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Digestive and Liver Disease

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Oral communications: 54th Annual Meeting of the Italian Association for the Study of the Liver – A.I.S.F. (Rome, March 24th-25th, 2022)

OC-1

Humoral, cellular, clinical responses and safety of two doses of SARS-CoV-2 Messenger RNA vaccine in patients with compensated and decompensated cirrhosis: a long-term single center prospective study

M. Iavarone [1,*], G. Tosetti [1,*], F. Facchetti [1], M. Topa [1], A. Lombardi [2], R. D'Ambrosio [1], E. Degasperi [1], A. Loglio [1], C. Oggioni [3], A. Bandera [2], A. Gori [2], F. Ceriotti [4], L. Scudeller [5], A. Bertoletti [6,7], P. Lampertico [1,8]

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Background and Aims: SARS-CoV-2 mRNA vaccines have been approved to prevent COVID-19. We assessed immunogenicity, effectiveness and safety of vaccines in patients with compensated and decompesated cirrhosis.
Method: This is a prospective single center study assessing humoral and cellular responses in cirrhotics compared to healthy controls, incidence post-vaccination SARS-CoV-2 infections and adverse events (AEs). Antibodies against the spike- and nucleocapside-protein (anti-S and anti-N) were tested at baseline, 21 days after the first and second doses and during follow-up. Spike-specific T-cells quantity assessment was longitudinally conducted by the stimulation of whole blood with peptides covering the SARS-CoV-2 spike protein, followed by IFN-γ and IL-2 measurement.
Results: 182 cirrhotics (61 years, 75% males, 45% viral-related, 74% Child-Pugh A, 31% HCC, 85% COVID-19 naïve) and 38 healthy subjects were enrolled. Previous SARS-CoV-2 infection predicted higher anti-S titres at all time points after vaccination, in both groups. COVID-19 naïve cirrhotics showed significantly lower anti-S titres compared to controls [998.5 (0.4-12,500) vs 1,520 (259-12,500) U/mL, p=0.048], anti-S titres significantly decreased after a median of 133 (70-182) days [536 (0.4-8,777) U/mL, p<0.0001] and were lower in decompensated vs compensated cirrhosis [632 (0.4-12,500) vs 1,377 (0.4-12,500) U/mL, p=0.028]. By multivariable analysis in COVID-19 naïve cirrhotics, independent predictors of lower anti-S were active HCC, immunocompromised conditions, BNT162b2 and lower anti-S after first dose. The spike-specific T-cell response was evaluated in 14 cirrhotics, showing a heterogeneous magnitude of response, but on average the quantity and kinetics of decline of the spike-specific cellular responses diverged in cirrhotics compared to controls, with lower concentrations of both IFN-γ and IL-2. During follow-up, 4/133 (3%) COVID-19 naïve cirrhotics tested positive for anti-N, all asymptomatic. Neither unexpected nor severe AEs emerged.
Conclusion: Humoral and cellular responses to SARS-CoV-2 mRNA vaccines appeared suboptimal in patients with cirrhosis, however the rate of post-vaccination infection seems low.

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OC-2

Clinical and prognostic characterization of the patterns of decompensation of liver cirrhosis

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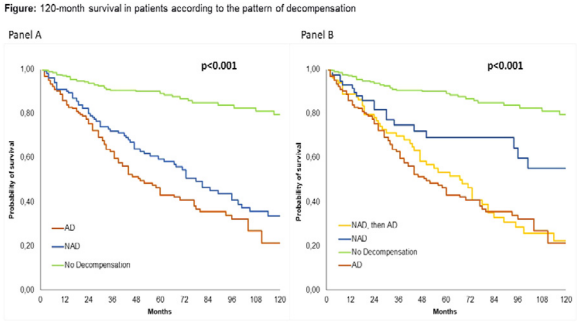
Background: The occurrence of decompensation is associated with poor prognosis in patients with cirrhosis. Recently, Acute Decompensation (AD, i.e. the development of complications that require hospitalization), has been characterized. However, complications of cirrhosis can develop progressively without needing hospitalization, a condition recently defined Non Acute Decompensation (NAD), whose characterization is still unclear. The aim of the study was to evaluate the incidence and the prognostic impact of NAD and AD in outpatients with cirrhosis.
Methods: Seven-hundred-forty-nine cirrhotic outpatients were enrolled and consequently followed up until death, liver transplantation or the end of the study (August 2021). The development of

complications during follow up was considered as AD if it resulted in hospitalization or NAD if the complication was managed at outpatient clinic.

Results: Three-hundred-seventy-nine patients (50.6%) did not develop any decompensation, 163 (21.8%) had NAD as first decompensation and 207 (27.6%) AD. During follow up, 216 patients (28.8%) died and 145 (19.4%) were transplanted. Ten-year survival was significantly higher in patients without decompensations (79.6%) than in patients with NAD or AD (33.7% and 21.3%, respectively; p<0.001, Fig.A). Eighty-three patients with NAD (50.9%) subsequently developed AD. No significant difference in 10-year survival between patients who developed AD after NAD and those who only had AD was identified, while both of these groups showed shorter survival than patients who had only NAD. In multivariable 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.



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OC-3

Trientine tetrahydrochloride versus d-Penicillamine for the management of patients with Wilson Disease: results from the CHELATE trial a year after randomisation

M. Zuin [1], A. Czlonkowska [2], D. Cassiman [3], A. Poujois [4], P. Ott [5], N. Dubois [6], K.H. Weiss [7], S. Monico [1], P.M. Battezzati [1], G. Carnevali [8], M.L. Schilsky [9], on behalf of Chelate Trial Investigators

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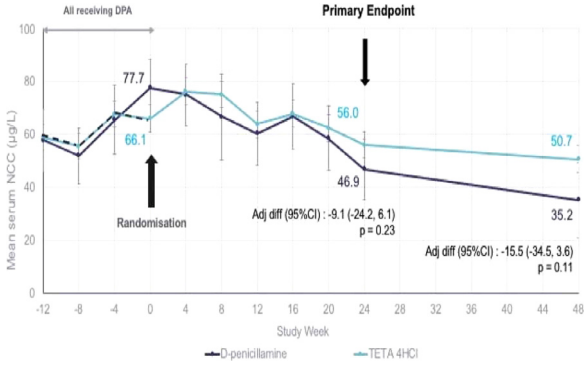
Introduction and Aims: Treatment of Wilson Disease (WD) with chelating agents such as d-Penicillamine (DPA) or trientine decreases the pathologic accumulation of copper and removes circulating non-ceruloplasmin bound copper (NCC). There are no prior controlled studies comparing DPA with trientine. The study aim is to determine if maintenance therapy for WD with a novel tetrahydrochloride trientine formulation (TETA4) is safe and effective when compared to DPA.

Materials and Methods Results: Multicentre, non-inferiority randomised controlled trial (TETA4 vs. DPA) in clinically stable adult WD patients (Leipzig score > 4) on DPA. Treatment endpoints were serum NCC (primary) measured by liquid chromatography inductively coupled plasma mass spectroscopy (LC-ICP-MS), 24-h urinary copper excretion (UCE) and blinded clinical assessment compared to baseline. Subjects were monitored by laboratory and clinical evaluation, including neurological assessment (UWDRS). After the primary endpoint, subjects entered an extension phase continuing with allocated therapy for a further 24w.

The mean (95% CI) difference in serum NCC after 24w and 48 w was - 9.1 (-24.2, 6.1) mcg/L and – 15.5 (-34.5, 3.6) mcg/L respectively; (non-inferiority margin -50 mcg/L). At randomisation mean (SD) UCE was comparable [DPA 516 (262) vs TETA4 547 (299) mcg/24hr]. After 24w and 48w, UCE was lower with TETA4; mean (95%CI) difference 232.7 (111, 361) mcg/24 hr (p= 0.0004) and 123.9 (1.9, 245.8) mcg/24 hr (p= 0.047) respectfully. Data on liver tests, changes in clinical condition including UWDRS were all either not clinically or statistically different from baseline. There were 5 SAEs with DPA; none for TETA4. All AEs resolved and were mild to moderate in nature.

Conclusions: TETA4 is an effective and safe treatment for WD. TETA4 effectively controlled serum NCC despite lower post-treatment UCE compared to DPA over 48w and with fewer treatment associated adverse events. NCC determined by LC-ICP-MS maybe useful for monitoring WD therapy. (ClinicalTrials.gov number: NCT03539952)



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OC-4

Genomic and metabolomic profiles and their correlations with preclinical signs of endothelial dysfunction measured by Peripheral Arterial Tonometry in Non Alcoholic Fatty Liver Disease

M. Masarone [1], J. Troisi [2,3], B. Motta [1], M. Lombardi [2,3], P. Torre [1], R. Sciorio [1], M. Aquino [1], M. Persico [1]

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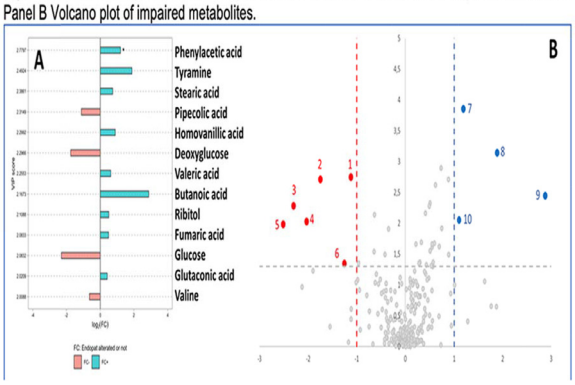
Background and Aims: NAFLD is associated with insulin resistance, metabolic syndrome (MS) and diabetes and it is an independent CVD risk factor. Endothelial Dysfunction (ED) plays a central role in the pathogenesis of CVD. Preclinical ED can be detected by vascular reactivity studies, such as Peripheral Arterial Tonometry (PAT). Genome Wide Studies (GWAS) identified Single Nucleotide Polymorphisms (SNPs) associated to NAFLD progression. Some of them (ie TM6SF2) have been postulated to influence CVD risk. The use of specific biomarkers related to ED presence in NAFLD may allow an early identification of CVD risk and provide crucial insights into its pathophysiology. This could be addressed through untargeted metabolomics and genomic approaches. Aims: to identify metabolomics signatures able to discriminate the presence of ED by combining data provided by metabolomics analyses with those from PAT, and to correlate them with anthropometric, laboratory and genomic profiles of NAFLD subjects.
Methods: Serum was collected from 107 subjects with biopsy-proven NAFLD (55.9% NAFL; 26.6% NASH; 17.5% NASH-Cirrhosis) without clinically evident CVD. Metabolomics analysis was performed by mass spectrometry. The resulting profiles were correlated with PAT scores, revealed by an EndoPAT-2000 device, and with genomic profiles of 4 SNPs of NAFLD (PNAPL3; TM6SF2; GKR; MBOAT).
Results: Class separation in metabolomics profiles between patients with and without ED (EndoPAT cut-off =0.51) was obtained through a "Partial Least Square Discriminant Analysis" (PLS-DA), which was also used to identify the discriminating metabolites. According to the PLS-DA score plot, two metabolomics profiles were identified, significantly different, in the two groups ($R2 = 0.98$, $p < 0.001$). The metabolites profiles are presented in figure 1. By comparing PAT scores of patients with simple steatosis (NAFL) (n:61, 19 with ED), NASH (n:29, 12 with ED), and NASH-cirrhosis (n:17, 9 with ED) no significant difference was observed ($p = 0.34$), suggesting that CVD risk is not associated with the degree of liver disease. Moreover, the clinical and genetic parameters associated to ED were type 2 diabetes, MS and BMI (directly) and TM6SF2 dominant model (CC+CT) (inversely) at the univariate and only MS at a multivariate analysis.
Conclusion: NAFLD patients with and without ED exhibit significant differences in their metabolomics profiles, demonstrating that they could be a useful early diagnostic tool for assessing CVD risk and providing an in-depth understanding of its underlying mechanisms. Among the NAFLD associated SNPs, only TM6SF2 mutation was correlated to a reduced prevalence of ED, but the only independent factor for ED was MS presence.

Figure 1: Metabolomic profiles of NAFLD patients with and without ED. Panel A: Impaired Metabolites. Panel B Volcano plot of impaired metabolites.



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OC-5

Potential feasibility of atezolizumab-bevacizumab therapy in patients with hepatocellular carcinoma treated with tyrosin-kinase inhibitors: a real-world analysis

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Background and Aims: Front-line systemic therapy for patients with unresectable hepatocellular carcinoma (HCC) not amenable/responding to locoregional treatments includes, beside tyrosine-kinase inhibitors (TKIs) sorafenib and lenvatinib, the combination of atezolizumab-bevacizumab (Atezo-Beva) which has become the standard of care for these patients, showing a clear superiority on sorafenib in terms of overall survival (OS) and Quality of Life.

This study aimed at assessing the real-world potential feasibility of the Atezo-Beva therapy in a large cohort of HCC patients treated with TKIs.
Methods: We retrospectively analysed 1448 patients diagnosed with unresectable HCC not amenable/not responding to locoregional treatments, treated with TKIs (sorafenib 98%, lenvatinib 2%) from January 2010 to December 2020 in 24 Italian centres. The percentage of patients potentially amenable to Atezo-Beva treatment (according to IMBrave-150 trial criteria) and the OS of eligible and non-eligible patients were assessed.
Results: 423 (29.2%) resulted to be qualified for the Atezo-Beva therapy. The main exclusion causes were Child-Pugh class >A (399 cases) and Performance Status >1 (187 cases). Adopting the more liberal selection criterion of the SHARP study (platelet count to >60,000 mmc, Child-Pugh Class B7, and Performance Status ≤2) the proportion of eligible cases increased to 536 patients (37.0%). Median OS of the whole population was 14.9 months (95% CI 16.0-13.7). It was better in eligible patients (18.0 months, 95% CI 20.3-15.8) than in the counterpart (13.0 months, 95% CI 14.4-11.7; p=0.017), likely due to better baseline Child-Pugh score, MELD score, platelet count, BCLC stage and alpha-fetoprotein level.
Conclusions. Real-world data indicate that no more than one-third of HCC patients treated with TKIs are potentially eligible for Atezo-Beva therapy according to the registration trial criteria. These patients have a better OS than non-eligible ones, owing to a better baseline clinical profile. Therefore, TKIs will remain the front-line approach for most HCC patients qualified for systemic therapy, due to the current stringent inclusion criteria endorsed by immunotherapy trials.

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OC-6

Different immunological microenvironment in patients with different cirrhosis etiology and hepatocellular carcinoma

A. Dalbeni [1,2], L.A. Natola [1,2], S. Cicco [6], F. Cattazzo [1,2], A. Vella [3], M. Bevilacqua [1,2], J. Kassem [2], A. Mantovani [1,2], S. Conci [4], T. Campagnaro [4], A. Guglielmi [4], M. Milella [5], D. Sacerdoti [6]

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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 chronic liver disease. The advanced stages of HCC are amendable only to systemic treatment. Systemic therapy 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 was to identify differences in immune cell population of patients with HCC, according to etiopathogenesis of cirrhosis, in order to identify different patterns that may be targeted for immunotherapy.
Patients and Methods: We analyzed 50 leukocyte sub-populations, using flow cytometric technique, in a cohort of 111 consecutive HCC cirrhotic patients with different etiopathogenesis. Differences between groups were analyzed with the Mann-Whitney U test.
Results: We divided HCC patients with cirrhosis into five groups according to etiology of liver disease: alcoholic, viral (HCV/HBV), metabolic (NAFLD/NASH), overlap between etiological factors and other etiology. Leukocyte sub-populations were significantly different in two groups. Specifically in the group 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 group there were increased levels of T cells CD57-RA+(4-8-) ($p=0.007$) and T cell CD3+ (4-8-) ($p=0.009$). No specific leukocyte subpopulation was significantly increased in the other groups, in particular in the metabolic one.
Conclusions: These data suggest that in liver disease with different etiopathogenesis there are different immunological microenvironments. Innate and innate-like cells are the principal regulators of immune response in alcoholic HCC, while adaptive immune system is predominant in viral etiology. This suggests that differences in cancer-mediated immune escape could explain the different response to immunotherapy and may be helpful in identification of responder patients to new HCC therapy

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OC-7

Role of immune activation and senescent profile as prognostic markers for cancer onset in patients undergoing liver transplantation

S. Shalaby [1,*], M.R. Petrara [2,*], E. Ruffoni [3], M. Taborelli [4], F. Carmona [3], P. Del Bianco [3], P. Piselli [5], F. D'Arcangelo [1], D. Bizzaro [1], M. Senzolo [1], F.P. Russo [1], U. Cillo [6], D. Serraino [4], P. Burra [1], A. De Rossi [2,3]

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[*] Shalaby S and Petrara MR share co-first Authorship

Background: Patients with hepatocellular carcinoma (HCC) are at higher risk for post-transplant malignancies (PTM). Immune activation and senescence have been frequently implicated in cancer development, however, no data are available concerning their prognostic role in patients undergoing liver transplant (LT). The aim of the study was to analyze these profiles in patients transplanted for HCC (LT-HCC) and for other causes (LT-non-HCC).
Methods: Patients who underwent LT between October 2016 and February 2021 at Multivisceral Transplant Unit, Padua University-Hospital were enrolled. Patients characteristics, HCC presence and features and immunosuppression were recorded. Exclusion criteria: ≤18 years old, follow-up shorter than 30 days or previous neoplastic history other than HCC. All PTM were registered. Markers of T (CD3+CD4/8+CD38+) and B (CD19+CD10-CD21-CD27+) cell activation, T (CD3+CD4/8+CD28-CD57+) and B (CD19+IgD-CD27-) cell senescence were evaluated by flow cytometry at transplantation (baseline).
Results: A total of 116 patients were included: 45 LT-HCC and 71 LT-non-HCC. LT-HCC patients were older than LT-non-HCC (median 60 vs 53 years, $p=0.011$), but comparable for sex, liver disease etiology, immunosuppressive schedule. At baseline, levels of activated CD8, memory B cells and senescent CD4, CD8 and B-cells were significantly higher in LT-HCC patients than LT-non-HCC ones (Table 1).

Table 1. Differences of immunological parameters between LT-HCC and LT-non-HCC at baseline

Median (IQR)	LT-HCC (N=45)	LT-non-HCC (N=71)	p value*
%CD8 activation (CD8+CD38+HLA-DR+)	10.89 (5.61-18.52)	6.59 (4.26-9.25)	**0.003**
%CD4 activation (CD4+CD38+HLA-DR+)	7.23 (4.11-14.12)	6.21 (3.49-9.23)	0.092
%B activated memory (CD19+CD10-CD21-D27+)	10.97 (5.59-20.68)	7.60 (3.00-13.72)	**0.040**
%CD8 senescence (CD8+CD28-CD57+)	11.06 (6.24-25.16)	5.92 (3.54-10.97)	**0.006**
%CD4 senescence (CD4+CD28-CD57+)	3.80 (1.36-14.03)	1.80 (0.48-3.41)	**0.002**
%B senescence (CD19+CD27-IgD-)	12.20 (6.28-17.67)	6.59 (4.24-12.50)	**0.019**

*adjusted by age

During 27.4 (7.7-41.7) months of follow-up, 6 PTM occurred: 4 in LT-HCC (8.9%) and 2 in LT-non-HCC (2.8%). Patients developing PTM showed significantly higher baseline levels of immune activation than patients without malignancies. Within LT-HCC group, levels of senescent cells were significantly higher in patients with PTM compared to the others [%CD8+CD28-CD57+: 22.45(17.72-25.86) vs 10.82(5.21-25.16), $p=0.098$; %CD4+CD28-CD57+: 14.33(10.23-21.12) vs 2.65(1.10-13.11), $p<0.001$].
Conclusion: Our findings suggest that patients undergoing LT for HCC have a higher immune activation and senescence profile compared to other recipients, possibly representing an additional risk factor for PTM. Moreover, immune activation and senescence may be prognostic factors for PTM occurrence regardless the cause of transplantation.

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OC-8

Steroidomic profiles across the spectrum of liver damage in non-alcoholic fatty liver disease

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Introduction. The onset and progression of liver damage in non-alcoholic fatty liver disease (NAFLD) is tightly associated with metabolic derangements. Steroids may affect lipid metabolism but their alterations in the setting of NAFLD remain to be fully explored.
Patients&Methods. We analyzed data from 121 patients with biopsy-proven NAFLD and 108 controls (CT). A panel of 26 steroids (including glucocorticoids, mineralocorticoids, androgens and progestogens as well as representative glucuro- and sulphoconjugated metabolites) were measured on plasma samples by liquid chromatography coupled to mass spectrometry (LC-MS/MS). Severe hepatic fibrosis was defined by F≥3.
Results. Compared to CT, NAFLD patients were older (median age 51vs43, p<0.001) and were characterized by a higher rate of MS (47%vs2%, p<0.001). More than a half of steroids were deregulated in patients compared to CT. At liver histology, the prevalence of absent/mild, moderate and severe fibrosis was 50.4%, 10.8% and 38.8%, respectively. Circulating levels of 16 compounds showed a significant stepwise decrease according to the degree of hepatic fibrosis. At univariate analysis, testosterone and its derivatives, androsterone metabolites, etiocholanolone metabolites and glicoandrogens metabolites were differentially expressed in patients with severe fibrosis compared to those with absent/moderate fibrosis. After multivariable logistic regression analysis adjusted for age, sex and type 2 diabetes, epitestosterone sulphate, 5α-androstan-3α,17β-diol-3-glucuronide and androsterone sulphate levels were significantly associated with F≥3. The diagnostic accuracy of the model for the identification of F≥3 was 0.91 with a sensitivity and specificity of 87% and 85 %, respectively, and with a positive and negative predictive value of 78% and 91%, respectively.
Conclusions. In NAFLD patients, alterations in androgens and their glucuro- and sulphoconjugated metabolites levels are expression of compromised steroid homeostasis regulation by the liver and are associated with severe fibrosis.

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OC-9

The co-presence of PNPLA3, MBOAT7 and TM6SF2 loss-of-functions impairs mitochondrial morphology and number in severe NAFLD patients

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Background: Mitochondrial(mt-) dysfunction represents a hallmark of NAFLD progression up to HCC. We demonstrated that PNPLA3, MBOAT7 and TM6SF2 deficiency in human HepG2 cells induced an enrichment of mt-mass and damaged mitochondriaalongside mt-functional defects.
Aims: To assess: 1) whether mt-morphology, circulating D-loop copy number and expression, which reflect mt-mass, correlated with disease severity and number of 3 at-risk variants (NRV=3) in biopsied NAFLD subjects (n=26, Discovery cohort); 2) circulating D-loop levels in a larger cohort of biopsied NAFLD patients (n=773, Validation cohort), including n=101 NAFLD-HCC. Hepatic D-loop content was evaluated in intra- and extra-tumoral tissues of 3 NAFLD-HCC individuals.
Methods: NAFLD patients were stratified according to NRV and NAFLD activity score (NAS). Mt- morphology was assessed by transmission electron microscopy (TEM).
Results: In the Discovery cohort, patients with NRV=3 showed NAS=5-7 along with the highest D-loop content compared to patients with 1-2 or no variants (p<0.01), resembling what observed in vitro. At TEM, patients carrying NRV=3 increased mt-mass and showed an elevated pattern of mt-morphological alterations as swollen shapes with loss of matrix, rupture of double membranes or giant/elongated mitochondria. In the Validation cohort, the NRV=3 associated with NAS and HCC risk (p<0.05) at multivariate analysis adjusted for age, sex, BMI and diabetes. At ordinal regression analysis adjusted as above plus the presence of NRV=3, circulating D-loop levels were independently associated with steatosis, necroinflammation, ballooning, fibrosis, and NAS (p<0.001) and were significantly increased in NAFLD patients with NRV=3 (p=0.03). In 3 NALFD-HCC patients, D-loopcopies were higher in the intra-tumoral tissues compared to extra-tumoral ones, showing the highest number in one patient carrying all 3 at-risk variants.
Conclusions: *PNPLA3, MBOAT7 and TM6SF2* loss-of-functions impair mt-morphology and mass in NAFLD patients. The assessment of D-loop copies may aid the non-invasive evaluation of disease course in genetically-predisposed subjects.

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OC-10

Cross-talk between MerTK-expressing stromal cells and cholangiocarcinoma

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Background and Aims: A typical feature of cholangiocarcinoma (CCA) is a dense stromal reaction populated by fibrogenic myofibroblasts and immune cells, creating a complex tumor microenvironment where malignant cells survive and proliferate. Cancer stem cells (CSCs) have been proposed as a driving force of tumor initiation, dissemination and drug-resistance in many solid tumors, including cholangiocarcinoma (CCA). Increasing evidence indicates that myeloid-epithelial-reproductive tyrosine kinase (MerTK) is highly expressed by a macrophage subset defined as M2c. The present study aims to investigate whether signals generated by MerTK-expressing macrophages modulate the biology of CCA.
Methods: 3D-tumor sphere cultures enriched in CSC were generated from intrahepatic CCA cell lines (HuCCT-1 and CCLP-1). Circulating monocytes were differentiated into M2c macrophages *in vitro*. Recombinant Gas-6, a MerTK ligand, was used to activate this receptor. *MERTK* mRNA expression in human CCA tissues was also analyzed.
Results: In CCA cell lines cultured with conditioned medium from Gas-6-stimulated M2c macrophages, cell survival, invasion, sphere-forming efficiency and drug resistance were significantly increased. These effects were reduced following macrophage pre-treatment with the MerTK inhibitor, UNC2025. Analysis of the transcriptome of laser-captured, micro-dissected epithelium and stroma from 23 CCA patients showed that MerTK mRNA expression is significantly higher in intratumoral stroma. Single-cell RNA sequencing of $CD45^+$ sorted cells from paired non-tumoral and tumoral specimens from iCCA patients (n=6) defined eleven clusters characterized by their gene expression profiles. A further reclustering of myeloid cells showed MerTK expression in Kupffer cells, lipid macrophages, $TREM2^+$ macrophages, and non-classical monocytes.
Conclusions: These data suggest a cross-talk between MerTK-expressing cells in the stroma and CCA cells, to induce increased malignant features.

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OC-11

Low hemoglobin predicts early readmission for liver-related causes in patients with cirrhosis discharged after an acute decompensation

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Introduction: Patients with decompensated cirrhosis present a high risk of early re-hospitalization with relevant clinical and socio-economic impacts.
Aim: This study aims to identify predictors of re-hospitalization for liver-related causes within 30 days (early readmission) after an index hospitalization for acute decompensation (AD).
Patients and Methods: 329 patients discharged after hospitalization due to AD were included in a prospective observational study. Laboratory and clinical data at admission, during hospital stay and at discharge of the index hospitalization were collected. Readmissions and its causes, and mortality were recorded up to 1 year.
Results: 182 patients were readmitted at least once within 1 year and 98 (30%) more than once. Cumulative incidence of readmission was 20% at 30 days, 39% at 90 days and 55% at 1 year. Early readmission was associated with a higher 1-year mortality (50vs33%, p=0.012). The most frequent causes of early readmission were hepatic encephalopathy (27%), bacterial infection (24%), and ascites (18%), while in 14% of patients the cause of hospitalization was not liver related. Data collected both at admission (Child-Pugh, MELD-Na score, diabetes), during hospital stay (development of acute-on-chronic liver failure [ACLF]) and at discharge (hemoglobin value, MELD-Na score, length of hospitalization) were significantly associated with early readmission due to liver-related cause. Multivariable Cox regression analysis showed that hemoglobin level lower than 8.75 mg/dL(HR 3.301[95%CI 1.763-6.178], p<0.001) and the development of ACLF during index hospitalization (HR 2.132 [95%CI 1.070-4.246], p=0.031) were independent predictors of early readmission.
Conclusions: Almost one patient out of five is readmitted for liver-related causes within 30 days after a hospitalization due to AD. In addition to the development of ACLF, hemoglobin values lower than 8.75 mg/dl also emerged as a new risk factor for early readmission. Thus, patients with low hemoglobin levels at discharge merit a closer post-hospitalization surveillance.

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OC-12

Natural history of hepatic encephalopathy (HE) in a tertiary referral centre for hepatology

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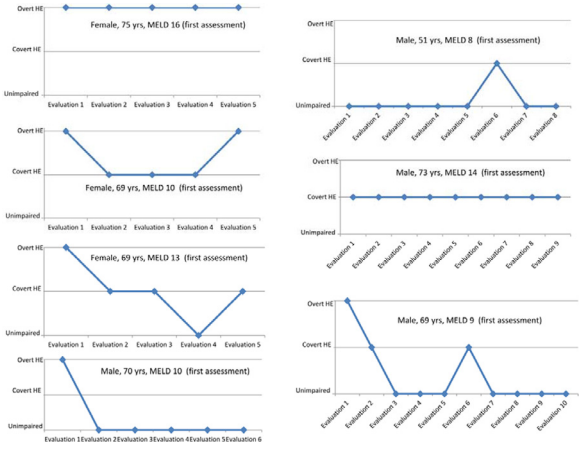
Introduction: The occurrence/recurrence of HE mark significant progression in the natural history of cirrhosis. While is well known that HE is an unfavorable prognostic factor, few data on its evolution over time are available.
Aim: To study the evolution of HE (neuropsychiatric indices, also in relation to HE treatment and severity of liver disease) in patients with varying degree of HE on first assessment.
Material and Methods: 87 patients with cirrhosis (age 58±11 years; 72 males) referred to the HE outpatient clinic at Padova University Hospital between 2009 and 2019 were included, and evaluated at varying time-intervals (2-10 times), for liver transplantation selection, differential diagnosis or treatment optimization. The presence/severity of HE was assessed by clinical, neuropsychological (PHES) and neurophysiological (EEG) tools. Severity of liver disease was assessed by MELD score. Treatment was instituted/modified according to guidelines and local experience after each evaluation.
Results: On first assessment, 23 patients were classed as unimpaired, 32 as having covert and 32 as having overt HE. Amongst unimpaired patients, on second/third evaluation 56%/6% remained unimpaired, 35%/3% developed covert HE, 9%/0% developed overt HE. Amongst patients with covert HE, 25%/10% became unimpaired, 44%/19% remained covert, 31%/13% developed overt HE. Finally, amongst patients with overt HE, 19%/16% became unimpaired, 25%/13% became covert and 56%/25% remained overt. Over

time, PHES results tended to improve in patients with overt HE and the EEG worsened (despite remaining normal) in unimpaired patients. These trends were not confirmed after adjustment for HE history, HE treatment and MELD. In patients with multiple evaluations, HE evolution was manifold and difficult to predict (Fig.1).
Conclusions: While there is obvious HE risk associated with HE on first assessment, our data suggest that evolution over time is extremely variable and largely dependent on HE history/management and MELD, and that HE is an essentially reversible condition.



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OC-13

Non-invasive diagnosis of clinically significant portal hypertension and treatment with non-selective beta-blockers: a new paradigm

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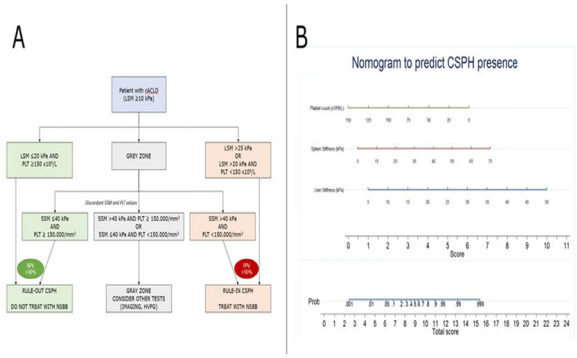
Introduction: Non-selective beta-blockers (NSBB) may reduce the risk of decompensation in patients with clinically significant portal hypertension (CSPH).
Aim: We aimed to improve the available algorithms for the non-invasive diagnosis of CSPH by evaluating spleen stiffness measurement (SSM) in patients with compensated advanced chronic liver disease (cACLD).
Method: This is a retrospective study in patients with liver stiffness measurement (LSM) ≥10 kPa, no previous decompensation, and available measurements of hepatic venous pressure gradient (HVPG), LSM and SSM referring to our tertiary center in Bologna. The diagnostic algorithms were adequate if negative (NPV) and positive predictive value (PPV) >90% when ruling-out and in CSPH, respectively. These models were validated in a cohort from Verona. The 5-year decompensation rate was reported in each risk group.
Results: One-hundred-fourteen patients were included in the derivation cohort (CSPH prevalence 62.3%). Available algorithms based on LSM and platelet count (PLT) (LSM >25 kPa or LSM >20 kPa and PLT <150.000/mm^3 for ruling-in CSPH and LSM ≤15 kPa or LSM ≤20 kPa and PLT ≥150.000/mm^3 for ruling out-CSPH) were validated. However, a large number of patients (40-60%) remained in the grey zone with indeterminate results for CSPH presence. The application of SSM cut-off 40 kPa and PLT 150.000/mm^3 in the "grey zone" patients allowed to significantly reduce the rate of indeterminate results to 15-23%, maintaining adequate NPV and PPV (above 90%) (**Figure 1A**). The combined algorithms were validated in an independent (Verona) cohort of eighty-one patients. A nomogram based on LSM, SSM and PLT was developed to predict the individual probability of CSPH presence (AUROC= 0.940) (**Figure 1B**); the model performed significantly better than the Anticipate model ($p<0.05$). During follow-up, up to 58% of the first decompensation events occurred in the patients within the "grey zone" according to the models based only on LSM and PLT, whereas all decompensation events occurred in the "rule-in" zone defined by the models including SSM.
Conclusion: The addition of SSM significantly improves the clinical applicability of the algorithms based on LSM and platelet count for CSPH diagnosis. Our models can be used to non-invasively identify candidates for NSBB treatment and patients at high-risk of decompensation.



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OC-14

Transjugular intra-hepatic portosystemic shunt (TIPS) in elderly patients: preliminary analysis of a multicenter retrospective cohort.

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Background and aim: TIPS is largely used in patients with cirrhosis affected by portal hypertensive (PH) complications such as bleeding gastro-esophageal varices (GEV) or refractory ascites (RA). However, data regarding its effectiveness and safety in elderly patients are limited. The objective of this study was to evaluate if TIPS might represent an effective and safe option in this group of patients.
Materials and methods: We retrospectively analyzed patients with cirrhosis who underwent TIPS implantation for RA and/or bleeding GEV at three Italian referral centers (Florence, Modena, Padua) between 2004 to 2021. A cut-off value of 70 years was considered to define elderly patients. Control of PH consequences, such as ascites and/or bleeding GEV, incidence of complications such as hepatic encephalopathy and deterioration of hepatocellular function, and death were evaluated in the two groups.
Results: A total of 347 consecutive patients, mean age 63.4±8.2y, 74% males, 35.7% alcohol, 27% HCV and 20% NASH, with a median follow-up of 609 days (IQR 1035) were included and divided into two groups: 252 (72%) were 69 years old or younger (<70y, mean age 59.4±5.5y) and 95 (28%) were 70 years or older (≥70y, mean age 74±3.2y). There were no statistically significant differences between the two groups before TIPS when comparing gender, BMI, TIPS indication, MELD or porta-caval gradient. In the <70y group there was a higher number of patients with more advanced liver disease (Child-Pugh B and C 68.9% vs 59.3% and 7.5% vs 3.3%, respectively, p=0.027), while in the ≥70y group there were significantly more patients with at least one comorbidity (>0.001). During follow-up, no significant differences between the two groups were observed in the overall incidence of all-grade encephalopathy or rebleeding episodes. Moreover, control of ascites or deterioration of hepatocellular function, evaluated at 1, 3, 6, and 12 months, were similar in the two groups. Regarding ascites control, similar results were obtained when the groups were stratified for Child-Pugh classification. Mortality was slightly higher in the >70y group (p=0.04). However, the survival trend between the two groups differs after 5 years from the procedure (Log Rank Mantel-Cox: p=0.113) and MELD (OR: 1.11, 95%CI: 1.06-1.18, p>0.001) and class C of Child-Pugh score (OR: 2.65, 95%CI: 1.22-5.74, p=0.014) before TIPS were the only predictors of mortality.
Conclusion: In elderly patients, TIPS implantation is an effective and safe option for the treatment of complications of PH in properly selected patients. Moreover, in this population, the incidence of post-derivative encephalopathy and deterioration of liver function are similar to those observed in younger patients.

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OC-15

Diagnostic and prognostic role of urinary Neutrophil Gelatinase-associated Lipocalin in patients with cirrhosis and acute kidney injury

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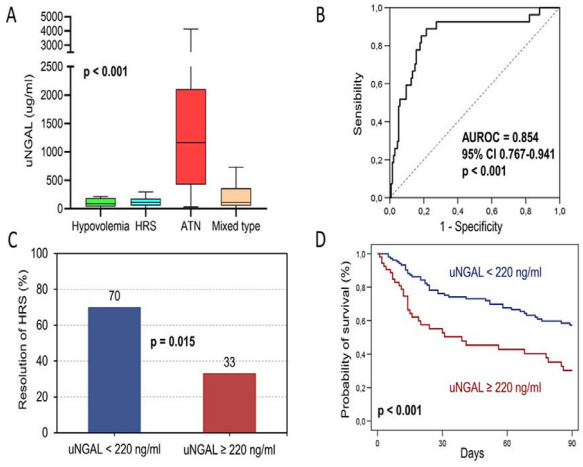
Background: Acute Kidney Injury (AKI) commonly occurs in patients with decompensated cirrhosis. Urinary Neutrophil Gelatinase-associated Lipocalin (uNGAL) could help in discriminating between different etiologies of AKI. The aim of this study was to investigate the use of uNGAL in: a) differential diagnosis of AKI; b) predicting the response to terlipressin and albumin in patients with Hepatorenal Syndrome (HRS-AKI); c) predicting in-hospital and 90-day mortality.
Methods: Consecutive patients with cirrhosis and AKI lasting >48 hours were included from 2015 to 2020. uNGAL and standard urinary biomarkers were measured. Data on treatment, type and resolution of AKI were collected. Patients were followed-up until transplant, death or 90 days.
Results: We enrolled 162 patients (mean age=62±10 years, male=77%; 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. uNGAL values were significantly higher in ATN-AKI than in 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), the best threshold was 220 ng/ml (sensitivity 89%; specificity 78%).

Among 62 patients with HRS-AKI treated with terlipressin and albumin, those with uNGAL≥220 ng/ml had a significantly lower rate of response (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 (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).
Conclusions: uNGAL is an excellent biomarker for differential diagnosis of AKI in cirrhosis, it predicts response to terlipressin and albumin in patients with HRS-AKI and is an independent predictor of mortality.



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OC-16

A new high-throughput HBV integration sequencing approach shows that mitochondrial DNA is frequently targeted by virus integration in liver cells with active HBV replication

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Background: Although research on HBV DNA integration has made relevant progress, important aspects remain unclear. Development of new integration detection methods may help in improving knowledge in the field and in HBV-related tumorigenesis.
Aim: To conduct a high-throughput HBV integration detection on tumor (T) and non-tumor tissues (NT) from HBsAg-positive patients with HCC and on HepaD38 cells using highly sensitive methods.
Methods. Identification of HBV DNA integration was performed by modifying an integration sequencing method described to study HIV integration (Cohn, 2015). Libraries were subjected to paired-end sequencing on Illumina MiSeq. Analysis of chimeric viral-human transcripts in HepAD38 cells was performed by RNASeq on Illumina HiSeq 2500 platform.
Results. A total of 3,339 unique HBV integrations were detected in the 7 patients: 2,913 in T and 426 in NT. The average number of integrations in T and NT was 416 and 71, respectively. Integration sites were randomly distributed across the whole genome and no hotspot was detected. An enrichment of virus integrations was observed in mitochondrial-DNA (mtDNA) both in T and NT. We found 20 unique HBV integrations in mtDNA from tissue specimens of 4/7 patients (17 breakpoints in T from 4/4 patients, 3 breakpoints in NT from 2/4 patients). HBV integration in mtDNA was associated with higher amount of HBV DNA (P=0.01) and pgRNA (P=0.02). In mtDNA, integrations were preferentially located in genes in T (17/17 vs 0/3; P<0.017) and in the D-loop region in NT (2/17 vs 3/3; P=0.008). RNR2, ATP6, ND4, and ND5 mitochondrial genes were recurrent sites of integration in T. Interestingly, HBV RNAs are imported into mitochondria, and fusion viral-mitochondrial transcripts are produced in HepAD38 cells.
Conclusions. The new HBV integration sequencing method importantly increases the detection efficiency of viral integrations. MtDNA is frequently targeted by HBV integration, which preferentially involves OXPHOS genes in T. HBV-replicating HepAD38 cells produce chimeric viral-mitochondrial transcripts.

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OC-17

Development and validation of a deep learning model for the prediction of hepatocellular cancer recurrence after transplantation: an international study

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Introduction: Identifying patients at high risk for recurrence of hepatocellular carcinoma (HCC) after liver transplantation (LT) represents a challenging issue.
Aim: The present study aims at developing an accurate post-LT recurrence prediction calculator using the machine learning method (Time_Radiological-response_Alpha-fetoproteIN_Artificial-Intelligence, TRAIN-AI).
Materials and methods: 3,381 patients with HCC listed for LT from 2000 to 2018 and coming from 17 centers from North America, Europe, and Asia were included in the study. The original dataset was split to generate the two main data sets used for the research. The Training Set was composed of 70% of the records of the original dataset, and the Test Set was composed of the remaining 30%. A prognostic model for HCC recurrence was developed using the Training Set data with a Deep Surv model, and a Cox proportional hazards deep neural network was constructed. Validation of the model was done using the Test Set. The TRAIN-AI was compared using the DeLong test with Metroticket 2.0 Score, AFP-French Model, Milan Criteria, San Francisco Criteria, Up-to-Seven Criteria, TRAIN Score, NYCA Score, and HALT-HCC Score.
Results: The developed TRAIN-AI model showed an escellent c-statistics, with an AUC=0.78 (95%CI=0.73-0.82). The TRAIN-AI always outperformed the other scores: Metroticket 2.0 Score AUC=0.66, P<0.0001; AFP-French Model AUC=0.65, P<0.0001; Milan Criteria AUC=0.63, P<0.0001; San Francisco Criteria AUC=0.61, P<0.0001; Up-to-Seven Criteria AUC=0.60, P<0.0001; TRAIN Score AUC=0.59, P<0.0001; NYCA Score AUC=0.58, P<0.0001; HALT-HCC Score AUC=0.57, P<0.0001.
Conclusions: The proposed TRAIN-AI score showed higher accuracy than other available risk scores regarding post-LT recurrence risk. Further validation is required. A web calculator has been developed to improve the model user-friendly availability.

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OC-18

Prognostic Models predicting allograft failure at 90 and 365 days after liver transplantation. Call for an international Est to West prospective observational study to guide re-transplantation

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Allograft failure (AF) at 90 days after LT has been recently predicted by externally validated kinetic models based on graft performance during early post-operative days (North American L-GrAFT score,[(1)] European EASE score[(2)]), which identify patients at high risk of AF who benefit from early retransplantation (C-statistic ≥85%).

However, with increasing utilization of ECD or DCD allografts, a higher incidence of ischemic cholangiopathy has been reported at 12 months, which is not captured when evaluating short-term outcomes.

Furthermore, other hepatological factors not routinely evaluated (e.g., frailty, sarcopenia, nutritional status, other organ failure, infections) often contribute to AF. Finally, the role of graft steatosis and the protective effect of perfusion machines are yet to be analyzed in a large multicentric prospective study. These factors may hamper or contraindicate a timely and efficacious re-transplantation.

Methods: We call for an International, Prospective, Non-competitive, Observational study[(3)] to validate-optimize prediction models of AF at 90 days and one year after LT by collecting data on current practice, various donor types (DBD, DCD, living donors [LD]) with non-competitive balanced international enrollment, homogeneous center volume, and evaluation of various mitigation strategies (e.g. perfusion machines). The study protocol has been designed by an [(*)]International Steering Committee. It includes both a prospective cohort (high-volume centers with ≥65 LT per year, 50 pts each) to develop new predictive models and a retrospective cohort (intermediate and low-volume centers, 75 pts each) to validate them. Secondary objectives include:

-developing a novel time-based dynamic algorithm, with increasing accuracy from day 3 to 7;

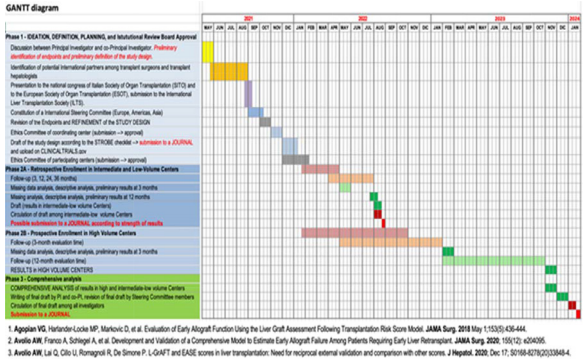
-identifying the optimal temporal window for re-transplantation;

-investigating differences in AF among DBD, DCD, LD grafts;

-evaluating strategies (e.g. perfusion machines) that mitigate AF;

-evaluating the ability to predict complications (AKI, ischemic cholangiopathy) and mortality (futility threshold).

A follow-up of at least 365 days is foreseen.



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OC-19

Radiomics-based model for outcome prediction in primary sclerosing cholangitis

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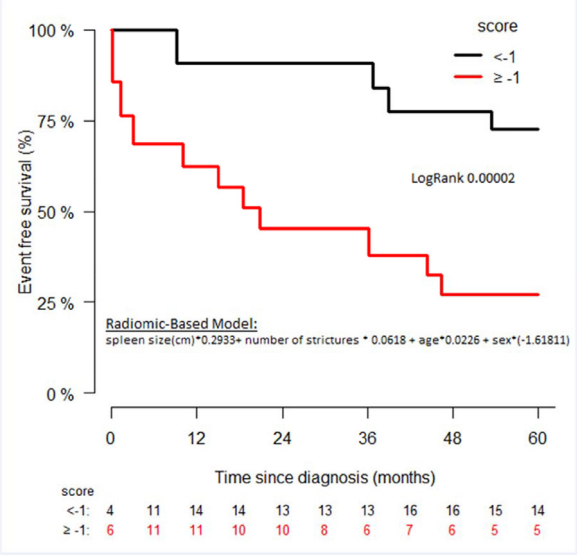
Introduction: Magnetic resonance cholangiopancreatography(MRCP) is the gold standard for diagnosis and follow-up of patients with primary sclerosing cholangitis(PSC). The semi-quantitative MRCP-derived ANALI score, while performant in risk stratification, has poor-to-moderate inter-reader agreement.
Aim: Aim of this study is to evaluate the prognostic performance of quantitative MRCP in PSC.
Methods: This is a retrospective study of a PSC cohort (2012-2019). MRCP images have been analysed using MRCP+ software(Perspectum,Oxford) that provides quantitative metrics of the bile ducts (number, length and severity of strictures and dilations, biliary tree volume). The prognostic value of radiomics biomarkers has been assessed towards both soft (hepatic decompensation, variceal bleeding, bacterial cholangitis and hepatobiliary neoplasia) and hard endpoints(death or liver transplantation, LT).
Results: 115 PSC patients with MRCP were evaluated; 90 MRCPs passed the quality control. Median age was 41(IQR 26-51) years, 61% were male, with a follow up from MRCP to event/censoring of 242 patient-years. An adverse outcome occurred in 28 patients (25.2%)(8 LT, 3 liver-related death, 5 liver decompensation, 10 bacterial cholangitis, 2 cholangiocarcinoma). Univariate analysis showed a good prognostic performance of all radiomics features evaluated. At multivariable analysis, adjusted for age and sex, the number of strictures and the spleen length were independently associated with the occurrence of adverse event with an HR of 1.06(per unit, CI 95% 1.03-1.09, $p<0.0001$) and 1.34(per cm, CI 95% 1.11-1.6, $p=0.002$), respectively and a C-statistics of 0.81. The model, after internal validation, outperformed the ANALI score in our cohort (C-statistics of 0.72vs0.6). Using as cut-off the mean value, the model enables to risk-stratify PSC patients (Figure).
Conclusions: A radiomics-based model, which includes the number of strictures and the spleen length, can identify PSC patients at higher risk of adverse outcome and outperforms the available radiological scores. MRCP+ features represent a novel biomarker for disease monitoring and a potential surrogate endpoint for clinical trials.



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OC-20

Persistent biochemical alteration at one year can lead to worse clinical outcomes in autoimmune hepatitis

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Background: Patients with AIH and slow biochemical remission frequently show a lack of transaminase normalization at 1 year (1Y-normal ALT) and a worse prognosis.
Aim: To identify predictive parameters of lack of 1Y-normal ALT and of clinical outcomes.
Methods: A retrospective cohort study in consecutive patients with biopsy-proven AIH with at least 1-year follow-up was performed. Exclusion criteria included presence of overlap syndromes, concomitant liver diseases and unavailable 1-year biochemistry. Decompensation-free survival was calculated according to Kaplan-Meier estimates; data were censored at the date of last visit or the occurrence of cirrhosis decompensation.
Results: 138 patients with AIH were included (84% female, aged 50±10 years), 20% of whom had cirrhosis at diagnosis and 28% had an acute onset; 114 patients(83%) reached a 1Y-normal ALT. A lack of 1Y-normal ALT was significantly associated with delayed(after 6

months) add-on introduction of azathioprine (35% vs.8%, p<0.001). Moreover, patients with lack of 1Y-normal ALT had significantly higher BMI at baseline (30.9 vs.24.6, p=0.03) and gained body weight during the first year (+8% vs.-1%, p=0.03). No differences regarding clinical onset, weight-based prednisone starting dose, liver histology and biochemical parameters were observed between the 2 groups. During a follow-up of 61 months (range 30-132 months) patients not achieving 1Y-normal ALT had more frequently cirrhosis decompensation, liver transplant, liver-related death(26% vs. 10% p=0.04) and showed a lower decompensation-free survival (OR 4.06, p=0.04). Lack of 1Y-normal ALT was positively associated with prednisone monotherapy during the first 6 months (r=0.17, p=0.05) and BMI (r=0.29,p=0.03), and a trend of significance between the lack of 1-Y normal ALT the combination of both factors was observed (r=0.32,p=0.06).

Conclusions: Delayed add-on introduction of azathioprine in combination with steroids, high BMI at diagnosis and body weight gain during the first one-year treatment are associated with lack of 1Y-normal ALT and with a lower decompensation-free survival.

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OC-21

Gamma Glutamyl Transferase as a marker of risk of progression to cirrhosis in patients with Primary Biliary Cholangitis

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Background and Aims: In the setting of primary biliary cholangitis (PBC), gamma-glutamyltransferase (GGT) is usually elevated in parallel to alkaline phosphatase (ALP) at onset, but may remain raised when ALP has normalized under ursodeoxycholic acid (UDCA). Since ALP is a prognostic marker for progression to cirrhosis in patients with PBC, we investigated whether the behaviour of GGT on UDCA has a prognostic value in such patients.

Methods: We assessed patients with PBC from the Rete CBP Sicilia Study Group, encompassing 13centers in Sicily, Italy, andobtained measurements of serum GGT at baseline and after 12 months of treatment. Results were plotted by Cox model hazard ratios to evaluate the association betweenGGT and progression to cirrhosis .

Results: 56 of the 351 patients included in the web network were excluded because of cirrhosis at baseline and 69 due to lack of an adequate follow up. 226 patients were analysed. Mean age at diagnosis was 55 years, 92% being women.

147 (65%) were responder to UDCA (ALP < 1.5). Thirteen patients (5.7%) progressed to cirrhosis during a median follow up of 49 months. Of them, 6 were among the 147 responders(4%) and 7 among the 79 non responder to UDCA (9%), p= 0.09.

Levels of GGT at 12 months after treatment higher than 3.2-fold the upper limit of normal (ULN) (1) identified patients who developed cirrhosis during FU (HR: 2.05; CI95% 1.07-7.44; p = 0.045). By converse, ALP at the same times were unrelated with progression of cirrhosis (HR: 1.35; CI95% 0.91-2.01; p = 0.130).

Along the same line, GGT levels higher than 3.2-fold (ULN) were associated with development of cirrhosis also among the patients who responded to UDCA (HR: 6.7: CI95%: 1.03-58.58; p = 0.041).

Conclusion: A raised level of GGT under UDCA treatment identifies patients with PBC still at risk for development of cirrhosis even when ALP has normalized.

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Transplantation or Death in Patients With Primary Biliary Cholangitis. CGH 2020.

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OC-22

Predictors of Serious Adverse Event and Non-response in Cirrhotic Patients With Primary Biliary Cholangitis under Obeticholic Acid

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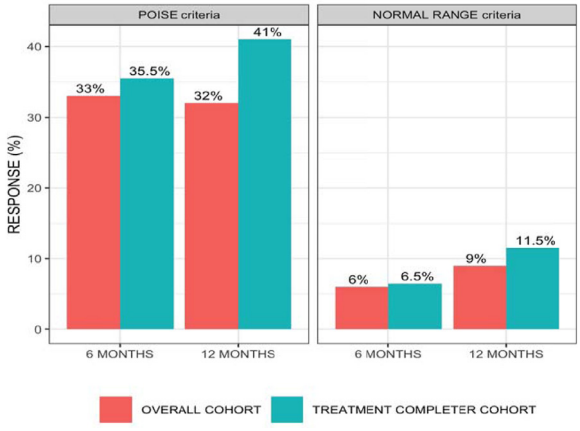
Background & Aims. Obeticholic acid (OCA) has recently been restricted in patients with primary biliary cholangitis (PBC) with "advanced cirrhosis" because of its narrow therapeutic index. Aim of this study was to better define the predicting factors of hepatic serious adverse events (SAEs) and non-response in cirrhotic patients undergoing OCA therapy.
Methods. Safety and efficacy of treatment were evaluated in a cohort of consecutive PBC cirrhotic patients started with OCA from the Italian PBC Registry. OCA response was evaluated according to the Poise criteria. Risk factors for hepatic SAEs and non-response were reported as risk ratios (RR) with 95% confidence intervals (CIs).
Results. One-hundred PBC cirrhotics were included, 97 Child-Pugh class A and 3 class B. Thirty-one had esophageal varices, 5 had history of ascites. Thirty-three% and 32% of patients achieved a biochemical response at 6 and 12 months, respectively. Male-sex (adjusted- RR 1.75, 95%CI 1.42-2.12), INR (1.37,1.00-1.87), Child-Pugh score (1.79,1.28-2.50), MELD (1.17,1.04- 1.30), and total bilirubin (1.83,1.11-3.01) were independently associated with non-response to OCA. Twenty- two patients discontinued OCA within 12 months: 10 for pruritus, 9 for hepatic SAEs (5 for jaundice and/or ascitic decompensation; 4 for upper digestive bleeding). INR (adjusted-RR 1.91,95%CI 1.10-3.36), lower albumin levels (0.18,0.06-0.51), Child-Pugh score (2.43,1.50-4.04), history of ascites (3.5,1.85-6.5), and total bilirubin (1.30,1.05-1.56), were associated with hepatic SAEs. A total bilirubin≥1.4mg/dL at baseline was the most accurate biochemical predictor of hepatic SAEs under OCA.
Conclusions. An accurate baseline assessment is crucial to select cirrhotic patients who can benefit from OCA. Although OCA is effective in one third of cirrhotics, bilirubin level ≥ 1.4mg/dL should discourage from its use.

Characteristic		N = 100
Sex, female		95 (95%)
Age at OCA start, years		62 (54, 67)
Age at PBC diagnosis, years		52 (43, 56)
AMA positivity		83 (83%)
ANA positivity		52 (52%)
PBC-AIH overlap		14 (14%)
Child-Pugh class		
	A[$]	97 (97%)
	B	3 (3%)
	C	0 (0%)
MELD		6.9 (6.4, 8.5)
Ascites, absence		95 (95%)
Ascites controlled with diuretics		4 (4%)
Ascites, presence		1 (1%)
Hepatic encephalopathy		0 (0%)
Esophageal varices, presence		31 (31%)
OCA start for inadequate response to UDCA		100 (100%)
ALP/ULN at baseline		2.10 (1.72, 2.89)
ALT/ULN at baseline		1.07 (0.78, 1.76)
AST/ULN at baseline		1.23 (0.90, 1.83)
GGT/ULN at baseline		4.5 (2.8, 7.0)
Total Bilirubin/ULN at baseline		0.90 (0.70, 1.21)
Albumin, g/dL		4.00 (3.60, 4.24)
INR		1.00 (0.97, 1.10)
Creatinine, mg/dL		0.70 (0.60, 0.80)



	Cut-off	Accuracy	Sensitivity	Specificity	PPV	NPV
Continuous variables						
Total bilirubin	≥1.4	0.86	0.67	0.88	0.35	0.96
Albumin	<3.7	0.71	0.88	0.69	0.23	0.98
Child-Pugh score	≥6	0.81	0.56	0.84	0.25	0.95
MELD	≥7.6	0.71	0.78	0.71	0.23	0.96
Categorical variables						
History of ascites	Presence	0.92	0.33	0.98	0.60	0.94
Esophageal varices	Presence	0.70	0.55	0.71	0.16	0.94

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OC-23

SARS-CoV-2 infection in liver transplantation is associated with favorable outcomes: an Italian transplant registry study

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Background and aims: Solid organ transplant recipients (SOTRs) have been considered as an extremely vulnerable population in respect to SARS-CoV-2 infection. We aimed to assess the incidence and lethality rate of SARS-CoV-2 infection in different organ transplant settings using the liver as a comparator.
Methods: In this nationwide population-based study we compared the crude incidence and lethality rates of SARS-CoV-2 infection [95% Bonferroni adjusted CI (Ba-CI)] among Italian LTRs as compared to non-liver SOTRs and to general population. The following independent groups had been compared: Italian general population, all SOTRs, liver transplant recipients (LTRs) and non-Liver SOTRs in area with different incidence of infection. Incidence rate ratio (IRR) and lethality rate ratio (LRR) was assessed. Community risk exposures in transplant settings were assessed.
Results: From February 21 to June 22, 2020, there were 450 cases of SARS-CoV-2 infections over 14168 LTRs (n=89) and 29815 non-liver SOTRs (n= 361). A significantly lower risk of infection [IRR 0.56 (Ba-CI 0.34-0.92), 0.45 (Ba-CI 0.26-0.79), 0.52 (Ba-CI 0.36-0.75)] and a lower lethality rate ratio [(LRR 0.61 (Ba-CI 0.23-1.57), 0.37 (0.08-1.76), 0.52 (0.23-1.18] was found among LTRs as compared to non-liver SOTRs in the three areas. Excluding Lombardy, the risk of infection and lethality in LTRs was lower compared to general population. Non-Liver SOTRs showed an increased risk of infection and lethality at all geographic levels compared to general population. No significant difference in the adherence to mitigation policies was found.
Conclusions: Liver transplantation was associated with a significantly lower risk of SARS-CoV-2 infection and lethality in respect to non-liver solid organ transplants. A separate evaluation of organ-specific risk stratification analysis and vaccination responses in transplant population is needed.

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OC-24

Long-term outcomes in pediatric liver transplantation: a single center 20 years- experience

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Introduction: Liver transplantation (LT) in pediatric age is a relatively recent reality with limited information about long-term natural history.

Aim: This study aimed to describe long-term outcomes in LT children followed-up for more than two decades, with particular interest to late post-transplant complications and patient survival rates.
Methods: We conducted a single-center retrospective study including all paediatric patients who underwent LT from 1987 to 2010 and followed-up until 2021 at the "Federico II" University Hospital of Naples.
Results: A total of 117 patients have been enrolled, 61 males and 57 females, with a mean age of 24.8±7.9 years. Mean age at LT time was 3.9±2.4 years, with a mean follow-up of 21.6±10.9 years.

The main indication for LT was biliary atresia (63.24%), followed by liver-based metabolic defects (9.4%), cholestatic disorders (9.4%) and autoimmune hepatitis (4.27%). Twenty-one re-transplantations were performed in 12 patients with a 15-year graft survival rate of 79.48%. Vascular complications represented the most frequent cause of graft failure (8/21).

The most common comorbidity was food allergy (17%). Long-term immunosuppression-related complications included arterial hypertension (10.2%) and chronic kidney dysfunction (10.2%). De novo malignancies occurred in 20 patients (17%), in particular lymphoproliferative disorders (18/20). No skin neoplasms were reported. Six deaths have been registered (for malignancies in 2 cases, for sepsis in 2 cases and for cirrhosis in 2 cases) with a 20-year survival rate of 95.72%.
Conclusions: The present study shows a significant increase in survival of LT pediatric patient and graft and confirms the less frequent onset of complications compared to adult setting but also highlights the emerging and still unresolved issues.

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OC-25

Effectiveness and safety of bulevirtide monotherapy 2 mg/die in hdv patients with compensated cirrhosis and clinically significant portal hypertension

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Introduction: Bulevirtide (BLV) has been recently approved for the treatment of HDV-related chronic hepatitis or compensated cirrhosis in Europe, but its effectiveness and safety in patients with advanced cirrhosis and severe portal hypertension are still unknown.
Methods: All consecutive HDV patients with advanced compensated cirrhosis who started BLV 2 mg/day were enrolled in this prospective single-centre study. All clinical/virological characteristics were collected at treatment baseline, weeks 4, 8 and every 8 weeks thereafter. HDV RNA was quantified by Robogene 2.0 (LOQ 6 IU/mL), HBcrAg by LUMIPULSE® G (LOQ 3 Log U/mL), HBV RNA by cobas® 6800 (LOQ 10 cp/mL).
Results: 18 patients were enrolled: 48 (29-77) years, 67% males, all Caucasian with HDV genotype-1 and cirrhosis (Child-Pugh A5 in 72%), 94% with CSPH, 11% with active HCC, Fibroscan® 16.4 (7.8-57.8) kPa, all under NUC therapy. At BLV baseline: ALT 106 (32-222) U/L, HBsAg 3.7 (2.5-4.3) Log IU/mL, HDV RNA 4.9 (3.3-6.6) Log IU/mL, HBcrAg 3.8 (2.3-5) Log U/mL, HBV RNA undetectable in all. During 6 months of BLV monotherapy, ALT normalized in 78% of patients; HDV RNA showed a 2.6 (0.6-3.9) Log IU/mL reduction, becoming undetectable in 2 (11%) patients. HDV RNA undetectable or ≥2 Log IU/mL decline was observed in 15 (83%) patients while a combined biochemical and virological response in 12 (67%). Two patients (11%) had virological non response (<1 log decline of HDV RNA at week 24). While platelets, albumin, AFP and HBsAg remained unchanged, IgG significantly declined. BLV was well tolerated, the only side effect being a fully asymptomatic increase of bile acids that rose to 48 (11-710) µmol/L.
Conclusions: This study demonstrates the effectiveness and safety of BLV monotherapy 2 mg/die even in difficult-to treat HDV patients with compensated cirrhosis and clinically significant portal hypertension who have been excluded from phase II and III studies.

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OC-26

Epidemiological, virological and clinical profile of HBsAg positive individuals in Italian hospital settings: interim results of the HBV/HDV PITER cohort

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Introduction: The increasing flows of migrants from endemic area is changing the burden of HBV infection in Italy in the last few decades.
Aim: We aimed to evaluate the epidemiological, virological and clinical profile of HBsAg positive subjects in order toupdate the HBV epidemiology in the hospital setting and the natural history of chronic HBV infection in a multi-ethnic context.
Method: Consecutive HBsAg positive patients were enrolled during 2019-2021 in the PITER cohort from 41 Italian clinical centers.
Results: 3141 patients (75.5% Italian and 25.5% non-Italian native) were enrolled; mean age: 58 years (range 16-93); 62% male; 73% genotype D, 65% in ongoing treatment. The 2 cohorts differed significantly (p=0.000) for gender: female 36.0% vs 48.1%, HBV genotype D: 80.0% vs 57.6%, HBeAg positivity: 4.5% vs 1.9% in Italian vs non-Italian natives, respectively. Italian patients were older (median 61 y vs 48 y p=0.0001) had more severe liver disease: cirrhosis 22.0% vs 4.0%, HCC 5.0% vs 1% p=0.000, higher rate (p=0.000) of liver disease cofactors and comorbidities mainly steatosis (25.1% vs 15,1%), cardiovascular disease (28.6% vs 9.0%), dislipidemia (10.4% vs 5.2%), diabetes (10.2% vs 3.7%). Anti-HDV was tested in 76% of patients and it was positive in 8% (7.5 % Italian vs 9.5% non-Italian natives). Median age of HBD/HDV patients was 55 years (range 21-80); 65% had cirrhosis, 13% had HCC. HDV-RNA was tested in 72% of anti-HDV positive patients: HDV RNA was positive in 61% of them. 79% of the HDV-RNA positive patients were mostly on NUCs treatment (90%).
Conclusion: Significantly different HBV epidemiological, virological and clinical profiles have been observed in Italians versus non-Italian native patients by demographic, infection/coinfection and comorbidity patterns. Such evidences underline the need of updated healthcare strategies for an effective control of HBV infection, well diagnostic and treatment algorithms for an appropriate management of HBV and HBV/HDV patients.

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OC-27

Increased platelet aggregation in decompensated cirrhosis indicates higher risks of further decompensation and liver-related mortality

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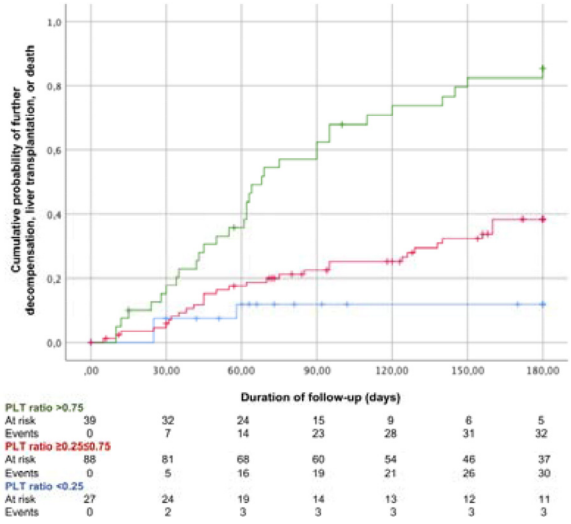
Background: Studies on platelet aggregation in cirrhosis are controversial because interpretation of platelet function is challenged by thrombocytopenia.
Aims: In this two-part study, we investigated platelet aggregation in cirrhosis and its correlation with liver-related events.
Materials and Methods: Aggregation was assessed by whole blood aggregometry (Multiplate®). To overcome the influence of platelet count and compare cirrhosis with thrombocytopenia and controls with normal platelet count (study part #1), we calculated a platelet ratio between platelet aggregation and platelet count (PLT ratio). Then, we prospectively followed patients with cirrhosis and investigated predictors of hepatic decompensation, transplantation, and death (study part #2).
Results: Two-hundred and three patients with cirrhosis were prospectively recruited (77% decompensated; median MELD 14). The PLT ratio was significantly higher in patients with cirrhosis than in chronic hepatitis and healthy subjects (0.44 vs. 0.25 and 0.26, respectively; p<0.0001). In cirrhosis, the ratio increased with disease severity (Child C>B>A) and was particularly elevated in decompensated patients with severe thrombocytopenia. During a 6-month follow-up, among decompensated patients, 65 had further decompensation, transplantation, or died. On multivariate analysis, PLT ratio (OR: 22.17, CI95%: 5.88-83.61; p<0.0001) and MELD score (OR: 1.07, CI95%: 1.01-1.13; p=0.03) were independently predictive of outcome. As indicated in the Figure, the rel-

ative risk of liver-related events was 7.5-fold higher in patients with a PLT ratio >0.75 vs. patients with a PLT ratio <0.25 (RR: 7.5, 95%CI: 2.5-21.9; p=0.003).

Conclusions: Patients with cirrhosis, particularly when decompensated, have a significantly increased platelet aggregation. Among decompensated patients, those with a PLT ratio >0.75 have an 80% probability of progressing towards further decompensation, transplantation, or liver-related death within 6 months.



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OC-28

Increased burden of inherited IRF3 rare genetic variants in Europeans with severe NAFLD

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Background/Aims: Inflammation is involved in the progression of non-alcoholic fatty liver disease (NAFLD) to to severe disease due to advanced fibrosis and hepatocellular carcinoma (HCC). By performing whole exome sequencing in 72 severe NAFLD patients vs 50 healthy controls plus 33,123 ExAC-NFE individuals, we detected increased risk in carriers of interferon regulatory factor (IRF3) rs141490768, encoding for the p.A418T IRF3-CL isoform variant (exome-wide adjusted p=0.015).The aim was to validate these initial results and examine IRF3 role across the NAFLD-spectrum.

Methods: IRF3 rs141490768 C>T was genotyped in a Validation cohort (n=241) with severe NAFLD, vs. GnomAD-NFE 32,537 controls (no-ExAC). We tested the enrichment in IRF3 rare variants (allelic frequency<0.01) by ProxECAT (Proxy External Controls Association Test) in 443 severe NAFLD cases vs GnomAD-NFE (n=64,603).

IRF3/pIRF3 immunohistochemistry (IHC) was performed in 16 patients stratified by disease severity.

IRF3 transcriptional activity was assessed in 125 obese individuals (transcriptomic cohort).

Results: We confirmed an enrichment of rs141490768 in the validation (p=0.044) and in overall cohorts (OR 13.6, 95%CI 6.3–29.5;$p=1.5\times10^{-6}$), as well as in IRF3 rare variants in severe NAFLD vs. controls (functional mutations to proxies ratio: 7.0 in cases vs 0.3 in controls, relative risk 23.3; $p=1.2\times10^{-7}$).

We observed a progressive increase in nuclear pIRF3 staining in hepatocytes and non-parenchymal cells with NAFLD severity, paralleled by increased expression of transcriptional targets (beta=0.022; p=0.013).

IRF3-/-, IRF3-CL+/-, and rs141490768 knock-in clones were generated in HepG2 to study the functional impact of IRF3 variation on inflammation and fibrogenesis in 3D multilineage spheroids with hepatocytes/stellate cells.

Conclusion: We found an enrichment of IRF3 rare variants in patients with severe NAFLD and IRF3 activity was upregulated across NAFLD spectrum. Additional studies are required to uncover the mechanism underpinning predisposition to disease progression in carriers of IRF3 variants.

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OC-29

AGILE-3 Score for the diagnosis of advanced fibrosis and for predicting liver-related events in nonalcoholic fatty liver disease

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Introduction: Noninvasive scores like FIB-4, NAFLD Fibrosis Score (NFS) and liver stiffness measurement (LSM) by transient elastography (TE) have acceptable accuracy for excluding advanced fibrosis in nonalcoholic fatty liver disease (NAFLD) and to stratify the risk of developing LRE. A recently developed score, namely AGILE-

3, and based on the combination of AST/ALT ratio, platelet count, diabetes status, sex, age and LSM, has been developed showing a slight improvement in AUROC and PPV for the diagnosis of advanced fibrosis. We aimed to assess the diagnostic accuracy of AGILE-3, respect to FIB-4, NFS e LSM, for the diagnosis of advanced fibrosis and for the prediction of LRE event occurrence in NAFLD patients.

Methods: 666 consecutive patients with biopsy-proven NAFLD or a clinical diagnosis of NAFLD-related compensated cirrhosis (LSM11.5 kPa for M probe or >11 kPa for XL probe) were enrolled. LRE were recorded during follow-up. FIB-4, NFS, LSM by TE and AGILE-3 score were measured. Patients were classified as at low, intermedium and high risk of F3-F4 fibrosis according to published cut-offs (FIB-4:<1.30,1.30-2.67,>2.67; NFS:<-1.455,-1.455-<=0.675,>0.675; LSM:<8 KPa,8-9.6 KPa,>9.6 KPa; AGILE-3:<0.45,0.45-<0.68,³0.68). The diagnostic performance of non-invasive criteria for advanced fibrosis and for the prediction of LRE was assessed by area under the receiver operating characteristic (AUROC) curve.

Results: In the cross-sectional study AGILE-3 and LSM had the higher AUC (0.89 and 0.88, respectively) and were better than both FIB-4 and NFS(0.80 and 0.79, respectively) for staging F3-F4 fibrosis. In the prospective study, the 3-,5- and 10-year AUCs for the occurrence of LRE of were 0.94,0.95 and 0.94 for FIB-4,0.92,0.91 and 0.91 for NFS,0.94,0.93 and 0.94 for AGILE-3, and 0.89,0.88 and 0.90 for LSM, respectively.

Conclusions: LSM had the better diagnostic accuracy for ruling-in and ruling-out advanced fibrosis in NAFLD,while FIB-4 and AGILE-3 better predict LRE occurrence.

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P-01

Humoral response to 2-dose BNT162b2 mRNA vaccine for Covid-19 in liver transplant recipients

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Introduction: In the context of the Italian SARS-CoV-2 vaccination program, liver transplant (LT) recipients were prioritized for vaccine administration, although the lower response to vaccines is a well known problem in this population.
Aim: We aimed to evaluate immunogenicity of BNT162b2 mRNA vaccine in LT recipients and healthy controls and to identify factors associated with negative response to vaccine.
Materials and Methods: We prospectively evaluated a cohort of adult LT patients the humoral response (with anti-Spike protein IgG-LIAISON SARS-CoV-2 S1/S2-IgG chemiluminescent assay) at 1 and 3 months after 2-dose vaccination. A group of 307 vaccinated healthcare workers, matched by age and sex, served as controls.
Results: Overall, 492 LT patients were enrolled (75.41% male, median age 64.85 years). Detectable antibodies were observed in the 75% of patients with a median value of 73.9 AU/mL after 3 months from 2-dose vaccination. At multivariable analysis, older age (>40years, p=0.016), shorter time from liver transplantation (<5years, p=0.004), and immunosuppression with antimetabolites (p=0.029) were significantly associated with non-response to vaccination. Moreover, the LT recipients showed antibody titers statistically lower than the control group (103 vs 261 AU/ml, p<0.0001) (fig. 1). Finally, both in controls and LT patients we found a trend of inverse correlation between age and antibody titers (correlation coefficient: -0.2023 and -0.2345, respectively).

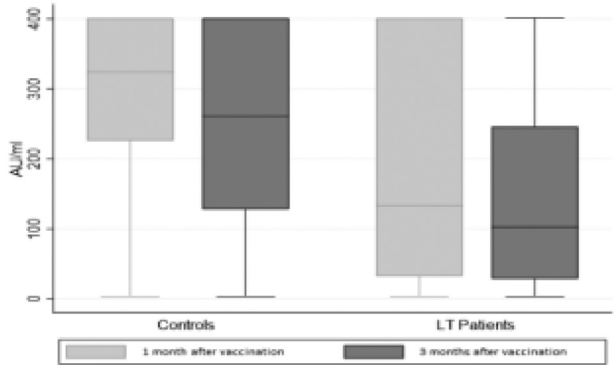

Figure 1. Humoral response to 2-dose BNT162b2 vaccine after 1 and 3 months in LT patients and healthcare workers (controls).

Conclusions: Three months after vaccination, LT recipients showed humoral response in 75% of cases. Older age, shorter time from transplantation and use of antimetabolites were factors associated with non-response to vaccination and needed to be kept under close monitoring.

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P-02

The use of Spleen Stiffness Measurement for the detection of high-risk esophageal varices in patients with portal hypertension

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Introduction: Endoscopic surveillance for esophageal varices (EV) is part of the routine workup for individuals with portal hypertension. High-risk esophageal varices (HR-EV) represent a rele-

vant morbid condition for this population. Recently, spleen stiffness measurement (SSM) has been suggested to stratify patients with EV. We aimed to assess the accuracy of SSM for the detection of HR-EV in individuals with portal hypertension undergoing surveillance endoscopy.
Materials and Methods: Outpatients with cCALD (chronic compensated advanced liver disease) according to Baveno VI criteria were included in this study. Clinical and biochemical data were collected for each patient at the day of endoscopy. Liver stiffness measurement (LSM), SSM, spleen size and volume were measured using the Fibroscan 630 Expert at 100 mHz. At least 10 SSM measurements per subject were recorded and analyzed after reaching a steady state. Grade 1 EV were considered as low-risk (LR-EV) and grades 2-3 EV were considered HR-EV.
Results: We enrolled 76 outpatients from May to October 2021. Median age was 58 years [IQR 51.5 – 64.5] and 57.9% was male. Most represented etiologies were alcohol-related (29%) and viral (12%). EV were detected in 85.5% of cases, of which 35.5% were considered HR-EV. Median longitudinal spleen size was 15.9 cm [IQR 13 – 17.4] and median spleen volume was 579 mm^3 [325.9 – 867.5]. Median SSM was 57.9 kPa [IQR 39.1 – 87.6], with significantly higher values in individuals with HR-EV, compared to those with no/LR-EV (medians of 86.8 kPa [IQR 51.1 – 99.5] versus 55.5 kPa [IQR 37.2 – 67.7], $p = 0.001$). There was a positive correlation between SSM and both longitudinal spleen size ($r = 0.43$, $p < 0.001$) and spleen volume ($r = 0.40$, $p = 0.036$). In multivariable logistic regression analysis, SSM and LSM > 20 kPa were significantly associated with the presence of HR-EV (OR 1,03 [95% CI 1.01 – 1.06] and 3,82 [1.00 – 14.6]). SSM had an Area Under the Curve of 0.72 for the detection of HR-EV. In this cohort, the ideal cut-off according to Youden's Index was 71.7 kPa, with a sensitivity of 63% and specificity of 84%. (Figure 1).
Conclusions: In this interim analysis, SSM correlates with longitudinal spleen size and volume. In addition, SSM is associated with the presence of HR-EV and suggests that it may be useful to assess the risk of HR-EV. A more detailed analysis of SSM including prospective data is needed to confirm the reproducibility of these results.

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P-03

Early post-liver transplant HCV eradication with sofosbuvir/velpatasvir/voxilaprevir in NS5A-inhibitor experienced patients

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Introduction: DAA revolutionized HCV treatment landscape. In HCV viremic patients at liver transplant (LT), early post-LT DAA therapy prevents graft damage and extrahepatic HCV involvement. Few data are available regarding patients who are HCV NS5B+NS5A inhibitors experienced at LT. We aimed to describe our first 6 patients treated early post-LT with sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) for 12 weeks.
Method: From 01/01/2019 to 01/11/2021, 436 patients underwent LT in our Center. Among 46 patients viremic at LT, 6 were experienced to NS5A inhibitors. SOF/VEL/VOX was started as soon as graft function was optimal with stable immunosuppression therapy (steroid, tacrolimus, mycophenolate).
Results: At LT, the median age was 54 years, median MELD 13. Median donor age: 70 years. Median cold ischemia time: 448 minutes. Patient#4 received a 50% macrovescicular steatosis graft and patient#6 a graft from a 82-year-old donor; both grafts underwent hypothermic oxygenated machine perfusion. Five patients were HCV-GT3 and one GT1a. Patient#6 received HCV-viremic donor (naïve GT2; Ishak: grading 3/18, fibrosis 1/6) and donor HCV strains replaced the recipient's (from GT3 to GT2). Median time from LT to DAA was 15 days. Four patients reached SVR12 by the end of therapy and remained negative (median follow-up 587 days). Patient#6 is still on therapy (week 3, HCV-RNA<15). Patient#3 interrupted SOF/VEL/VOX at week 8 for cholestatic hepatitis (GGT/ALP 576/1294 UI/L, bilirubin 12 mg/dL); liver biopsy was consistent with drug-induced hepatitis. Bilirubin dropped to 4 mg/dL at day 7 post-therapy withdrawal and normalized within 28 days; HCV-RNA became negative from day 14 of therapy. Immunosuppression levels remained stable.
Conclusions: Early use of post-LT SOF/VEL/VOX was successful in patients who were HCV viremic at LT and experienced to NS5B+NS5A inhibitors. One patient developed cholestatic hepatitis which reverted after therapy interruption. Early post-LT DAA prevented liver damage by HCV and allowed the use of suboptimal grafts.

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RECIPIENTS								DONORS			AFTER-LT				
Pt #	Age, years	Sex	HCC	MELD at LT	HCV GT	Previous DAA	HCV RNA at LT (UI/mL)	Macrovesicular Steatosis	Age, years	CIT (min)	Days from LT to DAA	HCV RNA pre DAA	HCV RNA < 15 UI/mL	SVR12	Follow-up from the end of therapy, days
1	46	M	No	14	3	SOF/VEL	1370000	<5%	55	312	6	26500	Week 1	Y	371
2	56	M	Yes	8	3	SOF/VEL	7066296	<5%	76	439	9	211200	Week 2	Y	804
3	48	M	Yes	15	3	SOF/VEL	62400	25%	43	391	21	779000	Week 1	Y	400
4	57	M	No	20	1a	SOF/LED	3716	50%	63	456	47	457360	Week 2	Y	831
5	58	M	Yes	9	3	SOF/VEL	1250000	10%	83	511	20	18500000	Week 3	Y	42
6	51	M	No	11	3	SOF/VEL	1490000	0%	82	578	8	5370000	Week 3	/	/

P-04

Morphological features and biological aggressiveness of hepatocellular carcinomas with TERT and TP53 mutations. Preliminary monocentric results on resected patients

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Introduction. Recently proposed prognostic classifications of hepatocellular carcinoma (HCC) included the mutations of TP53 and CTNNB1. The activation of the promoter gene telomerase reverse transcriptase (TERT) is observed in more than 50% of advanced HCC.
Aims. To compare the mutations harboured in advanced resected HCC with the main histological features of tumor progression.
Materials and Methods. In this prospective monocentric study, 27 surgically resected HCC were enrolled so far; clinical and histological variables were collected. Next Generation Sequencing (NGS) was carried out with a laboratory-developed multi-gene panel using Gene-Studio S5 sequencer. Due to their incidence, we focused on TERT, TP53 and CTNNB1.
Results. We recorded mutations in TERT promoter alone in 5 (18.6%) cases, in TP53 alone in 4 (14.8%), in CTNNB1 alone in 2 (7.4%); TERT and CTNNB1 were mutated together in 7 (25.9%) cases, TERT and TP53 in 6 (22.2%); none of the three mutations were observed in 3 (11.1%) cases. HCC mutation profile correlated with tumor architecture: all 5 cases with no mutations or only CTNNB1 mutations showed microtrabecular and/or acinar structure, while all cases with macrotrabecular and solid structure were observed in the other groups ($p<.001$, t-test). The presence of TERT promoter mutations, alone or in combination with other mutations, correlated with high-grade HCC: particularly, the 7 HCC with Edmondson's grade G4 in our series had pathogenic substitutions in TERT promoter regions ($p=.046$; Figure 1). No correlations were found between mutations and tumor dimensions.
Conclusions. The presence of TERT promoter mutations, alone or in combination with TP53/CTNNB1 alterations, correlates with a morphological progression in HCC, in terms of a higher tumor grade and a more "aggressive" architecture (solid, macrotrabecular), but not of a dimensional evolution, indicating that small HCC can be aggressive from a molecular and morphological point of view. Post-surgical follow-up will confirm these observations.

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P-05

Irisin alleviates liver oxidative stress in non-obese, non-diabetic individuals with Non-Alcoholic Fatty Liver Disease

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Introduction. Insulin resistance and oxidative stress play a relevant role in the onset of non-alcoholic fatty liver disease (NAFLD) and its progression to non-alcoholic steatohepatitis (NASH) and fibrosis. Irisin is an exercise-induced myokine involved in the regulation of energy homeostasis and glucose metabolism. Additionally, pre-clinical models have shown a potential role of irisin in the pathogenesis of NAFLD.
Aim. The aim of this study is to explore the association between irisin and indirect markers of oxidative stress and liver fibrogenesis in a well-characterized cohort of non-diabetic, non-obese, biopsy-proven NAFLD individuals.
Materials and methods. 41 patients with histological evidence of NAFLD were included. Circulating irisin and direct markers of fibrogenesis N-terminal type III collagen propeptide (PRO-C3) and type VI collagen cleavage product (PRO-C6) were measured by ELISA. The index of glutathione turnover derived from amino acid composition (GSGi) was used as indirect marker of liver oxidative stress.
Results. Median age of the cohort was 45 years [41-51] and 80.4% were male. Significant fibrosis (stage $\geq$ 2) was present in 36.6% of cases. Circulating irisin, PRO-C3 and PRO-C6 levels were significantly higher in subjects with fibrosis stage $\geq$ 2 when compared to those with fibrosis stage $<$ 2 (8.08 ng/ml [$\pm$ 4.88] versus 5.69 ng/ml [$\pm$ 5.4], $p=0.0326$; 13.8 ng/ml [$\pm$ 13.4] versus 7.6 ng/ml [$\pm$ 4.6], $p=0.046$; 7.3 ng/ml [$\pm$ 3.3] versus 5.4 ng/ml [$\pm$ 2.2], $p=0.0267$, respectively). Circulating irisin positively correlated with both PRO-C3 and PRO-C6 levels ($r=0.43$, $p=0.008$ and $r=0.49$, $p=0.002$). Conversely, circulating irisin, PRO-C3 and PRO-C6 levels inversely correlated with GSGi ($r=-0.55$, $p<0.001$; $r=-0.52$, $p=0.001$; $r=-0.57$, $p<0.001$). At multivariate regression analysis adjusted for age and gender, GSGi resulted significantly associated with circulating irisin ($t=-2.26$, $p=0.031$).
Conclusions. Increased circulating irisin levels may alleviate hepatic oxidative stress and may identify a more aggressive phenotype of liver disease.

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P-06

Longevity of seropositivity after anti SARS-CoV-2 vaccination in patients awaiting liver transplant

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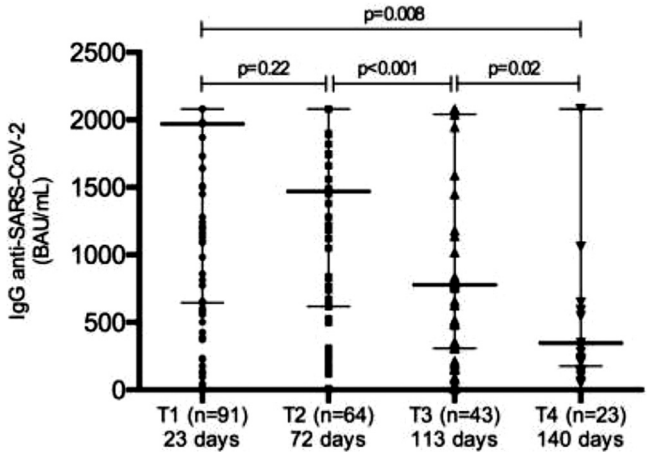
Introduction: Anti-SARS-CoV-2 vaccines demonstrated a high rate of success in preventing severe COVID-19 and decreasing infection rate. Few data are available in pre-liver transplant (LT) patients. IgG anti-Spike reflect humoral response to vaccination.
Aims: We aimed to evaluate longevity of humoral response to mRNA vaccine in our pre-LT patients.
Methods: From 01/2021 to 10/2021 we enrolled all pre-LT patients who completed anti-SARS-CoV-2 mRNA vaccination. Patients with previous COVID-19 received 1 vaccine dose within 6 months after infection. All the others received 2 doses. Patients were tested for IgG (LIAISON® SARS-CoV-2 TrimericS, positivity≥33.8 BAU/mL) 1 month post-vaccination and then every 2 months until LT.
Results: During study period, 91 pre-LT patients completed anti-SARS-CoV-2 vaccination: 80 patients received 2 doses, 11 patients 1 dose, as per protocol (94% Pfizer-BioNTech, 6% Moderna-COVID-19). 69% male, median age 56 years, BMI 25kg/m^2, eGFR 95ml/min, MELD 12; 43% HCC; 6 patients on steroids for autoimmune cirrhosis. **23 days** post-vaccination (**T1**), 86/91 (95%) seroconverted (median titer 1970 BAU/mL). During follow-up none of retested patients became IgG negative, however their titer progressively dropped: **72 days** post-vaccination (**T2**), 61/64 (95%) tested again IgG positive (median titer 1480); at **T3** (**113 days** post-vaccination) 42/43 (98%) patients remained positive and their titer significantly decreased (779); 23 pts were retested at **T4** (**140 days** post-vaccination) and all of them remained IgG positive (median titer 320). (T1vsT2, p=0.22; T2vsT3 p<0.001; T3vsT4, p=0.02; T1vsT4, p=0.008). At the end of a median follow-up of 190 days from vaccination, none of the patients developed COVID-19. No serious adverse events were registered.
Conclusions: In our 91 pre-LT patients, mRNA anti-SARS-CoV-2 vaccination elicited a high rate of seroconversion (95%) within 1 month. We observed a progressive significant decrease in IgG titer during a median follow-up of 190 days after vaccination. Nevertheless, none of our pre-LT patients developed COVID-19.



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P-07

Nash up, virus down: how is changing the waiting list for liver transplantation: a single center experience from Italy

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Introduction. Non-alcoholic steatohepatitis (NASH) has become the leading indication for liver transplantation in many Countries, with a growing rate in the Western World. This has contributed to a significant change of common features of the liver transplant candidate over time, since NASH patients are older, share higher risk of comorbidities, and cancer risk than patients with viral and/or alcoholic etiology.
Aims. To evaluate waiting list (WL) registration and liver transplantation rates in patients with NASH related cirrhosis at Padua University Hospital in the last fifteen years (2006-2020); to compare clinical characteristics and indications to liver transplantation between patients with and without NAFLD, as well as the WL survival and the post-transplant outcome.
Methods. All adult patients with cirrhosis listed for liver transplantation at Padua University Hospital between 2006 and 2020 were retrospectively collected using a prospectively-updated database; patients with NASH-related cirrhosis will be divided by indication for liver transplantation [dec-NASH vs HCC-NASH] and compared with patients with other etiologies of liver disease. Similarly, the outcomes in terms of waiting list survival and post-transplant outcome were assessed.
Results. 1,491 adult patients with cirrhosis were waitlisted in the study period. NASH patients accounted for 12% of all WL registrations, showing an increasing trend over time (from 2.5% in 2006 to 23% in 2020). In the last five years, NASH was the third, but the most rapidly growing indication to liver transplantation at Our Center. This trend was confirmed both for patients with decompensated cirrhosis (from 1.8% to 18%) and HCC as leading indication to transplantation (from 4% to 30%). NASH patients were older than non-NASH patients (mean±SD age 59±9 vs. 56±9 years; p<0.01), whereas no difference was found about gender, Child-Pugh and MELD score at WL registration. 60.9% NASH patients underwent liver transplantation, showing a 1-, 5- and 10-yr post-transplant survival of 86%, 73% and 60%, respectively.
Conclusion. NASH cirrhosis has become a rapidly growing indication to liver transplantation at Our Center, both for HCC and decompensated disease, with good post-transplant survival.

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P-08

Oleuropein prevents liver damage in NAFL mice by modulating copper-catalyzed dicarbonyl stress

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Introduction: The Nonalcoholic Fatty Liver Disease (NAFLD) is one of the major forms of chronic liver disease. NAFLD is considered the hepatic manifestation of the metabolic syndrome, thus, a new and more appropriate nomenclature has been suggested: Metabolic Associated Fatty Liver Disease (MAFLD). An imbalance of copper homeostasis has been described in the progression of NAFLD/MAFLD toward Nonalcoholic steatohepatitis (NASH), or Metabolic-associated Steatohepatitis (MASH).
Aim: We were interested in understanding whether the chelating activity of Oleuropein (Ole) was able to improve the copper accumulation and the related pro-oxidant and glycative damage in the liver of mice fed HFD.
Material and Methods Results: Twelve C57BL/6J mice fed normal diet (ND) or high-fat diet (HFD) for 16 weeks and then thirtytwo female and male mice fed ND or HFD for 8 weeks adding Ole for the following 8 weeks were studied. Copper was evaluated in the serum and liver tissues by atomic absorption spectroscopy. Dicarbonyl stress was assessed by ELISA kit. Our data show that altered expression of copper-trafficking genes and proteins (CTR1, CTR2, ATP7B, COX17, CCS, and ATOX1) induced imbalance of copper homeostasis combined with an increase in dicarbonyl stress in the liver of HFD fed mice. Interestingly enough, glyoxalase system was improved by Ole administration and the Ole related protective effects differ in the two sexes of mice.
Conclusions: Our study highlights the role of the dicarbonyl stress in the pathogenesis of NAFLD and suggests Ole as a natural copper chelator to prevent the liver damage induced by methyglyoxal pathway derangement.

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P-09

Impact of renaming NAFLD to MAFLD in a single Italian center

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Background and Aim: Metabolic Associated Fatty Liver Disease (MAFLD) is the novel definition and the new paradigm of NAFLD introduced in 2020, but its clinical and health public implications remain under evaluation. The aims of this study are to analyze the prevalence of MAFLD and NAFLD and compare them in a well-defined cohort of patients with liver steatosis.
Methods: A cross-sectional study was conducted in a single Liver Unit in Italy. Clinical, laboratory and imaging data were collected. NAFLD and MAFLD were defined according to international expert consensus.
Results: A total of 404 patients with ultrasound steatosis were included. The mean age was 61.6±13.4 years (61.8% male). The mean body mass index (BMI) was 29.2±5.2 kg/m^2. Most of them (84.1%) were overweight/obese, 216 (53.4%) had arterial hypertension, 86 (21.2%) had type 2 diabetes and 178 (44%) had dyslipidemia. MAFLD was present in 340 (84.1%) patients, while NAFLD in 138 (34.1%) of them. The increased prevalence of MAFLD in this cohort was driven by dual etiology of liver disease (29.1% of previous HCV infection; 30.2% of virologically suppressed HBV patients). All participants classified as NAFLD met the new definition of MAFLD. Compared with NAFLD subjects, MAFLD patients had higher ALT (p=0.01), AST (p=0.009), GGT (0.0038) and FIB-4 (p=0.02) values. No significant differences in the others non-invasive markers of fibrosis or steatosis (liver stiffness, NAFLD score, Controlled Attenuation Parameter) were observed.
Conclusions: Metabolic-associated fatty liver disease is a highly prevalent condition in this well-defined cohort. Application of these new criteria for MAFLD definition will increase the prevalence of fatty liver due to the inclusion of patients with dual etiology of liver disease.

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P-10

Interleukin-6 as a new marker for advanced sarcopenic HCC patients with different cirrhotic aetiology

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Introduction and aims: Hepatocellular carcinoma (HCC) is a major cause of liver cancer-related death worldwide. It usually occurs in cirrhosis with different aetiopathogenesis. Serum 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 signalling leads to tumour progression or local recurrence. Aim of our study is to clarify if the levels of IL-6 are associated with HCC progression and its different aetiopathogenesis in cirrhotic patients.
Methods: 111 consecutive HCC cirrhotic patients (with different stages and aetiopathogenesis) were enrolled and compared with 36 cirrhotic patients without HCC. Patients were divided according to Child Pugh (CP) class and severity of HCC disease (BCLC). The major anthropometric and biochemical parameters, particularly serum IL-6, were collected. The degree of sarcopenia was also considered using TC dedicated software.
Results: IL-6 levels were different between advanced and not advanced HCC (p=0.01), while no difference in IL-6 levels was documented in CP-C with and without HCC; however, IL-6 levels were higher in advanced HCC (OR 4.58 CI: 1.19-17.55; p < 0.001). IL-6 levels were different also between different aetiologies of cirrhosis; in particular, no differences in viral and metabolic cirrhosis, low levels (p< 0.001) in alcoholic and higher in autoimmune HCC or in combination of different aetiologies. IL-6 correlated also with sarcopenia severity (p<0.001) especially in advanced HCC patients (p<0.001). In no HCC CP-C patients, IL 6 was not correlated with sarcopenia. In linear regression IL-6 was correlated with AFP (p < 0,001, r = 0.57). In multivariate analysis IL-6 was linked with aetiopathogenesis, cancer progression, sarcopenia, CP and lymphocytes count.
Conclusions: These data suggest that IL-6 is higher in inflammatory states (like cirrhosis with CP-C) but it has a closer relation

with advanced HCC and could be a marker for the disease itself. IL-6 seems to be also a predictor of sarcopenia especially in advanced HCC patients. Also, cirrhosis aetiopathogenesis has shown different IL-6 levels, documenting a different inflammatory setting. IL-6 could be a new marker to classify advanced HCC and a possible future drug target considering the different cirrhotic aetiopathogenesis.

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P-11

Metabolic dysfunction-associated fatty liver disease and liver fibrosis score in patients with COVID-19 as predictors of adverse clinical outcomes: an artificial intelligent application through machine learning

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Introduction and aims. Patients with coronavirus disease-2019 (COVID-19) and metabolic-dysfunction associated fatty liver disease (MAFLD) appear to be at higher risk for severe manifestations like acute respiratory distress syndrome, especially in the youngest decades. Our aim was to examine whether patients with imaging-defined MAFLD and/or with increased non-invasive liver fibrosis scores (FIB-4) are at higher risk for severe illness from COVID-19, using a machine learning model.
Methods. In this retrospective cohort study, we included 672 patients admitted for SARS-CoV-2 pneumonia between February the 28th 2020 and May the 1st 2021. Hepatic steatosis was detected by ultrasound or computed tomography (CT), whereas FIB-4 score was used to define the risk of advanced liver fibrosis. We used a machine learning (ML) model to evaluate the risks of both in-hospital death and prolonged hospitalizations (>28 days), considering MAFLD, a set of blood tests (hepatic profile; HP), and the FIB-4 score, either separately and together.
Results. Three hundred-thirty-three (49.6% of total) had imaging-defined MAFLD. The accuracy in predicting in-hospital death in the whole sample was 0.709 for the HP alone, and 0.721 for HP+FIB-4 combined together; in the 55-to-75 age subgroup, the accuracies were respectively 0.842 and 0.855 for HP alone and HP+FIB-4 together. In the MAFLD subgroup, the accuracy in predicting death was 0.739 considering HP alone, and 0.772 when considering HP+FIB-4 together; whereas in the MAFLD 55-to-75 years cohort, the accuracies were respectively 0.825 for HP and 0.833 for HP+FIB-4. Similar results were obtained both in the entire cohort and in MAFLD patients when considering the accuracy in predicting prolonged hospitalization (>28 days).
Conclusions. In our cohort of COVID-19 patients, the presence of a worse HP and a higher FIB-4 correlated with a higher risk of death and prolonged hospitalization, regardless of the presence of MAFLD. These findings could improve the clinical risk stratification of patients diagnosed with SARS-CoV-2 pneumonia.

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P-12

Lifestyle in Primary Biliary Cholangitis: let's pay attention!

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Background and Aims: Primary Biliary Cholangitis (PBC), a chronic cholestatic liver disease, is frequently associated with severe hypercholesterolemia. The aim of this study is to evaluate whether the lifestyle of PBC patients is adequate to hypercholesterolemia.
Methods: In this multicenter study, PBC patients were subjected to a questionnaire on eating habits (daily caloric intake and diet composition) and physical activity to investigate their lifestyle.
Results: Seventy PBC patients were enrolled in two Italian centers. Characteristics of PBC patients are summarized in Table 1. The median age was 57.1 years and 94.1% of patients was female. The mean BMI was 26.6±3.8 Kg/m^2, the mean waist circumference was 89.79±13.75 cm and the mean waist/hip (W/H) ratio was 0.83±0.08. All these measures were higher than the reference values. Coexisting MAFLD (Metabolic Associated Fatty Liver Disease) was present in 48 (68.6%) patients. The average daily kilocalories were 1785.1 ± 568.1 kcal with 52% of lipids (mean satured fats 23.8±8.48 g) and 47% of carbohydrates. In particular, the average cholesterol content of diet was 293.88±114.57 mg, much greater than recommended. Finally, only the 38.6% of PBC patients practiced regular physical activity (200 min/week), while the majority of them had sedentary lifestyle.
Conclusions: Although PBC is often associated with hypercholesterolemia, the majority of patients are overweight, with waist circumference and W/H ratio values at high risk for metabolic comorbidities. Moreover, patient's lifestyle is mainly sedentary and with a high dietary fat content. Hepatologists should pay attention to this problem and recommend a lifestyle change also in PBC patients.

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P-13

Bulevirtide monotherapy at low and high dose in patients with chronic hepatitis delta: 24 weeks interim data of the phase 3 MYR301 study

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Aims: 24-week interim analysis of the MYR301 phase 3 study in chronic HDV patients receiving 2mg/qd or 10mg/qd dose of bulevirtide monotherapy compared to observation.
Method: 150 patients were randomized 1:1:1 to no antiviral treatment for 48 weeks followed by BLV 10mg/qd for 96 weeks (arm A, n=51), treatment with BLV 2 mg (arm B, n=49) or BLV 10 mg (arm C, n=50) for 144 weeks with a treatment-free follow-up of 96 weeks. The combined primary endpoint is defined as undetectable HDV RNA (<LoD) or decrease by ≥2log10 IU/ml and ALT normalization at week 48.
Results: 57.3% were male, 82.7% were White and mean age was 41.8 years. Baseline HDV RNA levels were 5.05 log10 IU/mL and ALT mean levels were 110.9 U/L. BLV was well tolerated during the first 24 weeks: overall, 421 treatment emergent adverse events (TEAE) were reported; 55 TEAE in 26 patients in the arm A, 121 TEAE in 32 patients in the arm B and 245 TEAE in 36 patients in the arm C. 48 TEAE in arm B and 100 TEAE in arm C were assessed as possibly related to BLV. At week 24, 36.7% of patients in arm B and 28.0% in arm C achieved combined virological and biochemical response (vs. 0% in arm A, $p<0.0001$). HDV RNA decrease by ≥2 log10 IU/mL at week 24 from baseline was observed in 55.1% of patients in arm B and 68% in arm C (vs. 3.8% in arm A, $p<0.0001$). ALT normalization was achieved in 53.1% of arm B, 38% of arm C (vs. 5.9% in arm A, $p<0.0001$).
Conclusion: Monotherapy with BLV is safe and well tolerated in patients with chronic HDV. 24-week treatment with BLV was associated with significant HDV RNA declines and improvements in biochemical disease activity.

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P-14

Obeticholic acid restores hepatic RECK content in a diet-induced ob/ob mouse model of NASH

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We have previously shown that obeticholic acid (OCA) restores hepatic levels of RECK, an MMP regulator tissue reversion-inducing cysteine rich protein with Kazal motifs, after ischemia/reperfusion injury. Here, the effect of OCA on hepatic RECK content was evaluated in a diet-induced NASH model in ob/ob mice.

$Lep^{ob/ob}$ (ob/ob) NASH mice fed the high fat (HF) diet (AMLN-diet; D09100301, with trans-fat, cholesterol and fructose) or control diet were used. After 9 weeks on diet, mice were treated with OCA dosed via dietary admixture 0.05% (30 mg/kg/d) or HF diet for 12 weeks. Liver weight, serum transaminase, alkaline phosphatase, bilirubin, cholesterol triglycerides and glucose, as well as hepatic RECK content, were quantified at the end of the study.

HF diet induced significant increase in liver weight compared to control diet group. OCA treatment restored liver weight when compared with HF-treated mice, to values comparable with those observed in the control diet group. Serum bilirubin and cholesterol increased in HF diet animals and OCA administration markedly counteracted these increases. OCA did not affect serum transaminase, alkaline phosphatase, glucose and triglycerides compared to HF diet mice. The downregulation of RECK observed in livers from HF diet mice was restored by OCA administration to values seen in control diet group.

Thus, OCA confers protection in a model of NASH, as shown by reduced serum bilirubin and cholesterol levels. This is the first study showing the positive effect of OCA on hepatic RECK levels in a NASH model, an intriguing finding considering the emerging role of RECK in regulating inflammatory and fibrogenic processes. Further studies are necessary to better understand the implications of OCA-induced increase in hepatic RECK expression, and its role in the therapy of NASH.

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P-15

Rectus femoris ultrasound is an easy bedside tool that identifies sarcopenia and predict a poor clinical course in patients with an acute decompensation of cirrhosis

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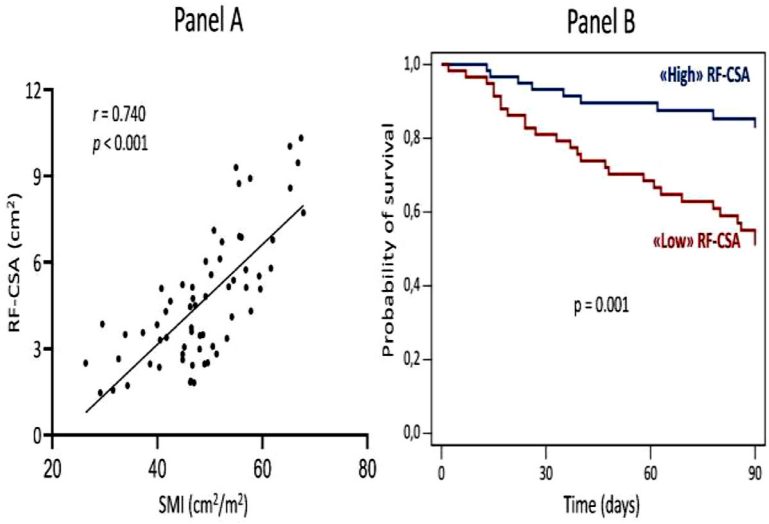

Background: Sarcopenia has been associated with poor outcomes in cirrhosis. The gold standard for assessing sarcopenia is the CT scan, with the measurement of skeletal muscle index(SMI) at L3. However, CT scan is expensive, exposes patients to radiations and SMI assessment requires a specific software. We evaluated: a)the accuracy of ultrasound measurement of rectus femoris cross sectional area(RF-CSA) in the assessment of sarcopenia; b)the prognostic value of RF-CSA in hospitalized patients with cirrhosis.
Methods: Phase1: abdominal CT scan and thigh ultrasound were performed in 64 patients with cirrhosis. RF-CSA was measured at two-thirds of the distance from the anterior superior iliac spine to the superior patellar border. Sarcopenia was defined by SMI(<39 cm^2/m^2 in women and <50 cm^2/m^2 in men). Independent predictors of sarcopenia were evaluated. Phase2: RF-CSA was measured in 120 consecutive patients hospitalized for decompensated cirrhosis. Patients were classified in two groups according to the median values of RF-CSA for males and females ("low"vs"high"). Patients were followed up until death, liver transplant or 90 days.
Results: RF-CSA showed a strong correlation with SMI (r=0.740;p<0.001;Fig.A) outperforming BMI and mid arm muscle circumference. RF-CSA was an independent predictor of sarcopenia (aOR=0.28;p=0.002) and showed a high discrimination ability for ruling out sarcopenia (AUROC=0.90 in male and 0.88 in female). Among inpatients (mean age=64±11 years, mean MELD-Na=20±7), those with "low" RF-CSA had a higher incidence of hepatic encephalopathy (63%vs39%;p=0.010), sepsis (36%vs10%;p=0.001), transfer to ICU (17%vs5%;p=0.042) and in-hospital mortality (27%vs8%;p=0.014), and a lower probability of 90-day survival (51%vs83%;p=0.001;Fig.B) than those with "high" RF-CSA. In multivariable analysis (adjusted for age, sex, MELD-Na and leukocytes), a "low" RF-CSA was an independent predictor of 90-day mortality (aHR=4.13;p<0.001).
Conclusions: Ultrasound measurement of RF-CSA is an easy bedside tool for the assessment of sarcopenia in patients with cirrhosis. Low RF-CSA values independently predict poor outcomes in hospitalized patients with cirrhosis.

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P-16

Impact of bacterial infections prior liver transplantation on post-transplant outcomes in patients with cirrhosis

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Background: Bacterial infections (BI) are frequent in cirrhosis and increase the risk of decompensation, death and drop-out from the liver transplant (LT) waitist. LT in patients with BI is frequently delayed due to the fear of poor outcomes. However there are few data on the impact of BI prior LT on post-LT outcomes. We evaluated the impact of pre-transplant BI on post-LT complications and survival.
Methods: From 2012 to 2018 we identified 109 LT candidates surviving an episode of BI within 3 months prior LT and 359 patients without BI prior LT. Demographic, clinical and laboratory data were collected at the time of LT. After LT data on complications, length of stay and survival were collected.
Results: Patients with pre-transplant BI had a higher MELD-Na score at transplant than those without. Donor characteristics, cold ischemia time and time of surgery were not significantly different between the 2 groups. Patients with pre-transplant BI had a more complex postoperative course with longer stays in intensive care unit (9 vs 6 days;p=0.010) and in-hospital (29 vs 21 days;p=0.002) and higher incidence of new BI (51% vs 29%;p<0.001), fungal infections (13 vs 4%;p=0.001) and septic shock (7 vs 1%;p=0.002;Fig.A). Nevertheless no difference was found in 1 and 5-year survival between patients with or without pre-transplant BI (Fig.B). In patients with pre-transplant BI no association was found between the time elapsed from the diagnosis of BI to LT and post LT outcomes.

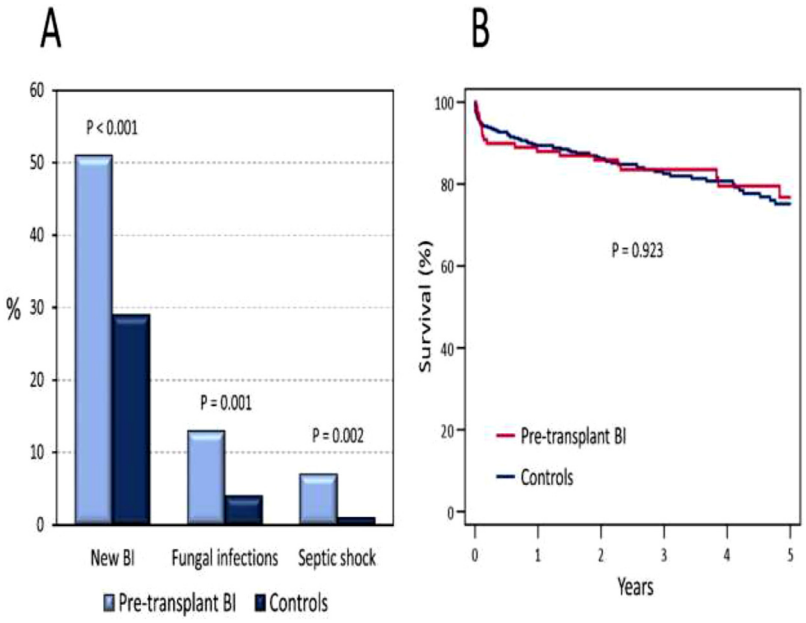

Figure: (A) Occurrence of bacterial infections (BI), fungal infections and septic shock after LT in patients with pre-transplant BI and controls; (B) Probability of survival after liver transplant in patients with pre-transplant BI and controls

Conclusions: Patients with BI prior LT have a more complex clinical course after LT and higher risk of new BI, fungal infections and septic shock. However post LT survival is excellent. Therefore, as soon as BI is resolving, it is safe to proceed with LT, but patients with pre-transplant BI require an active surveillance for infections after LT.

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P-17

Independent determinants of CAP values in healthy individuals with dysmetabolism

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Background: Controlled attenuation parameter (CAP) values determined during vibration controlled transient elastography correlate with hepatic fat content and can non-invasively assess the presence of fatty liver with moderate accuracy.
Aim: to examine the clinical and metabolic determinants of CAP in a cohort of apparently healthy individuals with dysmetabolism.

Method: We assessed CAP in 953 consecutive blood donors with ≥3 dysmetabolism features (hypertension, hyperglycemia, overweight/obesity, low HDL/high triglycerides), who participated in a primary prevention program (LIVER-BIBLE cohort up to July 2021). CAP determinants were assessed by generalized linear models.
Results: Mean age was 53.9±6.3 yrs, BMI 28.5±3.0 Kg/m^2, 158 (16.6%) participants were females, 35 (3.7%) diabetics, 704 (73.9%) had hypertension and 383 (40.2%) dyslipidemia, 463 (48.6%) had fatty liver (CAP>275 db/m), and 17 (1.8%) liver stiffness measurement (LSM) ≥8 kPa. CAP correlated with LSM ($p<10^{-16}$). CAP was associated with older age (p=0.02), higher BMI, abdominal circumference, glucose, insulin, ferritin (p<0.01 for all), and lower HDL (p=0.03). No consistent association with CRP, hypertension, diet/lifestyle factors was detected, except for alcohol consumption (p=0.003). At multivariable analysis, abdominal circumference was the main determinant of CAP ($p<10^{-9}$), with insulin ($p<10^{-6}$), HbA1c (p=0.006), ferritin (p=0.04) and HDL levels (p=0.04). Independent determinants of CAP≥275 dB/m were confirmed to be abdominal circumference ($p<10^{-5}$), insulin (p=0.0003), HDL, HbA1c, BMI and alcohol consumption (p<0.05 for all). Fatty liver index predicted CAP≥275 dB/m with low-moderate accuracy (AUROC=0.70), whereas ALT with low accuracy (AUROC=0.60). In the subset of the latest 352 enrolled participants for whom the information was available, we found an independent association between CAP and lower TSH levels (estimate -5.06±2.22, p=0.02).

	Overall LIVER-BIBLE Cohort			Subgroup with TSH determination (n=352)		
	Estimate	SE	P value	Estimate	SE	P value
Sex, F	1.99	1.84	0.28	3.33	2.76	0.23
Age, years	0.37	0.19	0.06	0.35	0.32	0.27
BMI, kg/m^2	0.79	0.62	0.21	0.42	0.95	0.66
Abdominal circumference, cm	1.41	0.22	$1.1*10^{-10}$	1.60	0.34	$1.9*10^{-6}$
HbA1c, mmol/mol	0.81	0.30	$6.4*10^{-3}$	0.31	0.45	0.49
Insulin, uU/ml	0.70	0.14	$2.8*10^{-7}$	0.95	0.22	$2.0*10^{-5}$
HDL, mg/dl	-0.25	0.13	$4.9*10^{-2}$	-0.15	0.20	0.45
Ferritin, log ng/ml	2.91	1.45	$4.4*10^{-2}$	1.88	2.40	0.43
Alcohol drinks, n/week	0.33	0.22	0.12	0.90	0.34	$8.0*10^{-3}$
TSH, mU/l	-	-	-	-5.06	2.22	$2.2*10^{-2}$

Independent predictors of CAP values in the LIVER-BIBLE cohort. F: female; BMI: body mass index; HbA1c: glycate hemoglobin; TSH: thyroid stimulating hormone; SE: standard error.

Conclusion: In healthy individuals with dysmetabolism, CAP values were most strongly associated with the severity of hyperinsulinemia and abdominal adiposity. The association between activation of the pituitary-thyroid axis and fatty liver is being evaluated in the whole updated cohort.

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P-18

SerpinB3/4 expression is associated with poor prognosis in patients with cholangiocarcinoma

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Introduction: Cholangiocarcinoma (CCA) is characterized by a very poor outcome and limited prognostic markers are currently available for this dismal tumor. The protease inhibitor SerpinB3 has been recently identified as a critical mediator of malignant phenotype in different tumors.
Aim: to analyze tissue and serum expression of SerpinB3/4 in human CCA, in relation to clinical outcome.
Materials and Methods: SerpinB3/4 was evaluated by tissue microarrays (TMAs) in 123 surgically resected CCAs, that were dichotomized into SerpinB3/4 high (2+/3+) versus SerpinB3/4 low (0/1+) groups. ELISA assays to detect free and IgM linked forms of this serpin in serum were carried out in additional 188 patients with CCA. Overall Survival was analyzed in relation to SerpinB3/4 expression and was estimated with Kaplan-Meier methods. Univariate and multivariate Cox models were used to evaluate independent variables associated with survival.
Results: Fifteen tumors (12.2%) showed high levels of SerpinB3/4 (TMA score 2+/3+). Patients with high SerpinB3/4 scores presented more frequently advanced TNM Stage (III/IV:64.3% vs. 31.3%, p=0.031), and had higher serum CA 19-9 levels (328 vs. 53 kU/L, p=0.001). Patients with high SerpinB3/4 scores had lower overall survival, independently of CCA subclass (iCCA: median 1.1 vs 2.4 years; p = 0.0007; eCCA: median 0.8 vs 2.2 years; p = 0.011). In a multivariate analysis, vascular invasion (p=0.027) and SerpinB3/4 score (p=0.0016) were independently associated with mortality. Patients who were positive for either free or IgM -linked SerpinB3/4 in serum showed poorer survival (1 vs 2.4 years for free SerpinB3/4, p 0.015; and 1 vs 2.6 years, p 0.0026 for SerpinB3/4-IgM).
Conclusions: High levels of tissue and serum expression of SerpinB3/4 in CCA are strongly associated with poor outcome after surgery, regardless of tumor subclass.

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P-19

Evaluation of allelic frequency and genetic risk score of non-alcoholic fatty liver disease in a population of Southern Italy

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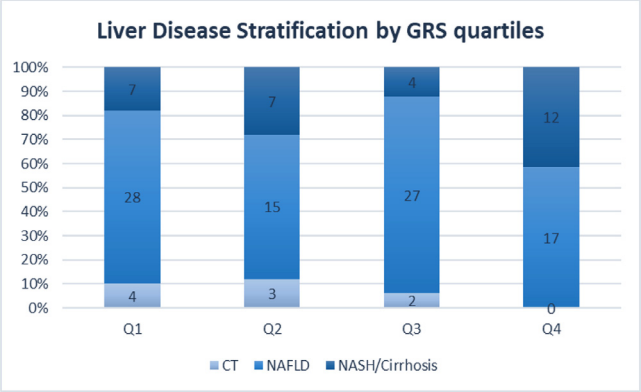
Background and Aims: Non-alcoholic fatty liver disease (NAFLD) is the leading cause of liver diseases, ranging from simple steatosis to non-alcoholic steatohepatitis (NASH). The risk of developing NAFLD is highly variable among individuals and determined by environmental and genetic factors. GWAS studies identified several genetic risk factors, and genetic risk scores (GRS) were developed for risk stratification. NAFLD susceptibility is significantly associated with four genetic variants: PNPLA3 rs738409 C>G, TM6SF2 rs58542926 C>T, rs641738 C>T close to MBOAT7 locus, GCKR rs1260326 C>T. Our aim was to evaluate how these variants are distributed in our population of Southern Italy and whether they predispose to severe liver disease in NAFLD patients by analysing allelic frequency and GRS.
Method: We enrolled 117 NAFLD patients and 9 controls, which were genotyped for rs738409, rs58542926, rs641738, rs1260326. We calculated a weighted GRS by multiplying beta-coefficient of NAFLD phenotype by respective risk alleles and summing the products.
Results: In our cohort, we observed a higher Minor Allele Frequency of PNPLA3 and GCKR variants compared to the ones reported in European population of 1000Genomes Project. The rs738409 G allele frequency is 34,1%, while in 1000Genomes Project is 23% (p<0.01). As expected, the G frequency increased from controls (5,6%) to NAFLD (31,8%) to NASH/cirrhosis (50%). The rs1260326 T allele frequency is 54,8% vs. 41% in 1000Genomes (p<0.01). Interestingly, T frequency is higher in controls (72,2%) than NAFLD (54%) and NASH/cirrhosis (51,7%),. MBOAT7 and TM6SF2 variants did not differ from reported frequencies. We eval-

uated the effect of the 4 variants on the risk of developing more severe liver disease by a weighted GRS, which increased from controls, to NAFLD, to NASH/cirrhosis.
Conclusion: This study suggests that in our population, GCKR T allele frequency is increased and that it is possible to use GRS to perform a genetic NAFLD risk stratification.



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P-20

Preclinical evaluations of a novel formulation of PD-L1-targeted liposomal doxorubicin for the treatment of hepatocellular carcinoma

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Introduction: Finding therapeutic options for hepatocellular carcinoma (HCC) is still an intriguing challenge, due to some drawbacks, as, for example, the shortage of effective pharmacological targets for drug development.
Aim: The aim of this study is to evaluate the in vitro and in vivo activity of a novel liposomal doxorubicin (DXR) formulation targeted with the PD-L1 checkpoint inhibitor atezolizumab, in order to deliver DXR selectively to cancer cells, enhancing its activity and decreasing its off-target toxicity.
Materials and Methods: Two liposomal formulations were tested, i.e., atezolizumab-targeted liposomal DXR (Stealth ImmunoLiposomes, SIL_atezolizumab) and untargeted liposomal DXR (Stealth Liposomes, SL). The in vitro cytotoxicity was evaluated on the three PD-L1 expressing HCC cell lines Hu7, HepG2 and Hepa1-6, after 72 h-treatment by means of the ATP assay. A syngeneic HCC mouse model was set up by injecting murine Hepa1-6 cells in C57BL/6J immunocompetent mice. SIL_atezolizumab and SL were administered e.v. once a week for 4 weeks. Tumor volumes were measured by an electronic caliper once a week and collected and weighed at sacrifice for further analyses.
Results: The in vitro cytotoxic effect of liposomal DXR in HepG2 and Hepa1-6 cells was increased by atezolizumab targeting, since IC50 values of SIL-atezolizumab were significantly lower with respect to SL ($p<0.01$ and $p<0.05$, respectively). In the Hepa1-6-injected syngeneic mice tumor growth was significantly reduced by the treatment with both SL and SIL_atezolizumab compared to untreated mice ($p<0.05$). Moreover, a slight increase of survival was observed in SIL_atezolizumab treated mice.
Conclusions: PD-L1-targeted liposomal doxorubicin limits HCC cell growth in vitro and in vivo. This approach, based on the combination of two already approved drugs joined in a novel liposomal formulation, could open new perspectives for the therapeutic management of HCC.

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P-21

Prognostic impact of sarcopenia on patients with advanced hepatocellular carcinoma treated with sorafenib

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Introduction Sarcopenia, defined as reduced muscle mass and function, has been associated with poor outcomes in patients with cirrhosis and hepatocellular carcinoma (HCC).
Aim To investigate the impact of sarcopenia on survival in patients with advanced HCC treated with sorafenib.
Materials and Methods Results The characteristics of 215 cirrhotic patients with HCC undergoing sorafenib and with abdominal computed tomography (CT) performed within 8 weeks from treatment start were retrospectively analyzed. Sarcopenia was defined by reduced Skeletal Muscle Index (SMI), calculated from an L3 section CT-image. Male patients with SMI < 53 cm2/m2 with a body mass index (BMI) ≥25 or with SMI <43 cm2/m2 with a BMI <25, and female patients with SMI <41 cm2/m2 regardless of BMI were defined as sarcopenic. Sarcopenia was present in 103 patients (48%). Sarcopenic patients did not differ from non-sarcopenics in respect to baseline data except for metastasis, more represented in sarcopenics (36 cases, 35% vs 22 cases, 19.5%; p=0.014). Sarcopenic patients showed a significant lower survival rate at 6 and 12 months (67% and 29%, respectively) compared to non-sarcopenics (74.1 and 45.5%; p=0.028). At multivariate Cox analysis sarcopenia [Hazard ratio (HR): 1.43, 95% confidence interval (95%CI) 1.02-2.01; p=0.03], Model for End stage Liver Disease (MELD) >9 (HR: 1.63, 95%CI 1.15-2.3; p=0.006) and alpha-fetoprotein (AFP) >25 ng/mL (HR 1.6, 95%CI 1.12-2.29: p=0.01) emerged as independent prognostic factors. Therefore, we classified patients according to the presence of the 3 aforementioned prognostic factors into two groups: group 1 (0-1 prognostic factor) and group 2 (2-3 prognostic factors). Group 1 showed a significantly better survival compared to group 2 (Figure).
Conclusions Sarcopenia is an independent predictor of poor survival in patients treated with sorafenib for advanced HCC. Its prognostic combination with MELD>9 and/or AFP >25 ng/mL could help to identify patients with shorter survival at 12 months.

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P-22

The impact of bacterial infections on cirrhosis complications in a cohort of cirrhotic patients in a northern Italian hospital

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Introduction: Bacterial infections represent a major cause of morbidity and mortality in patients with liver cirrhosis.
Aim: Our aim was to assess the prevalence of bacterial infectious events in a cohort of cirrhotic patients, the prevalence of multidrug resistant organisms (MDROs) and the association with hepatic complications.
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: 69 patients (30%) developed at least one bacterial infection during the study period (median follow-up 3.3 y). 101 bacterial infections were recorded, 33% 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%). 18.8% of all infections were sustained by MDROs, accounting for 46% of all culture-confirmed infections. Patients with at least one infection during the year were older (67±13 y, $p < .013$), with higher MELD and Child-Pugh scores at the enrolment ($p < .001$). In patients with at least one MDROs infection during the year, the mean MELD and Child-Pugh scores at the enrolment were higher ($p < .001$). Liver complications such as ascites ($p < .001$), bleeding ($p = .001$), portal vein thrombosis ($p = .001$), hepatorenal syndrome ($p < .001$) and hepatic encephalopathy ($p = .001$), occurred more frequently in infected than in uninfected 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.

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P-23

Laboratory diagnosis of HCV for elimination: shadows of the present and lights for the future

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Introduction. Hepatitis C virus diagnostics are essential to achieve global elimination. HCV is currently diagnosed first through the detection of HCV antibodies (anti-HCV) and, second, among those who are anti-HCV positive, active HCV infection is confirmed by HCV-RNA PCR and genotyping.
Aim. To assess if laboratory diagnosis of HCV infection is actually in accordance with our present epidemiological situation to find HCV missing patients providing a rapid linkage to care for starting DAAs.
Methods. We retrospectively evaluated anti-HCV serology results from 01.01.2019 to 31.12.2019 of Hub Hospital Pordenone (FVG). Using an extended database to 31.11.2021, we considered, among those who were anti-HCV positive, HCV-RNA result and if we detected positivity for HCV-RNA, we checked a control sample of negative HCV-RNA. Anti-HCV assays were performed using CLIA ADVIA-Centaur (Siemens Healthineers) and HCV-RNA RT-PCR molecular detection using COBAS 6800 (Roche) (Sensitivity 15 UI/ml).
Results. During the period assessed, 14.221 subjects were tested for HCV infection and 350 (2.4%) were identified as positive for anti-HCV. Of these 350, 101 (28.8%) patients were positive for serum HCV-RNA reporting prevalence of hepatitis C of 0.7% in our sample; 153 (43.7%) were negative and in 96 (27.4%) molecular test was not submitted. 40 subjects (39.6%) positive for HCV-RNA did not perform determinations of undetected HCV-RNA while we registered follow up negative HCV-RNA for 61 (60.4%) patients.
Conclusions. Even with limitations of performing exams and antiviral treatment in other locations, our results showed critical issues: 1) 27.4% anti-HCV positive subjects did not perform HCV-RNA PCR missing further diagnostic for dectectable HCV-RNA; 2) 39.6% HCV viremic patients did not reveal negative HCV-RNA suggesting missing linkage to care for starting DAAs. Our actual approach to laboratory diagnosis is not in accordance with the goal of HCV elimination. HCV reflex with laboratory alert in HCV-RNA positivity is urgently needed.

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P-24

Liver transplantation for hepatocellular carcinoma:outcome and prognostic factors for recurrence

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Introduction: HCC accounts for approximately 75% of primary liver cancers and is the fourth leading cause of death from malignancy worldwide.Liver transplant (LT) is a curative treatment in some patients. The post-transplant recurrence rate of HCC is very wide, between 5 and 30%, due also to different listing policies.
Aims: the aim of our study was to evaluate the recurrence rate of HCC after LT and to identify the main risk factors for recurrence.
Methods: 230 patients (84% male, mean age 59 yr) with HCC transplanted between February 2007 and December 2020 were followed until recurrence or death. The majority of patients had MELD scores $\leq$19, while 4.8% had scores $\geq$30. Milan criteria were applied for listing. Etiology, biochemical data, pre-transplant treat-

ments, and histological evaluation of the native liver were collected.
Results: 57% of patients had viral, 29.6% alcoholic, and 12.6% NAFLD cirrhosis. 69% of patients had undergone pre-transplant treatments (PEI, RFA,TACE, TARE, resection). The mean follow-up was 47+/-39 months, with 77.4% survival. Average survival of patients without HCC recurrence was 48.6+/- 39.4 months, with recurrence was 23+/-25.1 months. After LT, 9.1% of patients had HCC recurrence, and 22.6% died. Among those who had HCC recurrence, 57% of patients had recurrence within the first 12 months after transplantation; 19% at 24 months, 19% at 36 months, 5% at 60 months. In 66.6% of patients with relapsed HCC, the tumor started with extrahepatic localizations .

In the multivariate analysis the factors that predicted the outcome (death or 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 ($p< 0{,}04$).
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.

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P-25

Incidental findings of anti-mitochondrial antibodies without evidence of Primary Biliary Cholangitis

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Introduction and Aim: Anti-mitochondrial antibodies (AMA) are a specific diagnostic marker of Primary Biliary Cholangitis (PBC). The widespread use of auto-antibody test panels in non-hepatological settings allows incidental findings of AMA in patients without a history of liver disease. The aim of this study was to assess the evidence of significant liver disease in patients accidentally found positive for AMA testing.

Materials and Methods: From January 2020 to June 2021, forty-two adult patients without a known history of liver disease were occasionally found positive for immunofluorescent AMA testing during diagnostic evaluation for rheumatologic or endocrinologic conditions at our Institution. Immunoblotting confirmed M2 positivity in 37 patients. Evidence of concomitant liver disease was assessed by serum liver enzymes, Fib-4 score (based on age, platelet count, AST, and ALT values), abdominal ultrasound, and liver stiffness measurement (LSM) by 2D shear-wave elastography.
Results: Female sex was predominant (36/37, 97%), median age: 63 years (range: 37-81). In 32 (86.5%) and 33 (89.2%) patients, AST and ALT values were within the normal range, respectively. Alkaline phosphatase (ALP) was elevated in 13 (35.1%) patients: 166.8 $\pm$ 63.9 IU/L, and normal in 24 (64.9%): 74.0 $\pm$ 20.1 IU/L. Bilirubin levels were within the normal range in all but one patient (1.7 mg/dL in this one). The Fib-4 score resulted $<$ 1.3 in 23 (62.2%), between 1.3 and 2.67 in 11 (29.7%), and $>$ 2.67 in 3 (8.1%) patients. LSM showed kPa values $>$ 7 in only 3 patients (2 with elevated ALP and 1 with elevated AST). Figure summarises the distribution of AMA-positive patients according to liver enzymes, Fib-4 score, and liver elastography.
Conclusions: In most unselected consecutive adult patients with incidental findings of confirmed positive AMA, non-invasive biochemical and imaging evaluations did not show evidence of significant liver disease. Further longitudinal studies are needed to assess the clinical significance of AMA positivity in this set of subjects.

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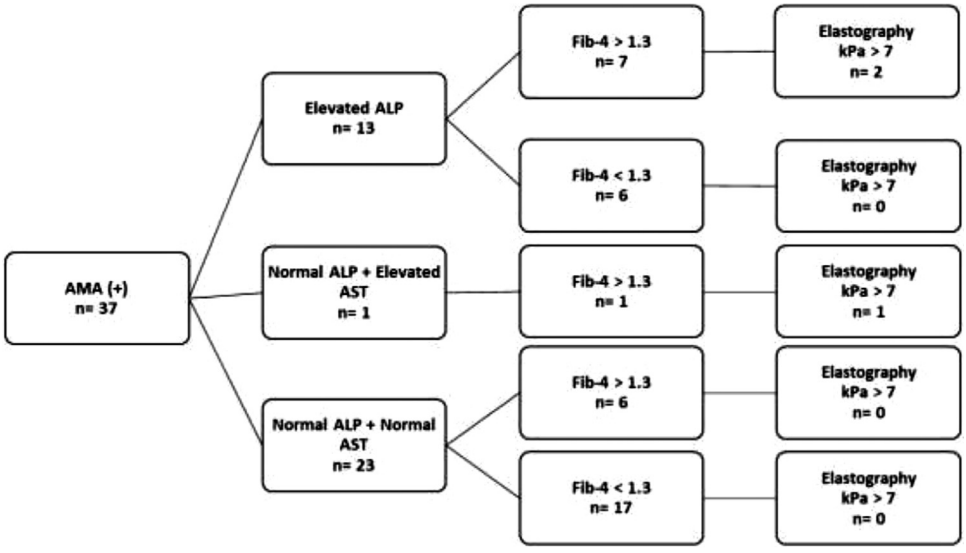

P-26

The forgotten ventricle: right ventricular (RV) evaluation in patients with cirrhosis listed for liver transplantation

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Introduction: The pre-operative evaluation of the right ventricle and its function is critical in the decision-making process on the eligibility for transplantation of the cirrhotic patient. Currently, RV assessment standards are based on measurement of heart chamber volume and systolic pulmonary artery pressure.
Aim: In our study we investigate the contractile capacity of RV and the degree of cardiac fibrosis in patients assessed for liver transplantation.
Materials and Methods: Patients undergoing LT evaluation between October 2020 to October 2021 were prospectively evaluated. RV global Longitudinal strain (RVGLS) and RV free wall strain (Rvfws) were measured by speckle tracking and indexed to echocardiographic estimated PASP. In a subgroup of patients with reduced RVGLS and Rvfws a cardiac Magnetic Resonance Imaging (c-MRI) was performed to define the abnormalities in the myocardium. Late gadolinium enhanced (LGE) in T1 phase was used as a marker of myocardial fibrosis. Results were compared to a retrospective group of 50 healthy patients.
Results: RV basal diameter and RV thickness were significantly higher in patients with end-stage liver disease compared to controls. Patients with cirrhosis had more impaired RV global longitudinal strain (-15.3 ± 6.2% compared to healthy controls, p= 0.009) and RV free wall longitudinal strain (-18.3 ± 5.1% compared to controls, p = 0.046). RV global longitudinal strain and RV-free wall strain in cirrhosis were significantly reduced in 48 patients than controls. RV strain reduction was found also in cirrhotic with normal RV volume and PASP (p=0.002). In those with RV strain reduction, c-MRI showed myocardial fibrosis; LGE (5.3 ± 3.1 vs. 0%, P < 0.001). LGE negatively correlated with RV ejection.
Conclusion: RV function in cirrhotic patients evaluated for LT is frequently impaired. A second-line evaluation based on echo strain and c-MRI allows to identify RV dysfunction.

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P-27

A non-invasive tests for the assessment of advanced liver fibrosis in patients with non-alcoholic fatty liver disease: a cross sectional study in a third referral centre

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Background and Aims: The prevalence of non-alcoholic fatty liver disease (NAFLD) is increasing, being the advanced fibrosis an independent risk factor for both hepatic and extrahepatic events, and mortality. For this reason, non-invasive tests are increasingly used to identify patients requiring referral to the specialists. Aim of the study was compare Liver Stiffness Measurement (LSM), Fibrosis-4 (FIB-4) and NAFLD fibrosis (NFS) scores in NAFLD patients, and the accuracy of FIB-4 in identifying patients with LSM ≥8 kPa.
Methods: A cross sectional retrospective study in all consecutive compensated HCC-free patients with fatty liver on liver ultrasound scan and without other comorbid liver diseases having baseline Fibroscan examination. Among 1.136 patients, a valid LSM was available in 1.117 (46% XL probe) [57% males, 60 years, 88% caucasian, BMI 28, 77% overweight, 51% arterial hypertension, 45% hyperlipidemia and 35% type 2 diabetes mellitus]. Cut-offs to rule-out and rule-in advanced fibrosis were FIB-4 <1.3, NFS <-1.455, LSM <8 kPa and FIB-4 >3.25, NFS >0,675, LSM >12 kPa, respectively.
Results: 52%, 50% and 69% of patients had FIB-4 <1.3, NFS <-1.455, LSM <8 kPa, whereas 9%, 14% and 15% of patients had FIB-4 >3.25, NFS >0,675, LSM >12 kPa, respectively. Among the 583 (52%) with FIB-4 <1.3, LSM was <8 kPa, between 8 and 12 kPa and >12 kPa in 494 (85%), 70 (12%) and 19 (3%); whereas among the 534 (48%) patients with FIB-4 ≥1.3, LSM was <8 kPa, between 8 and 12 kPa and >12 kPa in 272 (50%), 111 (21%) and 151 (29%), respectively.
Conclusions: 31% of patients have LSM ≥8 kPa (15% >12 kPa), however using the FIB-4 <1.3, as the cut-off to identify patients requiring referral to the liver clinic, we could miss 89/351 (25%) patients with LSM ≥8 kPa and 19/170 (11%) patients with LSM >12 kPa.

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P-28

Hepatocellular carcinoma with portal vein tumor thrombus: a single-center retrospective analysis

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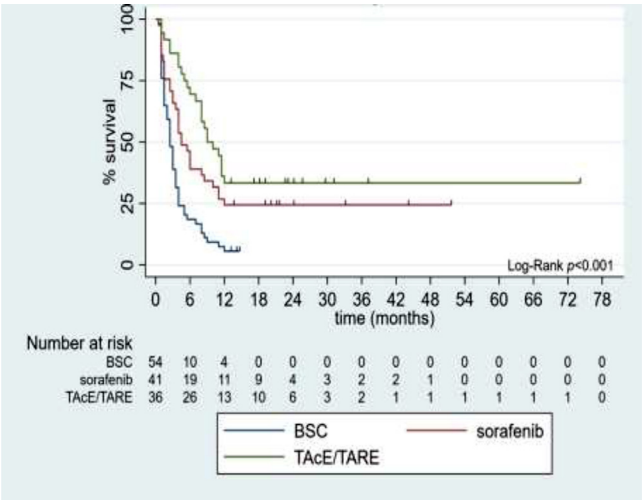
Background: Portal vein tumor thrombosis (PVTT) represents a serious complication of hepatocellular carcinoma (HCC). It rules out the possibility of liver transplantation and has a very poor prognosis. In the past two decades, clinical guidelines for HCC have been reviewed and validated. Japanese, Chinese and Hong Kong guidelines support the surgical resection in patients with Child-Pugh classes A/B cirrhosis. On the other hand, guidelines of EASl, AASLD and APASL indicate intra-arterial and systemic treatment.
Method In this observational, retrospective, single-center study, we evaluated patients with HCC followed-up in our Center from 2015 to 2019 and selected a cohort of 131 patients with HCC with PVTT. The primary endpoint was the overall survival at 6, 12 and 24 months; as secondary endpoint, we analysed all factors potentially associated with higher mortality rates.
Results: Mortality rates tend to increase over time, from the 37.4% at 3 mo. up to 93.4% at 24 mo. Age did not significantly affect these rates, as well as cirrhosis aetiology, comorbidities such as diabetes and obesity. We did observe a positive correlation towards a higher mortality risk with the female sex at 12 and 24 mo. Besides

this, the administration of a previous treatment exerted a significantly positive effect on survival, as well as the current administration of a therapy for HCC and PVTT, both with systemic therapy and endovascular therapy. Higher levels of alpha-fetoprotein and residual liver function represent a negative prognostic factor. The multivariable model confirmed albumin as independent negative prognostic factor. Conversely, current TACE/TARE therapy were independent positive prognostic factor.
Conclusion: HCC with PVTT has a poor prognosis. There is a diversity of approaches in PVTT patients between Western and Eastern countries. It is therefore necessary to review and expand the role of surgery and the systemic therapy.



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P-29

Pharmacological interventions effect on liver histology in non-alcoholic steatohepatitis: a network meta-analysis

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Background & Aim: The aims of this study were to quantify the histological improvement and its risk factors in patients with NASH enrolled in the placebo arms of randomized controlled trials(RCTs), and to indirectly compare the effect of several investigational drugs for NASH on validated histological outcomes.
Approach & Results: A comprehensive search was conducted to detect phase 2 and 3 RCTs comparing pharmacological interventions in patients with NASH. Resolution of NASH without worsening of fibrosis or ≥1 stage reduction of fibrosis without worsening of NASH were evaluated as outcomes validated by Food and Drug Administration. Meta-analysis and meta-regressions were conducted on placebo arms, while network meta-analysis was performed on intervention arms. A total of 15 RCTs met the eligibility criteria. The meta-analysis on placebo arms showed a pooled estimate rate of 17%(95%C.I. 12%-23%;I^2=86%;p<0.01) for NASH resolution without worsening of fibrosis and of 21%(95%C.I. 13%-31%;I^2=84%;p<0.01) for ≥1 stage improvement of fibrosis without worsening of NASH. Phase 3 RCTs, age and AST levels were significantly associated with progression of liver disease by univariate meta-regression. At network meta-analysis, Semaglutide(P-score 0.906), Pioglitazione alone(score 0.890) and plus Vitamin E(0.826) had the highest probability of being ranked the most effective intervention for NASH resolution without worsening of fibrosis, while Aldafermin(0.776), Lanifibranor(0.773) and Obeticholic acid(0.771) had the highest probability to achieve ≥1 stage of fibrosis improvement without worsening of NASH.
Conclusion: This study confirms the heterogeneity of histological progression of untreated patients with NASH and provides evidence for stratify patients according to identified risk factors in future RCTs of combination therapies.

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P-30

Patient-derived liver organoids as a 3D in vitro model to studyPNPLA3 I148M role in NAFLD

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Introduction and Aim: Non-alcoholic fatty liver disease (NAFLD) heritability is estimated to be within 25-75% and PNPLA3 rs738409 C>G p.I148M variant accounts for a large fraction of disease susceptibility. The p.I148M variant promotes intrahepatic lipid accumulation, progression to cirrhosis and hepatocellular carcinoma. A comprehensive human model to study the role and mechanisms of genetic variability in liver disease is still lacking. Aim of this study is to generate patient-derived human liver organoids (HLOs) to clarify the impact and role of PNPLA3 mutation in NAFLD onset and progression.
Methods: We isolated HLOs from 14 surgical resection specimens. PNPLA3 rs738409 was genotyped by 5' nuclease Taqman assays. Single cells were embedded in Matrigel and a complete organoid medium to instruct signaling cues crucial for the growth of liver epithelial cells. To model fatty liver, HLOs were differentiated toward a hepatocyte-like phenotype and exposed to free fatty acids (FFAs, 300/300 uM palmitic/oleic acid) for 3 days.
Results: We isolated, grew for > 150 days and biobanked organoids with different PNPLA3 p.I148M genotypes (7,1% GG, 42,8% CG, 50,1% CC). HLOs organize in a monolayer epithelial with a well-defined apical-basal polarity and show a cholangiocyte-like phenotype, expressing KRT19 and SOX9. Differentiated HLOs show high levels of hepatocyte markers (albumin, CYP2D6 and ApoA1, Fold Increase 85.8, p=0,0307; 1.27, p=ns and 324.8, p=0,0035 respectively; n=5), while the epithelial staminal marker LGR5 was suppressed. Moreover, both HLO and differentiated HLO retain PNPLA3 expression. When exposed to FFAs, differentiated organoids showed an accumulation of lipid droplets, as examined by Oil Red O staining (2.3 fold increase in organoid exposed vs. non-exposed).

Conclusions: We isolated, characterized and biobanked HLOs form 14 patient with different PNPLA3 genotypes, obtaining a 3D in vitro model for investigating NAFLD within a personalized medicine framework with high translational potential.

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P-31

Serum HBsAg and ddPCR HBV-DNA as predictive parameters of HBsAg loss after nucleo(s)tide analogue (NA) treatment discontinuation in non-cirrhotic patients with Chronic Hepatitis B

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Introduction: Stopping nucleo(s)tide analogue (NA) treatment in selected non-cirrhotic Chronic Hepatitis B (CHB) often leads to virus-induced flares, which may result to life-threatening liver failure.
Aim: to identify predictive parameters of off-NAs response at the end of treatment and their association with HBsAg loss or HBsAg <100IU/ml, for a safe discontinuation of treatment.
Materials and Methods: 38 non-cirrhotic CHB patients, with complete virological suppression (> 4 years), were prospectively monitored after suspending NA treatment for a median (IQR) time of 16 (10-19) months. Plasma samples at suspension date (baseline, BL) were collected and used to quantify serum HBV-DNA by highly sensitive droplet digital PCR (ddPCR). HBsAg was quantified by the ARCHITECT HBsAg assay at BL, every 2 weeks from suspension in the first month, followed by every month until the sixth month, then every 3 months.
Results: At BL, 28 (73.7%) pts had detectable serum HBV-DNA (median[IQR] 5[2-11] IU/mL), while 10 (26.3%) were completely negative to HBV-DNA. After NA suspension, 7 (18.4%) achieved HBsAg <100IU/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 <100IU/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 <100IU/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: Residual HBV replicative activity at NA suspension, measured by highly sensitive assays, provides an added value in identifying patients more prone to achieve HBV functional cure.

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Preprocedural prophylaxis with blood products in patients with cirrhosis: results from a survey of the Italian Association for the study of the Liver (AISF)

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Introduction: The new concept of rebalanced hemostasis in cirrhosis challenges the policy of transfusing plasma or platelets before invasive procedures in patients with prolonged PT or severe thrombocytopenia. Recent guidelines recommend against plasma transfusion and suggest avoiding/minimizing platelet transfusions.
Aim: We assessed how Italian hepato-gastroenterologists manage prolonged PT/INR or severe thrombocytopenia in cirrhosis before invasive procedures and whether their practice is influenced by recent guidelines.
Methods: On May 2021 members of the Italian Association for the Study of the Liver (AISF) were sent a questionnaire addressing the PT/INR and platelet count thresholds required before invasive procedures, the value given to other markers of bleeding risk, the pre-emptive use of other hemostatic treatments and the burden of blood products transfused.
Results: Sixty-two responders completed the survey. Of these, 94% and 100% use PT/INR and platelet count to assess the bleeding risk, only 37% require less conservative PT/INR and 32% require less conservative platelet count for low-risk procedures. The PT/INR threshold required prior to low- and high-risk procedures is <1.5 in 22% and 74% of centres, respectively. The platelet count threshold is $\geq 50 \times 10^9$/L in 25% and 90%, respectively. In centres where single thresholds for PT/INR and platelet count are applied, PT/INR< 1.5 and platelet count $\geq 50 \times 10^9$/L are required in 68% and 86%, respectively. Half centres use other indicators of bleeding risk besides PT/INR and platelet count and 63% use other hemostatic treatment besides plasma or platelet transfusion. Low-risk procedures account for 70% of invasive procedures, and for 50% and 59% of plasma and platelets units transfused, respectively.
Conclusions: This survey remarks the reluctance of Italian clinicians to comply with guidelines advising against pre-emptive plasma and platelet transfusions before invasive procedures and the need for further studies and inter-society consensus workshops.

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P-33

Investigating the effect of gender on liver fibrosis and associated sarcopenia

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Gender influences the incidence of liver fibrosis, which has a 2:1 male-to-female ratio and different outcomes in the two genders, including sarcopenia that affects 40-60% of patients with advanced liver fibrosis. Thus, we assessed the influence of gender in the pathophysiological mechanisms of liver fibrosis, regeneration and associated muscle dysfunction. A mouse model of liver fibrosis was obtained by injecting increasing doses of carbon tetrachloride (CCl_4, from 0.17 to 0.72 mL/g body weight) for a maximum of 12 weeks, followed by a 8 week-washout period. Muscle performance was assessed by the grid hanging and the grip strength test. Mice were sacrificed after 6 and 12 weeks of treatment, and after the washout period. Flow cytometry was used to analyze proinflammatory monocytes-derived macrophages recruited in the liver (MoMFs). Liver fibrosis was assessed by Masson's trichrome staining. Immunohistochemistry and qPCR were performed to measure the mRNA and protein expression of αSMA, col1a1, VEGFA, TGFβ, TNFα. After 6 weeks of CCl_4-treatment, male mice showed more fibrotic areas and activated stellate cells (HSCs) ($p < 0.05$), higher levels of the profibrotic agent TGFβ and proinflammatory MoMFS and worse motor performances with respect to females. After 12 weeks, females developed severe fibrosis with higher amounts of MoMFS, TGFβ and activated HSCs than males. During the washout, all the animals ameliorated their physical performances, although liver regeneration was not complete, especially in males, which still have fibrotic areas with the presence of some activated HSCs. This model, obtained by administering increasing doses of CCl_4, caused fibrosis, whose onset was faster in males and more progressive in females. CCl_4 administration was accompanied by a significant muscle weakness. Gender has an influence on the pivotal mechanisms regulating liver damage and regeneration, including the activation of HSCs and the recruitment of pro-inflammatory MoMFs.

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Controlled attenuation parameter in primary biliary cholangitis: a cross-sectional analysis

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Background and aims: Controlled Attenuation Parameter (CAP) is currently used to quantify steatosis in clinical practice. However, data in patients with primary biliary cholangitis (PBC) are lacking. Therefore, aim of our study was assessment of clinical features influencing CAP values in PBC patients.
Methods: PBC patients with liver stiffness measurement (LSM) and CAP values obtained between January 2020-May 2021 in a single center were included in a cross-sectional analysis. Blood tests and abdominal ultrasound (US) results were recorded ± 2 months from CAP assessment.
Results: Overall, 92 patients were included: 92% females, 87% AMA-positive, 91% on stable ursodeoxycholic acid (UDCA) treatment, 19% on second-line therapy due to UDCA non-response. At CAP assessment, median age was 63 (30-91) years, BMI 24 (17-38) kg/m^2, ALT 25 (6-233) U/L, ALP 120 (49-427) U/L (ULN: 104 U/L), GGT 41 (7-984) U/L, bilirubin 0.5 (0.1-3.6) mg/dL, albumin 4.2 (3.4-4.5) g/dL, total cholesterol 192 (112-365) mg/dL, HDL 69 (37-113) mg/dL. Median LSM was 5.8 (3.0-75.0) kPa, 20 (22%) patients had advanced fibrosis (>11 kPa). At US, steatosis was absent in 65 (70%) patients, mild in 19 (21%), moderate-severe in 8 (9%). Median CAP was 229 (166-354) dB/m: CAP resulted ≤248 dB/m (no steatosis) in 63 (68%) patients, >280 dB/m (moderate-severe steatosis) in 12 (13%). Median CAP values increased concomitantly to US steatosis, being 224 vs. 238 vs. 282 dB/m in patients with no vs. mild vs. moderate-severe steatosis, respectively (p=0.003). CAP values directly correlated with BMI (r=0.28, p=0.006) and inversely with HDL (r=0.27, p=0.01). Conversely, CAP was not influenced by total cholesterol, triglycerides, LSM, transaminases, cholestasis markers as well as UDCA response status.
Conclusions: In patients with PBC the prevalence of steatosis is low, when assessed either through US or CAP. In this setting, CAP values are influenced by metabolic features such as HDL and BMI.

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P-35

Diabetes and number of metabolic risk factors influence liver disease severity in patients with non-alcoholic fatty liver disease

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Background and Aims: Non-alcoholic fatty liver disease (NAFLD) has become a significant cause of liver disease also in Western Countries. Whilst several factors may be associated with NAFLD, type 2 diabetes mellitus (T2DM) and obesity have been associated with more severe fibrosis. We assessed liver disease severity through non-invasive tests according to the main metabolic risk factors (RF) for NAFLD: T2DM, obesity and dyslipidemia.
Methods: Consecutive NAFLD patients referred to our Center from January 2020 to May 2021 were included. They underwent liver stiffness measurement (LSM), controlled attenuation parameter (CAP) and serological non-invasive tests (NITs) for fibrosis (APRI, FIB-4, NFS, ELF, NASH test).
Results: Overall, 359 patients were analyzed: age was 57 (18-84) years, 204 (57%) males, 295 (82%) Caucasians, BMI 27.9 (19.0-47.5) kg/m^2. Median LSM and CAP values were 5.4 (2.0-72.0) kPa and

293 (107-395) dB/m, respectively. Forty-one (11%) had cirrhosis. 119 (33%) patients were obese, 87 (24%) had T2DM and 234 (65%) had dyslipidemia. Twenty-eight (8%) patients carried all 3 NAFLD RF, 117 (33%) two, 183 (51%) one and 31 (9%) none. The number of RF (0-1 vs. 2-3) influenced both LSM (p=0.0005) and CAP (p=0.0003). Despite similar ALT (p=0.70) and γGT (p=0.16) values, the number of RF influenced fibrosis through FIB-4 (p=0.001), NFS (p<0.0001), ELF (p<0.0001) and NASH test (p=0.012). Considering patients with only one RF, those with DMT2 had lower PLT (p=0.04) and higher LSM (p=0.04) values, and showed higher FIB-4 (p=0.05) and NFS (p<0.0001). Considering patients with two RF, those with DMT2 had the highest LSM values (p=0.001); conversely, CAP values were similar independently of RF combination (p=0.06).

Conclusions: In NAFLD patients, NITs and steatosis are influenced by the number of RF. Particularly, DMT2, but not obesity, is associated with more severe fibrosis either when analyzed alone or in combination with other RF.

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Switching tdf treated patients to taf is a safe and effective strategy even in difficult-to-manage elderly patients with hbv-related cirrhosis and significant comorbidities: a real-life prospective study

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Introduction. While registration studies clearly demonstrated the efficacy and safety of switching HBV patients from TDF to TAF, real life studies validating these results in difficult-to-manage elderly TDF-treated patients with significant comorbidities and proximal tubular damage have not been performed.

Methods. All consecutive patients switching from TDF to TAF from November 2019 to June 2020 in two EU Centers were enrolled in this prospective study. All lab/clinical parameters were recorded at TAF introduction (baseline), and at months 2, 6, 12, 18 and thereafter. Glomerular and tubular function was monitored by UBCR, UPCR, UACR, UCa/Cr while metabolic parameters included BMI, total cholesterol and triglycerides.

Results. 182 patients were switched to TAF after 123 (1-171) months of TDF treatment: age 69 (38-88) years, 99% Caucasian, 70% males, 42% compensated cirrhosis, 95% HBeAg-negative, 98% normal ALT, 95% HBV-DNA undetectable, 55% arterial hypertension/diabetes, 47% BMI >25 kg/m^2, 67% adefovir-exposed. TAF was initiated because of age (82% >60 years) or renal (59%) or bone (31%) disease. During 18 months of TAF treatment, BMI, total cholesterol and triglycerides levels remained unchanged. No significant changes of $eGFR_{CG}$ and $eGFR_{MDRD}$ levels were observed while the proportion of patients with eGFR<60 mL/min slightly increased (46à48%, and 35à43%). UPCR, UACR and uCa/Cr remained stable over time, while UBCR progressively improved, from 502 (14-81,299) to 208 (1-123,762) mg/g, normalizing in 59% of the patients. In 101 patients who switched to TAF from a TDF-reduced dose, $eGFR_{CG}$ and $eGFR_{MDRD}$ remained stable while UBCR improved (481à287 mg/g). Virological and biochemical responses were maintained over time with HBV-DNA undetectability rates exceeding 95% and ALT levels remaining within the normal range.

Conclusions. In-difficult-to manage elderly HBV patients with significant comorbidities exposed to TDF for many years, switching to TAF was effective and safe without significant changes of lipid profile or body weight.

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P-37

Implementation of hcv screening in the 1969-1989 birth-cohort undergoing covid-19 vaccination: a pivotal study in Italy

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Background and Aim: The World Health Organization (WHO) goal of hepatitis C virus (HCV) elimination by 2030 relies on the scaling-up of policies of both identification and linkage-to-care of the infected population, worldwide. In Italy, the estimated burden of HCV carriers who are unaware of their infection amounts to 200,000 persons, thus reinforcing the need for broadening population access to effective screening programs.

Methods: A pivotal screening program targeting subjects born between 1969 and 1989 has been conducted in Lombardy, where point-of-care (POC) testing was offered for free concomitantly to COVID-19 vaccination.

Results: Overall, 7,219 subjects underwent HCV screening in 4 vaccination hubs. Pivotal strategies varied according to each vaccination hub: each screening team has employed from 2-3 to 9-12 people daily, and took 16-128 hours to complete the screening program. Seven (0.1%) subjects tested anti-HCV positive and 5 (0.07%) had confirmed anti-HCV and HCV-RNA positivity by standard confirmation tests. Patients with HCV infection were all males, aged 41-46 years; only one of them came from Italy. Clinical data were available for 3 patients: all of them have altered transaminases values, without HBV or HIV co-infection; HCV genotypes were 1b, 3 and 4, and liver stiffness ranged between 4.5 and 10.3 kPa. All patients underwent oral anti-HCV therapies. The overall mean cost per test (including confirmation tests) was 9.8 €, of which 68.3% related to human resources (36.0% for clinicians, 21.8% for nurses, 10.5% for research assistants).

Conclusions: This pivotal study demonstrated the feasibility of a POC-based anti-HCV screening program in young adults undergoing COVID-19 vaccination. The prevalence of HCV infection in subjects born in the 1969-1989 cohort in Italy seems to be lower than previously estimated, thus raising the question whether more HCV carriers can be identified if screening is moved up to embrace subjects born before 1969.

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P-38

Prevalence of sarcopenia and cardiovascular alterations in a cohort of non-cirrhotic MAFLD patients

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Background and Aims: Metabolic dysfunction-associated fatty liver disease (MAFLD) is defined by hepatic steatosis associated with metabolic comorbidities. The prevalence of Sarcopenia, predictor of cardiovascular damage (CVD), in early stages of liver diseases is still debated as is the prevalence of CVD in MAFLD. Bioelectrical impedance analysis (BIA) non-invasively diagnoses sarcopenia by skeletal muscle index (SMI). An increased in carotid intima-media thickness (cIMT), the carotid plaques and the epicardial fat thickness (EFT) are validated markers of early CVD. Aims: to define the prevalence of 1) sarcopenia and associated factors in non-cirrhotic MAFLD patients; 2) CV alterations in the same cohorts.
Methods: 316 non-cirrhotic MAFLD patients were enrolled. Anthropometric parameters (BMI and waist circumference-WC), sarcopenia by BIA (SMI/height^2 $\leq$10.75/6.75 kg/m2 men/woman), cIMT ($>$0.9mm) and carotid plaques by ultrasound, EFT by echocardiography were evaluated.
Results: Mean age was 52 ys, 64% male. Sarcopenia was present in 34%, increased cIMT in 22% and carotid plaques in 32%. Median EFT was 7.6$\pm$2.6mm. Carotid plaques and EFT were higher in female than in male (41vs27, p=0.02; 8.3vs7.1mm, p=0.0003, respectively), while sarcopenia was more prevalent in male (53vs8%, p$<$0.001). At multivariate analysis, sarcopenia remained significantly associated to male sex, despite men were younger than women in our cohort. Moreover, at multivariate analysis cIMT was independently associated with sarcopenia (OR 6.6, CI 95% 1.9-23.3), while BMI (OR 0.3, CI 95% 0.2-0.5) and WC (OR 0.7, CI 95% 0.6-0.9) resulted inversely correlated with 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. CVD is higher prevalent in MAFLD, compared to literature data about non-alcoholic fatty liver disease. In patients with MAFLD, especially men, physicians must emphasize the role of nutrition and physical activities to prevent loss of skeletal muscle and progression of CVD.

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P-39

Hydroxytyrosol and vitamin E combination therapy exerts beneficial effects on NAFLD-related fibrosis

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Introduction: Liver fibrosis is the result of liver injury secondary to non-alcoholic fatty liver disease (NAFLD), imputable to the activation of hepatic stellate cells (HSCs), and consequent accumulation mostly of fibrillar collagens. To date, there is no approved pharmacological treatment for reversing of NAFLD-related fibrosis, thus this research field is extensively investigated. Natural antioxidants, such as hydroxytyrosol (HXT) and vitamin E (VitE), have been investigated as drugs both in vivo and in vitro, revealing that when combined they may exert anti-steatogenic and anti-inflammatory effects.
Aims: Here, we explored the anti-fibrotic effect of HXT and VitE combination therapy (HXT+VitE) in activated human HSCs and in children with NAFLD.
Materials and Methods: LX-2 cells, treated for 24 hours with 2 ng/mL of pro-fibrogenic stimulus transforming growth factor (TGF)-β1, were used as a model of activated human HSCs. Different concentrations of HXT and VitE were tested to decide no-toxic combinatorial amounts. TGF-activated cells were treated with 30μM HTX + 20 μM VitE for 48 hours. The mRNA/protein expression of pro-fibrogenic pathways and redox-active factors were performed. The potential reversal effect of HXT+VitE on fibrosis was investigated by evaluating circulating biomarkers (i.e. ProC3) in children with biopsy-proven NAFLD at baseline and 4 months after treatment with placebo or HXT+VitE.
Results: TGF-activated LX-2 cells treated with HXT+VitE exhibited a reduced pro-fibrogenic phenotype. In particular, the TGF-induced up-regulation of collagen type I alpha 1 chain (COL1A1) and collagen type III alpha 1 chain (COL3A1) genes was counteracted by the combined treatment. In addition, HXT+VitE antagonized TGF-induced up-regulation of pro-oxidant Nox2 gene by interfering with nuclear translocation of SMAD2/SMAD3 transcription factors. Accordingly, HXT+VitE treatment caused a decrease of circulating levels of ProC3 in children with NAFLD.
Conclusions: In conclusion, we reported that HXT+VitE may exert a promising ant-ifibrotic effect that deserves further investigation.

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The role of histidine-rich glycoprotein in non alcoholic steatohepatitis-related experimental liver carcinogenesis

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Introduction: Non-Alcoholic Fatty Liver Disease (NAFLD) has recently emerged as the leading cause of chronic liver disease in the general population in Europe and in the USA acquiring clinical relevance as a large percentage of NAFLD patients can develop steatohepatitis (NASH), fibrosis, cirrhosis and also hepatocellular carcinoma (HCC). Currently, the events, mechanisms and mediators involved in the evolution of NAFLD / NASH related HCC are still largely unknown.
Aim: In the present study we have investigated the possible pro-carcinogenic role of histidine-rich glycoprotein (HRG), a plasma protein abundantly produced by hepatocytes.
Material And Methods: The role of HRG, was investigated by morphological, cellular and molecular biology approaches in: a) HRG knock-out mice ($HRG^{-/-}$ mice) undergoing a NASH-related protocol of hepatocarcinogenesis; b) NAFLD patients carrying HCC; c) THP1 cells treated with purified HRG.
Results: Data obtained showed that HRG: a) is expressed in HCC nodules and released in plasma samples from NAFLD-related patients, b) exerts an M1-type pro-inflammatory action against monocytes / macrophages. Moreover, following the treatment with the DEN/CDAA protocol, $HRG^{-/-}$ mice showed a significant decrease in the volume and number of liver tumors as compared to wild-type mice. These effects were not associated with a modulation of cell proliferation process and may be attributable to a reduction in the angiogenic response together with an increase in the apoptotic process.
Conclusions: These results indicate that the release of HRG by hepatocytes has a critical role in the progression of experimental liver carcinogenesis in a dietary NAFLD/NASH-related environment.

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P-41

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 and 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.

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P-42

Divergent patterns of hbv-rna and hbcrag levels in untreated chronic hepatitis delta: a large european cross-sectional study

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Methods: Consecutive patients with untreated CHD were enrolled in this investigator driven cross-sectional study in two EU centers. All the standard clinical and virological characteristics were collected. HDV RNA was quantified by sensitive and specific assays (Robogene or a local validated in-house assay). Serum HBV RNA was quantified by an automated real-time PCR based investigational assay (cobas® 6800, Roche Diagnostics, Pleasanton, Ca, USA, LLOQ 10 cp/mL) while serum HBcrAg levels were measured using LUMIPULSE® G HBcrAg assay (Fujirebio Europe, LLOQ 3 $\log_{10}$ U/mL).
Results: Overall, 202 HDV patients were enrolled: median age 46 yrs, 61% males, 51% had cirrhosis, fibroscan 11 kpa, 58% on NUC therapy, HBsAg 3.8 logs IU/ml, 80% anti-HBe positive, 84% with elevated ALT levels, HDV RNA 4.9 logs IU/ml. HBV RNA tested positive (>10 cp/ml) in only 10% of the patients: median 43 cp/ml (range 13-82,000). In contrast, most patients (77%) tested positive for HBcrAg (>3.0 log IU//ml): 4.2 log IU/ml (range 3-8). By combining these biomarkers, 3 categories were identified: 23% double negative, 9% double positive and 68% negative for HBV RNA but positive for HBcrAg. HBV RNA levels were associated with younger age, higher HBV DNA, HDV RNA and HBcrAg while HBcrAg positivity correlated with higher HBsAg and HDV RNA levels. Double positive patients were younger, with higher HDV RNA levels and more likely of non-EU origin.
Conclusions: In untreated CHD patients, HBV RNA and HBcrAg show a divergent pattern: while HBV RNA was undetectable in most patients, most of them had quantifiable HBcrAg. Additional studies aimed to unravel the molecular mechanisms underlying these findings are warranted.

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P-43

Comparison of severity of liver damage and metabolic alterations in patients with NAFLD attending the hepatology clinic over the last three decades

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Introduction: Prevalence of NAFLD is progressively increasing possibly due to the evolving environment, unhealthy lifestyle and increasing prevalence of metabolic disease. Aim: to assess whether clinical presentation and severity of NAFLD changed over time.
Matherials and Methods and Results: We studied a cohort 418 patients (314 male, 104 female) with biopsy proven NAFLD enrolled from 1990 and 2021.The entire period of presentation was divided into 3 decades (1990-2000, 2001-2011, 2012-2021). Metabolic parameters, early atherosclerosis (by carotid intima media thickness and plaques) and histological liver damage (by NAS score, presence of NASH and significant fibrosis (>2)) were assessed at the time of biopsy. No differences in age of presentation, sex, early atherosclerosis and prevalence of dyslipidemia and hypertension were found across decades. Conversely, a higher prevalence of diabetes (22% vs 17% vs 30%, p=0.05), obesity (15% vs 27% vs 41%, p<0.001), increased levels of ALT (median 53 vs 51 vs 63 U/L, p=0.008) and GGT (median 79 vs 65 vs 98 U/L, p=0.03) were observed over time. At liver biopsy, a significant higher prevalence of NAS score > 4 (23%, 25% and 53%, p=0.001), NASH (42%, 44% and 78%, p=0.0001) and fibrosis >2 (20%, 25% and 44%, p=0.0005) was observed in the last decade compared to the previous ones. Considering the whole cohort, diabetes (OR 1.8, 95%CI 1.03-3.2) and BMI (OR 1.1, 95%CI 1.03-1.15) were independent risk factors for NASH, whereas age (1.06, 95%CI 1.03-1.08, p<0.001), diabetes (OR 2.7, 95%CI 1.5-4.8) and BMI (OR 1.08, 95%CI 1.02-1.14) for fibrosis.
Conclusions: Over the past 10 years compared to previous decades, patients with NAFLD presented to observation with a more severe liver disease, possibly paralleling the spread of diabetes and obesity. Our findings suggest the need, once a patient with NAFLD is diagnosed in primary care, to refer the patient to the hepatology center, promptly checking for advanced liver disease.

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P-44

Comparative performance analysis between manual and automatic RNA extraction to quantify HDV RNA by RoboGene 2.0 kit in untreated and bulevirtide-treated HDV patients

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Background & Aim. Diagnosis and management of Chronic Delta Hepatitis (CHD) requires highly sensitive and reliable tests for HDV RNA quantification coupled with automated lab procedures to optimize time and resources. Aim of the study was to compare two different extraction methods to quantify HDV RNA levels in untreated and Bulevertide (BLV)-treated HDV patients.
Methods. In this single-center retrospective study, frozen sera from consecutive untreated and BLV treated-HDV patients were tested for HDV RNA levels (Robogene 2.0, Roboscreen GmbH, Leipzig, Germany; LOQ 6 IU/mL, linear range 5 to 10^9 IU/mL) by using two different extraction methods: manual method, i.e. INSTANT Virus RNA/DNA kit (Analytik Jena AG, Jena, Germany) versus automatic method, i.e. EZ1 DSP Virus Kit (Qiagen, Hilden, Germany).
Results. 96 frozen sera collected from 18 Caucasians patients with CHD either untreated (baseline) or BLV treated were analyzed: 48 (29-77) years, 67% males, 100% HDV-GT1, 100% cirrhotics, all under TDF or ETV treatment; ALT 106 (32-222) U/L, HBsAg 3.7 (2.5-4.3) Log IU/mL, 94% HBeAg negative, 72% HBV DNA undetectable. Overall, HDV RNA levels were 3.61 (0.70-6.60) vs 2.66 (0.70-5.52) Log IU/mL, by manual vs automated extraction. Viremia tested <LOQ in 3 (3%) vs 14 (15%) patients, respectively. Compared to the automated method, manual RNA extraction reported higher HDV RNA levels in 90 samples [median 0.80 (0.07-2.11) Log IU/mL], similar levels in 3 [two <LOQ samples, and one 197 IU/mL], and lower levels in 3 [0.11 (0.09-0.17 Log IU/mL]. During the first 6 months of BLV monotherapy, HDV RNA progressively declined using both ex-

traction methods, but 11% vs 47% patients tested <LOQ at month 6, respectively.
Conclusions. Quantification of HDV RNA by Robogene 2.0 is significantly influenced by the extraction method, the manual extraction being more sensitive although more time consuming.

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P-45

Impact of deterioration of lifestyle and PNPLA3 genotype in NALFD patients during COVID-19 lockdown

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Introduction: Although quarantine measures have been effective in preventing the spread of SARS-COV2 infection, they have limited physical activity and changed dietary habits, factors known to predispose the progression of nonalcoholic fatty liver disease (NAFLD). A role of PNPLA3 in weight gain has been recently reported. Aim: to evaluate changes on metabolic and hepatic profile in NAFLD patients during COVID-19 pandemic and to investigate the impact of PNPLA3 on the effect of lifestyle.
Matherials and Methods and Results: 357 NAFLD patients who had a medical checkup no more than 6 months before COVID-19 blockade were included. Anthropometric, clinical and laboratory data and ultrasound grading of steatosis were collected before and after the blockade. Adherence to the Mediterranean Diet (MD) and physical activity (PA) was assessed at each visit. Genotyping for PNPLA3 was available in 188.After lockdown 48% patients gained weight and 16% worsened steatosis grade. Weight gain was associated with bad adherence to MD (p=0.005) and PA (p=0.03) and to PNPLA3 GG genotype (p=0.04). Interestingly, at multivariate analysis adjusted for sex, age, PA, MD and PNPLA3 GG, only PNPLA3 GG remained associated with weight gain (p=0.04). A higher glycemia (112±32 vs 106±25, p=0.002) and prevalence of increased transaminases (ALT 30% vs 21%, p= 0.02) were observed after lockdown only in patients who gained weight. Analyzing patients who gained weight according to age (i.e < or >67 ys), both older and younger patients showed less adherence to MD, but only younger patients had a significantly reduced PA during lockdown (23% vs 40%, p=0.002).
Conclusions: During lockdown nearly half of NAFLD patients gained weight with consequent worsening of metabolic and liver features, highlighting, independently of the pandemic, the beneficial role of correct lifestyle.More interestingly, PNPLA3 GG genotype emerged as an independent risk factor for weight gain, opening new perspectives in NAFLD patients care.

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P-46

Long-term albumin administration eases the management of hyponatremia in outpatients with decompensated cirrhosis: data from the ANSWER Trial

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Introduction. Hyponatremia is a frequent and ominous complication in patients with decompensated cirrhosis. Human albumin (HA) administration improves hyponatremia in patients with cirrhosis hospitalized because of acute decompensation, but no data are available on the effects of long-term HA administration.

Aims. To determine whether long-term HA administration could help in treating and preventing 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. Resolution rates of hyponatremia in hyponatremic patients, and 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 normonatremic patients. At baseline, 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: 45% vs 28% (p=0.042), 56% vs 32% (p=0.005), and 61% vs 38% (p=0.005) after 1, 2, and 3 months of treatment, respectively. 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, both in hyponatremic and non-hyponatremic patients (incidence rate ratios: 0.245 [CI 0.167-0.359, p<0.001] and 0.539 [CI 0.338-0.859, p=0.008], respectively.
Conclusions. Long-term HA administration appears an effective intervention in managing hyponatremia in outpatients with decompensated cirrhosis and ascites.

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P-47

Oncostatin M is overexpressed in NASH-related hepatocellular carcinoma and promotes cancer cell invasiveness and angiogenesis

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Introduction. Oncostatin M (OSM) is a pleiotropic cytokine of the interleukin (IL)-6 family that contributes to the progression of chronic liver disease.
Aim. Here we investigated the role of OSM in the development and progression of hepatocellular carcinoma (HCC) in NAFLD/NASH.
Material & Methods. The role of OSM was investigated in a) selected cohorts of NAFLD/NASH HCC patients, b) liver cancer cells exposed to human recombinant OSM or stably transfected to overexpress human OSM; c) murine HCC xenografts; d) a murine NASH-related model of hepatic carcinogenesis.
Results. OSM was selectively overexpressed in HCC cells of NAFLD/NASH patients, according to the tumor grading. OSM serum levels, barely detectable in patients with simple steatosis or NASH, were increased in patients with cirrhosis, and more evident in those carrying HCC. In this latter group, OSM serum levels were significantly higher in the subjects with intermediate/advanced HCCs and correlated with poor survival. Cell culture experiments indicate that OSM upregulation in hepatic cancer cells contributes to HCC progression by inducing epithelial-to-mesenchymal transition and increased invasiveness of cancer cells as well as, of critical relevance, by inducing angiogenesis. In murine xenografts, OSM overexpression was associated with slower tumor growth, but increased rate of lung metastases. Overexpression of OSM and its positive correlation with the angiogenic switch were also confirmed in a murine model of NAFLD/NASH-related hepatocarcinogenesis. Consistently, analysis of liver specimens from human NASH-related HCCs with vascular invasion showed that OSM was expressed by liver cancer cells invading hepatic vessels.
Conclusion. In conclusion, OSM up-regulation appears a specific feature of HCC arising on a NAFLD/NASH background and correlates with clinical parameters and disease outcome. Our data highlight a novel pro-carcinogenic contribution for OSM in NAFLD/NASH, suggesting a role of this factor as a prognostic marker and a target for therapy.

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P-48

Liver cancer-specific isoform of serine protease inhibitor Kazal for the detection of hepatocellular carcinoma in patients with non-alcoholic fatty liver disease

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Introduction. Surveillance of patients at risk of hepatocellular carcinoma (HCC) development mainly relies on ultrasound, while the role of serum biomarkers is still a matter of debate. Recent evidence highlighted a remarkable diagnostic accuracy of liver cancer-specific isoform of serine protease inhibitor Kazal (LC-SPIK) for the detection of HCC in patients with cirrhosis of viral etiology.
Aim. We investigated the performance of LC-SPIK, in comparison to standard serological biomarkers (i.e., AFP and PIVKA-II), for the detection of HCC in patients with non-alcoholic fatty liver disease (NAFLD).

Materials and methods. A total of 120 NAFLD patients with either cirrhosis (n=58, 29M/29F, median age 63 [57-68] years) or HCC (n=62, 49M/13F, median age 66 [62-70] years, 61.3% early-stage HCC) were retrospectively enrolled. HCC was classified according to the Barcelona Clinic Liver Cancer (BCLC) staging system. Serum LC-SPIK was measured by enzyme linked immunosorbent assay (ImCare Biotech, Doylestown, PA), while AFP and PIVKA-II by chemiluminescent immunoassay on Lumipulse® G600 System (Fujirebio Inc, Tokyo, Japan).
Results. Serum LC-SPIK values were significantly different between patients with or without HCC (24.3 [17.6-39.8] ng/mL vs. 11.7 [8.7-18.2] ng/mL, $p<0.001$, respectively). LC-SPIK showed an area under the curve (AUC) of 0.841 (cut-off 15 ng/mL, sensitivity=89% and specificity=67%) for the identification of patients with HCC; the accuracies of AFP and PIVKA-II were 0.719 and 0.853, respectively. Remarkably, the performance of LC-SPIK for HCC detection did not decrease neither in AFP-negative patients (AUC=0.849) nor in patients with early-stage HCC (AUC=0.831). Finally, in the overall population, the highest performance for HCC detection was obtained from the combination of LC-SPIK and PIVKA-II (AUC=0.908).
Conclusions. The encouraging performance of LC-SPIK warrants further prospective studies to assess the ability of the biomarker to predict HCC development in patients with NAFLD and advanced liver disease.

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P-49

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) related cirrhosis seems to be at higher risk of PVT development than patients with cirrhosis related to other causative factors. Nevertheless, definitively 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 November 1 st 2021 using predefined keywords to identify observational cohort studies. Meta-analysis was performed using random-effects modelling.
Results: We included seven articles published over the past 10-year period and reported a total of 231.399 patients from five different countries. NAFLD patients were 26853 (11,6%), while PVT incidence was 6.5% (n=1748). Meta-analysis demonstrated a significantly positive association between NAFLD and PVT (OR 1.37, 95% CI 1.06-1.78 p < 0,001). The between-study heterogeneity was substantial (I 2 = 92,73%). After stratifying the eligible cohort studies by country, we observed that compared to other regions, in European patients the incidence of PVT in NAFLD is higher (OR: 2.03, 95% CI 0.30-13.53) than in North-American patients (OR: 1.42, 95% CI 1.05-1.94) and Arabian patients (OR: 1.36, 95% CI 0.97-1.91). By a meta regression neither age nor percentage of diabetes seems to impact on the relationship between NAFLD and PVT.
Conclusions: This meta-analysis suggests that NASH is associated with an increased risk of developing PVT. Further research is required to decipher the complex link between NAFLD and PVT development.

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P-50

Liver disease and lipodystrophy: data from an Italian cohort

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Background: Lipodystrophy syndromes (LS) are a group of rare disorders characterized by selective deficiency of adipose tissue, metabolic syndrome and eventually non-alcoholic fatty liver disease (NAFLD). Four major groups are described based on etiology (genetic/ acquired) and distribution of adipose tissue loss (generalized/partial). Aim of the study was to describe liver profiles in a cohort of patients with congenital and acquired LS.
Patients: Patients (pts) with LS (non HIV-associated) followed at the LS center of Pisa from Jan 2017 to Dec 2020 were studied. All pts underwent evaluation including liver enzymes and functional tests; blood count; glucose, insulin, HOMA, total-cholesterol, LDL, HDL, triglycerides, adiponectin and leptin dosage. Pts were screened for LMNA, AGPAT2 and PPARγ genes mutations or submitted to NGS or gene panel screening for disease-causing mutations. All pts were assessed by liver ultrasound, transient Elastography (TE, Fibroscan®) and controlled attenuation parameter (CAP) measurements. Four patients underwent liver biopsy.
Results: 49 pts were included (M:F=9:40), 33 with congenital forms: 12 with type 1 and 8 with type 2 partial familial form, 9 with generalized LS including 6 with progeroid syndromes and 4 with generalized congenital forms. 16 pts had acquired LS: 14 partial and 2 generalized LS. Main characteristics are reported in the Table. Four patients with congenital LS (median age 46.7 yrs) had histologically or clinically diagnosis of cirrhosis.
Conclusions: High rate (~70 %) of NAFLD was confirmed in LS patients, who are young and with low BMI. LS should be suspected in lean individuals with NAFLD and unusual subcutaneous fat distribution. Higher risk of advanced liver disease was observed in pts with congenital forms, possibly because of a longer clinical history of disease. An early genetic diagnosis of congenital LS is mandatory for a timely monitoring and treatment.

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	ALL (49 pts)	Congenital Forms Lipodystrophy (33 pts)	Acquired Forms Lipodystrophy (16 pts)	
Age median (range) years	47.1 (5.8-78)	48 (5.8-78.1)	35.1 (8.5-76.1)	Ns
BMI kg/m²	22.4 (13.2-35.1)	24.4 (13.2-35.1)	21.1 (14-27)	0.029
LS duration (median years)	27.20 (±19.4)	33.1 (±18.2)	13.54 (±20.8)	*0.054*
IR and/or T2D	37 (75.5%)	28 (85 %)	9 (56%)	0.036
Leptin µg/l	6.1 (0.4-38)	6.3 (0.4-13.5)	5.7 (1.6-18.2)	Ns
Adiponectin µg/ml	2.85 (0.2-13.5)	2.25 (0.2-13.5)	6 (0.24-11.6)	Ns
Dyslipidemia	33 (67.3%)	24 (73%)	9 (56%)	Ns
Hypertension	20 (40.8 %)	16 (48 %)	4 (25%)	Ns
US steatosis	34 (69.4%)	25 (76%)	9 (56 %)	Ns
CAP > 290 db/m	20 (40.8%)	17 (51.5 %)	3 (19%)	0.035
TE > 8.0 kPa	9 (18.4%)	9 (27.3%)	0 (0%)	0.022
Cirrhosis	4 (8.2%)	4 (12.1%)	0	

P-51

High rates of histological findings compatible with porto-sinusoidal vascular liver disease in patients with constantly elevated gamma-glutamyl transferase levels undergoing a liver biopsy

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Isolated elevations in GGT levels are commonly found in patients referred to liver specialists, however their clinical impact is unknown. Data on the histological findings in these patients are scarce. All consecutive patients who underwent a liver biopsy between March 1st, 2015 and December 1st, 2020, in our Liver Unit for isolated and persistent (at least 2-fold ULN for three tests within 12 months) elevation of GGT value were retrospectively analyzed. Excluded were patients with concomitant ALT or AST elevation, intake of Hepato-toxic drugs, alcohol intake >20g/day and MAFLD. Data about age, gender, BMI, comorbidities including portal hypertension (PH), smoking habit and disease severity (APRI and FIB-4), were collected. All liver biopsies were blindly reviewed by 2 experts in liver pathology. During the study period a total of 640 patients performed a liver biopsy. 29 (4.5%) met the inclusion criteria and were enrolled. Most of them were males (19/29, 65.5%) and their mean age was 49.7±11.4 years (28-73). The mean BMI was 24.5±2.97 (18.8-30) and only two presented FIB-4 suggestive of advanced liver disease. The histological findings were compatible with PSVD in 13/29 (45%) patients, hepatic sarcoidosis in 3/29, NASH in 3 and congenital hepatic fibrosis (CHF) in 3. Histology did not allow a definite diagnosis in 6/29 (21%) patients. Patients with PSVD were male in 10/12 (%), with a mean age of 47±10.9 years (28-57), without any clinical signs of PH, in only one patient FIB-4 score was compatible with advanced liver disease. When comparing patients with PSVD to patients with any other liver etiology, we found no difference in gender, age, BMI, smoking habit, FIB-4, GGT, albumin and bilirubin values. Liver histology in patients with isolated elevated GGT levels is useful as it allows to diagnose chronic liver conditions associated with a significant impact on survival. The high rate of patients with histological findings compatible with PSVD in the absence of signs of PH, requires careful assessment on how to manage these patients in the long term.

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P-52

Bacterial infection 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.
Material and methods: We prospectively collected data of 229 consecutive cirrhotic patients followed 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, cholan-

gitis, 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 hepatocellular carcinoma (HCC) (OR 2.87 [95% CI 1.11 to 7.41; p = 0.029].

Conclusions: 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.

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P-53

Impact of polypharmacy and aging on the risk of multiple drug-drug interactions (DDIs) in HCV patients treated with pangenotypic direct-acting antivirals (pDAA)

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Background: Recent studies suggest that sofosbuvir-based regimens are preferred in HCV elderly patients for their slightly more user-friendly DDI profile compared to protease inhibitor-based regimens. Our aim was to explore the impact of polymedication and aging on multiple DDIs prevalence in patients treated with sofosbuvir/velpatasvir (SOF/VEL) or glecaprevir/pibrentasvir (GLE/PIB).

Methods. Retrospective observational study from an Italian database covering 6.9 million health-assisted individuals, including patients treated with SOF/VEL or GLE/PIB (2017-2020). Demographics, comedications, and DDIs were evaluated in the overall population and in patients receiving ≥ 2 comedications, assessing DDI risk and severity through the Liverpool University tool.

Results. 4,185 HCV patients were included (2,057 SOF/VEL and 2,128 GLE/PIB). Median age was 56 vs 52 years (p<0.001), with a higher percentage of patients over 50 yo in SOF/VEL vs GLE/PIB (72% vs 58%, p<0.001). The most prescribed comedications were cardiovascular drugs (43% SOF/VEL; 24% GLE/PIB), alimentary (37% SOF/VEL; 21% GLE/PIB) and nervous system (25% SOF/VEL; 15% GLE/PIB). Use of comedications was higher in SOF/VEL vs GLE/PIB (≥1 comed: 72% vs 50%, p<0.001; ≥2 comed: 57% vs 32%, p<0.001). Patients receiving ≥ 2 comed at risk of multi-DDI with pDAAs were 270 (14.6%) overall, 135 (12%) with SOF/VEL and 135 (20%) with GLE/PIB (p<0.001) and showed a slightly higher median age in SOF/VEL (74 vs 67 years, p<0.001), confirming the same trend observed in the overall population over 50 yo (94% vs 79%, p<0.001). Interestingly, the number of patients under 50 yo with multiple DDIs was three times more in GLE/PIB vs SOF/VEL (21% vs 6%, p<0.05).

Conclusion. In our sample population, PI-free pDAA regimen seems to be preferred in elderly patients particularly in those with ≥ 2 comed at risk of multi-DDI. The effects of DDIs are mainly related to increase of comedications among patients treated with PI-based pDAA.

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P-54

Risk of multiple drug interactions potentially linked to safety in patients receiving pangenotypic direct-acting antivirals for the treatment of hepatitis C

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Background: Previous studies evaluated the risk of drug-drug interactions (DDIs) in HCV patients receiving pangenotypic direct-acting antivirals (pDAA) on pairwise interaction. We aimed at describing the risk prevalence of potential multiple-DDI (multi-DDI) and its clinical impact in patients treated with pDAAs.

Methods: Retrospective observational study from a Spanish database of 1.8 million inhabitants, including patients treated with sofosbuvir/velpatasvir [SOF/VEL] or glecaprevir/pibrentasvir [GLE/PIB] (2017-2020). Demographics, comorbidities, comedications, and DDIs were evaluated assessing the impact of DDIs using the Liverpool University tool. Adverse drug reactions (SADR) were also registered through ICD-9 coding system. Effectiveness was indirectly evaluated as the number of new DAA-starts in the 6 months after end of therapy.

Results: 1620 patients were included; 730 with SOF/VEL (median age: 55 y; 62% men; 37.8% F3/4), 890 with GLE/PIB (53 y; 60% men; 28% F3/4). The most prescribed drugs were nervous drugs (35.8%), digestive (24.1%), cardiovascular (14.2%). 77.5% patients received ≥2 comedications; among them, 9,8% were at risk of multi-DDI (4,1% with SOF/VEL vs 5,7% with GLE/PIB). Risk of increase of comedication due to DDIs was higher with GLE/PIB (31%) compared to SOF/VEL (11%) (p <0.001). The risk of decreasing pDAA was 32% with GLE/PIB and 46% with SOF/VEL (p=NS). Higher number of SADR was registered with GLE/PIB (14) vs SOF/VEL (4) (p<0.05). Among patients at risk of multi-DDIs, SADR were 18% with GLE/PIB vs 6% with SOF/VEL (p<0.05); the most reported SADR were with statins with higher percentage with GLE/PIB vs SOF/VEL (p <0.05). 84% of patients with SADR had a multi-DDI profile. Both pDAAs

showed similar effectiveness (1.0% and 1.1% re-starts respectively, p=NS).
Conclusion: In Spain, about 10% of HCV patients taking ≥ 2 comedications are at risk of multiple DDIs with pDAAs. Potential risk of increased comedications and suspected adverse reactions were higher in GLE/PIB compared to SOF/VEL.

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P-55

Transient receptor potential cation channel subfamily member 7 liver tissue expression in cirrhotic patients correlates with disease severity and hepatocellular damage

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Introduction: Transient receptor potential cation channel subfamily member 7 (TRPM7) is a chanzyme permeable to divalent cation with an α-kinase domain. It is widely involved in cell cycle and metabolism, inflammation, apoptosis and in hepatic stellate cell activation and fibrosis. Data on TRPM7 liver tissue expression in cirrhotic patients are currently lacking.

Aim: The aim of this study was to evaluate the hepatic tissue expression of TRPM7 in cirrhosis, correlating it with the patient's clinical and biochemical data collected at the same time.
Materials and Methods: we retrospectively enrolled 26 cirrhotic patients undergoing liver transplantation. Samples of cirrhotic tissue, collected at transplantation, were analyzed by immunohistochemistry with anti-TRPM7 antibody staining. As control, 2 specimens from normal liver tissue were also stained. Tissue expression of TRPM7 was evaluated as a percentage of cells stained with TRPM7 in an area of 500 cells. The immunostaining level of each sample was expressed as the percentage of high and low intensity positive cells counted per area of interest. Clinical data were retrieved for all patients on the day of transplant.
Results: TRMP7 chanzyme was not detectable in normal liver tissue. In contrast, all cirrhotic liver samples were positive. Five (19%) had weak staining and 21 (81%) had both weakly stained and heavily stained hepatocytes. Interestingly, the patient's MELDNa score correlated positively with the total percentage of TRPM7 positive hepatocytes ($r = 0.479$; $p < 0.013$) and with the percentage of high intensity positive hepatocytes ($r = 0.732$; $p < 0.0001$). It was also observed that the percentage of high intensity TRPM7 positive hepatocytes correlated positively with the serum concentration of AST ($r = 502$; $p = 0.04$).
Conclusions: TRPM7 expression was found to be relevant in cirrhotic livers, but absent in normal ones. The degree of expression of TRPM7 correlated with the severity of the prognosis of cirrhosis and with serum transaminases, allowing to hypothesize its active role in liver damage and disease progression.

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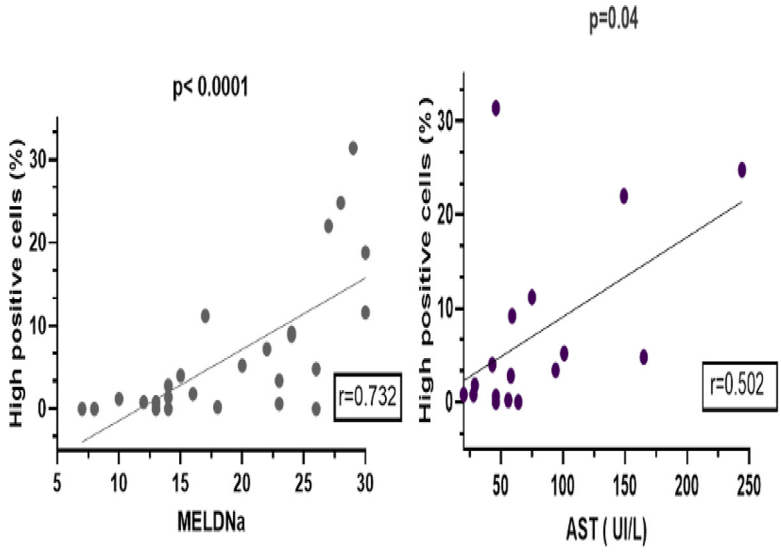

P-56

Sarcopenia predicts ascitic decompensation and mortality independently of portal hypertension status in patients with advanced chronic liver disease outside the liver transplantation setting

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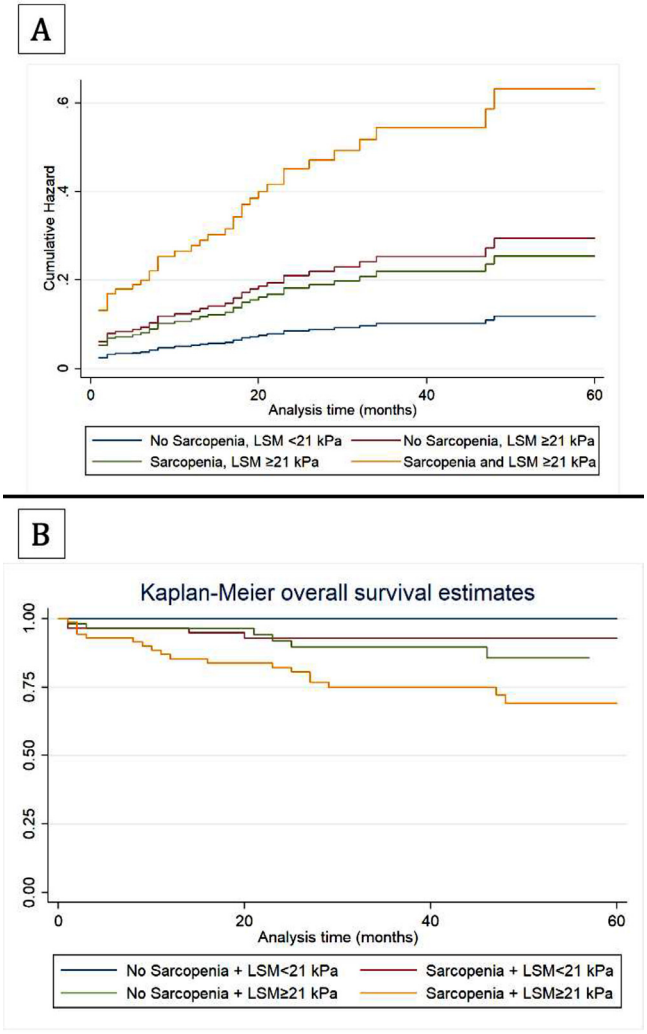
Introduction: Sarcopenia is mostly defined by a loss in muscle mass identified at cross-sectional imaging assessment by computed tomography (CT), where parameters such as skeletal muscle index (SMI) have been consistently associated with waitlist mortality in patients with end-stage liver disease, as well as with the hepatic encephalopathy, acute-on-chronic liver failure, and prognosis in patients with hepatocellular carcinoma. However, the role of sarcopenia in predicting hepatic decompensation other than hepatic encephalopathy is still unclear.
Aim: We aimed to evaluate the prognostic role of sarcopenia, assessed by computed tomography (CT), in the development of decompensation with ascites and overall mortality in patients with advanced chronic liver disease (ACLD) outside the liver transplantation (LT) setting.
Material and Methods: We retrospective evaluated ACLD patients with liver stiffness measurement (LSM) >10 kPa and an available CT scan within 6 months. Sarcopenia was defined as skeletal muscle index (SMI) <50 and <39 cm^2/m^3, respectively, in men and women. Cox proportional-hazards model models were used to assess the variables associated with the main outcomes.
Results: A total of 209 patients were included in the final analysis, and sarcopenia was present in 134 (64.1%) of the patients. During a median follow-up of 37 (20-63) months, 52 patients developed ascites and 30 died. Sarcopenia was found a predictive factor of decompensation with ascites (hazard ratio (HR) 2.148, 95%-Confidence-Interval: 1.136-4.060), independently from the features of clinically significant portal hypertension (CSPH; LSM≥21 kPa or presence of portosystemic shunts). Sarcopenia (HR: 2.604, 95%-CI: 1.005-6.749) and LSM≥21 kPa (HR: 4.139, 95%-CI: 1.493-11.474) were found independent risk factors for increased mortality.
Conclusions: Sarcopenia and CSPH are two major and independent risk factors for decompensation with ascites and overall mortality in cirrhotic patients outside the LT context.



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P-57

Surveillance of hepatobiliary cancers in primary sclerosing cholangitis: a preliminary study on the role of PET-MRI

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Introduction: Primary sclerosing cholangitis (PSC) is a rare chronic cholestatic disease with a progressive course toward cirrhosis and its complication. Moreover, these patients have an increased risk of hepatobiliary (HPB) and colorectal cancer. Current guidelines recommend performing annual ultrasound for gallbladder cancer surveillance, annual colonoscopy in patients with associated inflammatory bowel disease and 6-months ultrasound surveillance in cirrhotic patients. Despite the lack of evidence, most expert centers worldwide also perform annual MRI in combination with CA19-9 for HPB cancer surveillance. Positron emission tomography (PET)-MRI is a hybrid imaging technique combining metabolic and morpho-functional information but no data exists on its role in the diagnostic pathway of HPB cancer in PSC.
Aim: We thus performed an exploratory analysis of the role of PET-MRI in the diagnosis of HPB cancers in PSC.

Materials and methods: The study included all PSC patients followed in the outpatient clinic of the Gastroenterology Unit of the University Hospital of Padua who underwent PET-MRI during follow-up. "Whole-body" and abdominal MRI images, with magnetic resonance cholangiopancreatography(MRCP) and dynamic contrast-enhanced MRI using Gd-EOB-DTPA (Primovist®), were performed simultaneously with 18F-FDG-PET on a 3T-PET-MRI hybrid system. Reconstruction and processing were made by using a dedicated software, the semiquantitative PET parameter SUV max was calculated on different areas of interest.
Results: Sixteen patients were included and 6 (38%) of them showed positivities on PET. One patient was diagnosed with an intrahepatic cholangiocarcinoma by PET- MRI, not previously detected by MRI and CT scan. The remaining five patients with positive PET, showed, in most of case peribiliary uptakes compatible with history of recent or recurrent bacterial cholangitis.
Conclusions: These preliminary results suggest that PET-MRI may be used as a third level imaging in PSC patients, identifying patients with clinical and radiological worsening during follow-up as the possible target for further invasive exams.

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P-58

Real-life prevalence of Metabolic Associated Fatty Liver Disease (NAFLD) and non-alcoholic steatohepatitis (NASH) in a tertiary obesity clinic in Italy

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Introduction: Obesity is a major player of "metabolic dysfunction associated fatty liver disease" (MAFLD); however, scanty data is available on the prevalence of MAFLD and non-alcoholic steatohepatitis (NASH) in patients presenting with obesity to a specialist outpatient clinic; to date, data being available from bariatric surgery patient series only.

Aims: We aimed to evaluate the prevalence of MAFLD and the applicability of non-invasive tests (NITs) for fatty liver and liver fibrosis identification in an outpatient specialist clinic in Italy.
Material and Methods: We consecutively screened patients with obesity (PwO) who attended our outpatient obesity clinic from January 2020 to June 2021. Diagnosis of MAFLD was based on results from abdominal ultrasound (US); the anthropometric and laboratory data of the patients were collected, and the Fatty Liver Index (FLI), Fibrosis-4 (FIB4) and NAFLD (NFS) scores were calculated. Liver fibrosis was assessed within one month of the first visit using liver stiffness measurements (LSM) by transient elastography (FibroScan); Probe-specific LSM cut-offs were used to detect significant (F≥2) and advanced (F≥3) fibrosis and NASH cirrhosis. In a subgroup, hepatic fat was also evaluated through controlled attenuation parameters (CAP) with the FibroScan Expert 630 apparatus; all patients underwent oral glucose tolerance test (OGTT).
Results: Among 249 PwO, according to the WHO obesity classification, obesity I °, II °, III ° was classified in 144 (57.8%), 56 (22.5%), 49 (19.6 %), respectively. In addition, about half of the PwO had type 2 diabetes (T2DM) or impaired glucose tolerance (IGT) with a median HOMA index of 3.6 (IQR 2.44 - 4.94). According to US or FLI definitions, the prevalence of MAFLD was 90.4% and 91.6% and did not differ significantly in the different WHO categories of obesity (p-value 0.264). The distribution of hepatic steatosis classification on ultrasound was 25.8%, 38.7%, 35.6% for mild, moderate, and severe steatosis, respectively. The median CAP values were 287 dB/m (IQR 262-337). According to LSM values, 29%, 18% and 9.8% had significant fibrosis, advanced fibrosis, and NASH cirrhosis, respectively. The median LSM value was 5.4 kPa (IQR 4.3 – 7.5). The liver fibrosis prevalence significantly increased according to WHO categories of obesity (p-value <0.0001). Applying the screening with NITs, 10% and 9% of patients are wrongly classified, and this leads to misclassify about 50% and 11.4% of patients with advanced fibrosis using FIB-4 or NFS, respectively; moreover, 34.1% and 54.5% of patients with advanced fibrosis result in the grey area of the two tests respectively.
Conclusions: The results from the present study in a real-world setting strongly advocate for routine screening for MAFLD and NASH by LSM in PwO, regardless of WHO category, attending the outpatient specialist clinic for obesity.

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				Cirrhosis-NASH (9.8%)
			Advanced fibrosis (18%)	
	Absence of fibrosis (71%)	Significant fibrosis (29%)		
Patients (n.249)	F0-F1 [LSM <7]	F2 [LSM≥ 7 & <8.7]	F3 [LSM ≥8.7 & LSM<10.3]	F4 [LSM≥10.3]
Obesity I° [n.144]	117 (81.3%)	13 (9%)	9 (6.3%)	5 (3.4%)
Obesity II° [n.56]	39 (69.6%)	8 (14.3%)	3 (5.4%)	6 (10.7%)
Obesity III° [n.49]	21 (42.9%)	7 (14.3%)	8 (16.3%)	13 (26.5%)
DMT2/IGT (yes) [n.113]	63 (55.8%)	20 (17.7%)	13 (11.5%)	17 (15%)

P-59

Clinical features of patients with new onset of autoimmune hepatitis following SARS-CoV-2 vaccination

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Introduction: Autoimmune hepatitis (AIH) is a relatively rare chronic immune-mediated liver disease, which develops in genetically predisposed individuals following an environmental trigger. A few cases of AIH have been recently reported after the SARS-CoV-2 vaccination.
Aims: The aim of this study was to describe clinical-epidemiological profile of a series of adult patients who experienced AIH onset following SARS-CoV-2 vaccination.
Materials and Methods: This multicentric observational study collected clinical data of adult patients who had received SARS-CoV-2 vaccination and thereafter were diagnosed with AIH between 03/2021 and 10/2021 in Italy, using an online survey among members of the Italian Association for the study of the Liver (AISF).
Results: Among the 12 patients included: 50% were females, median age 62 years (range 32-80), 6 (50%) had preexisting extra-hepatic autoimmune disease (3 thyroiditis, 2 rheumatoid arthritis, 1 systemic lupus erythematosus), 7 patients have received Comirnaty (BioNTech/Pfizer) vaccine, 2 Spikevax (Moderna Biotech) and 3 Vaxzevria (AstraZeneca). Ten patients (83%) had acute onset of AIH with transaminase levels $\geq$10 times the upper limit of normal (ULN, range 13-77 x ULN), 8 (67%) with jaundice (total bilirubin 3.5-18.6 x ULN). At AIH diagnosis (median time from first and second vaccine dose: 48 and 10 days, respectively) median AST was 18 x ULN (range 5-85), ALT 23.8 x ULN (range 7-83), total bilirubin 3.8 x ULN (range 0.6-18.6), alkaline phosphatase 1.3 x ULN (range 0.8-7.1), immunoglobulin G 1.2 x ULN (median 0.8-1.5). Eight (67%) patients had autoantibodies: 6 ANA, 1 SMA, 1 LKM-1. Liver biopsy was typical for AIH in 8 and compatible in 3 patients. After 3 months 58% achieved complete biochemical response to standard immunosuppressive treatment.
Conclusion: While intensive vaccination against SARS-CoV-2 continues, the diagnosis of AIH secondary to vaccines should be included in the differential diagnosis in cases of acute hepatitis of unexplained aetiology.

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P-60

Biomarkers, imaging and safety in resmetirom 52 week non-cirrhotic NASH phase 3 clinical trial, completed open-label arm of maestro-NAFLD-1

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Background: MAESTRO-NASH (NCT03900429) and MAESTRO-NAFLD-1 (NCT04197479) are 52-week Phase 3 registrational double-blind placebo controlled clinical trials to study the effect of resmetirom, a selective thyroid receptor beta (THR-β) agonist in NASH patients. A goal of MAESTRO-NAFLD-1, a 1200 patient "real life" NASH study is to identify non-invasive markers that correlate with patient response to resmetirom treatment. The 171 patient 100 mg open label arm completed the 52-week study in July 2021.
Methods: Eligibility required at least 3 metabolic risk factors, transient elastography (TE) measured in kPa consistent with $\geq$F1, and MRI-PDFF $\geq$8%. The primary and key secondary endpoints of MAESTRO-NAFLD-1 include safety, relative percent reduction of MRI-PDFF (week 16) and LDL-C, Apolipoprotein-B, triglycerides (week 24).
Results: Statistically significant ($p<0.0001$) reduction of MRI-PDFF -53% (3.3 (SE)) at week 52. Liver volume (LV) was elevated at baseline (2202 cm3 (535)) by ~50% relative to normal controls and ~15% after correction for BMI. Resmetirom reduced LV by -21% (1.0), -23% (1.0) respectively, at weeks 16 and 52 ($p<0.0001$). LV reduction was greater than predicted by % reduction in MRI-PDFF; LV-corrected mean MRI-PDFF reduction at Week 52 was -61% (2.4). At week 52, MRE (-0.34, $p=0.03$); CAP (-39 (4.6)) and TE (-1.87, $p<0.0001$) were reduced relative to baseline. LDL-C (-21% (1.9)), apolipoprotein-B (-22% (1.6)) and triglycerides (-22% (2.6)) were statistically significantly reduced ($p<0.0001$). No safety flags were identified; BP (systolic, diastolic) was reduced by ~2-4 mmHg, bone mineral density (DEXA) was unchanged at 52 weeks.
Conclusion: Noninvasively identified patients with NASH treated with 100 mg per day of resmetirom for up to 52 weeks demonstrated rapid and sustained reduction in 1-hepatic fat and LV; 2-fibrosis, assessed by biomarkers, MRE and TE; 3- LDL and atherogenic lipids; 4-liver enzymes and inflammatory biomarkers, supporting the use of non-invasive tests to monitor NASH patient response to resmetirom.

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Arterial hypertension in cirrhotic patients is associated with older age and protects against liver decompensation independently of the etiology of the liver disease

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Background-Aims: Coexistence of liver cirrhosis (LC) and arterial hypertension (AH) has been insufficiently investigated. The aims of this study were to analyze prevalence and possible clinical impact of AH in LC patients.
Patients-Materials-Results: All 660 [423 (64.1%) males; mean age 68.7 years (± 11 SD)] cirrhotic individuals consecutively attending the outpatient clinic of a tertiary referral liver unit from January to December 2019 were analysed. Demographic, clinical, biochemical, ultrasonographic/radiologic, and endoscopic data were recorded from each subject. Patients were subgrouped by liver disease etiology also distinguishing, in each subgroup, cases with single or multifactorial causes. LC was: related to "metabolic disorders" (obesity ± diabetes ± dyslipidemia) in 391 (59.2%) cases ("metabolic disorders" as single cause in 170/391); HCV-related in 205 (31.1%) cases (HCV as "single cause" in 81/205); alcohol-related in 186 (28.2%) cases (74/186 alcohol as single cause); HBV-related in 60 (9.1%) cases (32/60 HBV as single cause); cryptogenic in 54 (8.2%) cases. At the visit, 468 patients (71%) were in Child-Pugh class A. Three-hundred-eighty patients (57.7%) presented or had history of hepatic decompensation (ascites, hepatic encephalopathy, variceal bleeding). Three-hundred-ninety-five patients (59.9%) had diagnosis of AH, a prevalence similar to that (57.4%) of the general Italian population aged 65-69 years. Mean age of patients with AH was 71.26 (±9.64) vs 64.21 (±11.47) years of patients without AH ($p<0.0001$); this significant difference was maintained in the compensated and decompensated subcategories (both $p<0.0001$). Multivariate logistic regression analysis revealed that AH was protective against decompensation ($p=0.004$, OR 0.5, CI 0.312-0.800), and this even within each etiological subgroup and independently of the class of antihypertensive drugs and of statin therapy.
Conclusions: AH in cirrhotic patients (1) has a prevalence comparable to that of the general population; (2) is significantly associated with older age; (3) is protective from hepatic decompensation independently of the disease etiology.

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De-novo occurrence of portal vein thrombosis in patients with HCV-related cirrhosis after sustained virological response: medium to long term observations from the ongoing PITER cohort

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Introduction: Achievement of sustained virological response (SVR) by direct-acting antiviral therapy (DAAs) ameliorates portal hypertension, and may reverse hyper-coagulability driven by cirrhosis.
Aim: We analyzed the long-term impact of SVR on the PVT development in patients with cirrhosis.
Methods: Consecutive DAA treated patients with liver cirrhosis in the PITER cohort were prospectively evaluated. Patients with history of PVT prior to DAA treatment were excluded. Cox regression analysis was used to evaluate factors independently associated with de-novo PVT. Kaplan Meier analysis and log rank test evaluated the PVT rates by DAA treatment response.
Results: Of 1632 patients evaluated, 40 (2.5%) developed PVT following DAA treatment. The two year PVT free survival was 99% for SVR patients and 93% for those who failed to achieve the SVR($p=0.002$). Of 1555 SVR patients (median age 65 years, 85% Child A, 15% Child B), 34 (2.2%) experienced PVT (median follow-up 36 months after EOT; IQR 24 - 44.7). Of them, 18 reported HCC (previous or after achieving the SVR); in 6 (17.6%) the PVT was neoplasm. In SVR patients the non-neoplastic PVT occurrence, was 1.8% (28 patients); the median occurrence time was 33.8 months (IQR 17- 45 months) after EOT. At pretreatment evaluation, patients with de-novo non-neoplastic PVT were more likely Child B (39.3% vs. 14.2%, $p<0.001$) and variables independently associated were: platelets $\leq 120.000/\mu L$ (aHR: 3.56, CI 95%: 1.03 - 12.33), albumin <3.5g/dL (aHR: 2.66, CI 95%: 1.15 - 6.15), bilirubin >1.1 mg/dL (aHR: 2.70, CI 95%:1.10 - 6.65). Patients with de-novo, non-neoplastic PVT had higher risks of decompensation (39.3% vs. 4.9%; $p<0.001$) and liver-related death (13% vs. 2%, $p<0.001$).
Conclusion: The risk of de-novo non-neoplastic PVT in patients with cirrhosis who achieved the SVR is low and mainly related to the liver disease severity. PVT development following the SVR may identify patients with higher decompensation and mortality risks.

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P-63

MiRNome profiling of circulating extracellular vesicles in patients with chronic hepatitis delta treated with pegylated interferon alpha

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Introduction: MicroRNAs (miRNAs) are short noncoding RNAs involved in the epigenetic regulation of multiple signalling pathways including modulation of viral replication and host immune antiviral response. Specific circulating miRNAs profiles have been associated both with the progression of chronic hepatitis C and with the response to interferon (IFN) treatment in chronic hepatitis B patients. However, data in patients with chronic hepatitis delta virus (HDV) infection are missing.
Aim: To analyse miRNAs profile of circulating extracellular vesicles (EVs) in chronic HDV patients under pegylated (Peg)-IFN-alpha (α) treatment and to evaluate the role of miRNAs as potential biomarkers for the prediction of treatment response.
Materials and Methods: We retrospectively enrolled 20 consecutive patients treated with Peg-IFNα (16M/4F; median age 44, 31-56, years); 8 patients were responders (R) while 12 were non-responders (NR). Circulating EVs were isolated from plasma samples collected at baseline (T0) and at 6 months (6M) of Peg-IFNα treatment; miRNAs expression was determined by Next Generation Sequencing approach using NEBNext Multiplex Small RNA Library PrepSet (NewEngland Biolabs) on NextSeq550 (Illumina Inc) platform.
Results: At T0, 21 miRNAs resulted differentially expressed between R and NR. Considering a $\log_2$ fold-change (FC)≥â",0.5â"„ the most significantly deregulated miRNAs were miR-1-3p ($\log_2$FC=1.60, p=0.002), miR-1246 ($\log_2$FC=1.57, p=0.002), miR-155-5p ($\log_2$FC=1.44, p=0.002), and miR-30d-5p ($\log_2$FC=-0.77, p=0.001). Consistently, miR-155-5p ($\log_2$FC=2.51, p<0.001) and miR-30d-5p ($\log_2$FC=-1.01, p=0.002) resulted significantly deregulated at 6M of therapy. MiR-155-5p showed an area under the curve (AUC) of 0.854 at T0 and 0.896 at 6M for the discrimination between R and NR, while miR-30d-5p showed AUC of 0.792 at T0 and 0.875 at 6M.
Conclusion: In patients with chronic HDV infection, we have identified a panel of differentially expressed EVs miRNAs according to treatment response. MiR-155-5p and miR-30d-5p may be useful biomarkers to tailor personalized treatment strategies in patients with chronic HDV infection undergoing Peg-IFNα therapy.

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Modeling KLB deficiency by genome editing in hepatocytes: from oxidative stress and inflammation towards enhanced proliferation

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Introduction: We previously reported that the rs17618244 G>A variant in the β-Klotho (KLB) gene, encoding the hepatic co-receptor of fibroblast growth factor receptor 4 (FGFR4), dampened KLB plasma levels, leading to inflammation, ballooning and fibrosis both in pediatric and adult patients with nonalcoholic fatty liver disease (NAFLD).
Aim: To evaluate the impact of KLB down-regulation on fat accumulation, oxidative/endoplasmic reticulum (ER) stress, inflammation and cell proliferation.
Materials and Methods: We generated, for the first time, a stable full knock-out model of KLB gene in HepG2 hepatoma cells (referred to as KLB$^{-/-}$) by Crispr/Cas9 technology. Then, markers of lipid metabolism, cellular stress and proliferation have been investigated.
Results: As expected, KLB mRNA and protein levels were strongly dampened in KLB$^{-/-}$ cells (p<0.01), along with the expression of genes implicated in cholesterol metabolism, suggesting an overall altered KLB signaling (p<0.05). KLB$^{-/-}$ cells displayed a reduced intra-cellular triglyceride (TG) content (p<0.05), related to the suppression of genes involved in lipogenesis and TG synthesis (p<0.05). Moreover, mRNA levels of genes-related to β-oxidation and lipoprotein assembly were also decreased (p<0.01). KLB deletion strongly induced oxidative and ER stress, increasing ROS/reactive nitrite species (RNS) production, aldehyde derivate concentrations and ROS-induced DNA damage (p<0.05) and the expression of ATF4/6, PERK and MnSOD2 (p<0.05). These events triggered the release of pro-inflammatory cytokines (TNFα, IL1β and IL6) into the KLB$^{-/-}$ cultured media (p<0.05). Finally, KLB$^{-/-}$ cells also showed an elevated proliferative rate and invasiveness (p<0.05).
Conclusions: We firstly generated a model of hepatocytes carrying a genetic ablation of KLB. Our preliminary results outlined that KLB shutdown may be causally involved in the switching towards progressive forms of liver damage, by inducing ER/oxidative stress, inflammation and enhanced proliferation, even in the absence of excessive fat accumulation. Thus, KLB may constitute a novel druggable target for the prevention of severe NAFLD.

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The I148M PNPLA3 variant mitigates Niacin beneficial effects: how the genetic screening in NAFLD patients gains value

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Introduction: The PNPLA3 p.I148M variant is the major genetic predictor of NAFLD and nutrients modulate its impact on fat accumulation. Niacin reduces triglycerides (TG) synthesis and ROS production in NAFLD patients.
Aims: To assess the dietary and circulating niacin levels in NAFLD patients stratified according to the presence of the p.I148M variant; to examine the efficacy of niacin in Hep3B and HepG2 cells, wild-type and homozygous for the p.I148M mutation, respectively.
Method: We enrolled 172 patients with non-invasively assessed NAFLD. Dietary niacin was collected from food diary, while serum niacin was quantified by ELISA. Hepatic expression of genes related to NAD metabolism was evaluated by RNAseq in bariatric NAFLD patients (n=125). Hepatoma cells were transfected with a siRNA targeting PNPLA3 and treated with palmitic acid 0.25mM alone/plus niacin 0.5mM for 24hrs.
Results: At bivariate analysis NAFLD patients showed reduced dietary niacin (p=0.01). The p.I148M variant was correlated with lower levels of alimentary and circulating niacin (p=0.01,p=0.03 vs non-carriers). At multivariate analysis, adjusted for sex, BMI, and alimentary niacin, the p.I148M mutation was associated with reduced serum niacin (β=-18.01;CI:-35.6–0.57;p=0.04), suggesting that it may independently modulate niacin systemic availability. The expression of enzymes related to NAD biosynthesis was impaired in p.I148M carriers (p=0.006). Niacin supplementation reduced TG synthesis alongside oxidative/ER stress in hepatoma cells ($p<0.001$,$p<0.05$ vs PA), although its efficacy was hidden by the p.I148M variant in HepG2 cells. PNPLA3 silencing masked the beneficial effect of niacin on TG overload in Hep3B cells, whereas it didn't affect niacin effectiveness on oxidative/ER stress in both cell lines ($p<0.001$,$p<0.05$ vs PA), suggesting that it mitigates the usefulness of niacin in lipid handling but not in hepatocellular damage.
Conclusion: Niacin levels were reduced in patients carrying the p.I48M variant. PNPLA3 silencing compromised the efficacy of niacin, thus suggesting its supplementation in NAFLD patients should be preceded by genetic screening.

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P-66

Referral and outcomes of patients with decompensated alcoholic liver disease: critical issues from our real life experience

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Introduction. Alcoholic liver disease (ALD) is one of the main indications for liver transplantation (LT).
Aim. To evaluate the referral to LT and the outcomes of patients with decompensated alcohol-related liver cirrhosis admitted to Internal Medicine Units of Azienda sanitaria Friuli Occidentale.
Methods. We retrospectively collected data of hospitalized patients at first episode of decompensation from 01.01.2018 to 31.12.2019. Follow up: up to 3 years. Results. 46 patients (37 males) were analysed. Median age was 58 with median value of Charlson Comorbidity Index equal to 7 [3-12]. Median MELD score was 17 [6-34], anemia was diagnosed in 28 (64%) and infection in 25 patients (54%). 2 patients had AAH. 18 (39%) patients were referred to LT Center and of these, 7 (15%) currently living patients were transplanted; one relapsed AUD after LT. 11 were not transplanted: 2 for lack of supportive/social integration, 2 died during ongoing evaluation for HCC progression, 2 died for ACLF, 2 were lost at follow up and 3 were never listed for absence of transplant benefit. The rule of 6-months abstinence was not strictly observed in the group referred to LT if MELD≥21 and if AAH existed. Of 46 patients, 20 (43%) died while 17 (37%) improved liver function without referring. Missing referral was related to: lack of 6-months abstinence (14/46), extrahepatic cancer (4/46), dilated cardiomyopathy (6/46), comorbidities (4/46). Patients who accepted to be referred to Addiction Unit were 24 (52%) but only 14 (30%) continued to attend Addiction Unit.
Conclusions. Even if sample is small, according to our real life, the mortality for ALD is high and the underreferral is present. The acceptance to attend Addiction Unit is poor. It is necessary to increase medical education in ALD to detect early complications. Partnership of Transplantation Unit with Hub/Spoke Hospitals and Addiction Units is needed too.

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Results from a retrospective, observational, multicentre study of patients with primary biliary cholangitis treated with obeticholic acid in real life in Italy (O-REAL)

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Sixty-seven patients enrolled in the O-REAL study who matched the inclusion criteria were analyzed. At baseline, 91% of the patients were female and 12% had a concomitant liver disease. Mean

age at start of OCA therapy was 57.64 (±10.87) years with mean time from diagnosis to start of OCA therapy of 8 years. At OCA start, rates of pruritus and fatigue were 24% (n=16) and 18% (n=12), respectively. Eleven patients 16.4%) had cirrhosis confirmed by biopsy. OCA treatment resulted in a mean ALP reduction from 301.01 (±149.16) U/L; to 211.67 (± 97.08) after 6 months of therapy, with a mean percentage change of -21.72% (±34.60). The proportion of patients with ALP ≤1.5xULN after 6 and 12 months of OCA treatment were, 42.2% and 51.7% respectively. After 12 months of OCA, 81.6% of patients with baseline ALP ≥1.67xULN had a reduction >15%. Additionally, ALP, GGT, alanine transaminase (ALT) and aspartate transaminase (AST) levels after 12 months of OCA therapy were significantly reduced compared to baseline (Table). However, changes in total bilirubin and albumin were not significant. Transient elastography was available and paired for 16 patients at baseline and month 12, with a mean at month 12 of -18.39% kPa (95% CI - 45.46-82.24). Among the 27 patients for which GLOBE score was calculated, 19 patients (70.37%) showed a score below the threshold of 0.3 and 8 above it after OCA treatment. Pruritus (n=31) and fatigue (n=3) were the most frequent adverse events. Nine patients developed pruritus after OCA therapy and 4 patients discontinued treatment, 3 due to adverse event (2 pruritus, 1 abdominal distention). No serious adverse events were reported.

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Expert consensus criteria and practical recommendations for pbc care in the covid-19 era and beyond

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Primary biliary cholangitis (PBC) is a chronic autoimmune cholestatic liver disease that can progress to liver fibrosis and cirrhosis, and requires timely diagnosis, optimal treatment, and risk stratification. Several guidelines for the management of PBC have been published, including the American Association for the Study of Liver Disease (AASLD) and European Association for the Study of the Liver (EASL) Clinical Practice Guidelines, which include goals for standards of PBC care. However, recent audits have identified deficiencies in real-world PBC care. In addition, the global coronavirus (COVID-19) pandemic has generally reduced access to care, diminished healthcare resources and accelerated the use of remote patient management. There is therefore a need for simple, actionable guidance that physicians can implement in order to maintain standards of care in PBC in the new environment.

A working group of ten PBC specialists from Europe and Canada were convened by Intercept Pharmaceuticals in January 2020 with the aim of defining key criteria for the care of patients with PBC. Following the outbreak of the COVID-19 pandemic, based on these criteria, a smaller working group of six PBC specialists developed practical recommendations to assist physicians in maintaining standards of care and to guide remote management of patients

The working group defined five key criteria for care in PBC, encompassing PBC diagnosis, initiation of first line therapy with ursodeoxycholic acid (UDCA), risk stratification on UDCA, symptom management, and initiation of 2L therapy. The group developed 21 practical recommendations for the management of patients with PBC in the COVID-19 environment including modality, frequency and timing of investigations and monitoring.

The delivery of PBC care during the COVID-19 pandemic carries significant challenges. These consensus criteria and practical recommendations provide guidance for the management of PBC during the pandemic era and beyond.

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P-69

Outcomes of three lines Atezolizumab plus Bevacizumab-based sequential treatment for hepatocellular carcinoma: a simulation model

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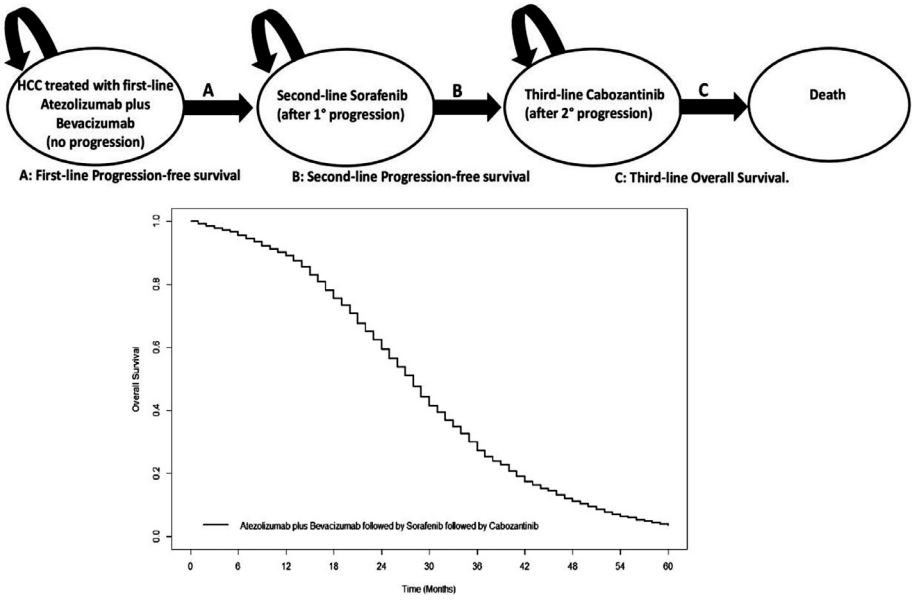
Introduction: The number of effective agents for systemic treatment of hepatocellular carcinoma (HCC) has rapidly increased in recent years and they should be combined in a rationale sequence to offer the best net health benefit. The combination of Atezolizumab plus Bevacizumab is now the standard of care first-line treatment in this setting, but the outcomes of subsequent treatment lines still remain unknown.
Aim To estimate the overall survival (OS) of the sequence of Atezolizumab plus Bevacizumab (first-line) followed by Sorafenib (second-line) followed by Cabozantinib (third-line), that represents the next available sequential strategy for the systemic treatment of patients with HCC in Italy.
Materials and Methods A Markov model was built to estimate the OS of the sequence Atezolizumab plus Bevacizumab (first-line) followed by Sorafenib (second-line) followed by Cabozantinib (third-line). The probability of transition between states (initial treatment, cancer progressions and death) was derived from published randomized controlled trials (RCTs). Survival estimate considered the proportion of patients who did not receive subsequent lines of therapy due to death. OS was the main outcome. Rates of severe adverse events (SAEs) (≥ grade 3) were calculated
Results The estimated median OS of the simulated sequential strategy is 28 months (95% Confidence Interval 27-29 months). Rate of SAEs is 67.5%.
Conclusions Our simulation model provides a forecast of the efficacy and safety of the next available sequential systemic treatment of patients with HCC. The sequence consisting in first-line Atezolizumab plus Bevacizuab followed by second-line Sorafenib followed by third-line Cabozantinib leads to median OS of more than two years, with about two thirds of patients experiencing



SAEs. Prospective real-world studies are needed to prove the net health benefit of this sequence.

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P-70

Recurrence of hepatocellular carcinoma and hepatitis delta infection in a liver transplant recipient: a case report

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A 52 years-old caucasian man, with HIV chronic infection, underwent a liver transplantation in 2012 because of end stage liver disease due to HCV/HBV/HDV and HCC. Tacrolimus monotherapy was started as immune-suppression. After transplant, the patient became spontaneously HCV-RNA negative, HBV-HDV recurrence was prevented by tenofovir and anti-HBs immunoglobulins infusion and the patient remained HBsAg neg. In 2018 anti-HBs levels started to decline despite regular immunoglobulin infusion. Frequency and dosage of immunoglobulin infusions were increased but by the end of the year the patient became HBsAg positive with an HDV-RNA >19000 copies/ml; HBV-DNA remained undetectable. HBsAb infusion was interrupted in January 2019. In March 2019 the patient developed acute hepatitis due to HDV reactivation. A liver biopsy showed no signs of acute or chronic rejection, immunocytochemistry was negative for HBsAg/HBcAg. An abdominal CT scan performed in April 2019 showed a 25 mm left adrenal gland lesion suggestive for HCC. Tumorectomy was performed in September 2019, histological analysis revealed undifferentiated HCC. Polymerase chain reaction (PCR) documented HBV-DNA within tumor without HBsAg-coding gene mutations. A rapid decrease of HBsAg was seen after surgery and HBsAg became undetectable after 3 weeks. Concurrently HDV-RNA levels declined, becoming undetectable after 2 months. HBsAb infusion was then restarted, immune-suppression was switched to everolimus. After sixteen months of well-being, in December 2020 HBsAb levels again started to decline; in order to prevent a new HDV hepatitis HBsAb infusion qod was started. No signs of recurrence at CT scan were reported until May 2021, when multiple HCC nodules involving both hepatic lobes were found. A transarterial chemoembolization was performed, but the following CT scan showed a new metastasis within the right adrenal gland. Systemic therapy with sorafenib was therefore started. In summary, we reported a unique case of post-OLT HDV-related hepatitis linked to extra-hepatic HCC recurrence. The absence of HBV expression in the transplanted liver together with the rapid decline of HBsAg levels within few days after tumorectomy strongly suggest that HCC metastasis was the site of HBsAg production.

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P-71

Hepatitis Delta in HIV: changes in attitude to testing and disease burden over time

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Introduction. Hepatitis Delta virus (HDV) causes severe liver disease. Due to similarities in transmission routes, persons living with HIV (PLWH) are at risk for HDV infection.

Aim. This analysis investigates prevalence and long-term clinical outcome of people with HDV in the large ICONA cohort of PLWH .
Materials and Methods. We retrieved HBsAg ± anti-HDV positive PLWH enrolled from 1997 to 2015 in the multicentre, prospective ICONA study The primary endpoint was a composite clinical outcome (CCO=having experienced ≥1 of the following: Fib4 score >3.25; diagnosis of cirrhosis; decompensation; hepatocellular carcinoma or liver-related death). Kaplan Meier curves and unweighted and weighted Cox regression models were used for data analysis.
Results. Overall, less than half of HBsAg positive patients had been tested for anti-HDV in clinical practice; the proportion of tested cases declined over the observation period (to 15%). After filling the gap by testing stored sera for anti-HDV and HDV-RNA, among 617 HBV/HIV cases, 115 (19%) were anti-HDV positive; 405 (65%) HBV monoinfected; 99(16%) undeterminate. The prevalence declined over the observation period. HDV-RNA was present in 21/38 tested cases (55%) and anti-HDV IgM in additional 11 (29%) patients. HDV patients were more often males, intravenous drug users, anti-HCV positive. After a median of 26 months, 55/115 (48%) developed CCO among HDV+; 98/403 (24%) among HBV monoinfected; 18/99 (18%) in HDV unknown (p<0.001). After controlling for geographical region, alcohol consumption, CD4 count, anti-HCV status and IFN-based therapies, the association with HDV retained statistical significance [HR=1.67 (1.15, 2.95; p=0.025)].
Conclusions. HDV infection among PLWH is underdiagnosed, although HDV entails an high risk of liver disease progression. Because effective drugs to treat HDV are now available, it is even more crucial to identify patients at an early stage of liver disease.

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P-72

Liver transplantation in HIV infected subjects: a long-term single-center experience

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Background: Cirrhosis and HCC represent one of the leading causes of death among HIV positive patients. Liver transplantation (LT) is a well-accepted option for end-stage liver diseases in these patients.
Aim: to analyze the results of LTs performed in our center comparing the outcome in HIV-positive and negative recipients, particularly in those with HCC.
Methods: All patients who underwent LT in our center between 2001-2020 were considered. Cox regression analysis, Kaplan-Meier method and log rank test were used for statistical analysis. A subgroup analysis was performed in LT patients with HCC.
Results: 928 LTs were performed between 2001 and 2020, 63 of them in HIV positive recipients. HIV positive patients were younger than HIV negative (49.4 vs 53.3 yrs, p= 0.001) while no difference was seen regarding MELD score at the time of LT (19 vs 19,1). Mean follow-up was 58 ± 55 months. Five years overall survival in HIV positive was 65.3%, 72.7% in negative LT recipients (p = ns). An improvement in 5 yrs survival was recorded over time in the HIV group: 46.9% in Era I (2003-2011), 80.6% in Era 2 (2012-2020, p<0.001). Independent predictive factors of survival in the HIV group were: age of donor, HCV-RNA detectable at time of transplant, and first Era of LT. 420 patients underwent LT for HCC, 34 HIV positive and 386 HIV negative. No significant differences between the two groups in terms of HCC characteristics were found. HIV positive subjects showed a better overall survival at 5 and 10 years, the difference being not significant (71.6% vs 69.6%, 71.6% vs 61%, p = ns).
Conclusions: Our study shows that HIV positive LT recipients have similar results to HIV negative in terms of survival; survival among HIV-infected LT subjects has improved over time, mainly because of DAAs introduction for HCV and better management of immunosuppression. Excellent results can be achieved for HIV-infected patients with HCC, even better than in HIV-negative patients in our experience, as long as a strategy of good selection of candidates and close surveillance of recurrence is adopted.

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P-73

Transarterial chemoembolization for hepatocellular carcinoma in clinical practice: temporal trends and survival outcomes over the last three decades in Italy

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Introduction and Aim: We aimed at evaluating whether transarterial chemoembolization (TACE) application, as well as the related survival, changed over the last three decades in Italy.
Methods: The 7,184 patients retrieved from the Italian Liver Cancer (ITA.LI.CA) database were divided in six groups according to the period of diagnosis: P1 (1988-1993), P2 (1994-1998), P3 (1999-2004), P4 (2005-2009), P5 (2010-2014), and P6 (2015-2019). The analyses were performed in the whole population and in Barcelona Clinic Liver Cancer (BCLC) B patients, those supposed to receive TACE according to guidelines. TACE was either defined as the first or the main (more radical) treatment.
Results: The proportion of patients receiving TACE as first or main therapy declined over time, and less than 50% of BCLC B patients were treated with TACE from P3 onwards. Conversely, TACE was widely used in other BCLC stages. Survival of TACE-treated patients progressively increased from P1 to P6, and this improvement was confirmed after adjustment for confounders. There percentage of patients receiving 2 or ≥3 TACE increased over time, and the overall survival of patients repeatedly treated was higher compared to those receiving TACE once (p<0.0001). Similar proportion of death from liver decompensation was shown in patients treated with 1, 2 and ≥3 TACE (20.2%, 19.3% and 19.9%, respectively). After a first-line TACE, curative treatments provided longer survival than iterative TACE (83.0 vs. 42.0 months; p<0.0001) that, in turn, was asso-

ciated with better prognosis compared to more palliative therapies (Figure).

Conclusion: Despite a decline over time in its use, TACE has still an important role in HCC management. Survival in TACE-treated patients improved over time, probably due to better patients' selection. Iterative TACE is effective, but an up-ward shift to curative therapies provides better outcomes while transition to systemic therapies and supportive care leads to a worse prognosis.

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P-74

Long term outcome of elderly recipients after liver transplantation. An Italian multicentric study

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In the last years, the number of elderly patients evaluated and considered for liver transplantation LT is increasing, due to the aging of the general population and the better management of hepatic diseases. However, the results in this category of recipients are controversial. This study aims to evaluate the outcome of liver transplantation in elderly recipients (age> 65 years) compared to recipients age 50-59 years, in Italian multicentric cohort.

During the study period 693 patients enrollable for the present study were transplanted.

Two cohorts were created consisting of, respectively, recipients aged 50–59 years (group A; n = 519 74,9%) and elderly recipients aged ≥65 years (group B; n = 174, 25,1%). Results was analyzed in the two groups before and after undergoing a stabilized inverse probability therapy weighting (IPTW).

The Group B patients more commonly presented an EAD defined according to Olthoff (23.9 vs. 23.9%, P=0.04). However, despite this datum, the Group A patients had longer hospital stays after LT (median: 14 vs. 13 days; P=0.02).

The Group B patients more commonly presented an Early Allograft Disfunction (EAD) (23.9 vs. 23.9%, P=0.04). However, the Group A patients had longer hospital stays after LT (median: 14 vs. 13 days; P=0.02). no substantial differences were reported in terms of median CCI® at discharge and CCI>42 in Groups A and B, respectively (P=0.20 and P=0,58). At multivariable Cox regression analysis, the risk factors for patient death and graft loss were patient age ≥65 years (HR=1.76; P=0.002 and HR=1.63; P=0.005), cold ischemia time (CIT) and cardiac arrest of the donor related to an increased risk.

The cumulative patient survival rates at3-month, 1-year, and 5-year survival rates were 91.1, 88.5, and 82.0% vs. 82.6, 79.8, and 66.4% in Groups A and B, respectively (log-rank P=0.001).

The graft survival rates at 3-month, 1-year, and 5-year survival rates were 90.2, 87.2, and 79.9% vs. 81.5, 78.7, and 66.0% in Groups A and B, respectively (log-rank P=0.003). when the CIT was ≤420 minutes, 3-month, 1-year, and 5-year survival rates were 92.0, 91.1, and 85.4% vs. 92.0, 89.3, and 81.2% in Groups A and B, respectively, not showing a statistical difference (log-rank P=0.30).

In conclusion, in the early course, no substantial differences exist in terms of morbidity between elderly and younger patients. However, the mid- and long-term results are poorer. Minimization or optimization of CIT are required to obtained good patient and graft survival.

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P-75

Efficacy and safety of pangenotypic DAAs for chronic HCV infection: real-world data from the RESIST-HCV cohort

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Background and aims: Real-world data on the efficacy and safety of pangenotypic direct antiviral agents (DAAs) for chronic HCV infection are limited. In this study we assessed the efficacy and safety of sofosbuvir/velpatasvir (SOF/VEL) and glecaprevir/pibrentasvir (GLE/PIB) in the RESIST-HCV cohort.

Methods: We studied an observational cohort of 1771 patients (age 62±14, male 51.8%) treated with SOF/VEL and GLE/PIB between October 2017 and January 2020 in Sicily.

Results: 1110 (62.7%) patients were treated with SOF/VEL and 661 (37.3%) with GLE/PIB. Overall, 1742 patients (98.36%) achieved a sustained virological response (SVR) to DAAs, and 29 (1.64%) were non responder/relapser. The two pangenotypic regimens were comparable in terms of SVR both in patients with chronic hepatitis (98.88% vs 98.39% for SOF/VEL vs GLE/PIB, p=0.488), or cirrhosis (97.05% vs 97.44% for SOF/VEL vs GLE/PIB, p=1.000). In a multiple logistic regression analysis, adjusted for drug, gender, diabetes, age, BMI and creatinine, in which liver disease severity was included as categorical variable (hepatitis, Child-A and Child-B), Child-B cirrhosis was associated with lack of SVR, when compared to chronic hepatitis (OR 0.14, CI 0.04-0.53; p=0.004). Consistently, when considering liver disease severity as an ordered variable (hepatitis, Child-A and Child-B), the transition from one stage to the next brought a lower chance of achieving SVR (OR 0.43, CI 0.23-0.80; p=0.011, per unit). In the multiple logistic regression analysis, creatinine was also showed as a predictor of lack of SVR regardless of

whether liver disease was introduced as ordered (OR 0.73, CI 0.55-0.96; p=0.024) or nominal categorical variable (OR 0.72, CI 0.55-0.95; p=0.020).
Conclusions: Real-world data from the RESIST-HCV cohort confirmed the similar efficacy of the two pangenotypic DAAs and showed liver disease severity and renal failure as main predictors of HCV recurrence/non response.

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P-76

Screening for HCV infection combined with SARS-CoV-2 vaccination in the Campania region

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Background and Aims: The health emergency caused by the SARS-CoV-2 pandemic has negatively impacted the management of HCV infection, potentially jeopardizing the achievement of the goal of eliminate hepatitis C by 2030. To take advantage of the current sanitary situation, associated screening for HCV and SARS-CoV-2 infection have been carried out. We decided to propose HCV screening also to people who undergone SARS-CoV-2 vaccination.

Methods: Screening for hepatitis C was carried out by finger-prick test to search for HCV antibodies. It took place in the minutes following the SARS-CoV-2 vaccination, in two different vaccination centers of the Campania region, and in two different time frames. In the period 1 May-20 July 2021, screening for hepatitis C was offered to the general population who got the vaccine at the Fisciano (province of Salerno) vaccination center. In the period 20 September-11 October 2021, screening for hepatitis C was offered to the general population who underwent vaccination at the San Leonardo Hospital (Castellammare di Stabia, metropolitan city of Naples). In both sites, Pfizer-BioNTech, Moderna, or Oxford-AstraZeneca vaccines were used.
Results: Out of 5095 people who underwent vaccination at the Fisciano vaccination center, 1952 (38,3%, average age 41,6 years) performed screening for hepatitis C. 5 of these (0,25%, average age 54,2 years) resulted HCV-Ab positive; all 5 were aware of their condition; 4 had previous treatment; 1 (0,05%) was found to have active HCV infection. Out of 2202 people vaccinated at the San Leonardo Hospital, 1207 (54,8%, average age 43,1 years) underwent screening for hepatitis C. Among these, 9 (0,7%, average age 54,3) resulted positive. 5/9 tested negative on the confirmatory test; 2/9 were aware of their condition and had previous treatment; 1 subject (0,08%) was found to have active HCV infection; 1 subject is awaiting the results at time of writing. In both sites a consistent percentage of people refused the HCV-Ab test. Moreover, the prevalence of HCV-Ab positivity and HCV active infection was found to be lower than the national data. Frequent reasons for refusing the test were lack of knowledge of the disease, fear of a positive result, and distrust in the test's effectiveness. Someone refused the test because vaccination was considered a particularly stressful event. The low prevalence of HCV infection found in these projects could be at least partly attributable to the underparticipation of the elderly, as at the time the screenings were carried out most of them had probably already received the expected doses of SARS-CoV-2 vaccine.
Conclusions: In conclusion, we believe that SARS-CoV-2 vaccination could be an opportunity to screen for HCV infection, but to maximize the benefits of this screening, the characteristics of the subjects to be tested should be reconsidered, by focusing particularly on the elderly population.

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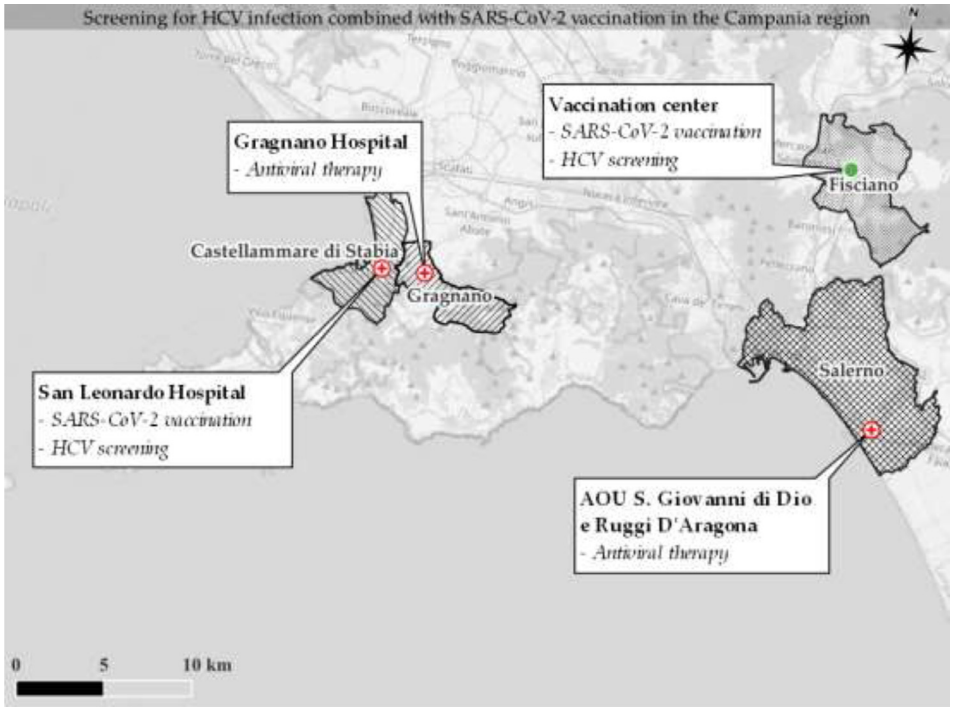

P-77

The synergic effect of non-alcoholic fatty liver disease and hypertension in the development of cardiovascular disease

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Background: Non-alcoholic fatty liver disease (NAFLD) is associated with an increased cardiovascular risk. However, it is still not clear whether NAFLD contributes independently from traditional cardiovascular risk factors to the development of cardiovascular disease. Our study aimed to assess the differences in indices of atherosclerosis, cardiac function and morphology between NAFLD patients with or without hypertension (HT).
Methods: 169 participants (age=50.4±10.2 yrs; males=73.6 %) were divided according to the presence of NAFLD and HT in three groups: only-NAFLD (55 patients), only-HT (49 patients) and NAFLD+HT (65 patients). NAFLD was detected through ultrasonography and excluded by MRI. Exclusion criteria were BMI≥35Kg/m^2 and the presence of diabetes mellitus. Carotid ultrasonography was performed to measure markers of arterial stiffness (pulse wave velocity [cf-PWV]) and subclinical (Carotid Intima–Media Thickness [cIMT]) or overt atherosclerosis (plaques). Cardiac function and morphology were analyzed using transthoracic echocardiography.
Results: Subjects with NAFLD+HT presented higher values of cIMT and cf-PWV as compared with only-NAFLD and only-HT patients ($p<0.001$). Furthermore, the prevalence of atherosclerotic plaques was significantly higher in the NAFLD+HT group compared to the only-NAFLD and only-HT groups: 43.1%, 10.9%, 22.4% ($p<0,001$). No significant differences were found among echocardiographic parameters. In multivariate regression analysis (after adjustment for age, sex, smoke, statins treatment, BMI, systolic blood pressure and liver stiffness) the coexistence of NAFLD+HT was independently associated with the presence of atherosclerotic plaques (OR=3.631; $p=0.04$), while no association was found when NAFLD or HT were considered alone. Conversely, the association of NAFLD and HT (either alone or combined) with cIMT and cf-PWV was no more significant after multivariate analysis.
Conclusion: Overt atherosclerosis and partly arterial stiffness were more pronounced in NAFLD+HT patients. This implies that the impact of NAFLD on vascular structure and function could partially be dependent on the coexistence of others major cardiovascular risk factors, such as hypertension.

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P-78

CONUT score predicts early morbidity after liver transplantation: a collaborative study

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Introduction: Liver transplantation (LT) is burdened by the risk of postoperative morbidity. Identifying patients at higher risk of developing complications can help allocate resources in the perioperative phase. Controlling Nutritional Status (CONUT) score, based on lymphocyte count, serum albumin and cholesterol levels, has been applied to various surgical specialties, proving reliable in predicting complications and prognosis. Our study aims to investigate the role of the CONUT score in predicting the development of early complications (within 90 days) after LT.
Methods: This is a retrospective analysis of 209 patients with a calculable CONUT score within two months before LT. The ability of the CONUT score to predict severe complications, defined as a Comprehensive Complication Index (CCI) ≥42.1, was examined. Inverse Probability Treatment Weighting was used to balance the study population against potential confounders.
Results: Patients with a CCI ≥42.1 had higher CONUT score values (median: 7 vs. 5, P-value <0.0001). The CONUT score showed a good diagnostic ability regarding post-LT morbidity, with an AUC=0.72 (95.0% CI=0.64-0.79; P-value <0.0001). The CONUT score was the only independent risk factor identified for a complicated post-LT course, with an odds ratio=1.39 (P-value <0.0001). The 90-day survival rate was 98.8% and 87.5% for patients with a CONUT score <8 and ≥8, respectively.
Conclusions: Pre-operative CONUT score is a helpful tool to identify patients at increased post-LT morbidity risk. Further refinements in the score composition, specific to the LT population, could be obtained with prospective studies.

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P-79

Liver cirrhosis in the Emergency Department: a change of paradigm in DAAs era

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Introduction Cirrhosis epidemiology is changing over the years with increase of NASH-related cirrhosis ad reduction of virus related cirrhosis. Since 2014, the introduction of Direct-acting antivirals (DAAs) modified the prognosis HCV-related cirrhosis.
Aim The primary aim of the study is to analyse changes in intra-hospital mortality of cirrhotic admitted in Emergency Department (ED) in the DAA era compared with previous years, with particular attention to HCV-related cirrhosis. Secondary aim of the study is the analysis of prognostic index of intra-hospital mortality.
Materials and Methods This is a retrospective, single Centre study, from a tertiary hospital's database, from 2015 to 2021. Association between predictor variables and survival in two subgroups (all-aetiology and HCV-cirrhotic patients) has been investigated through weighted cox regression in the pre and post DAA era. We defined "post-DAAs era" years from 2018 to 2021, because of the achievement of 100.000 Italian HCV treatments in 2018. The predictive power of the MELD derived scores and comorbidity scores have been compared though ROC curve.
Results 1790 patients were enrolled, most of them males (69.1%), alcohol abuse (25.5%) and HCV (24.0%) the prevalent aetiolo-

gies. Among HCV-cirrhotic, intra-hospital survival was improved in DAAs era (pre-DAAs HR 2.1, 95% CI 1.2 - 3.8; post- DAAs HR 0.48, 95% CI 0.3 - 0.9, p = 0.01), with MELDNa, presence of HCC, and triage code as the most important predictors of mortality. Mortality in cirrhotic patients with all other aetiologies was not modified in the DAA era. iMELD, UKELD, Updated MELD, MELDNa, MELD-Na, MELD, CLIF-AD and Charslon Comorbidity Index were analysed as prognostic scores. MELDNA and MELD-Na were identified as the best predictors of intra-hospital mortality.
Conclusions Intra-hospital mortality of HCV cirrhotic admitted in ED seems to be improved in the DAA era. Sodium-based MELD-derived scores have the best predictive power in ED setting.

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P-80

Ruling out Varices Needing Treatment with a non-invasive score in patients with compensated HBV cirrhosis

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Background & Aims: Non-invasive criteria to rule-out oesophageal varices needing treatment (VNT) in patients with compensated HBV cirrhosis on long-term treatment with nucleoside analogs(NUCs) are lacking. We have assessed the performance of an algorithm combining platelets and albumin (PLT-ALB) in a cohort of such patients under endoscopic (EGD) surveillance.
Approach & Results: All consecutive patients with compensated HBV cirrhosis who achieved HBV DNA suppression on NUCs since at least 1 year were classified at the moment of EGD as: PLT-ALB IN (low risk for VNT) if platelets were $>120 \times 10^9$/L plus serum albumin >3.6 g/dL–PLT-ALB OUT (high risk for VNT) if platelets were $<120 \times 10^9$/L and/or serum albumin <3.6 g/dL. Primary outcome was the finding of VNT at EGD. Performance of PLT-ALB scoring to predict the outcome was assessed measuring the the receiver operating characteristic (AUROC) curve.. 87 patients in Child-Pugh A class (mean age 52 years, 75.9% males) were assessed, 46treated with Entecavir and 41 with Tenofovir. Seven patients (8%) had VNT, all being PLT-ALB OUT. Among the 41 PLT-ALB IN patients (47.1%) no VNT were found (NPV 100%). The PLT-ALB algorithm showed an AUROC of 0.76, potentially saving 47% of EGDs, with a false negative rate (FNR) of 0% and a false positive rate (FPR) of 48.1%.
Conclusions: APLT-ALB algorithmic approach based on widely available noninvasive parameters can avoid up to 50% EGDs aimed to screen for high-risk varices patients with compensated HBV cirrhosis under NUC suppression . Further validation in larger cohorts are needed before translating this approach into practice.

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P-81

Mathematical modeling of cancer cells and vasculature dynamics with serological and imaging biomarkers suggests synergistic effects of TACE and TKIs in HCC patients

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Background and Aims: Transarterial-chemoembolization (TACE) and tyrosine-kinase inhibitors (TKI) represent first-line treatments in intermediate and advanced hepatocellular carcinoma (HCC). Deepening TKI and TACE response mechanisms may provide insights to optimize their combination. We developed a physic-mathematical model to analyze cancer cells and tumor vasculature dynamics in HCC patients (pts) using serum biomarkers combined with tumor digital imaging before and after TACE or TKI treatment.
Method: Ten pts (F/M: 2/8, median age: 65y, stage: 1 BCLC-B and 9 BCLC-C) who received TKIs (1 regorafenib, 9 sorafenib) and 8 pts (F/M: 5/3, median age: 77y, all BCLC-B) who underwent TACE (doxorubicin+DC-beads), with serological and imaging data suitable for modeling analysis, were enrolled. Circulating HCC biomarkers (alpha-fetoprotein, AFP and protein induced by vitamin K absence-II, PIVKA-II) were measured by commercial assays (Abbott, Fujirebio). HCC volume and densitometry were measured by CT scans (GE Advantage Workstation 4.6). The model used for fitting experimental data is described at https://doi.org/10.3390/cancers13092064
Results: The model was able to fit AFP and PIVKA-II measures independently on therapy response in both TKI [4 Complete Response (CR), 4 Partial Response (PR), 2 Progressive Disease (PD)] and TACE [2 CR, 5 PR, 1 PD] treated pts (Figure). The computed anti-angiogenetic and anti-proliferative effectiveness of TKIs were 13.7 and 7.0-fold higher as compared to TACE, by contrast TACE reached the maximal therapeutic effect in <1 day, and TKIs between 4.6-99.9 days. AFP decline after TACE followed its natural decay (0.10-0.16 day-1), whereas it occurred with delay in TKIs responders. An early spike of PIVKA-II levels was observed in most pts receiving TKIs, but not after TACE, suggesting that PIVKA-II production rate can increase only when the ischemia onset is slow. Anti-angiogenesis effectiveness was, on average, 8-fold higher in CR that in NON-CR pts, regardless to the type of treatment. CR pts showed an accelerated vasculature decay also, which was maintained in TKIs treated pts despite significant lowering of the doses.
Conclusion: Cancer cells and tumor vasculature dynamics in HCC patients can be analyzed by modeling the kinetics of serum biomarkers combined with tumor digital imaging. Our model supports potential synergic effects of TKIs and TACE, although further studies are required to define the best strategy of combination.

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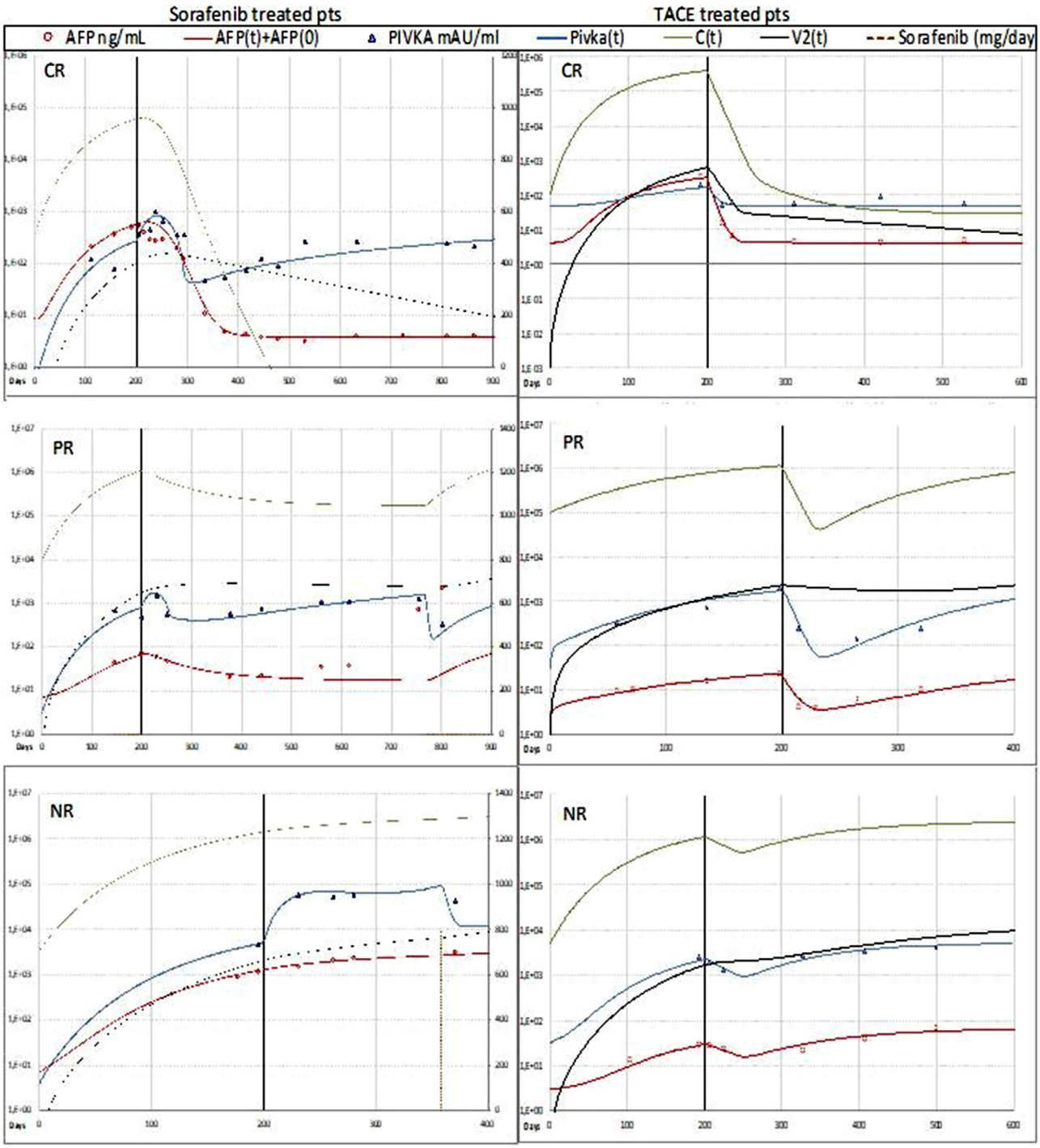

P-82

Predictors of survival of patients with hepatocellular carcinoma in best supportive care

C. Campani, L. Bucci, V. Adotti, M. Rosi, U. Arena, F. Trevisani, F. Marra, for the Ita.Li.Ca. group

Background and Aims: The prognosis of patients with hepatocellular carcinoma (HCC) is very variable. Patients unfit to receive any type of treatment are managed with best supportive care (BSC), and their median overall survival (OS) is around 3-6 months, although longer values may be observed in clinical practice. Aim of this study was to identify prognostic factors associated with longer survival in patients with HCC treated with BSC.

Method: We retrospectively evaluated the clinical characteristics of 916 patients, recorded in the Ita.Li.Ca. database, who had an indication for BSC. We analyzed both patient and tumor characteristics to identify predictors of better OS.

Results: Median age was 71y and 75% of patients were male. Etiology included chronic viral infection (48.7%), alcohol use disorder (20.7%) and non-alcoholic steatohepatitis (4.1%). Approximately 50% of patients had a performance status 0-1 and were in Child-Pugh B class. Median MELD was 13. 60% of patients had a multifocal HCC with a median number of 2 lesions and a median size of 35 mm. 369 patients had vascular invasion. Me-

dian alpha-fetoprotein was 63.2 ng/ml. The median OS was 9 months (CI 7.7;10.2). No differences in terms of OS were observed considering the etiology of liver disease. Among comorbidities, heart disease was associated with lower OS (p=0.015). Abdominal pain (p<0.001), vomiting (p=0.014), fatigue (p<0.001), edema (p<0.001), jaundice (p=0.01), higher PS (p=0.01), and a worse liver function (p<0.001) were associated with shorter OS. Patients with multifocal HCC had a better OS (12 mo; CI 10-13.9) compared to those with monofocal HCC (8 months; CI 6.5-9.5) (p<0.001). Lack of vascular invasion was also associated with a better OS (14 months, CI 12.2-15.7, p<0.001). No significant differences were observed comparing patients with or without metastasis (p=0.310). Patients who had an active treatment before BSC had significantly longer OS than those for whom BSC was the only treatment (561 patients, p<0.001). Survival in BCLC-A patients was longer than in other stages. No differences in OS were found comparing BCLC-B and -C groups. Patients in BSC with a median OS longer than 6 months had more lesions (p=0.005), higher levels of albumin (p=0.003), lower bilirubin (p<0,001) and alpha-fetoprotein (0,001), and a lower median MELD (p<0.001). A weak association was found between survival shorter than 6 months and the presence of cirrhosis (p=0.012), alcohol consumption (p=0.046), heart disease (p=0.007), obesity (p=0.025), hypercholesterolemia (p=0.002), hypertriglyceridemia (p=0.0036) symptoms (p=0.02), vascular invasion (p<0.001), and non-multifocal HCC (p<0.001). Similar results were found comparing patients with a mOS longer or shorter than 12 months.

Conclusion: In a large series of patients with HCC in BSC we identified several clinical and tumor characteristics associated with the length of survival.

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P-83

Comparison of therapeutic outcomes of liver resection and transarterial chemoembolization in multifocal HCC: a propensity score-matched analysis

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Background and Aims: Patients with multifocal hepatocellular carcinoma (HCC), preserved liver function, without cancer-related symptoms (PS 0), vascular invasion or extrahepatic spread represent a heterogeneous group. Although transarterial chemoembolization (TACE) is the most frequently employed treatment in this group of patients, previous data have indicated that liver resection (LR) could be a safe and effective procedure for multifocal HCC. Nevertheless, it is still debated whether better outcomes are achieved after surgery as compared to those obtained with TACE.

Method: We prospectively enrolled 58 patients with multifocal HCC who underwent a first procedure of LR (=25) or TACE (=33) between May 2011 and March 2021. For each patient, information regarding demographic and clinical variables was collected. A propensity score matching was used to adjust the baseline differences between patients undergoing LR and the TACE group (number and diameter of lesions, presence of cirrhosis, AFP values, and MELD score). TACE and LR were compared in terms of overall survival, disease-free survival and development of short-term (<7 days) complications.

Results: Median age was 68 and 70 years for LR and TACE, respectively. In both groups almost all patients were male and chronic viral infection was the most frequent etiology. The median MELD in the LR and TACE groups was 8 and 9, respectively and most patients had cirrhosis. Regarding tumor features the median number of lesions was 3, median size 65 mm and median alphafetoprotein 16 ng/ml. The development of short-term complication was significantly higher in patients with LR (49%) than in those subjected to TACE (8%, p=0.015). The majority of complication within the LR group were classified as Clavien-Dindo I-II. In contrast, disease-free susrvival was significantly longer in resected patients (18.8 vs 4.8 months; p=0.004). Although a trend toward better overall survival was observed in patients undergoing TACE (27.9 months) compared with the LR group (22,4 months), the difference was not statistically significant.

Conclusion: In patients with multifocal HCC, LR confers an advantage in terms of disease-free survival compared with patients who underwent TACE, but this does not reflects into differences in terms of overall survival.

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P-84

Modulation of the cholangiocarcinoma stem-like compartment by monounsaturated fatty acids

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Background and Aims: Identification of the molecular features of CCA may be helpful in designing new therapeutic approaches. Cancer cells are exposed to a metabolically challenging environment with scarce availability of nutrients, and alterations in lipid metabolism may affect the response of tumor cells to drugs. We hypothesize that fatty acids (FA) modulate the biology of CCA cells and the development of stemness features.

Methods: CCA cells (HuCCT-1 OR CCLP1) were treated with monounsaturated FA (132mcM oleic or 100mcM palmitoleic acid). Responsiveness of CCA cells to cytotoxic drugs was tested with crystal violet staining. Epithelial-mesenchymal transition program, stem-like markers, ABC transporters and metabolic markers, were tested with real-time PCR. Self-renewal ability was tested with a colony formation assay. Cancer stem cell- (CSC)-enriched spheres were obtained growing cells in anchorage-independent conditions and selective medium. Five-year overall survival (OS) was analyzed in 104 patients with cholangiocarcinoma sub-grouped based on fatty acid synthase (FASN) expression. NSG mice were injected with spheres obtained from CCLP1 cells and treated for four weeks with the FASN inhibitor orlistat (240mg/Kg).

Results: Exposure of CCA cell lines to FAs increased cell proliferation and activated growth and survival pathways, including AKT and ERK1/2. Exposure to FA before treatment with chemotherapeutic agents made CCA cells less sensitive to their toxic effects, and modulated the expression of ABC transporters involved in drug resistance. The colony forming ability of CCA cells was increased by FAs, and was associated with upregulation of genes controlling epithelial-mesenchymal transition and stemness. Expression levels of genes involved in lipid metabolism were upregulated in CSC-

enriched spheres. In a series of CCA patients, the expression of FASN correlated with OS. FASN inhibition by orlistat decreased cell proliferation and CSC or EMT markers. In a xenograft model of CCA, tumor volume of mice treated with orlistat was significantly lower than in control mice.
Conclusion: Exposure of CCA cells to FA increases growth, invasiveness and resistance to antineoplastic drugs, and modulates stem-like features and self-renewal abilities. In the CCA stem-like subset, several key genes involved in FA synthesis and transport were upregulated, and FASN inhibition decreased cell proliferation and downregulated CSC markers. and FASN expression levels correlate with survival in patients with CCA. These data suggest that lipid metabolism could be a new potential target to affect CCA progression, especially in CSCs subset.

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P-85

Macrophage MerTK promotes a profibrogenic cross-talk with hepatic stellate cells via soluble mediators

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Background and aims: Activation of Kupffer cells and recruitment of monocytes are key events in fibrogenesis. These cells release soluble mediators which induce the activation of hepatic stellate cells (HSC), the main fibrogenic cell type within the liver. Mer tyrosine kinase (MerTK) signaling regulates multiple processes in macrophages and has been implicated in the pathogenesis of NASH-related fibrosis. In this study, we explored if MerTK activation in macrophages influences the profibrogenic phenotype of HSCs.
Methods: M2c-like ($MerTK^+/CD206^+/CD163^+/CD209^-$) macrophages were differentiated from peripheral blood monocytes using M-CSF and IL-10. The role of MerTK was assessed by stimulation with the ligand Gas-6 and by pharmacologic inhibition with UNC569.
Results: $MerTK^+$ macrophages exhibited activation of STAT3, ERK1/2, and p38 and increased expression of VEGF-A. Exposure of $MerTK^+$ macrophages to Gas-6 increased activation of MerTK and downstream pathways. These events were reverted by pretreatment with UNC569. *MERTK* and *Gas-6* mRNA levels were gradually increased during macrophage polarization towards a M2c-like phenotype and were significantly greater in Kupffer cells than in peripheral blood monocytes. Gas-6 was released both by M2c-like macrophages and Kupffer cells. Activation of MerTK in macrophages induced a secretome which caused a significant increase in migration, proliferation, viability and expression of profibrogenic factors in HSCs. Conditioned medium of Gas-6-stimulated $MerTK^+$ macrophages also induced a significant increase in phosphorylation of STAT3 and p38 in HSCs, and upregulation of IL8 expression. These effects were specifically related to MerTK activity in macrophages, as indicated by pharmacologic inhibition.
Conclusions: MerTK activation in M2c-like macrophages modifies the secretome to promote HSC profibrogenic features, indicating that this receptor may be implicated in the pathogenesis of hepatic fibrosis.

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A.I.S.F. 2022 Abstracts Evaluation Procedure

Thanks to experts evaluating all the abstracts according to predetermined Clinical and Experimental categories.

The experts for the 2022 Annual Meeting are listed below:

Category A. "EXPERIMENTAL VIRAL HEPATITIS"
C. Ferrari, Parma - T. Pollicino, Messina - P. Pontisso, Padua - V. Svicher, Rome

Category B. "HEPATITIS B & DELTA CLINICAL"
B. Coco, Pisa - V. Di Marco, Palermo - A. Marzano, Turin

Category C. "HEPATITIS C CLINICAL"
A. Mangia, S.G. Rotondo (FG) - F. Morisco, Naples - M. Viganò, Milan - A.L. Zignego, Florence

Category D. "NAFLD & ALD EXPERIMENTAL"
A. Alisi, Rome - P. Dongiovanni, Milan - A. Federico, Naples - L. Valenti, Milan

Category E. "NAFLD & ALD CLINICAL"
E. Bugianesi, Turin - A. Fracanzani, Milan - G. Marchesini, Bologna - S. Petta, Palermo - F. Salomone, Catania

Category F. "AUTOIMMUNE HEPATITIS & BILIARY DISEASE"
M. Carbone, Milan - V. Cardinale, Rome - A. Floreani, Padua - L. Muratori, Bologna - C. Rigamonti, Novara

Category H. "EXPERIMENTAL LIVER DAMAGE, FIBROSIS, CIRRHOSIS & PORTAL HYPERTENSION"
M. Fraquelli, Milan - F. Marra, Florence - M. Parola, Turin - G. Svegliati-Baroni, Ancona

Category I. "FIBROSIS, CIRRHOSIS & PORTAL HYPERTENSION CLINICAL"
V. Calvaruso, Palermo - P. Caraceni, Bologna - V. La Mura, Milan - S. Piano, Padua - F. Schepis, Modena - M. Senzolo, Padua

Category L. "HEPATOCELLULAR CARCINOMA EXPERIMENTAL"
G. Missale, Parma - F. Farinati, Padua

Category M. "HEPATOCELLULAR CARCINOMA CLINICAL"
A. Cucchetti, Bologna - E. Giannini, Genoa - M. Guarino, Naples - M. Iavarone, Milan - F. Piscaglia, Bologna - F. Trevisani, Bologna

Category N. "LIVER FAILURE, HEPATOBILIARY SURGERY & TRANSPLANTATION"
L. Baiocchi, Rome - P. Burra, Padua - M.F. Donato, Milan - S. Ginanni Corradini, Rome - L. Pasulo, Bergamo

Category O. "MISCELLANEOUS: GENETIC, PEDIATRIC, NUTRACEUTICALS, DILI, OTHER"
A. Gasbarrini, Rome - A. Lleo, Rozzano (MI) - F.P. Russo, Padua

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1590-8658