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OC 01

Chronic exposure to microplastic-associated Bisphenol A drives progression of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) by promoting immunometabolic and epigenetic reprogramming of Trained Immunity

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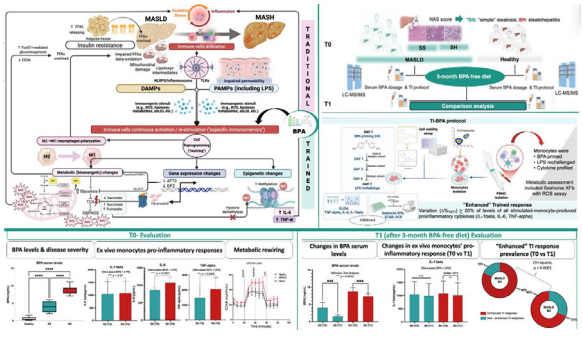
Background & Aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is driven by a complex interplay between metabolic, inflammatory, and environmental factors. Emerging evidence implicates microplastics and their associated endocrine-disrupting chemicals, including Bisphenol A (BPA), as contributors to metabolic and immune dysregulation. Trained immunity (TI), a memory-like functional reprogramming of innate immune cells sustained by coordinated epigenetic and metabolic rewiring, has emerged as a key mechanism linking environmental exposures to chronic inflammation. We investigated whether chronic exposure to BPA promotes MASLD progression through TI-related immunometabolic reprogramming.

Methods: Ten healthy controls and twenty biopsy-proven MASLD patients (10 MASLD with simple steatosis [MASLD-SS] and 10 with steatohepatitis [MASLD-SH]) were enrolled. At baseline (T0) and after a 3-month BPA-free diet (T1), serum BPA levels were quantified by liquid chromatography–tandem mass spectrometry (LC-MS/MS), and circulating IL-1β, IL-6, and TNF-α were measured by ELISA. Monocytes were isolated and subjected to a TI-BPA protocol consisting of BPA priming followed by lipopolysaccharide (LPS) rechallenge. Cytokine production, reactive oxygen species, cellular metabolism (Seahorse XF), and epigenetic remodeling, assessed through H3K4me3 enrichment at promoters of key pro-inflammatory genes, were evaluated (Figure).

Results: At baseline, BPA levels progressively increased from healthy controls to MASLD-SS and MASLD-SH, paralleled by significantly higher inflammatory cytokine concentrations in MASLD-SH compared with MASLD-SS (all $p<0.0001$). Following TI-BPA stimulation, monocytes from MASLD-SH patients produced significantly greater amounts of IL-1β, IL-6, and TNF-α than those from MASLD-SS and controls (all $p<0.001$). This enhanced inflammatory response was accompanied by increased H3K4me3 enrichment at the IL-1β, IL6, and TNF-α promoters (all $p<0.05$), consistent with persistent epigenetic activation of TI pathways. Seahorse analysis demonstrated increased glycolytic activity and reduced mitochondrial respiration in MASLD-SH compared with MASLD-SS (ECAR/OCR, all $p<0.0001$) (Figure).After the BPA-free diet, in parallel with a significant decline of serum BPA concentrations ($p=0.0002$), particularly in MASLD-SH patients, the prevalence of an enhanced TI response significantly decreased (82% vs 31%, $p<0.0001$), consistent with the attenuation of metabolic differences between groups (Figure).

Conclusions: Chronic exposure to BPA, a prototypical microplastic-associated endocrine disruptor, promotes TI in MASLD through coordinated epigenetic and immunometabolic reprogramming, amplifying inflammatory responses and promoting progression toward steatohepatitis. These findings identify microplastic-related environmental exposures as potentially modifiable drivers of MASLD, supporting the development of TI-targeted preventive and therapeutic strategies

Preliminary Figure BPA



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OC 02

Prevalence of elevated fibrosis-4 index in adults from primary care and associated clinical factors

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Background: Advanced hepatic fibrosis remains largely undetected in primary care. The Fibrosis-4 (FIB-4) index — computable from routine blood tests and guideline-endorsed as first-line triage — enables opportunistic, lab-only screening at near-zero marginal cost.
Objective: To estimate the prevalence of elevated FIB-4 and quantify the operational referral-alert burden of alternative FIB-4 thresholds across pragmatic patient-identification strategies in Italian primary care, with explicit attention to the proportion of alerts arising in patients without previously coded liver disease.
Design: Cross-sectional analysis of routinely collected data from 13 general practitioners in Ancona, Italy (January 2020–August 2025). Adults aged 18–80 years with computable FIB-4 (n=10,529) were analyzed across four prespecified cohorts: general 18–80, age 40–70, and a metabolic high-risk variant (≥1 of overweight, diabetes, hypertension, elevated triglycerides or low HDL-C). Parallel cohorts excluding patients with GP-recorded known liver disease (NKLD) were analyzed as sensitivity analyses.
Results: FIB-4 ≥ 2.67 was present in 3.2% (95% CI 2.9–3.6%) of the general 18–80 cohort (one alert per 31 tests), 2.25% (one per 44.5) in the 40–70 cohort, 5.1% (one per 19.6) in the 18–80 metabolic high-risk cohort, and 3.1% (one per 32.0) in the 40–70 high-risk cohort. Prevalence climbed from <1% before age 50 to 3.7% at 60–69 and 9.9% at 70–80. Male sex was the most consistent independent determinant across cohorts (OR 2.12–2.70); hypertension and diabetes showed positive associations in the general cohort. Crucially, 73–76% of primary-threshold alerts arose in patients with no prior GP-coded liver disease, identifying a substantial pool of case-finding candidates currently invisible to liver services. Likewise, 7% of elevated-transaminase values (AST or ALT > 40 U/L) occurred in the NKLD group.
Conclusion: In unselected Italian primary care, opportunistic FIB-4 ≥ 2.67 screening generates a manageable referral signal (≈31 tests per alert). Three of four alerts and 7% of high transaminase values were identified in previously unflagged case-finding candidates. Our study shows that GP databases contain an uncovered burden of liver disease, and this supports the need to set up dedicated pathways to identify patients at risk of cirrhosis and hepatocellular carcinoma. These data provide a quantitative framework for opportunistic FIB-4 screening within the Italian National Health Service and prospective implementation studies coupling lab-only triage with second-line non-invasive testing.

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OC 03

TM6SF2 rs58542926 impairs intestinal homeostasis and increases susceptibility to ex vivo microbiota-derived injury in paediatric MASLD

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common chronic liver disease worldwide, affecting 7–14% of children. MASLD is a multifactorial disorder resulting from interactions between genetic susceptibility and environmental factors, in which gut dysbiosis, increased intestinal permeability, oxidative stress, and inflammation contribute to disease progression. Among the genetic determinants of MASLD, the TM6SF2 rs58542926 C>T variant is a well-established risk factor for hepatic steatosis, although its role in intestinal homeostasis and gut–liver interactions remains poorly understood.
Aims: To investigate the impact of TM6SF2 and its rs58542926 C>T variant on intestinal barrier integrity and to explore genotype-dependent host-microbiota interactions upon exposure to fecal water (FW) from healthy subjects and MASLD patients.
Methods: Human intestinal (Caco-2), hepatocyte (HepG2), and hepatic stellate (LX-2) cell lines were engineered to generate TM6SF2 knockout (KO) models and the rescue systems expressing either the wild-type (pTM6SF2CC) or mutant (pTM6SF2TT) variant assessed. Caco-2 monolayers were exposed to FW from healthy children (HFW, n=4) or MASLD patients (MFW, n=4). Intestinal barrier function was evaluated by cell viability and apoptosis assays, transepithelial electrical resistance (TEER) measures, and tight junction protein expression. Conditioned media from Caco-2 cells were subsequently applied to HepG2 and LX-2 cells to assess gut–liver crosstalk. In hepatic cells, viability, apoptosis, lipid accumulation, and expression of lipid metabolism- and fibrosis-related genes were analyzed.
Results: TM6SF2 KO Caco-2 cells showed reduced viability, increased apoptosis, lower TEER values, and decreased expression of ZO-1, Occludin, and JAM-A compared with controls. Re-expression

of the pTM6SF2TT variant further exacerbated apoptosis and barrier dysfunction compared with pCTRL and pTM6SF2CC cells. Exposure to MFW impaired epithelial integrity in both genotypes, with more pronounced effects in pTM6SF2TT monolayers. Conditioned media from these cells reduced viability, increased apoptosis, lipid accumulation, and upregulated lipogenic genes in HepG2 cells, while activated fibrogenic pathways in LX-2 cells. Metagenomic and metabolomic analyses revealed alterations in the gut microbiota composition and fecal metabolic profiles in patients with MASLD. Notably, MFW displayed increased levels of acetic and propionic acids, which may act as contributors to the cellular damage observed in vitro.
Conclusions: The TM6SF2 rs58542926 C>T variant directly impairs intestinal epithelial barrier structure and function, increasing susceptibility to microbiota-derived injury. These findings suggest that TM6SF2 contributes to increased intestinal permeability and early activation of the gut–liver axis in MASLD, providing a mechanistic link between host genetics, dysbiosis, and disease progression.

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OC 04

MASLD-related Hepatocellular Carcinoma in Cirrhotic and Non-Cirrhotic Livers: A Real-World Insight from the ITA.Li.Ca. Cohort

Lucia Ragozzino [1], Claudia Campani [1], Alessio Mastro [1], Arianna Toscano [2], Tommaso Zurli [1], Tancredi Vincenzo Li Cavoli [1], Valentina Adotti [1], Fabio Marra [1]

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Metabolic dysfunction-associated steatotic liver disease (MASLD) is a leading cause of hepatocellular carcinoma (HCC), which may develop with or without cirrhosis. The study aimed to assess differences in tumour burden, treatment access, and outcomes between cirrhotic and non-cirrhotic MASLD-related HCC.Data from the ITA.Li.Ca. database (27 centres, 2003–2022) were retrospectively analysed. Patients with MASLD-related HCC and no other liver disease aetiologies were included. Baseline clinical, biochemical, and tumour features were compared according to cirrhosis status. Tumour response was classified according to mRECIST criteria.Among 903 eligible patients, 273 (30%) were non-cirrhotic. Only 25% were under ultrasound surveillance; 64% showed no significant fibrosis by FIB-4. Cirrhotic patients were more often obese and diabetic, with worse liver function (MELD 9.7 vs 8.5; $p<0.001$). Non-cirrhotic patients had larger tumours (≥50% parenchymal involvement 15% vs 8%; $p=0.01$) but similar rates of vascular invasion and metastases.Almost half of non-cirrhotic cases lacked histological confirmation despite recommendations.When we separately analysed cirrhotic and non-cirrhotic patients not undergoing surveillance, non-cirrhotic patients had bigger tumours (p value <0,001), although without differences in tumour spread.This difference was also confirmed in patients undergoing semi-annual surveillance (10% vs. 2.6%, $p=0.029$).In the whole cohort, no significant differences in overall survival were observed between cirrhotic and non-cirrhotic patients, regardless of the treatment they received.Non-cirrhotic patients underwent more resections (64% vs 31%), while cirrhotics received more ablation (27%) and transplantation (15%). Tumour burden remained higher in non-cirrhotics irrespective of surveillance. Overall survival did not differ by cirrhosis status or treatment type (log-rank $p>0.05$ for all).MASLD-related HCC in non-cirrhotic patients presents with greater tumour burden but comparable survival to cirrhotic HCC. Despite guideline recommendations, biopsy is often omitted in non-cirrhotic cases. Treatment selection should prioritise tumour and liver function characteristics rather than the presence of cirrhosis. These findings highlight the need for tailored surveillance strategies in non-cirrhotic MASLD.

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OC 05

Baseline phenotyping in MASLD-related compensated advanced chronic liver disease: a patient cohort study

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Background & Aims: Metabolic dysfunction-associated steatotic liver disease (MASLD)-related compensated advanced chronic liver disease (cACLD) carries the dual burden of hepatic events — decompensation and HCC — and non-hepatic events — cardiovascular disease and extrahepatic malignancies — that single-marker stratification cannot jointly capture. We aimed to identify data-driven baseline phenotypes and validate their prognostic relevance against competing hepatic and non-hepatic outcomes in a multicentre cohort.
Methods: Deep Dual Competitive Layer – Incremental Transformer – Tabular clustering was applied to 15 baseline variables in 2,639 patients with MASLD-related cACLD from a multicentre cohort (median follow-up 4.7 years). Six competing-risks endpoints were analysed: decompensation, HCC, composite liver events, cardiovascular events, extrahepatic cancer, and all-cause mortality. Cumulative incidence was estimated using the Aalen–Johansen method, and associations were assessed using centre-stratified cause-specific Cox models adjusted for age and sex.
Results: Four distinct phenotypes were identified: Metabolic (n=1,245; diabetes 88.7%, mean age 63 years), Non-metabolic (n=598; diabetes 2.7%, mean age 51.6 years), Liver (n=596; LSM 31.7 kPa, platelets 129.6×10^9/L, INR 1.3, albumin 3.8 g/dL), and Dyslipidemic (n=200; triglycerides 390.2 mg/dL, ALT 156.6 U/L, mean age 48 years). The Liver phenotype exhibited the highest hazard of hepatic events, including decompensation (HR 2.76, 95% CI 2.10–3.62), HCC (HR 1.61, 1.20–2.17), and composite liver events (HR 2.75, 2.14–3.53; all $p \leq 0.001$ vs Non-metabolic reference). It was also associated with increased risks of extrahepatic cancer (HR 1.40, 1.09–1.80; p=0.008), and all-cause mortality (HR 1.93, 1.46–2.54; $p < 0.0001$). Both the Metabolic and Liver phenotypes showed excess cardiovascular risk vs the Non-metabolic reference (HR 1.43, 1.16–1.77 and HR 1.53, 1.18–1.97, respectively; both p=0.001). The Non-metabolic phenotype had a lower HCC risk than the Metabolic phenotype (HR 0.71, 0.52–0.99; p=0.04). The Dyslipidemic phenotype did not differ significantly from the Non-metabolic reference for any endpoint.
Conclusions: Four baseline phenotypes with distinct hepatic and non-hepatic risk trajectories are identifiable from routinely collected variables in MASLD-related cACLD. The Liver phenotype exhibits the highest hepatic and extrahepatic risks and overall mortality; the Metabolic phenotype carries excess cardiovascular burden and higher HCC risk than the Non-metabolic phenotype; the Dyslipidemic phenotype is a young low-risk subgroup; the Non-metabolic phenotype is uniformly low-risk. This framework supports phenotype-based risk stratification and may facilitate more individualized management of MASLD-related cACLD.

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OC 06

Multisensory electronic technologies for the non-invasive identification of at-risk MASLD phenotypes: fibrotic MASH and advanced fibrosis.

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Background and Aims: Fibrotic MASH, defined by NAS ≥4 and fibrosis stage ≥2, together with advanced fibrosis (stage ≥3), represents the most prognostically relevant and treatment-targeted MASLD phenotype. This study evaluated the performance of electronic nose (e-nose) and tongue (e-tongue) technologies for identifying high-risk and treatment-eligible patients with MASLD.
Methods: Consecutive patients with MASLD or metabolic risk factors were prospectively enrolled between December 2022 and December 2025 at the Hepatology Unit of Fondazione Policlinico Universitario Campus Bio-Medico, Rome. Patients were classified non-invasively using FAST score and liver stiffness measurement (LSM), with liver biopsy available in a subset. FAST ≥0.35 defined at-risk fibrotic MASH, FAST ≥0.67 fibrotic MASH, and LSM ≥10 kPa advanced fibrosis. Histological fibrotic MASH was defined as MASH with NAS ≥4 and fibrosis stage ≥2, and advanced fibrosis as stage ≥3. All patients underwent breath sampling for BIONOTE e-nose analysis and urine and saliva sampling for BIONOTE e-tongue analysis. Supervised Random Forest models predicted predefined clinical categories, with performance reported as confusion matrices.
Results: A total of 215 patients were included (mean age 56.6 ± 13.9 years; 65% male; median BMI 31.1 kg/m²), including 57 with histological assessment. Overall, 81 patients (41.5%) had FAST ≥0.35, 16 (8%) had FAST ≥0.67, and 28 (13.4%) had LSM ≥10 kPa. In the histological cohort, fibrotic MASH was identified in 28 patients (49%) and advanced fibrosis in 17 (29.8%). In the overall cohort, e-nose and e-tongue identified patients at risk of fibrotic MASH according to FAST ≥0.35 with accuracies of 0.83, 0.81, and 0.87 for breath, urine, and saliva, respectively. For LSM-defined advanced fibrosis, the highest accuracies were observed for breath e-nose and urine e-tongue (0.95 and 0.94, respectively). In the histological cohort, breath e-nose identified biopsy-proven fibrotic MASH with an accuracy of 0.81, while urine and saliva e-tongue achieved accuracies of 0.91 and 0.88, respectively, reaching 1.00 when combined. Histological advanced fibrosis was identified with an accuracy of 0.84 for breath e-nose and 0.87 for combined urine–saliva e-tongue analysis. In the histological cohort, multisensory technologies outperformed FAST and LSM, which achieved accuracies of 0.71 and 0.68, respectively.
Conclusions: Multisensory electronic technologies showed good diagnostic performance for identifying high-risk MASLD phenotypes, including fibrotic MASH and advanced fibrosis, outperforming conventional FAST and LSM criteria in the histological cohort. These findings support their potential role in non-invasive risk stratification, although external validation is required.

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OC 07

Real-life performance of FIB-4-based algorithm for referral of MASLD subjects to hepatologic centers: a retrospective multicenter Italian study

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Introduction: Accurate detection of fibrosis in metabolic dysfunction–associated steatotic liver disease (MASLD) is crucial for timely referral to hepatology care, particularly in the era of emerging therapies. Current international guidelines recommend a two-step screening strategy using FIB-4 (cut-off 1.3 or 2.0 if >65 years) followed by liver stiffness measurement (LSM ≥8 kPa). We aimed to assess in a large Italian cohort the real-life performance of FIB-4 in MASLD patients referred to tertiary hepatology clinics and to identify factors influencing misclassification.
Methods: We retrospectively enrolled 2638 subjects with ultrasound-proven MASLD from 9 Italian hepatological centers at their first evaluation, before any dietary or pharmacological intervention. All subjects underwent simultaneous Fibroscan® and FIB-4 calculation within 6 months of their referral.
Results: Prevalence of LSM>8 was 21%. Out of 1815(68.8%) patients with FIB-4 <1.3/2 235 (13.2%) were false negatives (LSM >8 kPa), whereas out of 823 (31.2%) with FIB4>1.3/2, 483 (58.7%) were false positives (LSM<8kPa). Diabetes (OR 3.07[2.07–4.55], hypertension (OR 1.59[1.12–2.25], obesity (OR 6.65[2.83-15.62], increased ALT (OR 1.81 [1.30-2.51] and steatosis grade 3 (OR 1.7[1.17–2.54] were independently associated with false negative results. Similarly, age (OR 0.97[0.95-0.99], diabetes (OR 0.27[0.19–0.40], and increased ALT (OR 0.43[0.29-0.64] were independently inversely associated with false positive results. Overall, FIB-4 showed good specificity (77%) and negative predictive value (87%), but low sensitivity (59%), with an AUC of 0.72 [0.69–0.74]. Diagnostic accuracy increased with age without any difference between sexes (AUC 0.59 [0.51–0.66] in <45y vs 0.76 [0.73–0.81] in > 65 years). Cut-offs required to maintain 80% sensitivity and 95% specificity increased from 0.47 to 1.75 and from 1.30 to 3.34 in patients <45 years vs ≥65 years, respectively. Accuracy, progressively declined from lean to overweight to obese subjects (AUC 0.82 [0.74-0.91] to 0.73 [0.68-0.78] to 0.71[0.67-0.74]). Accordingly, lower rule-out thresholds were required in obese vs overweight vs lean subjects to maintain sensitivity at 80% (0.94 vs 1.04 vs 1.38), with superimposable thresholds for specificity (2.34, 2.34 and 2.3). Diagnostic accuracy of FIB-4 was significantly lower in patients with severe steatosis (AUC 0.64 [0.58-0.69] vs 0.76[0.73-0.80]). Similarly, lower cut-offs were required in patients with vs without severe steatosis for sensitivity at 80% (0.77 vs 1.09), with superimposable thresholds for specificity (2.24 vs 2.34).
Conclusions: FIB-4 showed only moderate performance for detecting elevated liver stiffness in MASLD as clinically relevant fibrosis was frequently missed in patients with cardiometabolic risk factors who may possibly benefit from direct assessment rather than a sequential testing approach. Future screening strategies should integrate metabolic risk factors and tailored

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OC 08

Metabolomic and lipidomic profiling revealed red flag signatures for the identification of MASLD risk across patients with dysmetabolic traits

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Background & Aims: Adolescents and adults with comparable cardiometabolic burden can either develop metabolic dysfunction-associated steatotic liver disease (MASLD) or don't show evidence of fatty liver. However, it is still unclear whether patients with MASLD exhibit a specific circulating metabolic fingerprint compared to non-MASLD dysmetabolic subjects. Therefore, we aimed to analyze the serum metabolomic/lipidomic (SML) profile in a dysmetabolic cohort (n=383), including pediatrics with MASLD (n=100, P-MASLD), adults with biopsy-proven (n=95, B-MASLD) or non-invasive MASLD (n=88, NI-MASLD) diagnosis, and a control group of dyslipidemic patients (n=100, Dys) without MASLD.
Method: SML was performed by UHPLC and analyzed through MetaboAnalyst 6.0.
Results: The P-MASLD group showed a higher rate of glucose intolerance compared to all the others whereas less dyslipidemia was detected in P/B-MASLD vs NI-MASLD/Dys patients. The P/B-MASLD groups showed severe disease in 58% and 47% of cases, compared to NI-MASLD (18%). SML analysis revealed two main hierarchical clusters across dysmetabolic patients, highlighting that P/B-MASLD and NI-MASLD/Dys showed a similar metabolic pattern, respectively. In particular, ~100 species were dysregulated (adjusted $p<0.05$ FDR) in P/B-MASLD vs NI-MASLD/Dys patients, and 64 metabolites were shared between the P/B-MASLD groups, suggestive of a conserved signature across pediatric and adult biopsied cases potentially due to the high percentage of severe disease. To discover candidate MASLD-specific biomarkers, we performed the intersection analysis of differentially abundant species across the 4 groups. Sixteen metabolites were consistently altered in all MASLD patients (P-, B-, NI-MASLD) vs Dys. Two of them, glutamic acid and phosphatidylcholine (PC) O-40:6, accurately discriminated MASLD from non-MASLD with 94% AUC (sens: 95%, spec: 88%), remaining stable after 10-fold cross-validation. Next, in the attempt to identify compounds with potential prognostic value, we stratified the dysmetabolic cohort according to MASLD severity. Nine metabolites were mainly dysregulated in severe disease vs controls (Dys). At multivariate and cross-validation analyses, a 5-metabolite model (Decanoylcarnitine, Ocatnoylcarnitine, Leucine, LysoPC 18:2, SM 41:2) achieved the best performance in distinguishing between severe MASLD vs controls (AUC 93%; sens: 87%; spec: 88%). The same panel performed less well in detecting cases with mild/moderate MASLD (81% and 87%) vs controls, indicating a higher specificity for advanced disease stage.
Conclusion: SML analysis captured a specific circulating profile shared across young and adult MASLD patients, possibly linked to an advanced clinical phenotype, which may be a red flag for cardiometabolic monitoring in pediatric cases. Still, we disclosed 2 compounds specific for MASLD and 5-metabolites highly predictive of severe MASLD.

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OC 09

MASLD Features and Potential Eligibility for Emerging MASH Therapies in Patients with Controlled HBV Infection and Cured HCV Infection: A Real-World Analysis from the Italian PITER Cohorts

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Background and Aims: As HBV replication becomes suppressed and HCV infection cured, metabolic dysfunction-associated steatotic liver disease (MASLD) features are emerging as major determinants of residual liver disease progression. In these patients, liver injury may reflect a mixed viral–metabolic phenotype. We performed a cross-sectional evaluation within the PITER cohorts to assess the prevalence of MASLD features, the multimorbidity burden, and the proportion of patients potentially eligible for emerging MASLD therapies according to the AISF STEPS-MASH framework.
Methods: We analysed 2,155 HBV patients with HBV-DNA <2,000 IU/mL and 3,002 HCV patients with sustained virological response. Patients with significant alcohol intake, hepatocellular carcinoma, decompensated cirrhosis, or Child-Pugh B/C disease were excluded. MASLD features were identified according to current criteria. Following AISF STEPS-MASH recommendations (AISF non-invasive criteria), fibrosis severity was estimated using liver stiffness measurement (LSM) and platelet count. Patients with LSM ≥8 and <20 kPa and platelets >150,000/μL were considered potentially eligible for pharmacological treatment.
Results: MASLD features were identified in 399/2,155 HBV patients (18.5%) and 962/3,002 HCV patients (32.0%). Patients with MASLD features were older (HBV: median age 63 vs 58 years; HCV: 67 vs 66 years) than those without MASLD features. Male sex was present in 55.9% of HBV-MASLD, and in 41.9% of HCV-

MASLD patients. According to AISF non-invasive criteria, 22.8% of HBV-MASLD and 33.3% of HCV-MASLD were identified as potentially eligible for treatment evaluation. This subgroup already displayed a marked metabolic and systemic burden. Overweight or obesity was present in 88.3% of HBV and 73.1% of HCV patients, diabetes in 25.4% and 30.1%, elevated GGT in 27.3% and 23.0%, creatinine >1.2 mg/dL in 21.4% and 7.7%, INR >1.1 in 23.4% and 30.6%, while albumin >3.5 g/dL remained preserved in 94.4% and 92.7%, respectively. Moreover, 49.2% of HBV and 56.5% of HCV patients had at least two comorbidities. Conversely, a further 25.1% of HBV and 37.5% of HCV patients exhibited fibrosis profiles suggestive of advanced liver disease (LSM ≥20 kPa or platelets ≤150,000/μL).
Conclusions: In this representative real-world Italian cohort, MASLD features identify a frequent viral–metabolic phenotype characterised by multimorbidity and residual risk of liver disease progression despite viral suppression or cure. Approximately one-third of patients fulfil AISF non-invasive criteria warranting evaluation for emerging metabolic therapies, while an additional one-third already exhibit advanced fibrosis profiles. Given the historically high burden of viral hepatitis in Italy, these findings suggest that a substantial number of patients with chronic liver disease may benefit from integrated hepatologic and metabolic management strategies in the post-viral era.

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OC 10

Clinical impact of the AISF STEPS-MASH algorithm: real-world application in tertiary hepatology practice

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Background and Aims: The recent approval of resmetirom and semaglutide for people living with metabolic dysfunction–associated steatohepatitis (MASH) and significant fibrosis has created a need for pragmatic strategies to identify treatment candidates in routine practice. We evaluated the real-world applicability of the AISF STEPS-MASH algorithm and estimated treatment eligibility in tertiary hepatology centres.
Methods: We retrospectively applied the AISF STEPS-MASH algorithm to all consecutive adults undergoing vibration-controlled transient elastography (VCTE) at nine Italian tertiary hepatology centres between January and June 2025. Stepwise attrition across steatosis identification (Step S), fibrosis risk stratification (Step T; CAP≥248 dB/m and LSM≥8 kPa), and exclusion assessment (Step E) was quantified. Eligibility for resmetirom and semaglutide was assessed according to framework-defined criteria.
Results: Among 8,194 screened people, 8,150 (99.5%) had complete CAP and LSM data and constituted the evaluable cohort. Overall, 4,371 people (53.6%) fulfilled step S criteria. Of these, 1,041 (23.8%) met the step T fibrosis-risk criteria. Within Step T 291 people (28.0%) were excluded for advanced liver disease and/or possible portal hypertension, leaving 750 people for final treatment assessment. Drug-specific exclusion criteria were more frequent for semaglutide than for resmetirom (21.5% vs. 7.2%), with concomitant GLP-1 receptor agonist therapy (15.3%) and gallbladder disease (5.7%) the most frequent semaglutide-related exclusions, and fibrate use (5.1%) the most common resmetirom-related exclusion. After application of all inclusion and exclusion criteria, 612 people (81.6% of the final Step T population) fulfilled strict eligibility criteria for at least one approved therapy. Strict eligibility was observed in 588 people (78.4%) for resmetirom and 322 (42.9%) for semaglutide, with 298 (39.7%) fulfilling criteria for both agents. Overall, strict eligibility corresponded to 7.5% of the entire evaluable VCTE population and 14.0% of people fulfilling Step S criteria, equivalent to 75 strictly eligible people per 1,000 VCTE examinations, corresponding to approximately one treatment candidate identified every 13 examinations performed.
Conclusions: The AISF STEPS-MASHalgorithm can be readily implemented using routinely collected non-invasive data in tertiary hepatology practice. Although only 7.5% of the overall VCTE population fulfilled strict eligibility criteria, more than 80% of patients reaching the final assessment step were eligible for at least one approved therapy. The algorithm thus efficiently enriches for treatment-eligible people.

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OC 11

Geographical distribution of MASLD and its drivers in Italian patients with cirrhosis

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) was the leading cause of newly diagnosed liver cirrhosis in Italy in 2024. However, MASLD is characterized by multiple disease drivers, and the Italian population exhibits geographical, socioeconomic, and lifestyle heterogeneity, warranting a deeper evaluation of regional differences in disease distribution.
Aim: To assess the geographical distribution of MASLD and its disease drivers among Italian patients with cirrhosis.
Patients and Methods: In this cross-sectional multicenter observational study, 1,195 consecutive patients with cirrhosis were enrolled from 11 tertiary hepatology centers across Italy. Eligible participants included patients at the first diagnosis of cirrhosis or presenting for the first evaluation at participating centers in 2024. Patients were stratified according to their area of residence into Northern/Central Italy (n=422) and Southern Italy (n=659). A total of 105 patients of non-Italian origin were excluded. Demographic, clinical and etiological variables were collected at baseline.
Results: MASLD was identified in 174 patients from Northern/Central Italy (41.2%) and 256 from Southern Italy (38.8%) (OR 1.10, 95% CI 0.86–1.42; p=0.434), no differences were found regarding MASLD prevalence between the two groups although MASLD associated with other cofactors of liver disease (i.e., viral hepatitis) was significantly more common in Northern/Central Italy (15.6% vs 8.3%; OR 2.04, 95% CI 1.40–2.98; p<0.001). Among metabolic drivers, arterial hypertension (54.3% vs 47.2%; OR 0.75, 95%CI 0.59–0.96; p=0.021), type 2 diabetes mellitus (43.9% vs 32.5%; OR 0.62, 95%CI 0.48–0.79; p<0.001), and obesity (30.7% vs 17.5%; OR 0.48, 95%CI 0.36–0.65; p<0.001) were more prevalent in Southern Italy, while dyslipidemia was more frequent in Northern/Central Italy (20.9% vs 7.4%; OR 3.28, 95%CI 2.26–4.77; p<0.001). Across both macro areas, MASLD represented the leading etiology among patients aged 60–79 years. Although MASLD was overall more prevalent among men, geographical differences in sex distribution were observed, with a predominance of male patients in Northern/Central Italy (78.2% vs 68%, OR 1.68, 95% CI 1.08–2.60) and a higher prevalence of female patients in Southern Italy (21.8% vs 32%, OR 0.59, 95%CI 0.38-0.93).
Conclusion: Marked geographical differences exist in the clinical and metabolic profile of MASLD-related cirrhosis across Italy. Although MASLD distribution was similar across the country, a higher burden of obesity, diabetes and hypertension was found in the South whereas a greater prevalence of dyslipidemia in Northern/Central Italy. These findings highlight the heterogeneous nature of MASLD-related cirrhosis across Italy and suggest that regional differences in metabolic drivers of the disease may contribute to distinct disease phenotypes. Future studies integrating genetic profiling may improve risk stratification and personalized management.

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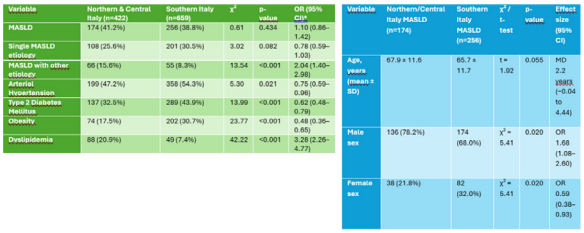

Variable	Northern & Central Italy (n=422)	Southern Italy (n=659)	χ^2	p-value	OR (95% CI)*
MASLD	174 (41.2%)	256 (38.8%)	0.61	0.434	1.10 (0.86–1.42)
Single MASLD etiology	108 (25.6%)	201 (30.5%)	3.02	0.082	0.78 (0.59–1.03)
MASLD with other etiology	66 (15.6%)	55 (8.3%)	13.54	<0.001	2.04 (1.40–2.98)
Arterial Hypertension	199 (47.2%)	358 (54.3%)	5.30	0.021	0.75 (0.59–0.96)
Type 2 Diabetes Mellitus	137 (32.5%)	289 (43.9%)	13.99	<0.001	0.62 (0.48–0.79)
Obesity	74 (17.5%)	202 (30.7%)	23.77	<0.001	0.48 (0.36–0.65)
Dyslipidemia	88 (20.9%)	49 (7.4%)	42.22	<0.001	3.28 (2.26–4.77)

Variable	Northern/Central Italy MASLD (n=174)	Southern Italy MASLD (n=256)	χ^2 / t-test	p-value	Effect size (95% CI)
Age, years (mean ± SD)	67.9 ± 11.6	65.7 ± 11.7	t = 1.92	0.055	MD 2.2 (−0.04 to 4.44)
Male sex	136 (78.2%)	174 (68.0%)	χ^2 = 5.41	0.020	OR 1.68 (1.08–2.60)
Female sex	38 (21.8%)	82 (32.0%)	χ^2 = 5.41	0.020	OR 0.59 (0.38–0.93)

Table 1: Prevalence of MASLD and its drivers and comparing of age and sex by geographic area

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OC 12

Beyond Aetiology: Outcome- and Etiology-Free Clinical Phenotypes in Matched Cirrhosis Emergency-Care Encounters

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Background: Etiologic classification alone may not capture the clinical heterogeneity of patients with cirrhosis presenting to emergency care. Phenotyping is most defensible when outcomes are kept outside the inputs and then used as external validators. Methods. In a matched cohort of 2,524 emergency department encounters from 1,176 patients, assembled as 1,262 MASLD/non-MASLD pairs, we performed outcome- and aetiology-free latent class analysis (LCA) and k-means clustering in 2,524 matched emergency department encounters. The purpose was to identify clinical phenotypes without allowing either acute outcomes or MASLD status to define the groups. Therefore, the class assignment used only presentation or baseline variables: age, sex, MELD-Na, CLIF-AD, mSOFA, triage, hepatocellular carcinoma, clinically significant portal hypertension, cardiovascular disease, diabetes, chronic kidney disease, cancer, and Charlson burden. Death/ICU, MACE, OHE, hospitalization, LOS >7 days, hepatic decompensation, AKI/HRS, and MASLD/pure/mixed status were added only after clustering as external descriptors/validators. LCA fit was compared across 2-, 3-, and 4-class solutions using AIC/BIC, relative entropy, and mean maximum posterior probability; k-means stability was assessed by bootstrap resampling.
Results: Outcome- and etiology-free LCA favoured a 4-class solution by BIC (34,088 vs. 34,658 for 3 classes and 35,602 for 2 classes), with acceptable separation (relative entropy 0.856; mean maximum posterior probability 0.921). The classes described clinically distinct strata. Class 1 was cardiometabolic/high-utilization, with diabetes 63.0%, cardiovascular disease 53.4%, high hospitalization, LOS >7 days 65.6%, and MACE 30.8%; MASLD enrichment in this class (60.5%) was observed after class construction, not used to generate it. Class 2 was a lower-severity phenotype with low death/ICU (2.3%), MACE (11.2%), OHE (2.6%), hepatic decompensa-

tion (27.1%), and AKI/HRS (0.6%). Class 3 represented hepatic-renal severity, with near-universal high MELD-Na/CLIF-AD, high chronic kidney disease, death/ICU 23.5%, hepatic decompensation 89.3%, and AKI/HRS 52.2%. Class 4 was a portal-hypertension/OHE phenotype, with CSPH 96.7%, mSOFA $\geq$3 in 84.6%, OHE 20.7%, and relatively low MACE (8.2%). K-means provided convergent support for a high-severity cluster with death/ICU 28.0%, MACE 29.3%, hepatic decompensation 88.6%, AKI/HRS 63.3%, median MELD-Na 24, and median CLIF-AD 43. Bootstrap resampling generally supported cluster stability.

Conclusions: With outcomes and aetiology excluded from phenotype construction, emergency-care cirrhosis presentations organized into hepatic-renal, portal-hypertension/OHE, cardiometabolic/high-utilization, and lower-severity strata. These exploratory, internally stable patterns support phenotype-based interpretation beyond binary MASLD status and require external validation.

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Thursday Posters: Monothematic Conference of the Italian Association for the Study of the Liver – A.I.S.F. (Palermo, September 24th-25th, 2026)

T-01

Metabolic dysfunction is associated with a higher risk of further hepatic decompensation despite carvedilol in decompensated advanced chronic liver disease

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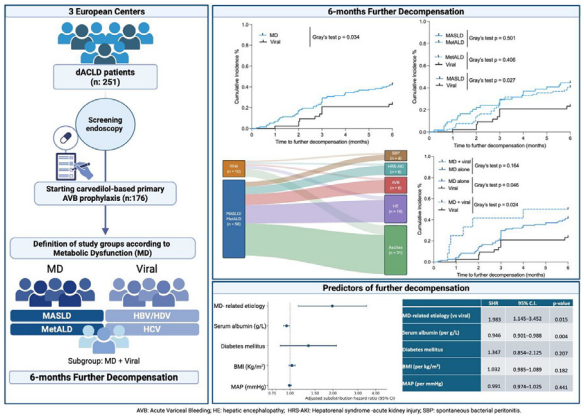
Background and Aims: Metabolic dysfunction (MD) is increasingly recognized as a major determinant of cirrhosis progression and may attenuate the response to non-selective beta-blockers (NSBBs). Whether MD influences the risk of further hepatic decompensation in patients with decompensated advanced chronic liver disease (dACLD) receiving carvedilol-based primary prophylaxis for acute variceal bleeding (AVB) remains unknown.
Methods: In this multicenter cohort study, consecutive adults with dACLD and esophageal varices requiring primary prophylaxis were enrolled at three European tertiary centers. All patients started carvedilol and were prospectively followed for 6 months. Patients were classified according to the presence of MD, including metabolic dysfunction-associated steatotic liver disease (MASLD), metabolic dysfunction-associated alcohol-related liver disease (MetALD), and mixed metabolic plus viral etiologies, and were compared with patients with viral-related cirrhosis without MD. The primary endpoint was first further hepatic decompensation, defined as new or recurrent ascites, overt hepatic encephalopathy, acute variceal bleeding, spontaneous bacterial peritonitis, or hepatorenal syndrome–acute kidney injury. Death and liver transplantation were treated as competing events.
Results: Among 176 included patients, 133 (75.6%) had MD and 43 (24.4%) had viral-related cirrhosis without MD. Baseline liver function, Child-Pugh class, MELD score, and variceal characteristics were comparable between groups. During follow-up, 66 patients (37.5%) developed further hepatic decompensation. The 6-month cumulative incidence was significantly higher in patients with MD (42.1% vs 23.3%) than in those without MD (SHR 2.06, 95% CI 1.19–3.52; p=0.009) (Figure). After adjustment for serum albumin, diabetes, body mass index, mean arterial pressure, and recruiting center, MD remained independently associated with the outcome (adjusted SHR 1.98, 95% CI 1.15–3.45; p=0.015). Lower serum albumin was also independently associated with further decompensation. Excess risk was driven predominantly by non-bleeding events, particularly ascites (Figure). Carvedilol exposure, target dose achievement, hemodynamic changes, and treatment discontinuation rates were similar across etiological groups. No significant differences were observed between MASLD and MetALD patients (Figure).
Conclusions: MD is independently associated with a higher risk of further hepatic decompensation despite guideline-directed carvedilol therapy in dACLD. These findings support the concept of a distinct metabolic phenotype of portal hypertension and suggest that patients with MD may require closer monitoring and personalized management strategies beyond standard therapeutic approaches.

Preliminary Figure NSBB MALSD



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T-02

Comparative Performance of MAFLD and MASLD Criteria for Predicting de novo Hepatocellular Carcinoma in HCV-Infected Patients After Sustained Virological Response

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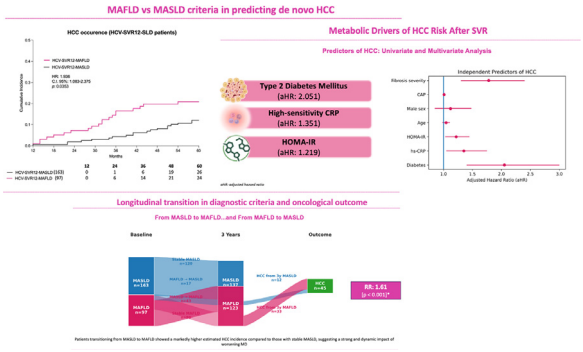
Background and Aims: Direct-acting antivirals (DAAs) have dramatically reduced liver-related complications in patients with chronic hepatitis C virus (HCV) infection. However, a substantial residual risk of de novo hepatocellular carcinoma (HCC) persists after sustained virological response (SVR), particularly in individuals with coexisting metabolic dysfunction (MD). The recent transition from metabolic dysfunction-associated fatty liver disease (MAFLD) to metabolic dysfunction-associated steatotic liver disease (MASLD) has generated debate regarding the prognostic performance of these definitions. We aimed to compare MAFLD and MASLD criteria in predicting de novo HCC in HCV-cured patients and to assess whether dynamic worsening of MD further influences oncological risk.
Methods: We retrospectively analyzed 650 consecutive HCV-infected patients with hepatic steatosis who achieved SVR after DAA therapy and were followed for 5 years. At baseline, all patients were classified by applying MASLD and MAFLD criteria. Three groups were identified: “pure MASLD” (n=163), overlap MASLD/MAFLD (n=390), and “pure MAFLD” (n=97). Baseline demographic, biochemical, and clinical variables were collected. The primary endpoint was de novo HCC. Kaplan–Meier curves, Cox proportional hazards models, and exploratory longitudinal analyses of transitions between diagnostic categories were performed.
Results: Baseline clinical, biochemical, and fibrosis-related features were comparable among the three groups. During follow-up, “pure MAFLD” patients showed a significantly higher cumulative incidence of de novo HCC compared with “pure MASLD” individuals [HR: 1.936; p=0.035]. This finding remained consistent after stratification by fibrosis severity. In multivariable Cox regression analysis adjusted for age, sex, steatosis severity, fibrosis, and concomitant medications, independent predictors of HCC included diabetes (aHR 2.05, 95% CI 1.40–3.00; p=0.001), hs-CRP (aHR 1.35, 95% CI 1.05–1.75; p=0.02), and HOMA-IR (aHR 1.22, 95% CI 1.03–1.45; p=0.02). In exploratory longitudinal analyses, patients transitioning from MASLD to MAFLD during follow-up experienced a significantly increased HCC risk compared with those with stable MASLD (relative risk 1.61; p<0.001), suggesting that progressive metabolic deterioration dynamically amplifies oncogenic potential (Figure).
Conclusions: MD remains a major determinant of de novo HCC in HCV-SVR patients. In this real-world cohort, MAFLD criteria outperformed MASLD in identifying patients at the highest oncological risk, likely because they better capture insulin resistance and systemic inflammation by including HOMA-IR and hs-CRP. Dynamic progression from MASLD to MAFLD may define an especially high-risk phenotype. These findings support integration of comprehensive metabolic profiling into post-SVR surveillance strategies and reinforce the role of precision hepatology in tailoring HCC risk assessment.

Preliminary Figure MAFLD



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T-03

Predictive Value of Endoscopic Ultrasound Portal Hemodynamics in Patients with Metabolic Dysfunction-Associated Steatohepatitis (MASH)

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Background: Non-invasive assessment of portal hypertension in metabolic dysfunction-associated steatohepatitis (MASH) remains a clinical challenge. We aimed to evaluate the baseline clinical characteristics of patients with MASH and identify hemodynamic and clinical predictors of subsequent decompensation/clinical events.
Method: A cohort of 51 MASH patients (mean age 65 years, 51% males) was longitudinally evaluated. Portal hemodynamic parameters—including portal venous pressure (PVP) and portal pressure gradient (PPG)—clinical scores (Fib4, MELD), and non-invasive markers (LSM, SSM) were analyzed. Diagnostic accuracy for clinical outcomes was determined using AUROC and Kaplan-Meier survival curves.
Results: Over the follow-up period, 12 patients (23.5%) experienced a clinical event. At baseline, patients who subsequently developed clinical events exhibited significantly higher Fib4 scores (6.96 vs. 3.23, p=0.001), higher INR (1.20 vs. 1.10, p=0.016), lower platelet counts (75.5 10^9/L} vs. 123.0 10^9/L}, p=0.009), and lower albumin levels (3.50 vs. 4.08 g/dL, p=0.004). Notably, the presence of cirrhosis (100% vs. 56.4%, p=0.005) and esophageal varices (75% vs. 33.3%, p=0.001) was significantly more frequent in the event group. Regarding portal hemodynamics, both baseline PVP (26.5 vs. 17.3 mmHg, p<0.001) and PPG (17.0 vs. 10.0 mmHg, p<0.001) were markedly elevated in patients with poor outcomes. Multivariate logistic regression identified PVP (OR: 1.32, 95% CI: 1.06–1.65, p=0.01) and Fib4 (OR: 1.33, 95% CI: 1.01–1.76, p=0.04) as independent predictors of clinical events. ROC analysis demonstrated excellent diagnostic accuracy for both parameters: PVP: AUROC = 0.834 (Best cut-off >22 mmHg}, Sensibility: 0.83, Specificity: 0.74, p<0.001); PPG: AUROC = 0.828 (Best cut-off >11 mmHg, Sensibility: 0.83, Specificity: 0.76, p<0.001). Kaplan-Meier estimates confirmed significantly impaired decompensation-free survival in

patients exceeding these thresholds, with PVP >22 mmHg showing a stronger stratification capacity (log-rank p=0.002) compared to PPG >11 mmHg (log-rank p=0.04). ConclusionIn patients with MASH, direct portal hemodynamic assessment via PVP and PPG provides robust prognostic stratification. Baseline PVP >22 mmHg and PPG >11 mmHg identify patients at critical risk of hepatic decompensation, highlighting their potential role in tailoring intensive monitoring and therapeutic strategies.

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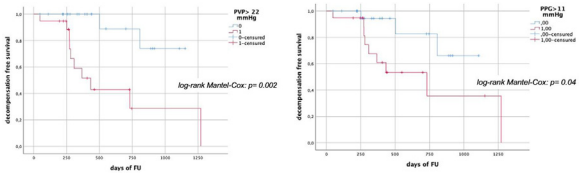

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T-04

When Wellness Turns Harmful: Green Tea–Associated Liver Injury in a Patient with MASH

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A 34-year-old woman with no prior liver disease was referred to our Hepatology Clinic after routine laboratory tests detected markedly elevated liver enzymes (AST 88 U/L, ALT 194 U/L, GGT 85 U/L). Abdominal ultrasound showed a moderately steatotic liver. Her medical history included insulin resistance with impaired fasting glucose, androgenetic alopecia, and a small colloid-cystic euthyroid thyroid nodule. She denied alcohol consumption, smoking, and any risk factors for viral hepatitis. Her diet was generally balanced, though she reported consuming 1–1.5 liters daily of green tea prepared by infusion of whole leaves. There was no family history of liver disease or malignancy. Comprehensive laboratory evaluation—including viral hepatitis serologies (HAV, HBV, HCV), autoimmune markers (ANA, AMA, ENA, ANCA, ASMA, LKM), iron and copper metabolism tests, alpha-1 antitrypsin, thyroid function, and celiac screening—was normal. MRI of the abdomen confirmed hepatic steatosis without biliary or vascular abnormalities.Due to persistent enzyme elevation without clear etiology, a liver biopsy was performed. Histology demonstrated preserved lobular architecture, extensive macro- and microvesicular steatosis, mild pericellular fibrosis, and minimal intralobular lymphogranulocytic inflammation. These findings supported a diagnosis of steatohepatitis, most likely metabolic in origin, although green tea–related hepatotoxicity could not be excluded.The patient was advised to discontinue green tea consumption, adopt a hypocaloric diet, and begin physical activity. After two months, liver enzymes showed marked improvement (AST 43, ALT 82, GGT 88, ALP 94 U/L), despite no major lifestyle changes aside from stopping green tea. At six months, values had nearly normalized (AST 32, ALT 47, GGT 51 U/L), suggesting a reversible liver injury potentially triggered or exacerbated by green tea intake.Green tea (Camellia sinensis) is widely consumed for its perceived health benefits, attributed largely to catechins such as epigallocatechin-3-gallate (EGCG). Nevertheless, idiosyncratic hepatotoxicity has been reported, most commonly with concentrated extracts but also with traditional infusions. Individual susceptibility plays a central role, and the HLA B*35:01 allele has been associated with increased risk. This case highlights a possible synergistic mechanism in a patient with underlying metabolic dysfunction. Although MAFLD was evident histologically, the substantial biochemical improvement following discontinuation of green tea suggests an additional toxic component. The pathogenesis is linked to its catechins like EGCG, and the mechanism involves oxidative stress, mitochondrial dysfunction, and potentially idiosyncratic immune responses. Clinicians should remain aware of the hepatotoxic potential of green tea, even in infusion form, and should routinely inquire about herbal and dietary supplement use in the evaluation of abnormal liver enzymes.

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T-05

LOW BURDEN OF CARDIOMETABOLIC RISK FACTORS IN HDV-RELATED LIVER DISEASE: A EUROPEAN POOLED ANALYSIS OF THE SAVE-D AND D-SHIELD COHORTS

Maria Paola Anolli [1], Elisabetta Degasperi [1], Liana Gheorghe [2], Alessandro Loglio [3], Alessia Ciancio [4], Gianpiero D'Offizi [5], Mathias Jachs [6], Thomas Reiberger [6], Cristoph Schramm [7], Maurizia Brunetto [8], Florian Van Bommel [9], Serena Zaltron [10], Laura Turco [11], Caroline Zöllner [12], Teresa Santantonio [13], Ivana Carey [14], Alessandro Federico [15], Mariarosa Tamè [16], Andrea Di Lorenzo [17], Maria Buti [18], Filipe Calinas [19], Filomena Morisco [20], Margarita Papatheodoridi [21], Francesco Paolo Russo [22], Alessandra Mangia [23], Pierluigi Toniutto [24], Nicola Coppola [25], Cristopher Dietz-Fricke [26], Jèrome Dumortier [27], Edoardo Giovanni Giannini [28], Elena Rosselli Del Turco [29], Soo Aleman [30], Stella De Nicola [31], Monia Maracci [32], Letizia Marinaro [33], Michele Milella [34], Adriano Pellicelli [35], Biagio Pinchera [36], Massimo Puoti [37], Dominique Roulot [38], Lory Saveria Crocè [39], Ivana Maida [40], Uta Merle [41], Mariana Cardoso [42], Alessia Zoncada [43], Pietro Torre [44], Francesca Pileri [45], Antonietta Romano [46], Matteo Tonnini [47], Paola Vitiello [48], Rosa Zampino [49], Pietro Lampertico [1]

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Background and Aim: Chronic hepatitis Delta is the most severe form of viral hepatitis, with accelerated progression to cirrhosis and increased hepatocellular carcinoma (HCC) risk. While cardiometabolic risk factors influence outcomes in other chronic liver diseases, their prevalence and clinical relevance in CHD remain poorly defined.
Methods: CHD patients included in the retrospective multicenter real-world European SAVE-D study and in the prospective multicenter Italian D-SHIELD study were included. The prevalence of cardiometabolic risk factors (arterial hypertension, type 2 diabetes, overweight/obesity) were evaluated at BLV start.
Results: 828 patients treated with BLV 2 mg/day subcutaneous monotherapy up to 144 weeks were included in this analysis: age 52 (IQR 42-60) years, 57% men, 698 (84%) with cirrhosis, median BMI was 24.8 (22.7-27.4). 39 (5%) patients had type 2 diabetes (T2DM), and 126 (15%) patients had arterial hypertension (AHTN), 85 (10%) patients had obesity (defined as BMI ≥30), of whom 13 (15%) grade II obesity (BMI 35-39) and 2 (2%) grade III obesity (BMI≥40). Controlled Attenuation Parameter (CAP) on Fibroscan® was available in 484 (59%) patients: median CAP values were 209 (181-238) dB/m. 50 (5%) patients showed hepatic steatosis (by CAP >275 dB/m): median BMI in these patients was 28.4, 6 (12%) patients had T2DM, 11 (22%) AHTN. Overall, median alanine aminotransferase (ALT) levels were 79 (50-129) U/L and 62 (47-94) in patients without and with T2DM, respectively (p=0.04). Median gamma glutamyl transferase (gGT) were 58 (35-97) and 44 (27-74) U/L in patients without and with T2DM, respectively (p=0.03). When analyzing the impact of cardiometabolic risk factors (AHTN, T2DM), BMI and CAP values on responses rates to BLV, only CAP values predicted the achievement of a biochemical response at on-treatment week 48 (OR 1.01 95% CI 1.00-1.02, p=0.02). Conversely, none of the baseline features predicted the achievement of a virological response, combined response, and of HDV RNA undetectability at week 48 of BLV monotherapy.
Conclusions: European patients with CHD exhibited an unexpectedly low prevalence of cardiometabolic risk factors (MetHDV), compared to other viral hepatitis, with no measurable effect on BLV treatment responses during the first year of therapy.

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T-06

Clinical Obesity Refines Longitudinal Risk Stratification for Liver-related and Cardiometabolic Outcomes Beyond BMI

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Background and Aims: The Lancet Diabetes & Endocrinology Commission recently proposed a classification of obesity distinguishing preclinical from clinical obesity by integrating excess adiposity with obesity-related organ dysfunction. Whether this classification improves longitudinal risk stratification for liver-related and cardiometabolic outcomes beyond conventional body mass index (BMI)-defined obesity remains unclear.
Methods: We analysed 282,719 European-ancestry adults from the UK Biobank (UKBB) and 460,507 predominantly older Korean adults from the Korean National Health Insurance Service (KNHIS) Senior Cohort. Participants were classified according to BMI categories (normal weight, overweight, obesity) and Lancet Commission criteria as having no obesity, preclinical obesity, or clinical obesity. Cox models estimated adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) for incident liver-related events, cardiovascular events, and all-cause mortality. Transition from preclinical to clinical obesity was assessed in UKBB.
Results: In UKBB, over a median follow-up of 14.2 years, both BMI-based and Lancet Commission classifications showed a graded increase in liver-related risk. Compared with normal weight, overweight and BMI-defined obesity were associated with liver-related events with aHRs of 1.09 (95% CI 1.00–1.18; p=0.043) and 1.78 (1.63–1.94; p<0.001), respectively. Under the Lancet Commission classification, preclinical obesity showed intermediate liver-related risk (aHR 1.24, 1.14–1.35; p<0.001), while clinical obesity showed the highest risk (aHR 1.98, 1.83–2.15; p<0.001), compared with no obesity. Compared with BMI-defined obesity, clinical obesity also showed stronger associations with cardiovascular events (aHR 2.05 vs. 1.82; both p<0.001) and all-cause mortality (aHR 1.63 vs. 1.43; both p<0.001). In KNHIS, clinical obesity showed consistent associations with liver-related events (aHR 1.36, 1.28–1.44; p<0.001) and cardiovascular events (aHR 1.25, 1.23–1.27; p<0.001), whereas mortality associations differed from UKBB, likely reflecting age-modified relationships. Among 90,386 UKBB participants with preclinical obesity at baseline, 33,434 (37%) progressed to clinical obesity with a median transition time of 8.0 years.
Conclusions: The Lancet Commission obesity classification refines longitudinal risk stratification beyond BMI-defined obesity, particularly for liver-related and cardiovascular outcomes, by identifying both a high-risk clinical obesity group and an intermediate preclinical stage. Preclinical obesity is a dynamic condition with substantial progression to clinical obesity, highlighting a potential window for early intervention in people at metabolic risk.

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T-07

Sleep Duration and Liver Fibrosis in Metabolic Dysfunction-Associated Steatotic Liver Disease: Evidence from the NHANES 2017–2022 Cohort

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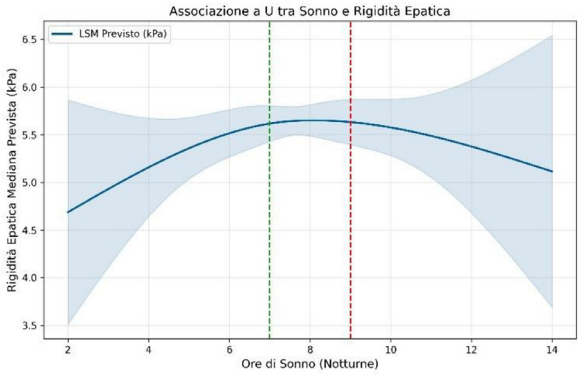
Background and Aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a leading cause of chronic liver disease worldwide. Lifestyle factors, including sleep habits, may influence fibrosis progression. We investigated the association between sleep duration, healthy lifestyle behaviors, and significant liver fibrosis in adults with MASLD from the National Health and Nutrition Examination Survey (NHANES) 2017–2022.
Methods: Among 27,493 NHANES participants, individuals aged <18 or >80 years, pregnant women, subjects with viral hepatitis B/C, excessive alcohol consumption, other chronic liver diseases, or missing key data were excluded. Participants meeting MASLD diagnostic criteria were included, yielding a final cohort of 11,142 subjects. Missing data were handled using Multiple Imputation by Chained Equations (MICE). Significant fibrosis (≥F2) was defined as liver stiffness measurement (LSM) ≥8.0 kPa by vibration-controlled transient elastography. A Healthy Lifestyle Score (0–5) was constructed by assigning one point for each of the following: sleep duration 7–9 h/night, social jetlag <1 h, ≥150 min/week of moderate-to-vigorous physical activity, sedentary time <360 min/day, and adequate dietary fiber intake according to sex-specific recommendations. Multivariable logistic regression, restricted cubic spline analyses, and causal mediation analyses were performed.
Results: Each one-point increase in the Healthy Lifestyle Score was independently associated with a 19–32% lower odds of significant fibrosis across adjusted models (OR 0.81, 95% CI 0.75–0.88; p<0.001), including adjustment for BMI and type 2 diabetes. Participants in the highest lifestyle score tertile had a 41% lower fibrosis risk than those in the lowest tertile (OR 0.59, 95% CI 0.48–0.73; p-trend <0.001). Restricted cubic spline analysis demonstrated a U-shaped association between sleep duration and LSM, with the lowest predicted stiffness observed at 7–8 h/night. Both short (≤6

h) and prolonged sleep duration were associated with higher liver stiffness. BMI mediated 52% of the lifestyle–fibrosis association in men, whereas a predominantly direct effect was observed in women (58.8%).
Conclusions: Optimal sleep duration (7–8 h/night) is independently associated with lower liver stiffness in MASLD. Sleep health should be considered an integral component of lifestyle interventions aimed at preventing fibrosis progression.

Sleep Duration and Liver Fibrosis in MASLD.pdf



Restricted Cubic Splines tra la relazione non lineare tra ore di sonno notturne e LSM in kPa aggiustata per Età, Sesso e BMI

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T-08

Eligibility for MASH Therapy in Chronic HBV with MASLD: Application of the AISF STEPS-MASH Framework in a Real-world Cohort

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Background and aims: Steatotic liver disease frequently coexists with chronic hepatitis B virus (HBV) infection. With the approval of pharmacological therapies for non-cirrhotic metabolic dysfunction-associated steatohepatitis (MASH), the proportion of people living with chronic HBV and concomitant metabolic dysfunction-associated steatotic liver disease (MASLD) who may be eligible for treatment remains undefined. We applied the recently published AISF STEPS-MASH clinical framework to a real-world single-centre chronic HBV cohort to identify the proportion and clinical features of patients potentially eligible for MASH pharmacotherapy.
Methods: We analysed 160 consecutive adults with chronic HBV infection. Hepatic steatosis was defined by ultrasound or controlled attenuation parameter (CAP) ≥248 dB/m, and MASLD by steatosis plus at least one cardiometabolic risk factor. Eligibility for MASH-directed pharmacotherapy was assessed using the STEPS-MASH approach: documented steatosis, significant fibrosis on vibration-controlled transient elastography (liver stiffness measurement [LSM] ≥8 kPa and <20 kPa), and exclusion of cirrhosis based on LSM ≥20 kPa or radiological signs.
Results: Median age was 63 years, 67.5% were men, and 91% were receiving nucleos(t)ide analogue therapy. Hepatic steatosis was documented in 95 patients (59.4%), and at least one cardiometabolic risk factor was present in 124 (77.5%). Overall, MASLD was identified in 81 patients (50.6%). Applying the STEPS-MASH criteria, 13 patients were potentially eligible for MASH-directed pharmacotherapy, corresponding to 8.1% of the whole cohort and 16.0% of those with MASLD. Eligible patients had a median age of 72 years, were all receiving nucleos(t)ide analogue therapy, and had a median LSM of 9.5 kPa; 9 had LSM 8–10 kPa and 4 had LSM 10–20 kPa. Median BMI was 27.6 kg/m², and only one eligible patient had diabetes.
Conclusions: In this real-world chronic HBV cohort, MASLD was present in approximately half of patients, but only a minority fulfilled non-invasive STEPS-MASH criteria for MASH-directed pharmacotherapy. Systematic assessment of steatosis, cardiometabolic risk, and fibrosis may help identify patients with concomitant MASLD who could benefit from targeted treatment.

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T-09

LINKING OBESITY TO MILD COGNITIVE IMPAIRMENT IN METABOLIC-ASSOCIATED STEATOTIC LIVER DISEASE

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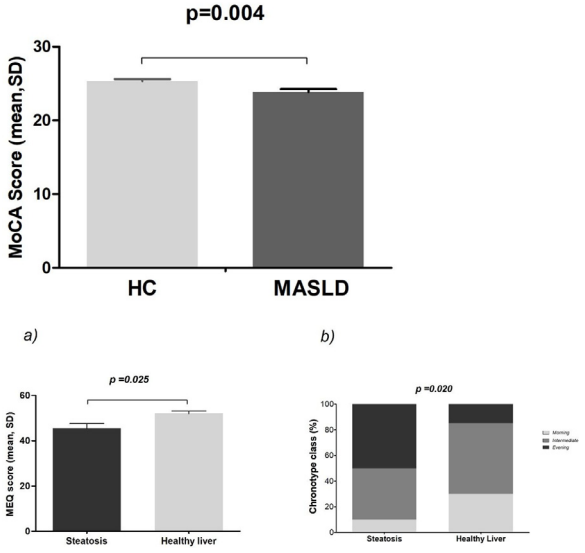
Background: Metabolic dysfunction–associated steatotic liver disease (MASLD) is the most prevalent chronic liver disease worldwide, with increasing incidence in both adults and children. Beyond liver involvement, MASLD has been linked to extrahepatic manifestations, including mild cognitive impairment (MCI), potentially driven by systemic low-grade inflammation and neuroinflammatory mechanisms. However, it remains unclear whether cognitive decline is primarily related to liver pathology or to associated metabolic risk factors. We aimed to assess MCI prevalence in MASLD patients compared with healthy controls (HC) and to identify factors predictive of cognitive decline.
Methods: We enrolled adult patients (18–65 years) with ultrasound-confirmed MASLD attending our tertiary centre. Exclusion criteria included non-metabolic liver diseases, risk of advanced fibrosis (ruled out by a FIB-4 score ≥1.3), cirrhosis, psychiatric or neurological disorders, severe systemic diseases, and use of steatogenic medications. Demographic, clinical, anthropometric, and lifestyle data were collected. Cognitive function was assessed using the digital Montreal Cognitive Assessment (MoCA) test, with scores ≥26 considered normal. Anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS).
Results: The ANCOVA model revealed a significant impact of years of schooling ($p < 0.001$) and age ($p = 0.005$) on cognitive performance. After adjusting for these covariates (evaluated at a mean age of 48.3 years and 12.0 years of education), MASLD patients showed significantly lower adjusted MoCA scores (23.86 ± 0.40 vs. 25.33 ± 0.28; $p = 0.004$) (Figure 1) and a higher prevalence of MoCA scores below the normal threshold (66.7% vs. 42.7%, $p = 0.010$) compared with HC (Figure 2). Domain-specific analyses revealed poorer performance in language ($p < 0.001$) and memory ($p = 0.011$). Multivariate logistic regression showed that MASLD is a strong, independent predictor of pathological MoCA,

tripling the risk of cognitive impairment (OR = 3.03, 95%CI: 1.14 - 8.01,p = 0.026). HADS scores indicated minimal anxiety or depression in both groups. Within the MASLD cohort, obesity was the only metabolic comorbidity significantly associated with pathological MoCA (p = 0.021), while diabetes (p = 0.052), hypertension (p = 0.125), and hypercholesterolemia (p = 0.826) showed no significant association. In the final stepwise model, years of schooling remained the dominant independent protective factor (OR = 0.70, p = 0.002).

Conclusions: MCI is more prevalent in MASLD patients than in HC, particularly affecting memory and language domains. While lower educational attainment stands out as the main baseline predictor of cognitive status, obesity emerges as the primary modifiable clinical risk factor among metabolic comorbidities. Early interventions targeting obesity may help prevent or mitigate cognitive impairment in this population.

FIGURE_1.jpg

FIGURE_2.jpg



doi: 10.1016/j.dld.2026.07.038

T-10

HEPATIC STEATOSIS IN HEALTHY YOUNG ADULTS: A LINK WITH THE EVENING CHRONOTYPE

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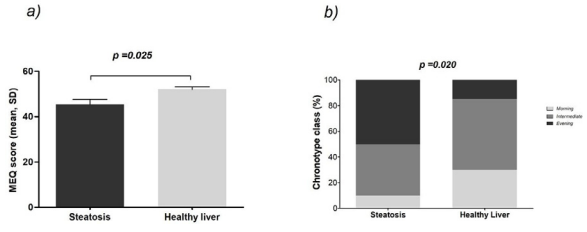
Background and Aims: Beyond classical metabolic risk factors, circadian rhythm disruption and individual chronotype have recently emerged as potential contributors to metabolic dysregulation. While an evening chronotype is known to correlate with worse MASLD severity in individuals with obesity, its impact on early liver steatosis among healthy young adults remains poorly characterized. This study aimed to evaluate the prevalence of liver steatosis in a healthy young population and identify associated risk factors, focusing specifically on chronotype. Material and

Methods: Healthy volunteers aged 18–30 years, with a normal BMI (18.5–24.9 kg/m²), stable body weight, and no history of acute or chronic diseases or alcohol use (assessed via AUDIT-C), were consecutively enrolled. Chronotype was determined using the Morningness-Eveningness Questionnaire (MEQ). Sleep quality, adherence to the Mediterranean diet, and physical activity were measured using the Pittsburgh Sleep Quality Index (PSQI), the MEDI-LITE score, and digital step counts, respectively. Body composition was measured by BIA. Hepatic steatosis and fibrosis were assessed by abdominal ultrasound and FibroScan®, with steatosis defined as CAP ≥248 dB/m. Morning salivary cortisol was collected at 8:00 AM. Independent predictors of steatosis were identified using multivariable logistic regression analyses.

Results: Liver steatosis was detected in 10 out of 77 participants (13%). No significant differences regarding age, sex, family history of metabolic diseases, physical activity, dietary patterns, or body composition parameters were found between the groups. However, participants with liver steatosis displayed significantly lower MEQ scores (45.5 ± 6.5 vs 52.1 ± 8.6; p = 0.025) (Figure 1, panel a), a higher prevalence of an evening chronotype (50% vs 15%; p = 0.020) (Figure 1, panel b), and significantly higher morning salivary cortisol levels (9.5 ± 4.1 vs 6.8 ± 3.7 mcg/L; p = 0.045). In the multivariable logistic regression analysis, the MEQ score was independently associated with hepatic steatosis, exerting a significant protective effect (OR 0.90, 95% CI 0.81–0.99; p = 0.034), demonstrating that a morning-oriented chronotype lowers the likelihood of hepatic fat accumulation. A secondary exploratory model suggested a borderline significant interaction trend between sleep quality and chronotype (PSQI × MEQ; OR 1.90, 95% CI 0.96–3.74; p = 0.064).

Conclusions: In healthy young adults, an evening chronotype is independently associated with early hepatic steatosis, regardless of sex, diet, and physical activity. These findings suggest that circadian misalignment may contribute to early liver fat accumulation and support chronotype assessment as a potential tool for identifying at-risk individuals and guiding targeted circadian-based preventive interventions.

FIGURE_1_ABSTRACT.jpg



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T-11

Prevalence and clinical impact of metabolic dysfunction-associated steatotic liver disease in primary biliary cholangitis: a tertiary-center experience

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Background and Aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is frequent among general population, as such might coexist with other chronic liver condition such as primary biliary cholangitis (PBC). However, its clinical relevance

remains uncertain. While current management effectively targets cholestasis, it is unclear whether patients with concomitant MASLD differ in disease progression. We aimed to assess MASLD prevalence in a tertiary-care PBC cohort, assessing their treatment response and disease course compared with PBC alone.
Method: We conducted a single-centre, retrospective, observational study of consecutive patients with PBC. MASLD was defined by evidence of hepatic steatosis on imaging in the presence of cardiometabolic risk factors. Fibrosis stage was assessed by liver biopsy or liver stiffness measurement. Metabolic dysfunction–associated steatohepatitis (MASH) was defined histologically. Clinical outcomes were assessed at the last available follow-up.
Results: Among 160 patients with PBC, 50 (31%) had concomitant MASLD. Baseline alkaline phosphatase levels were comparable between patients with and without MASLD (median 220, IQR 145-321 vs median 211, IQR 151-381 respectively, $p = 0.80$), while gamma glutamyltransferase levels were higher in MASLD patients without being statically significant (median 224, IQR 123-438 vs median 274, IQR 167-538, respectively, $p = 0.30$). Liver stiffness measurements were similar between groups, whereas CAP values were significantly higher in patients with MASLD (median 201, IQR 181-233 vs median 255, IQR 227-293, $p < 0.05$). Response to UDCA did not differ between groups. Cirrhosis was less frequent among patients with MASLD compared with those without MASLD (14% vs 32%, $p = 0.029$). Hepatic decompensation occurred in 4% of patients with MASLD and 12% of those without MASLD, without a statistically significant difference between groups. Among patients with MASLD, 8 (18.6%) had fibrosis stage F2–F3; histological MASH was identified in 3 patients.
Conclusion: MASLD was a common overlapping condition in patients with PBC, yet its presence was not associated with clear differences in cholestatic treatment response or short-term clinical outcomes in this cohort. These findings raise the hypothesis that MASLD may have a limited impact on the clinical course of established PBC, although longer follow-up and larger prospective studies are needed.

Conflict of interest

Pietro Meschisi: None declared, Riccardo Plebani: None declared, Maria Pia Calabrese: None declared, Antonella Ruiu: None declared, Stella De Nicola: None declared, Nicola Pugliese: None declared, Vincenzo Ronca Ipsen, Gilead, Dr Falk, Alessio Aghemo: None declared, Ana Lleo: Advanz Pharma, GSK, Ipsen, Gilead, Dr Falk, AlfaSigma, Takeda, Gilead, Abbvie, MSD, Incyte

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T-12

Phase Angle as non-invasive indicator of liver disease severity and muscle strength in MASLD patients

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Background and aim: The evaluation of nutritional status with bioelectrical impedence analysis (BIA) plays an important role in the multidisciplinary management of MASLD patients. Phase angle (PhA) is gaining attention because it is a proxy of water distribution and body cell mass with high values suggesting cellular integrity and function. This study aimed to evaluate the role of PhA in MASLD patients, investigating its association with liver disease severity.
Methods: This is a monocentric study enrolling all consecutive MASLD patients observed between January and May 2026 at Diseases of the Liver and Biliary System Unit of Federico II University Hospital. All patient underwent anthropometric, clinical and biochemical evaluation. At enrollment, nutritional status was assessed with BIA and liver fibrosis and steatosis was evaluated non-invasively using Transient Elastography (TE) and Controlled Attenuation Parameter (CAP). The cohort was stratified according to PhA values in two groups (group A: PhA $<6°$ and group B PhA $\geq 6°$). A multivariable logistic regression analysis was conducted to identify factors independently associated with PhA values.
Results: A total of 100 MASLD patients (56% male, mean age 55.1 years) were enrolled. Group A was older and with higher BMI and hip circumferences than group B. Regarding nutritional status, group A showed lower total body water ($p=0.002$) and free fat mass ($p<0.001$) and higher fat mass ($p<0.001$) than group B. The skeletal muscle index (SMI) did not differ between groups, but patients with low PhA showed significantly lower handgrip values (27.3 ± 10.4 vs 40 ± 8.9, $p<0.001$) and ate less protein ($p=0.005$). Moreover, liver stiffness (LSM) was significantly higher in group A ($p=0.02$), while CAP was similar between groups. At multivariable analysis, the factors independently associated with high PhA values were liver stiffness (LSM), showing a significant inverse association (OR 0.63, 95%CI 0.41-0.98, $p=0.04$), and handgrip strength, which have direct association (OR 1.55, 95%CI 1.11-2.17, $p=0.01$) Conclusions In MASLD patients, the reduction of PhA is independently driven by increased LSM and reduced muscle strength. Therefore, the PhA could be used by in clinical and nutritional practice as a simple, non-invasive tool to track the progression of liver disease and refer to hepatologists patients with lower values.

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T-13

Sex-Specific Statin Effects on Hepatic Fibrosis in MASLD — Evidence from a Nationally Representative IPTW-Weighted Cohort

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Background and Aims: In patients with metabolic dysfunction-associated steatotic liver disease (MASLD), the hepatoprotective potential of statins is difficult to assess due to confounding by indication, as these drugs are preferentially prescribed to patients with

worse metabolic profiles. To overcome this limitation, we investigated sex-specific associations between statin use and liver stiffness measurement (LSM) using inverse probability of treatment weighting (IPTW). We further evaluated the adequacy of lipid-lowering therapy according to 2025 ESC cardiovascular risk guidelines, and examined how clinically significant fibrosis (LSM $\geq$ 8.0 kPa) impacts LDL target attainment across both sexes.
Methods: We analyzed 2,110 adults from NHANES 2017–2023 with valid vibration-controlled transient elastography. After excluding individuals with significant alcohol use, viral hepatitis, and enforcing strict age criteria (20-80 years), IPTW was applied—stratified by sex—to balance baseline covariates between statin users and non-users. Weighted linear regression assessed statin effects on LSM. LDL target attainment was evaluated using ESC 2025 criteria and the SCORE2 algorithm.
Results: Independent baseline predictors of LSM included BMI ($\beta = 0.205$; $p < 0.001$), diabetes ($\beta = 1.792$; $p < 0.001$), and female sex ($\beta = -0.966$; $p < 0.001$). Post-IPTW, statins reduced LSM overall ($\beta = -0.589$ kPa; $p = 0.007$). Sex stratification revealed profound dimorphism (interaction $p = 0.059$): women derived substantial hepatoprotection ($\beta = -0.934$ kPa; $p = 0.002$), consistent across pre-menopausal ($\beta = -1.013$ kPa; $p = <0.001$) and post-menopausal ($\beta = -0.844$ kPa; $p = 0.022$) status. Men showed no significant benefit ($\beta = -0.102$ kPa; $p = 0.733$). Despite superior hepatic responsiveness, women experienced systematic LDL under-treatment; among High-Risk patients on statins, only 22.8% of women achieved ESC targets (< 70 mg/dL), compared to 37.9% of men.
Conclusions: Statins exert a sex-specific hepatoprotective effect in MASLD, significantly reducing liver stiffness in women. The systematic under-treatment of dyslipidaemia in women represents a critical therapeutic paradox. Integrating sex-specific aggressive lipid management while controlling primary fibrotic drivers like adiposity and diabetes is urgently needed to optimize care.

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T-14

Peripheral Serotonin Signaling and 5-HT2B Modulation as Emerging Metabolic Targets in MASLD: Translational Evidence from Preclinical Models and Early Clinical Development

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is increasingly recognized as a systemic metabolic disorder driven by complex interactions between hepatocytes, non-parenchymal liver cells, and extrahepatic signaling pathways. Among these, peripheral serotonin has emerged as a regulator of lipid metabolism, inflammation, and fibrogenesis. Activation of the serotonin receptor 5-HT2B promotes hepatic stellate cell activation and fibrosis, suggesting a potential role in MASLD progression. We investigated whether pharmacological modulation of hepatic serotonergic signaling could influence steatosis and fibrogenesis and explored the translational feasibility of a low-dose modified-release psilocybin formulation acting through this pathway.
Methods: Psilocin (10 μM) was evaluated in steatotic HepG2 cells, including CRISPR/Cas9-generated 5-HT2A-mutant lines, and compared with a selective 5-HT2B inhibitor. Fibrogenic responses were assessed in TGF-β-activated LX-2 hepatic stellate cells by immunocytochemistry and RT-PCR. In vivo, male mice fed a Gubra-Amylin NASH (GAN) diet received oral sub-psychedelic psilocybin (0.05 mg/kg) from weeks 20–32, followed by histological, ultrastructural, and molecular liver analyses. Translational development was further explored in a Phase I randomized, double-blind, placebo-controlled study evaluating safety and pharmacokinetics of a modified-release psilocybin formulation (REL-P11) in normal-weight and overweight/obese participants.
Results: Psilocin significantly reduced lipid accumulation in steatotic hepatocytes, an effect maintained in 5-HT2A-mutant cells and reproduced by selective 5-HT2B inhibition, indicating a predominant role for 5-HT2B signaling. In activated LX-2 cells, psilocin downregulated key fibrogenic markers, including α-SMA, collagen I, vimentin, ACTA2, and MMP2, mirroring the effects of selective 5-HT2B blockade. In GAN-fed mice, low-dose psilocybin improved mitochondrial and endoplasmic reticulum ultrastructure and attenuated early fibrotic remodeling without worsening steatosis. In the Phase I study, REL-P11 demonstrated favorable safety and tolerability, proportional psilocin exposure, low interindividual variability, and no clinically relevant impact of obesity on pharmacokinetics.
Conclusions: These findings identify hepatic serotonin signaling, particularly through the 5-HT2B receptor, as a pivotal metabolic pathway contributing to MASLD progression. Pharmacological modulation of this axis improves steatotic and fibrogenic features across complementary preclinical models and supports the development of mechanism-based therapeutic strategies targeting metabolic liver disease. Low-dose modified-release psilocybin provides a feasible translational approach to engage this pathway while avoiding measurable psychoactive effects.

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T-15

Cardiac remodelling in a mouse model of progressive metabolic dysfunction-associated steatotic liver disease

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Background: The increasing prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD), and its progressive subtype, metabolic dysfunction-associated steatohepatitis (MASH) and liver fibrosis, establishes MASLD as a major cardiometabolic disorder. Growing evidence has strongly documented a complex, bidirectional crosstalk between the liver and heart as a central driver of cardiometabolic disease, including hypertension and atherogenic dyslipidaemia. Human and preclinical studies recently indicated that, beyond endothelial dysfunction and atherosclerosis, MASLD can be associated with adverse cardiac remodelling, including cardiac hypertrophy.
Aims: In this study, we aimed to evaluate the pattern of pathological cardiac remodelling in a mouse model of early-established progressive MASLD to investigate the relationship between liver and cardiac tissue damage.

Methods: A MASLD mouse model was established using streptozotocin combined with a high-fat (SHF) diet and compared with standard chow-fed controls (CTRL). Mice from both groups were sacrificed at 8, 16, and 20 weeks old to assess disease progression. Biochemical and metabolic parameters were measured by colorimetric assays, while hepatic and cardiac tissue damage were evaluated on FFPE sections by haematoxylin/eosin and Masson's trichrome staining. Gene expression analysis was performed by qRT-PCR to assess alterations in hepatic lipid metabolism and fibrogenesis and to identify markers of cardiac remodelling.
Results: Anthropometric and biochemical analyses revealed a progressive disease phenotype in SHF mice, characterised by increased body and liver weights, elevated metabolic parameters and elevated liver enzymes compared with CTRL. Histological staining showed a progressive increase in steatosis and fibrosis across all SHF groups compared with their respective CTRL groups. Interestingly, the progressive liver damage was parallel to cellular and structural changes occurring in cardiac tissue, such as signs of hypertrophy with irregular vacuolization, evidence of ectopic lipid accumulation, extensive disorganisation and an increase in collagen deposition. These findings were confirmed by gene expression data, including upregulation of the Collagen type 1 (Col1a1) and 3 (Col3a1) and Fatty acid synthase (Fasn) mRNA levels in both hepatic and cardiac tissues of SHF mice. The hypertrophic remodelling was confirmed by increased expression of natriuretic peptide A (Nppa), B (Nppb), and beta-myosin heavy chain (Myh7) and decreased expression of alpha-myosin heavy chain (Myh6).
Conclusions: Overall, our preliminary data suggest that hepatometabolic dysfunction during MASLD progression is associated with cardiac hypertrophy, a fibrotic phenotype and altered lipid metabolism, supporting lipotoxicity as a potential driver of cardiomyocyte remodelling that warrants further exploration to elucidate the causal connection between dual organ damage.

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T-16

Targeting RuvBL1 mitigates mTOR-driven hepatocarcinogenesis by activating the AMPK-TFEB-PPARα lipid catabolic axis

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Background: Hepatocellular carcinoma is a global health challenge, with annual new cases projected to exceed one million by 2025. The rising prevalence of metabolic-associated fatty liver disease highlights the critical role of metabolic dysregulation in liver pathogenesis. The PI3K/Akt/mTOR pathway is hyperactivated in 40-50% of HCC cases, where the AAA+ ATPase RuvBL1 serves as a key regulator of mTORC1. RuvBL1 is frequently overexpressed in human HCC, and high levels are strongly correlated with poor patient prognosis. This study aims to investigate the role of RuvBL1 in liver metabolism and its potential as a therapeutic target in mTOR-driven hepatocarcinogenesis.
Materials and Methods: To investigate RuvBL1 role in liver metabolism, we first generated a hepatocyte-specific haploinsufficient mouse model (RuvBL1hep±). Then, we crossed RuvBL1hep± with liver-specific PTEN-deficient mice (PTENhep-/-), which mimic human NASH through mTOR-induced lipogenesis. Phenotypic and survival analyses were performed on PTENhep-/-RuvBL1hep± mice at 10 weeks and 15 months of age. In vitro, CRISPR-Cas9 was used to generate AML-12 PTEN KO cells. The RuvBL1 ATPase inhibitor CB-6644 was employed to assess its effects on lipid accumulation and metabolic signalling.
Results: RuvBL1hep± mice displayed a distinct metabolic profile compared to WT, characterized by elevated blood glucose, impaired glucose clearance, insulin resistance, and increased hepatic gluconeogenesis. These first results showed us that RuvBL1 haploinsufficiency altered the PI3K/Akt/mTOR pathway, impacting liver function and hepatocyte proliferation. Furthermore, RuvBL1 haploinsufficiency significantly improved the NASH metabolic phenotype, reduced HCC tumor number and grade, and markedly prolonged survival of PTENhep-/- mice. Mechanistically, mice did not show the expected decrease in expression of mTORC1 target lipogenic genes; instead, they exhibited a significant upregulation of lipolytic genes (Ppargc1a, Cpt1a, Acadm, Acadl, Acadvl, Acsl1), suggesting that the improvement was driven by enhanced lipid catabolism. In AML-12 cells, CB-6644 treatment reduced lipid droplet accumulation and stimulated mitochondrial oxidation. CB-6644 induced AMPK activation and TFEB-mediated upregulation of PGC1α and PPARα, identifying the AMPK-TFEB-PPARα axis as the primary driver of this metabolic shift. TCGA database analysis further confirmed that RuvBL1 expression in human HCC positively correlates with mTOR hyperactivation and negatively correlates with key regulators of lipid catabolism.
Conclusions: These findings identify RuvBL1 as a critical regulator of the crosstalk between the mTOR and AMPK pathways. By modulating the AMPK-TFEB-PPARα axis, RuvBL1 targeting promotes lipid mobilization and counteracts pathological lipid accumulation and tumor progression driven by mTOR hyperactivation. RuvBL1 represents a promising therapeutic target for the prevention and treatment of metabolic-driven HCC.

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T-17

Liver involvement in latent autoimmune diabetes in adults: a matched comparison with type 2 diabetes

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Background and aims: Latent autoimmune diabetes in adults (LADA) is an adult-onset autoimmune form of diabetes, whose hepatic phenotype remains poorly characterised. We aimed to assess liver involvement in people living with LADA compared with individuals with type 2 diabetes (T2D).
Methods: In this single-centre, cross-sectional study, 22 people living with LADA were matched 1:1 to 22 people with T2D by sex, age and body mass index (BMI). All participants underwent vibration-controlled transient elastography (VCTE) with controlled attenuation parameter (CAP) and liver stiffness measurement (LSM). Hepatic steatosis was defined as CAP $\geq$248 dB/m; given the presence of diabetes as a cardiometabolic risk factor, this threshold was used to define MASLD. Data are reported as median [IQR] or n (%). Between-group comparisons were performed using the Wilcoxon rank-sum test and Fisher's exact test. Among people with LADA, predictors of CAP were explored using linear regression.

Results: After matching, the LADA and T2D groups were comparable for sex distribution (59% men), age (median 59 years), and BMI (median 24 kg/m²). Compared with individuals with T2D, people with LADA had lower median CAP values (204 [188–236] vs 285 [256–316] dB/m; p<0.001) and a lower prevalence of MASLD (4/22, 18% vs 18/22, 82%; p<0.001). LSM was also lower in LADA than in T2D (4.50 [3.62–5.07] vs 4.95 [4.23–6.78] kPa; p=0.021). Among people with LADA, CAP was associated with BMI (β=9.5 dB/m per kg/m²; p=0.004), but not with HbA1c, diabetes duration, or lipid profile.
Conclusions: At comparable BMI, people with LADA showed a substantially lower burden of hepatic steatosis and lower liver stiffness than individuals with T2D. Within LADA, steatosis was primarily associated with body mass rather than glycaemic control or diabetes duration. These findings suggest that LADA may be characterised by a distinct, lower-risk hepatic phenotype compared with T2D, and that MASLD screening approaches developed for T2D may require specific validation in this population.

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T-18

Mental Health in MASLD: Binge eating, depression and anxiety. A multicentre study

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Background and Aims: Despite the well-established cardiometabolic burden of MASLD, evidence regarding its association with binge eating, depression, and anxiety remains limited. We compared the prevalence of these conditions between patients with MASLD and non-MASLD chronic liver disease controls and investigated their relationship with liver fibrosis.
Methods: Across three tertiary centres (two in Italy and one in Canada), 151 people living with MASLD and 68 non-MASLD controls (people living with HBV, HCV or primary biliary cholangitis) completed four validated questionnaires: Binge Eating Scale (BES), Beck Depression Inventory-II (BDI-II) and State-Trait Anxiety Inventory (STAI-Y1 state, STAI-Y2 trait). Active malignancy and active psychiatric disorders were exclusion criteria. Clinical, demographic and socioeconomic data were collected. Continuous variables were compared by Mann-Whitney U test and categorical variables by chi-square or Fisher's exact test; correlation between questionnaire scores and liver stiffness (LSM) evaluated with vibration-controlled transient elastography was assessed by Spearman's coefficient.
Results: The two groups were comparable for sex (women 46.4% vs 48.5%) and age (median 60 vs 57 years, p=0.37). People living with MASLD showed higher BMI (29.3 vs 23.5 kg/m²), CAP (284 vs 233 dB/m) and prevalence of type 2 diabetes (37.7% vs 4.4%), hypertension (57.0% vs 25.0%), dyslipidemia (70.9% vs 20.6%) and metabolic syndrome (75.5% vs 17.6%) (all p<0.001), with similar LSM (6.9 vs 8.8 kPa, p=0.69). BES scores were significantly higher in the MASLD group (median 4, IQR 1-9, vs 1, IQR 0-4; p<0.001), and probable binge eating disorder (BES>26) was present only in people living with MASLD (4 participants, 2.7%). BDI-II scores were also higher in MASLD (6, IQR 2-13, vs 3, IQR 1-6; p=0.006), with moderate-to-severe depression in 12.7% vs 6.2% and all severe cases occurring in the MASLD group. Anxiety showed a non-significant trend towards higher trait and total scores in MASLD (STAI-Y2 40 vs 37, p=0.069; STAI total p=0.068), while state anxiety did not differ (STAI-Y1 40 vs 38, p=0.14). No questionnaire score correlated with LSM (all p>0.4).
Conclusions: In this multicentre cohort, MASLD was associated with higher binge eating and depressive symptom scores, whereas only a non-significant trend was observed for anxiety. These psychological manifestations were not associated with fibrosis severity, suggesting that they are more closely linked to the metabolic and behavioural milieu of MASLD than to the stage of liver disease. Our findings support the routine assessment of disordered eating and mood disturbances in individuals with MASLD using brief validated instruments such as the BES and BDI-II. Integrating psychological support into multidisciplinary care pathways may enhance adherence to lifestyle and pharmacological interventions, ultimately improving metabolic and clinical outcomes.

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T-19

From Emergency Department to Community Care: Opportunistic Screening as a New Paradigm for Hospital–Territory Integration. The multicentre Pre-DEA study

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Background and Aims: Chronic non-communicable diseases often progress silently for years and remain underdiagnosed until advanced stages, when complications have already developed, resulting in increased morbidity, mortality, and healthcare costs. MASLD represents a paradigmatic example of this hidden burden.Emergency Departments (EDs), increasingly accessed by patients assigned low-priority triage codes, may provide a valuable opportunity for opportunistic screening and early detection of previously unrecognized chronic diseases. Beyond MASLD, conditions such as chronic kidney disease, COPD, type 2 diabetes, osteoporosis, frailty, cognitive impairment, and hypertension could similarly benefit from early identification and referral to integrated hospital-community care pathways. This study aimed to assess the prevalence and awareness of MASLD among low-acuity ED attendees and to explore the role of EDs as gateways to integrated chronic disease management.
Methods: Pre-DEA, a prospective multicenter study involved five ED located in different Italian regions. Adults (≥18 years) triaged as non-urgent or less-urgent were enrolled at presentation. Participants underwent a structured evaluation including medical history, anthropometric assessment, laboratory testing, physical examina-

tion, and focused abdominal ultrasound. Awareness of liver steatosis was also assessed.
Results: Overall, 1138 eligible patients were enrolled. Pre-DEA screening identified steatotic liver disease (SLD) in 31.3% of the cohort. In Lombardy, 58.0% of subjects were steatotic, and 41.0% had a mild disease. In Abruzzo, prevalence was 34.0%, with mild disease in 76.0% of cases. Within this region, Avezzano displayed a site-specific rate of 42.7%. In Apulia, liver steatosis was present in 22.1% of participants, with mild disease in 63.7% of cases. The majority of participants were unaware of their hepatic steatosis status, with an overall unawareness rate of 87%. Regional differences were observed, with unawareness rates of 70% in Lombardy, 92% in Abruzzo, and 98% in Apulia.These findings indicate that SLD was largely hidden and unrecognized, with significant regional differences ($p<0.05$), possibly reflecting heterogeneous environmental or population-related factors.
Conclusions: The greatest benefit of the Pre-DEA model lies in the creation of structured referral pathways linking EDs with primary care physicians, community services, specialist outpatient clinics, and telemedicine programs. This approach may help overcome the persistent fragmentation between hospital and community care, ensuring continuity of care, earlier intervention, and more effective management of chronic diseases. Such integration may facilitate earlier diagnosis, improve risk stratification, promote preventive interventions, reduce avoidable hospitalizations, and slow disease progression.

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T-20

Genetic Clues to Advanced Liver Fibrosis In Italian Patients With Metabolic Dysfunction-Associated Steatotic Liver Disease

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Introduction: Metabolic dysfunction-associated steatotic liver disease (MASLD) is now a leading global cause of chronic liver disease, with the potential to progress to advanced fibrosis and cirrhosis. Growing evidence linking multiple genetic variants to disease progression underscores the substantial heritable component of MASLD. This provides a strong rationale for the use of genetic risk scores (GRS), which integrate key risk alleles, to identify individuals at increased risk of liver fibrosis.
Aims & Methods: This study aimed to investigate the association between a GRS composed of 12 liver-related genetic variants and fibrosis severity in adult patients with MASLD. A total of two-hundred eighty-five adults with MASLD (176 males and 108 females; mean age 64 years) were prospectively enrolled. Liver fibrosis was assessed by liver stiffness measurement (LSM) using FibroScan, and the FIB-4 index, calculated from laboratory data. Genotyping of selected variants was carried out using TaqMan allelic discrimination assays. A GRS was computed by integrating the effect of the 12 genetic variants (rs738409 PNPLA3, rs641738 MBOAT7, rs58542926 TM6SF2, rs17618244 KLB, rs17580 SERPINA1, rs12904 EFNA1, rs429358 APOE, rs7029757 TOR1B, rs888655 ARHGEF28, rs72613567 HSD17B13 T>TA, rs2642438 MARC1, rs12152703 KLB G>T). Participants were categorized into low-risk (GRS < 2, $n = 78$) and high-risk (GRS ≥ 2, $n = 207$) groups. Differences in LSM and FIB-4 across GRS groups were assessed using Mann-Whitney U tests. Multivariable logistic regression models, adjusted for age, sex, and BMI, were performed to evaluate the association between GRS risk categories and liver fibrosis outcomes, defined as LSM $\geq$ 8.0 kPa and FIB-4 $\geq$ 2.67.ResultsPatients in the high-risk GRS group exhibited significantly higher median LSM values (13.5 kPa vs 11.7 kPa; $p = 0.029$) and significantly higher FIB-4 scores (2.5 vs 1.9; $p = 0.034$) compared with the low-risk GRS group. When applying clinically relevant thresholds for significant fibrosis, LSM $\geq$ 8 kPa was detected in 44/78 (56%) patients with low GRS and in 145/207 (70%) with high GRS. The logistic regression analysis showed that high GRS was independently associated with increased odds of elevated LSM (OR 1.86, 95% CI 1.07–3.24; $p = 0.027$). Similarly, advanced fibrosis defined by a FIB-4 score $\geq$ 2.67 was observed in 24/78 (30.8%) low-risk GRS patients and in 93/207 (44.9%) high-risk GRS patients, and the logistic regression analysis showed that high genetic risk was significantly associated with elevated FIB-4 values (OR 1.84, 95% CI 1.06–3.22; $p = 0.031$).
Conclusion: Taken together, these findings highlight the potential clinical relevance of a genetic risk score for identifying patients with MASLD at increased risk of advanced fibrosis. Further studies involving larger, independent cohorts are needed to validate these findings and determine the role of GRS in clinical decision-making.

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T-21

Hepatology referral for MASLD: reflections from the perspective of a tertiary center

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Introduction: MASLD is the most common cause of chronic liver disease worldwide. Case finding and referral of patients with advanced fibrosis are crucial. Fibrosis stage remains the strongest predictor of liver-related outcome and mortality. However, hepatology referral for MASLD varies widely.
Aim: To assess determinants of MASLD referral to our tertiary hepatology center. To explore correlation between FIB-4 score and liver stiffness (LS) in our cohort considering which FIB-4 cutoff value detects significant liver fibrosis.
Method: Retrospective data of referred patients with MASLD were reviewed within Hepatology and Transplant Unit at Udine Hub Hospital (Friuli Venezia Giulia) over a 12-month period. Inclusion was based on imaging evidence of hepatic steatosis after exclusion of secondary causes of steatotic liver disease (SLD). Demographic and biochemical features, LS, controlled attenuation pa-

rameter (CAP) measures, ultrasound findings were recorded. Statistical analysis was performed using T-test MedCalc version 23.5.0.
Results: From 01.05.2025 to 01.05.2026, of 264 first visits performed, 103 (43%) were consistent with MASLD referral. Median age of MASLD patients was 58 years old and 56 (54%) were males. The most prevalent associated cardiometabolic factor was obesity (56%). 83 subjects (80%) were referred from general practitioners (GPs) while the remnants from specialists (diabetologist, endocrinologist, internist). Reasons of referral were as follows: MASLD +normal liver function tests (LFTs) in 33 patients (32%) (group A), MASLD +abnormal LFTs in 45 (43%) (group B), focal liver lesions (FLL) (excluding HCC) in MASLD in 11 (11%) (group C), burning-out MASLD advanced chronic liver disease (ACLD) ± HCC ± decompensation in 14 patients (14%) (group D). Median FIB-4 value was equal to 1.2, 1.6 and 2.0 in group A, B, C respectively. In addition to 14 patients with ACLD (group D); overall, in group A, B, C, we registered 6 patients (6.7%) with LS≥8 kPa and 3 patients (3.3%) with LS ≥12 kPa. FIB-4 ≥1.84 identified advanced fibrosis yielding an area under the curve (AUC) of 0.949 (CI: 0.87, 0.98), regardless of age.
Conclusion: Our data evidence referral for MASLD is heterogeneous, emerging different clinical awareness. The majority of patients seems to be referred too early, in absence of significant fibrosis. Use of the revised FIB-4 scores should be considered to diagnose patients at high risk of liver disease progression, particularly in obese subjects. Referral strategies for MASLD should be optimized according to primary and specialist care.

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T-22

Impact of MASLD on the natural history of chronic hepatitis delta: a retrospective single-center study of the MetHDV phenotype

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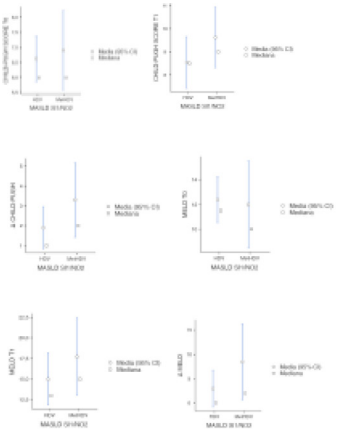
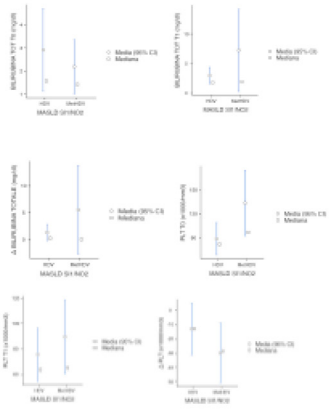
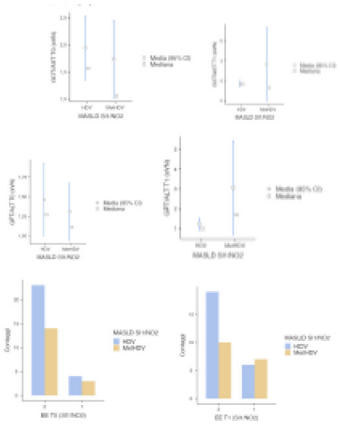
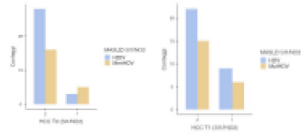
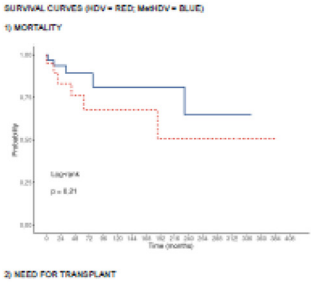
Background and aims: MASLD is the leading etiology of chronic liver disease, and its coexistence with chronic viral hepatitis can worsen liver outcomes. However, its impact on chronic delta hepatitis remains insufficiently investigated. The present study aims to compare clinical characteristics and long-term outcomes between patients with chronic HDV and patients with HDV+MASLD ("MetHDV").
Materials and methods: A single-center retrospective cohort study was conducted enrolling 58 patients with chronic HDV infection followed for a mean follow-up of 6.3 years. Patients with HCV or alcohol-related liver disease were excluded. MASLD was defined according to EASL–EASD–EASO 2024 criteria (steatosis + ≥1 cardiometabolic risk factor). Patients were stratified into two groups: HDV without MASLD (n=35) and MetHDV (n=23). Clinical, biochemical, virological, ultrasound/elastographic parameters and primary outcomes-mortality, liver transplantation, and hepatocellular carcinoma (HCC) development-were assessed.
Results: The two groups were comparable in age and follow-up duration. As expected, MetHDV patients had a significantly worse metabolic profile, with higher BMI (26.6 vs. 21.4 kg/m²; p<0.001), a higher prevalence of overweight/obesity (78.9% vs. 6.3%; p<0.001), and diabetes (21.1% vs. 0%; p=0.021). Virological parameters and response to antiviral therapy did not differ significantly between groups. Although no significant differences were observed in the prevalence of cirrhosis or portal hypertension-related complications, the MetHDV group showed a trend toward greater worsening in liver function over time, with increases in MELD, Child-Pugh, and bilirubin, and a progressive reduction in platelet count. Furthermore, transaminase levels tended to increase only in the MetHDV group (ALT at T1: 3.06 vs. 1.23 xULN; p=0.085). Regarding long-term outcomes, no significant differences were observed in overall mortality (HR 1.03; p=0.959) or the need for liver transplantation (HR 0.93; p=0.899). Analysis of HCC development, however, highlighted the most significant finding: MetHDV patients had a shorter HCC-free survival (63 vs. 233 months) and a more than twofold increased risk of developing HCC compared to patients with HDV alone (HR 2.11; 95% CI 0.63-7.02), although the results were not statistically significant, likely due to the limited sample size.
Conclusions: The presence of MASLD in patients with chronic delta hepatitis may identify a clinically distinct phenotype, characterized by progressive biochemical worsening of liver function and a possible increased risk of HCC, although it does not influence mortality or transplantation in this cohort. Given the limited sample size, larger multicenter studies are warranted to confirm these data findings.

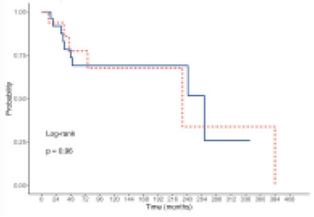


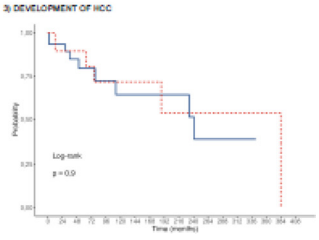












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T-23

Screening for MASLD-Related Fibrosis in Primary Care: Adherence to EASL-EASD-EASO Guidelines and FIB-4 Application in the Verona Cohort

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Background and Aims: Metabolic-associated fatty liver disease (MASLD) is one of the most common liver diseases in industrialized countries and is closely associated with the presence of cardiometabolic risk factors. Early identification of patients at risk of fibrotic progression is crucial, and in this context, non-invasive tools, such as the FIB-4 index, can support screening in general practice. The aim of the study was to evaluate, in a general pop-

ulation of patients attending general practice in the Verona area, adherence to the recommendations of the EASL-EASD-EASO (2024) guidelines regarding MASLD screening, as well as the identification of patients at risk of liver fibrosis.
Materials and Methods: An observational study was conducted based on the analysis of clinical and laboratory data obtained from a population of 1,300 patients cared for by a general practitioner. Patients were selected based on the presence of at least one metabolic risk factor and divided into two groups: patients > 65 years of age with FIB-4 >2 and patients ≤ 65 years of age with FIB-4 > 1.3. AST, ALT and platelets were necessary available in the least two years.
Results: Of 1,300 patients, 56% patients were identified with at least 1 metabolic risk factor. FIB-4 could not be calculated in 21.3% (data non available), while it was calculated in 453, of whom 31% had FIB-4 > 1.3/2.Arterial hypertension is the most frequent comorbidity in the older population (75.3%), while dyslipidaemia and glucose load alterations were identified in younger patients. In patients at risk of fibrosis, transaminase values were within normal limits or below reference cutoffs.
Conclusions: The study results confirm a high prevalence of metabolic risk factors that require screening according to the most recent guidelines, which, however, are still under-applied in the general population. The association between metabolic risk factors and the possible presence of liver fibrosis is confirmed. The use of non-invasive tools based on routine laboratory data, such as FIB-4, may represent a useful strategy to improve screening for MASLD at risk of fibrosis. However, given the high number of patients eligible for second-level screening, it will be necessary to optimize the early identification of patients at risk of fibrosis.

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T-24

Feasibility of Remote Completion of Patient-Centred Questionnaires in Patients with MASLD

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Background and Aims: The burden of Metabolic dysfunction-associated steatotic liver disease (MASLD) has dramatically increased in recent years, consequently the number of patients requiring follow-up in hepatologic centres is steadily growing. Several questionnaires that evaluate health-related quality of life are currently validated for patients with MASLD; however, due to the increasing number of patients, their use in clinical practice is challenging. Thus, to collect this relevant information, we asked our patients to complete questionnaires at home after receiving them via email. The feasibility of this approach in a frail population is uncertain due to their limited digital literacy. Therefore, we aimed to evaluate both the ability and the willingness of patients to complete the questionnaires.
Methods: We conducted a restrospective cross-sectional study to analyze the ability and the willingness of fibrotic MASLD patients to answer validated questionnaires for MASLD (Chronic Liver Disease Questionnaire for NAFLD - CLDQ, Rapid Eating Assessment for Participants - REAPS, FACT-Hep) at home when sent by email. We included consecutive patients with MASLD and significant fibrosis who were visited in our center between September 2025 and May 2026 and agreed to receive questionnaires via email and complete them. Then we analysed whether frailty or comorbidities affected their ability or willingness to fill the questionnaires.
Results: After excluding 244 patients because of the absence of significant fibrosis, we enrolled 60 patients who received the questionnaires by email. In our population, 27 were female (45%), the median age was 62 years (IQR 54.0-69.25), 19 patients (31.7%) had F4 according to FibroScan values and 15 patients (25%) had three or more diseases. Overall, 43 (71.7%) completed at least one questionnaire. When we compared patients who completed at least one questionnaire (n=43) and those who did not complete any (n=17), we observed that Type 2 diabetes (T2D) was significantly more prevalent in the non-completers (88.2% vs. 44.2%; p=0.003). Among non-completers, there was a significantly higher prevalence of F4 fibrosis (52.9% vs 23.8%; p=0.049) and a larger number of frail patients. Specifically, 88.2% of these patients had at least two comorbidities and 35.3% had three or more (vs. 39.5% and 20.9%, respectively, among patients who completed at least one questionnaire). Interestingly the mean age was not different among the two groups (61.1 years of non-completers, vs. 59.4 of completers; p=0.974)
Conclusion: Our findings suggest that innovative approaches are feasible and could reduce both the in-hospital time for patients and the administrative burden for physicians in the majority of fibrotic patients with MASLD, particularly in those with lower degree of fibrosis and who are less frail.

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F-01

Metabolic ferroptosis as targetable signature for the genetic subtype of MASLD

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Background and Aims: The co-presence of the I148M-PNPLA3, rs641738-MBOAT7 and E167K-TM6SF2 polymorphisms (3NRV) enhances the risk of severe MASLD. Emerging evidence highlighted that ferroptosis is essential for developing MASLD/MASH since it promotes oxidative stress, lipid peroxidation and inflammation although the underlying mechanisms are still unknown. Thus, this study investigated the possible crosslink between ferroptosis and the three mutations, by dissecting the metabolism of hepatocytes (HEPs) and non-parenchymal cells (NPCs) in hepatic biopsies of MASLD patients, through a spatial transcriptomic approach.
Method: Spatial transcriptomics was performed by Visium CytAssist (10x Genomics). Patients, featured by a similar histological severity (NAS≥4) and comorbidities (gender, age, BMI, absence of T2D), were wild type (WT), homozygous for PNPLA3, MBOAT7, TM6SF2 polymorphisms and 3NRV carriers.
Results: All samples were integrated and clustered as follows: cl0 enriched in periportal HEPs; cl1 in immune cells; cl2 in pericentral HEPs; cl3 in cholangiocytes; cl4 in endothelial cells (ENDOs); cl5 in immune cells; cl6 in NPCs (HSCs, immune cells and ENDOs); cl7 in HEPs. Firstly, we observed that cl4 was more abundant in PNPLA3, MBOAT7, TM6SF2 and 3NRV samples compared to WT, whereas cl6 was mainly enriched in 3NRV patients vs all. At Pathway-enrichment analysis 3NRV exhibited increased lipid metabolism, oxidative damage, inflammation, fibrosis, and ferroptosis reflecting a worse clinical scenario in all clusters vs the other samples. By focusing on the ferroptosis pathway, we found that in patients carrying TM6SF2 and MBOAT7 variants, it was mainly espressed in macrophages whereas in PNPLA3 and 3NRV, also in HEPs. Moreover, cl6 showed the strongest upregulation of a "metabolic" ferroptosis, driven by lipid buildup and mitochondrial dysfunction. It was designed by a signature of 51 unique genes, which was uregulated only in 3NRV patients, thus rappresenting a pathognonomic feature of the "genetic" subtype of MASLD. To exclude that ferroptosis is driven by iron overload, Perls' staining showed no evidence of hepatic iron depots across groups, supporting its modulation by genetic background. Moreover, hepatic ACSL4, an activator of ferroptosis, was significantly increased in 3NRV patients, whereas GPX4, a key suppressor of ferroptosis, was mainly expressed in WT samples. Finally, an in vitro model generated by CRISPR/Cas9-mediated silencing of MBOAT7 and/or TM6SF2 in HEPG2 cells further confirmed the ferroptotic phenotype in double knock-out model. Consistently, the restoration of both WT MBOAT7 and TM6SF2 through lentiviral transduction strongly reduced ferroptosis activation.
Conclusion: The co-presence of PNPLA3, MBOAT7, and TM6SF2 variants may accelerate liver injury by triggering "metabolic" ferroptosis in both HEPs and NPCs, addressing it as a potential druggable signature to tackle 3NRV MASLD patients.

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F-02

Oxidized LDL reflects inflammatory activity while Lipoprotein(a) tracks fibrotic progression in MASLD

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Background: Oxidized low–density lipoproteins (ox–LDLs) are key mediators of oxidative stress and inflammation, two central players in metabolic dysfunction–associated steatotic liver disease (MASLD) progression towards steatohepatitis (MASH), fibrosis, cirrhosis and hepatocarcinoma (HCC). Although ox–LDLs have been

implicated in cardiometabolic damage, their relationship with MASLD spectrum remains unclear. Another lipid-related biomarker, Lipoprotein(a) [Lp(a)], a genetically determined lipoprotein synthesized in the liver, has been previously associated with advanced fibrosis, but its relationship with ox–LDL and the diagnostic value of their combination is unknown. Aim of this study was to examine the association between ox–LDL and progressive MASLD, and to determine whether its integration with Lp(a) may improve the non–invasive stratification of disease severity.

Methods: We evaluated circulating ox–LDLs in 587 biopsy–proven MASLD patients and assessed their association with histological features, metabolic traits, and serum Lp(a). Hepatic ox–LDL content and expression of scavenger receptors (CD36, LOX–1) were quantified in liver tissues from a subset of 50 patients. Multivariable regression and ROC analyses were performed to determine the independent and combined predictive value of ox–LDL and Lp(a).

Results: Circulating ox–LDLs were associated with lobular inflammation, ballooning, NAS, and MASH, after adjustment for metabolic risk factors and statin use ($p<0.05$ for all comparisons). No association with fibrosis was observed. Hepatic ox–LDL levels were higher than circulating concentrations and progressively increased from steatosis to cirrhosis, suggesting enhanced intrahepatic retention and oxidative remodelling in advanced disease. Accordingly, CD36 and LOX–1 protein levels were increased across disease, especially in cirrhosis (adjusted $p<0.05$ vs steatosis). Ox–LDL and Lp(a) showed an inverse correlation and reflect distinct histological MASLD stages. Indeed, at multivariate analysis, ox–LDL was associated with inflammation whereas low Lp(a) with advanced fibrosis. Unsupervised clustering integrating both biomarkers revealed a high–risk phenotype (high ox–LDL + low Lp(a)) with strong discriminative accuracy for MASH with moderate fibrosis (AUC=0.80).

Conclusions: Circulating ox–LDLs mirror the inflammatory stages of MASLD, whereas reduced Lp(a) reflects fibrotic progression. Their combination delineates a high–risk phenotype that identify both conditions, improving non–invasive stratification and personalized management of MASLD.

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F-03

Nutrigenomic Effects of High-Polyphenol EVOO in MASLD Patients: Impact on Inflammation, ER Stress, and Lipogenic Pathways

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Background: Metabolic Syndrome (MetS) and metabolic dysfunction-associated steatotic liver disease (MASLD) significantly increase cardiovascular risk and mortality. Lifestyle modifications, including the Mediterranean Diet (MD) with Extra Virgin Olive Oil (EVOO) as a key component, represent the cornerstone of treatment.

Aims: This study compared the impact of a high-polyphenol EVOO (HPPE) vs. standard EVOO (SE) dietary intervention in MetS/MASLD patients. We evaluated: 1) clinical, instrumental, and laboratory profiles related to cardiovascular and hepatic health; 2) systemic inflammatory status via cytokine patterns; 3) transcriptional modulation in PBMCs, targeting lipid metabolism and endoplasmic reticulum (ER) stress pathways. Materials and

Methods: Ninety consecutive MetS/MASLD patients were enrolled in a single-center, double-blind prospective study and randomized to supplement the MD with either HPPE or SE (40 ml/day for 6 months). Anthropometric measures, liver function, metabolic/inflammatory status, flow-mediated dilatation (FMD), liver ultrasound (US), and abdominal fat thickness were analyzed at baseline (T0) and after 6 months (T6). Plasma cytokines/chemokines (IL-1β, IL-10, IL-17A, MCP-1, TNF-α) were quantified using a Luminex multiplex immunoassay. Gene expression in PBMCs for pathways involving ER/oxidative stress, lipid metabolism, and steatosis was analyzed via RT-PCR. Genetic polymorphisms (PNPLA3, TM6SF2, PCSK9, GCKR) were also screened.

Results: From T0 to T6, waist circumference, HbA1C, and visceral/subcutaneous fat thickness significantly improved in both the HPPE ($p<0.0001$, $p<0.03$, $p<0.04$) and SE groups ($p<0.0001$, $p<0.04$, $p<0.03$). Conversely, insulinemia ($p<0.03$), HOMA-IR ($p<0.03$), AST ($p<0.01$), and FMD ($p<0.001$) improved exclusively in the HPPE group. Both groups showed a downward trend in liver steatosis at US, particularly in moderate-to-severe stages. The entire cohort exhibited a significant reduction in inflammatory markers: IL-1β ($p<0.0001$), IL-10 ($p<0.0001$), IL-17A ($p<0.0001$), MCP-1 ($p=0.0058$), and TNF-α ($p=0.013$). In PBMCs, the HPPE group showed a significant downregulation of TRB3 (ER stress), FASN, SREBP1, PPARalpha, PPARgamma, and CPT1a (lipid metabolism). In contrast, the SE group showed a significant increase in TRB3 and FASN expression, with no changes in other genes. Polymorphism frequencies were equivalent to the general population in both groups.

Conclusions: MD supplemented with HPPE EVOO effectively mitigates metabolic risk factors and restores endothelial function in MASLD patients. The concurrent reduction in pro-inflammatory cytokines and the downregulation of key lipogenic genes (SREBP1, FASN) provide a molecular rationale for these clinical improvements, suggesting that dietary polyphenols directly target hepatic steatogenesis pathways.

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F-04

Muscle mass and function in MASLD patients eligible for incretin-based therapies: a cross-sectional study from a tertiary referral center

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Background and Aims: Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) is an emerging indication for incretin-based therapies. As these treatments are increasingly adopted, interest has grown in understanding body composition changes accompanying weight reduction, particularly regarding skeletal muscle preservation. Since the clinical consequences of lean tissue loss may depend on baseline muscle reserves, we aimed to characterize body composition and muscle function in MASLD patients potentially eligible for incretin-based therapy.
Methods: In this prospective cross-sectional study, consecutive MASLD patients were enrolled at a tertiary referral center between 2025 and 2026. Participants underwent anthropometric assessment, bioelectrical impedance analysis (Akern®), and handgrip strength testing. Body composition was characterized using fat-free mass index (FFMI) and appendicular skeletal muscle mass index (ASMI). Low muscle mass was defined according to ESPEN-recommended cut-offs, while reduced muscle strength was identified according to EWGSOP2 criteria. Eligibility for incretin-based therapies was assessed using either weight-based criteria or liver disease–based criteria (AISF STEP-MASH criteria).
Results: After exclusion, 65 patients with MASLD were included. Median age was 63 years (IQR 55.0–71.0), median BMI 33.4 kg/m² (IQR 30.2–37.7), with a high prevalence of hypertension (69.2%) and dysglycaemia (70.8%), including type 2 diabetes in 49.2%. Liver disease severity was heterogeneous, with 16.9% of patients showing LSM <8 kPa, 63.1% between 8 and 20 kPa, and 20.0% >20 kPa. Fifty patients (76.9%) fulfilled weight-based eligibility criteria and 24 (36.9%) met STEP-MASH–based eligibility criteria. No patient met ESPEN criteria for low muscle mass and no participant had ASMI values below EWGSOP2 thresholds. Median FFMI and ASMI remained consistently above diagnostic cut-offs across all eligibility groups (FFMI 22.4–25.4 kg/m²; ASMI 8.8–10.2 kg/m²), suggesting substantial baseline lean tissue reserves. Reduced muscle strength was observed in a subset of patients, with low handgrip strength detected in 14.7% of men overall and more frequently among those meeting STEP-MASH–based eligibility criteria than in the weight-based subgroup (33.3% vs 13.0%).
Conclusions: MASLD patients meeting current eligibility criteria for incretin-based therapies generally show preserved muscle mass despite reduced muscle strength in a subset of individuals. Muscle function assessment may represent a practical first-line screening tool, while comprehensive body composition evaluation could be prioritized in older or more vulnerable patients. The relevance of this approach may increase if future indications expand to more advanced stages of liver disease.

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F-05

Biopsy Fragmentation Influences Steatosis Quantification Discordance in MASLD Diagnosis

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Rationale: Traditional liver biopsy adequacy criteria (i.e, portal tract number and biopsy length) are currently used for steatosis liver disease (SLD) diagnosis. However, these criteria were developed for portal-based hepatitis diagnosis, whereas steatosis and steatohepatitis are mainly lobular events. In this study, we tested whether innovative (i.e., tissue fragment number, total area, weighted fragment length (WFL), weighted fragment area (WFA), and dispersed versus clustered spatial pattern) biopsy adequacy criteria are more supportive of MASLD pathology diagnosis and explain discordance between artificial intelligence (AI) and pathologist steatosis assessment.
Methods: Whole-slide images from 57 SLD liver biopsies were analyzed for steatosis estimates by an AI-based algorithm and a pathologist with dedicated training. Discordance between evaluators was defined as the absolute difference between the AI and pathologist steatosis percentage. Overall agreement was assessed with the intraclass correlation coefficient (ICC). Correlation of traditional and innovative liver biopsy metrics was assessed via Spearman correlation.
Results: Across the 57 SLD biopsies, median AI-estimated and pathologist steatosis assessments were 34.6% and 32.0%, respectively. Overall agreement between AI and pathologist assessment was high (ICC: 0.936). Among the evaluated liver biopsy adequacy criteria, the total number of fragments was positively correlated with absolute discordance (Spearman rho=0.882, $p<0.001$), indicating that higher fragmentation was associated with greater disagreement. Furthermore, WFL (rho=−0.822, $p<0.001$) and WFA (rho=−0.803, $p<0.001$) indicated that a smaller average fragment size was associated with higher AI–pathologist discordance. Spatial fragmentation pattern was also relevant: among cases with evaluable classification (i.e., with more than one fragment), a dispersed fragment pattern was associated with higher discordance (rho=0.588, $p<0.001$). In contrast, traditional adequacy or size metrics were not significantly associated with discordance, including portal tract number (rho=−0.111, p=0.409), portal tract density (rho=−0.135, p=0.318), total biopsy length (rho=0.122, p=0.367), and total biopsy area (rho=0.012, p=0.930).
Conclusion: In this SLD biopsy series, AI-pathologist steatosis agreement was high, but discordance was driven primarily by tissue fragmentation and related spatial dispersion rather than by portal tract count and biopsy length. These findings suggest that biopsy architecture should be incorporated into quality-control metrics for SLD steatosis assessment, particularly when highly fragmented samples are evaluated.

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F-06

Liver-oriented non-invasive tests and cardiovascular and liver-related outcomes in the UK Biobank

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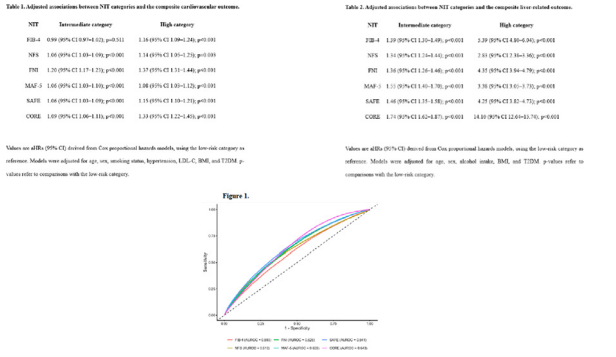
Background and Aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is linked to cardiometabolic dysfunction. Several liver-oriented non-invasive tests (NITs) integrate hepatic and metabolic variables, but their ability to capture cardiovascular disease (CVD) risk remains unclear. We evaluated the association of the Fibrosis-4 Index (FIB-4), non-alcoholic fatty liver disease fibrosis score (NFS), fibrotic non-alcoholic steatohepatitis index (FNI), Metabolic Dysfunction-Associated Fibrosis 5 (MAF-5), Steatosis-Associated Fibrosis Estimator (SAFE), and Cirrhosis Outcome Risk Estimator (CORE) with cardiovascular and liver-related outcomes in UK Biobank participants.
Methods: Two cohorts were derived from UK Biobank Europeans after outcome-specific exclusions. Composite cardiovascular outcome was defined as atherosclerotic CVD events, coronary revascularization, or CVD-related death; liver-related outcome as cirrhosis, portal hypertension complications, hepatocellular carcinoma, liver transplantation, or liver-related death. Cox proportional hazards models compared NIT categories with the low-risk reference. Cardiovascular models were adjusted for age, sex, smoking, hypertension, low-density lipoprotein cholesterol (LDL-C), body mass index (BMI), and type 2 diabetes mellitus (T2DM); liver-related models were adjusted for age, sex, alcohol intake, BMI, and T2DM. Ten-year time-dependent AUROCs were estimated for the composite cardiovascular outcome. Fine–Gray models were used for competing-risk analyses (non-CVD death as competing event). Systematic Coronary Risk Evaluation 2 (SCORE2) and Systematic Coronary Risk Evaluation 2-Diabetes (SCORE2-Diabetes) were evaluated across FNI categories.
Results: The cardiovascular and liver-related cohorts included 248,951 and 259,290 participants, with about 14 years of follow-up. For the composite cardiovascular outcome, adjusted Cox estimates are reported in Table 1. In competing-risk analyses, FNI showed subdistribution hazard ratios (sHRs) of 1.20 (95% confidence interval [CI], 1.16–1.23; p<0.001) and 1.35 (95% CI, 1.29–1.41; p<0.001). For CORE, Fine–Gray estimates were lower than Cox estimates (sHR 1.08, 95% CI, 1.05–1.11; p<0.001 and sHR 1.19, 95% CI, 1.09–1.31; p<0.001). Cardiovascular discrimination was limited across NITs, as shown in Figure 1. SCORE2 and SCORE2-Diabetes increased across FNI categories (3.4%, 5.1%, 5.3%; and 7.0%, 8.5%, 9.2%; all p<0.001). Liver-related associations were stronger (Table 2), with CORE showing the largest association with the composite liver-related outcome.
Conclusions: Liver-oriented NITs capture modest cardiovascular risk signals, particularly FNI, but show limited discrimination and should not replace dedicated CVD risk algorithms. Their associations with liver-related outcomes are stronger, especially for CORE. When calculated for hepatological purposes, elevated NIT categories may help identify individuals who warrant formal CVD risk assessment.



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F-07

FIB-4–Guided Vibration-Controlled Transient Elastography Reveals a High Burden of Liver Fibrosis and Steatosis in Patients with Diabetes: A Real-World Study

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Background and Aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is common in patients with diabetes and may progress silently to advanced liver disease. Guidelines recommend sequential risk stratification using FIB-4 followed by vibration-controlled transient elastography (VCTE), but implementation may be hindered by patient volumes, FIB-4 age-related limitations, and incomplete linkage to second-level assessment. We aimed to evaluate the application of a stepwise FIB-4/VCTE strategy in a real-world diabetes cohort.

Methods: This prospective, single-centre observational study was conducted at the Diabetes Centre and Hepatology Outpatient Clinic of the academic hospital in Novara. Between May 2025 and May 2026, patients with diabetes mellitus and FIB-4 ≥1.3 were deemed eligible for VCTE (FibroScan®, Echosens). Patients with ≥20-30 g/day alcohol consumption were excluded. Liver stiffness measurement (LSM) ≥8 kPa was the threshold for hepatology referral. According to Baveno VII, LSM ≥10 kPa and ≥15 kPa were considered suggestive and highly suggestive of compensated advanced chronic liver disease, respectively. Controlled attenuation parameter (CAP) values ≥248 and ≥280 dB/m defined steatosis and severe steatosis, respectively. FIB-4 was centrally recalculated; patients with FIB-4 <1.3 and one patient with an acute, non-representative elevation were excluded. Statistical analyses were performed using jamovi 2.7.

Results: Among 7,461 patients referred to Endocrinology Unit during the study period, 3,423 (45.9%) had FIB-4 ≥1.3. Of these, 213 (6.2%) were referred for VCTE and 205 were analysed. Median age was 70 years (IQR 64–76); 70 patients (34.1%) were female, 153 (74.6%) were overweight/obese, 161 (78.5%) had arterial hypertension, 70 (34.1%) had low HDL cholesterol, and 47 (22.9%) had hypertriglyceridaemia. LSM ≥8 kPa was observed in 50 patients (24.4%); LSM ≥10 kPa and ≥15 kPa were observed in 38 (18.5%) and 18 (8.8%), respectively. CAP ≥248 dB/m was present in 135 (65.9%) and CAP ≥280 dB/m in 99 (48.3%). Female sex (OR 2.77, p=0.009) and a doubling of GGT levels (OR 2.35, p<0.001) were independently associated with LSM ≥8 kPa. Severe steatosis was independently associated with each 5-kg/m² increase in BMI (OR 2.22, p<0.001) and each 50-mg/dL increase in triglycerides (OR 1.43, p=0.018). Among 73 patients aged >65 years with 1.3≤FIB-4<2.0, 9 (12.3%) had LSM ≥8 kPa and 6 (8.2%) had LSM ≥10 kPa, representing 18.0% and 15.8% of all cases above these thresholds, respectively.

Conclusions: A FIB-4-based referral strategy identified a high burden of liver disease, with approximately one quarter showing increased liver stiffness. Applying a FIB-4 cut-off of 2.0 in patients aged >65 years would have reduced referrals but missed 18.0% of patients with LSM ≥8 kPa and 15.8% of those with LSM ≥10 kPa. Structured diabetes–hepatology pathways are needed to improve risk stratification and facilitate specialist referral.

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F-08

Liver Fibrosis and IRS1 rs2972146 Are Associated With Insufficient Weight Loss After Bariatric Metabolic Surgery

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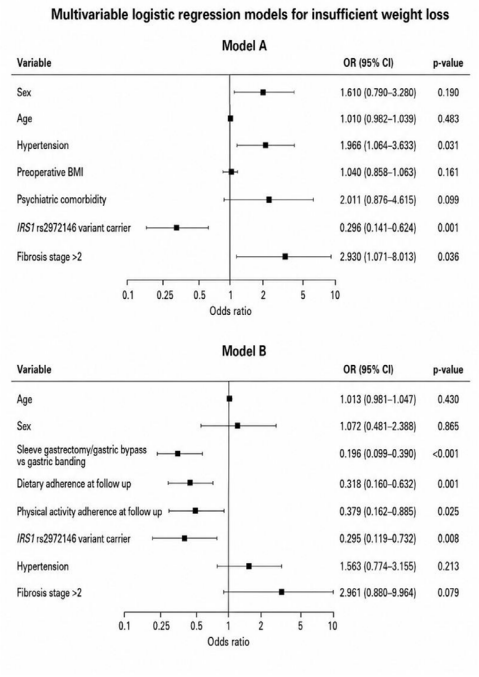
Background and Aims: Metabolic dysfunction associated steatotic liver disease (MASLD), the leading cause of chronic liver disease worldwide, is highly prevalent in patients with obesity. Weight loss is the cornerstone of treatment, with bariatric metabolic surgery (BMS) providing durable weight reduction in severe obesity. However, insufficient weight loss (IWL) and weight regain (WR) may limit its liver-related benefits. We aim to evaluate the role of MASLD severity and MASLD-related genetic variants in post-BMS outcomes.

Methods: We retrospectively included 351 consecutive adults who underwent BMS at Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, between 2008 and 2023. IWL was defined at 18 months as <50% excess weight loss and/or BMI ≥35 kg/m², WR was defined as ≥10% increase from postoperative weight nadir. MASLD severity was assessed histologically. Genetic susceptibility was evaluated using TaqMan assays for PNPLA3, TM6SF2, GCKR, HSD17B13 and IRS1 variants.

Results: Among 351 patients, MASLD was present in 298 patients (84.9%), metabolic-dysfunction associated steatohepatitis (MASH) in 43 (12.3%) and significant fibrosis >2 in 26 (7.4%). Overall, 109 (31.1%) patients developed IWL. MASLD and MASH were not associated with IWL, while fibrosis >2 was more frequent in patients with versus without IWL (13.8% vs. 4.6%, p=0.002). IRS1 rs2972146 variant carriage was less frequent in patients with IWL versus without IWL (79.4% vs 89.2%, p=0.024), whereas no associations were observed for the other genetic variants. In multivariable models, fibrosis >2 (OR 2.93, 95% CI 1.07–8.01) and IRS1 rs2972146 variant (OR 0.30, 95% CI 0.14–0.62), remained independently associated with IWL, after correction for type of surgical intervention, hypertension, dietary adherence and physical activity (Figure). WR data were available for 280 patients, of whom 91 (32.5%) developed WR after a median follow-up of 43 months. MASLD, MASH, liver fibrosis and MASLD related genetic variants were not associated with WR. In multivariable analysis WR was independently associated with psychiatric comorbidity (OR 3.63, 95% CI 1.55–8.49), higher preoperative BMI (OR 0.92, 95% CI 0.87–0.97), sleeve gastrectomy or gastric bypass (OR 0.41, 95% CI 0.21–0.80), and dietary adherence (OR 0.30, 95% CI 0.16–0.55).

Conclusions: In this bariatric cohort, MASLD and liver fibrosis were highly prevalent, and the severity of liver disease appeared to influence the response to BMS. Both IWL and WR affected nearly one-third of patients. Liver fibrosis was independently associated with a higher risk of IWL, whereas WR was mainly driven by behavioral and psychiatric factors. A novel finding was the potential protective role of the IRS1 rs2972146 variant, a gene involved in insulin signaling, against IWL. Overall, these findings support the need for multidisciplinary management of MASLD in patients undergoing BMS, even in the context of an interventional weight-loss approach.



Note: **Model A** evaluated baseline host-related factors only, including age, sex, preoperative BMI, psychiatric comorbidity, hypertension, significant fibrosis, and IRS1 rs2972146 variant carrier status. **Model B** extended Model A by additionally including procedure- and postoperative lifestyle-related factors, namely bariatric procedure type, dietary adherence at follow-up, and physical activity adherence at follow-up.

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F-09

Dual-Axis Phenotyping Reveals Distinct Cardiometabolic and Liver-Specific Disease Patterns in biopsy-proven MASLD

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Background: MASH is a clinically heterogeneous disease:some patients carry a predominant cardiometabolic burden, others exhibit severe liver-specific histological injury regardless of metabolic comorbidities. We aimed to classify biopsy-proven MASH into four clinical phenotypes using a dual-axis approach and compare portal-splenic involvement and non-invasive test performance across groups.
Methods: Single-centre retrospective study, with 75 histologically confirmed MASH patients; all other aetiologies were excluded. A dual-axis 2 × 2 matrix defined four phenotypes:(1)Metabolic burden score 0–5 (type 2 diabetes, obesity BMI≥30, hypertension, dyslipidaemia, CKD/CVD): High if ≥3;(2)Liver-specific histological burden per SAF score:High if SAF-F≥3 (sufficient criterion) or SAF-A≥3 AND SAF-S=3. Phenotypes: Low-risk, Cardiometabolic, Liver-specific, Mixed systemic. Primary outcome: portal-splenic involvement (splenomegaly, varices, ascites, encephalopathy, collaterals). Baseline comparisons used Kruskal-Wallis and chi-square/Fisher; portal-splenic involvement was tested with chi-square and pairwise Fisher vs Low-risk; multivariable logistic regression assessed independent phenotype effects; continuous portal-splenic surrogates were compared with Kruskal-Wallis/Mann-Whitney; elastometry was stratified by fibrosis stage; FIB-4 ≥2.67 performance for SAF-F≥3 was evaluated by sensitivity/specificity.
Results: Low-risk 29%, Cardiometabolic 12%, Liver-specific 32%,Mixed systemic 27%. SAF-F≥3 was present in 0% of low liver-burden phenotypes vs 95–96% of Liver-specific/Mixed (p<0.001). The cumulative number of portal-splenic components was significantly higher in Mixed systemic MASH (Kruskal-Wallis p<0.001). Cardiometabolic and Liver-specific MASH showed comparable portal-splenic rates (33% vs 38%, p=1.000) despite opposite fibrosis (SAF-F 2.0 vs 4.0, p<0.001). Liver stiffness differed across phenotypes (p=0.001): Cardiometabolic MASH showed elevated elastometry vs Low-risk (11.0 vs 7.3 kPa) at identical fibrosis stage. FIB-4 ≥2.67 achieved only 29% sensitivity for SAF-F≥3. (Fig1)
Conclusions: A dual-axis classification based on metabolic comorbidities and histological burden identifies four distinct MASH phenotypes. Mixed systemic MASH carries the greatest portal-splenic load, representing the most advanced disease expression. Cardiometabolic and Liver-specific MASH share a comparable prevalence of portal-splenic involvement despite opposite fibrosis profiles, suggesting that metabolic burden independently drives portal injury through mechanisms beyond fibrosis alone. Furthermore, liver stiffness overestimates fibrosis in the cardiometabolic phenotype, likely reflecting metabolic inflammation and haemodynamics. Finally, FIB-4 thresholds fail to detect advanced fibrosis in a substantial proportion of patients. These findings highlight the limitations of conventional stratification frameworks in capturing MASH heterogeneity supporting phenotype-based assessment.

Figure 1. Dual-axis phenotypic classification of biopsy-proven MASH: portal-splenic burden and liver stiffness across phenotypes (n=75)

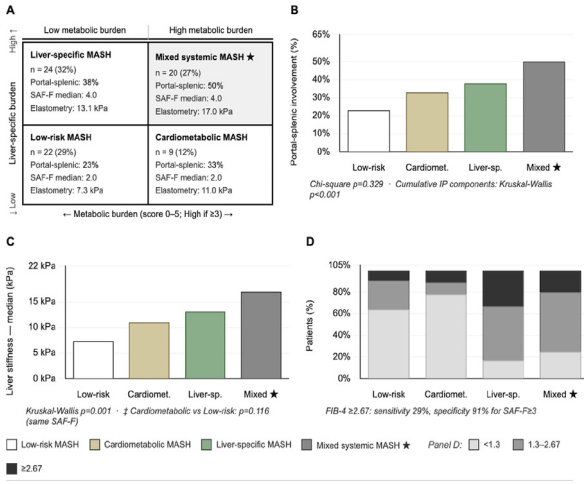

Figure 1. (A) Dual-axis 2×2 phenotypic matrix. Metabolic burden score: one point each for type 2 diabetes, obesity (BMI≥30 kg/m²), hypertension, dyslipidaemia, CKD/CVD (high if ≥3). Liver-specific burden: high if SAF-F≥3 (sufficient criterion) or SAF-A≥3 AND SAF-S=3. Cell values indicate portal-splenic prevalence and median liver stiffness. **(B)** Portal-splenic involvement by phenotype. **(C)** Median liver stiffness by phenotype — note disproportionate elevation in Cardiometabolic MASH at identical fibrosis stage (SAF-F 1–2) as Low-risk. **(D)** FIB-4 category distribution across phenotypes. ★ Highest cumulative portal-splenic burden (Kruskal-Wallis p<0.001). SAF, Steatosis-Activity-Fibrosis; kPa, kilopascal.

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F-10

Spleen Stiffness Measurement for Detection of Advanced Fibrosis and Prognostication in MASH: A Prospective Study Protocol

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Background and Aims: Spleen stiffness measurement (SSM) using the novel 100-Hz probe (Fibroscan F630 Expert) has emerged as a promising non-invasive tool for assessing portal hypertension and advanced chronic liver disease in patients with metabolic dysfunction-associated steatotic liver disease (MASLD). However, its role in prognostic stratification and in improving diagnostic accuracy for compensated advanced chronic liver disease (cACLD) remains unclear. Here, we present the protocol of the "S-MASH study", which aims to evaluate the diagnostic and prognostic performance of SSM in MASLD-related cACLD.
Methods: S-MASH is an Italian multicenter, ambispective observational study coordinated by Policlinico Universitario A. Gemelli IRCCS (Rome) and University of Torino, Italy. More than 500 adult patients with MASLD and cACLD will be enrolled across 28 hepatology centers. cACLD is defined by histological fibrosis stage F3–F4 and/or liver stiffness measurement (LSM) by vibration controlled transient elastography (VCTE) >15 kPa; patients with LSM >8 kPa undergoing liver biopsy according to clinical practice are also eligible.The primary aim is to evaluate whether baseline and longitudinal SSM measurements predict major adverse liver outcomes (MALOs), defined as hepatic decompensation, hepatocellular carcinoma, liver transplantation, or liver-related death. Secondary objectives of the first aim include assessing the technical feasibility of SSM and evaluating the relationship between SSM dynamics and development of clinically significant portal hypertension (CSPH). The secondary aim is to assess the diagnostic accuracy of SSM, alone or combined with established non-invasive tests (FIB-4, LSM, Agile 3+, Agile 4), for histological diagnosis of cACLD. A two-step diagnostic algorithm integrating SSM with current non-invasive tests will also be developed to reduce indeterminate cases and improve rule-in/rule-out performance. For both aims, the met-ALD population will be enrolled as exploratory cohort. VCTE data will be collected at baseline and at 12 month follow up. Patients will be followed up for 60 months.
Expected Results: The study is expected to clarify the role of SSM as a complementary non-invasive biomarker for both diagnosis and prognostic stratification in MASLD-related cACLD, potentially improving identification of patients at higher risk of MALOs and reducing the indeterminate area of current VCTE-based algorithms.
Conclusions: S-MASH may support the integration of SSM into future non-invasive pathways for risk stratification and longitudinal monitoring of MASLD-related cACLD.

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F-11

Toward a Spatially Resolved Human MASLD Meta-Atlas: A Systematic Review and Technical Audit of Single-Cell and Spatial Datasets

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Introduction: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common chronic liver disease worldwide, and its progression from simple steatosis through steatohepatitis (MASH), fibrosis, cirrhosis and hepatocellular carcinoma (HCC) is driven by cellular transitions that bulk transcriptomics cannot resolve. Single-cell, single-nucleus and spatial technologies have transformed this landscape, but the resulting human datasets are fragmented and technically heterogeneous, limiting the cross-study integration that a unified molecular map would require. Existing reviews synthesise biology rather than assessing whether the underlying datasets are actually accessible, annotated and suitable for an integrated spatially resolved human MASLD progression meta-atlas.
Methods: We aimed to systematically catalogue and grade the actionability of human liver single-cell and spatial transcriptomic datasets across the entire MASLD axis. Following PRISMA 2020, we

searched PubMed (frozen March 2026), supplemented by backward and forward citation searching, and screened 2,357 unique records. Eligible studies generated de novo high-resolution transcriptomic data. For each, we extracted disease context, tissue source, modality, platform, yield, repository accessions and metadata, and graded integration-readiness across data accessibility, granularity, metadata completeness and technical harmonisability.
Results: Seventy-eight datasets met eligibility (35 core-metabolic data producers, 10 foundational healthy ref, 33 secondary HCC ref), published 2017–2026, with 83% appearing from 2022 onward. scRNA-seq predominated (47/78), followed by spatial methods (33), snRNA-seq (21) and multiome/ATAC (8); 19 datasets combined single-cell and spatial profiling, the configuration most useful for integration. Disease-axis coverage was uneven: MASH (52/78) and HCC-containing tissue (51/78) dominated and 38 datasets included healthy reference tissue, whereas early MASL/simple steatosis was captured in only 11 datasets. On integration-readiness, 42/78 datasets (54%) were openly reusable, 31 (40%) conditionally integrable (controlled access, author request, or pending publication) and 5 (6%) not obtainable; controlled-access deposition (26 datasets, concentrated among genotype-/eQTL-linked cohorts) and incomplete metadata were the principal barriers.
Conclusion: Human single-cell and spatial profiling of the MASLD axis is rich but uneven and fragmented, and only about half of it is openly integration-ready. The dominant obstacles to a unified molecular map are infrastructural rather than biological: sparse early-disease sampling, controlled-access deposition and inconsistent metadata. This audit provides a reproducible, curated roadmap and identifies spatially resolved profiling of early MASL and bridging fibrosis, with standardised metadata and open deposition, as the field's most actionable priorities for assembling a spatially resolved human MASLD meta-atlas.

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F-12

Psychological vulnerability is associated with compensated advanced chronic liver disease (cACLD) in patients with metabolic dysfunction–associated steatotic liver disease (MASLD): a Case Control study

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Introduction and Aim: Metabolic dysfunction–associated steatotic liver disease (MASLD) requires sustained lifestyle modification, however psychological vulnerability that may influence both metabolic control and adherence remain additional and less visible determinants. The aim of the study is to evaluate the association between psychological profiles and advanced liver disease in patients with MASLD, focusing on depression, anxiety, emotional dysregulation, worry, and coping.
Materials and Methods: Consecutive adults with MASLD completed validated validated self-report instruments: BDI-II (depression), STAI-Y (anxiety), DERS (emotional dysregulation), Brief-COPE (coping strategies), and PSWQ (worry). Disease severity was defined by Baveno VII criteria for compensated advanced chronic liver disease (cACLD) and clinically significant portal hypertension (CSPH). Multivariable logistic regression adjusted for sex, age, diabetes, and obesity was used to evaluate associations between psychological measures and cACLD. Two psychological phenotypes were derived by Ward's hierarchical clustering, a primary non-residualized phenotype and a companion residualized phenotype; clustering was exploratory.
Results: Of 172 enrolled patients, 162 were analysed, 67.3% were male, the age was 53.7 ± 12.7 years, 24.1% had cACLD and 10.5% had CSPH. cACLD was associated with higher depression, state anxiety, and emotional dysregulation. In adjusted models, STAI-Y State, BDI-II Total/Somatic-Affective scores, DERS above cut-off, DERS Non-acceptance, DERS Impulse, and DERS Strategies were associated with cACLD; Brief-COPE Avoidance was borderline. The primary high-burden phenotype was associated with cACLD (adjusted OR 2.97, 95% CI 1.24–7.08; p=0.014) and CSPH (adjusted OR 3.09, 95% CI 1.04–9.15; p=0.042) with concordant estimates for the residualized phenotype.
Conclusions: Psychological vulnerability is common in MASLD and is associated with advanced liver disease, particularly through depression, state anxiety, and emotional dysregulation. These findings support the integration of psychological assessment into routine MASLD care and highlight emotional regulation as a potential target for behavioral interventions.

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F-13

Integrated phenotyping of the gut-platelet-liver axis in the progression of MASLD-related chronic liver disease

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Introduction: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common chronic liver disease, with MASH representing its progressive inflammatory form. Increasing evidence suggests that gut microbiota-derived metabolites modulate platelet function, supporting the existence of a gut–platelet–liver axis involved in disease progression and thrombotic complications.We aim to identify platelet characteristics associated with the progression of liver disease and to investigate the mechanistic relationship between gut dysbiosis and platelet activation.
Methods: In this case-control study 34 participants have been involved: 4 healthy controls, 10 MASLD, 10 MASH and 10 Cirrhotic patients. Fecal eluates were prepared from patient stool samples by homogenisation in phosphate-buffered saline (PBS), followed by centrifugation and filtration, and subsequently inactivated by UV irradiation to inactivate bacteria and thus prevent platelet damage;

efficacy was assessed by aerobic and anaerobic cultures before and after treatment. Platelet-rich plasma (PRP), obtained by centrifugation blood from healthy controls, was incubated with the patients' fecal eluates for 60 and 120 minutes. Platelet activation was assessed by flow cytometry, analysing markers of activation and degranulation (GPIIb/IIIa/PAC-1, P-selectin/CD62p, CD63), with TRAP as a positive control. Fecal samples were also collected for microbiota profiling, with 16S rRNA sequencing (NGS).
Results: Cirrhotic patients showed increased CD62p up to 365% and PAC-1 up to 161% at 60 min ($p<0.05$), with CD63 stable or slightly reduced. MASH patients showed marked platelet activation, with CD62p up to 340% at 60 minutes and 187% at 120 minutes ($p<0.05$). Patients with MASLD showed a significant increase in CD62p levels of up to 1013% at 60 minutes, which persisted even at 120 minutes. Microbiota analysis in 10 patients (3 MASLD, 5 MASH, 2 Cirrhotic) showed inter-individual variability. Alpha diversity was higher in MASLD, while reduced in MASH and Cirrhotics. Beta diversity showed partial separation by disease stage: MASLD clustered more closely, MASH showed greater heterogeneity, and cirrhotics tended to segregate. Functional analysis revealed distinct metabolic signatures, with PCoA explaining 52.2% of variance; MASH displayed marked heterogeneity.
Conclusions: These findings support the existence of a functional gut–platelet–liver axis in MASLD. Fecal eluates from patients with MASLD, MASH, and cirrhosis contain factors capable of inducing platelet activation, which increases with disease severity. In parallel, disease progression is associated with reduced microbial diversity and distinct functional microbiome signatures. Gut dysbiosis may therefore contribute to platelet activation, thrombotic risk, and liver disease progression, suggesting the microbiota as a potential therapeutic target in MASLD.

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F-14

Optimising hepatology referral in metabolic dysfunction: diabetes and obesity drive advanced fibrosis while GLP-1 receptor agonists remain underused

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Background & Aims: Validated noninvasive tools to help non-hepatology clinicians identify metabolic-dysfunction patients needing referral for advanced fibrosis remain scarce. We evaluated the real-world performance of blood-based fibrosis (FIB-4) and steatosis (HSI) scores against vibration-controlled transient elastography (VCTE), and explored associations between GLP-1RA use and liver disease at referral.
Methods: 795 patients consecutively referred by non-hepatology clinicians (Jan2025–Jun2026) at first evaluation for at least 1 metabolic risk factor (type 2 diabetes, obesity, dyslipidaemia, or arterial hypertension) had complete FIB-4, HSI, VCTE and controlled attenuation parameter (CAP) data. Liver stiffness (LSM) >8;>10;>12 kPa flagged increasing likelihood of advanced fibrosis; CAP ≥248; ≥280 dB/m defined steatosis (≥S1) and severe steatosis (≥S3). Performance was assessed by AUROC and guideline dual cut-offs strategies; multivariable logistic regression identified independent associations.
Results: LSM >8;>10;>12 kPa prevalence was 9.6%; 4.5%; 2.9%; CAP ≥248; ≥280, 68.1%, 45.3%. Diabetes (OR 1.82) and obesity (OR 2.10) independently predicted LSM >8 kPa, whereas GLP-1RA use was associated with lower adjusted odds (OR 0.50, 95%CI 0.27–0.93). Obesity independently predicted steatosis (OR 2.98). FIB-4 discrimination rose with stiffness threshold (AUROC 0.58; 0.66; 0.72) and was higher when steatosis coexisted (CAP-by-FIB-4 interaction, p=0.01), consistent with reports that metabolic phenotype modulates FIB-4. The low cut-off (<1.30) retained rule-out value; HSI's low cut-off was non-discriminatory (only 1.6% classified low-risk). Notably, 27% (n=215) of patients were on GLP-1RA therapy, 76 had Diabetes and obesity (35.3%), 77 had only diabetes (35.8%), 49 had only obesity (22.8%) and 13 were only overweight (6.1%).Among patients with both CAP>248 dB/m and LSM>8kPa (n=61), 46 (75%) were not taking GLP1-RA despite 80% of them were diabetic od obese.
Conclusions: In a real-world metabolic dysfunction referral cohort, diabetes and obesity are independent drivers of significant fibrosis. FIB-4 accuracy is meaningfully enhanced by concomitant steatosis and retains its established role as a reliable rule-out tool for liver fibrosis. While HSI achieves acceptable sensitivity at the high cut-off, its near-absent specificity at the low cutoff precludes its use as a reliable rule-out instrument. GLP-1RA is markedly underused in potential eligible patients, supporting structured, metabolic-informed referral pathways.

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F-15

Reduced cardiorespiratory fitness with a peripheral-metabolic limitation pattern in patients with MASLD: a pilot CPET study

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Background: Patients with metabolic dysfunction associated steatotic liver disease (MASLD) frequently show reduced exercise capacity and increased cardiovascular risk. However, the mechanisms underlying impaired functional performance remain incompletely understood. We aimed to characterize cardiopulmonary exercise patterns in MASLD patients undergoing CPET.
Methods: We conducted a cross-sectional pilot study including 27 MASLD patients. All patients underwent comprehensive clinical evaluation, liver stiffness measurement (LSM) by transient elastography and symptom-limited cardiopulmonary exercise testing (CPET). CPET was performed on a cycle ergometer using an incremental ramp (15 watt) protocol. Reduced cardiorespiratory fitness was defined according to VO_2 peak values adjusted for age and sex. Ventilatory limitation was assessed through breathing reserve(BR), with preserved ventilatory reserve defined as BR >30%. Ventilatory efficiency was considered preserved in patients with VE/VCO_2 <34. The primary endpoint was peak oxygen uptake (VO_2 peak, mL/kg/min) as a measure of cardiorespiratory fitness. Secondary CPET variables, including BR and VE/VCO_2, were analyzed to characterize the predominant mechanism underlying exercise limitation.
Results: Patients included in the study have a median age and BMI of 64 years and 28.3 kg/m². Hypertension and diabetes were present in 78%, 50% of patients. Compensated advanced chronic liver disease (cACLD) was observed in 12 patients (41.4%), while 8 (27.6%) met criteria for clinically significant portal hyperten-

sion (CSPH). Overall, cardiorespiratory fitness was reduced, with a median VO_2peak of 16.4 mL/kg/min (IQR 13.2–19.7). Despite this impairment, ventilatory reserve was preserved, with a median BR of 65.0% (IQR 57.9–71.2), and ventilatory efficiency remained within normal limits (median VE/VCO_2 32.4, IQR 29.1–33.9). No significant differences in CPET-derived parameters were observed between patients with or without cACLD. Conversely, patients with CSPH showed a trend toward lower cardiorespiratory fitness (VO_2peak 13.7 vs 16.6 mL/kg/min, p=0.089). Diabetic patients exhibited significantly lower cardiorespiratory fitness compared with non-diabetic subjects (median VO_2peak 13.3 vs 17.0 mL/kg/min, p=0.021). No differences were observed in breathing reserve (65.0% vs 65.7%, p=0.830), while a trend toward higher VE/VCO_2 values was observed among diabetic patients (33.4 vs 30.4, p=0.073).
Conclusions: In this pilot cohort, impaired fitness in MASLD patients appeared to be more closely associated with type 2 diabetes than with advanced liver fibrosis, highlighting the potential role of metabolic dysfunction as a key determinant of functional impairment. The observed reduction in peak VO_2, occurring in the presence of preserved BR and normal VE/VCO_2, suggests that the exercise limitation is primarily driven by peripheral muscle metabolic dysfunction or impaired oxygen delivery rather than ventilatory limitation.

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F-16

Metabolic Dysfunction-Associated Steatotic Liver Disease and Acute Outcomes in Matched Cirrhosis Emergency-Care Encounters

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is increasingly represented among patients with cirrhosis and is linked to cardiometabolic comorbidity. In emergency care, whether MASLD independently worsens acute outcomes or marks accumulated vulnerability remains uncertain.
Methods: We analyzed 2,524 emergency department encounters from 1,176 patients with cirrhosis, assembled as 1,262 severity- and missingness-matched MASLD/non-MASLD pairs. The primary outcome was death or intensive care unit (ICU) admission. Secondary outcomes included MACE, OHE, hospitalization, length of stay, hepatic decompensation, and AKI/HRS. Multivariable logistic models used patient-clustered standard errors and adjusted for age, sex, calendar year, MELD-Na, Charlson hepatic score, hepatocellular carcinoma, clinically significant portal hypertension, cardiovascular disease, diabetes, chronic kidney disease, and triage. Robustness analyses addressed repeated encounters, control reuse, broad no-replacement matching, absolute risks, staged adjustment, missingness/IPW, COVID-era effects, and MACE among patients without prior cardiovascular disease.
Results: Death or ICU admission was similar in MASLD and matched non-MASLD encounters (10.7% vs. 11.6%). After adjustment, MASLD was not associated with death/ICU (OR, 0.90; 95% CI, 0.55 to 1.46; P=0.669); adjusted absolute risks were 13.1% vs. 14.2% (risk difference, -1.1 percentage points).
Results: were directionally consistent in first-encounter (OR, 0.74), unique-control (OR, 0.66), broad no-replacement (OR, 0.81), and reuse-weighted analyses (OR, 0.66). MACE was more frequent in MASLD encounters before adjustment (24.6% vs. 14.1%). The association attenuated across staged models: crude OR 1.99, severity-adjusted OR 1.92, plus Charlson OR 1.30, plus cardiometabolic burden OR 1.05, and full-model OR 1.03 (P=0.922). Among patients without prior cardiovascular disease, MASLD was not associated with MACE (OR, 0.99). MASLD was inversely associated with hepatic decompensation in the primary adjusted model (adjusted risk difference, -9.6 percentage points; OR, 0.46; P<0.001). AKI/HRS remained a secondary, less stable signal.
Conclusions: Across matched, patient-level, reuse-weighted, and broad no-replacement sensitivity analyses, MASLD was not associated with increased short-term death/ICU risk. The crude MACE excess was largely attenuated after accounting for measured cardiometabolic burden, especially prior cardiovascular disease, rather than MASLD itself.

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F-17

Behavioural and multidimensional factors associated with MASLD progression toward cACLD and portal hypertension

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Background: MASLD spans a wide spectrum, from simple steatosis to compensated advanced chronic liver disease (cACLD) and clinically significant portal hypertension (CSPH). How metabolic load, health-related behaviours, frailty, cognition, and psychological distress vary across this spectrum is incompletely characterised. We assessed these dimensions in a prospective, multicentre Italian cohort.
Methods: Prospective observational study in three tertiary Italian centres (Rome, Palermo, Naples). Patients underwent VCTE (FibroScan®); cACLD was defined as LSM ≥15 kPa and CSPH per Baveno VII. Assessment included HOMA-IR, TyG index, waist-to-height ratio (WHtR), Mediterranean Diet score (MDS), AUDIT-C, IPAQ, Liver Frailty Index (LFI), Animal Naming Test (ANT), MMSE, DASS-21, DERS, and CLDQ. Given the tertiary setting, the cohort is enriched for advanced disease.
Results: Among 411 patients (median age 65 [57–71]; 37.7% female), 70.4% had hypertension, 49.8% diabetes, and 78.6% were overweight/obese. Median LSM was 11.7 kPa (8.3–17.8); cACLD prevalence was 35% and CSPH 27.5%.Diabetes was more frequent in cACLD (59.7% vs 40.3%, p<0.01), with higher HOMA-IR (5.04 vs 3.71, p=0.02; interpretation limited by insulin therapy), whereas the TyG index did not differ (8.59 vs 8.56, p=0.47). WHtR was higher in cACLD (0.64 vs 0.61, p<0.05), while BMI showed only a trend (29.2 vs 28.1, p=0.06). All three adiposity measures correlated weakly with CAP (WHtR r=0.29, TyG r=0.31, BMI r=0.34; p<0.01). Health-related behaviours were uniformly poor across stages: 49% were current/former smokers, 54.9% re-

ported low or absent physical activity, and MDS, energy from sweetened/alcoholic drinks, and AUDIT-C did not differ between groups.The continuous LFI did not differ by cACLD (3.89 vs 4.01, p=0.68) or CSPH (median 4.21, p=0.14); however, the proportion classified pre-frail/frail was higher in CSPH (95.8% vs 84.4%, p=0.04). ANT was lower in cACLD (16 vs 18, p<0.01), consistent with subtle covert cognitive change, whereas MMSE did not differ (27.0 vs 26.5, p=0.28; overall mild-to-severe cognitive impairment 16.8%). On DASS-21, depression and stress scales were comparable; severe anxiety was more frequent in cACLD (14.5% vs 6.5%, p=0.05) and reached 17.0% in CSPH. On CLDQ, the activity/energy domain was modestly lower in cACLD (6.0 vs 6.2, p=0.04) and CSPH (5.8, p=0.02).

Conclusions: In a tertiary MASLD cohort, progression to cACLD and CSPH was accompanied by greater metabolic load, emerging pre-frailty (in CSPH), subtle covert cognitive change, and unadjusted signals of anxiety and reduced energy. Most strikingly, adverse lifestyle behaviours were uniformly poor across all stages, identifying a persistent, undermanaged behavioural burden.These findings support a multidimensional MASLD model integrating structured lifestyle and metabolic intervention at every stage, with cognitive and psychological screening targeted to advanced disease

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F-18

Internal and Temporal Risk Discrimination in MASLD-Related Cirrhosis Presenting to Emergency Care

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Background: Risk stratification in MASLD-related cirrhosis presenting to emergency care requires integration of hepatic severity, comorbidity, cardiometabolic burden, and acute presentation. Because AUROC only measures how well a model ranks patients by risk, calibration and temporal validation are needed to assess whether predicted risks remain reliable over time.

Methods: Among 1,262 MASLD encounters from a matched cohort, we fit six separate multivariable logistic regression models for complete-case MASLD encounters with available prediction features, one for each endpoint: death/ICU, death, ICU admission, MACE, hepatic decompensation, and OHE. For comparability and to avoid endpoint-specific predictor selection, all models used the same prespecified candidate predictors: age, sex, calendar year, MELD-Na, Charlson hepatic score, hepatocellular carcinoma, clinically significant portal hypertension, cardiovascular disease, diabetes, chronic kidney disease, triage, and mSOFA. Coefficients and predicted risks were estimated separately for each endpoint. Internal validation used patient-level cross-validation. Performance was summarized with AUROC and patient-level bootstrap 95% CI, Brier score, calibration intercept, and calibration slope. Temporal validation trained models in 2016–2021 period and tested them in 2022–2024 period. Standard scores, including MELD, MELD-Na, CLIF-AD, Charlson, qSOFA, and mSOFA, were retained as comparators.

Results: In MASLD encounters, the endpoint-specific logistic models showed the highest cross-validated discrimination for hepatic decompensation (AUROC, 0.864; 95% CI, 0.839 to 0.884; Brier 0.141; calibration slope 0.938) and MACE (AUROC, 0.845; 95% CI, 0.816 to 0.871; Brier 0.125; slope 0.934). OHE prediction was also useful (AUROC, 0.809; 95% CI, 0.777 to 0.839; Brier 0.112; slope 0.819). Death/ICU showed more modest discrimination (AUROC, 0.702; 95% CI, 0.654 to 0.749; Brier 0.105; slope 0.845). Temporal validation preserved useful ranking but showed weaker calibration: AUROC 0.834 for hepatic decompensation, 0.789 for MACE, 0.783 for OHE, and 0.685 for death/ICU, with slopes between 0.59 and 0.77 for several endpoints. MACE prediction depended substantially on cardiovascular history: AUROC was 0.845 with cardiovascular disease included and 0.731 without it. Single liver-score benchmarks approached the multivariable death/ICU model but did not capture cardiometabolic outcomes as well.

Conclusions: Six endpoint-specific multivariable logistic models showed useful internal discrimination for MACE, OHE, and hepatic decompensation in MASLD-related cirrhosis. However, temporal calibration was imperfect. These models should be interpreted as risk-stratification tools requiring recalibration and external validation before clinical implementation.

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F-19

MASLD and Coronary Artery Disease in Liver Transplant Candidates: A Hidden Burden Beyond Calcium Scoring

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Introduction: Cardiovascular disease is common among liver transplant candidates, but its burden and clinical impact vary by liver disease etiology. Patients with metabolic dysfunction–associated steatotic liver disease (MASLD) have a higher prevalence of cardiovascular risk factors and may be at increased risk of clinically significant coronary artery disease. However, the optimal strategy for cardiovascular risk stratification in this population remains uncertain. This study aimed to compare cardiovascular risk factors, coronary calcium burden, and coronary intervention rates between MASLD and non-MASLD liver transplant candidates.

Aims: Evaluate differences in cardiovascular risk factors, coronary calcium burden, coronary angiography, and coronary revascularization between MASLD and non-MASLD liver transplant candidates.

Methods: Single-center retrospective cohort study of adults evaluated for liver transplantation at San Camillo Forlanini Hospital be-

tween 2022 and 2025. All patients underwent standardized pre-transplant assessment including cardiovascular risk stratification, transthoracic echocardiography, coronary CT with calcium scoring, and coronary angiography with revascularization when indicated.
Results: A total of 299 patients were evaluated, including 70 (23.4%) with MASLD and 229 (76.6%) with non-MASLD. MASLD patients had a higher prevalence of diabetes (64.3% vs 19.2%), hypertension (58.6% vs 26.6%), dyslipidemia (40.0% vs 10.5%), ≥2 cardiovascular risk factors (64.3% vs 37.1%), and higher mean BMI (28.9 vs 26.2 kg/m²). Coronary CT angiography was performed more frequently in MASLD patients (74.3% vs 60.3%; OR 1.90, 95% CI 1.05–3.46, p=0.034). Among those undergoing CT, coronary calcium score distributions were similar between groups. Coronary angiography was performed in 32.9% of MASLD and 25.8% of non-MASLD patients (OR 1.41, 95% CI 0.79–2.52, p=0.284). Percutaneous coronary intervention (PCI) was significantly more frequent in MASLD patients (11.4% vs 4.4%; OR 2.83, 95% CI 1.07–7.47, p=0.042). Although representing only 23.4% of the cohort, MASLD patients accounted for 44.4% of all PCI procedures (8/18). PCI occurred across all coronary calcium strata in MASLD patients, including CAC <100, whereas in non-MASLD patients it was largely confined to higher calcium strata.
Conclusion: MASLD liver transplant candidates have a substantially greater cardiovascular risk burden and nearly threefold higher odds of requiring coronary revascularization during transplant evaluation. Despite similar coronary calcium scores, MASLD patients accounted for almost half of all PCI procedures. These findings suggest that coronary calcium burden alone may underestimate clinically significant coronary artery disease in MASLD and support more intensive cardiovascular assessment in this high-risk population.

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F-20

Echocardiographic Correlates of Liver and Spleen Stiffness in Metabolic Dysfunction–Associated Steatotic Liver Disease

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Background and Aims: Metabolic dysfunction–associated steatotic liver disease (MASLD) is a systemic condition associated with increased cardiovascular risk. While liver stiffness (LS) is a validated non-invasive marker of hepatic fibrosis, spleen stiffness (SS) is emerging as a sensitive indicator of portal hemodynamics. This study aimed to evaluate the association between non-invasive elastometric measures (LS and SS) and echocardiographic parameters in a cohort of patients with MASLD.
Methods: We prospectively enrolled patients with MASLD attending the Metabolic Outpatient Clinic of the University Hospital of Modena. Participants underwent comprehensive clinical evaluation, anthropometric assessment, and review of laboratory tests. Transient elastography (FibroScan®) was used to assess LS, SS, and controlled attenuation parameter (CAP), while a complete transthoracic echocardiogram was performed by a certified specialist. Subclinical systolic function was assessed using global longitudinal strain (GLS).
Results: A total of 49 patients were included. Mean age was 59.3±9.5 years, and 30.6% were female. Mean BMI was 30.7±4.6 kg/m², with 51% classified as obese; mean waist-to-height ratio was 0.627±0.063. Cardiometabolic comorbidities were highly prevalent: hypertension in 49%, hyperlipidaemia in 91.8%, and diabetes in 20.4%. Mean estimated 10-year cardiovascular risk was 7.63 ± 3.89%. According to FIB-4, 52.8% had low probability, 41.7% intermediate probability, and 5.6% high probability of advanced fibrosis.Median LS was 5.80 kPa, median CAP 276 dB/m, and median SS 24.6 kPa. Nine patients (18.4%) had LS ≥ 8 kPa.Echocardiography showed preserved cardiac structure and function overall. Mean LVEF was 58.8 ± 4.2% and GLS −19.4 ± 2.2%. Diastolic indices suggested mild relaxation impairment, while structural parameters indicated a tendency toward left ventricular remodelling. LS correlated positively with PAPs($r = 0.446$, $p = 0.004$) and LVMi ($\rho = 0.326$, $p = 0.031$), with a positive trend toward IVC diameter. Patients with LS ≥ 8 kPa showed higher cardiovascular risk ($p = 0.015$), WC ($p = 0.038$), FIB-4 ($p = 0.045$), and HbA1c ($p < 0.001$), with a higher prevalence of diabetes and hypertension. IVS was significantly increased in this group ($p = 0.043$), while LVMi and LA area showed non-significant increases, consistent with cardiometabolic-related remodelling. Patients with elevated SS had higher BMI ($p = 0.015$), with a non-significant trend for hypertension. FIB-4 was higher in the SS > 25 kPa group and LS and SS were positively correlated ($r = 0.315$, $p = 0.035$).
Conclusions: in this preliminary study, liver stiffness was associated with higher CV risk marker and early cardiac remodeling, especially in LS ≥ 8 kPa. Spleen stiffness correlated with metabolic burden and liver stiffness, supporting a shared pathophysiological link. Combined hepatic and splenic elastography with echocardiography may improve cardiometabolic risk stratification in MASLD.

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F-21

Aspirin and Liver-Related Outcomes in Metabolic Dysfunction-Associated Steatotic Liver Disease: A Systematic Review and Meta-analysis

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Background and Aims: Aspirin has plausible anti-inflammatory, anti-fibrotic, and anti-carcinogenic effects in metabolic dysfunction-associated steatotic liver disease/metabolic dysfunction-associated steatohepatitis (MASLD/MASH), but its clinical effectiveness and safety in patients with established disease remain uncertain. A systematic review and meta-analysis of aspirin use versus non-use or placebo in adults with established MASLD/MASH was performed, including legacy NAFLD/NASH cohorts.
Methods: PubMed/MEDLINE, CENTRAL, Scopus, and Web of Science were searched using an aspirin plus MASLD/MASH-spectrum strategy. Randomized and non-randomised evidence were synthesised separately. Adjusted time-to-event estimates were prioritized; cause-specific hazard ratios (HRs) and subdistribution hazard ratios (SHRs) were not combined. Random-effects meta-analyses were performed when at least two clinically comparable estimates were available. Risk of bias was assessed.

Results: 2,557 records were identified, of which 1,960 remained after deduplication. After title/abstract screening, 19 reports underwent full-text review: 10 were initially included, and 9 were added after resolution of 27 screening conflicts. Twelve articles met eligibility after full-text review, and citation snowballing identified 2 additional articles, yielding 14 included articles. Most evidence was observational and at serious risk of bias; trial-derived evidence had some concerns. In the primary overlap-corrected analysis, aspirin use was associated with lower incident HCC risk (pooled HR 0.47, 95% CI 0.38-0.58; k=2; I^2=0%). Sensitivity analyses were directionally consistent but less stable, including pooled HRs of 0.52 (95% CI 0.36-0.75) and 0.63 (95% CI 0.35-1.12), and competing-risk pooled SHRs of 0.85 (95% CI 0.74-0.97) and 0.74 (95% CI 0.57-0.98). All-cause mortality showed no consistent association (pooled HR 0.99, 95% CI 0.72-1.37; k=2; I^2=88.7%). Evidence for liver-related events, liver-related mortality, cardiovascular outcomes, and bleeding was sparse and imprecise. One longitudinal cohort reported lower incident advanced fibrosis with daily aspirin, and one randomized trial showed short-term reductions in liver stiffness and hepatic fat. Major bleeding estimates were uncertain and did not exclude clinically important harm.
Conclusions: In adults with established MASLD/MASH, aspirin use was associated with a lower risk of incident HCC and favourable short-term surrogate liver outcomes, but the evidence is largely observational, heterogeneous, and vulnerable to confounding and time-related biases. No consistent survival benefit was observed, and safety estimates remain imprecise.

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F-22

Inhibition of the renin–angiotensin system does not improve the outcomes of hepatocellular carcinoma treated with atezolizumab–bevacizumab

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Hepatocellular carcinoma (HCC) remains a leading cause of cancer-related mortality worldwide. Although atezolizumab plus bevacizumab is a standard first-line treatment for unresectable HCC, outcomes remain heterogeneous. Angiotensin-converting enzyme inhibitors (ACE-i) and angiotensin receptor blockers (ARBs) may influence fibrosis, angiogenesis, and the tumor microenvironment, but their impact during immune checkpoint inhibitor-based therapy is unclear. We evaluated the association between concomitant ACE-i/ARB use and outcomes in patients with unresectable HCC treated with first-line atezolizumab plus bevacizumab. Methods: We conducted a multicenter real-world study within the national ARTE (Atezolizumab–Bevacizumab Real-life Experience) cohort, including consecutive adults with unresectable HCC treated with first-line atezolizumab plus bevacizumab between October 2020 and July 2025. Patients were classified according to baseline ACE-i/ARB exposure. Primary endpoints were overall survival (OS) and progression-free survival (PFS); secondary endpoints were objective response rate (ORR) and disease control rate (DCR) according to RECIST 1.1. Survival was analyzed using Kaplan–Meier and Cox models. Multivariable analyses and propensity score subclassification were applied to account for baseline imbalances. Predefined subgroup analyses were performed in MASLD-related and viral-related HCC. Results: Among 538 patients, 194 (36.1%) received ACE-i/ARB therapy and 344 (63.9%) did not. ACE-i/ARB users were older and more frequently had MASLD, diabetes, obesity, and cardiovascular comorbidities, while tumor burden was comparable and liver function was generally better preserved. In unadjusted analyses, median PFS was 8.9 versus 10.9 months and median OS was 17 versus 22 months in ACE-i/ARB users and non-users, respectively, with no significant differences (OS HR 1.23, 95% CI 0.97–1.57; p=0.092). Multivariable analysis showed no survival benefit and a borderline association with worse OS (HR 1.29, 95% CI 1.00–1.66; p=0.051). No improvement in tumor response was observed, with a non-significant trend toward lower DCR (OR 0.63, 95% CI 0.39–1.02; p=0.06). After propensity score subclassification (182 users, 325 controls), no significant association emerged between ACE-i/ARB use and PFS or OS (adjusted OS HR 1.14, 95% CI 0.86–1.51; p=0.36). Findings were consistent across MASLD-related and viral-related HCC subgroups. Conclusions: In this large multicenter real-world cohort, concomitant ACE-i/ARB therapy was not associated with improved survival or response outcomes in patients with unresectable HCC receiving first-line atezolizumab plus bevacizumab. These findings remained consistent after adjustment for confounding and across major etiologic subgroups, suggesting no clinically meaningful benefit of baseline RAS inhibition in this setting.

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F-23

Efficacy of a Brown Algae-Based Nutraceutical Combined with a Hypocaloric Mediterranean Diet on Metabolic Dysfunction in Hepatic Steatosis: The Gdue® Study

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is closely linked to excess adiposity, insulin resis-

tance and cardiometabolic risk. Lifestyle modification remains the cornerstone of treatment, but adjunctive strategies may help enhance its metabolic and hepatic benefits.

Methods: This six-month randomized, double-blind, placebo-controlled, parallel-group trial evaluated the efficacy of Gdue®, a brown algae-based nutraceutical containing Ascophyllum nodosum, Fucus vesiculosus and chromium picolinate, combined with a personalized hypocaloric Mediterranean diet in adults with MASLD and metabolic syndrome. Anthropometric, biochemical and insulin resistance parameters were assessed at baseline, 3 months and 6 months. Body composition and liver steatosis, assessed by controlled attenuation parameter (CAP), were evaluated at baseline and 6 months.

Results: Of 112 randomized patients, 101 were included in the modified intention-to-treat analysis: 49 in the placebo group and 52 in the Gdue® group. At 3 months, BMI (28.2 vs 29.9 kg/m²; p=0.029) and fasting insulin (10.15 vs 11.80 µIU/mL; p=0.033) were significantly lower with Gdue® than placebo. At 6 months, Gdue® was associated with lower BMI (28.0 vs 29.2 kg/m²; p=0.045), lower body fat percentage (28.8% vs 34.5%; p=0.018), higher HDL-C (51 vs 45 mg/dL; p=0.041) and lower HOMA-IR (2.20 vs 2.64; p=0.049). CAP was also lower in the Gdue® group (258.5 vs 275.0 dB/m; p=0.039), and persistent moderate-to-severe steatosis was less frequent with Gdue® than placebo (50.0% vs 69.4%; p=0.047). The intervention was well tolerated.

Conclusions: Gdue® combined with a hypocaloric Mediterranean diet was associated with greater improvements in adiposity, insulin resistance, HDL-C and hepatic steatosis than diet plus placebo.

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