extrinsic in many aspects, both subclinical and clinical, confirming a need for a major "internistic" global approach to the evaluation of chronic respiratory diseases

## 448. DO NOT WATER THAT TREE!

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The re-expansion pulmonary edema is a rare and potentially fatal undesirable effect of chest drainage.
It presents with dyspnea, tachycardia and hypotension after thoracentesis or chest drainage tube positioning.
The aim of this case report is to witness our experience about this circum-

stance and to underline the risk factors, the key point for a rapid diagnosis and a correct clinical management.
We expose the case of a 49-years-old woman with a recent diagnosis of pulmonary adenocarcinoma who was admitted to ER due to dyspnea. The X-ray showed a massive pleural effusion associated to a mediastinal shift; a CT total body was executed in order to have a more detailed imaging: pulmonary embolism was found in the other lung, the one free from effusion.
The patient was then approached step by step starting from the effusion and then treating the emboli. Due to possible complications of the procedure, the lung drainage was positioned by thoracic surgeons assisted by an equipe of intensive care specialists.
Then we accepted the patient in our ward noticing an high outer pressure of the drainage, an additional clue to treat the effusion carefully. We decided to start prophylactic antibiotics to take care of potentially infections of the liquid and according to pulmonary embolism we started anticoagulant therapy with low-molecular-weight heparin (enoxaparin) 6000 UI bid.
Later the same day, the woman started to complain symptoms like dyspnea cough associated, hypotension, tachycardia, sweating and anxiety. The clinical examination demonstrated the presence of crackles in all the fields of the right lung, no evidence of pathological findings was found in the left one. Due to hypotension it was impossible to perform an arteriosus blood gas analysis. The short of breath was not responsive to Reservoire mask and high dose intravenous steroids so ICU was necessary anew. Meanwhile another X-Ray was performed showing a one-sided pulmonary edema from unknown cause.
C-PAP helmet allowed to treat and stabilize the episodes in less than few minutes. A second CT documented a remaining pleural effusion in the right lung and describing "gingko biloba leaf" sign which is compatible with alveolar edema. Intravenous steroids and loop diuretics were continued. The following day the clinical conditions improved: no more dyspnea was observed and only an intermittent oxygen supply was necessary to prevent re-exacerbation.
The pathogenesis of re-expansion edema is still unknown and probably multifactorial; the mechanisms that play an important role are the increase of hydrostatic pressure and a drop of surfactant production. The main risk factors include young age, the lasting and severity of the effusion, technique of drainage and a quick lung re-expansion. These risk factors should be evaluated prior to the insertion of chest tubes.
The mortality swings between 15% and 20% and the therapeutic approach is usually supportive and symptomatic; it consists of analgesic drugs, oxygen therapy and non-invasive-ventilation. Blood plessure support might be necessary in more dramatic cases.

## REUMATOLOGIA

### 449. ADULT-ONSET STILL'S DISEASE (AOSD) IN A YOUNG WOMAN AFTER COVID-19 VACCINATION

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**Background:** Adult-Onset Still's disease (AOSD) is a rare multisystem inflammatory disorder that mostly affects young adults (16-35 years), and it is typically diagnosed after exclusion of other, more common aetiologies.1
Its pathogenesis is suspected to involve aberrant activation of the innate immune system leading to an overproduction of proinflammatory cytokines (e.g., IL-1, IL-6 and IL-8), but the exact mechanism is still unknown.
It has been hypothesized that the SARS-CoV-2 spike protein can induce inflammation via the toll-like receptors (TLR) -pathogen-associate molecular pattern (PAMP) pathway. Similarly, mRNA anti SARS-CoV2 vaccines, by translation of mRNA into the antigenic protein, might induce some of these pro-inflammatory mechanisms possibly implicated in the pathogenesis of AOSD1.
**Objectives:** to describe a case of a young woman who developed AOSD-like symptoms after SARS-CoV2 vaccination, successfully treated with selective IL-1 inhibition treatment.
**Methods:** A 18-year-old woman was admitted to our ward with persistent daily fever (up to 39.5 °C), sore throat, migrating arthralgias and a fleeting, salmon-coloured rash on the limbs. Such symptoms appeared a few days after receiving the second dose of mRNA BNT162b2 COVID-19 vaccine (Pfizer/BioNTech). No significant past medical history was reported.
At admission, blood tests showed a neutrophilic leucocytosis, a mild normocytic anemia, increased ESR and CRP and serum ferritin, normal liver function tests.
**Results:** Tests for infectious diseases were negative. The autoimmunity panel only showed a low-titre positivity for ANA (1: 160). A total body CT scan showed latero-cervical, axillary and mesenterial lymphadenopathy. A total body PET-CT excluded vasculitis and neoplasm; a hematologic disorder was also ruled-out, while a trans-thoracic cardiac ECD ruled-out pericarditis. Empiric therapy with methylprednisolone 1 mg/kg was started, obtaining only a partial response. In accordance with the Yamaguchi criteria, a diagnosis of Adult-Onset Still's disease (AOSD) was hypothesized and anakinra 100 mg daily was added, with a significant and rapid clinical improvement.
**Conclusions:** Although a causal association could not be demonstrated, the close temporal association between the onset of symptoms and the vaccination, the absence of other aetiologies and the good response to anakinra strongly support the hypothesis of a vaccine-triggered AOSD or AOSD-like syndrome.
These observations are in line with other, recently described cases of AOSD after COVID-19 vaccine1-3 and highlight the central role of IL-1 in hyperinflammation during both COVID-19 and AOSD3, supporting a therapeutic role of anakinra in these patients1-3.
**References:** 1. Leone F, Cerasuolo PG, Bosello SL, Verardi L, Fiori E, Cocciolillo F, Merlino B, Zoli A, D'Agostino MA. Adult-onset Still's disease following COVID-19 vaccination. Lancet Rheumatol. 2021 Oct;3(10): e678-e680 - 2. Magliulo D, Narayan S, Ue F, Boulougoura A, Badlissi F. Adult-onset Still's disease after mRNA COVID-19 vaccine. Lancet Rheumatol. 2021 Oct;3(10): e680-e682. - 3. Bamidis AD, Koehler P, di Cristanziano V, Rasche K, Demirel B, Bacher P, Hallek M, Kochanek M, Klein F, Hofmann SC, Wesselmann U, Kofler DM. First manifestation of adult-onset Still's disease after COVID-19. Lancet Rheumatol. 2021 May;3(5): e319-e321.

### 450. OVERLAP SYNDROME OR MISDIAGNOSIS? NOT AN INFREQUENT PICTURE IN RHEUMATOLOGY

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**Introduction:** Patients with Overlap Syndromes who cannot be definitely diagnosed with a well characterized systemic rheumatic disease include 25% of rheumatology patients. They often exhibit one of several disease patterns, manifesting multiple nonspecific clinical or serologic abnormalities of more than one defined rheumatic disorder, making clinical management challenging. We here present a case of possible overlap syndrome, previously labeled as rheumatoid arthritis.
**Case Presentation:** A 75 year-old woman was admitted at the Emergency Department (ED) of our hospital for persistent worsening pain and tenderness of the left shoulder refractory to paracetamol and nonsteroidal antinflammatory drugs (NSAIDs). An accidental fall had occurred in the preceding month without any direct trauma involving the shoulder. Nevertheless, the specific pain had been erroneously ascribed, by her general physician, to the event without any further investigations. Her medical history accounted for paroxismal atrial fibrillation under apixaban, arterial hypertension, obesity (BMI 31kg/m2), multifactorial chronic anaemia secondary to a myelodysplastic syndrome (on hematological follow up) and to previous upper gastrointestinal bleeding for gastric ulcer, and a seronegative rheumatoid arthritis not on medication (previously treated with steroids) associated to arthrosis.
Clinical examination at the ED was unremarkable except for the local pain and swelling of the left shoulder, exacerbated with the movement of the ipsilateral arm, that was constrained. Blood examinations confirmed presence of inflammation (C-Reactive protein (CRP) 16 mg/dl, with normal WBC count), chronic anemia, (Hb 9 g/dl, MCV 76 fL, MCHC 31 g/dl, fer-

ritine 523 ng/ml, sideremia 46 mcg/dl, transferrin 154 mg/dl), and kidney injury (creatinine 2.5mg/dl, azotemia 170mg/dl). Electrocardiogram (ECG) showed a sinus tachycardia (100 bpm) with normal atrioventricular and intraventricular conduction with diffuse non-specific ventricular repolarization abnormalities. A left shoulder X-Ray excluded local fractures highlighting several peri-articular micro-calcifications.
She was therefore admitted to our Emergency Medicine ward, where she underwent a CT scan of the left shoulder that highlighted a severe arthrosis characterized by disruption of the normal articular anatomy associated to a remarkable distension of the articular capsule and periarticular bursae for high density sinovial fluid, with local gasseous micro-nuclei, several focal calcifications, and several hemorragic spots.
An orthopedic consultation excluded a surgical indication and, in the hypothesis of a secondary periarthritis, an antibiotic empirical therapy with piperacillin/tazobactam and levofloxacin was initiated with meager clinical relief and laboratory variation (CRP remained stable at 7mg/dl). An autoimmune involvement of the enthesoarthritis was thus suspected and a specific laboratory screening with an X-Ray study of the hands were performed. The first resulted positive for anti-centromere antibodies (ACAs), and the second showed symmetrical degenerative alterations accompanied by arthritis of the proximal interphalangeal joints of the second and third fingers of both hands. A poliarticular inflammatory arthritis secondary to underlying subclinical systemic sclerosis was hence diagnosed, antibiotic therapy was withdrawn and a high-dose methylprednisolone (0.75 mg/kg) was started with an immediate clinical benefit. In the following five days she not only regained capability in brachial movements, but also reported pain relief of the small joints of the hands. Steroid medication was thereby slowly tapered and the patient was discharged and adressed to our Reumathology outpatient center.
**Discussion and Conclusion:**
A heterogeneous group of patients may exhibit signs of inflammatory arthritis suggestive but not diagnostic of rheumatoid arthritis. About 10 % of them ultimately fulfill criteria for another systemic rheumatic disease, and 10 % will acquire other features of systemic rheumatic disease but still cannot be diagnosed with a specific well-differentiated rheumatic disorder.
With our clinical case we want to highlight how a specific diagnosis should be made only when patients fulfill appropriate classification criteria. Assigning diagnostic labels to patients implies confidence and certainty in pathogenesis, prognosis, and outcomes, with a risk, in the thinking of the health care provider, to inappropiately circumscribe the clinical picture, leading to eventual inappropiate management and possible harm.
**Bibliography:** 1- Jones R, Barraclough K, Dowrick C. When no diagnostic label is applied. BMJ 2010; 340: c2683. - 2- Hitchon CA, Peschken CA, Shaikh S, El-Gabalawy HS. Early undifferentiated arthritis. Rheum Dis Clin North Am 2005; 31: 605. - 3- Cervera R, Khamashta MA, Hughes GR. Overlap syndromes. Ann Rhem Dis 1990; 49: 947.

## 451. RITIRATO

## 452. A PERSISTENT FEVER

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The patient, 40 years old, smoker, went to the emergency room of a local hospital for fever and edema of the lower limbs with arthralgia and erythema. Therefore he performed chest CT (two pulmonary thickening areas and lymphadenomegaly in the right hilar site) and venous doppler (not deep vein thrombosis) and was discharged at home with indication of empirical antibiotic therapy. For persistence of fever, he went again to the emergency room and was admitted to the medical ward. He also presented a clinical history of previous varicocele surgery and previous pleurisy. He was alert, cooperative, oriented, hemodynamically stable, eupnoic in ambient air, feverish. There was edema in the lower limbs with skin, bilateral tibial level, erythematous and hot. The remaining objectivity was normal. Blood chemistry tests showed increased inflammation indices (CRP 8.21 mg / dl, fibrinogen 730 mg / dl) and D-Dimer (5.47 ng / ml). Serologies were negative for ongoing infection (Borrelia, Mycoplasma, weil felix reaction, CMV, EBV, HCV). Autoimmunity (ANA reflex), cryoglobulin detection and urinary antigens for Legionella and Pneumococcus were negative. Previous HBV infection (HBsAb positive) was reported. The instrumental investigations (abdominal ultrasound, skin-subcutaneous ultrasound of the lower limbs, venous doppler of the lower limbs, transthoracic echocardiogram) did not document any significant alterations. After a collegial discussion with a specialist colleague, second level investigations (PET-CT and bronchoscopy) were requested, indicative of Lofgren's syndrome. Therefore steroid therapy was set and continued at home with benefit and regression of the symptoms. The patient is followed up in a pneumological clinic for interstitial diseases. To exclude systemic implications, he performed brain MRI and eye examination, as normal.

## 453. RISK OF SEVERE INFECTION AMONG RHEUMATOID ARTHRITIS PATIENTS ON BIOLOGICAL DMARDS: A POPULATION-BASED COHORT STUDY

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**Background:** Biological disease modifying anti-rheumatic drugs (bDMARDs) are widely used for the management of rheumatoid arthritis (RA), although their benefits are counterweight by an increased risk of infections. In the present study, we used administrative data to compare the risk of severe infections requiring hospital admission among different classes of bDMARDs..
**Methods:** A retrospective cohort study was conducted using Administrative Health Databases of the Piedmont Region, Italy. Relevant data were obtained from: 1) inhabitants registry, 2) hospital discharge records, and 3) co-payment exemption registry; 4) drug claims registry. Fine and Gray competing risk models were fitted to evaluate the association between use of different types of bDMARDs and occurrence of severe infection accounting for treatment interruption as competing risk.
**Results:** A total of 1,780 new users of bDMARDs were identified. Among them, 50 hospitalizations for infection occurred during the study period. Use of Tocilizumab was associated with an increased risk of infection, compared to TNF inhibitor drugs (sub-distribution hazard ratios -sHR: 2.510; 95CI: 1.279-4.926), while no difference in the risk of severe infection was found for abatacept (sHR: 0.584; 95CI: 0.234-1.457).
**Conclusions:** bDMARDs treatment is generally safe in clinical practice with slight but important differences among classes. The increased risk of infection associated with tocilizumab use should be taken into account when balancing risk and benefits of starting a treatment with this drug.

## 454. POLYMYALGIA RHEUMATICA OR RS3PE SYNDROME: IDIOPATHIC OR FOLLOWING MRNA COVID-19 VACCINATION? A CASE REPORT

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**Background:** Among the side effects of the mRNA COVID-19 vaccines pathologies affecting the musculoskeletal system have been reported. Of all UK spontaneous reports received up to 06/04/ 2022 for Pfizer/BioNTech vaccine, out of a total of 168,927 Yellow-Cards, 55,737 reports of muscle and tissue disorders have been described, including 88 polymyalgia rheumatica (PMR) (1).
**Case Presentation:** A 74-year-old Caucasian man, in full well-being, undergoes the anti-Covid-19 vaccine with mRNA Comirnaty (2^dose) on may2021. After three weeks they appeared cervical and right shoulder pain treated with initial benefit through NSAIDs and betamethasone. Right shoulder MRI showed acromioclavicular arthrosis and supraspinatus tendinosis. After a few days, stiff neck, pain in the shoulders and also in the pelvic girdles, pain in the hands and arms associated with functional limitation, pain in the knees and, subsequently, edematous swelling of the hands appeared. Suspected polyarthritis with polymyalgia, intramuscular dexamethasone therapy was applied. Irregular cortisone treatment, associated with various oral NSAIDS, lasted for several months, but with poor result. Hands x-ray: osteoarthritis, no erosion. EMG: carpal tunnel syndrome. Blood tests performed in September showed: CRP 8.6 mg/L (<5), RBC 3.73x10^12/L, Hb 10.3 g/dL, MCV 86 fl, MCH 27 pg, gammaglobulin 5.9 g/L (nv>6.4); normal: renal, hepatic, thyroid function tests, RF, transferrin, ferritin, CPK, folic acid, vit. B12, fecal calproctectin, αFP, CEA, CA 19-9, PSA; fecal occult blood positive. EGDS and colonoscopy: gastric hyperplastic polyp and tubulo-villous adenoma in sigma diverticulosis. In December the symptoms worsened with the onset in the lower limbs improntable

oedema, dyspnea from exertion, marked accentuation of the livedo reticularis present for many years, erectile dysfunction. The pains in the upper limbs and the edema of the hands had increased. The patient comes to our observation in February 2022 after performing mRNA Spikevax vaccine booster dose. Medical history: psoriasis at a young age, arterial hypertension, carotid atheromasia, mild chronic normocytic normochromic anemia, dyslipidemia, hyperuricaemia, cervicoarthrosis, mild hypogammaglobulinemia. Ongoing therapy: atorvastatin, aspirin, candesartan+HCTZ, allopurinol, esomeprazole. Physical examination: symmetrical pitting oedema in the back of both hands and wrist (boxing-glove), shoulders movement deficit, lower limbs and feet oedema, with diffuse livedo reticularis, small palpable lymph nodes in the groins, bilateral hydrocele, enlarged right calf, small psoriatic area left hand. Laboratory checks: CRP 55, D-dimer 2211 µg/L (nv<200), fibrinogen 4.90 g/L (nv<4), haptglobin 3.97 g/L (nv<2), magnesium 0.56 mmol/L (nv 0.75-1.04); 25-OH vit. D 59 nmol/L (insufficiency); SOB absent. ANA, ENA, anti-CCP, C3c, C4, Ig G, A, M, Ig E, INR, aPTT, calcium, phosphate normal; cryoglobulins absent; ACL, anti-β2 GPI, markers for HCV and HBV negative. Abdominal ultrasound negative. Right shoulder ultrasound: long-had-biceps tenosynovitis and subadeltoid bursitis. Chest-X-ray negative. Echocardiogram: EF> 60%, left atrial enlargement, aortosclerosis. Lower limbs US: subcutaneous soft tissues oedema, fluid dissociation of the adipose lobules, no DVT, bilateral Baker's cyst, hematoma in the medial twin muscle (previous exertional muscle tear). The patient was treated with oral methylprednisolone (8 mg/day), cholecalciferol, furosemide, enoxaparine, magnesium. The oedema in the hands and legs quickly regressed, the weight was reduced by 2 kg in a week, pain disappeared, cenesthesis improved. Laboratory testing: RBC 4.21x10^12/L, Hb 10.6, MCV 84, CRP 1.84, D-dimer 371, Mg 0.68, gammaglobulin 10; JAK2 V617F mutation negative. Increased D-dimer was associated with right calf hematoma, hypomagne saemia may be related to PPI therapy.

**Conclusions:** We report a case of probable rheumatic polymyalgia arising three weeks after second dose of the mRNA vaccine and evolving into remitting seronegative symmetrical synovitis with pitting oedema. RS3PE, considered as an edematous variant of PMR, it is rare, affects elderly males and is characterized by acute onset of symmetrical oedema and small joint synovitis involving mainly the hands and, less often, the feet. Although most cases are idiopathic, RS3PE has been associated with other rheumatic conditions, malignancies, parvovirus infection, intravesical BCG instillation and more recently with immunotherapies. For now, we have excluded an association with neoplastic pathology. The vaccine association remains plausible even if so far only three cases have been described in the literature (2,3).

**References:** 1..COVID-19 mRNA Pfizer-BioNTech Vaccine Analysis Print. Report Run Date: 07-Apr-2022, page 1-117. 2.Watad A, De Marco G, et al. Immune-mediated disease flares or new-onset disease in 27 subjects following mRNA/DNA SARS-CoV-2 vaccination. Vaccines 2021; 9: 435.3.Parperis K, Constantinou M. Remitting seronegative symmetrical synovitis with pitting oedema following BNT162b2 mRNA COVID-19 vaccination. BMJ Rep 2021;14: e244479

## 455. CARDIOVASCULAR RISK AND OSTEOMETABOLIC ALTERATIONS IN PATIENTS WITH RHEUMATOID ARTHRITIS: PRELIMINARY RESULTS FROM A MULTIDISCIPLINARY STUDY

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**Background and Objective:** Rheumatoid Arthritis (RA) is associated with increased cardiovascular (CV) morbidity and mortality and osteometabolic alterations. Traditional risk factors can play a role on this increased risk, but other causes should be involved, such as the chronic inflammation, which can lead to insulin resistance and accelerated atherogenesis, the use of non-steroidal anti-inflammatory drugs and glucocorticoids and the reduced physical exercise due to functional limitation. The objective of the present study is to cross-sectionally estimate cardiovascular risk and osteometabolic status in patients with RA and to evaluate the association with some disease parameters such as positivity of autoantibodies, disease activity and steroid therapy.

**Material and Methods:** At the current time, 61 consecutive patients with diagnosis of RA, admitted to the Rheumatology Unit of the City of Health and Science University Hospital of Turin, were prospectively recruited and assessed for cardiometabolic risk by the Endocrinology Unit of the same hospital. Subjects underwent medical examination, laboratory and instrumental tests, to define his own cardiometabolic risk profile.

**Preliminary Results:**The prevalence of the major cardiovascular risk factors and osteometabolic alterations was the subsequent: arterial hypertension (52%), type 2 diabetes mellitus (7%), dyslipidemia (56%), smoking habit (18%), obesity (15%), osteoporosis (42%), and vertebral fragility fracture (30%). At the univariate analysis, the enrolled population was divided according to serodiagnosis, steroid therapy and disease remission, the latter depending on DAS28-PCR. No statistically significant results were highlighted stratifying population by serodiagnosis. While considering osteometabolic parameters, patients with high disease activity (DAS28-PCR >2.6) showed lower bone mineral density (BMD) values [BMD femoral trochanter: 0.53± 0.08 vs 0.60 ± 0.08 (g/m2), p=0.031; BMD L2: 0.82 ± 0.01 vs 0.94 ± 0.14 (g/m2), p=0.036] and T-score value on bone densitometry [T-score Femoral total: -1.88 ± 0.53 vs -1.07 ± 0.83, p=0.005], higher percentage of osteoporosis [67% vs 27%, p=0.047] and vertebral fragility fractures [60% vs 12%, p=0.001], and higher sarcopenia score [SARC-F: 5 (3-7) vs 2 (2-4), p=0.020], in comparison with subjects with remission disease. These differences were not confirmed when the population was divided according to the use of steroid therapy. For cardiovascular and metabolic variables, disease activity group showed higher rate of previous CV events [10% vs 5%, p=0.464] and of type 2 diabetes mellitus [11% vs 6% p=0.603], higher value of HbA1c [5.7 (5.5-5.8) vs 5.5 (5.4-5.8) (%), p=0.332] and lower of LDL cholesterol [115.28 ± 35.12 vs 126.81 ± 31.09 (mg/dl), p=0.239], compared to remission group, but without reaching statistical significance. Lower value of LDLc cholesterol in RA patients with high disease activity, even without reaching statistical significance, reflects the typical lipid paradox observed in subjects with active systemic inflammation. At the multivariate linear regression analysis, advanced age (p=0.001), steroid therapy (p=0.021) and copeptin (p=0.002) showed an inverse association and lumbar T-score (p=0.002) a direct one with lumbar trabecular bone score (TBS). Moreover, male gender (p=0.001) revealed a direct and significant association, while copeptin (p=0.086) an inverse and not significant one with percentage of lean mass on total body dual energy X-ray absorptiometry, correcting for advanced age, duration of disease, steroid therapy, and disease activity. In the last model, advanced age (p<0.001) and copeptin (p<0.001) showed a direct and significant association with a CV risk score (HeartSCORE), correcting for parameters of disease while serodiagnosis, duration of disease, steroid therapy, and disease activity.

**Conclusions:** Preliminary results of this study showed that osteometabolic alterations and cardiovascular risk factor were associated with disease activity, an expression of systemic chronic inflammation, but not with steroid therapy and serodiagnosis. At the multivariate analysis, the association of disease activity and TBS values, did not reach the statistical significance, probably for the loss of statistical power. However, steroid therapy, as well as advanced age, low lumbar T-score and high value of copeptin, remained independently associated with lower TBS value. Disease parameters were not associated with lower percentage of lean mass at total body densitometry and higher HeartSCORE values, while advanced age and copeptin were associated with bone health and cardiovascular risk. In particular, copeptin, in this cohort of RA patients, demonstrated a significant inverse association with percentage of lean mass at total body densitometry, and a direct one with HeartSCORE.

## 456. INVOLVEMENT OF THE HEART IN SCLERODERMA: A CASE REPORT

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A 56- years old woman was admitted to our department because of the onset of chest pain modifiable with trunk movements for 15 days, attenuated by the intake of anti-inflammatory drugs, associated with exertional dyspnea, persistent and worsening asthenia, cold sweating in the absence of fever and / or syncope. In addition, she reported the appearance of Raynaud's phenomenon for about seven months. Family history was negative for cardiovascular events and autoimmune diseases. Only previous ovarian cyst removal surgery (15 years earlier) was present in her clinical history. Phisical examination revealed sclerodactyly in the hands in the absence of calcinosis or telangiectasias. The echocardiogram showed non-dilated left ventricle with preserved systolic function, in the absence of alterations in the kinetics, non-dilated right sections and circumferential pericardial effusion of a maximum size of 3 cm in the posterior area conditioning a

partial collapse of the right atrium. Another echocardiogram performed after 24 hours revealed right ventricle free wall collapse. She subsequently underwent evacuative and exploratory pericardiocentesis with withdrawal of 500 cc of macroscopically serum-haematic liquid. The investigations carried out on the pericardial fluid were compatible with an exudate with negativity of cytological and microbiological examinations (on pericardial fluid and serum). Blood tests revealed high levels of inflammation indices, positivity for ANA at high title and anti-centromere antibodies, suggestive for limited cutaneus systemic sclerosis. Otherwise, in order to exclude the neoplastic etiology of the pericardial effusion, total body CT scan, complete gynecological consultation and bilateral mammography were performed and resulted all negative for significant alterations. For diagnostic completion the patient underwent total body PET / CT with 18F-FDG which did not show metabolically active lesions, thus excluding both heteroplasia and vasculitis of the great vessels. Anti-inflammatory therapy with ibuprofen and colchicine at adequate dosage was started with progressive improvement of the clinical and humoral picture. Before discharge, the patient underwent echocardiographic evaluation which showed a slight detachment at the level of right sections without hemodynamic significance. This case report confirmes that acute pericarditis can be a manifestation of limited cutaneous systemic sclerosis. Although pericardial involvement is frequent in scleroderma (symptomatic pericarditis in 16% of patients with diffuse scleroderma and about 30 % of patients with limited scleroderma), acute pericarditis with large pericardial effusion and signs of cardiac tamponade is exceptional in these patients. It is suggested that pericardial fibrosis in scleroderma may predispose to cardiac tamponade. Although no specific therapy exists for scleroderma heart disease, early recognition of the presence and type of scleroderma heart disease may lead to more effective management of patients with scleroderma.

## 457. ACUTE PANCREATITIS: A COMMON DISEASE WITH A RARE AETIOLOGY. A CASE OF SJOGREN'S SYNDROME DIAGNOSED IN A 78-YEAR-OLD WOMAN

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**Introduction:** Sjögren's syndrome (SS) is a systemic autoimmune disorder characterized by chronic inflammation of exocrine glands. SS typically involves salivary and lachrymal glands, leading to xerostomia and xerophthalmia (1), namely sicca syndrome. Systemic manifestations include fatigue, musculoskeletal complaints, hepatic, pulmonary, renal, and nervous system involvement. Pancreas is, in part, an exocrine gland that is functionally and histologically comparable to the salivary glands; however, its involvement is debated (2). Here, we report a case of acute pancreatitis that permitted to diagnose the Sjögren's syndrome in a 78-year-old woman.
**Methods:** A Caucasian 78-year-old woman was admitted to the emergency department with epigastric pain, nausea, asthenia, and weight loss (9 kg within 5 months). At admission, she presented mild thrombocytopenia (122x 103/ul), GOT and GPT x 2 ULN, GGT x 1.5 ULN, amylase x 6 ULN, lipase x 21 ULN, ESR 27 mm/h, CRP 1.9 mg/l. The patient was treated with fasting, enteral nutrition, analgesics, potassium supplement and antiemetics with no resolution of symptoms. The computed tomography (CT) and magnetic resonance imaging (MRI) revealed intrahepatic bile ducts and common bile duct (CBD) dilatation with pancreas head inhomogeneity. Common causes of acute pancreatitis were excluded (alcohol use, gallstones, hypertriglyceridemia, hypercalcemia, medications, ERCP). However, a more accurate anamnesis described a history of dry mouth, recurrent keratoconjunctivitis and vaginal dryness. Additional investigation showed normal levels of C3 and C4, rheumatoid factor (RF), IgA, IgM, proteinogram, while IgG4 was reduced (0.6 mg/dl; n.v. 3- 200 mg/dl). Antinuclear antibodies resulted positive (1: 320, granular pattern) and anti-SSA/B antibodies were negative. Therefore, a Schirmer's test was carried out, resulting positive (5 mm/5min on at least one eye) and the salivary gland biopsy revealed the presence of focal sialadenitis with lymphocytic and plasma cell inflammatory infiltrate (Grade III, Chisholm e Mason score). According to EULAR classification criteria (2016) we diagnosed primary SS.
**Results:** The patient was treated with prednisolone 1 mg/kg/day (slow-tapering regimen for 6 weeks) and hydroxychloroquine 200 mg b.i.d.. A complete symptom resolution occurred after 1 week, in parallel with a significant reduction of pancreatic enzymes. After 6 months, the patient showed pancreatic enzymes within normal limits, and echo-endoscopy was carried out, revealing dilation of intrahepatic bile ducts and normal diameter of CBD (3 mm at the hilum).
**Conclusion:** In approximately 10-40% of patients with acute pancreatitis the cause remains elusive (3). Ramos-Casals et al demonstrated that, in a cohort of patients with SS (1010 patients), the prevalence of acute pancreatitis was 0.5% (4). A nationwide, population-based study in Taiwan described that patients with SS have a higher risk of acute pancreatitis compared with general population, while the use of hydroxychloroquine was protective (5). In conclusion, limited studies reported the correlation of SS with acute pancreatitis, and comprehensive long-term investigation will be necessary to fully understand this association.

## 458. LIVER INVOLVEMENT IN A PATIENT WITH SYSTEMIC SCLEROSIS

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**Case Presentation:** In October 2021, a 82-year-old Caucasian man was admitted to our Internal Medicine Unit because of the onset of increased abdomen volume and dyspnoea. He was affected by Systemic sclerosis (SSc) since 1999, initially treated with methotrexate, corticosteroids, azathioprine and finally with miycophenolate. Furthermore, the patient suffered from third stage chronic kidney disease, low platelet count of unknown origin and aortic valv stenosis (treated with transcatheter aortic valve implantation in July 2021). During hospitalization, edematous-ascitic decompensation was diagnosed, for which the patient underwent several evacuative paracenteses. Neoplastic cells and peritoneal carcinosis were excluded, while liver ecography showed dilated portal vein (13.8 mm) and portal hypertension, paraumbilical collateral venous circulation, and no focal lesions. Blood tests were in range except for hypoalbuminemia and low platelet count. Anamnesis excluded alcoholic intake. HIV, HCV, HBV, AMA, ASMA and LKM antibodies tests were negative; ceruloplasmin, transferrin saturation and IgG classes were normal. Transtoracic echocardiography was negative for both right and left heart failure. Liver biopsy could not be performed due to patient age and thrombocytopenia. Because of persistence of high inflammatory indexes despite piperacillin-tazobactam treatment, even if without hyperpyrexia, chest and abdomen computed tomography (CT) scan and urine and blood cultures were performed. CT scan revealed abundant pleural effusion with consensual disventilatory phenomena in an anasarcatic state, chronic obstructive pulmonary disease and a suspected ischemic splenic triangular-reflective area plus a suspected intestinal ischemic area too. Blood cultures were positive for S. Epidermidis MRSE and Candida Albicans. In addition, the patient progressively showed several painless bleeding skin spots on the palms and soles of the feet which were suggestive of Janeway lesions, and subcongiuntival hemorragy. Transesophageal echocardiography was then performed, showing infective endocarditis on protesic valve with adjoining circumferential abscess of the mitroaortic junction. Ocular involvement was excluded. Cardiac surgery was contraindicated due to the severity of the patient clinical condition and low performance status; antimicrobic targeted therapy with daptomycin and caspofungin was then started and immunosuppressive therapy was suspended. Three days after starting specific antibiotic therapy, blood cultures became negative; moreover, the patient showed a strong diuretic response so that paracentesis were no more needed. After few more days, however, the patient progressively worsened and developed refractory ascites; thereafter was transferred to a territorial hospice, where died on day five from discharge.
**Conclusion:** It is known that liver is unusually involved in SSc. Primary biliary cirrhosis is the most commonly associated hepatic disorder, occurring in 2.5% of patients with SSc, followed by autoimmune hepatitis. Rarely, other hepatic pathologies have been reported, including primary sclerosing cholangitis, nodular regenerative hyperplasia, idiopathic noncirrhotic portal hypertension, infarction as a result of vasospasm, and vasculitis.
As autoimmune, alcoholic, infective and cardiogenic etiology were excluded, we explained ascites as consequence of idiopathic portal hypertension in cryptogenetic hepatic involvement. In light of the infectious state, the patient was unable to resume immunosuppressive therapy. Therefore, this clinical case shows the complex work-up and the fragile balance between autoimmune and infective state both coexisting and their association with liver decompensation.

## 459. THE IMPORTANCE OF CT- PET TOTAL BODY WITH18 F-FDG TO DIAGNOSE VASCULITIDES OF LARGE VESSELS

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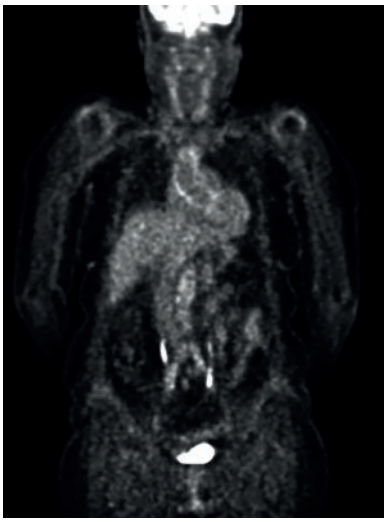
**Background:** Vasculitides belong to a heterogeneous group of..conditions characterized by inflammation of the blood vessel wall. Each type of vessel can be affected by the inflammatory process. This explains the extreme polymorphism of the clinical presentation, which makes difficult a diagnostic classification especially in the early phase. Vasculitides are commonly classified on the basis of the caliber of the affected vessels: large, medium and small. The most common causes of large vessel vasculitides are giant cell arteritis and Takayasu's arteritis.
**Case Report:** 70-year-old female patient with history of chronic migratory arthralgias responsive to Nimesulide; arterial hypertension under treatment; vaccinated with first dose of Astrazeneca vaccine. She accessed the hospital for cervical pain, chewing pain, loss of appetite, low-grade fever and weight loss (5 kg) with general malaise. In the emergency room, blood chemistry tests showed an increase in the indices of inflammation (CRP 90.35 mg/l), ESR 90 mm and fibrinogen 600 mg/dl. The patient underwent molecular swab for Sars Cov 2 with negative results and blood tests such as: urine culture; blood cultures for bacteria and fungi; beta D glucan; HIV and serum tests for brucella, rickettsia coronii, borrelia, coxiella burnetii, typhus and paratyphus; autoimmunity anti-nucleus antibodies, anti native DNA, Anti ENA, Anti CCP, anti mitochondria, anti gastric wall,hip, myositis immunoblot resulted negative. During the hospitalization chest-X-ray, chest-neck- abdomen, brain and cervical spine CT,abdomen ultrasound,echocardiogram,resulted negative.CT-Pet showed vascular uptake of the carotids, subclavian, thoracic and abdominal aorta, common iliac. This pattern was compatible with inflammatory processof arterial trii in active phase
**Conclusions:** Our case report demonstrates that CT-PET scan could be considered useful tool for evaluation of patients withvasculitides. The rationale for the use of 18 F-FDG, a tracer of glucose metabolism, to evaluate inflammatory processes is due to accumulation of this radioactive substance in the leukocytes activated within the site of inflammation.



## 460. A CASE OF MAN WITH BLADDER CANCER AND SEVERE POLYARTHRITIS

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A 66-year-old Caucasian man presented to our Emergency Department because of dysuria and legs pain. In his clinical history: appendicectomy, a previous diagnosis of bladder cancer treated with trans urethral resection and periodic Bacille Calmette-Guerin (BCG) intravescical instillations. The family history was positive for rheumatoid arthritis. The last BCG intravescical instillation was performed 7 days before the hospital admission. At physical examination, the patient was awake, oriented, and hemodynamically stable. He presented with swelling of the lower limbs associated with pain localized at large joints (both knees and ankles). Blood tests showed neutrophilic leucocytosis (WBC 11550, N 79%, L 10.6%) and increased serum C-reactive protein (7.54 mg/dL, normal value <0.5 mg/dl). The doppler ultrasound of the vascular axis of the lower limbs excluded the presence of deep vein thrombosis and the microbiological tests (i.e., blood and urine cultures, urethral swab for the detection of chlamydia, acid-fast bacillus culture on urine, serology for HBV, HCV and HIV) were negative.
During the hospitalization, the patient developed a frank polyarthritis involving both ankles and knees and the right wrist with abundant amount of intraarticular effusion and evidence of bursitis at the ultrasound of the knees, confirmed by MRI. An arthrocentesis of the left knee was performed and analysis of the fluid showed high amount of red blood cells, low number of leukocytes, whereas no crystals detected. Immunological serum tests revealed an aplotype HLA B49 and B51.
Therefore, taking into account all this information, our primary diagnostic hypothesis was BCG instillation–related arthritis (and cystitis) and the patient was treated with anti-inflammatory therapy (ibuprofen and glucocorticoids for 6 weeks), with complete resolution of the symptoms.

## 461. FEVER OF UNKNOWN ORIGIN AND CHEST PAIN: A RARE CASE OF GIANT CELL ARTERITIS ASSOCIATED WITH ACUTE PERICARDITIS

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**Introduction:** Giant cell arteritis (GCA) is a granulomatous vasculitis of the large vessels which mainly involves extracranial branches of the carotid artery. The typical presentation is an abrupt onset retro-orbital headache, jaw and tongue claudication, visual loss (amaurosis fugax), and temporal artery tenderness, but it can ensue also with a subtle and nonspecific systemic presentation, including constitutional symptoms, fever, weight loss.
Cardiac involvement is uncommon in GCA, with myocardial infarction and aortic aneurysm being severe complications of the disease. Pericardial involvement is quite rare and has been only documented in case reports and small observational studies.
We report a case of GCA in which the patient presented with fever of unknown origin associated with incidental finding of pericardial effusion at transthoracic echocardiography.
**Case Presentation:** A 55 year-old woman was admitted to our ward because of relapsing fever (up to 38°C) in the past month, associated with retrosternal and interscapular pain, radiating to the cervical area. She also reported night sweats and weight loss (approximately 4 kg). She had already been treated by the general practitioner with a cycle of antibiotics (cephalosporins) and a cycle of corticosteroids (prednisone 25 mg) without resolution of symptoms. In her past medical history, she was diagnosed with breast cancer in 2011, with negative follow-up to date, and hypertension.
At the emergency department her physical examination was unremarkable. The patient denied any urinary or gastrointestinal discomfort or dyspnea. A 12-lead ECG showed normal sinus rhythm without alteration in the ST and PR segments. Blood tests showed increased inflammatory markers (CRP 13 mg/dL, ESR 136 mm/h, ferritin 1205 ng/mL) and leukocytosis, mild elevation in liver function tests, spontaneously normalized during the hospitalization, and normocytic anemia (Hb 8.4 g/dL). Chest X-ray was negative, as well as nasopharyngeal swab for SARS-CoV2 (PCR), blood cultures and urine cultures. Because of the patient's clinical stability and the lack of evidence of an infective process, empiric antibiotic therapy was not started and the patient was transferred to our unit.
During hospitalization, further diagnostic tests were conducted. In particular, serology for HBV, HAV, HCV, HIV, HHV-6, Mycoplasma pneumoniae, Chlamydia pneumoniae, Toxoplasma were performed, with only evidence of a previous infection from HAV. In addition, IgM anti-Chlamydia Trachomatis came out positive, but an infectivology consult ruled it out as the cause of the clinical picture. The patient was also tested for EBV, CMV and parvovirus DNA, all negative, as well as Widal-Wright and Weil-Felix serology. Because of fever, sweating and systemic symptoms, quantiferon assay was required but excluded any previous contact with mycobacterium tuberculosis. Screening for autoimmunity was negative (ANA, ENA, RF,

anti-CCP, C3 and C4, anti-dsDNA, anti-SM, ANCA).
During hospital stay, the patient reported the persistence of retrosternal and interscapular pain, exacerbated by deep inspiration and trunk flexion, worsening during febrile episodes and partially responsive to paracetamol. These findings elicited a strong clinical suspicion for acute pericarditis. A transthoracic echocardiography indicated the presence of mild pericardial effusion without hemodynamic impairment. No valve vegetations were found. Cardiac enzymes were within normal range. Treatment with colchicine and ibuprofen was then started, with only partial clinical benefit.
Being the clinical picture suggestive but not conclusive for acute pericarditis, an FDG-PET/CT scan was requested to rule out other causes of the fever (mainly neoplastic). Interestingly, along with confirming the diagnosis of pericarditis, with a strong pathological diffuse uptake of the radio-marker within the pericardium, the exam highlighted also a mild-moderate uptake at the level of the subclavian arteries bilaterally, compatible with large vessel vasculitis. Our hypothesis was corroborated by a rheumatological consult, that concluded for Giant Cell Arteritis (based on the clinical manifestation and the age group) associated with acute pericarditis. Colchicine and ibuprofen were stopped and treatment with high dose prednisone (1 mg/kg) was started, with substantial clinical and biochemical improvement (CRP 5.21 mg/dL on a decreasing trend). After 14 days of hospitalization, the patient was discharged with a corticosteroid tapering regimen, PCP prophylaxis and was referred to an outpatient rheumatological follow up.
In conclusion, GCA is quite uncommonly associated with acute pericarditis, but if recognized promptly, treatment with high dose corticosteroids is effective, with complete remission of symptoms, avoidance of complications and preservation of the patient's quality of life. Diagnosis in a patient that presents with fever of unknown origin can be challenging and often can't be reached. Rheumatologic etiology must always be considered, even when the clinical picture is not typical and lays out an unusual presentation.

## 462. CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME (CAPS) IN AN AFRICAN PATIENT WITH MULTI-ORGAN FAILURE: A CASE REPORT

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Catastrophic antiphospholipid syndrome (CAPS) is a rare, life-threatening variant of antiphospholipid syndrome which can lead to multi-organ failure caused by autoimmune-mediated small vessel occlusion. Although it can be very challenging, its diagnosis should be rapid because of its high rate of mortality. In scientific literature there are only few studies about pathophysiologic mechanisms of the CAPS, as it is difficult to collect serum samples during an acute episode due to low prevalence and high mortality of this autoimmune disease. We present a rare case of an African woman who developed multi-organ failure involving lungs, liver, kidneys and brain, and a severe anaemia. A high titre of lupus anticoagulant (LAC) antibodies was found, while anti-β2-glycoprotein I (aβ2GPI) and anti-cardiolipin antibodies were in range. A clinical diagnosis of catastrophic antiphospholipid syndrome (CAPS) was made and a rapid treatment with repeated plasma exchange, anticoagulant and immunosuppressive drugs were started, observing a progressive regression of symptoms. This case highlights how a rare disease like catastrophic antiphospholipid syndrome should be considered in the differential diagnosis of a critical patient with multi-organ failure: a prompt diagnosis with subsequent adequate therapy can be crucial for saving the patient's life.

## 463. ANTI-MPO ASSOCIATED INTERSTITIAL LUNG DISEASE: A CLINICAL PICTURE WITH LACK OF INTERNATIONAL CONSENSUS

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**Introduction:** Connective tissue diseases (CTD) are a wide group of pathologies that can interest almost each organ of human body with various combination. However, patients with CTD rarely only have some - clinical, laboratoristic, radiologic - feature of autoimmunity with a specific organ impairment. So, these forms often "elude" classic definitions and criteria of CTD with a consequent difficult clinical management. For example, European Respiratory Society and American Thoracic Society proposed classification criteria for patients with interstitial pneumonia and features of autoimmunity that do not meet CTD criteria, naming these diseases IPAF (Intestinal Pneumonia with Autoimmunity Features). However, also this new classification seems to "miss" some – not so – rare clinical picture. We admitted a patient with diagnosed "ANCA (anti-MPO)- related interstitial pneumopathy" that showed a disease progression despite antifibrotic therapy.
**Case Report:** A 67-year-old man admitted at the Emergency department after 1 month of intermittent fever not responsible to various antibiotic therapies, associated with cough with clear sputum and some haemoptysis episode. 2 years ago, he was diagnosed a "ANCA (anti-MPO) related interstitial pneumopathy", based upon thorax CT scan and serologic findings of high title of anti-MPO antibodies, treated as an IPF with nintedanib (drug reduction after diarrheal appearance, suspended at the admission). In anamnesis MD type 2 and Forrestier syndrome; he also referred weight loss (15 kg in 1 year) and asthenia. He had a characteristic objective find at thorax auscultation, bilateral crackles "velcro-like". At the basal blood sample only an increase of CRP (81 mg/dl) was found.Our primary differential diagnostic aim was to exclude an infectious form: we performed both blood tests (haemoculture) and BAL (bronchoalveolar lavage) with microbiologic and PCR samples which were negative for infections. The patient was apyretic during almost the whole recovery. We reconsidered the admitting diagnosis and consequent therapy to differentiate an "IPF with ANCA" by a more complex disease, that could be included in the "IPAF spectre". The essential difference between these two groups is that the second shows also pulmonary inflammation overlap to the underlying fibrosis and can be responsive to immunosuppressant drugs. This second scenario fitted with the clinical worsening of the patient and imposed further in-depth analysis. We planned a thorax magnetic resonance with specific sequences to assess if there were pulmonary active flogistic areas at basal time (T0) and after 5 days of high-dose of intravenous corticosteroids (250 mg of 6-metil-prednisolone, T1). We observed an initial pulmonary flogosis (and well-known fibrosis) at T0 with a subsequent mild reduction at T1 of inflammations with a clear clinical improvement. So, after excluding occult infections (negative Quantiferon test, HIV, HBV and HCV serology) and cancer (negative total-body CT with intravenous contrast) we decided to start the induction-dose of rituximab (1000 mg iv). A second infusion was planned at 15 days based on the clinical response.
**Conclusion:** It may be very complex to manage this type of patients in absence of definite classifications and literature evidence. In this difficult context, clinical, laboratoristic and radiologic features, also with specific and dedicated imaging, can lead therapeutic decisions in patients that do not respond to first line therapy, together with an accurate exclusion of infective intercurrent causes. Particularly, we consider essential to discern if patients with interstitial pneumopathy with autoimmunity features shows an "IPF-like" phenotype with predominant fibrosis or an "IPAF-like" phenotype, with also a relevant inflammatory component. In conclusion, this clinical case underlines the urgent need of statistically relevant clinical trials for almost two reasons:

## 464. WHEN IT RAINS, IT POURS: THE ALLIANCE BETWEEN IMMUNOSUPPRESSIVE THERAPY, PARVOVIRUS B19 AND LEISHMANIA

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Herein we present the case of a patient with enteropathic artopathy who came to our attention because of persistent trilinear cytopenia and worsening splenomegaly mimicking a lymphoproliferative disease. A careful differential diagnosis allowed the identification of a co-infection by Parvovirus B19 and leishmania. The use of a complex immunosuppressive therapy for the management of the underlying inflammatory diseases contributed to the patient's greater susceptibility to opportunistic infections.
A-65-year-old man with a known history of Crohn's disease, in follow-up at our rheumatology clinic for an axial spondylarthritis came for a scheduled visit at our department. His past medical history comprised appendectomy, hemorrhoidectomy and right inguinal hernia repair; a diagnosis of Crohn's disease with joint involvement was made 4 years earlier. He already underwent to surgical resection 3 years before. The patient had been previously treated with sulfasalazine, suspended for primary failure, and with azathioprine, suspended because of pancreatic toxicity. He later started adalimumab and methotrexate (MTX), along with moderate prednisone dose (10 mg/day) obtaining a good disease control. During the visit

the patient reported low-grade evening fever, weight loss, pharyngodynia and productive cough for about three weeks. Because of these symptoms, his general practitioner had previously prescribed a chest X-ray, which was unremarkable and started antibiotic therapy with amoxicillin/clavulanic acid, without obvious clinical response. Blood work-up, performed 10 days before the scheduled visit, had revealed a slight decrease in white blood cells count (WBC 4180/mcl), normochromic normocytic anemia (9.1 g/dl) and a slight decrease in platelets values (150000/mcl); erythrocite sedimentation rate was elevated, as well as C reactive protein. The serology for HIV, HBV and HCV turned out negative, stool calprotectin level was in range. During the visit, the patient repeated blood tests, which demonstrated a decrease of WBC and hemoglobin levels, with a reduced reticulocyte index. Ferritin, vitamin B12 and folate resulted normal. The patient was admitted to our ward; the immunosuppressive therapy with MTX and adalimumab was stopped while the steroid therapy and the ongoing antibiotic therapy was maintained. A peripheral-blood smear was performed, excluding immature elements or other pathological alterations. One urine culture and two blood cultures resulted negative. The flu swab test, the CMV-DNA research and EBV serology were negative. Conversely, Parvovirus B19 IgM and IgG index titers were positive and qualitative molecular biology confirmed the infection. At discharge, 5 days after admission, hemoglobin was 8.6 g/dl and WBC 3750/mcl. Two weeks after discharge the patient presented again fever associated with sweating. Moreover, although improved, blood tests showed persistence of leukopenia and anemia. The patient was hospitalized again. Physical examination was regular, except for an evident splenomegaly. A chest x-ray was again unremarkable, urine culture and two blood cultures resulted negatives. In the suspicion of a lymphoproliferative disease, flow cytometry examination was also performed on peripheral blood and bone marrow biopsy was programmed. CT scan of the thorax and abdomen was normal, except for splenomegaly. A series of serological test were also repeated: the CMV-DNA research and EBV serology were confirmed negative while the search for leishmania proteins resulted positive. Bone marrow biopsy showed the presence of trophozoites inside the macrophages and the remaining hemopoietic lines with normal morphology and maturation. The patient was later transferred to the infectious disease department and started the appropriate therapy with amphotericin B. After the eradication it was observed complete resolution of fever and malaise. Two weeks later the complete blood count was normal.

This case describes an acute episode of severe anemia, leukopenia and splenomegaly in a patient with Crohn's disease under immunosuppressive therapy with different agents. The MTX effect on cellular and humoral immunity together with adalimumab activity has probably compromised the immune response both against Parvovirus B19 and leishmania. In literature only one case of co-infection by these two pathogen is described while several cases of anti-TNF alfa drugs used along with MTX and the infection of opportunistic pathogens is frequently reported. It is now difficult to determine whether Parovovirus B19 or leishmania infected first the patient but both could have participated in the impairment of the host's defenses and therefore in the mutual manifestation.

This case underlines the importance of a careful differential diagnosis between malignancies and infectious diseases which both can cause similar manifestations. This diagnosis is even more important in patients undergoing immunosuppressive therapies because the early and right treatment can prove to be fundamental for survival.

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