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Oral communications: 55th Annual Meeting of the Italian Association for the Study of the Liver – A.I.S.F. (Rome, March 16th-17th, 2023)

OC-01

Nationwide survey of liver transplantation for Primary Sclerosing Cholangitis in Italy

M.C. Morelli [1], M. Gambato [2], S. Martini [3], P. Carrai [4], P. Toniutto [5], V. Giannelli [6], F. Donato [7], I. Lenci [8], L. Pasulo [9], C. Mazzarelli [10], A. Ferrarese [11], M. Rendina [12], A. Grieco [13], A. Galeota Lanza [14], G. Svegliati-Baroni [15], N. De Maria [16], S. Marenco [17], L. Mameli [18], P. Burra [2]

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Introduction: Primary Sclerosing Cholangitis (PSC) is a rare condition with low incidence in countries of the Mediterranean Basin, such as Italy; the timing for listing and the indication for liver transplantation (LT) are not entirely stated.
Aim: To investigate the Italian trend in indication, timing, and outcome for PSC LT.
Materials and Methods: In April 2022, we conducted a nationwide survey of LT in PSC over the last 15 years. 85% of Italian LT Centers took part in the project. Clinical features, indications and outcomes were evaluated.
Results: From January 2007 to December 2021, 445 PSC patients have been included in the Italian LT waiting-lists, and 411 underwent LT. The median age at LT was 46 years (18-73), with a high prevalence of males (n=287, 70%). Over 15 years, the number of transplants for PSC increased from 20 to 42 per year, reaching 3.0% of all indications in 2021. Recurring cholangitis and hepatic decompensation were the main indications for listing. The dropout rate from the waiting-list was 6% (26/445), cholangiocarcinoma (CCA) not eligible for LT and being too sick were the leading causes.

71% of the LT Centers utilized induction therapy with Basiliximab. Tacrolimus+MMF was the combined therapy of choice.

Overall post-LT mortality was 15% (66/441): 24 patients died in the first year (50% due to surgical complications and 25% infections); 33 patients died between 1 to 5 years (36% PSC recurrence, 21% occult CCA-recurrence) and 9 patients after 5 years (56% cancer, 44% PSC recurrence).
Conclusions: Likewise other Countries, PSC has been an increasing indication for LT in Italy. The dropout rate from LT waiting-list was relatively low, and CCA not eligible for transplantation or being too sick for surgery were the leading causes. 5-year post-LT survival was 87%, being PSC-recurrence or neoplastic disease the main causes of death.

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OC-02

SIRT5 rs12216101 T>G variant is associated with oxidative stress and mitochondrial dysfunction in patients with non-alcoholic fatty liver disease

F. Salomone [1], R.M. Pipitone [2], M. Longo [3], F. Malvestiti [4], E. Casirati [4], A. Distefano [5], M. Amorini [5], G. Li Volti [5], E. Ciociola [6], G. Lazzarino [5], A. Craxì [2], A.L. Fracanzani [3], P. Dongiovanni [3], L. Valenti [3], S. Petta [2], S. Grimaudo [2]

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Introduction: Sirtuin 5 (SIRT5) is a NAD+-dependent deacylase that modulates mitochondrial processes and the antioxidant defense through post-translational modifications of target proteins.
Aim: In this study, we aimed to evaluate the impact of *SIRT5* rs12216101 T>G on disease severity in patients with non-alcoholic fatty liver disease (NAFLD). We also aimed to assess if *SIRT5* rs12216101 T>G genotype may influence mitochondrial function and oxidative stress in NAFLD.
Materials and Methods: The rs12216101 was genotyped in 2606 consecutive European patients with biopsy-proven NAFLD. Genotyping of *SIRT5* rs12216101 variants was performed by TaqMan assays. Parameters of mitochondrial function and oxidative stress were evaluated in a sub-cohort of 28 patients. Effects of SIRT5 pharmacological inhibition was evaluated in HepG2 cells exposed to free fatty acids (FFA) and mitochondrial energetics was investigated by HPLC.
Results: At multivariate logistic regression analysis adjusted for gender, age>50 years, diabetes, and *PNPLA3* rs738409 status, *SIRT5* rs12216101 T>G variant was associated with presence of F2-F4 fibrosis (OR 1.18, 95% C.I. 1.00-1.37). Parameters of oxidative stress including reactive oxygen species, reactive nitrogen species and malondialdehyde were higher in patients carrying the T>G allele, whereas liver ATP was significantly lower. Exposure of HepG2 to FFA impaired mitochondrial energetics and determined oxidative stress. Administration of a pharmacological SIRT5 inhibitor to HepG2 treated with FFA preserved mitochondrial function as evidenced by restored ATP/ADP, NAD+/NADH and NADP+/NADPH ratios.
Conclusions: The *SIRT5* rs12216101 T>G variant is associated with liver damage, impaired mitochondrial function and oxidative stress in patients with NAFLD.

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OC-03

Increased level of presepsin in patients with acutely decompensated cirrhosis predicts development of acute-on-chronic liver failure

A. Zanetto [1,2], M.M. Mion [3], A. Ferrarese [4], S. Shalaby [1,2], G. Germani [1,2], M. Gambato [1,2], F.P. Russo [1,2], F. Farinati [1,2], D. Basso [3], P. Burra [1,2], M. Senzolo [1,2,5]

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Introduction: The clinical course of acutely decompensated cirrhosis (AD) is heterogeneous. Presepsin (PSP) is a soluble CD14-subtype biomarker that reflects Toll-like receptor activity as the immune response to endotoxaemia and bacterial infections, and it has regulatory properties of the adaptive immune system.
Aim: We conducted a prospective study to assess whether, in hospitalized patients with AD, plasmatic PSP could predict development of ACLF.
Material and Methods: AD patients were recruited at admission and underwent determination of PSP (chemiluminescent immunoassay). All patients were followed for 1 year, and predictors of ACLF were assessed by Cox analysis.
Results: 99 AD patients were included (median age: 61 years; 65% had alcohol-related cirrhosis). The main reasons for AD were infections and alcoholic hepatitis (52% and 22%, respectively). Median MELD and CLIF-C AD scores were 18 and 54, respectively. Median PCP was 674 U/L (308-1700). Thirty-six patients developed ACLF. PSP was higher in patients who experienced ACLF vs those who did not (1253 [670-2562] vs 375 [245-722], respectively; $p<0.0001$). Among patients who didn't develop ACLF, PSP was comparable between those who were re-hospitalized due to cirrhosis complications and those who were not re-hospitalized (432 vs 355, respectively). Cox analysis demonstrated that PSP was independently associated with ACLF (Table). PSP AUROC was good and comparable to CLIF-C AD score (0.78 vs 0.79, respectively). A PSP value > 660 had 77% sensitivity and 70% specificity for the development of ACLF. In a sub-analysis including patients at lower risk of ACLF (i.e. CLIF-C AD score ≤50 and Child B), PSP was significantly higher in those who developed ACLF than in those who did not (1054 vs 250, respectively).

Conclusion: PSP can be a useful, single and independent biomarker to identify trajectories of AD, even in patients at lower risk of ACLF, if this is confirmed in larger cohorts.

Table. Variables associated with development of ACLF (Cox-regression analyses).

Variables	HR	95%CI	P value
Univariate			
CLIF-C AD score (>54)	4.8	2.3-10.1	<0.0001
Presepsin, ng/L (>674)	3.9	1.9-8.5	<0.0001
MELD score (>18)	3.1	1.5-6.0	0.002
Child class C vs B	5.7	2.4-13.7	<0.0001
C-reactive protein, mg/dL (>21)	3.4	1.6-7.1	0.001
Infection (YES/NO)	1.8	0.93-3.45	0.08
Hemoglobin, mg/dL	0.9	0.8-1.2	0.8
Multivariate model#1			
Presepsin, ng/L (>674)	2.7	1.2-5.9	0.01
CLIF-C AD score (>54)	2.4	1.1-5.5	0.03
C-reactive protein, mg/dL (>21)	1.6	0.7-3.5	0.2
Child class C vs B	2.9	1.2-7.4	0.02
Multivariate model#2			
Presepsin, ng/L (>674)	2.5	1.1-5.6	0.02
CLIF-C AD score (>54)	3.1	1.4-6.8	<0.01
C-reactive protein, mg/dL (>21)	1.6	0.7-3.5	0.2
MELD score (>18)	1.5	0.7-3.1	0.3
Multivariate model #3			
Infection (YES/NO)	1.2	0.6-2.6	0.4
Presepsin, ng/L (>674)	2.5	1.1-5.6	0.02
CLIF-C AD score (>54)	3.2	1.5-7.2	0.003
MELD score (>18)	1.6	0.7-3.5	0.2

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OC-04

Network meta-analysis of first-line systemic therapies for advanced hepatocellular carcinoma: Who is the winner?

C. Celsa [1], G. Cabibbo [1], G.E.M. Rizzo [1], P. Giuffrida [1], M. Enea [2], G. Di Maria [1], M. Antonucci [3], C.M. Giacchetto [1], G. Rancatore [1], M.V. Grassini [1], R. Ciccia [1], A. Grova [1], M. Salvato [1], S. Battaglia [4], M. Vaccaro [1], C. Cammà [1]

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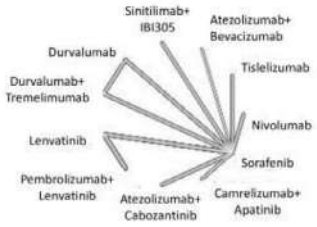
Introduction: Atezolizumab plus Bevacizumab represents the current standard of care for first-line treatment of advanced HCC. However, direct comparison with other combination treatments including immune-checkpoint inhibitors (ICI) plus tyrosine-kinase inhibitors (TKIs) or anti-CTLA4 are lacking.
Aim: The aim of this network meta-analysis (NMA) is to indirectly compare the efficacy and the safety of first-line systemic treatments.
Materials and Methods: Literature search of MEDLINE, EMBASE and SCOPUS databases was conducted up to October, 2022. Phase 3 randomized controlled trials (RCTs) testing TKIs, including Sorafenib and Lenvatinib, or ICIs reporting overall survival (OS) and progression-free survival (PFS) were included. Individual survival data were extracted from OS and PFS curves to calculate restricted mean survival time (RMST). A Bayesian NMA was performed to compare treatments in terms of efficacy (15- and 30-month OS, 6-month PFS) and safety, represented by grade≥3 (severe) adverse events (SAEs). The incremental safety-effectiveness ratio (ISER) as measure of net health benefit was calculated as the difference in probability of SAEs divided by difference in survival between the 2 most effective treatments.
Results: Nine RCTs enrolling 6600 patients were included. Atezolizumab+bevacizumab showed the highest probability (88%) of being the best in 30-month OS. Pembrolizumab+lenvatinib showed the highest probability (94%) of being the best in terms of PFS. ICI monotherapies were the most safe combination. At a willingness-to-risk threshold of 10% of SAEs for month-year gained, atezolizumab+bevacizumab was favored in 76% of cases, while at a threshold of 30% of SAEs for month-year gained, pembrolizumab+lenvatinib was favored in 72% of cases.
Conclusions: Atezolizumab plus Bevacizumab is the preferred option in unfit patients with high tumor burden, while Pembrolizumab plus Lenvatinib could be preferred for fit patients with less advanced vascular tumor spread



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OC-05

The invasion of the biliary epithelial cells by CD103$^+$ CD69$^+$ intraepithelial cells CD8$^+$ T lymphocyte and its role in the pathogenesis of primary biliary cholangitis

V. Ronca [1,2,3,4], S. Davies [1], G. Wootton [1], N. Krajewska [1], G. Reynolds [1], Y. Oo [1,2]

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Introduction: The pathogenesis of primary biliary cholangitis (PBC) remains elusive and the mechanism of the biliary injury is yet to be clarified. Cell-in-cell structures (CICs) formed from lymphocytes have been reported in the liver. These are predominantly found within hepatocytes and have been associated with autoimmunity.
Aims: We report for the first time the internalisation of CD8$^+$ T cells in biliary epithelial cells in PBC. Our aim is to characterise the mechanism of the internalisation and explore its role in the pathogenesis of PBC.
Materials and Methods Results: Immunofluorescence staining was used to identify and characterise CD8$^+$ T cells internalised by BECs. Primary T cells were co-cultured with human BECs *in vitro* to assess the mechanism of internalisation. Morphology of co-cultured T cells and epithelial cells was visualised using confocal and electron microscopy, high-content imaging and flow cytometry. Internalised CD8$^+$ T cells were found with higher frequency in PBC patients compared with diseased liver tissue. They were found to

express CD103$^+$ CD69$^+$ and being significantly larger than liver parenchymal CD8$^+$ T cells. Cells stimulation significantly increase their ability to invade BECs *in vitro*. Furthermore, the increased exposure to activation stimuli positively correlated with cell size and frequency of internalisation. Transmission electron microscopy confirmed complete internalisation *in vitro* and showed the lack of an additional membrane containing the T cell. Scanning electron microscopy revealed the polarisation of T cells prior to their internalisation and the absence of BEC membrane rearrangements associated with capture processes. These behaviours were not observed with matched CD4$^+$ T cells.

Conclusions: We described and characterised a population of hyper-activated CD8$^+$ T Intraepithelial lymphocytes (IELs) which can invade cholangiocytes in patients with PBC. We reported for the first time the mechanism of this CiC process, demonstrating a novel ability of IELs to invade epithelial cells.

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OC-06

Prediction of response to obeticholic acid in primary biliary cholangitis: Development and validation of the OCA response score (ORS)

A. De Vincentis [1], F. Terracciani [1], D. D'Amato [2], P. Invernizzi [3], A. Morgando [4], E. Vanni [4], M. Viganò [5], D. Alvaro [6], R. Venere [7], A. Lleo [8], F. Colapietro [9], E. Degasperi [10], R. Viganò [11], E.G. Giannini [12], S. Labanca [13], V. Feletti [14], A. Mussetto [14], R. Cozzolongo [15], F. Losito [16], M. Pompili [17], F.R. Ponziani [17], G.A. Niro [18], R. Cotugno [19], P. Pozzoni [20], L. Chessa [21], G. Cuccorese [22], V. Pace Palitti [23], M. Russello [24], M. Cannavò [25], E. Frazzetto [26], G. Bertino [26], M. Marzioni [27], N. Terreni [28], T. Zolfino [29], C. Saitta [30], A. Pellicelli [31], B. Coco [32], M. Brunetto [32], N. Cazzagon [33], A. Floreani [34], L. Muratori [35], F. Rosina [36], M. Di Stefano [37], G. Scifo [38], L. Baiocchi [39], G. Grassi [40], R. Sacco [41], A. Izzi [42], Saveria Lory Crocè [43,44], Cecilia Fiorini [45], Fabio Marra [45], Loredana Simone [46], Olivia Morelli [47], L. Abenavoli [48], F. Pizzolante [49], N. De Matthaeis [49], M. Scaravaglio [50], G. Gimignani [51], V. Boano [52], G.F. Manfredi [53], M. Marignani [54], S. Fanella [54], M. Giacchetto [55], A. Castellaneta [56], G. Poggi [57], V. Buzzanca [27], P. Scivetti [58], A. Tortora [17], S. Casella [59], V. Bellia [60], B.F. Omazzi [61], G. Alagna [62], C. Ricci [63], P. Poisa [64], C. Rigamonti [65], V. Calvaruso [55], U. Vespasiani-Gentilucci [1], M. Carbone [3], on behalf of the Club Epatologi Ospedalieri (CLEO)/Associazione Italiana Gastroenterologi ed Endoscopisti Digestivi Ospedalieri (AIGO) PBC Study Group, the Sicilian PBC Network, the PBC Project Piemonte-Liguria-Valle D'Aosta and the Italian PBC Registry

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Introduction: Obeticholic acid (OCA) is the approved second-line treatment for patients with primary biliary cholangitis (PBC). Biochemical response by POISE criteria is achieved in ∼40% of patients, according to registrative and post-marketing studies.
Aim: To derive the OCA response score (ORS) for predicting response to OCA at 12 and 24 months, according to the POISE (alkaline phosphatase(ALP)/upper limit of normal(ULN) <1.67 with a reduction of at least 15%, and a normal bilirubin) and ALP/ULN<1.67 criteria.
Materials and Methods: We used the Italian RECAPITULATE database including centers from Italian PBC Registry, the Sicilian PBC Network, the PBC Project Piemonte-Liguria-Valle D'Aosta and CLEO/AIGO PBC study group. Multivariable Cox's regressions with backward selection method were applied to obtain parsimonious predictive models, including pre-treatment variables and/or the change of ALP/ULN and total bilirubin after 6 months' therapy. Discrimination and calibration were evaluated by c-statistics and comparing observed and predicted probabilities, and internally validated with bootstrap resampling procedure.
Results: 441 PBC patients (median age 58, women 88%, cirrhosis 34%, median follow-up 24 months) with at least 6 months' observation after of OCA prescription, were included for ORS derivation. The observed 12 and 24 months' response probabilities were 38% , 47% for POISE and 58%, 67% for ALP/ULN<1.67 criteria. A score including age, pre-treatment pruritus, cirrhosis, ALP/ULN, GGT/ULN and bilirubin (ORS), and one that includes also the relative change of ALP/ULN and total bilirubin after 6 months (ORS+), showed good discrimination for response by POISE (c-statistics=0.76 and 0.84, for ORS and ORS+, respectively) and by ALP/ULN<1.67 (c-statistics=0.78 and 0.89, for ORS and ORS+, respectively). Bootstrap validation evidenced modest overfitting (slopes>0.90) and consistent discriminative performance. Mean absolute errors <0.04 were observed for prediction of POISE and ALP/ULN<1.67 response at 24 months according to ORS and ORS+.
Conclusions: The ORS accurately predicts OCA response at 12 and 24 months. This will enable to enhance allocation of second-line therapies in PBC with a personalised medicine approach.

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OC-07

Interferon gamma-induced protein 10 levels are associated with insulin resistant components in subjects with non-alcoholic fatty liver disease

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Introdution and aim: The most important determinant of the progression of non-alcoholic fatty liver disease (NAFLD) to non-alcoholic steatohepatitis (NASH) and fibrosis is insulin resistance (IR). Interferon gamma-induced protein 10 (IP-10), a proinflammatory chemokine, plays a crucial role in inflammatory diseases but its interaction with IR in the setting of NAFLD is not clear.
Methods: We analysed data from 200 patients with biopsy proven NAFLD (M/F 121/79; mean age 47±12). A subgroup of 46 non-diabetic NAFLD subjects underwent tracers studies (6,6-D2-glucose and [2H5]glycerol). Tracers enrichment was determined by GC-MS and data were used to calculate hepatic (Hep)-IR and adipose tissue (AT)-IR components. Serum IP-10 levels were assessed by Bio-Plex (BioRad Laboratories).
Results: Overall, 81/200 (40.5%) patients had F≥2 and 151/200 (75.5%) had NASH. The prevalence of type 2 diabetes was 27.5% and 47.5% of the patients were obese. IP-10 levels significantly increased across lean to overweight to obese subjects (p=0.009), showed a stepwise increase according to the stages of hepatic fibrosis (p=0.006) and were significantly higher in patients with NASH compared to those with NAFL (457pg/ml vs 383pg/ml, p=0.039). Moreover, IP-10 levels were increased in diabetic compared to non-diabetic patients (491pg/ml vs 393pg/ml, p=0.021) and showed a significant correlation with HOMA-IR (r=0.30, p=0.006). In the subgroup of non-obese, non-diabetic NAFLD patients who underwent tracers' studies, IP-10 levels showed a significant correlation with both Hep-IR and AT-IR (r=0.32, p=0.030 and r=0.33, p=0.049, respectively). At multivariate analysis, IP-10 was independently associated to the degree of hepatic fibrosis (r_p=0.3, p=0.05).
Conclusions: IP-10 may be involved in the complex pathogenesis of NAFLD. Further studies are needed to demonstrate its causality in determining liver damage.

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OC-08

Detection of hepatocellular carcinoma's microvascular invasion at the preoperative CT scan: Artificial intelligence meets radiomics

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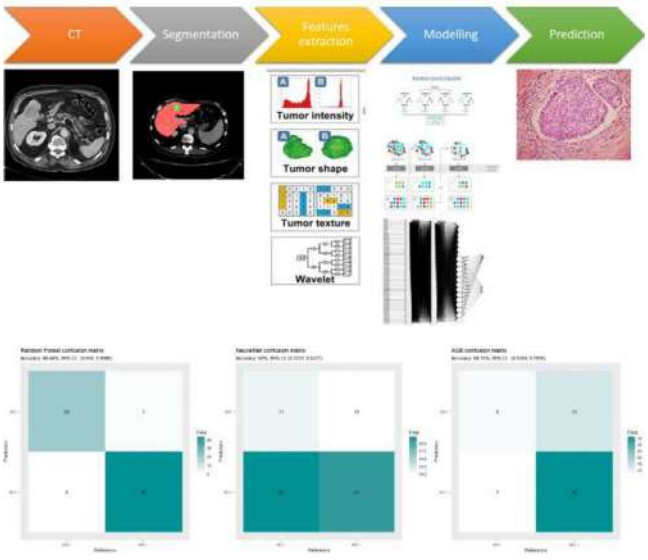
Introduction: Microvascular invasion(MVI) is the main risk factor for overall mortality and recurrence after surgery for hepatocellular carcinoma(HCC). Its diagnosis can be made only postoperatively on the histological specimen.
Aim: to train machine-learning models to predict MVI on preoperative CT scan (fig.1).
Methods: Clinical data and 3-phases CT scans were retrospectively collected among 4 Italian centres. After an initial manual segmentation, an algorithm was developed to automatically identify the liver and the tumor on CT scans. Radiomics features were automatically extracted from the tumoral, peritumoral and healthy liver areas in each phase. Principal component analysis (PCA) was performed to reduce the dimensions of the dataset. Data were divided between training (70%) and test (30%) sets. Random-Forest (RF), fully connected Artificial neural network (neuralnet) and extreme gradient boosting (XGB) models were fitted to predict MVI. Hyperparameters tuning was made to reduce the out-of-bag error.
Results: Between 2008 and 2022, 218 consecutive preoperative CT scans of patients affected by HCC and submitted to surgery were collected. At the histological specimen 33.02% patients had MVI. The Jaccard index between manual and algorithm segmentations was 90%. First and second order radiomics features were extracted, obtaining 672 variables per patient. PCA selected 58 dimensions explaining >95% of the variance. After standardization and normalization, RF, neuralnet and XGB were fitted to predict the presence of MVI. Tuning parameters were: 1) RF: n.tree=500, mtry=30; 2) Neuralnet: 2 hidden layer with 40 and 20 neurons, learning rate= 0.001, threshold for termination= 1%, activation function= sigmoid; 3) XGB: nrounds = 100, max_depth = 3, eta = 0.3. The models were then fitted in the testset to estimate prediction accuracy by confusion-matrix. RF was the best performer (Acc=98.4%, 95%CI: 0.91-0.99, Sens: 95.2%, Spec: 100%, PPV: 100% and NPV: 97.7%, fig.2).
Conclusion: RF model predicted automatically MVI with a never-before reached accuracy



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OC-09

Predictors of clinical trajectories in patients admitted for acutely decompensated cirrhosis: An external validation of the PREDICT study

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Introduction: The PREDICT study has recently shown that acutely decompensated (AD) cirrhotic patients without acute-on-chronic liver failure (ACLF) present three different clinical trajectories and mortality rates: pre-ACLF, developing ACLF within 90 days; Unstable Decompensated Cirrhosis (UDC), who were readmitted within 90-days or die without ACLF; and Stable Decompensated Cirrhosis (SDC), without ACLF or readmissions.
Aims: This study aimed to i) validate the existence of three distinct trajectories in AD patients, and ii) identify predictors for the occurrence of each trajectory.
Methods: Baseline data, 3-months ACLF and readmission incidence, and 1-year survival were analyzed in a prospective cohort of patients admitted for AD. A pre-specified multinomial multivariable model (MNM) was used to evaluate the association between baseline features and the clinical trajectories.
Results: Of the 311 patients enrolled, 169 (55%) met the criteria for SDC, 57 (18%) for UDC, and 85 (27%) for pre-ACLF. The 1-year mortality was significantly different between the three groups: pre-ACLF 65%, UDC 46% and SDC 21% ($p<0.001$). Marginal changes of the probability of pre-ACLF, SDC and UDC attributable to the

predictors are reported in Figure 1. Among clinical parameters, the presence of hepatic encephalopathy was associated to UDC (p=0.043), while the absence of ascites to SDC (p=0.017). Among lab parameters, an increase of MELD-Na (p=0.000) and C-Reactive Protein (p=0.009) and a decrease of hemoglobin (p=0.004) and albumin (p=0.008) levels were associated to pre-ACLF.
Conclusion: The present study confirms that patients with AD have 3 different clinical trajectories associated to different mortality rates. Besides severity of cirrhosis, the association with CRP supports the predominant role of systemic inflammation in ACLF pathophysiology. Moreover, low hemoglobin levels also predict ACLF within 90 days. Finally, HE is associated to the UDC trajectory highlighting the need of a better management of this complication after discharge.

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OC-10

Extension of Bulevirtide monotherapy to 72 weeks in HDV patients with compensated cirrhosis: Efficacy and safety from the italian multicenter study (HEP4Di)

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Background and aim: In phase II and III trials, Bulevirtide (BLV) significantly reduced HDV-RNA and aminotransferase (ALT) levels in patients with chronic hepatitis Delta virus (HDV) infection, however, data on efficacy and safety beyond week 48 in real-world settings are limited.
Methods: HDV patients with compensated cirrhosis treated with BLV 2 mg monotherapy up to 72 weeks were retrospectively evaluated in this multicenter Italian real-life study. Clinical and virological variables were collected at baseline, weeks 4, 8 and every 8 weeks thereafter.
Results: 93 patients were included: median age 52 years, 52% males, liver stiffness measurement (LSM) 17.4 kPa, 55% with varices, 22% with previous ascites, 53% IFN-experienced, 97% under nucleos(t)ide (NUC) treatment. Median ALT levels were 79 U/L, albumin 3.9 g/dL, platelets 70 x 10^3/mm^3, HDV RNA 5.2 Log IU/mL, CPT score A in all patients. A virological response (undetectable HDV RNA or ≥2 Log decline *vs.* baseline) was achieved by 67%, 77% and 75% of patients at weeks 24, 48 and 72, respectively, HDV RNA becoming undetectable in 10%, 16% and 38%. At the same timepoints, ALT normalization was observed in 67%, 67% and 81% of the patients while a combined response (virological + biochemical) was achieved by 45%, 56% and 63%. Besides ALT, significant on-treatment declines were also observed for AST, GGT, IgG (p<0.001 *vs.* baseline), while albumin values increased (p=0.02). Platelets, LSM and HBsAg levels remained unchanged. BLV was well tolerated, no patient discontinued treatment for adverse events, an asymptomatic increase in bile acids occurred in all patients. During BLV treatment, liver decompensation occurred in one patient, de-novo HCC in two, three underwent liver transplantation and one died for BLV-unrelated causes.
Conclusions: Extension of BLV monotherapy to 72 weeks is safe and effective in patients with HDV-related compensated cirrhosis. Virological and clinical responses increase overtime.

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OC-11

Programmed cell death 1 genetic variant and liver damage in nonalcoholic fatty liver disease

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Background and Aims: Programmed cell death 1/programmed cell death-ligand 1 (PD-1/PDL-1) axis has been reported to modulate liver inflammation and progression to hepatocellular carcinoma (HCC) in patients with nonalcoholic fatty liver disease (NAFLD). Here, we examined whether the *PDCD1* variation associates with NAFLD severity in individuals with liver biopsy.
Methods: We examined the impact of *PDCD1* gene variants on HCC, as robust severe liver disease phenotype in UK Biobank participants. The strongest genetic association with the rs13023138 G>C variation was subsequently tested for association with liver damage in 2,889 individuals who underwent liver biopsy for suspected nonalcoholic steatohepatitis (NASH). Hepatic transcriptome was examined by RNASeq in a subset of NAFLD individuals (n=121). Transcriptomic and deconvolution analyses were performed to identify biological pathways modulated by the risk allele.
Results: The rs13023138 C>G showed the most robust association with HCC in UK Biobank *(P = 5.28E-4, OR=1.32, 95% CI [1.1, 1.5])*. In the liver biopsy cohort, *rs13023138* G allele was independently associated with severe steatosis (OR 1.17, 95%C.I. 1.02-1.34; p=0.01), NASH (OR 1.22, 95%C.I. 1.09-1.37; p<0.001) and advanced fibrosis (OR 1.26, 95%C.I. 1.06-1.50; p=0.07). At deconvolution analysis, rs13023138 G>C allele was linked to higher hepatic representation of M1 macrophages, paralleled by upregulation of pathways related to inflammation and higher expression of CXCR6.
Conclusions: The *PDCD1 rs13023138* G allele was associated with HCC development in general population and with liver disease severity in patients at high risk of NASH.

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OC-12

Cholangiocarcinoma-on-chip: A 3D liver tumor platform for personalized medicine

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Intrahepatic cholangiocarcinoma (iCCA) is a deadly cancer of biliary epithelium with generally unsuccessful therapeutic options. This highlights the importance of deeper decipher iCCA mechanisms to develop new effective therapeutic strategies. Nevertheless, *in-vivo*cell interaction complexity has hindered an effective recapitulation of the *in-vitro* human milieu through 2D culture systems. In the last years, strong efforts were focused on the Organ-On-Chip (OoC) as promising models to faithfully recapitulate the *in-vivo* tumor niche.

In this study, we aimed to develop an *in-vitro* 3D microfluidic device by co-culturing three cell types involved in iCCA.

Primary iCCA cells were isolated from patients surgically resected at Humanitas Research Hospital. The microfluidic device was fabricated at Polytechnic of Milan, composed of three microfluidically interconnected channels.

iCCA microenvironment was recapitulated by co-culturing iCCA cells and cancer-associated fibroblasts (CAFs) in the central channel with an *ad hoc* medium and embedded in an optimized hydrogel, flanked by an endothelial tubule in the lateral channel. The 3D cellular organization was visualized using confocal microscopy and the significant increase in the expression of key phenotypic cell markers was assessed by *q*RT-PCR, compared to 2D culture system. Diffusion assays at small and large molecules showed the high biocompatibility of this platform and the functional integrity of the endothelial tubule. Subsequently, the mechanical and biological proprieties of the platform were evaluated overtime in culture, showing that the cross-talk established between iCCA cells and CAFs within the chip led to a deep extracellular matrix remodeling. Indeed, scanning electron microscopy (SEM) allowed to measure the dimension of the matrix pores and immunofluorescence assay revealed a significant increase in the collagen IV deposition within the hydrogel.

Our results showed that iCCA-on-chip provides a reliable 3D platform able to mimic the *in-vivo* iCCA microenvironment and may represent useful tool to investigate patient-specific therapeutic strategies.

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OC-13

Incidence and predictors of hepatocellular carcinoma in autoimmune hepatitis: A multicenter international study

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Background and Aim: Survival in patients with Autoimmune Hepatitis (AIH) is impaired mostly due to potential evolution to liver cirrhosis. While cirrhosis is a well-known precursor of Hepatocellular Carcinoma (HCC), the risk of HCC in AIH remains unclear. Aim of our research was to investigate the risk of HCC across a global AIH cohort and to identify predictive factors.
Methods: We performed a retrospective, observational, and multicentric study of data collected within the International Autoimmune Hepatitis Group (IAIHG) Retrospective Registry. All adult and pediatric patients with regular and complete follow-up concerning demographic, clinical, biochemical and treatment data were included. Outcome considered was HCC development.
Results: 1421 patients from 22 centers across Europe and Canada were included, with a median follow-up of 11.6 years. 285 (20.9%) patients were already cirrhotic at diagnosis, PBC and PSC variant syndromes were observed in 119 (8.4%) and 95 (6.7%) patients. During follow up, 24 patients developed HCC (1.7 %) with cumulative incidence of HCC of 0.6% (95% CI 0.3-1.2) at 5 years, 0.7% (95% CI 0.4-1.3) at 10 years, 2.6% (1.4-4.3) at 20 years, and 6.4% (3.0-11.6) at 30 years of follow-up. Patients developing cirrhosis during follow-up had a significantly higher incidence of HCC with a cumulative risk increasing over time from 3.1% at 5 years to 12% at 30 years from AIH diagnosis. Older age (HR 3.96, $p = 0.01$), obesity (HR 3.62, $p = 0.04$), cirrhosis (HR 3.44, $p = 0.02$), and PSC variant (HR 8.80, $p < 0.001$) at baseline resulted independent risk factors for HCC development at multivariate analysis stratified by center.
Conclusion: The incidence of HCC in AIH is low even after cirrhosis development; age more than 40 years, obesity, cirrhosis, and PSC variant syndrome at baseline represent independent risk factors for HCC development. Further studies are needed to identify predictive tools for enhanced stratification of the at-risk population to design "a la carte" surveillance strategies.

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OC-14

Role of extracellular vesicles in sarcopenia associated to chronic liver diseases

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Introduction: A loss of muscle mass and strength, referred as sarcopenia, is a condition highly prevalent in patients with chronic liver disease. Pathogenesis of sarcopenia is multifactorial and mainly results from an imbalance between protein synthesis and degradation. Mechanisms underlying sarcopenia in liver disease are still not completely understood as the mediators of the liver-muscle axis have not yet been identified.
Aim: Given the close metabolic interplay between skeletal muscle and liver and the emerging role of extracellular vesicles (EVs) in mediating intercellular communication, we evaluated whether circulating EVs in liver disease could vehicle to skeletal muscle microRNAs able to induce or contribute to sarcopenia.
Materials and Methods: Primary human myoblasts were exposed to serum EVs from healthy (H-EVs; n=9) and cirrhotic individuals (C-EVs; n=13) and analysed for their ability to differentiate and for the expression of markers of protein synthesis and degradation. Moreover, expression levels of microRNAs involved both in liver disease and in muscle development were examined in C-EVs and compared to those of H-EVs.
Results and Conclusion: We demonstrated that circulating EVs were efficiently internalized by skeletal muscle cells and that C-EVs were able to cause *in vitro* muscle atrophy, inducing a decrease in muscle differentiation, highlighted by a reduced fusion index and a downregulation of Myosin protein amount ($p<0.05$) and an increase in protein degradation, revealed by an upregulation of *Murf-1* and *Atrogin-1* mRNA expression levels ($p<0.05$), compared to H-EVs.Furthermore, we showed that C-EVs exhibited significant higher expression levels of microRNAs, such as miR-223, –133a, -29a, -128a, -21, and -199a-3p, targeting the two most important signaling pathways in muscle tissue: the TGF-β/myostatin/BMP and PI3K/AKT/mTOR pathways, regulating protein and synthesis and degradation respectively. Therefore, circulating EVs could be key players of the liver-muscle axis in sarcopenia associated to liver disease.

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OC-15

Serum procalcitonin predicts mortality independently of the presence of ACLF in patients with cirrhosis and ascites hospitalized for suspicious infection and treated with empiric antibiotic therapy

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Introduction: Patients with cirrhosis and ascites are at high risk of infections, which increase mortality and trigger acute-on-chronic liver failure (ACLF).

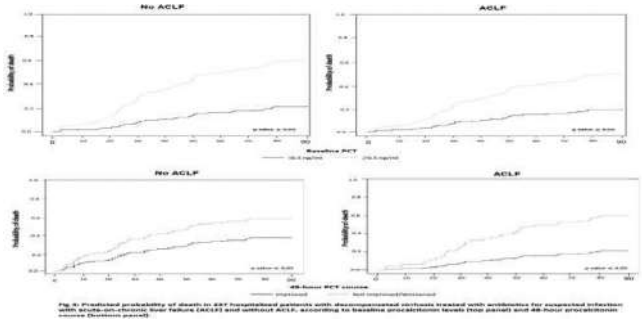
Aim: To evaluate procalcitonin (PCT) as risk factor for 28- and 90-day mortality in patients with decompensated cirrhosis with or without ACLF hospitalized for suspected infection and treated with empiric antibiotic therapy.

Materials and Methods: Two-hundred thirty-seven patients with ascites admitted at two Italian referral centers were prospectively evaluated. Risk factors for 28- and 90-day mortality were assessed by multivariate competing risks analysis, with liver transplant (LT) as competing event.

Results: Infection was confirmed in 83% of patients; 53% had ACLF; 88 (37%) died and 52 (22%) underwent LT within 90 days from admission. Creatinine [Hazard Ratio (HR)] 1.18, 95% Confidence Interval [95%CI] 1.01-1.38, p=0.039), grade III-IV hepatic encephalopathy (HR 2.32, 95%CI 1.15-4.65, p<0.018), septic shock (HR 2.77, 95%CI 1.39-5.53, p=0.004), baseline PCT>0.5 ng/mL (HR 4.10, 95%CI 1.24-13.38, p=0.021) or 48-hour PCT unfavorable course (HR 3.08, 95%CI 1.49-6.42, p=0.003) were risk factors for 28-day mortality by multivariate analysis (AUC 0.84). The same risk factors plus age (HR 1.03, 95%CI 1.01-1.05, p=0.001) were predictive for 90-day mortality (AUC 0.78). When ACLF was included in the multivariate model, instead of the single covariates, both ACLF and PCT (baseline levels and 48-hour course) were independently associated with 28- and 90-day mortality (AUC 0.83 and 0.72 respectively). When either baseline or 48-hour course PCT were combined with ACLF grade the prediction of 28- and 90- day mortality significantly increased.

Conclusions: PCT both at baseline and 48-hour after starting empiric antibiotic treatment significantly predicts 28- and 90-day mortality in patients with decompensated cirrhosis presenting with or without ACLF at admission.

Keywords: Decompensated cirrhosis, infections, empiric antibiotic treatment, ACLF, procalcitonin



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OC-16

Long-term outcomes of patients with chronic HBe-negative infection: Differences and transition between inactive carriers and low viremic carriers

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Background: Chronic HBeAg-negative infection with low viral load levels (< 2000 IU/mL), previously named "inactive carrier" (IC), usually has no indication for starting antiviral treatment, but patients with HBeAg-negative chronic infection may be characterize by the presence of viral load between 2,000-20,000 IU/mL, called "Low Viremic Carriers" (LVC), which belong to a "grey area". IC have a survival comparable to that of the non-infected general population. LWC have shown low risk of progression to cirrhosis or HCC.

Materials and Methods: The aim of our study was to evaluate the natural history of a cohort of HBeAg-negative chronic infection with viral load <20,000 IU /mL followed up in our tertiary center from 1999 to 2022. Decompensation, HCC development, loss of HBsAg with or without the appearance of anti-HBs and change of virological status (defined as an increase/decrease in HBV-DNA levels compared to the cut-off of 2,000 IU/ml in at least two consecutive evaluations at 12 and 24 months) were evaluated.

Results: We identified 156 patients with HBeAg-negative chronic infection, labeled as chronic carriers. Of them, we identified 106 patients as IC and 40 patients as LCV, showing no statistically significant difference. The long-term follow up (mean 95 ± 162) confirm that the identification of IC status has relevant prognostic implications since these patients are more likely to lose HBsAg (12.3% in IC vs 2.5% in LVC) low incidence (5.6%) of transition from IC to LVC status. Furthermore, 40% of LVC patients transited to IC status and the residual 60% of LVC did not show any negative clinical event.

Conclusions: Our data confirm that all HBeAg-negative patients with serum HBV-DNA < 20,000 IU/mL has a benign natural course even without antiviral therapy. HBsAg loss is unlikely in the group of patients with HBV-DNA levels between 2,000 IU/mL and 20,000 IU/mL.

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OC-17

Highlighting sex dimorphism in the molecular mechanisms responsible for sarcopenia in a murine model of liver fibrosis

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Introduction: Sarcopenia is present in about 25-70% of patients with chronic liver diseases (CLDs), with higher rates in males. Understanding the mechanisms of CLD-related sarcopenia is mandatory for its management.
Aim: We investigated the mechanism of sarcopenia in a murine model of liver fibrosis, focusing on sex-related differences, as well as the mechanisms involved in its resolution during liver regeneration.
Materials and Methods: Liver fibrosis was induced in female and male mice by injecting increasing doses of carbon tetrachloride (CCl_4, from 0.17 to 0.72 mL/Kg*bw) for 12 weeks. Muscle function and strength were evaluated by the grid hanging and the grip strength test. Mice were sacrificed after 6 and 12 weeks of CCl_4-treatment, and after the 8-week washout period to study regeneration. H&E staining was used to calculate the cross-sectional area (CSA) of muscle quadriceps fibers. Muscle pAkt and p4EBP1 protein expression was assessed by western blot, mRNA expression of Musa, Atrogin-1, Murf-1, and Bnip3 by qRT-PCR.
Results: Liver fibrosis was associated to a progressive loss of muscle strength in both sexes as demonstrated by the statistically significant reduction of CSA. pAkt and p4EBP1 levels, promoters of muscle protein synthesis, were not affected by fibrosis development. However, autophagy-related genes (Musa, Atrogin-1, Murf-1, and Bnip3), responsible for the breakdown of muscle proteins, were significantly upregulated in fibrotic mice with respect to controls, especially in females ($p<0.05$). After the washout period, males recovered muscle strength and CSA, although liver fibrosis was still present, whereas females were characterized by an amelioration of liver histology, not accompanied by a recovery of the muscle function.
Conclusion: Sarcopenia is differently affected by CLD in males and females and is not correlated to the degree of liver fibrosis. Muscle atrophy, due to an increase of protein degradation, is more evident and persistent in females than in males.

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OC-18

PNPLA3, MBOAT7 and TM6SF2 modify mitochondrial dynamics in NAFLD patients: Dissecting the role of cell-free circulating mtDNA and copy number

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Background: Mitochondrial (mt) dysfunction is a hallmark of progressive NAFLD. MtDNA copy number (mtDNA-CN) and cell-free circulating mtDNA (ccf-mtDNA), which reflect mt-mass and mt-dysfunction, respectively, are gaining attention for NAFLD non-invasive assessment. We demonstrated that *PNPLA3*, *MBOAT7* and *TM6SF2* deficiency in HepG2 cells increased mt-mass, mtDNA-CN and ccf-mtDNA.
Aims: To assess the genetic contribution on mt-dynamics, mtDNA-CN and ccf-mtDNA in 1) primary mouse hepatocytes silenced for *PNPLA3*/*MBOAT7*/*TM6SF2* genes; 2) Discovery (n=28) and Validation (n=773) cohorts, including biopsied NAFLD patients, stratified according to number of risk variants (NRV=3).
Methods: Mt-morphology was assessed by TEM. mtDNA-CN was measured in the entire Validation cohort (n=773), while ccf-mtDNA in a subgroup (n=300) with available serum samples. mtDNA-CN and mt-related genes were evaluated in liver biopsies.
Results: Primary mouse hepatocytes challenged with fat overload or *PNPLA3*/*TM6SF2*/*MBOAT7* co-silencing lowered mt-fusion paralleled by higher mt-fission and ccf-mtDNA release, suggesting that lipid accumulation and genetics may independently unbalance mt-dynamics. In the Discovery cohort, NRV=3 patients showed the highest mtDNA-CN compared to those with 1-2 or no variants. At TEM, NRV=3 carriers increased mt-mass and presented an elevated pattern of mt-morphological alterations (swollen shapes, double membranes rupture). In the Validation cohort, mtDNA-CN associated with the NAFLD histological spectrum and NRV=3 at multivariate analyses, supporting that both NAFLD severity and genetics may modulate mt-dynamics. In liver biopsies, mtDNA-CN was higher in NRV=3 patients together with reduction of mt-fusion and activation of mt-fission, resembling what observed in hepatocytes. Ccf-mtDNA was augmented in NRV=3 patients with low-moderate/severe NAFLD, thereby sustaining that this effect was amenable to the 3 at-risk polymorphisms. ROC curves showed that mtDNA-CN discriminated NAFLD subjects *vs* controls (AUC: 0.71), while ccf-mtDNA was highly predictive of NAFLD-HCC vs NALFD (AUC: 0.79).
Conclusions: mtDNA-CN and ccf-mtDNA may have pathological and predictive significance in NAFLD patients at high-risk, especially in those genetically-predisposed.

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OC-19

Validation of a targeted gene panel sequencing for the diagnosis of hereditary chronic liver diseases

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Introduction: The cause of chronic liver diseases (CLD) remains undiagnosed in up to 30% of adult patients. Whole-Exome Sequencing (WES) could improve the diagnostic rate of genetic conditions, but it is not yet widely clinically available, due to the costs and the difficulties in results interpretation. Targeted panel sequencing (TS) represents an alternative more focused diagnostic approach.
Aims: To validate a customized TS for hereditary CLD diagnosis.
Materials and Methods: We designed a customized panel including 82 CLD-associated genes (iron overload, lipid metabolism, cholestatic diseases, storage diseases, specific hereditary CLD). DNA samples from 19 unrelated adult patients with undiagnosed CLD were analyzed with both TS (HaloPlex) and WES (SureSelect Human All Exon kit v5) and the performances were compared.
Results: The mean depth of the target regions obtained with TS was higher than WES (300X vs 102X). Moreover, TS yielded higher average coverage per gene and lower fraction of exons with low coverage. Overall, 374 unique variants were identified across all samples, 100 of which were "Pathogenic" or "Likely Pathogenic" variants with a high functional impact (HFI). The majority of HFI variants (80%) were detected by both methods; 14 were uniquely identified by TS and 6 by WES. Discrepancies in variant calling were mainly due to variability in read depth and insufficient coverage in the corresponding target regions. All variants were confirmed by Sanger sequencing except two uniquely detected by TS. Detection rate of TS was 94% while that of WES was 88%.
Conclusion: TS was confirmed to be a valid first-tier genetic test, less laborious and with a detection rate comparable to or higher than WES, useful to support clinical and instrumental evaluation for hereditary CLD diagnosis.

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OC-20

Noninvasive assessment of liver disease severity in patients with nonalcoholic fatty liver disease and type 2 diabetes

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Background: The aim of this study was to evaluate the diagnostic accuracy of simple non-invasive tests (NITs) in NAFLD patients with type 2 diabetes(T2D).
Methods: This was an individual patient data meta-analysis of 1780 patients with biopsy-proven NAFLD and T2D. The index tests of interest were FIB-4, NAFLD Fibrosis Score (NFS), APRI, liver stiffness measurement (LSM) by vibration-controlled transient elastography (VCTE) and AGILE 3+. The target conditions were advanced fibrosis, nonalcoholic steatohepatitis (NASH) and fibrotic NASH(NASH plus F2-F4 fibrosis). The diagnostic performance of NITs individually or in sequential combination was assessed by area under receiver operating characteristic curve(AUROC) and by decision curve analysis(DCA). Comparison with 2278 NAFLD patients without T2D was also made.

Results: In NAFLD with T2D LSM and AGILE 3+ outperformed both NFS and FIB-4 for advanced fibrosis(AUROC:LSM 0.82,AGILE 3+ 0.82,NFS 0.72,FIB-4 0.75,APRI 0.68;p<0.001 of LSM-based vs simple serum tests), with an uncertainty area of 12%-20%.The combination of serum-based with LSM-based tests for advanced fibrosis led to a reduction of 40% to 60% in necessary LSM tests. DCA showed that all scores had modest net benefit for ruling-out advanced fibrosis at the risk threshold of 5%-10% of missing advanced fibrosis. LSM and AGILE 3+ outperformed both NFS and FIB-4 for fibrotic NASH(AUROC LSM 0.79,AGILE 3+ 0.77,NFS 0.71,FIB-4 0.71;p<0.001 of LSM-based vs simple serum tests). All noninvasive scores were sub-optimal for diagnosing NASH. In comparison to NAFLD patients without T2D, the overall accuracy of NITs for advanced fibrosis was similar even if with a lower net benefit mainly related to lower specificity and higher uncertainty area, while that for fibrotic NASH was lower.
Conclusions: LSM and AGILE 3+ individually or in low availability setting in sequential combination after FIB-4 or NFS have a similar good diagnostic accuracy for advanced fibrosis and an acceptable diagnostic accuracy for fibrotic NASH in NAFLD patients with T2D.

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OC-21

A functional interaction between hepatic estrogen receptor-α and PNPLA3 p.I148M inherited variant drives fatty liver disease susceptibility in women

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Introduction: Fatty liver disease (FLD) related to metabolic dysfunction and excessive alcohol affects almost one third of the global population and is a leading cause of liver related mortality. The *PNPLA3* p.I148M variant accounts for the largest fraction of FLD heritability. Although women are protected during the reproductive age, especially after menopause some are susceptible to FLD, but this sexual dimorphism is neglected in clinical studies. The aim was to examine the *PNPLA3* p.I148M*female sex interaction in FLD development, and to investigate the underlying mechanism.
Methods: The female sex**PNPLA3* p.I148M interaction on FLD was tested in the Liver Biopsy (n=1861), severe FLD case-control (n=4374), Liver-Bible-2021 (n=817) and UK Biobank (n=347,127) cohorts. PNPLA3 expression was determined in transcriptomic cohort (n=107). HepG2 cells were used for estrogen receptor (ER) modulation and fatty acid treatment, and to generate PNPLA3-ER element (ERE) knock-out clones.
Results: In all cohorts we observed an interaction between female sex and *PNPLA3* p.I148M, but not other FLD genetic risk variants, in determining FLD development and progression, with a larger effect in postmenopausal women (p<0.05). Higher hepatic PNPLA3 mRNA expression was independently associated with the p.I148M variant and female sex (p=0.002 and p=0.007, respectively). At chromatin immunoprecipitation, ERα agonists induced the ER binding to a specific ERE at a *PNPLA3* enhancer site, enhancing its transcriptional activity at luciferase assays. PNPLA3 mRNA and protein expression was upregulated via direct ERα agonists, leading to intracellular fat accumulation in p.I148M homozygous HepG2 cells, but not in wild-type hepatocytes. Genetic deletion of the PNPLA3-ERE by Crispr/Cas9 editing in HepG2 abolished the ERα-induced PNPLA3 and intracellular lipid accumulation in response to fatty acids.
Conclusions: We identified a driver of FLD acceleration occurring in a subset of women with metabolic dysfunction at menopause, highlighting at the same time a therapeutic target of particular relevance.

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OC-22

A simple characterization of dynamic changes in circulating CD8+PD1+ lymphocytes early predicts response to atezolizumab-bevacizumab in hepatocellular carcinoma

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Atezolizumab+bevacizumab improves survival of patients with advanced Hepatocarcinoma (HCC) in comparison to Sorafenib. No biomarker predicts responders from non-responders to atezolizumab+bevacizumab or patients who benefit from this combination instead of TKIs. To identify early on treatment predictive biomarkers, we investigated whether baseline and early on treatment variation of CD8+, PD1+, PD-L1+, CD8+PD1+, CD8+PDL1+ peripheral lymphocytes might offer a non-invasive, cheap and feasible assay.
Methods A prospective cohort of 31 patients treated with atezolizumab+bevacizumab and a control prospective cohort of 15 patients treated with sorafenib or lenvatinib were subjected to repeated blood tests, at baseline and during the course of treatments. At first imaging re-evaluation, 11 patients receiving atezolizumab+bevacizumab showed objective response, 13 stable disease, accounting for the responder group, while 7 patients displayed tumor progression, corresponding to primary non-response. Baseline and early on treatment variation of CD8+, PD1+, PD-L1+, CD8+PD1+, CD8+PDL1+ peripheral lymphocytes were tested by cytofluorimetric analysis and compared in responders and non-responders.

Results Baseline CD8+ and CD8+PDL1+ peripheral lymphocytes were lower in responders versus non-responders (mean±SD CD8+: 68±30 vs 95±5; T-test, p<0.0001; mean ±SD CD8+PD-L1+: 77± 9.4 vs 82±4.6; T-test: p=0.004 respectively). Dynamic changes in CD8+PD1+ lymphocytes assessed at 3-weeks, before the second drug infusion, were the most informative test: 22 of 24 responders displayed a rise of CD8+PD1+ peripheral lymphocytes with a positive mean fold change of 4.63 (±5.5 SD). Conversely, 6 of 7 non-responders displayed a negative mean fold change of 0.89 (±0.84 SD) of CD8+PD1+ lymphocytes. These changes were restricted to patients treated with atezolizumab+bevacizumab, while they were not documented in TKI patients, irrespective of the response.
Conclusion. Early changes in circulating PD1+CD8+ lymphocytes predict the type of response to atezolizumab+bevacizumab and encourage evaluating this minimally invasive, cheap, easy and repeatable test in a larger cohort of patients to confirm its informativeness in this setting.

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OC-23

Fatty Acid Synthase expression promotes the malignant features of cholangiocarcinoma cells and predicts shorter survival in patients

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Background and Aims: Cancer cells are exposed to a metabolically challenging environment with scarce availability of nutrients, and alterations in lipid metabolism may affect the cellular response to drugs. We hypothesize that fatty acids (FA) modulate the biology of cholangiocarcinoma (CCA) cells and the development of stemness features.
Method: CCA cells (HuCCT-1 or CCLP1) were treated with monounsaturated FAs (132μM oleic or 100μM palmitoleic acid). 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 34 patients with CCA subgrouped based on fatty acid synthase (FASN) expression. Desaturation index and triglyceride de novo synthesis were performed by lipidomic analysis. NSG mice were injected with CCLP1 spheres and treated with the FASN inhibitor orlistat (240mg/Kg). Tumor volume was measured with Vevo LAZR-X imaging station. RTPCR array on tumor masses was performed using the QuantiNova LNA PCR Panel.
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 made CCA cells less sensitive to the toxic effects of chemotherapeutic agents, 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 as well as the percentage of desaturated TGs. FASN inhibition by orlistat decreased cell proliferation and CSC or EMT markers. In a xenograft model of CCA, tumor volume was significantly lower in mice treated with orlistat. Accordingly, expression of genes involved in cell proliferation was downregulated while the one of tumor suppressor genes increased. In a series of CCA patients, the expression of FASN correlated with OS.
Conclusion: FA promote malignant features of CCA and increase CSC markers. FASN expression levels correlate with survival in patients with CCA and promote CCA growth in mice. Lipid metabolism could be a new target to block CCA progression.

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OC-24

Patient-derived liver organoids as an in vitro model to study new personalized therapies targeting VDAC1 in intrahepatic cholangiocarcinoma

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Introduction and Aim: Intrahepatic cholangiocarcinoma (iCCA) is characterized by a very poor outcome, and reliable biomarkers as well as new therapeutic strategies are urgently needed. As a main actor in the regulation of mitochondria-mediated cell death and survival signaling pathways, Voltage Dependence Anion Selective Channel isoform 1 (VDAC1) became an attractive pharmacologic target. Many molecules have been conceived, however, due to promiscuity and side effects, none of them have been extensively used to treat patients. The aim of this study was to test a new class of small molecules targeting VDAC1 to induce activation of the apoptotic pathway in iCCA patient-derived liver cells and organoids.
Methods: To generate organoids, we minced tumor and paired non-tumor biopsies and shortly digested in small cell clusters that are seeded into Matrigel. After characterization using immunofluorescence and qPCR techniques, we treated primary cell cultures and organoids with different concentrations of small molecules targeting VDAC1, monitoring cell viability and ROS production, to verify the in vitro effects and the efficiency of these compounds on cells.
Results: We developed and established a biobank of human iCCA-derived organoids, evaluating the morphological characteristics and assessing a mathematical tool to model tumor growth. In addition, we analysed the presence of typical CCA markers (EpCAM, CK19, CK7, E-Cadherin, Ki67). We also investigated VDAC1 expression underlying higher levels in iCCA cells in comparison with non-tumor cells (p<0.005). We subsequently examined the efficiency of new small molecules targeting VDAC1, at different time points and concentrations, both in patient-derived cell cultures and organoids. In particular, we showed a significant decrease in viability in tumor cells only and a modulation in ROS production.
Conclusion: We developed and characterized a well-defined iCCA in vitro model that allowed us to investigate the effect of small molecules targeting VDAC1 as a new personalized therapy.

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OC-25

CAR-OLT score predicts cardiac contraindications to liver transplant and 1-year cardiovascular complications after transplant

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Background: Accurate pre-Liver Transplant(LT) cardiac risk estimation is paramount to guide graft allocation and to improve post-LT outcome. CAR-OLT-score predicts major 1-year post-LT cardiovascular complications(CVD-Com), but external validation is lacking. We aimed to test the performance of the score in identifying cardiac contraindication(Ca-Con) to LT-listing and to validate CAR-OLT-score to predict major 1-year CVD-Com post-LT.
Patients and Methods: We consecutive enrolled all adult cirrhotics who underwent first pre-LT evaluation in Rome-Gemelli-Center(RO-cohort, N=342, from 2015 to 2019) and Turin-Center(TU-cohort, N=302, from 2015 to 2017). The main outcome measures were Ca-Con to listing(after center-specific cardiology work-up) and major 1-year CVD-Com post-transplant(death/hospitalization for CVD event). Discriminative performance of CAR-OLT-score was evaluated by area-under-the-ROC-curve(AUROC) method.
Results: Among 644 pre-LT cirrhotics, 23(3.6%) received a Ca-Con to listing (52.2% because of coronary artery disease, CAD). CAD, heart failure and atrial fibrillation were independent predictors of Ca-Con to listing. Among 431 first-LT recipients, 38(8.8%) patients experienced 1-year major CVD-Com (39.5% atrial-fibrillation, 23.7% heart-failure, 21% myocardial infarction). Diabetes, pulmonary hypertension, non-active workers were independent predictors of 1-year major CVD-Com.

RO-cohort had higher prevalence of hypertensive, obese, diabetic, alcoholic patients and higher burden of CAD, atrial-fibrillation, heart-failure, peripheral vasculopathy compared with TU-cohort. CAR-OLT-score predicts Ca-Con to listing in RO-cohort (AUROC 0.806) and TU-cohort (AUROC 0.978) and 1-year major CVD-Com in RO-cohort (AUROC 0.746) and TU-cohort (AUROC 0.640).

193(29.9%) candidates had CAR-OLT-score ≤23. This cut-off had 99% NPV for Ca-Con to listing and 95% NPV for 1-year major CVD-Com post-LT. Candidates with CAR-OLT-score ≤23 underwent 18 cardiac-exercise-stress-test, 89 myocardial-perfusion-imaging, 24 dobutamine-stress-echocardiography, 10 coronary-computed-tomography, 17 coronary-angiography pre-listing, with estimated costs of 68.090€.
Conclusion: CAR-OLT-score ≤23 identified candidates who can be safely listed without provocative cardiac tests, allowing time and cost savings and we validated CAR-OLT-score as predictor of major 1-year CVD-Com in an Italian cohort of LT recipients.

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OC-26

Validation of elastography criteria and cACLD Risk Model for diagnosis of compensated Advanced Chronic Liver Disease (cACLD) in NAFLD patients

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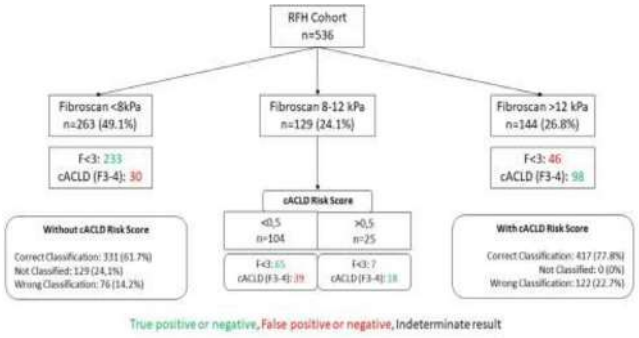
Introduction: Fibroscan is a well-established NIT for the diagnosis of advanced fibrosis (F>2) in patients with NAFLD, recently defined as compensated advanced chronic liver disease (cACLD). EASL Guidelines proposed 8 and 12 kPa, respectively, as rule-out and rule-in cut-offs for cACLD. Patients with Fibroscan measurement between 8 and 12 fall in a grey zone where further investigations are recommended. We recently proposed the cACLD Risk Score to further stratify this population.
Aim: The main aim of this study was to test the diagnostic performance of the main NITs in a two European cohorts of patients with histological diagnosis of NAFLD. Secondly, we assessed the performance of the cACLD risk score to further stratify patients in the Fibroscan's grey zone.
Materials and Methods: This is a retrospective observational study. We enrolled consecutive patients with histological diagnosis of NAFLD/NASH from January 2014 to December 2021 at two tertiary liver units in UK (the Royal Free Hospital, London - RFH) and Italy (Fondazione Universitaria Policlinico A. Gemelli IRCCS, Rome – FPG). We excluded patients who did not perform at least one of these NITs at time of biopsy (± 6 months): FIB4, NAFLD Fibrosis score (NFS), Fibroscan, APRI, AGILE3+, cACLD Risk Score. We performed a ROC analysis to explore the diagnostic performance of NITs for cACLD (F>2). Secondly, in patients with intermediate Fibroscan results (between 8-12 kPa), we tested the diagnostic performance of cACLD Risk Score.
Results: We included 536 patients;201 were female, median age was 53 years, and 44% had diabetes.

Fibroscan and AGILE3+ score had the best diagnostic performances for cACLD with an AUROC of 0.81 and 0.83 respectively. (Fig. 1) EASL criteria showed a high sensitivity and high specificity for 8 kPa and 12 kPa cutoffs, respectively (Sens 84.3%; Spec 86.6%), wrong classification of 14.2% and 129 patients (24.1%) in the grey zone (between 8 and 12 kPa). Diagnostic performance of cACLD Risk Score in Fibroscan's grey zone was suboptimal (AUROC: 0.682).

The use of Fibroscan+cACLD Risk Score vs Fibroscan alone showed a better overall accuracy (77.8% vs 61.7%) and a slight worsening of overall wrong classification rate (22.7% vs 14.2%) mainly due to a higher number of false negative than false positive. Among patients with intermediate Fibroscan (8-12 kPa), cACLD risk score correctly classify 64.4% of patients with a PPV of 72.0% and NPV of 62.5%.
Conclusions: Our results suggest that cACLD Risk Score should be used in patients with indeterminate Fibroscan results in order to

further stratify their risk of cACLD. The use of cACLD Risk Score improve the performance in identifying patients with cACLD (high PPV) although its false negative rate could lead to missed diagnosis (suboptimal NPV). Patients with intermediate fibroscan and low cACLD risk score should be still considered for further investigation (liver biopsy).



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OC-27

Risk factors for viral reactivation in patients with overt or occult Hepatitis B Virus infection receiving immunosuppressive treatments: A systematic review and meta-analysis with decision curve analysis

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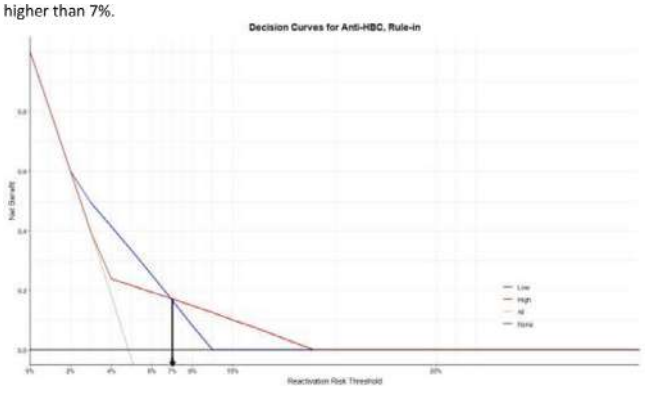
Introduction: Patients with Hepatitis B virus (HBV) infection receiving immunosuppressive treatments are at risk of HBV reactivation (rHBV).
Aims: We performed a systematic review with meta-analysis to estimate the risk of rHBV among patients naïve to antiviral prophylaxis and to identify factors associated with rHBV.
Methods: Studies of immunosuppressive treatments in HBV patients were identified through literature search using PubMed, MEDLINE, and EMBASE until October 2022. Pooled estimates were obtained using random-effects model. Subgroup analyses were performed according to viral status, drug class and underlying disease. Decision curve analysis(DCA) was used to identify the risk threshold associated with the best net benefit of administering antiviral prophylaxis in HBsAg negative anti-HBc positive patients.
Results: Seventy-nine studies (48 retrospective and 31 prospective) were selected, including 9946 patients (1108 HBsAg positive, 8203 anti-HBc positive and 635 isolated anti-HBs positive). Pooled rHBV rate was 6%(95% CI 5-8%; I^2 79%; P<0.001) with a rate of 23%(95% CI 16-31%), 4.6%(95% CI, 3.4-6.1%) and 2.9%(95% CI 1.5-10%) in HBsAg positive, anti-HBc positive and isolated anti-HBs positive patients, respectively.

In HBsAg positive patients, the risk for rHBV ranged from 22%(95%CI 11-39%) in patients with autoimmune disease receiving immunosuppressants to 30% (95%CI 5-79%) in patients with cancer receiving chemotherapy.

In anti-HBc positive patients with cancer, chemotherapy, targeted-therapy and monoclonal antibodies were associated with risk of rHBV of 9%(95%CI 5-15%), 7%(95% CI 1-43%) and 5%(95%CI 2-10%), respectively; in anti-HBc positive with autoimmune diseases, the risk of rHBV was 3%(95% CI 2-4%), 4%(95% CI 2-8%) and 3%(95%CI 1-13%) for anti-TNFα, other monoclonal antibodies and immunosuppressants, respectively. DCA showed that the risk threshold of rHBV associated with the best net benefit of administering antiviral prophylaxis in anti-HBc positive patients was 7%.
Conclusions: The risk of rHBV is highly heterogeneous according to viral status, underlying diseases and drug class. In anti-HBcore positive patients, antiviral prophylaxis should be considered when the risk of rHBV is higher than 7%.

higher than 7%.



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OC-28

Lack of substantial improvements in the landscape of alcohol-related hepatocellular carcinoma in the last 15 years: The need to improve cancer prevention and surveillance

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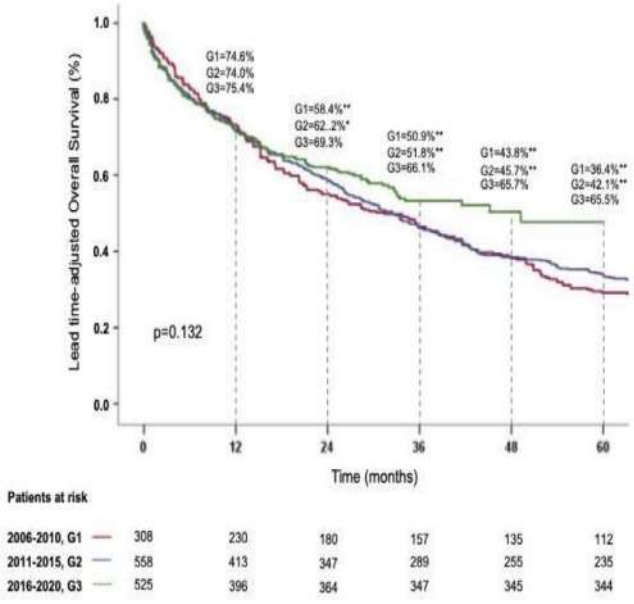
Introduction: Alcohol abuse and metabolic disorders are leading causes of hepatocellular carcinoma (HCC) worldwide. Alcoholic aetiology associates with a worse prognosis compared to hepatitis B and C infections, due to a lower percentage of HCCs diagnosed under regular surveillance and a higher comorbidity burden in alcoholic patients.
Aim: This study aimed at describing the evolving clinical scenario of alcohol-related HCC over a 15-year period (2006-2020) in Italy.
Material and Methods: Data of the Italian Liver Cancer (ITA.LI.CA) registry were used: 1391 alcoholic patients were allocated to 3 groups based on the year of cancer diagnosis (2006-2010; 2011-2015; 2016-2020) and patient characteristics, HCC treatment and overall survival were compared among groups. Survival predictors were also investigated.
Results: Around 80% of alcoholic patients were classified as metabolic dysfunction-associated fatty liver disease (MAFLD) cases. Throughout the quinquennia, <50% of HCCs were detected by surveillance programs. The tumour burden at diagnosis slightly decreased but not enough to change the distribution of ITA.LI.CA cancer stages. The use of intra-arterial and targeting systemic therapies increased across quinquennia. A modest improvement of survival was observed in the last quinquennia, particularly after 24 months of patient observation. Cancer stage, HCC treatment and presence of oesophageal varices were independent predictors of survival.
Conclusion: In the last 15 years, minor improvements have been obtained in the outcome of alcohol-related HCC, mainly because of a persistent underuse of surveillance programs and the consequent steadily low amenability to curative treatments. Oesophageal varices are an independent grim prognosticator and therefore this variable should be included in prognostic systems. MAFLD is a widespread condition in alcohol abusers, but its presence did not achieve a pivotal prognostic role once HCC has developed.



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OC-29

Prospective evaluation of screening strategies for NAFLD in people with type-2 diabetes mellitus in the community

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Background: We investigated the prevalence of significant and advanced non-alcoholic fatty liver disease (NAFLD) in patients with type 2 diabetes mellitus(T2DM) in primary care.As screening and risk-stratification pathways are not established in this population

we evaluated the diagnostic performance and the cost-utility of different screening strategies for NAFLD in the diabetic community.
Methods: Consecutive T2DM patients underwent screening for liver diseases, including transient elastography (TE).Binary logistic was used to predict factors associated with significant fibrosis.We used independent predictors of significant and advanced fibrosis to generate a predictive score for this population(BIMAST; based on AST and BMI)and validated it internally and externally.Six screening strategies were compared against standard of care: BIMAST score, ultrasound plus abnormal liver function tests, FIB-4, NAFLD fibrosis score, ELF and TE.A Markov model was built using four health states based on fibrosis status.We generated the cost per quality-adjusted life year(QALY)gained and calculated the incremental cost-effectiveness ratio(ICER)in the base-case analysis conducted over a lifetime horizon.

Results: Among 300 patients enrolled (287 included), 64%(186) had NAFLD and 10% (28) other causes of liver disease.Patients with significant fibrosis, advanced fibrosis, and cirrhosis due to NAFLD accounted for 17% (50/287), 11% (31/287), and 3% (8/287), respectively.BIMAST score validation showed an excellent diagnostic performance in primary care reducing false negatives from 54% (ELF) and 38% (FIB-4) to 10% (Figure 1).In the cost-utility analysis, ICER was £2,337.92/QALY for BIMAST and £2,480/QALY for TE (Table 1).When transition probabilities, utilities, screening effect, and cost inputs were varied in sensitivity analysis, we found a >99% probability of NAFLD screening tests being cost-effective compared to standard of care in all evaluated scenarios.
Conclusion: Traditional screening strategies, including FIB-4 and ELF, underestimate the presence of significant liver disease in diabetics in the community.Screening for NAFLD in diabetic patients in primary care is cost-effective and should become part of the holistic assessment.

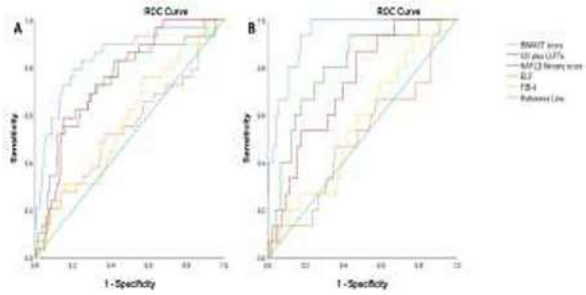

Figure 1. BIMAST score vs conventional screening methods for predicting significant and advanced fibrosis in the diabetic primary care population (whole study population). The figure illustrates the receiver operating characteristic curve of the BIMAST score vs conventional methods for predicting LSM ≥ 8.1 kPa (Figure 1A) and for predicting LSM ≥ 12.1 kPa (Figure 1B) in the whole study population.
Abbreviations: US: ultrasound; LFTs: liver function tests.

Screening strategy 1: US + LFTs	Screening	Standard of care
Discounted life expectancy, entire cohort (years)	3,751.88	3,594.85
QALYs gained, entire cohort (years)	138.19	-
Increase in correct diagnoses compared to baseline screening (%)	10.73	-
Lifetime discounted per person cost (£)	13,542.93	12,295.53
Incremental cost per person (£)	0.0008	-
Incremental cost-effectiveness ratio (£/QALY)	**2,337.92**	-
Screening strategy 2: FIB-4		
Discounted life expectancy, entire cohort (years)	3,747.62	3,594.85
QALYs gained, entire cohort (years)	134.07	-
Increase in correct diagnoses compared to baseline screening (%)	8.29	-
Lifetime discounted per person cost (£)	13,361.87	12,295.53
Incremental cost per person (£)	0.0009	-
Incremental cost-effectiveness ratio (£/QALY)	**2,059.98**	-
Screening strategy 3: NAFLD fibrosis score		
Discounted life expectancy, entire cohort (years)	3,734.50	3,594.85
QALYs gained, entire cohort (years)	121.25	-
Increase in correct diagnoses compared to baseline screening (%)	-2.32	-
Lifetime discounted per person cost (£)	13,275.08	12,295.53
Incremental cost per person (£)	0.0010	-
Incremental cost-effectiveness ratio (£/QALY)	**2,092.47**	-
Screening strategy 4: BIMAST score		
Discounted life expectancy, entire cohort (years)	3,754.88	3,594.85
QALYs gained, entire cohort (years)	141.01	-
Increase in correct diagnoses compared to baseline screening (%)	10.76	-
Lifetime discounted per person cost (£)	13,366.51	12,295.53
Incremental cost per person (£)	0.0009	-
Incremental cost-effectiveness ratio (£/QALY	**1,967.11**	-
Screening strategy 5: ELF test		
Discounted life expectancy, entire cohort (years)	3[illegible]	3[illegible]
QALYs gained, entire cohort (years)	1[illegible]	--
Increase in correct diagnoses compared to baseline screening (%)	8[illegible]	--
Lifetime discounted per person cost (£)	13[illegible]	12[illegible]
Incremental cost per person (£)	0[illegible]	--
Incremental cost-effectiveness ratio (£/QALY)	**2[illegible]**	--
Screening strategy 6: Transient elastography		
Discounted life expectancy, entire cohort (years)	3,762.89	3,594.85
QALYs gained, entire cohort (years)	148.73	-
Increase in correct diagnoses compared to baseline screening (%)	15.05	-
Lifetime discounted per person cost (£)	13,717.67	12,295.53
Incremental cost per person (£)	0.0007	-
Incremental cost-effectiveness ratio (£/QALY)	**2,476.57**	-

Table 1. Base-case cost-effectiveness analysis of NAFLD screening strategies versus standard of care (baseline screening).
Abbreviations: US: ultrasound; LFTs: liver function tests; ELF test: Enhanced liver fibrosis test.

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T-01

Long-term results of ab-initio introduction of everolimus after liver transplantation

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Introduction: Ab-initio introduction of Everolimus in liver transplantation immunosuppression regimens allows weaning of Calcineurin Inhibitors (CNI) and Mycophenolate levels consequently reducing the common complications associated to their use.
Aim: The primary aim of our study was the analysis of graft and recipient survival at the 5- and 10-year follow-up timepoints. The secondary aim was to assess the acute and chronic rejection incidence, renal function, and incidence of complications in our cohort.
Materials and Methods Results: Observational retrospective monocentric study analyzing all patients undergoing liver transplantation between September 2009 and March 2020, with a minimum follow-up length of 3 months, in whom Everolimus was introduced on post-operative day 1 along with low-dose CNI and Mycophenolate on a steroid-free protocol. One-hundred and sixty-six patients [135 (81%) males, mean age 58 y.o. (20-72)] were included. The overall graft and recipient survivals were 70% and 60% at the 5- and 10-year timepoint respectively. The incidence of acute rejection was 3%. In all the 17 (10%) patients suffering from hepatorenal syndrome at transplant [mean Serum Creatinine 0,9 mg/dL (1,6-3,49)] we observed normalization of the renal function. De-novo malignancies incidence and HCC recurrence were 14% and 1% respectively. In 37 (22%) patients, we were able to taper CNIs up to a Everolimus monotherapy.
Conclusions: Ab-initio introduction of Everolimus in liver transplant immunosuppression schemes is safe and associated to a low incidence of acute and chronic rejection. Also, thanks to the reduction of post-operative complications it allows tapering of other immunosuppressants and complete wean-off in 22% of the patients.

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T-02

Prevalence of hepatitis delta virus among chronic hbvcarriers at AOU Federico II

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Background/Aim: In Italy, the prevalence of HDV infection in HBsAg carriers is about 9.9% (6.4% in Italian natives and 26.4% in immigrants). However, the actual prevalence is probably underestimated because the anti-HDV test is not performed routinely in all HBsAg carriers. The HDV causes a rapidly progressive liver disease and as new antiviral therapies are coming, it is fundamental to known the exact HDV prevalence. The aim of this study was to assess the real HDV prevalence in the AOU Federico II.
Methods: From April 2021 to July 2022, reflex test for the detection of total HDV antibodies was performed in all HBsAg positive subjects observed at AOU Federico II. Demographic, clinical and laboratory data were collected. Liver fibrosis was evaluated with FIB-4. Sera were evaluated with ADVIA Centaur HBsAgII Qualitative, Liaison Murex HBsAg Quantitative and Liaison Murex Total Anti-HDV Qualitative.
Results: Of 365 HBsAg carriers, 46 (12.6%) resulted positive for total anti-HDV. The majority of them (89.2%) were Italian natives and only 5 (10.8%) of them were immigrants. Twenty-one (45.6%) were males with a median age of 62.2 years. Thirty-five (76%) patients were already aware of HBV/HDV coinfection. HDV-RNA was performed in 18 (39.1%) subjects and resulted detectable in 15 (83.3%) of them, with a median HDV-RNA level of 84.300 [25th – 75th percentiles: 1.685-547.796] IU/ml. Twenty (43.5%) anti-HDV positive subjects had advanced liver fibrosis.
Conclusions: Our data showed that the HDV prevalence is higher than expected, demonstrating that the reflex test in HBsAg carri-

ers could be a useful approach to identify the real prevalence of HDV infection. Moreover, the HDV-RNA is performed only in the minority of the anti-HDV positive subjects. In this setting, due to the forthcoming approval of specific anti-HDV drugs, a reflex test for HDV-RNA should be implemented to identify viremic patients needing antiviral treatment.

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T-03

Safety and immunogenicity of booster dose in patients with chronic liver disease

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Background/Aims: Several studies showed that patients with liver cirrhosis have an immune dysregulation leading to poor immunological response to vaccination. However, in literature there are few data about the response to SARS-CoV-2 vaccination in patients with chronic liver disease (CLD). Aims of the study are (is) the evaluation of safety and immunogenicity of booster dose in patients with CLD.
Methods: From September 2021 to April 2022, all consecutive outpatients with CLD who completed the primary vaccination course and the booster dose for anti-SARS-CoV-2 vaccination were enrolled. Blood samples were collected 12-16 weeks after second dose and after booster dose. Collected samples were analyzed for detecting anti-Spike protein IgG using LIAISON TrimericS IgG chemiluminescent assay (Diasorin, Italy).
Results: We enrolled 340 patients (187 Males, mean age:64.32±17.34years). Stratified by the presence of cirrhosis, 249 had CLD and 91 were cirrhotic whose 57 (62.24%) had portal hypertension. At the end of the primary vaccination course, 60 patients (17.65%) did not develop a protective antibody titer, with no statistically significant differences between the two groups (19.7% in cirrhotic vs 16.8% in non-cirrhotic; p=0.076). The majority of them (53/60 patients; 88.3%) developed a protective titer after booster dose, without differences between cirrhotics and non-cirrhotics (p=0.089). At multivariate analysis, factors associated with a higher humoral response after booster dose were young age (p=0.0098); porto-sinusoidal vascular disorder (p=0.005), none or a single comorbidity rather than two or more (p=0.05) and Spikevax booster dose compared with Comirnaty (p=0.001). Moreover, the antibody titer is inversely related to age (p=0.000).
Conclusions: In a large cohort of patients with CLD booster dose of anti-Sars-CoV-2 vaccine has an excellent immunogenicity and leads to an adequate antibody response even in those who had not produced a protective titer after the primary vaccination course. Cirrhosis is not associated with a reduced humoral response.

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T-04

The role of thyroid hormone signalling in liver carcinogenesis: A proof of knowledge

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Background/Aim: Emerging reports suggest a relationship between thyroid hormones (TH) signalling pathways and liver diseases, including hepatocellular carcinoma (HCC). Although it has been proven that the expression of deiodinases type 1 and 3 (D1-3) changes during induced liver injury, their role is still poorly understood in hepatocarcinogenesis. We aimed to evaluate the role of deiodinases and their regulation in liver carcinogenesis.
Methods: This is a proof of knowledge introductory to an ongoing monocentric prospective study. We enrolled 19 patients underwent liver surgery for HCC (10 cases) or for other non-neoplastic liver diseases in non-cirrhotic context (9 controls). We evaluated genes and protein expression of the main TH metabolism factors (D1, Monocarboxylate transporter-MCT8, Thyroid receptors-TR alpha and beta and Kruppel-like factor-KLF-9), with RT-PCR and Western blot analysis in HCC, cirrhotic tissue and healthy liver samples.
Results: **RT**-PCR analysis showed a progressive statistically significant decrease of D1 (p=0.004), MCT-8 (p=0.001) and TRα (p=0.02) mRNA expression from healthy liver to HCC. The expression of KLF9, involved in cell differentiation and proliferation, decreased accordingly (p=0.03). Western Blot analysis showed a decreased expression of D1 protein in all cirrhotic samples (p=0.01), while D3 increased in 50% of HCC (p=0.02)**.** Among HCC patients, D3 expression was associated with more severe liver stiffness (32 kPa, IQR:23.47-35.5, p=0.002) and high BMI (p=0.004). A statistically significant overall survival (OS) difference between D3 positive and D3 negative HCC patients was observed (log rank p=0.003), with a median OS of 17.9 (IQR:15.5-18.7) months for D3 positive vs 41.3 (IQR:35.1-43.8) months in D3 negative**.** Furthermore, a shorter Progression Free Survival and an increased recurrence rate was observed in D3 positive patients, even if not statistically significant.
Conclusions: These preliminary data showed that D3 expression could define a more severe phenotype of HCC and it could be used in clinical practice as negative prognostic biomarker.

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T-05

Presence and severity of esophageal varices drives portal hypertension-related complications in compensated advanced nonalcoholic fatty liver disease

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Background/Aim: We aimed to evaluate the impact of esophageal varices(EV) and their changes during follow-up on the risk of developing liver events in patients with compensated advanced chronic liver disease(cACLD) due to NAFLD. We also assessed diagnostic accuracy of noninvasive scores for predicting the development of liver events and for identifying patients at low risk of high-risk EV.
Materials/Methods: We assessed 629 patients with NAFLD-related cACLD who had baseline and follow-up esophagogastroduodenoscopy(EGD), and clinical follow-up to record decompensation, portal vein thrombosis(PVT) and hepatocellular carcinoma.
Results: Small and large EV were observed at baseline in 30% and 15.9% of patients, respectively. The 4-year rate of EV development from absence at baseline, and of progression from small to large EV were 16.3% and 22.4%, respectively. Presence of diabetes and ≥5% increase in BMI were associated with worsening of EV status. At multivariate Cox regression analysis, small(HR 2.24, 95%C.I. 1.47-3.41) and large (HR 3.86, 95%C.I. 2.34-6.39) EV were independently associated with decompensation. When considering EV status and EV trajectories, baseline and/or follow-up small EV(HR 2.65, 95%C.I. 1.39-5.05), and baseline and/or follow-up large EV(HR 4.90, 95%C.I. 2.49-9.63) were independently associated with decompensation as compared to baseline and/or follow-up absence of EV. Presence of small(HR 2.8 (95%C.I.1.16-6.74) and large(HR 5.29, 95%C.I. 1.96-14.2) EV were also independently associated with PVT occurrence.
Conclusion: In NAFLD-related cACLD, the presence, severity and evolution of EV well stratify the risk of developing decompensation and PVT.

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T-06

TERT-mutated hepatocellular carcinomas have a higher risk of recurrence after surgical resection. A monocentric prospective study

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Introduction: The mutational profile of hepatocellular carcinoma (HCC) is still poorly understood, hampering the development of target therapies for these heterogeneous cancers. Few studies found CTNNB1 and TP53 mutations to correlate with HCC prognosis, while even less is known about the role of the promoter TERT gene, despite the high frequency of its mutations.
Aim: To identify the prognostic role of the mutations in TERT, with or without concomitant CTNNB1 and TP53, in HCC after surgical resection.
Materials and Methods: This is a prospective monocentric study on *ex vivo* tissue; 65 patients were enrolled so far, undergone to liver resection for histologically-proven HCC (not previously treated). After routine histological analysis, next-generation sequencing (NGS) was carried out with a laboratory-developed multi-gene panel using Gene-Studio S5 sequencer.
Results: The incidence of TERT, TP53 and CTNNB1 mutations was 63%, 35% and 26%, respectively; as expected, TP53 and CTNNB1 mutations were mutually exclusive. TP53-mutated HCCs had a significantly higher incidence of poorly differentiated grade (Edmondson's G4, p=0.039 chi-square, OR 3.5) and of macrotrabecular or solid architecture (p=0.032 chi-square, OR 3.4).

TERT mutation showed to correlate with post-resection HCC recurrence on both multivariate (Exp(B): 39, Cox regression analysis) and univariate (p=0.041, log rank) analysis: in particular, 27.5% TERT-mutated HCCs experienced tumor recurrence, while no cases of tumor recurrence were recorded among the cases without mutations.

The concomitant mutations of both TERT and TP53 showed an even more dramatic recurrence rate than TERT-mutated alone cases (p=0.039, OR 6.4).
Conclusions: Mutation of the TERT promoter correlates with a higher risk of recurrence after surgical resection. TP53 mutation

characterizes the histologically advanced HCCs, with high grade and macrotrabecular or solid architecture; combined TERT and TP53 mutations worsen the recurrence rate.

The possibility of identifying these mutations before surgery opens new scenarios for a personalized therapy for advanced HCC.

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T-07

Magnetic Resonance-based fibrosis markers in patients with Non-Alcoholic Fatty Liver Disease: Exploratory data from the Turin cohort

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Introduction: In the setting of non-alcoholic fatty liver disease(NAFLD), liver fibrosis(LF) is the most relevant prognostic factor. Several non-invasive tests have been proposed to assess LF; among them, Magnetic resonance elastography(MRE) is so far the most accurate. Compared to the traditional magnetic resonance(MR), MRE requires an additional hardware with increasing procedure costs, with limited application in clinical practice. Quantitative T1-MR imaging is an emerging tool for the evaluation of LF,but its potential use has not yet been fully investigated.

Aim: We aimed to explore the correlations between T1 measured on vendor specific(vendor-T1) and LivermultiScan MOLLI(LMS-T1) sequences, with MRE and vibration controlled transient elastography(VCTE) parameters, in a cohort of NAFLD patients.

Methods: Between June 2021 and October 2022, we prospectively enrolled 24 NAFLD patients who underwent concomitant MR and VCTE. We extracted the following MR data(Philips Achieva 1,5T): from MRE, stiffness measured on FFE and EPI sequences; from multiparametric liver MR, T1 with vendor specific and LMS sequences, T2, proton-density-fat-fraction(PDFF); from VCTE(Fibroscan,Echosense), stiffness and controlled attenuation parameter(CAP).

Results: Median age was 54 years(interquartile range[IQR], 45-63) and 52% of the cases were males. Median liver stiffness value by VCTE was 5.9 kPa(IQR 4.4-8.4), while median CAP value was 313 dB/m(IQR 290-334). MRE-EPI stiffness showed significant correlation with MRE-FFE stiffness(r= 0.84, p<0.001), VCTE stiffness(r= 0.71, p<0.001),T1(r= 0.61, p<0.005) and T2(r= 0.42, p<0.05). LMS-T1 correlated to MRE-FFE stiffness(r=0.537, p < 0.02), while T1 correlated to MRE-EPI stiffness(r=0.616, p< 0.005). At multivariate regression analysis adjusted for T2 and PDFF, both vendor-T1 and LMS-T1 were significantly and independently associated with MRE-EPI stiffness(t=3.64, p=0.002 and t=2.4, p=0.027, respectively).

Conclusions: In NAFLD patients, T1 sequences may be used for the non-invasive assessment of LF. Further data from larger cohorts are needed to assess its potential use in clinical practice.

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Table 1. Characteristics of the study cohort

Variables	Median (IQR)
Age, y	54 (45-63)
Male gender, n (%)	13 (52%)
BMI, kg/m^2	30.9 (28.1-34.5)
Weight, kg	86 (76-93)
Height, m	1.67 (1.60-1.75)
Obesity, n (%)	13 (52%)
Type 2 diabetes, n (%)	5 (20%)
Hypertension, n (%)	12 (48%)
AST, U/l	34 (30-42)
ALT, U/l	39 (32-76)
GGT, U/l	44 (30-64)
PLT, x10^9/l	242 (194-277)
VCTE parameters	
Stiffness, kPa	5.9 (4.4-8.4)
CAP, dB/m	313 (290-334)
MRE parameters	
FFE stiffness, kPa	2.53 (2.08-2.84)
EPI stiffness, kPa	2.14 (1.58-2.59)
MR parameters	
Vendor T1, ms	530 (470-605)
LMS MOLLI T1, ms	655 (620-730)
T2, ms	27 (25-31)
PDFF, %	15.2 (10.3-27.0)

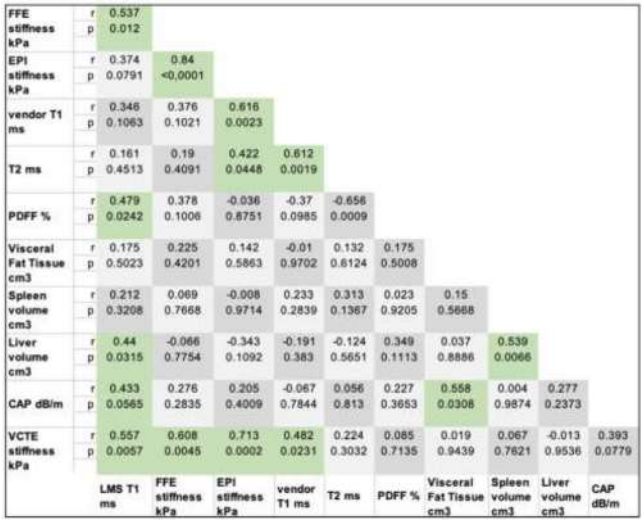

Figure 1. Correlation table. R = Spearman rank correlation coefficient

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T-08

Prognostic value of simple non-invasive tests for the risk stratification of hcc development in patients with cirrhosis due to non-alcoholic fatty liver disease

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Introduction: Hepatocellular Carcinoma (HCC) represents a major clinical event in the cirrhotic population, leading to a significant incidence of morbidity and mortality.
Aim: To assess the prognostic value of simple non-invasive tests (NITs) for the stratification of the risk of HCC development in a Non-Alcoholic Fatty Liver Disease (NAFLD) cirrhotic population on long-term follow-up (FU).
Materials and Methods: A total of 122 patients with NAFLD-cirrhosis (median age: 62 years; males 52.5%; median BMI 30.5 kg/m^2; prevalence of type-2 diabetes: 57.4%) were retrospectively analyzed. Cirrhosis diagnosis was achieved by either liver histology, instrumental findings and/or clinical evidence of portal hypertension. Clinical and biochemical data were collected at the time of diagnosis; the following NITs were calculated: FIB-4, AST to Platelet Ratio Index (APRI) gamma-glutamyl transpeptidase-to-platelet ratio (GPR), BARD.
Results: During a median FU of 6 (IQR 3.2-9.3) years, 13 (10.7%) patients developed HCC. Baseline FIB-4 (HR=1.27, 95%CI 1.03–1.58, p=0.027) and GPR (HR=1.44, 95%CI 1.11–1.85, p=0.005) values resulted significantly associated to HCC occurrence. Conversely, no association was observed for APRI and BARD. Conventional FIB-4 cut-off values allowed a proper patients' stratification into 3 risk categories with different HCC incidence: FIB-4<1.3 = 0/18 (0%), FIB-4 between 1.3–3.25 = 7/73 (9.6%), and FIB-4>3.25 = 6/31 (19.4%) (Log-rank test: p=0.009). Likewise, the cumulative HCC incidence according to GPR tertiles risk groups was: 3/41 (7.3%), 4/40 (10.0%) and 6/41 (14.6%) (Log-rank test: p=0.041).
Conclusions: Baseline FIB-4 could stratify patients with NAFLD-cirrhosis on long-term FU according to their individual risk of HCC development. In such patients, this simple NIT may be useful to optimize tailored HCC surveillance strategies.

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T-09

Low adherence to Mediterranean Diet is associated to sCD163 levels in patients with MAFLD

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Introduction&Aim: Low adherence to the Mediterranean Diet (MedDiet) has been associated with an increased risk of metabolic associated fatty liver disease (MAFLD), a clinical condition characterized by low grade chronic inflammation. The aim of this study was to assess whether the adherence to the Mediterranean diet is associated with biomarkers of inflammation in patients with MAFLD.
Method: A total of 40 patients with MAFLD were evaluated. Liver fibrosis was assessed by transient electrography (Fibroscan®530). Anthropometric, clinical and biochemical parameters were collected at enrolment. We measured the soluble CD163 (sCD163) levels by ELISA as indirect biomarker of both hepatic inflammation and fibrosis. Adherence to the MedDiet was assessed using a validated 14-item Mediterranean diet adherence questionnaire; low and high adherence were defined by the median value of the final score.
Results: Overall, the median age was 51 years (IQR 44;62), 52.00% of subjects were female and 32.00% had diabetes. Median liver stiffness was 6.6 (IQR 4.9;8.8), while sCD163 levels were 657 (IQR 553.5;813.5). Consistently, liver stiffness was significantly correlated to both MedDiet adherence and sCD163 concentrations (MedDiet: r= -0.38, p=0.006; sCD163: r=0.66, p<0.001, respectively). In addition, in patients with a low adherence to MedDiet significantly higher levels of sCD163 were observed (771.3 *vs.* 629.0, p=0.035). Interestingly, at multiple regression analysis, both low adherence to MedDiet adherence and sCD163 values (750-1303 ng/mL) were significantly associated with liver stiffness independently of age, sex, body mass index and diabetes.
Conclusion: In conclusion, in subjects with MAFLD low adherence to MedDiet is associated to a pro-inflammatory profile and is associated with the degree of hepatic fibrosis. *This work has received support from the EU/EFPIA Innovative Medicines Initiaive 2 Joint Undertaking (LITMUS grant no. 777377).*

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T-10

A nutrigenetic precision approach for the management of NAFLD

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Introduction and Aim: The Patatin-like phospholipase domain–containing 3 (*PNPLA3*) rs738409 single nucleotide polymorphism (SNP) is one of the major genetic determinant of NAFLD and is strongly regulated by changes in energy balance and dietary factors. The aim of this study was to investigate the association between the *PNPLA3* rs738409 SNP, nutrient intake and NAFLD severity.
Method: *PNPLA3*-rs738409 genetic variant was genotyped in 181 patients with hepatic steatosis who completed the EPIC Food Frequency Questionnaire. Liver steatosis was evaluated by Controlled

Attenuation Parameter (CAP) (Fibroscan®530). According to the established cut-off, a CAP value ≥300 was used to identify steatosis (S3). Subsequently, a validation analysis was performed in 47 biopsy-proven NAFLD where significant steatosis was classified as steatosis ≥ 33% and advance fibrosis as ≥F3 according to Kleinert score. Anthropometric, clinical and biochemical parameters were collected at the time of enrolment.
Results: Overall, median age was 53 years (IQR 44;62) and 60.22% of patients were male. 102 subjects (56.35%) had severe steatosis and showed increased liver stiffness ($p<0.001$), AST ($p=0.003$) and ALT levels ($p<0.001$) compared to those with CAP<300. At logistic regression analyses we found that the interaction between carbohydrates intake and the carriers of the *PNPLA3* G risk allele was significantly associated with severe steatosis ($p=0.001$). The same result was confirmed in a subgroup of patients who underwent liver biopsy, were the interaction between carbohydrate intake and *PNPLA3* SNP was significantly associated with steatosis ≥33% and advanced fibrosis (≥F3) ($p=0.017$ and $p=0.050$, respectively)
Conclusion: The intake of greater than or equal to 48% carbohydrate carrying the CG/GG allele of *PNPLA3* rs738409 may increase the risk of steatosis and fibrosis in patients with NAFLD. *This work has received support from EU/EFPIA/IM2 Joint Undertaking (LITMUS grant no.777377) and Italian Ministry for Education, University and Research (MIUR) under the programme "Dipartimenti di Eccellenza 2018-2022" n.D15D18000410001.*

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T-11

Social jetlag and mediterranean diet adherence are associated to liver fibrosis in patients with non-alcoholic fatty liver disease

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Introduction and Aim: The discrepancy in a person's sleep pattern between working days and days off is called Social Jetlag (SJL). The aim of this work was to investigate the potential impact of Mediterranean Diet (MedDiet) on the risk of significant liver fibrosis (F≥2) in individuals with non-alcoholic fatty liver disease (NAFLD), according to SJL.
Methods: A total of 148 patients diagnosed with NAFLD by ultrasound underwent assessment of liver stiffness + controlled attenuation parameter (CAP) (FibroScan® 530). F≥2 was defined by liver stiffness values ≥7.1kPa. The adherence to the MedDiet was assessed by the Mediterranean diet score questionnaire; low and high adherence were defined by the median value of the score. SJL was defined by the Munich Chronotype Questionnaire as the absolute difference between mid-sleep on free days and mid-sleep on workdays. According to the median value, we defined small and large SJL.
Results: The median age was 52 (42-61.5) years and the main comorbidities were type-2 diabetes mellitus (T2DM) (26.35%), arterial hypertension (49.3%), dyslipidemia (64.9%), obstructive sleep apnea (OSAS) (5.4%), and depression (6.1%). Median liver stiffness and CAP values were 5.1kPa (F≥2; 13.5%) and 301db/m, respectively. The prevalence of large SJL was significantly higher in patients with F≤2 compared to those with F≥2 (57.46% vs. 28.57%, p=0.039), while no significant difference was found in the adherence to MedDiet between groups. At multivariate logistic regression analysis adjusted for sex, age, BMI, T2DM, OSAS, arterial hypertension, dyslipidemia, and depression, we found that the interaction between a large SJL and a high adherence to MedDiet was significantly associated to F≥2 (OR=0.02, p=0.049).
Conclusion: Models integrating diet and SJL/sleep pattern characteristics may unveil potential pathogenetic mechanisms associated to liver fibrosis risk in patients with NAFLD. *Italian Ministry for Education, University and Research (MIUR) under the programme "Dipartimenti di Eccellenza 2018-2022" n.D15D18000410001*

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T-12

A new metabolic comorbidity score predicts risk of death among cirrhotic patients on waiting list for liver transplantation

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Background: Liver transplant (LT) candidates are becoming older and more comorbid, with significant increase of metabolic associated fatty liver disease (MAFLD). The Charlson comorbidity index (CCI) is frequently used for risk stratification, even in the LT setting, but not for prediction of waitlist outcomes. We built a new risk score based on comorbidities, named Charlson Metabolic Comorbidity score (CMC-Score), adding within the CCI the clinical features of the metabolic syndrome not present. We then compared the new CMC-Score with the CCI regarding the ability to predict survival on the waiting list.
Methods: All consecutive cirrhotic patients listed at our Liver Transplant Center from 2005 to 2019 were retrospectively analyzed. The CMC-Score was constructed by adding one point to the CCI for each clinical variable present among overweight/obesity, arterial hypertension, and dyslipidemia. Fine Gray multivariable competing risk analysis was employed to investigate risk factors for patients' death considering LT as competing event.
Results: 385 cirrhotic patients were enrolled, 45% had HCC and 70% had MAFLD. In the multivariate analysis, conducted considering the entire study population, the CMC-Score [SHR=1.260 (95.0%CI= 1.014-1.56); p=0.037], but not the CCI [SHR= 1.005 (95.0%CI=0.811 1.25); p=0.960], was the only statistically significant risk factor for death, adjusting for age, sex, MELDNa and presence of HCC. In a sub-analysis conducted in patients with HCC, the CMC-Score [SHR=1.604 (95.0%CI= 1.145-2.25); p=0.006], but not the CCI [SHR= 1.156 (95.0% CI= 0.815 1.64); p=0.42], was confirmed to be a relevant risk factor for death by adjusting for age, sex, MELDNa and the Up To Seven score of the HCC.
Conclusions: The new CMC-Score is useful for identifying patients on the LT waiting list at increased risk of death. Further adjustments in the composition of the score and its validation should be made with multicenter and prospective studies.

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T-13

Primary biliary cholangitis case-finding: Monocentrical study on patients with incidental finding of anti-mitochondrial antibodies

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Introduction: Anti-mitochondrial antibodies (AMA) are a specific diagnostic marker of Primary Biliary Cholangitis In a lot of situation, in our hospital, thanks to our multidisciplinary group formed by hepatologist and rheumatologist we find some rheumatological patients, with AMA positivity that is sent to Hepatologist for an evaluation, or simply, some patients that casually find in autoimmunity exam this value and laboratory send him to hepatologist. The aims of this observational prospective study were to assess the proportion of AMA positive subjects referred to hepatological evaluation and the evidence of significant liver disease found in these patients.
Methods: From September 2020 to August 2021, 44 consecutive adult patients without a known history of liver disease were incidentally found positive for immunofluorescent AMA testing, with immunoblotting con-firmed M2 positivity, during diagnostic evaluation mainly for rheumatologic or endocrinologic conditions at San Bonifacio Hospital in Verona, Italy. Referral of these subjects to hepatological evaluation was recorded until February 2022. Evidence of concomitant liver disease was assessed by serum liver enzymes and Fib-4 score (based on age, platelet count, AST, and ALT values) and on sign as fatigue or pruritus.
Results: Among patients who were referral to hepatologist 19/44 (43,1%), at the visit admit to suffer of pruritus or fatigue (calculate with fatigue severity scale), all patients permorf elastosonografy, but 100% had low fibrosis value (median value 4,3 Kpa range 3,2-5,7), in 5/44 case we found High value of ALP, that was related with stronger symptomatology. At one year follow up, we found all patients in better condition, the 5 patients with high level of ALP returned in range and of the 19 patients who had symptoms 10 did not suffer anymore, the other 9 maybe suffer for other condition.
Conclusion: AMA positive in patients without a history of liver disease evaluated by hepatologist, about 43% show evidence of liver disease, suggestive of PBC. Patients without current evidence of PBC should be monitored and followed up, and begin as soon as possible UDCA. Our results indicate the need for an informational and educational campaign among rheumatologists and endocrinologists on the importance of a hepatological evaluation of patients with incidental AMA positivity.

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T-14

The rs1468615 T>C in ABCB4 confers protection against gallstone disease but not against severe liver disease

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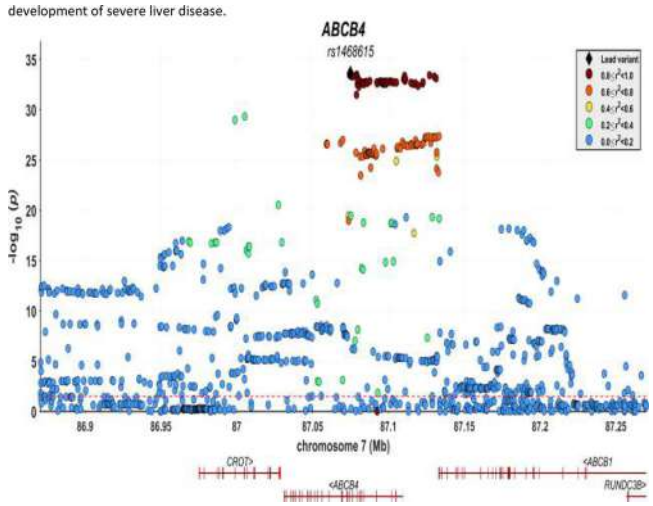
Background: Growing evidence suggests that cholestatic and fatty liver disease share common pathophysiological mechanisms. Rare loss-of-function variants in the ATP binding cassette subfamily B member 4 (*ABCB4*) gene have been associated with gallstone disease and with a spectrum of cholestatic liver diseases, ranging from progressive familial intrahepatic cholestasis to less severe conditions, like low phospholipid-associated cholelithiasis or intrahepatic cholestasis during pregnancy. Whole-genome sequencing of Icelanders revealed the common variant rs2109505 T>A in *ABCB4*, conferring protection against gallstone disease and being associated with lower transaminases.
Aim: To identify common variants in *ABCB4* associated with severe liver disease.
Methods: We examined the association of missense and nonsense common variants (minor allele frequency >1%) at the *ABCB4 locus* with ALT in 412,912 Europeans from the UK Biobank using a whole-genome regression model. Next, we tested the association of the lead variant in the region with liver-related traits and incident severe liver disease in a subset of 365,449 unrelated Europeans by multiple linear/logistic regression models and Cox proportional hazards models, respectively. Analyses were adjusted for age, gender, BMI, type 2 diabetes, alcohol intake, and first 10 PCs of ancestry.
Results: We identified the *ABCB4* rs1468615 T>C as the lead variant independently associated with ALT ($P = 2.26 \times 10^{-34}$). The rs1468615 is an intronic variant in high linkage disequilibrium with the rs2109505 ($r^2 = 0.94$). The rs1468615 was associated with lower risk of gallstone disease ($P = 8.56 \times 10^{-12}$) and with lower liver enzymes ($P = 2.28 \times 10^{-30}$, $P = 8.31 \times 10^{-09}$, and $P = 8.08 \times 10^{-04}$ for ALT, AST, and GGT respectively). No association was found with liver cirrhosis, liver cancer, and gallbladder/biliary tract cancer. No association was found with incident severe liver disease.

Conclusions: The rs1468615 T>C in *ABCB4* confers protection against gallstone disease but not against the development of severe liver disease.



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T-15

Glecaprevir/Pibrentasvir is safe and effective in Italian patients with chronic Hepatitis C aged 75 years or older: A multicenter study

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Glecaprevir and Pibrentasvir (G/P) determines high rates of sustained virologic response (SVR) with optimal safety profile in patients with chronic hepatitis C virus (HCV) infection. The efficacy and safety of G/P in Caucasian patients aged 75 years and older has not been widely analyzed. This is a retrospective multicenter real-world study enrolling all consecutive patients 75 years and older who received G/P between October 2017 and January 2022 at 5 referral centers in Italy. SVR was analyzed by Intention to Treat (ITT) and Per Protocol analysis (PP). 570 patients met the inclusion criteria and were analyzed: mean age was 80 (75-97) years, 356 were females, 52% (298/570) had HCV-1 and 44% (252/570) had HCV-2. 137 (24%) patients had liver cirrhosis. 463 (81%) patients were taking at least 1 concomitant drug, with 144 (25%) taking ≥5 concomitant drugs. G/P was given for 8 weeks in 488 patients (86%). During treatment 48 patients (8%) reported side effects, with 10 (2%) patients discontinuing treatment prematurely. Two patients developed treatment unrelated serious adverse events. Overall, the SVR rate was 97.9% (558/570) by ITT analysis and 99.6% (558/560) by PP analysis. SVR rates remained consistently high among subgroup analysis stratified by genotype, treatment duration, fibrosis stage and concomitant medications. Treatment with G/P achieved 97.9% SVR rates in HCV patients older than 75 years of age. Safety was optimal with only 2% of patients discontinuing early.

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T-16

Liver transplantation for polycystic disease: A cumbersome benign disease

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Background: Liver transplantation (LT) or simultaneous liver-kidney transplantation (SLKT) remain the curative treatment for liver (PCLD) and liver-kidney (PCLKD) polycystic disease. We aimed at describing pre- and post-transplant characteristics of polycystic patients undergoing LT/SLKT.
Methods: Patients who underwent LT/SLKT for polycystosis in our Centre from 01/01/2010 to 30/06/2022 were enrolled. Follow-up ended on 30/11/2022.
Results: among 1754 LTs, 63(3.6%) were performed for polycystosis (45/63 SLKT). 48/63(76.2%) female; median age 52 years[IQR 48-56]; median BMI 23.7 kg/m^2[22.6-26.0]. Median serum creatinine 5.7 mg/dL[4.1-7.8], eGFR 12.2 mL/min[7.8-17.7] for SLKT patients (60.4% on pre-LT dialysis). Nine patients had pre-transplant cyst interventions. 58/63(92.1%) underwent LT due to abdominal fullness with sarcopenia (median liver weight 3950g[2450-6750]; median largest cyst size 7.0 cm[5.0-9.2]); 19/63(30.2%) showed refractory ascites. 10/63(15.9%) were pre-LT colonized by multidrug-resistant bacteria. During transplant: 6(9.5%) patients underwent venous-venous bypass and 9(14.2%) temporary porto-cava shunt; 18/63 (28.6%) piggy-back technique. Median liver cold ischemia time was 447 min[369-504]; median number of red blood cell transfusion was 7[3-16]. Among 48 patients listed for SLKT, 7/48(14.6%) underwent a delayed kidney transplantation from the same liver donor and 3/48(6.3%) due to the complexity of LT surgery, were then listed for sequential kidney transplant. After transplant: 41/69(65.1%) were extubated within 48-hours; median ICU-stay was 5 days[3-9] and hospital length-of-stay 17 days[12-25]. Two patients underwent re-LT for primary non-function and 28/63(44.4%) post-transplant surgical revisions. After a median follow-up of 4.1 years [1.6-7.7]: 59/63(93.7%) were alive; 3 patients died for sepsis 3 weeks after transplant and 1 patient for HHV8-induced hemophagocytic syndrome 3 years later.
Conclusions: PCLD/PCLKD is a cumbersome and insidious benign disease. 16% of our patients were pre-transplant colonized by multidrug-resistant bacteria and post-transplant early surgical re-

visions were needed in 44% of the patients. However, the expertise of a high-volume transplant Centre allowed to achieve a 3-year survival rate of 93.7%.

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T-17

Liver transplantation for portopulmonary hypertension responsive to targeted therapy

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Background and Aims: In the current era of pulmonary arterial hypertension (PAH) therapy (tx), patients (pts) affected by liver disease with mild portopulmonary hypertension (POPH) can experience significant improvement after liver transplant (LT). We described characteristics of POPH pts who underwent LT in our Center.
Methods: Among 1135 LT performed between 05/2013-05/2021 in our Center, we enrolled 10 cirrhotics with POPH. Diagnosis was made accordingto right heart catheterization (RHC) criteria: mean PA pressure(mPAP) >25 mmHg, PA wedge pressure(CAP)≤ 15 mmHg, pulmonary vascular resistance(PVR)>3WU. To achieve LT criteria (mPAP<35 mmHg, PVR<5 WU or mPAP 35-44 mmHg and PVR<3 WU) pts received phosphodiesterase-5-inhibitors(P-5i) and/or endothelin-receptor antagonists(ERA) and/or prostacyclin receptor-agonists. Follow-up was closed on 30/11/2022.
Results: Recipients (**Table 1**): median age 53 years, 80% male, BMI 26Kg/m^2, 100% HCV cirrhosis, 20% HCC, 60% with large portosystemic-shunt, MELD 12. PAH-tx: pts#1-5 underwent ERA-tx; pts#6-8 ERA+P-5i; pt#9 and#10 prostacyclin+P-5i+ERA. Six pts (#1,#2,#4,#5,#9,#10) achieved POPH LT criteria after 4 mo of PAH-tx; 2 pts (#3,#6) after 8 mo, pt #8 after 12 mo.The 10 pts were transplanted after 0.3 y from registration on LT waiting list. Donors: median age 49 y, DRI 1.6. Post-LT: 3 pts developed early allograft dysfunction. All except pt #7 were extubated within day 2 post-LT; median hospital length of stay was 16 days. Pt#7 died after 18 days for cardiac failure.At a median follow-up of 2.9 y, 7 patients persistently discontinued PAH-tx.
Conclusion: In our high-volume LT center, in the last 8 y we transplanted 10 cirrhotic pts affected by POPH and responsive to targeted therapy. LT offered a POPH resolution in 78% of the pts who were weaned off all PAH-tx without RHC evidence of POPH recurrence. One pt died early post-LT for cardiac failure. Careful patient and donor selection and proper timing of LT remain pivotal to obtain good outcomes.

Pt	Baseline				At LT						Post-LT		
N	mPAP mmHg	CAP mmHg	PVR WU	CI l/min/m^2	MAP mmHg	mPAP mmHg	CAP mmHg	PVR WU	CI l/min/m^2	MELD	Alive	EAD	Stop PAH- tx
#1	35	10	4.2	3.1	60	33	15	2.9	3.3	11	Yes	No	Yes
#2	38	10	5.8	2.5	60	31	12	2.4	4.0	13	Yes	No	Yes
#3	45	14	6.5	1.9	58	34	15	3.8	3.0	10	Yes	No	No
#4	51	10	5.9	3.2	68	34	17	1.7	4.9	14	No	No	Yes
#5	45	11	4.9	3.4	68	27	12	1.8	4.1	10	Yes	No	No
#6	60	13	6.3	3.9	50	31	13	1.7	5.3	20	Yes	Yes	Yes
#7	47	10	9.0	2.6	58	40	15	2.9	5.8	27	No	Yes	No
#8	41	14	4.2	2.9	69	32	19	2.4	2.6	10	Yes	No	Yes
#9	46	10	13.0	1.8	88	27	16	1.6	4.3	8	Yes	No	Yes
#10	47	10	10.9	1.6	70	24	11	1.2	5.3	13	Yes	Yes	Yes

Abbreviations: LT, liver transplant; mPAP, mean pulmonary arterial pressure; CAP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; CI, cardiac index; MAP, mean arterial pressure; EAD: early allograft dysfunction according to Olthoff's definition; PA-Tx: pulmonary arterial targeted therapy.

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T-18

Medium-term outcome of liver recipients from COVID-19 donors

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Background: COVID-19 is associated with thrombotic complications and can result in hepatobiliary injury. Excellent early outcomes have been reported in recipients of solid non-lungs organs from SARS-CoV-2-infected donors, however longer follow-up data are lacking. We aimed to describe the medium-term outcome of our liver transplants (LT) from COVID-19 donors.
Methods: From 11/2020 to 03/2022, we consecutively enrolled all patients who received a graft from COVID-19 donor in our Centre. Protocol liver biopsy and magnetic resonance cholangiopancreatography (MRCP) after 1-year from LT were reported.
Results: In the study period 12/213 (5.6%) adult LT patients received a COVID-19 donor (11 active, 1 resolved COVID-19)[1]. Eleven patients underwent end-to-end biliary anastomosis and 1 biliodigestive anastomosis. Recipients' and donors' characteristics are reported in **table 1**. Two recipients tested SARS-CoV-2 RNA positive on nasopharyngeal swab at LT and one was treated with sotrovimab on day-1 after LT. None of the patients developed COVID-19 after LT. One patient underwent hepatic artery thrombectomy at day-1 and died after 320 days for HCC recurrence. Until now: -10 patients underwent protocol MRCP (median time from LT 562 days, IQR 245-614), which showed: 7 no visible abnormalities, 1 donor-recipient's bile duct size discrepancy, 2 caliber changes <50% at the anastomotic level (untreated for the absence of cholestasis); -7 patients underwent protocol liver biopsy (median time from LT 553 days, IQR 311-557) which showed 1 acute cellular rejection (RAI 4/9) successfully treated with steroids; no signs of fibrosis, rejection or biliopathy in the other 6 patients.
Conclusions: 11/12 patients who received a LT from COVID-19 donors are alive, without evidence of SARS-CoV-2 transmission. At a median follow-up of 1.5 years, protocol liver biopsy and MRCP did not show biliopathy, supporting the utilization of COVID-19 donors to expand the donor pool and reduce the waiting list mortality.

Table 1. Recipients' and donors' characteristics at LT	Donors n = 12	Recipients n = 12
Age, years	59 [52- 63]	61 [56-65]
Sex, male	8 (67%)	9 (75%)
Body mass index, kg/m^2	25 [24-27]	27 [24-28]
Hepatocellular carcinoma	/	9 (75%)
Model for end stage liver disease at LT	/	10 [8- 14]
Anti-SARS-CoV-2 vaccination before LT	/	4 (33%)
SARS-CoV-2 IgG positive before LT	/	12 (100%)
SARS-CoV-2 RNA swab positive at LT	2/3 (67%)*	2 (17%)
SARS-CoV-2 RNA bronchoalveolar lavage positive at LT	9/9 (100%)*	/
Donor risk index	2 (1.6-2.2)	/
Donation after brain death	12 (100%)	/
Hypothermic machine perfusion	3 (25%)	/
Normothermic machine perfusion	1 (8%)	/
SARS-CoV-2 RNA PCR negative on liver biopsy	11/11 (100%)^	/

*11 active COVID-19 donors and 1 resolved COVID-19 donor. ^The COVID-19 resolved donor was not tested.

[1]Peghin M. J Hepatol. 2022;77(4):1198-1204.

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T-19

Liver transplant outcome of cirrhotic patients treated with coronary stenting and early discontinuation of dual antiplatelet therapy

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Background: Significant coronary artery disease (CAD) should be treated with percutaneous revascularization in pre-liver transplant (LT) work-up. New-generation drug-eluting stents (DES) allow early discontinuation of dual antiplatelet therapy (DAPT). We aimed to describe pre-LT management and early post-LT outcome of our patients with CAD who underwent Percutaneous Coronary Intervention (PCI).
Methods: We enrolled all patients transplanted in our Centre from 01/2018 to 04/2022 who underwent pre-LT cardiac catheterization (CATH). Stenosis ≥50% in a major-vessel or stenosis ≥70% in a moderate-sized branch vessel indicated significant CAD.
Results: Among 638 adult patients who received LT, 33 underwent pre-LT CATH (5%) due to previous history of obstructive CAD (18%), positive noninvasive stress-test (61%), inconclusive noninvasive test (15%) or CAD symptoms (6%). CATH showed normal coronaries in 6/33 (18%), non-obstructive CAD in 15/33 (46%) and significant CAD in 12/33 (36%). These 12 patients were all male, median age 64 years, 75% diabetics, 83% smokers, median BMI 26kg/m^2 and underwent PCI with single (6/12) or ≥ 2 coronary arteries stenting (6/12). Patients received 31 days (IQR 31-41) of DAPT (clopidogrel+cardioaspirin), followed by aspirin monotherapy; anemia was a concern, without pre-LT major bleeding. Registration on the LT waiting list and LT occurred after 14 days (7-87) and 77 days (12-172) respectively from DAPT discontinuation. The median number of red blood cell units transfused during LT was 5 (2-7). At the end of LT, median arterial lactate and noradrenaline requirement were 1.9 mmol/L and 0.13 γ/Kg/min (**Table 1**). After a median follow-up of 321 days from LT: patient #1 experienced acute heart failure at month 4th (EF 35%), following major gastrointestinal bleeding (hemoglobin 4.2 g/dL); CATH was unchanged; patient improved with blood transfusion (EF at discharge 45%).
Conclusion: Coronary DES revascularization and early clopidogrel discontinuation was safe in cirrhotic patients with significant CAD and allowed timely LT.

Table 1. Characteristics of patients with significant coronary artery diseases

	CATH	LT		At the end of LT			
Pt	Stenosis treated with DES	MELD	Donor age (years)	Blood transfusion (unit)	Lactate (mmoL/L)	Noradrenaline (γ/Kg/min)	Post reperfusion syndrome
#1	LCX 90% RCA 80%	20	68	10	3.2	0.3	Moderate
#2	LAD 90%	10	47	3	1.8	0.2	Mild
#3	LAD 70% RCA 70%	11	36	5	1.6	0.1	Moderate
#4	LAD 60% LCX 80%	13	75	7	2.3	0.5	Moderate
#5	RCA 99%	11	62	4	3.4	0	Moderate
#6	RCA 90%	10	62	7	1.9	0.05	Mild
#7	LAD 60% RCA 60%	9	82	2	1.5	0.15	Mild
#8	RCA 80%	13	54	1	1.1	0.4	Severe
#9	LAD 75	30	45	14	4.1	0.3	Moderate
#10	LCX 80% PDA 90%	7	79	0	1.2	0	Mild
#11	LM 90%	12	63	0	1.2	0.1	Mild
#12	LAD 80%	32	63	8	2.3	0.05	Mild

LCX, left circumflex artery; RCA, right coronary artery; LAD, left anterior descending artery; PDA, posterior descending artery; LM, left main artery.

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T-20

The enigmatic immunoglobulin G4-related disease: A single-centre experience

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Introduction: Immunoglobulin G4 (IgG4)-related disease (RD) is an immune-mediated disease, characterized by fibrosis and inflammatory pseudotumors. It affects multiple organs, being pancreas (P) and hepatobiliary tree (HB) the main targets. The diagnosis is usually complex, and the clinical manifestations provide the treatment indication.
Aim: Our aim was to study the clinical, radiological, and histological behavior of a cohort of patients with IgG4-RD.
Material and Methods: A retrospective analysis of IgG4-RD patients prospectively collected between May 2012 and October 2022 was performed. Clinical, serologic, radiologic, and histopathologic data were collected, together with therapeutic strategy.
Results: A total of 13 IgG4- RD patients were included (84.6% male, 65.8 years). Twelve had HB involvement. Eight had both P and HB involvement, 2 of whom also had other organs (lacrimal and salivary glands, lungs). One patient had isolated P. The main clinical manifestation was cholestasis (92.3%), followed by cholangitis (53.8%) and pancreatic pain (53.8%). Circulating IgG4 levels were high in all tested patients (10 of 13), but above 4ULN in only 2. Two of the 9 patients with P involvement developed diabetes. Liver or pancreas biopsy was performed in 6 patients, lymphoplasmacytic infiltrate was the most common finding. Of these, IgG4 immunohistochemistry was performed in 4 patients, 2 of whom were above the 10/HPF diagnostic cutoff. The most common CT-scan/MRI finding was swollen pancreas, followed by biliary tract irregularities. One P and 1 HB pseudotumors, but no malignancies were described. Mean delay in diagnosis was 6 months (1-48). Eleven patients were treated with steroids, with good response. Of them, 3

patients were switched to azathioprine maintenance therapy. One steroid-refractory patient received rituximab.
Conclusions: Despite the limited number of patients, this study confirms the heterogeneity of IgG4- RD manifestations, diagnostic challenges, and response to therapy. Further studies are needed to better understand this enigmatic disease.

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T-21

Improvement of clinical parameters in HDV patients with advanced compensated cirrhosis treated with Bulevirtide monotherapy for 48 weeks

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Background and Aim: Bulevirtide (BLV) has been conditionally approved for treatment of compensated chronic hepatitis Delta in Europe, however long-term outcomes of HDV patients with compensated cirrhosis treated with BLV monotherapy are currently unknown.
Methods: Consecutive HDV patients with compensated cirrhosis who received BLV monotherapy for 48 weeks were enrolled in this single-center study. Clinical variables were collected at baseline, weeks 4, 8 and every 8 weeks thereafter.
Results: 20 Caucasian patients under nucleos(t)ide analogue (NUC) treatment were included: median age 49 years, 65% males, liver stiffness measurement (LSM) 16.8 kPa, 80% with varices. At baseline, ALT levels were 110 U/L, AST 92 U/L, GGT 52 U/L, albumin 3.9 g/dL, platelets $72 \times 10^3/mm^3$, IgG 2285 mg/dL, HDV RNA 4.9 UI/mL. CPT score was A in all patients. Following 48 weeks of BLV monotherapy (2 mg/day in n=18 and 10 mg/day in n=2), HDV RNA declined by 3.1 Log IU/mL and became undetectable in 39%; 89% of patients achieved a virological response (undetectable HDV RNA or ≥2 Log decline *vs.* baseline). At week 48, most biochemical parameters improved: ALT (normalizing in 85% of patients), AST, GGT, IgG and albumin ($p<0.001$ for all comparisons). Four out of 5 patients with CPT score A6 improved to A5 at week 48. Bilirubin, platelets and HBsAg remained unchanged, LSM significantly declined in viral responder patients ($p=0.03$). Among 9 patients with baseline small varices not needing prophylaxis, varices disappeared in 2 cases. De-novo decompensation due to portal vein thrombosis occurred in one patient, de-novo HCC in two, three underwent liver transplantation and one patient died due to BLV-unrelated causes. BLV was well tolerated, an asymptomatic increase in bile acids occurred.
Conclusions: Liver function parameters improved in HDV patients with compensated cirrhosis treated with BLV monotherapy for 48 weeks. Esophageal varices disappeared in some patients.

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T-22

It takes a team for HCC: The adverse events reduction in first line HCC systemic therapies with the multidisciplinary ambulatory

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Introduction and aim: Hepatocellular carcinoma (HCC) is the major cause of liverâ€ related death worldwide. In the last 2 years, a new approach with immune checkpoint inhibitors (ICIs) started to gain attention in HCC setting. With these new therapies multidisciplinary team (MDT) discussion become necessary to increased curative treatment, frequency of stage migration, higher treatment rates and reduced mortality. In Verona hospital in addition to MDT discussion, a LIVER-MDT ambulatory was created, to our knowledge the first in the Italian health system. Aim of this study was to verify if the LIVER-MDT ambulatory is useful to reduce adverse effects and mortality compared to a similar cohort (ELEVETOR cohort, Liver cancer 2022).
Patients and Methods: we collected data from patients attended the LIVER-MDT ambulatory. Major, minor adverse effects (MAE and mAE) and antitumoral dose were collected. Death and progression free survival (PFS) were also recorded.
Results: 834 patients were evaluated at the MDT discussion from 2021; 40 patients also referred to LIVER-MDT ambulatory to start systemic treatment. Median age was 69.5 (53-82), 82.5% were male. Cirrhosis etiology were 45% viral (HCV/HBV), 37.5% MAFLD and 10% alcohol. Compared to ELEVATOR cohort, less MAE were recorded (20% vs 32.7%, $p<0.01$). In addition, MAE strictly due to the systemic therapy developed in 7.5%. Anyone developed uncontrolled and resistance arterial hypertension or heart failure during the treatment. 32.5% died, with a median PFS of 8.85±6.03 (median in ELEVATOR 6.4). Only 15 % of patients documented a reduction of antitumoral drug dose (vs 50% in ELEVATOR).
Conclusion: LIVER-MDT ambulatory is linked with a reduction in MAE and mAE in particular any patients developed hypertension or heart failure. Also, a small reduction of antitumoral dose was documented. The multidisciplinary approach (MDT and LIVER-MDT) seems to be the best approach for HCC patients and possible collateral events drug correlated.

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T-23

Mitochondrial Complex I modulator (CIM) reduces lipid accumulation and inflammation in MCD-diet fed rats

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Introduction and Aim: Inflammation, ROS and mitochondrial dysfunction play a key role in NAFLD progression. Currently no treatments are available, but the finding that metformin targets mitochondrial Complex I opens a new challenge for the research. Aim of this work was to investigate if the selective modulation of mitochondrial Complex I, which is the main ROS producer in mitochondria, could play a role in decreasing lipid accumulation and NAFLD progression.
Materials and Methods: male Wistar rats, fed by a Methionine and Choline deficient (MCD) diet or Control diet for 6 weeks, were orally administered, starting from the fourth week, with Complex I Modulator (CIM, Boehringer Ingelheim) 10mg/Kg/day or vehicle for 3 weeks. TBARS, ROS, ATP content, NAD(P)H bound/free ratio, Nitrate and Nitrite, total lipid content and the area of lipid droplets in the liver were evaluated.
Results: TBARS increased in MCD-treated rats compared with Controls, without changes after CIM administration. ROS increased in MCD groups, but a significant reduction in CIM-treated Controls was detected. ATP decreased in CIM-treated Controls, however no differences were appreciated in MCD-treated groups. The same trend was observed for NAD(P)H bound/free ratio. Nitrate and Nitrite were reduced in CIM-treated MCD rats, compared with vehicle-treated MCD rats. Total lipid content displayed a significant reduction in CIM-treated MCD rats and a significant reduction in lipid droplet areas was also observed in CIM-treated MCD rats, compared with untreated MCD group. Inflammatory cell infiltration was significantly reduced in CIM-treated MCD rats and a significant decrease in AST and ALT was observed in CIM-treated Control rats, compared with untreated controls.
Conclusions: This is the first attempt to demonstrate a possible role of Complex I Modulator in reducing lipid accumulation and inflammation in a model of benign steatosis, although further investigation are needed to clarify the underling mechanisms of this process.

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T-24

Obeticholic acid reduces lipid accumulation and fibrosis in a diet-induced ob/ob mouse model of NASH

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We previously reported that Obeticholic acid (OCA), a potent Farnesoid X receptor (FXR) agonist, restores RECK, an inverse modulator of metalloproteases, involved in fibrogenic processes. Recently, hepatic eNOS, a key regulator of liver vascular tone, was found strongly associated with the progression of NAFLD to NASH. Here, the effect of OCA was evaluated on hepatic eNOS content, lipid accumulation and fibrosis in a diet-induced ob/ob mouse model of NASH. 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, bilirubin, cholesterol as well as hepatic eNOS and histological analysis of lipid droplets and fibrosis (by Sirius Red) were quantified. A marked increase in eNOS was observed in livers from HF diet mice treated with OCA compared with HF diet group. Histological results showed an accumulation of large lipid droplets in HF diet mice and reduced number and diameter of lipid droplets following OCA treatment. The same trend occurred for collagen deposition. Liver eNOS shows a marked inverse correlation with lipid droplets (number and diameter) and fibrosis. OCA treatment restored liver weight, serum bilirubin and cholesterol compared with HF-treated mice. No changes in serum transaminase were found. In conclusion, OCA confers liver protection in a NASH model as shown by reduced hepatic lipid accumulation and fibrosis as well as serum bilirubin and cholesterol. This study also shows increased hepatic eNOS levels following OCA treatment associated with reduced lipid accumulation and fibrosis. Our data support the emerging role of eNOS as a key regulator of NAFLD progression to NASH.

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T-25

Prospective study on the prevalence of HCV infection in consecutive adult inpatients in a hospital division of Internal Medicine in Tuscany

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Introduction: Prevalence of HCV infection in adults in Italy ranges between 0.5 and 3% across the country. Free HCV screening is offered to subjects born after 1969, but little is known about the prevalence of HCV infection in elder subjects.
Aim: This prospective study aimed to evaluate the prevalence and significance of HCV infection in consecutive adult inpatients without a history of hepatitis C during their stay in a large division of Internal Medicine in Tuscany.
Materials and Methods: Between October 2021 and July 2022, all the consecutive adult inpatients born before 1969, without a history of hepatitis C, and admitted to the Division of Internal Medicine at the University Hospital in Siena (AOU Senese) were tested for antibody to HCV (anti-HCV). In addition, demographic characteristics and liver test results were collected.
Results: A total of 571 consecutive adult patients (307 males, 264 females) without a history of hepatitis C were evaluated. Median age was 82 yrs. (range: 52 - 99). Unknown HCV infection was detected in 12 patients (2.1%). Characteristics of the HCV-positive patients are summarized as follows (values are expressed as median and range):Sex (M/F): 7/5, Age (yrs): 74 (54 – 84), AST (IU/L): 25.5 (14 – 163), ALT (IU/L): 19 (11 – 89), Bilirubin (mg/dL): 0.8 (0.2 – 3.3) Among the 12 HCV-positive patients without a history of hepatitis C, clinical signs of liver cirrhosis were present in 1, and hepatocellular carcinoma was first detected in another patient.
Conclusions: Routine detection of anti-HCV in all adult inpatients consecutively admitted in a division of Internal Medicine in a large hospital in Tuscany allowed estimation of a 2.1% HCV infection prevalence rate. Evidence of advanced liver disease was not found in many of them but let the detection of previously undiagnosed clinically significant liver cirrhosis and hepatocellular carcinoma.

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T-26

HBV/HDV coinfection: A long-lasting indication for liver transplantation

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Background: Liver transplantation(LT) remains the only therapeutic option for decompensated HDV-liver disease. We aimed to compare the characteristics of HBV- versus HBV/HDV-positive LT recipients in our high-volume Center in the last 12 years.
Methods: All HBsAg+ patients who underwent LT in our Centre from January 2010 to December 2021 were included. Post-LT anti-HBV prophylaxis was performed with anti-HBs immunoglobulins and nucleos(t)idic analogues. Immunosuppression was based on calcineurin inhibitors, mycophenolate, and steroids (tapered to suspension in 6 months).
Results: In the study period, 1710 LTs were performed in our Centre. LT indication was HBsAg+ liver disease in 290 patients (17.0%). 147/290 patients (50.7%) were HBV monoinfected, while 143 (49.3%) were HBV/HDV coinfected.

Median age was lower in HBV/HDV patients (55.2 years, IQR 49.1-60.2) compared to HBV patients (59.0 years, IQR 55.2-63.1), $p<0.001$. Female gender was more frequent in HBV/HDV group (28.7% vs. 11.6%, $p<0.001$). Median MELD was higher in HBV/HDV coinfected LT recipients (15 vs 11, $p<0.001$). Hepatocellular carcinoma (HCC) was the main LT indication in both groups, with higher prevalence in HBV monoinfected patients (74.1% vs 54.5%, $p<0.001$). The proportion of foreign-origin patients increased in the HBV/HDV group from 9.7% in 2010-2015 to 42.0% in 2016-2021 one ($p<0.001$), whereas it remained stable in the monoinfected group (9.9% vs 16.7%, $p=0.22$) (**Table 1**). Median post-LT follow-up time was 6.9 years (IQR 4.0-9.9). Overall 5-year survival was 92.2%: 95.5% in HBV/HDV and 88.9% in HBV group, $p=0.009$. All patients remained HBV-DNA negative after LT.
Conclusions: Our experience shows that HDV still represents a noteworthy indication for LT, accounting for up to 50% of transplants performed for HBV, with a prevalence of 61.2% in the foreign subgroup. Coinfected patients need LT at a younger age and with higher MELD score compared with the HBV population, but they show an excellent 5-year post-LT survival.

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T-27

Coronary computed tomography angiography in pre-liver transplant cardiac work-up

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Background: Controversies persist about the screening of pre-liver transplant(LT) patients for coronary artery disease(CAD). Dobutamine-stress-echocardiography(DSE) is used in many centers but it performs poorly. Coronary-computed-tomography-angiography(CCTA) is a promising tool to detect CAD and we aimed to describe its role in the the pre-LT setting.
Materials and Methods: We included all patients who underwent CCTA during pre-LT work-up from 01/2022 to 11/2022 in our Centre. CCTA was performed in patients with at least one major cardiovascular risk factor (age>65 years, insulin-dependent diabetes, NASH-cirrhosis, severe peripheral vascular disease, previous stroke). Significant CAD(S-CAD) was defined as ≥50% stenosis in major-vessels or ≥70% stenosis in moderate-sized vessels. Patients with S-CAD or non-diagnostic CCTA underwent cardiac catheterization(CATH).
Results: During the study period, 119 patients underwent pre-LT work-up in our Centre. CCTA was performed in 39/119(33%) patients, with median age 65 years (IQR 60-68): 22/39(56%) diabetics, 15/39(38%) with NASH-cirrhosis, 3/39(8%) peripheral vascular disease, 4/39(10%) previous stroke, 18/39(46%) arterial hypertension, 9/39(23%) dyslipidemia, 15/39(38%) active smokers. CCTA identified S-CAD in 15/39(38%) patients and was non-diagnostic in 2(5%); 14 of these 17 patients underwent CATH which diagnosed S-CAD needing revascularization in 7 patients. 6/7(86%) underwent percutaneous coronary intervention (PCI) (one complicated by myocardial infarction) with 1 month of dual-antiplatelet-therapy; 1/7(14%) required surgical-bypass. After revascularization: 2 patients were listed for LT, 1 died, 2 are still on dual-antiplatelet-therapy, 2 excluded from LT for extra-cardiac reasons. 2/7 patients before revascularization underwent DSE which tested negative. Until now, 10/22(45%) patients without S-CAD on CCTA underwent LT without early cardiological events and among the remaining 17 patients, 2 (S-CAD not requiring revascularization) underwent uneventful LT.
Conclusions: In our pre-LT cohort with at least one cardiovascular risk factor, CCTA identified S-CAD in 15/39 patients (38%). 7 patients needed pre-LT PCI/bypass. CCTA appears to be a precious tool for detecting CAD in pre-LT work-up.

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T-28

The use of AGILE 3+ and AGILE 4 for the prediction of advanced fibrosis and cirrhosis in patients with Non-Alcoholic Fatty Liver Disease

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Introduction: non-invasive assessment of advanced fibrosis in Non-Alcoholic Fatty Liver Disease (NAFLD) is crucial for the identification of patients at greatest risk of progression. Among non-invasive tests, AGILE 3+ and AGILE 4 have been recently proposed, combining liver stiffness measurement (LSM) by vibration-controlled transient elastography (FibroScan) with clinical-biochemical variables.

Aim: we aimed to assess the accuracy of AGILE 3+ and AGILE 4 for the identification of advanced fibrosis (F3-F4) and cirrhosis (F4), respectively, against LSM in individuals with biopsy-proven NAFLD.
Methods: we retrospectively included 315 biopsy-proven NAFLD patients. No clinical, radiological or biochemical signs of cirrhosis were present at inclusion. Clinical-biochemical data and LSM were collected at time of the biopsy.
Results: median age was 48 (IQR 38-47) years, 62% were male. Median LSM was 7.5 kPa (IQR 5.8-10.1). Advanced fibrosis was present in 28%, cirrhosis in 10% and NASH in 28% of cases. Eighty subjects had type 2 diabetes. At Area Under the Curve (AUC) analysis, LSM had a value of 0.807 (Se 70%, Sp 80%) for advanced fibrosis and 0.877 (Se 88%, Sp 76%) for cirrhosis. AGILE 3+ had AUC of 0.77 for advanced fibrosis (cut-off by Youden index 0.30, Se 68%, Sp 78%), while AGILE 4 had AUC of 0.78 for cirrhosis (cut-off by Youden index 0.11, Se 55%, Sp 89%). Comparison of AUC showed that AGILE 3+ was similar to LSM for identifying advanced fibrosis (DeLong p= 0.254). Similarly, AUC comparison between LSM and AGILE 4 for cirrhosis was not different (DeLong p=0.739).
Conclusion: when compared to LSM, AGILE 3+ and AGILE 4 had similar accuracy for the detection of advanced fibrosis and cirrhosis in NAFLD patients. This research was supported by the Italian MIUR "Dipartimenti di Eccellenza 2018-2022" D15D18000410001 and by *Horizon 2020, no.777377, LITMUS.*

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T-29

Fully automated approach of machine learning combined with deep learning: How to predict the onset of major cardiovascular events in NAFLD patients

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Introduction: Growing evidence indicates that the presence of NAFLD increases cardiovascular (CV) morbidity and mortality.

Coronary arteries disease (CAD) is detected by Coronary CT, moreover CT is used also for the determination liver steatosis.
Aim: The aim of our study was to perform a prognostic's stratification risk of presence of CAD with a combined ML/DL approach in NAFLD patients
Materials and Methods: Our retrospective study analyzed clinical data and CT images of 401 patients (217 males and 184 females), who underwent coronary CT between 2017 and 2021. Hounsfield Unit (HU), Agatston score, Fib-4 score were used to measure radiodensity, calcium score (CS) and the degree of fibrosis, respectively. Fully automated algorithms were trained with clinical data, among them the best were Support vector machine, Random Forest and XGBoost for ML, while Fully Convolutional Network and Long short-term memory for DL.
Results: We performed a binary classification to compare the most used ML (XGBoost, RF, SVM) and DL (FCN, LSTM) algorithms for clinical data. Our algorithms predicted absent and severe CAD with a mean accuracy of 96% and a mean specificity of 97%. After using a multiclassification approach our algorithms were able to distinguish patients in 5 classes from healthy patients to patients affected by NAFLD and CVD, with a mean accuracy of 87% and a mean specificity of 86% for ML/DL. To improve the performance of this prediction models, we are integrating them with DL algorithms for liver CT images (e.g. 3D-UNet)
Conclusion: Our integrated ML/DL approach could be used in practice to flag NAFLD patients at high risk of CVD.

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T-30

Combined hepatic and adipose tissue transcriptomics highlights circulating NASH biomarkers

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Introduction: Obesity represents the main contributor to nonalcoholic fatty liver disease (NAFLD) and adipose tissue is strongly interlaced with the liver in the disease pathogenesis and progression. Previous studies were restricted to investigate the hepatic transcriptome across the entire spectrum of NAFLD, whereas the transcriptomic changes which occur in white adipose tissue (WAT) in relation to liver damage have been poorly investigated.
Aim: Therefore, we aimed to compare hepatic and adipose tissue transcriptome in NAFLD patients with the purpose to identify shared biomarkers useful for the diagnosis of advanced liver damage.
Materials and Methods: We performed high-throughput RNA-sequencing in 167 hepatic samples from obese patients and in a subset of 79 matched adipose tissues. Patients were subdivided in normal liver, mild and severe NAFLD according to histology. Circulating cathepsin D (CTSD) was assessed by ELISA.
Results: We identified a specific transcriptomic signature that may discriminate patients with severe NAFLD and isolated steatosis, including 424 deregulated genes in liver and 209 in adipose tissue. According to pathway and network analyses, inflammation, ECM remodeling and mitochondrial dysfunction were upregulated whereas oxidative phosphorylation was downregulated in both tissues. We highlighted 13 genes commonly deregulated in both tissues and among them, CTSD showed the most robust diagnostic accuracy in discriminating mild and severe NAFLD. In 52 obese subjects and in a validation cohort of 432 histologically-characterized NAFLD patients, serum CTSD progressively increased

from normal liver to severe NAFLD and it was associated with steatosis, necroinflammation, fibrosis, steatohepatitis (NASH) and NAS>5. The area under the curve (AUC) weighted for transaminases to foresee severe NAFLD *versus* mild and normal liver was 0.78 and 0.87, respectively.
Conclusions: CTSD may be a possible biomarker of severe NAFLD since its hepatic/adipose tissue expression as well as circulating levels correlated with liver damage thus allowing to discriminate advanced disease.

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T-31

The overexpression of TM6SF2 and/or MBOAT7 wild-type genes restores the mitochondrial lifecycle and activity in an in vitro NAFLD model

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Introduction: Mitochondrial dysfunction is a key player in the transition from NASH to HCC. The knock-out (KO) of *MBOAT7* and/or *TM6SF2* hampers the mitochondrial dynamics in Hepg2 cells resulting in an enrichment of misshapen and failed mitochondria. The overexpression of *MBOAT7* and/or *TM6SF2* wild-type genes in KO models through lentiviral vectors decreases the number of damaged-globular mitochondria, while increases the normo-shaped ones.
Aims: To deepen the impact of *PNPLA3/MBOAT7/TM6SF2* loss-of-function mutations on mitochondrial aberrances, we investigated the mitochondrial lifecycle and activity in KO cells overexpressed for the wild-type forms of *MBOAT7* and/or *TM6SF2*.
Method: Mitochondrial lifecycle and activity were assessed through RT-PCR, Western Blot, Seahorse assay and immunohistochemistry.
Results: The overexpression of *MBOAT7*, *TM6SF2* or both decreased PGC1α, the master regulator of mitobiogenesis, which was activated in KO cells in response to fusion-fission unbalance, boosted the expression of Mfn1/Mfn2 (mitochondrial outer membranes proteins involved in fusion) and OPA1 (inner mitochondrial membranes fusion protein) whereas decreased FIS1 and DRP1 (fission proteins) levels, thus re-establishing the mitochondrial turnover. Consistently, the mitophagy pathways (PINK/PARKIN/BNIP3/BNIP3-L/LC3/phospho-UBIQUITIN) increased after the *MBOAT7* and/or *TM6SF2* overexpression, prompting the disruption of damaged mitochondria. The balance of mitochondrial biogenesis is essential for organelles' homeostasis and activity. Indeed, the overexpressed models augmented the COX-I/SDHA ratio, COX-III, and citrate synthase activity alongside the oxygen consumption rate, recovering the OXPHOS capacity and Krebs cycle which were impaired in KO cells. Finally, lactate levels decreased after the upregulation of *MBOAT7* and/or *TM6SF2* wild-type genes together with the glycolytic/extracellular acidification rate, thus inhibiting the switch to anerobic glycolysis which was promoted in KO cells to trigger tumorigenesis.
Conclusion: Genetics impacts on mitochondrial maladaptation during NAFLD and the overexpression of *MBOAT7* and/or *TM6SF2* wild-type genes in KO HepG2 cells re-balances the mitochondrial lifecycle and turnover, thus ensuring the organelles' function and possibly reversing hepatocellular damage.

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T-32

B-Klotho deficiency in hepatic stellate cells (HSCs) prompts inflammation, oxidative stress and a pro-fibrotic phenotype

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Introduction: β-Klotho (*KLB*) gene encodes the hepatic co-receptor of fibroblast growth factor receptor 4 (FGFR4). We previously reported that the rs17618244 G>A *KLB* gene variant dampened KLB hepatic and plasma levels, leading to inflammation, ballooning and fibrosis both in pediatric and adult patients with nonalcoholic fatty liver disease (NAFLD). Hepatic stellate cells (HSCs) are directly involved in the fibrotic processes, playing a crucial role in the switching to severe forms of NAFLD.
Aim: To generate a new cell line of hepatic stellate cells (HSCs), responsible for hepatic fibrosis, which are deleted for *KLB*, by using Crispr/Cas9 and to investigate the impact of its deficiency on their pro-fibrotic phenotype, inflammation and oxidative stress.
Materials and Methods: We stably silenced *KLB* gene in LX2 cells (referred to as HSCs $KLB^{-/-}$) by Crispr-Cas9 technology. Then, markers of activation, cellular stress, inflammation and proliferation have been investigated.
Results: KLB mRNA and protein levels were reduced in HSC $KLB^{-/-}$ cells ($p<0.05$). Markers of activation (i.e., *aSMA, COL1A1/3A1/4A1, TGFb, PDGFRB, BAMBI*) were increased in $KLB^{-/-}$ cells at both gene and protein levels. Accordingly, retinol synthesis (*RALDH*) was reduced ($p<0.05$), suggesting a more pro-fibrotic phenotype. Moreover, *KLB* deletion strongly induced oxidative stress, enhancing ROS/reactive nitrite species (RNS) and lactate production, aldehyde derivate concentrations (MDA) ($p<0.05$). These events triggered the release of pro-inflammatory cytokines (TNFα, IL1β and IL6) into the $KLB^{-/-}$ cultured media. Finally, $KLB^{-/-}$ cells also showed an elevated proliferative rate ($p<0.05$).
Conclusions: We generated, for the first time, a stable knock-out of *KLB* in HSCs. Our preliminary results outlined that *KLB* deficiency induced an enhanced pro-fibrotic phenotype with increased proliferation, inflammation and oxidative stress, thus possibly explaining the association between the rs17618244 *KLB* at-risk variant and more severe forms of liver damage. Altogether, these observations pointed KLB a novel target to prevent severe NAFLD.

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T-33

Omicron SARS-CoV-2 variant outbreak in vaccinated liver transplant (LT) recipients in 2022: A large spread of infection, a mild disease

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Background: From January 2022 the Omicron SARS-CoV-2 variant became the dominant circulating variant worldwide, showing increased transmissibility and the ability to evade immunity. Booster vaccinations improved the protective effects of neutralizing antibodies and might have lowered the risk of hospitalization and mortality, as recently observed.
Aim: to evaluate the prevalence and outcome of Omicron-related infection in a cohort of liver transplant (LT) recipients.
Material and Methods: From January to September 2022, we enrolled in a longitudinal study all LT recipients who became SARS-CoV-2 infected (95% vaccinated; 88% receiving a 1st booster dose and 25% a 2nd booster). All patients were included in a protocol of testing anti-spike (a-S) and anti-nucleocapsid (a-N) antibodies titres before/after each dose (Elecsys Anti-SARS-CoV-2, Roche Diagnostic). Diagnostic criteria for SARS-CoV-2 infection were 1) presence of a positive nasopharyngeal swab (NFS) by PCR or antigenic assays or 2) presence of a-N seroconversion (if previously a-N negative). Reinfection was defined by a new NFS positivity or an increased value of a-N titre.
Results: Overall, 201 LT-recipients have been infected by SARS-CoV-2 (62% males, median age=61yr, 50% viral-etiology, 35% with HCC, all received a CNI-based regimen, plus MMF=63%). Most of infections were diagnosed by NFS (72%); mild flu-like symptoms were observed in 59% of our LT recipients; 72% of them remained untreated, while 28% received antivirals (11%) or monoclonal antibodies (17%). Fifteen LT recipients were hospitalized, 6 of them for interstitial pneumonia and 2 (both with previous lung diseases) died for COVID-19.
Conclusions: A mild or asymptomatic infection occurred frequently in our LT recipients with a less severe outcome than the past waves. A possible explanation could be the high prevalence of vaccinated patients in our cohort. Interestingly, the overall prevalence of SARS Cov2 infection might be underestimated without a careful monitoring of SARS-CoV-2 serology against nucleocapsid.

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T-34

Oncostatin M is overexpressed in NASH-related hepatocellular carcinoma and promotes a pro-tumorigenic inflammatory response

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Introduction: Oncostatin M (OSM) is a pleiotropic cytokine belonging to the interleukin (IL)-6 family that has been proposed to contribute to the progression of chronic liver diseases, hepatocellular carcinoma (HCC) development and metastasis. High levels of OSM was observed in cirrhotic patients with different etiology carrying HCC.
Aim: Here we investigated the role of OSM in relation to the development of HCC in non-alcoholic steatohepatitis (NASH) background.
Methods: We investigated the role of OSM in NASH-related HCC taking advantage of: a) cohort of NASH patients with/without HCC; b) mouse model of NASH-related liver carcinogenesis (DEN/CDAA protocol); c) human macrophage cell lines exposed to human recombinant OSM (hrOSM).
Results: OSM serum levels are significantly higher in patients carrying NASH-related HCC, as compared to those whit viral aetiologies, and their increase is paralleled the disease progression from simple steatosis to HCC. Noteworthy, OSM serum levels are significantly higher in patients with intermediate/advanced HCC and correlate with poor survival. In patients with NASH-related HCC, OSM is expressed in cancer cells in relation to the staging of HCC as well as to macrophages infiltrating tumour. Accordingly, OSM expression is increased in murine NASH-related liver tumours and correlates with F4/80 gene expression, suggesting an interplay between OSM and macrophages recruitment/functions in the tumor microenvironment. In particular, OSM transcript levels correlate with canonical M1and M2 macrophage polarization markers and with newly identified NASH-associated macrophages (NAM) markers (TREM-2, CD-9). The ability of OSM to promote M2 polarization, observed in human THP1 macrophages exposed to hrOSM, is due to activation of STAT3 and PI-3K/Akt signaling pathways.
Conclusions: Patients with HCC arising on a NASH background showed increased OSM serum levels that correlate with clinical parameters and disease outcome. Experimental data highlight a pro-carcinogenic contribution for OSM in NASH, by promoting pro-tumorigenic inflammation and eventually modulating tumor escape.

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T-35

Circulating interleukin-32 levels are associated with arterial hypertension in individuals at risk of NAFLD

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Background: Nonalcoholic fatty liver disease (NAFLD) is associated with metabolic comorbidities such as arterial hypertension and increased risk of cardiovascular disease (CVD), but the mechanism remains unclear. We recently reported that Interleukin-32 (IL32) is strongly upregulated and secreted in patients with severe NAFLD, correlating with liver damage. Accumulating evidence suggests that IL32 affects endothelial function and may contribute to CVD.
Aim: To examine the relationship between circulating IL32 and metabolic comorbidities in healthy individuals with metabolic risk factors for NAFLD.
Methods: IL32 plasma levels were measured by Human IL-32 DuoSet ELISA (R&D Systems) in the prospective LiverBible cohort 2020 (n=949, age 53.9±6.4 years, 83.3% males). Inclusion criteria were age 40-65 and ≥3 among: BMI≥25 Kg/m2, glucose≥100mg/dl, triglycerides≥150mg/dl, HDL<45/55 mg/dl in M/F, impaired blood pressure control (systolic/diastolic>130/80mmHg). Multivariable generalized linear models were used to analyse the independent determinants of log normalized IL32 levels.
Results: Among participants, 470 (49.5%) had NAFLD (CAP≥275), 20 (2.1%) liver stiffness measurement (LSM)≥8. Of these, 31.4% showed low circulating IL32 (<10pg/mL); median IL32 concentration was 559 pg/mL (IQR: 6258-4936 pg/mL). High circulating levels of IL32 were associated with female sex (p=.0498), as well as impaired blood pressure control (p=.0007), detected in 68.9% of participants. Notably, IL32 levels were correlated with systolic but not diastolic blood pressure (p=.017), while the use of some antihypertensive agents including beta-blockers and ace-inhibitors was inversely associated (p=.047 and p=.029 respectively). Among other liver disease predictors, plasma IL32 resulted inversely correlated with HbA1c (p=.051), but not with fasting insulin, circulating lipids and ferritin/CRP. The independent determinants of circulating IL32 levels are shown in the Table 1.
Conclusion: Results suggest a potential cross-talk between IL32 and CVD in individuals with metabolic risk factors. Additional studies are warranted to examine the possible role of IL32 as therapeutic target to reduce NAFLD comorbidities.

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T-36

Clinical utility of a targeted panel sequencing for the diagnosis of chronic hereditary liver diseases in adult patients

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Introduction: The pathogenesis of chronic liver diseases (CLD) remains often unexplained despite extended clinical and instrumental evaluations. Next-generation sequencing (Whole Exome [WES] or Targeted Panel Sequencing [TS]), may improve the diagnostic rate of rare genetic disorders also in adults, but they are not yet widely clinically available.
Aim: To evaluate the clinical utility of a TS approach in diagnosis CLD in adult patients.
Materials and Methods: We analyzed 57 unrelated adult patients with CLD of suspected hereditary etiology, using a Haloplex Customized TS including 82 selected liver-diseases causing genes. Sequencing was performed on MiSeq and data were analyzed using SureCall and wANNOVAR softwares. All variants were confirmed by Sanger sequencing.
Results: Patients' phenotypes were divided into four categories: iron overload, dyslipidemia, cholestatic diseases and fatty liver diseases. Overall, TS allowed to reach a definitive genetic diagnosis in 15 patients (diagnostic yield: 26%). Likely pathogenic variants or rare variants of unknown significance, (VUS) but with a high likelihood of altering protein function, were identified in 26 patients, providing a diagnostic rate of 46% for genetic contribution to the phenotype. A total of 16 cases (28%) remained undiagnosed. Stratifying according to the clinical phenotypes, the higher diagnostic yield was obtained in patients with dyslipidemia (36%) and iron overload (30%) (Table 1).
Conclusion: TS proved to be a useful first-tier genetic test for the diagnosis of selected adult patients with CLD, mainly if the clinical phenotype is well defined, as in dyslipidemia or iron overload cases. Moreover, TS allowed to identify genetic variants possibly contributing to disease phenotype in a high number of patients, expanding disease pathogenesis understanding. In undiagnosed cases, more extensive analysis, such as WES and determination of genetic predisposition to fatty liver disease progression, as captured by polygenic risk scores, should be performed.

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T-37

Echocardiography-based markers of subclinical cardiac dysfunction in individuals with Non-Alcoholic Fatty Liver Disease and preserved ejection fraction: Interim data from a prospective study

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Introduction: Individuals with Non-Alcoholic Fatty Liver Disease (NAFLD) have abnormal myocardial energy metabolism and reduced coronary functional capacity, even in the absence of risk factors for cardiovascular disease (CVD).
Aim: We aimed to evaluate diastolic and systolic function in NAFLD individuals with preserved ejection fraction without overt CVD.
Material and Method: We prospectively included 95 patients (median age 53.0 [IQR 44.5-62.5] years, male sex 44.6%) with ultrasound-diagnosed NAFLD undergoing echocardiographic evaluation, which included speckle tracking analysis with left ventricular global longitudinal strain (GLS) measurement (Philips, Andover, US). Diastolic dysfunction was defined by mitral E/E'>9 and systolic dysfunction was defined by GLS >-18. Significant liver fibrosis (SLF) was defined by Fibrosis-4 (FIB-4) score>1.3.
Results: Obesity, type 2 diabetes (T2D), arterial hypertension and dyslipidemia were present in 43.3%, 21.1%, 46.2% and 57.8% of cases, while median FIB-4 was 0.97 [0.67-1.24]. SLF, diastolic and systolic dysfunction were found in 20%, 17% and 18.3% of the total. Higher FIB-4 levels were found in both diastolic and systolic dysfunction (p=0.003 and p=0.001). SLF was associated with diastolic dysfunction (OR 6.8 [95%CI 1.8-25.5], p=0.004), showing an Area Under the Curve of 0.76 (Se 76.9%, Sp 72.2%, PPV 33.3%, NPV 94.5%). In a multiple stepwise logistic regression model including T2D, obesity, arterial hypertension, dyslipidemia, male sex and SLF, both SLF and T2D were significantly and independently associated with diastolic dysfunction (aOR of SLF 6.2 [95%CI 1.5-25.1, p=0.011). In the same regression model for systolic dysfunction, only T2D showed a significant association (aOR 4.6 [95%CI 1.3-16.8], p=0.021).
Conclusion: In NAFLD patients with preserved ejection fraction, SLF by FIB-4 is associated with diastolic dysfunction independently of major risk factors for CVD. Screening echocardiography may be recommended in this population. *Funding: the Italian Ministry for Education, University and Research (MIUR) under the programme "Dipartimenti di Eccellenza 2018-2022" Project code D15D18000410001.*

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T-38

Trans-splenic anterograde coil assisted transvenous occlusion (TACATO) of gastric varices associated with gastrorenal shunt

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Background: The management of gastric varices (GV) depends on anatomical and hemodynamic features and balloon-occluded retrograde transvenous obliteration (BRTO) is recommended for the occlusion of GV-associated with gastro-renal shunts (GRS). We report a prospective case-series in which we used the trans-splenic route to perform occlusion of GV for prophylaxis of variceal bleeding or refractory encephalopathy.
Methods: Trans-splenic access was obtained by puncturing a splenic venous branch under ultrasound/fluoroscopic guidance. Through a 5-Fr sheath a 2.7"microcatheter was introduced into the varices and embolization was performed using detachable microcoils +/- a mixture of N-butyl-cyanoacrylate (NCBA)-Lipiodol. A venography was performed to assess technical success. The percutaneous tract was embolized using a NBCA-Lipiodol mixture. All patients underwent upper gastrointestinal-endoscopy at follow up to evaluate worsening of esophageal varices and amelioration of GV.
Results: Ten patients with different indications were enrolled: 3 for primary prophylaxis (1 GOV1, 2 IGV1), 6 for secondary prophylaxis (1 GOV1, 5 GOV2) of GV bleeding and 1 for post-transplant shunt-related persistent encephalopathy (IGV1). In all patients, the GRS [median size 22mm (range 15-32mm)]was accessed by trans-splenic route and the GV was embolized with a median of 10 microcoils (range 5-18), with addition of NBCA-Lipiodol in 6patients. The mean time in the angiography suite was 135min (range 105-180min), while the mean procedure-time was 75min (range 45-120min). Besides mild local abdominal pain at access, 3 patients presented acute partial splenic +/- portal thrombosis, which regressed in all with anticoagulation. During follow-up (median 5months, range 1-12months) no bleeding was observed, liver function remained stable and no patient developed/worsened ascites. Endoscopic follow-up showed a significant reduction of GV or filling with coils (Fig.1), without worsening of esophageal varices.
Conclusions: TACATO seems to be a safe and efficient method to obliterate GV associated with GRS and it can be considered as alternative to BRTO in the algorithm of treatment.

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T-39

Phenotypical and molecular landscape of B lymphocytes in patients with Intrahepatic Cholangiocarcinoma

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Intrahepatic cholangiocarcinoma (iCCA) is a heterogeneous biliary tract cancer whose incidence is rising worldwide. Due to the aggressive evolution of the disease, there is an urgent need for diagnostic and therapeutic alternatives. The immune infiltrate, key component of the tumor microenvironment (TME), remains poorly characterized, limiting development of successful immunotherapies. Herein, we aimed to define phenotypical and molecular characteristics of B lymphocytes, whose role in iCCA development is still controversial. Single-cell RNA-sequencing analysis of $CD20^{+}$ cells in iCCA patients identified four main subclusters of B and revealed a downregulation of B cell activation/inflammatory genes in intratumoral compared to adjacent non-malignant tissue, suggesting that B cells play a protective role in iCCA progression. Multicolor flow cytometry analysis demonstrated an abundant infiltration of immature naïve B cells respect to the memory phenotype. A reduction in B-cell effector functions was also detected, probably due to the cellular components of the TME. Immunohistochemical analyses showed that B cells, when infiltrate the tumor tissue, create cellular aggregates similar to tertiary lymphoid structures. Overall, these observations suggest that iCCA tissue may contain various B cells subtypes with protective role, probably limited by TME. However, a comprehensive characterization of B cell property, organization and crosstalk with other cells of iCCA milieu will elucidate mechanisms of tumor progression or control, exploitable for the development of novel immunotherapeutic approaches. *The present work was partially funded by the Associazione Italiana per la Ricerca sul Cancro (IG AIRC 2019 – ID 23408 to A. Lleo)*

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T-40

Role of non neoplastic portal vein thrombosis in natural history of patients with cirrhosis and hepatocellular carcinoma

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Background: Hepatocellular carcinoma (HCC) increases the risk of non-neoplastic portal vein thrombosis (PVT) in cirrhosis. However, data on its natural history and prognostic role in HCC-patients are lacking.
Methods: Cirrhotic HCC-patients undergoing laparoscopic ablation were consecutively enrolled (2015-2018) and followed until transplantation or up to 36months. HCC and PVT (baseline and incident) characteristics, and their evolution in the first 12months, were reviewed by a single radiologist. PVT evolution was categorized according to changes in occlusion (cut-off 20%) and extension to other segments as: 'complete/progressive': partial-PVT progressing to complete, complete-PVT not improving or, PVT extending to other segments; 'partial/ameliorated': partial-PVT improving or remaining stable, complete-PVT improving. Variables associated with presence of PVT and evolution patterns were analyzed, as well as its impact on survival.
Results: Seven-hundreds-fifty patients were included, 88 with PVT (78.4% partial, 43.2% extended to mesenteric and/or splenic vein). On multivariate analysis, presence of PVT was associated with pre-treatment total-tumor-volume (TTV) (OR1.10, p<.0001) and clinically-significant portal hypertension (OR2.90, p=.0046). During follow-up, 46 incident PVT occurred, 27/46 (58.7%) in the presence of viable tumor. Among total 115 PVT diagnosed in presence of HCC, 83 had available radiological follow-up (77.1% partial, 41% extended to the mesenteric and/or splenic vein), and 22 were anticoagulated. The 'complete/progressive' evolution pattern was associated with occlusive PVT at diagnosis and absence of anticoagulation in all PVT; whereas to Child C score and non-response to HCC treatment in non-anticoagulated patients. Overall survival was lower in presence of PVT, specifically for 'complete/progressive' PVT [HR3.9, p<0.001]. A higher cumulative risk of death emerged for 'complete/progressive' PVT, both for HCC-related (p<0.001) and non-HCC-related (p<0.001) death.
Conclusions: Non neoplastic PVT in HCC seems to be characterized by a higher risk of progression when not anticoagulated, correlated with the HCC activity. Complete/progressive PVT is an independent factor associated with mortality, regardless of HCC evolution.

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T-41

Lusutrombopag treatment in cirrhotic patients with low platelets count scheduled to undergo invasive procedures: A multicenter experience

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Introduction: Lusutrombopag (LUS) is a small thrombopoietin receptor (TPO)-agonist used to treat severe thrombocytopenia, a rare evidence (1%) in cirrhotic patients scheduled to undergo invasive procedures.
Matherials and methods: Between December 2021 and August 2022, 11 cirrhotic patients, presenting with severe thrombocytopenia (PLT count<50,000uL), were enrolled (CPS A/B, mean MELD 12, no portal thrombosis) to undergo high bleeding risk procedures (5 banding ligations, 2 liver biopsies, 1 TACE, 2 surgical and 1 endoscopic resection). Patients were treated as follows: baseline PLT count check 15 days at least before the procedure(**T1**); administration of LUS (3 mg od) for 7 days(**T2**); PLT count check 9-14 days after starting LUS(**T3**); invasive procedure(**T4**).
Results: Mean PLT count pre-drug administration, the day of procedure and 7-30 days after was 37,000uL (25-49,000uL), 54,000uL (30-90,000uL) and 53,000uL (31-97,000uL), respectively. Nine patients (81.8%) reached the PLT count target and two required preemptive PLT infusion; ten patients (90.9%) did not experienced bleeding after the procedure, while one developed a periprocedural bleeding after liver biopsy, followed by arterioportal fistulas and porto-mesenteric thrombosis by CT-scan performed 7 days later (PLT 69,000uL), treated with LMWH.
Conclusions: LUS treatment requires careful schedule (TI-T4) and organization; the drug was able to significatively increase mean platelets count (≥50,000uL) in 81.8% of patients and only two patients needed PLT transfusion. Moreover, PLT≥50,000uL was manteined for at least 7-30 days after the procedure, unlike temporary effect of PLT transfusion, possibly reducing bleeding risk either in short and medium term. However, one patient experienced bleeding and developed thrombosis 7 days after the procedure, probably related to the rapid increase of portal pressure due to arterioportal fistulas and consumption coagulopaty related to early bleeding, rather then the thrombophilic effect of TPO-agonist (normal thrombophilic screening). Larger clinical practice experiences are needed to confirm efficacy, practical feasability and safety of LUS.

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T-42

RESIST Criteria: A biochemical algorithm to reduce the number of unnecessary upper endoscopies for the evaluation of portal hypertension in compensated HBV-cirrhotic patients

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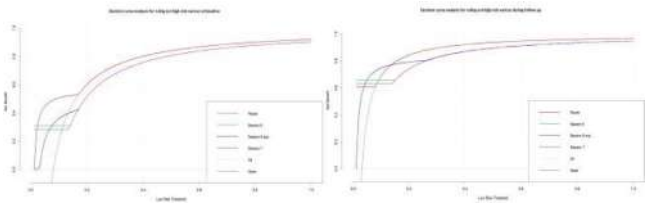
Introduction: Non-invasive criteria to identify patients with compensated hepatitis B virus (HBV) cirrhosis who can avoid esophagogastroduodenoscopy(EGD) and predict the progression of low-risk esophageal varices(EV) are lacking.
Aims: To evaluate the diagnostic performance of RESIST criteria: 1)to rule out high-risk EV(HRV) in viremic patients with compensated HBV cirrhosis at baseline; 2)to predict progression to HRV after viral suppression with nucleos(t)idic analogues(NUCs) in patients without HRV at baseline.
Methods: All consecutive patients observed at 2 Italian referral centers with compensated viremic HBV cirrhosis who received NUCs therapy during follow-up were classified as RESIST low-risk if platelets were$>120\times10^9$/L and serum albumin>3.6 g/dL or RESIST high-risk if platelets were$<120\times10^9$/L or albumin<3.6 g/dL, before and after viral suppression. Outcomes were the presence of HRV at baseline and the progression to HRV during follow-up after viral suppression. Area under the receiver operating characteristic curve(AUROC) and decision curve analysis(DCA) were calculated for RESIST and compared with elastography-based criteria (Baveno VI, Expanded Baveno VI, and Baveno VII).
Results: One-hundred-thirty-five Child-Pugh class A patients(mean age 50.8 years, 83.7% males) were included. At baseline, 35 patients(25.9%) had low-risk varices and 13(9.7%) had HRV. HRV were correctly classified in all 13 patients(100%) by Baveno VII and Baveno VI, in 12(92.3%) by RESIST and in 11(84.6%) by Expanded Baveno VI. Although RESIST missed 1 patient with HRV, they had the highest AUROC(0.73) and DCA demonstrates a higher net benefit compared to elastography-based criteria for ruling out HRV. After a median follow-up of 16.8 years, 9 out of 87(10.3%) patients without HRV at baseline developed HRV. RESIST showed higher specificity(85%) versus Baveno VII(59%) and VI(63%), avoiding a higher number(80%) of unnecessary endoscopies and showing the highest AUROC(0.90) and the highest net benefit in ruling out HRV compared to elastography-based scores.
Discussion: RESIST criteria are useful to accurately predict HRV at baseline and the development of HRV after viral suppression by NUCs in patients with compensated HBV cirrhosis.



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T-43

The impact of metabolic comorbidities and alcohol consumption on FIB-4 and NFS performance in MAFLD: A multicentric preliminary data

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Background/Aims: Metabolic dysfunction-associated fatty liver disease (MAFLD) is defined by liver steatosis with metabolic comorbidities, with different degree of disease severity. Fibrosis-4 Index (FIB-4) and NAFLD fibrosis score (NFS) are non-invasive tests (NITs) of fibrosis widely used in NAFLD, while FibroScan®, by liver stiffness measurement (LSM), evaluate the fibrosis degree. Aims:

to evaluate in patients with MAFLD the performance of scores in comparison with LSM and to define the impact of metabolic comorbidities and alcohol intake on NITs performance.
Method: 600 patients with MAFLD referring to liver clinic in Lisbon and Milan. Clinical, laboratory data and FibroScan® were performed. LSM≥10/9.3kPa for M/XL probes suggested advanced fibrosis. Daily alcohol consumption: abstainers, low (<30/20gr), moderate (30-40 and 20-30gr) and heavy (≥40/≥30gr) for men and women respectively. FIB-4<1.45 and NFS<-1.455 ruled out advanced liver fibrosis while FIB-4>3.25 and NFS>0.676 rule in.
Results: Mean age 54 yrs, 60% male, 54% obese, 30% diabetic. 61% abstainers, 13% had moderate-high alcohol consumption. LSM≥10 kPa in 15%, FIB-4<1.45 in 74%, FIB-4>3.25 in 4% and indeterminate in 22%, NFS<-1.455 in 70%, NFS>0.676 in 2% and indeterminate in 28%. Compared to LSM, FIB-4 and NFS had AUROCs of 0.58 and 0.52 for advanced fibrosis and of 0.66 and 0.72 for the exclusion. For both detection and exclusion of advanced fibrosis, FIB-4 performed worse in obese versus non-obese (AUROCs 0.55vs0.63; AUROCs 0.64vs0.72), while no differences were found regarding NFS (AUROCs 0.51vs0.52; AUROCs 0.71vs0.70). FIB-4 and NFS performed poorly in T2DM for advanced fibrosis (AUROCs<0.60). There was a negative impact of alcohol consumption on diagnostic performance for advanced liver fibrosis, particularly for NFS (AUROCs 0.50 for high alcohol).
Conclusion: Metabolic comorbidities and alcohol consumption negatively impact the ability of NITs in identifying advanced fibrosis in MAFLD. Revision of values may be necessary to avoid misdiagnosis in patients with advanced liver disease.

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T-44

The CCAAT/Enhancer-Binding Protein beta - SerpinB3 axis inhibition as a novel strategy for Non-Alcoholic Steatohepatitis treatment

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Introduction: The liver has a key role in maintaining metabolic homeostasis. The serine protease inhibitor SerpinB3 has been described as critical mediator of liver inflammation and fibrosis. 1-Piperidine Propionic Acid (1-PPA) has been recently proposed as a specific SerpinB3 inhibitor.
Aim: To assess a targeted therapeutic strategy for NASH, using 1-PPA in *in vitro* and *in vivo* models of NASH.
Methods: SerpinB3-transgenic (TG) and SerpinB3-KO mice were fed on MCD and CDAA diets to induce experimental NASH. Starting from the second month, mice were injected with 1-PPA (70 ng/g) and at sacrifice liver specimens were analyzed for histological parameters and for molecular and protein gene expression. Fibrosis and inflammation genes were assessed in LX2 and THP1 cell lines, exposed to human SerpinB3 (100ng/ml) alone or with 1-PPA (100ng/ml) after 24 hours incubation. The expression of CCAAT Enhancer Binding Protein Beta (CEPB-b), a SerpinB3 transcriptor factor, also involved in metabolic disturbances and inflammatory response, was assessed in different cell lines with or without 1-PPA and in mouse livers in relation to SerpinB3 expression.
Results: SerpinB3-KO mice showed significantly lower steatosis, inflammation and fibrosis after both dietary regimens, while opposite findings were observed in SerpinB3-TG mice, where treatment with 1-PPA reverted these features. This effect was associated to a parallel reduction of genes involved in adipogenesis, inflammation and fibrosis. These findings were confirmed in LX2 or THP1 cells exposed to SerpinB3. At mechanistic level C/EBP-β induced SerpinB3 and was in turn induced by this serpin, generating a positive loop. 1-PPA was able to inhibit the C/EBP-β - SerpinB3 axis.
Conclusions: SerpinB3 - C/EBP-b axis could be relevant in the development of NASH and the SerpinB3 inhibitor 1-PPA is effective in the control of adipogenesis, inflammation and fibrosis *in vitro* and in NASH models, supporting this approach for a targeted therapy of NASH.

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T-45

Comparison of metabolic alterations, hepatic and cardiovascular damage between primary NAFLD and HIV-associated NAFLD: Role of low visceral adiposity

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People with HIV (PWH) are at risk of developing NAFLD due to frequent metabolic comorbidities, chronic HIV-related inflammation, and exposure to antiretroviral therapy. However, whether HIV-associated NAFLD differs in clinical presentation from primary NAFLD is still unknown. To compare metabolic, hepatic and cardiovascular (CV) alterations in PWH with hepatic steatosis (HS) and primary NAFLD patients. 30 consecutive HIV mono-infected patients (mean age 46+12 years, male 81%; 90% with viral suppression) with HS at ultrasound, in absence of alcohol abuse, were compared to 60 NAFLD patients matched for sex and age. For all subjects, anthropometric parameters, metabolic comorbidities, fat mass and sarcopenia by bioimpedance, liver damage by transaminases and Fibroscan (advanced fibrosis>F3 for LSM>8.9/7.2kPa M/XL probe), CV damage by carotid ultrasound (plaques, arterial stiffness by radiofrequency as pulse wave velocity) and heart ultrasound (systolic and diastolic function and epicardial adipose tissue - EAT) were assessed. PWH with HS presented lower BMI (27.1+4 vs 29.1+4.3 Kg/m^2, p=0.04), waist circumference (98+9 vs 103.1+10.3 cm, p=0.03) and trunk fat mass (9.8+3.3 vs 12.4+4.7 Kg, p=0.02) compared to primary NAFLD patients. Nevertheless, the prevalence of metabolic alterations (type 2 diabetes 13% vs 13%; hypertension 47% vs 42%; dyslipidemia 83% vs 85%) and sarcopenia (40% vs 52%) was similar among the two groups, with superimposable liver damage (increased transaminases 17% vs 20%; advanced fibrosis 17% vs 12%) and CV damage (high CV risk 84% vs 83%; carotid plaques 39% vs 28%; increased EAT 20% vs 17%; systolic dysfunction 6% vs 5%; diastolic dysfunction 7% vs 6%; pulse wave velocity values 7.4+2 vs 6.9+1.4 m/s). PWH with HIV-

associated NAFLD have lower BMI and lower visceral adiposity compared to primary NAFLD patients despite similar prevalence of metabolic, liver and CV damage. Therefore, screening and follow up for HS in HIV patients is mandatory independently of their body weight.

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T-46

Which is the best therapy for not transplantable patients with multinodular early HCC?

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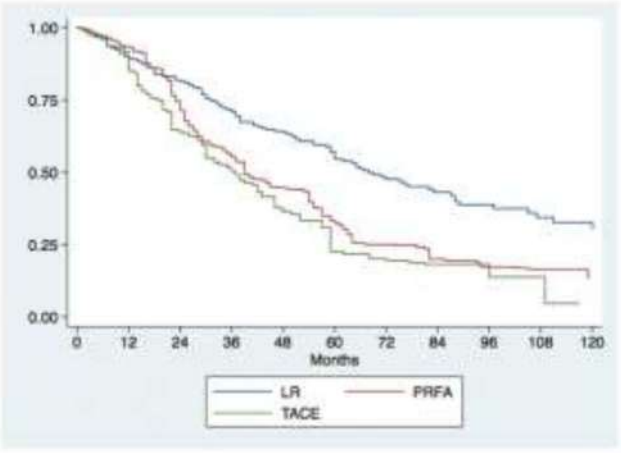
Introduction: The 2022 version of the BCLC staging system recommends a treatment stage migration from liver transplantation (LT) directly to trans-arterial chemo-embolization (TACE) in patients with multinodular early stage HCC, when LT is not feasible. We sought to compare the effectiveness of liver resection (LR), percutaneous radiofrequency ablation (PRA), and TACE in patients with not transplantable but potentially resectable multinodular early HCC.
Methods: Only multinodular not transplantable early stage (2 or 3 nodules ≤3 cm) HCC patients were considered. LR patients were obtained from the HE.RC.O.LE.S. register, whereas PRA and TACE patients were obtained from the ITA.LI.CA register. Since the aim of this study was to compare the effectiveness of three potential treatments in resectable patients, the statistical method "matching-adjusted indirect comparison" (MAIC) was used to match the PRA and TACE groups to the LR group.
Results: Between 2008 and 2020, 655 HCC cirrhotic patients were enrolled: 303 in LR, 204 in PRA, and 148 in TACE groups. Age, sex, Charlson Comorbidity index, Child-Pugh grade, MELD, platelets count, aetiology of cirrhosis, number and diameter of nodules, and alpha-fetoprotein were weighted by MAIC to create two PRA and TACE pseudo-populations balanced with the LR group. After MAIC, 1-3-5 years OS was 88%, 71%, 56% for LR (median survival 67 months), 97%, 63%, 22% for PRA (median survival 53 months), and 88%, 58%, 32% for TACE (median survival 41 months)($P < 0.001$). At Cox multivariable weighted regression, the survival benefit of LR over alternative treatments was confirmed: LR group as reference; PRA (hazard ratio 1.44; 95% confidence interval 1.19-1.84; $P = 0.0045$); TACE (hazard ratio 1.70; 95% confidence interval 1.25-2.31; $P = 0.0007$).
Conclusions: In multinodular early not transplantable HCC, LR should be the first option, followed by PRA and TACE only when LR is not feasible.



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T-47

Cholestatic HCV-related cryoglobulinemia: A new clinical and pathological entity

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Introduction and Aim: Mixed cryoglobulinemia (MC), the most common extrahepatic manifestation in chronic hepatitis C (CHC), can persist even after virus eradication, and it is a risk factor for development of cirrhosis. Up today, the relationship between MC and liver pathophysiology remains controversial, especially regarding intrahepatic cholestasis. This study aims to investigate the correlation between MC and intrahepatic cholestasis in CHC patients.
Methods: 32 not yet eradicated HCV+ MC+ patients were enrolled, matched for age, sex and HCV genotype with 31 HCV+ MC-. For each participant, cholestatic parameters (direct bilirubin, alkaline phosphatase and gamma-glutamyl transferase), HCV-RNA, HCV genotype, plasma MC were measured; liver histology and plasma cells (aggregation and distribution), observed blinded by two operators, were analyzed. Patients with known autoimmune diseases were excluded from the study. Results were evaluated by the Mann-Whitney U or the Chi-squared tests and by stepwise multivariate analysis ($p < 0.05$).
Results: 63 participants (mean age 57.1±11.1 years; males=50.8%) with CHC were enrolled. Serum cholestasis (2 or more increased cholestatic parameters) was significantly higher in MC+ group (p=0.025) and correlated in univariate analysis with cryoglobulinemia (OR 4.05; p=0.031). Plasma cells on liver histology were found in a significantly higher number in MC+ group (p=0.004) and tended to form aggregates more than in the control group (p=0.024). In stepwise multivariate analysis with genotype, HCV-RNA, steatosis, gender and age, cholestasis was only related to MC+ (OR 5.76; p=0.024).

Conclusions: Our study identified for the first time a correlation between MC, cholestasis and intrahepatic plasma cells in patients with CHC before virus eradication. Future studies are needed to understand how MC causes cholestasis.

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T-48

Salivary Analytical Device (SAD), a good tool for monitoring the metabolic status of patients with fatty liver disease

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Introduction: Physical inactivity and sedentary lifestyle have contributed to the epidemic of obesity and non-alcoholic fatty liver disease (NAFLD), the most common cause of chronic liver disease. Monitoring NAFLD patients at risk of developing complications by using a more effective health technology would allow the implementation of preventive strategies and follow-up programs that would bring important benefits to the individual and reduce the burden of this disease on the health care system.
Aim: The purpose of the study was to develop a device that could use saliva to monitor patients with dysmetabolism and derive reliable values comparable with blood values so as to allow telematic control of the patient.
Material and methods: In a small cohort of thirty patients we evaluated and compared values of lipid profile (total cholesterol, HDL, triglycerides) and glucose, detected in blood samples, with those identified in saliva samples by using commercial enzymatic kit assay. Besides that, hematological parameters were measured in saliva samples by a lab on chip to validate a prototype created in collaboration with electronic engineers and called SAD, Salivary Analytical Device.
Results: We obtained a good degree of correlation between blood and salivary values of total cholesterol (r=0.65, P=0.04), HDL (r=0.73, P=0.04), triglycerides (r=0.84, P=0.02) and glucose (r=0.98, P=0.003) both using commercial kits. Moreover SAD prototype displayed an excellent reliability for salivary parameters evaluation.
Conclusions: Although our results need to be validated on a larger cohort of patients, our preliminary data confirm that SAD can be a good tool for monitoring total cholesterol, HDL, triglycerides and glucose levels in saliva samples.

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T-49

FVIII/PC and ADAMTS13/VWF ratio to predict liver-related events and mortality in patients with ACLD

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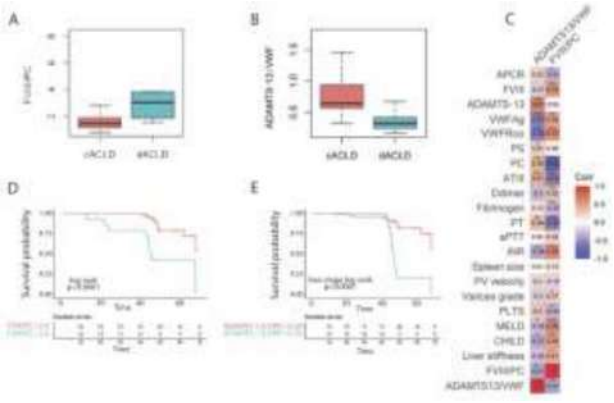
Introduction: Recent studies analyzed the prognostic role of coagulation parameters such as factor VIII (FVIII) /protein C (PC) ratio on advanced chronic liver disease (ACLD) decompensation or liver-related outcomes [1]. We recently demonstrated that a disintegrin and metalloprotease with thrombospondin 1 repeats number 13 (ADAMTS-13)/von Willebrand factor (VWF) ratio is useful to predict the development of portal vein thrombosis (PVT) [2], but little is known about its role as marker of decompensated ACLD (dACLD).
Aim: To investigate the prognostic role of ADAMTS13/VWF ratio on the development of dACLD and compare it with FIII/VWF ratio.
Materials and Methods Results: We assessed 86 patients with ACLD (median age 66 years; 65.47% male; etiology viral/nonviral 50%/50%; Child Pugh A/B/C 80.2%/15.1%/4.7% and median model for end-stage liver disease [MELD] 8). 20 patients (23.25%) developed decompensated ACLD after a median of 48.8 months and presented a significantly a lower ADAMTS-13/VWF ratio and a higher FVIII/PC ratio compared to their counterparts maintaining compensated ACLD (ADAMTS-13/VWF 0.26 [0.22-0.41] vs 0.52 [0.16-0.62], p<0.0001; FVIII/PC 2.62 [1.87-3.81] vs 1.44 [1.13-1.77], p<0.0001 Figure 1A-B). Both these indices correlated with Child Pugh and MELD score, although FVIII/PC ratio showed the strongest correlation with clinical and coagulation parameters (Figure 1C). Moreover, ADAMTS-13/VWF ratio or FVIII/PC ratio showed a good prognostic ability on dACLD-free survival and liver-related death (p<0.0001, Figure 1D-E), although ADAMTS-13/VWF ratio showed a limitation in identifying clinically relevant early events. Finally, the four patients who developed portal vein thrombosis (PVT) had a lower ADAMTS-13/VWF or a higher FVIII/PC compared to their counterparts.
Conclusions: Coagulation parameters, historically used only for assessing bleeding risk in patients with ACLD, are instead harbingers of important prognostic information. Indeed, ADAMTS13/VWF ratio and FVIII/PC ratio correlate with liver disease severity and can predict liver-related death or decompensation in patients with ACLD.



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T-50

Prognostic impact of metastatic site in patients receiving first-line sorafenib therapy for advanced hepatocellular carcinoma

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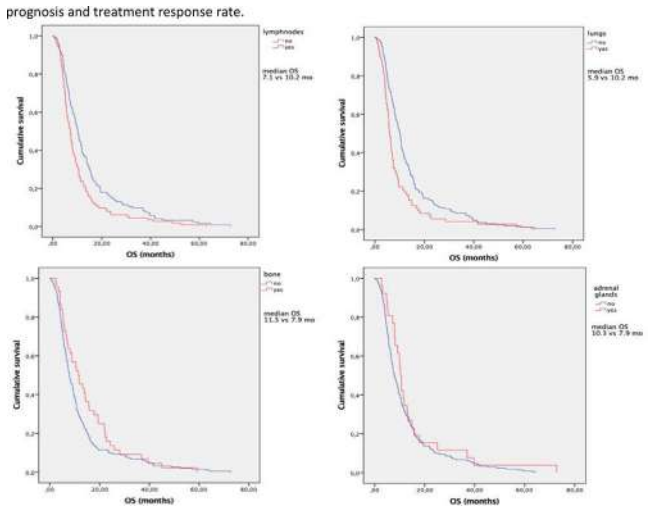
Extrahepatic spread is a well-known negative prognostic factor in patients with advanced hepatocellular carcinoma (HCC). The prognostic role of different metastatic sites and their response rate to systemic treatment is still being debated. We considered 237 metastatic HCC patients treated with sorafenib as first-line therapy in five different Italian centers from 2010 to 2020. The most common metastatic sites were lymph nodes, lungs, bone and adrenal glands. In survival analysis, the presence of dissemination to lymph nodes (OS 7.1 vs 10.2 months; $p = 0.007$) and lungs (OS 5.9 vs 10.2 months; $p < 0.001$) were significantly related to a worse survival. In the subgroup analysis of patients with a single metastatic site, this prognostic relationship remained statistically significant. Palliative radiation therapy on bone metastases significantly prolonged the survival in this cohort of patients (OS 19.4 vs 6.5 months; $p < 0.001$). Furthermore, patients with lymph node and lung metastases had a worse disease control rate (39.4% and 30.5%, respectively) and a shorter radiological progression-free survival (3.4 and 3.1 months, respectively). Different site of metastases has a prognostic impact on survival; in particular, lymph node and lung metastases have worse prognosis and treatment response rate.



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T-51

SGLT2 inhibitors improve hepatic fibrosis assessed by Fibroscan in NAFLD patients with type 2 diabetes: A five-year follow-up study

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Introduction: Subjects with non-alcoholic fatty liver disease (NAFLD) and type 2 diabetes mellitus (T2DM) present high progression of liver disease. Data are accumulating on the benefits of sodium glucose cotransporter 2 inhibitors (SGLT-2i) on hepatic fibrosis mainly in pharmacologic or retrospective studies.
Aim: to prospectively evaluate change in hepatic fibrosis assessed by Fibroscan (liver stiffness measurement LSM) in patients with NAFLD and T2DM and predisposing factors.
Materials and Methods and Results: 237 patients with NAFLD (mean age 67 ±9 years, 54% male) were enrolled at the diabetology outpatient clinics and re-evaluated after 5 years. Information about diabetic control, metabolic comorbidities and medications were collected at baseline and follow-up. Additionally, NAFLD was assessed by liver ultrasonography, whereas LSM was detected by Fibroscan® at baseline and after 5 years. During follow-up, we observed an increase in LSM mean values (6.0±2.8 vs. 5.8±2.7 kPa, $p=0.02$). LSM worsened in 133(56%) subjects, with 92 (39%) having a worsening of >10% and 20 (8%) of at least 1 fibrosis stage at Fibroscan from baseline. Moreover, a higher prescription of SGLT2i was seen (21% vs 6%, $p<0.001$). Compared with those with no worsening of LSM, patients with worsening of LSM had an increase in BMI during follow-up. In multivariate analysis, after adjustment for age, sex, liver enzymes and HbA1c, use of SGLT2-inhibitors at follow-up (adjusted-odds ratio 0.46; 95% confidence interval 0.22-0.96) was associated with a reduced risk of worsening of LSM by Fibroscan. However, this association was markedly attenuated after further adjusting for change in BMI over time.
Conclusions: Despite a high prevalence of fibrosis progression in NAFLD subjects with T2DM, we showed a potential effect of SGLT2-inhibitors in reducing the risk of worsening of liver stiffness. Moreover, data suggest the need of weight control in these patients.

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T-52

Contribution of GD2 ganglioside to aggressivness of human cholangiocarcinoma

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Background: Glycosphingolipids (GSL), a peculiar class of plasma membrane lipids, are prevalently expressed in cancer stem cells (CSC). Gangliosides (GS), sialic acid-containing GSL, regulate the malignant phenotype of several cancers. This study aims to provide a GSL and GS profiling of both stem-like subsets and their parental cells in human CCA.
Methods: Stem-like subset was enriched by sphere culture (SPH) in CCA cells (HUCCT1, CCLP1). CCA GS patterns were determined by chromatographic procedures. Identification of GSL and GS molecular species and assessment of GS turnover were evaluated by feeding cells with 3H-sphingosine. GS role was investigated using PPMP, a glucosylceramide synthase inhibitor. FACS-sorted GD2+ SPH cells were examined for stem-like gene expression compared to GD2-SPH. Enzymes of GS biosynthesis were analyzed at different times of spherogenesis.
Results: In both CCA lines, compared to monolayers (MON), SPH showed changes in specific sphingolipids (Cer, Gb3, SM), and in the amount of total GS. CCA-SPH showed increase content of GM3 and GD1a, and reduction of GM2, Appearance of GD2 was observed, a finding corroborated by high level expression of GM3 synthase as well as GD3- and GM2/GD2 in CCA-SPH. Sphere-forming ability and expression of CSC-related genes were affected by PPMP. CSC features related on GD2 availability were not dependent on GD2 synthase, but on GD3S, the synthase that provides the precursor (GD3) of ganglioside GD2. We then stably transfected both CCLP1 and HUCCT1 cells with the GD3S gene. GD3S-transfected MON cells showed enhanced sphere-forming ability, superior invasive properties, as well as higher drug resistance when treated with cisplatin and oxaliplatin. Global transcriptomic analysis indicated that GD2+ SPH cells were enriched with CSC-markers in addition to several genes involved in pluripotency, self-renewal, and EMT, compared to GD2-SPH. Notably, expression of GM2/GD2 synthases was significantly expressed in tumor samples compared to paired non-tumoral liver tissue of CCA patients (n=104) and correlated with presence of satellite nodules, lymph node invasion, and recurrence.
Conclusions: We show for the first time that the CCA stem-like properties may be associated with GS synthetic pathway and pattern. GS synthases could represent potential markers for CCA.

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T-53

Screening rate for Hepatitis D in Hepatitis B patients: Tips and tricks

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Introduction: Hepatitis B virus (HBV) and its satellite virus hepatitis D (HDV) are common worldwide hepatotrophic infections responsible for cirrhosis and hepatocellular carcinoma. EASL practice guidelines recommend HDV screening in all Hep B patients. Novel therapies for Hep D are promising.
Aim: To determine screening rates for HDV in HBV patients referred to our Laboratory of Hub Hospital Pordenone (Friuli Venezia Giulia).
Methods: We retrospectively considered HBsAg positive results from 01.01.2018 to 31.12.2021. Using an extended database to 30.11.2022, we considered, among those were HBsAg positive, anti-HDV results and if we detected positivity for anti-HDV, we checked if HDV-RNA was performed.
Results: 931 patients (55% non-Italian native) positive for hepatitis B surface antigen were studied with a majority male patients (65%). Of 931, 470 (50%) Hep B patients were screened for Hep D and 13 (1.4%) (9 non-Italian native) were positive for anti-HDV. Of 13, 6 were positive for serum HDV-RNA; 3 subjects were negative for HDV-RNA while 4 patients did not perform HDV-RNA. 10 Hep-B patients (1%) negative for anti-HDV at first time were re-tested for anti-HDV more than once. Comparing 2018-2019 vs 2020-2021, screening rate for Hep D decreased from 56% to 40%.
Conclusions: Despite current HDV guidelines, in our Hospital HDV screening is suboptimal and it is actually declining. In fact COVID-19 has caused the slowing down of hepatitis testing program. Therefore we suggest: 1) anti-HDV simplified and automated reflex testing algorithms in Hep B patients for an early diagnosis and linkage to care of HDV infection; 2) enhancement of molecular biology for HDV-RNA assay in our Italian Labs; 3) repeating more than once anti-HDV especially in high-risk HBV patients. Furthermore, we need to be careful for Hep B vaccine to reduce Hep D screening and disease burden.

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T-54

Preliminary results of intrahospital HCV screening for elimination: A single center experience

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Introduction: New HCV models of care aimed to elimination are emerging. In particular, hospitalized patients may represent an ideal population for HCV screening and for referral treatment.
Aim: To evaluate the feasibility of an opportunistic hospital-based HCV screening and its linkage to care in our Hub Hospital Pordenone (Friuli Venezia Giulia).
Methods: All patients consecutively admitted to Internal Medicine, Neurology, Gynecology and Surgery from 5.09.2022 to 5.12.2022 were screened with in-hospital reflex HCV testing. During the hospital stay, Hepatologysts examined all viremic subjects, as the result of Laboratory alert or Specialist advice.
Results: Among 1.176 (median age: 70 years old, 59% female) inpatients consecutively screened, 40 (3.4%) were HCV-Ab positive. Among patients positive for HCV-Ab, 9 had been previously treated for HCV infection with SVR and were excluded. Of 31 patients (HCV-Ab+) patients who were tested for HCV-RNA, 15 (1.2%) were HCV-RNA positive. The highest prevalence of HCV-RNA positivity (86%) was found in patients admitted to Internal Medicine. Of 15 patients HCV-RNA+: 2 patients died during hospital admission, 1 refused treatment with DAAs, 7 patients were evaluated for antiviral therapy but were excluded due to severe comorbidities, short life expectancy (<6 months) and elderly age, 2 (13%) patients started DAAs. Antiviral treatment was planned for the remaining 3 patients, after the resolution of the acute event that led to hospitalization (sepsis, pneumonia, heart failure). For all patients with hepatitis C, HCV counselling for caregivers was explained. 5 patients (33%) were unaware of HCV infection.
Conclusions: Hospital HCV screening is feasible because HCV active infection has been frequently found in patients with comorbidities admitted in our Hospital.In fact submerged/unaware people with hepatitis C still exist. In-hospital reflex HCV testing has enabled optimal linkage to care for the first visit. However, reasons for hospital admission and severe comorbidities may delay antiviral treatment reducing the HCV treatment cascade.

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T-55

Hepatitis D: A still relevant disease

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Introduction: Hepatitis D virus (HDV) affects approximately 5% of chronically infected hepatitis B (HBV) patients and remains a common indication for liver transplantation (LT), which is the only therapeutic option for patients with end-stage liver disease and unresectable hepatocellular carcinoma (HCC).
Aim: Our aim was to investigate the different characteristics, indications to LT and long-term patient survival of HDV-coinfected patients compared to HBV-monoinfected patients.
Matherials & Methods Results: All patients waitlisted for LT at our Center between 2006 and 2020 were retrospectively evaluated. Demographic characteristics, indication to LT, liver function, type of antiviral therapy before and after LT were recorded. A total of 1555 patients were included in the waiting list (WL): 18.2% of patients were HBsAg positive of which 32.6% were HDV-coinfected. At the time of admission to WL, HBVD patients differed significantly from HBV-monoinfected patients in terms of gender (females 42.4% vs 14%, p<0.001), and age (54, IQR 45 – 56 vs. 56, IQR 51 – 61, p=0.017). HDV-coinfected patients had significantly lower rate of HCC diagnoses (36/92 – 22% vs 128/192 – 66%, p<0.001) and HCC as indication to LT (21/92 – 17.2% vs 101/192 – 52.6%, p<0.001). Patients with HBVD had similar probability to LT (65.7% vs 64.7%, OR 1.046 CI95% 0.5-2.3, p=0.9) and death (21% vs 19%, OR 1.13 CI95% 0.5-2.8, p=0.8) than monoinfected patients, but they were less often excluded from WL due to stability of disease (1% vs. 5%). HBVD patients had similar patient survival (p=0.981) as HBV-monoinfected patients. Post-transplant prophylaxis was based on combination therapy with NUCs and HBIG. HDV-coinfected patients did not experience viral relapse after LT.
Conclusions: Hepatis D infection is still significantly prevalent among HBsAg carriers. LT is the only curative approach for end-stage liver disease. Survival after LT was comparable to that of HBV-monoinfected patients.

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T-56

Long-term results from the Italian real-world experience on obeticholic acid treatment in primary biliary cholangitis: The RECAPITULATE study

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Introduction: Obeticholic acid (OCA) is the only licensed second-line therapy for PBC patients non-responders/intolerant to UDCA. Real-world experiences on OCA therapy are somehow limited by reduced sample sizes and short follow-up.
Aim: Aim of the RECAPITULATE study is to provide long-term real-world data on OCA therapy in a large Italian cohort of patients with PBC.
Methods: Data on patients in OCA therapy from centres belonging to "Italian PBC registry", "CLEO/AIGO", "Sicilian PBC Network" and "PBC Project Piemonte-Liguria-Valle-D'Aosta" were captured. Cumulative incidences of OCA response and discontinuation were evaluated through Aalen-Johansen (taking into account the competing risk of discontinuation) and Kaplan-Meier estimators, respectively.
Results: 441 PBC patients (median age 58, women 88%) on OCA therapy for at least 6 months were enrolled from 50 Italian centres, with a median time on OCA therapy of 24 months (IQR 12-36, max 48). Cirrhotics were 152 (34%), PBC/autoimmune hepatitis (AIH) overlap were 59 (13%). According to POISE, response probabilities were 37.5/43.5/47.2% at 12/24/36 months. Discontinuation probabilities were 12.8/17.7/22.9% at 12/24/36 months, with pruritus (41 patients, 48%) and hepatic events (18 patients, 21%) as leading causes. In cirrhotics, probabilities of response were lower (25.9/27.7/34.8% at 12/24/36 months; $p<0.01$ Vs non-cirrhotics), due to higher discontinuation rates (19.9/27.6/34.6% at 12/24/36 months; $p<0.01$ Vs non-cirrhotics), while patients with PBC/AIH overlap did not show significantly different probabilities of response and discontinuation ($p=0.20$). Results of Vibration-Controlled-Transient-Elastography (VCTE) were available from 309/114/69 patients at 0/12/24 months. Liver stiffness measurement (LSM) was stable at 12 months in both OCA responders and non-responders, while a significant reduction was observed at 24 months only in responders ($p=0.01$).
Conclusions: Our results confirm long-term efficacy and safety of OCA therapy in a large real-world cohort of PBC patients. These first results concerning LSM variation over time under OCA treatment need to be confirmed in a larger subgroup of patients.

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T-57

Intestinal activation of the lxr-α receptor protects the liver from NASH-related damage

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Introduction: Non-Alcoholic fatty liver disease (NAFLD) is the most common liver disorder in western countries, with an estimated global prevalence of 25%, with differences according to the age, sex and ethnicity. NAFLD is characterized by the accumulation of different lipid species within hepatocytes and encompasses a spectrum of conditions including simple steatosis and non-alcoholic steatohepatitis (NASH). Liver X receptors (LXRs) are master regulators of whole-body cholesterol homeostasis and also exert anti-inflammatory effects, but its effects in the treatment of NASH are controversial.
Aim: Assess in an experimental model of NAFLD, whether the activation of the LXR receptor in the intestine leads to a reduction of the damage, and in particular the accumulation of lipids and inflammation, characteristics of the metabolic syndrome.
Materials and Method: We used FVBN (controls) and iVP16-LXRα (with constitutively activated LXRα in enterocytes) mice treated for 12 weeks with a control diet, or with CCl_4 (Carbon tetrachloride) combined with a Western Diet (WD) as a model of NASH.
Results: The results show a reduction in hepatic weight, hepatic triglyceride and cholesterol content, as well as a reduction in hepatic expression of genes involved in lipid absorption and storage and de novo lipogenesis (FABP4, CD36 and FAS) in WD/CCl_4 iVP16-LXRα compared to WD/CCl4 FVBN. Also, FVBN controls showed a raised number of CD68+ macrophages compared to iVP16-LXRα WD/CCl_4, suggesting an increased inflammation, unlike iVP16-LXRα which show preferentially anti-inflammatory M2 macrophages and a reduction in both systemic and hepatic inflammation (as measured by inflammatory antibody arrays and OpenArray gene expression technology). Furthermore, treated iVP16-LXRα mice showed a reduced deposition of hepatic collagen and down-expression of the main fibrogenic genes (α-SMA, TGF-β and type 1 and 3 collagen). These results indicate a possible anti-inflammatory effect exerted by HDL via the SRB1 receptor, a mechanism that needs to be further investigated.
Conclusion: The present work demonstrates that a specific activation of intestinal LXRα may exert beneficial effects and could represent a novel therapy for the treatment of NASH.

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F-01

MiR-494 induces metabolic reprogramming through G6pc targeting and modulates sorafenib response in hepatocellular carcinoma

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Introduction: The epidemiology of hepatocellular carcinoma (HCC) in industrialized countries is increasingly related to metabolic syndrome and non-alcoholic steatohepatitis (NASH). Despite the approval of molecular targeted drugs, including immune checkpoint inhibitors, the lack of circulating biomarkers still impacts patient responsiveness to treatments, as evidenced by reduced sensitivity to immunotherapy in NASH-associated HCCs. In this context, there is an urgent need to identify new biomarkers to help stratify patients according to personalized therapeutic regimens.
Aim: The aims of this work are to study metabolic mechanisms underlying miR-494 overexpression in HCC preclinical models and to assess miR-494 as a circulating biomarker associated with metabolic features and sorafenib resistance in HCC patients.
Materials and Methods: We identified miR-494 metabolic targets through bioinformatics analysis. QPCR analysis of glucose 6-phosphatase catalytic subunit (G6pc) was performed in preclinical models and HCC patients. Functional and metabolic analyses assessed G6pc targeting and miR-494 involvement in metabolic change, mitochondrial dysfunction, and ROS production in HCC cells. Live-imaging analysis elucidated the involvement of miR-494/G6pc axis in cell proliferation of HCC cells under stressful conditions. Circulating miR-494 levels were assayed in sorafenib-treated HCC patients and DEN-HCC rats.
Results: We demonstrated that miR-494 promote a metabolic shift of HCC cells towards a glycolytic phenotype trough G6pc targeting. The miR-494/G6pc axis exhibits an active role in the metabolic plasticity of tumor cells promoted by glycogen and lipid droplets accumulation to be used under detrimental conditions. High miR-494 serum levels are predictive of sorafenib resistance in a small cohort of HCCs and identify patients with metabolic derangements. AntagomiR-494-based strategies showed a synergic effect with metabolic inhibitors and sorafenib in HCC cells.
Conclusions: Our preliminary data suggest miR-494 as a possible target for combined treatments and a promising biomarker for the identification of patients with dysmetabolic HCCs who may be refractory to currently approved treatments.

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F-02

Myosteatosis is not associated with complications or survival in HCC patients undergoing transarterial embolization

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Background and aims: Alterations in nutritional and metabolic status, in particular sarcopenia, have been extensively associated with a poor prognosis in cirrhotic patients regardless of the etiology of liver disease. Less is known about predictive value of myosteatosis, defined as pathological fat infiltration into the skeletal muscle, in this context.
Methods: We retrospectively analyzed a cohort of 151 cirrhotic patients with unresectable hepatocellular carcinoma (HCC) who underwent their 1st trans-arterial embolization (TAE) between March 1st 2011 and July 1st 2019 in our Institution. Demographic, clinical and biochemical data were collected. Sarcopenia was assessed using the L3-SMI method. We calculated myosteatosis with a dedicated segmentation suite (3D Slicer), using a single slice at an axial plane located at L3 and calculating the IMAC (Intramuscular Adipose Tissue Content Index). The sex-specific cut-off values for defining myosteatosis were IMAC > -0.44 in male and > -0.31 in female.
Results: In our cohort of 151 patients, 115 (76%) patients were included in the myosteatosis group; 128 (85%) patients had a coexistent diagnosis of sarcopenia. Patients with myosteatosis were significantly older and showed higher BMI than patients without myosteatosis: male gender and alcoholic or metabolic-related cirrhosis were most represented in the myosteatosis group. Myosteatosis was not associated with different HCC burden, length of hospitalization, complication rates and readmission in the first 30 days after discharge. Overall survival was not influenced by the presence of myosteatosis.
Conclusions: Myosteatosis didn't significantly affect the main outcomes of cirrhotic patients with HCC undergoing locoregional treatments.

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F-03

Prevalence and predictiors of porto-sinusoidal vascular disorder in patients with constantly elevated gamma-glutamyl transferase levels: A multicenter Italian study

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PSVD includes a group of vascular diseases featuring lesions encompassing portal venules and sinusoids, irrespective of the presence of portal hypertension (PH). Liver biopsy (LB) is fundamental for diagnosis. A recent monocenter study showed high rates of PSVD in patients with isolated and unexplained GGT elevation who underwent a LB; due to the small sample, the study could not identify factors associated with PSVD.

Aim of this study was to validate in a multicenter cohort the rate of PSVD in patients with isolated GGT elevation and identify clinical factors associated with PSVD.

We retrospectively included all patients who underwent a LB for unexplained isolated and persistent GGT elevation in five Italian Hepatology Units from March, 2015 to December, 2021. All LB specimens were reviewed by hepatopathologists.

144 patients met the inclusion criteria and were enrolled in the study. Most patients were males (76/144, 53%) with the mean age being 52 years (range 19-74). 11 patients (7.6%) presented liver stiffness (LS) suggestive of advanced liver disease (>10 kPa) but none showed clinical features of PH. The histological findings were compatible with PSVD in 96 out of 144 patients (67%). In 13 patients (9%) histology was compatible with NASH, in 3 patients (2%) with hepatic sarcoidosis and in 3 patients with congenital hepatic fibrosis (CHF). Histology showed healthy liver in 29 (20%) patients. At univariate analyses male sex, LS <10 kPa and GGT <214 UI/L were associated with PSVD ($p<0.05$). The same factors were confirmed by logistic regression: LS <10 kPa (OR 7.5 (95%, CI 1.7-32.3), GGT <214 UI/L (OR 2.8 (95%, CI 1.29-6.28) and male gender (OR 2.5 (95%, CI 1.19-5.58).

PSVD is common in patients with elevated GGT and no signs of PH. Male gender, LS and GGT levels can be used to identify these patients a priori.

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F-04

Glomerular Hyperfiltration is a new marker of fibrosis severity in non-cirrhotic NAFLD

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Background: Non-alcoholic fatty liver disease (NAFLD) represents a risk factor for development of cardiovascular disease and chronic kidney failure, early expressed by glomerular hyperfiltration (GH). GH shares the same cardiovascular and metabolic risk factors as NAFLD. Their association has already been evaluated in adults with metabolic syndrome. Despite that, association between GH and NAFLD fibrosis is not described in literature.
Methods: 597 patients, with an age between 18 and 60 years old, from three centers (Verona, Milan and London) with non-cirrhotic NAFLD diagnosed by abdominal ultrasound, were enrolled. The degree of steatosis and stiffness were assessed by sonography and Fibroscan (echoSense), respectively. Glomerular filtration rate (GFR)

was estimated using 2021CKD-EPI formula. Two different classes were defined: normal (<110 and >60 mL/min)(nGFR) and hyperfiltration (≥110 mL/min)(hGFR). Main anthropometric and biochemical indexes, medical history, current therapy and smoke habits were recorded.
Results: Of the 597 (mean age 51.2±5.41, 64% male) enrolled patients, 541 had nGFR, 56 hGFR. The hGFR group was characterized by a younger age (47.2 ± 5.2 vs 51.6 ± 5.3, p<0.001), reduced use of beta blockers (2.9% vs 14.7% p=0.03), lower s-creatinine [61.0 (CI 52.5 – 67.0) vs 75.0 (CI 67.0 – 86.0), p<0.01]. Mean stiffness was 6.30 (CI 4.85–9.65) kPa in hGFR, compared to 5.90 (CI 4.50–8.00) kPa in nGFR (p=0.030) and grade 3 steatosis was more frequent in hGFR group (54.4% vs 36.4%, p=0.03). Using univariate and multivariate models with GFR as dependent variable, age, male sex and stiffness were independent variables (OR 0.8, 0.03, 5.78, respectively). The collinearity showed a strong link between hyperfiltration and stiffness (VIF=1).
Conclusions: GH correlates with a worse degree of liver stiffness. Therefore, hGFR could be considered an early marker of liver fibrosis in non-cirrhotic NAFLD patients.

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F-05

Hepatocyte depletion of ERK5 impairs the response to lipotoxic oxidative stress resulting in defective insulin receptor signaling

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Background/aims: Insulin resistance is an early event in nonalcoholic fatty liver disease (NAFLD), but the molecular mechanisms underlying the reduced response to insulin are still elusive. The mitogen-activated protein kinase ERK5 has been implicated in the development of hepatic fibrosis and cancer. Aim of this study was to investigate the role of ERK5 in the regulation of hepatocyte sensitivity to insulin.
Methods: A murine hepatocyte cell line (MMH) was silenced using lentiviral vectors encoding shRNA for the ERK5 gene. Mitochondrial depolarization was assayed using the TMRE staining protocol. OXPHOS was measured by Seahorse. Mice with hepatocyte-specific deletion of ERK5 (ERK5ΔHep) were fed with a high-fat diet (HFD) for 16 weeks. For Glucose and insulin tolerance tests were conducted injecting 1 g/kg BW glucose or 0.8 U/kg BW insulin, respectively, i.p.
Results: MMH stably silenced for ERK5 showed reduced Akt activation following insulin stimulation. When ERK5-silenced cells were exposed to palmitic acid and then stimulated with insulin, Akt activation was abrogated, and expression of the insulin receptor (IR) reduced. Additionally, ERK5 silencing induced phosphorylation and activation of JNK, resulting in phosphorylation of IRS-1 on inhibitory residues (S307). In parallel, an increase of mitochondrial ROS generation was observed in ERK5-depleted MMH. ERK5 is known to induce a NRF2-dependent anti-oxidative stress response. Expression of the NRF2-target genes HMOX1 and NQO1 was reduced in ERK5-silenced MMH. Treatment with NAC, a free-radical scavenger, prevented the downregulation of the IR and the increase in IRS1 phosphorylation on S307. Measurement of the mitochondrial membrane potential indicated a strong depolarization in ERK5-silenced cells, together with an impairment of mitochondrial OXPHOS, associated with up-regulated expression of PGC-1alpha and TRIB3, a negative regulator of insulin signalling through inhibition of Akt. ERK5ΔHep mice exhibited impaired glucose tolerance and reduced insulin sensitivity. Hepatocyte depletion of ERK5 in vivo was also associated with reduced expression of IR, and increased expression of PGC-1α and TRIB3
Conclusion: We have elucidated a new role of ERK5 in maintaining hepatocyte insulin sensitivity, via an antioxidant response involving IRS-1, PGC-1α, and TRIB3, and converging on Akt activation.

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F-06

Role of the interplay between ERK5 and hypoxia in intrahepatic cholangiocarcinoma cells

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Background/Aims: Intrahepatic cholangiocarcinoma (iCCA) is an aggressive liver malignancy with limited therapeutic options, and its incidence is increasing in the Western countries. ERK5, a kinase belonging to the mitogen-activated protein kinase family, has been recently shown to be involved in iCCA progression. Hypoxia, a condition that occurs in solid tumors, is involved in malignant transformation mainly activating hypoxia inducible factors (HIF) 1/2 α. This study was undertaken to investigate a possible interaction between hypoxia and ERK5 and to unveil a possible interplay between two potential targets in iCCA.
Methods: Two iCCA cell lines (HuCCT-1 and CCLP-1) were used. ERK5, phospho-ERK5, HIF-1α, Glut1 and CAIX were investigated by Western blotting. Gene silencing was performed with shRNA. Pharmacologic inhibitors of ERK5 activity and HIF-1/2 α were used. Quantitative RT-PCR was employed to analyze HIF 1/2 α mRNA expression. MTT and crystal violet assays were used to evaluate cell viability.
Results: HIF-1α and HIF-2α mRNA expression was increased in iCCA cells compared to normal human cholangiocytes. HIF-1α protein levels were increased upon hypoxic (0.2% O_2) conditions with the subsequent upregulated expression of its two targets Glut1 and CAIX. An increase of ERK5 phosphorylation was observed upon hypoxia, while in ERK5-depleted cells an enhancement of total and nuclear HIF-1α was found, indicating an interplay among the two signaling pathways. Combined treatment with HIF and ERK5 inhibitors synergized to reduce cell viability compared to single treatments. Among the different HIF and ERK5 inhibitors used, KC7F2 and JWG071 resulted the more efficient combination.
Conclusions: ERK5 is activated upon hypoxic conditions and cross-talks with HIF in CCA cells.

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F-07

Impact of Endoscopic Band Ligation on Bleeding Incidence in Patients with Chronic Liver Disease and High-Risk Varices

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Introduction: Baveno VII guidelines preferred the use of non-selective beta-blockers (NSBB) as primary prophylaxis (PP) of high-risk varices (HRV) in patients with chronic liver disease in accordance with data showing that the 2-year bleeding rates of 14% in patients undergoing NSBB treatment.
Aim: evaluate the cumulative incidence of esophageal varices bleeding in patients with chronic liver diseases treated with endoscopic band ligation (EBL).
Material and Methods: We enrolled 153 consecutive patients referred to the Liver Clinic from 01/01/2016 to 31/12/2019, with chronic liver disease undergoing variceal endoscopic screening and evidence of HRV, not in PP for any kind of intervention (i.e., EBL and NSBB) or with previous events of variceal bleeding. After the first EBL, each patient was followed-up every 21 days upon variceal eradication. After successful eradication, endoscopy was repeated after 1-3 months and then after 6-12 months. Data were analyzed according to competitive risk analyses (competitive event=death), and predictors of variceal bleeding were described with sub-hazard ratios (sHR).
Results: Patients were predominantly males (62%), with a median age of 72 (61;80) years. The most prevalent etiology of chronic liver disease was alcohol (37.2%). 65.4% and 18.3% of patients were in Child-Pugh (CP) classes B and C, respectively. Forty-nine (32%) patients had at least one episode of variceal bleeding during the follow-up period. In particular, the cumulative incidence of bleeding (*Figure*) varies from 2% (10 months after EBL) to 26% (60 months after EBL). Total bilirubin (sHR 1.40 [95% C.I. 1.20-1.90], p=0.001), INR (sHR 2.7 [95% C.I. 1.4-5.6], p<0.001) and Platelet Count < 100.000 (sHR 3.2 [1.9-6.10], p=0.039) were the most significant predictors of variceal bleeding.
Conclusion: patients with higher CP scores show high rates of variceal bleeding despite successful eradication and appropriate follow-up, showing that in view of long-term follow-up, other interventional strategies for PP should be preferred.

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F-08

Individualized HBIG withdrawal in an historical cohort of liver transplant recipients in Italy

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Introduction: Since the advent of third-generation Nucleoside-Analogues (3-NA) characterized by strong potency and high genetic barrier, the role of long-term HBIG has been questioned to the extent that Scientific Societies suggest that HBIG should be used for a finite duration, specifically in compliant patients without Delta co-infection. The same guidance applies to historical patients. Surprisinglly, many LT centres across Europe are reluctant to change and prefer continuing with HBIG-NA long term
Aim: To report the results of HBV prophylaxis according to the ELITA Guidelines in a cohort of historical liver transplant recipients.
Material and methods: All consecutive adherent HBV LT recipients without HDV coinfection and in regular follow-up in 7 italian sites. Patients on Lamivudine shifted to 3⁻NA before HBIG-withdrawal. A prospective observational Registry for monitoring serological and biochemical paramethers was implemented.
Results: 136 patients were considered for HBIG withdrawal with 2 being excluded: one refused, the other excluded for poor-compliance. One additional patient on LAM/HBIG did not tolerate shifting from LAM to entecavir.

133 patients stopped HBIG after a median time of 7 years from LT (range 1-27). HBV-Dna at LT was positive in 63%, negative in 12% and unavailable in 25% of the cases.

100 and 56 patients have a follow up of at least 3 and 6 months with 98 (98%) and 54 (96%) currently HBsAg-ve. All patients remained HBV-DNa –ve, asymptomatic and with normal liver function tests.

Assuming a maintenance dose of 1000 IU every 4 weeks, the cost saving per-patient would be of at least 4.000 Euro for each additional year. For centres who have many patients in follow-up the cost saving would be substantial.
Conclusion: HBIG withdrawal in adherent HBV+/HDV- patients on lifelong 3NAs is safe and associated with HBsAg negativity in the vast majority of cases. The substantial cost-saving could cover different needs.

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F-09

Long-term survival in patients undergoing trans jugular intrahepatic portosystemic shunt placement after liver transplantation

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Introduction: Trans jugular Intrahepatic Portosystemic Shunt (TIPS) insertion after liver transplantation (LT) has been reported in a limited number of patients, with controversial results. The absence of long-term survival studies has not allowed the clear definition of a prognosis of these patients. This study aims at evaluating the long-term graft- and patient-survival in this subset of patients.
Methods: Patients receiving a TIPS for post-LT portal hypertension-or venous-related complications in our Transplant Center were retrospectively evaluated. Clinical success was defined as the resolution of the complication that led to the TIPS insertion. Procedure-

related complications were documented. Patients' follow up was defined until death or at June 30th 2020.

Results: Between 2001 and 2015, 25 LT patients and 2 re-LT patients underwent TIPS insertion. Patients were more frequently males (77.8%), with a median age at LT (or re-LT) of 52 years (range 24-69) and predominantly viral aethiology (74.1%). TIPS placement was performed after a median of 91 days (27-787) following LT. The more frequent indications for post-LT TIPS insertion were Veno-Occlusive Disease-related ascites (48.2%), non-VOD ascites (33.3%), portal vein thrombosis (7.4%). Mean pre-TIPS MELD-score was 12.5±4.4; mean HVPG was 16.1±6.5 mmHg pre-TIPS and 7.9±4.1 mmHg post-TIPS. Clinical success was achieved in 20 patients (74.1%). The rate of procedure-related complications was 40.7%, no procedure-related deaths occurred. During the follow-up, 12 patients (44.4%) developed at least one episode of encephalopathy, shunt occlusion was recorded in 8 patients (29.6%). Graft- and patient-survival rates at 1, 3 and 5 years post-TIPS were 77.8%, 63.0%, 44.4% and 85.2%, 74.1%, 55.6% respectively. Graft-survival rates were greater in patients with pre-TIPS MELD<14 (75.0% and 56.3% at 3 and 5 years; p=0.028).

Conclusions: Patients undergoing TIPS insertion after LT showed a 5-year graft survival post-TIPS of nearly 45%; therefore they need a careful follow-up for a possible re-transplantation candidacy.

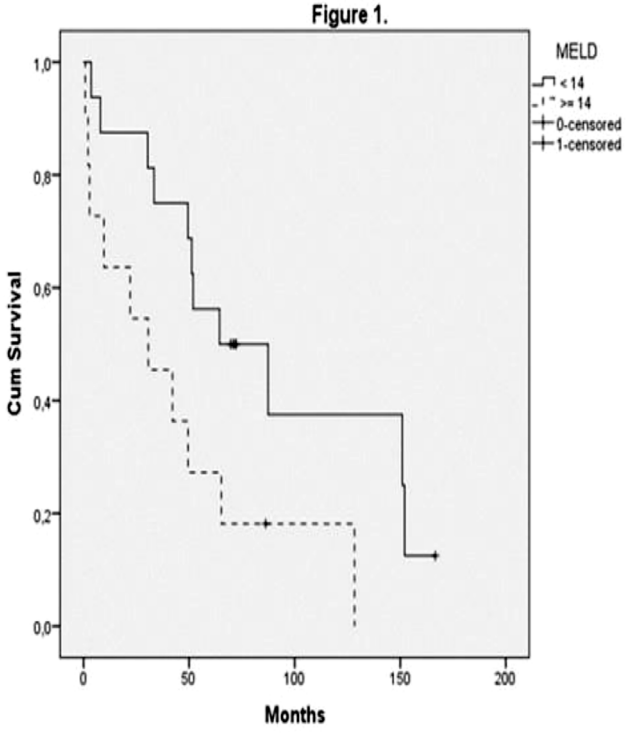

Figure 1. Kaplan-Meier curves of post-TIPS graft-survival grouped by pre-TIPS MELD score; MELD <14 (solid line) vs MELD ≥14 (dotted line) - Log-Rank p< 0.05

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F-10

High Incidence of sepsis caused by MDR bacteria in patients undergoing Percutaneous biliary drainage for the treatment of biliary obstruction

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Percutaneous biliary drainage (PTBD) is indicated in the management of jaundice and cholangitis caused by biliary obstructions. In an era of increasing prevalence of multidrug resistant (MDR) bacteria the risk of post-PTBD infection is not well established.

The aim of our study was to assess the prevalence of post PTBD sepsis driven by MDR bacteria and to identify clinical and epidemiological variables associated with MDR Bacteria.

We retrospectively collected data of all consecutive patients who underwent PTBD in our Hospital from January 2015 to January 2020.We recorded the overall incidence of post-procedural sepsis and analyzed various clinical features for their contribution to MDR-sepsis incidence using multivariate linear regression analysis.

A total of 99 PTBD were performed in 73 patients during the selected period. The most frequent etiology of biliary obstruction was malignant: Cholangiocarcinoma in 40(54%), Hepatocellular Carcinoma(HCC) in 10(13%) and biliary involvement from other neoplasms in 15 (20%). The median age was 68(range 31-86), male sex was predominant (61%) with 23% of patients having a concomitant chronic liver disease.

The majority of patients received cancer treatment prior to PTBD (surgery in 36%, chemotherapy 27%, locoregional treatment in 19%, radiotherapy 19%). Twenty-nine patients (39%) had at baseline a bacterial cholangitis, with only 1 patient infected by a MDR microorganism prior to PTBD. After PTBD 34/73 (46%) patients developed sepsis, in 9 cases (9/34,26%) was caused by MDR bacteria(5 ESBL, 2 Amp-C, 2 VRE). At multivariate analysis the only risk factors associated with MDR sepsis were previous local radiotherapy (p=0.01) and baseline AST value (p=0.009).

Post PTBD sepsis is frequent in patients undergoing treatment of biliary obstruction. MDR sepsis was found mostly in patients who underwent radiotherapy and had high AST values. Further studies to assess the need for pre PTBD screening for MDR colonization are warranted

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F-11

Predictors of extrahepatic recurrence after transarterial chemoembolization as first-line therapy for hepatocellular carcinoma

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Introduction: The literature regarding the risk of progression to extrahepatic disease and clinical factors associated with the development of metastases in patients with hepatocellular carcinoma (HCC) treated with transarterial chemoembolization (TACE) is sparse.
Aim: We aimed to assess the incidence of extrahepatic recurrence and to identify clinically relevant risk factors for the development of metastases in patients with HCC undergoing TACE as first-line treatment.
Materials and Methods: From the Italian Liver Cancer (ITA.LI.CA) database, data of 981 HCC patients undergoing TACE as first-line treatment were retrieved and retrospectively analyzed. Incidence of extrahepatic recurrence was compared between two groups according to the diameter of the largest liver lesion at the time of TACE (HCC $\leq$ 3 cm vs. HCC $>$ 3 cm). Multivariate Cox regression was used to identify predictor of extrahepatic recurrence.
Results: During a median follow-up of 27.0 months, the overall recurrence rate was 75.4%. Only 8.0% of patients had metastases at first recurrence (5.4% in the $\leq$3 cm group and 10.7% in the $>$3 group; p=0.002), while the overall extrahepatic recurrence rate was 26.0% (21.2% and 31.0% patients in the $\leq$3 cm and $>$3 cm groups, respectively; p=0.0006) (Figure 1). Compared to those with larger tumors, patients with HCC $\leq$ 3 cm had a significantly longer recurrence-free survival (12.0 [95% CI 10.7-13.3] vs. 9.7 [95% CI 8.2-11.2] months; p=0.02) and overall survival (52.5 [95% CI 45.5-59.4] vs. 34.7 [95% CI 30.7-38.7] months; p$<$0.0001). HCC size $\geq$ 3 cm, multifocality and AFP levels were independent predictors of extrahepatic recurrence.
Conclusions: Although the majority of patients treated with TACE do not develop extrahepatic recurrence, the incidence of early metastases (within one year) is not negligible at all (8%). The identification of the risk factors involved (HCC size, multifocality, AFP levels) may help to assess patient prognosis and to evaluate the opportunity of an adjuvant treatment, when this will be available.

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F-12

Preoperative predictors of recurrence beyond Milan criteria in hepatocellular carcinoma patients treated with frontline liver resection

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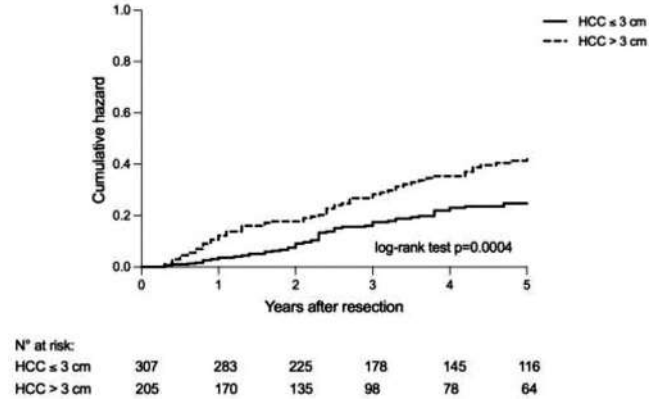
Introduction: Hepatocellular carcinoma (HCC) recurrence is common in patients treated with liver resection (LR). Salvage liver transplantation (LT) may be an option provided that a transplantable recurrence has occurred.
Aim: We aimed to assess incidence and preoperative predictors of recurrence beyond Milan criteria (MC) in patients with small ($\leq$ 5 cm) single HCC treated with first-line LR.
Materials and Methods: Data of 512 patients with single HCC $\leq$5 cm treated with frontline LR were retrieved from the Italian Liver Cancer (ITA.LI.CA) database. Incidence and predictors of recurrence beyond MC was compared across two groups according to tumor diameter (HCC $\leq$3 cm vs. $>$3 cm).
Results: During a median follow-up of 4.2 years, the overall recurrence rate was 55.9%. Only 18.0% of patients had a first recurrence beyond MC (14.0% in the $\leq$3 cm group and 23.9% in the $>$3

group; p=0.005), while the overall recurrence rate beyond MC was 30.3% (25.1% and 38.0% patients in the ≤3 cm and >3 cm groups, respectively; p=0.002) (Figure). Compared to those with larger tumors, patients with HCC ≤3 cm had a longer recurrence-free survival (4.0 [95% CI 3.3-4.7] vs. 2.5 [95% CI 2.0-3.0] years; p=0.002) and overall survival (9.9 [95% CI 6.5-13.4] vs. 7.8 [95% CI 5.7-9.9] years; p=0.008). HCC size and alpha-fetoprotein (AFP) level at the time of LR were independent predictors of recurrence beyond MC. A subanalysis in patients with "ab initio" potentially transplantable HCC confirmed these results.

Conclusions: Despite the high recurrence rate, LR for single HCC ≤ 5 cm offers excellent long-term survival. Recurrence beyond MC is predicted by HCC size and AFP levels. Referral for salvage LT should be immediate at the first HCC recurrence, but high-risk patients (HCC >3 cm and high AFP) could be considered for frontline LT or listed for transplantation even before recurrence.



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F-13

Independent determinants and predictors of controlled attenuation parameter (CAP) values in 1,230 individuals with metabolic dysfunction

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Background: Hepatic fat content, a key driver of liver disease, can be non-invasively assessed by controlled attenuation parameter (CAP) during vibration controlled transient elastography (VCTE).
Aim: Examine clinical and metabolic determinants and predictors of CAP values in a cohort of apparently healthy individuals at high risk of fatty liver disease (FLD) due to metabolic dysfunction.
Methods: We enrolled 1,230 consecutive blood donors (LIVER-BIBLE-cohort up to June 2022) with ≥3 features of dysmetabolism (overweight/obesity, hyperglycemia, hypertension, low HDL/high triglycerides) who underwent a cardiometabolic evaluation. CAP was measured by VCTE with Fibroscan; CAP determinants and predictors were identified by backward stepwise analysis and introduced in generalized linear models.
Results: Participants were predominantly males (82.9%), mean age was 53.8+6.4 yrs, 600 (48.8%) had steatosis (CAP≥275 dB/m) and 27 (2.2%) had liver stiffness measurement (LSM)>8 kPa. CAP values correlated with higher LSM ($p<10^{-22}$). At multivariable analysis, fasting insulin and abdominal circumference (AC) were the main independent determinants of CAP ($p<10^{-7}$), together with body mass index (BMI; $p<10^{-4}$), age, diabetes, triglycerides, ferritin, and lower HDL and thyroid stimulating hormone (TSH; p<0.05). AC was also an independent determinant of CAP>275 dB/m ($p<10^{-5}$), with insulin and diabetes, BMI, and lower HDL and TSH (p<0.05). In a subset of 592 participants, we found an independent association between higher fT3 levels, correlating with higher TSH, and CAP values (estimate 11.78+3.92, p=0.0027), independently of TSH and of levothyroxine treatment. A clinical score based on BMI, AC, HbA1c and ALT predicted CAP≥275 dB/m with moderate accuracy (AUROC=0.73), which was better than that of fatty liver index (AUROC=0.69) and ALT (AUROC=0.61).
Conclusion: Severity of insulin resistance and abdominal adiposity were the main independent determinants of CAP in individuals with dysmetabolism, and may improve the risk stratification of early FLD. Higher CAP was associated with a modulation of the hypophysis-thyroid-axis and fT3 conversion.

Independent determinants of CAP values in the LIVER-BIBLE-2022 cohort.

	Overall Liver-Bible-2022 cohort (n=1,230)			Subgroup with fT3/T4 determination (n=592)		
	Estimate	SE	p-value°	Estimate	SE	p-value°
Age, years	0.59	0.17	**0.0005**	0.47	0.24	**0.0491**
Sex, F	0.95	1.59	0.5514	0.94	2.29	0.6829
BMI, Kg/m^2	2.22	0.55	**5.06*10^{-5}**	2.05	0.80	**0.0101**
AC, cm	1.07	0.20	**9.28*10^{-8}**	1.07	0.29	**0.0002**
Glucose, mg/dL	0.14	0.07	0.0634	0.19	0.11	0.0860
Insulin, mIU/L	0.68	0.12	**1.61*10^{-8}**	0.50	0.17	**0.0034**
T2D, yes	10.48	4.46	**0.0189**	17.13	6.81	**0.0120**
HDL-C, mg/dL	-0.28	0.11	**0.0149**			
TG, mg/dL	0.03	0.01	**0.0382**			
Ferritin, log ng/mL	3.63	1.27	**0.0042**			
TSH, mU/L	-1.46	0.72	**0.0445**			
fT3, ng/L				11.78	3.92	**0.0027**

° At GLM, adjusted for ethnicity and reported variables (identified at backward stepwise analysis, not shown).
AC: abdominal circumference; BMI: body mass index; F: female; fT3: free triiodothyronine; HDL-C: high-density lipoprotein cholesterol; SE: standard error; T2D: type 2 diabetes; TG: triglycerides; TSH: thyroid stimulating hormone.

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F-14

HDV epidemic in Central Italy is stable over the last two decades and is characterized by the circulation of multiple HDV subgenotypes 1 inducing different inflammatory stimuli

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Background: In Italy, HDV-prevalence and its fluctuations over time are controversial while an extensive characterization of HDV-infected patients is missing.
Aim: To assess HDV-seroprevalence in a large cohort of HBsAg-positive subjects, followed in Central Italy over time, and the epidemiological/virological characteristics of HDV-infected patients.
Methods: 1,579 consecutive and well-characterized HBsAg-positive patients, firstly referred to Tor Vergata-University-Hospital from 2005-2022, were included. HDV-RNA was quantified by a commercial assay (LLOQ:100copies/ml) and HDV sub-genotypes were defined by phylogenetic-analysis.
Results: Among 1,579 HBsAg-positive patients, 45.3% (715/1579) received HDV-screening with an increasing temporal-trend: 17.1% (2005-2010), 43.2% (2011-2015), 56.5% (2016-2019), 75.8% (2020-2022). The lack of HDV-screening significantly correlated with normal ALT (OR[95%CI]:1.69[1.28-2.22], P<0.001) and being Italian (OR[95%CI]:1.4[1.12-184], P=0.005), while no factors were identified in 2020-2022. Overall, this suggests a higher awareness towards HDV-screening in all HBsAg+ in recent years.

13.4% (96/715) of HDV-screened patients resulted anti-HDV+ with a stable temporal trend: 10.7% (2005-2010), 15.6% (2011-2015), 10.8% (2016-2019), 10% (2020-2022). Among them, 80.5% had detectable HDV-RNA (median[IQR]log:4.6[3.6-5.6]copies/ml) with altered ALT in 89.3% (median[IQR]:92[62-177]U/L).

Anti-HDV positivity was higher in patients from Eastern Europe than from Italy (23.6% versus 12.9%, P=0.002). Notably, anti-HDV+ patients from Eastern Europe were younger (44[37-54] versus 53[47-62]years, P<0.001) with higher HDV-RNA (4.8[3.6-5.8] versus 3.9[1.4-4.9]copies/ml, P=0.016) and HBsAg (9,461[4,159-24,532] versus 4,447[737-13,336]IU/ml), P=0.032), indicating more pronounced HDV-replication.

Phylogenetic-analysis revealed the circulation of HDV sub-genotype 1a (25.9%), 1b (33.4%), 1c (25.9) and 1d (14.8%). Notably, sub-genotype 1a and 1c correlated with 3xULN ALT compared to 1b and 1d (75%% versus 27.3%, P=0.039).
Conclusions: The awareness to request HDV-screening is increasing over time even if some gaps remain to achieve HDV-screening in all HBsAg-positive patients. Immigration from Eastern Europe contributes to the circulation of HDV-strains with enhanced replication. The detection of different sub-genotypes, triggering variable inflammatory stimuli, supports the need to expand HDV molecular characterization.

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F-15

Group therapy for alcohol addiction treatment before liver transplantation reduces post-transplant alcohol relapse: preliminary results of a monocentric retrospective study

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Introduction: Long-term survival of patients with end-stage alcoholic liver disease is excellent after liver transplantation (LT), but the predisposition to alcohol relapse (AR) in these patients can reduce such a beneficial effect.
Aim: To assess whether participation in group therapy for alcohol addiction treatment before LT can reduce post-transplant AR.
Materials: Clinical and social informations of 16 consecutive liver transplanted patients (age 57±8 years, 3 females) were collected from January 2019 to December 2022 and patients were followed for median 12.5 months (interquartile range 3.8-25.6). Difference between participants and not participants in group therapy was assessed by restricted mean event time analysis. Alcohol addiction was diagnosed by Diagnostic and Statistical Manual of Mental Health-IV criteria and alcohol abstinence was assessed by patient or caregiver interview and confirmed by urinary sample analysis.
Results: AR was observed in 4 patients (25%), 3 patients after 12 months from LT and earlier in 1 patient. Two patients among those with AR became heavy drinkers. Eight patients participated in group therapy before LT, whereas the others refused it. In participants in group therapy, no AR was observed, whereas in not participants AR was observed in 4/8 patients (0% vs 50%, respectively, p=0.077). Not significant differences in age, sex, marital status, caregiver presence, alcohol addiction severity, 6-month alcohol abstinence, and MELD score were observed before LT between participants and not-participants in group therapy. The mean time to AR in the not participants in group therapy was 17.6 months (95% confidence interval 8.6-27.5), whereas the mean observation time of participants without AR was 34 months (p=0.011).
Conclusions: This study shows that participation in group therapy for alcohol addiction treatment before LT can reduce post-transplant AR. This preliminary result justifies the design of confirmatory prospective clinical trials.

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F-16

Prognostic impact of previous intraarterial treatment in patients with hcc treated with sorafenib

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Introduction and Aim: Hepatocellular carcinoma (HCC) can be treated with different treatment options, TACE is among the most effective options in patients at intermediate stage (BCLC B), however failure rate and its risk of liver function impairment are also well-known. Depending on local expertise patients belonging to BCLC-B stage are often treated with multiple loco-regional treatments even if unsuccessful rather than receive systemic therapy upfront. In this study we aimed to evaluate the impact of previous TACE on patients who received Sorafenib.
Method: Multicentric retrospective study involving patients who received Sorafenib between January 2010 and December 2018 in 6 different Italian hospitals. We included 668 patients from the ARPES database, 116 patients (17.6%) received more than two intraarterial treatments, 129 received only one treatment and 102 received 2 different TACE, while the remaining part of the population did not receive any TACE. We used a Cox-regression analysis to find predictors of survival.
Results: No changes in term of OS were found between patients who received >2 TACE (mOS 11.1 months) and patients who received two or less (mOS 12.4), a closer look to the curve shows how after the first 12 months there is a sustained separation between these groups.

Thus we stratified our population according to response to sorafenib, median OS in Non-responder was not affected from the number of TACE they received, whereas in the Responder group patients who received ≤2 TACE had a significant prolonged median OS than patients who received ≥3 TACE (22.6 months vs 15.6 months, p=0.04). This was confirmed in the multivariate analysis where TACE was an independent predictor of mortality with an hazard ratio of 1,547 (p= 0,016).
Conclusion: This study demonstrates how having received more than two TACE is an independent risk factor for mortality in patients who respond to Sorafenib.

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F-17

Quality of life outcomes in people with Primary Biliary Cholangitis treated with obeticholic acid: results of a phase 4 real life observational trial

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Introduction: Primary biliary cholangitis (PBC) can be associated with impaired health-related quality of life (HRQoL) caused by symptoms, mainly pruritus and fatigue, and eventually depression.Treatment confidence strongly affects HRQoL in PBC, and UDCA has been reported to be a positive factor in enhancing trust therapy. No real-life data on this and HRQoL exist regarding obeticholic acid (OCA) second-line therapy.
Aim: To assess the impact of OCA on biochemistry, patients' illness perception and HRQoL of PBC patients
Methods: We designed a phase 4 observational open label study (Protocol AOP1515) and collected at baseline and every 6 months from starting OCA biochemistry, adverse events, reported symptoms and the results of following questionnaires: PBC-40, Fatigue Impact Scale(FIS), 5-D Itch scale, EuroQoL-5D-5L. Changes in symptoms after OCA introduction were assessed by Wilcoxon paired rank test.
Results: Nineteen (60%) over 32 patients who started OCA treatment between March 2018 and April 2022 for insufficient response to UDCA agreed to participate. Median duration of OCA treatment was 32(15-53) months with no drug discontinuation due to adverse events. A decrease of alkaline phosphatase compared to baseline below 1.5xULN and 1xULN was observed in 47%,67%,64%,67% and 16%,21%,35%,17% patients at 6,12,18,24 months, respectively. At the time of starting OCA, significant pruritus, fatigue, cognitive and social dysfunction, emotional impairment, and general symptoms were present in 5%,32%,11%,53%,37%, 21% patients, respectively. No significant aggravation of itch or other symptoms was observed after OCA introduction, except for a transient aggravation in emotional domain at 12 months (8[5-10]*vs.*14[9-19], p=0.005). A trend over a significant reduction of fatigue evaluated by FIS at 36 months was observed (45[0-82]*vs.*10.5[0-42],p=0.06). All patients reported a significant and persistent general improvement after OCA introduction.
Conclusion: People with PBC and insufficient response to UDCA experienced a biochemical and subjective improvement after OCA introduction and no aggravation of objectively assessed HRQoL.

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F-18

RuvBL1 haploinsufficiency promotes hepatic lipid catabolism hampering NASH-HCC progression in mice

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RuvBL1 is a AAA$^+$ATPase involved in several cellular processes including DNA repair, gene expression, telomerase complex assembly and mTOR pathway activity. It is deregulated in various human cancers and its expression correlates with a worse prognosis in HCC patients. We have previously demonstrated that RuvBL1 haploinsufficiency impairs insulin signalling affecting the PI3K/Akt/mTOR pathway.
Given the relevance of mTOR pathway hyperactivation in HCC, we tested if RuvBL1 genetic targeting could reduce mTOR-driven hepatocarcinogenesis in Pten$^{hep-/-}$ mice.
Pten$^{hep-/-}$ and Ruvbl1$^{hep+/-}$ mice were crossed to generate Pten$^{hep-/-}$Ruvbl1$^{hep+/-}$ mice. Oil red, Sirius red and F4/80 staining revealed a significant reduction of steatosis, fibrosis, and inflammation in Pten$^{hep-/-}$Ruvbl1$^{hep+/-}$ compared to Pten$^{hep-/-}$ at 12 weeks of age. Similar mRNA expression of mTOR-driven lipogenic targets was found in the two mice models. However, expression of *Ppara* and its target CPT1 was increased in Pten$^{hep-/-}$Ruvbl1$^{hep+/-}$, indicating a lipid-lowering action mediated by PPARalpha in this mouse model. Moreover, promoter reporter experiments revealed that inhibition of RuvBL1 activity by CB-6644 increases PPARalpha transcriptional activity in AML-12 hepatocytic cell line. Next, MS proteomics analysis of RuvBL1 immunoprecipitation in murine AML-12 and Hepa1-6 cells revealed that RuvBL1 interacts with several members of the lysosomal AMPK complex (V-ATPase, LAMTOR1, LAMTOR4, Rag C).
Furthermore, p-AMPK and p-RAPTOR were increased in Pten$^{hep-/-}$Ruvbl1$^{hep+/-}$ compared to Pten$^{hep-/-}$mice, suggesting a role of RuvBL1 at the interplay between mTOR and AMPK in

hepatic lipid metabolism. Finally, Pten$^{hep-/-}$Ruvbl1$^{hep+/-}$mice aged to 15 months showed better survival than Pten$^{hep-/-}$ which developed significantly more HCC and of higher grade. qPCR analysis showed a significant upregulation of key lipolytic genes, such as *Cpt1a, Acadl, Acadvl* and *Ppara,* in Pten$^{hep-/-}$Ruvbl1$^{hep+/-}$ at 15 months of age.
In conclusion, RuvBL1 targeting mitigates the NASH metabolic and tumorigenic phenotype driven by mTOR hyperactivation in Pten$^{hep-/-}$ mice, likely promoting the switch from mTOR-driven lipogenesis to AMPK-induced fatty acid catabolism.

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F-19

TIPS under-dilation strategy with new controlled expansion endoprosthesis: A hemodynamic and imaging confirmation of its feasibility

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Introduction: The use of small caliber (<8 mm) transjugular intrahepatic portosystemic shunt (TIPS) is a promising approach to reduce shunt-related complications. Its feasibility with the new controlled expansion endoprosthesis (GORE® VIATORR® CX 8-10 mm) has not yet been explored.
Aim: To investigate whether GORE® VIATORR® CX self-expands over time at portal vein wall (PVW) and hepatic vein wall (HVW) when under-dilated to <8 mm at TIPS placement.
Material & Methods: We prospectively enrolled consecutive patients with cirrhosis who received under-dilated TIPS between June 2020 and September 2022 at our tertiary referral Center in Modena, Italy. All patients underwent hemodynamic measurements a) immediately before and after TIPS placement, b) 6-7 days and c) ≥1 month after the procedure. We measured average pressure values in different sites along the TIPS: portal-vein tract (PV), intra-parenchymal tract (IP), hepatic-vein tract (HV) and inferior vena cava (IVC). A subgroup of patients underwent serial CT scans within 24h (T0), at 6-7 days (T1) and at ≥1 month after TIPS (T2). Average maximal inner diameter of endoprosthesis was measured at 5 standard sites: PV, PVW, IP, HVW and distal HV.
Results: Sixty-four patients underwent hemodynamic assessments: 25, 29 and 10 received TIPS under-dilated to 5, 6 and 7 mm, respectively. A significant drop of pressure was observed while crossing PVW and HVW in all under-dilated groups (Figure 1A). Forty-three of these patients underwent CT scans: 17, 19 and 7 were dilated to 5, 6 and 7 mm, respectively. PVW and HVW sites maintained under-dilation overtime (Figure 1B). No TIPS dysfunction occurred during a mean follow up period of 363 days.
Conclusion: Under-dilation TIPS strategy performed with GORE® VIATORR® CX is feasible. Evaluation of clinical outcomes after applying this strategy are awaited.

Figure 1A Average pressure at each standard site in hemodynamic assessment time points (immediate post-TIPS, 6-7 days and ≥ 1 months after TIPS)

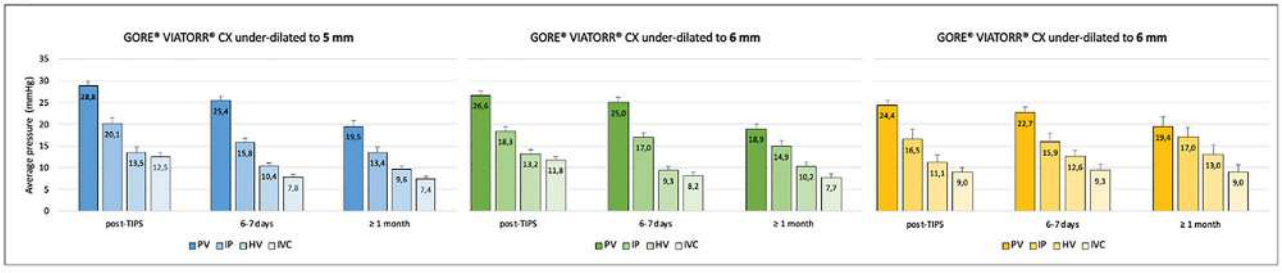
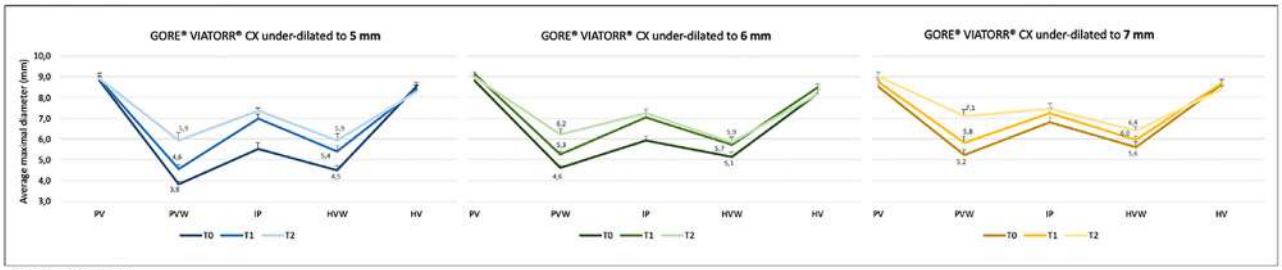


Figure 1B Average maximal inner diameters at each standard site in CTs time points (T0, T1 and T2)



Bars represent mean±SE
HVW, hepatic vein wall; HV, hepatic vein lumen; IP, TIPS intra-parenchymal tract; IVC, inferior vena cava lumen; PV, portal vein lumen; PVW, portal vein wall.

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F-20

Genetic characterization of a dysmetabolic and obese population of Southern Italy

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Background and Aims: Non-alcoholic fatty liver disease (NAFLD) is the leading cause of liver diseases, and the susceptibility to develop NAFLD is highly variable and influenced by environmental and genetic factors. The gold standard for diagnosis and staging of NAFLD is liver biopsy, however, it is an invasive procedure, subject to sampling errors and inter-observer variability. Several non-invasive methods aim at diagnosing hepatic steatosis and predicting significant/advanced fibrosis. GWAS studies identified genetic risk factors, and genetic risk scores (GRS) were developed for risk stratification. NAFLD susceptibility is associated with four genetic variants: *PNPLA3* rs738409, *TM6SF2* rs58542926, rs641738 close to *MBOAT7* locus, *GCKR* rs1260326. Our aim was to evaluate how these variants are distributed in an obese and dysmetabolic population of Southern Italy and how GRS correlates with biochemical phenotypes.
Method: We enrolled 184 patients attending our Hepatology Clinic and Surgery department, 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. Anthropometric data, FibroScan, and blood test results were collected.
Results: In our cohort, we observed a higher MAF of PNPLA3 and GCKR variants compared to the ones reported in European population of 1000Genomes Project ($p<0.0001$). The rs738409 G allele frequency is 35,1% vs. 23%. The rs1260326 T allele frequency is 52,7% vs. 41%. In a sub-cohort of 65 patients, we recorded Fibroscan parameters and biochemical data and evaluated the effect of the 4 variants together by GRS. GRS increased proportionally with ALT levels ($p=0.01$), and AST, total cholesterol, triglycerides, and CAP (p=N.S). Considering a CAP value of 275 as discriminant for moderate/severe steatosis, GRS is significantly higher in the CAP>275 subjects ($p<0.05$).
Conclusion: This study shows that in our population, PNPLA3 and GCKR risk alleles frequency are higher, and GRS correlates with biochemical and Fibroscan parameters, identifying the most dysmetabolic subjects.

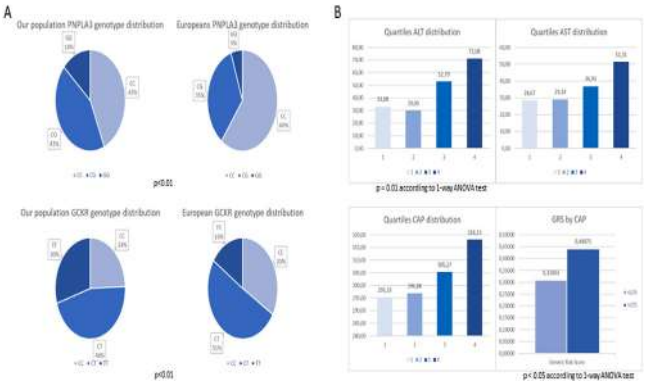

Figure 1. Characterization of dysmetabolic and obese population. A) PNPLA3 and GCKR variants distribution. Chi-Square test. B) Biochemical parameters straified by GRS. One-way ANOVA test.

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F-21

Enhanced detection of overt HBV infection in chronic HCV carriers

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Introduction: Hepatitis B (HBV) and hepatitis C (HCV) virus coinfection are frequent in subjects at high-risk, with most HBV infections in chronic HCV carriers being apparently inactive (HBsAg negative and anti-HBc positive). HCV treatment may lead to HBV reactivation, more frequently in cases with a low-level HBV replication undetectable by current HBV serological assays.
Aim: To unveil active HBV infections in a cohort of HCV-infected individuals by employing an HBsAg assay with higher sensitivity.
Methods: We selected a single sample from each of 100 HCV-RNA positive, untreated patients admitted over the last three years. Sera were analyzed by Abbott ARCHITECT assays for HBsAg, by both the current (HBsAg Qual II) and a new (HBsAg Next) version, and for anti-HBc, anti-HBs and HIV.
Results: Sixty-six were males and the median age was not significantly different between genders, with 87% of all subjects aged >43 years. The median HCV-RNA levels were 5.98 log10 IU/mL in females and 5.73 log10 IU/mL in males; 40 subjects were HIV infected, 29 of those virally suppressed. Markers of HBV infection were identified in 81.8% of males vs. 47.1% of females ($p<0.05$) and 70% overall, with 6% more being positive only for anti-HBs. The most common pattern was anti-HBc alone (37%) followed by anti-HBc + anti-HBs (33%) and HBsAg + anti-HBc + anti-HBs in one case (male, 54 years, HIV coinfected). HBsAg Next identified four more positive: one female, three males, three HIV-coinfected, two positive for anti-HBc + anti-HBs, two only for anti-HBc. No significant correlation between HCV-RNA levels and HBsAg positivity was found.
Conclusions: There's a high rate of HBV coinfection in chronic, unvaccinated HCV carriers. The frequency of overt HBV infection, detected by a highly sensitive HBsAg assays, is relevant and monitoring HBV infection during and after DAA treatment for HCV shall be warranted.

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F-22

Efficacy of a polyphenols enriched EVOO in MAFLD patients: a preliminary evaluation on cardiovascular risk, metabolism and liver function parameters.

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Introduction: Mediterranean Diet (MD) has protective effect on mortality and survival free from cardiovascular events. The added value of MD is extra virgin olive oil (EVOO), a food with monounsaturated fatty acids and polyphenols high-content.
Aim: We evaluated, in MAFLD patients, polyphenols-enriched EVOO (PPE) intake efficacy on clinical and laboratory parameters inferring with cardiovascular risk, metabolism and liver function. We present preliminary results of the 1st of a 3-years study co-financed by the European Union - PON Research and Innovation 2014-2020 - DM1062/2021.
Materials and Methods: Thirty consecutive MAFLD patients enrolled at University Hospital of Palermo were randomized, in double-blind, to add PPE or standard EVOO (SE) (40ml/daily for 6 months) to a MD. Anthropometric/demographic measures, liver function, metabolic and inflammatory status, flow mediated dilatation (FMD), ultrasound liver and abdominal fat features were analyzed at baseline (T0) and after 6 months (T6).
Results: All patients had good adherence to MD (mean Perceived Dietary Adherence Questionnaire: 45 in both groups) and consumed EVOO 40ml/daily-dose. No differences were found at T0 between groups. In SE group, from T0 to T6, a significant ($p<0.05$) reduction was proved for waist circumference (WC), HbA1c, subcutaneous fat thickness (SFT), and FMD. In PPE group, a significant ($p<0.05$) reduction was proved for BMI, WC, HbA1c, insulinemia, HOMA-IR, SFT and FMD.

When comparing the two groups at T6, no difference was proved, even if major reduction was shown in PPE group for BMI, WC, ALT, HbA1C, triglycerides, total and LDL-cholesterol, FMD, SFT and visceral fat thickness.
Conclusions: MD *plus* EVOO for 6 months can improve both metabolic and cardiovascular parameters in MAFLD, without differences between PPE and SE. No effect was proved over liver function and US features. Our preliminary data have been conditioned by low number of patients and we hope to prove significancy completing the study.

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F-23

Impact of complications on long-term survival after pediatric liver transplantation

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INTRODUCTION: Pediatric Liver Transplantation (PLT) usually benefits of excellent long-term patient-survival rates. However, data are sparse regarding the impact of post-transplant complications on the quality of life and survival of these patients.
Methods: Patients receiving PLT in a single referral Center were retrospectively evaluated. Complications after LT were collected, defined as early- or late- if before or after 3 months post-LT. Patients' follow-up was defined until death or at March 31st 2022.
Results: Between 1997 and 2004, 232 patients underwent PLT; excluding patients with combined transplantation, intra-operative death and incomplete follow-up, 130 patients were regularly followed. Median age at LT was 14.3 months (range 1.0 month-17.7 years). Major indications for LT were Biliary Atresia (59.2%), Alagille syndrome (10%), Metabolic Liver Disease (8.5%) and Hepatoblastoma (4.6%). Median follow-up was 19.2 years. Thirty-one patients underwent liver re-transplantation. At the end of follow-up, 90 patients were alive. Among the remaining 40 patients 13 died within 3 months from LT. Excluding perioperative deaths, patient-survival rates at 1, 5, 10 and 20 years after LT, were 91.7%, 84.3%, 80.2% and 74.4% respectively. At least one vascular complication occurred in 38.5% of patients (20% hepatic artery thrombosis, 74% portal thrombosis), biliary complications in 27.7% (stenosis). Fifty-six patients (43.1%) presented at least one acute rejection episode, sixty-eight patients (52.3%) showed histological signs of chronic rejection at liver biopsy. Twenty-four patients (18.5%) developed a neoplastic pathology during follow-up (71% PTLD). No differences were observed in survival-rates between patients who did or did not develop biliary, late-vascular complications or episodes of acute rejection. Statistically significant differences in survival-rates were found in patients who developed early vascular complication or post-LT tumours.
Conclusions: Our study showed that only the onset of early vascular complications (but not late ones) or post-LT neoplastic complications significantly affect long-term survival of pediatric LT patients.

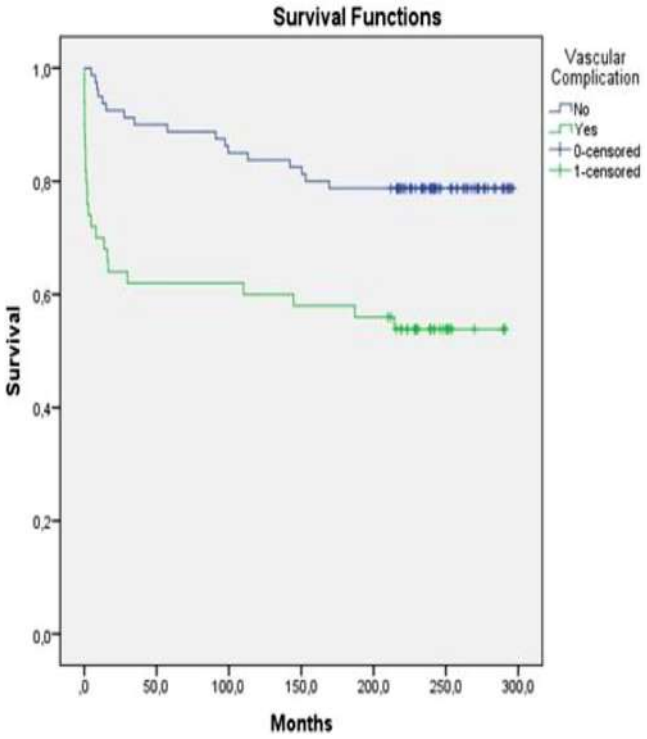

Figure 1. Kaplan-Meier curves of PLT patients who developed vascular complication (green curve) vs patients who did not (blue curve) - Long-Rank $p<0.05$.

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F-24

RuvBL1 ATPase activity is essential for mitochondrial integrity and function in HCC cells

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RuvBL1 is a AAA+ ATPase involved in multiple cellular activities, such as cell proliferation, chromatin remodeling, DNA repair, transcription, translation and mTOR pathway activity. High RuvBL1 expression in HCC correlates with worse prognosis. We previously demonstrated that RuvBL1 is a key regulator of liver metabolism and glucose homeostasis, suggesting that this ATPase may also participate in the metabolic rewiring of HCC cells.
We therefore aimed at dissecting RuvBL1 role in HCC cell metabolism.
Metabolomics performed by GC/MS in RuvBL1-silenced Huh7 cells highlighted altered intermediates of glucose, TCA and aminoacid metabolism. Pathway enrichment analysis of modulated metabolites showed a significant association with processes related to cancer metabolic reprogramming and centered in mitochondria.
RuvBL1 targeting by RNAi or by the selective inhibitor CB-6644 significantly impaired OXPHOS and ATP production in a dose- and time-dependent manner in AML-12, Hepa1-6, Huh7, Hep3B and HepG2 cell lines. Mitochondrial morphology assessed by Mitotracker and TEM was severely affected by RuvBL1 inhibition, that caused a reduction in matrix electrondensity, disruption of the cristae, swelling and fragmentation. Using superresolution STED microscopy and immunoglold/TEM, we detected RuvBL1 within mitochondria. Thus, we performed MS analysis of RuvBL1 co-immunoprecipitated complexes from purified mitochondria. Gene ontology analysis of mitochondrial RuvBL1-interactome revealed that this ATPase impact on TCA, aminoacid, purines, and lipid metabolism, mito-ribosome assembly, mitochondrial transmembrane transport, and membrane organization. Intriguingly, several members of the MIB complex (SAMM50, Mic19, Mic60), which plays a crucial role in shaping mitochondrial cristae, were identified in the RuvBL1-interactome. In the TCGA-LIHC dataset, RuvBL1 expression positively correlates with 9 out of 14 principal members of the MIB complex and genes differentially expressed between HCC with high- vs low-RuvBL1 were significantly enriched in mitochondria-related GO terms.
Our data uncover a novel localization and function of RuvBL1 in mitochondria, and suggest that RuvBL1 overexpression support mitochondria-related processes in HCC.

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F-25

The burden of HDV infection: A ten-years' experience of a sicilian tertiary centre of liver disease

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Introduction: Hepatitis B virus (HBV) and Hepatitis D virus (HDV) super-infection is considered as one of the most dangerous forms of chronic viral hepatitis, but the burden of the HDV infection worldwide could be underestimated. The aim of our study is to evaluate the burden of HDV among a cohort of HBV patients with a long-term follow-up (more than 10 years).
Methods: This retrospective study enrolled HBV patients from a tertiary liver centre between 1998 and 2022. We performed screening for HDV including anti-HDV antibodies at baseline and during the last year of follow-up. We estimated the prevalence of HDV infection among those patients with HBsAg positivity. Disease outcomes as progression to advanced liver disease, decompensation of liver cirrhosis, development of hepatocellular carcinoma (HCC), portal thrombosis or death were collected and estimated using Kaplan-meier curves.
Results: We evaluated a total of 616 HBsAg positive patients who attended our liver tertiary (78% males; mean age 62 years). At the end of our retrospective analysis, we identified 52 patients (8.4%) with HBV / HDV coinfection Of these forty-two were italians (80%) while ten (20%) were foreigners9 of 10 of the foreigners patients10 were Romanians. At baseline, 3 of 52 HBV-HDV coinfected patients had a chronic asymptomatic infection (5.7%), 14 had a chronic hepatitis (26.9%) and 35 had a liver cirrhosis (67.3%). In the subgroup of 35 cirrhotic patients, 19 patients (54.2%) developed at least decompensation of their iver disease and 13 patients (37.1%) developed HCC. Overall, 15 patients (28.9%) died during a mean follow up of 115 months.
Discussion: Our retrospective study confirms that HBV / HDV coinfection is still widespread in cohorts of patients with chronic HBV infection and that it results in severe liver disease with a high risk of developing heart failure, HCC and death.

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F-26

Long-term treatment with fibrates and ursodeoxycholic acid in people with Primary Sclerosing Cholangitis is safe and associated with persistent clinical and biochemical improvement

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Introduction: People with Primary Sclerosing Cholangitis(PSC) have no effective medical treatment for delaying disease progression. Ursodeoxycholic acid(UDCA) improves liver tests(LFTs) and prognostic markers. Fibrates, PPARs agonists, are recommended as first-line therapy for pruritus in PSC. However, long-term data on safety and effectiveness of fibrates on pruritus, LFTs and prognostic markers in PSC are lacking.
Aim: To assess long-term safety and effectiveness of fibrates in PSC.
Methods: Retrospectively, we collected data of PSC people treated with fenofibrate (200 mg/day) or bezafibrate (400 mg/day) for at least 6 months in addition to UDCA, for persistent alkaline phosphatase (ALP) elevation (>1.5xULN), pruritus or dyslipidemia. Changes in LFTs, liver stiffness by VCTE, symptoms, prognostic scores and occurrence of adverse events every 6 months after fibrates introduction were collected.

Results: Twenty-seven consecutive PSC people who started fibrates (fenofibrate n=25, bezafibrate n=2) between 2017 and 2020 were included. Median age at diagnosis was 31(21-35). Upon treatment with fibrates (median duration of 33.3[20.8-51.2] months), we observed a significant reduction of ALP, GGT and transaminases. A decrease of ALP levels of 41%,52%,46%,54% at 6,12,18,24 months compared to baseline values, respectively, was observed. Nearly a third of people achieved ALP normalization at semestral evaluations. The Amsterdam-Oxford score significantly improved after 12 months (1.75*vs.*1.35, p=0.03). Liver stiffness showed a non-significant reduction on long-term. Number of patients experiencing pruritus significantly decreased at each time point, as well as fatigue at 18 months (p=0.03). One third of people interrupted fibrates for non-response, but no adverse events related to fibrate treatment occurred during follow-up.
Conclusions: Long-term combination of fibrates and UDCA in people with PSC is safe and associated with persistent clinical and biochemical improvement. While awaiting the results of ongoing phase 3 study, we consider fibrates as a valid therapeutic option in people with PSC and elevated liver tests despite UDCA.

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F-27

Recurrence of primary sclerosing cholangitis after liver transplantation: A single center data

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Introduction and Aim of the Study: Recurrence of primary sclerosing cholangitis (rPSC) after liver transplantation (LT) is a significant concern without any possibility of prevention. This study aimed to analyze the disease recurrence and long-term outcome after LT in a single center and investigate potentially modifiable risk factors.
Materials and Methods: We performed a retrospective analysis of patients who underwent a first LT for PSC, using demographic and clinical data before and after LT and donor features. Only patients with at least one-year post-transplant follow-up were included.
Results: Thirty-three patients who underwent LT for PSC between 1993 and 2021 were included. Median age at LT was 44 years (31.3–56.7), 52% were female and 73% had inflammatory bowel disease (IBD) (73%). Twenty-three patients underwent LT for decompensated cirrhosis (70%) 9 for recurrent cholangitis (27%) and 1 for perihilar cholangiocarcinoma (CCA) (3%). Median donor age was 52 years (26.5-68.6); median cold ischemia time (CIT) was 8 hours. Nine patients (27%) developed rPSC during a median follow-up of 60 months, with no significant difference across recipient gender and age. Longer CIT (p=0.0260) and female donor gender (p=0.049) were associated with the risk of rPSC, while donor age was not. An association between IBD reactivation after LT and a higher risk of rPSC was found (p=0.005). Performing biliodigestive anastomosis at LT was associated with a higher risk of recurrence (p=0.019). We observed a graft survival of 94%, 86%, and 74% and patient survival of 97%, 89%, and 77% at 1, 5, and 10 years after LT, respectively, with no significant differences in rPSC and no rPSC groups.
Conclusions: The identification of predictive factors for rPSC is challenging. Some donor features could increase rPSC risk. IBD reactivation might have a pathogenic role in rPSC. The use of biliodigestive anastomosis might influence recurrence development. In our cohort, PSC did not affect patient and graft survival.

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F-28

Clinical impact and treatment of veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) after liver transplant (LT). The role of transjugular intrahepatic portosystemic shunt (TIPS)

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Background: VOD/SOS occurring after LT is a rare complication that raises some questions about its significance and treatment.
Aim: to evaluate the clinical outcome of VOD/SOS after LT.
Materials and Methods: The clinical data of 1123 patients >18 years transplanted at our center in the last twenty years were retrospectively evaluated. In patients who developed portal hypertension with or without ascites after LT the diagnosis of VOD/SOS was established by liver biopsy and HVPG.
Results: 18/1123(1,6%) had histological VOD/SOS diagnosis with ascites (90% males, mean age 58yrs, 100% received steroids, 17/18(94%) tacrolimus, 1/18(5%) tacrolimus+mycofenolic acid, 1/18(5%) cyclosporin). Median time of VOD/SOS development after LT was 2 (range1-12) months. In 2/18 patients(11%) the VOD/SOS was associated to acute cellular rejection. Median HVPG at VOD/SOS diagnosis was 14mmHg. 1/18(5%) was treated with defibrotide, 1/18(5%) underwent spontaneous improvement, 16/18(90%) patients underwent TIPS with median HVPG reduction to 7mmHg, 14/16(87%) patients with TIPS solved ascites after a mean time of three months. 2/16(12%) developed encephalopathy, one solved with medical therapy and one with TIPS caliper reduction, 3/16(19%) needed TIPS enlargement within one year due to stent dysfunction and ascites relapse. Patient treated with defibrotide had onset of ascites after one year (without VOD/SOS relapse at liver biopsy). Among 16 patients with TIPS 2(12%) needed re-transplantation, one after five years for TIPS infection and one after 14 years for graft dysfunction. During a median follow up of 11 years (range1 months-20 years) 6/18 patients(33%) died (one patient without TIPS, one patient who received defibrotide). The mean yearly mortality rate of the overall cohort was 4%, corresponding to a 1-, 3- and 5-year overall survival of 100%, 89% and 78% respectively.
Conclusions: VOD/SOS is a rare complication potentially at risk for graft loss. TIPS might be a safe and effective treatment for clinical significant VOD/SOS.

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F-29

Single centre experience with Nivolumab as monotherapy in chirrotic patients with advanced HCC.

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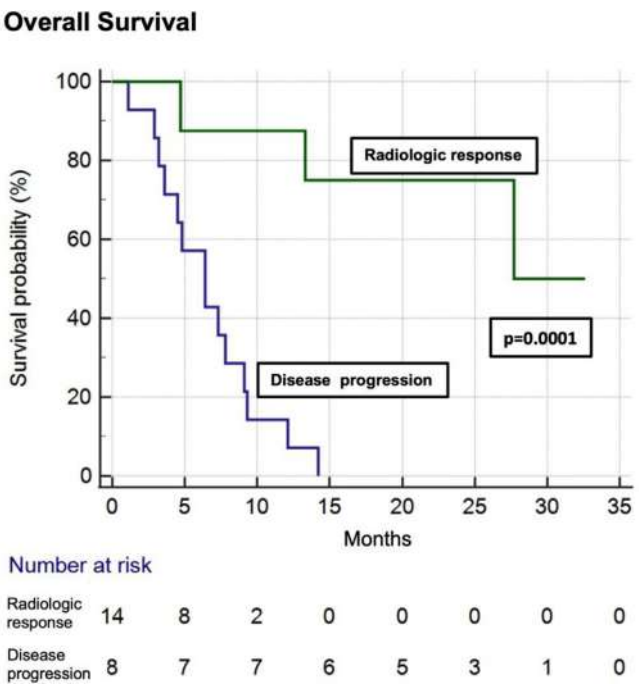
Nivolumab monotherapy has proven to be effective sometimes for advanced HCC and could be a valuable treatment option for patients outside current treatment indications and reimbursement criteria for the standard of care.
Aim: To evaluate the effectiveness of nivolumab off label monotherapy in patients with advanced HCC who are not eligible for other treatments.
Methods: This is a retrospective study including 22 patients with advanced HCC from A.O.U. Città della Salute e della Scienza di Torino. Patients had prior sistemic therapy or were intolerant or ineligible for other treatments. They received nivolumab 3 mg/kg in monotherapy, every two weeks intravenously until disease progression, severe adverse events or death.
Overall Survival (OS), Radiological Response (RR) (defined as stable disease, complete or partial response), Biological Response (BR) (defined as a decrease of $\geq$ 25% in AFP blood level at 3 months) are reported. A safety profile is reported.
Results: OS was 7.8 months (95% CI 4,7-14,2, range: 1.1-32.6 months).
The RR rate at 3 months was 36% (8/22 pts) and BR was 46% (6/13 pts).
OS was significantly associated to the RR at 3 months (p 0.0001) and to BR (p 0.0001). Median OS in patients with Radiological response at 3 months was 27.7 months (CI 95% 4.7-27.7) vs 6.4 months in patients with disease progression (95% CI 3.2-9.1, p 0.0001).
At baseline, performance status (ECOG), presence of metastatic lymph-nodes, bilobar hepatic involvement vs monolobar were related to a better OS (p 0.003).
Grade 2 or 3 adverse events occurred in 36% of patients. No patients ceased nivolumab due to directly related adverse events.
Conclusion: Nivolumab monotherapy could be a good treatment choice in selected patients with HCC who are ineligible for the standard of care. Radiological and biological response at 3 months predict long survivors. Overall Nivolumab was well tollerated.



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F-30

Epidemiological and clinical profile of HDV infected people in care in Italy: Interim analysis from the ongoing PITER cohort

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Introduction: With the new therapeutic options available for hepatitis delta infection, epidemiological and clinical profile of patients in care are useful to determine better treatment appropriateness. We aimed to describe the updated epidemiological and clinical profile of HDV infected patients in the PITER HBV cohort.
Methods: Data from consecutive HBsAg positive patients enrolled from 2019 up to October 2022 by 50 Clinical centers were evaluated.
Results: Of 4729 patients of whom 1,010 (21%) were non-Italian natives, the anti-HDV prevalence was 9.3% (343 of 3679 anti-HDV tested patients): 8.3% (median age 57.5; IQR 53-64) Italian, 13.0% (median age 43 years IQR 43 -53 years) non-Italian natives ($p<0.001$); 22% (1,050) have never been tested for HDV infection (23% in Italian and 19% in non-Italian; $p<0.001$), of whom 21% with liver cirrhosis. Of anti-HDV positive patients, 212 (62%) were tested for HDV RNA, of whom 140 (66%) were HDV RNA positive. Of anti-HDV positive patients, transaminase levels were altered in 63%, cirrhosis was present in 70% (57.5% in Italian and 75.5% in non-Italians; $p=0.001$), of whom portal hypertension signs in 55%, cirrhosis complications and/or HCC development in 37.5%. Liver disease progression cofactors were present as follows: alcohol use 35.6% (similar in Italians and non-Italians), HCV infection in 11.1% (15.5% in Italian and 1.8% in non-Italian, $p<0.001$), diabetes in 6.1% (7.5% in Italians and 1.9 in non-Italian $p<0.001$), other features of potential metabolic syndrome in 23.9%. Overall, 52.8% of patients have no comorbidities, 40.8% has 1-2, 6.4% more than 2 comorbidities.
Conclusions: The updated picture of patients in care in Italy confirms the older Italian cohort and significantly younger non-Italian cohort of patients in care with HDV infection, both with signifi-

cant proportion of liver cirrhosis. The dysmetabolic comorbidities are more represented in Italians, but the overall comorbidity profile is similar between two cohorts.

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F-31

Post-liver transplantation recurrence of primary sclerosing cholangitis: role of autologous hematopoietic stem cell transplantation

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Background: Primary sclerosing cholangitis (PSC) represents 5% of the indications for liver transplantation (LT). Recurrence of PSC (rPSC) is reported to occur in 8-27% and it has a great impact on both graft and patient survival.
Methods: the clinical data of 35 patients with PSC who underwent LT at our center in the last 20 years were retrospectively evaluated. Twentyfive were male (71,4%) with a history of IBD before OLT (67%). Tacrolimus+steroid was the most frequent immunosoppressive schedule (84.8%). Five patients (15.1%) underwent re-OLT (3 for rPSC, 2 for immunological damage). Graft and patient survival at 5 years were 73.6% and 88%. A female transplanted for the first time at the age of 17 years, redeveloped aggressive rPSC, with the need for a third LT. The time interval between second and third LT was much shorter than between the first and second LT (2015-2019-2021). In order to modulate the patient's immune reactivity, within 3 months from the 3rdLT, stem cell mobilization (cyclophosphamide+G-CSF) was performed, and CD34+ cells were selected: the patient eventually underwent autologous hematopoietic stem cell transplantation (aHSCT), preceded by a conditioning regimen (melphalan+rabbit antithymocyte globulin). In the immediate post-aHSCT, the patient experienced a *E. Coli*-related sepsis. The full immunosuppressive regimen was reintroduced 18days after aHSTC. Three and 14 months after aHSCT, she underwent follow-up liver biopsies which excluded rPSC and showed a picture of mild ectasia of centrolobular veins and pericentral sinusoids, associated with initial aspects of sclero-atrophy of the bile ducts, consistent with liver injury secondary to chemotherapy. Liver test were maintained normal.
Conclusion: ReLT is the only treatment option for aggressive rPSC. Our patient succesfully underwent 3rd R-LT combined with aHSCT with no evidence of rPSC at over 14 months follow-up: this may represent a successful approach as a preemptive strategy in selected cases of reLT for rPSC.

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F-32

ePRO Diary: an App-based linkage to care model to promote compliance in pediatric liver transplant recipients in transition to adulthood

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Introduction: Adolescent liver transplant recipients represent a clinical challenge in the transition to adulthood. In particular, compliance remains the Achilles heel in this specific population. Low executive functions and quality of life markers were found to be similar to those observed in other chronic disease conditions of the childhhod.
Methods: at our liver Transplant Center both adult and pediatric liver transplantations are performed (1024 adults and 677 pediatric LT from November 1997 to November 2022). Currently, 167 patients in the transition phase to adulthood, are being followed in our dedicated transitional outpatient clinic. In this setting, adolescents are evaluated jointly by pediatric- and adult- hepatologist with the concomitant support of the psychologist. A web base APPLICATION (downloadable on patient' own device) has been designed aiming to improve both the compliance and the relationship between transitioning adolescents and physicians. The APP allows the set-up of reminders for both drug intake and follow-up testings/exams, together with the recording of therapeutic schedule changes, blood tests results. A specific session dedicated to patients reported outcome with both psycologic and QoL testing) has been developed. The data entered in the app can be extracted online as chart output by both health care personnel and patients.
Conclusion: ePRO Diary Liver has been built and approved within the ATRA(transitional outpatient clinic) project. The APP is currently available and patient enrollment is ongoing. This app can provide an updated support to young "native digital" liver transplant recipients during their transition to adulthood. This simple and intuitive application allows adolescent patients (and their caregivers, when needed) to insert reminders, appointments and blood tests in order to improve adherence to therapies and treatment plan. All data are shared with the transplant center, who can monitor the clinical situation in real time.

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F-33

HBsAg kinetics during and after nucleos(t)ide analogues described by mathematical modeling

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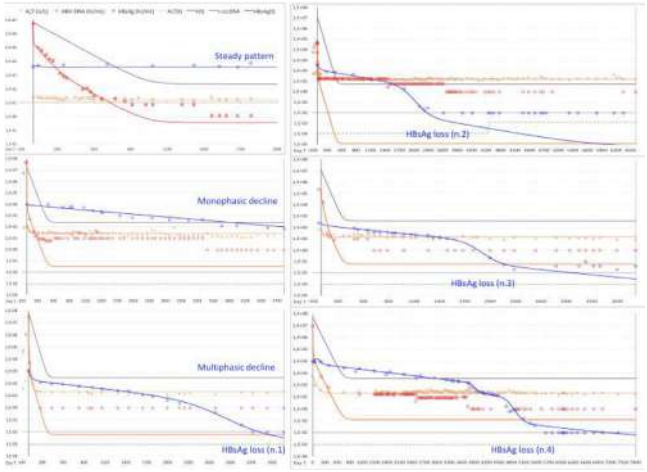
Introduction: HBsAg clearance (functional cure) is the optimal endpoint of chronic hepatitis B treatment. Nucleo(s)tide analogues (NAs) have a limited impact on HBsAg decline, however achieving low HBsAg serum levels correlates with loss after discontinuation.
Aim: To investigate mechanisms of HBsAg decline during NAs.
Materials and Methods: We set up a mathematical model describing: 1) dynamics of replication-competent hepatocytes (cccDNA>1

copy/cell) producing HBsAg by either cccDNA or integrated DNA (intDNA); 2) cccDNA turnover; 3) dynamics of non-replication-competent hepatocytes which lost cccDNA by cell division, but still produce HBsAg by intDNA. Baseline $I_{0\text{-cccDNA}}$ and their immune-mediated clearance rate were computed by ALT decline upon NAs block of HBV replication; cccDNA lifetime by fitting ALT, HBV-DNA and HBsAg; HBsAg production rate constants (from $I_{0\text{-cccDNA}}$ and $I_{0\text{-intDNA}}$), $I_{0\text{-intDNA}}$ and their lifetime by fitting HBsAg. We applied the model in 29 HBeAg-neg and 2 HBeAg-pos patients, median age 56.1(30-76.6) years, 21(65.6%) males, 17(54.8%) with cirrhosis. Median NAs treatment was 123.1(41.2-260.1) months. HBV-DNA (COBAS-TaqMan, Roche) and HBsAg (Architect, Abbott) were tested every six months.

Results: HBsAg during NAs showed 3 different patterns: steady (3;9.6%), monophasic (18;58.1%) and multiphasic (10;32.3%) decline. Mean baseline ALT and HBsAg were lower in monophasic (121±95vs666±565 U/L, p=0.0004 and 4,421.9±2,876,2vs18,846.8±22,861.3 IU/mL, p=0.0272). Overall, 6(19.4%) lost HBsAg: 5(17.2%) HBeAg-neg (4 during, 1 after NAs) and 1 (50%) HBeAg-pos (after discontinuation-retreatment). Patients who lost HBsAg on-therapy had multiphasic declines, successfully described by the model (Figure). Monophasic patients had lower $I_{0\text{-cccDNA}}$ (22.0%±15.4%vs54.8%±27.3%, p=0.0159) and HBsAg production by cccDNA (1.7%±2.3vs53.3%±27.3%, p<0.0001). Lifetime of I_{intDNA} was longer in monophasic (3,938±2,681 vs 1,340±875 days, p=0.0065), cccDNA lifetime was similar (52±52vs31±14 days, p=0.2288).

Conclusions: Mathematical modeling showed that faster HBsAg decline after NAs was associated with higher disease activity and prevalent HBsAg production from cccDNA, with lifetime shorter of intDNA. HBsAg loss was characterized by multiphasic declines.



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F-34

People with autoimmune hepatitis and celiac disease have a milder liver disease course and a better chance of immunosuppressive treatment withdrawal.

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Background: In people with Autoimmune Hepatitis (AIH), the diagnosis of Celiac Disease(CD) is 3-times more frequent than in general population. In paediatric patients with AIH and CD a milder course of AIH and higher chances of immunosuppressive therapy withdrawal were reported.

Aim: To assess frequency of CD in AIH, and to analyse the features and the long-term response to immunosuppressive treatment in patients with AIH associated with CD(AIH-CD) compared to patients without CD(AIH-non-CD).

Methods: A retrospective cohort study including all consecutive people with an established diagnosis of AIH in adulthood was performed. Exclusion criteria were the presence of overlap syndromes or concomitant liver diseases. 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: 166 consecutive people(80% female, median age 52) with diagnosis of AIH between 1990 and 2021 and followed-up for a median of 63(24-125) months at the Gastroenterology Unit of the University Hospital of Padova were included. Eighteen percent had cirrhosis at diagnosis. Nine people (5.4%) had a histologically confirmed diagnosis of CD. People with AIH-CD were treated with significantly lower doses of prednisone at 2 years from diagnosis (2.5*vs.*5 mg/day,p= 0.007) and at 3 years from diagnosis were more likely to have stopped steroids (83%*vs.*31%,p=0.007) compared to AIH-non-CD. On long-term observation, immunosuppressive therapy withdrawal was more frequent in AIH-CD compared to AIH-non-CD (44%*vs.*13%, p=0.01) and the need for immunosuppressive reintroduction was similar (p=n.s.). On the other hand, we did not found differences regarding cirrhosis development, cirrhosis decompensation, liver-related deaths or number of relapses between people with AIH-CD and AIH-non-CD.

Conclusions: In our cohort, CD is present in 5.4% of people with AIH. In people with AIH-CD we observed a milder course and immunosuppressive therapy has been effectively withdrawn more frequently compared to AIH-non-CD.

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F-35

Characteristics and medium-term outcomes of a retrospective cohort of patients with non-malignant, non-cirrhotic splanchnic vein thrombosis

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Introduction: Non-malignant, non-cirrhotic splanchnic vein thrombosis (NC-SVT) is an infrequent yet not negligible cause of portal hypertension (PHT). Despite often associated with myeloproliferative neoplasms (MPN), prothrombotic disorders (PD) or local factors (LF), up to 30% of cases are idiopathic. Long-term management is debated, especially for cases with no underlying factors.

Aim: To describe the clinical course and management of a single-centre NC-SVT-patients cohort.
Methods: A retrospective analysis of NC-SVT patients referred to our centre between November 2009 and September 2021, with at least three-months follow-up, was performed. Etiology, thrombosis extension, clinical presentation, and therapeutic strategy at SVT onset were retrieved. After referral, clinical, biochemical, and radiological outcomes were analyzed.
Results: A total of 22 NC-SVT patients were included (50% male, mean age at referral 53.1 years). Mean follow-up time was 29 months (10-66). The most frequent cause was MPN (31.2%), followed by LF (27.3%), and PD (13.6%). Most SVT (95.5%) involved the portal vein, six of which with spleno/mesenteric extension. One case had isolated intrahepatic involvement. Seven (15%) presented with PHT-related complications (three ascites, four variceal bleeding) and nine (40.1%) developed esophageal varices. All MPS and PD received long-term anticoagulation, except four cases (three excessive bleeding risk, one patient refusal). Most MPS cases (57%) underwent etiological therapy. Eight patients received beta-blockers at SVT onset, four of which as secondary prophylaxis of variceal bleeding. At referral, beta-blockers were added in two cases with radiological/biochemical evidence of PHT progression. During follow-up, four patients developed esophageal varices, but no PHT-related complications occurred. No significant variation from referral of biochemical parameters (platelet count, coagulation, bilirubin, albumin, aminotransferases) was detected. All SVT (100%) were stable/improved, and spleen length showed no significant variation. A single case of extrasplanchnic thrombosis occurred.
Conclusions: We report excellent mid-term outcomes in a well-phenotyped NC-SVT-patients cohort. Additional prospective studies are needed.

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F-36

Red rice (Monakoline K) effects on oxidative stress parameters and biomarkers of steatosis in mild hypercholesterolemic NAFLD patients

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Introduction: The first cause in the pathogenesis of NAFLD is oxidative stress. Hypercholesterolemia is frequent in NAFLD patients. Red rice is administered in patients with mild hypercholesterolemia or in patients intolerant to statins. Red rice is rich in sterols and isoflavonoids with potential effects on oxidative stress.
Aims: to evaluate the role of red rice on parameters of oxidative stress and on biomarkers of liver steatosis in patients with NAFLD.
Methods: we studied 24 patients (14 F, 10 M) with mean age ± SD (50.9±11.9 yrs) affected by NAFLD, with mild hypercholesterolemia. Patients with Type 2 diabetes and patients on treatment with statins were excluded. We measured the following parameters of oxidative stress: Malondialdehyde (MDA) and Glutathione-disulfide (GSSG). Calculated the scores of liver steatosis (FLI, HIS, NAFLD-LFS) and the scores of fibrosis (APRI, FIB-4, NFS). The liver fibrosis was also detected by ARFI methods (Simens S-2000). The body composition was calculated with Bioimpedentiometry (BIA). All the parameters were detected at T=0 and after 6 months (T=6) of therapy with 10 mg of Monakoline K.
Results: all the patients completed the study. The body weight was stable, and no modifications on BIA parameters were observed. The total cholesterol and total triglycerides declined (232 .05±22.01 mg/dl to 204.15± 35.80 mg/dl $p < 0.003$; 135.60±99.90, to 130,80±46.80 mg/dl $p< 0.026$, respectively). ALT was also reduced (51.45±26.86 U/L to 34.40±17.57 U/L $p< 0.18$). MDA and GSSG decreased significantly (10.90 ±4.20 mM to 5.15±2.78 mM $p< 0.0001$; 3.15±1.83 µM to 1.02±0.98 µM $p<0.0001$, respectively). The FLI was reduced by 75.69±18.01 to 64.93±4.96 $p< 0.035$, while HIS and NAFLD-LFS and scores of fibrosis were unchanged.
Conclusions: Red Rice after six months of therapy in patients with NAFLD and mild Hypercholesterolemia reduced significantly the parameters of oxidative stress, the score of fatty liver FLI, and the parameters of hepatic cytonecrosis.

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F-37

NAFLD and weight loss: The Salerno experience on close monitoring

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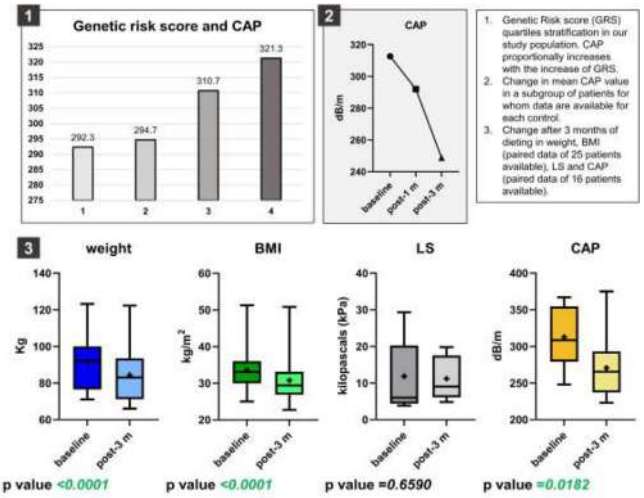
Introduction: Weight loss is the cornerstone in the treatment of NAFLD and was found associated with a histological improvement proportional to its extent. However, it is a difficult goal to achieve and maintain. Moreover, the precise link between weight changes and NAFLD is not fully understood.
Aims: To describe the possible positive influences of a nutritionist-guided low-glycemic index diet on anthropometric parameters, Transient Elastography (TE), Controlled Attenuation Parameter (CAP, with the *SmartExam* software), and blood chemistry in overweight or obese NAFLD patients. The genetic correlation with TE/CAP measurements was also taken into account.
Patients and Methods: 69/106 patients who were attending our Hepatology Unit, with NAFLD, aged ≥ 18, and with a BMI ≥ 25 accepted to start the nutritionist-guided diet. Baseline anthropometric data, TE/CAP, and blood test results were recorded. Single nucleotide polymorphisms in NAFLD risk genes were analyzed and genetic risk score (GRS) was calculated. Control visits were scheduled after 1 and 3 months. TE/CAP was performed during each visit, and after 3 months blood tests were repeated.
Results: 57/69 patients (82.61%) attended at least one of the control visits. A significant difference from baseline was observed at both 1-month and 3-month visit in weight (-4.26 kg [-4.78%] $p <0.0001$, and -7.67 kg [-8.43%] $p <0.0001$), BMI (-1.55 Kg/m^2, $p <0.0001$, and -2.75 Kg/m^2, $p <0.0001$), and CAP (-27.67 dB/m, $p =0.0062$, and -42 dB/m, $p =0.0182$). Changes in CAP were proportional to the extent of weight loss, whereas mean liver stiffness remained almost unchanged. Baseline CAP was proportional to GRS; high GRS patients presented a higher decrease in TE/CAP values after 3 months of diet. After 3 months of diet, significant differences in glycemia and triglycerides were observed; AST, ALT, total cholesterol and HDL cholesterol also improved.
Conclusions: In our NAFLD population, after diet-induced weight loss, an improvement in metabolic parameters was observed. The early reduction of CAP could increase patient awareness of the ongoing improvements. Genetics could influence the reduction of steatosis during weight loss.



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Quantitative HBV/HDV markers help to distinguish different clinic/virologic phases of chronic hepatitis delta

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Introduction and aim: New therapy options for Chronic hepatitis delta (CHD) urge a better clinical/virologic stratification of patients(pts). We quantified HDV/HBV markers to investigate their correlation with disease activity/stage in untreated and Interferon(IFN)-treated pts.
Methods: One hundred forty-six consecutive anti-HDV+pts admitted at Pisa University Hospital were classified based on biochemical/histological/imaging data in:1)Pts without liver disease (no-CHD)[ALT<40U/L, LS<6kPa];2)CHD without cirrhosis;3)CHD with cirrhosis;4)CHD with advanced cirrhosis [varices/decompensation/HCC]. HDV-RNA (RoboGeneKit2.0;RoboscreenDiagnostics), anti-HDV(Liaison®XLmurexAnti-HDV,DiaSorin) and HBV markers (HBV-DNA/HBsAg/HBcrAg/anti-HBc-IgG) were tested at baseline(BL) in the overall cohort, and at end-of-therapy(EOT),6-months after EOT (6mFU) and end-of-follow-up(EOF) in 31(21.2%) IFN-treated pts. Virologic response was defined by qualitative HDV-RNA (in house-PCR).
Results: Table1 shows the BL characteristics of the overall cohort. Eleven (7.6%) subjects were classified as no-CHD; 10/11(90.9%) had HDV-RNA serum levels(sl)<1000 IU/mL. Among 135 CHD pts, HDV-RNA sl were higher in pts with cirrhosis compared to CHD without cirrhosis or with advanced cirrhosis. All no-CHD subjects had anti-HDV titer≤1:100; 132/135 CHD pts (97.8%) had anti-HDV≥1:1000. At multivariate analyses, HDV-RNA[OR=1.816/P=0.007], anti-HDV[OR=4.429/P=0.012] and anti-HBc-IgG[O7R=3.260/P=0.041] associated with higher disease activity(ALT>100U/L); Age[OR=1.059/P=0.032] and HDV-RNA [OR=1.643/P=0.006] associated with cirrhosis. Among 31 IFN-treated-pts [duration 12.4(2.0/91.7) months], 13(41.9%) had virologic response, 3 (9.7%) relapsed and 15(48.4%) were non-responders at 6mFU. At EOF [median 4.6(1.3-18)years], 14 pts maintained undetectable qualitative HDV-RNA and normal ALT, all of them showing HDV-RNA sl<1000 IU/mL, 12/14 (85.7%) anti-HDV≤1:100. The remaining pts with CHD at EOF had HDV-RNA sl>1000 IU/mL and anti-HDV≥1:1000 in 92.3% and 100% of cases, respectively.
Conclusions: In CHD pts HDV-RNA sl independently correlate with biochemical activity and stage of liver disease. HDV infection can persist without active liver damage in a status, either spontaneously-acquired or IFN-induced, characterized by low levels of viral replication (HDV-RNA<1000 IU/mL) and anti-HDV titer (≤1:100) The quantitative analysis of HDV/HBV markers qualifies as a useful tool for clinic-virological classification and treatment monitoring of CHD pts.
Table 1.

	A	B	C	D	*P values*		
	no-CHD n=11	CHD without cirrhosis n=24	CHD with cirrhosis n=73	CHD with Advanced Cirrhosis n=38	*A vs B+C+D*	*B vs C+D*	*C vs D*
Age (yrs)	34.7 (22.2/70.3)	39.7 (17.9/54.4)	42.3 (19.1/69.1)	51.8 (25.0/71.7)	0.906	*0.062*	**0.005**
LS (kPa)	5.2 (3.4/6.0)	7.0 (4.3/12.0)	16.0 (7.0/69.0)	23.5 (11.1/66.4)	**<0.001**	**<0.001**	**<0.001**
ALT (U/L)	17 (10/40)	75 (12/194)	73 (5/500)	62 (26/206)	**<0.001**	0.364	*0.087*
HDV-RNA (Log IU/mL)	2.28 (0.82/4.14)	4.39 (0.70/6.75)	5.55 (0.70/7.73)	4.81 (0.70/6.48)	**<0.001**	**0.002**	**0.008**
Anti-HDV (< / ≥ 1:1000)	11 (100) -	- 24 (100)	3 (4.1) 70 (95.9)	- 38 (100)	**<0.001**	0.959	0.516
HBsAg (Log IU/mL)	2.88 (-1.40/3.53)	3.90 (1.59/4.59)	3.90 (-1.40/4.57)	3.80 (-1.40/4.50)	**<0.001**	0.993	0.234
HBV-DNA (Log IU/mL)	1.00 (0.70/3.87)	1.28 (0.70/7.61)	1.24 (0.70/5.94)	1.53 (0.70/5.34)	0.912	0.363	0.447
HBcrAg (Log IU/mL)	2.00 (2.00/3.00)	3.47 (2.00/6.97)	3.60 (2.00/7.19)	3.69 (2.0/6.17)	**<0.001**	0.930	0.859
Anti-HBc IgG (Log COI)	278.6 (23.0/2314.0)	265.8 (28.2/2355)	158.9 (7.7/2678)	152.9 (7.0/841.0)	0.333	*0.065*	0.265

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Liver health in patients with hemophilia: Residual risk factors of liver-related complications after HCV-clearance

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Background and Aim: HCV is highly prevalent in hemophilia. Nowadays DAA warrants 80-100% rate of sustained virological response (SVR) but no studies have described the clinical outcome post-SVR in patients with hemophilia. We conducted a prospective screening to detect any relevant risk-factor of liver-complications after HCV-clearance in this setting.
Methods: 119 HCV-patients (median age:54 years;range:36-87): 108/11 hemophilia A/B. SVR was achieved after interferon-based therapies in 43 patients (36%), after DAA in 53 (45%). Twelve patients (10%) had spontaneous HCV-clearance. Any active factor of chronic liver damage was registered along with biochemistry, liver stiffness measurement (LSM) and ultrasound (US) to rule-in/out advanced fibrosis/cirrhosis. A pre/post-SVR sub-analysis was conducted in 57 patients with LSM, US, non-invasive tests of fibro-

sis (NITs) (e.g.FIB-4, APRI) simultaneously available to show their change.
Results: Ninety-six patients (81%) presented at least one active risk-factor of chronic liver-damage, metabolic factors were the most prevalent (77%). Ten patients (8%) were HIV and 4 (4%) HBV, both infections under control at time of the screening. After our evaluation, 51 patients (43%) had US-steatosis. Twenty-one patients (18%) had clinical, biochemical, liver-morphology and/or LSM suggestive of advanced fibrosis/cirrhosis. Furthermore, 10 patients (8%) had esophageal varices, 3 (3%) hepatocellular carcinomas (HCC). One HCC was detected in a non-cirrhotic liver but associated with metabolic comorbidities, 2 HCC were Milan-out and were addressed to a down-staging approach. All HCC were finally transplanted. In the sub-analysis, LSM and NITs were reduced after SVR ($p<0.05$), while morphological US-signs specific of cirrhosis did not change. Overall, after HCV-clearance, 13/67 patients (19%) with LSM≤8KPa had at least one US-sign suggestive of advanced fibrosis/cirrhosis.
Conclusions: Residual risk-factors of chronic liver damage after HCV-clearance are frequent. LSM and NITs significantly change after SVR and could be inaccurate to rule-out advanced fibrosis/cirrhosis. A specific diagnostic work-up is warranted to maintain liver-health in hemophilia.

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F-40

Tyrosol attenuates hepatic steatosis and fibrosis in a mouse model of NASH

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Introduction: Nonalcoholic steatohepatitis (NASH), characterized by lipid accumulation, inflammation, hepatocellular damage, represents a major health problem due to its increasing incidence. Some preclinical and clinical evidence suggests that hydroxytirosol (HT) may improve NASH progression and fibrosis.
Aim: to dissect the effect of the HT precursor tyrosol on hepatic fat accumulation and NASH-related fibrosis in a mouse model.
Materials and Methods: Male C57BL6 mice were fed with a high fructose-high fat diet (HFHFD) for 14 weeks, and treated with CCl_4 (IP, 0.05 mg/kg) during the last 4 weeks. Tyrosol (10 mg/kg) was administered daily by oral gavage starting from week 4. Extrahepatic manifestations of NASH, i.e. sarcopenia and mood disorders, were evaluated by behavioral and motor tests (Gripping, grid, rotarod, open field and forced swim test). After sacrifice, liver histology was assessed by means of H&E, Oil Red O and Masson's trichrome staining. Flow cytometry was performed to analyze liver and blood CD4+, CD8+ lymphocytes, M1 and M2 macrophages and natural killer (NK) cells.
Results: Tyrosol attenuated the physical dysfunction and anxious behavior associated to NASH development. Moreover, it significantly improved hepatic steatosis and fibrosis in NASH animal ($p<0.01$). Tyrosol-treated animals had less hepatic inflammatory foci than untreated NASH mice ($p<0.05$), and a significant reduction of hepatic proinflammatory M1-type macrophages ($p<0.05$), CD4+ ($p<0.05$) and T helper effector lymphocytes ($p<0.05$). A significant increase of Treg cells ($p<0.05$) was observed in Tyrosol-treated animals.
Conclusions: Tyrosol may represent a novel strategy to counteract hepatic steatosis, fibrosis and inflammation associated to NASH development by modulating the recruitment of immune cells in the liver.

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Oleocanthalic acid extracted form extravirgin olive oil reduces fatty acid accumulation and fibrogenesis in experimental in vitro models of NAFLD and NASH

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Introduction: The extravirgin olive oil (EVOO) phenol oleocanthal was demonstrated to exert an antifibrotic effect in preclinical models, counteracting the upregulation of NADPH oxidases, proinflammatory cytokines and metalloproteinases. Its mono-oxidized derivative oleochantalic acid (OcA) has recently been identified in aged EVOO, and limited information is available about its biological activities.
Aim: to assess the effect of OcA against fibrogenesis and lipid accumulation in 2D and 3D cellular models.
Materials and Methods: The effect of 24-h OcA treatment on fatty acid (FA) uptake was assessed in a 2D model of NAFLD obtained treating HepG2 cells with palmitic acid/oleic acid (PA/OA1:1, 0.1 mM) and in a 3D spheroid coculture of HepG2 and LX-2 cells treated with PA/OA by means of Bodipy and Nile red stain, respectively. To assess the effect of OcA on FA uptake in an inflammatory NASH-like microenvironment, PA/OA-treated HepG2 cells were co-cultured with THP-1-derived M1 proinflammatory macrophages. The effect of 24-h OcA treatment on fibrogenesis was also evaluated in LX-2 cells activated with TGFb1 (2ng/mL) and in cocultures of HepG2 and THP-1 derived M0 macrophages. aSMA expression, marker of LX-2 activation, was assessed by ICC.
Results: OcA significantly reduced the uptake of FAs in PA/OA-treated HepG2 cells in a dose dependent manner. The same effect ($p<0.0001$) could be observed in HepG2 cells cocultured with proinflammatory M1 macrophages, mimicking a NASH microenvironment, as well as in 3D spheroid coculture of HepG2 and LX-2 cells treated with PA/OA ($p<0.01$). Moreover, OcA significantly reduced LX-2 cell activation induced by both TGFb1 treatment and by coculture with HepG2 and M0 macrophages ($p<0.0001$).
Conclusions: This preliminary *in vitro* evaluation of OcA demonstrated a significant improvement of FA accumulation and HSC activation, which are both pivotal mechanisms in the development of NASH.

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The dietary supplementation with brown seaweeds and chromium picolinate improves NAFLD and NASH by modulating lipid metabolism and inflammation

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Introduction: According to preclinical and clinical evidence, brown seaweeds improve liver function and reduce metabolic-associated risk factors, by virtue of the high amounts of bioactive compounds. Moreover, chromium, an essential mineral, can improve glucose homeostasis and insulin resistance.
Aim: to assess the effect of supplementation with brown seaweed extracts and chromium picolinate on hepatic steatosis of different severities in rat models of NAFLD and NASH.
Materials and Methods: NAFLD or NASH were induced in Sprague-Dawley male rats by high fructose-high fat diet (HFHFD) administration for 12 and 18 weeks, respectively. Rats were treated by daily gavage with a nutraceutical formulation (7.5 mg/kg·bw) containing water extracts of two brown seaweeds (*Ascophyllum nodosum* and *Fucus vesiculosus*) and chromium picolinate or vehicle. After sacrifice, liver steatosis was assessed by the ORO staining. mRNA levels of hepatic DGAT1, DGAT2, SREBP-1, FASN and PLIN-2 were assessed by qPCR; myeloperoxidase (MPO) hepatic expression was evaluated by IHC. Plasma inflammatory cytokines were measured by ELISA.
Results: The supplementation with algal extract and chromium picolinate led to a significant drop of hepatic fat in both models ($p<0.01$ vs. vehicle-treated animals), accompanied by a reduction in plasma inflammatory cytokines (IL6, TNFa and C reactive protein), and in hepatic MPO expression. Furthermore, a significant reduction of the mRNA expression of FASN, DGAT1 and 2, SREBP-1 and the lipid transporter perilipin-2, was observed in both treated NAFLD and NASH rats in comparison to vehicle-treated ones.
Conclusions: The supplementation with brown seaweed extracts and chromium picolinate reduces hepatic steatosis and inflammation, thus representing a promising therapeutic option for NAFLD and NASH, valuable of further clinical investigations.

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F-43

Incidence and risk factors of esophagogastric varices bleeding in cirrhotic patients with advanced hepatocellular carcinoma treated with lenvatinib

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Background and aims: Lenvatinib is indicated for the forefront treatment of advanced hepatocellular carcinoma (aHCC) but its use it is eventually limited by presence of esophagogastric varices (EGV) and bleeding-risk. This study aimed to assess prevalence and risk factors of EGV and bleeding in lenvatinib-treated patients with HCC.
Methods: In this multicenter international retrospective study, cirrhotic patients treated with lenvatinib for aHCC with an upper-gastrointestinal endoscopy performed <6 months before treatment were enrolled. Primary endpoint: incidence and risk factors of EGV bleeding during treatment. Secondary endpoints: prevalence and risk factors for EGV and high-risk EGV (HR-EGV) at baseline.
Results: 535 patients were enrolled [median age 72 years, 78% male, 63% viral aetiology, 89% Child-Pugh-A, 16% neoplastic portal vein thrombosis (nPVT), 56% BCLC-C]: 301 (56%) patients were EGV-free, 234 had EGV (44%) and 70 (30%) HR-EGV. Presence of EGV and of HR-EGV were independently associated with Child-

Pugh-B (OR 2.12; 95%CI 1.08-4.17, p=0.03), nPVT (OR 2.54; 95%CI 1.40-4.61, p=0.002) and platelets<150.000/uL (OR 2.47; 95%CI 1.35-4.50, p=0.003). During lenvatinib treatment, 17 patients bled from EGV, the 12-month cumulative incidence being 3%. The only independent predictor of bleeding was presence of HR-EGV (HR 6.94, 95% CI 2.23-21.57, p=0.001). Risk of EGV bleeding can be stratified according to Child-Pugh-B, presence of nPVT and platelets<150.000/uL into low (0/3 risk factors, 6-months cumulative incidence 0.77%), intermediate (1/3 risk factors, 6-months cumulative incidence 2.31%) and high (2/3 or 3/3 risk factors, 6-months cumulative incidence 7.40%). Among the 476 Child-Pugh-A patients, independent predictors of HR-EGV were nPVT (OR 2.53; 95%CI 1.24-5.16, p=0.008) and platelets<150.000/uL (OR 2.56; 95%CI 1.28-5.10, p=0.01).
Conclusion: In HCC patients treated with lenvatinib, the risk of EGV bleeding is low but it increases in patients with HR-EGV at baseline. A risk stratification for HR-EGV can be applied according to liver reserve, platelet count and nPVT.

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Lenvatinib for treatment of recurrence hepatocellular carcinoma after liver transplantation: A case series

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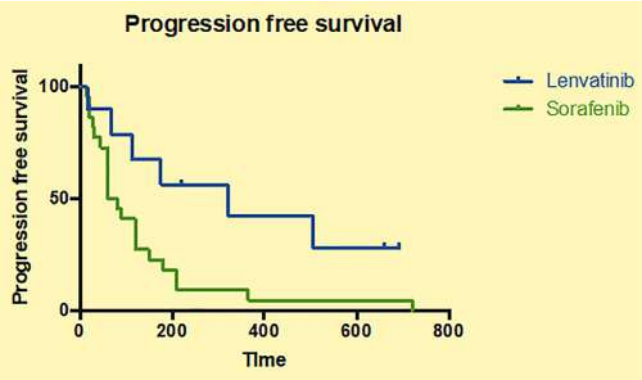
Background and Aims: Lenvatinib (Len), an oral inhibitor of multiple receptor tyrosine kinases, is approved as first-line treatment in patients with advanced hepatocellular carcinoma (HCC). Limited data have been published regarding the efficacy and safety of Len in patients with HCC recurrence after liver transplantation (LT).
Method: Retrospective study including 9 patients with HCC recurrence post-LT treated with Len as first-line regimen. Baseline characteristics and adverse events during treatment were analysed. Progression-free survival and overall survival in the Len group were compared with a historical cohort of patients with HCC recurrence after LT treated with Sorafenib (SOR).
Results: 8/9 patients were male, with a median age of 60 years. (IQR 56-77). HCC recurrence was both intra and extra-hepatic in 6/9 patients (66%), only extrahepatic in 2 cases (22%) and only intrahepatic in 1 case. Median time from LT to start of Lenvatinib was 4.3 years. Before starting Lenvatinib, 5/9 patients (55%) had already received surgery or locoregional treatment for HCC. The most common adverse events (AEs) were hypertension and fatigue with a single patient experiencing a grade 3 adverse event (proteinuria in the nephrotic range) requiring drug withdrawal. No rejections were observed. Three patients required modification of immunosuppression during the the first 8 weeks of Len treatment. The progression-free survival (PFS) from Len initiation was 321 days. Seven patients experienced disease progression under Len treatment and were shifted to SOR as second-line treatment. A single patient with progressive disease died 2 months after Len withdrawal for tumor progression. When comparing the 9 patients with HCC recurrence treated with LEN, with a balanced cohort of 22 historical patients treated with SOR, LEN was associated with a better progression-free survival (p=0.02) and overall survival (p=0.011) **(Fig. 1)**



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Transarterial Radioembolization for Unresectable Hepatocellular Carcinoma: A single-center experience

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Background: Transarterial radioembolization (TARE) has become widely used for the treatment of Hepatocellular carcinoma (HCC). TARE is a microembolic procedure that minimizes alterations to hepatic arterial flow, and thus can be safely performed in patients with HCC and portal vein tumor thrombus (PVTT).
Aim: The long-term clinical outcomes of 38 patients with HCC treated with TARE at Niguarda Hospital from 2105 and 2022 were analyzed.
Results: Patients were stratified according to the BCLC Staging system. 27 patients (71%) were in advanced stage, 10 (26%) in intermediate stage and 1 in early-stage HCC (3%). All patients had an Eastern Cooperative Oncology Group (ECOG) score of 0-1 and their Child-Pugh class was A-B7. Bilirubin was < 1,2 mg/dl in 33 patients (87%) and tumor burden was <50% in 35 patients (84%). 24 patients (73%) had a PVVT: ten PV1 (segmental), seven PV2 (second order) and seven PV3 (main right/left).

A complete and partial response to treatment was observed in 7 (18%) and 15 patients (40%) respectively. During the follow-up period (mean time 20 months), overall survival (OS) was 39%. Median OS in complete, partial response and tumor progression group was 29 months, 25 months and 6 months respectively.
Conclusion: TARE is a potential effective treatment in intermediate to advanced HCC, particularly in the case of PVTT.

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Efficacy of lenvatinib in intermediate stage and advanced hepatocellular carcinoma: Results of monotherapy and combination with locoregional treatment

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Introduction: Lenvatinib is the one of the two mainstay first-line therapy for unresectable Hepatocellular carcinoma (HCC). Combined treatment with locoregional treatment and Lenvatinib has been proposed as an alternative strategy in more advanced disease. Real-world study comparison of efficacy and safety between these two regimens is limited, previous studies suggested a higher response rate from locoregional plus systemic treatment than chemotherapy alone.
Aim: In this study, we aimed to evaluate the efficacy of lenvatinib in intermediate and advanced stage HCC.
Materials and Methods: 46 patients with Child-Pugh score 5-7 and ECOG PS 0-1 who received Lenvatinib for Intermediate or Advanced stage HCC from April 2020 to October 2022 at our hospital were enrolled. First, landmark analyses were performed to evaluate the association between radiological response and prognosis. Univariate and multivariate analyses were then performed to search for factors contributing to OS and Response Rate.
Results: Median age was 72,5 years, Child-Pugh score was 5 in 35 patients, 6 in 5 patients, 7 in 6 patients. 35 patients were started in the first line Lenvatinib and 11 patients were treated with TACE/TARE during the period of lenvatinib. The median OS in 46 patients were 47 weeks, and the ORR was 62 %, in the best response by mRECIST. In a landmark analysis comparing the responder and non-responder groups, the complete responder group (12%) was treated with combined treatment. Multivariate analysis showed that relative tumor volume, AFP value before induction, first response, and combination of Lenvatinib with locoregional treatment were independent predictors of OS.
Conclusion: The efficacy of lenvatinib in the treatment of intermediate/advance stage HCC was favorable. The combination of lenvatinib and locoregional treatment may improve further prognosis, even in those patients who are refractory or unsuitable for TACE.

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Verona liver day: Data of liver health from the Arena

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Background: Liver diseases affect millions of people worldwide, with different etiologies between countries. The incidence of viral hepatitis is waning as a result of advances in prevention and new therapies. In contrast, with the improvement in living standards, the incidence of metabolic liver diseases including non-alcoholic fatty liver disease and alcohol-related liver disease is set to rise.
Aim: On the 14th of May 2022 the Liver Unit Team of Azienda Ospedaliera Universitaria Integrata of Verona organized a "Liver Day" for the general population with educational and preventive aim. Using a mobile medical center with an ultrasound scanner, a fibroscan and HCV test kits, 110 people were visited and screened. Many other people had only information.
Results: From the anamnestic data collected, alcohol consumption (> 100 g/week) was detected in 36.5%, hypertension in treatment in 39%, dyslipidemia in 35.6%, type 2 diabetes in 6.7% of our population. We confirmed HCV Ab in 6 patients, nobody with unknown HCV was detected. Based on these collected data, a sample of people was subjected to a fibroscan method and/or an abdominal ultrasound and 40% had steatosis. MAFLD was detected in 28.7% of cases. Liver stiffness (LS) measured with Fibroscan was 5.11±1.28 kPa; only one patient had LS> 8 kPa. LS was higher in MAFLD group. MAFLD patients (n=30) had higher BMI (median BMI 28.3 (IQR 5.10) vs 23.7 (IQR 4.50) and higher waist circumference (median 99±14.18 vs 87±15.20 cm).
Conclusions: Data from Verona general population confirms the relevant prevalence of risk factors (alcohol and MAFLD) which can lead to chronic liver disease.

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F-48

Survey on hepatic sarcoidosis in Italy

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Introduction: Sarcoidosis is a granulomatous disease that can potentially involve all body tissues, including the liver in about 10-20% of cases (1-4). High quality data on the management of hepatic sarcoidosis (HS) are scarce. In absence of national and international guidelines, management of HS is still experienced-based.
Aim: This survey was carried out amongst Italian hepatologists to describe their practices in the management of patients with HS.
Methods, Results: 1985 questionnaires were forwarded, of which 37 were completed and returned. Thirty-three centers reported managing patients with HS, 17 (51%) of these reported managing more than one patient. Twenty-seven (81%) centers obtained the diagnosis by liver biopsy, the remaining centers by radiological techniques or biopsy in other sites. In coexistence with HS, the pulmonary sarcoidosis was reported from 18 (54%) centers, while patients with no other localization, except for the hepatic one, were followed up in 6 (18%) centers. Twenty-two (66%) centers treated such patients with first-line steroid therapy, the remainders reported using other drugs. Finally, 3 (9%) centers reported the presence of transplant patients, other 3 (9%) centers of deceased patients.
Conclusion: HS is a rare entity in Italy and there is a wide variation in diagnostics and therapeutics. A multicentric, prospective, national cohort study is needed to study this disease.

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F-49

Characterization of sarcopenia with ultrasound-based measurements in patients with advanced chronic liver disease.

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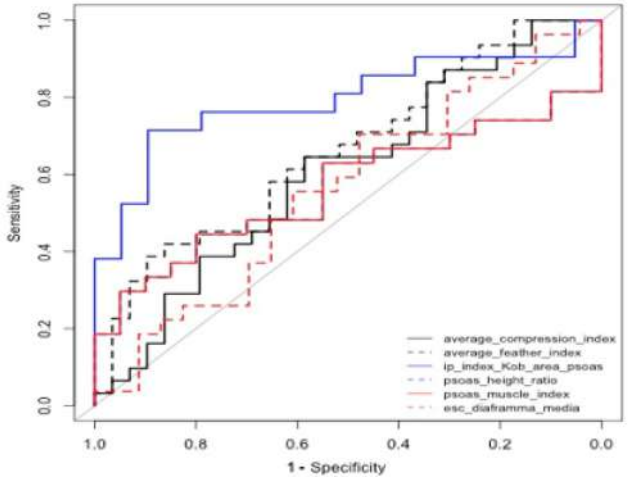
Introduction: Sarcopenia is a very common complication of cirrhosis. In the clinical setting, it is usually diagnosed using operational definitions based on low muscle mass. Muscle ultrasound-based measurement has recently achieved attention because of its easier feasibility; however, only a few studies evaluating this approach have been reported.
Aim: We aimed to validate ultrasound-derived measurements for the assessment of sarcopenia in a cohort of patients with chronic liver disease (CLD) evaluated by computed tomography (CT) or magnetic resonance imaging (MR) during follow-up for hepatocellular carcinoma (HCC).
Materials and methods: Consecutive adult outpatients attending our Hepato-Oncology Unit were included in the study. CT\MR scans were imported and analysed, and the L3-skeletal mass index was calculated. Ultrasound was performed to obtain muscle thickness and derived indices according to different previously described techniques. Receiver operating characteristic (ROC) curve analysis was performed to assess the diagnostic accuracy of each technique with respect to sarcopenia as determined by CT and/or MR analyses.
Results: 51 patients were included. The average age was 74 years (±7.07), with a prevalence of male gender (70.6%). Mean BMI was 27.4 kg/m2. The most common etiology of cirrhosis was metabolic (41.2%), and more than half of the patients (68%) had a preserved liver function. Logistic regression analysis identified the average feather index [OR 13.64 (1.25-196.17), p 0.04] and the ileopsoas(IP)-index [OR 1.01 (1-1.02), p 0.01] as significantly associated with a low muscle mass expressed with CT/MR. The IP-index was the only one showing an adequate discriminative ability, with an AUROC of 0.79 (0.65-094) (Figure 1).
Conclusions: Our preliminary results show a statistically significant association between some ultrasound-based techniques and reduced muscle mass. If these results will be confirmed in larger and external series, ultrasound would represent a feasible and cheap tool for assessing sarcopenia at least in patients with CLD.

Figure 1.

ULTRASOUND INDICES	Discriminative ability (AUROC)
Average compression index	0.61 (0.46-0.75)
Average feather index	0.66 (0.52-0.8)
IP-index	0.79 (0.65-0.94)
Ultrasound-Psoas height ratio	0.57 (0.4-0.73)
Ultrasound-Poas muscle index	0.57 (0.4-0.73)
Diaphragmatic excursion	0.56 (0.4-0.73)
Diaphragmatic thickness inspirium	0.56 (0.41-0.72)
Diaphragmatic thickness espirium	0.56 (0.4-0.71)



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F-50

Use of psychiatric medication and drug interactions in patients with hcv infection treated with pangenotypic direct-acting antivirals

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Background: Previous studies have shown that nervous system (NS) drugs were the most prescribed in patients with chronic C-hepatitis. The aim of this sub-analysis was to analyze the presence and severity of drug-drug interactions (DDIs) in patients using antipsychotics and treated with Pangenotypic Direct-Acting Antivirals (pDAA) in a real-life cohort.
Methods: Retrospective, multicenter, observational study, using the BIG-PAC database (Atrys Health), in adult HCV patients treated with Sofosbuvir/Velpatasvir [SOF/VEL] and Glecaprevir/Pibrentasvir [GLE/PIB] (years 2017-2020). Variables collected were: age, sex; fibrosis degree, addiction/substance abuse; pharmacotherapeutic; adverse events; type of pDAA prescribed and presence or absence of psychiatric co-medications. Potential DDIs between concomitant medication and pDAA were assessed using the University of Liverpool database.
Results: 1620 patients were included (median age: 54 years; men: 61%; F3/4: 32.4%). 61% had addictions/substance abuse. NS drugs were the most prescribed (35.8%): among those, psycholeptics (N05) accounted for 40% (being quetiapine the most represented). 12% of the total population was under antipsychotics (N05A), characterized by younger age and higher fibrosis degree (F3/F4) than the total population [median age: 53 years; men: 59%; F3/4: 44%]. 75% of patients with antipsychotics had addictions/substance abuse and 14% of patients with addictions/substance abuse were prescribed antipsychotics, being this percentage lower in the general population, 7%; $p<0.001$. In terms of potential interactions, 28% of patients with antipsychotics were at risk of DDIs with DAAs; this percentage is numerically higher in patients with addictions/substance abuse, 30% vs. 23% of the general population ($p=0.336$). Two adverse events were reported in the GLE/PIB treated group, 1 with quetiapine (resulting in DAA discontinuation) and 1 with paliperidone. No adverse events were reported in the group treated with SOF/VEL.
Conclusion: In patients with C-hepatitis and treated with antipsychotics, the presence of potential interactions is high, requiring a comprehensive approach to their follow-up to achieve therapy optimization

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Changing HCV patient profiles: insights from a large multinational real-world sofosbuvir/velpatasvir (SOF/VEL) dataset

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Background and aims: The profile of HCV patients being started on direct-acting antivirals (DAAs) has shifted towards more vulnerable populations. This large real-world analysis describes the diverse profile of these populations according to age and sex.
Method: Adult HCV patients from 37 clinical cohorts across nine Countries treated with SOF/VEL for 12 weeks without ribavirin were included. Those with a history of decompensation or prior NS5A-inhibitor exposure were excluded. Patients' characteristics, time to treatment, and sustained virological response ≥12 weeks after end of treatment (SVR), stratified by age and sex, were analyzed.
Results: Among 6356 patients, 2274 were aged <50 y, 2568 50−65 y, and 1514 > 65 y. Within these age strata, 73%, 65%, and 45%, respectively, were male. Vulnerable populations were well represented, and ∼20% of all patients had a history of IV drug use. Male patients were more likely to have compensated cirrhosis and to be infected with HCV genotype 3. Significantly fewer mental health disorders were seen in male patients. However, use of antipsychotics appeared similar, irrespective of sex. Median TT was shorter in male patients across the age spectrum. In 5845 patients with a valid result, SVR was high across age ranges, with no significant differences observed between males and females (<50 y: female 98.7%, male 99.2%; 50−65 y: female 98.7%, male 98.1%; >65 y: female 99.3%, male 98.3%). 475 pts did not achieve SVR for a non-virological reason: mostly loss to follow-up, with no differences between males and females across age strata.
Conclusion: SOF/VEL shows high cure rates across different age and sex groups. Antipsychotic drug use appeared similar in males and females, despite significantly fewer mental health disorders in male pts. TT varied from 1 day to >6 months and was shorter in males.

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Clinical application of NGS in the diagnosis of iron overload disorders or hyperferritinemia of genetic origin

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Background: The liver is central in the pathophysiology and clinical manifestations of most genetic iron-loading disorders. Although HFE- hemochromatosis is the most prevalent condition of hereditary iron overload in Caucasians, a significant portion of patients with clinical suspicion of iron-loading disorder or hyperferritinemia of genetic origin do not have a diagnostic HFE genotype.
Aim: To investigate, through Next Generation Sequencing (NGS) technology, the presence of pathogenic variants in candidate "iron genes" in patients with clinical suspicion of genetic iron overload disorders and/or hyperferritinemia.
Materials and Methods: 94 patients with a hemochromatosis-like phenotype (HC-group) and 55 cases with clinical suspicion of hereditary hyperferritinemia (HF-group) were enrolled. A custom AmpliSeqTM NGS panel of 32 genes involved in iron homeostasis was tested using the Ion Torrent PGM platform. Literature information and in silico predictions were used for the prioritization of possibly pathogenic variants.
Results: In both groups, HFE and CP were respectively the first and second most frequently mutated genes, followed by TFR2 in HC-group and SLC40A1 in HF-group. In HC-group, 43.7% of patients carried a genotype diagnostic for hemochromatosis; in HF-group, 23.6% of patients carried a genotype known to cause hyperferritinemia. Most patients presented single-gene variants: the iron genes that emerged as solely mutated are HFE, HJV, TFR2, TF, and SLC40A1 for HC-group and HFE, SLC40A1, CP, FTL, TMPRSS6, NEO1, and TFRC for HF-group. Novel variants were identified in some of these genes. In HC-group, 40.5% of patients carried only heterozygous variants and always presented at least one variant in HFE, HJV, TFR2, SLC40A1, or TF.
Conclusion: NGS contributes to the diagnostic workup of patients with non-HFE hemochromatosis or other iron disorders by identifying possible pathogenic variants or disease contributors/modifiers. Our data support the polygenic origin of certain phenotypes and indicate novel variants to take forward for functional or experimental validation.

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Bulevirtide improves health-related quality of life measured by EQ-5D VAS in patients with chronic hepatitis delta: An exploratory analysis of a Phase 3 trial at 48 weeks

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Introduction: Chronic hepatitis delta (CHD) is the most severe form of viral hepatitis and is associated with rapid progression to cirrhosis, decompensation, hepatocellular carcinoma, and end-stage liver disease.
Aim: We report an exploratory analysis of EuroQol 5D visual analog scale (EQ-5D VAS) scores in patients with CHD after 48 weeks of treatment with bulevirtide (BLV) in an ongoing Phase 3 trial.
Methods and Results: MYR301 (NCT03852719) is a randomized, open-label, parallel-group, multicenter trial that assigned 150 patients with CHD (1:1:1) to BLV 2 mg (n=49), BLV 10 mg (n=50), or control (n=51) for up to 3 years. Control patients received no

BLV treatment until week 48 (W48). The EQ-5D VAS is a self-completed rating of patients' quality of life (QOL) with a range of 0–100 (100=best health state). The QOL analysis was based on EQ-5D VAS scores at baseline and W48.

Baseline characteristics were well balanced across groups. At W48, patients with CHD treated with BLV 2 mg reported statistically significant improvement in QOL (by EQ-5D VAS) and significantly better EQ-5D VAS change from baseline scores when compared with control patients **(Table).** Changes from BL with BLV 10 mg were not statistically significant at W48 A cirrhosis-specific subgroup analysis indicated similar improvement trends among patients with or without cirrhosis; however, statistical significance was not reached.

Conclusion: Patients with CHD treated with BLV 2 mg experienced improvements in QOL measured by the EQ-5D VAS at W48. EQ-5D VAS scores significantly improved in the BLV 2 mg group compared with baseline and compared with controls at W48 but did not in the BLV 10 mg group. Further investigation is needed to understand the impact of BLV 10 mg and the long-term effects of BLV treatment.

Table. Baseline characteristics and change from baseline in EQ-5D VAS with bulevirtide 2 mg, 10 mg, and control at week 48

	Control (n=51)	Bulevirtide 2 mg/day (n=49)	Bulevirtide 10 mg/day (n=50)
Baseline characteristics			
Mean age (years)	41	44	41
BMI (kg/m²)	25	24	25
Male (%)	51	61	60
White (%)	78	84	86
Compensated cirrhosis (%)	47	47	48
Results: Change from baseline in EQ-5D VAS at week 48			
Baseline, mean (SD)	72.0 (18.4) n =51	73.1 (16.2) n=49	73.9 (19.3) n=50
Week 48, mean (SD)	75.9 (18.3) n=50	82.1 (10.3) n=48	76.2 (15.1) n=45
CFB, mean (95% CI)	3.3 (−0.3, 6.9) n=50	8.6 (4.9, 12.3) n=48	3.6 (−0.4, 7.7) n=42
Difference vs control	-	**5.3 (0.1, 10.5); *P* = .0449**	0.4 (−5.1, 5.8); *P* = .8975

BMI, body mass index; CFB, change from baseline; EQ: EuroQol; VAS, visual analogue scale.

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F-54

Efficacy of bulevirtide as monotherapy for chronic hepatitis D (CHD): Week 48 results from an integrated analysis

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Introduction: Bulevirtide (BLV) is a novel first-in-class entry inhibitor for the treatment of chronic hepatitis delta virus (HDV) infection (CHD) that was conditionally approved in the EU in July 2020. Patients treated with BLV had pronounced HDV RNA and alanine transaminase (ALT) declines through 48 weeks (W) in a Phase 2 study (MYR203; NCT02888106) and 24W in a Phase 3 study (MYR301; NCT03852719).

Aim: We present an integrated analysis of 48W efficacy derived from MYR203/MYR301.

Method and Results: Patients with CHD (N=180) ± compensated cirrhosis were included in a pooled 48W analysis of BLV 2 (n=64) or 10 mg (n=65) given subcutaneously once daily vs no active anti-HDV treatment (n=51; control). The primary efficacy endpoint was combined response (CR; undetectable HDV RNA or decrease by ≥2 $\log_{10}$ IU/mL from baseline and ALT normalization); additional endpoints included viral response, ALT normalization, and $\log_{10}$ change in HDV RNA levels.

Baseline demographics were well balanced across groups. The 48W CR rate was similar in the BLV 2 vs 10 mg groups (46.9% vs 46.2%) and higher than control (2.0%). While rates of ALT normalization at 48W were similar for those treated with BLV 2 and 10 mg (56.3% and 52.3%), the viral response rate was numerically lower in the BLV 2 than in the BLV 10 mg group (68.8% and 78.5%), with mean change from baseline in HDV RNA of −2.60 and −3.29 $\log_{10}$ IU/mL. All efficacy endpoint response rates were higher in the BLV groups vs the control group. Treatment benefit was consistent across subgroups treated with BLV.

Conclusion: Among patients with CHD, efficacy at 48W was comparable between BLV 2 and 10 mg, and both were better than control. These results provide additional support for the use of BLV 2 mg for treatment of compensated CHD.

Table: Efficacy at week 48

	BLV 2 mg (n=64)	BLV 10 mg (n=65)	Control (n=51)
Combined response[1]: Responder at week 48	30 (46.9%)	30 (46.2%)	1 (2.0%)
95% CI	(34.3%, 59.8%)	(33.7%, 59.0%)	(0.0%, 10.4%)
Viral response[2]: Responder at week 48	44 (68.8%)	51 (78.5%)	2 (3.9%)
95% CI	(55.9%, 79.8%)	(66.5%, 87.7%)	(0.5%, 13.5%)
HDV RNA ($\log_{10}$ IU/mL): Mean (SD) change from baseline at week 48	n=62 −2.60 (1.453)	n=61 −3.29 (1.492)	n=50 −0.05 (1.047)
Biochemical response[3]: Responder at Week 48	36 (56.3%)	34 (52.3%)	6 (11.8%)
95% CI	(43.3%, 68.6%)	(39.5%, 64.9%)	(4.4%, 23.9%)
Liver stiffness (kPa): Mean (SD) change from baseline at week 48	−2.6 (5.34)	−2.8 (3.94)	0.7 (7.49)

[1]Undetectable HDV RNA or decrease by ≥2log10 IU/mL from baseline and ALT normalization.
[2]Undetectable HDV RNA or decrease by ≥2log10 IU/mL from baseline.
[3]ALT normalization.
Undetectable HDV RNA defined as HDV RNA less than LOD, which was 10 and 6 IU/mL in Studies MYR203 and MYR301, respectively. Normalization of ALT was defined as an ALT value within the normal range, as defined by central laboratories (all sites in Study MYR203 and Russian sites in Study MYR301: ≤31 U/L for females and ≤41 U/L for males; all other sites in Study MYR301: ≤34 U/L for females and ≤49 U/L for males).
ALT, alanine transaminase; BLV, bulevirtide; HDV, hepatitis delta virus; LOD, limit of detection.

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F-55

Bulevirtide monotherapy is safe and well tolerated in patients with chronic hepatitis D (CHD): An integrated safety analysis of 48-week data

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Introduction: Bulevirtide (BLV), a novel first-in-class entry inhibitor of the hepatitis delta virus (HDV) that was conditionally approved for treatment of chronic HDV (CHD) in the EU in July 2020, was generally safe and well tolerated in Phase 2 (MYR 203, NCT02888106 and MYR 204, NCT03852433) and Phase 3 (MYR301, NCT03852719) studies.
Aim: We present an integrated safety analysis of 48-week (48W) data from these studies.
Methods and Results: In a pooled analysis, treatment-emergent adverse events (AEs), serious adverse events (SAEs), discontinuations, and laboratory abnormalities were assessed in patients treated with BLV alone at 2 or 10 mg for 48W, compared with patients receiving no active anti-HDV treatment (control) and those receiving the current standard of care (SOC; pegylated-interferon alfa [Peg-IFNα]).

A total of 269 patients with CHD were included; the baseline demographics of all groups were well balanced. At 48W, overall incidence of AEs was similar in BLV 2 and 10 mg groups at 85.9% and 86.1%, respectively, compared with rates of 89.7% with Peg-IFNα and 76.5% for controls. There were no BLV-related SAEs and no AEs leading to BLV discontinuation. AE profiles were similar between BLV and control groups, with a few exceptions, including higher rates of headache, injection-site reactions (ISRs), pruritus, fatigue, dizziness, nausea, and eosinophilia in the BLV groups. As expected, asymptomatic dose-dependent increases in serum bile acids were observed. Most AEs were mild/moderate in severity. ISRs were more common in the BLV 10 mg group (who received 2 daily subcutaneous injections) vs 2 mg. BLV safety did not differ between patients with and without cirrhosis.
Conclusion: BLV 2 mg monotherapy was safe and well tolerated through 48W, including among patients with compensated cirrhosis and those previously exposed to interferon. The frequency of AEs was similar with both BLV dosages and lower compared to SOC.

Table. Adverse events and laboratory abnormalities by week 48

Number (%) of patients with any AE	Control (n=51)	BLV 2 mg (n=64)	BLV 10 mg (n=115)	Peg-IFNα (n=39)
AE	39 (76.5%)	55 (85.9%)	99 (86.1%)	35 (89.7%)
AE with Grade 3–4[a]	3 (5.9%)	7 (10.9%)	13 (11.3%)	20 (51.3%)
Grade 3 or 4 TE laboratory abnormalities	6 (11.8%)	13 (20.3%)	16 (13.9%)	25 (67.6%)[b]
AE related to BLV	N/A	38 (59.4%)	72 (62.6%)	N/A
SAE	1 (2%)	2 (3.1%)	2 (1.7%)	3 (7.7%)
AEs of interest:				
Injection-site reactions	0	10 (15.6%)	23 (20%)	1 (2.6%)

[a]Related to BLV: 2 (3.1%) patients in the BLV 2 mg group and 5 (4.3%) in the BLV 10 mg group.
[b]Of 37 patients with post-baseline values available.
AEs were coded according to MedDRA Version 24.0.
Severity grades were defined by the CTCAE. All AEs are treatment emergent.
AE, adverse event; BLV, bulevirtide; CTCAE, Common Terminology Criteria for Adverse Events; Peg-IFNα, pegylated-interferon alfa; N/A, not applicable; SAE, serious adverse event; TE, treatment-emergent.

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F-56

Liver function is a predictor of survival in patients with hepatocellular carcinoma in best supportive care

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Background and Aims: The prognosis of patients with hepatocellular carcinoma (HCC) is very variable, and the relative contribution of tumor burden and liver dysfunction to survival is uncertain. Median overall survival (OS) of patients managed with best supportive care is around 3-6 months, although longer values may be observed in clinical practice. Aim of this study was to identify the factors linked to tumor or liver dysfunction associated with survival in patients with HCC treated with BSC.
Methods: We retrospectively evaluated the clinical characteristics of 1414 patients who had an indication for BSC recorded in the Ita.Li.Ca. database between 2000 and 2020. We analyzed both patient and tumor characteristics to identify predictors of OS.
Results: Median age was 69y and 76% of patients were male. Etiology included chronic viral infection (68.3%), alcohol use disorder (30.9%) and non-alcoholic steatohepatitis (8.3%). 67.4% of patients had a performance status 0-1 and 41.4% were in Child-Pugh B class. Median MELD was 13. 60% of patients had a multifocal HCC with a median number of 3 lesions and a median size of 33mm. 533 patients had vascular invasion. Median alpha-fetoprotein was 49.25 ng/ml. 111 patients were classified as BCLC-A, 148 as BCLC-B, 791 as BCLC-C and 325 as BCLC-D (12 unknown). No differences in terms of OS were observed considering the etiology of liver disease or the presence of cirrhosis. Obesity ($p<0.001$), hypercholesterolemia ($p=0.036$) and hypertriglyceridemia ($p=0.034$) were associated with lower OS. Absence of symptoms (6 vs 10 months, $p<0.001$), lack of vascular invasion (9.1 vs 5.03, $p<0.001$), and absence of metastasis (8.167 vs 4.733 $p<0.001$) were associated with a better OS. Survival in BCLC-A patients was longer than in stages B or C. Survival progressively declined according to severity of liver function using three different scores (CPS, ALBI, pALBI, $p<001$). Women tended to survive longer 23 vs. 19 months, $p=0.053$). Comparing patients surviving more or less than 12 months (398 vs. 1016), age, size of lesions, albumin, bilirubin, alpha-fetoprotein, and MELD were significantly different. At Cox univariate analysis presence of cirrhosis, number and size of lesions, vascular invasion, metastasis, ALBI and pALBI grades, MELD, and CPS were signifi-

cantly associated with OS. Using different models to avoid colinearity ALBI, pALBI, and CPS maintained an independent prognostic role on OS.

Conclusion: In a large series of patients with HCC in BSC, parameters of liver function are strongly associated with survival.

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