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Oral communications: 57th Annual Meeting of the Italian Association for the Study of the Liver – A.I.S.F. (Rome, March 27th-28th, 2025)

OC-01

Terminology, diagnosis and management of primary biliary cholangitis -autoimmune hepatitis variant syndrome (PBC-AIH): results from an international Delphi consensus process

A. Gerussi [1,2], M. Sebode [3,4], E. Nofit [1,2], A. Stoelinga [5], D. Bernasconi [2,6], A. Leburgue [7], P. Invernizzi [1,2], C. Schramm [4,5], B. Van Hoek [3], D. Tiniakos [8,9], L. Terracciano [10,11], M. Carbone [2,12], A. Lohse [4,5], On behalf of the ERN RARE-LIVER, Global PBC Study Group and International Autoimmune Hepatitis Group (IAIHG)

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Introduction: Heterogeneity in definition, diagnosis and treatment of primary biliary cholangitis - autoimmune hepatitis variant syndrome (PBC-AIH) is present in guidelines and daily practice.
Aim: This initiative aimed to bring together global experts to achieve consensus on the terminology, diagnosis and management of PBC-AIH.
Materials and Methods: The initiative was endorsed by the ERN RARE-LIVER, the Global PBC Study Group and the IAIHG. The Delphi process included two rounds of voting, and followed a modified approach according to the "RAND/UCLA Appropriateness Method". A core group of experts identified the unmet needs and areas of uncertainty, identified panelists worldwide, drafted the first set of statements, analyzed and discussed the results of the first round, organized a physical meeting at EASL 2024 in Milan, and drafted a second round of statements restricted to those areas that did not reach consensus after the first round.
Results: The first round included 92 participants, while 82 took part in the second one, representing a geographically diverse panel of 78 hepatologists and 14 liver pathologists. Consensus was reached on definition (variants), suspicion criteria (incomplete response to UDCA with disproportionate elevation of transaminases compared to cholestasis), liver biopsy indications to diagnose PBC-AIH (mandatory in PBC patients, need for revision of the index biopsy in AIH patients first). The panel agreed that diagnosis should be periodically re-evaluated, since features can occur sequentially, and that PBC-AIH is associated with worse prognosis as compared to PBC alone. Severe interface hepatitis in patients with PBC would require immunosuppression, but age, comorbidities, stage and patient preferences should be considered.
Conclusions: This Delphi initiative successfully convened PBC and AIH experts to establish consensus in a complex, understudied area lacking evidence-based guidelines. The resulting statements offer a basis for prospective studies and standardized clinical protocols, aiming to enhance consistent management of PBC-AIH.

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OC-02

Metabolic and Functional Characterization of CD8+ T-Cell Subpopulations in Hepatocellular Carcinoma: Implications of Tumor Microenvironment on T-Cell Dysfunction

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Introduction: CD8 T-cells are crucial in adaptive immune response, against viral infections and tumors. The tumor immune microenvironment (TIME) can disrupt immunological pathways. In hepatocellular carcinoma, CD8 T-cell functional defects correlate with disease stage and clinical outcomes, but the molecular bases of their dysfunction are not fully understood.
Aim and Methods: This study aims to characterize metabolic and functional differences between tumor-infiltrating and liver-infiltrating CD8+ T-cell subpopulations. We performed phenotypic expression of surface markers (CD103, CD39 and PD1) that can define CD8 subsets: Tissue resident memory (TRM), Tumor reactive (Tr) and Terminally exhausted cells (TEX). By analyzing metabolic status, DNA damage response, and cytokine production, we seek to elucidate TIME's impact on T-cell functionality.
Results: The tumor microenvironment was enriched of TEX cells (CD39+ CD103- PD1+) and Tr cells (CD39+/CD103+) compared to the surrounding liver. Moreover, PD1 and Tim3 co-expression was significantly enriched in all subsets from the tumor as well as frequency of PD1hi CD8 T-cells.

Metabolic analyses revealed that tumor-infiltrating subpopulations had lower glucose uptake and higher mitochondrial membrane depolarization, indicating significant metabolic strain, and higher histone H2AX phosphorylation, indicating more DNA damage. TEX showed highest H2AX phosphorylation, while TRM the lowest. In tumor-infiltrating CD8+ T-cells, mitochondrial membrane depolarization correlated positively with p-H2AX+ cells and negatively with glucose uptake. Functional analysis revealed an overall lack of functionality in tumor-infiltrating TEX cells. Finally, patients with larger tumor nodules showed an enrichment of TEX cells and reduction of Tumor-reactive and TRM cells.
Conclusions: The TIME imposes significant metabolic and DNA damage stress on CD8+ T-cell subpopulations, leading to functional impairments. Therapeutic strategies targeting these metabolic challenges are essential for enhancing anti-tumor immunity.

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OC-03

Exploring the impact of mitochondrial biomarkers on HCC risk according to etiologic drivers: a multicenter study

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Introduction: Metabolic dysfunction-associated steatotic liver disease (MASLD) overcame both viral (V) and alcohol (ALD) hepatitis, becoming the main cause of hepatocellular carcinoma (HCC). We recently showed that circulating mitochondrial (mt-) biomarkers (*D-loop*, ccf-COXIII) increases in MASLD patients. *D-loop* progressively raised with histological damage, resulting an early MASLD prognostic indicator. Instead, ccf-COXIII was closely related to advanced MASLD (cirrhosis, HCC). Still, combination of both accurately predicted HCC risk (86%). However, it remains to be elucidated whether these biomarkers are MASLD-specific. Then, we assess *D-loop* and ccf-COXIII levels across different etiologies (V, ALD and MASLD) in a multicenter cohort of 260 HCC patients.
Material and Methods Results: *D-loop* and ccf-mtDNA were measured in PBMCs and serum samples, respectively. MASLD-HCC subjects had higher BMI, presence of diabetes (T2DM) and serum lipids compared to ALD-HCCs and V-HCCs ($p<0.05$). The highest transaminases and alpha-fetoprotein levels were found in V-HCC patients. The mean size of HCC nodules was larger in MASLD-HCCs and V-HCCs rather than ALD-HCCs. ccf-COXIII levels were higher in V-HCC patients compared to non-viral HCCs ($p<0.001$) at bivariate analysis and at generalized linear model adjusted for sex, age at diagnosis, BMI, T2DM and ALD/MASLD etiologies. At nominal logistic analysis adjusted as above, ccf-COXIII correlated with increased risk of developing HCC from viral infections (OR:1.27 95% CI:1.08-1.5, $p=0.0009$). Conversely, the highest levels of circulating *D-loop* were observed in MASLD-HCC patients at bivariate and multivariate analyses and correlated with tumor size. Alongside, elevated *D-loop* levels correlated with enhanced cancer risk of metabolic origin (OR:1.62 95% CI:1.0-2.5, $p=0.02$), even after adjustment for the presence of cirrhosis.
Conclusions: Mt-biomarkers differently feature HCC patients according to etiology. ccf-COXIII rises most with virus infections in a condition of advanced liver disease, while *D-loop* seems to be MASLD-specific, possibly identifying HCC cases also in the absence of cirrhosis.

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OC-04

Coronary angiography in liver transplant work-up: report from a large multicenter Italian cohort

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Background: Evaluating coronary artery disease(CAD) is critical in liver transplant(LT) candidates. Coronary-angiography (CATH) is the invasive gold standard for CAD diagnosis. We aimed to assess CATH role in Italian multicenter pre-LT cohort.
Methods: 18/21 Italian adult LT centers participated, enrolling cirrhotics who underwent CATH during cardiac work-up between 2018-2022. We evaluated: CATH indications, significant-coronary-stenosis rate (SCS: ≥50% major-vessels or ≥70% moderate-branches), post-LT major cardiovascular events(MACEs), and survival.
Results: Between 2018-2022, the 18 centers performed 5336 LTs from deceased donors. 305 pts underwent pre-LT CATH and constituted our study cohort. Median age 62 years; 85% male; BMI 27kg/m^2; 68% smokers; 57% diabetes; 55% arterial hypertension; 13% CAD history, 9% peripheral artery disease, 26% CAD family history. Liver etiology was 34% viral, 27% alcohol, 15% MASLD, 12% alcohol+MASLD, MELD 13(IQR 9-18), 61% HCC Indications for CATH were: 31% positive coronary-CT, 25% ≥3 cardiovascular risk factors, 12% cardiac consultation, 11% positive myocardial scintigraphy, 9% positive stress-echocardiography, 8% CAD history, 4% resting echocardiographic abnormalities.

CATH complications occurred in 16 pts (5%). SCS was detected in 120(39%) patients, 54% underwent revascularization. At univariate analysis, SCS was associated with male (OR=2.02,CI:1.00-4.09,p=0.049) and smoking history (OR:1.92,CI:1.07-3.47,p=0.029). At multivariable analysis, active smoking (OR2.02,CI:1.07-3.88,p=0.037) and MASLD (OR1.89,CI:1.02-3.55,p=0.044) were independent predictors of SCS. Positive predictive value (PPV) of CCTA and stress-echocardiography was 57% and 35%, respectively.

After CATH,259/305 pts were placed on LT waiting list. By 30/06/2023, 230 underwent LT (21% after pre-LT revascularization). 28(12%) MACEs occurred within 2 y after LT with 3 related deaths. 1- and 2-y patient survival 92% and 90%.
Conclusions: Cardiac work-up varies across our 18 LT centers. CCTA showed a PPV of 57%. 39% of pts selected for CATH had SCS, 54% requiring revascularization. National efforts should be made to share a unified cardiac work-up protocol tailored for our LT recipients.

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OC-05

Role of spleen stiffness measurement by vibration-controlled transient elastography at 100Hz in guiding invasive hemodynamic reassessments after underdilated TIPS

D. Saltini [1], T. Guasconi [1,2], C. Caporali [3], M. Bianchini [1], F. Casari [3], F. Prampolini [3], B. Lei [2], M. Scoppettuolo [2], F. Ascari [3], A.S. Velasco Mayorga [2], A. Piscopo [2], A. Colecchia [2], F. Schepis [1]

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Introduction: Underdilated Transjugular Intrahepatic Portosystemic Shunt (udTIPS) effectively manages portal hypertension complications while minimizing shunt-related adverse events. Spleen Stiffness (SS) measured by vibration-controlled transient elastography has shown high accuracy in detecting clinically significant portal hypertension when compared to the gold standard hepatovenous pressure gradient.
Aim: To evaluate SS as a non-invasive tool for identifying patients with Porto-Caval Pressure Gradient (PCPG) <12 mmHg after udTIPS.
Materials and Methods: We prospectively enrolled patients with cirrhosis undergoing udTIPS at our referral center (January 2023–September 2024). Both invasive PCPG assessment and SS measurement with the spleen-dedicated 100Hz probe by FibroScan® were performed at three time-points: before TIPS, immediately post-TIPS, and one-month after the procedure.
Results: The study included 51 patients (mean age 62±12 years, 63% male) with preserved liver function [median Child-Pugh score 7 (IQR 3), MELD-Na 13 (IQR 6)]. TIPS indications were secondary prophylaxis for variceal bleeding (65%) and refractory ascites (35%). Median udTIPS dilation diameter was 6 (IQR 1) mm. PCPG progressively decreased from 22 (IQR 7) pre-TIPS to 15 (IQR 4) immediately post-TIPS and 11 (IQR 5) mmHg at one-month. Correspondingly, SS decreased from 74.5 (IQR 5) to 55.5 (IQR 21) and 41.6 (IQR 19) kPa. All SS measurements strongly correlated with PCPG values (ρ=0.72, p<0.0001). SS demonstrated an excellent diagnostic discrimination for PCPG <12 mmHg [AUC=0.90 (95% CI 0.84-0.96)]. The cut-off of <35 kPa accurately ruled in patients with post-TIPS PCPG <12 mmHg (97.8% specificity, 88.2% PPV, 21.3 positive likelihood ratio).
Conclusion: SS measured with the spleen-dedicated 100Hz probe strongly correlates with PCPG over time and reliably identifies patients achieving PCPG <12 mmHg after udTIPS. If validated in larger cohorts, SS may become a non-invasive tool for tailoring invasive hemodynamic reassessments in post-TIPS monitoring protocols.

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OC-06

Trends in complications and mortality among individuals with chronic liver disease and cirrhosis: a population-based cohort study

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Background: Current trends in complications and mortality among individuals with chronic liver disease (CLD) and cirrhosis are largely unknown.

This study **aimed** to: (1) explore changes in mortality trends among patients with cirrhosis and CLD based on its aetiology; (2) disentangle mortality between liver and non-liver causes, before and during the COVID-19 pandemic; and (3) determine trends in the development of cirrhosis complications.

Material and Methods: Three subsequent population-based cohorts of individuals with CLD/cirrhosis were identified (4.9 million residents): the first enrolled before introduction of direct-acting antivirals (DAA); the second corresponding to full availability of DAA treatment; the last enrolled at the beginning of the pandemic. Risk of liver decompensation and death – liver and non-liver related – were recorded for each cohort during a 3-year follow-up. Changes in the risk of death across cohorts were measured by risk ratios (RR) obtained through Poisson regression models with robust error variance.

Results: Across the 3 cohorts spanning over 10 years, we found that the number of individuals with CLD and cirrhosis remained stable at about 40,000 and 10,000, respectively. The 3-year risk of ascites, hepatorenal syndrome, hepatic encephalopathy, and HCC decreased across the study period. The overall 3-year mortality risk declined by 14% (liver cirrhosis, subjects enrolled in 2020 vs. 2013: RR=0.86, 95%CI 0.83-0.89), especially among those with viral aetiology. By contrast, mortality due to alcohol-related CLD/cirrhosis was stable or increasing during the COVID-19 pandemic, especially for non-liver causes of death.

Conclusions: Despite increased awareness and proactive enrollment into patient care, CLD and cirrhosis remain a significant health-care challenge. The reduction in HCV-related mortality underscores the impact of antiviral treatments, while the persistently high mortality risk in alcohol-related disease highlights the need for targeted interventions.

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OC-07

Influence of the MBOAT7 rs641738 polymorphism on the prognosis of patients with metabolic dysfunction-associated steatotic liver disease and hepatocellular carcinoma

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Introduction and Aim: Several genetic factors have been associated to liver disease onset and progression in patients with metabolic dysfunction-associated steatotic liver disease (MASLD). In particular, genetic variants predisposing to liver fat accumulation (i.e. *PNPLA3*, *TM6SF2*, *MBOAT7*, *GCKR*, and *HSD17B13*) were associated with increased risk of hepatocellular carcinoma (HCC) development. We aimed to investigate the association between genetic variants and prognosis of patients with MASLD-HCC.

Methods: A total of 225 MASLD patients (median age: 74, IQR 49–97 years; males: 195, 86.7%) with a diagnosis of HCC were retrospectively enrolled. Most patients had an early stage HCC (BCLC: 0/A, n=145, 64.4%); patients with BCLC stage D were excluded from the analysis. Genotyping for *PNPLA3* rs738409 C>G, *MBOAT7* rs641738 C>T, *TM6SF2* rs58542926 C>T, *GCKR* rs780094 C>T, *HSD17B13* rs72613567: TA was performed by real-time allelic discrimination assay (TaqMan SNP Genotyping Assay, Applied Biosystems). Primary end-point was overall survival (OS).

Results: Overall, median OS was 29.1 (95%CI 21.4–32.7) months. Among the five genetic variants analysed, only *MBOAT7* rs641738 showed significant results at survival analysis. Specifically, patients who carried the TT risk genotype (n=59) showed reduced OS compared to those with CC/CT genotype (n=167) (OS=19.8, 95%CI 16.4–27.0 months vs. 32.2, 95%CI 28.5–53.9 months, respectively; p=0.007). At multivariate logistic regression analysis, *MBOAT7* rs641738 TT genotype resulted associated to reduced OS (OR=1.62, 95%CI 1.04–2.51) independently from BCLC stage (OR=2.12, 95%CI 1.68–2.68).

Conclusion: *MBOAT7* rs641738 (C>T) variant was associated to poor prognosis in patients with MASLD-HCC. In such patients, *MBOAT7* rs641738 genotyping may be useful to improve clinical management and to support decision-making.

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OC-08

Effect of Protease-Activated Receptor 2 inhibition by 1-Piperidinepropionic acid in lipid accumulation, inflammation and hepatocellular carcinoma development

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Introduction: Hepatocellular carcinoma (HCC) and Metabolic-Associated Steatohepatitis (MASH) are major challenges in modern hepatology. 1-Piperidinepropionic Acid (1-PPA) is a novel inhibitor of Protease-Activated Receptor 2 (PAR2), which is involved in inflammation, lipid accumulation and tumour development. This

study aims to evaluate the effect of 1-PPA on liver steatosis, inflammation and HCC development.
Materials: C57BL/6J mice transgenic overexpressing SerpinB3 (C57/TG), fed on a CDAA diet and injected with diethylnitrosamine (DEN) were divided into two groups (n=8 each) and treated with 1-PPA or placebo. HCC development was confirmed by liver histology. Microsomal triglyceride transfer protein (MTP) activity was quantified in liver tissue using a specific assay. qPCR of macrophage M2-polarization markers was carried out. Human liver organoids were cultured with Oleic Acid and SB3, and treated with 1-PPA and lomitapide, an inhibitor of VLDL export. Lipid and ROS accumulation was quantified using BodiPY and MitoSOX respectively.
Results: C57/TG mice treated with 1-PPA developed a lower mean number of nodules (1.5 vs 5, $p < 0.05$), a reduced mean tumoral mass (0.04 vs 0.1 g, $p < 0.01$) and a blunted expression of M2-polarization macrophage markers. MTP activity was increased in the liver of mice treated with 1-PPA. Human liver organoids showed a significant increase in lipid and ROS accumulation after Oleic Acid administration. Treatment with 1-PPA significantly lower lipid and ROS accumulation, however contemporary treatment with lomitapide reverted this effect, suggesting a role in VLDL export.
Conclusion: 1-PPA treatment reduced HCC development by reducing lipid accumulation and M2-macrophage polarization in a mouse model of NASH-induced liver carcinogenesis. 1-PPA treatment reduced lipid accumulation by stimulating VLDL formation and secretion both in a mouse model of MASH-induced liver carcinogenesis and in human liver organoids.

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OC-09

Genome-wide association study of noninvasive scores of fibrotic MASLD in an Italian population

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Background: Metabolic Associated Steatotic Liver Disease (MASLD) is the most prevalent chronic liver disease. It can progress to metabolic steatohepatitis (MASH), resulting in cirrhosis and hepatocellular carcinoma. A large fraction of MASLD heritability remains unexplained, and few genomic data are available in the Italian population. Genome-wide association studies (GWAS) offer a powerful method to identify genetic risk variants for risk stratification and therapeutic strategies.
Methods: The Milano BioBank is a multi-center effort which is gathering genomic and phenotypic data of Italian individuals enriched for the presence of metabolic dysfunction and MASLD (currently n=5875). Global Screening Array 3.0 (Illumina) and Michigan Imputation Server (GRCh38 TOPMed freeze 5) were used for SNP detection and imputation. We considered as main outcome the Fibrosis-4 Index (FIB-4) and secondary the Fibrotic NASH Index (FNI) and liver enzymes, as first-line clinical tests to identify at-risk MASLD (quantitative traits) adjusting the REGENIE regression models for age, sex, BMI, ethnicity.
Results: We confirmed a genome-wide significant association of *PNPLA3* locus with FIB-4 and FNI (rs738409 p.I148M; β=0.132, p= 3.06*10-22 and β=0.233, p=3.59*10-16 respectively) and with circulating ALT (rs3747207; β=0.145, p=2.64*10-16), AST (rs738408; β=0.186, p=1.48*10-23), and GGT (rs738409;β=0.109, p=1.28*10-11) levels. Additionally, *HAPLN4-TM6SF2* locus was associated with FNI (current top hit rs150641967 intronic variant; β=0.374, p=5.55*10-10), *ERLIN1* locus was associated with circulating ALT (rs10883451; β=-0.099, p=2.64*10-9) while *GGT1* (rs2073397, β=0.157, p=4.21*10-22), *RORA* (rs339969, β=0.108, p=5.84*10-11) and *EXOC3L4* (rs944002, β=0.108, p=8.22*10-10) loci associated with GGT.
Conclusions: We confirmed that single nucleotide polymorphisms in genes involved in hepatic lipid retention are the main genetic determinants of at risk of MASLD in the Italian population. These findings reinforce the role of *PNPLA3* as a key genetic determinant of MASLD, suggest the possible presence of additional contributors to liver disease at the *TM6SF2* locus and support the use of FNI to detect fibrosing MASH.

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OC-10

Impact of sexual dimorphism on liver damage in patients with metabolic-dysfunction associated steatotic liver disease

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Introduction: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a sexually dimorphic condition, characterized by a high prevalence in men compared to premenopausal women, but the reverse is true after menopause. Steroids, including glucocorticoids and sex hormones, regulate both glucose and lipid metabolism, and their perturbation may exert a detrimental effect on metabolic pathways promoting liver damage.

Aim: The aim of this study was to shed light on sexual dimorphism in patients with MASLD through a targeted steroidomic approach.
Materials and Methods: We enrolled 463 consecutive patients (males n=275 [59%]; females n=188 [41%]) with biopsy-proven MASLD and 112 healthy controls (HC) (males n=55 [49%]; females n=57 [51%]). A panel of 26 steroids (including glucocorticoids, androgens and their representative glucuro- and sulpho-conjugated metabolites) was measured by liquid chromatography coupled to tandem mass spectrometry. For statistical analysis, we stratified the whole cohort according to sex and age, using 50 years(y) as a cut-off. Advanced fibrosis was defined as F≥3.
Results: By comparing MASLD subjects and HC, we observed an increase in glucocorticoid levels in MASLD men<50y, and an increase in testosterone levels in MASLD women ≥50y compared to the corresponding HC groups. Concerning MASLD group, the prevalence of F≥3 was 36% (men/women 31%/45%, p=0.061). Similarly, we observed an increase in glucocorticoids levels in both MASLD men and women <50y with F≥3 compared to those without advanced hepatic fibrosis. In addition, in MASLD women with F≥3, regardless of age, we observed an increase in androgens metabolites, but a decrease in sulphate compounds.
Conclusions: In patients with MASLD, we identified different steroids profiles according to gender and age that varied according to the severity of hepatic fibrosis. Further studies are needed to understand the molecular basis of sexual dimorphism in the context of MASLD.

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OC-11

Burden of Hepatitis D Virus infection in Italy: final results from the HDV Describe study

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Introduction: Migratory flows are reconstituting the HDV reservoir in Italy, displacing the infection in Italians.
Aim: To compare the features of contemporary Chronic Hepatitis D (CHD) in native Italians (**It**) and foreign-born (**Fb**) patients.
Materials and Methods: Consecutive HBsAg carriers positive for antibodies to HDV (anti-HD) referred to 32 Italian Centers, were prospectively enrolled from 08/2022 to 07/2024. Sera were centralized in Torino for virologic assessment.
Results: Overall, 432 of 515 (83.9%) patients were HDV-RNA-positive (4.39, IQR 1.30–5.82 Log IU/mL; 99.0% HDV genotype-1). HDV-RNA levels correlated with ALT (r_s=0.58, 0.51–0.63) and liver stiffness (r_s=0.28, 0.19–0.37). The 317 **It** (61%) were older than the 198 **Fb** (39%) (median age 60, IQR 55–65 vs 46, IQR 39–54 years; $p<0.001$) with more advanced liver disease (cirrhosis: 223/317 [70.3%] vs 100/198 [50.5%]; $p<0.001$). Most (70.3%) of the ageing **It** had a cirrhosis acquired long ago. However, 29.7% (94/317) had no cirrhosis: their features denoted an active and viremic CHD in 44.7% (42/94) and an inactive/minimal disease with low viremia (<3 Log) in 55.3% (52/94), presumably acquired as a slow infection decades before. Despite the younger age, **Fb** already exhibited a 50.5% rate (100/198) of symptom-free compensated cirrhosis (median albumin: 4.1, IQR 3.8–4.4 g/dL); in the other 45.5% (98/198), 50 (51.0%) had an active CHD and 48 (49.0%) an inactive/mild infection with low viremia (<3 Log).
Conclusion: In Italy, the current scenario of chronic HDV infection is more heterogeneous than expected, changing the perspective of CHD as a most severe disease; about a quarter of **It** and **Fb** had a lingering less virulent CHD, and half of **Fb** presented with recently acquired cirrhosis, which was compatible with a stable clinical condition.

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OC-12

Duodenal organoids from patients with MASLD-cirrhosis display impaired mitochondrial energy metabolism and antioxidant defense

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Introduction: Gut-liver axis has been implicated in the pathogenesis of cirrhosis related to metabolic dysfunction-associated steatotic liver disease (MASLD). However so far no study has evaluated the pathogenetic involvement of the duodenum in this setting.
Aim: In this study we aimed to assess functional differences between intestinal organoids derived from subjects with steatosis without clinically significant fibrosis versus patients with MASLD and portal hypertension, i.e. the two extremes of the disorder.
Materials and Methods: Intestinal organoids were obtained from duodenal samples of subjects with simple steatosis and from cirrhotic patients. After 7-10 days of culture, RNA extraction, microarray analysis and Real-time PCR were performed. Mitochondrial energetics *in vitro* was evaluated by chromatographic analysis.
Results: Microarray analysis showed 600 dysregulated transcripts in organoids isolated from patients with MASLD-cirrhosis compared to patients with simple steatosis. Bioinformatic analysis indicated that dysregulated transcripts were involved in pathways regulating mitochondrial metabolism, hypoxia, inflammation and pluripotency of stem cells. Overall, chromatographic analysis demonstrated that mitocondrial energy metabolism was remarkably impaired in both differentiated intestinal epithelia cells and undifferentiated precursors from cirrhotic patients compared to steatotic subjects. In either undifferentiated or differentiated organoids from patients with cirrhosis, the triphosphate sum and the ATP/ADP, NAD+/NADH, NADP+/NADPH ratios were markedly lower, indicating a decline of the of phosphorylating capacity and a mitochondrial derangement of duodenal cells. In agreement with these findings, we also found lower levels of reduced glutathione and of total oxypurines in undifferentiated and differentiated cells from cirrhotics, and lower levels of the UDP-glucuronic acid, indicating impairment of antioxidant defense and of response to xenobiotics.
Conclusion: Deregulation of mitochondrial energy metabolism and of several pathways in the duodenum may contribute to pathophysiology of MASLD-cirrhosis.

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OC-13

High burden of MASLD and metALD in People with HIV: a call for liver fibrosis screening prioritization

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Background: Evidence suggests that metabolic dysfunction-associated steatotic liver disease (MASLD) has heightened severity in people with HIV (PWH). However, hepatology guidelines do not recognize HIV as a risk factor for MASLD and fibrosis. Most data rely on the outdated NAFLD nomenclature, emphasizing the need for research within the MASLD framework.
Aim: to assess the prevalence and factors associated with steatotic liver disease (SLD), its subcategories, and significant liver fibrosis in PWH.
Methods: We analyzed data from clinical centers in Canada, Italy and Germany on consecutive PWH undergoing unselected screening for SLD and liver fibrosis. SLD was defined as controlled attenuation parameter >248 dB/m. MASLD was defined as SLD plus ≥1 cardiometabolic factor without alcohol intake >20-30g/day. Metabolic dysfunction- and alcohol-associated liver disease (MetALD) was defined as SLD with ≥1 cardiometabolic factor and alcohol intake 20-60g/day. Alcohol-associated liver disease (ALD) was defined as SLD with alcohol intake >60g/day. Cryptogenic SLD (cSLD) was defined as SLD without cardiometabolic risk factors or other causes of SLD. Significant liver fibrosis and cirrhosis were diagnosed by liver stiffness measurement >8 kPa and >13 kPa, respectively. Logistic regression was used to investigate factors associated with MASLD and fibrosis.
Results: Among 3,006 PWH (median age 53, 25% female, all on ART, 85% with undetectable HIV viral load), 14% had HCV coinfection and 3% had HBV coinfection. SLD, MASLD, MetALD, cSLD, and ALD prevalence were 43.4%, 26.2%, 9.8%, 5.2%, and 2.2%, respectively. Overall, 11.2% had significant fibrosis, and 3.5% had cirrhosis. PWH with MASLD and MetALD had a significantly higher prevalence of significant fibrosis and cirrhosis compared to those without SLD (Figure). In multivariable analysis, body mass index (OR 1.28, 95% CI: 1.21–1.32) and age >50 (OR 1.47, 95% CI: 1.07–2.08) were independently associated with MASLD after adjusting for sex, duration of HIV infection, ALT, GGT, nadir CD4 <200 cells/uL, and use of integrase inhibitors. Significant fibrosis was associated with age (OR 1.01, 95% CI: 1.00–1.06), male sex (OR 1.53, 95% CI: 1.13–2.25), MASLD (OR 2.55, 95% CI: 1.70–3.25), MetALD (OR 1.89, 95% CI: 1.17–2.99), integrase inhibitor use (OR 1.65, 95% CI: 1.17–2.24), nadir CD4 <200 cells/uL (OR 1.45, 95% CI: 1.06–1.98), and HCV coinfection (OR 3.41, 95% CI: 2.46–4.71), while HBV coinfection was not.
Conclusion: The updated SLD definition reveals a high prevalence of significant liver fibrosis in PWH, driven by hepatic steatosis with metabolic alterations (MASLD and MetALD), HIV-related factors, and HCV coinfection. PWH should be globally recognized as a high-risk population for MASLD and prioritized for liver fibrosis screening.

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OC-14

Involvement of the ERG1 potassium channel in cholangiocarcinoma cell biology

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Background and Aim: Due to the lack of proper biomarkers and potentially effective treatments, the management of cholangiocarcinoma (CCA) is still challenging. In this view, ion channels have been proven to be novel biomarkers as well as new targets for cancer therapy, due to their easy druggability. The voltage-gated K+ channel hERG1 exert pleiotropic effects in cancer cells. Thus, this study explored the influence of hERG1 in intrahepatic CCA (iCCA) susceptibility.
Methods: Validation of h*ERG1* in iCCA tissues was performed in TCGA database. In vitro experiments were assessed to estimate the impact of h*ERG1 inhibition* on cell function in iCCA cell lines (HUCCT1, CCLP1, CCA4).
Results: Significant difference in h*ERG1* gene expression was observed between iCCA and normal tissue samples. Similarly, iCCA cell lines significantly showed high protein content of hERG1 compared to normal cholangiocytes (NHC3).

Treatment with E4031, a selective hERG1 inhibitor as well genetic depletion (siRNA), showed, albeit limited impact of cell growth, a substantial reduction of invasive capability of iCCA cells. Moreover, immunoprecipitation assay and immunofluorescence revealed the formation of an active macromolecular complex with $\beta 1$ integrin responsible for VEGF-A activation through the phosphorylation of AKT signaling.

Furthermore, treatment with the bispecific antibody (scDb: single-chain Diabody) that binds the hERG1-$\beta 1$ complex, negatively impacted invasiveness of iCCA cells as well as expression of epithelial to mesenchymal genes. Importantly in vitro co-treatment with scDb and cisplatin-gemcitabine, significantly reduced growth of iCCA cells.
Conclusions: This study suggests that hERG1 may play a critical role in the initiation and progression of intrahepatic CCA, highlighting its potential as a therapeutic target.

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OC-15

Real-world practice patterns on the use of terlipressin in patients with cirrhosis and acute kidney injury - results from the ICA-GLOBAL AKI study

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Background: Terlipressin is indicated for the treatment of HRS-AKI. However, real-world practice patterns on the use of terlipressin in AKI in general as well as outcomes in non HRS-AKI remain largely unknown.
Method: International prospective study including patients hospitalized for decompensated cirrhosis from July 2022 to May 2023. This was a subgroup analysis of patients who received terlipressin for AKI treatment. Primary outcome was absence of AKI resolution (return of serum creatinine to a value within 0.3 mg/dl of the baseline). Secondary outcomes were incidence of respiratory failure, and 28-day mortality.
Results: Among 1,456 patients with cirrhosis and AKI, 243 (17%) received terlipressin for AKI treatment. Terlipressin was predominantly administered in continuous infusion (75%) at a median maximum daily dose of 3 mg [IQR=2-4] and median duration of 5 days [IQR=3-8]. The AKI phenotype was HRS-AKI in 50%, ATN in 17%, hypovolemia-induced in 25%. Complete AKI resolution occurred in 49% of patients. Lack of AKI resolution was highest in ATN (71%), followed by HRS-AKI (49%). On multivariable analysis ATN was independently associated with lack of AKI resolution (OR 2.77; p=0.016) compared to HRS-AKI, along with AKI stage 3 and ACLF stages 2-3. *De novo* respiratory failure occurred

in 20% of patients treated with terlipressin. No significant differences were found in albumin and terlipressin doses in patients who did and did not developed respiratory failure. Pneumonia (OR=8.29; p<0.001) and lack of volume loss/hypovolemia before AKI (OR=2.70; p=0.029) were independent predictors of respiratory failure. On multivariable analysis, age, ATN, hospital-acquired AKI and MELD score were independent predictors of 28-day mortality.
Conclusion: Terlipressin is often used for treatment of AKI outside its primary indication of HRS-AKI. Since AKI response and clinical outcomes are very poor in ATN, terlipressin should be used with caution in this setting as its risks may outweigh benefits.

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OC-16

Feasibility and effectiveness of liver transplantation following immunotherapy in patients with hepatocellular carcinoma

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Introduction: Immunotherapy is an attractive strategy for downstaging/bridging hepatocellular carcinoma (HCC) to liver transplantation (LT).
Aims: This multicenter study reports the results of HCC-transplanted patients in ten French liver transplant centers in this context.
Patients and Methods: Clinical, biological, and radiological data were collected for each patient at the beginning and end of immunotherapy and before LT. The primary endpoint was the tolerance and effectiveness of LT.
Results: Twenty-one patients [majority of men (17/21); median age 62 years (57-64), BCLC B stage in 14/21 patients (66.7%)] who underwent LT for HCC after immunotherapy were included. HCC was multi-nodular in 17/21 (81%) cases, with a median size of the largest nodule of 36 mm (21-60). Thirteen patients had an AFP score >2 (downstaging group) and 8 of ≤2 (bridging group). Patients in the downstaging group were beyond Milan criteria, and 3 in the bridging group (p=0.006). Sixteen patients (76.2%) received Atezolizumab/Bevacizumab during 8.5 cycles (4.7-14). At the end of immunotherapy, most patients shifted to an early/intermediate BCLC stage (p=0.001) and reached Milan criteria (57.1%, p=0.023). The AFP score remained >2 in 2 cases (9.5%) (p=0.003). The median interval between the last immunotherapy cycle and LT was 5.1 (2.7-9.3) months. All patients except 3 received standard immunosuppressive treatment. Two cases (10%) of rejection occurred, resolved after increasing immunosuppression. Early serious adverse events occurred in 6 patients (28.5%), 5 being fatal (27%). Two patients (10.5%) had an HCC recurrence post-LT. On explant pathology, no residual tumor was detected in 6 cases (28.6%) and partial necrosis in 7 (41.2%). The R3-AFP score stratified patients into 3 at very low (14.3%), 8 at low (38.1%), and 10 at high (47.6%) recurrence risk.
Conclusion: LT following immunotherapy is feasible in selected patients with HCC and has an acceptable risk of rejection. However, the high immediate mortality observed requires further exploration in prospective studies.

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OC-17

One-year changes in alt and lsm, not in cap, predict long-term liver outcomes in patients with metabolic dysfunction-associated steatotic liver disease

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Background & Aim: The availability of new drugs for the treatment of patients with metabolic dysfunction-associated steatotic liver disease(MASLD) underlines the need of early predictors of response to such therapies. This study evaluated the impact of 1-year changes in liver stiffness measurement by Vibration-Controlled Transient Elastography(LSM by VCTE), controlled attenuation parameters(CAP), and serum alanine aminotransferase (ALT) on liver outcomes in patients with MASLD-related liver disease.
Methods: A large multicentre cohort of MASLD patients with LSM≥8kPa and prospective follow-up was enrolled. Liver-related events(LRE), including hepatocellular carcinoma (HCC) and liver decompensation(LD), were evaluated during follow-up. LSM,CAP, and ALT were assessed at baseline and at 1-year follow-up. Cumulative incidence functions and cause-specific Cox regression analyses were performed to correlate 1-year reduction in LSM,CAP, and ALT with the risk of developing LRE,LD and HCC.
Results: In 4662 patients with MASLD and LSM≥8kPa, a 1-year reduction in ALT of 17 IU/L(HR 0.62;95% CI 0.41-0.95;p=0.02)and a 20% reduction in LSM(HR 0.44;95% CI 0.29-0.67;p<0.001)were both independently associated with a lower risk of LRE. Similarly, in 3044 patients with MASLD and LSM≥10kPa, a 1-year reduction in ALT of 17 IU/L(HR 0.62;95% CI 0.39-0.98;p=0.04)and a 20% reduction in LSM(HR 0.42;95% CI 0.27-0.66;p<0.001)were independently associated with a decreased risk of LRE. Comparable results were observed when considering LD separately, but not for HCC. One-year changes in CAP did not predict liver outcomes. When combining 1-year reduction in ALT of 17 IU/L and a 1-year 20% reduction in LSM, the 5-year probabilities of LRE ranged from 2.1% in the best profile to 5% in the worst profile in patients with LSM≥8kPa, and from 3.3% to 8.1% in those with LSM≥10kPa.
Conclusions: One-year reductions in ALT of 17 IU/L and in LSM by 20%, not changes in CAP, reduce long-term liver outcomes in patients with MASLD, providing a new perspective on monitoring therapy effectiveness.

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OC-18

The early dynamic changes of radiological and biochemical scores help identify a more aggressive PSC phenotype

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Introduction: The natural course of Primary Sclerosing Cholangitis (PSC) is generally progressive towards cirrhosis and its complications. Predicting the prognosis in PSC is still a matter of debate. Several prognostic factors associated with transplant-free survival have been identified, including serum markers, composite scores, biliary and parenchymal changes and elastography.
Aim: The aim of this study was to assess whether the evolution of biochemical and magnetic resonance imaging (MRI) scores is associated with an increased risk of developing clinical outcomes.
Material and Methods: We conducted a retrospective analysis of patients diagnosed with large ducts, non-cirrhotic PSC, who underwent regular clinical and radiological follow-up with at least two consecutive MRIs closest to the diagnosis, available for review by an expert radiologist. The ANALI scores with and without gadolinium (Gd) were assessed in the two MRIs, and any increase in the ANALI scores was considered as radiological worsening. Demographic data and liver function tests were collected at the same timepoints as the MRI scans, and two scores, the Amsterdam Oxford Model (AOM) and the Mayo Risk Score (MRS), were calculated and stratified into low, intermediate and high-risk categories. The progression of AOM and MRS was defined by the upgrade from one category to a higher one. Clinical outcomes considered included the development of recurrent cholangitis, cirrhosis, liver transplantation (LT), death from liver disease, and the development of hepatobiliary malignancies.
Results: A total of 45 patients were included. Median age was 30 (21-38) years at diagnosis and 36 (28-50) years at inclusion. The median interval between the two MRIs was 24 (16–38) months. Twenty-eight (62%) patients were male. The median follow-up after the second MRI was 69 (50-90) months. Thirteen (29%) patients experienced radiological worsening, while 8 (18%) and 7 (16%) patients showed progression of the AOM and the MRS, respectively. The increases in ANALI with and without Gd and the MRS were associated with the risk of development cirrhosis during follow-up (p=0.032, p=0.003 and p=0.001, respectively). Additionally, the increase in ANALI without Gd during follow-up was significantly associated with the need for LT (p=0.001). A trend towards a significant association between the increase in MRS and LT was observed

(p=0.085). Finally, patients who developed recurrent cholangitis during follow-up exhibited a progressive increase in ANALI without Gd (p=0.003).
Conclusions: The early dynamic changes in radiological and biochemical scores help identify a more aggressive PSC phenotype. These preliminary findings suggest the potential utility of dynamic assessment of radiologic and biochemical scores for prognostic purposes and risk stratification. Further validation in larger cohorts is warranted.

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OC-19

MASLD and FIB4 are independent predictors of major adverse liver outcomes and cardiovascular events in type 2 diabetes: findings from a single-center cohort using AI-driven machine learning

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Introduction: MASLD and liver fibrosis are common in type 2 diabetes(T2D), and the FIB-4 index is reliable marker of liver fibrosis. However, data on the specific predictive role of FIB-4 in identifying the risk of major adverse liver outcomes(MALOs) in T2D remain limited.

The primary objective was to evaluate whether the presence of MASLD and elevated FIB-4 predict an increased incidence of MALO in T2D. Secondary objectives included assessing whether MASLD and FIB-4 serve as predictors of MACE, and identifying any additional variables associated with MALO and MACE.
Materials and Methods: This retrospective cohort study analyzed T2D patients from January-2016 to January-2022 at the Gemelli Polyclinic outpatient diabetes clinic. Clinical data were collected using an AI-driven system. FIB-4 score>2.67 was considered indicative of a high probability of advanced liver fibrosis.

Multivariable logistic regression models were developed. Each model was adjusted for clinically relevant covariates, significance was considered as p<0.05.
Results: The study included 1,711 patients, 67(3.9%) experienced a MALO and 203(11.86%) a MACE. MASLD significantly increased the risk of MALO(OR 2.03,p=0.024) and MACE(OR 1.40,p=0.042). A FIB-4>2.67 was strongly associated with higher risks of MALO(OR 6.92,p<0.001) and MACE(OR 2.39,p<0.001). In the model, which excluded cirrhosis at baseline, MASLD(OR 2.51, p=0.040) andFIB-4 >2.67(OR 3.02,p=0.007) remained significant predictors of MALO. Additionally, HbA1c was a significant predictor in both models(OR 1.02, 95%-CI 1.01–1.04, p=0.009).
Conclusion: The study found that MASLD and elevated FIB-4 are independent predictors of MALOs and MACE in T2D-patients, highlighting the importance of routine non-invasive screening for liver fibrosis and MASLD. HbA1c was also identified as independent predictor of adverse outcomes. Early detection and optimal glycemic control can help mitigate liver and cardiovascular complications. Furthermore, the use of AI-driven data extraction demonstrates the potential for enhancing clinical research and improving patient management in real-world settings.

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OC-20

The early impact of bariatric surgery on liver fibrosis and steatosis in MASLD patients

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Background: Metabolic-dysfunction-associated-steatotic liver disease (MASLD) affects more than half of obese subjects. To date, weight reduction by diet and physical activity is recommended to improve liver injury. Recent studies have shown that bariatric surgery induces stable weight loss and ameliorates metabolic parameters. Aim of this study is to evaluate the effect of bariatric surgery on liver steatosis and fibrosis.
Methods: This is a monocentric prospective study including all patients with severe obesity and MASLD candidates for bariatric surgery in a single Italian-center. Other causes of chronic liver disease were an exclusion criteria. Clinical and biochemical data were collected. Liver fibrosis and steatosis were non-invasively assessed with Liver Stiffness Measurements (LSM) and Controlled Attenuation Parameter (CAP) by Fibroscan at three time-points: before surgery, 6- and 12-months after surgery.
Results: A total of 112 patients (63.4% female, mean age 41.5 years) were enrolled. Before bariatric surgery, the BMI was 43.6±6.2kg/m², the LSM was 8±5.8kPa and the CAP was 319.7±57.8dB/m. Ninety-six patients continued follow-up up after surgery. These patients demonstrated a significant reduction in BMI and CAP as early as 6-months post-surgery, while a significant decrease in LSM was observed only after 12-months. Specifically, the mean BMI was 31.9±5.1kg/m² after 6 months and 28.0±3.5kg/m² after 12-months, representing an overall decrease of 35.9% from baseline (p<0.0001). The mean CAP was 264.5±57dB/m after 6-months and 214.8±47.8dB/m after 12-months, reflecting an overall decrease of 32.8% from baseline (p<0.0001). Finally, the mean LSM was 6.3±2.5kPa after 6-months and 5.8±1.9kPa after 12-months, showing an overall decrease of 21.6% from baseline (p=0.02).
Conclusions: This study demonstrated a significant weight loss and liver steatosis decrease already at 6-months after surgery, while liver fibrosis reduction takes longer at 12-months after surgery. Therefore, in adults with MASLD and severe obesity, bariatric surgery should be considered as a valid therapeutic option for improving the liver damage

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OC-21

HDV persistence acts independently from HBV reservoir extent and is sustained by HBsAg production mainly derived from integrated HBV-DNA

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Introduction&Aim: HDV exploits HBV surface-glycoproteins (HBsAg) for viral infectivity. Here, we investigate HBV and HDV activities and their interplay in liver biopsies from patients with chronic HDV infection (CHD) and HBV mono-infection (CHB).
Methods: 70 HBeAg-negative patients (74% NUC-treated) are included: 35 with CHD and 35 with CHB. Droplet-digital PCR was used to quantify intrahepatic levels of cccDNA, pgRNA, HDV-RNA and HBs-transcripts from cccDNA and from integrated HBV-DNA (Grudda, 2022). Ad-hoc ELISAs were used to quantify HBs isoforms.
Results: CHD and CHB are comparable in terms of age and NUC-treatment duration. CHD has lower serum HBV-DNA than CHB (median[IQR]: 26[14-58] vs 4,100[225-76,515]IU/ml,P<0.0001).

Median(IQR) serum HDV-RNA is 6.0(4.0-6.9)logIU/ml, positively correlated with intrahepatic HDV-RNA (Rho=0.62,P=0.006; 787[1-7,596]copies/1000cells).

CHD presents lower levels of cccDNA and pgRNA (median[IQR]: 1(0.02-12) vs 24(8-93)copies/1000cells and 8[1-147] vs 518[57-3,894]copies/1000cells,P<0.0001 for both comparisons), but a substantial HBs-transcripts production comparable to CHB (median[IQR]: 6,041[323-29,446] and 12,776[4,570-55,977]), with >99% of them from integrated HBV-DNA.

By stratifying CHD-patients according to cccDNA-size, lower levels of HBV intrahepatic-markers are observed in those with smaller cccDNA (median[IQR] pgRNA and cccDNA-derived transcripts: 1.4[0.4-25] vs 89[6-238],P=0.005 and 0.3[0.1-0.9] vs 41[7-179]copies/1000cells,P=0.002 in cccDNA<1 vs cccDNA>1copy/1000cells). Conversely, no differences are observed for intrahepatic HDV-RNA (median[IQR]: 782[1-5,559] vs 1,026[40-6,984]copies/1000cells,P=0.5). Moreover, 8 out of 35 CHD-patients with undetectable cccDNA, cccDNAderived-HBs transcripts and serum HBV-DNA present considerable levels of intrahepatic and serum HDV-RNA (median[IQR]: 5,495[976-14,946]copies/1000cells and 6.0[4.8-6.9]logIU/ml, respectively), as well as of integrated HBV-DNA derived HBs-transcripts (median[IQR]: 3[1-497]copies/1000 cells) and of all the three HBs-isoforms (median[IQR]ng/ml: 1,116[123-3,987] for S-HBs, 368[8-1,894] for M-HBs and 1.4[5.9-7.3] for L-HBs).
Conclusions: Pathways sustaining HDV-persistence act independently from HBV reservoir extent and are fueled by an intense HBs-transcripts production, mainly sustained by integrated HBV-DNA, capable to produce all three HBs-isoforms. In this light, pharmacological strategies should take into account HBsAg production from integrated HBV-DNA for achieving HDV cure.

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OC-22

Expert-Validated Framework for Large Language Models in HCV Care: A Comparative Analysis of RAG and Fine-Tuning Using Clinical Guidelines

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Introduction: Large language models (LLMs) show promise for transforming chronic disease management, but their accuracy in medical applications remains variable.
Aim: This study aims to evaluates how retrieval augmented generation (RAG) and supervised fine-tuning (SFT) impact the accuracy and clarity of LLM recommendations for Hepatitis C Virus (HCV) management.
Methods: We compared three configurations: baseline GPT-4 Turbo, RAG-enhanced GPT-4 Turbo using the 2020 HCV EASL guidelines, and GPT-3.5 Turbo with SFT. Fifteen questions across general, patient, and physician perspectives were carefully designed and reviewed by a lead author of the EASL HCV guidelines. These questions were evaluated by four expert hepatologists who authored the same guidelines. Responses were scored on a binary evaluations for accuracy (distinguishing completely accurate responses from those with any degree of inaccuracy) and clarity. Additionally, gold standard answers were created and reviewed by the guideline author to enable text similarity analysis using OpenAI's text-embedding-3-large model for embedding-based metrics.

Results: The RAG-enhanced model showed significantly higher accuracy (83.3% vs 36.6%, p<0.001) and clarity (91.6% vs 46.6%, p<0.001) compared to baseline. Similarly, the SFT model demonstrated improved accuracy (80% vs 36.6%, p<0.001) and clarity (86.6% vs 46.6%, p<0.001). Inter-rater agreement was excellent for the 10-point scale (ICC=0.82-0.86) but only moderate for binary evaluations (Kappa=0.41-0.54). Both enhanced models performed particularly well with patient-oriented questions, achieving 95% (RAG) and 85% (SFT) accuracy. Text similarity analysis using cosine similarity showed the highest scores for RAG-generated responses (0.59) compared to baseline (0.48) and SFT (0.51), particularly in patient-oriented responses where RAG achieved a cosine similarity of 0.65.
Conclusions: RAG and SFT significantly improve the accuracy and clarity of HCV management recommendations compared to baseline LLMs. The involvement of guideline authors in both question design and evaluation provides robust validation of these improvements. However, moderate inter-rater agreement on binary metrics suggests the need for standardized evaluation frameworks. These findings support the potential of enhanced LLMs for clinical decision support while highlighting the importance of rigorous evaluation methods for safe implementation in healthcare settings.

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OC-23

Changes in body mass composition do not predict post-transplant outcome in cirrhosis patients with hepatocellular carcinoma undergoing liver transplantation

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Introduction: Sarcopenia and adipose tissue alterations may predict liver decompensation and reduced survival before and after liver transplant(LT). However, the evolution of body composition from pre- to post-transplant and its outcomes association are poorly understood.
Aim: To assess the evolution of sarcopenia and adipose tissue alterations from pre- to post-LT and their potential impact on patient outcomes.
Methods: Adult patients with hepatocellular carcinoma(HCC) who underwent LT at Padua University Hospital between January 2015 and March 2022 were retrospectively included. Body composition was assessed via CT scans within six months pre-LT and at 3-,6-, and 12-months post-LT. The Skeletal Muscle Index(SMI), Visceral Adipose Tissue Index(VATI), and Subcutaneous Adipose Tissue Index(SATI) were calculated. Uni and multivariate Cox regression analysis was used to evaluate the association with clinical outcomes.
Results: 164 patients(85.3%male, median age 62 years) were included. HCV infection was the most common aetiology of liver disease, followed by alcohol-related liver disease(20%); Prevalence of sarcopenia was 45%(median SMI of 50 cm^2/m^2;IQR 56.43–45.03), while VAT and SAT alterations were observed in 22.4% and 49.4% of patients. Sarcopenia prevalence slightly increased from 45.1% pre-LT to 56.1% at 12 months. VAT alterations increased consistently, from 40.6% pre-LT to 60% at 12 months post-LT, whereas SAT alterations remained largely stable. Pre-transplant body composition alterations were not associated with decreased survival at 1, 3, or 5 years (sarcopenia:p=0.21;VATI alteration:p=0.20;SATI alteration:p=0.28). No association was found between changes in body composition and survival (sarcopenia:p=0.43; VATI alteration:p=0.50; SATI alteration:p=0.43) nor the risk of HCC recurrence. In multivariate analysis, COPD(OR:0.9;95%CI 0.7–9.1;p=0.042) and CKD(OR:1.7;95%CI 1.8–17.9;p=0.003) were the only independent predictors of survival.
Conclusions: Sarcopenia and adipose tissue alterations are common in cirrhosis and HCC patients undergoing transplantation. Significant body composition changes occur within a year post-LT but are not linked to complications or survival. These findings do not support body composition assessment for LT evaluation or early post-LT risk stratification in compensated cirrhosis with HCC.

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OC-24

Non-invasive follow-up of cardiac hemodynamics after trans-jugular intrahepatic portosystemic shunt: focus on left ventricular global longitudinal strain

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Introduction: In patients with clinical significant portal hypertension, especially in those with variceal bleeding or stable decompensated cirrhosis with refractory ascites, trans-jugular intrahepatic portosystemic shunt (TIPS) implantation is a well-established second-line treatment. TIPS leads to immediate changes in both systemic and portal hemodynamics, as the procedure effectively reduces portal pressure and shifts blood flow from the splanchnic circulation to the systemic circulation. This shift increases preload, boosting central blood volume and cardiac output. Pre-TIPS workup should include abdominal imaging to delineate the hepatic vascular anatomy and an echocardiogram to assess cardiac function, particularly for the presence and severity of systolic and diastolic dysfunction, as well as for signs of pulmonary hypertension. Novel echocardiographic index, such as speckle tracking echocardiography (STE), particularly left-ventricle global longitudinal strain (LV-GLS), is more sensitive in identifying subclinical myocardial dysfunction in cirrhotic patients.
Aim: We evaluated the impact of TIPS placement on cardiac hemodynamics by employing standard and advanced echocardiography. Specifically, we sought to explore the utility of global longitudinal strain (GLS) in detecting changes in left ventricular function pre- and post-TIPS, and to correlate these findings with clinical outcomes.
Material and Methods: We consecutively enrolled 19 patients underwent TIPS placement. Each patient underwent echocardiography and abdominal Doppler ultrasound before and 3 months after TIPS insertion.
Results: Echocardiographic follow-up showed that left ventricular end diastolic volume (+13.5%, p<0.05), left atrium indexed volume (+21%, p<0.005) and right atrial area increased after TIPS (+26%,

p = 0.01). Left ventricular GLS significantly reduced (became less negative) after TIPS (+14%, p<0.02).
Conclusion: Our data indicates that after three months of TIPS placement, GLS reduced approximately more than 2 percentage points, suggesting a "pseudo-normalization" of cardiac hemodynamic. In the context of TIPS, identifying patients with impaired GLS, could help stratify those at higher risk of post-TIPS acute on chronic liver failure.

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OC-25

Thrombus generation under flow conditions in patients with cirrhosis and thrombocytopenia: the CirTAS-study

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Introduction: Thrombocytopenia is common in cirrhosis and its predictive role for the hemorrhagic risk is still controversial. Along with thrombocytopenia, the most advanced stages of cirrhosis are associated with high levels of von Willebrand factor (VWF). This, under flow conditions, may allow platelets to provide effective hemostasis in-vivo, however most global hemostasis tests are static and do not capture this phenomenon.
Aim: The CirTAS-study aimed to explore the reliability of a new point-of-care device to evaluate thrombus generation under flow conditions in patients with cirrhosis and thrombocytopenia.
Materials and Methods: The Total Thrombus Analysis System (T-TAS) was used to evaluate the thrombus generation of whole blood under high shear stress in a flow chamber (HD-CHIP) designed to test hemostasis in patients with platelet count $<100 \times 10^3/mm^3$. All measurements were duplicated and the reproducibility was tested by intraclass correlation coefficients (ICC). The ability of the device to evidence a disease gradient effect on hemostasis was explored by comparing three groups of patients at a different stage of severity: 1-Child A (n=20), 2-Child B/C with decompensation without acute infection (N=41), 3-Child B/C with decompensation and acute infection (N=20). We also measured: factor VIII (FVIII), protein C (PC), VWF:Ag, VWF:Rco.
Results: Clinical and biochemical data were consistent with a gradient of disease severity among the groups (p<0.05). T-TAS parameters were reproducible (ICC≥0.9) and showed the existence of a disease gradient effect on hemostasis, being Child B/C patients with decompensation and acute infection the group with the slowest and lowest in-vitro thrombus generation under flow (p<0.05). Low platelet count, and, at least in part, FVIII were the most important determinants of thrombus formation in the whole series.
Conclusions: T-TAS is a reliable point-of-care device to explore new laboratory-based algorithms for the management of the hemorrhagic risk in patients with cirrhosis and thrombocytopenia.

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OC-26

Prognostic role of endoscopic ultrasound guided direct portal pressure gradient measurement in porto-sinusoidal vascular disorder

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Introduction: HVPG is the gold standard for the diagnosis of clinically significant portal hypertension (CSPH), a condition associated with the risk of developing hepatic decompensation events. However, HVPG is an indirect method to measure portal pressure and its application in pre-sinusoidal form of portal hypertension (PH), as in porto- sinusoidal vascular disorder (PSVD), is hindered by low accuracy. Recently, endoscopic ultrasound (EUS)-guided Portal Pressure Gradient (PPG) measurement, which allows direct measurement of portal pressure, is emerging as a safe method and may overcome the limitation of HVPG. However, data in patients with CSPH and pre-sinusoidal form of PH are still missing.
Aims: This study aims to evaluate the safety and usefulness of EUS-PPG compared to HVPG in a cohort of patients with PSVD and CSPH.
Materials and Methods: in this prospective single center study, patients with a diagnosis of PSVD who presented a clinical suspicion of CSPH underwent HVPG and EUS-guided PPG baseline measurements. A second EUS-PPG measurement was performed in patients naïve to non-selective beta-blockers (NSBBs) to evaluate hemodynamic response to therapy.
Results: Twenty patients were enrolled and a total of 20 HVPG and 27 EUS-PPG measurements were performed, without any adverse events. Mean EUS-PPG was 18.2 ± 4.5 mmHg, significantly higher than mean HVPG value (5.9 ± 2.9 mmHg). At logistic regression, EUS-PPG was associated with hepatic decompensation.
Conclusions: EUS-PPG measurement is safe and might have a prognostic role in patients with PSVD and CSPH, outperforming HVPG.

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OC-27

Unravelling MASLD heterogeneity at single cell level in the switching towards progressive disease

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Introduction: Metabolic dysfunction-associated steatotic liver disease (MASLD) embraces different conditions, including metabolic dysfunction-associated steatohepatitis (MASH), fibrosis/cirrhosis and hepatocarcinoma. The landscape of cellular abnormalities occurring in the different stages of MASLD and the processes which drive its evolution are not elucidated.
Aim: We aimed to investigate cell population heterogeneity involved in progressive MASLD at single cell resolution, to define the role of hepatic cell types in the disease transition.
Materials and Methods Results: C57Bl6 male mice were fed standard (SD) or high fat high fructose (AMLN) diets for 14 (steatosis), 22 (MASH) and 28 (MASH-fibrosis) weeks to resemble human MASLD. Single cell RNA-sequencing (scRNAseq) was applied to decipher cell populations, differentiation and genes/pathways guiding MASLD progression.

By considering the expression of canonical markers, we classified 32 clusters (Cls), including hepatocytes (HEPs), hepatic stellate cells (HSCs), endothelial cells (Endo), Kupffer cells (KCs), and immune cells. We observed changes in HEPs Cls across disease severity, with a mixed pericentral/periportal localization in steatosis and a periportal one in MASH and MASH-fibrosis, reflecting the advanced damage in this area. The latter conditions were featured by Endo Cls which induced the expression of vascular angiogenesis and ECM molecules whereas endothelial mesenchymal transition (EndMT) markers gradually appeared during the disease. Among KCs, we found Cls of resident cells and immune cells recruited from the circulation with a M1 phenotype which increased throughout diet exposure. Regarding HSCs, MASH-fibrosis was featured by Cls with mesenchymal markers. Among the 32 Cls, we identified 5 chimeric populations named HSCs/Endo (Cl 21), HEPs/Endo (Cl 15), KCs/Endo (Cl 26) and HEPs/KCs (Cl 10 and Cl 17). Evolutionary trajectory outlined the directions of cell differentiation, which was more pronounced in MASH-fibrosis.
Conclusions: We observed an evolution of cellular heterogeneity during MASLD and identified chimeric populations in the advanced stages thus suggesting their involvement in disease progression.

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OC-28

Systemic oxidative stress correlates with sarcopenia and pruritus severity: two independent relationships simultaneously burdening the quality of life in patients with Primary Biliary Cholangitis

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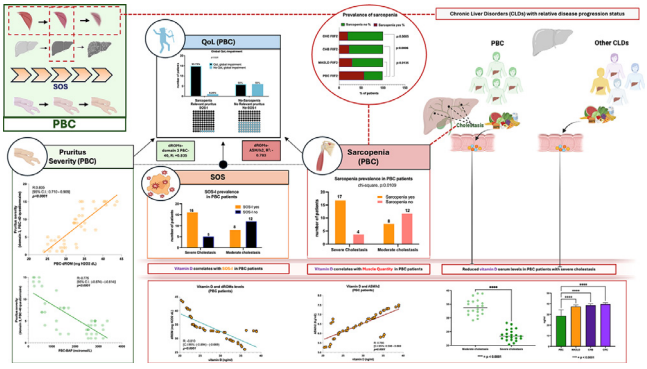
Introduction: In chronic liver disorders (CLDs), systemic oxidative stress (SOS) worsens in parallel with liver disease progression status (DPS) exclusively in Primary Biliary Cholangitis (PBC). Sarcopenia severely burdens outcomes even in PBC. However, the SOS-Muscle Quantity (MQ) relationship has never been investigated. In PBC, cholestasis impairs vitamin D absorption, promoting malnutrition-sarcopenia. The relationship between vitamin D levels-MQ and vitamin D levels-SOS has never been directly evaluated. Cholestasis-related pruritus represents a main quality of life (QoL) determinant in PBC. Although SOS influences various central/peripheral pathogenetic itch pathways, the correlation with pruritus severity remains unexplored in PBC.
Aim: To investigate the relationship between SOS and sarcopenia severity in PBC patients compared with other CLDs, as well as, by focusing on the PBC, to evaluate the relationship between SOS and pruritus severity and the simultaneous impact of sarcopenia-SOS-pruritus on QoL.
Material and Methods: 40 MASLD, 52 chronic-HBV-infection (CHB), 50 chronic-HCV-infection (CHC), and 41 ursodeoxycholic-acid/antioxidants-naïve PBC patients were enrolled. Biochemical, nutritional, and Liver Stiffness data were collected after a normalizing 3-month equally prescribed dietetic-physical exercise regimen. EWGSOP2 criteria diagnosed sarcopenia. The d-ROMs/BAP tests evaluated SOS. The "PBC-40 questionnaire" estimated pruritus QoL.
Results: Unlike other CLDs, in PBC, sarcopenia was more prevalent in initial-mild fibrosis (PBC: 57.10% vs MASLD: 30.76%, CHB: 22.60%, CHC: 20.70%, all $p<0.0001$), and SOS significantly correlated with MQ (dROMs-ASM/h^2, p:0.0002; BAP- ASM/h^2: p:0.0092). PBC patients presented lower vitamin D levels and a significant correlation of these with both SOS and MQ ($p < 0.0001$). In PBC, SOS correlated with pruritus severity (dROMs, R:0.835; BAP, R: - 0.775, $p<0.0001$). A QoL impairment was significantly more represented in PBC individuals simultaneously showing sarcopenia, SOS imbalance, and relevant pruritus (p: 0.0228).
Conclusions: In PBC, SOS simultaneously correlates with sarcopenia and pruritus severity, configuring a QoL-burdening scenario.



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OC-29

Bulevirtide for patients with chronic Hepatitis D (CHD) in Italy: a multicenter prospective nationwide real-life study (D-Shield)

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Background: Bulevirtide (BLV) has been available in Italy since May 2023 for patients with chronic hepatitis Delta (CHD), but no studies have addressed features of patients treated with BLV and their responses to treatment yet.
Methods: CHD patients starting BLV 2 mg/day as monotherapy or in combination with pegIFNα were included in a multicenter prospective real-life Italian study (D-SHIELD). Patients' characteristics and treatment responses were assessed at baseline and trimonthly afterwards.
Results: 369 patients from 36 centers were enrolled in this ongoing study. 99% received BLV 2 mg/day monotherapy: age 54 (28-82) years, 55% men, 76% cirrhotics, 96% on NUC therapy. Among cirrhotics, 39% had varices, 10% history of HCC, 10% of ascites, 3% of varices hemorrhage, 7% were decompensated. As of November 2024, 170 patients have completed 48 weeks of treatment. ALT declined: from 75 (16-1,074) U/l at baseline to 34 (7-198), 34 (7-236), and 32 (11-216) U/L at week 24, 32 and 48, respectively ($p<0,0001$). HDV RNA declined from 5.3 (1.5-8.2) at baseline to 3.4 (0.3-7.3), 2.8 (0.2-7.2), and 2.5 (0.3-7.3) at week 24, 32 and 48, respectively ($p<0,0001$). Virological, biochemical and combined responses were achieved by 42%, 65% and 31% of patients at week 24; 61%, 67% and 43% of patients at week 32, and by 64% 70% and 47% of patients at week 48. Among non-virological responders, 61%, 46% and 47% achieved a partial virological response (HDV RNA decline >1 but <2 Log IU/mL, compared to baseline) at week 24, 32, and 48. Moreover, 11%, 21% and 22% of patients achieved HDV RNA undetectable at week 24, 32 and 48, respectively.
Conclusions: D-SHIELD is the largest single country study on BLV treatment for CHD in Europe. Almost all patients started BLV as monotherapy. Virological, biochemical and combined responses at week 48 compared with previous retrospective studies.

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OC-30

Oncostatin M modulates the biology of cholangiocarcinoma cells and the tumor microenvironment

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Background and Aims: Cholangiocarcinoma (CCA) is a highly aggressive tumor characterized by high resistance to chemotherapy and poor prognosis. Increasing evidence highlights that oncostatin M (OSM) regulates the tumor microenvironment (TME) and orchestrates the crosstalk between cancer and stromal cells. This project aims at elucidating the involvement of this factor and its receptor in iCCA progression, as well as in tumor-stroma interaction.
Method: Expression of OSM and its receptor was analysed in patients with iCCA by immunohistochemistry or RT-PCR. Two human iCCA cell lines (HuCCT-1 and CCLP-1) and two type of cultured stromal cells have been used in this study. Cell migration and invasiveness of iCCA cells has been evaluated by performing chemotaxis and invasion assays. Knockdown of OSMR and gp130 was carried out with specific siRNA in iCCA cells.
Results: iCCA cells expressed both OSM receptors and OSM at protein levels. In human CCA specimens, OSM was expressed at higher levels in cancer cells and in the tumor microenvironment with respect to peritumoral tissue. In addition, OSMR mRNA levels were higher in CCA. Exposure of iCCA to OSM induced a dose-dependent increase in cell migration and invasion. These effects were mediated by cytoskeletal rearrangement (increased expression of p-FAK, p-paxillin and p-MLC2), and inducing EMT. OSM also upregulated cancer-associated pathways including c-Myc, G6PD, p-Rb, and p-Akt The ability of OSM to induce iCCA cell migration and invasion was reduced after knockdown of the OSMR or of gp130, or treatment with ruxolitinib. Incubation of primary hepatic stellate cells, HSCs or cancer-associated fibroblasts, CAFs with conditioned medium collected from iCCA cells treated with OSM resulted in increased cell migration, suggesting a role in the formation of a dense fibrotic tumor microenvironment.
Conclusions: This study identifies the OSM/OSMR axis as a novel system potentially implicated in cholangiocarcinogenesis with modulation of the tumor microenvironment.

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OC-31

Investigating Notch3 expression in hepatocellular carcinoma and its interplay with KDM2A

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Introduction: Notch3 receptor is involved in different aspects of hepatocellular carcinoma (HCC). Nevertheless, to unlock Notch3 therapeutic/diagnostic/prognostic potential a deeper understanding of its role in HCC onset/progression is needed. KDM2A demethylase epigenetically regulates gene expression. Its levels increase with HCC grading.
Aim: To investigate the involvement of KDM2A in controlling Notch3 expression in HCC.
Material and Methods: An expression analysis of Notch3 and KDM2A was conducted by Real-Time PCR on mRNA from formalin-fixed paraffin-embedded (FFPE) HCCs and peritumoral tissue (PT). Huh7 cells were transiently silenced for KDM2A using siRNAs for a first evaluation of Notch3/KDM2A association. KDM2A and Notch3 levels after silencing were assessed by Real-Time PCR and Western-Blotting (WB). The stem-cell marker CD133, associated with Epithelial Mesenchymal Transition, was evaluated in Notch3-silenced cells. Immunohistochemistry (IHC) was conducted using anti-Notch3 and anti-KDM2A antibodies.
Results: Notch3 and KDM2A in FFPE samples were higher in HCCs compared to PT ($p<0.001$ and $p<0.01$, respectively) and increased from G1 to G3 HCC. In well differentiated HCC the staining was mainly localized in the vascular endothelium while in G3 HCC it involved clusters of tumoral hepatocytes, sometimes invading portal areas. CD34 staining showed that the Notch3 positive blood vessels were consequences of neo-angiogenesis. The transient KDM2A silencing resulted in Notch3 transcript downregulation ($p\leq0.001$), confirmed by WB ($p\leq0.01$). CD133 was downregulated in Notch3-silenced Huh7 ($p\leq0.0001$).
Conclusions: An increasing Notch3 expression was observed during HCC progression. IHC revealed the involvement of Notch3 in neo-angiogenesis in early HCC and a role in invasiveness of stromal portal areas in G3 tumors. This latter, together with Notch3/CD133 association, suggests an involvement of Notch3 in local invasiveness. Furthermore, we found an association between Notch3 and KDM2A suggesting a possible mechanism of epigenetic regulation that could be responsible for the higher Notch3 expression in poorly differentiated HCC with high KDM2A levels.

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OC-32

Characterization of the intrahepatic immune microenvironment in a large cohort of patients with untreated hepatitis B virus infection

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Introduction: Chronic hepatitis B virus (HBV) infection progresses through distinct clinical phases, with some patients falling into a "gray zone" (GZ), the management of which remains poorly understood.
Aims: To characterize the intrahepatic immune microenvironment and gene expression profiles across different clinical phases in a large cohort of untreated HBV patients.
Materials and Methods: Three hundred forty-nine HBV patients who underwent liver biopsy between 2005 and 2020 at Henri-Mondor University Hospital (Créteil, France) were evaluated and classified according to the EASL criteria into four phases [chronic infection (CI)/chronic hepatitis B (CHB), HBeAg±]. Those not fitting into these phases were categorized as GZ-1 (HBeAg+) and GZ-2 (HBeAg-). RNA sequencing was performed to assess gene expression profiles, and supervised clustering was applied. Immune infiltrations were estimated by the MCP counter. Statistical analyses were performed with R4.2.0.
Results: One-hundred twenty-four HBV patients [93 males, median age 39 years (32-50)] were included in the analysis: 28 HBeAg+ (4 CI, 11 CHB, 13 GZ-1), 96 HBeAg- (15 CI, 53 CHB, 28 GZ-2). In HBeAg+ phases, gene-expression analysis revealed 276 differently expressed genes (DEGs) in CI*vs*.GZ-1, 91 in CHB*vs*.GZ-1, and 301 *vs*.CI. At enrichment analysis, GZ-1*vs*.CI showed *over*-expression of adaptive immune-activation gene-set pathways, CHB*vs*.GZ-1 *under*-expression of immune response, metabolism/oxidative stress involved-genes sets, but CHB*vs*.CI *over*-expressed immune activation/cytokine-signaling pathways. GZ-1 microenvironment (*vs*.CI) was richer in cytotoxic lymphocytes (p=0.003) and B/T-cells (p=0.01; p=0.045); no significant differences were observed in GZ-1*vs*.CHB. In HBeAg- phases, 74 DEGs were found in GZ-2*vs*.CI, 231 in CHB*vs*.CI. GZ-2*vs*.CI showed *over*-expressed immune response related-gene pathways, CHB*vs*.GZ-2 *down*-regulated metabolism/hepatocyte processes gene pathways, and *vs*.CI *up*-regulated immune response/liver tissue regeneration pathways. CHB liver microenvironment (*vs*.GZ-2) had more B-cells (p=0.034) and fibroblasts (p=0.0078) than CI and fibroblasts (p=0.029). No differences were observed in GZ-2*vs*.CHB liver tissues.
Conclusion: GZ profiles, like CHB, showed significant immune activation, warranting closer monitoring and potentially early antiviral therapy.

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OC-33

Fibrates in Primary Sclerosing Cholangitis: a multicenter retrospective observational study

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Introduction: Primary Sclerosing Cholangitis(PSC) is a chronic cholestatic liver disease with no medical treatment options registered. Bezafibrate is recommended as first-line treatment for pruritus. Small series showed promising data on fibrates' efficacy on disease progression and a randomized clinical trial is ongoing in France to confirm these findings. Data on safety in PSC are limited.
Aim: To assess safety and efficacy of fibrates in a multicenter series of PSC patients across Europe and United States.
Materials and Methods: Patients with a diagnosis with classic PSC treated with both bezafibrates and fenofibrates, at University Hospitals of Monza, Milan, Yale, Hamburg and Oxford, with at least six months of follow-up, were retrospectively included in this study. Liver biochemistry and liver stiffness measurement(LSM) were assessed at baseline and over follow-up. Safety was evalu-

ated through discontinuation rates and clinical outcomes. A mixed linear model was used to assess temporal trends.

Results: Seventy-two PSC patients were included: 40(55.6%) received bezafibrate, 32(44.4%) fenofibrate. Median age at diagnosis was 30.5years (IQR 23.8–45.3); 48(66.7%) were male. Fifty-two (72.2%) had IBD (56.9% ulcerative colitis), and 14(9.4%) had overlap with autoimmune hepatitis. Indication for therapy was: cholestasis (58.3%), pruritus (31.9%), and both (9.7%). Median follow-up was 24 months. Over time, ALP levels significantly decreased ($p=0.0053$) with no differences between bezafibrate and fenofibrate($p=0.6262$). 18(23.6%) patients achieved normalization after 6 months of treatment with stable trend over follow-up(Fig.1). LSM remained stable after 12 months of therapy($p>0.05$). Twenty patients(27.8%) discontinued treatment: 7(35%) due to inefficacy, 5(25%) due to adverse events, 5(25%) due to clinical outcomes, and 3(15%) by personal choice.

Conclusions: In PSC patients, fibrates demonstrated significant ALP reduction, with 23.6% achieving normalization in 6 months. LSM remained stable at 12months. Safety was acceptable, with discontinuation driven mainly by inefficacy. Fibrates may be valuable for managing cholestasis in PSC, warranting further prospective studies.

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P-01

When glecaprevir/pibrentasvir ultra-short therapy is enough to eradicate HCV infection

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Introduction: There is general agreement about the fact that at least 8 weeks of therapy with direct-acting anti-viral agents (DAA) are necessary to achieve definitive hepatitis C virus (HCV) eradication but, probably, the real impact of DAA in HCV replication is not yet completely known.
Aim: To retrospectively evaluate if and when shorter DAA therapy may be enough to eradicate HCV chronic infection
Methods and Results: From January 2018 to December 2023, 302 HCV-RNA+ve patients completed 8-12 weeks of glecaprevir/ pibrentasvir (G/P) antiviral treatment and 12 weeks post treatment follow up. Sustained virological response (SVR) was globally obtained in 297 patients (98.3%). Ten patients prematurely suspended treatment (median duration of treatment 7 days, range 4-28 days), mainly for slight side effects (itching, headache weakness). The main characteristics of these 10 patients are reported in the table.

Nine of them (90%) were HCV RNA negative at the end of treatment and six of them (60%) resulted SVR; three (30%) relapsed 12 weeks post the end of treatment and only one (10%) resulted non responder.

SVR patients showed pre-treatment ALT level lower than non SVR patients (IU median values: 39 vs 131, p=0.017).

Age, gender, liver fibrosis score, genotype, pre-treatment HCV RNA and duration of therapy where not significantly different in the two groups.
Conclusion: In this tiny series of patients, HCV eradication was obtained in 60% of cases with (even extremely) reduced duration of treatment with G/P. Apparently SVR resulted more probable when pre-treatment degree of HCV related hepatic cyto-necrosis was low.

More studies about this topic would be important to eventually permit ultra-short scheduled of treatment to eradicate HCV infection. This should strengthen the case for offering treatment with DAAs to all HCV+ve people, even to subjects with presumed reduced compliance with therapy (prisoners, drug addicts, etc) in accordance with the World Health Organisation (WHO) program to eliminate HCV infection within 2030.

Patient (Initials)	AL1	DB	LC	AG	DG	GF	AL2	FC	OG	AV
Age (years)	54	72	66	60	52	83	40	79	55	83
Gender (Male/Female)	M	F	M	M	M	F	M	F	M	M
Fibrosis (Metavir)	F2	F1	F3	F2	F1	F3	F1	F4	F4	F2
Genotype	1b	2	3	1a	4	1b	3	2	3	2
HCV RNA pre-treatment (log)	5	6	5	6	5	4	4	4	5	7
ALT pre-treatment (UI/ml)	89	248	38	6	34	23	138	58	73	49
Duration of treatment (days)	5	6	4	10	5	8	4	20	28	16
Side effects leading to premature withdrawal of treatment	confusion weakness	itching	itching	depression anxiety	pneumo-nia	itching	headache weakness	itching	none	none
Side effects related to DAA treatment?	probable	probable	probable	unlikely	unlikely	probable	probable	probable		
HCV RNA at the end of treatment (log)	negative	negative	not done	not done	negative	negative	5	negative	negative	negative
HCV RNA 12 weeks post treatment (log)	5	7	negative	negative	negative	negative	4	negative	negative	6

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P-02

Early hepatic decompensation is the main driver of mortality in patients with hepatocellular carcinoma treated with Atezolizumab plus Bevacizumab or Sorafenib

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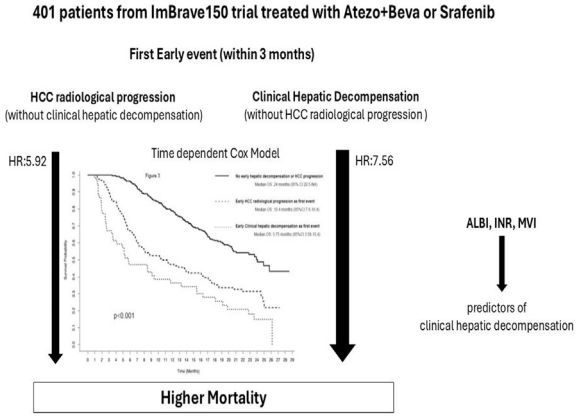
Introduction: The prognosis of patients with unresectable hepatocellular carcinoma (uHCC) and compensated cirrhosis is influenced by cancer progression. Data on the incidence and the prognostic role of clinical hepatic decompensation following immune checkpoint inhibitor therapy are lacking.
Aim: We aimed to assess whether early clinical hepatic decompensation (CHD) within 3 months from commencement of systemic therapy affects overall survival (OS) of patients treated with Atezolizumab plus Bevacizumab or Sorafenib
Materials and Methods: Individual patient data from IMbrave150 trial were analyzed through Vivli platform. Cumulative incidence of CHD was assessed by competing risks analysis against HCC radiological progression. Early CHD and HCC radiological progression were assessed as predictors of OS by time-dependent Cox model.
Results: The 3- and 12-month rates of CHD were 7% and 12%, respectively, while the 3- and 12-month rates of HCC radiological progression were 23% and 52%. Albumin-bilirubin(ALBI)grade 2 (Sub-distribution hazard ratio[sHR] 1.79, 95%CI 1.01-3.19, p=0.049), INR(sHR 1.97, 95%CI 1.64-2.37, p<0.001) and presence of neoplastic macrovascular invasion (sHR 2.01, 95%CI 1.14-3.54, p=0.020) were independently associated with higher risk of CHD. Early CHD(HR 7.56, 95%CI 4.47-12.8) and early HCC radiological progression(HR 5.92, 95%CI 4.03-8.69), as first events, were independently associated with higher mortality.
Conclusions: This study provides robust evidence that early CHD is associated with the highest risk of death in patients with uHCC undergoing systemic treatment. Within well-compensated participants, ALBI, INR and macrovascular invasion identify a population at higher risk of decompensation. Inclusion of clinical decompensation events in future prospective clinical trials may improve characterization of OS from systemic therapy of HCC.



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P-03

The spleen area affects the performance of the platelet count-based non-invasive tools in predicting hepatic decompensation in MASLD-related advanced chronic liver disease

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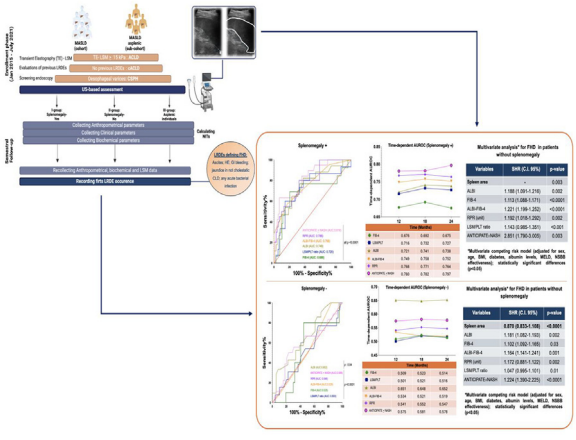
Introduction: Most of the currently available non-invasive tools (NITs) predicting hepatic decompensation (HD) in advanced chronic liver disease (ACLD) include the platelet (PLT) count. However, a non-negligible proportion of Metabolic dysfunction-associated Steatotic Liver Disease (MASLD)-related compensated ACLD patients with clinically significant portal hypertension (CSPH) do not show splenomegaly and hypersplenism-related thrombocytopenia.
Aim: The present research explored the performance of NITs in predicting a 3-year first HD according to spleen size.
Materials and Methods: 148 splenic and 27 asplenic (ASP: 25-splenectomized; 2-agenesis) MASLD-cACLD patients receiving an endoscopy evidencing CSPH were enrolled. Ultrasound artificial intelligence (AI)-based tools distinguished splenomegaly-affected (SAP: 91) and normal spleen patients (NSP: 57). Albumin-bilirubin (ALBI) score and PLT count-based NITs (PLNs) [Fibrosis-4 (FIB-4), ALBI-FIB-4 score, red-cell-distribution-width/PLT-ratio (RPR), Liver Stiffness Measurement (LSM)/PLT-ratio (LSM/PLTr), and ANTICIPATE+NASH] were determined. During a 3-year semiannual follow-up, NITs and spleen size were reassessed, as well as the HD occurrence was recorded.
Results: Limitedly to SAP, Spleen Area inversely correlated with PLT count (R: -0.981; p<0.0001), confirming the predominant role of splenomegaly-related hypersplenism in conditioning thrombocytopenia. HD occurred similarly in SAP (20.48%), NSP (21.15%), and ASP (25%) (chi-square, p:0.198). In NSP, PLNs showed a reduced influence on HD [FIB-4 (p: 0.03), ALBI-FIB-4 (p:0.001), RPR (p:0.002), LSM/PLT ratio (p:0.01), and ANTICIPATE ± NASH (p:0.001)] compared to SAP. In NSP, the Spleen Area was inversely associated (aSHR: 0.870) and more significantly (p<0.0001) impacted HD. Consistently, unlike SAP, in NSP and ASP, PLNs showed poor performance, and exclusively ALBI maintained a good accuracy (NSP: AUC 0.651, p:0.04; ASP: AUC:0.625, p:0.03) in predicting 3-year HD.
Conclusions: Spleen size dramatically affects the predictive performance of the PLNs in CSPH-affected MASLD-cACLD patients.



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P-04

The prognostic impact of comorbidities in patients with hepatocellular carcinoma: a multicenter observational study

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Introduction: Charlson Comorbidity Index (CCI) could be used to assess the burden of comorbidities in different clinical settings, but few data are available in patients with hepatocellular carcinoma (HCC).
Aim: We aimed to evaluate the CCI as a prognostic predictor in HCC patients, as well as to derive a modified CCI specifically developed in this patient population.
Method: From the ITA.LI.CA database, data of 8945 patients were retrieved. In order to recalibrate the CCI in the HCC population, the independent effect on survival of each comorbidity included in the original CCI was assessed with a multivariate Cox regression analysis. The CCI-HCC score was then calculated adding the points for each independent comorbidity (equal to the hazard ratio rounded to the nearest integer) to the points derived from age (as in the original CCI).
Results: The median CCI in the entire cohort was 7 (IQR, 6 – 9). Higher CCI values were independently associated with a worse survival (HR 1.05, 95% CI 1.03 – 1.07). Among individual components of CCI, myocardial infarction (HR 1.15, 95% CI 1.06 – 1.25), chronic kidney disease (HR 1.17, 95% CI 1.04 – 1.32) and chronic obstructive pulmonary disease (HR 1.18, 95% CI 1.08 – 1.28) emerged as independent predictors of survival, and were included in the CCI-HCC score. The median overall survival was 56.0 months (95% CI 48.6 – 63.4), 46.0 months (95% CI 43.9 – 48.1) and 31.5 months (95% CI 29.2 – 33.9) in patients with CCI-HCC score of 0 – 1, 2 – 3 and $\geq$ 4, respectively ($p<0.001$). Moreover, the CCI-HCC score maintained an independent association with prognosis (HR 1.03, 95% CI 1.01 – 1.06).
Conclusion: In patients with HCC, CCI is associated with survival. However, a modified simple comorbidity index (CCI-HCC) specifically derived in this population may be useful to assess prognosis.

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P-05

Workforce reintegration for liver transplant recipients: interdisciplinary assessment of unemployment risk factors

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Background: Return to work is crucial for liver transplant (LT) recipients, yet there are no specific recommendations for this process. The BRIC-2022-ID25 project evaluates how liver disease and transplantation impact work ability by analyzing correlations between clinical, social, and employment status before and after LT, aiming to improve professional outcomes.
Methods: In collaboration with the occupational medicine department, we enrolled patients who underwent LT at our center from 2018 to 2023, aged 18 to 68 years, who were not retired before LT. Participants completed the WHODAS 2.0 (World Health Organization Disability Assessment Schedule) and Work Ability Index (WAI) questionnaires, supplemented with clinical and occupational data. Interim analyses were conducted on patients interviewed from January to June 2024.
Results: A total of 140 recipients were included; 76% had liver cirrhosis (49% with hepatocellular carcinoma - HCC), and 19% had hepatic/hepato-renal polycystosis. The mean age was 55 years (24-69), 64% of the respondents were males, with an average of 42 months between LT and interview. FIfty percent of participants had a middle-school education. After LT, 49% were unemployed, and 62% reported that health issues affected their job search. Significant correlations were found between unemployment and factors such as pre-LT alcohol abuse (p=0.005), age over 60 at LT (p=0.02), caregiver outside household (p=0.004) and a higher number of post-LT hospitalizations (p=0.05). Low self-perception of work capacity (WAS) was linked to age over 50 (p=0.02), low education (p=0.04), pre-OLT HCC (p=0.02), and MELD<14 at LT (p=0.04). Worse disability scores (WHODAS) correlated with female sex (p=0.02), caregiver outside family (p=0.04) and non-Italian nationality (p=0.002).
Conclusions: Interim analyses show a 49% unemployment rate post-LT. Factors such as caregiver, education, nationality, and gender, along with age, pre-LT HCC and pre-LT complications, significantly influence work ability. More efforts are needed to ensure equal work access for transplant recipients.

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P-06

Hepatitis delta virus (hdv) replication through hbv integrants in hcc recurrence after liver transplantation

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A PWID man, HCV/HBV-HDV/HIV-infected, underwent liver transplantation (LT) for HCC in 2012 at the age of 52 years. HCC tissue showed high HDV-RNA (88,400 copies/cell), low total HBV-DNA (0.00001 c/c), and HBVcccDNA0.00008 c/c), without detectable HBV-RNA. High-throughput HBV integration sequencing (HBIS) identified 657 HBV integration sites.HBV integrants were predominantly represented by HBx gene sequences. After LT, Tacrolimus, Bictegravir/Emtricitabine/TAF, and anti-HBs immunoglobulin were administered, yielding HBsAg, HDV-RNA, and HCV-RNA negativity.

In 2018, HBsAg reversion was observed with undetectable HBV-DNA and HDV-RNA >19,000 c/ml.

In 2019, HDV-related hepatitis occurred. Intrahepatic HBcAg, HBsAgHBV DNA, HBVcccDNA, and HBV-RNA were undetectable. HDV RNA concentrations were very high in the liver (3,920,000 c/c) but low in the serum (214 IU/mL). CT scan (CTs) suspected an isolated HCC recurrence in the left adrenal gland, confirmed by adrenalectomy. Real-time PCR in the tumor from the adrenal gland revealed high levels of HDV RNA (5.5 c/c) but low levels of HBV DNA (0.00009 c/c) and HBVcccDNA (0.00001 c/c). HBV RNA was undetectable. HBIS identified 3497 HBV integrations, most of which included HBs gene sequences. After adrenalectomy, HBsAg and HDV-RNA became undetectable. Anti-HBs immunoglobulin was continued with Everolimus.

In 2021, CTs showed two HCC nodules in the liver and one in the right adrenal gland. TACE was performed, and TKI therapy was started.

In 2023, new HDV hepatitis occurred, with HDV-RNA>3,631,360 UI/ml and HBV-DNA <10UI/ml. For the progression of HCC, RFA on the right adrenal gland was performed, and Bulevirtide was started. After 3 months, HDV-RNA was 48,638 c/ml, and transaminases were normal.

This case demonstrates HDV replication in extrahepatic HCC recurrence, despite low levels of HBVcccDNA. The decreased HDV RNA levels after RFA and BLV therapy suggest that HCC metastases may serve as HBsAg production sites following HBV integration.

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P-07

Outcomes and safety of DAA treatment in HCV cirrhotic patients treated with Atezolizumab- Bevacizumab for hepatocellular carcinoma

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Background and Aims: Hepatitis C virus (HCV) infection is a critical driver of hepatocellular carcinoma (HCC) development and progression. Concurrent HCV treatment during systemic HCC therapy has not shown consistent benefits on survival and disease progression. This study aimed to evaluate safety and efficacy of Direct-Acting Antiviral (DAA) therapy in HCV-related HCC patients undergoing Atezolizumab-Bevacizumab (A/B), analysing its effects on overall survival (OS), time to progression (TTP), progression-free survival (PFS), liver decompensation rates.
Method: A total of 135 patients with HCV-related cirrhosis undergoing A/B treatment for HCC were enrolled from 2021 to 2024 and divided into groups based on HCV treatment status: an "active eradication" group (18 patients) who achieved sustained virological response (SVR) after DAA therapy concurrent with A/B treatment, a "prior eradication" group (95 patients) that reached SVR with DAAs or IFN-based regimens at least six months before starting A/B, and a "no eradication" group (22 patients) who did not obtain SVR at all.
Results: 19 patients received SOF/VEL for 12 weeks achieving a 94.7% SVR rate, mostly due to elevated ALT and AST levels (94.4%). No adverse events (AEs) related to DAA therapy occurred during the treatment course.

The active eradication group demonstrated a significantly improved median OS that was not reached compared to the no eradication group (NA, 95% CI: 22.8–NA vs 20.0 months, 95% CI: 15.5–NA; $p = 0.026$). Regarding TTP, the active eradication group showed a median of 41.20 months (95% CI: 18.6– NA) compared to 21.3 months (95% CI: 5.13–NA) in no eradication group ($p = 0.008$). PFS results further supported the benefits of active eradication, with a median PFS of 41.17 months (95% CI: 22.80–NA) compared to 7.76 months (95% CI: 4.53–NA) in the no eradication group ($p = 0.012$). In contrast, the prior eradication group did not show significant survival benefits compared to the no eradication group for all outcomes. Liver decompensation rates did not differ significantly among groups ($p > 0.05$).
Conclusion: DAA therapy was safe and effective in patients with unresectable HCC receiving A/B treatment. DAA therapy during A/B significantly improved OS, TTP, and PFS in patients with HCV-related HCC, likely enhancing the A/B treatment effect through immunomodulatory mechanisms. This is particularly relevant in settings where maximizing disease control is critical, such as down-staging in patients undergoing liver transplantation.

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P-08

AI-Driven Diagnosis: Enhancing HCV-Related Cirrhosis Detection with Multilayer Perceptron Networks

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Introduction: Liver cirrhosis, particularly due to chronic HCV infection, is a leading cause of liver-related complications and mortality worldwide. Traditional diagnostic methods include clinical assessments, imaging, and invasive procedures, such as liver biopsy, which, despite their accuracy, carry limitations related to invasiveness and cost. Advances in artificial intelligence (AI), especially machine learning (ML), provide promising tools for more efficient, non-invasive diagnostic solutions. This study explores the utility of a multilayer perceptron (MLP) neural network to differentiate chronic hepatitis from cirrhosis in patients with HCV, aiming to improve diagnostic precision and reduce invasive testing.
Aim: The study's main objective was to assess the accuracy of an MLP neural network model trained on clinical and laboratory data to diagnose HCV-related cirrhosis. The model's performance was compared with established non-invasive tests (APRI, FIB-4, and VCTE) commonly used in clinical practice.
Materials and Methods Results: The MLP model demonstrated robust performance in diagnosing HCV-related cirrhosis, achieving an accuracy of 87.74%. It correctly classified 346 cases of chronic hepatitis and 284 cases of cirrhosis. The AUROC values were 0.927 for chronic hepatitis and 0.934 for cirrhosis, indicating excellent discriminative capability. Sensitivity and specificity of the MLP model were superior to those of conventional non-invasive
Methods: APRI (AUROC 0.834) and FIB-4 (AUROC 0.868). For chronic hepatitis, the model achieved a precision of 87.8% and a recall of 89.6%, while for cirrhosis, it demonstrated a precision of 87.7% and a recall of 85.5%. The F1 scores for chronic hepatitis and cirrhosis were 0.887 and 0.866, respectively, highlighting a balanced performance in identifying true positives and minimizing false positives and negatives. The mean absolute error (MAE) of 0.146 and root mean square error (RMSE) of 0.3111 indicated that the predictions were closely aligned with actual classifications, with minimal significant errors. Key attributes influencing the model's predictions included liver stiffness (FibroScan), INR, platelet count, and diabetes, emphasizing their relevance in distinguishing between chronic hepatitis and cirrhosis.

Conclusions: The study highlights the potential of AI, specifically MLP neural networks, as a non-invasive diagnostic tool for HCV-related cirrhosis. The MLP model's superior performance compared to standard methods supports its potential use in clinical practice, where it could reduce the need for invasive procedures like liver biopsy and provide personalized risk assessment for patients. Future research should focus on validating this model across diverse patient populations and exploring other ML algorithms to enhance diagnostic accuracy.

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P-09

Evidence of durable response to bepirovirsen in B-Clear On-NA responders: B-Sure second report ☆

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Introduction: Bepirovirsen (BPV) is an unconjugated antisense oligonucleotide, for the treatment of chronic hepatitis B (HBV) infection. Data from a Phase 2b study (B-Clear) indicated that a subset of participants (pts) achieved a response at the end of treatment, sustained for 24 weeks. This occurred in pts on and not on nucleos(t)ide analog (NA) therapy. Pts who had a complete (CR) or partial (PR) response at the end of B-Clear were eligible for this long-term durability study (B-Sure).
Aim: Here, we present data on the durability of response for B-Clear On-NA CRs and PRs who entered B-Sure.
Methods: CR defined as hepatitis B surface antigen (HBsAg) <0.05 IU/mL and HBV DNA <lower limit of quantification (LLOQ), and PR as HBsAg <100 IU/mL and HBV DNA <LLOQ. If eligible, pts discontinued NA treatment 3 months into B-Sure and were followed to determine the durability of response off all HBV therapy. Adverse events were recorded.
Results: 11 CRs and 29 PRs entered B-Sure (Figure). In B-Clear, 77% of pts were HBeAg negative, 19/44 (43%, and 32/44 (73%) had HBsAg ≤1000 IU/mL. For CR pts, 9/11 (82%) discontinued NAs 3 months after rollover into B-Sure; 7/9 (78%) maintained a CR to 6 months post NA cessation, thus achieving functional cure (FC). For PR pts, 23 pts discontinued NAs 3 months after rollover into B-Sure. 8/23 of PR pts either maintained PR status (5/23) or had achieved and maintained a CR (3/23) 6 months post NA cessation (i.e. FC). None of the 9 CRs who discontinued NAs had restarted NA therapy by 9 months post NA cessation. Of the PRs who discontinued NAs, 8 had restarted NAs within 6 months post NA cessation due to virological breakthrough.
Conclusions: These data provide evidence of the durability of FC, particularly in CRs.

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P-10

Analysis of HBV genotype association to bepirovirsen treatment response in patients with chronic HBV infection (Phase 2b B-Clear study) ☆

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☆ JB, RE, PY, SY, ASY, AN, JC, GQ, FC, MP and DT are/were GSK employees and hold stock/shares in GSK

Introduction: B-Clear is a phase-2b trial testing Bepirovirsen (BPV) 12 or 24weeks (wks) treatment in patients (pts) with chronic hepatitis B (CHB) where hepatitis B surface antigen (HBsAg) reductions and seroclearance have been observed.

Aim: Here we present the HBsAg response for pts by viral genotype.
Methods: Pts from 22 countries received either nucleos(t)ide analogue therapy (on-NA) or not NA (not-on-NA) and randomised to receive BPV 300mg weekly either for 24wks (Arm 1); 12wks then 150mg for 12wks (Arm 2); 12wks then placebo (PBO) for 12wks (Arm 3); or PBO for 12wks then BPV 300mg for 12wks (Arm 4). A loading dose of BPV (Arms 1-3) or PBO (Arm 4) was given on days 4 and 11. Pts were followed for 24 wks after end of treatment (EOT).
Results: Genotypes observed: A, B, C, D, E, F and H; in majority B and C in Asia, A and D in Europe, A, B, C and D in the Americas. **Not-on-NA,** (GT) C (31%, 70/229 pts), GT-B (21%), GT-D (20%), GT-A (18%), other (6%) and undetermined (4%). Pts with GT-B had the lowest mean HBsAg level at baseline (3.155 log IU/mL) and GT-A the highest (3.982 log IU/mL). **On-NA,** GT-C (31%, 70/226 pts), GT-B (9%), GT-D, GT-A (8% each), others (3%). On-NA pts had low/undetectable RNA/DNA resulting in a high proportion of undetermined genotypes (41%). GT-B pts had the lowest mean HBsAg level at baseline (3.090 log IU/mL) and GT-A the highest (3.724 log IU/mL). Table 1 shows treatment response by genotype.
Conclusion: In both not-on-NA and NA cohorts, GT-B had the lowest baseline HBsAg and demonstrated the greatest log reduction in HBsAg, consistent with lower baseline HBsAg predicting the ability to achieve HBsAg seroclearance. Seroclearance 24wks off-BPV treatment was achieved in HBV genotypes A, B, C and D.

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P-11

Bepirovirsen immune mechanism of action may potentiate infected hepatocyte killing: Indirect evidence from B-together peripheral longitudinal biomarker analysis ☆

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☆ SJ, JF, JMS, LF, SD, MP, DT and JW are GSK employees and hold stock/shares in GSK. SJ holds an international patent: WO 2020/239478 A1. JS holds two US patents: #11,021,502 and #11,873,312. LF, SD and DT hold provisional US patents.

Introduction: B-Together tested sequential bepirovirsen (BPV) followed by pegylated interferon (PegIFN) in participants (pts) with chronic hepatitis B virus (HBV) infection. Previously, we demonstrated that pts treated with BPV may experience transient alanine transaminase (ALT) increases. We investigated BPV's immune mechanism of action with respect to virological response (VR) and surrogate markers associated with hepatocyte cell death.
Method: Pts were randomised to receive BPV for 12 or 24 weeks followed by up to 24 weeks of PegIFN. Primary endpoint: proportion of pts with hepatitis B surface antigen and HBV DNA below the limit of detection for 24 weeks after end of treatment (tx). Peripheral blood mononuclear cells, blood, and serum samples were subjected to flow cytometry, whole blood transcriptomics (WBT) and proteomics analyses.
Results: By Week 3, BPV led to a significant increase from BL in mean expression of serum proteins, independent of arms or VR subgroups, showing enrichment in immune effector response and apoptotic pathways. After 4wks, upward trends in proliferating activated CD8+ T-cells and B-cells were observed with a significant increase in mean expression of some genes associated with proliferation in WBT independent of arms or response subgroups. After 7wks of BPV tx, liver and apoptosis-specific proteins showed increased abundance in serum, (more pronounced in BPV-responders). Abundance of these proteins was highly correlated with ALT levels, which was sometimes associated with transient low level HBV DNA elevations in serum; indirectly linking the observation to infected hepatocyte death.
Conclusion: Three observations provide indirect evidence of a role for BPV in infected hepatocyte death: 1) presence of proliferating, activated adaptive immune cells in all subgroups before rise in ALT; 2) increases in liver and apoptosis-specific proteins in the serum concomitant with ALT elevations; 3) intermittent increase in HBV DNA during ALT elevations occurring more frequently in BPV responders.

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P-12

Investigation of linerixibat 40 mg BID for cholestatic pruritus of primary biliary cholangitis (PBC); further data from the Phase 2b GLIMMER study to support the Phase 3 GLISTEN study ☆

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Introduction: GLIMMER was a Phase-2b randomized, double-blind, placebo-controlled, dose response study of linerixibat, an ileal BA transporter inhibitor, in PBC patients with moderate-severe pruritus. Data were reanalyzed to assess itch responder definitions in the linerixibat 40mg BID group.
Methods: Patients (N=147) assessed itch daily. Proportion of responders was assessed using reductions in monthly itch score (MIS) at week 16 compared to baseline (BL). An empirical cumulative distribution function (eCDF) graph was generated for the percentage of patients with change from BL in MIS for the linerixibat 40mg BID (N=23) and placebo (N=36) groups. BA samples were reanalyzed using an enzymatic assay. TSBA changes from BL were analyzed using a mixed model repeated measures (MMRM) analysis.
Results: The eCDF curves showed separation of linerixibat 40 mg BID and placebo groups. The percentages of patients with a MIS improvement from BL at week 16 were greater in the linerixibat

group for a wide range of responder thresholds. The largest differences were observed between thresholds of -3 to -2, where the cumulative percentages were >20% greater in the linerixibat group. Linerixibat 40mg BID (n=22) reduced mean TSBA from a BL of 18.6 µM (21.8) by -6.94 µM (17.5) after 12-weeks' treatment. A MMRM analysis showed a significant 39% decrease (p=0.0001) from BL and 37% (p=0.0030) from placebo (n=36) over the 12-week double-blind treatment period.

Discussion: 40mg BID linerixibat resulted in significant TSBA reductions. The proportion of patients with MIS change from BL at week 16 was greater in the linerixibat 40mg BID group over a range of responder threshold values. Linerixibat 40mg BID is being studied in the ongoing phase-3 GLISTEN study. Responder thresholds of 2-, 3- and 4-point MIS improvements compared to BL are key secondary endpoints.

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P-13

Mri-based clinical-radiomics analyses of colorectal liver metastases to predict tumor growth patterns by machine learning approach

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Introduction: Tumor growth patterns in colorectal liver metastases (CRLM) were associated with different recurrence risk after liver resection, but this information is not available before therapy decision. This study explores a combined clinical-radiomic approach to perform MRI analysis of hepatic metastases with the aim to predict tumor growth patterns by different machine learning algorithms, specifically distinguishing between replacement and desmoplastic/pushing types.

Methods: 3-phases MRI scans were retrospectively collected among 2 Italian centers. DICOM files were manually segmented to detect the tumor (core) and the peritumoral area (ring). Clinical variables association with the outcome (replacement vs. desmoplastic/pushing pattern) was assessed via statistical analysis. Radiomics features were extracted in the hepatobiliary phase using Pyradiomics and ComBat harmonization was applied to features to reduce inter-centers variability effects. Features selection was performed via minimum redundancy maximum relevance (MRMR) approach. Models of different complexity, including logistic regression, Random Forest, XGBoost and SVM were evaluated. The area under the curve (AUC) of the receiver operating characteristics (ROC), together with sensitivity and specificity were computed to assess model performance.

Results: Two hundred-twelve patients were enrolled, dividing them into training (148 patients, 70%) and test (64 patients, 30%) cohorts. Harmonization via ComBat reduced feature instability related to imaging protocol variances, enhancing the overall reliability of the feature set. Feature selection on the training set yielded 1 clinical variable (tumor size) and 5 radiomics features. The Random Forest model showed the best performance with the combined clinical-radiomic approach, yielding an AUC of 0.91, sensitivity of 0.87, and specificity of 0.79 on the training set. On the test set, these metrics were lower (AUC 0.70, sensitivity 0.73, specificity 0.60, figure 1), demonstrating a good calibration.

Conclusions: The clinical-radiomic modeling approach shows promising potential for accurately predicting growth patterns of hepatic metastases in MRI.

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P-14

Efficacy and safety of atezolizumab/bevacizumab for hepatocellular carcinoma in a real-life prospective cohort: A 2024 update

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Introduction: Atezolizumab/bevacizumab (atezo/bev) is a standard-of-care for patients with unresectable hepatocellular carcinoma (HCC). Most efficacy and safety data, however, stem from clinical trials, with relatively limited evidence from real-world practice.
Aim: To provide real-life clinical data of HCC patients treated with atezo/bev.
Methods: We analyzed clinical data and outcomes for HCC patients enrolled in the ARTE database between March 2022 and November 2024. The ARTE study group prospectively collects data from patients who initiated atezo/bev outside of clinical trials.
Results: Data from 397 patients across 15 centers were included. The majority had advanced HCC (59.9%). Sixty patients (15.1%) presented with one or more conditions outside the IMbrave-150 enrollment criteria (thrombocytopenia <70,000/mmc [n=26], concurrent/recent malignancy [n=13], concurrent anticoagulation [n=9], arrhythmia [n=8], HIV infection [n=4], chronic heart failure [n=2]). Hepatitis C virus (HCV) was the most common risk factor (45.1%), followed by metabolic-associated steatotic liver disease (MASLD, 33.0%), alcohol-related liver disease (ALD, 27.7%), and hepatitis B virus (HBV, 15.9%). A total of 103 patients (25.9%) reported multiple risk factors. Performance status (ECOG-PS) >0, macrovascular invasion (MVI), extrahepatic spread, and alpha-fetoprotein (AFP) >400 ng/ml were observed in 31.5%, 32.7%, 39.0%, and 28.0% of patients, respectively. Fifty-three patients (13.4%) received non-systemic therapies after starting atezo/bev, including surgical (transplant n=8, resection n=4), percutaneous (n=9), and trans-arterial procedures (n=18), or non-liver-directed radiotherapy (n=20).

Median overall and progression-free survivals were 20.4 (95% CI 17.8-23.0) and 9.6 months (8.4-12.8), respectively. ECOG-PS>0, MVI, AFP>400 ng/ml, ALBI grade>1, and neutrophils-to-lymphocytes ratio>3 were independent negative prognostic factors. Progression due to new extrahepatic lesions/macrovascular invasion led to worse outcomes.

The most common treatment-related adverse events (AEs) included fatigue (45.1%), hypertension (24.7%), anorexia (17.1%), and diarrhoea (13.9%). Most common treatment-related Grade 3-4 AEs were: hypertension (5.3%), variceal bleeding (3.5%), increased aminotransferases (2.8%), and digestive non-variceal bleeding (2.5%).
Conclusions: real-life data confirm previous efficacy and safety information of atezo/bev. Multiple HCC risk factors, comorbidities, and combination with surgical/locoregional treatments are common in clinical practice and warrant dedicated studies.

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P-15

Management of ascites in elderly patients with cirrhosis: results of an Italian survey

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Introduction: The management of ascites in elderly cirrhotic patients is challenging, given comorbidities and frailty that limit therapies, interventions, and transplantation.
Aim: We assessed how physicians in Italy manage ascites decompensation in elderly patients (>70 years) with cirrhosis.
Materials and Methods: AISF members received a 49-question survey addressing care settings, centre expertise, radiology and transplant services, patient comorbidities, ascites therapies, and management challenges. Respondents also identified the main problem in managing these patients.
Results: Twenty-two centres (54.5% from university hospitals) responded. Half of the respondents were gastroenterologists. Day hospital services were available in 90.9% of centres, but only 45.5% performed TIPS directly. A total of 1,064 elderly patients with ascites were included. Alcohol was the main etiology. Two hundred and forty-two (22.7%) patients had refractory or intractable ascites, with kidney injury being the leading cause, followed by hepatic encephalopathy and electrolyte imbalance. Diuretics were the main therapy (63.2%), while 21.7% required periodic paracentesis; procedural complications occurred in 17% of patients. Spontaneous bacterial peritonitis (61 cases) and hepatorenal syndrome (42 cases) were common complications, but the majority of physicians (81%) avoided vasopressor therapy due to age and comorbidities. TIPS was evaluated in 50 patients, but were denied in 26 cases; nine patients underwent transplantation despite their age. Forty-six patients required long-term care, and 209 (19.6%) died, with infections and ACLF as leading causes. Over half were dependent on caregivers, and 566 (53.2%) were malnourished, though only 259 received nutritional support. Respondents highlighted insufficient community medical support and undervalued caregiver roles as key issues.
Conclusions: Elderly patients with ascites face limited therapeutic options. Comprehensive care strategies, enhanced community support, caregiver integration, and targeted nutritional programmes are crucial to improving outcomes in this vulnerable population.

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P-16

Prevalence of HBV and HCV infections among at-risk migrant and refugee populations in Italy: 2-year results of the VH-COMSAVAC European project

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Background and Aims: VH-COMSAVAC is a European project, co-funded by the European Commission and involving institutions in Greece, Italy and Spain, to offer community-based HBV and HCV testing, HBV vaccination, and linkage-to-care strategies to migrant and refugee populations from countries with high HBV and HCV prevalence. The project is based on simplified tools and person-centered referral processes, to ultimately reduce liver cancer-associated mortality.
Methods: Decentralized HBV and HCV testing was offered in community and faith-based organizations using HBV surface antigen (HBsAg) and anti-HCV rapid diagnostic tests (RDTs). Participants with a positive RDT were referred to our clinics to confirm an active infection and start appropriate anti-viral treatment.
Results: To date 423 individuals have been recruited and screened for HBV and/or HCV, 56% men, with a median age of 47 years (18-79). Overall HBsAg+ and anti-HCV+ prevalence was 1.7% and 2.1%,

respectively. Most participants were born in Latin America (40%) followed by North Africa (19%), Central Africa (12%), Asia (13%) and Eastern Europe (8%).

Of the 7 HBsAg+ individuals 2 originated from Bangladesh and the remaining from China, Dominican Republic, Ghana, Romania and Senegal. Among anti-HCV+ participants 5 were from Egypt and the remaining from Colombia, Pakistan, Russia and Ukraine. Among positive participants, three (23%) were linked to care, and 13 are in the process of being admitted to our clinics.

Conclusion: VH-COMSAVAC has been successful in screening at-risk migrant and refugee populations in Italy, supporting the HCV and HBV micro-elimination strategy based on fragile populations migrating from high prevalence countries.

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P-17

MPEP combines mGluR5 inhibition and AMPK activation to reduce hepatic steatosis

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Introduction and Aim: Recent studies highlight the role of metabotropic glutamate receptor type 5 (mGluR5) in hepatic steatosis, where its hyperactivation in hepatic stellate cells (HSCs) drives fat accumulation in hepatocytes (Choi et al., 2019). Previous research demonstrated that 2-methyl-6-(phenylethynyl)pyridine (MPEP), a negative allosteric modulator of mGluR5, reduces lipid deposition in HepG2 cells exposed to an oleate/palmitate-induced steatosis model (Ferrigno et al., 2020). This study aimed to evaluate mGluR5's role in lipid metabolism using negative allosteric modulators (MPEP, Fenobam), an orthosteric antagonist (carboxyphenylglycine, CPG), and an orthosteric agonist ((S)-3,5-dihydroxyphenylglycine, DHPG). Additionally, we explored whether MPEP's effects involve activation of AMP-activated protein kinase (AMPK), a critical regulator of lipid metabolism linked to ATP depletion (Ferrigno et al., 2018).

Materials and Methods: Lipid accumulation was induced in HepG2 cells using 2 mM oleate/palmitate (O/P) for 24 hours. Cells were treated with MPEP (0.3-3-30 μM), Fenobam (1-25-50 μM), and CPG (100-150-200 μM), alone or with the AMPK inhibitor (Compound C 0.1-1-10 μM). Non-steatotic cells received DHPG (100-200-300 μM) alone or with 30 μM MPEP. Lipid content was visualized with Nile Red dye and quantified via ImageJ; cell viability was assessed via MTT assay. ATP levels were measured using a luciferin-luciferase assay, and the p-AMPK/AMPK ratio was analyzed by Western blot.

Results: In steatotic HepG2 cells, MPEP, Fenobam, and CPG significantly reduced lipid accumulation dose-dependently. DHPG increased lipid content in non-steatotic cells, but co-treatment with MPEP reversed this effect. MPEP, uniquely among the compounds, depleted ATP levels and activated AMPK. Compound C abolished MPEP's lipid-lowering effects, confirming AMPK's role. Western blot showed increased p-AMPK/AMPK ratios in MPEP-treated steatotic cells.

Conclusion: mGluR5 inhibition reduces lipid accumulation in an in vitro steatosis model. MPEP engages an AMPK-mediated pathway, providing a dual mechanism against hepatic steatosis and highlighting its therapeutic potential.

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P-18

Enterobius vermicularis infection mimicking liver malignancy

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Background: *Enterobius vermicularis* is a common worm infestation of the bowel lumen; it has rarely been found outside the gastrointestinal tract. We review a case of hepatic enterobiasis mimicking haematologic disease.

Case description: In November 2021 and 2022 a 55 yo man developed two episodes of urticaria treated with steroids. During the first episode groin itching was also reported.

Blood tests showed eosinophilia (WBC 19030/mm3, Eos 67.1%), augmented total IgE (2108 IU/mL) and LFTs (liver function tests) (AST 69 IU/L, ALT 91 IU/L, GGT 127 IU/L) with negative viral hepatitis serologies as well as autoimmunity (ANA, antiDNA AMA, ASMA, antiLKM, ENA, ANCA). No ova nor worms were found in faeces (single sample tested). Sinus and chest CT scan showed no signs of Churg Strauss syndrome.

Liver ultrasound (LUS) showed mild hepatomegaly, non-homogeneous echo pattern with centimetric hypoechoic areas (Dec/2022). Abdomen MRI showed multiple and diffuse subverted structures of the liver (suggestive of lymphoma) and multiple lymph nodes (Apr/2023).

Due to persisting eosinophilia (WBC 8400/mm3, Eos 33.4%) and augmented total IgE (752 IU/mL) with abnormal LFTs (AST 59 IU/L, ALT 51 IU/L, GGT 138 IU/L, ALP 226 IU/L), patient underwent a first liver biopsy, suggestive of infectious etiopathogenesis: massive and confluent necrosis surrounded by histiocytes and numerous eosinophils, mild cholestasis and some eosinophils within the lobules, lymphohistiocytic inflammation with some eosinophils in the pericentral location; PAS, GMS, GROCOTT, WS and ZN stains were negative.

In May 2023 faeces were tested again: 1 out of 3 samples revealed *Enterobius vermicularis* ova. Serologies for *Schistosoma* and *Trichinella* were negative, as well as endoscopic searching for *Anisakis*.

Albendazole treatment (400mg once/weekly for 8 weeks) was administered, resulting in normalization of eosinophils count (4.8%, 300/mm3) and LFTs (AST 24 IU/L, ALT 27 IU/L, GGT 64 IU/L); moreover, a second liver biopsy showing normal pattern was performed after the aforementioned therapy, 6 months after the first one. Finally, a liver MRI confirmed the complete resolution of the abnormalities previously reported.

Conclusions: Ectopic localization of *Enterobius vermicularis* is rare. International literature reports six cases of liver infection, only two with modern imaging available, describing liver lesions as ill-defined, while diffuse hypoechoic areas were observed in our imaging. Treatment with albendazole (chronic recurrent course) resulted in normalization of the eosinophil count and LFTs; further-

more, histopathological lesions (necrosis and eosinophils infiltration) were no longer observed on the liver biopsy after appropriate therapy.

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P-19

Predictors of esophago-gastric varices and variceal bleeding in patients receiving atezolizumab/bevacizumab for unresectable hepatocellular carcinoma

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Introduction: Atezolizumab/bevacizumab (atezo/bev) is a standard treatment for unresectable hepatocellular carcinoma (HCC). Bevacizumab may increase the risk of bleeding, causing concerns of variceal bleeding in patients with cirrhosis.
Aim: Assess the predictors of esofago-gastric varices, high-risk varices (according to the Baveno criteria), and variceal bleeding in a population receiving atezo/bev for HCC.
Method: Analysis of prospectively collected data from 15 Italian centers included in the ARTE database (March 2022-June2024). Logistic regressions were run for predictors of varices amongst patients who had received an upper-gastrointestinal endoscopy (UGE) <6 months before starting treatment. Competing-risk analyses were performed to assess the predictors of variceal bleeding.
Results: Among 317 patients treated with atezo/bev included in the ARTE database, 256 had a recently performed UGE and were considered for this study. The main characteristcs of the study population were: median age 70 years, 83% male, 58% viral etiology, 88% Child-Pugh A, 52% ALBIgrade 1, 34.3% neoplastic portal vein thrombosis (nPVT), 59.9% Barcelona Clinic Liver Cancer-C stage. At treatment start, 27.3% of patients were receiving non-selective beta-blockers, and 5.8% had received a prior elastica band ligation. The prevalence of any-type and high-risk varices was 32.0 and 8.6%, respectively. Independent predictors of varices were: platelet count < 150.000/mmc (OR 3.69, 95%CI 2.06-6.61), ALBI grade >1 (OR 1.95, 95%CI 1.09-3.48), and nPVT (OR 1.78, 95%CI 1.01-3.18). High risk varices were independently associated platelet count < 150.000/mmc (OR 5.81, 95%CI 1.91-17.67) and ALBI grade >1 (OR 2.44, 95% CI 1.02-5.77). Nine patients had variceal bleeding during the follow-up (G3: n=6; G4: n=2; G5: n=1), accounting for a 3.5% 12-month cumulative incidence. Amongst patients with varices, high-risk varices were the only factor associated with bleeding (sHR 4.06, 95% CI 1.14-14.46) at the competing risk analysis. In these patients the 12-month risk was 12.7%.
Conclusion: The risk of variceal bleeding was low, but non negligible in the subgroup of patients with high-risk varices at baseline. UGE should be performed in all patients before starting treatment: patients with platelet count < 150.000/mmc, ALBI grade > 1 or neoplastic portal vein thrombosis are at increased risk of varices.

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P-20

Long-term outcomes after Combined Liver-Kidney Transplantation: a single center experience

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Introduction: Combined Liver-Kidney Transplantation (CLKT) is a consolidated therapeutic option for patients with end-stage liver and renal disease or irreversible hepatorenal syndrome. Despite a prolonged operative time and greater technical complexity, CLKT is often preferable to Liver Transplantation (LT) alone in selected cirrhotic patients with renal failure. This study aims at evaluating the long-term graft-/patient-survival of these patients.
Methods: Consecutive patients receiving CLKT at our Transplant Center were included in the study. Characteristics of patients, indications to CLKT, and graft variables were retrospectively evaluated. Patients' follow-up was defined until death or at October 31st 2024.
Results: Between 1999 and 2024, 36 patients underwent CLKT. Patients were primarily males (63.9%), median age at CLKT 52 years (range 18-64). The most common indication was polycystic kidney disease (17 patients; 47.2%), with polycystic liver disease in 14 and congenital hepatic fibrosis in 3. Other causes of liver failure were viral cirrhosis (27.8%), alcoholic cirrhosis (8.3%) and primary biliary cholangitis (5.6%); other causes of kidney failure were hepatorenal syndrome (8.3%), glomerulonephritis (8.3%), diabetic nephropathy (5.6%) and multifactorial disease (13.9%). At the time of CLKT, 22 patients (61.1%) were on dialysis. All patients received grafts from deceased donors: whole-liver grafts in 32 (88.9%), 4 split-extended-right liver grafts. Median follow-up was 77.5 months. At last follow up, 4 patients were on dialysis and 1 patient had developed liver graft failure. None of the patients underwent liver or kidney re-transplantation. Patient-survival rates at 1, 3, 5 and 10

years post-CLKT were 91.7%, 88.0%, 80.7% and 72.2%. In our Centre, patients undergoing LT in the same period showed survival rates at 1, 3, 5 and 10 years of 88.1%, 81.6%, 77.3% and 66.8% respectively.
Conclusions: Despite the complexity of the procedure, CLKT showed excellent long term survival rates, even better than those of LT alone [Figure 1].

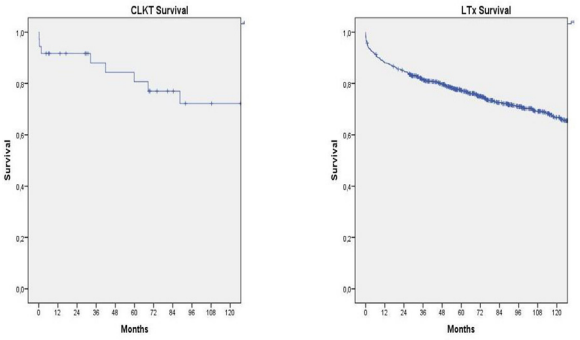

Figure 1. Kaplan-Meier curves of CLKT vs LT long-term patient-survival

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P-21

To re-transplant, or not to re-transplant, that is the question

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Introduction: The outcomes of Liver Re-Transplantation (Re-LT) have improved over the decades but remain worse (5-year graft survival rate 45-55%) than those of primary LT. Several studies, mostly dated, have analyzed the predictive factors of post-Re-LT failure, aiming to increase the survival rates and to avoid "futile" Re-LT, however the question is still open to debate.
Methods: Consecutive adult patients undergoing Re-LT in our Transplant Center were included. Both recipient- and donor-predictive factors were evaluated. Patients' follow-up was until death or September 30th 2024.
Results: Between 2000 and 2023, 79 patients underwent Re-LT (whole graft) at our Transplant Centre. Patients were more frequently males (76.0%), median age at Re-LT 55 years (range 19-70). Re-LT was performed after a median of 4.2 months (1 d-200.6 m) following LT. The main indications were: Delayed Graft Function (22.8%), Hepatic Artery Thrombosis (20.3%), Primary Non Function (13.9%) and Secondary Biliary Cirrhosis (7.6%). Median donor age was 56 years (15-82) and most liver-grafts derived from brain-dead donors (97.5%). At the time of Re-LT, mean MELD-score was 24.9±10.8, 36% of patients were receiving vasopressors, 30.7% were on mechanical ventilation and 32.9% had severe renal insufficiency (creatinine ≥3.5 mg/dl) or required ultrafiltration. Median follow up was 64.3 months. Graft- and patient-survival rates at 1, 3 and 5 years post-Re-LT were 64.6%, 60.4%, 48.2% and 77.2%, 68.0%, 62.1% respectively. No correlations between donor or graft variables and graft-survival emerged. Graft-survival rates were significantly worst in patients with age at Re-LT> 60 years, a MELD≥ 30, hyperlactatemia (≥2.2 mmol/l) and use of vasopressors or ultrafiltration at the time of Re-LT; patients with a pre-Re-LT CLIF-Organ Failure score > 60 have a 6 months graft-survival of 31.3%. [Figure 1].
Conclusions: A correct patient selection is critical to minimize "futile" liver retransplants and improve survival rate after Re-LT.

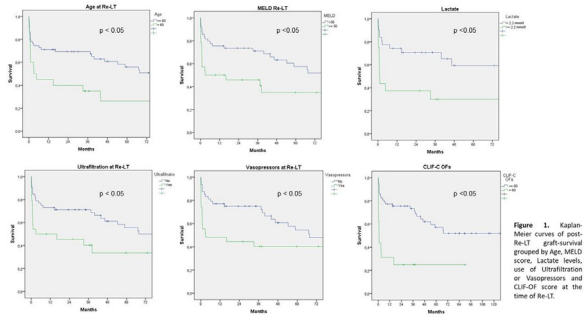

Figure 1. Kaplan-Meier curves of post-Re-LT graft-survival grouped by Age, MELD score, Lactate levels, use of Ultrafiltration or Vasopressors and CLIF-OF score at the time of Re-LT.

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P-22

AI-AD score: a novel Machine Learning-based model for predicting Acute Liver Decompensation progression – a prospective observational study

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Background: Patients with advanced chronic liver disease (ACLD), including the new form of non-acute decompensated (NAD), are at risk for acute decompensation (AD) or acute-on-chronic liver failure (ACLF), with an increased risk of mortality. To date, no specific score has been developed for AD onset. The well-known CLIF-C AD score is the only score to predict prognosis in hospitalized cirrhotic patients, but not designed for AD onset.
Aims: develop and validate, using artificial intelligence (AI) techniques, the AI-AD score, a prognostic score for outpatients with ACLD who may develop AD, and to compare its performance with CLIF-C AD, Child-Pugh, and MELD scores.
Patients and Methods: a single-center cohort study enrolled consecutive ACLD patients, followed at Liver Unit in Verona between January 2017 and December 2022. AI-AD score was developed using machine learning and pattern recognition techniques, focusing on classification and feature selection. AI was able to select the feature most relevant for predicting AD onset and trough a linear classifier to applied it. The score was validated in both an internal and a validation cohort. To assess the performance of the different scores, we used the classic AUC.
Results: 456 patients (70.6% male, mean age 64 ± 11 years) were enrolled for a median follow-up of 43.3 months. Among ACLD patients, 91 developed AD, 62 developed ACLF, while 79 NAD pa-

tients progressed to AD. The selected features for AI-AD score were: previous hospital admissions, infection episodes before enrollment, history of ascites and encephalopathy, portal vein thrombosis, serum creatinine and albumin values. AUC for the AI-AD score was 0.80 (CI 95%:0.73-0.86), higher than other scores (Fig 1).
Conclusion: AI-AD score effectively predicts AD onset in ACLD patients. history of infections and PVT, were identified as a crucial complication in cirrhotic patients and may predispose individuals to AD and ACLF.

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P-23

Statins in patients with advanced hcc treated with atezolizumab/bevacizumab: a propensity score-matched cohort analysis from arte an Italian prospective multicentric dataset

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Background and Aims: Statins have been suggested to exert anticancer properties by modulating angiogenesis, fibrosis, inflammation, and the tumor microenvironment, generating interest in their clinical use for chronic liver diseases (CLD) and hepatocellular carcinoma (HCC) chemoprevention. However, the effects of statin therapy in patients treated with immune checkpoint inhibitors for CLD-associated HCC remain unknown. This study primarily aimed to assess the potential effect of statins on overall survival (OS) mand progression-free survival (PFS) in patients with advanced HCC treated with atezolizumab and bevacizumab (A+B).
Method: The ARTE dataset, a retro-prospectively maintained database, includes 305 consecutive patients with unresectable HCC treated with A+B, enrolled from 12 tertiary care centers in Italy. From the original cohort, a 1:1 propensity score matching was performed to balance potential confounding factors between 63 patients on statin therapy and those who were not. The primary outcomes were OS and PFS, while secondary outcomes included all-cause mortality, liver-related death, treatment interruption, and incidence of liver decompensation events.
Results: Among the matched population of 126 patients, 75% had liver cirrhosis, with metabolic disfunction-associated steatotic liver disease (MASLD) being the most common etiology. Ninety-seven patients (32%) had diabetes. No significant differences were found between statin users and non-users for OS, PFS, or liver-related death. Additionally, the log-rank test revealed no significant difference between the groups in terms of treatment interruption due to liver decompensation events (p=0.28).
Conclusion: Statin use did not show any impact on OS, PFS, or reduction in mortality or treatment interruption due to liver-related decompensation events in patients with advanced HCC treated with A+B.

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P-24

RuvBL1/2 ATPase activity is required for HSF1-mediated stress response in hepatocellular carcinoma

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RuvBL1 is an AAA+ ATPase involved in multiple cellular activities including proliferation, chromatin remodeling, gene expression and translation. RuvBL1 expression correlates with a poor prognosis in Hepatocellular Carcinoma (HCC) and other human tumors. Emerging data suggests that RuvBL1 could exert co-chaperone functions. Aim of this study is to investigate the potential axis between RuvBL1 and molecular chaperones in HCC. Analysis of hu-

man HCC samples in the TGCA shows that RuvBL1 significantly correlates with the expression of HSPs family members, of TCP-1 ring complex (TRiC) genes and with the transcription factor HSF1. RuvBL1 and TRiCs are among the top-scoring genes associated with a worse survival in the TCGA_LIHC cohort. The expression of selected targets was evaluated by qPCR in AML-12 and Huh7 cells treated with the RuvBL1/2 ATPase inhibitor CB6644 during Heat Shock response (HS) or mitochondrial Unfolded-Protein Response (mtUPR). HSPs and TRiC genes were induced by HS- or mtUPR in a context-dependent way, but consistently repressed by CB6644. HSF1 transcriptional activity measured through a luciferase-reporter assay was induced by HS or mtUPR and completely abrogated by CB6644. Proximity ligation assay revealed a constitutive HSF1-RuvBL1 nuclear interaction, which was disrupted by CB6644. Finaly, the inhibition of RuvBL1/2 ATPase activity by CB-6644 potentiate the growth inhibitory effect of HSP90 inhibitors such as 17-AAG and VER-50589 and also of the TKI inhibitor Sorafenib. In conclusion, RuvBL1/2 ATPase activity is required for HSPs and TRiC gene expression and its targeting may be exploited to impair HSF1-mediated stress-response in HCC.

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P-25

Features and factors related to intensive care unit admission of cirrhotic patients with Acute-on-Chronic Liver Failure: a single-center observational study

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Introduction and Aims: Acute-on-chronic liver failure (ACLF) is a severe form of acutely decompensated cirrhosis. Infections play a crucial role in precipitating and complicating ACLF. This study aimed to evaluate the characteristics of a population of patients with ACLF admitted to our unit, with the goal of identifying factors predisposing to intensive care unit (ICU) admission and to death or liver transplantation (LT).
Materials and Methods: This is a single-center prospective study conducted from January 2018 to July 2024. Demographic, clinical, laboratory, and radiologic data of 94 consecutive cirrhotic patients diagnosed with ACLF and admitted to our department were collected and analyzed. ACLF-related ICU admission, mortality, or LT were recorded. Infections that triggered ACLF or occurred during hospitalization for ACLF, prior to potential ICU admission, were categorized.
Results: During hospitalization, 37% of patients were admitted to ICU. 80% of the patients either died or underwent LT. Infections, either triggering or complicating ACLF occurred in 87% of patients prior to potential admission to the ICU. In survival analysis, ACLF patients who had undergone tertiary hepatological follow-up for at least six months prior to hospitalization (49%) exhibited a significantly reduced risk of ICU admission following ACLF (HR 0.21, 95% CI 0.07–0.37, $p<0.001$), and a reduced risk of ACLF-related death or need of LT (HR 0.12, 95% CI 0.07–0.24, $p<0.001$). Fungal infections, on the other hand, were strongly associated with a higher likelihood of ICU admission (HR 2.93, 95% CI 1.31–6.54, $p=0.009$), and multidrug-resistant (MDR) infections markedly increased the risk of death or LT (HR 2.16, 95% CI 1.13–4.10, $p=0.019$).
Conclusions: Fungal infections have been identified as a risk factor for ICU admission in patients with ACLF. Moreover, MDR infections significantly increase the risk of ACLF-related death or LT. Therefore, strategies aimed at preventing and rapidly managing these infections are essential. Finally, outpatient tertiary hepatological follow-up appears to be protective in cirrhotic patients, reducing the risk of ICU admission, as well as of death or LT when developing ACLF.

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P-26

The real life use of bulevirtide for treatment of chronic HDV infection: an interim analysis in the PITER cohort ☆

PITER Collaborating Investigators

☆ www.progettopiter.it

Introduction and Aim: We aimed to update the status of patients with chronic HDV infection enrolled in the PITER HBV/HDV cohort after one year from bulevirtide approval.
Methods: This is an interim analysis of consecutive anti-HDV-positive patients enrolled in the PITER cohort. The chi-square test was used to analyze differences in proportions between treated and untreated patients. Following the data validation, multivariable analysis will be performed.
Results: Of 640 anti-HDV positive patients, 358 (56%) tested HDV-RNA positive, of whom 181 (51%) were on bulevirtide therapy. Of the HDV–RNA positive, treated patients, 19 (10%) tested HDV-RNA negative et enrolment, of whom 16 (84%) had liver cirrhosis, and 11 (58%) had altered transaminase levels. Cirrhosis was reported in 82% and 74% ($p=0.057$) of treated and untreated patients, respectively. Child A and Child B cirrhosis were reported in 93% and 87% of treated patients and 76% and 22% ($p=0.02$) of untreated patients, respectively. HCC was reported in 8% and 16% of treated and untreated patients, respectively ($p=0.03$). Ongoing NUC therapy was reported in 91% of treated and 76% ($p=0.001$) of untreated patients. No significant differences were observed in the age distribution, country of birth, gender, transaminase and gamma-GT levels, HBV-DNA positivity, previous Interferon use, and years of NUC therapy ($p > 0.05$). During the first year of follow-up, 1.1% and 9% ($p=0.002$) of patients died in the treated and untreated group, respectively. Both groups had similar liver decompensation (0.7% and 0.8%) and HCC incidence (0.6%).
Conclusions: During the first year of bulevirtide therapy, patients with more severe liver disease were prioritized for treatment. About 50% of patients with an active HDV infection, of whom 25% have cirrhosis, still need to be treated. Negative HDV-RNA should be confirmed with current, more sensitive tests in anti-HDV-positive patients with cirrhosis and altered transaminase levels.

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P-27

Antinuclear antibodies target unknown autoantigens in porto-sinusoidal vascular disorder (PSVD) without portal hypertension

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Recent evidence links PSVD to connective tissue diseases. Antinuclear antibodies (ANA) are a hallmark of these conditions, but their prevalence and significance in patients with PSVD without portal hypertension (noPH-PSVD) remain unclear.

Sera from noPH-PSVD patients were analyzed for ANA using indirect immunofluorescence (IIF) on HEp-2 substrates (HEp-2 IIF). ANA-positive cases underwent RNA immunoprecipitation (RNA-IP) to identify autoantibodies for specific ribonuclear proteins. Patients with cytoplasmic staining on Hep-2 IIF, underwent ELISA for antimitochondrial antibodies (AMA), targeting the E2 subunit of the pyruvate dehydrogenase complex (anti-E2-PDH).

Sixteen patients were enrolled, with a median age of 42 years (range 22–58), 56% were female. Autoimmune comorbidities included thyroiditis in 4 patients, multiple sclerosis in one. PSVD diagnosis was based on histological evidence of nodular regenerative hyperplasia on liver biopsy performed for unexplained liver enzyme abnormalities. ANA were found in 8 out of 16 (50%) patients using HEp-2 IIF with titers ranging from 1:80 to 1:320. A cytoplasmic reticular/AMA-like pattern was observed in 4/16 (25%) patients, a speckled pattern in 1/16 (6.25%), a nucleolar pattern in 2/16 (12.5%; one co-occurring with a cytoplasmic reticular pattern) and a mitotic pattern (mitotic centrosome and NuMA-like) in 2 out of 16 (12.5%) cases. RNA-IP did not identify autoantibodies against specific ribonuclear proteins in any patient. Moreover, none of the patients with a cytoplasmic reticular/AMA-like pattern tested positive for anti-E2-PDH autoantibodies via ELISA.

In this noPH-PSVD cohort, ANA were detected in 50% of cases using gold-standard techniques. Despite 25% showing an AMA-like pattern, anti-E2-PDH testing by ELISA was negative, suggesting these ANA may target antigens distinct from those in primary biliary cholangitis. A notable proportion of ANA-positive patients showed mitotic staining, uncommon in connective tissue diseases. Although ANA prevalence was high, RNA-IP did not reveal specific autoantibodies, highlighting the need for further investigation.

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P-28

Assessing the diagnostic accuracy of ChatGPT-4 in the histopathological evaluation of liver fibrosis in metabolic dysfunction-associated steatotic liver disease

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Large language models like ChatGPT have demonstrated potential in medical image interpretation, but their efficacy in histopathological analysis, particularly for liver diseases, remains largely unexplored. This study aims to assess ChatGPT-4-vision's diagnostic accuracy, compared to liver pathologists' performance, in evaluating liver fibrosis (stage) in Metabolic Dysfunction-Associated SteatoHepatitis (MASH).

Digitized Sirius Red stained images for 59 MASH tissue biopsy specimens were evaluated by ChatGPT-4 and four pathologists using the NASH-CRN staging system. Fields of view (FOVs) at increasing magnification levels, extracted by a senior pathologist or randomly selected from the whole slide images, were shown to ChatGPT-4, asking for fibrosis staging. The diagnostic accuracy of ChatGPT-4 was compared with pathologists' evaluations and correlated to the collagen proportionate area (CPA) for additional insights.

ChatGPT-4′s diagnostic accuracy was 81% when using images selected by a pathologist, while it decreases to 54% with randomly cropped FOVs. In the F1-F3 fibrosis stages, ChatGPT-4 performed comparably to expert liver pathologists. However, in the F4 stage, ChatGPT-4′s diagnostic accuracy (40%) was lower than that obtained by all the involved pathologists. The study also highlighted a moderate to strong correlation between ChatGPT-4′s fibrosis staging and CPA.

ChatGPT-4 showed remarkable results with a diagnostic accuracy overlapping those of expert liver pathologists. Surprisingly, the diagnostic accuracy dropped with F4 cases, which are consistently recognized also by non-expert liver pathologists. This aspect, together with the low accuracy observed with unselected images, makes, at the moment, this AI tool unreliable as an assistant in diagnostic pathology.

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P-29

Fibrate-Oca (FI-OCA) Study - a Global snapshot of PBC practice around the Globe

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Introduction: The introduction of obeticholic acid (OCA) and the emerging evidence on the efficacy of fibrates and other PPAR-agonists have shifted the treatment paradigm for primary biliary cholangitis (PBC) away from the UDCA-only approach. This expanded drug armamentarium has increased the complexity of disease management, resulting in heterogeneous and diverse PBC practices worldwide. We aimed to define who are the patients offered second line treatment and what is the dynamic of add-on, switches or stop of second line treatment across the Globe.
Material and Methods: We conducted a retrospective, international, multicentric cohort study involving PBC patients who began second-line treatment with either fibric acid derivatives (fibrates) or OCA in 40 tertiary centres across Europe, Japan, South America, and North America. We collected clinical, biochemical, and treatment data at diagnosis and at the initiation of second-line treatment. Adverse effects and treatment changes during follow-up were also recorded.
Results: We accrued data on 1,831 patients, 917 initiated on OCA (901 already on UDCA) and 868 on fibrates (863 on UDCA). Among these, 635 patients started on bezafibrate and 233 on fenofibrate. 276 of the patients on Bezafibrate were from 18 centres with restricted access to OCA, in Japan, Argentina and Netherlands. Only 17 patients began bezafibrate and OCA simultaneously. The sex distribution did not differ significantly between the fibrate and OCA groups (female: 87.9% vs 88.9%, p=0.570). Baseline mean ALT, ALP, GGT, and bilirubin (ratios to the upper limit of normal) were 1.47 (±1.29) vs 1.63 (±1.58) (p=0.100), 2.64 (±1.55) vs 2.43 (±2.47) (p=0.070), 5.39 (±4.20) vs 5.06 (±4.79) (p=0.453), and 0.98 (±0.94) vs 0.98 (±0.64) (p=0.986), respectively. Baseline cirrhosis was more frequent in OCA patients (28.3.0%, n=216; vs 19.5%, n=83, p=0.01). Most cirrhotic patients on OCA were Child A (97.7%) compared with 64% on fibrates. The median time from UDCA initiation to second-line treatment was longer for OCA patients (70.7 (28-132) months vs 53 (15-123) months, p< 0.001). During follow-up, 96 OCA patients added a fibrate, while 22 fibrate patients added OCA. OCA was discontinued by 302 patients (33%), primarily due to pruritus (33%). 128 of them switched to fibrates. Fibrates were discontinued by 182 patients (21%) due to increased transaminases (18%) or worsening renal function (10%); 39 switched to OCA. The median time before adding a third medication or switching treatments was 23.5 (12.0-39.8) months for OCA and 27.0 (12.5-53.0) months for fibrates.
Conclusions: The management of PBC involves dynamic adjustments to second-line treatments. The high rates of treatment discontinuation and changes highlight the need for better tools to allocate second-line treatments more effectively. Additionally, these data suggest that second-line treatments should be offered earlier in the disease course to optimize management strategies.

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P-30

Somatic copy number alterations in circulating cell-free DNA as a predictive biomarker for hepatocellular carcinoma: insights from a proof-of-concept study

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Background and Aims: Despite improvements in hepatocellular carcinoma (HCC) management, its prognosis remains poor. Diagnosis at advanced stages often precludes curative treatment options, and currently available biomarkers (e.g., alpha-fetoprotein (AFP)) offer limited utility in early diagnosis and prognostic stratification. Liquid biopsy has emerged as a promising tool for early HCC detection and prognostic evaluation, and the analysis of circulating cell-free DNA (ccfDNA) hold significant potential as a diagnostic tool. This proof-of-concept study aimed to investigate the potential role of tumor fraction (TF) within ccfDNA as a biomarker in HCC patients.
Method: A total of 60 patients were recruited, including 13 with chronic liver disease (CLD), 24 with cirrhosis, and 23 with HCC. Plasma samples were collected, and ccfDNA was extracted for genomic analysis. TF was calculated by focusing on somatic copy number alterations (SCNAs) within the ccfDNA.
Results: In patients with CLD and cirrhosis (n = 37), circulating tumor DNA (ctDNA) was undetectable with the exception of one cirrhotic patient, who presented a significant TF (17 %) and displayed HCC shortly after. Conversely, 5 out of 22 HCC patients (21.7 %) exhibited detectable ctDNA, with TF levels ranging from 3.0 % to 32.6 %. Patients with higher TF levels were characterized by more aggressive disease features, including elevated AFP levels, larger tumor sizes, multiple tumor nodules, and advanced-stage disease.

Conclusion: Preliminary evidence from this study suggests that the analysis of TF, specifically through the detection of SCNAs, could serve as a promising non-invasive tool for the identification and evaluation of HCC. The innovative approach has the potential to significantly enhance early diagnosis and may also improve prognostic stratification in HCC patients.

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P-31

Prognostic value of a composite biomarker score for predicting overall survival in HCC patients

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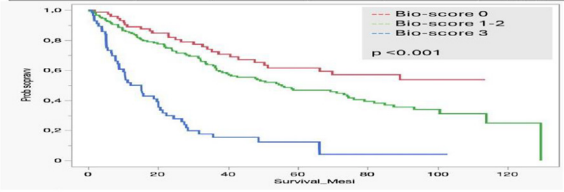
Background: Despite advances in diagnosis and treatment of Hepatocellular Carcinoma (HCC), its management remains challenging. Tumor stage and liver function, that impact overall survival (OS), currently guide treatment algorithms. Lacking histology in most cases, serum biomarkers might provide additional insights to characterize tumor biology. Alpha-fetoprotein (AFP), Prothrombin induced by vitamin K absence-II (PIVKA-II), and glypican-3 (GPC-3) have been separately used for diagnosis and monitoring, whether their measure can better stratify survival is unknown.
Material and Methods: In this retrospective cohort 275 patients admitted at the Hepatology-Unit of Pisa University Hospital and at the Gastroenterology-Unit of the Molinette-Hospital, Turin with a first diagnosis of HCC had AFP, PIVKA-II, and GPC-3 measured at diagnosis. Setting pathological cut-offs (AFP>10 ng/mL, PIVKA-II>200 mAU/mL, GPC-3>100 pg/mL) each patient received a "bio-score" based on the number of elevated biomarkers (0-3). Kaplan-Meier and Cox regression analyses were used to evaluate the relationship between the bio-score and OS.
Results: The bio-score demonstrated a significant association with OS (p<0.001), with higher scores correlating with worse outcomes. Patients with a bio-score of 3 had the poorest survival, while lower scores were associated with progressively better survival rates (Figure-1). In the multivariate analysis (Table-1), the bio- score emerged as an independent predictor of OS (p=0.027-HR=5.316 for score "3"), overtaking individual biomarkers in predictive power. The other independent variables associated with OS at multivariate analysis were the BCLC stage (p<0.001), the presence of ascites (p=0.003), ALBI grade (p=0.007) and the number of lesions (p=0.036).
Conclusion: Combining AFP, PIVKA-II, and GPC-3 as a composite biomarker score provides superior predictive accuracy for OS in HCC patients compared to individual biomarkers. This multi-biomarker approach could offer a valuable, noninvasive prognostic tool, allowing for more personalized management of HCC patients based on survival probability. Further studies are recommended to validate this model in larger

Variable	Category	N/median	P	OR	IC
Age at Diagnosis	years	69.7	0.484	1.006	0.989-1.023
Cirrhosis	Yes	239	0.996	1.001	0.565-1.776
	No	36			
Child-Pugh	A	241	0.455	0.770	0.388-1.528
	B-C	34			
Ascites	Yes	41	**0.003**	2.353	1.329-4.166
	No	234			
Portal Hypertension	Yes	184	0.835	0.958	0.637-1.439
	No	91			
Portal Vein Thrombosis	Yes	31	0.796	1.083	0.593-1.977
	No	244			
MELD SCORE		8.1	0.883	1.005	0.936-1.080
ALBI score	Grade 1	160	**0.007**	1.669	1.150-2.423
	Grado 2-3	115			
HCC Diameter max	cm	3.00	0.151	1.063	0.978-1.156
Number of HCC lesions	<1	132	**0.036**	1.521	1.029-2.250
	>1	143			
BCLC	0	36	**<0.001**		
	A	116	*0.089*	2.034	0.898-4.607
	B	71	**0.012**	3.200	1.293-7.917
	C	46	**<0.001**	6.833	2.413-19.353
	D	6	**<0.001**	18.982	4.865-74.071
AFP	< 10ng/ml	148	0.110	0.635	0.364-1.108
	>10ng/ml	127			
PIVKA	<200 mAU/ml	140	0.788	1.094	0.568-2.108
	>200 mAU/ml	135			
GPC-3	<100 pg/ml	147	0.319	0.757	0.437-1.310
	>100 pg/ml	128			
Bio-score	0 pt	72	**0.027**		
	1-2 pts	147	0.157	**1.830**	**0.792-4.228**
	3 pts	56	**0.027**	**5.316**	**1.214-23.276**



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P-32

Creatinine as a predictor of clinical events in Metabolic Dysfunction-Associated Steatotic Liver Disease

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Background: Metabolic dysnfuction-associated steatotic liver disease (MASLD) is the leading cause of chronic liver disease, and liver fibrosis is the primary predictor of liver-related events and mortality. Identifying patients at higher risk of progression is crucial for improving outcomes.
Aim: to characterize patients referred for hepatic steatosis to the Metabolic Clinic of AOU Policlinico of Modena with a minimum follow-up of 10 years and to assess the incidence and predictors of clinical events of interest.
Material and Methods: we prospectively enrolled all patients referred to the Metabolic Clinic for suspected NAFLD in the first years from its foundation (2011-2012). Retrospective data on cardiovascular events, liver-related events and mortality were collected. NITs for liver fibrosis were calculated and elastometric and histologic data were collected when available. Cox regression analysis was used to identify predictors of: 1) liver-related events, 2) cardiovascular events, 3) composite of death, hepatic decompensation, or cardiovascular events.
Results: the study population included 120 patients (33,3% females, mean age 53,32 ± 11,8 years). At baseline, 41 patients (37,3%) were obese (BMI of 29,02 ± 4,03), with T2DM, hypertension and dyslipidaemia prevalence of 14,2%, 26,7% and 76,7%, respectively (Figure 1). Over a mean follow-up of 11 years, 13 patients (10,8%) progressed to cirrhosis: 3 (5%) experienced hepatic decompensations, 3 developed HCC; 15 (12,5%) developed cardiovascular events, and 4 (3,3%) died.

Baseline Fib4 and APRI correlated with the composite outcome in univariate analysis, but not AGILE3. At the multivariate analysis, age, BMI and creatinine remained significant predictors (Figure2).
Conclusion: Creatinine levels may serve as an additional marker for identifying patients with MASLD who are at higher risk of clinical events, highlighting the possible, often subclinical, organ damage in this patient group.

Age (years) ± SD	53,32 ± 11,8
Male	80 (66,7%)
Body mass index (kg/m^2)	29,02 ± 4,03
Normal weight	14 (12,7%)
Overweight	55 (50 %)
Obese	41 (37,3%)
Diabetes mellitus	17 (14,2)
IFG or IGT	18 (15%)
Hypertension	32 (26,7%)
Dyslipidaemia	92 (76,7%)
Previous CV events	6 (5%)
History of viral hepatitis	26 (21,7%)
Hyperferritinaemia	22 (47,8%)
Current smoker	20 (16,7%)
Excess alcohol ever	9 (7,5%)
Alcohol (g/week)	12 (84)
APRI	0,428 (0,4)
APRI < 0.5	40 (58,8%)
APRI 0.5-1.5	28 (41,2%)
APRI > 1.5	0 (0%)
Fib4	1,160 (0,8)
Fib4 < 1,3	36 (58,1%)
Fib4 1,3-2,67	26 (41,9%)
Fib4 > 2,67	0

UNIVARIATE			MULTIVARIATE		
	HR 95% CI	p		HR 95% CI	p
Age	1,076 (1,031-1,123)	0,001	**MODEL1**		
BMI	1,13 (1,032-1,253)	0,009	Age	1,095 (1,010-1,187)	0,027
Hypertension	3,68 (1,493-9,083)	0,005	BMI	1,256 (1,040-1,515)	0,018
Diabetes	4,37 (1,717-11,17)	0,002	Hypertension	-	ns
CV events	5,30 (1,163-24,198)	0,031	N.Medications	-	ns
Comorbidities	1,887 (1,145-3,078)	0,013	Creatinin	197,0(2,56-15154,29)	0,017
N.Medications	1,37 (1,1,93-1,581)	<0,001	Platelets	-	ns
Statin	2,563 (1,006-6,531)	0,049	Glucose	-	ns
Creatinin	95,76 (2,92-313,05)	0,010	**MODEL 2**		
Platelets	0,99 (0,97-1,00)	0,084	BMI	1,55 (1,07-2,24)	0,021
Glucose	1,01 (1,00-1,02)	0,012	Hypertension	-	ns
Uric Acid	2,112 (0,99-4,605)	0,060	N.Medications	14,26 (1,14-178,57)	0,039
Fib4	7,29 (1,73-30,61)	0,007	Creatinin	138,96 (0,69-27713,88)	0,068
APRI	29,21 (1,89-449,57)	0,016	Fib4	-	ns
Never smoker	0,316 (1,49-9,08)	0,041	Diabetes	-	ns

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P-33

The changing epidemiology of patients with HCC receiving a first-line systemic therapy: insights from ARPES and ARTE databases (2008-2024)

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Introduction: The epidemiological characteristics of patients starting first-line systemic therapy for hepatocellular carcinoma (HCC) have changed over time.
Aim: This study examines shifts in demographics and disease profiles since the first systemic therapy was introduced.

Material and Methods Results: We compared baseline characteristics of patients receiving frontline systemic treatments from two Italian multicenter nationwide datasets of systemic treatments: ARPES (sorafenib, 656 patients, 2008-2019) and ARTE (atezolizumab and bevacizumab [atezo/bev], 393 patients, 2022-2024). ARPES included cardiometabolic risk factors, allowing reclassification from NAFLD to MASLD.

Compared to ARPES, patients in ARTE showed a higher prevalence of females (19.9% vs. 15.1%; p=0.047), a trend toward older age, and an increase in single-etiology MASLD (17.6% vs. 8.8%, p<0.001), with fewer viral cases. More patients with HCV were in sustained virologic response at treatment start (72.8 vs 9.1%, p<0.001). Additionally, patients included in ARTE had better liver function (ALBI grade-1: 52.6 vs 18.7%, p<0.001), highest rate of no prior surgical/locoregional HCC treatments (38.5% vs. 28.1%, p<0.001), less prevalent BCLC-C stage due to fewer cases with macrovascular invasion (31.0% vs. 43.1%, p<0.001) and similar rate of metastatic disease. Lower likelihood of previous surgical/locoregional treatments was confirmed in the intermediate-stage subgroup (19.9 vs 35.2%, p<0.001). Tumors larger>6 cm (14.9% vs. 10.0%, p<0.001) and ECOG-PS>0, (32.0% vs. 23.3%, p<0.001) were also more common in the ARTE database.

Conclusions: The increased prevalence of MASLD, a decline in viral cases, high SVR rates in HCV, and less previous locoregional treatments are likely to contribute to better liver function and more patients with intermediate stage. The challenges of surveillance in patients with MASLD may explain the increase in cases with no prior treatment, larger tumors, and higher ECOG-PS scores.

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P-34

Multiparametric ultrasound-based algorithm SteatoScore2.0 versus monoparametric Controlled Attenuation Parameter in clinical practice: a comparison study in a monocentric MASLD cohort

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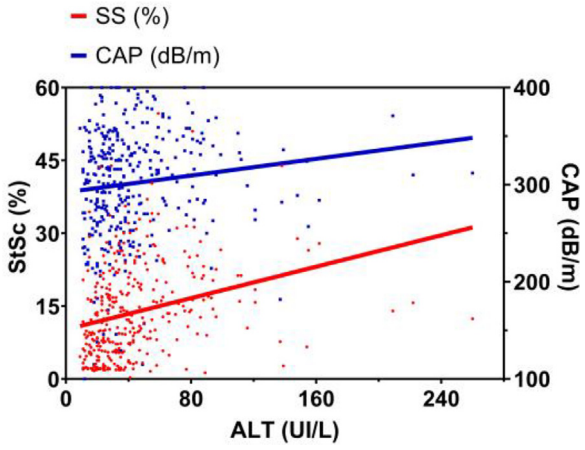
Introduction: A quantitative, accurate and non-invasive measurement of liver fat content (LFC) is an unmet need of clinical practice for Steatotic Liver Disease (SLD) evaluation. The most widespread non-invasive tests in clinical practice is controlled attenuation parameter (CAP) by FibroScan®. Multiparamatric Steatoscore 2.0 (StSc) was shown recently to provide LFC measures highly comparable to MRI-PDFF.

Aim: Aim of the study was to analyze the StSc-CAP agreement in patients with metabolic dysfunction-associated SLD (MASLD) spectrum and their correlation with clinical/biochemical parameters.

Materials and Methods: 450 patients consecutively evaluated from January 2019 to October 2024 for SLD at the Hepatology Unit of Pisa University Hospital were enrolled at MASLD diagnosis. Clinical, anthropometric, biochemical and instrumental data were collected. LFC was simultaneously measured with CAP and StSc and liver fibro-inflammatory one with FibroScan® liver stiffness measurement (LSM).

Results: Overall CAP and StSc were significantly correlated (r=0.485, p<0.001[sc1]), but the agreement was poor and varied by LSM categories (<8kPa: r=0.485, p<0.001; 8-12kPa: r=0.462, p=0.001; 12-20kPa: r=0.494 p=0.005, >20kPa r=-0.326 p=0.330) and BMI classes (normal weight: r=0.501 p<0.001, overweight: r=0.546 p<0.001, obese: r=0.385 p=0.001). StSc correlated inversely with age (r=-0.111 p=0.025) and directly with overweight (r=0.133 p=0.047), while CAP did not. In non-advanced MASLD cohort (LSM<12 kPa) we found a difference in correlation of StSc and CAP with AST (StSc r=0.290 p<0.001 vs CAP r=0.167 p<0.001, p for comparison=0.010) and ALT (StSc r=0.358 p<0.001 vs CAP r=0.191 p=0.001, p for comparison=0.0005).

Conclusions: In a MASLD cohort LFC measures by StSc and CAP were correlated but their agreement varied consistently along the spectrum of liver disease stage stratified non-invasively by LSM. Multiparametric StSc outperformed mono-parametric CAP and significantly correlates with body weight. In earlier forms of MASLD StSc correlated better than CAP with liver enzymes in patients with progressive steato-hepatitis.



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P-35

Activation of AMPK by a novel complex I modulator (CIM) reduces lipid accumulation and mitigates fibrosis in an in vivo model of MASLD

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Introduction: Mitochondrial complex I dysfunction is linked to lipid accumulation and excessive ROS production, contributing to MASLD progression. Metformin, a known complex I inhibitor, promotes lipolysis and β-oxidation *via* AMP-activated protein kinase (AMPK), a key regulator of lipid metabolism. This study aims to assess whether a novel complex I modulator (CIM) regulates lipid metabolism and hepatic fibrosis with a similar mechanism.

Materials and Methods: male Wistar rats, fed with a Methionine and Choline deficient (MCD) diet or Control diet for 6 weeks, were

orally administered with complex I modulator (CIM, 10mg/Kg/day) or vehicle for the last 3 weeks. ATP content, NAD(P)H bound/free ratio, lipid accumulation, collagen deposition, protein and mRNA expression of key lipid and fibrosis markers were analyzed.
Results: CIM administration significantly reduced intrahepatic lipid content in MCD-fed rats, compared with untreated ones. Histological analysis revealed a significant reduction in lipid droplets in both CIM-treated groups, compared with untreated ones. ATP and NAD(P)H bound/free ratio decreased in CIM-treated controls, *versus* vehicle-treated rats. Activated AMPK increased in both CIM-treated groups, but the effect was significant only in control diet rats. Nuclear PPAR-a levels significantly rose in CIM-treated MCD-fed rats, relative to the untreated ones, while its cytoplasmic levels were significantly reduced in the same samples. CIM administration significantly decreased mRNA expression of *Srebp1c* and its target genes *Acaca* and *Fasn* in CIM-treated controls, with a similar trend observed in SREBP1c and mTOR protein levels. CIM-treated rats also showed a significant reduction in collagen deposition in both control rats and rats fed with MCD diet, along with a significant decrease in a-SMA protein expression in CIM-treated MCD rats. The same trend, although not significant, was observed for fibronectin protein expression.
Conclusions: CIM appears to be a promising strategy to improve liver lipids metabolism and is beneficial to hepatic steatosis and fibrosis.

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P-36

Usefulness of cardiology specialist follow up after liver transplant

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Introduction: Major adverse cardiovascular events (MACE) are a leading cause of mortality following liver transplantation (LT), and the age of LT recipients is progressively increasing. As a consequence, pre-transplant cardiological evaluations have become more thorough; however, less attention has been given to identifying the most effective cardiac monitoring protocol post-LT.
Aim: The aim of this study is to evaluate the diagnostic and therapeutic value of specialised cardiovascular assessments following LT, and to identify the most common diagnoses and therapeutic interventions they facilitate.
Materials and Methods: We retrospectively analysed the medical records of all deceased LT recipients referred to our non-transplant centre. The total number of post-LT specialised cardiology consultations was recorded, and each visit was classified as either diagnostic or therapeutic. The incidence of MACE and causes of death were also assessed.
Results: A total of 48 patients were included in the study, who underwent 194 specialised cardiology consultations, with a mean of 4.04 visits per patient over a median overall survival after LT of 8.39 years. Three patients experienced a MACE (**Table 1**), but none died from cardiovascular disease. Ten out of 194 cardiologic visits were diagnostic, with the most frequent diagnoses being arterial hypertension or hypertensive cardiopathy (6/10), and valvular disease (4/10). Cardiologists prescribed or adjusted medications in 18 visits, 17 of which involved antihypertensive therapy.
Conclusions: Specialised cardiology follow-up should be personalized and both general practitioners and hepatologists should provide vigilant management of antihypertensive therapy.

Patient	Cardiology consultations	Diagnostic cardiology consultations	Diagnoses at cardiology consultation	Therapeutic cardiology consultations	New or modified cardiovascular medication at cardiology consultation	MACE	Survival after LT (years)
#1	8	1	Valvulopathy; hypertensive cardiopathy	0	None	Stroke	8
#2	0	0	None	0	None	Stroke	4
#3	13	2	Valvulopathy; hypertensive cardiopathy	1	Change of anti-hypertensive drug	Stroke	25

Table 1 *Characteristics of patients who suffered a major cardiovascular event. Abbreviations: MACE = major cardiovascular event; LT = liver transplantation*

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P-37

Wilson disease: presentation, clinical course and complications in a large cohort of patients attending San Paolo Hospital of Milan

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Wilson disease (WD) is a rare hereditary illness characterised by pathological copper accumulation due to mutation in ATPTB, a gene that transcribes a protein involved in copper metabolism.

The present study aimed to describe the clinical course and treatment strategies in a cohort of 193 patients (100 M, 93 F) suffering from WD, followed in our center between 1972 and 2023. The mean follow-up time was 12 years (from 0 to 49 years).

Patients were classified according to presentation: investigations for familiarity with WD (IFW – 17%), hepatological involvement (HEP – 56%), neuropsychiatric presentation (NP – 22%) and mixed presentation (HNP – 5%), with neuropsychiatric symptoms associated with hepatological alterations.

The mean age at the onset of disease was 18.5 (±14) years. Patients in the HEP group were the youngest at the time of presentation, with a mean age of 14.7 years, in comparison to the NP group (22 years - *p value=0,001)* and HNP group (38.5 years - *p value=0,0007*).

In the study population, liver cirrhosis was present in a relevant percentage of subjects at the time of presentation (44%). Interestingly, the frequency of liver cirrhosis was elevated even in patients diagnosed after investigations for familiarity (IFW) representing the 42% of patients of this group.

Among patients with cirrhosis, one third experienced at least one major complication including ascites, variceal bleeding, hepatic encephalopathy and hepatobiliary neoplasms during follow-up.

Regarding survival, within our cohort, 8 patients performed liver transplantation, while 9 died during the observation period, 5 from causes related to WD, of which 2 because of hepatobiliary neoplasms.

Regarding treatment strategies, D-Penicillamine was the most chosen drug, mostly as first line therapy. The second most used was zinc, mainly as second line therapy in patients intolerant to D-penicillamine or as maintenance therapy. Trientine, recently available in Italy, have had a more limited use.

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P-38

Quantitative morphometric analysis via artificial intelligence-driven image analysis in autoimmune hepatitis: a multi-center study

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Introduction: Clinical-pathological correlations in autoimmune hepatitis (AIH) remain challenging due to significant variability in clinical and pathological presentations and diverse subtypes.
Aim: This study employed computer vision on digital slides to derive quantitative morphometric parameters, aiming to improve diagnostic accuracy and strengthen correlations with clinical markers.
Materials and Methods: Clinical data and hematoxylin and eosin (H&E)-stained histological slides from diagnosis were collected from two Italian and one German tertiary referral centers. Images were processed with tissue and portal tract segmentation, and a nucleus classifier to differentiate hepatocytes and inflammatory cells. For each case, ten morphometric parameters, six classical histological metrics (mhAI and Ishak fibrosis scores), and over fifty clinical parameters were analyzed (Figure).
Results: The study includes a cohort of 128 patients with confirmed AIH; mean age at diagnosis was 54±17 years, with 66% females. After feature selection, the following morphometric parameters were prioritized for clinico-pathological correlations: 'inflammatory cell-to-hepatocyte ratio', 'mean distance between inflammatory cells', 'functional liver area' and 'cell density in portal tracts'. The 'inflammatory cell-to-hepatocyte ratio' in the lobule ($p<0.01$) and the 'mean distance between inflammatory cells' ($p<0.01$) showed strong correlations with mhAI score. When compared to traditional histological mHAI and Ishak Fibrosis scores, morphometric parameters demonstrated stronger correlations with AST and ALT levels in multiple linear regression. Patients with higher values of AST and ALT at diagnosis showed significantly higher values of 'inflammatory cell-to-hepatocyte ratio' ($p<0.001$) and lower values of 'mean distance between inflammatory cells' ($p=0.02$). The 'functional liver area' and 'cell density in portal tracts' were higher in patients with lower platelets ($p<0.01$ and $p=0.01$, respectively).
Conclusions: Artificial intelligence-driven image analysis enables more reproducible quantification of histological parameters and enhances the correlation with clinical findings, complementing existing semi-quantitative scoring systems.

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P-39

Characterization of a cohort of liver transplant patients for HBV and/or HBV/HDV related complications: results of a Campania multicenter study

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Introduction: Liver transplantation is a life-saving treatment option for patients with complications related to HBV and/or HBV/HDV-related liver disease.
Methods: A multicenter retrospective study was conducted including 5 infectious disease or hepatology units in Campania. Patients receiving liver transplants for HBV and/or HBV/HDV-related complications were enrolled in post-transplant follow-up from 1 to a maximum of 20 years. The characteristics of patients with monoinfection were compared with those of HBV/HDV coinfected patients.
Results: We enrolled 233 patients, 109 of whom had confirmed HVB/HDV coinfection. Patients were predominantly male (76.4%), with a median age of 56 years, of whom 9.6% were HCVAb positive and 0.7% HIVAb positive; the median years of liver transplantation was 8 years. 64.5% of patients had a diagnosis of HCC at the time of transplantation. The comparison between the subjects transplanted for HBV and HBV/HDV did not show statistically significant epidemiological and demographic differences (table 1). During follow-up, 31.6% of patients had a clinical event: 6.4% liver-related and 27.8% not liver-related. Renal failure (20.9%) and cancer (12.85%) were the most frequent new-onset clinical events, with similar incidence between HBV patients and those with HBV/HDV coinfection (table 2). Patients in whom an adverse clinical event occurred were mostly men (79.7%, n.s.) (table 3). Only 4.2% of patients died during follow-up and of these only one death was related to a hepatic event (table 2). Comparing the characteristics (Table 4): they were all men (100% vs 75.3%; $p=0.122$), they had been transplanted for longer (16 years vs 8; $p=0.059$), 50% had been transplanted before 2010 and 50% of them were HDV coinfected (50%vs62.7%;$p=0.674$).
Conclusions: our study highlights a good outcome during follow-up and does not show different clinical evolution between liver

transplant patients for HBV monoinfection and HBV/HDV coinfection.

Table 1

	Total HBV pts	Only HBV pts	Only HBV/HDV pts	p
Total patients observed	233	66	109	
Gender M n° (%)	178(76,4%)	50 (75,8%)	74 (67,9%)	0,267
Age at transplant Median and range	56 (50;62)	57 (50;63)	55(50;60)	0,294
No° (%)* patients with				
- IVDA	15 (6,7%)	4(6,3%)	9 (8,5%)	0,416
- Ethyl abuse	31 (13,8%)	13 (20%)	13 (12,4%)	0,180
- Familiarity with HbsAg	71(41,5%)	21 (36,2%)	29(36,7%)	0,952
Years of transplant Median (range)	8(4;12)	8 (5;17)	7 (4;10)	0,126
No° (%) transplant patients				0,005
- <2010	45 (19,4%)	21 (31,85)	14 (12,8%)	
- 2010-2015	61 (26,3%)	8 (12,1%)	32 (29,4%)	
- 2015-2020	87(37,5%)	25 (37,9%)	42 (38,5%)	
- >2020	39(16,8%)	12 (18,2%)	21 (19,3%)	
Transplanted for				
- Cirrhosis n (%)	176 (97,2%)	45 (91,8%)	90 (98,9%)	0,051
- HCC n (%)	109 (64,5%)	31 (64,6%)	50 (57,5%)	0,419
No° (%)/ tested* transplant patients				
- with NUC	151/151(100%)	34/34(100%)	75/75 (100%)	0,052
- HBV DNA neg	69/91(75,8%)	30/40 (75%)	37/49 (75,5%)	0,956
- HDV RNA pos	6/10(60%)	0/3 (0%)	6/7 (85,7%)	0,033
- Anti-HCV	22/228 (9,6%)	4/65 (6,2%)	10/107(9,3%)	0,458
- Anti-HIV	1/145(0,7%)	0/66 (0%)	1/77 (1,3%)	1
No° (%)/ tested* transplant patients				
- With diabetes mellitus	36/156(23,1%)	8/49(16,3%)	18/82 (22%)	0,435
- CKD	14/154 (9,1%)	2/49 (4,1%)	6/81 (7,4%)	0,709
- Heart disease	13/160 (8,1%)	2/49 (4,1%)	2/82 (2,4%)	0,630
- Cancer	16/161 (9,9%)	1/49 (2%)	11/82 (13,4%)	0,031
- Psychiatric pathology	15/145 (10,3%)	0/48 (0%)	13/76 (17,1%)	0,002

Table 2: Post-transplant follow-up events in enrolled patients, by HDV status.

	Total HBV pts	Only HBV pts	Only HBV/HDV pts	p
N° (%)patients with at least one hepatic event (cirrhosis, HCC, HBV relapse, decompensation)	15 (6,4%)	4 (6,1%)	6 (5,5%)	1
N° (%)patients with at least one hepatic event				0,444
- In the first 5 years after transplant	10(71,4%)	4 (100%)	3 (60%)	
- From the 6th to the 10th year post transplant	3(21,4%)		2 (40%)	
- After the 10th year post transplant	1(7,1%)			
N° (%)patients with at least one extra-hepatic event (renal failure, new onset neoplasm)	65(27,8%)	22 (33,3%)	22 (20,2%)	0,52
N° (%) patients with at least one extra-hepatic event				1
- In the first 5 years after transplant	57(87,7%)	20 (90,9%)	20 (90,9%)	
- From the 6th to the 10th year post transplant	7 (10,8%)	2 (9,1%)	2(9,1%)	
- After the 10th year post transplant	1 (1,5%)			
N° (%)patients with at least one clinical event (hepatic or extra-hepatic)	74(31,6%)	25 (37,9%)	27 (24,8%)	0,066
N° (%)patients with at least one clinical event				0,668
- In the first 5 years after transplant	63(86,3%)	23 (92%)	22 (84,6%)	
- From the 6th to the 10th year post transplant	9(12,3%)	2 (8%)	4 (15,4%)	
- After the 10th year post transplant	1(1,4%)			
N° (%) patients with				
- HBV relapse	4 (1,7%)	2 (3%)	1 (0,9%)	0,558
- HCC	5 (2,1%)	2 (3%)	1 (0,9%)	0,558
- cirrhosis	6 (2,6%)	1 (1,5%)	2 (1,8%)	1
- hepatic decompensation	3 (1,3%)	0 (0%)	2 (1,8%)	0,527
- renal failure	49(20,9%)	17 (25,8%)	16 (14,7%)	0,069
- new onset cancer	30(12,8%)	10 (15,2%)	9 (8,3%)	0,155
N° (%) patients with				
- death related to hepatic event	1(0,4%)	0 (0%)	0 (0%)	0,674
- death not related to hepatic event	9(3,8%)	3 (4,5%)	3 (2,8%)	
- overall deaths	10(4,2%)	3 (4,5%)	3 (2,8%)	0,674
N° (%)patients with liver-related death				
- In the first 5 years after transplant	1 (100%)			
- From the 6th to the 10th year post transplant				
- After the 10th year post transplant				
N° (%)patients with death not related to hepatic events				0,400
- In the first 5 years after transplant	3 (33,3%)		2 (66,7%)	
- From the 6th to the 10th year post transplant	5 (55,6%)	3 (100%)	1 (33,3%)	
- After the 10th year post transplant	1(11,1%)			
N° (%)patients with overall death				0,400
- In the first 5 years after transplant	4 (40%)		2 (66,7%)	
- From the 6th to the 10th year post transplant	5(50%)	3 (100%)	1 (33,3%)	
- After the 10th year post transplant	1(10%)			

Table 3: demographic, virological and clinical data associated with at least one post-transplant event

	Patients with clinical event	Patients without clinical event	p
Gender M n° (%)	59 (79,7%)	119 (74,8%)	0,413
Age at transplant Median and range	58 (52;63)	56 (50;61)	0,094
Median years of transplant (range)	8 (5;11)	8 (4;12)	0,458
No. (%) of transplanted patients			0,545
- <2010	11 (14,9%)	34 (21,5%)	
- 2010-2015	21 (28,4%)	40 (25,3%)	
- 2015-2020	31 (41,9%)	56 (35,4%)	
- >2020	11 (14,9%)	28 (17,7%)	
Transplanted for			
- Cirrhosis n (%)	64 (98,5%)	112 (96,6%)	0,656
- HCC n (%)	43 (70,5%)	66 (61,1%)	0,221
Coinfection, n° (%)			
- HDV	27 (51,9%)	82 (66,7%)	0,066
- HCV	6 (8,2%)	16 (10,3%)	0,616
- HIV	0 (0%)	1 (1,1%)	1
Comorbidities at the time of transplant no° (%)			
- diabetes mellitus	18 (30%)	18 (18,8%)	0,105
- IRC	11 (18,3%)	3 (3,2%)	0,001
- Heart disease	7 (11,3%)	6 (6,1%)	0,244
- Cancer	4 (6,3%)	12 (12,2%)	0,222
- Psychiatric pathology	5 (9,1%)	10 (11,1%)	0,698
At least 1 year history of immunosuppressive medication , no° (%)			0,736
- Ciclosporina	5 (7%)	8 (5,3%)	
- Tacrolimus	20 (28,2%)	49(32,7%)	
- Micofenolato	2 (2,8%)	4 (2,7%)	
- Everolimus	10 (14,1%)	23 (15,3%)	
- Association therapies	34 (47,9%)	61 (40,7%)	
History of at least 1 year of anti-HBV therapy with NUC, n° (%)			0,447
-Lamivudina	9 (13,6%)	28 (20,9%)	
-Entecavir	44 (66,7%)	85 (63,4%)	

-Tenofovir	12 (18,3%)	20 (14,95)	
-others	1 (1,5%)	1 (0,7%)	
History of at least 1 year of administration of anti-HBs immunoglobulin, n° (%)			0,793
-ev			
- intramuscular	3 (4,8%)	8 (5,6%)	
-sc	37(59,7%)	78 (54,5%)	
	22 (35,5%)	57 (39,9%)	

Table 4: demographic, virological and clinical data associated with overall mortality

	Deceased patients	Non-deceased patients	p
- Gender M n° (%)	10 (100%)	168 (75,3%)	0,122
Age at transplant Median and range	58(50;65)	56(50;61)	0,742
Median years of transplant (range)	16(6;19)	8(4;11)	0,059
No. (%) of transplanted patients			0,088
- <2010	5 (50%)	40 (18%)	
- 2010-2015	1 (10%)	60 (27%)	
- 2015-2020	3(30%)	84 (37,8%)	
- >2020	1(10%)	38 (17,1%)	
Transplanted for			
- Cirrhosis n (%)	6(100%)	170 (97,1%)	1
- HCC n (%)	5 (100%)	104 (63,4%)	0,162
Coinfection, n° (%)			
- HDV	3 (50%)	106 (62,7%)	0,674
- HCV	0 (0%)	22(10,1%)	0,604
- HIV	0(0%)	1(0,7%)	1
Comorbidities at the time of transplant no° (%)			0,574
- diabetes mellitus	0(0%)	36 (23,7%)	1
- - IRC	0(0%)	14 (9,3%)	1
- - Heart disease	0(0%)	13 (8,3%)	0,050
- - Neoplasm	2 (2%)	14 (8,9%)	1
- - Psychiatric pathology	0 (0%)	15 (10,6%)	
At least 1 year history of immunosuppressive medication , no° (%)			0,185
- Ciclosporina	0(0%)	13 (6,1%)	
- Tacrolimus	3(33,3%)	66 (31,1%)	
- Micofenolato	1(11,1%)	5 (2,4%)	
- Everolimus	2 (22,2%)	31 (14,6%)	
- Association therapies	2(22,2%)	93 (43,9%)	

History of at least 1 year of anti-HBV therapy with NUC, n° (%)			0,006
-Lamivudina	2 (28,6%)	35 (18,1%)	
-Entecavir	4 (57,1%)	125 (64,8%)	
-Tenofovir	0 (0%)	32 (16,6%)	
-others	1 (14,3%)	1 (0,5%)	
History of at least 1 year of administration of anti-HBs immunoglobulin, n° (%)			0,009
-ev			
-intramuscular	2 (22,2%)	9(4,6%)	
-sc	7 (77,8%)	108(55,1%)	
	0 (0%)	79(40,3%)	

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P-40

AI-based estimation of cardiovascular risk in MASLD patients using non-contrast CT imaging and clinical data

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Introduction: Accurate cardiovascular risk (CVR) assessment is crucial for apparently healthy individuals. Metabolic-dysfunction associated steatotic liver disease (MASLD), formerly NAFLD, affects 38% of the population worldwide and the cardiovascular diseases (CVD) represent the primary cause of death in these patients, suggesting that MASLD could be considered as an independent risk factor for a novel CVR assessment score.
Aim: our study aims at modelling non-contrast Cardio-CT scans and clinical data with artificial intelligence (AI) approaches to develop a predictive model for CVR assessment in MASLD.
Materials and Methods, Results: A retrospective study analyzed clinical and imaging data from 174 patients who underwent Cardio-CT in S.Salvatore Hospital in L'Aquila and S.Pertini Hospital in Rome. Based on Coronary Artery Calcium (CAC) scores and Hunsfield units (HU), 50% of patients were affected by MASLD and CVD, the rest of patients were healthy controls. 96 Patients were enlisted for training and 78 for the internal validation cohort to obtain performance metrics.

A U-Net convolutional neural network was used to segment liver parenchyma, and a Gray-Level Co-occurrence Matrix (GLCM) was applied to extract radiomic features and evaluate levels of steatosis. The relevant features were combined with clinical data and used as input into a multilayer perceptron neural network to perform binary classification of CAC.
Results: Our trained algorithm automatically defines the severity of CAC, based on liver steatosis and patient clinical data, thereby assessing the level of CVR. Notably, the related important features were represented by dyslipidemia, diabetes and age. By testing images and clinical data from both centers, the most performing model was the Stacking Model achieving an AUC of 80%.
Conclusion: Our AI model estimates CVR in MASLD patients undergoing abdominal CT, integrating radiomic and clinical data, it could be useful also for cirrhotic patients undergoing HCC screening or awaiting OLT.

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P-41

One-year efficacy and safety of tacrolimus in chronic autoimmune hepatitis

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Introduction: Treatment of Autoimmune hepatitis (AIH) in patients difficult-to-treat or intolerant to standard of care (SOC) can include Tacrolimus (TAC) but evidence on its efficacy and safety is still limited.
Aim: To evaluate the efficacy and safety of TAC in difficult-to-treat and intolerant AIH patients.

Materials and Methods: Patients with AIH followed at Fondazione IRCCS San Gerardo dei Tintori, Monza, for 12 months of follow-up since initiating TAC were included in the study. Biochemical parameters (AST, ALT, GGT, bilirubin, albumin, IgG) were monitored at treatment initiation and during follow-up at 1, 3, 6, and 12 months.
Results: Twenty-seven AIH patients, 22 refractory and five intolerant to SOC, were included. Median age was 46 years (IQR 37, 57), with 63% female. Regarding ethnicity, 23 were Caucasian, three patients were Hispanic and one was Asian. The median bilirubin at enrollment was 0.73 (0.60, 1.39) times the upper limit of normal (ULN), median albumin was 3.71 mg/dl and median gamma globulins were 1.02 (0.72, 1.62). After 12 months of TAC therapy, a significant reduction in AST levels (from 1.8 to 0.8 times ULN) and ALT levels (from 2.5 to 0.7 times ULN) was observed, with the greatest improvements occurring within the first three months. In the 22 refractory cases, AST levels declined from 2.4 times ULN to 0.9 times ULN, and ALT levels declined from 2.7 x ULN to 0.8 times ULN. Adverse events were observed in 67% of patients. Nine patients experienced an infection, one died due to pneumonia. Four patients experienced arthralgias and three experienced headache. Tacrolimus was never discontinued due to adverse events.
Conclusion: TAC can be a viable therapy for AIH patients non-responders or intolerant to the standard of care in the chronic setting, significantly improving biochemical markers within 12 months. Side effects are frequent and require monitoring. Multicenter studies are needed.

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P-42

The use of Controlled Attenuation Parameter for the assessment of treatment response in patients with Metabolic Dysfunction-Associated Steatotic Liver Disease undergoing a lifestyle intervention program

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Introduction: Non-invasive biomarkers for the assessment of treatment response are highly needed in the clinical setting for Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD).
Aim: This study evaluates the role of Controlled Attenuation Parameter (CAP) by Vibration-Controlled Transient Elastography and PNPLA3 gene variants for the assessment of weight loss and BMI reduction in MASLD patients undergoing a 6-month dietary intervention.
Materials and Methods: 94 MASLD patients were randomly assigned to 3 arms: Mediterranean Diet (MD), Low-Charb Diet (LCD), and Control Diet (CD). Inclusion criteria were BMI 26-35 kg/m², CAP≥248 dB/m, Liver Stiffness Measurement (LSM)<12 kPa. Primary endpoints was ≥7% weight loss. Clinical/biochemical parameters and VCTE were assessment at baseline and after 6 months.
Results: Median age was 50.5 [IQR 43.0-61.0] years and 71.3% was male. Type 2 diabetes (T2D) was present in 17% of cases and PNPLA3 GG was present in 19.1% of cases. After 6 months, 28.7% of patients achieved ≥7% weight loss, with the highest proportion in LCD group (36.2%). In all patients achieving weight loss, CAP significantly decreased (from median 294 to median 246 dB/m, p<0.0001), as compared to CAP changes that were observed in those who did not achieve weight loss (inter-group p-value=0.001). Delta CAP values were higher in LCD group (p=0.040). A stepwise increase in the delta CAP values was observed across incremental weight loss categories (<5%, 5-10%,>10%) (p=0.02). In patients achieving≥7% weight loss, delta CAP values were higher in patients with CC/CG genotype (p=0.0004), as compared to GG carriers (p=0.79).
Conclusions: In patients with MASLD undergoing lifestyle intervention, weight loss≥7% was associated with significant decreases in CAP values. PNPLA3 genotyping may be useful for further patient stratification.

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P-43

The association between non-invasive tests of liver fibrosis and early diastolic dysfunction in patients with Metabolic Dysfunction-Associated Steatotic Liver Disease

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Introduction: Metabolic dysfunction-Associated Steatotic Liver Disease (MASLD) may contribute to cardiac impairment through diastolic dysfunction. Non-invasive tests (NITs) for liver fibrosis offer valuable tools for risk stratification, though their utility in identifying patients with early or established diastolic dysfunction remains uncertain.
Aim: Identify the association between liver NITs (FIB-4 and liver stiffness measurement [LSM]) and echocardiographic markers of diastolic dysfunction.
Materials and Methods Results: We prospectively enrolled 150 MASLD patients without cardiovascular disease history. All patients underwent clinical-biochemical evaluation, vibration-controlled transient elastography for LSM, echocardiography with speckle tracking analysis. Significant fibrosis was defined by FIB-4 >1.3 or LSM ≥7 kPa. Diastolic dysfunction was defined by mitral E/E' ratio >9, while early diastolic dysfunction was defined by left atrial strain reservoir (LARS) (<22%) and left atrial stiffness index (LASi) ≥25 kPa. Pericardial fat was also assessed.

Increased FIB-4 was found in 23,3% patients (median age 62) with prevalence of type 2 diabetes (T2DM), hypertension and dyslipidemia respectively at 20%, 74,3%, 62,9%. For low FIB-4 group (median age 49), prevalences were 15%, 36,5%, 55,7%. Obesity overall was 43,9%. Compared to patients with low FIB-4, those with FIB-4 >1.3 had increased E/E' ratio, LASI and pericardial fat (respectively median 8.0 [6,0 – 9,2], p =0.007; 0.34 kPa [0,20 - 0,42], p <0.0001; 12.5 mm [8,5 – 17,2], p <0.0001), and had reduced LARS (26.5% [19,0 – 33,0], p <0.0001). In a 3 model multivariable regression analysis, FIB-4 >1.3 was independently associated with diastolic dysfunction (aOR 3.41 [1.08 – 10.74]) and early diastolic dysfunction (aOR for reduced LARS 10.03 [2.01 – 49.8]; aOR for reduced LASi 4.24 [1.16 – 15.5]). Finally, FIB-4 displayed Area Under the Curve (AUC) of 0.83 for the prediction of reduced LARS.
Conclusion: In MASLD patients without cardiac disease, FIB-4 may be useful to identify a higher risk with early cardiac dysfunction, suggesting tailored echocardiography surveillance

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P-44

Incidence of clinical outcomes in patients with MASLD and long-term follow up: results from a single center cohort study

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Introduction: The natural history of MASLD results from environmental and genetic factors, impacting hepatic and extrahepatic outcomes. This study aims to elucidate the incidence of clinical outcomes, and the impact of non-invasive tests (NITs) and genetic factors.

Materials and methods: A retrospective study was conducted on patients undergoing vibration-controlled transient elastography (VCTE) for liver stiffness measurement (LSM), with at least 6 months follow-up. Other etiologies than MASLD, previous decompensation or hepatocarcinoma (HCC) were excluded. Significant liver fibrosis was defined by LSM≥8 Kpa, clinically significant portal hypertension (CSPH) by LSM≥25 Kpa. Primary endpoints included incidence of major adverse liver outcomes (MALOs): cirrhosis, liver decompensation (ascites, encephalopathy, variceal bleeding), HCC and liver transplant.

Results: 504 patients were selected (61.7% males, median age 59 years [IQR 50.0-67.0]), with a median follow-up of 45.5 months [9.5-94.5]. Median LSM was 6.4 Kpa [5.0-9.0], 21% had PNPLA3 GG. Overall, 11.3% experienced MALOs (33.3% liver decompensation), 2.6% died (46.2% liver-related events). Significant fibrosis increased MALOs incidence (log rank p<0.0001, HR14.4, 95%CI 5.5-13.3). CSPH raised liver decompensation occurrence (p=0.007, HR 6.1, 95%CI 3.3-22.4). Type 2 diabetes (T2D) and PNPLA3 GG increased MALOs incidence (p<0.001, HR 3.8, 95%CI 2.03-6.2; p=0.004, HR 2.3, 95%CI 1.38-5.61). Obese/overweight patients had higher MALOs incidence than lean individuals (p=0.008, HR 2.67, 95% Cl 1.31-3.94). Multivariable Cox regression analysis showed that significant fibrosis by LSM was independently associated with MALOs (aHR 18.5, p<0.0001, 95%Cl 5.65-60.7).

Conclusions: Overweight/obesity and T2D increase incidence of MALOs. LSM by VCTE and PNPLA3 genotyping are useful tools for risk stratification.

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P-45

Perception and management of liver enzymes abnormalities among IBD specialists: Insights from an IG-IBD survey

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Liver diseases are common in patients with Inflammatory Bowel Diseases (IBD). Despite their burden, little is known about how specialists perceive and manage liver enzyme abnormalities. This study investigates current practices, challenges, and educational needs of IBD specialists in the management of liver enzyme abnormalities.

A 22-question web-based survey was distributed to IG-IBD member physicians, covering their demographics, workplace features and approach to managing liver enzyme abnormalities in

The survey was completed by 205/439 (46.7%) participants. The majority of respondents were over 45 years old (39%) and worked in Northern Italy (62%). Most were gastroenterologists (86%) working in public community hospitals (46%), with only 21% having a dedicated Liver Unit with a clear referral pathway for IBD patients. Forty-eight percent of physicians reported regular monitoring of liver enzymes such as AST and ALT at each visit, while 41% similarly monitored GGT and 28% monitored ALP (with 24% monitoring it only in the presence of signs of liver disease). In the case of abnormal liver enzymes, over 70% chose to order additional tests independently. The conditions considered most likely in case of mild transaminase elevations were metabolic dysfunction-associated steatotic liver disease (MASLD) (71%) and drug-induced liver injury (DILI) (17%). The least likely diagnosis was porto-sinusoidal vascular disorder (PSVD; 58%). Routine upper abdominal ultrasound was performed only by 50% of physicians. A significant proportion of physicians (57%) reported that their training in the management of liver enzyme abnormalities was adequate, but they would benefit from additional education. The main barriers identified were a lack of specific guideline (62%) and limited access to tools for in-depth diagnosis (52%).

This survey reveals heterogeneity in monitoring and management of liver enzyme abnormalities among IBD specialists. Most physicians recognize the need for improved training and guidelines.

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P-46

Dynopenia predicts mortality in patients with liver cirrhosis and hepatocellular carcinoma

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Introduction: Sarcopenia is a common complication in patients with liver cirrhosis and hepatocellular carcinoma (HCC). Traditionally, its diagnosis has been based on the assessment of muscle

mass. However, recent advances in geriatric research have led to a paradigm shift, identifying low muscle strength as the primary determinant of negative outcomes in sarcopenia. However, few studies have thoroughly investigated the clinical impact of muscle strength.
Aim: The aim of this study was to evaluate the role of dynopenia (reduced muscle strength) compared with reduced muscle mass in predicting mortality among patients with liver cirrhosis and HCC.
Materials and Methods: The study included consecutive adult outpatients attending the Hepatology Unit of the Fondazione Policlinico Campus Bio-Medico of Rome. Muscle mass was assessed by bioimpedance analysis (appendicular skeletal muscle mass calculated according to the Sergi equation -EWGSOP 2019) and ultrasound (quadriceps mean compression and feather index; iliopsoas area and thickness; and diaphragm thickness). Muscle strength was assessed using handgrip dynamometry, following the recommendations of the EWGSOP 2019 (< 27 kg for men and < 16 kg for women). Diaphragmatic excursion was assessed with ultrasound and considered a proxy of low muscle strength. The associations between sarcopenia proxies and 24-month all-cause mortality were evaluated using both crude and adjusted Cox regression models. Survival was estimated through Kaplan–Meier estimates, and survival curves were compared using the log-rank test.
Results: A total of 65 patients were included in the analysis [mean age 72.9 years (SD 7.5), 78% male, mean BMI 27 kg/m^2 (SD 5.2)]. Viral cirrhosis represented the most common aetiology (42%), with 80% of patients classified as Child-Pugh class A. Active HCC was observed in 68% of patients, most of whom were classified as BCLC stage A or B (73%). Dynopenia was the only factor independently associated with 24-month mortality [aHR 1.96(1.15-3.35), p=0.014] after correction for age, gender and MELD. Diaphragmatic excursion showed a trend towards significance [HR 0.48 (0.22-1.04), p=0.06]. Conversely, none of the muscle mass indices showed an association with all-cause mortality. Finally, Kaplan–Meier analysis (Figure 1) showed a significantly reduced survival in patients with dynopenia compared to those without (log-rank test p=0.0068).
Conclusions: Dynopenia has emerged as a key prognostic determinant in cirrhotic patients with HCC, particularly in the earlier stages of the disease. In our small cohort, it was identified as the only muscle-related parameter significantly associated with mortality. If validated in larger, independent cohorts, dynopenia could serve as a robust early marker to identify patients at higher risk of poor outcomes.

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P-47

Automatic generation of learning material for residential students in Emergency Departments (ED): evaluation of AI-generated flashcards for supporting medical management of gastrointestinal emergencies

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Introduction: In Emergency Departments (ED) gastrointestinal emergencies represent daily challenges for physicians. Given this, a proper formation and support are crucial for ED residents. Flashcards are a valuable tool in medical education, helping memory and supporting learning. Large Language Models (LLMs), like those developed by OpenAI, are becoming promising tools for automating content generation in medical education and clinical practice.
Aim: The objective of the study is to generate LLMs-based flashcards with content related to gastrointestinal emergencies and evaluate the corresponding quality and reliability.
Materials and Methods: A medical team manually elaborated flashcard content based on current clinical guidelines. Then, a multidisciplinary team of both physicians and informaticians, used Open AI platform for developing prompt engineering process aimed at the creation of automatically generated flashcards. The obtained content was iteratively reviewed, and the prompt was refined to obtain comprehensive, correct content updated with the latest guidelines. Eventually, the comparison between the manually curated and AI-generated flashcards was performed using dedicated measures (cosine similarity, Word Mover's Distance (WMD) and Likert scales).
Results: AI-generated flashcards showed high semantic similarity with those manually curated (cosine similarity=0.86, CI 0.84-0.87; WMD=0.13, CI 0.12-0.14) and also high values for clarity (4.86/5, CI 4.79-4.93), correctness (4.84/5, CI 4.77-4.91) and relevance (4.82/5, CI 4.74-4.90) in clinical evaluation phase. Informativeness was lower (4.42/5, CI 4.30-3.55). In fact, some discrepancies were found in differential diagnoses, instrumental tests and reliance on outdated guidelines.
Conclusions: LLM-based approach enabled a rapid and accurate generation of content, supporting physicians in understanding and managing gastrointestinal emergencies. Human intervention remains crucial to improve informativeness of the LLMs generated content. Using an app, we will test flashcards in a multicenter study involving over 200 Italian ED residents to obtain a feedback useful for enhancing the AI pipeline and obtain an improved content.

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P-48

Large Language Model Agent-Based Framework for automated Treatment Prescription in Patients with Chronic Hepatitis C Virus Infection

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Background: Large Language Models (LLMs) may be useful for clinical tasks that require reasoning over different information sources. LLMs could be regarded as intelligent "agents" with internal planning abilities, enabling them to engage in multi-step reasoning and interact with other agents or external users. Hepatitis C Virus (HCV) management is a potential area where LLM-enabled agents could be useful, since treatment decisions require consideration of genotype, treatment history, liver fibrosis extent, and drug-drug interactions.
Aim: To evaluate the performance of different LLM agent-based configurations in automating HCV treatment decisions and to determine whether specialized multi-agent architectures improve prescription accuracy compared to single-agent approaches.
Material and Methods: We developed 50 clinical cases focusing on therapeutic regimen prescription. Cases included genotype, prior

treatment history, fibrosis status, and concurrent medications. We compared multiple configurations using OpenAI's GPT-3.5 and GPT-4o, fine-tuned with HCV treatment guidelines. Different agent architectures were tested: single agent (one LLM extracting all data), multi-agent (three specialized LLMs for data extraction plus prescriber), and specialized multi-agent (four specialized extraction agents plus prescriber). Each agent accessed specific guideline sections relevant to its task. Performance was compared to baseline fine-tuned models.
Results: Using GPT-3.5, the baseline model achieved 24% prescription accuracy. The single agent configuration reached 50% ($p=0.007$), multi-agent 76% ($p<0.001$), and specialized multi-agent 89% ($p<0.001$). With GPT-4, performance improved significantly: baseline 35% accuracy, single agent 65% ($p=0.005$), multi-agent 88% ($p<0.001$), and specialized multi-agent 94% ($p<0.001$).
Conclusions: Specialized multi-agent LLM frameworks significantly improve HCV treatment recommendation accuracy, with GPT-4 showing superior performance. The agent-based approach demonstrates the potential for complex clinical decision-making. Future work should validate these findings in real-world settings and explore integration with clinical decision-support systems.

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P-49

Treatment of portal hypertension through transjugular intrahepatic portosystemic shunt (TIPS) in patients with porto-sinusoidal vascular disease (PSVD)

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Introduction: Porto sinusoidal vascular disease (PSVD) defines a vascular liver disease (VLD) with specific histological lesions in absence of cirrhosis, complicated by portal hypertension (PH). The management of PH complications aligns with the guidelines of cirrhosis. Data on the use of transjugular intrahepatic portosystemic shunt (TIPS) in PSVD are scant.
Aim: To evaluate the effect of TIPS in treating PH complications in patients with PSVD and difference between patients with PSVD and cirrhosis.
Methods: We conduct a retrospective study on patients with TIPS placed at out institution between February 2016 and August 2023. Patients with VLD qualified as PSVD were included and subsequently matched (1:2) with a control group of patients with cirrhosis.
Results: 22 patients were included (68 % male, mean age 50 years). Portal vein thrombosis (PVT) was present in 20 patients (90.9%), being the most frequent indication to TIPS (19, 86.4%), followed by variceal bleeding (9, 40.9%). Liver-related events occurred in 8 patients (36.4%). Univariate analysis showed higher albumin levels associated with better prognosis (HR 0.15, CI 0.02-0.96, $p=0.044$), as well as the use of anticoagulant therapy pre-TIPS (HR 0.16, CI 0.03-0.85, $p=0.032$), but only albumin was confirmed at the multivariable analysis (HR 0.15, CI 0.02-0.955, $p=0.044$). When comparing the PSVD group with the matched cohort of cirrhotic patients, we observed higher incidence of immediate post-TIPS complications (10 vs. 7 patients, $p=0.01$), while recurrent ascites and hepatocellular carcinoma occurred only in the control group ($p=0.032$ and $p=0.048$, respectively). In the PSVD group, 1-year transplant-free survival rate of 81.8 % and an overall survival rate of 86.4% vs 65.9 and 79.5 % of the control group (log rank not significant).
Conclusions: Despite the complexity of the procedure, TIPS may represent a possible strategy to counteract the complication of PH in patients with PSVD with an excellent survival rate.

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P-50

Portal Vein Recanalization-Transjugular Intrahepatic Portosystemic Shunt (PVR-TIPS) in patients with anatomical portal contraindication to liver transplantation: feasibility and clinical implication

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Introduction: Portal vein thrombosis (PVT) may represent a relative contraindication to liver transplantation (LT). Transjugular intrahepatic portosystemic shunt (TIPS), a procedure intended to treat complications of portal hypertension, may allow portal vein (PV) recanalization (PVR).
Aim: We describe our single-center experience with PVR-TIPS in patients who are clinically candidates for LT but contraindicated because of PV anatomy.
Methods: We included consecutive patients who underwent PVT-TIPS at our center from February 2014 to May 2023. Patients with previous LT or vascular liver disease were excluded. Clinical variables at TIPS placement and LT were collected.
Results: We found 25 patients (19 males [76%], mean age 56 years [IQR 51-62]) in whom PVR-TIPS was offered for considering LT otherwise contraindicated because of PV anatomy. Twelve (48%) patients showed main PV thrombosis (PVT), 8 (32%) had cavernoma and 5 (20%) had PV with very small diameter. The main indication for LT was hepatocellular carcinoma (HCC) (10 patients, 40%), with 8 patients (32%) having active HCC at the time of PVR-TIPS. PVR-TIPS was successfully achieved in all but one patient. Concurrently, 9 patients (38%) underwent endovascular closure of porto-systemic shunts. All patients were listed post-PVR-TIPS with MELD at listing higher than pre-PVR-TIPS MELD (16 ± 3 vs. 21 ± 6, $p<0.001$). Overall, 3 patients (12%) were delisted due to improvement in clinical status, 2 (8%) died on the waiting list, 14 (56%) underwent LT, while 5

(21%) are still on WL. LT was technically feasible with standard PV anastomosis. One patient died 141 days after LT due to endocarditis, while another was successfully retransplanted due to primary graft dysfunction.
Conclusions: PVR-TIPS may be a strategy to allow LT in patients otherwise excluded due to PV anatomy. It requires a high level of technical expertise and is often associated with a deterioration of liver function.

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P-51

Strategies to enhance Natural Killer cell response in Hepatocellular Carcinoma: The role of TGFβ in NK-Cells (dys)function and plasticity

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Introduction: The tumor immune microenvironment (TIME), characterized by elevated transforming growth factor-β (TGF-β) levels, alongside hypoxia and nutrient deprivation, often leads to tumor-infiltrating NK (TINK) cells dysfunction. TGF-β is a key regulator within TIME, influencing NK cell plasticity and functionality. Despite its well-established immunosuppressive effects, the molecular mechanisms underlying TGF-β's impact on NK cells remain incompletely understood, and its role may not be entirely deleterious, reflecting a complex and context-dependent function.
Aim and Methods: This study investigates the impact of TGF-β on TINK subsets, focusing on ILC1-like, CD56Bright CD49a+ and conventional NK (cNK) cells. Given TGF-β's role in driving the phenotypic plasticity of these cells, the activation of both SMAD- and TAK1-dependent TGF-β pathways was evaluated. By analyzing mitochondrial membrane depolarization, DNA damage response, and cytokine production, we seek to elucidate TGF-β's impact on NK-cell functionality.
Results: CD56bright/CD49a+ and ILC1-like (CD103+CD49a+CD9+) NK-cells were enriched in the tumor microenvironment, particularly in viral-related hepatocellular carcinoma (HCC), and nearly absent in the liver. TAK1-dependent TGF-β pathway activation was significantly higher in the tumor compared to the liver, and overall, greater than SMAD-dependent activation with highest levels in ILC1-like cells. CD56Bright CD49a+, ILC1-like and cNK (negative for CD103, CD49a and CD9) exhibited higher H2AX phosphorylation in the tumor compartment and an interesting positive correlation was found between mitochondrial depolarization and both H2AX and TAK1 phosphorylation. Finally, ILC1-like TINKs showed higher TNF-α production than their liver counterpart and tumor infiltrating cNK and opposite behavior for IFN-γ production.
Conclusions: TGF-β impacts NK cell functionality and phenotypic plasticity within the TIME and, particularly through the TAK1 pathway, leads to mitochondrial dysfunction, DNA damage and a shift in cytokine profiles that might aid immune evasion. These findings highlight TGF-β's complex role and suggest targeting its pathway to enhance NK cell function in cancer.

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P-52

Oncostatin M contributes to liver steatosis in experimental conditions of Metabolic dysfuntion - Associated Steatotic Liver Disease

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Introduction: Oncostatin M (OSM), a cytokine belonging to the IL-6 family, has been recently proposed as a pro-inflammatory and profibrogenic mediator involved in the progression of either experimental and clinical conditions of Metabolic dysfunction – Associated Steatotic Liver Disease (MASLD). In this study we provide experimental evidence that OSM in the MASLD scenario can also contribute to hepatocyte accumulation of triglicerydes.
Materials and Methods: In this study we employed mice genetically manipulated to delete OSM β receptor (OSMβR$^{-/-}$ mice) in hepatocyte and related wild type (WT) control littermates fed on a Choline-Devoided, AminoAcid-refined (CDAA) lipogenic diet to develop a murine MASLD-like condition.
Results: Hepatocyte conditional deletion of OSMβR, that abrogates OSM/STAT3-related signaling in hepatocytes, resulted in a significant reduction of liver steatosis in OSMβR$^{-/-}$ mice vs related WT mice fed on CDAA diet, as for morphological analysis and evaluation of liver triglicerydes content. This was accompanied by a number of observations suggesting a correlation of OSM/OSMβR axis and lipid metabolism in hepatocytes, including: i) a reduction of total macrophage infiltration paralled by a significant increase in TREM2+ macrophages as well as in Osteopontin (OPN) expression observed in OSMβR$^{-/-}$ mice vs WT mice; ii) OSMβR$^{-/-}$ mice, as compared to WT mice, were also characterized by a significantly reduced expression of genes involved in the regulation of lipid metabolism, including CD36, carnitine-palmitoyl transferase 1 (Cpt1) and medium-chain acyl-CoA dehydrogenase (MCAD)
Conclusions: These results indicate that the pro-inflammatory and pro-fibrogenic cytokine OSM, by acting on OSMβR expressed by hepatocytes, can also contribute to liver steatosis in a murine condition of dietary induced MASLD.

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Long-term Bulevirtide monotherapy in patients with HDV-related compensated cirrhosis: effectiveness, safety and clinical outcomes from the retrospective multicenter european study (Save-D)

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Background: Bulevirtide (BLV) has been approved by EMA for treatment of compensated chronic hepatitis D virus (HDV) infection, however, long-term real-life effectiveness and safety data in large cohorts of HDV patients with cirrhosis treated beyond week 48 are lacking.
Methods: Consecutive HDV patients with cirrhosis starting BLV 2 mg/day sc since September 2019 were included in a retrospective multicenter real-life European study (SAVE-D). Virological (HDV-RNA undetectable or $\geq$2-log decline *vs.* baseline), biochemical (ALT $<$40 U/L), combined response (biochemical + virological), adverse events and liver-related outcomes were assessed.
Results: 244 patients treated with BLV monotherapy up to 120 weeks [median follow-up: 92 (range 24-120) weeks] were included: age 49 years, 61% men, ALT 80 U/L, LSM 18.3 kPa, platelets $94 \times 10^3/mm^3$, 95% CPT score A, 54% with varices, 10% HIV-positive, 15% with a history of ascites, 6% with active HCC, 92% on NUC. Baseline HDV-RNA and HBsAg levels were 5.4 (4.1-6.5) log IU/mL and 3.8 (3.4-4.1) log IU/mL. Virological, biochemical and combined responses at W48, W96, W120 were 64%, 71%, and 74%, 58%, 63%, 59% and 43%, 51%, 49%, respectively. HDV RNA undetectability was achieved by 27%, 40%, and 41%. Baseline HDV-RNA $<$5 LogIU/mL was the only predictor of HDV-RNA undetectability at week 48. AST, GGT, albumin, IgG and LSM values significantly improved during treatment. Bile acids significantly increased but only 11% of patients reported mild and transient pruritus. The W120 cumulative incidences of de-novo HCC and decompensation were 6.1% (95% CI 3-9%) and 3.3% (95% CI 1-6%), respectively. 18 patients underwent liver transplantation (HCC n=15; decompensation n=3), 8 patients died due to BLV-unrelated causes.

Conclusions: BLV 2 mg/day monotherapy up to 120 weeks was safe and effective in patients with HDV-related cirrhosis. Virological and clinical responses continued to increase and only few patients experienced liver-related complications.

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Autoimmunity in chronic HDV infection: results from the HDV Describe study cohort

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Introduction: Chronic liver disease induced by hepatitis D virus (HDV) infection is associated with autoimmune manifestations.

Aim: The present study investigated the prevalence of autoantibodies (auto-ab) and their association with clinical and virologic features in patients with chronic HDV infection.
Materials and Methods: We studied 494 patients with chronic HDV infection from the HDV Describe study cohort. Non-organ-specific auto-ab (e.g., anti-nuclear auto-ab [ANA], anti-smooth muscle auto-ab [ASMA], anti-mitochondrial auto-ab [AMA], and anti-liver-kidney microsomal auto-ab [LKM]) were tested in diluted serum samples (1:80) by indirect immunofluorescence (IIF) on rat kidney/stomach/liver tissue slides (Euroimmun, Germany). Selected serum samples were analysed by immunoblot (IB) (Euroimmun, Germany) to detect antigen-specific auto-ab.
Results: The prevalence of ANA, ASMA, AMA, and LKM by IIF was 9.9% (n=49), 12.3% (n=61), 2.0% (n=10), and 1.8% (n=9), respectively. Among LKM+ patients, only one patient was LKM-1+ at IB. A high proportion of patients had anti-brush border auto-ab (n=99; 20.0%); 9 patients were anti-parietal cells auto-ab+, 1 was anti-reticulin auto-ab+, and 1 was anti-lysosome auto-ab+. ASMA+ was associated with liver cirrhosis (OR=2.00, 1.08–3.70) and HDV RNA >3 Log IU/mL (OR=1.91, 1.03–3.52), whereas no association was observed between ASMA+ and ALT >40 U/L (OR=1.12, 0.65–1.93). At multivariate analysis, ASMA+ resulted significantly associated with liver cirrhosis (OR=1.89, 1.01–3.51) independently from HDV RNA (OR=1.57, 1.01–2.42) and ALT (OR=1.22, 0.79–1.87).
Conclusion: The assessment of circulating auto-ab by IIF may represent a valuable and inexpensive tool for identifying patients with high HDV replication and advanced liver disease.

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Differential patterns of HBV RNA and HBcrAg levels in a large european cross-sectional study of untreated patients with chronic Hepatitis Delta

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Background and Aim: Serum HBV RNA and HBcrAg levels have been proposed as useful biomarkers in the management of HBV patients, however their role in chronic hepatitis Delta (CHD) is currently unknown.
Methods: Consecutive untreated CHD patients were enrolled in a cross-sectional study in three EU centers. Clinical and virological characteristics were collected. Serum HBV RNA and HBcrAg levels were quantified by an automated real-time investigational assay (Cobas® 6800, Roche Diagnostics, Pleasanton, Ca, USA) and by LUMIPULSE® G HBcrAg assay (Fujirebio Europe), respectively. In 18 patients with available liver biopsies, intrahepatic analyses were performed.
Results: Overall, 240 HDV patients were enrolled: median age 46 years, 62% males, 53% cirrhotics, 57% NUC-treated, median ALT 70 U/L, HBsAg 3.8 $\log_{10}$ IU/mL, 88% HBeAg-negative, median HDV RNA 4.9 $\log_{10}$ IU/mL. HBV RNA tested positive (>10 cp/mL) in only 8% of the patients [median 40 (13-82,000) cp/mL], whereas HBcrAg was ≥3 $\log_{10}$ U/mL in 77% [median 4.2 (3.0-8.0) $\log_{10}$ U/mL]. By combining these biomarkers, 3 categories were identified: 23% double negative (HBV RNA neg/HBcrAg neg), 9% double positive (HBV RNA pos/HBcrAg pos) and 68% HBV RNA negative/HBcrAg positive. HBV RNA levels positively correlated with male sex and detectable HBV DNA, while positive HBcrAg correlated with higher HBsAg levels. Double positive patients were younger, non-European, with elevated ALT and HDV RNA levels and detectable HBV DNA. Intrahepatic HDV RNA and HBV RNA were positive in most samples, while intrahepatic levels of covalently closed circular (ccc)DNA were low.
Conclusions: In untreated CHD, most patients had undetectable HBV RNA but quantifiable HBcrAg ("divergent pattern") in the absence of HBeAg. Additional studies aimed to unravel the molecular mechanisms underlying these findings are warranted.

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Diagnostic yield of whole exome sequencing in adult-onset cholestatic liver disease

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Introduction: Cholestatic liver diseases are a heterogeneous group of conditions that can progress to end-stage liver disease. One quarter of unexplained child-onset cholestasis has been associated with an expanding set of genetic disorders. In adults inherited conditions may similarly underly a significant number of unexplained cholestasis cases. However, genetic testing has been focused only on progressive familial intrahepatic cholestasis (PFIC) genes or has not been integrated at all in the management of adult-onset cholestatic liver disease so far.
Aim: This study assessed the diagnostic utility of whole-exome sequencing (WES) in adult-onset cholestatic liver disease, targeting a wide list of genes tied to inherited cholestatic and liver conditions.
Materials and Methods: WES was performed on adults with unexplained or unusual cholestatic liver disease from one referral centre. Pathogenic and rare functional variants in candidate cholestatic and liver disease genes were prioritised, and genotype-phenotype correlations were conducted.
Results: Twenty-one patients were included in the study. The mean age at disease presentation and at genetic analysis was 33.7±11.4 and 42.8 ±10.8 years, respectively. Familiarity for cholestatic liver disease was present in 7 (33.3%) patients. WES yielded a genetic diagnosis of inherited cholestatic or liver disorder mimicking the cholestatic phenotype in five (23.8%) cases. *ABCB4* was the causative gene in two cases (40.0%), while genes outside the PFIC spectrum (*ABCC2*, *PPOX*, *APOB*) accounted for the other three (60.0%). In fourteen additional patients (66.7%), we selected 28 rare functional heterozygous variants with a possible contribution to the cholestatic phenotype in 21 different genes known to play a role in mitochondrial hepatopathies, defects in biliary acids synthesis, ciliopathies, errors of metabolism and alfa-1-antitrypsin deficiency.
Conclusions: This pilot study highlights the value of WES in the diagnostic workup of adult-onset cholestatic liver disease and expands our understanding of its genetic landscape, paving the way for larger-scale studies.

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Prevalence and impact of Clinically Significant Portal Hypertension (CSPH) in patients with Hepatocellular Carcinoma (HCC): a multicenter cohort study on the ITA.LI.CA database

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Background and Aims: Clinically significant portal hypertension (CSPH) is a known independent predictor of hepatocellular carcinoma (HCC) development and prognosis, influencing patient access to oncological treatments. This study aims to evaluate the prevalence of CSPH and its impact across different HCC stages according to the Barcelona Clinic Liver Cancer (BCLC) staging system.
Method: A retrospective analysis was conducted on HCC patients registered in the Italian Liver Cancer (ITA.LI.CA) database between January 1987 and December 2022. Patients in BCLC stage D or stage C without extrahepatic metastasis or macrovascular invasion and those with Child-Pugh score > B7, were excluded. The presence of CSPH was assessed through esophageal/gastric varices, tense ascites, or liver stiffness > 25 kPa.
Results: Of 10,907 total patients, 7,069 were included, with 2,652 diagnosed with CSPH. CSPH prevalence was highest in alcoholic etiology and BCLC stage C (44.7%), followed by stages A (39.1%), B (33.9%), and 0 (19.6%). CSPH correlated with reduced survival overall, particularly in stages A, B, and C in univariate analysis, but not in stage 0. Multivariate analysis confirmed this association for

stages A and B, but not for stage C. Only 9.7% of CSPH patients were on non-selective beta-blockers (NSBB), and although NSBB use improved survival in univariate analysis, it did not in multivariate analysis.

Conclusion: This study found that CSPH significantly impacts survival in early and intermediate stages of HCC, but not in very early or advanced stages, likely due to milder liver disease in very early stages (or more frequent access to liver transplantation) or a dominant oncological burden in advanced stages. CSPH is common in advanced HCC patients, who often require anti-angiogenic therapies that necessitate careful management due to the presence of CSPH. Further analysis is underway, including a subgroup analysis of BCLC-C patients based on venous invasion.

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P-58

Ultrasound muscular thickness-based model to identify sarcopenia in patients with portal hypertension (PH): a cross-sectional single-center observational study

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Background: Sarcopenia is a frequent complication of cirrhosis (40–70%) and is an independent prognostic factor of worse outcome. Currently, CT scan is the gold standard to identify this condition, but new user friendly and reliable non-invasive screening tools are needed.

Methods: This single center prospective study includes consecutive outpatients with portal hypertension and abdominal CT who underwent US assessment of biceps brachii (BB), rectus abdominis (RA), rectus femoris (RF) and thigh muscle (TM), performed by two blinded trained investigators.

The sum of both-side muscle thickness was adjusted for height obtaining an index (mm/m).

Sarcopenia was defined using CT by L3-SMI cut-offs prosed by EASL/AASLD. Association between sarcopenia and US parameters, anthropometric, clinical, biochemical and nutritional data was assessed.

Results: 103 patients were enrolled (median age 61 ys, 63% men, 84% cirrhotic, median BMI 25,7 kg/m^2). Prevalence of sarcopenia was high among both cirrhotic and non-cirrhotic portal hypertension patients (54.1% vs 61.5%, p = ns), without statistically significant difference between women and men.

Among US measurements and anthropometric data, RF index and BMI showed the best inverse-correlation with sarcopenia with an OR of 0.79 (95% CI: 0.69-0.91, p <0.01) and 0.80 (95% CI: 0.63-0.910, p <0.01), respectively.

Based on these findings, a gender specific integrated model to identify sarcopenia was proposed with best results among cirrhotic men and women overall where BMI threshold of 28 and 23.9 kg/m^2 and RF index of 14.8 and 13.4 mm/m showed the highest positive (73% and 78%) and negative (81% and 74%) predictive value, with a ROC of 0.81 and 0.80 respectively.

Moreover, US muscular measurements showed high intra/inter-operator reliability.

Conclusions: US can be a bedside, non-invasive and reproducible tool to assess muscle thickness with a good capability in a model with BMI to discriminate patients with sarcopenia.

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P-59

Comparison of diagnostic performances of HDV RNA quantification assays used in clinical practice in Italy: data from the first national quality control multicenter study

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Introduction: A reliable quantification of serum hepatitis D virus (HDV) RNA is of paramount importance for a proper monitoring of patients under antiviral therapy.
Aim: This quality-control study compares the diagnostic performances of quantitative HDV-RNA assays, used in clinical-practice.
Methods: Two HDV-RNA sample panels were quantified at 30 laboratories by 6 commercial assays: RoboGene(N=9 laboratories), Eurobio/EliTech-platform(N=7), Altona(N=5), Anatolia(N=3), DiaPro(N=2), Nuclear-Laser-Medicine(N=1) and 3 in-house assays. Panel-A and -B comprised 8 serial dilutions of WHO/HDV standard(range:5-0.5logIU/ml) and 20 clinical samples(range:6-0.5logIU/ml), respectively. Laboratories quantified dilutions of Panel-A and -B 9 and 5 times, respectively, in order to define for each assay: i)sensitivity by 95%LOD(limit of detection), ii)precision by intra- and inter-run CV(coefficient of variation), iii)accuracy by the differences between expected-observed HDV-RNA loads, iv)linearity by linear-regression analysis.
Results: In Panel-A, 95%LOD varied across the assays underlining heterogeneous sensitivities: Altona had the lowest median 95%LOD (10[min-max:3-316]IU/ml), followed by Robogene (31[3-316] IU/ml), Nuclear-Laser-Medicine (31IU/ml) and EliTech (100[100-316]IU/ml). Moreover, 5 assays (Robogene/EliTech/Altona, Nuclear-Laser-Medicine/In-house) showed $<$0.5logIU/ml differences between expected and observed HDV-RNA for all dilutions while the remaining assays had HDV-RNA underestimations$>$1logIU/ml. In Panel-B, Altona and EliTech had the highest precision (mean intra-run CV$<$20%), followed by Robogene and Nuclear-Laser-Medicine ($<$30%). Inter-run CV was higher for all assays with only Altona, Nuclear-Laser-Medicine and EliTech maintaining this parameter$<$25%. Five assays (Robogene/Altona/EliTech/Nuclear-Laser-Medicine/In-house) showed a good linearity($R^2>0.9$) between LLOQ and 6.7logIU/ml. Conversely, a linearity drop emerged for HDV-RNA$<$1000IU/ml, with only Altona and Robogene retaining $R^2>0.85$.
Conclusions: This study underlines heterogeneous sensitivities (inter- and intra-assays), that could hamper the proper HDV-RNA quantification, particularly at low viral-loads. This raises the need to improve the diagnostic performance of most assays for properly identifying virological response to anti-HDV drugs.

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P-60

Assessing portal hypertension with endoscopic ultrasound portal pressure gradient (eus-ppg): clinical correlations and procedural outcomes

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Background and Aim: Portal hypertension (PH) is a critical complication in chronic liver diseases, notably cirrhosis, and often precedes severe outcomes. Recent advancements have introduced endoscopic ultrasound-guided PPG (EUS-PPG) as a method for directly measuring the portal pressure gradient, potentially overcoming the limitations of traditional indirect measures like the hepatic venous pressure gradient (HVPG). This interim analysis aims to evaluate the technical success, safety, and correlation of EUS-PPG with clinical and laboratory indicators of portal hypertension.
Material and Methods: The study involved a cohort of patients with suspected or confirmed PH who underwent EUS-PPG using a linear echoendoscope, a 25G fine needle aspiration needle, and a compact manometer with non-compressible tubing. All procedures were performed by the same operator under conscious sedation. For each patient, at least three measurements were taken in the portal vein and three in the hepatic vein or retrohepatic inferior vena cava, with the gradient calculated as the difference between the means of these measurements. Clinical and laboratory data were collected for each patient to assess potential correlations with EUS-PPG values.
Results: A total of 32 patients underwent EUS-PPG. Descriptive analysis of demographic, clinical, and laboratory characteristics, as well as procedural details, is provided in Table 1,2.Technical success was achieved in 100% of cases, with only minor complications (9%), such as mild post-procedural abdominal pain.

For statistical analysis, a Student's t-test was conducted to compare PPG values between patients with a low probability versus a high probability of PH (defined as the presence of one specific sign of PH or, in its absence, at least two non-specific signs of PH). Results showed significantly higher PPG values in the high-probability group (p 0,0011).

Spearman's correlation analysis was performed to evaluate the association between EUS-PPG values and portal hypertension severity, defined as the sum of specific and non-specific signs of PH. This analysis revealed a positive correlation, with an increase in PPG associated with greater PH severity (Spearman's $\rho = 0.6283$, $p = 0.0003$). Similarly, Spearman's correlation was used to assess the relationship between EUS-PPG values and platelet count, liver stiffness, and spleen stiffness. An inverse correlation was observed

between PPG and platelet count ($\rho = -0.5323$, $p = 0.0030$), while positive correlations were found with liver stiffness ($\rho = 0.6320$, $p = 0.0028$) and spleen stiffness ($\rho = 0.5812$, $p = 0.0231$).
Conclusion: EUS-PPG demonstrated high technical success and safety in evaluating PH, with meaningful correlations between PPG values and clinical and laboratory indicators of PH severity. These findings support the potential of EUS-PPG as a valuable tool in the direct assessment of portal hypertension, warranting further studies to confirm its clinical applicability.

Table 1. Clinical features of patients who underwent EUS-PPG procedure

Patients' demographics		
Patients, n		32
Female, n (%)		19 (41%)
Age (y), median (IQR)		55 (15.75)
Etiology/indication		
MASH, n (%)		13 (41%)
PSVD, n (%)		5 (16%)
PBC, n (%)		4 (13%)
ALD, n (%)		3 (9%)
Cardiac disease, n (%)		3 (9%)
Genetic disease GLID, n (%)		1 (3%)
Cryptogenic, n (%)		3 (9%)
NSBB		
Yes, n (%)		17 (53%)
	Carvedilol, n (%)	11 (65%)
	Propranolol, n (%)	6 (35%)
	Primary prophylaxis, n (%)	13 (76%)
	Secondary prophylaxis, n (%)	4 (24%)
Specific signs of PH		
Yes, n (%)		19 (59%)
	Single sign of PH, n (%)	9 (28%)
	Multiple signs of PH, n (%)	10 (31%)
	Esophageal varices, n (%)	19 (59%)
	Gastric varices, n (%)	2 (6%)
	Previous portal hypertensive bleeding, n (%)	4 (13%)
	Porto-systemic collateral at imaging, n (%)	4 (13%)
Nonspecific signs of PH		
Yes, n (%)		29 (91%)
	Single sign of PH, n (%)	8 (25%)
	Multiple signs of PH, n (%)	20 (63%)
	Thrombocytopenia, n (%)	20 (63%)
	Ascites, n (%)	10 (31%)
	Splenomegaly, n (%)	23 (72%)
	Spleen size if splenomegaly, median (IQR)	16.3 cm (4.5 cm)
	PLT count if thrombocytopenia, median (IQR)	72.500/mm³ (63.000/mm³)
	PLT count < 50.000/mm³, n (%)	6 (19%)
Clinical probability of PH		
High, n (%)		22 (69%)
Low, n (%)		10 (31%)
Severity of PH		
Sum of PH signs, median (IQR)		3 (2)
Transient elastography		
LSM, n (%)		23 (72%)
LSM, median (IQR)		10.1 kPa (18 kPa)
SSM, n (%)		18 (56%)
SSM, median (IQR)		71.7 kPa (54.0 kPa)

ALD, alcohol-related liver disease; GLID, granulomatous liver idiopathic disease; LSM, liver stiffness measurement; MASH, metabolic dysfunction-associated steatohepatitis; NSBB, nonselective beta-blockers; PBC, primary biliary cholangitis; PH, portal hypertension; PLT, platelets; PSVD, porto-sinusoidal vascular disorder; SSM, spleen stiffness measurement.

Table 2. Technical and procedural features

Procedural specifics		
EUS-PPG procedural time, median (IQR)		35' (12.3')
HV pressure measurement, n (%)		25 (78%)
HV mean pressure, median (IQR)		14 mmHg (9.5 mmHg)
ICV pressure measurement, n (%)		16 (50%)
ICV mean pressure, median (IQR)		12 mmHg (11 mmHg)
PV pressure measurement, n (%)		32 (100%)
PV mean pressure, median (IQR)		24.5 mmHg (15.75 mmHg)
PPG measurement, n (%)		32 (100%)
PPG mean, median (IQR)		10.5 mmHg (9 mmHg)
Technical success, n (%)		32 (100%)
Major complications, n (%)		0 (0%)
Minor complications, n (%)		3 (9%)
Technical difficulties		
Yes, n (%)		14 (44%)
	HV sampling, n (%)	7 (50%)
	PV sampling, n (%)	6 (43%)
	Multiple hepatic cysts, n (%)	1 (7%)
EUS-LB		
Yes, n (%)		18 (56%)
	Left lobe, n (%)	4 (22%)
	Bilobar, n (%)	14 (78%)
	22 G needle, n (%)	4 (22%)
	19 G needle, n (%)	14 (78%)
	Macroscopic specimen adequacy*, n (%)	18 (100%)
	Microscopic specimen adequacy*, n (%)	17 (94%)

EUS-LB, EUS liver biopsy; EUS-PPG, EUS-guided portal pressure gradient; HV, hepatic vein; ICV, inferior vena cava; PPG, portal pressure gradient; PV, portal vein.
* According to AASLD criteria

Liver biopsy. Don C Rockey 1, Stephen H Caldwell, Zachary D Goodman. Hepatology 2009 Mar;49(3):1017-44.

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P-61

Spatial transcriptomics maps the metabolic zonation of hepatocytes in MASLD I148M-PNPLA3 carriers

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Introduction: The I148M *PNPLA3* polymorphism is the main genetic predictor of MASLD. Few data showed that I148M overexpression in hepatocytes correlated with metabolic switching and mitochondrial (mt)-dysfunction.
Aims: To deepen the impact of *PNPLA3* variation on mt-function by overexpressing I148M protein in HepG2 and Hep3B cells, to force or introduce the mutation, respectively; to dissect hepatocytes metabolic zonation in liver biopsies of MASLD patients, wild-type (WT) and homozygous for PNPLA3-I148M with similar disease severity (NAS=4), through spatial transcriptomic.
Materials and Methods Results: PNPLA3-I148M protein was upregulated in hepatoma cells by lentiviral transfection. Spatial transcriptomics was performed by Visium CytAssist (10X-Genomics). I148M-protein upregulation in hepatoma cells fostered lipid accumulation, thus increasing PGC1a to clear fat. Both I148M-overexpressed models showed lower OXPHOS capacity and ATP production alongside higher release of ROS and mtDNA fragments, corroborating the I148M-mediated mt-dysfunction. To explore the role of PNPLA3 I148M in hepatocytes zonation, we spatially mapped pericentral (PC) and periportal (PP) hepatocytes of WT and I148M MASLD-biopsies by using *CYP3A4/CYP2E1* and *HAL/SDS* genes as zonation markers, respectively. Among DEGs, we found increased lipogenesis (*SREPF1, DGAT2, ACACA, FABP1)* and mitobiogenesis (*PGC1a*), the latter as response to fat accumulation, in both WT-I148M-PP areas. However, WT-PP zones showed high expression of DEGs related to physiologic fusion-mitophagy (Mfn1, Mfn2, Opa1, BnipL, Bnip3), ðœ·-oxidation (PPAR*a)* and mt-respiration (SDHA, ATP5MF), that conversely were decreased in I148M-PP areas suggesting a mt-impairment. As concern pathways related to glycolysis, fatty acids metabolism, autophagy/mitophagy and PPAR/Wnt signaling, we observed an opposite trend between WT and I148M as they were enhanced in PC zones in the former and PP areas in the latter.
Conclusion: The *in vitro* I148M overexpression dampens mitochondrial respiration triggering oxidative stress. In MASLD patients, the I148M mutation leads to unbalanced PC-PP metabolic zonation providing new insights into its impact in the disease progression.

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Mapping the hepatic mtDNA genomic landscape in patients with MASLD: The Era of GPT-4 Artificial Intelligence

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Introduction: Artificial intelligence (AI) enables big data mining even without high-tech resources.
Aims: We exploited AI tool (GPT-4) to assist in analyzing -omics data from a anonymized cohort of MASLD patients, who underwent hepatic mitochondrial (mt-)DNA whole-genome sequencing (WGS cohort, n=39). We then investigated the correlation among mtDNA variants and: a) hepatic mt-respiration in 80 MASLD patients (Seahorse cohort); b) histological damage and serum cell-free circulating (ccf-) mtDNA fragments in biopsied MASLD patients (Hepatology service cohort, n=555).
Material and Methods Results: A customized GPT-4 model with coding skills was used for genomic data analysis (mtGPT-4). In the WGS cohort, 520 mtDNA nonsynonymous variants were detected. At unbiased analysis, ten mutations, affecting mt-tRNAs, correlated

with NAS≥5, while nine located in respiratory complexes' genes associated with advanced fibrosis, supporting that mt-respiration fails during disease severity. We asked mtGPT-4 to perform a phylogenetic analysis to assess the impact of clustered mtDNA mutations on MASLD progression. Patients belonging to T phylocluster exhibited severe steatosis, NAS≥5 and advanced fibrosis compared to non-T. Among the T patients, seven T subgroups were recorded, each including a specific mtDNA mutation panel. We thus requested mtGPT-4 which mtDNA variants were shared across T haplotypes. Eight mtDNA variants were extrapolated and two of them [*MT-ND1* T>C (p.Y304H); *MT-TR* ($tRNA^{Arg}$) T>C)], correlated with steatosis, NAS and fibrosis. Both mutations individually emerged from the unbiased analysis and occurred in combination in phylocluster T, driving its association with MASLD. A preliminary validation of the *MT-ND1* genotype in the Seahorse cohort revealed a poor hepatic complex I activity and OCR in carriers compared to noncarriers. In the Hepatology service cohort, the *MT-ND1* variant associated with elevated ccf-ND1, NAS and fibrosis at multivariate analysis adjusted for both environmental and genetic factors.
Conclusions: GPT-4 facilitated -omic data manipulation, identifying novel mtDNA mutations contributing to MASLD pathogenesis.

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P-63

Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) in Italian women: is liver fibrosis independent from menopause?

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Background and Aims: Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) is an emerging health concern among women, with menopause influencing its onset and progression. This study aimed to explore the connection between menopause and liver fibrosis in MASLD.
Method: Between October 2014 and September 2024, 149 non-cirrhotic women were enrolled and underwent comprehensive evaluations, including physical activity and diet quality assessments (IPAQ and REAP-S scores). Significant liver fibrosis was defined as liver stiffness ≥ 7 kPa on 2D-elastography. Cardiovascular risk was assessed with ESC scores, and insulin resistance with TyG index.
Results: Of 149 women, 41 were pre-menopausal (median age 46, 17.1% fibrotic) and 108 post-menopausal (median age 61, 27.8% fibrotic). Fibrotic women were older (median age 64 vs. 56, $p < 0.001$) and had higher rates of hypertension (64.9% vs. 43.8%, $p = 0.026$), type 2 diabetes (T2DM 40.5% vs. 16.1%, $p = 0.002$), and insulin resistance (TyG index: 4.9 vs. 4.7, $p = 0.024$). BMI, menopause status, age at menopause were similar between fibrotic and non-fibrotic women. Multivariate analysis revealed that age (OR 1.068, $p = 0.002$) and T2DM (OR 3.633, $p = 0.004$) were independently associated with fibrosis. Compared to non-fibrotic, fibrotic post-menopausal women had poorer diet quality (REAPS score: 26 vs. 31, $p = 0.018$), higher rates of hypertension (73.3% vs. 46.2%, $p = 0.011$) and T2DM (40% vs. 17.9%, $p = 0.016$), and a higher risk of CV events (11.1% vs. 6.1%, $p < 0.001$). Multivariate analysis confirmed that hypertension (OR 2.959, $p = 0.024$) and T2DM (OR 2.752, $p = 0.039$) were independently associated with fibrosis in post-menopausal women.
Conclusion: T2DM drives liver fibrosis in both pre- and post-menopausal women, while hypertension is linked to fibrosis only in post-menopausal women, with diet quality posing additional challenges, particularly for post-menopausal women, possibly due to socioeconomic factors.

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Prevalence and predictors of steatotic liver disease and significant liver fibrosis in an integrated hepatological and non-hepatological healthcare pathway model

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Introduction: An integrated healthcare pathway model for metabolic-dysfunction associated steatotic liver disease (MASLD) is recommended for a comprehensive evaluation of the metabolic health.
Aim: In this prospective study we aimed to assess prevalence and predictors of steatotic liver disease (SLD) and significant liver fibrosis (SLF) in consecutive patients first referred for type 2 diabetes mellitus (T2DM) or SLD in two different settings (diabetology and hepatology clinics) of the "AOU Città della Salute e della Scienza di Torino" University Hospital.
Materials and Methods: All patients underwent vibration-controlled transient elastography for liver stiffness measurement (LSM) and controlled attenuation parameter (CAP), and echocardiography with speckle tracking analysis. SLD was defined by CAP>247 dB/m. SLF was defined by LSM>7 kPa. Diastolic dysfunction was defined by mitral E/E' ratio>9 and systolic dysfunction by left ventricular global longitudinal strain (GLS)>-18.
Results: 544 patients (59% in the liver clinic group [LCG] and 41% in the diabetes clinic group [DCG]) were enrolled. In the LCG all patients fulfilled the criteria for MASLD; prevalence of T2DM and obesity were 21.8% and 42.7%; 4.7% were referred to the DCG for first diagnosed or decompensated T2DM. Median LSM was 5.1 [4.6 – 6.3] kPa and SLF was detected in 17.8% of cases. In the DCG prevalence of obesity was 52.0% and median LSM was 4.9 [4.1 – 5.9] kPa. SLD was present in 67.7% of cases, of which 59.6% MASLD, 1.3% ALD (alcohol-related liver disease) and 6.7% metALD. SLF was detected in 13.5% of cases, which were referred to the LCG for hepatological evaluation. A known cardiovascular disease (CVD) was found in 9.7% and 50.2% of patients in the LCG and DCG, respectively. A high Framingham risk score (>20%) was detected in 12.9% in the LCG and 1.3% in the DCG. Prevalence of diastolic and systolic dysfunctions in those without CVD were 27.4% and 18.2% in the LCG and 8.9% and 3.6% in the DCG. In the LCG, Body

Mass Index (BMI) and T2DM were the strongest predictors of SLF (aOR 1.13[95%CI 1.06-1.21], p=0.0002 and 5.66 [95%CI 2.64-12.07], p<0.001). In the DCG, only transaminases were independent predictors of SLF (aOR 1.11 [95%CI 1.04-1.19], p=0.001), while BMI was the only predictor of SLD (aOR 1.09 [95%CI 1.03-1.16], p=0.001).
Conclusions: Two thirds of SLD in the non-hepatology setting are due to MASLD and associated with BMI. Prevalence of SLF is similar in hepatology and non-hepatology settings, but presence of T2DM results in the strongest association independent of other metabolic risk factors. A higher prevalence of pre-clinical CVD is detected in the hepatology setting by advanced echocardiography, consistent with a higher 10-year risk of CVD-related mortality.

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Liver transplants in untreated vs Bulevirtide-treated patients with chronic Hepatits Delta: a cross-sectional, intrahepatic analysis

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Background and Aim: Bulevirtide (BLV) was approved by EMA for CHD treatment, however no data exist about intrahepatic features of BLV-treated patients who underwent liver transplantation (LT). Aim of the study was to compare intrahepatic and clinical features of untreated and BLV-treated CHD patients who received LT.
Material and Methods: BLV-treated (SAVE-D study) and untreated CHD patients who underwent LT were compared. Clinical and virological features were collected at LT; HDV RNA was quantified with Robogene® 2.0. Intrahepatic (i) HDAg, HBsAg, and HBcAg staining were performed by immunohistochemistry (Ventana Benchmark Ultra System).
Results: 24 LT were studied, 14 untreated patients and 10 BLV-treated patients [14 (5-18) months therapy]. BLV-treated and untreated patients were similar in term of age at LT (56 *vs.* 49 years), male gender (60% *vs.* 29%), indication for LT (HCC 50% *vs.* 50%), HBsAg levels (3.6 *vs.* 3.8 LogIU/mL), NUC therapy (100%) and undetectable HBV DNA (100%). By contrast, BLV-treated patients had lower MELD (10 *vs.* 16, p=0.01), lower ALT (41 *vs.* 59, p=0.04) and lower HDV RNA (3.4 vs 5.2 LogIU/mL, p=0.08). At histology, iHBcAg stained negative in all patients, while iHBsAg stained negative in 2 (8%), 10-30% positive in 7 (29%), >30% in 15 (63%), without differences between groups. iHBsAg levels correlated with serum HBsAg (p=0.01), but not with serum HDV RNA. iHDAg stained negative in 2 patients (8%), 1-5% positive in 12 (50%), 10-50% in 7 (29%) and >50 in 3 (13%), without significant differences between groups, diffuse (46%) and focal (29%) being the most prevalent patterns. iHDAg correlated with serum HDV RNA (p=0.07), but not with serum HBsAg or iHBsAg.
Conclusions: In CHD patients undergoing LT, iHBsAg was positive in most patients and correlated with serum HBsAg, while iHDAg staining was low and poorly correlated with serum HDV RNA, independently of BLV-treatment.

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Similar Rates of Biochemical Response Are Observed Across Virologic Response Categories Over 96 Weeks of Bulevirtide Monotherapy in Patients With Chronic Hepatitis Delta

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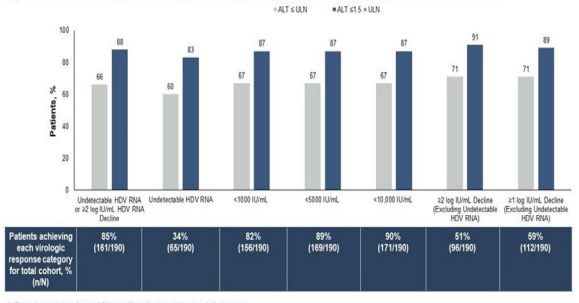
Introduction: Bulevirtide (BLV) is approved for treatment for chronic hepatitis delta (CHD) in Europe. BLV is not a direct antiviral but prevents liver spreading of HDV; biochemical response (BR; alanine aminotransferase [ALT] normalisation) can be observed independently of virologic response (VR) likely due to prevention of de novo infection of hepatocytes.
Aim: Previous analyses using 48-week (W) treatment data described similar rates of BR across multiple HDV RNA response cutoffs. We examined whether this effect persists beyond 48W of BLV monotherapy.
Materials and Methods: Pooled W96 BLV (2mg/day, 10mg/day) data from 2 clinical studies were analysed. VR categories included log10 declines from baseline (BL), undetectable HDV RNA, and absolute value HDV RNA cutoffs (1000–10,000 IU/mL). ALT response (ALT ≤ upper limit of normal [ULN] or ALT ≤1.5 × ULN) was evaluated in each VR category.
Results: Included were 190 patients with CHD (BLV 2mg, n=47; BLV 10mg, n=143). After 96W of BLV monotherapy, 34% to 90% of patients achieved VR across the VR categories (Figure); 85% had VR (HDV RNA undetectable or ≥2-log10 decline from BL in HDV RNA). ALT ≤ULN or ≤1.5 × ULN was achieved by 64% and 83% of patients, respectively. Proportions achieving VR were similar: 88%

of patients with ALT ≤ULN and 89% with ALT ≤1.5 × ULN. HDV RNA <10,000 IU/mL was the most inclusive metric for detecting ALT response, capturing 94% of those with ALT ≤ULN and 94% of those with ALT ≤1.5 × ULN. The proportions of patients with VR with or without BR were similar regardless of the VR cutoff.
Conclusion: The use of a less stringent cutoff for VR (ie, HDV RNA <10,000 IU/mL) over the standard VR definition can capture additional cases of ALT response. Like previous findings, similar rates of ALT responses were observed across the evaluated VR subgroups after 96W of BLV monotherapy.

Figure. Biochemical Responses Among Patients Achieving Different Virologic Response Criteria at Week 96



Patients achieving each virologic response category for total cohort, % (n/N)	85% (161/190)	34% (65/190)	82% (156/190)	89% (169/190)	90% (171/190)	51% (96/190)	59% (112/190)

ALT, alanine aminotransferase; HDV, hepatitis delta virus; ULN, upper limit of normal.

ALT, alanine aminotransferase; HDV, hepatitis delta virus; ULN, upper limit of normal.

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P-67

Anticoagulation in Patients with Liver Cirrhosis and Portal Vein Thrombosis

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Introduction: Anticoagulation may have protective effects in patients with liver cirrhosis, regardless of portal vein thrombosis (PVT). This study aimed to evaluate the efficacy of anticoagulation, compared to no treatment, in preventing acute decompensation (AD) in cirrhotic patients with PVT.
Methods: Four hundred fifty-nine cirrhotic patients were retrospectively evaluated for study eligibility from January 2018 to January 2024 and. Forty-three patients patients with a diagnosis of PVT were finally included in the analysis. The first available abdominal imaging, conducted approximately 6 ± 3 months after enrollment, was collected to assess the status of PVT. During a 24-month follow-up, the incidence of AD, bleeding events, mortality, and liver transplantation were recorded.
Results: Forty-three patients (mean age 63.7±10.9 years; males 83.7%; median follow-up 19 months [IQR 9-24]) were included and divided into two groups based on the clinician's decision to initiate anticoagulation: 22 patients not anticoagulated and 21 patients anticoagulated (with either Fondaparinux or direct oral anticoagulants). Thrombosis improved more frequently in the treatment group, with progression in only one anticoagulated patient. Anticoagulation was discontinued in 7 patients due to regression of thrombosis with a PVT recurrence of 71.4%. AD occurred more frequently in untreated patients (50% vs. 9.5%, p<0.004). Cox regression analysis confirmed anticoagulation's protective effect against AD (HR 0.19, 95% CI 0.04–0.85), even after adjusting for confounders. No significant differences in overall or transplant-free survival were observed. Bleeding incidence was similar between the two groups.
Conclusions: Our study provides evidence supporting the use of anticoagulation in patients with liver cirrhosis and PVT. Due to its protective role against both the occurrence and recurrence of AD, anticoagulation should be considered regardless of thrombosis severity and extension and may be maintained long term due to the elevated risk of recurrence.

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P-68

Prevalence of steatotic liver disease and steatohepatitis in a population of healthy workers

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Introduction: Steatotic Liver Disease (SLD) may silently evolve into Steatohepatitis (SH). In clinical practice, elevation of liver enzymes (LE) is used as a surrogate marker of liver inflammation. Screening of liver disease is gaining attention and novel strategies need to be found. We aimed to study the prevalence and associated factors of SLD and SH in a population of healthy workers.
Methods: 780 healthy workers were prospectively enrolled during yearly health checkups (from January to September 2024) at Bridgestone factory (Bilbao, Spain). Ultrasound, anthropometric and biochemical data were collected. 335 patients with all available data were further analysed. Patients were divided into the following groups: no steatosis and normal LE (Healthy), steatosis and normal LE (SLD), steatosis and elevated LE (SH), no steatosis and elevated LE (Hepatitis).
Results: The Healthy Group accounted for half of the patients (57%), while the remaining patients were divided into the other three groups (SLD 20%; SH 11%; Hepatitis 12%). The analysis of variance showed differences in age, BMI, HDL, triglycerides, glucose and haemoglobin. At post-hoc analysis only BMI increased significantly between Healthy (25.10 [23.15, 27.16]), SLD (26.87 [24.97, 30.05]) and SH Groups (30.38 [27.59, 33.18]). Multivariate logistic regression for risk factors for SLD showed: BMI (aOR 1.21 [1.11, 1.31], p < 0.001), and hypertension (aOR 2.19 [1.10, 4.37], p = 0.026). The only significant risk factor for SH after adjustment was BMI (aOR 1.31 [1.18, 1.48], p < 0.001).
Conclusion: The inclusion of liver ultrasound and transaminases in healthy workers' checkups can be effective in identifying patients with metabolic liver disease.

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P-69

Efficacy and safety of BLV monotherapy for chronic hepatitis delta: posttreatment results through 48 weeks after the end of treatment from an interim analysis of a randomised Phase 3 study MYR301

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Introduction: Bulevirtide (BLV) is approved in Europe for chronic hepatitis delta (CHD). MYR301 (NCT03852719) showed BLV 2 d or 10 mg/d monotherapy was efficacious and safe through 144 weeks(w) of treatment.
Aim: To present MYR301 results through 48w after the end of treatment (EOT; FU48).
Materials and Methods: We randomised 150 patients with CHD (stratified by presence/absence of compensated cirrhosis [CC]) in a 1:1:1 ratio to Arm A: no active anti-hepatitis delta virus (HDV) treatment for 48w followed by BLV 10 mg/d for 96w (n=51), or Arm B: BLV 2 mg/d (n=49) or Arm C: BLV 10 mg/d (n=50) for 144w. Patients were followed for 96w after EOT. Endpoints included combined response (CR) defined as virologic response (VR; undetectable HDV RNA or a decrease by ≥2 log10 IU/mL from baseline) and ALT normalisation, VR, ALT normalisation, undetectable HDV RNA, liver stiffness, and liver-related outcomes.
Results: Among patients, 47% had CC; 72% reached FU48. All response rates decreased after EOT due to viral relapses or rebounds, which mainly occurred over the first 24w after EOT. CR and ALT normalisation rates were similar regardless of dose/duration. VR and undetectable HDV RNA rates after EOT were higher with BLV 10 vs 2 mg or delayed treatment. Only 2 liver-related events were reported after EOT: ascites (Arm A) and oesophageal variceal bleed (Arm B). More patients in Arm A had serious adverse events (SAEs) and grade ≥3 AEs after EOT vs Arms B and C. Of 13 patients who reported an SAE that started after EOT, 9 had posttreatment flare with ALT and HDV RNA increases (5/9 cirrhotic).
Conclusion: A subset of patients treated with BLV monotherapy for 2-3 years maintained virologic and biochemical responses 1 year after stopping BLV. Liver-related event rates 1 year after completing BLV monotherapy were low.

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P-70

The asymmetry of the liver and spleen stiffness measures between patients with chronic hepatitis B and D reflects clinic-pathologic differences

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Background: Chronic Hepatitis D (CHD) infection causes an additional pathologic burden in patients (pts) with Chronic Hepatitis B Virus (CHB), leading to worse outcomes. We evaluated liver (LSM) and spleen (SSM) stiffness measurements in CHB and CHD pts to assess the added value of SSM in this clinical setting.
Methods: We studied 119-HBsAg+ pts, 71-CHB and 48-CHD [30(42.3%) and 27(56.3%) with cirrhosis, respectively] undergoing regular follow-up at the Hepatology-Unit of Pisa University Hospital. Physical examination, ultrasound scan, LSM and SSM (FibroScan-Echosens,France) were performed on the same day, liver biochemistry and virological assays within one week.
Results: Demographical, clinical and laboratory features are reported in Table-1a. Median LSM was lower in CHB than in CHD pts [6.2(2.8–71) vs 8.1(2.8–33.1) kPa, (p=0.004)], whereas SSM was similar [25.6(9.3–87.6) vs. 26.8(4.8–100) kPa, p=0.569]. Median SSM/LSM-ratio was lower in CHD than in CHB [2.98(1.00-9.64) vs 3.88(1.09-16.25), p=0.003]. Median spleen diameter (SD) was similar between CHB and CHD (11.0(7.0-18.0) cm vs 12.0(6.5-23.0)cm, p=0.079). CHD showed a significantly lower SD/LSM-ratio [1.33(0.36-3.89) vs 1.78(0.21-4.08), p=0.007], but similar SD/SSM ratio [0.44(0.14-2.06) vs 0.43(0.14-1.07), p=0.688]. Also in cirrhotic pts, median LSM was significantly lower in CHB pts [9.7(3.7-71) vs 13.3(5.6-33.1) kPa,p=0.022], whereas SSM was similar [34.0(9.9-87.6) vs 33.3(14.5-100) kPa,p=0.842]. The SD/LSM-ratio showed a trend to be lower in cirrhotic-CHD [0.92(0.36-2.09) vs 1.20(0.21-2.89); p=0.054]. In CHD, SSM correlated better with LSM, SD and PLT-count overall and in cirrhotics **(table 1-b).**
Conclusion: Combining LSM and SSM provides a useful differential clinic pathologic characterization of liver disease in pts with CHB and CHD. The significantly lower SD/LSM-ratio found in CHD pts, suggests the specific role of HDV induced necro-inflammation as a driver of disease progression with splenomegaly and platelet count

reduction. Longer follow up in CHD treated patients are needed to define the curative impact of the current antivirals.

Variables		HDV N=48	HBV N=71	P
Age	yrs	47.8 (20.2-74.8)	58.9 (28.9-86.4)	**<0.001**
Gender	F M	21 (43.8) 27 (56.3)	17 (23.9) 54 (76.1)	**0.038**
Country	Italy Other	18 (37.5) 30 (62.5)	52 (73.2) 19 (26.8)	**<0.001**
BMI	Kg/m^2	24.6 (17.3-43.1)	24.9 (18.8-51.8)	0.497
Cofactors	MASLD HCV (SVR) Alcohol	21 (43.8) 5 (10.4) 5 (10.4)	22 (31.0) 4 (5.6) 9 (12.7)	0.220 0.539 0.932
Cirrhosis	Yes No	27 (56.3) 21 (43.8)	30 (42.3) 41 (57.7)	0.189
HBV Genotype	D Non D	18 (90.0) 2 (10.0)	43 (72.9) 16 (27.1)	0.204
HBV DNA	Log IU/mL	1.00 (0.70-4.38)	0.70 (0.70-8.30)	0.951
HBsAg	Log IU/mL	3.65 (-0.70 / 4.75)	2.61 (-0.70 / 5.07)	**<0.001**
NUC Therapy	Yes No	34 (70.8) 14 (29.2)	51 (71.8) 20 (28.2)	1.000
AST	U/L	28 (11 - 155)	24 (11 - 218)	**0.014**
ALT	U/L	27 (9 - 160)	19 (5 - 219)	**0.001**
gGT	U/L	24 (11 - 152)	20 (8 - 290)	*0.082*
ALP	U/L	87 (36 - 141)	76 (39 - 161)	**0.044**
Albumin	g/dL	4.3 (3.2 - 4.9)	4.5 (2.8 - 5.1)	**0.002**
PLTs	n/mmc	176 (33 - 341)	187 (20 - 489)	*0.066*
INR		1.06 (0.90 - 1.49)	1.04 (0.87 - 2.84)	0.476
AFP	ng/mL	3.3 (0.9 - 60.9)	2.3 (0.9 - 79.4)	**0.005**
Bilirubin	mg/dL	0.66 (0.13 - 3.05)	0.59 (0.18 - 2.58)	0.358

		Overall (n=119)	Cirrhosis (n=51)	HBV n=71	HBV-Cirrhosis n=24	HDV n=48	HDV-Cirrhosis n=27
LSM	ρ	0.567	0.579	0.465	0.432	0.761	0.799
	P	**<0.001**	**<0.001**	**<0.001**	**0.022**	**<0.001**	**<0.001**
median	kPa	7.2	10.5	6.2	9.7	8.1	13.3
SD	ρ	0.534	0.537	0.489	0.524	0.643	0.647
	P	**<0.001**	**<0.001**	**<0.001**	**0.004**	**<0.001**	**<0.001**
median	cm	11.5	12.8	11.0	12.1	12.0	13.0
PLT	ρ	-0.538	-0.666	-0.498	-0.638	-0.617	-0.726
	P	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
median	n	180	132	187	142	176	106
ALT	ρ	0.002	0.017	0.011	0.144	-0.021	-0.042
	P	0.266	0.263	0.197	**0.041**	0.891	0.809
median	U/L	21	22	19	18	27	28

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P-71

Impact of liver transplantation on spleen stiffness: early findings from a single-centre study

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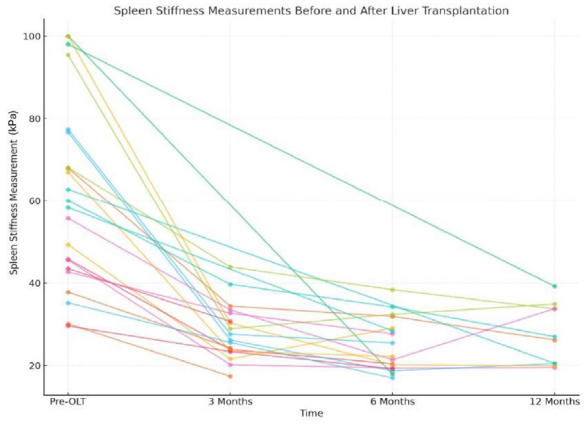
Introduction: Vibration controlled transient elastography (VCTE; Fibroscan®) is a non-invasive method to assess liver stiffness measurement (LSM) and evaluate liver fibrosis. VCTE has also been widely used in post-liver transplantation (LT) setting to identify graft damage. Spleen stiffness measurement (SSM) is known to improve non-invasive diagnosis of clinically significant portal hypertension (CSPH) but data on SSM in the post-LT setting is limited.

Aim: To evaluate changes in SSM, spleen size and liver stiffness following LT.

Materials and Methods: From January 2022 to July 2024, we prospectively enrolled all consecutive LT recipients transplanted at our centre with available SSM pre-LT. Patients with re-LT, splenectomy or without SSM pre-LT were excluded. SSM was measured by VCTE Fibroscan® (Echosens, Paris) before LT and at 3-6-12 months after surgery when available, while LSM was assessed only after LT at the same time points. Ultrasonographic and biochemical data were also collected.

Results: Twenty-two recipients (median age 61.5 years, 55% males, 45% viral-etiology, 32% with HCC; 4 DCD grafts; donor age 58 years, 100% on CNI-based immunosuppression) were enrolled. Median SSM significantly decreased from 59 kPa pre-LT to 27, 22, 27 kPa at 3, 6, 12 months, respectively ($p<0.05$, **figure),** with 44% having more than 50% decrease already at month 3. Spleen diameter reduced from 15 cm pre-LT to 14, 13, 11 cm at 3, 6, 12 months ($p<0.05$), and median platelet count (65,000, 153,000, 148,000, 157,000 per mm^3, $p<0.05$) significantly improved over time ($p<0.05$). Median LSM did not significantly change post-LT (from 7 at 3 months to 6 and 5 kPa at 6 and 12 months, respectively, $p>0.05$).

Conclusions: Our study demonstrates a significant reduction of SSM and spleen diameter occurring within three months and remaining stable during the first year after LT. These results are consistent with the early reversal of CSPH after LT.



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P-72

Patients with cirrhosis and ascites treated with long-term albumin: An integrated management proposal based on a real-life study

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Background and Aims: Long-term albumin (LTA) is widely used in Italy in patients with cirrhosis and ascites. This study aims to analyze clinical courses and outcomes of patients receiving LTA.
Methods: Secondary analysis of "Real-ANSWER", an Italian multicenter, retrospective, real-world study.
Results: Of the 312 patients included (median Child-Pugh 8, MELD 15), after 3 months of LTA, 34% resolved ascites to grade 0-1 (responders), 33% had persistent ascites but no need for paracentesis (partial responders) and 33% still received paracentesis to control ascites (non-responders). At baseline, non-responders had more severe ascites, higher white blood cell count (6.00 vs 4.80 vs 4.90 10^9/L, p=0.001) and creatinine (1.1 vs 0.9 vs 0.9 mg/dl, p=0.003) compared to other groups, while no differences were found in etiology of cirrhosis, serum albumin, MELD and Child-Pugh. Among responders, 40% discontinued LTA due to improvement (median: 7 months; IQR 4-12), 26% received a transplant, 15% died. Among non-responders, 18% received TIPS (median: 5 months; IQR 3-12), 33% died, 11% received a transplant. Interestingly, 15% discontinued LTA due to subsequent improvement (median: 14 months; IQR 10-22), half of whom received etiological treatments. Among partial responders, 16% discontinued LTA due to improvement (median: 10 months; IQR 5-22), 21% received a transplant and 42% died. The cumulative incidence of 18-month mortality was lower in responders (18%) compared to partial responders (46%) and non-responders (42%, p<0.001).
Conclusion: Based on the ascites response after 3 months of LTA, three categories with different clinical courses can be identified, which would help in the decision-making process. Non-responders should receive TIPS whenever possible, except for those undergoing effective etiological treatment who can be reassessed later. Responders should continue with LTA as they have the highest chance of survival, resolution of ascites and likely recompensation. Treatment should be tailored on a case-by-case basis in partial responders.

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P-73

A dynamic contrast enhanced ultrasound based risk prediction model for the diagnosis of hepatocellular carcinoma in the grey area of ceus li-rads: The person4 model

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Background: Hepatocellular carcinoma (HCC) in patients with liver cirrhosis is characterized by a distinct dynamic vascular pattern, marked by arterial hyperenhancement followed by late and mild wash-out in the portal-venous phase. However, a substantial proportion of HCC cases exhibit atypical imaging features. Dynamic Contrast-Enhanced Ultrasound (D-CEUS) employing standardized software emerges as a promising tool, potentially enhancing the accuracy of tumor perfusion assessment.
Aim: This study aims to investigate the utility of integrating D-CEUS into the diagnostic algorithm for HCC in patients currently identified as candidates for liver biopsy.
Methods: From January 2021 to November 2023, consecutive patients with chronic liver disease and liver nodules candidated to liver biopsy were enrolled in this prospective monocentric cohort study. Contrast enhanced ultrasound (CEUS) was perfomed in all patients before biopsy and assessed by CEUS LI-RADS. Clips were examined by VueBox® software to obtain the time intensity curves. Baseline clinical characteristics and D-CEUS based quantitative parameters were compared among the different histological entities. Univariable analysis was employed, and relevant parameters were incorporated into a logistic regression model for HCC diagnosis. The diagnostic accuracy of the identified model was evaluated by Receiver Operating Characteristic (ROC) curve and relative Area Under the Curve (AUC).
Results: A total of 58 patients (mean age 67, 36 men) were enrolled, including 32 HCC, 15 intrahepatic cholangiocarcinoma (ICC) and 11 liver metastasis (LM). According to CEUS LI- RADS, 45 patients were classified as LI-RADS M, 5 as LI-RADS 3, and 8 as LI-RADS 4. Statistically significant differences between HCC and non-HCC patients were observed for variables such as the number of nodules ≥4 (p=0.03), irregular margins (p=0.01), peripheral rim-like hyperenhancement (p=0.002), and Peak Enhancement (PE) percentage change (p=0.006). The optimal logistic regression model was identified incorporating the following predictive variables: sex, number of nodules ≥4, peripheral rim-like hyperenhancement, and PE percent change. The model showed high accuracy (AUC 0.91) for the diagnosis of HCC.
Conclusions: A risk assessment model, combining clinical and D-CEUS data, has the potential to enhance the diagnostic performance of standard CEUS LI-RADS criteria for non-invasive HCC diagnosis in high-risk patients. If our data will be confirmed in larger multicenter studies, the proposed diagnostic model could revolutionize the non-invasive diagnosis of HCC in over 60% of patients currently considered candidates for liver biopsy.

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P-74

Quantification of plasma HDV RNA in untreated and Bulevirtide-treated patients with CHD: a comparison between Robogene 2.0, Eurobioplex EBX071 and Altostar

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Background and Aim: Accurate quantification of HDV-RNA is essential for diagnosing and managing chronic hepatitis Delta (CHD), but there is considerable variability between different assays. In this study, we compared three methods for HDV-RNA quantification in both untreated and Bulevirtide (BLV)-treated CHD patients.

Methods: Frozen plasma samples from untreated and BLV–treated CHD patients were tested in a single-center retrospective study by 3 different assays: Robogene HDV-RNA Quantification Kit 2.0 [Roboscreen GmbH; Lower Limit of Detection (LOD) <6 IU/mL, Lower Limit of Quantification (LOQ) 60 IU/mL on 7500 Fast Real-Time PCR System (Applied Byosystem)], EurobioPlex HDV PCR quantitative EBX071 [Eurobio Scientific, LOD <20 UI/mL, LOQ 50 UI/mL on CFX96™ real-time PCR detection system (Bio-Rad)] and AltoStar HDV RT-PCR RUO Kit 1.5 (Altona Diagnostics, estimated LOD <10 IU/mL estimated LOQ 20 UI/mL on AltoStar®AM16).
Results: 112 plasma samples from 79 CHD (10 untreated and 69 BLV-treated) patients were studied by 3 different assays (total 336 tests). All patients were HDV genotype 1 (available in 70). Median HDV RNA was 3.05 (-0.04-6.69) Log IU/mL with Robogene 2.0, 3.78 (-0.83-7.78) IU/mL with EurobioPlex EBX071, 3.22 (-0.31-7.03) IU/mL with AltoStar (Robogene *vs.* EurobioPlex p=0.005; Robogene *vs.* AltoStar p<0.0001; EurobioPlex *vs.* AltoStar p=0.5; overall p<0.0001). Compared to Robogene 2.0, EurobioPlex EBX071 reported higher (>0.5 Log IU/mL) HDV RNA levels in 33% samples, similar levels (<±0.5 Log IU/mL) in 55%. Likewise, compared to Robogene 2.0, AltoStar reported higher HDV RNA levels in 18% of positive samples, similar levels in 82%. Robogene tested target not detected (TND) or <LOQ in 33% samples, EurobioPlex in 36%, AltoStar in 20%, the difference in identifying as either positive or negative samples being statistically significant (p<0.01).
Conclusions: HDV-RNA levels quantified by EurobioPlex EBX071 and Altostar were similar to Robogene 2.0 in most samples. However, HDV-RNA undetectability rates significantly differed across assays.

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P-75

An easy and reproducible strategy to improve the structural integrity of the albumin molecule in commercial vials

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Background and Aims: Human albumin in commercial preparations present structural damages that may dampen its therapeutic potential in patients with decompensated cirrhosis as well as in other clinical settings. The aim of this study is to identify the pattern and timing of the onset of structural damage to albumin in commercial vials, and to develop a strategy to easily obtain a high-quality albumin solution in clinical practice.
Methods: Albumin structure was investigated by LC-MS throughout the manufacturing process and in a prospective study at different times of shelf-life of standard commercial vials. The impact of cold-storage and glutathione supplementation, alone or in combination, on albumin structure was also investigated.
Results: Contrary to the manufacturing process, storage at room temperature significantly impair the structural integrity of albumin already after 1 year, with a significant increase of the oxidized (HNA1: +24%; HNA2: +3%) and truncated (N-terminal: +12%) forms and a concomitant decrease of the reduced (HMA: -27%) and native (-30%) forms. Storage at 2-8°C minimizes oxidative and non-oxidative damage during shelf-life, while the addition of glutathione to commercial albumin vials almost completely reduced the Cys-34 residue. No other changes in albumin structure or binding activity were detected in the glutathione-mixed albumin solution, which remained stable up to 7 days at room temperature and was safe in animal experiments. After 24 months of shelf life the highest level of the native form of albumin was achieved by the combination of both strategies (64±1%) when compared to cold storage (43±1%) and glutathione addition (50±2%) alone.
Conclusions: This study describes a simple, low-cost, reproducible and safe method for the bedside preparation of a high-quality albumin solution with very high levels of native form from standard commercial albumin vials and provides the basis for the evaluation of its safety and efficacy in clinical trials.

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P-76

Outcome of hepatic resection for hepatocellular carcinoma in ideal and non-ideal candidates

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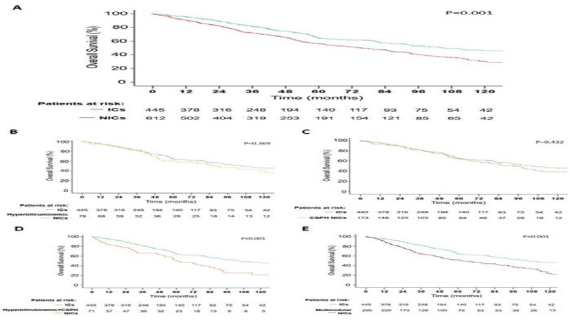
Introduction: Hepatic resection (HR) is a mainstay treatment for hepatocellular carcinoma (HCC). Current guidelines recommend HR in "ideal candidates" (ICs), i.e. patients with single lesion, normal bilirubin and no clinically significant portal hypertension (CSPH). â€¯
Aim: The objective of this study was to compare, in real-world practice, the outcome of HR between ICs and non-ICs.
Materials and Methods Results: Data from 1,057 Child-Pugh A patients without extrahepatic tumour spread undergoing HR for HCC over three periods (2000-2008, 2009-2015, 2016-2022) were retrospectively analyzed. CSPH was defined as presence of gastro-oesophageal varices and/or platelet count <100,000/mmc. Hyperbilirubinemia was accepted up to 2 mg/dL. Overall survival (OS) was measured from HR to death, loss to or end of follow-up (31/12/22). Patients undergoing liver transplantation (LT) were censored at the time of LT.

In each period non-ICs prevailed over ICs. Among non-ICs, the proportion of patients with isolated CSPH did not change over time, while that of patients with multinodular HCC (mHCC) increased. A decrease occurred for patients with hyperbilirubinemia (20.4% vs 10.1%; p=0.036) or hyperbilirubinemia+CSPH (21.5% vs 9.4%; p=0.005).

Over a median followâ€ up of 41.0 months, median OS was higher in ICs compared to non-ICs (104.9 vs. 75.3 months; p<0.001).â€¯However, compared to ICs, median OS did not significantly differ in patients with isolated CSPH (93.1 months; p=0.432) or isolated hyperbilirubinemia (86.0 months; p=0.369), while it was lower in those with hyperbilirubinemia+CSPH (60.0 months; p<0.001) or mHCC (61.9 months; p<0.001).

Compared to ICs, only hyperbilirubinemia+CSPH patients showed a significantly higher perioperative mortality.
Conclusions: In real-world practice, the proportion of ICs remained lower than that of non-ICs since 2000. Patients with CSPH or modest hyperbilirubinemia can receive HR without compromising their outcome. Studies comparing HR vs. non-surgical therapies are warranted for patients with both these features or mHCC, as they generate a poorer prognosis.



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P-77

The svr10k study: a real-world data with pangenotypic direct-acting antivirals across multiple diverse regions

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Introduction: Real-world data previously showed high effectiveness of sofosbuvir/velpatasvir (SOF/VEL) without ribavirin (RBV) in >6,000 HCV patients across 12 clinical cohorts in Australia, Canada, Europe, and the USA. Expanding this research to additional geographical areas assesses SOF/VEL effectiveness across diverse populations and evaluates HCV characteristics in Western countries, Asia, the Middle East, and Latin America (LATAM) (ongoing SVR10K study).
Methods: This analysis includes HCV patients ≥18 years treated with SOF/VEL (no RBV) for 12 weeks, as decided by the treating HCP, from 10 sites: Brazil, Hong Kong, Mexico, Singapore, Sweden, Spain, Taiwan, and the UAE, grouped into five regions: LATAM, Asia, Nordic, Southern Europe, and Middle East. Age, sex, treatment experience (TE), cirrhosis (F4, no decompensation), genotype, coinfections, time to treatment initiation (TTI), and overall SVR were analyzed.
Results: 6,633 patients were included, with Asian sites contributing over half, and LATAM sites with 496. Median age was 55 years [IQR 46-64]; highest in Asia (57 yo) and lowest in the Middle East (31 yo). Patients ≥ 50 years were 65% of the total, with the highest percentage in Asia and Southern Europe sites (71%%) and lowest in the Middle East (28%). Cirrhosis was reported in 20% [18%-24%],

with the highest rates in LATAM. Overall GT3 and GT1 were most common (31% and 30%); GT3 dominated in Nordic sites (57%), GT1 in the Middle East (49%). The TTI was available for 72% (n = 4,772) of the sample, with 13% treated in ≤30 days. Overall, SVR was 99% [97.1%-100%].

Conclusion: SOF/VEL efficacy remains consistently high across diverse populations. Improvements in timely treatment initiation are essential to meet the WHO 2030 HCV elimination goal.

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P-78

Systolic and diastolic dysfunction, but not cardiac hypercontractility, are unrelated to liver disease severity: a multicentric cohort study

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Introduction and Aim: Systolic dysfunction (SD, defined as impaired left-ventricle global longitudinal strain, LV-GLS > -18% or left-ventricle ejection fraction < 50%) or relevant diastolic dysfunction (DD) have been recently proposed as diagnostic criteria of cirrhotic cardiomyopathy (CCM). Both prevalence and prognostic implications of CCM have been largely explored in previous studies, but with conflicting results; similarly, liver disease severity has not been clearly recognized as risk factor for CCM. Furthermore, cardiac hyper-contractility (CH, LV-GLS < -22%) has been related to a more advanced liver disease and a reduced transplant-free survival. The aim of the study was to evaluate prevalence and associated factors of CCM and CH in a cohort of cirrhotic patients.

Patients and

Methods: Outpatient subjects with liver cirrhosis of any etiology and Child-Pugh (CP) class and without previous significant heart diseases were evaluated. A complete standard Color- and Tissue-Doppler echocardiography was performed; in particular, LV GLS was obtained in each patient.

Results: 101 subjects (76 males, median age 62 years, 43 CP A, 32 CP B, 26 CP C, alcoholic etiology 64%) were evaluated. Patients were paired for age, gender and prevalence of alcoholic etiology among CP classes. SD and DD were present in 15 (14.8%) and 17 (16.8%) subjects, respectively; in both, at multivariate analysis, age (OR 1.12, IC 95% [1.05-1.16], p=0.050), type II diabetes (OR 3.4, IC 95% [1.1-10.5], p=0.033, for SD) and baseline body mass index (OR 1.17 95% I.C. [1.03-1.37], p=0.043, for SD) resulted significantly associated. CH was more prevalent in subjects with higher CP score (14.6% of CP A, 40.0% of CP B, 59.1% of CP C, p<0.001); CP score (OR 3.7, IC 95% [1.99-6.88], p=0.001) or MELD score (OR 1.12, IC 95% [1.03-1.20], p=0.005) were independently associated in multivariate analysis.

Conclusion: Our data suggest that CH is associated to the severity of cirrhosis while both SD and DD are related only to age and metabolic risk factors, questioning the real etiological cause-effect relationship of liver disease and the so-called cirrhotic cardiomyopathy.

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P-79

Carriage of rare pathogenic apob variants predispose to severe masld and hcc

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Background and Aims: Metabolic dysfunction associated steatotic liver disease (MASLD) has a strong inherited component, which is not fully accounted by common genetic variation. Carriage of rare loss-of-function (LoF) variants in Apolipoprotein B (*APOB*) has been linked to increased susceptibility to steatosis, but the contribution to cirrhosis and hepatocellular carcinoma (HCC) is still disputed.

Methods: We investigated the impact of LoF *APOB* variants in a clinical cohort of people with MASLD and advanced fibrosis or HCC (advanced MASLD; n=510) vs. healthy controls, a family study (n=43 and a meta-analysis of literature), and the population-based UK Biobank cohort (n=416,331) on clinical outcomes and lipidomics/metabolomics/proteomics.

Results: LoF *APOB* variants were strongly enriched in patients with advanced MASLD vs. healthy controls (aOR 13.8, 95% c.i. 2.7-70.7, p=0.002), being observed in 1 in 22 cases, and associated with lower circulating lipids, but higher disease activity and fibrosis scores (p<0.05). Through familial studies of probands with advanced MASLD, *APOB* variants segregated with inheritance of liver steatosis and fibrosis (p<0.05). In UKBB, we observed increased risk of cirrhosis and HCC (aOR 2.01, 1.51-2.53 and 4.01, 3.09-5.15, respectively), the effect being larger for rarer variants (aOR 9.88, 8.8-10.96 and aOR 27.2, 25.26-29.08, respectively). Remarkably, we observed a dissociation between the impact of variants affecting specifically ApoB100 and very low-density lipoprotein secretion, with a larger impact on circulating lipoprotein levels and the risk of cirrhosis, and those impairing also ApoB48 and chylomicron secretion, associated with immunological biomarkers and a selective increase in the risk of HCC (aOR 5.9, 4.8-6.9).
Conclusions: carriage of rare LoF *APOB* variants are associated with advanced MASLD, with distinct contributions from impaired secretion of VLDL and chylomicrons, and genotyping may improve risk stratification and case finding.

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P-80

Outcomes of patients with alcohol-related cirrhosis referred to a hepatology outpatient clinic

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Background and Aims: Achieving abstinence is the most effective treatment of alcohol-related cirrhosis even if already decompensated. Patients with cirrhosis and alcohol use disorder (AUD) represents a special population and should be treated by a multidisciplinary team with a mandatory experience in addiction medicine (2020 AISF guidelines). This study aims to assess the outcome of patients with cirrhosis and alcohol-related cirrhosis referred to a hepatological service provided of an internal multidisciplinary alcohol unit.
Methods: Retrospective observational study assessing clinical trajectories and survival of patients with alcoholic cirrhosis referred to our hepatological service from 2016 to 2022 Prolonged abstinence was assessed by means of clinical and laboratory parameters.
Results: 175 patients (median age: 54 years; 77% male) were included. About 35% of patients had also a viral etiology and 26% MASLD. About 60% were decompensated, median MELD was 13 and MELD-Na 16. About 40% patients discontinued alcohol consumption at the hepatological evaluation without referral to the alcohol unit. About 45% accepted to be followed by the multidisciplinary alcohol team; of these patients, almost 35% achieved prolonged abstinence, while the remaining had several episodes of AUD recurrence alternating periods of abstinence in most cases. Interestingly, these latter patients showed an intermediate survival between abstinent individuals and active drinkers. Only 15% of patients refused any support and continued alcohol consumption. Clinical and socio-economic differences were observed among groups.
Conclusions: This study showed that, besides many patients able to stop drinking at the time of diagnosis of cirrhosis, combining a multidisciplinary alcohol unit embedded in a hepatological service is an effective approach for patients with cirrhosis and DUA even when prolonged abstinence is not fully achieved.

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P-81

Use of proton pump inhibitors among German Hepatitis C patients treated with sofosbuvir/velpatasvir: data from the German hepatitis C-Registry (2016â€“2022)

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Introduction: Pharmacokinetic studies suggest velpatasvir bioavailability may be reduced with concomitant proton pump inhibitor (PPI) use. This study examined the clinical relationship between PPI use and sustained virologic response (SVR) rates in patients treated with sofosbuvir/velpatasvir (SOF/VEL) ± ribavirin (RBV) in a real-world, multicenter, observational DHC-R Registry.
Method: Data from 1,154 patients (2016–2022) treated with SOF/VEL, with or without PPIs, were analyzed. Baseline characteristics and SVR rates (modified intention-to-treat [mITT], including ITT SVR and relapses) were assessed. Metamizole use, sharing a similar drug-drug interaction (DDI) profile, was also evaluated to assess multi-DDI effects.
Results: PPI users accounted for 8.5% (98/1,154) of patients. The most common PPI was pantoprazole (78/98), with doses of 20 mg (28/78), 40 mg (29/78), 80 mg (2/78), or unspecified (19/78). Other PPIs included omeprazole (19/98, doses of 20 mg: 14/19; 40 mg: 2/19; unspecified: 3/19) and esomeprazole (1/98, 80 mg). Among SOF/VEL+PPI users, 9.2% also took metamizole. PPI users were older (≥50 years: 59% vs. 37%), more often female (38% vs. 27%), had less genotype 3 (47% vs. 62%), and higher cirrhosis rates (compensated: 50% vs. 32%; decompensated: 17% vs. 4%).

SVR rates were comparable between groups, even in cirrhosis (=98%) across all genotypes, including genotype 3 with cirrhosis (≥96%). Metamizole use did not affect SVR (=100%). No dose-dependent SVR trend was noted for PPI doses (20 mg: 96–100%, 40 mg: 91–100%, 80 mg: 100%, unspecified: 100%).
Conclusion: PPI co-use during SOF/VEL therapy in the DHC-R study did not impact SVR, regardless of cirrhosis, PPI dose, or multi-DDI scenarios

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P-82

Atezolizumab plus Bevacizumab does not cause subclinical cardiotoxicity evaluated by Left-Ventricular Global Longitudinal Strain

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Introduction and Aim: The association of atezolizumab plus bevacizumab (AB) has been recently approved as a first-line treatment for advanced unresectable hepatocellular carcinoma (HCC). As a combination of an immune-stimulating and an antiangiogenetic agent, several cardiovascular adverse (CV) events/reactions had been shown, such as hypertension, heart failure, myocarditis and CV events. Since the exact prevalence of cardiac dysfunction after AB is unknown, the aim of the study was to evaluate its possible subclinical cardiotoxicity in a cohort of advanced HCC subjects particularly focusing on left-ventricle global longitudinal strain (LV-GLS)
Patients and Methods: Subjects with advanced unresectable HCC candidate to receive AB were enrolled from June 2022 to May 2024. For each patient, a complete echocardiographic examination was performed (VIVID T8 equipment) before and 6 months after the beginning of AB; LV-GLS was obtained according to ESC guidelines. Patients with advanced liver disease (Child-Pugh B and C) and previous CV events were excluded.
Results: Twenty-three subjects (95.8% males, median age 63.5 years, 78% with liver cirrhosis) completed the follow-up. No significant differences were found in standard left and right morphological and functional parameters between baseline and follow-up. A slight but non statistically significant reduction of LV-GLS (-19.5% [-18.6—20.7] vs -18.3 % [-17.7—20.1], p=0.120) was observed. Only 1 patient (4.3%) developed a significant reduction of LV-GLS < -15%) and none had new-onset diastolic dysfunction.
Conclusion: Our data suggest that, at least in our cohort, treatment with AB is generally safe in terms of cardiotoxicity. However, our study population had good cardiac function at baseline and a strict control of CV risk factors during observation, in particular hypertension. This underlines the importance of a global CV assessment in HCC patients undergoing chemo-immunotherapy.

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P-83

Liver and spleen stiffness measure by transient elastograghy: a promising tool for the clinical management of patients after Fontan-type surgery circulation

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Background: Haemodynamic changes after Fontan palliation in infant patients with univentricular heart promote so-called Fontan-associated-liver-disease (FALD). FALD is not adequately monitored by traditional liver clinical scores (e.g. MELD-XI, VAST score) and progression risk biomarkers and non-invasive tools are missing. Liver and spleen stiffness (LSM and SSM) measured by transient elastography might be useful technique.
Aim was to study correlations between LSM-SSM and FALD stages in adult post-Fontan patients.
Materials and Methods: 31 consecutive pts with compensated FALD (median age 27 y, 23.1-37.7 y; 8 F) were studied. We recorded liver morphology/structure by ultrasound-scan, LSM and SSM (Fibroscan®), biochemical liver tests, radiologic and/or upper endoscopic signs of portal hypertension and cardiological functional parameters.
Results: Median LSM and SSM were 16.8 (13.7-24.1) kPa and 30.4 (24.4-42.8) kPa respectively and significantly correlated (r=0.492, p=0.0058). LSM correlated with g-GT levels (r=0.452, p=0.0139) and caudate lobe hypertrophy (r=0.449; p=0.0127), while SSM did't. Patients with advanced liver involvement had significantly higher LSM [18.5 (16.6-38.8) kPa in VAST>1 vs 16.2 (13.1-20.8) kPa in VAST£1 pts (p=0.0499)]. LSM for VAST score>1 identified an AUROC of 0.750 (p=0.0136) and a 16.4 kPa cut off with 100% sensitivity and 50% specificity. SSM was not correlated with FALD stage. SSM was correlated to left ventriculus disfunction in logistic regression (r=0.384, p=0.461) and it was higher in pts on beta-blockers (34.0 vs 26.7 kPa, p=0.0294) or diuretics (39.1 vs 26.7 kPa, p=0.0401) reflecting a worse hemodynamic condition.
Conclusions: LSM and SSM appear promising tools for the clinical management of pts with Fontan circulation. LSM >16.4 kPa predicted with high sensitivity advanced FALD. SSM is significantly higher in patients requiring on diuretics, suggesting its potential role in the prognostic stratification of this challenging population. These preliminary results prompt prospective studies on larger cohorts of pts after Fontan's surgery.

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P-84

Use of Glucagon-like Peptide-1 Receptor Agonist is associated with reduced risk of major liver-related events: a meta-analysis

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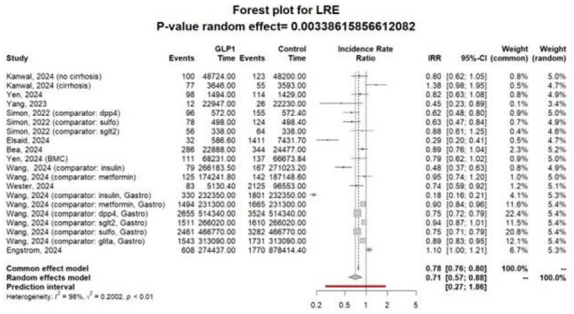
Introduction: Metabolic dysfunction-associated steatotic liver disease (MASLD) represents a leading cause of chronic liver disease worldwide. While glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have shown promise in managing metabolic-related outcomes, evidence regarding their impact on major liver-related outcomes (MALOs) remains heterogeneous.
Aim: This meta-analysis aimed to evaluate the incidence of MALOs, specifically hepatocellular carcinoma (HCC) and hepatic decompensation, in patients using GLP-1 RAs compared to non-users or users of other antidiabetic therapies.
Methods: Medical databases were searched through November 2024. Eligible studies included adult patients with type 2 diabetes treated with GLP-1 RAs, reporting the incidence of MALOs (defined as decompensated cirrhosis, hepatocellular carcinoma, hepatic failure, liver transplant or liver-related death), with appropriate adjustment for confounding factors. Incidence rates were extracted as events per person-year and pooled using random effect model.

Results: Eleven observational studies, including 647903 GLP-1 RA users and 819317 non-users, were included in the meta-analysis for MALOs. GLP-1 RA use was associated with a significant 29% reduction in MALOs risk compared to non-users, with a pooled incidence rate ratio(IRR) of 0.71(95%CI 0.57-0.88). Subgroup analysis according to the control group showed a significant decrease of the risk of LRE with GLP-1 RA compared to SGLT-2. Use of GLP-1 RA was associated with a significant reduction of 30% in the risk of hepatic decompensation, with a pooled IRR of 0.70(0.52-0.94)(6 studies). GLP-1 RA was associated with a non-significant decrease of 18% in the risk of HCC, with a pooled IRR of 0.82 (95% 0.61-1.11)(8 studies).
Conclusions: This meta-analysis demonstrates that GLP-1 RA use is associated with significant reductions in major liver-related outcomes and hepatic decompensation in patients with type 2 diabetes, while showing a non-significant trend toward reduced hepatocellular carcinoma risk. These findings support the potential therapeutic value of GLP-1 RAs in preventing progression of liver disease towards complications.



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P-85

Skin injuries prevention during TIPS creation: use of “alert levels” and “trigger levels” in a high volume TIPS referral hospital (>20 procedures/year)

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Background: TIPS creation is a highly challenging and radiation-intensive procedure in abdominal interventional radiology. Performing at least 20 TIPS procedures annually is associated with better patient outcomes and lower in-patient mortality rates, which can define a hospital as experienced in TIPS creation. However, the procedure carries significant risks, including skin injuries due to high radiation exposure, making it one of the most radiation-intensive procedures in interventional radiology.
Aim: To assess, in a high volume TIPS referral hospital, the application of “alert” and “trigger” levels for skin injuries prevention, in patients undergoing TIPS
Materials & Methods: Between 7/2017 and 2/2024, 286 consecutive TIPS were performed, in a single high volume TIPS referral hospital. “Alerts” were setted at 2Gy and 3Gy Cumulative air kerma at a reference point (Ka,r) and “trigger” at 5Gy. Fluoroscopy time (FT) was recorded and considered as surrogate of procedural complexity.
Results: 282 TIPS were performed on adult and 4 on pediatric patients. Median Ka,r was 0.11Gy (Q3 0.20Gy). Ka,r alerts and trigger levels were never encountered (alert quota 0%). The highest Ka,r was 1.56Gy in a TIPS performed on an adult patient with cavernoma after liver transplantation, for which FT was 65 min. No skin injuries were reported in the follow up of all patients
Conclusion: The low Ka,r values obtained suggest that the use of real-time ultrasound guidance and radiologists’experience, in a high volume TIPS referral hospital, allowed all TIPS to remain below the alert and trigger levels threshold at wich a skin reaction can occur (2Gy according to IAEA indication).

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P-86

The relationship between serum bile acids and event-free survival following the use of maralixibat for progressive familial intrahepatic cholestasis: data from MARCH/MARCH-ON

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Background: Maralixibat, an inhibitor of the ileal bile acid transporter, is approved in the EU for treatment of Progressive Familial Intrahepatic Cholestasis (PFIC) in individuals ≥3 months. Prior analyses in ALGS have demonstrated improved event-free survival (EFS) following use of maralixibat and this improvement is associated with reductions in sBA. Data from MARCH/MARCH-ON, a clinical trial of maralixibat for individuals with PFIC, demonstrated reductions in sBA. In this analysis, we evaluated the impact of sBA reduction on EFS.
Methods: The design of MARCH/MARCH-ON have been previously described. Data were administratively censored in June, 2023. First events (i.e., liver transplant, decompensation, surgical biliary diversion [SBD], or death) were identified for different PFIC types. For individuals with nt-BSEP and FIC1, 2-year EFS was calculated and stratified by sBA response at Week 26 (averaged over last 12 weeks) using thresholds developed by the NAPPED Consortium (BSEP: >75% reduction or <102 µmol/L; FIC1: <65 µmol/L).
Results: There were 5 events (nt-BSEP: 1 transplant, 1 decompensation; FIC1: 1 death, 1 SBD; and MDR3: 1 transplant) among 72 individuals with a median (Q1, Q3) follow-up of 94 (68, 110) weeks. The overall EFS was 92%. Among individuals with nt-BSEP, an sBA response was achieved in 12 of 27 (44%), and this group had no events yielding an EFS of 100%; an insufficient sBA response was observed in 15 (56%) and this group had 2 events yielding an EFS of 84%. The sBA reduction for the 2 patients with events were 19% and 26%. Among individuals with FIC1, an sBA response was achieved in 3 of 12 (25%) and this group had no events yielding an EFS of 100%; an insufficient sBA response was observed in 9 (75%) and this group had 2 events for an EFS of 78%. The sBA reduction for the 2 patients with events were 18% and 16%. When nt-BSEP and FIC1 were analyzed together, sBA responders had an EFS of 100% whereas sBA non-responders had an EFS of 81%. For the individual with MDR3 disease requiring a transplant, the sBA reduction was 44%.

Conclusion: Consistent with sBA response thresholds from the NAPPED Consortium that are associated with EFS, individuals in MARCH/MARCH-ON who reduced sBA levels below the threshold did not have a clinically meaningful event whereas some individuals who had lower reductions in sBA experienced events. These data support the importance of sBA reduction in PFIC and the potential of maralixibat to facilitate this biochemical change.

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P-87

Characterization of transcriptional and functional CD8 T cell heterogeneity to design individualized correction strategies for chronic HBV infection

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Introduction: HBV-specific CD8 T cells are exhausted/dysfunctional in chronic HBV patients. Simultaneous staining with the exhaustion (PD-1) and memory (CD127) markers identifies two main subsets of HBV-specific CD8 T cells ($PD1^{hi}CD127^{low/-}$ and PD1+CD127+) variably distributed in individual patients with HBeAg- chronic hepatitis.
Aim: To characterize the transcriptional profiling and functional features of HBV-specific CD8 T cell subsets in patients with HBeAg-untreated chronic active hepatitis (CH) and in CH patients who achieved HBsAg clearance either spontaneously or by NUC therapy (Re) to better understand their role in HBV pathogenesis and to identify intracellular pathways relevant for HBV functional cure.
Materials and Methods: Gene expression profiles of individual HBV $core^{18-27}$-specific CD8 T cell subsets sorted by PD-1 and CD127 co-staining were analyzed by Nanostring, adapted for low-input samples (e.g. 1-10 cells) in 5 HBeAg- CH patients and in 6 Re patients. The analysis of checkpoint/differentiation molecules (CD39, Bcl-2), transcription factors (TOX, TCF1) and cytokines (TNF-a and IFN-g) by flow cytometry was performed in an expanded cohort of 21 CH and 11 Re patients.
Results: Transcriptional analysis of HBV-specific CD8 T cell subsets shows an enrichment in exhaustion-related genes in the $PD1^{hi}CD127^{low/-}$ subset as compared to $PD1^{+}CD127^{+}$ *memory like* (*ML*) cells in CH patients, which is even more significant when the comparison focuses on $PD1^{+}CD127^{+}$ *ML* cells of Re patients. A signature of 13 genes identifies the progressive transition from the more exhaustion-oriented $PD1^{hi}CD127^{low/-}$ CD8 T cells of CH patients to the intermediate phenotype of $PD1^{+}CD127^{+}$ T cells of CH patients and the more memory-oriented $PD1^{+}CD127^{+}$ *ML* T cells of Re HBsAg- patients.
Conclusions: Our study identifies distinct exhaustion signatures in the different HBV-specific CD8 T cell subsets that coexist at different ratios in the distinct phases of the disease and that may guide individualized transcriptional/functional correction therapies for CHB patients.

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P-88

Assessing perilipin-2 as a liver-specific biomarker: lack of correlation between cardiac damage and its levels in heart failure patients

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Perilipin 2 (PLIN2) is linked to lipid deposition in non-adipose tissues, and its increased expression is associated with various metabolic diseases. Recently, PLIN2 has been proposed as a specific and sensitive biomarker for detecting MASLD and/or liver fibrosis.

The aim of this study is to confirm the role of PLIN2 as a specific biomarker of liver damage, excluding its correlation with cardiac damage in patients with cardiovascular disease.

This is a case-control study to assess the association between PLIN2 levels and cardiac damage in patients affected by heart failure (HF) compared to PLIN2 levels in MASLD patients. A total of 50 patients affected by HF, without history of MASLD as determined by non-invasive scoring methods, were enrolled. Patients were divided into two subgroups based on history of coronary artery disease (CAD) and degree of systolic dysfunction, expressed as ejection fraction (EF): patients with a previous history of CAD and EF $<$ 50% (CAD n=33) and patients without history of CAD and EF $\geq$ 50% (HFpEF n=17). A total of 20 controls with histological proven MASLD without history of HF were included. PLIN2 monocyte expression was assess by flow cytometry. Data were analyzed by Mann-Whitney U test and expressed as mean±SEM.

PLIN2 protein level was significantly lower in subjects with HFnoMASLD (3.68±1.13 MFI; $p<0.0001$) compared to MASLD patient (19.10±8.48 MFI; $p<0.0001$). Moreover, there was no difference in PLIN2 level between patients with CAD or HFpEF (3.68±0.97 and 3.61±1,30 MFI; $p=0.24$), highlighting the lack of association between PLIN2 levels and HF.

Preliminary data show that there is no correlation between HF and PLIN2 levels, regardless of ischemic or non-ischemic etiology. This study reinforces the role of PLIN2 as a specific biomarker of liver damage despite the crucial role of monocytes and lipids accumulation in the pathogenesis of CAD.

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P-89

Clinical benefits of maralixibat for patients with Alagille syndrome are durable through 7 years of treatment: data from the MERGE study

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Introduction: Maralixibat, an ileal bile acid transport inhibitor (IBATi), is approved for the treatment of cholestatic pruritus in patients with Alagille Syndrome (ALGS) ≥2 months of age in Europe. Improvements in pruritus, serum bile acids (sBA), and height have been demonstrated from prior clinical trials including ICONIC, which followed participants up to 4 years, as well as IMAGO/IMAGINE and ITCH/IMAGINE-II, which reported outcomes to approximately 1.5 years. Participants from ICONIC, IMAGINE, and IMAGINE-II trials were invited to enroll in MERGE for additional long-term follow-up (LTFU); prior long-term survival outcomes (e.g., liver transplant, death) for this group have been previously reported.
Aim: Here we report on efficacy in participants with additional LTFU from MERGE, including some participants that have received treatment for 7 years.
Methods and Method Results: All participants from ICONIC, IMAGINE and IMAGINE-II were included in the analysis. Impact of maralixibat was assessed for pruritus [ItchRO(Obs) 0-4 scale, with a ≥1-point reduction considered clinically meaningful], sBA, height and weight z-scores, ALT, total bilirubin (TB) and direct bilirubin (DB). Change from Baseline (CFB) was determined by comparing median (Q1, Q3) values from enrolment in the initial trial (i.e., ICONIC, IMAGO, or ITCH) to data from the visit in MERGE that best aligned with an annual visit. Data were analyzed for 86 participants at Baseline, with follow-up to 1 year for 76 participants, 4 years for 42 participants, and 7 years for 23 participants. Of the 86 participants, 84 had a genetic diagnosis of ALGS via the *JAG1* mutation, 2 participants had a genetic diagnosis of ALGS via the *NOTCH2* mutation, and 1 participant had an unidentified mutation. Baseline mean (SD) ItchRO(Obs) was 2.65 (0.75) and clinically meaningful reductions over time with CFB of -1.57 (-0.83, -2.14), -2.00 (-1.43, -2.56), and -2.14 (-1.43, -3.00) at 1 year, 4 years and 7 years, respectively. Likewise, Baseline sBA was 254 (207) µmol/L and decreased with CFB of -57 (8, -150) µmol/L, -62 (-32, -152) µmol/L, and -105 (-41, -266) µmol/L at 1 year, 4 years and 7 years. Improvement was observed in height, with Baseline z-score of -1.7 (1.27) and CFB of 0.1 (-0.1, 0.3), 0.3 (0.0, 1.0), and 0.7 (0.0, 1.2) at 1 year, 4 years and 7 years while weight z-scores were largely unchanged. Reductions in TB and DB were observed after treatment with maralixibat. No clinically meaningful changes in ALT or AST were observed with maralixibat treatment. There were no new safety signals.
Conclusions: In this unmatched cohort, the benefit of maralixibat in ALGS patients, including both improvements in clinical outcomes and sBA, persist through 7 years of treatment. No new safety concerns were identified in the long-term.

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P-90

Gaps in metabolic dysfunction-associated steatotic liver disease (MASLD) screening and management: a retrospective audit of patients at cardiometabolic risk in secondary care

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Introduction and Aim: Significant gaps exist between cross-specialty guidelines and the management of cardiometabolic patients at high risk for MASLD, particularly those referred to secondary specialist settings. Fragmented care approaches and insufficient communication hinder effective disease management, exacerbating the MASLD burden. The OPTIMA-NASH study (Optimizing Management of Comorbid NASH through Multidisciplinary Integration and Artificial Intelligence Alliance) aims to identify and address these practice gaps.
Methods: This single-center, retrospective, longitudinal practice improvement initiative, based on a clinical audit, included patients with at least one cardiometabolic risk factor (prediabetes, type 2 diabetes, obesity, dyslipidemia, arterial hypertension, or atherosclerotic cardiovascular disease) evaluated at Niguarda outpatient clinics over 24 months.
Results: Of 854 patients (mean age 65.8±15 years, 56.8% male), 41.3% had diabetes, 27.5% were obese (mean BMI 27.9±4.9 kg/m²), 29.6% had mixed dyslipidemia, and 59.3% were hypertensive. Additional comorbidities included ischemic heart disease (15.6%), atrial fibrillation (25.1%), heart failure (2.8%), a history of TIA/stroke (4.8%), and chronic kidney dysfunction (10.2%). Most patients (81%) had ≥2 risk factors, reflecting a very high-risk population. Data to calculate the FIB-4 score were available for 311 patients, of whom 51% had a FIB-4 >1.3 (mean 1.7±1.67), warranting further assessment with transient elastography (TE). NAFLD Fibrosis Score (NFS) data were available for 162 patients, with 52% exceeding the threshold of -1.455 (mean -1.224±1.733). TE was performed for 153 patients (mean 8±6.9 kPa). Both FIB-4 and NFS demonstrated moderate predictive accuracy for advanced fibrosis (AUROC 0.768 and 0.739, respectively). Controlled attenuation parameter (CAP) values, available for 80 patients, showed 77.5% exceeded 275 dB/m.
Conclusion: Screening for MASLD in high-risk cardiometabolic patients within secondary care is suboptimal. This highlights the need for enhanced protocols and improved communication between specialties to enable timely screenings and interventions. Addressing these gaps can facilitate better MASLD management and reduce its burden in at-risk populations.

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P-91

Liver disease is highly prevalent in patients with hereditary transthyretin-related amyloidosis

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Introduction: Hereditary transthyretin-related amyloidosis [ATTRv amyloidosis (AA)] is a rare and progressive disease characterized by the deposition of transthyretin amyloid in various organs, mostly in the heart (cardiac phenotype) and peripheral nerves (neurological phenotype). However, data on the possible co-presence of liver damage in patients with AA are scant.
Aims: To assess prevalence and characteristics of possible liver disease in a quite large cohort of patients with AA.
Materials and Methods: Patients with AA, regularly followed up at the Cardiology and Neurology referral centers of the University Hospital of Messina, were evaluated at the Unit of Medicine and Hepatology by means of liver biochemistry/elastography/ultrasonography. Liver stiffness measurement (LSM) was considered abnormal when stiffness values were above 8 kPa, and ultrasonography when signs of chronic or cirrhotic liver disease were present.
Results: Fourty-six patients (37 males, mean age 70.3±11 years) were enrolled. Twenty-five (54.3%) had cardiac phenotype, 13 (28.3%) neurological manifestations, and 8 (17.4%) mixed phenotype. Overall, 19/46 (41.3%) patients had alteration of liver biochemistry and/or stiffness and/or ultrasonography. No patient had viral or autoimmune hepatitis, nor alcohol use disorder. Fourteen/46 patients (30.4%) had LSM >8 kPa, and they were older (median age 76.8 vs 67.7 years, p=0.007), with larger spleen diameter (11 vs 10 cm, p=0.02) and lower platelet count (150×10^9/L vs 212.5×10^9/L, p<0.0001) than patients with lower LSM; no differences in prevalence of diabetes, obesity and dyslipidemia was found between patients with different LSMs. Ten/14 patients with LSM >8 kPa had cardiac and 4/14 a neurological phenotype, while patients with LSM <8 kPa had cardiac phenotype in 15/32 cases, neurological in 9/32, and mixed in 8/32 (p= n.s.). Overall, liver stiffness was directly correlated with NT-proBNP values (p=0.003) and inversely related to platelet count and portal vein flow (p<0.0001 and p=0.02, respectively).
Conclusions: patients with AA show a high prevalence of liver disease and should therefore promptly be referred to a liver center for a careful assessment of possible liver damage.

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Relationship between recipient/donor features and liver stiffness measurement in the first year after liver transplantation

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Introduction: liver stiffness measurement (LSM) is widely used in the management of long-term liver transplant (LT) recipients to non-invasively evaluate graft function. However, its clinical application in the early period post-LT needs further investigations.
Aim: to evaluate the relationship between LSM trend during the first 12 months post-LT and recipient and donor features at LT.
Materials and Methods: This is a single-centre retrospective study enrolling consecutive patients undergoing LT between 2015 and 2023. Deceased LT recipients within 6 months as well as those undergoing re-LT or without LSM were excluded. LSM was performed at 6 and 12 months by vibration-controlled transient elastography (Fibroscan©, Echosens, Paris). We investigated the association between LSM>8 kPa (defining presumptive graft damage) and donor/recipients features at LT.
Results: 326 LT recipients were enrolled, median age 58 years (18-72), 73% males. Liver diseases pre-LT were viral hepatitis (54%), Met-ALD (29%), immune-mediated (10%) and others (7%). 55% were transplanted for HCC, 38% for decompensated cirrhosis. Eight percent of grafts were DCD, all patients were on CNI-based immunosuppressive regimen. Median LSM was 6.6 (2.5-30.5) kPa with 87 patients (27%) showing LSM>8 kPa at 6 months and 6.1 (range 2.5-24.1, p=0.02) kPa with 65 patients (20%) with LSM>8 kPa at 12 months. By univariate analysis, among all the LT features, including type of grafts (DCD, DBD, split), donor features (age, sex, BMI) and recipients characteristics (aetiology, MELD, BMI, diabetes), only donor age was associated with LSM>8 kPa both at 6 and 12 months (6-month OR=1.04, 95%CI 1.02-1.05, p<0.01; 12-month OR=1.03, 95%CI 1.01-1.06, p<0.01).
Conclusions: Our study shows that recipient and graft features do not significantly affect LSM trends during the first year post-LT except for donor age. The negative impact of older donors on early LSM needs to be confirmed on long-term graft outcomes.

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Bone fragility and fracture risk assessment in metabolic disfunction-associated steatotic liver disease

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Introduction: Metabolic dysfunction-associated steatotic liver disease (MASLD) and Type 2 diabetes (T2D) share several risk factors for bone fragility despite the precise mechanism implied in fracture development is not defined.
Aims: This study aims to evaluate fracture bone risk in patients with MASLD and T2D using the trabecular bone score (TBS), an index of bone microarchitecture quality.
Materials and Methods: One-hundred-eight patients with MASLD and T2D (median age 62 years, 54% male, 26 cirrhotic, 47% with BMI>30 kg/m^2) who consecutively attended the Hepatology Unit of the University Hospital of Messina from February 1st,2024,

to October 31st,2024, were enrolled. Exclusion criteria were the presence of decompensated cirrhosis, thyroid/parathyroid diseases, chronic kidney disease, heart failure, active malignant neoplasia, and bone metabolism therapies used for >3 months. All patients underwent liver stiffness measurements (LSM)/Controlled Attenuation Parameter (CAP) evaluation by fibroscan and dual-energy X-ray absorptiometry (DEXA) with TBS assessment.
Results: Overall, study population presented median LSM and CAP values of 7.5 kPa (5.8-13.9) and 298 dB/m (255-324) respectively. Sixty-three patients (58.9%) had a pathological TBS (cut-off <1.350), and 55 (52%) presented sub-clinical vertebral fractures at DEXA. Patients with pathological TBS showed higher BMI values (p<0.0001), LSM>8 kPa (p=0.038), higher CAP levels (p=0.007), and LDL-c (p=0.035) compared to patients without. TBS values were inversely correlated with CAP and visceral adiposity index (p=0.006; p=0.003, respectively) and directly with L1-L4 and femur BMD (p<0.0001, p=0.002). Patients with vertebral fractures showed higher BMI levels (p=0.001), LSM (p=0.027), CAP (p=0.010) values, and pathological TBS (p<0.001). At logistic univariate and multivariate regression analysis, independent variables associated with the presence of a pathological TBS score were BMI>30kg/m^2 (p<0.001), CAP>298dB/m (p=0.020), and higher values of total FRAX score (p=0.027).
Conclusions: Evaluation of TBS in MASLD and T2D patients could be useful for assessing bone fragility and enabling an early fracture diagnosis.

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Direct effects of psilocybin on serotonin receptors regulate lipid accumulation in hepatic cells and adipocytes

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Introduction: The serotonin receptor (5-HTR) agonist psilocybin, an alkaloid of *Psilocybe* mushrooms, is the prodrug of the active compound psilocin, known for its central psychedelic effects exerted by agonism to the 5-HT2AR isoform. Psilocybin reduced MASLD, insulin resistance and body weight gain in animal models, when used at non-psychedelic doses. However, nothing is known about psilocybin action on peripheral 5-HTRs.
Aim: This study aimed at confirming the existence of a direct effect of psilocin on hepatic cells and adipocytes and unravelling the molecular mechanism of this metabolic effects.
Methods: The in vitro effect of psilocin (10 µM) on lipid accumulation was assessed on HepG2 and HUH-7 cells treated with a mixture of palmitic and oleic acid (PA:OA). Further evaluations were performed on spheroids of 3T3L1-derived adipocytes. The mRNA and protein expression of 5-HT2AR and 5-HT2BR was evaluated by qPCR and western blot, respectively.
Results: 5-HT2AR and 5-HT2BR are both expressed in hepatic cell lines. The direct antisteatotic effect of psilocin was demonstrated in HepG2 and HUH-7 cells, where it induced a significant reduction in the number and area of â€<â€<lipid droplets respect to PA:OA treated cells. In HepG2 cells, this effect was reverted by the concomitant treatment with an excess of the 5-HT2AR antagonist ketanserin. Notably, we observed that psilocin increased the expression of 5-HT2BR in HepG2 cells (p<0.05 vs control cells), suggesting a possible effect also on this isoform, known for its role in hepatic fibrogenesis. In spheroids obtained with 3T3L1-derived adipocytes, a significant reduction of lipid accumulation after psilocin treatment was observed.
Conclusions: The results of these studies suggest that psilocin, previously known primarily for its central agonistic activity at the 5-HT2AR, also exerts peripheral metabolic effects in hepatic cells and adipocytes through its action on serotonergic receptors.

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Beneficial effect of the combination psilocybin-semaglutide in a murine model of Steatotic Liver Disease

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Introduction: MASLD pathogenesis is correlated with insulin-resistance, and recently glucagon-like peptide-1 (GLP-1) receptor agonists gained interest in MASLD therapy. Psilocybin has been reported to ameliorate the phenotype of a MASLD mouse model. Serotonin (5-HT) acts in combination with GLP-1 agonists to control feeding behaviors and modulates the nutrient-induced release of GLP-1 in the ileum.
Aim: the 5-HT/GLP-1 axis has not been fully explored as pharmacological target, therefore here we evaluated GLP-1 mimetic semaglutide and 5HT2AR agonist prodrug psilocybin combined effects in a mouse model of MASLD.
Materials and Methods: an *in vivo* model of MASLD was obtained by feeding C57BL6 mice (n=10 per group) with a high fat (60% kcal from fat) and high fructose (30% fructose) diet. Semaglutide (40 mcg twice weekly, s.c.) and psilocybin (0.05 mg/Kg daily, p.o.) were administered alone or in combination. A control group of mice (n=10) fed with standard diet was used.
Results: Body weight gain was significantly reduced by all treatments, particularly with semaglutide-psilocybin combination. Liver steatosis was reduced by all treatments. Although all treated groups showed a significant reduction of fasting glucose, insulin and HOMA index (p<0.05 vs HFHFD untreated mice), only combination-treated mice showed a drop of insulin (3-fold-decrease, p<0.05) and glucose (1.5-fold-decrease, p<0.05) area in the ipGTT. Grid test was used to evaluate muscular strength. Psilocybin alone or in combination delayed motor performance deterioration, which was rapidly reached by the untreated and semaglutide-treated MASLD mice. mRNA levels of perilipin-4, which plays a detrimental role in myosteatosis, were reduced (p<0.05) in quadriceps of psilocybin-treated mice.
Conclusions: Psilocybin- semaglutide-treated MASLD mice showed an improvement of metabolism and liver steatosis. The combination psilocybin-semaglutide further ameliorated insulin sensitivity and preserved muscle function, indicating potential advantages of combination therapy.

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Outcome and predictors of major adverse cardiovascular events after liver transplantation: a single center experience

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Introduction: Liver transplantation (LT) is the only life-saving treatment option for end-stage liver disease. However, major adverse cardiovascular events (MACE) are a leading cause of morbidity and mortality after LT, accounting for over 40% of early deaths (<30 days) after surgery.
Aim: To assess the incidence, predictors and outcome of post-LT MACE.
Methods: All consecutive adult patients who underwent LT between January 2018 to February 2023 in our Center were retrospectively evaluated. Each patient was represented only once in the cohort. MACE were defined as: congestive heart failure, acute coronary syndrome, arrhythmia, ischemic stroke, peripheral artery disease. Continuous variables were shown as median (IQR) while categorical variables were shown as percentages. Logistic regression was used to evaluate association between variables and outcomes.
Results: A total of 235 patients were included (baseline characteristics shown in the Table). During a mean follow up of 33 (range 1-60) months, 36 (15%) LT recipients experienced a MACE. The early mortality rate (<30 days from OLT) for cardiovascular events was 33% (4/12). 20% of MACE occurred during LT or < 48 hours after surgery, reaching 80,5% within 30 days from OLT and 86% at 1 year post-LT. The most frequent event was arrythmia (56%), followed by acute coronary syndrome (22%) and congestive heart failure (19%). Previous history of arrhythmia (OR=7.86, 95% CI 1.98-33.3, p=0.003) and obesity (OR=2.55, 95% CI 1.03-5.96, p=0.035) were significantly associated with MACE occurrence. The concomitant presence of more than one cardiovascular risk factor (diabetes+hypertension+age >60 years) was way more frequent in MACE cohort compared to no-MACE cohort (16% vs 5%, p=0.02).
Conclusion: Despite the accurate patient's selection pre-LT, 15% of patients developed an early post-LT MACE, being arrythmias the most frequent event. Previous history of atrial fibrillation and obesity were strongly associated with MACE.

Characteristic	N = 235
Age at LT, Median (IQR)	58 (51 – 63)
Male, n (%)	162 (69%)
BMI, Median (IQR)	24.8 (22.7 – 28.4)
Etiology of liver disease	n (%)
HCV	54 (23%)
ETOH	57 (24%)
HBV	31 (13%)
Dismetabolic	6 (3%)
Autoimmune disease	23 (10%)
ADPKD	9 (4%)
Other	55 (23%)
HCC at LT	90 (38%)
Type 2 diabetes	62 (26%)
Arterial hypertension	68 (29%)
BMI ≥30 kg/m²	32 (14%)
History of coronary disease	10 (4.3%)
History of arrhythmia	9 (3.8%)
History of congestive heart failure	2 (0.9%)

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Improving effects of sacubitril/valsartan on hepatic fibrosis in MASLD patients with heart failure

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Introduction: Metabolic associated steatosic liver disease (MASLD) is associated with cardiovascular events and increased mortality. Liver fibrosis is a major determinant for chronic liver disease (CLD) progression and is associated with previous history of coronary heart disease, atrial fibrillation, heart failure correlating with poor prognosis. Liver fibrosis has no current approved drugs and its identification by non-invasive tests (NIT) (such as Fib-4, NFS, NAFLD Fibrosis Score, FAST, Agile 4) or non-invasive imaging (Fibroscan or T1-mapping MRI) is still a matter of controversy.

Sacubitril/valsartan is a new drug for the heart failure treatment, improving myocardial function and reducing myocardial fibrosis. In this setting, our study aims to evaluate in patients with MASLD with mild-reduced ejection fraction (HF r or m EF), the effects on liver fibrosis assessed by liver stiffness measurement (LSM) with Fibroscan.
Material and Methods: In this prospective cohort, data were collected from subjects attending the clinical cardiology (either ward or outpatients setting) of the Azienda Ospedaliera Universitaria Integrata di Verona –AOUI -, Veneto region, Italy, enrolled in the Heart Failure registry of AOUI Verona, with a chronic HF r o m EF. Echocardiography and Fibroscan were performed before and 6-month after sacubitril/valsartan administration, following optimization of all the other HF therapies. No signs of clinical or ultrasound congestion were documented.
Results: Twenty-seven patients were enrolled (male 89%, median age 61). Median HF was 30%. Six months therapy with sacubitril/valsartan led to an HF improvement from 30 to 38%. In 9 patients (33.3%) with hepatic fibrosis (LSM at the baseline > 8kPa, F1), we found a significant decrease in LSM from 9.8 to 7.8 kPa (p=0.008), whereas Fib score did not show any significant difference.
ConclusionS: Though in a small sample, we reported the beneficial effects of sacubitril/valsartan on hepatic fibrosis of MASLD patients. This finding paves the way to analysis of larger series of patients.

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A multicenter analysis on efficacy and safety of Tenofovir alafenamide (TAF) in a wide cohort of patients with chronic hepatitis B (CHB)

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Introduction: First (Lamivudine-LAM), second (Telbivudin, Adefovir-ADV), and third (Tenofovir-TDF, Entecavir) generation Nucleos(t)ide analogues (NAs) changed the natural history of CHB, leading to high rates of virological suppression, despite a not negligible risk of virologic resistance and nephrotoxicity (mostly ADV and TDF).
Aim: To investigate clinical and virological outcomes of patients treated with TAF, the most recent NA approved for HBV therapy.
Methods: We retrospectively enrolled 381 patients with CHB (median age: 72, IQR 66–77 years; males: 69.3%; liver cirrhosis: 38.3%) treated with TAF (median treatment duration: 3.7, IQR 2.5–4.5 years) in three Northern-Italian centers. Data were collected at TAF introduction (T0) and last follow-up (FU).
Results: Median NAs treatment duration before TAF initiation was 15.5 (12.5–18.3) years (LAM: 317, 83.4%; ADV: 215, 56.4%; LAM+ADV: 190, 49.9%). Thirteen (4.3%) patients had previous kidney transplant, 175 (45.9%) had chronic kidney disease and 190 (49.9%) needed NAs dose reduction due to renal impairment. The main indications for switching to TAF were age >60 years, virologic resistance, and Reduced glomerular filtration rate (GFR). From T0 to last FU, we did not observe any variation in creatinine values (1.10, 0.90–1.30 mg/dL vs 1.09, 0.90 – 1.30 mg/dL; p=0.660) and GFR-MDRD4 (66.9, 52.4–80.9 mL/min vs 66.1, 52.8–80.6 ml/min; p=0.470), while ALT values further decreased from 21 (17–27) U/L to 20 (15–26) U/L (p<0.001). At T0, 361 (94.7%) were HBV-DNA-negative, and none had a virological relapse; for the other 20 (5.3%) viremic patients, only 4 were still HBV-DNA-positive at last FU (2 of whom had FU<4 months). During TAF, 8 (2.4%) patients had de-novo HCC, and 33 (8.7%) died, mostly for non-liver-related causes (60.6%).
Conclusions: TAF treatment was effective in inducing and maintaining virologic and biochemical remission. No significant safety concerns were observed in patients with renal impairment.

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P-99

Prognostic value of liver stiffness trends vs. absolute values after sustained virological response in HCV-related advanced chronic liver disease. a monocentric retrospective study

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Background and Aim: SVR achievement in patients with ACLD is associated with a range of positive outcomes, including liver health improvement. Favorable outcomes have been reported in patients [BA1] with persistent absence of symptoms associated with LSM <20kPa and [BA2] in those with a decrease in LSM ≥20% and/or LSM decrease below 10kPa[BA3] . However, this criteria still require validation in independent series. Indeed it is still unclear whether the best prognostic stratification can be achieved by using the absolute LSM achieved after SVR, or the relative change as compared to the pre-treatment value. The aim of the study was to clarify this issue in a cohort of HCV patients undergoing SVR.
Methods: 135 patients with compensated ACLD (cACLD) treated between December 2014-March 2022 at our Hepatology Unit and who underwent at least 2 LSMs and followed-up until February 2024 were evaluated for inclusion in this retrospective longitudinal cohort study.
Results: 135 cACLD patients were included in our cohort and in the analysis; 56% male, with a median age of 69 ys. Median-LSM was 18kPa (IQR 15-23). LSM at the first FU post-therapy (FU-LSM) showed good predictive ability for decompensation within the first 3-years after treatment. Similar to FU-LSM, both FIB-4 and APRI measured at baseline or first FU post treatment showed good predictive abilities for decompensation for the first 36 months. Evaluation of Baveno-VII criteria through three separate models demonstrated that only FU-LSM > 20kPa was significantly associated with decompensation, while changes of LSM vs. pre-treatment values were not.
Conclusions: In conclusion, our findings support the EASL and Baveno-VII guidelines recommending repeated liver stiffness measurements (LSM) during the follow-up of patients receiving etiologic treatment for HCV-related liver disease. Furthermore, our data confirms that the absolute LSM values during follow-up is the strongest prognostic indicator for predicting a high risk of liver-related events.

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P-100

Epidemiologic features influencing the selection of direct acting antivirals (DAA) in HCV patients: an Italian real-world study

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Introduction: Pangenotypic direct-acting antivirals (pDAAs) have significantly improved HCV management. Despite comparable efficacy and safety profiles, the choice between available pDAAs often depends on regimen and/or patients features. Given the high prevalence of comorbidities and polypharmacy among HCV patients, understanding the clinical drivers of pDAA selection is crucial, particularly concerning potential drug–drug interactions (DDIs).

Aim: To investigate clinical, pharmacological and epidemiological drivers influencing pDAA regimen choice in Italy and identify possible gaps in personalized treatment.
Materials and Methods: Between 2018 and 2023, HCV-infected patients were identified from administrative databases of healthcare entities covering ~3.7 million citizens, distributed in the principle Italian Regions. Then, pDAA-treated patients receiving SOF/VEL or GLE/PIB (mutually exclusive cohorts) were compared for demographic, clinical and therapeutic features.
Results: Among 5,565 HCV patients, 51% received SOF/VEL and 49% GLE/PIB. SOF/VEL-treated patients were older (60.8 vs 57.6 years, $p<0.001$), showed higher comorbidities rates, including diabetes, mental disorders, cancer and cardiovascular diseases, were more frequently hospitalized (particularly for hepatobiliary morbidities: 16% vs 10.3%, $p<0.001$), and had more exemption codes for chronic illnesses (mainly chronic hepatitis, hypertension and diabetes). Additionally, polypharmacy was more common in SOF/VEL group, with 25% receiving $\geq$10 drugs compared to 17% in GLE/PIB group, with a larger number of drugs prescribed other than pDAAs (6.3 ± 5.6.vs 4.9 ± 5.2; $p<0.001$).
Conclusions: SOF/VEL-treated patients represent an older, frailer population with a heavier comorbidity burden and greater polypharmacy. The lack of a protease inhibitor (PI) in SOF/VEL regimen may reduce DDI risk and also be preferable for advanced liver disease. These findings offer insight into evolving prescribing trends and current HCV management in Italy. Despite the cohort has been extracted by the 6% of Italian heath-assisted population, a study limitation is the possible underestimation of HCV and pDAA-treated patients due to identification methodology.

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P-101

Pathogenic pathways in MASLD: comparison between "Metabolic" and "Genetic" MASLD, a multiOmics cohort study

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Background: The pathogenesis of MASLD can be explained in part by a metabolic component, including obesity, and in part by a genetic component. In fact, several single nucleotide polymorphisms (SNPs) have been correlated with high risk of fibrosis/inflammation in patients with MASLD and, on this basis, even a "genetic risk score" (GRS) has been validated. Recently, it has been hypothesized that "metabolic MASLD"(MM - without any genetic mutation) may have a different pathophysiology in respect to "genetic MASLD" (GM). However, this has been only partially demonstrated by indirect evaluations. Aims: To investigate, in a large cohort of MASLD patients of Southern Italy, if, and how, the metabolomic profiles of patients with GM are different from MM ones and in respect to healthy controls.
Patients and Methods: 270 MASLD patients from a tertiary center of Southern Italy and 102 controls were characterized by performing clinical, laboratory, genetic and untageted metabolomic evaluations. Inclusion criteria: presence of US evidence of steatosis in absence of any other liver disease. Every patient was classified based on of fibrosis risk in three groups: low-risk, high risk of fibrosis and cirrhosis, by clinical/laboratory parameters, liver stiffness and/or liver biopsy as by European guidelines. All the subjects were genotyped for *PNPLA3*, *MBOAT7*, *GCKR*, and *TM6SF2* SNPs by TaqMan 5′-nuclease assays. Patients were defined as GM if they had any of the analyzed SNPs at-risk mutations, and MM if they did not, also categorizing them into high and low genetic risk groups on the basis of a weighted GRS. Untargeted metabolomics analysis was performed through Gas Chromatography-Mass Spectrometry (Shimadzu 2010 SE), after metabolome extraction, purification and derivatization using the MetaboPrep GC-kit.
Results: Patients with GM were the majority (216/270:80%). However, GM and MM patients did not differ for clinical parameters other than BMI (higher in MM, p:0.029) GGT (higher in GM, p:0.019) and Ferritin (higher in GM. P0.033). The prevalence of at-risk SNP mutations was not different in patients vs controls except for PNPLA3 dominant model (59.25% in patients vs 47.05% in controls, p:0.033).PLS-DA was employed to reveal class separation and identify key metabolites based on VIP scores. For disease severity analysis, the model demonstrated progressive separation, with key metabolites including lactic acid, urea, pyroglutamic acid, hydroxydecanoic acid, 2-hydroxyisocaproic acid, and acetoacetic acid. Pathway analysis highlighted alterations in starch, sucrose, galactose, and amino sugar metabolism. In a separate PLS-DA model focused on genetic risk, significant separation was observed between High- and Low-Risk groups. Metabolites with high VIP scores in this analysis included palmitic, mandelic, pyroglutamic, lactic, and ribonic acids. Altered pathways involved phenylalanine, tyrosine, and tryptophan biosynthesis, as well as valine, leucine, and isoleucine metabolism.
Conclusions: Clinical and laboratory evaluation was not able to discriminate between "genetic" and "metabolic" MASLD. On the contrary, the untargeted metabolomic analysis was able to exhibit progressive metabolic alterations according to the severity of the disease. Moreover, a marked separation emerged between high- and low-genetic-risk groups, indicating potential for early diagnostics and stratified patient management. This approach may offer promising avenues for personalized therapeutic strategies, ultimately supporting more effective and individualized care at the dawn of pharmacological treatment of MASLD.

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P-102

Outcomes of HBV and HCV testing in Italyâ€™s marginalized communities: a step towards WHO plan to end viral hepatitis as a public health threat by 2030

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Introduction: The health of the marginalized communities is crucial for public health and inequalities. The WHO Global Hepatitis Report 2024 stated that over 304 million people were living with HBV/HCV infection in 2022.
Aim: We performed HBV/HCV screenings among marginalized people to reveal hidden infections and link-to-care positive individuals.
Materials and Methods: From January 2019 to May 2024, fingerprick tests were used to conduct on-site screenings at non-profit organizations (meal centers, shelters for migrants, and help centers for othervulnerable people) in the metropolitan areas of Florence, Prato, and Pistoia, three cities in Tuscany, Italy.

Positive participants were referred to the closest outpatient clinic to be linked to care.
Results: Eighty/1812 (4·4%) participants were HBsAg+, mostly men ($p<0·001$) and non-Italian natives compared to those HBsAg- ($p<0·001$). Fifty-two/1812 (2·9%) were anti-HCV+ with a higher proportion of Italians ($p<0·001$) and lower education level ($p<0·01$) compared to the anti-HCV-. Intravenous drug use was an independent factor for being anti-HCV+ ($p<0·0001$). Among the HBsAg+ individuals, 66·3% (53/80) were linked and 90·4% (48/53) retained in care (treated/monitored). Of the anti-HCV participants requiring clinical evaluation, 37·8% (14/37) were linked to care, and all the 11/14 (88·6%) viremic patients were successfully treated.
Conclusions: We found higher HBV/HCV positivity compared to national prevalences. Participation and linkage to care were successful. The young mean age (33·6 yrs) of HBsAg+ individuals, primarily from regions with low vaccinal adherence, indicated geographical origin as a key risk factor. The profile of the HCV+ individual was that of a person experiencing extreme marginalization, who engages in risky behaviors, and whose priorities do not include their health. The results stress the need to implement the marginalized groups screening to target hidden HBV/HCV infections, reducing disparities in healthcare and advancing towards the WHO plan to end viral hepatitis as a public health threat by 2030.

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P-103

Exploring the interplay between sarcopenia, liver and cardiovascular damage in non-cirrhotic masld patients: a genetic perspective

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Background and Aims: Sarcopenia is associated with liver fibrosis and cardiovascular(CV) risk, both heightened in metabolic-dysfunction associated steatotic liver disease(MASLD). Genetic variants, including PNPLA3, TM6SF2, and HSD17B13, influence MASLD risk but their association with sarcopenia and CV damage remains unclear.
Aim: To assess the impact of sarcopenia and genetic variants on liver and CV damage in 841 MASLD patients.
Method: Fibrosis and steatosis were assessed using liver stiffness measurement (LSM≥8 kPa for advanced fibrosis) and controlled attenuation parameter (CAP>280 dB/m for severe steatosis) at Fibroscan. Sarcopenia was defined as the lowest tertile of skeletal muscle index (SMI=skeletal muscle mass/height^2) at bioelectrical impedance analysis(BIA). CV damage markers included carotid intima-media thickness(cIMT)≥0.9 mm, carotid plaques, epicardial fat thickness(EFT)≥5.2 mm. Genetic polymorphisms were assessed in 424 patients.
Results: Mean age was 51 ys, 63% male. 24% had advanced fibrosis, 22% increased cIMT, 35% carotid plaques, 83% increased EFT. Sarcopenia was linked to older age (54vs48 years,p<0.001), lower BMI (27vs33.4 kg/m2,p<0.001), WC (99vs110 cm,p<0.001), CAP (293vs317 dB/m,p<0.001), and LSM (4.9vs6.4 kPa,p<0.001). Sarcopenic had higher dyslipidemia (56%vs46%,p=0.03), increased cIMT (28%vs18%,p=0.01), EFT (85%vs77%,p=0.05). At multivariate analysis, sarcopenia remained associated with low BMI (OR 0.61;95%CI 0.5-0.7,p<0.001), WC (OR 0.92;95%CI 0.8-0.97,p=0.001), female sex (OR 2.21;95%CI 1.2-4.0,p=0.008), increased cIMT (OR 2.1;95%CI 1.1-3.97,p=0.003).

In sarcopenic, PNPLA3 CG/GG was linked to increased LSM (OR 1.82,95%CI 1.1-3.1,p=0.03) but lower cIMT (OR 0.39,95%CI 0.15-0.96,p=0.04). TM6SF2 wild-type was associated with increased cIMT (OR 3.4,95%CI 1.3-5.8,p=0.004), and WC (OR 2.3,95%CI 1.4-3.6,p=0.001). HSD17B13 showed no significant impact.
Conclusion: Sarcopenia independently correlates with atherosclerosis in MASLD but not advanced liver damage, possibly due to lower visceral fat. In sarcopenic, PNPLA3 variant correlated with increased liver damage but lower subclinical atherosclerosis, while TM6SF2 polymorphism was protective against CV damage. Combining imaging and genetic data may better clarify the impact of sarcopenia on liver and CV damage in MASLD.

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Prognostic implications of minimal serum creatinine fluctuations in acutely decompensated cirrhosis

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Introduction: Renal dysfunction is common in cirrhosis, affecting prognosis. If subtle increases in serum creatinine (sCr) significantly impact on outcomes in patients hospitalized for acute decompensation (AD) remains unclear.
Methods: Patients with cirrhosis hospitalized for AD from July 2022 to October 2024 were prospectively evaluated. Stable renal function (SRF) was defined as sCr level at or below patients baseline value defined as per International Club of Ascites (ICA); minimal renal dysfunction (MRD) was defined as any sCr level exceeding the baseline without fulfilling acute kidney injury (AKI) or acute kidney disease criteria as per ICA definitions. Follow-up ended at liver transplantation (LT) or death.
Results: 304 patients were enrolled. Median age was 60 years. The most frequent cause of hospitalization was ascites (60%). Alcohol-related liver disease was the most prevalent etiology (45%). Patients were classified as follows: 13% SRF, 39% MRD, 28% AKI, 12% chronic kidney disease (CKD) and 8% acute-on-chronic kidney disease. Median follow-up was 5.7 months (1.7-13.2). Overall, 87 (29%) patients underwent LT and 69 (23%) died. Among the 105 patients with follow-up ≥ 3 months, 14 (13%) developed new-

onset CKD. The incidence was 0/31 for SRF, 7/47 (15%) for MRD and 7/27 (26%) for AKI (MRD *vs* SRF, p=0.038; MRD *vs* AKI, p=0.36). 104/278 (37%) patients discharged from index hospitalization were re-hospitalized. The 3-month cumulative incidence of rehospitalization was comparable across groups (42%, 32%, and 39%; log-rank p=0.73). The 6- and 12-month LT-free survival were respectively 97% and 94% in SRF, 88% and 78% in MRD, 64% and 52% in AKI (MRD *vs* SRF, p=0.028; MRD *vs* AKI, p<0.001).
Conclusions: MRD is very common among patients hospitalized for decompensated cirrhosis. Our preliminary results suggest that MRD may be clinically meaningful as it entails intermediate prognosis between SRF and AKI. These patients may then need careful monitoring to prevent negative outcomes.

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P-105

Baseline liver elastography and its longitudinal changes predict liver related outcomes in patients with Metabolic dysfunction Associated Steatotic Liver Disease (MASLD)

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Introduction: Liver fibrosis is the primary prognostic factor in MASLD. Liver biopsy is the gold standard for staging fibrosis, although it is invasive and expensive procedure. Currently, non-invasive methods are available to stratify the degree of fibrosis.The aim of this study is to validate liver stiffness as a prognostic factor both at baseline and in its variation over time during follow-up.
Method: This is a retrospective single-center cohort study including 389 patients who underwent at least two Fibroscan liver stiffness measurements, with a minimum 6-month interval between scans, from January 2011 to December 2023. They were stratified into 3 risk groups according to Baseline liver stiffness measurements (LSM) (<10, 10-20, >20 kPa). Primary outcome was a composite of Liver Related Events (LRE), death or liver transplantation. Kaplan-Meier curves were generated for time to primary outcome stratified by Baseline LSM and Δ% Fibroscan categories (worsening: LSM increase >20%, stable, improved: LSM decrease >20%). Multivariable Cox regression analysis, adjusted for age, gender, BMI and type 2 diabetes, was used to assess the association of baseline LSM and Δ% fibroscan with primary outcome event. Cumulative incidence curves and incidence rates have been assessed and compared for each risk subgroup.
Results: During a median follow-up of 28 months (IQR 14.4 – 43.4), 29 (7.5%) patients experienced the composite primary endpoint. These patients were older and had a higher LSM at baseline (median 23.3 vs 6.2 kPa, p <0.01) and higher Δ% fibroscan (median 16.9% vs -3.5%, p <0.01) than patients who did not experienced a LRE. Baseline LSM show a good predictive performance for the composite endpoint events with an AUC of 0.897 (95% CI 0.845 – 0.948). Compared to patients with an LSM <10, patients with LSM between 10 and 20 kPa had a 9.7 fold higher risk for the primary outcome (HR 9.7 [2.05 – 45.79], p ≤0.01) and those with LSM>20 had a 55.6-fold higher risk (HR 55.63 [12.15 – 254.74], p ≤0.01). Multivariate Cox regression analysis also revealed significantly lower risk of developing LRE for high-risk patients (>20 kPa) who showed longitudinal improvements (Δ%LSM > -20%) on fibroscan results (HR 0.16, 95%CI 0.04 – 0.68, p=0.01), and a significantly higher risk of developing LRE in intermediate patients (10-20 kPa) who showed worsening longitudinal changes (Δ%LSM > 20%) on fibroscan results (HR 6.66, 95%CI 1.69 – 26.23, p<0.01). Incidence rate of composite outcome per 1000 person-year was 15.5, 19.7, 81.4 for LSM improved, stable or worsened groups respectively.
Conclusion: Our study strengthens the use of LSM both at baseline and during follow up as reliable prognostic factors in MASLD able to identify the subgroups of patients with MASLD at risk of LREs. In patients with intermediate or high risk of events at baseline, elastography surveillance should be encouraged.

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Coagulation imbalance is associated with hepatic and vascular complications in patients with MASLD and diabetes: key role of factor VIII

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Introduction: Metabolic-dysfunction associated steatotic liver disease (MASLD) promotes fibrosis and vascular complications, especially if associated to type 2 diabetes (T2DM), and both diseases present a procoagulant imbalance.
Aim: to evaluate the association between hypercoagulability, hepatic and vascular damage in a cohort of MASLD diabetic patients.
Materials and Methods: 185 MASLD diabetic patients (mean age 62 ± 11 ys, 59% males) underwent assessment of coagulation factors (fibrinogen, FII, FVIII, protein C and antithrombin; FVIII/PC considered a hypercoagulability index), FibroScan® (LSM>8 kPa), macro/microvascular complications. In 96 patient genotyping for PNPLA3 and thrombin generation assay (peak-thrombin: greatest amount of generated thrombin; endogenous thrombin potential (ETP):total amount of generated thrombin), expressed as ratio in presence/absence of trombomodulin-TM as index of procoagulant imbalance) were also available. 192 healthy controls were tested for coagulation parameters.
Results: MASLD diabetic patients presented a hypercoagulable state compared to controls. In patients, ETP-TM ratio and FVIII/proteinC increased over LSM quartiles (from 1 to 4: 0.63±0.12 to 0.89±0.42, pANOVA=0.012; 1.18±0.35 to 1.57±0.68, pANOVA=0.003) and independently associated with increasing LSM values (b-coefficient, 6.11; CI 95% 3.59-8.64; b-coefficient, 4.80; CI 95% 2.28-7.32). Antithrombin and proteinC independently correlated to LSM> 8kpa (OR 0.92, CI 95% 0.88-0.97; OR 0.97, CI 95% 0.94-0.99). Added to the model, PNPLA3 hampered these associations and remained independently associated with increased peak thrombin ratio (b-coefficient 0.063; CI 95% 0.001; 0.126) and decreased antithrombin (b-coefficient -6.14; CI 95% -11.82; -0.46). Increased FVIII and fibrinogen were risk factors with microvascu-

lar complications (OR 1.01, CI 95% 1.00-1.02; OR 1.01; CI 95% 1.00-1.01).
Conclusion: MASLD diabetic patients display a procoagulant profile which seems mainly associated with increased FVIII levels and which is independently related to the severity of hepatic fibrosis by Fibroscan and microvascular complications. A possible interplay between coagulation and PNPLA3 in determining fibrosis has emerged, however further studies are warranted to elucidate this mechanism.

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MiR-22-3p targets the G2/M checkpoint inhibitor Wee1 and represents a possible biomarker of TACE response in hepatocellular carcinoma

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Background and Aims: Hepatocellular carcinoma (HCC) is a hypervascular tumor and derive most of its blood supply from the hepatic artery. The locoregional treatment transarterial chemoembolization (TACE) represents the gold standard for HCC patients at intermediated stage, with survival rates ranging from 20 to 36 months. Despite the proven effectiveness of TACE, the identification of biomarkers predictive of response to the first or subsequent TACE cycle remains an unmet clinical need. MicroRNAs are pivotal players in drug resistance in HCC and show ideal characteristics as circulating biomarkers. MiR-22-3p is a tumor suppressor gene in several cancers, including HCC. Here, we aimed at identifying novel miR-22-3p targets involved in TACE resistance and at exploring circulating miR-22 as a candidate of TACE response.
Method: Serum and tissue miR-22-3p and WEE1 levels were quantified by qPCR and digital droplets PCR in HCC patients at early and intermediate stages, as well as in HCC cell lines. Functional analysis and luciferase reporter assay assessed WEE1 targeting by miR-22-3p in HCC cell lines and xenograft mice. Flow cytometric analysis evaluated cell cycle modulation after miR-22 overexpression or silencing in HCC cells. Live imaging and WB analyses evaluated cell growth and apoptotic cell death in miR-22 modulated HCC cells subjected to hypoxia and doxorubicin treatment. Statistical analysis was performed to investigate clinicopathological associations in TACE-treated patients.
Results: An inverse correlation between serum and tissue miR-22 levels was detected in surgically resected HCC patients. Functional analysis and luciferase reporter assay demonstrated WEE1 targeting by miR-22-3p in HCC cell lines and xenograft mice. Cell cycle and BrdU analyses showed a downregulation of G2/M in miR-22-overexpressing cells, and an upregulation in miR-22 stably silenced cells. An increase of cell growth and an inhibition of apoptotic markers was shown in miR-22 silenced cells undergoing hypoxia and doxorubicin treatment. Increased miR-22 serum levels were observed after each TACE cycle with respect to pre-treatment levels. Higher miR-22 levels associated with TACE resistance at 3 and 6 months of follow-up when assessed two days after treatment. Post-treatment miR-22 levels associated with alfa-fetoprotein and tumor size in TACE-treated patients.
Conclusion: The cell cycle checkpoint inhibitor WEE1 is a novel miR-22-3p target in HCC and contributes to TACE resistance in low miR-22-expressing HCC cells. If validated in larger cohorts, miR-22-3p represents a promising circulating biomarker of TACE response when analyzed few days after treatment.

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Prevalence and influence of diabetes mellitus on clinical outcomes in patients hospitalized for acutely decompensated cirrhosis

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Introduction: Diabetes mellitus (DM) is common in patients with chronic liver disease and significantly increases the risk of liver-related complications. However, its impact on decompensated hospitalized patients remains poorly addressed.
Methods: Patients with cirrhosis hospitalized for acute decompensation (AD) between July 2022 and October 2024 were prospectively evaluated and followed-up until liver transplantation (LT) or death.
Results: 304 patients were included. One-third had DM (101/304, 33%). Compared to non-DM patients, DM patients were older (66 *vs* 57 years, $p<0.001$) and with higher rates of arterial hypertension (45% *vs* 26%, $p=0.002$); the prevalence of chronic kidney disease was similar (24% *vs* 19%, $p=0.36$). The predominant etiology was metabolic dysfunction-associated steatotic liver disease (MASLD) in DM patients (30% vs. 8%, $p<0.001$) and alcohol-related liver disease in non-DM patients (26% *vs* 54%, $p<0.001$). The most common reason for hospitalization in each group was ascites (63% and 58%, respectively). Both groups had a median MELD-Na score of 20.

Acute kidney injury (AKI) occurred in 36% in both groups during index hospitalization ($p=0.89$). AKI stage$\geq$2 was more frequent in DM patients, although not significantly (47% *vs* 30%, $p=0.09$).

Among patients discharged from the index hospitalization (278), 33/93 (35%) of DM patients and 71/185 (38%) of non-DM patients experienced further hospitalizations ($p=0.69$). The 3-month cumulative probability of rehospitalization was similar (25% *vs* 29%, log-rank $p=0.84$). After a median follow-up of 5.7 (IQR 1.7-13.2) months, a comparable number of patients with- and without DM died (27% *vs* 26%, $p=0.89$) or underwent LT (27% *vs* 30%, $p=0.69$). The 6-month LT-free survival was 78.8% and 79.1%, respectively (log-rank $p=0.99$).

Conclusion: Diabetes mellitus is frequently observed in patients with cirrhosis hospitalized for AD, particularly among older individuals and those with MASLD. It does not appear to significantly impact short- or medium-term outcomes, as evidenced by similar AKI rates, rehospitalization risk and 6-month LT-free survival.

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Checkpoint inhibitor-induced liver injury (ChILI) in patients with advanced skin cancer: a single center experience

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Introduction: Immune checkpoint inhibitors (ICIs) are first-line treatments for advanced melanoma and non-melanoma skin cancers. Liver injury (ChILI) affects ~10% of patients. It remains unclear whether to permanently discontinue ICIs after ChILI or safely resume therapy or cross to a different class of ICI. Here we report the experience of ChILI on patients attending a third-level center for the treatment of skin neoplasms.
Methods: This retrospective study included patients treated with ICIs for advanced skin cancers at Fondazione Policlinico Universitario "A. Gemelli" IRCCS (Rome) from June 2016 to April 2024. ChILI was diagnosed using CTCAE v5.0 criteria. Liver function tests (LFTs) at baseline, after 3 cycles of therapy and at ChILI suspicion of appearance have been retrieved, alongside ChILI management and outcome.
Results: Among 111 patients (32.4% female, median age 75), 70 (63.1%) had advanced melanoma, and 41 (36.9%) had advanced squamous cell carcinoma. ICIs included anti-PD1 (95.5%), anti-CTLA4 (2.7%) or their combination (1.8%). Over a median therapy duration of 10 months (IQR 5-21), 9 patients (8.1%) developed ChILI. CTCAE severity: grade 2 (n=2), grade 3 (n=5), grade 4 (n=2). Pattern of liver damage: 5 hepatocellular, 3 cholestatic, 1 mixed. 3 patients showed ANA positivity, 1 showed ENA positivity and 2 had previously diagnosed autoimmune disorder. All patients discontinued ICIs; 5 recovered spontaneously while 4 required steroids. No drug rechallenges occurred, but 2 switched to other ICIs without early or late ChILI recurrence. ChILI patients had higher rates of diarrhea (33%) and rash (44%) compared to non-ChILI patients (4.8% and 13.5%, $p<0.05$). Baseline and 3rd-infusion LFTs showed no significant differences among ChILI and non-ChILI patients ($p>0.05$).
Conclusions: ChILI incidence aligns with literature, occurring after multiple cycles, suggesting an indirect damage mechanism. Dermatological or gastrointestinal AEs often preceded ChILI, highlighting potential early warning signs for clinicians to enable timely intervention.

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Rectus femoris cross sectional area predicts 90-day readmission in patients hospitalized for an acute decompensation of cirrhosis

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Background and Aims: Sarcopenia is frequent in patients with cirrhosis and linked to poor clinical outcomes. Ultrasound measurement of rectus femoris cross sectional area (RF-CSA) is an easy bedside tool for assessing sarcopenia in patients with cirrhosis. The aim of this study was to evaluate the ability of RF-CSA in predicting 90-day readmission in patients hospitalized for an acute decompensation (AD) of cirrhosis.
Method: We prospectively enrolled cirrhotic patients surviving a hospitalization for AD between 2019 and 2024. At discharge, clinical, demographic and laboratory data were collected, and RF-CSA was measured at two-thirds of the distance from the anterior superior iliac spine to the superior patellar border. Patients were classified in two groups according to the median values of RF-CSA for males (3.34 cm^2) and females (2.42 cm^2): "high" if the RF-CSA value was above or equal to the median, and "low" if it was below the median. Follow-up continued until death, liver transplant, or 90 days, during which readmissions were documented.
Results: We enrolled 164 patients (mean age 64±10 years, median MELD 16), the majority had alcohol-related cirrhosis (59%) and ascites (70%). During the 90-day follow-up 73 patients were readmitted (45%). They were older (67 vs 62 years; p=0.004) and had lower RF-CSA (2.88 vs 3.63 cm^2; p=0.002). Patients with "low" RF-CSA had a higher probability of 90-day readmission than those with "high" RF-CSA (59 vs 36%; p=0.002). In multivariable analysis (adjusted for age, sex, MELD and hepatic encephalopathy), RF-CSA was an independent predictor of 90-day readmission ("high" vs "low" sHR=0.54; p=0.011), along with MELD (sHR=1.05; p=0.037) and age (sHR=1.03; p=0.005).
Conclusion: Low muscle mass assessed by RF-CSA independently predicts 90 day-readmission in cirrhotic patients surviving a hospitalization for AD. Preventing muscle loss and/or promoting increases in muscle mass could be potential targets for strategies aimed at preventing readmissions.

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Determinants of liver stiffness measurements changes in Metabolic dysfunction-Associated Steatotic Liver Disease: insights from two cohorts

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Introduction: Liver stiffness measurement (LSM) is essential for monitoring disease progression in Metabolic dysfunction-

Associated Steatotic Liver Disease (MASLD). Identifying predictors of LSM change could enhance prognosis and guide management.
Aim: This study evaluated metabolic and clinical factors affecting LSM changes in two large MASLD cohorts.
Methods: MASLD patients with ≥2 outpatient visits from 2014 to 2022 were included. Follow-up LSM was >6 months after baseline. LSM worsening was defined as >30% increase if baseline LSM was ≥5 kPa, or follow-up LSM >6 kPa if baseline was <5 kPa. LSM improvement was defined as >30% decrease (if baseline >6 kPa). Alternate analyses used a >40% change cut-off. Significant weight and HbA1c changes were >5% and >10%, respectively.

The difference between actual and "expected" FIB-4 at follow-up (calculated using the patient's age at follow-up but baseline blood tests) was assessed. "Expected" Fibroscan improvement or worsening was based on weight, HbA1c, ALT, and FIB-4 changes, with at least one variable showing improvement or worsening while the others remained stable.
Results: Among 400 patients (mean age 54, 70% male), median follow-up was 20 months. LSM improved >30% in 13.5% and worsened >30% in 11.3%; using a >40% cut-off, 6.5% improved and 6.0% worsened. Only one-third of patients with >30% or >40% LSM changes showed corresponding FIB-4 shifts. LSM worsening >30% was independently associated with increased HbA1c (OR 1.03), longer follow-up (OR 1.07), and cholesterol change (OR 0.97). Weight reduction predicted LSM improvement >30% (OR 0.89). "Expected" Fibroscan improvement strongly correlated with actual LSM reduction (p=0.002, NPV: 92–96%), while expected worsening did not predict LSM increase (NPV: 72–89%).
Conclusion: Around 20% of MASLD patients experienced significant LSM changes. Weight reduction improved LSM, while increased HbA1c predicted worsening. "Expected" Fibroscan changes may guide pathways but require a comprehensive, multidisciplinary model of care.

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Liver stiffness measurement by SuperSonic Imagine two-dimensional shear wave elastography to predict hepatocellular carcinoma in non-cirrhotic metabolic dysfunction-associated steatotic liver disease

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Background and Aims: Hepatocellular carcinoma (HCC) commonly develops in patients with liver cirrhosis; however, non-cirrhotic metabolic dysfunction-associated steatotic liver disease (MASLD) also presents a significant HCC risk. Developing effective screening protocols for MASLD-HCC necessitates identifying "at-risk" patients for targeted surveillance. Liver stiffness measurement (LSM) using two-dimensional shear wave elastography (2D-SWE), together with clinical and demographic parameters could enhance MASLD-HCC risk stratification. The utility of LSM performed with the SuperSonic Imagine (SSI) ultrasound machine was evaluated to predict HCC risk in MASLD patients.
Method: Retrospective study conducted on a consecutive prospective cohort of MASLD patients from a tertiary liver disease center in Bologna. All patients underwent baseline LSM-SSI and attended follow-up visits every 6-12 months. Patients with less than 6 months follow-up, unavailable baseline 2D-SWE, or prior HCC were excluded. LSM-SSI cut-offs based on recent meta-analysis data were applied. Primary endpoint was the incidence of de novo HCC, with hepatic decompensation and portal vein thrombosis (PVT) as competing risks. Univariate competing-risks regression (CRR), using Fine and Gray's proportional subhazards method, identified HCC risk predictors.
Results: Among 352 patients (mean follow-up: 38 ± 26 months), the average age was 56.4 ± 13.4 years, and the BMI was 29.6 ± 4.4 kg/m². At baseline, 73% of patients had LSM-SSI <7.37 kPa, 27%≥7.37 kPa, and 8% >15.59 kPa. All patients with liver events had baseline LSM-SSI ≥7.37 kPa. Among these, 9.5% developed HCC, 6.3% experienced the first liver decompensation, and 2.1% developed PVT. For non-cirrhotic patients (LSM-SSI ≤15.6 kPa), baseline LSM-SSI was significantly associated with HCC risk (HR 1.542, 95% CI 1.269-1.875, p<0.0001). Using a significant fibrosis cutoff of 8.28 kPa, LSM-SSI demonstrated 66.7% sensitivity, 88.1% specificity, and 99.6% negative predictive value for HCC (AUC: 0.770) and a number needed to diagnose of 25.2. Multivariate analysis identified LSM-SSI (HR 1.052, 95% CI 1.030-1.075, p<0.001), type 2 diabetes mellitus (HR 4.555, p=0.038), and gamma-glutamyl transferase (HR 1.004, p=0.003) as independent predictors of MASLD-HCC.
Conclusion: For non-cirrhotic MASLD, an LSM-SSI <7.37 kPa effectively rules-out the need for HCC screening, whereas patients with significant fibrosis may benefit from HCC surveillance based on elevated LSM-SSI and other identified risk factors.

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A peculiar composition of HBsAg isoforms characterizes chronic HDV coinfection respect to HBV mono-infection with higher middle- and large-HBs levels reflecting a more intense HDV activity

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Introduction: HBV surface proteins (HBsAg) drive HBV and HDV entry and morphogenesis. Total HBsAg comprises 3 different forms: Large- (L-HBs), Middle- (M-HBs) and Small-HBs (S-HBs) with L-HBs found in virions rather than subviral particles.
Aim: Te investigate the levels of HBs isoforms in the setting of chronic HBV mono-infection (CHB) and HDV coinfection (CHD).
Methods: This study includes 262 plasma samples from HBeAg-negative patients: 143 CHD and 119 CHB. Total HBsAg is measured

by COBAS HBsAg II assays (Roche), HBs forms by ad-hoc designed ELISAs (Beacle) and HDV-RNA was quantified by Robogene assay.
Results: CHD and CHB patients have comparable age and rate of NUC treatment. CHD have lower HBV-DNA (median [IQR]: 1.3[0.0-2.3], 1.6[1.2-3.4] logIU/ml; P=0.002), higher ALT (median[IQR]: 79[50-113], 36[22-63]U/L; P<0.001) and total HBsAg levels (median[IQR]: 5206[827-8555], 1776[354-6936]IU/ml; P=0.008). Median(IQR) HDV-RNA is 5.2 (3.4-6.0)logIU/ml. CHD correlate with higher M- and L-HBs respect to CHB (median[IQR]: 1127[145-2301] vs 142[25-707] and 2.0[0.2-6.3] vs 0.06[0.2-0.5]ng/ml); P<0.001), despite similar S-HBs levels (median [IQR]: 3221[587-6497], 1039[239-5438]ng/ml). Datum confirmed by multivariable analysis (OR[95%CI]: 4.7[1.7-12-4], 6.2[2.2-17.9]; P<0.002). Among CHD, HBs forms positively correlate with HDV-RNA levels (Rho=0.48, 0.49, 0.43 for S-/M-/L-HBs; P<0.001) while in CHB, L-HBs correlates weakly with HBV-DNA levels (Rho=0.29, 0.02).

Patients with HDV-RNA>3log U/ml show significantly higher levels of all HBs forms than lowly-replicating HDV (median[IQR]ng/ml: 4431[1251-6950] vs 274[25-2640] for S-HBs; 1404[191-2484] vs127[4-1242] for M-HBs; 3.3[0.2-7.8] vs 0.3[0.04-1.1] for L-HBs; P<0.001 for all). M-HBs>200ng/ml is the best cut-off predicting altered ALT (70% M-HBs>200ng/ml vs 30% M-HBs<200ng/ml has ALT>40U/L; PPV=70%, NPV=76.9%; P=0.04).
Conclusions: HBsAg form composition differs in CHD vs CHB, with CHD showing higher M-HBs and L-HBs, along with HDV replication, potentially reflecting a variation in the proportion of circulating viral and subviral particles for CHD and CHB. Overall, HBs forms can aid in prioritizing treatment against liver disease progression.

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Evaluation of the intratumoral immune microenvironment in hepatocellular carcinoma treated with liver surgery after selective internal radiation therapy

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Introduction: Selective internal radiation therapy (SIRT) has emerged as a promising treatment for locally advanced HCC, particularly as a bridge to liver resection (LR) or transplantation (LT), but its effect on tumor microenvironment/immune activation must be understood.
Aims: To evaluate the intra-tumoral immune microenvironment and gene expression profiles in HCC patients who underwent LR or LT post-SIRT and its impact on survival outcomes.
Patients and Methods: Thirty-six HCC patients treated with SIRT followed by LR or LT at two French University Hospitals between 2014 and 2023 were included. RNA was extracted from tumoral tissue of formalin-fixed paraffin-embedded surgical liver samples. RNA sequencing was performed to identify differentially expressed genes (DEGs). Immune infiltrates were estimated using the MCP-counter method.
Results: Twenty-five HCC patients (84% male, median age 67 years, 80% with cirrhosis) treated with LR/LT post-SIRT were included in the final analysis. Thirteen patients (52%) were BCLC-C, 10 BCLC-B (40%), 2 BCLC-A (8%). Ten patients (40%) achieved a complete response (CR) 6-months post-SIRT, 12 (48%) partial response (PR), and 3 (12%) stable disease (SD). Fourteen patients (56%) experienced tumor recurrence post-surgery, 11 (44%) died. Sixty-five DEGs were found in CR *vs.* others. Enrichment analysis revealed *under*-expressed immune response gene-set pathways in CR cases and *over*-expressed pathways related to more aggressive HCC subtypes in non-responders. SD milieu showed significantly lower neutrophils (p=0.027) and myeloid dendritic cells (p=0.049) than CR/PR. No significant differences in immune infiltrates were observed between patients with and without HCC recurrence. Gene enrichment analysis showed immune response gene-expression profiles in patients with recurrence than those without. Multivariate Cox analysis identified age>60 years (p=0.039), cirrhosis (p=0.032), and satellite nodules in liver samples (p=0.012) as independent predictors of death.
Conclusion: SIRT modulates the HCC immune microenvironment, with CR showing a downregulated immune response. Residual tumors after SIRT may require combined immunotherapy and surgery to enhance antitumor responses and reduce the risk of recurrence.

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Cardiopulmonary hemodynamics and liver stiffness changes in predicting cardiac decompensation after TIPS: a prospective study

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Introduction: Transjugular intrahepatic portosystemic shunt (TIPS) can induce significant cardiovascular distress in patients with cirrhosis. Despite its therapeutic benefits, post-TIPS cardiac decompensation (CD) remains a serious concern, with early predictive factors still incompletely characterized.
Aim: To identify reliable predictive factors of post-TIPS symptomatic CD (AHA stage C-D).
Materials & Methods: We prospectively enrolled consecutive patients with cirrhosis undergoing TIPS between May 2022 and May 2024 at our tertiary referral center. Baseline clinical and biochemi-

cal parameters were recorded. Right-heart catheterization was performed at three time points: pre-TIPS, immediately post-TIPS, and one-month post-procedure. Liver stiffness measurement (LSM) by vibration-controlled transient elastography was performed at corresponding intervals.
Results: Among 53 patients treated with TIPS for secondary prophylaxis of variceal bleeding (59%) or refractory ascites (41%), with a median Child-Pugh score of 7 (IQR 3) and a MELD-Na score of 12 (IQR 6), CD developed in 20% of patients, with a median onset of 3.3 months (IQR 5.8). At univariable Cox regression analysis, factors associated with CD were advanced age (71 vs. 59 years; HR 1.10, p=0.010), presence of post-capillary pulmonary hypertension (pcPH) at one-month (82% vs. 26%; HR 6.33, p=0.018), and the evidence of increased LSM at one-month follow-up (73% vs. 19%; HR 6.42, p=0.006). The median LSM increased by +22% in patients who developed CD, in contrast to a -23% decrease observed in those who did not (p=0.012).
Conclusion: Presence of pcPH and increase of LSM at one-month follow-up are strongly associated with the development of post-TIPS CD. This is the first demonstration that gold-standard diagnosis of pcPH few weeks after TIPS can predict evolution towards CD. Further studies are required to investigate the relationship between LSM changes and cardiac adaptation following TIPS.

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The impact of first and further decompensation in patients with metabolic-dysfunction associated compensated advanced chronic liver disease

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Background&Aim: The first and further decompensation mark the natural history and the risk of mortality in patients with cirrhosis. We assessed the cumulative incidence of first and further (acute and non-acute) decompensation and evaluated their impact on both liver-related death (LR-D) in patients with compensated advanced chronic liver disease (cACLD) due to metabolic dysfunction-associated steatotic liver disease (MASLD).
Methods: Consecutive patients with clinical (LSM>10 kPa) or biopsy-proven (F3-F4 fibrosis) diagnosis of cACLD due to MASLD were included. First and further decompensation were defined according to Baveno VII criteria. Competing risk analysis and cumulative incidence functions were assessed by Fine and Gray. Cause-specific Cox models with baseline and time-dependent variables were applied. Multistate model was built to better assess the clinical course of cACLD due to MASLD.
Results: The cumulative incidence of the first decompensation was 3.5% at 5 years, increasing 20-fold the risk of LR-D at cause-specific Cox analysis; the cumulative incidence of further decompensation was 44% at 5 years among patients with first decompensation, additionally increasing 1.6-times the risk of LR-D. Ascites, followed by variceal bleeding, were the most common events in both first and further decompensation. Hepatocellular carcinoma (HCC) further independently increased the risk of LR-D of 3.2-times and 1.6-fold, respectively, in the whole cohort of cACLD due to MASLD and in those who experienced first decompensation.
ConclusionS: The first and further decompensations represent tipping points in the clinical course of patients with cACLD due to MASLD, increasing 20-times and additionally 1.6-times the risk of LR-D. HCC is an independent predictor of LR-D in patients with cACLD due to MASLD, resulting in an additional risk of LR-D when associated with both first and further decompensation.

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Our Hub Hospital experience with adult liver transplantation referral in hepatic cirrhosis

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Introduction: Liver transplantation (LT) is the only curative treatment for end-stage liver disease (ESLD). Referral from Hub/Spoke Hospitals to LT Centers is the critical first step in accessing LT programs. However, inconsistent referral methods and timing can influence patient evaluation, eligibility, and outcomes.
Aim: To describe the referral process for cirrhotic patients managed at our Internal Medicine Unit in Pordenone (FVG) from January 2020 to October 2024 and evaluate their characteristics and outcomes.
Materials and Methods: Referral requires submitting an LT referral form via email, with an additional mandatory phone call for acute-on-chronic liver failure (ACLF) cases. Waiting times for the first visit depend on MELD and CLIF-C ACLF/AD scores. Hospitalized patients are co-managed by transplant hepatologists and intensivists. Candidate evaluations follow LT Center protocols. Regular meetings organized by the LT Center aim to raise awareness of ESLD diagnosis and treatment.
Results: From January 2020 to October 2024, 48 cirrhotic patients (75% male, median age 57) were referred to the LT Center. The median MELD score was 20, with alcohol and MASLD being the most common ESLD causes. Referral indications included MELD >15 (18 patients), hepatocellular carcinoma (HCC, 12), extra-MELD criteria (14), and ACLF (4). Among these, 26 patients (54%) underwent transplantation, with a 100% one-year survival for those transplanted by 2023. One patient remains listed, three are completing evaluations for listing, and one awaits re-transplantation for ischemic cholangiopathy. Eighteen patients (37%) were not transplanted due to factors such as recompensation, active malignancy, severe pulmonary hypertension, inadequate social support, HCC with vascular invasion, or uncontrolled sepsis.
Conclusions: Effective collaboration between the Hub Hospital and LT Center is crucial to optimize the referral process and improve patient outcomes.

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Prevalence and clinical impact of rectal colonization by multidrug-resistant (MDR) bacteria in patients with acute decompensation of cirrhosis

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Background: MDR bacterial infections are frequent and difficult to treat in patients with cirrhosis. In addition to standard risk factors (epidemiology, antibiotic/healthcare exposure), colonization by MDR may increase the risk of MDR. The screening for rectal colonization by MDR pathogens could be a valuable tool to identify patients with cirrhosis at risk for MDR infection.
Aim: Assess the prevalence and clinical impact of rectal colonization by MDR organisms in hospitalized patients with acute decompensation (AD) of cirrhosis.
Methods: Consecutive patients admitted for AD and available rectal swab screening for MDR colonization at admission were enrolled. The following clinical endpoints were assessed: development of bacterial/MDR bacterial infection during hospitalization; transfer to intensive care unit (ICU); development of acute-on-chronic liver failure (ACLF); in-hospital mortality; 28- day mortality; 90-day mortality.
Results: 204 patients underwent rectal swab, and 37 (18.1%) tested positive for colonization by MDRO (carbapenem-resistant *enterobacteriaceae* accounted for 60% of cases). Patients colonized by MDRO had higher incidence of MDR infections (29,2 vs 6,2%; p=0,006), ACLF (43,2 vs 21%; p=0,009), transfer to ICU (16,2 vs 8,4%; p=0,018) and 90 days mortality (51,3 vs 14,3%; p<0,001). Almost two third of MDR infections were sustained by the same pathogen identified in rectal swab. In multivariable analysis, patients with MDR colonization had higher risk of developing MDR infections [HR=5.22; p=0.003], an increased risk of developing ACLF [OR=3.50, p=0.005], of being transferred to the ICU [OR=3.03; p=0.016], and of experiencing mortality during hospitalization [OR=9.38; p<0.001], as well as at 28 days [sHR=5.11; p<0.001] and 90 days [sHR=4.89; p<0.001].
Conclusion: Colonization by MDR organisms is associated with increased risk of developing MDR infections, organ failures and mortality in patients with AD of cirrhosis. Rectal swab could be a valuable screening tool for the clinical management of these patients.

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More advanced presentation but similar survival for hepatocellular carcinoma in HIV positive compared to HIV-negative patients: a retrospective cohort analysis

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Background and Aims: Conflicting data on survival of people with HIV (PWH) who develop hepatocellular carcinoma (HCC) could depend on inequal access to curative treatments. We compared two cohorts of patients with HCC, HIV-positive and negative.
Methods: Patients from four referral centers, with a first HCC diagnosis (01/2005-03/2024) were included in a retrospective analysis. Clinical characteristics, access to treatment and survival (OS) were described, according to HIV status. Cox regression models were used to identify predictors of mortality and recurrence. Inverse probability weighting (IPW) and propensity score (PS) methods were used to estimate the HIV-status effect.
Results: 606 patients were enrolled (143 PWH, 463 HIV-negative): PWH were younger (53 vs 68 years, p<0.001), mainly males (87% vs 75%, p=0.004), prevalent viral etiology (99% vs 77%), less frequently Child-Pugh A (71% vs 76%, p=0.01). PWH had a higher proportion of advanced Barcelona Clinical Liver Cancer (BCLC) stage (22% vs 10%, p<0.001), and higher rates of AFP>200 ng/mL (28% vs 15%, p=0.001), macrovascular invasion and/or extrahepatic spread (27% vs 11%, p<0.001), despite similar rate of surveillance (91% vs 88%). Median follow-up was 32 (11-78) months for PWH and 36 (19-84) for HIV-negative. The 5-year OS rate was 43.4% for PWH vs 44.1% in HIV-negative (log rank p=0.97). Independent predictors of mortality in PWH were: presence of esophagogastric varices (HR 2.45, 95%CI 1.16-5.15, p=0.02), AFP >200 ng/mL (HR 3.13, 95%CI 1.73-5.70, p<0.001), advanced/end-stage HCC (C: HR 5.74, 95%CI 1.93-17.08, p=0.002; D: HR 16.73, 95%CI 3.59-78.03, p<0.001) and no active treatment (HR 5.86, 95%CI 1.20-28.49, p=0.03). After IPWT/PS, PWH showed higher 2-year recurrence rate (47.39% [95%CI 32.6-64.9] vs 22.8% [95%CI 17.6-29.2], p=0.03).
Conclusion: Overall survival was similar in PWH and HIV-negative individuals with HCC, despite more advanced tumors at presentation and higher recurrence rates: aggressive downstaging strategies to provide curative options granted prolonged survival.

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Clinical characterization and evolution of disease in a large cohort of 196 patient with autoimmune hepatitis in a referral center

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Autoimmune Hepatitis (AIH) is a rare, heterogeneous disease with an estimated prevalence of 17.4/100000 worldwide, more frequently women. Both presentation and clinical course are extremely variable. The present study aimed to describe the clinical features of patients with AIH and their clinical course in a large cohort of patients consecutively enrolled and followed at our center between 1984 and 2024. Of the 196 patients, 143 (73%) were female and 53 (27 %) male. Mean age at presentation was 51 years (range, 15-83). AIH was associated with other immune related disorders. At least one autoimmune disease was present in 127 patients (64.8%), more frequently (p <0.001) in the female than in the male sex. Autoimmune thyroiditis, rheumatoid arthritis and Sjogren syndrome were found in 47 (33 %) female patients and in 5 (9%) male patients. We also found an association with Inflammatory Bowel Diseases (IBD): 5 (2.6%) patients had Ulcerative Colitis and 1 (0.5%) had Crohn, with higher prevalence in male patients (p =0.006). By the end of follow up, 69 patients (35 %) had developed cirrhosis, with major complications of portal hypertension being present in 14.2% at that time. Among the 53 men, the cumulative incidence of major clinical events (liver decompensation, liver transplantation or death) during follow up was significantly higher (p =0.005). The 48 patients with cirrhosis at presentation showed a significantly (p <0.0001) higher cumulative incidence of major clinical events. Incidence of major clinical events was also higher (p <0.0001) in patients with ANCA positive test. Compared to patients with no liver comorbidities, prognosis was significantly (p = 0.016) poorer in patients with an overlap syndrome. During the follow up, liver neoplasm (either hepatocellular carcinoma (HCC) or cholangiocarcinoma (CCA)) was detected in 3 patients (2 HCC and 1 CCA, confirming the low figures reported in literature.

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Assessment of response and impact of safety treatment with bulevirtide in patients with chronic delta virus infection: an observational trial for evaluating long-term efficacy. the ARISTOTELE pilot study

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Introduction: Hepatitis D virus (HDV) infection remains a significant global health challenge due to its severity and high risk of progression to cirrhosis and hepatocellular carcinoma (HCC). Bulevirtide, a novel HDV entry inhibitor, has shown promise in managing chronic hepatitis D by blocking viral entry into hepatocytes.
Aim: This study evaluated the efficacy and safety of bulevirtide in reducing HDV RNA levels and improving liver function in a real-life cohort of Italian patients with HDV infection.
Materials, Methods and Results: This multicenter prospective trial enrolled 85 consecutive patients with chronic HDV infection, from June 2023 to June 2024, who received 2 mg/day of bulevirtide as monotherapy or in combination with a nucleoside/nucleotide analogue for hepatitis B virus (HBV) infection. Patients with any stage of liver fibrosis or compensated cirrhosis were included. Data collected included demographic and clinical characteristics, liver function tests, HDV RNA levels, and adverse events at baseline and 6 months.

The virological response was achieved in 55.7% of patients (n=47), with 32 demonstrating undetectable HDV RNA levels. Among responders, ALT levels decreased significantly from 66.0 U/mL (IQR 46.5–120.0) to 31.5 U/mL (IQR 25.0–37.0, $p < 0.001$), and AST levels from 71.0 U/mL (IQR 48.5–94.5) to 31.0 U/mL (IQR 27.0–38.5, $p = 0.021$). Median HDV RNA dropped from 16,410 IU/mL (IQR 2,530–339,400) to 0 IU/mL (IQR 0–84,000, $p < 0.001$). No significant predictors of response emerged. Mild adverse events, including pruritus (7.1%) and injection-site reactions (2.4%), were reported, with no treatment discontinuation.
Conclusions: Bulevirtide effectively reduces HDV RNA levels and improves liver function with a favorable safety profile, offering a promising therapeutic option for chronic hepatitis D. Further large-scale studies are needed to confirm these findings and explore long-term outcomes.

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Outcomes of durvalumab with or without tremelimumab in routine clinical practice according to HIMALAYA Trial Eligibility: preliminary results of the international DT-real study

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Introduction: HIMALAYA showed that Durvalumab+Tremelimumab(D+T) and Durvalumab(D) are effective options for unresectable hepatocellular carcinoma(uHCC).
Aim: To investigate the outcomes of D+T and D in uHCC patients according to their adherence to the HIMALAYA inclusion criteria in routine clinical practice
Materials and Methods: Within a prospectively maintained database including 1293 patients with uHCC treated with immunotherapy, we analysed patients treated with D+T or D across 8 centres in USA, Asia and Europe. Patients meeting >1 key exclusion criterion of HIMALAYA(prior systemic therapy, Child-Pugh class B-C, Vp4 thrombosis) were defined HIMALAYA-OUT and compared with HIMALAYA-IN patients for overall survival(OS), progression-free survival(PFS), objective response rate(ORR) and disease control rate(DCR) by RECIST 1.1, and treatment-related adverse events(TRAEs) per CTCAEv.5.0.
Results: 108 patients(mean age 66 years, male sex 81%) started D+T(n=69, 64%) or D(n=39, 36%). 62 patients(57%) were treated in 1° line and 46(43%) in>2°line. Child-Pugh class was A in 67 patients(62%). Vp4 was present in 17 patients(16%). 31 patients(29%)were HIMALAYA-IN and 19/31(61%)received D+T. After a median follow-up of 4.3 months(m, 95%CI 3.3-4.9), median OS(mOS)was 11.5 m and 12-m OS rate was 42%. mOS was not reached in HIMALAYA-IN patients(12-m OS rate 62%) and 8.9 m(95%CI 6.0-12.1) in HIMALAYA-OUT patients. OS hazard ratio(HR) for HIMALAYA IN vs OUT was 0.28(95%CI 0.09-0.93, p=0.037). Median PFS was 2.6 m(95% CI 2.2-5.2) overall, 4.6 m(95%CI 2.1-8.5) in HIMALAYA-IN and 2.6 m(95%CI 1.9-5.2) in HIMALAYA-OUT patients(HR 0.70, 95%CI 0.38-1.30, p=0.266). ORR and DCR(evaluable in 53 patients, 49%) were 15.1%(95%CI 6.5-29.7%) and 43.4%(95%CI 27.5-65.1)(Table). Any-grade TRAEs occurred in 31.5%(95%CI 21.8-44.0%), grade 3-4 TRAEs in 8.3%(95%CI 3.8-15.8%), TRAEs requiring systemic corticosteroids in 8.3%(95%CI 3.8-15.8%) and discontinuation due to toxicity in 3.7%(95%CI 1.0-9.5%).
Conclusions: Preliminary observational data from DT-Real study suggest a reproducible efficacy and safety of D+T and D in patients with uHCC fitting the inclusion criteria of HIMALAYA in routine clinical practice.

	HIMALAYA IN (n=31)	HIMALAYA IN		HIMALAYA OUT (n=77)	HIMALAYA OUT	
		D+T (n=19)	D (n=12)		D+T (n=50)	D (n=27)
mOS (m, 95%CI)	NR	NR	NR	8.9 (6.0-12.2)	11.2 (6.6-13.2)	4.9 (2.6-12.2)
12-m OS (%)	61.8	63	88.9	37.2	37.4	44.4
mPFS (m, 95%CI)	4.6 (2.1-8.4)	8.5 (2.1-8.5)	2.4 (1.6-2.5)	2.6 (1.9-5.2)	2.4 (1.8-6.7)	2.6 (1.8-5.2)
ORR (%,95%CI) (N=53)	23.1 (4.8-67.4)	25.0 (5.1-73.1)	0	12.5 (4.1-29.2)	13.8 (3.8-35.3)	9.1 (0.2-50.6)
DCR (%, 95%CI)	46.2 (16.9-100)	50.0 (18.3-100)	0	42.5 (24.8-68.1)	41.4 (21.4-72.2)	45.4 (14.8-100)
Any grade TRAEs (%,95%CI)	32.3 (15.5-59.3)	31.6 (11.6-68.7)	33.3 (9.1-85.4)	31.2 (20.0-46.4)	28.0 (15.3-47.0)	37.1 (17.8-68.1)
Grade 3-4 TRAEs (%, 95%CI)	9.7 (2.0-28.3)	15.8 (3.3-46.1)	0	7.8 (2.9-17.0)	4.0 (0.5-14.4)	14.8 (4.0-38.0)

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Multiparametric ultrasound for the prediction of the outcomes of endoscopic variceal band ligation

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Introduction: Endoscopic Variceal Band Ligation(EVBL) represents a pivotal treatment in the prophylaxis of esophageal varices bleeding in patients with cirrhosis, but in most cases a single session of EVBL is unable to eradicate esophageal varices completely, and a control endoscopy after 2-4 weeks is required to assess eradication and/or the need for another band ligation. To date, there are no instruments able to predict noninvasively the outcome of EVBL.
Aim: To identify noninvasive predictors of varices eradication after EVBL through multiparametric ultrasound.
Materials and Methods: We prospectively enrolled consecutive cirrhotic patients untolerant or with contraindications to beta-blockers undergoing EVBL for bleeding prophylaxis. Before the procedure(T0), patients underwent abdominal ultrasound with liver and spleen 2D-ShearWave Elastography and Dynamic contrast-enhanced ultrasound(DCE-US) with analysis of time-intensity curves through VueBox® software in two regions of interest placed on liver parenchyma and portal vein. After one month(T1), we performed the same exams before the control endoscopy to verify varices eradication, intended as either the absence of varices or residual varices not requiring further ligations.
Results: We enrolled 41 patients(mean age 63±7.5 years, 75.6% males). After EVBL at T0, 28 patients(68.3%) reached varices eradication while 13(31.7%) required a second EVBL at T1. Patients who achieved eradication showed a significant decrease in spleen stiffness(SS) at T1(39 kPa vs 52.5 kPa,p=0.014). Logistic regression analysis further demonstrated that the percentage reduction in spleen stiffness was a strong predictor of variceal eradication(OR=1.156,p=0.033). Additionally, changes in DCE-US parameters between T0 and T1 were predictive of eradication. Specifically, the percentage increase in peak enhancement(PE; OR=0.905,p=0.003) and area under the curve(AUC; OR=0.957,p=0.009) for liver parenchyma, as well as percentage increase in PE(OR=0.947, p=0.003), AUC (OR=0.947,p=0.006), and wash-in rate (OR=0.973,p=0.029) for the portal vein, were significant predictors.
Conclusions: Our study showed the spleen stiffness and DCE-US are reliable predictors of varices eradication after EVBL.

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The prognostic role of LiverRisk score in patients with compensated cirrhosis

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Introduction: The LiverRisk score is a non-invasive test that has been recently proposed for assessing the risk of compensated advanced chronic liver disease and liver-related events in patients without known chronic liver disease. Recently, its diagnostic and prognostic ability in tertiary settings was questioned.
Aim: The aim of this study was the evaluation of the ability of LiverRisk score in predicting first decompensating event and mortality in outpatients with compensated cirrhosis.
Material and Methods: 271 outpatients with compensated cirrhosis and different etiologies evaluated at the Care Management Program of the University Hospital of Padova from 2004 to 2023 were enrolled in the study. LiverRisk score was calculated for each patient using biochemical parameters at inclusion. Patients were followed until death, liver transplantation or the end of follow up (October 2023).
Results: 271 outpatients (64% males, mean age 56.7±13.0 years, mainly HCV cirrhosis [48.7%], median MELD and CTP 8 and 6, respectively) were included in the study. During follow up, 60 patients developed ascites (22.1%, and 6 developed refractory ascites), 30 hepatic encephalopathy (11.1%), 17 variceal bleeding (6.3%). Fiftysix patients died (20.7%, 33 for hepatic cause) and 31 were transplanted (11.4%). At multivariable analysis (adjusted for age, MELD, varices at inclusion and effective etiological treatment), LiverRisk score was associated with development of decompensation (HR 1.08, 95% CI 1.02-1.14, p=0.015) and in particular with development of ascites (HR 1.07, 95% CI 1.02-1.13, p=0.012), but not with mortality (HR 1.06, 95% CI 0.96-1.18, p=0.245).
Conclusions: LiverRisk score is associated with a high risk of decompensation in patients with compensated cirrhosis, however it is not significantly associated with mortality.

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Survey on acute on chronic liver failure in internal medicine departments and transplant centers of lazio

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Introduction: Acute-on-chronic liver failure is a cause of decompensation of liver cirrhosis and an indication for liver transplantation, however there are no data about its prevalence in the Internal Medicine Departments and in the Transplant Centers of Lazio. From the ECLIS study it appears that in Italy out of 7 Centers with 359 transplants for Decompensated Cirrhosis, 49 were for ACLF 2-3 (13.6%).
Aim: To collect data of Lazio, a questionnaire was submitted to the Internal Medicine Departments and a letter sent to the Transplant Centers of Rome.
Methods: A 22-items on-line questionnaire (Google Forms), discussed within the hepatology area of â€<â€<FADOI Lazio, was administered from 01/02/2024 to 01/04/2024 to the medical departments of Lazio.
Results: 15 Depts responded, for 80 % of them decompensated cirrhosis represented 3-8% of the total diagnosis. For 60% etiology was alcoholic in 30-50% of cases, for 60% was Metabolic in 10-30%, for 53.3% was viral in <10%, for 92.9% was autoimmune in <10%, for 73,3% was unknown in <10%. 20-50% of patients admitted for acute decompensation met the EASL-CLIF criteria of ACLF. Patients discharged/transferred to a transplant department varied from center to center (range 20-80%), like patients sent to palliative care or who have died. The primary cause of ACLF was > 1 factor in 46.7% of cases, alcohol abuse in 33%, bacterial infections in 13.3%. Data from the transplant centers are as follows: Policlinico Umberto I from 2013 to 2024 had had 12/251 (4.8%) transplants for ACLF, Policlinico Tor Vergata in the last 4 years 3/140 (2.1%), San Camillo Hospital in the last 5 years 55/397 (13.8%).
Conclusions: The data collected will serve to improve the questionnaire to be presented as a national survey. Data from the Transplant Centers varied from center to center and were not comparable due to the different observation periods.

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The changing scenario in hepatocellular carcinoma management: the Niguarda experience

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Background: Over the last decade, the management of patients with Hepatocellular carcinoma (HCC) has significantly evolved, with great advances in therapeutic techniques and systemic therapies.
Aim: This study analyzed the distribution and changes in systemic treatment and surgical and locoregional procedures in HCC management in our hospital, from 2017 to 2023.
Results: The total number of liver transplants remained relatively stable over the study period. However, in 2020 and 2021, a significant drop in HCC transplants was observed. The reduction can be attributed to several actors, such as low referral of HCC patients or prioritization of urgent medical cases during the pandemic. The annual number of procedures slightly increased over the analyzed period (from 176 in 2017 to 212 in 2023). Among curative treatments, surgery remained relatively stable, with a slight increase from 40 in 2017 to 57 in 2023. The number of radiofrequency ablation (RFA) remained stable. A peak was observed in 2020, reaching the value of 35 ablations (Figure 1). Notably, in 2023, laparoscopic RFA showed a significant increase. Percutaneous ethanol injection (PEI) was a standard treatment in the early 2000s. In our experience, this technique has been progressively abandoned, favouring newer and safer approaches, such as Stereotactic Radiation Therapy (SRBT). Trans-arterial chemoembolization (TACE) was the most frequently performed technical procedure. However, TACE decreased from 50% of total procedures in 2017 to 30% in 2023. The percentage of patients eligible for curative treatment (Resection/Laparoscopic and Percutaneous ablation) has slightly increased over the study period, reflecting an improvement in patient selection, diagnostic techniques, and treatment strategies. Finally, systemic therapy showed a substantial rise, from 16 first-line treatments prescribed in 2017 to 34 in 2023, reflecting an increasing use of TKI and immunotherapy in the setting of intermediate and advanced HCC.
Conclusion: our study highlights the evolving landscape of HCC treatment, with notable changes in both locoregional and systemic approaches over the past several years.

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Safety considerations for finite nucleos(t)ide analogue (NA) in Chronic Hepatitis B infection, a single-center, observational and restrospective study

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Introduction: Since 2016, international guidelines have recognized finite nucleos(t)ide analogue (NA) therapy as an option for selected chronic hepatitis B patients.
Materials and Methods Results: We conducted a pilot study to evaluate the feasibility and outcomes of applying a finite NA strategy in a hepatology outpatient clinic. Of 126 HBsAg-positive patients, 13 received finite NA therapy for immunosuppressive regimens and were excluded. Among the remaining 113 patients, three groups were identified: 72 were ineligible for therapy discontinuation (Group 3), 13 were eligible (i.e. on NA for at least 3 years, HBV DNA undetectable in three separate occasions, qHBsAg<1000mUI/ml) but continued therapy (Group 0), and 28 discontinued treatment (Group 1). The primary antivirals used were entecavir (57–80%) and tenofovir disoproxil fumarate (7–39%). Group 3 patients had a significantly shorter median treatment duration (6 years, IQR 2.2–10) compared to Groups 1 and 0 (13 years, IQR 8–21, and 16 years, IQR 7–20, respectively). Patients in Group 1 who discontinued NA therapy showed a higher likelihood of achieving HBsAg loss, with functional cure observed in 25% (7/28) compared to none in Group 0 (0/13), with a trend towards statistical significance (p=0.077). Among ineligible patients in Group 3, only one achieved HBsAg loss (1/72). Uncontrolled viral replication requiring therapy restart occurred in 35% of Group 1

patients (10/28), while breakthrough replication requiring NA antiviral therapy was rare, observed in only one Group 0 patient (1/13).
Conclusions: Despite the small sample size, this pilot study provides real-world insights into the application of a finite NA strategy for CHB patients. The findings suggest that treatment discontinuation is feasible and may enhance the chances of functional cure in selected patients, though further research is needed to confirm its safety and long-term efficacy.

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NON INVASIVE TESTS TO RULE OUT CLINICAL SIGNIFICANT PORTAL HYPERTENSION AND HIGH- RISK VARICES IN AUTOIMMUNE HEPATITIS

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Introduction: Autoimmune hepatitis (AIH) causes hepatic inflammation, potentially impacting liver stiffness and non-invasive test (NIT) accuracy for diagnosing clinically significant portal hypertension (CSPH). This study evaluated NIT performance in ruling out CSPH or high-risk esophageal varices (HRV) in AIH-related compensated advanced chronic liver disease (cACLD) and assess the influence of hepatic cytolysis on NIT accuracy.
Materials and Methods: A total of 184 AIH-related cACLD patients from two Italian centers were included. All underwent esophagogastroduodenoscopy (EGDS) for portal hypertension signs within six months of liver stiffness measurement (LSM) and biochemical evaluation. Remission was defined using standard criteria, and deep remission as AST and/or ALT $\leq$ 0.5 times the upper limit of normal (ULN). RESIST, Baveno VI (BVI), and Expanded Baveno VI (EBVI) criteria were tested to rule out HRV. Baveno VII (BVII) criteria were validated in the AIH cohort to rule out varices as CSPH signs. Decision curve analysis (DCA) assessed NITs' net benefit.
Results: Of 184 patients, 118(64.1%) had no varices, 58(31.5%) had low-risk varices, and eight(4.4%) had HRV. Remission occurred in 147(79.9%), with deep remission in 36(19.6%). The negative predictive value for HRV was 100% for RESIST, BVI, and EBVI criteria (0% false negative rate - FNR), sparing endoscopy in 55.4%, 54.2%, and 65.9%, respectively. Baveno VII criteria showed an FNR of 19.6% for any size EV to rule out CSPH. In remission, BVII criteria had a lower FNR than non-remission (19.2% vs. 25%), with deep remission showing a significantly lower FNR (11.8%) compared to those with AST/ALT $>$ 0.5 ULN (23.1%). DCA analysis is shown in the figure.
Conclusions: Biochemical-based RESIST criteria show similar net benefit to elastography-based criteria for ruling out HRV. Hepatic cytolysis severity affects NIT performance in ruling out CSPH. Baveno VII criteria are more accurate in ruling out CSPH in patients with deep remission.

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Longitudinal analysis of viral profiles in chronic HBV/HDV coinfected patients

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Background and Aims: Interactions between HBV and HDV in coinfected patients and the role of HDV genetic variability remain poorly understood. This study aimed to assess serum samples from HBV/HDV coinfected patients to provide a comprehensive analysis of viral profiles and HDV RNA variability.
Materials and Methods: Serum samples collected over time from 43 consecutive patients (32 male, 74.4%; median age 46 years, IQR:39-59; all infected with HDV genotype 1) were analyzed. HDV RNA levels were quantified using the RoboGene HDV RNA Quantification Kit (Roboscreen), while HBsAg and HBcrAg levels were measured using the Elecsys HBsAg II quant II (Roche Diagnostics) and Lumipulse G HBcrAg assays (Fujirebio), respectively. HDV genetic variability was assessed using next-generation sequencing (NGS) on the Illumina MiSeq platform.
Results: In 10/43 patients (all on NUC therapy) with two serum samples collected over 1.8 to 5.8 years (mean 2.6 years), HBV DNA was undetectable or at very low levels ($<$20 IU/mL), while HDV RNA, HBsAg, and HBcrAg remained at elevated levels. Specifically, median HDV RNA levels were 158,000 IU/mL (1st sample) and 82,900 IU/mL (2nd sample; $P = 0.7$), HBsAg levels were 5,562 IU/mL (1st sample) and 1,861 IU/mL (2nd sample; $P = 0.1$), and HBcrAg levels were 3.16 kU/mL (1st sample) and 3.35 kU/mL (2nd sample; $P = 0.2$). NGS revealed that 3/43 patients (6.3%) had high-frequency mutations in Cys211 (Cys211Ser) and Gln214 (Gln214Leu) of the CXXQ isoprenylation site of HDAg. Additionally, 41/43 patients (95%) had highly frequent mutations in the nuclear export signal (aa 198-211) and lower HBsAg levels. Notably, unedited HDV (producing a higher amount of small HDAg than large HDAg) predominated in 40/43 patients (93%).
Conclusions: Our findings demonstrate that HBsAg and HBcrAg are produced during HDV infection independently of HBV replication. Furthermore, the high frequency of mutations in specific HDAg regions and the predominance of unedited HDV genomes suggest potential mechanisms involved in viral adaptation and persistence.

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Etiology-specific Coronary Artery Calcium Score thresholds for cardiovascular risk stratification in liver transplant candidates

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Introduction: Screening for coronary artery disease (CAD) in liver transplant candidates is challenging and often inefficient, with many unnecessary invasive tests. The Coronary Artery Calcium (CAC) Score has been proposed as a risk marker for CAD, but its predictive value in this specific population is not well studied.
Aim: This study aims to examine clinical differences in transplant candidates with elevated CAC-Scores (≥400) compared to those with lower scores and to propose new CAC-Score cut-offs tailored to different cirrhosis etiologies for identifying patients with significant CAD who may benefit from revascularization.
Materials and Methods: Out of 239 patients undergoing evaluation at the POIT of San Camillo Forlanini Hospital, 151 underwent coronary CT to measure CAC-Score, excluding those with pre-existing stents or other exclusion criteria. Patients were divided into two groups (CAC-Score ≥400 and <400) to compare clinical variables.
Results: Patients with CAC-Scores ≥400 were older on average (60 vs. 59 years, $p = 0.036$) and had a higher prevalence of previous CAD ($p = 0.02$), while other traditional risk factors showed no significant differences. Analysis by cirrhosis etiology revealed that elevated CAC-Scores were more frequent in patients with alcohol-related cirrhosis (POTUS, $p = 0.004$), whereas no significant associations were observed in patients with viral cirrhosis or MASLD. Additionally, patients with CAC-Scores ≥400 had significantly more areas of fibrosis (LGE) on cardiac MRI compared to those with lower scores ($p = 0.037$). ROC curves were generated to define optimal cut-offs for each etiology. For MASLD, the optimal cut-off was 150 (AUC 0.79, $p = 0.05$); for viral hepatitis, 234 (AUC 0.877, $p = 0.003$); and for POTUS, 696 (AUC 0.733, $p = 0.005$).
Conclusions: Tailored CAC-Score cut-offs based on cirrhosis etiology could improve diagnostic accuracy in liver transplant candidates, reducing unnecessary coronary angiographies and enabling a more targeted diagnostic approach.

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Alkaline Phosphatase Changes With Seladelpar Across Subgroups Of Primary Biliary Cholangitis Patients In The Response Trial

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Introduction: ALP is a key marker in PBC linked to disease progression risk. In the phase 3 RESPONSE trial (NCT04620733), seladelpar, a selective PPAR-δ agonist, led to a significantly higher percentage of PBC patients achieving the composite biochemical endpoint compared to placebo (61.7% vs 20%) and decreased mean ALP levels (-42.4% vs -4.3%) after one year.
Aim: To report additional ALP data from the RESPONSE trial.
Materials and Methods: PBC patients who received UDCA for ≥12 months or were UDCA intolerant with ALP ≥1.67x ULN and TB ≤2x ULN were randomized 2:1 to seladelpar 10 mg or placebo. ALP changes were analyzed across demographic subgroups, baseline ALP quartiles, and in patients not meeting the composite endpoint. We also evaluated worsening ALP (increase >0 U/L) and safety by baseline ALP.
Results: Among patients who received seladelpar (n=128) and placebo (n=65), mean baseline ALP was similar (314.6 U/L vs 313.8 U/L). Seladelpar consistently reduced ALP across all subgroups, including those with cirrhosis or Hispanic/Latino ethnicity. Patients with baseline ALP ≥350 U/L showed greater decreases with seladelpar (-44.8%; -216.1 U/L) than placebo (-11.6%; -56.4 U/L). Among those not meeting the composite endpoint, seladelpar decreased ALP by -129.9 U/L vs -6.4 U/L with placebo. ALP worsening occurred in 5.5% of seladelpar patients vs 29.2% with placebo. AEs were reported in similar proportions in patients with baseline ALP <350 U/L (86.4%) and ≥350 U/L (84.9%).
Conclusion: Seladelpar led to robust, consistent ALP reductions across subgroups and among patients not meeting composite criteria. It was safe and well tolerated regardless of baseline ALP.

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Long-Term Efficacy and Safety of Open-Label Seladelpar Treatment in Patients With Primary Biliary Cholangitis: Pooled Interim Results for up to 3 Years From the ASSURE Study

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Introduction: ASSURE (NCT03301506) is an ongoing, open-label, long-term, Phase 3 trial of seladelpar—a novel delpar (selective PPARδ agonist)—in patients (pts) with primary biliary cholangitis who rolled over from the Phase 3, placebo-controlled RESPONSE trial (NCT04620733) and from legacy trials (ENHANCE [NCT03602560], CB8025-21629 [NCT02955602], CB8025-31731 [NCT03301506], CB8025-21838 [NCT04950764]). Eligibility criteria included inadequate response or intolerance to ursodeoxycholic acid.
Aim: To present pooled interim efficacy and safety results from the RESPONSE trial and from legacy trials.
Materials and Methods: Data cutoff: January 31, 2024. Patient exposure to seladelpar in ASSURE was analyzed. Key efficacy endpoints included composite biochemical response (CBR; ALP $<1.67 \times$ ULN, ALP decrease $\geq$15%, TB $\leq$ULN) and ALP normalization. Pruritus was assessed using a numeric rating scale (NRS; 0–10) through month (M) 6; change from baseline (BL) was assessed at M6 in pts with moderate-to-severe pruritus (NRS $\geq$4) . Adjusted adverse events (AEs) were calculated per 100 pt-years. Baseline included first exposure to seladelpar in ASSURE or RESPONSE.
Results: 337 pts received 10 mg of seladelpar daily. At BL, mean age was 58.1 (9.7) years, 94% were female, mean ALP was 287.5 (128.4) U/L, TB was 0.75 (0.34) mg/dL, and 16% had cirrhosis. At M12, M24, and M30, 204/280 (73%), 90/124 (73%), and 30/37 (81%) achieved the CBR endpoint, respectively, with ALP normalization in 38%, 38%, and 41%. Mean NRS pruritus change at M6 was −3.3 (SE 0.24) among 99 pts. Exposure-adjusted AEs occurred in 86, 70, and 63 pts per 100 pt-years by M12, M24, and M36, respectively. No serious treatment-related AEs were reported.
Conclusions: Seladelpar showed durable biochemical response by M30, with 81% achieving CBR, 41% attaining ALP normalization, and robust pruritus improvement. It remained safe and well tolerated, showing consistent safety over 3 years.

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At the boundaries: analyzing short and long-term outcome after paediatric liver transplantation: Padua experience

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Introduction: Pediatric liver transplantation (pLT) offers excellent survival rates, enabling many patients to reach adulthood and transition to the adult healthcare service (AHS).
Aim: To describe the short- and long-term outcomes of patients who underwent pLT at Padua University Hospital, focusing on the achievement of ideal outcome after transitioning to AHS.
Materials and Methods: All patients who underwent pLT between 1993 and 2022 were included. Short-term (i.e.,6 months) and long-term (i.e.,≥20 years) outcomes were assessed. For those who transitioned to AHS, the rate of achieving an ideal outcome—defined as a combination of perfect graft function, no immunosuppression side effects, and no late reLT—was evaluated.
Results: 197 pLTs were performed in 167 children (90 males [53.8%], median age at transplant 4 years). Among 30 re-LTs (15.2%), 21 (10.6%) were performed urgently. Biliary atresia was the most common underlying condition (31%), while oncological indications accounted for 16%cases. Patient and graft survival rates at 1, 5, 10, and 20 years were 87%, 84%, 80%, and 76%, and 76%, 75%, 70%, and 63%, respectively (Fig.1). Nineteen (11%) patients did not survive beyond 6 months after their first pLT, with the need for urgent re-LT identified as an independent predictor of survival in multivariate analysis ($p = 0.05$). Among 27 patients who, at the time of analysis, had survived ≥20 years after pLT, all but one were still receiving immunosuppression; 7(26%) developed at least one major medical complication, 1(3.7%) underwent re-LT due to chronic rejection, and 1(3.7%) died of sepsis. Of the 48 patients who transitioned to AHS, an ideal outcome was achieved in 47%, 44%, and 45% of patients at 12, 36, and 60 months after transition, respectively.
ConclusionS: Medical complications, whether related or unrelated to the graft, during the long-term follow-up of patients undergoing pLT significantly impact global health and the achievement of an ideal outcome.

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A proof of concept study evaluating the role of lipopolysaccharide-induced tumor necrosis factor in hepatocellular carcinoma

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Introduction: The identification of novel predictive and prognostic biomarkers for hepatocellular carcinoma (HCC) is a crucial issue. The lipopolysaccharide Induced TNF Factor (LITAF) regulating pro-inflammatory cytokine release and cellular apoptosis may exert a protective effect on cancer and was found downregulated in several cancer types, including HCC.
Aim: Here, we investigated the LITAF role in liver cancer by using knockout (KO) cell models.
Materials and Methods: HepG2 and PLC HCC cells KO for LITAF were established by CRISPR-Cas9 technology. KO validation was performed through rt-PCR, Western Blotting (WB) and immunofluorescence (IF). Cell proliferation was analyzed by using the Incucyte® SX5 platform. Cell cycle was evaluated by Fluorescence-activated cell sorting (FACS). Inflammation was evaluated via WB and IF for NF-κB, and with TaqMan® OpenArray® Human Inflammation Panel. Tumorigenicity was assessed through spheroid (TS) growth assays on the Incucyte® SX5 platform.
Results: LITAF expression was drastically reduced in HepG2 and PLC LITAF KO compared to wild-type (CTR) cells. LITAF KO cells exhibited reduced cellular viability as determined by the XTT assay, a higher proliferation rate than CTR cells, and a significant increase in the proportion of cells in the S-phase and G2/M phase of the cell cycle, further confirmed by PCNA expression up-regulation in the absence of LITAF. In the HepG2 LITAF KO model, inflammatory pathway activation, mediated by the phosphorylation of p65NF-κB was found. In our model, the analysis of the expression of 586 inflammation-related genes revealed the up-regulation of 118 genes, including those involved in cytokine and interleukin

signalling. Additionally, HepG2 LITAF KO cells showed increased TS growth compared to CTR cells.
Conclusions: Our findings reveal that LITAF loss promotes tumour cell proliferation, activates tumour inflammation and enhances tumorigenic potential in HCC models. These results highlight that further exploration of LITAF's role in HCC may reveal its effective translation relevance.

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The devastating impact of severe pruritus in primary biliary cholangitis ☆

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☆ COI: H.T.S., M. M. M., S. D., A. R., P. J. T., with GSK; P.A. no COI., A. K. with Intercept pharma, AbbVIe, GSK, BMS, CymaBay therapeutics, Eisai, Escient, Falk, Gilead, Lilly, Mirum, MSD, Vifor, Zambon; D.J. with GSK, Intercept, Falk, Pfizer, Abbott, Novartis

Introduction: PBC-pruritus' impact on quality of life (QoL) is measured using the EuroQol-5-Dimension-5-Level (EQ-5D-5L) health utility score. Phase 2b GLIMMER post-hoc analyses showed: mean (standard deviation [SD]) baseline (BL) utility was 0.69 (0.23); patients with mild or moderate pruritus at BL had similar utilities (0.75 [0.17] and 0.76 [0.17] whereas patients with severe pruritus at BL had notably worse utility (0.49 [0.28]).
Aim: To look at factors impacting QoL in patients with PBC and pruritus.
Methods: GLIMMER patients completed BL EQ-5D-5L score ranging from 1 "health" to 0 "death" and Beck Depression Inventory (BDI-II) evaluating symptoms of depression. Patients' classification: mild (<4, BL all mild were ≥3–<4), moderate (≥4–<7) or severe pruritus (≥7–10) using the mean worst daily itch score. Sleep disturbance severity was based on the same rating scale.
Results: There were associations between itch severity, sleep disturbance, and health utility. Overall mean (SD) health utility was highest in those with mild sleep impairment 0.83 (0.126). Those with severe sleep impairment had lower scores and those with severe itch and severe sleep disturbance even lower (0.52 [0.30] and 0.47 [0.31]). No patients with mild itch had severe sleep impairment; no patients with severe itch had mild sleep impairment. Health utility was lower with worse depression; from 0.81 (0.18) with minimal depression to 0.39 (0.31) for those with severe depression; amongst those with moderate or severe depression the incremental impact of severe pruritus on health utility was striking, with utilities of 0.32 and 0.26. Over 80% of patients with mild and moderate itch have minimal or mild depression; with severe itch, 49% had moderate or severe depression.
Conclusion: Sleep disturbance and moderate/severe depression were more common in patients with severe pruritus. In patients suffering with both severe pruritus and moderate to severe depression, health utility was severely impaired.

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Domino liver transplantation from an adult patient with propionic acidemia: a case report of the first documented case worldwide

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Introduction: Propionic acidemia (PA) is an inherited metabolic disorder of branch-chain amino acid and odd-chain fatty acid metabolism; the defect of propionyl-CoA carboxylase activity leads to the accumulation of toxic metabolites with the risk of decompensations potentially lethal and to neurological impairment. Liver transplantation (LT), the only curative option for end-stage liver disease, is a valid therapeutic option for PA in case of unresponsiveness to medical therapy; considering the shortage of organs, domino liver transplantation (DLT) has been performed for around 30 years; reviewing the literature, only one case of DLT in PA has been performed on pediatric patients.
Aim: We present the case of a 70-year-old woman who underwent DLT because of Hepatocellular Carcinoma on cryptogenic hepatic cirrhosis, receiving a graft from an adult donor affected by PA.
Materials and Methods: Data was collected during both inpatient and outpatient evaluations from the multidisciplinary team that cares for the patient, according to clinical practice. Informed consent was signed.
Results: No episodes of decompensation were observed in the months before transplantation, and the patient was cared for in outpatient; at hospitalization for DLT, she appeared clinically stable. The DLT procedure took place without any relevant complications. Oral feeding was well tolerated, and no relevant events were observed in the postoperative days. Laboratory data is presented in Table 1. Note that we observed a mild augmentation of the levels of propionic acid and propionyl-carnitine, which are of no clinical relevance, as they do not put the patient in danger of developing any complication in the long term.
Conclusion: Considering the three months after DLT, it proved a safe option, with no metabolic decompensation and no sign of significant enzymatic activity deficiency in the receiver. While it's preliminary data, DLT in adult patients with PA should be considered as a viable therapeutic option.

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A.I.S.F. 2025: Abstracts Evaluation Procedure

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

The experts for the 2025 Annual Meeting are listed below:

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

Category M. "HEPATOCELLULAR CARCINOMA CLINICAL"
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Category O. "MISCELLANEOUS: GENETIC, PEDIATRIC, NUTRACEUTICALS, DILI, OTHER"
A. Licata, Palermo - A. Lleo, Rozzano (MI) - A. Russo, Padua - A. Zocco, Rome

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