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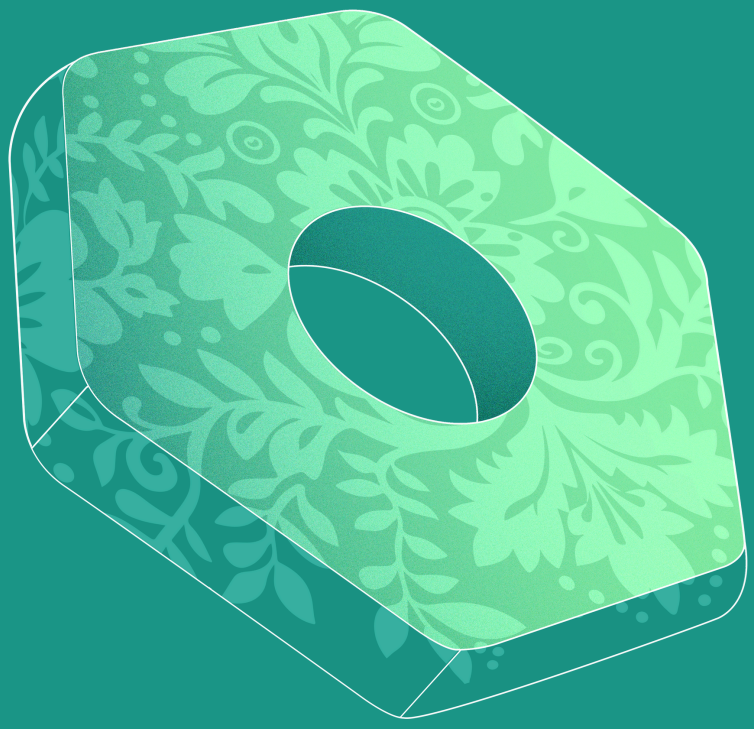

ABSTRACT BOOK

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Contents

ORAL ABSTRACT PRESENTATIONS

OS-1-YI

Refining and validating screening indicators for MASLD-related advanced chronic liver disease in the general population

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Background and aims: Diabetes, obesity, and elevated ALT are indicators to screen for advanced chronic liver disease. Yet, guidelines differ on which features should trigger screening. Given the increasing prevalence of metabolic comorbidities and feasibility issues of screening programs, we sought to refine screening criteria using population-based data.

Method: We included nationally representative adults aged 18–80 years from NHANES 2017-2020 with BMI ≥18.5 kg/m², without excessive alcohol consumption, and with complete screening indicator data. Weighted proportions of individuals meeting EASL, AASLD, AGA, and ADA screening criteria were estimated. We assessed the prevalence of liver stiffness measurement (LSM) ≥8 kPa across screening indicators using stratified analyses. The refined criteria were validated in three independent general population cohorts from Rotterdam, Barcelona and the US.

Results: The derivation cohort included 5,904 adults (mean age 47 years, 49% male), of whom 8.9% had LSM ≥ 8 kPa. Current guidelines target 60–76% for screening, yielding a positive predictive value (PPV) of 11.1-13.5% and a negative predictive value (NPV) of 98.0-98.2% for LSM ≥8 kPa. Certain subgroups were not at increased risk, such as individuals with diabetes and normal ALT levels without obesity, or those with class I-II obesity without diabetes and normal ALT. Based on these findings, a refined screening strategy recommended screening in only 22% of the US population, whilst maintaining a high NPV of 96.3% and improved PPV of 27.7% for LSM ≥8 kPa. The validation cohort included 13,244 participants, of whom 6.9% had LSM ≥8 kPa. Application of the algorithm indicated that 13.8% required screening, yielding similar results: PPV 22.2% and NPV 95.6% for LSM ≥8 kPa, PPV 12.7% and NPV 98.3% for LSM ≥10 kPa and PPV 7.4% and NPV 99.1% for LSM ≥12 kPa.

Conclusion: Current guidelines target 60-76% of the US adult population for MASLD-induced advanced chronic liver disease screening, creating a diagnostic capacity challenge that hinders implementation. To overcome this, we developed and validated in 19,148 adults a refined set of indicators for screening prioritisation: (1) T2DM with elevated ALT or obesity (any class); (2) Obesity class III; and (3) Elevated ALT with obesity class I and ≥ 3 metabolic risk factors, obesity class II-III or T2DM. These refined criteria target a more feasible 22% of the adult US population and 14% of our validation cohort, whilst maintaining a high NPV for increased LSM.

OS-2-YI

Exploring the potential of circulating epigenetic marks for monitoring paediatric metabolic dysfunction-associated steatotic liver disease progression through a machine learning approach

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Background and aims: There is an urgent need for non-invasive biomarkers to monitor the progression of metabolic dysfunction-associated steatotic liver disease (MASLD) to steatohepatitis (MASH) and fibrosis. Lipotoxicity, necroinflammation and autophagy were associated with metabolic and liver cellular damage, MASH and fibrosis. A few studies highlighted that tissue events could be associated with the release of cellular biomarkers. Among them, epigenetic marks such as cell-free DNA (cfDNA), cell-free RNA (cfRNA), and DNA-associated histone proteins are still unexplored particularly in paediatric MASLD. Here, we investigated whether circulating epigenetic marks correlated with MASH in children with biopsy-proven MASLD by machine learning (ML) approaches.

Method: The study included 252 children with biopsy-proven MASLD, stratified by MASH (n = 167) or non-MASH (n = 85) condition. Circulating cfDNA and cfRNA were extracted from plasma using commercial kits and characterised using TapeStation. The levels of cfDNA 5-methylcytosine methylation (cfDNA-5mC-me), nucleosomes, total histone H3, H3 trimethylated (me3) or acetylated (ac) in lysine (K) (H3K27me3, H3K27ac, H3K4me3, H3K9me3, H3K18ac), and inflammatory biomarkers were assessed in plasma by immunoassays. Cf mitochondrial DNA (cf-mtDNA) was calculated using a qPCR method. The Mann-Whitney U test was used to compare two groups, and three ML models were tested. Finally, the SHapley Additive exPlanations (SHAP) method was applied.

Results: Children with MASH had significantly increased plasma levels of cfDNA-5mC-me, cf-mtDNA, nucleosomes, histone H3, H3K27me3, H3K27ac, and H3K4me3 compared with non-MASH, while the levels of cfRNA decreased. MASH patients had higher levels of IL-1beta and lower levels of IL-10. Among the tested ML approaches, the Linear Discriminant Analysis model was the most effective in discriminating MASH (AUC = 0.84), with the most significant contribution provided by cfDNA-5mC-me, HDL cholesterol, cfDNA concentration and fragment size, nucleosomes, H3K18ac, AST, triglycerides, H3K9me3, and GGT levels as revealed by SHAP method.

Conclusion: Our preliminary analysis corroborated the hypothesis of a connection between circulating epigenetic marks and MASH. Combining epigenetic and clinical data enabled accurate discrimination of MASH using a ML approach**.** Further studies are required for validating circulating epigenetic signatures as non-invasive tools for MASLD monitoring and stratification.

OS-3-YI

HCC incidence and risk stratification in patients with metabolic dysfunction-associated steatotic liver disease on long-term follow-up: a retrospective multicentre study

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is projected to become the leading cause of hepatocellular carcinoma (HCC) globally. We aimed (i) to investigate the incidence of HCC in patients with MASLD according to baseline liver disease severity, and (ii) to assess the performance of non-invasive and biomarker-based prognostic tools for HCC prediction and risk stratification.

Method: We retrospectively enrolled 942 consecutive patients with MASLD (median age: 60 [IQR 51–67] years; males: 553 [58.7%]; T2DM: 516 [54.8%]; median BMI: 30.8 [27.7–34.1] kg/m^2) and significant liver fibrosis (liver stiffness measurement [LSM]≥8 kPa or F≥2 at liver biopsy). Of these, 680 (72.2%) met criteria for compensated advanced chronic liver disease (cACLD; LSM ≥10 kPa or F≥3 at liver biopsy), within which 344 (50.6%; 36.5% of the overall cohort) had cirrhosis by clinical or histologic criteria. All patients had at least 6 months of follow-up (FU) with regular ultrasound surveillance. At baseline, we computed the Fibrosis-4 (FIB-4) score, the aMAP prognostic index, and the age-sex-AFP-PIVKA-II (ASAP) score. Serum AFP and PIVKA-II were centrally measured by CLEIA (Lumipulse®G600II, Fujirebio) under blinded conditions.

Results: During a median FU of 2.4 (IQR 1.0–4.3) years, 49/942 (5.2%) patients developed HCC (incidence rate [IR]: 1.67 per 100 person/years [PY]). At baseline, 36/49 (73.5%) had cirrhosis, 12/49 (24.5%) had F3 fibrosis, and 1/49 (2.0%) had F2 fibrosis. The HCC IR among patients with liver cirrhosis was 3.75 per 100 PY, while among patients with F3 and F2 fibrosis was 1.09 and 0.11 per 100 PY, respectively. At HCC diagnosis, BCLC stage was 0 in 11 (22.4%) patients, A in 25 (51.0%), B in 5 (10.2%), C in 2 (4.1%); BCLC stage was unknown in 6 patients. In the overall population, the integrated

area under the curve (iAUC) from 1 to 5 years was 0.794 (95% CI 0.694–0.884) for aMAP, 0.792 (95% CI, 0.710–0.859) for ASAP, and 0.730 (95% CI 0.625–0.833) for FIB-4. Among patients with cACLD, the corresponding iAUC values were 0.759 (95% CI 0.643–0.865), 0.758 (95% CI 0.664–0.837), and 0.698 (95% CI 0.564–0.816), respectively. aMAP and ASAP score outperformed FIB-4 in both the overall cohort and the cACLD subgroup.

Conclusion: Our results support HCC surveillance in MASLD patients with advanced liver disease; aMAP and ASAP score may help to define personalized, risk-adapted surveillance according to individual HCC risk.

OS-4-YI
Isogenic hiPSC derived liver-on-chip system : A valuable tool for modelling fibrosis

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Background and aims: Modeling the human liver in vitro is a challenging task. Yet information from such models about the architecture of the liver is important for the development of drugs and the study of different liver diseases. The functional characterization of these components remains difficult owing in part to a scarcity of human model systems.To improve the predictive power of in-vitro models, (HLA-matched) hiPSCs from a healthy and diseased donor were used in this study to generate parenchyma and non-parenchyma liver-like cells, through tissue engineering approaches interfaced with organ-on-chip technology.

Method: This system was designed to allow for long-term investigation of tissue-tissue crosstalk without any bias and recapitulation of micro-environmental cues in a 3D culture format. The platform is intended for the culture and co-culture of isogenic cells (hepatocytes, stellate cells, endothelial cells (EC), and macrophages) and its application in the context of disease modeling. Firstly, HLA-matched hiPSC-derived liver cells were generated, functionally characterized, and bio-banked. To investigate vascular-immune cellular crosstalk, hiPSC-derived endothelial cells were co-cultured with polarized macrophages, on-chip under static and dynamic flow conditions.

Results: Fibrosis phenotype was validated based on endothelial cell dysfunction, stellate cell activation, and deposition of extracellular matrix. This phenotype was more pronounced in LoC models treated with TGFβ compared to untreated controls. The TGFβ treated models were characterized by the extracellular deposition of collagen, upregulation of fibrosis markers (Alpha- smooth muscle actin, Fibronectin, Glial fibrillary acidic protein, Col1ά1, PDGRFβ), and activation of stellate cells as indicative markers related to fibrosis development. Thus, the data suggest that the dynamic interactions between different liver cell types via soluble mediators and cytokines play an important role in the progression of fibrosis.

Conclusion: This lays the groundwork for its use in preclinical studies and the investigation of the effects of new molecules such as short-chain fatty acids and bile acids on disease progression or therapeutics for disease intervention. Therefore, these LoC systems offer the advantage of the combination of different liver cells with HLA-matched donors with individualized study of monogenic diseases.The model-system will be useful for pharmacological interventions and large-scale therapeutics development in the future.

OS-5-YI
PNPLA3 beyond the liver: exploring its impact on body composition in MASLD

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Background and aims: The PNPLA3 I48M variant is the main genetic determinant linked to the progression of metabolic-dysfunction associated steatotic liver disease (MASLD). Although PNPLA3 is primarily expressed in the liver, its expression in adipose tissue suggests a potential role in body composition. Aim: to assess the association between PNPLA3 genotype and body composition in MASLD patients.

Method: We enrolled 497 MASLD patients (mean age 50±12 ys, 65% male) attending the Metabolic Liver Disease outpatient clinic at Policlinico Hospital, Milan. Body composition, including total, trunk and appendicular muscle and adipose mass, was assessed by bioimpedance analysis (BIA) under fasting conditions. Skeletal muscle mass index (SMI) and adipose tissue index (ATI) were calculated as mass/height2 (kg/m2) and analyzed by sex. Genotyping for PNPLA3 (rs738409) was performed using TaqMan assays for all patients.

Results: The distribution of PNPLA3 genotypes was 16% GG (homozygous variant), 44% CG (heterozygous), and 40% CC (wild-type). Mean SMI was 10.7±1.2 kg/m2 in men and 8.2±1.1 kg/m2 in women; ATI was 8.5±3.4 kg/m2 in men and 12.2±4.2 kg/m2 in women. Compared with CC carriers, PNPLA3 GG homozygotes showed lower SMI (9.4 vs 10.2 kg/m2, p=0.03), with no differences in mean ATI (p=0.09).

Moreover, patients with the PNPLA3 GG genotype showed lower trunk muscle mass (3.0 vs 3.4 kg/m2, p=0.04) and higher trunk adipose mass, the latter observed only in women (4.9 vs 4.0 kg/m2, p=0.02). No significant differences were detected in appendicular muscle (p=0.27) or fat mass (p=0.06).

The associations between PNPLA3 GG and both lower SMI (b= -0.8 kg/m2, 95% CI -1.2 to -0.2, p=0.03) and lower trunk muscle mass (b= -0.4 kg/m2, 95% CI -0.8 to -0.03, p=0.04) remained significant after adjustment for age, fibrosis stage, BMI, and diabetes.

Conclusion: Although PNPLA3 is well known for its hepatic effects, its impact on body composition has been poorly characterized. Our findings reveal an independent association of the PNPLA3 GG variant with lower skeletal muscle mass and, notably, with increased trunk adiposity, especially among women, who generally exhibit higher adipose mass than men. These results highlight the extrahepatic role of PNPLA3 in regulating muscle-fat distribution, potentially contributing to adverse musculoskeletal phenotypes in MASLD. Genetic profiling may help identify MASLD patients at risk for unfavorable liver and muscle outcomes.

OS-6

Tofogliflozin and glimepiride on liver and serum metabolites in persons with metabolic dysfunction-associated steatotic liver disease and type 2 diabetes mellitus: a post hoc analysis

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Background and aims: The mechanism by which sodium-glucose cotransporter 2 (SGLT2) inhibitors and sulfonylureas alter liver metabolism in humans with metabolic dysfunction-associated steatotic liver disease (MASLD) and type 2 diabetes mellitus remains unknown.

Method: This 48-week, randomized, open-label, parallel-group trial involved patients with type 2 diabetes with biopsy-confirmed MASLD. Forty participants were randomly assigned to receive tofogliflozin or glimepiride once daily. The study outcomes were the changes in serum and liver metabolites and their association with liver histology, serum liver enzymes, and metabolic markers.

Results: Hepatic glucose 1-phosphate and acetyl-CoA were elevated in the tofogliflozin group. Among the tricarboxylic acid cycle intermediates, the serum citrate and succinate levels were elevated and reduced, respectively, in the tofogliflozin group with no hepatic level changes. Serum succinate reduction was associated with AST, ALT, and GGT reductions, and higher baseline serum succinate levels predicted improved ballooning and inflammation scores and AST, ALT, and GGT reductions in the tofogliflozin group. The hepatic branched-chain amino acids (BCAAs) were reduced in the glimepiride group, but not in the tofogliflozin group. Liver BCAA reduction was related to the reductions in liver ballooning and steatosis in the tofogliflozin and glimepiride groups, respectively. In the tofogliflozin group, the serum urea cycle intermediate levels were elevated without hepatic level changes, whereas the glimepiride group showed an opposite trend.

Conclusion: The metabolic signature of the SGLT2 inhibitor was associated with starvation-induced glucose production and hypovolemia-induced aestivation-like response in the liver. The serum succinate level may be a biomarker reflecting MASLD pathology.

OS-7-YI

Prognostic performance of phosphatidylethanol with non-invasive liver fibrosis tests for individuals at-risk of alcohol-related liver disease

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Background and aims: Alcohol is a key driver of liver-related mortality, while phosphatidylethanol (PEth) is a direct biomarker of alcohol intake. We investigated the prognostic performance of PEth with non-invasive liver fibrosis tests (NITs) for predicting hepatic decompensation in an alcohol-related liver disease (ALD) at-risk population.

Method: Prospective cohort study with 411 at risk of ALD of whom 162 had a follow-up PEth. PEth was measured from whole blood by liquid chromatography-mass spectrometry. PEth, self-reported alcohol intake, and three NITs: Enhanced Liver Fibrosis (ELF) test, an algorithm incorporating PRO-C3 (ADAPT) and transient elastography (TE) were assessed at baseline. By review of medical records, participants were followed for up to 5 years for hepatic decompensation.

Results: Baseline PEth was 338 ng/mL (IQR: 32-921 ng/mL), while median time to follow-up PEth was 26 months (IQR: 17-33). Baseline PEth was associated with decompensation (sHR per 100 ng/mL: 1.04; 95%CI: 1.01–1.06), independently of NITs. Liver fibrosis NITs were the strongest individual predictors, but PEth added incremental 6-month prognostic value. Discriminatory accuracy of PEth declined with an AUC of 0.77 at 6 months to 0.62 at 2 years, while fibrosis-based NITs maintained an AUC ~0.90. Of those with a follow-up PEth, 79 (49%) had increased PEth levels compared to baseline, while 83 (51%) had stable or lowered PEth. An increased follow-up PEth was significantly associated with a higher risk of subsequent hepatic decompensation (sHR=4.92, 95%CI: 1.09-22.34, p=0.039).

Conclusion: PEth predicts hepatic decompensation independently of fibrosis-based NITs in individuals at risk of ALD. Although its prognostic performance declines rapidly, repeated PEth measurements maintain prognostic discrimination.

OS-8

The genetic architecture by genome- and exome-wide association study of chronically elevated ALT in a British South Asian community study of 57,000 participants

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Background and aims: Genome-wide association studies (GWASs) in metabolic dysfunction-associated steatotic liver disease (MASLD) have advanced our understanding of the underlying genetic architecture, yet these studies have largely been conducted in Caucasian cohorts. South Asians, who appear to be at higher risk of developing MASLD and related cardiometabolic conditions, are historically under-represented. To understand the genetic architecture of MASLD in South Asians, we performed a binary GWAS and exome-wide association study (ExWAS) in the Genes and Health (G&H) cohort consisting of over 57,000 individuals of Bangladeshi and Pakistani ethnicity living in Britain.

Method: The G&H cohort has genotype data and linked healthcare data. Cases were defined using a 'chronically elevated alanine aminotransferase (ALT) [cALT]' phenotype, a validated proxy for MASLD: individuals with ≥ 2 elevated ALT readings > 6 months apart, within 2 years. Controls were those not meeting cALT criteria and those with coded MASLD were excluded. Participants with alternative causes of liver disease were excluded from both cases and controls. Genetic analysis was run on REGENIE, with TOPMED r3 imputation and pre-defined covariates.

Results: There were 6,384 cALT cases and 25,148 controls. The cases were enriched for cardiometabolic comorbidities: 53.6% had type 2 diabetes, 51.8% were obese and 20.1% had cardiovascular disease, compared to 21.2%, 36.1% and 9.7% respectively in controls ($p<0.001$ for all).

GWAS identified 5 variants meeting significance ($p < 5.0 \times 10^{-8}$). Variants with the lowest p-values mapped to *PNPLA3* (rs12483959, $p = 1.46 \times 10^{-35}$), *AKNA* (rs10733608, 5.62×10^{-21}) and *TM6SF2* (rs58542926, 3.67×10^{-13}). All 5 variants were known or map to genes with known associations with liver traits.

ExWAS identified 22 variants reaching significance ($p < 1.04 \times 10^{-6}$). The variant with the lowest p-value mapped to *PNPLA3* ($p = 7.9 \times 10^{-34}$), followed by a missense variant in *SAMM50* ($p = 4.6 \times 10^{-23}$). 9 variants were novel, including in *CHUK*, encoding a protein kinase, and *PBX4*, encoding a transcription factor.

Conclusion: This is the largest GWAS and only ExWAS to be performed in a purely South Asian cohort. Our work has identified exciting new variants and, by extension, possible causal genes for further investigation and understanding the differences in ethnic risk for MASLD.

OS-9
Multiomic profiling of liver sinusoidal endothelial cells reveals steatotic liver disease mechanisms

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is underlined by a combination of cardiometabolic and genetic risk factors. Recent genome-wide association studies have uncovered thousands of genetic risk variants for histologically proven MASLD and/or MASLD proxy traits. Liver sinusoidal endothelial cells (LSECs) form a discontinuous and highly permeable barrier at the interface between hepatocytes and the blood. LSEC dysfunction has been observed at different stages of MASLD and inducing LSEC dysfunction in animal models causes liver fibrosis and other features of hepatopathy. Nevertheless, the degree to which LSEC contribute to MASLD genetic risk remains largely unexplored. In this study, we aimed to characterize the transcriptomic and chromatin landscape of human LSEC and their contribution to MASLD genetic risk.

Method: We profiled primary human LSECs by RNA-seq, ATAC-seq and ChIP-seq (H3K27ac, H3K4me3), under basal and lipotoxic conditions (320 µM palmitic acid +/- 320 µM oleic acid, 18 hours). LSEC cis-regulatory elements (CREs) were tested for MASLD risk variant enrichment using different tools. CRISPR-mediated activation (CRISPRa) and targeted chromosome conformation capture (UMI-4C) were used to identify targets of noncoding risk variants.

Results: Integration of chromatin accessibility and active histone mark profiles uncovered >160 thousand CREs. Palmitic acid induced broad gene expression and chromatin changes, implicating disease-relevant pathways such as activation of cell stress response and immune signaling, as well as loss of LSEC identity. Combining our data with MASLD liver transcriptomic datasets allowed prioritization of transcription factors (TFs) driving the observed loss of LSEC identity, including *GATA4*, a TF essential for liver metabolic homeostasis. Furthermore, we observed enrichment of MASLD risk variants at LSEC CREs. TF motif disruption analysis revealed that risk variants within LSEC CREs may alter TF affinity and CRE activity, which we validated for select candidates. Targeting of noncoding variants using CRISPRa along with UMI-4C enabled us to nominate disease effector genes at specific loci.

Conclusion: We demonstrate that a subset of MASLD genetic risk variants is predicted to disrupt LSEC regulatory elements. LSEC-specific regulatory maps revealed new candidate variants and target genes at several risk loci. This work demonstrates the importance of studying minority cell types to uncover causal mechanisms of disease susceptibility.

OS-11

Machine Learning Models of Non-invasive tests to predict MASH and fibrosis stage based on MAESTRO-NAFLD-1 and MAESTRO-NASH liver biopsies

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Background and aims: Fibrosis stage in patients with Metabolic Dysfunction-Associated Steatohepatitis (MASH) is currently diagnosed by liver biopsy for the purpose of staging in clinical trials. Although non-invasive tools have emerged, no consensus method exists for staging fibrosis and/or diagnosing MASH with moderate to advanced liver fibrosis, a progressive liver disease. We aimed to develop machine learning (ML) methods to predict fibrosis stage and MASH with F2/F3 Fibrosis using non-invasive biomarkers.

Method: Data from 1,970 biopsy-confirmed patients who screened for phase 3 resmetirom trials (MAESTRO-NASH, MAESTRO-NAFLD-1) were retrospectively analyzed. Outcomes included predictions of fibrosis stage and "MASH with F2/F3 Fibrosis" (NAS ≥4 and moderate-to-advanced noncirrhotic fibrosis) based on thirty-seven predictors (including clinical, laboratory, and imaging measures). Models using random forest were developed, selected for accuracy and stability, in two settings: full predictor models (using all 37 variables) and "lean" models (a subset of predictors routinely available in clinical practice). Performance was evaluated with 4-fold cross-validation via area under the curve (AUC).

Results: Random forest models to predict three classes of fibrosis stages (F0/F1 vs. F2/F3 vs. F4) resulted in one vs-rest cross-validation mean AUCs for the full data model (0.76, 0.75, and 0.94, respectively) and best performing lean model (0.83, 0.78, and 0.89, respectively). The most important factors included liver stiffness measures (MRE (magnetic resonance elastography), TE (transient elastography)) and MASH composite algorithms. In a model predicting MASH with significant (i.e., Stage 2/3) liver fibrosis, the full and lean models achieved AUCs of 0.75 and 0.79, respectively.

Conclusion: ML models using non-invasive biomarkers, with routinely available clinical predictors, accurately predict fibrosis stage and MASH with F2/F3 Fibrosis, supporting their potential to identify patients with MASH and moderate to advanced liver fibrosis for clinical trials or clinical practice.

OS-12-YI

Blood-based non-invasive tests differentiate individuals with persistent liver stiffness elevation from those who normalise during follow-up: Longitudinal results from the LiverScreen consortium

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Background and aims: Liver stiffness measurements (LSM) are widely used in liver disease screening programs, but high regression rates on repeat assessment raise concerns about false-positive results. Blood-based non-invasive tests (NITs) may help distinguish individuals with persistent LSM elevation from those who normalise during follow-up. We aimed to evaluate whether NITs can predict long-term persistence of elevated LSM and distinguish individuals who normalise during follow-up.

Method: This prospective, longitudinal study was conducted at three European centres (Barcelona, Rotterdam, Odense), within the LiverScreen consortium. Baseline and follow-up LSM were obtained at a 4-year interval. Unreliable measurements were excluded (IQR >30% for LSM ≥7.1 kPa). Persistent LSM elevation was defined as LSM ≥8 kPa at both baseline and follow-up; normalisation was defined as a decrease to <8 kPa at follow-up. FIB-4, MAF-5, LRS, and LiverPRO scores were calculated. Their ability to predict persistent LSM elevation was assessed using area under the receiver operating curve (AUC) analyses. In addition, established NIT-specific rule-out cut-offs were applied to evaluate the prognostic performance of baseline NIT scores alongside LSM using descriptive statistics.

Results: Among 4536 participants (median follow-up 4.3 years [IQR 4.1–8.2]; median age 62 years [56–68]; 52% female), 5.5% had a baseline LSM ≥8 kPa. Of these, 38% showed persistent elevation at follow-up. Analysed NITs demonstrated moderate to high discrimination for persistent LSM elevation (MAF-5: 0.875; LiverPRO: 0.853; LRS: 0.852; FIB-4: 0.700). LSM normalisation was observed in 62% of participants with baseline LSM elevation. Normalisation was more frequent among individuals with low baseline NIT scores (low LiverPRO: 81%; low LRS: 81%; low MAF-5: 79%; low FIB-4: 67%). Conversely, high baseline NIT scores demonstrated a greater likelihood of persistent LSM elevation, with persistence increasing from 38% to 47% (MAF-5), 47% (FIB-4), and 46% (LRS) and 43% (LiverPRO).

Conclusion: During long-term follow-up, LSM normalisation among those with initial elevated values is common, suggesting a high rate of false positives in screening. Among the assessed NITs, MAF-5, LRS, and LiverPRO provide excellent predictive value for long-term persistent LSM elevation and can help identify individuals at greatest risk of true liver fibrosis. When combined with baseline LSM, low NIT scores ruled out persistent LSM elevation in up to 81% of cases.

POSTER TOUR PRESENTATIONS

PT1-02-YI

Steatotic liver disease is associated with frailty and lower muscle density compared to other liver diseases in patients with cirrhosis evaluated for liver transplantation: a cross-sectional study

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Background and aims: Myosteatosis, defined as reduced muscle density on computed tomography (CT) reflecting fat infiltration of skeletal muscle, is a classical feature and an independent predictor of mortality in patients with cirrhosis. However, its relationship with the underlying etiology of cirrhosis remains unclear. Our aim is to characterize muscle alterations across etiological subtypes of cirrhosis, focusing on steatotic liver disease (SLD).

Method: A total of 191 cirrhotic patients evaluated for liver transplantation were prospectively included. Frailty was assessed using the Liver Frailty Index (LFI). All patients underwent abdominal CT scan at the third lumbar vertebra level (L3) to assess the following muscle parameters: skeletal muscle area (cm^2), skeletal muscle index (SMI, cm^2/m^2), skeletal muscle density (HU) and skeletal muscle density index (SMDI, HU/cm^2).

Results: Among the 191 patients, 124 had a SLD: 23 with metabolic dysfunction–associated steatotic liver disease (MASLD), 90 with alcohol-related liver disease (ALD), and 11 with mixed etiology (MetALD). The remaining 67 patients had other disease causes (viral hepatitis, autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis, etc.). Patients with SLD were significantly older and had a higher body mass index (BMI) than non-SLD patients (61 vs 52 years; 27.7 vs 22.8 kg/m^2; both $p < 0.0001$), even though they had similar MELD scores. They were also frailer according to the LFI (3.9 vs 3.5; $p < 0.05$). On imaging, SLD patients showed higher muscle area and SMI values than other etiologies (164 vs 141 cm^2; 54 vs 47 cm^2/m^2; $p = 0.0012$ and $p = 0.003$, respectively). In contrast, muscle density and the skeletal muscle density index (SMDI) were significantly lower in SLD patients (42 vs 49 HU; 0.26 vs 0.35 HU/cm^2; $p = 0.0002$ and $p < 0.0001$), indicating increased muscle fat infiltration. These differences remained significant after adjustment for sex, age, and BMI in multivariate analysis.

Conclusion: Patients with cirrhosis display distinct muscle alterations depending on the underlying etiology. SLD is associated with a muscle phenotype characterized by increased muscle mass, greater fat infiltration and muscle function impairment, suggesting a specific metabolic-driven muscle profile unique to these etiologies. These findings suggest specific approaches to nutritional and metabolic management in SLD-related cirrhosis.

PT1-03

Withdrawal of semaglutide results in weight regain, increased alcohol intake and metabolic disorders in a diet-induced obese hamster model of MetALD

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Background and aims: As an alternative to mice and rats, we have developed a free-choice diet-induced obese hamster model, that exhibits human-like dyslipidemia, MASH, heart failure with preserved ejection fraction (HFpEF) and a spontaneous preference for alcohol. In a recent publication (Briand et al. *Eur J Pharmacol*, 2025), we have demonstrated that semaglutide shows multiple cardiometabolic benefits in our model, including improved HFpEF and reduced alcohol consumption. In the present study, we evaluated the effects of semaglutide withdrawal in diet-induced obese hamsters with free access to alcohol, as a model of MetALD.

Method: Diet-induced obese hamsters, with free access to chow or high fat diet, tap water or fructose/alcohol water, were treated s.c. three times per week with vehicle for 4 weeks or semaglutide 15nmol/kg for 2 weeks, followed by a 2-week withdrawal period.

Results: Compared to vehicle, semaglutide for two weeks resulted in significant weight loss (-11%), including reductions in both fat and lean mass, and reduced high fat diet as well as fructose/alcohol water intake. Semaglutide significantly decreased fasting glycaemia and insulinemia, leading to a strong reduction in the HOMA-IR index of insulin resistance (-73%, $p<0.01$). Semaglutide also reduced levels of fasting plasma free fatty acids, triglycerides and total cholesterol (all $p<0.05$).

During the two-week period of semaglutide withdrawal, the hamsters rapidly regained their initial body weight and fat mass. This was accompanied by an increase in their intake of high-fat diet and fructose/alcohol water. At the end of the 2-week period, withdrawal of semaglutide led to similar HOMA-IR index and plasma total cholesterol levels, as well as significantly higher plasma free fatty acids (+52%) and triglycerides (+80%) levels, as compared to vehicle. This dyslipidemic profile was confirmed by FPLC analysis. While it did not change liver fat content and NAFLD activity scoring, semaglutide withdrawal tended to worsen liver fibrosis with a significantly greater expression of genes involved in fibrosis, as well as higher % Sirius Red labelling.

Conclusion: Withdrawal from semaglutide results in rapid weight regain, increased intake of high-fat diet and fructose/alcohol in the drinking water, dyslipidemia and worsening liver fibrosis. This preclinical hamster model could be used to evaluate novel therapies that would prevent metabolic disorders following semaglutide withdrawal.

PT1-07-YI

The pFIB scores for pediatric MASLD fibrosis associate with the risk of youth-onset type 2 diabetes in children with obesity

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) has become the most common liver disease worldwide in children and adolescents just as in adults. We recently developed a novel risk score, the pFIB-c, and a simplified version, the pFIB-6, for the diagnosis of significant liver fibrosis in pediatric MASLD. Still, no pediatric scores have been evaluated for their prognostic value in longitudinal studies. In this study, we hypothesized that the pFIB scores are associated with the risk of type 2 diabetes (T2D) in adolescence and young adulthood, underpinning their clinical utility.

Method: A cohort study was conducted using the Swedish Childhood Obesity Treatment Register (BORIS, 2005-2020) linked with national registers, from which T2D was ascertained. We included 4856 children with obesity and 23,758 general population comparators. The pFIB-c (https://www.mdcalc.com/calc/10615/pediatric-fibrosis-score-continuous-pFIB-c) and simplified pFIB-6 scores were calculated as published at the time of patient inclusion in the database. The incidence rate per 10,000 person-years (PY) were calculated for the general population and individuals with obesity with or without elevated pFIB scores. Time-to-event analysis yielding hazard ratio (HR) was performed using Cox regression and flexible parametric survival models.

Results: Among children with obesity, 12.4% (n = 602) had a high pFIB-6 (≥ 4). The HRs for T2D were not proportional over time, with an inflection point in late adolescence. A high pFIB-c score increased the risk for T2D at 9-19 years of age (adjusted HR 3.03, 95% CI 2.19-4.19, $p < 0.001$). The incidence rate was 1.02 (95% CI 0.61-1.72) per 10,000 PY in the general population comparators, 45.5 (95% CI 37.8-54.7) in individuals with obesity and a pFIB-6 < 4, and 161.7 (95% CI 122.2-213.9) when the pFIB-6 ≥ 4. Among individual score components, hypertension, ALT and HOMA-IR were associated with a greater likelihood of incident T2D, with ALT being the strongest predictor. Male sex reduced predictive performance, as girls were at higher risk of T2D. In contrast, neither score, measured at pediatric age, predicted T2D risk at 20-25 years of age.

Conclusion: This is the first evidence of a pediatric fibrosis score that correlates with clinically meaningful outcomes. These findings support the scores' integration into risk stratification tools for children with MASLD, while highlighting the need for longer follow-up to assess cardiovascular and liver outcomes.

PT1-08
Mediterranean diet improves metabolic outcomes and reprograms immune-cell bioenergetics in adults with MASLD

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Background and aims: Metabolic dysfunction–associated steatotic liver disease (MASLD) lacks effective pharmacotherapy, highlighting the need for dietary approaches. We examined whether a Mediterranean diet (MD), enriched with ω-3 PUFAs containing food, improves metabolic health and peripheral immune-cells (PBMCs) bioenergetics in MASLD.

Method: Thirty (30) adults with obesity and MASLD were enrolled in a diet-induced weight loss (WL) program: ~1800 kcal/day (men) or ~1400 kcal/day (women) based on an MD pattern plus flaxseed (≈10 g/day: ~2.2 g ω-3) and oily fish ≥3 times/week. At baseline and after 6 months, anthropometric data, routine blood test and PBMC samples were collected, together with assessment of body composition (Bioelectrical Impedance Analysis) and hepatic steatosis by measuring controlled attenuation parameter (CAP) with FibroScan®. PBMCs bioenergetics was determined by Seahorse XF Analyzer as proton efflux rate and oxygen consumption rate, indices of glycolysis (GLY) and mitochondrial respiration (MR). Respiratory-chain (RC) activity and gene expression of 78 targets (mostly RC subunits) were measured by spectrophotometer and qPCR (PrimePCR array Mitochondria Energy Metabolism Plus). 17/30 patients completed the program with full compliance, hence included in the analyses. 10 age-matched healthy people served as bioenergetics control.

Results: Participants (67.6% male, BMI=36.8±7.1Kg/m^2) achieved moderate WL (~10%) with broad metabolic benefits: fasting glucose −11.8% (107.6→95.0 mg/dL, p=0.006), HbA1c −5.8% (p=0.013), total cholesterol −12.8% (p=0.018), LDL −14.4% (p=0.032), AST −18.2% (p=0.0005), ALT −41.7% (p<0.0001), CAP −11.9% (p=0.003); fat mass (kg) decreased by 21.4%, while skeletal muscle mass (%) rose by 7.1% (p<0.05).
Interestingly, at baseline MASLD PBMCs exhibited a clear hypometabolic signature, with significantly reduced MR and GLY on Seahorse assays (lower OCR- and PER-derived indices), corroborated by diminished RC complex II activity and reduced ATP content vs healthy controls. Following WL, PBMC bioenergetics shifted toward a “healthy” state, with higher basal, maximal, and ATP-linked respiration and increases in both basal and compensatory GLY. These functional gains paralleled a recovery of complex-II activity and the coordinated upregulation of multiple RC subunits, indicating a systemic immunometabolic reset.

Conclusion: An MD-induced WL promotes a metabolic reactivation in MASLD, improving clinical and hepatic endpoints and restoring immune-cell bioenergetic competence.

PT1-09-YI
Platelet phenotype and function throughout the spectrum of Metabolic dysfunction-Associated Steatotic Liver Disease

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Background and aims: Metabolic dysfunction-Associated Steatotic Liver Disease (MASLD) is a major cause of chronic liver disease, progressing from steatosis to cirrhosis. Platelets are increasingly recognised as contributors to its pathogenesis, yet their phenotype and function across disease stages remain unclear. We aimed to characterise platelet activation and function in MASLD with mild fibrosis (≤F2) and advanced fibrosis/cirrhosis (F3-F4) versus healthy controls. A secondary aim was to assess coagulation factor profiles and the possible platelet role in their transport.

Method: In this cross-sectional study, 192 subjects were included: 62 healthy controls, 82 MASLD ≤F2, and 48 MASLD F3-F4. Platelet activation was assessed by urinary 11-dehydro-thromboxane B2 (11-dh-TXB2) and plasma soluble P-selectin; platelet adhesion under flow by microfluidics; and flow cytometry analysed fibrinogen receptor activation, Annexin V binding, and platelet-leukocyte aggregates. Coagulation parameters (PT, aPTT, fibrinogen, FVII, FVIII, FIX, FX, FXII, FXIII, and vWF) were measured in platelet-rich and platelet-poor plasma. Combination assays mixing patient platelets with control plasma and vice versa evaluated whether platelets contribute to coagulation factor transport.

Results: Both 11-dh-TXB2 and soluble P-selectin rose progressively with fibrosis severity and correlated with FIB-4 and liver stiffness ($p<0.001$). Microfluidic assays showed enhanced platelet adhesiveness in MASLD ≤F2 and F3-F4 versus controls. Flow cytometry showed an increased proportion of Annexin V-positive procoagulant platelets in ≤F2 patients, while F3-F4 exhibited reduced fibrinogen receptor activation and lower platelet-monocyte aggregates, suggesting exhaustion. Advanced fibrosis/cirrhosis was associated with prolonged PT/aPTT and reduced FVII, FVIII, FIX, FX, FXII, and FXIII, alongside elevated vWF. Combination experiments demonstrated that differences were plasma-driven, excluding a relevant platelet-mediated transport role.

Conclusion: Distinct platelet phenotypes characterise MASLD progression. Early disease (≤F2) shows increased platelet activation and procoagulant potential, while advanced fibrosis/cirrhosis displays reduced responsiveness despite systemic activation and thrombocytopenia. Coagulation abnormalities mainly reflect plasma defects rather than platelet carriage. These findings identify platelets as active players in MASLD pathogenesis and support their potential as biomarkers and therapeutic targets in chronic liver disease.

PT1-10-YI

Biomarkers of collagen formation and degradation are associated with major adverse liver outcomes and esophageal varices

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Background and aims: As management of liver cirrhosis shifts from reactive to proactive, a key challenge is identifying patients at risk of decompensation and other major adverse liver outcomes (MALO) before these events occur. Chronic inflammation and extracellular matrix (ECM) remodeling drive disease progression. Pro-C3, a marker of type III collagen formation, and C4G, a marker of granzyme B–mediated degradation of type IV collagen, may together capture both fibrogenesis and inflammation-driven degradation of ECM.

This study aims to evaluate the prognostic value of Pro-C3 and C4G in predicting MALO and the development of non-bleeding esophageal varices in patients with liver cirrhosis.

Method: ACCESS-ESLD is a prospective multi-center cohort study of 150 patients with liver cirrhosis. Baseline serum nordicPro-C3 (ELISA) for activity fibrogenesis and nordicC4G for T-cell activity were analyzed. Follow-up occurred every six months with clinical data collection. Major adverse liver outcomes (MALO) were defined as decompensation event, liver transplantation, or liver-related death. Data collection is continuously ongoing.

Results: The median follow-up time by the time of analysis was 18 months. Patients were stratified into four groups based on upper quartile cut-offs for Pro-C3 (32.8 ng/mL) and C4G (73.4 ng/mL). The 1-year event-free probabilities for MALO or non-bleeding esophageal varices were 95% for low Pro-C3/low C4G, 83% for low Pro-C3/high C4G, 80% for high Pro-C3/high C4G, and 58% for high Pro-C3/low C4G (log-rank p = 0.003).

Using the low Pro-C3/low C4G as reference, the hazard ratios were 3.5 (95% CI: 0.7 – 17.3, p = 0.13) for low Pro-C3/high C4G, 4.0 (95% CI: 0.4 – 38.9, p = 0.23) for high Pro-C3/high C4G, and 9.3 (95% CI: 2.3 – 37.0, p = 0.002) for high Pro-C3/low C4G.

When analyzed individually, high Pro-C3 was associated with a hazard ratio of 4.9 (95% CI: 1.9 – 13.0, p = 0.001) compared with low Pro-C3, whereas high C4G showed a non-significant association (HR 1.5, 95% CI: 0.5 – 4.8, p = 0.53).

Conclusion: High fibrogenesis levels (Pro-C3) identified patients at increased risk of MALO and esophageal varices. Combining systemically assessed Pro-C3 with C4G, which reflect fibrogenesis and inflammation-driven ECM degradation respectively, improves prognostic performance compared with Pro-C3 alone. Larger studies with longer follow-up are needed to confirm these findings.

PT2-01-YI

A novel machine learning-based algorithm improves risk stratification of patients with MASLD compared to FIB-4

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Background and aims: MASLD is the most common cause of chronic liver disease worldwide. Early identification of advanced fibrosis is crucial, as fibrosis stage remains the strongest predictor of liver-related outcomes and mortality. Current guidelines recommend FIB-4 as the first-line non-invasive test in primary care, yet its limited accuracy in younger and older individuals and high rate of indeterminate results highlight the need for more reliable tools. LiverPRO, a novel machine learning-based algorithm, has recently been proposed as an alternative. The aim of this study is to compare the performance of LiverPRO F3 and FIB-4 for first-line risk stratification of advanced fibrosis in patients with MASLD, by comparing the impact of a LiverPRO-based referral pathway with standard referral strategy.

Method: This is a retrospective cross-sectional study of 1818 consecutive MASLD patients referred to the hepatology clinic of the Royal Free Hospital, London (2016-2024). Two parallel referral pathways were constructed, using either FIB-4 or LiverPRO F3 as the first-line test for advanced fibrosis. Patients were stratified into low-, intermediate-, and high-risk categories. Diagnostic performance of both pathways was assessed against a composite reference standard for advanced fibrosis, defined as the presence of either: 1) histological stage F3 or higher, 2) liver stiffness >12 kPa, or 3) liver stiffness >8 kPa combined with an ELF score > 9.8. Net reclassification improvement (NRI) was used to quantify the added value of LiverPRO versus FIB-4. In addition, the performance of LiverPRO was validated VCTE and liver biopsy, separately.

Results: Among 1703 patients with valid reference standards, 389 (23%) had advanced fibrosis. Using FIB-4, 695 patients (41%) were classified as indeterminate and 108 patients (13%) in the low-risk group had advanced fibrosis. Compared with FIB-4, LiverPRO F3 identified 206 patients (12%) with advanced fibrosis at the high-risk threshold versus 78 (5%) with FIB-4 ($p < 0.0001$), reduced the number of missed cases in the low-risk group to 50 (8%) vs. 108 patients (13%) with FIB-4 ($p = 0.001$), and decreased the number of patients in the indeterminate-risk category to 606 (36%) vs. 695 (41%) ($p = 0.002$). Overall, LiverPRO F3 achieved a NRI of 21% compared with FIB-4.

Conclusion: In this large real-world MASLD cohort, LiverPRO F3 significantly improved first-line risk stratification of advanced fibrosis compared with FIB-4, supporting its integration into non-invasive care pathways.

PT2-02-YI

Impact of fibrotic MASH as a new indication on semaglutide eligibility in the U.S. adult population

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Background and aims: Semaglutide, a glucagon-like peptide-1 receptor agonist, is effective in the treatment of fibrotic (F2-F3) metabolic dysfunction-associated steatohepatitis (MASH) and has recently received accelerated FDA approval. However, the extent to which this new indication expands treatment eligibility beyond existing approvals for type 2 diabetes mellitus (T2DM) and obesity remains unclear.

Method: We analyzed nationally representative NHANES data (2017–2020) on U.S. adults, excluding individuals with viral hepatitis or excessive alcohol consumption. Semaglutide eligibility was defined according to FDA-approved indications for weight loss (BMI ≥ 27 kg/m^2 with weight related comorbidity), high-risk T2DM (T2DM with CVD or high risk of CVD or impaired renal function), or fibrotic MASH (LSM 8-15 kPa with MASLD [CAP ≥ 275 db/m + metabolic dysfunction]). Findings were validated in the Mainz (Germany) biopsy cohort (n = 213) with biopsy-proven MASLD and F2–F3 fibrosis.

Results: We included 6,936 adults, the weighted median age was 47 years [32 - 61], 47.9% were male, MASLD was present in 41.0% and fibrotic MASH in 5.2%. In the adult U.S. general population, 51.5% met indications for semaglutide for weight loss (41.8 of 51.5%), high-risk T2DM (2.0 of 51.5%) or both (7.7 of 51.5%). Among individuals with MASLD, 80.9% qualified for treatment based on conventional indications, increasing to 95.4% in those with fibrotic MASH. Including fibrotic MASH as an additional indication marginally increased overall eligibility (from 51.5% to 51.8%), reflecting that most individuals with fibrotic MASH already met eligibility criteria through obesity or high-risk T2DM. In the Mainz cohort, 80.3% of patients with biopsy-proven F2–F3 fibrosis were eligible for semaglutide irrespective of fibrotic MASH, in agreement with the findings from the general population.

Conclusion: Semaglutide eligibility is high among U.S. adults. The new fibrotic MASH indication largely overlaps with pre-existing indications, primarily obesity, which uses the same dose as fibrotic MASH. These findings highlight the intertwined nature of metabolic comorbidities and liver disease and emphasize the need for an integrated, patient-centred approach to semaglutide, alongside policies that improve access and reimbursement.

PT2-03
Acute response of hepatic fat content to consuming simple sugar alongside fat

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD, formerly NAFLD) is a growing global health concern characterized by excessive fat accumulation in the liver. While the exact mechanisms are complex and multifactorial, dietary factors, particularly the consumption of fructose, have been implicated in its development and progression. In a previous study (doi:10.1093/ajcn/nqy386), we demonstrated that fructose, if provided together with a high fat load, led to accumulation of fat in the liver in non-obese subjects after 6 hours. On the contrary the coadministration of glucose with high fat load did not affect hepatic fat content (HFC). In this study we tested whether such effect is preserved in obese subjects, and how both groups would react to sucrose.

Method: Ten obese and six non-obese subjects underwent three separate interventions in randomized order. In each of these interventions the HFC (HFC_0) was measured by magnetic resonance spectroscopy (MRS) after overnight fasting. Then, subjects consumed 150 g of fat alongside 50 g of sugar (glucose, fructose, or sucrose). The same sugar was given to them again after 2 and 4 hours, and after 6 hours, they underwent a second MRS (HFC_6). Blood was collected before the first consumption and then repeatedly during intervention for determination of triacylglycerols (TAG), free fatty acids (FFA), glucose, insulin, uric acid and 3-hydroxybutyrat.

Results: In the non-obese subjects, the HFC increased after the high fat load with fructose (HFC_6/HFC_0 = 117 ± 18 %) but remained unchanged in interventions with glucose and sucrose. In the obese subjects, there were no changes in HFC across any of three interventions. In each intervention, the insulin secretion was higher in obese group, while blood glucose response did not differ between groups. FFA and TAG remain unchanged in both groups across any of three interventions.

Conclusion: In this study we confirmed that HFC in non-obese subjects increased after high fat load with fructose, but not after high fat load with glucose. No changes in HFC were also observed after consumption of sucrose with high fat load. On the contrary, we were unable to detect any change in HFC in the same experiments in obese individuals. Based on the analysis of biochemical data, we conclude that increase in HFC after six hours in non-obese group were due to *de novo* lipogenesis from dietary fructose.

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PT2-04-YI

The chronic exposure to Bisphenol A influences trained immunity and induces immunometabolic innate cells reprogramming, promoting metabolic dysfunction associated steatotic liver disease progression

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a growing global health concern, often progressing to steatohepatitis (MASH) and advanced fibrosis (AF). Beyond insulin resistance, recent evidence implicates damage-associated molecular patterns (DAMPs) and gut-derived pathogen-associated molecular patterns (PAMPs), such as lipopolysaccharide (LPS), in driving MASLD progression via innate immune activation, inflammation, and reactive oxygen species (ROS) generation. The concept of trained immunity (TI)—a memory-like response in innate immune cells—has emerged as a key mechanism, involving metabolic reprogramming and heightened inflammatory output. Bisphenol A (BPA), a widespread endocrine disruptor, has been identified as a TI trigger capable of inducing immunometabolic remodeling in monocytes. This study investigates the role of chronic BPA exposure in MASLD progression through TI-mediated innate immune activation.

Method: Ten healthy controls and twenty MASLD patients (10 MASLD-SS, 10 MASLD-SH) undergoing liver biopsy were enrolled. At baseline (T0) and after a 3-month BPA-free diet (T1), BPA serum levels were quantified (LC-MS/MS), and cytokines (IL-1beta, IL-6, TNF-alpha) were assessed (ELISA). Monocytes were isolated and subjected to a TI-BPA protocol (BPA priming, LPS rechallenge), followed by cytokine profiling and metabolic assessment (Seahorse XFb, ROS assay).

Results: At T0, BPA levels progressively increased from controls to MASLD-SS and MASLD-SH, with significantly elevated cytokines in MASLD-SH vs MASLD-SS (all $p < 0.0001$). TI-BPA-stimulated MASLD-SH monocytes produced higher IL-1beta, IL-6, and TNF-alpha than other groups (all $p < 0.001$). Seahorse analysis revealed increased glycolysis and reduced mitochondrial respiration in MASLD-SH vs MASLD-SS (ECAR/OCR, all $p < 0.0001$). The BPA-free diet significantly reduced BPA levels (T1 vs T0, $p = 0.0002$), especially in MASLD-SH. At T1, “enhanced trained response” prevalence was higher in MASLD-SH vs MASLD-SS (82 % vs 31 %, $p < 0.0001$), with no metabolic differences between groups.

Conclusion: BPA promotes trained immunity and immunometabolic reprogramming in MASLD, exacerbating inflammation and disease progression. These findings underscore the impact of environmental exposures and support TI-targeted interventions in MASLD management.

PT2-05-YI

Modulation of interactions between mitochondria and the endoplasmic reticulum by resmetirom in MASLD

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Background and aims: Poor calcium coupling between the endoplasmic reticulum (ER) and mitochondria, at contact points called mitochondria-associated ER membranes (MAMs), plays a role in the development of insulin resistance and metabolic dysfunction-associated steatotic liver disease (MASLD). Recently, resmetirom (a thyroid hormone receptor agonist, THR-beta) has been approved as a treatment for fibrotic metabolic dysfunction-associated steatohepatitis (MASH). We investigated whether the mechanism of action of resmetirom depends on the integrity of hepatic MAMs.

Method: We studied the effect of resmetirom (1 µM) on MAMs (in situ PLA), lipid accumulation (Bodipy), insulin resistance (Western blot P-AKT/AKT), lipid metabolism (RT-PCR) in Huh7 cells under preventive (24-hour co-treatment with 200 µM palmitate) and curative (8 hours of 100 µM palmitate, followed by 24 hours of resmetirom) conditions.

Results: The efficacy of resmetirom treatment is demonstrated by the induction of THR-β target genes DIO1 in Huh7 cells. Palmitate induces an increase in lipid droplet size (+ 113 %, $p < 0.0001$), which is partially prevented by resmetirom (+ 59 %, $p = 0.0001$), i.e., delta -25%, $p < 0.0001$. Similarly, the reduction in MAMs induced by palmitate (- 46 %, $p < 0.0001$) is partially prevented by resmetirom (- 26 %, $p < 0.0001$), i.e., delta +37 %, $p < 0.0001$. In addition, resmetirom increases the P-AKT/AKT ratio in the presence of palmitate (delta + 48 %). Finally, resmestirom stimulates the expression of key lipid metabolism genes, such as CPT1A. Under curative conditions, resmetirom reduces palmitate-induced steatosis (delta – 13 %, $p < 0.05$) and the integrity of MAMs is currently being analyzed.

Conclusion: These preliminary results suggest that resmetirom could prevent and improve lipid accumulation and hepatic insulin resistance induced by palmitate through the regulation of the integrity of MAMs. An in vivo protocol in a MASLD mouse model, with or without hepatic MAM disruption induced by a molecular spacer, will serve to confirm these data.

PT2-06

CD8+ T cells are pro-inflammatory, cytotoxic, and clonally expanded in the early stages of fibrosis due to metabolic dysfunction-associated steatohepatitis (MASH)

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Background and aims: Metabolic dysfunction-associated steatohepatitis (MASH) can progress to fibrosis. We previously found an increased number and activation of peripheral blood T cells in patients with MASH compared to steatosis and healthy controls. However, clonality and activation status of T cells in early stages of MASH fibrosis remain unclear and may give unique insights into pathogenesis. Here, we characterised the phenotype and T cell receptor repertoire of T cells in blood, liver, and adipose tissue sampled simultaneously from patients ranging from healthy to non-cirrhotic fibrosis.

Method: We performed CITE-seq and TCR sequencing on CD45+ immune cells from liver, subcutaneous (SAT), visceral adipose tissue (VAT), and peripheral blood (PBMC) of 19 MASLD patients (F0-F3 fibrosis) and one healthy control. Histology was assessed using NASH CRN criteria.

Results: TCR sequencing revealed progressive TCR diversity loss and increased clonal expansion from health to MASLD with fibrosis, with expanded clones enriched in different subsets of CD8 T cells (effector memory, cytotoxic, and NK-like). Clonotype tracking demonstrated shared expanded clones across tissues, often targeting non-infectious antigens. Cell-cell interaction analysis identified clonally expanded CD8 T cells as major signal recipients and TAGLN EndoMT-like endothelial cells as dominant senders in fibrosis. Gene set enrichment of expanded clones in fibrotic tissues showed metabolic rewiring, suppression of exhaustion programs, and tissue-specific signaling, consistent with immunometabolic adaptation.

Conclusion: Clonal expansion of CD8 T cells with cytotoxic and pro-inflammatory expression profiles occurs early in MASH-related fibrosis and may be a key pathogenic factor in progressive disease.

POSTER ABSTRACT PRESENTATIONS

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Basic and Translational Science

PO1-01-YI

Cardiometabolic stratification reveals heterogeneous hepatocellular carcinoma risk in MASLD with advanced fibrosis

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Background and aims: Metabolic dysfunction (MD)-associated steatotic liver disease (MASLD) is defined by steatotic liver disease (SLD) in the presence of at least one cardiometabolic risk factor (CMRF)—obesity, type 2 diabetes, dyslipidemia, or hypertension—in the absence of alternative causes. MASLD may progress to steatohepatitis (MASH) and advanced fibrosis (AF), significantly increasing the risk of hepatocellular carcinoma (HCC). While cardiovascular risk is known to escalate with MD severity, the impact of cumulative CMRF burden on HCC development remains poorly characterized. This study aimed to assess differential HCC risk and timing by stratifying MASLD-AF patients according to distinct CMRF combinations.

Method: Biochemical, clinical, and Liver Stiffness (LSM) data from 1921 SLD individuals, archived in the Health Documents Digitization Repository of the "Luigi Vanvitelli" University Hospital (January 2010 – Oct 2020), were retrospectively analyzed to identify subjects fulfilling EASL-proposed MASLD criteria and exhibiting LSM-AF. A non-redundant permutation of CMRFs—obesity (Obe), dysglycaemia or type 2 diabetes (Gly), dyslipidemia (Lip), and elevated blood pressure (Press)—was applied, yielding 4 groups with 15 distinct MD profiles: Group 1) One CMRF (n: 311) [1a: Obe (n: 130); 1b: Gly (n: 40); 1c: Lip (n: 91); 1d: Press (n: 50)]; Group 2) Two CMRFs (n: 840) [2a: Obe-Gly (n: 140); 2b: Obe-Lip (n: 120); 2c: Obe-Press (n: 150); 2d: Gly-Lip (n: 130); 2e: Gly-Press (n: 140); 2f: Lip-Press (n: 160)]; Group 3) Three CMRFs (n: 680) [3a: Obe-Gly-Lip (n: 190); 3b: Obe-Lip-Press (n: 170); 3c: Obe-Gly-Press (n: 140); 3d: Gly-Lip-Press (n: 180)]; Group 4) Four CMRFs (Obe-Gly-Lip-Press) (n: 90). HCC diagnosis and staging (BCLC) were retrospectively recorded over a 5-year follow-up.

Results: Patients with ≥3 CMRFs exhibited significantly higher HCC risk [HR: 3.12, p: 0.001]. Within this subgroup, Gly-Lip-Press, Obe-Gly-Lip [HR: 1.129, p: 0.034], and Obe-Gly-Lip-Press [HR: 2.21, p: 0.002] showed progressively increasing 5-year HCC incidence and decreasing median time to occurrence (48.2 vs 41.3 vs 28.1 months; $p < 0.0001$). Notably, the BCLC-C stage at diagnosis was more frequent in Obe-Gly-Lip (31 %) compared to other Group 3 profiles (< 10 %; $p < 0.0001$).

Conclusion: CMRF-based stratification reveals substantial heterogeneity in HCC risk among MASLD-AF patients, supporting the implementation of personalized surveillance strategies taking into account the metabolic burden.

PO1-07-YI

Anti-sonic hedgehog immunohistochemistry accurately diagnosis ballooning degeneration in both metabolic dysfunction-associated steatotic liver disease and alcohol-related liver disease

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Background and aims: Ballooning degeneration is a key histological marker of steatotic liver disease (SLD) severity, but it remains difficult to identify reliably and shows poor inter-observer agreement. Sonic hedgehog pathway is involved in ballooning pathogenesis. Our objective was to assess the diagnostic accuracy of anti-SHH immunohistochemistry (IHC) for the diagnosis of ballooning degeneration in SLD.

Method: Recruited participants with a diagnosis of SLD (MASLD or ALD) on imaging and increased liver stiffness (≥ 9kPa, M probe, Fibroscan®) underwent liver biopsy. Four blinded pathologists scored hematoxylin-eosin stained slides for steatosis and activity including ballooning. Anti-SHH IHC was performed on the same liver samples and quantified manually (positive cells per field at 40-fold magnification) by two untrained observers blinded to the pathology score.

Results: Eighty-eight participants with SLD (52 with MASLD, 36 with ALD) were prospectively recruited and underwent liver biopsy. Median self-reported alcohol consumption was 80 units per week in the ALD group. Mean BMI was significantly higher in the MASLD group (34.7 kg/m²) compared to the ALD group (27.3 kg/m²; $p < 0.0001$). 38% of cases were classified by pathologists as fibrosis grade 0-1 (F0-1), 30% as F2, 26% as F3 and 6% as F4 in the pooled SLD group. 46% of MASLD cases were classified as ballooning grade 0 (B0), 27% as B1 and 27% as B2 while 61% of ALD were classified as B0, 14% as B1 and 25% as B2. The count of SHH positive cells strongly correlated between untrained observers ($r = 0.89$, $p < 0.0001$) across the whole SLD cohort. SHH positive density positively correlated with ballooning grades in MASLD ($r = 0.71$, $p < 0.0001$), ALD ($r = 0.75$, $p < 0.0001$) and pooled SLD ($r = 0.69$, $p < 0.0001$). In particular, the median SHH density was 0.03 for B0, 0.16 for B1 and 0.96 for B2 in the pooled SLD group ($p < 0.0001$). SHH density showed a very high diagnostic accuracy for the diagnosis of ballooning in MASLD (AUC = 0.83, $p < 0.0001$), ALD (AUC = 0.94, $p < 0.0001$) and pooled SLD (AUC = 0.86, $p < 0.0001$).

Conclusion: Anti-SHH IHC is a highly accurate tool for the diagnosis of ballooning by untrained observers in MASLD and ALD highlighting its potential utility in clinical practice and research in the topic of SLD.

PO1-10-YI

Epigenetic alterations in patients with metabolic dysfunction-associated steatotic liverdisease differ by anthropometric status

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Background and aims: Body mass index (BMI) and waist-to-hip ratio (WHR) reflect different aspects of adiposity and may exert distinct metabolic and inflammatory effects in patients with metabolic dysfunction-associated steatotic liver disease (MASLD), potentially shaping their epigenetic profile. This study aimed to evaluate how anthropometric status relates to specific epigenetic biomarkers.

Method: We examined 50 patients with MASLD (median age 54.1 [48.7; 59.3] years; 60% men), stratified by BMI (< or ≥30 kg/m²) and WHR (< or ≥0.90 in men; < or ≥0.85 in women). All patients with elevated BMI also had increased WHR, resulting in no subgroup with high BMI but normal WHR. Anthropometric indices, biochemical and hematological parameters (including CRP), 5-methylcytosine (5-mC) as a marker of global DNA methylation, telomere length (TL), and phenotypic age (PA) according to the Levine M. et al. (2018) were assessed.

Results: Patients with obesity (OB) based on BMI demonstrated a more adverse metabolic profile and higher 5-mC levels ($p = 0.048$) compared with those without OB. When compared specifically to patients who had neither OB nor elevated WHR, 5-mC remained significantly higher ($p = 0.019$). In contrast, increased WHR without elevated BMI was accompanied only by metabolic and inflammatory changes, without a rise in 5-mC levels. PA was paradoxically lower in this group ($p < 0.001$), most likely reflecting a transient compensatory shift in circulating biomarkers included in the PA evaluation rather than genuine biological rejuvenation. TL did not differ across anthropometric groups, which may be explained by the modest sample size and age heterogeneity. In the linear regression model among all patients with MASLD, a direct association between 5-mC and PA was observed ($R^2 = 0.092$; $B = 0.033$; $\beta = 0.303$; $p = 0.033$).

Conclusion: Global DNA methylation was higher in patients with MASLD and OB defined by BMI but not in those with increased WHR alone, suggesting that global DNA methylation may represent an early epigenetic indicator of obesity-related metabolic burden. The longitudinal behaviour of PA in relation to changes in central adiposity warrants further investigation as a potential marker of early epigenetic response in MASLD.

PO2-05-YI

Association of anthropometabolic indicators with telomere length in patients with metabolic dysfunction-associated steatotic liver disease

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Background and aims: Although various anthropometric indices are used to estimate metabolic risk in metabolic dysfunction-associated steatotic liver disease (MASLD) patients, their relationship with epigenetic ageing—particularly telomere shortening—remains insufficiently defined. This study aimed to identify anthropo-metabolic indicators associated with reduced telomere length (TL) in MASLD patients.

Method: A total of 324 patients with MASLD (median age 54.3 [49.5; 59.9] years; 69% men) examined in 2022–2025 were included. Patients were stratified into two groups according to TL: preserved (≥1.0; n = 174) and shortened (<1.0; n = 150), matched for age and sex. Anthropometric and biochemical parameters were assessed together with calculated indices: body mass index (BMI), waist-to-hip ratio (**WHR**), waist-to-height ratio (**WHtR**), waist–triglyceride index (WTI), triglyceride–glucose index (**TyG**), TyG myltiplied by waist circumference (**TyG–WC**), TyG myltiplied by WHtR, TyG myltiplied by BMI.

Results: The TyG–WC index was significantly higher in patients with shortened TL (p = 0.020). These patients also had higher fasting glucose (p < 0.001), direct bilirubin (p = 0.001), and very-low-density lipoprotein cholesterol (p = 0.039). The MASLD cohort demonstrated a high burden of cardiometabolic risk: overweight/obesity (92%), prediabetes/diabetes (37%), hypertriglyceridemia (44%), reduced high-density lipoprotein cholesterol (23%), and hypertension (84%). Dysglycemia and excess weight were more prevalent in the shortened TL group (48% vs 28%, p < 0.001; 96% vs 88%, p = 0.009). However, no significant differences were found between obesity-related categories defined by BMI (≥30 kg/m²), WC (≥94 cm in men, ≥80 cm in women), WHR (≥0.9 in men, ≥0.85 in women), or WHtR (≥0.6), suggesting that the **type and metabolic activity of adiposity, rather than its presence alone, may determine TL dynamics**. Recent data also indicate that fluctuations in body weight (in both directions) may accelerate telomere erosion and could partly explain the observed findings.

Conclusion: TyG–WC, reflecting combined abdominal adiposity and insulin resistance, appears to be a more sensitive indicator of telomere shortening in MASLD than traditional anthropometric indices. Screening based solely on BMI, WC, WHR, or WHtR—without metabolic context or monitoring of weight variability—may overlook individuals at risk of accelerated biological ageing.

PO2-06-YI

Pilot case-control GWAS approach to discover novel genetic variants associated with Metabolic Dysfunction-Associated Steatotic Liver Disease

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common chronic liver disease worldwide, with a prevalence of > 25 % in the adult population. Genome-wide association studies (GWAS), have demonstrated that genetic factors play a fundamental role in the predisposition to MASLD. Several genetic variants (e.g., *PNPLA3*, *TM6SF2*, *MBOAT7*) have already been identified as contributors to the development of MASLD and represent potential therapeutical targets. We designed a pilot case-control GWAS aimed at identifying novel genetic variants associated with MASLD.

Method: For this study, we enrolled 141 caucasian patients with MASLD at Liver Outpatient clinic at Policlinico A. Gemelli, Rome. Medical and pharmacological anamnesis, anthropometric measurements and laboratory tests were obtained for all patients. Next generation sequencing (NGS)-based “Clinical Exome Solution (CES)” (Sophia Genetics) panel was performed for all patients. We also retrospectively selected 72 controls, with absence of MASLD and risk factors MASLD-related, analyzed with CES. Raw data collected from all the study cohort was analyzed with a GWAS approach.

Results: Our study enabled the identification of 44 variants (91 % SNPs; 9 % INDELs) significantly associated with the MASLD phenotype ($p \leq 3.79 \times 10^{-6}$), belonging to 30 distinct genes. Among these genes, four (*CELSR2*, *EDAR*, *SULT1A2*, *CYP4A11*) are known to be associated with MASLD, seven with its risk factors (dyslipidemia, obesity, diabetes), and twelve with the development and progression of HCC. Additionally, we observed an overlap of genes implicated both in the regulation of risk factors and in the progression of MASLD and HCC—such as *CELSR2*, *MCCC1*, *CNOT4*, and *EDAR*—highlighting how genetic variants associated with steatosis and fibrosis may ultimately predispose to hepatic oncogenesis and may display a prognostic role.

Conclusion: This study allowed us to explore CES as an approach for the diagnosis of MASLD, which proved to be effective and biologically consistent. The identification of novel variants that may have a prognostic role in HCC development could lead to the creation of personalized gene panels for MASLD patients and contribute to a better understanding of the molecular mechanisms underlying the disease.

PO2-13
Di-lineage liver organoids from human donors recapitulate steatotic liver disease

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common chronic liver disorder and a major contributor to liver-related morbidity and mortality. Existing *in vitro* models either depend on complex differentiation protocols, or hepatocyte-only 3D-models or immortalized cell models that fail to capture fibrosis driven by hepatic stellate cells. Here, we present a di-lineage human hepatic organoid model that represents the key pathological features of MASLD.

Method: Organoids were generated using primary hepatocytes (PHHs) and primary hepatic stellate cells (PHSCs) from several human donors in a pre-defined 24:1 ratio. Steatosis and fibrotic-like conditions were induced by incubation with a mixture of fatty acids (oleic and palmitic acid in a 2:1 ratio, at a final concentration of 500 µM) and TGFB1 (10 ng/ml).

Results: Our model recapitulated the hallmarks of MASLD, including elevated neutral lipid accumulation, increased COL1A1 deposition, lower β-oxidation and reduced ApoB100 secretion. Transcriptomic and proteomic analyses demonstrated changes in the expression of genes and protein levels associated with extracellular matrix (ECM) and metabolic pathways, key features of MASLD. Results were validated in RNA seq data from people with the entire spectrum of fibrosis severity. Incubation with resmetirom or obeticholic acid reversed lipid accumulation and collagen deposition, consistent with clinical trials.

Conclusion: This di-lineage human hepatic organoid model offers a physiologically relevant and scalable system that effectively recapitulates the hallmarks of MASLD. Moreover, this model offers a valuable platform for the discovery and validation of treatment for MASLD.

PO2-16-YI

Brightfield features for discriminating organoids for application in steatotic liver disease: a pilot study by using artificial intelligence

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Background and aims: Hepatocyte organoids (HO) are emerging 3D in vitro systems for exploring disease mechanisms and response to therapies in liver pathologies, such as steatotic liver disease (SLD). One source for developing HOs is patient hepatic progenitors. Upon differentiation and treatment, HOs undergo morphological and structural changes that are difficult to monitor but critical for disease model development. Machine learning (ML) approaches may help researchers with HO morphological analysis. Here, we combined manual segmentation and ML to evaluate differential features in a HO model that mimics SLD.

Method: HO were developed from liver biopsy of healthy tissue by differentiation medium (DM) culture. Palmitic and oleic acid (PA/OA) in a ratio 1:2 were administered to HO to mimic in vitro SLD. HO segmentation was performed on brightfield (BF) images using ImageJ. Python was used to extract and analyse features using ML approaches, including Principal Component Analysis (PCA) and Support Vector Machine (SVM).

Results: HO cultures were optimised for daily live-cell BF imaging during their differentiation and subsequent PA/OA treatment. Growth curve analysis revealed that upon differentiation HOs decreased in area ($p < 0.001$). Among the features, significant changes occurred in the Grey Level Co-occurrence Matrix (GLCM)-Contrast at day 18 of differentiation ($p < 0.05$). Thus, this timepoint was set in the next experiments as the time for treating organoids with PA/OA. The ANOVA test revealed significant differences in the intensity features of mean grey, modal grey, and grey integrated density between untreated and PA/OA-treated HO, with significant differences observed at 24 hours and throughout the treatment (96 hours) ($p < 0.001$). Texture analysis highlighted differences in GLCM-Homogeneity between DM and PA/OA conditions. Finally, PCA showed a progressive separation of the conditions over time, with the first three components represented by shape, GLCM-Homogeneity, GLCM-Energy, GLCM-Contrast, and grey intensity. These components enabled the separation of two clusters, as demonstrated by SVM classifier (ACC = 95%). Bodipy 493/503 staining confirmed that these differences were associated with increased lipid accumulation ($p = 0.036$).

Conclusion: Our pilot study demonstrates that AI tools may support the development and analysis of an HO model of SLD, and further studies could enable the development of a computer-assisted system for monitoring treatment response and drug screening.

PO3-02
PNPLA3 and TM6SF2 genotypes with diabetes identify MASLD patients at high risk of advanced fibrosis

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Background and aims: Genetic information is not yet used for the clinical diagnosis of advanced fibrosis in patients with metabolic dysfunction-associated steatotic liver disease (MASLD). Here we investigated whether incorporating genetic information regarding *PNPLA3* and *TM6SF2* into existing non-invasive fibrosis scoring systems could enhance the predictive accuracy, with particular emphasis on reducing indeterminate diagnostic zones and assessing potential benefits in patients with type 2 diabetes mellitus (T2DM).

Method: Data were collected from a cohort of 637 patients with biopsy-proven MASLD. All participants underwent liver stiffness measurement (LSM), serum marker analysis, and genotyping for *PNPLA3* (rs738409), *TM6SF2* (rs58542926), and other relevant SNPs. We evaluated the benefit of adding genetic information to existing non-invasive tests (NITs)—including the Agile 3+, Fibrosis-4 (FIB-4) index, and NAFLD fibrosis score (NFS).

Results: Decision curve analysis demonstrated that adding genotype data into each model provided higher net benefits and reduced indeterminate risk zones compared to models without genetic information. Notably, in the key high-risk of patients with T2DM, incorporating genetic information enhanced predictive accuracy, with NFS and FIB-4 showing statistically significant improvements in AUROC (increases of 0.053, $p = 0.001$ and 0.058, $p = 0.010$, respectively). The Agile 3+ model showed a similar trend, although it did not reach statistical significance (increase of 0.016, $p = 0.058$).

Conclusion: Incorporating genetic information regarding *PNPLA3* and *TM6SF2* into non-invasive fibrosis scoring systems for MASLD enhances predictive accuracy, particularly in T2DM patients, and reduces indeterminate zones. This approach offers a more reliable tool for identifying individuals at risk for advanced fibrosis, potentially improving clinical decision-making and outcomes.

PO3-04-YI
The potential role of a gut hormone expression in MASLD patients

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Background and aims: Ghrelin, an orexigenic peptide predominantly secreted by the stomach, exerts diverse systemic effects beyond appetite regulation, including modulation of energy balance, glucose metabolism, and inflammation. Among its bioactive isoforms, acyl-ghrelin plays a pivotal role in metabolic regulation. Conversely, nuclear factor-kappa B (NF-κB) is a key transcription factor mediating cellular responses to metabolic and inflammatory stress, contributing to insulin resistance, adipose inflammation, and hepatocellular injury. Despite increasing evidence on their individual roles, the interplay between ghrelin and NF-κB in metabolic dysfunction–associated steatotic liver disease (MASLD) pathogenesis remains insufficiently defined. We investigated the relationship between circulating acyl-ghrelin levels and NF-κB gene expression, and their potential roles in lipid dysregulation, insulin resistance, and hepatic inflammation in MASLD.

Method: Ninety-three adults were enrolled and classified into three groups: 30 patients with biopsy-confirmed metabolic dysfunction–associated steatohepatitis (MASH), 38 with simple steatosis, and 25 age-, sex-, and BMI-matched healthy controls. All participants underwent clinical evaluation, abdominal ultrasonography, laboratory investigations, including liver tests, lipid profile, fasting glucose, insulin, C-peptide, plasma acyl-ghrelin levels *and ,where indicated, liver biopsy*. NF-κB mRNA expression was quantified by real-time reverse transcription polymerase chain reaction.

Results: Compared with controls, MASLD patients exhibited significantly higher fasting insulin, C-peptide, HOMA-IR, AST, ALT, and γ-glutamyl transferase (γ-GT), and lower HDL-cholesterol. Within the MASLD spectrum, the MASH subgroup showed greater elevations in ALT, γ-GT, fasting insulin, C-peptide, and HOMA-IR than those with simple steatosis. Circulating acyl-ghrelin levels were significantly reduced in MASLD, particularly in MASH, whereas NF-κB mRNA expression was markedly elevated. NF-κB expression correlated positively with BMI, HOMA-IR, ALT, fasting insulin, C-peptide, and histological severity, while acyl-ghrelin showed inverse correlations with these variables. Both markers were significantly associated with HDL-C.

Conclusion: Reduced acyl-ghrelin levels and increased NF-κB expression exhibit reciprocal associations reflecting opposing influences on metabolic and inflammatory pathways in MASLD. Acyl-ghrelin may confer hepatoprotective effects by attenuating NF-κB–mediated inflammation.

PO3-07-YI

Global but not liver-specific deletion of the NO receptor protect mice from metabolic dysfunction-associated steatotic liver disease

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Background and aims: NO-sensitive guanylyl cyclase (NO-GC) acts as the main receptor for NO. Within the liver, NO-GC is expressed in hepatic stellate cells and smooth muscle cells. Preclinical reports have investigated the therapeutic effects of NO-GC stimulators in metabolic dysfunction-associated steatotic liver disease (MASLD). However, no study has thoroughly characterized the role of NO-GC in MASLD. Therefore, in the present study, we explored the role of hepatic NO-GC in mice lacking NO-GC globally (GCKO) and specifically in liver (Lrat-GCKO) in Western diet-fed mice.

Method: 8-10-week-old male mice carrying a global (GCKO) and liver-specific (Lrat-GCKO) deletion of NO-GC were received control diet or Western diet (21 % fat, 0.2 % cholesterol) supplemented with 42 g/l fructose in drinking water for 16 weeks and 32 weeks. Thereafter, mice were sacrificed, and liver tissues were fixed in 4 % paraformaldehyde for histological evaluation to assess the rate of disease progression. Analyses included HE, Sirius red staining, immunofluorescence, and confocal microscopy.

Results: GCKO mice spontaneously develop a mild PSC like phenotype (PSC stage 1 - 2) which worsened upon feeding Western diet (≥stage 2). This phenotype was not seen in Lrat-GCKO animals. Interestingly, in contrast to control siblings, GCKO mice did not develop MASLD features upon Western diet; however, mice lacking NO-GC only in liver developed a MASLD phenotype.

Conclusion: We postulate that extra-hepatic NO-GC prevents Western diet-induced MASLD features in mice.

PO3-09
Metabolomic fingerprints differentiate disease severity in Metabolic dysfunction-associated steatotic liver disease

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common chronic liver disease worldwide, closely linked to the rising incidence of type 2 diabetes mellitus (T2DM) and obesity. Affecting approximately one-third of the adult population, MASLD is a significant public health challenge. There is an urgent need for non-invasive strategies to monitor and predict disease progression. Metabolomics represents a powerful platform for identifying disease-specific metabolic profiles, providing mechanistic insights and potential biomarkers for MASLD. This cross-sectional study explores metabolomic signatures associated with T2DM and MASLD, across different stages of hepatic involvement.

Method: Untargeted ultra-high performance liquid chromatography-quadrupole time-of-flight mass spectrometry (UHPLC-QTOF) data derived from plasma were obtained from 100 patients with T2DM from two large Swedish cohorts with or without MASLD. Data were preprocessed with the 'XCMS' package in R and subjected to multivariate analysis in SIMCA. Model performance was assessed using R^2 and Q^2 values and reliability was evaluated with CV-ANOVA, where p-values < 0.05 were considered statistically significant. To study disease trajectory, patients were stratified into four groups: those without MASLD (n = 26), MASLD without significant fibrosis (n = 28), MASLD with significant fibrosis (n = 19), and MASLD with liver cirrhosis (n = 27).

Results: Analysis with orthogonal-partial least squares discriminant analysis (OPLS-DA) revealed discrimination between all patient groups and a model robustness reporting R^2 and Q^2 of 0.648 and 0.413 along with a CV-ANOVA of $p < 0.001$. The final model presented 449 significant features with a variable influence on projection (VIP) score above 1. Annotation and further modeling against clinical data are currently ongoing.

Conclusion: Preliminary findings demonstrate a robust model distinguishing distinct metabolomic profiles across the MASLD disease spectrum. Numerous key metabolic features driving group separation were identified, highlighting key mechanistic alterations in regulatory pathways associated with disease progression.

PO3-12-YI

Microalgae supplementation attenuates malnutrition-induced steatohepatitis by modulating hepatic lipid metabolism, iron balance, and gut barrier function in Rats

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Background and aims: Malnutrition is a major global health concern that heightens susceptibility to metabolic disorders, including metabolic dysfunction-associated steatotic liver disease (MASLD). Conventional fortified foods have limited effectiveness due to low nutrient bioavailability. Microalgae are rich in proteins, lipids, and antioxidants, making them promising dietary supplements. This study evaluated the nutritional benefits and hepatoprotective efficacy of *Spirulina platensis* and *Chlorella pyrenoidosa* against malnutrition-induced steatohepatitis in rats.

Method: Malnutrition was induced using a low-protein-iron-deficient (*LPI*) diet, followed by a recovery phase with diets fortified with *Spirulina* or *Chlorella* biomass. Physiological, biochemical, molecular, and histological analyses were performed to assess recovery outcomes.

Results: Microalgal-enriched recovery diets significantly restored body weight and improved hematological indices. Liver function markers (ALT, AST), glucose, total protein, TSI, TIBC, and hepcidin levels were normalized. Histopathology revealed marked reductions in hepatic fat accumulation and collagen deposition. Supplementation downregulated lipogenic genes (*Srebp1c, Fas, Acc*), reduced inflammation and fibrosis markers, and enhanced antioxidant enzyme activities (SOD, CAT, GPx). Upregulation of *Pgc-1alpha* and *Tfam* indicated improved mitochondrial biogenesis. Transcriptomic analysis showed suppression of NAFLD-associated pathways, while lipidomics revealed decreased ceramide and sphingolipid levels. Moreover, *Spirulina* and *Chlorella* improved intestinal structure and barrier integrity, as evidenced by the modulation of claudin-2, COX2, NF-kappaB, and HIF-2alpha expression.

Conclusion: *Spirulina* and *Chlorella*-fortified diets effectively counteract malnutrition-induced hepatic and metabolic dysfunction by enhancing lipid metabolism, antioxidant defense, and gut–liver axis integrity, highlighting their potential as sustainable nutritional interventions against metabolic liver diseases.

PO4-03
MARC1 p.A165 ablation reduces hepatocellular carcinoma aggressiveness in vitro and in vivo

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Background and aims: Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related mortality worldwide and is driven by metabolic reprogramming that supports tumor growth and progression. A common missense genetic variant (rs2642438, p.A165T) in Mitochondrial amidoxime reducing component 1 (*MARC1*), identified as protective against liver disease, has been recently associated with lower prevalence of cirrhosis and of HCC. However, the mechanistic role of MARC1 in HCC remains poorly understood. Therefore, we sought to decipher the role of MARC1 in HCC.

Method: We investigated the role of MARC1 in HCC by performing siRNA-mediated knockdown across human immortalized HCC cell lines (Hep3B2, HuH7, HepG2, and HepaRG) homozygous for the risk allele (p.A165) and by generating stable CRISPR-Cas9 knockout (KO) models. Next, we assessed the effect of MARC1 loss on cell proliferation, migration, lipid metabolism, fatty acid oxidation *in vitro*, and tumor aggressiveness in a subcutaneous xenograft mouse model. Additionally, we performed global proteomics in both *in vitro* and xenograft models.

Results: Transient knockdown of *MARC1* p.A165 reduced proliferation in HCC cell lines. CRISPR-Cas9-mediated stable *MARC1* p.A165 KO in Hep3B2 cells led to decreased neutral lipid intracellular accumulation, enhanced β-oxidation, and reduced cell migration. MARC1 KO xenograft reduced tumor volume and tumor weight. Proteomic analyses of both *in vitro* HCC cells and xenograft tumors revealed inhibition of oncogenic pathways and activation of anti-proliferative proteins.

Conclusion: Downregulation of *MARC1* p.A165 inhibits lipid accumulation, dampens tumor-promoting pathways, and restricts tumor growth, highlighting MARC1 as a promising therapeutic target for HCC.

PO4-04

Circulating cell-free DNA and 5-methylcytosine correlated with hepatic damage and death patterns in a progressive model of metabolic dysfunction-associated steatotic liver disease

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) encompasses a spectrum of liver patterns, including simple steatosis (MASL), steatohepatitis (MASH), and fibrosis that may progress into cirrhosis. Since apoptosis is associated with MASH, previous studies highlighted that circulating apoptosis signals (i.e. cytokeratin 18 fragments) could be used to distinguish MASL from MASH, even though data on the specificity of these molecules are controversial. Recently, cell-free DNAs (cfDNAs) have been reported as an epigenetic biomarker for other diseases, but there is little evidence in MASLD. Here, we analysed the cfDNA signature in a mouse model of early progressive MASLD to evaluate its potential to identify hepatic MASH and fibrosis features.

Method: A mouse model of MASLD was generated by combining streptozotocin with a high-fat (SHF) diet, compared with untreated standard chow-fed mice (CTL). Groups were terminated at different timepoints (8, 13, and 16 weeks) to evaluate disease progression by histological and metabolic analyses. Apoptotic death was monitored by quantitative immunofluorescence of hepatic cleaved Caspase 3 and 8 and evaluation of total and fragmented cfDNA by TapeStation, cfDNA 5-methylcytosine (5mC) methylation (cfDNA-5mC-me) by ELISA assay, and mitochondrial cfDNA (mt-cfDNA) by qPCR.

Results: Our mouse model of MASLD (SHF) had a significant increase in body and liver weight, ALT, glucose and insulin levels compared to CTL, which increased alongside the timepoints. Histological staining revealed a progressive liver damage with mild MASH and fibrotic patterns at 13 weeks, and more severe damage at 16 weeks. The progressive up-regulation of the cleaved-caspase 3 and 8 expression in SHF mice highlighted an increasing cell death liver pattern. Total cfDNA concentrations and cfDNA-5mC-me levels were increased in SHF mice, with a trend toward higher levels at 8, 13, and 16 weeks. Spearman correlation analysis revealed that cfDNA concentrations and cfDNA-5mC-me levels correlated with a more severe liver damage and death pattern.

Conclusion: Our murine model of MASLD successfully recapitulated histopathological and metabolic features of MASLD. The release of total and cfDNA-5mC-me was associated with hepatic damage and progression to MASH and fibrosis. These results suggest that cfDNA profiling may be a promising non-invasive biomarker for MASLD detection and staging, even if further analysis is required.

PO4-07-YI

In silico electrophysiological investigation reveals cardiotoxicity induced by tecentric in hepatocellular carcinoma via sodium current inhibition

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Background and aims: Tecentric (atezolizumab), a PD-L1 inhibitor used in hepatocellular, urothelial, and small-cell lung cancers, has been linked to sinus bradycardia. The cellular electrophysiology underlying this event remains unclear. We used in silico modeling of the human sinoatrial node (SAN) to determine whether Tecentric alters pacemaker excitability via effects on ion channels—focusing on the fast sodium current (INa, Nav1.5)—and to quantify downstream changes in action potential (AP) shape and firing rate consistent with bradycardia.

Method: A validated SAN cell model incorporating Nav1.5-mediated INa, L-type calcium (ICa,L), inward rectifier and delayed rectifier potassium currents (IK1, IKr, IKs), Na^+/Ca^{2+} exchange, and intracellular Ca^{2+} handling was implemented. Tecentric exposure (0.1–10 µmol/L) was simulated by scaling Nav1.5 conductance and adjusting activation parameters during 200 ms drug pulses. Voltage-clamp protocols (steps −90 to +60 mV) generated current–voltage (I–V) relations and half-activation (V½). Current-clamp simulations assessed AP amplitude, dV/dtmax, diastolic depolarization slope, APD90, and spontaneous firing frequency. Outputs were normalized to drug-free control.

Results: Tecentric produced a concentration-dependent reduction of INa. At 10 µmol/L, peak inward current fell to ~26% of control; the I–V curve shifted positively (~20%), and V½ depolarized (~28%), indicating reduced channel availability. In the integrated SAN model, these changes slowed phase-0 upstroke and flattened the diastolic depolarization, prolonging repolarization (↑APD90) and lowering automaticity. Firing rate declined by ~35% at 5 µmol/L and ~60% at 10 µmol/L. Secondary effects included reduced Ca^{2+} loading via Na^+/Ca^{2+} exchange and modest attenuation of ICa,L, further stabilizing the bradycardic phenotype. Simulated traces reproduced control pacemaking versus Tecentric-exposed APs with fewer beats per time window.

Conclusion: In silico electrophysiology indicates that Tecentric suppresses Nav1.5-dependent sodium current and shifts activation to more positive potentials, diminishing SAN excitability and spontaneous rate. These mechanisms provide a parsimonious explanation for Tecentric-associated sinus bradycardia. Dose optimization and rhythm monitoring (e.g., baseline and on-therapy ECGs) are advisable, especially in patients with conduction disease or concomitant QT-active drugs.

PO4-12-YI
MPEP attenuates hepatic steatosis via mGluR5/PKC inhibition and AMPK activation in hepatocytes and liver organoids

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Background and aims: Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) is a major cause of chronic liver disease, linked to obesity, insulin resistance, and dyslipidemia. It is characterized by hepatic lipid accumulation due to altered lipid metabolism, which can progress to steatohepatitis, cirrhosis, and hepatocarcinoma. The glutamatergic system, and in particular mGluR5, has been identified as a regulator of hepatic lipid metabolism. Our previous studies showed that the mGluR5 antagonist MPEP reduces hepatic fat accumulation in obese mouse models of steatosis and decreases ATP levels in liver tissue, an effect observed only with MPEP, suggesting involvement of the AMPK pathway. Building on this evidence, the present study investigated the mechanisms underlying MPEP effects on steatosis in HepG2 and HuH7.5 cells and in non-cancer patient-derived liver organoids.

Method: Steatosis was induced with a 2 mM oleate/palmitate mixture for 24 h. Hepatocytes were treated with mGluR5 antagonists (MPEP, Fenobam, CPG), alone or with the AMPK inhibitor Compound C, the PKC activator PMA, or the PKC inhibitor Ro 31-8220 to dissect mGluR5-PKC-AMPK signaling. Non-steatotic cells were exposed to the agonist DHPG, alone or with MPEP, to confirm receptor activity. Organoids were treated with MPEP after oleic acid exposure. Lipid and ATP content and cell viability were measured, while proteins involved in the AMPK pathway were analyzed by western blotting.

Results: All antagonists reduced lipid accumulation in hepatocytes, confirming the role of glutamatergic signaling. Only MPEP decreased intracellular ATP and increased AMPK pathway activation, indicating a distinct mechanism. Its lipid-lowering effect was abolished by Compound C, confirming AMPK involvement. Fenobam and CPG reduced lipid levels independently of AMPK modulation. PKC activation by PMA enhanced steatosis, while Ro 31-8220 reduced the pro-steatotic effect of DHPG, confirming PKC as a downstream effector of mGluR5. In organoids, MPEP significantly reduced lipid accumulation after oleic acid, reproducing the anti-steatotic effect seen in hepatocytes.

Conclusion: MPEP acts through dual mechanisms: inhibition of mGluR5/PKC signaling and activation of AMPK via ATP depletion, leading to a strong anti-steatotic effect. Unlike Fenobam and CPG, MPEP directly engages AMPK, making it a unique tool to study metabolic regulation. Its efficacy in hepatocytes and organoids highlights MPEP as a promising candidate for novel therapeutic strategies against MASLD.

PO4-13-YI

The beneficial effect of extra virgin olive oil major phenolic compounds in an in vitro model of metabolic associated steatohepatitis

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Background and aims: Metabolic dysfunction–associated steatotic liver disease (MASLD) affects 38% of adults global popultaion and is the leading cause of liver-related morbidity and mortality. With no approved pharmacological therapy, lifestyle interventions remain the primary management strategy. Extra virgin olive oil (EVOO) and its phenolic compounds such as hydroxytyrosol (HT), oleuropein (OLE), and oleocanthal (OC) were associated with various health benefits. However, the molecular mechanisms underlying these benefits in the context of MASLD remain unclear. This study investigates the effects of EVOO phenolic compounds in a well-established *in vitro* model of metabolic dysfunction–associated steatohepatitis (MASH) using HuH7 hepatocytes exposed to 1200 µM free fatty acids (FFA) for 24h, alone or in combination with HT, OLE, and OC.

Method: Experimental doses were selected using cell viability assays. Oxidative stress was assessed by measuring reactive oxygen species production (ROS)and mitochondrial membrane potential (MMP), the latter using the JC-1 assay. Inflammatory response was assessed by real-time PCR analysis of interleukin-8 (IL-8) and tumor necrosis factor-alpha (TNF-α). Steatosis was determined by quantifying intracellular lipid accumulation using BODIPY 493/503 staining. Data from three biological replicates were analyzed using one-way ANOVA or Student's t-test, and represented as mean ± SD with significance set at $p < 0.05$.

Results: The obtained optimal non-toxic concentrations of EVOO phenolic compounds (10 µM for HT, 40 µM for OLE, and 30 µM for OC) correspond to the concentration present in the recommended daily intake of EVOO (20g/day). HT and OLE significantly decreased ROS levels by 34% ($p < 0.05$). HT showed significant MMP activity, maintaining mitochondrial function and potentially reducing oxidative stress. Gene expression analysis revealed that FFA exposure increased IL-8 and TNF-α expression six-fold compared to control. HT and OLE significantly downregulated TNF-α by 60%, while OLE and OC also reduced IL-8 levels by 80% ($p < 0.05$). None of the compounds affected FFA-induced intracellular lipid accumulation.

Conclusion: This study shows that the main polyphenols present in the recommended daily intake of EVOO beneficially modulate key pathophysiological mechanisms of MASH, such as oxidative stress and inflammation. Notably, these compounds exhibit complementary biological activities, supporting the use of EVOO as a dietary fat source for the prevention and management of MASLD.

PO5-02-YI

Gut dysbiosis and metabolic alterations contribute to hepatic iron overload in a high-fat diet induced rat model of metabolic-dysfunction associated steatotic liver disease

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Background and aims: Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) has been linked to dysmetabolic iron overload syndrome and contributes to disease progression toward dysfunction-associated steatohepatitis (MASH), cirrhosis, and hepatocellular carcinoma (HCC). The current study aimed to investigating the effect of high fat diet (*Hfd)* on hepatic iron overload *via* transcriptomic, lipidomic as well as gut microbiome alterations.

Method: To assess the impact of fatty acid treatment on iron metabolism, Huh7 cells were treated with a cocktail of sodium palmitate and sodium oleate. Cell viability, lipid accumulation through Nile Red staining, and triglycerides were quantified along with the expression of iron regulatory genes. *In-vivo,* Sprague Dawley rats were subjected to either *Hfd*or standard chow diet for 6 months. The effect of *Hfd* on iron metabolism was assessed by gene expression, histopathology, lipidomic, transcriptomics in liver tissue and gut microbiome analysis.

Results: *In vitro*, the treatment reduced cell viability, increased triglycerides, and lipids. Significant changes were observed in the expression of iron-related genes. *In vivo,* the *Hfd* group had elevated body weight, liver weight, and increased ALT, AST, ALP and triglycerides indicating liver injury and dyslipidaemia. The transcriptomic as well as lipidomic profile also revealed the alterations in pathways related to fatty acid metabolism and involvement of genes related to the MASLD. High serum iron, low total iron binding capacity, and hepcidin indicate impaired iron metabolism. Histopathology revealed lipid accumulation and Prussian blue staining showed increased iron deposition in HFD liver. Immunohistochemistry revealed increase in Divalent metal transporter, Hypoxia Inducible factor-1 alpha, and 2-alpha in liver and small intestine indicating compensatory iron uptake. Decreased gene expression of hepcidin and ferroportin and elevated expression of ferritin indicate increased hepatic iron stores. The gut microbiome profile further revealed the reduction in beneficial bacteria which further contribute to the progression of hepatic iron overload.

Conclusion: Lipid accumulation significantly disrupts iron metabolism by altering the expression of key regulatory genes involved in maintaining iron homeostasis. These findings suggest that metabolic stress and iron dysregulation act synergistically in driving liver injury.

PO5-04
Combined drug and diet treatment lead to lipid remodeling, mitochondrial repair in Metabolic dysfunction-associated steatotic hepatitis

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Background and aims: Metabolic dysfunction–associated steatohepatitis (MASH) is characterized by excessive lipid accumulation (steatosis), inflammation, and progressive fibrosis. We observed a strong link between transcription alterations in NRF2 regulation and lipid metabolism in human MASH. NRF2, a master regulator of antioxidant defense and cellular homeostasis, may participate in lipid remodeling and detoxification during MASH regression. We hypothesize that NRF2 activation would reduce lipid peroxidation and de novo lipogenesis, while improving fatty acid B-oxidation, leading to MASH resolution.

Method: We evaluated the impact of pharmacological NRF2 activation, alone or combined with a recovery diet, in diet- and chemical-induced MASH model using system biology approach.

Results: The combined dietary and NRF2 intervention led to the most pronounced histological regression, with significant reductions in steatosis, inflammation, and fibrosis. Transcriptional analyses revealed more effective modulation of genes in lipid metabolism (Elovl6, Cpt1a), fibrogenesis (Col1a1, Lgals3), and oxidative stress (Gpx4, Nox2), while significantly affecting inflammatory markers (Crp, Tgfa) from control to MASH, following recovery and NRF2 activation. Transcriptomics-driven metabolic pathway analysis showed the treatment could potentially restore enzymes in mitochondrial B-oxidation, cholesterol and fatty acid biosynthesis, and reduce peroxidation. Scd1 and Elovl6 were elevated in MASH but reduced by the combination treatment, confirmed by lipidomics. Cholesterol esters were increased in MASH, and Acat1 overexpression partially corrected. Oxidized lipids were elevated in MASH and partially restored by NRF2 activation, with strongest effect under combined treatment. Mitochondrial dysfunction showed an elevated MLCL/CL ratio and PGC-1alpha, Timm23 overexpression, partially improved by NRF2 activation and further restored by the combined intervention. NRF2 alone tended to decrease their expression, diet recovery partially restored it, and the combination led to a synergistic effect. Finally, in accordance to transcriptional changes, medium- and long-chain acylcarnitines were elevated in MASH and reduced by combined treatment, indicating improved mitochondrial fatty acid transport and B-oxidation.

Conclusion: NRF2 activation could potentially lead to MASH regression by reducing lipotoxicity, improving mitochondrial function, and remodeling lipid metabolism. Combined with diet, it provides a synergistic multitarget strategy.

PO5-07
Refined deuterium tracing of hepatic de novo lipogenesis reveals lipid fraction–specific effects of obesogenic diets

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Background and aims: De novo lipogenesis (DNL) actively contributes to the development of MASLD. Accurate measurement of DNL is crucial in animal models, but there is no standardised method. The impact of obesogenic diet on DNL rates in mice is therefore currently unclear, limiting the translatability of research. Clearer data is needed on how obesogenic diets impact DNL in mouse models.

Lee et al. (1994) describe methods for measuring lipogenesis in Sprague-Dawley rats, using fractional synthesis rate (FSR), reflecting the proportion of de novo synthesised palmitate. This model is commonly applied to mouse models, however, calculating the overall synthesis rate is challenging. Mice have high hepatic DNL rates, leading to a likely early saturation of the dynamic lipid pool, which can lead to underestimated lipogenic rates. As such this method requires adaptation for mouse models.

Therefore, our aims were to establish standardised methods for accurately measuring hepatic DNL rates in vivo and to determine DNL rates in mouse models of obesity.

Method: Chow or high fat diet (HFD)-fed C57BL6 mice received intraperitoneal injection and drinking water supplementation with D_2O. Animals were culled 24 or 48 hours post D_2O exposure. Neutral and polar lipids were extracted and analysed by GC-MS. FSR was measured as previously described (Bidault, 2021).

Results: FSR following 24 or 48 hours of D2O exposure was similar, indicating that the labelable lipid pool approaches saturation by 24 hours. This suggests that conventional methods underestimate true DNL rates. Applying our exponential model, we used the experimentally derived maximum labelled fraction, to solve for lipogenic rate, based on the proximity of animals to this plateau at 24 hours. Using this approach, we found that existing methods may underestimate lipogenic rates by up to 10x.

Furthermore, our analysis showed that phospholipid and triglyceride metabolism is differentially affected by HFD feeding. While HFD is typically thought to suppress DNL, our findings indicate that this suppression is specific to the phospholipid fraction, while triglycerides synthesis remains unchanged or elevated.

Conclusion: Our data demonstrate that the current standard methods in mice do not account for early saturation of the labelable lipid pool. Here we present a viable approach to overcome this limitation and obtain more accurate lipogenic rate estimates. Furthermore, we show that phospholipid and triglyceride fractions are differentially affected by HFD feeding.

PO5-08-YI
Early periportal fibrosis and intrahepatic lipid accumulation in a pig model of obesity

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Background and aims: Metabolic-Associated Steatotic Liver Disease (MASLD) is a multifactorial and chronic disease of the liver that can manifest as simple steatosis, steatohepatitis, fibrosis, and cirrhosis. Tracking the early, subclinical progression of MASLD in humans is limited by the impracticality of repeated biopsies and frequent late-stage diagnosis. We utilised a short-term, diet-induced obesity model in the obese-prone Mangalitsa pig to characterise the early histological and physiological markers of the pathology.

Method: Six adult female pigs underwent MRI (Siemens MAGNETOM Skyra 3T, Dixon method) and laparoscopic liver biopsies before and after 15 weeks of high fat diet (Control chow 3% vs HFD 23% palm oil). Formalin fixed and paraffin embedded sections (2/pig) were stained with haematoxylin and eosin (H&E) and picrosirius red (PSR). Frozen sections were stained with oil red (ORO). H&E sections were evaluated by two independent observers using an adapted MASLD scoring scale to evaluate steatosis and inflammation (H&E), while fibrosis (PSR) and lipid droplets size and number (ORO) were quantified via imaging analysis in Fiji. Liver fat fraction was calculated before and after HFD, and liver enzymes monitored.

Results: HFD resulted in a 62% increase in body weight, and final body fat % was 41±6. MASLD score (inflammation+steatosis) increased (baseline1.5±0.5 vs HFD 3±0.6). None of the pigs developed macrovesicular steatosis. Microscopic fat droplets total area increased (baseline 231±188 vs HFD 640±317 um^2, $p<0.05$) while droplets number was highly (baseline 1180±740 vs HFD 1855±1078). Collagen deposition was greater after the HFD, especially periportally (N of pixels $167.91x10^9$ ± $86.25x10^9$ vs $241.17x10^9$± $48.88x10^9$, $p<0.05$). Liver enzymes were unchanged. MRI did not detect any change in liver fat fraction throughout the study (2.5±0.4 vs 3±0.4 %), implying that this modality did not have sufficient resolution needed to detect these subclinical differences.

Conclusion: Interestingly in this model fibrosis was an early event in MASLD development, occurring even in the absence of macrovesicular steatosis or severe inflammation. These findings challenge the traditional requirement for severe steatohepatitis for fibrosis development and highlight that HFD resulting in obesity and degree of intrahepatic lipid accumulation in MRI may drive inflammation and periportal collagen deposition.

PO6-01-YI
Hepatocyte-specific DNMT1 deficiency aggravates hepatic inflammation and fibrosis in MASH

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) has emerged as one of the most common and clinically significant chronic liver disorders. Its pathogenesis is mainly driven by lipid overload in hepatocytes, leading to lipotoxic stress and impaired mitochondrial function. Epigenetic alterations, especially changes in DNA methylation, are increasingly recognized as critical contributors to chronic liver injury and inflammation. Yet, the specific involvement of aberrant DNA methylation in the development and progression of MASLD remains poorly defined.

Method: Hepatocyte-specific *Dnmt1* knockout mice (*Dnmt1*$^{flox/flox;Alb\text{-}Cre}$) and their wild-type littermates (*Dnmt1*$^{flox/flox}$) were fed either a Western diet (WD) or a control diet (CD) from 6 - 8 weeks of age for up to six months to induce metabolic dysfunction-associated steatohepatitis (MASH). Serum biochemistry and histopathological analyses, including immunohistochemistry, were carried out to evaluate liver injury and inflammation. In addition, liver tissues were subjected to RNA sequencing and metabolomic profiling to capture transcriptomic and metabolic alterations associated with *Dnmt1* loss.

Results: Compared with wild-type (WT) controls, *Dnmt1* knockout (KO) mice showed less body weight gain and a blunted hyperinsulinemic response. Despite similar hepatic triglyceride accumulation across both genotypes, KO animals developed a marked increase in intrahepatic cholesterol after six months of Western diet feeding. Remarkably, KO mice exhibited elevated serum alkaline phosphatase (ALP) concentrations after three months on WD. Histological examination revealed increased infiltration of immune cells, including F4/80$^+$ macrophages and CD8$^+$ T lymphocytes. Advanced hepatic fibrosis was observed exclusively in *Dnmt1*-deficient livers after six months of WD. Transcriptomic profiling indicated strong enrichment of oxidative stress- and mitochondrial dysfunction-related signatures. Metabolomic analysis further demonstrated increased glutamate and reduced glutathione levels in *Dnmt1* KO livers.

Conclusion: Hepatocyte-specific loss of *Dnmt1* exacerbates immune cell infiltration during the development of MASLD/MASH, resulting in aggravated hepatic injury and fibrosis. These data highlight epigenetic dysregulation as a critical driver of disease progression and point to DNMT1-dependent mechanisms as potential therapeutic targets.

PO6-03
Metabolic overload alters secretion and molecular signature of extracellular vesicles released by hepatocytes and stellate cells

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Background and aims: Extracellular vesicles (EVs) represent a potential source of biomarkers due to their stability, abundance in the blood and their molecular cargo reflecting status of the cell of origin. The aim of our study was to characterize liver cells derived EVs as perspective circulating MASLD biomarker.

Method: MASLD-like condition was induced in HepG2 hepatocytes and primary human hepatic stellate cells (HSCs) by supplementation of high glucose, fructose, insulin and palmitate to culture medium. EVs secreted by the cells under standard or metabolically stressed conditions were isolated using size exclusion chromatography. Particle concentration and size of EVs were analyzed by Nanoparticle tracking analyzer. Proteomic composition of EVs was characterized by mass spectrometry.

Results: Metabolic stress significantly enhances EVs secretion from both hepatocytes and HSCs ($p < 0.01$) in addition to alterations in nanoparticle size disribution ($p < 0.05$). Untargeted proteomic characterization of EVs secreted by hepatocytes and activated HSCs under metabolic stress identified enrichment of proteins related to cytokine signalling and extracellular matrix organisation, respectively, as altered biological processes according to Reactome pathway analysis. Interestingly, similar pattern was also observed on the level of EVs surface proteins.

Conclusion: EVs release and cargo mirror metabolic overload of hepatocytes as well as HSCs activation. These findings show that EVs signature clearly differentiate cellular states and highlight the potential of EVs as non-invasive biomarkers. Particularly, deciphering the surfaceome of liver cells derived EVs offers a promising strategy to monitor MASLD onset and progression in the blood by tracking specific EVs subpopulations.

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PO6-06-YI

Picroside I and II prevent fatty acid induced steatosis via modulation of mitochondrial biogenesis and autophagy in Huh 7 cells

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Background and aims: Steatotic Liver Disease (SLD) is a broad term that refers to conditions where fat accumulates in hepatocytes, exceeding 5% of liver weight or affecting more than 5% of hepatocytes histologically. Picrosides are bioactive iridoid glycosides found primarily in the medicinal plant *Picrorhiza kurroa*, known for their potent hepatoprotective, antioxidant, and anti-inflammatory properties. There is currently no approved pharmacological treatment for SLD, with management relying primarily on lifestyle modification. In the present study, the protective efficacy of picroside I and II against steatosis was studied using combination of *in silico* and *in vitro* approaches.

Method: Receptor protein structures were retrieved from the Protein Data Bank, refined using PyMol and Chimera for energy minimization, and converted to .pdbqt format in AutoDock Tools. Physicochemical, pharmacokinetic, and toxicity profiles were predicted using ADMETLab-3.0, ProTox-3.0, and CarcinoPred-EL, followed by protein–ligand docking with InstaDock (QuickVina-W) and visualization in PyMol. Cytoprotective effects were evaluated against palmitate oleate (PO) induced toxicity using MTT assay. Intracellular ROS, lipid accumulation, and mitochondrial potential were analyzed using DCFDA, Nile red, and JC-1 staining, respectively, with fluorescence microscopy and ImageJ quantification. Further analyses included ELISA for cytokines, qRT-PCR for gene expression and mtDNA copy number, western blotting for protein expression validation.

Results: Docking studies showed that picrosides I and II had moderate to high binding affinity with proteins regulating mitochondrial biogenesis and autophagy. In PO-induced steatotic Huh7 cells, picrosides significantly reduced lipid accumulation, triglycerides, ROS, and lipid peroxidation, while improving mitochondrial membrane potential and mtDNA copy number. Picrosides, mainly picroside II downregulated lipogenic genes and upregulated mitochondrial biogenesis related genes. Autophagy impairment was indicated by the altered expressions of autophagy markers in the PO-treated Huh7 cells. Picroside I and II treatment helped to restore the autophagic flux by improving the expressions of various autophagy biomarkers.

Conclusion: In conclusion, the picroside I and II effectively prevented the steatosis by lowering the lipogenesis and oxidative stress which improved the mitochondrial biogenesis and autophagic reflux in the hepatic cells.

PO6-08
Fumaric acid as a novel non-invasive biomarker for identifying metabolic dysfunction-associated steatohepatitis in obese subjects

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Background and aims: Metabolic dysfunction-associated steatohepatitis (MASH) represents the progressive and clinically significant stage of metabolic dysfunction-associated steatotic liver disease (MASLD), closely linked to hepatic fibrosis, liver-related mortality, and cardiometabolic complications. Mitochondrial dysfunction and impaired tricarboxylic acid (TCA) cycle flux are key metabolic features underlying the progression from simple steatosis to steatohepatitis. Fumaric acid, a major intermediate in the TCA cycle, may therefore serve as a potential non-invasive biomarker reflecting mitochondrial dysfunction in MASH.

Method: A total of 64 patients who underwent histologically confirmed evaluation for MASLD at Gachon University Gil Medical Center between March 2018 and January 2023 were included in this study. The mean age was 65 ± 10 years, 75% were female, and the mean body mass index (BMI) was 37.1 ± 5.9 kg/m². Based on histologic findings, 16 patients were classified as MASH (NAS≥5) and 48 as non-MASH (NAS<5). Plasma metabolomic profiling was performed to analyze fatty acids, organic acids, and amino acids using GC–MS/MS after derivatization as tert-butyldimethylsilyl (TBDMS)-, methoxime (MO)-TBDMS-, and ethoxycarbonyl (EOC)-TBDMS derivatives, respectively.

Results: Plasma fumaric acid levels were significantly lower in MASH compared with non-MASH subjects (2.35 vs. 3.80 ng/L, $p < 0.01$). When analyzed as a continuous variable, lower fumaric acid levels were independently associated with the presence of MASH (odds ratio 0.52, 95% CI 0.33–0.81, $p = 0.004$). A cutoff value of < 2.5 ng/L yielded a sensitivity of 75.0%, specificity of 81.2%, and AUROC 0.781 (95% CI 0.642–0.921, $p = 0.001$) for diagnosis of MASH.

Conclusion: Plasma fumaric acid levels are significantly decreased in histologically confirmed MASH, likely reflecting impaired mitochondrial TCA cycle activity. These findings suggest that fumaric acid may serve as a simple and reliable non-invasive biomarker for identifying MASH among patients with MASLD.

PO6-09-YI

Attenuation versus backscatter for the non-invasive quantification of hepatic steatosis in metabolic dysfunction–associated steatotic liver disease

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Background and aims: Quantitative ultrasound techniques are increasingly used as non-invasive tools for assessing steatotic liver disease (SLD), particularly metabolic dysfunction–associated steatotic liver disease (MASLD). Among them, Quantification Attenuation Imaging (QAI, Esaote) and Quantification Scattering Imaging (QSI, Esaote) provide attenuation- and backscatter-based parameters for hepatic steatosis evaluation. However, their clinical performance and mutual relationship have not yet been systematically validated. This study aimed to investigate the correlation of QAI and QSI with histological steatosis grade, their distribution across steatosis categories, and their diagnostic accuracy, both individually and in combination.

Method: This prospective monocentric study included 66 patients (27 men, 39 women; mean age 57.9 ± 15.2 years; mean body mass index [BMI] 30.3 ± 7.0 kg/m²) who underwent liver biopsy and multiparametric ultrasound examination. Histological steatosis was graded from S0 to S3. Spearman's rank correlation coefficients between QAI, QSI, and the histological percentage of steatosis were calculated. Differences among grades were tested using the Kruskal–Wallis and Mann–Whitney tests. Diagnostic accuracy for ≥S1 and ≥S2 steatosis was assessed through receiver operating characteristic analysis using predefined and Youden index–optimized cut-offs.

Results: QAI and QSI were moderately correlated with each other ($\rho = 0.38$, $p < 0.01$) and strongly correlated with histological steatosis (QAI $\rho = 0.73$; QSI $\rho = 0.68$; both $p < 0.0001$). The combined QAI–QSI index achieved an even stronger correlation ($\rho = 0.81$, $p < 0.0001$). Median QAI and QSI values increased progressively from S0 to S3 (QAI: 0.51, 0.58, 0.70, 0.75 dB/cm/MHz; QSI: 0.86, 0.99, 1.04, 1.07; $p < 0.001$ for both), with significant differences between S0–S1 and S1–S2 for QAI, and between S0–S1 for QSI. Area under the receiver operating characteristic curve (AUC) values were 0.83 and 0.93 for QAI (≥S1, ≥S2), 0.87 for QSI (≥S1), and 0.93 and 0.94 for the combined index, with sensitivity range 92–100% and specificity 81–84%.

Conclusion: QAI and QSI show strong correlation with histological steatosis grade and high diagnostic accuracy. Their combination further improves performance, suggesting that attenuation- and backscatter-based quantitative ultrasound parameters may serve as reliable non-invasive biomarkers for hepatic steatosis within the spectrum of metabolic dysfunction–associated steatotic liver disease.

PO7-01
Genetic and pharmaceutical manipulation of H3K9 methyltransferase Suv39h1 promotes liver regeneration by unleashing HMGB2 transcription

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Background and aims: The liver possesses a remarkable capacity to regenerate after injury,but the underlying epigenetic mechanisms controlling this process remain incompletely understood. This study investigates the role of Suv39h1, a histone methyltransferase that modifies H3K9, in regulating liver regeneration. The aim was to determine how this epigenetic regulator influences the liver's regenerative capacity and to identify the molecular pathway involved.

Method: The research employed a comprehensive approach using mouse models of partial hepatectomy.Genetic strategies included both systemic and hepatocyte-specific deletion of Suv39h1. Pharmacological inhibition was achieved using chaetocin. Molecular analyses included RNA sequencing to identify targets, HMGB2 knockdown experiments, and transcriptomic analysis. Human validation was performed using samples from acute liver failure patients.

Results: The study yielded a clear mechanistic pathway.First, Suv39h1 was found to be actively repressed during regeneration, a process controlled by another enzyme, DNMT1. Genetically deleting Suv39h1 in mice significantly enhanced liver regrowth and improved survival after surgery. RNA sequencing identified the High-mobility group protein B2 (HMGB2) as a critical downstream target gene normally repressed by Suv39h1. The mechanism involves the removal of Suv39h1, which then allows the transcription factor E2F1 to bind to and activate the HMGB2 gene. The importance of HMGB2 was confirmed, as silencing it blocked liver cell proliferation and impaired regeneration. Crucially, treating mice with the drug chaetocin successfully boosted regeneration, mirroring the genetic results. Finally, in human patients, a significant correlation was found where low SUV39H1 levels corresponded with high HMGB2 and high levels of cell proliferation markers, underscoring the pathway's relevance to human disease.

Conclusion: This research identifies Suv39h1 as a major epigenetic brake on liver regeneration.It operates by repressing the HMGB2 gene, and when this brake is released—either genetically or pharmacologically—HMGB2 expression drives a pro-regenerative program. The findings demonstrate that targeting Suv39h1 is a viable and promising therapeutic strategy to enhance the liver's innate healing capacity, potentially benefiting patients recovering from liver surgery or acute injury.

PO7-03-YI

Modulation of inflammation in the liver–adipose tissue axis by extra virgin olive oil–derived polyphenolic compounds in metabolic dysfunction–associated steatohepatitis

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) affects over 30% of adults worldwide, is strongly associated with obesity, and currently lacks approved pharmacological therapies. Dysfunctional visceral adipose tissue (VAT) is considered a key driver of progression towards metabolic dysfunction-associated steatohepatitis (MASH), thus representing a potential therapeutic target. Extra virgin olive oil (EVOO)-derived polyphenolic compounds, known for their multiple beneficial effects, may offer a promising strategy to target the liver-VAT axis in MASH.

Method: The *in vitro* liver-VAT co-culture model was established using Huh7 hepatocytes and VAT explants from morbidly obese subjects with histologically confirmed MASLD. Hepatocyte intracellular lipid accumulation (steatosis) was quantified by BODIPY 493/503 staining. Inflammatory response was assessed by real-time PCR of interleukin-8 (IL-8), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-alpha), and by ELISA for TNF-alpha. Oleocanthal (OC), a representative polyphenolic compound of EVOO, at the daily recommended dose of 30 µM, was used to test the effects on the liver-VAT axis.

Results: Direct co-culture with VAT induced lipid accumulation in hepatocytes by approximately 25% ($p < 0.05$). VAT exposure also upregulated the expression of several proinflammatory cytokines in hepatocytes, including IL-8, IL-6, and TNF-alpha (4.1-,1.5-, and 1.8-fold increases, respectively; $p < 0.05$). Treatment with OC (30 µM) significantly reduced the expression of these cytokines in hepatocytes co-cultured with VAT (1.4-, 1.6-, and 2.2-fold decreases, respectively; $p < 0.05$). Moreover, OC attenuated inflammation within VAT itself by lowering IL-8, IL-6, and TNF-alpha expression (1.9-, 1.4-, and 1.2-fold decreases, respectively; $p < 0.05$), as well as secreted TNF-alpha levels (2.1-fold decrease; $p < 0.05$). However, OC did not significantly affect VAT-induced steatosis in hepatocytes.

Conclusion: This study demonstrated that VAT explants from MASLD patients could induce MASH phenotype in hepatocytes by promoting steatosis and inflammation in direct co-culture. A major EVOO polyphenolic compound, OC, exerted anti-inflammatory effects on the liver-VAT axis, suggesting a modulatory role in MASH-associated pathophysiological mechanisms in obesity. These findings support a potential protective role of EVOO consumption in preventing or attenuating MASLD progression.

PO7-06-YI

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 enhance 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 (ST) approach.

Method: ST was performed by Visium CytAssist and data were analyzed using the Spaceranger count pipeline (10x Genomics). Patients, featured by a similar histological severity, were wild type (WT), homozygous for PNPLA3, MBOAT7, TM6SF2 polymorphisms and carriers of the 3 at-risk variants (3NRV) (n=2/group).

Results: All samples were integrated and clustered at 0.5 resolution allowing the identification of 7 clusters (cl), annotated 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 and cl6 were more abundant in 3NRV patients compared to WT. Then, we conducted a Pathway-enrichment analysis by considering differentially expressed genes (DEGs; Log2FC>0.5 and padj<0.05) of 3NRV *vs* all samples. The former exhibited increased lipid metabolism, oxidative damage, inflammation, fibrosis, and ferroptosis reflecting a worse clinical *scenario*. In details, we found that in patients carrying TM6SF2 and MBOAT7 variants, ferroptosis was mainly espressed in immune cells whereas in *PNPLA3* and more so in those with 3NRV it featured also HEPs. Moreover, cl6 showed the strongest upregulation of a metabolic ferroptosis, driven by lipid buildup and mitocondrial dysfunction. Finally, we discriminated a signature of 51 unique genes related to ferroptosis and to its regulatory pathways, which were uregulated only in 3NRV patients, thus rappresenting a pathognonomic feature of the “genetic” subtype of MASLD.

Conclusion: The co-presence of *PNPLA3*, *MBOAT7*, and *TM6SF2* variants may accelerate liver injury by triggering a lipid-metabolism and mitochondrial ferroptosis in both HEPs and NPCs. Thus, ferroptosis could be a potential druggable signature to tackle 3NRV MASLD patients.

PO7-07

Combined effect of Atorvastatin and Ambrisentan on the hemodynamic alterations and liver fibrosis in a translational rat model of MASLD with advanced fibrosis

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Background and aims: Metabolic-dysfunction Associated Steatotic Liver Disease (MASLD) is characterized by hepatic steatosis, which can progress to inflammation, fibrosis, and portal hypertension (PH). Previously, our group developed a non-fibrotic NASH model, which, when treated with Atorvastatin (Ato) and Ambrisentan (Amb) reduced steatohepatitis and PH. Considering the results in the NASH model, here we evaluate the combined effect of Ato and Amb on liver fibrosis, endothelial dysfunction, and hemodynamic alterations in a recently developed translational model of MASLD with advanced fibrosis.

Method: For model development, male Sprague-Dawley rats were fed for 20 weeks with control diet or high-fat high-cholesterol diet (2% Chol + 0.1% Cholic Acid) with glucose/fructose beverage. During the last four weeks the rats received daily vehicle, 10 mg/kg Ato, 2 mg/kg Amb, or both. At end-point liver hemodynamic was assessed. Blood and liver samples were used for histological evaluation (H&E and Sirius Red), and gene and protein analysis for fibrosis, insulin signaling and endothelial function.

Results: MASLD rats exhibited increased AST/ALT, PH, insulin resistance, steatohepatitis and advanced fibrosis, corresponding to our known model features. Neither Ato nor Amb alone or combined reduced body weight or reverted insulin resistance. Endothelial dysfunction was mildly reversed by AtoAmb, indicated by restored levels of P-Enos and KLF2. Markedly, AtoAmb led to fibrosis regression, evidenced by 1) decreased histological fibrosis stage, 2) reduced collagen deposition, 3) downregulation of Col1, alpha-SMA to near-control levels, and 4) lower levels of metalloprotease inhibitor TIMP1. However, severe steatosis and PH remained largely unaffected. Correlation analyses showed poor association between portal pressure and fibrosis, but a stronger correlation between portal pressure and steatosis severity, suggesting steatosis as the main driver to sinusoidal compression and so PH.

Conclusion: The combination of Ato and Amb demonstrated a synergistic effect reversing liver fibrosis in a translational rat model of MASLD but failed to reduce PH, likely due to persistent severe steatosis and sinusoidal compression. These findings highlight the dissociation between fibrosis and portal pressure in advanced MASLD and emphasize the need for multi-targeted strategies addressing both lipid accumulation and fibrosis for effective PH management.

PO7-10-YI
Chaperone-mediated autophagy modulates the hepatic proteome and disease severity in MASH

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Background and aims: Chaperone-mediated autophagy (CMA) is a selective type of autophagy which facilitates the lysosomal degradation of a broad group of proteins involved in the regulation of key metabolic pathways, the cell cycle, and cell death, among others. Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common chronic liver disease in western countries, representing the beginning of a spectrum of disease that can progress to metabolic dysfunction-associated steatohepatitis (MASH), liver fibrosis and cirrhosis, and ultimately hepatocellular carcinoma (HCC). More severe presentations of disease are more likely as patient age increases; concurrent with and potentially underlying this increased risk is a decline in CMA activity with age. Considering the well-established roles of CMA in the regulation of liver metabolism, we hypothesized that CMA failure with age may exacerbate MASLD severity.

Method: In order to investigate alterations in CMA activity during MASLD development and progression, as well as the consequences of CMA decline, we have used publicly available human datasets from patients with MASLD and its more progressive manifestations and applied chemical-plus-diet models of MASLD and its progression to HCC to transgenic mice that constitutively express a fluorescent reporter of CMA activity or lack CMA either systemically or specifically in hepatocytes. We have used orally bioavailable compounds that selectively modulate CMA to evaluate the therapeutic potential of this pathway during MASH.

Results: There is a cell type-specific upregulation of CMA activity in the livers of mice with MASLD that tapers as disease becomes more severe, mirroring CMA alterations seen in the human condition. This early upregulation of CMA is protective, as exposure of mice that lack CMA to the same interventions results in worsened disease, including steatosis reduction, increased liver fibrosis, and increased hepatic immune infiltration. These alterations are mediated by a failure of CMA-dependent degradation of proteins involved in cellular pathways related to inflammation, mitochondrial integrity and cellular respiration, and protein translation. In the setting of MASH, pharmacologic CMA upregulation ameliorates disease severity, resulting in reduced steatosis, fibrosis, and lobular inflammation.

Conclusion: Our results reveal a previously unexplored role of CMA in modulating MASLD progression and severity, as well as a novel therapeutic avenue for patients affected by MASH.

PO7-15-YI
Dysregulation of the urea cycle enzymes determines a more severe MASLD phenotype in a DIAMOND preclinical model

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Background and aims: (i) to characterize the DIAMOND model under different dietary regimens and (ii) to evaluate changes in urea cycle enzymes (UCEs) in DIAMOND.

Method: DIAMOND mice (n = 35) were randomized to three dietary regimens and duration: high-fat diet supplemented with fructose/glucose in drinking water (HF-HFD; 21w, 30w and 52w), choline-deficient high-fat diet model supplemented with 0.1% methionine (CDA-HFD, 16w) or chow diet (21w, 30w and 52w). Anthropometric, biochemical, and hepatic profiles were evaluated, and animals were included in metabolic cages. TUNEL assay, a panel of pro-inflammatory and pro-fibrogenic markers, and hepatic expression of UCEs by qRT-PCR were performed. Finally, an oral glutamine challenge (OGC), microbiota analysis and histopathological evaluation by an expert pathologist were performed.

Results: HF-HFD mice developed metabolic syndrome, unlike CDA-HFD mice. HOMA-IR and HOMA-beta showed insulin resistance with partial depletion of beta-cell function in HF-HFD mice. CDA-HFD mice showed insulin sensitivity and normal beta-cell function. Both interventions increased profibrogenic, proinflammatory and apoptotic markers, especially in CDA-HFD and HF-HFD mice at 30 weeks. Both groups showed NAS Scores > 5, with ballooning and grade 1 of fibrosis. A decrease in the expression of UCEs was observed: carbamoyl phosphate synthetase I (CPS1) (fold change (FC) 0.66; $p = 0.05$), argininosuccinate synthase 1 (ASS1) (FC 0.57; $p < 0.05$) and argininosuccinate lyase (ASL) (FC 0.42; $p < 0.05$) in the presence of ballooning, and CPS1 (FC 0.58; $p < 0.01$), ornithine carbamoyltransferase (OTC1) (FC 0.82;$p < 0.05$) and ASL (FC 0.42; $p = 0.05$) in fibrosis. A significant increase in GLS1 was observed in the presence of ballooning (FC 2.50; $p < 0.01$) and fibrosis (FC 2.90; $p < 0.0001$). Ammonia production after SOG was significantly higher in CDA-HFD (AUC = 7269 ± 1276, $p < 0.05$) and HF-HFD at 52w (AUC = 10755 ± 1452, $p < 0.05$) compared to baseline controls (AUC = 3855 ± 187.7). Microbiota analysis revealed that groups differed in their bacterial species composition, and PICRUST analysis identified 17 differentially expressed pathways with ammonia as an intermediate or end product.

Conclusion: DIAMOND mice showed urea cycle dysregulation under different dietary interventions leading to a compromised ammonia metabolism. CDA-HFD induced a faster and more aggressive liver phenotype without the presence of metabolic syndrome, whereas HF-HFD more closely mirrored the metabolic phenotype seen in humans.

PO8-02-YI
Targeting RIPK3 as a mediator of hepatocyte-macrophage crosstalk in MASLD

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Background and aims: RIPK3 contributes to metabolic dysfunction-associated steatotic liver disease (MASLD) pathogenesis, but its cell-specific roles remain unclear. Here, we aimed to examine RIPK3 function in hepatocytes and macrophages under metabolic stress and develop novel chemical RIPK3 inhibitors.

Method: Co-cultures using wild-type (WT) and *Ripk3*-deficient AML12 hepatocytes and J774A.1 macrophages were treated with palmitic acid (PA), followed by evaluation of cell death and inflammatory responses. Dose-response assays were performed in L929 and HT29 cells to assess the potency of candidate RIPK3 inhibitors.

Results: *Ripk3* deletion protected hepatocytes from PA-induced cell death. Strikingly, *Ripk3* deletion in hepatocytes induced pro-inflammatory markers in macrophages, alongside upregulation of the anti-inflammatory *Arg1*, suggesting RIPK3 role in macrophage polarization and possibly linking inflammatory response to tissue repair under metabolic stress. In line, when co-cultured with macrophages, PA-treated *Ripk3*$^{-/-}$ hepatocytes exhibited enhanced repair capacity compared to their WT counterparts, reinforcing the therapeutic potential of RIPK3 inhibition.

To further explore RIPK3-targeted therapies, initial structure-activity relationship studies were conducted based on hits from previous high-throughput screening. These studies revealed a strong correlation in compound activity between human and murine cells and identified critical loss-of-function substitutions, supporting the translational potential of the chemical series and informing the design of more potent and selective RIPK3 inhibitors.

Conclusion: Overall, our findings support RIPK3 as a promising therapeutic target in MASLD, capable of limiting hepatocellular death and promoting repair. Continued development of selective RIPK3 inhibitors may open new avenues for treating MASLD.

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PO8-12-YI

Transcriptional dysregulation of hepatocyte-specific factors in chronic liver disease: A potential biomarker panel

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Background and aims: Chronic liver disease (CLD) remains a major global health burden, with limited biomarkers available for early diagnosis and disease progression monitoring. This study investigates the differential expression of hepatocyte transcription factors in various stages of CLD and their correlation with biochemical and clinical parameters. The aim is to identify potential molecular biomarkers that can aid in early diagnosis and improve disease prognosis.

Method: A total of 100 patients with chronic liver disease (CLD), including (NAFLD, N= 30), (ALD, N= 30), and (DCLD,N= 30), were enrolled in the study, along with 10 controls. Venous blood samples were collected from all participants and processed for RNA extraction followed by reverse-transcription into cDNA. Quantitative qPCR was performed to evaluate the expression of key hepatocyte transcription factors, including HNF1A, HNF4A, APO, CEBPA, and EGR, with GAPDH as the control. Fold-change analysis and Statistical analyses was conducted to determine expression patterns, comparing transcription factor expression levels and evaluating the significance.

Results: Fold-change analysis demonstrated transcriptional dysregulation of hepatocyte-specific factors in patients with chronic liver disease (CLD) relative to healthy controls. HNF1A and HNF4A were markedly
downregulated in decompensated chronic liver disease (DCLD), reflecting impaired hepatocyte functionality and structural integrity. CEBPA and APO exhibited distinct expression patterns in NAFLD and ALD cohorts, underscoring their involvement in lipid homeostasis and inflammatory modulation. EGR expression was highly heterogeneous across disease phenotypes, suggesting a context-dependent
role in hepatic regeneration and fibrogenesis. Crucially, these transcriptional alterations displayed correlations with biochemical indices as well as key clinical parameters, reinforcing their relevance as candidate non-invasive biomarkers for monitoring liver function, disease progression, and prognostic stratification in CLD.

Conclusion: Our study highlights the potential of hepatocyte-specific transcription factors as novel molecular biomarkers for chronic liver disease. The observed transcriptional dysregulation suggests their critical role in disease progression and supports the possibility of early diagnostic applications. Further
validation in a larger cohort with diverse etiologies could strengthen the clinical utility of these biomarkers for evidence based clinical decisionmaking in hepatology.

PO8-15
SIRT4 enhances NK cell cytotoxicity against hepatic stellate cells and reverses liver fibrosis via the AMPKα/p53/NKG2DL axis

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Background and aims: Natural killer (NK) cells possess potent antifibrotic activity in liver fibrosis (LF) by directly targeting and suppressing activated hepatic stellate cells (HSCs). SIRT4, a key mitochondrial regulatory protein, is known to bridge cellular energy metabolism and viability. Nevertheless, its specific role in regulating NK cell-mediated cytotoxicity against HSCs has remained undefined.

Method: We employed in vitro cellular assays and in vivo liver fibrosis mouse models to investigate SIRT4 function. We assessed NK cell cytotoxicity against HSCs via LDH release and CD107a degranulation assays, and detected AMPKα-p53-ULBP1/2 pathway activation using Western blotting and qRT-PCR. We further validated therapeutic efficacy by delivering HSC-targeted SIRT4 vectors to fibrosis mice, with fibrosis severity evaluated via H&E, Masson's trichrome staining and fibrosis marker quantification.

Results: We observed a significant downregulation of SIRT4 in activated HSCs, in mouse models of LF (induced by CCl_4 or DDC), and in liver tissues from patients with fibrosis. Functional studies revealed that SIRT4 overexpression in HSCs enhanced their susceptibility to NK cell-mediated killing, whereas SIRT4 knockdown impaired it. Mechanistically, SIRT4 activates AMPKα, leading to enhanced phosphorylation and nuclear translocation of p53. Activated p53 directly binds to the promoters of ULBP1 and ULBP2, key ligands for the NKG2D receptor, and transactivates their expression. This SIRT4-AMPKα-p53 signaling axis thereby upregulates NKG2D ligands on HSCs, promoting NK cell recognition and cytotoxicity. Therapeutically, HSC-specific overexpression of SIRT4 via an adeno-associated virus vector (AAV8-pGAFP-SIRT4) activated hepatic NK cells, enhanced the clearance of activated HSCs, and effectively attenuated liver injury and fibrosis in mice. This antifibrotic effect was abolished upon NK cell depletion.

Conclusion: Our findings establish SIRT4 as a critical regulator of NK cell cytotoxicity against HSCs, operating through the novel AMPKα-p53-ULBP1/2 pathway. HSC-targeted SIRT4 gene therapy represents a promising and novel therapeutic strategy for the treatment of liver fibrosis.

POSTER ABSTRACT PRESENTATIONS

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Clinical Science

PO1-03-YI

Simplified metabolic dysfunction Associated Fibrosis-5 (sMAF-5) score to identify at-risk liver fibrosis and to predict prognosis

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Background and aims: Metabolic dysfunction Associated Fibrosis - 5 (MAF-5), a waist-circumference-based non-invasive test (NIT) for fibrosis risk stratification, has emerged as a well-performing test in low-prevalence populations. Waist circumference is often not available, which hampers the utility of the MAF-5. Therefore, we developed and validated the simplified MAF-5 (sMAF-5), which could be used when waist circumference is unavailable.

Method: US representative individuals from NHANES 2017-2020 with metabolic dysfunction were selected with complete data on score components, and the outcome was defined as LSM ≥ 8 kPa. Correlation between MAF-5 and sMAF-5 was assessed using Pearson's correlation coefficient. AUC analysis was used to compare sMAF-5 to other scores with the DeLong test for assessing statistically significant differences. sMAF-5 was validated in US representative adults (NHANES 2021-2023) and MASLD patients across a pooled cohort of 16 tertiary referral centres in the US, Europe, and Asia (VCTE Prognosis Study Group) for the presence of LSM ≥ 8 kPa and liver-related events (LRE) defined as hepatic decompensation and HCC.

Results: The derivation cohort included 6.191 adults (49% male, mean age 52 years) of whom 10.1% had LSM ≥ 8 kPa. The sMAF-5, comprising BMI, diabetes, AST, platelets, and sex, was strongly correlated with MAF-5 (r = 0.97). With sMAF-5, 61.6% were classified as low risk (sMAF-5 < 0), 14.0% as intermediate risk (0–1), and 24.4% as high risk (≥ 1), with observed LSM ≥ 8 kPa prevalence of 3.4%, 9.2%, and 27.7%, respectively. The AUC of sMAF-5 (AUC 0.803) did not significantly differ from the original MAF-5 (AUC 0.808), but was significantly better than SAFE (0.739), LiverRisk (0.715), LiverPRO (0.715), and FIB-4 (0.667). Results were validated in the independent NHANES 2021-2023 cohort (n = 4.202), yielding similar results. In the VCTE prognosis study group (12,330 MASLD patients), sMAF-5 was associated with LRE where the time-dependent AUC for LRE (all), hepatic decompensation, and HCC was 0.757, 0.793, and 0.723, respectively. The cumulative incidence of LRE was 0.6% in individuals with sMAF-5 < 0 and 4.0% (6.3 times higher) for sMAF-5 ≥ 1 in MASLD patients.

Conclusion: sMAF-5 is a valuable replacement for the original MAF-5 as a first-line test in screening algorithms when waist circumference is unavailable, enabling the identification of adult community-dwelling individuals at high risk of liver fibrosis and future liver-related events.

PO1-05-YI
The potential role of resistin, interleukin-6, and NT-proBNP in the development of cardiac disease among patients with Type 2 diabetes mellitus

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Background and aims: Epidemiological and genetic investigations have consistently demonstrated an association between proinflammatory cytokines and the development of insulin resistance, type 2 diabetes mellitus (T2DM), and cardiovascular diseases. Among the inflammatory mediators implicated, interleukin-6 (IL-6), NH_2-terminal pro–brain natriuretic peptide (NT-proBNP), and resistin precise roles in the pathogenesis of left ventricular systolic dysfunction (LVSD) and hypertrophy remain controversial. The present study aimed to elucidate the relationship between these biomarkers and left ventricular structural and functional alterations in patients with T2DM, and to explore their potential utility as non-invasive indicators for early prediction of left ventricular remodeling.

Method: This case–control study included 150 participants, categorized according to echocardiographic findings. Group 1a consisted of 46 T2DM patients with echocardiographic evidence of systolic dysfunction, group 1b included 54 T2DM patients with preserved systolic function, while group 2 comprised 50 apparently healthy controls. All participants underwent detailed clinical evaluation, comprehensive laboratory investigations—complete blood count, liver and renal function tests, lipid profile—and serum measurement of IL-6, NT-proBNP, and resistin. Standard transthoracic echocardiography was performed with particular attention to left ventricular systolic function, assessed primarily through ejection fraction and left ventricular mass index (LVMI).

Results: The results revealed a significant elevation in serum IL-6, NT-proBNP, and resistin levels in group 1a compared with group 1b and control subjects. Echocardiographic parameters demonstrated notable increases in LVMI, posterior wall thickness, interventricular septal thickness, and left ventricular mass among patients with impaired systolic function. Furthermore, elevated levels of IL-6, NT-proBNP, and resistin exhibited strong positive correlations with increased LVMI, indicating their contributory role in myocardial remodeling and systolic impairment.

Conclusion: The close interplay between systemic inflammation, metabolic dysfunction, and cardiac structural changes in T2DM reflecting elevated IL-6, NT-proBNP, and resistin levels are significantly associated with left ventricular systolic dysfunction & hypertrophy, suggesting their potential use as early, non-invasive biomarkers for detecting subclinical myocardial damage and predicting adverse cardiac remodeling in diabetic patients.

PO1-06-YI
Comparative performance of non-invasive models for detecting clinically significant portal hypertension in MASLD

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Background and aims: Portal hypertension (PH) underpins complications of chronic liver disease, but its gold-standard assessment via hepatic venous pressure gradient (HVPG) is invasive. Non-invasive tests (NITs) offer alternatives for risk stratification, but data in metabolic dysfunction-associated steatotic liver disease (MASLD) are limited. This study systematically compared NIT performance for detecting PH and clinically significant PH (CSPH).

Method: We analysed 232 consecutive MASLD patients who underwent HVPG and liver biopsy between January 2018 and December 2024. The following NITs were compared with HVPG: NICER; MODEL-3P (PROB10, PRED); MODEL-5P (PROB10, PRED); ANTICIPATE (RISK CSPH); ANTICIPATE NASH (RISK CSPH); LSPS; Lok; FIB-4+; FIB-4; MAF-5; APRI; Forns Index; AGILE3P+; AGILE4. Diagnostic performance was assessed by AUC, sensitivity, specificity, PPV, and NPV.

Results: Of 232 patients, 81 (66%) had PH (HVPG ≥5 mmHg; mean 12.8 ± 5.9), 47 (38%) had CSPH (HVPG ≥10 mmHg; mean 17.0 ± 3.8), and 42 (18%) had normal portal pressure (mean HVPG 3.24 ± 0.88).
For PH, several NITs showed excellent performance (AUC ≥0.90). NICER (AUC 0.929; sensitivity 0.86, specificity 1.00, PPV 1.00, NPV 0.69), ANTICIPATE (AUC 0.912; sensitivity 0.93, specificity 0.70), ANTICIPATE NASH (AUC 0.909; sensitivity 0.93, specificity 0.70), and Lok (AUC 0.923) demonstrated strong accuracy. FIB-4+ also performed well (AUC 0.907). For CSPH, models maintained high performance (AUC ≥0.90). AGILE4 (AUC 0.936; sensitivity 0.93, specificity 0.70), AGILE3P+ (AUC 0.918), and NICER (AUC 0.904; sensitivity 0.95, NPV 0.95) were particularly effective in ruling out CSPH. ANTICIPATE (AUC 0.917) and ANTICIPATE NASH (AUC 0.914) showed sensitivities and NPVs >0.88.

Conclusion: In MASLD, non-invasive models integrating elastography showed high accuracy, with strong sensitivity and excellent NPVs. NITs developed for PH/CSPH outperformed fibrosis-based models. Portal-specific NITs incorporating elastography are reliable alternatives to invasive HVPG, especially for excluding CSPH in MASLD.

PO1-08-YI

Association of steatotic liver disease with hypertensive disorders of pregnancy: a systematic review and meta analysis of 74.5 million pregnant individuals

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Background and aims: The prevalence of steatotic liver disease (SLD) in pregnancy has tripled over the past decade, now affecting up to 18% of pregnant individuals. Hypertensive disorders of pregnancy (HDP), including gestational hypertension (GHTN), preeclampsia (PE), eclampsia, and HELLP syndrome, are a leading cause of pregnancy-related morbidity and mortality. While some studies demonstrate an association between SLD and HDP, emerging data are conflicting.

Method: We conducted a systematic review and meta-analysis querying PubMed, Embase, and Web of Science for articles that report on HDP in pregnant patients with SLD. Two independent reviewers screened all titles and abstracts, full texts, and extracted data. Studies were split into three groups depending on their reported outcomes: GHTN, PE, and composite outcomes of HDP. The pooled prevalence of SLD and odds ratios (OR) were calculated using random-effects models in Stata 19.

Results: Seventeen studies with 74.5 million pregnant patients and 86,525 cases of SLD were identified. Among seven studies reporting SLD prevalence, the pooled prevalence was 12% (95% CI, 7–20%). Reported SLD diagnosis methods included imaging (n=10), HSI (n=2), and ICD codes (n=4). Studies were conducted in the United States (4), Asia (9), Europe (2), Australia (1), and Africa (1). The mean age was 31.0 (3.5) among patients with SLD and 28.6 (2.3) for non-SLD patients. The pooled ORs evaluating outcomes of interest were 2.72 (95% CI, 1.79–4.13) for studies reporting on PE (n=10), 2.24 (95% CI, 1.75–2.88) for those reporting on GHTN (n=7), and 3.44 (95% CI, 2.70–4.38) for studies evaluating a composite outcome of HDP (n=10). There was significant heterogeneity across studies (I^2 = 93–97%); however, heterogeneity was decreased when studies were stratified by method of diagnosis and country. In subgroup analyses of studies that diagnosed SLD using imaging, the association between SLD and PE was no longer significant (OR = 1.69; 0.91–3.13), but the association with GHTN remained significant (OR = 2.41; 1.46–3.96).

Conclusion: Our study suggests that SLD may be associated with increased risk of HDP, including GHTN and PE. These findings highlight the role of close blood pressure monitoring and aspirin use in pregnant patients with SLD to prevent adverse outcomes. Given the high heterogeneity across studies, our future directions include conducting an individual participant data meta-analysis to better characterize patients with SLD who are at risk for HDP.

PO1-09-YI

Sacubitril/Valsartan reduced liver fibrosis in patients with MASLD and heart failure with reduction ejection fraction: an Italian pilot study

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Background and aims: Metabolic dysfunction-Associated Steatotic Liver Disease (MASLD) frequently coexists with heart failure (HF), sharing common pathophysiological mechanisms over the metabolic dysfunction, such as neurohormonal activation, systemic inflammation. Sacubitril/valsartan, an angiotensin receptor-neprilysin inhibitor (ARNI), has demonstrated significant cardiovascular benefits in heart failure patients, but its impact on hepatic fibrosis in MASLD patients remains unexplored. The cardio-hepatic crosstalk suggests that therapies targeting neurohormonal pathways may have dual organ benefits. To evaluate the effects of sacubitril/valsartan on hepatic fibrosis markers in patients with MASLD and compensated chronic heart failure with reduced ejection fraction.

Method: This prospective pilot study included 30 patients with MASLD and compensated heart failure in which treatment was initiated with sacubitril/valsartan according to current guidelines. Hepatic fibrosis was assessed using transient elastography (FibroScan) and FIB-4 score at baseline and after 6 months of treatment. Cardiac parameters including left ventricular dimensions and pulmonary artery pressures were evaluated by echocardiography. Subgroup analyses were performed based on baseline liver stiffness measurement (LSM <8 vs ³ 8 kPa).

Results: Median LSM was 7.2 kPa (IQR 5.8-9.4 kPa), and 40% (12/30) with a a LSV >8Kpa. After 6 months of sacubitril/valsartan therapy, significant improvements were observed in hepatic fibrosis markers. Overall LSM values decreased significantly (p=0.003), with more pronounced benefits in patients with baseline LSM values < 8 kPa (p=0.008) compared to those with >8 kPa (p=0.233). FIB-4 scores showed a trend toward improvement (p=0.318). Significant cardiac reverse remodelling was evident with reductions in left ventricular dimensions (p<0.0001) and improvements in ejection fraction (p=0.035). Pulmonary artery pressures showed a trend toward reduction (p=0.055). The differential response based on baseline fibrosis severity suggests that earlier intervention may be more effective.

Conclusion: This pilot study provides the first clinical evidence that sacubitril/valsartan may have beneficial effects on hepatic fibrosis in MASLD patients with heart failure, beyond its established cardiovascular benefits. Larger randomized controlled trials are warranted to confirm these preliminary observations and establish the hepatoprotective potential of sacubitril/valsartan in this high-risk population.

PO1-11-YI

Cardiovascular mortality trends in patients with metabolic dysfunction-associated Steatotic Liver Disease in the United States, 1999-2020: A population-based epidemiological study

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD), which now replaces the term NAFLD, affects over 25% of adults globally. Although MASLD can progress to severe hepatic complications, cardiovascular disease remains the primary cause of death. We utilized the CDC WONDER database to analyze cardiovascular mortality trends in individuals with MASLD in the U.S.

Method: This retrospective, population-based epidemiological study used the CDC WONDER database to identify deaths. We identified MASLD-related deaths via ICD-10 code K76.0 and circulatory system deaths using codes I00-I99. Crude (CMRs) and age-adjusted mortality rates (AMRs) were then computed, with stratification by sex, race/ethnicity, census region, and age group.

Results: Our analysis of data from 1999-2020 revealed 14,528 circulatory system-related deaths in individuals with MASLD, marking an 81.4% increase. AMRs were higher in males, White individuals, and residents of the West, whereas CMRs were higher for adults ≥ 35 years. The most significant AMR increases were among females (111.8%), White individuals (37%), and those in the Midwest (159%). The largest CMR increase was in the 75-84 age group (210.4%). The top five causes of death included atherosclerotic cardiovascular disease (2,479), atherosclerotic heart disease (2,429), hypertensive heart disease (1,958), cardiomegaly (1,056), and dilated cardiomyopathy (1,034).

Conclusion: Cardiovascular mortality among patients with MASLD has increased substantially, showing disparities by sex, race/ethnicity, age, and region. The observed increases, especially in females, White individuals, and Midwest residents, emphasize the importance of targeted prevention and management. Because cardiovascular disease is the leading cause of death in this population, integrating cardiovascular risk assessment into MASLD care pathways is critical to alleviate this rising mortality burden.

PO1-12-YI

Comparative evaluation of MAFLD versus MASLD diagnostic criteria for predicting de novo hepatocellular carcinoma risk in HCV-infected individuals following sustained virological response

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Background and aims: Patients with chronic hepatitis C virus (HCV) infection who achieve sustained virological response (SVR12) following direct-acting antiviral (DAA) therapy and present with Steatotic Liver Disease (SLD) and cardiometabolic risk factors (CMRFs) indicative of metabolic dysfunction (MD) are known to exhibit an increased risk of hepatocellular carcinoma (HCC). Two years after the Delphi consensus, the comparative utility of Metabolic dysfunction-Associated Steatotic Liver Disease (MASLD) versus Metabolic dysfunction-Associated Fatty Liver Disease (MAFLD) criteria in predicting disease progression remains unclear. This study aimed to assess the performance of MASLD and MAFLD definitions in estimating 5-year de novo HCC risk among SLD patients achieving DAA-induced HCV SVR12.

Method: Clinical, anthropometric, biochemical, Liver Stiffness Measurement (LSM), and Controlled Attenuation Parameter (CAP) data from 751 HCV-SVR12-SLD patients (January 2015 – May 2020) archived at “Luigi Vanvitelli” University Hospital were retrospectively analyzed. After excluding lean individuals (BMI < 25 kg/m²) and those with alternative etiologies of chronic liver disease (n = 101), MASLD and MAFLD criteria were independently applied, yielding three cohorts: HCV-SVR12-MASLD (n = 163), HCV-SVR12-MASLD/MAFLD (n = 390), and HCV-SVR12-MAFLD (n = 97). HCC diagnosis followed EASL guidelines and was documented over a 5-year follow-up.

Results: Baseline characteristics and prevalence of LSM-defined advanced fibrosis (AF) were comparable between HCV-SVR12-MASLD and HCV-SVR12-MAFLD groups [53 (32.51 %) vs 34 (35.05 %), p > 0.05]. MAFLD criteria demonstrated superior predictive accuracy for HCC risk compared to MASLD [HR: 1.936; 95 % CI: 1.083 – 2.375; p = 0.035], including stratification by AF status (p < 0.0001). Multivariate competing risk analysis (adjusted for sex, age, diabetes, steatosis, SVR timing, CAP, and fibrosis stage) identified diabetes (aHR: 2.051; p = 0.001), high-sensitivity C-reactive protein (aHR: 1.351; p = 0.02), and HOMA-IR (aHR: 1.219; p = 0.02) as independent predictors of HCC occurrence.

Conclusion: MAFLD criteria more accurately stratify de novo HCC risk in SLD patients achieving SVR12 following DAA therapy for HCV.

PO1-13

Steatosis speaks to the heart: early left ventricular global longitudinal strain impairment in metabolic dysfunction-associated steatotic liver disease

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) and Heart failure (HF) are rapidly growing clinical challenges. MASLD affects approximately 25% of adults worldwide and associates with a higher risk of HF. Early myocardial dysfunction, as reflected by reduced left ventricular global longitudinal strain (LVGLS) often precedes the decline in ejection fraction (EF). Understanding the relation between MASLD and impaired systolic function may provide insights for HF prevention. Our study aimed to investigate the association between MASLD and LVGLS in patients without overt cardiovascular disease.

Method: We retrospectively evaluated 58 patients with MASLD and no history of heart disease, followed at our outpatient clinic; of these 32 underwent 2D transthoracic echocardiography with speckle-tracking analysis of myocardial strain in all cardiac chambers. Diastolic dysfunction was defined as mitral E/E' > 9, systolic dysfunction as LVGLS > 17.5%. Severe liver steatosis was defined as controlled attenuation parameter (CAP) > 290 dB/m and significant liver stiffness measurement (LSM) was definied as LSM > 7 kPa. Informed consent was obtained for all participants.

Results: A total of 58 patients were included (mean age 59.4 ± 10.3 years; 48.3 % female). The mean BMI was 30.5 ± 4.6 kg/m². The most frequent comorbidities were arterial hypertension (60.3 %) and dyslipidemia (79.3 %). Hepatic steatosis was distributed as mild (10.3 %), moderate (15.5 %), and severe (36.2 %). Among the 32 patients who underwent echocardiography, the mean LVGLS was –16.9 ± 4.0. Patients with severe steatosis had significantly less negative LVGLS values compared to those without severe steatosis (- 15.4 vs - 18.7; p = 0.024); all patients had normal values of EF. Patients with LSM ≥ 7 kPa had less negative LVGLS compared to those with < 7 kPa (- 16.5 vs - 17.7), although the difference was not statistically significant (p = 0.49). Metabolic parameters (glycemia, cholesterol, insulin) were not significantly associated to LVGLS.

Conclusion: MASLD patients with severe steatosis have a significantly high frequency of impaired LVGLS, independent of age, sex, and conventional cardiovascular risk factors. LVGLS deterioration appears early in MASLD, before ejection fraction declines. Our findings support echocardiographic screening for heart failure in all patients with liver steatosis and MASLD screening for all cardiac patients.

PO1-14-YI
Non-invasive assessment of liver histology in masld using multiparametric ultrasound

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Background and aims: MASLD is an increasing cause of cirrhosis. Histology is the reference standard for assessing hepatic steatosis, inflammation and fibrosis, but its invasiveness limits follow-up use. Multiparametric ultrasound (MPUS) combining attenuation (USAT), elastography (E) and viscosity (Vi) may offer a non-invasive alternative. The study aimed to evaluate the correlation between MPUS parameters and histological findings in patients with MASLD.

Method: Prospective single-center study including 42 adult patients undergoing same day MPUS and percutaneous liver biopsy for MASLD-related indications. USAT, E and Vi were acquired as the mean of five valid measurements (IQR/M ≤30%), following WFUMB recommendations. SAF (Steatosis, Activity, Fibrosis) score and NAS (NAFLD Activity Score) score were used to grade histological steatosis, inflammation and fibrosis, and overall disease activity.

Results: 18 males and 24 females (mean age 52.9 years, BMI 30.9 kg/m²) were included. USAT values increased with steatosis grade (0.54 dB/cm/MHz in S0 to 0.82 in S3, $p < 0.0001$), showed significant association with both inflammatory activity ($p = 0.0068$) and fibrosis stage ($p = 0.023$). USAT strongly correlated with histological fat content ($\rho = 0.86$, $p < 0.001$) and differed across NAS categories ($p < 0.0001$), with higher values in NAS ≥ 5 (0.79 ± 0.08) Vs NAS ≤ 2 (0.55 ± 0.06) patients. E and Vi showed no significant correlation with fibrosis or inflammation, respectively. ROC analysis confirmed the diagnostic value of USAT for steatosis grading: AUC = 0.62 (S0 Vs S1), 0.81 (S1 Vs S2), 0.76 (S2 Vs S3). The best discrimination was between mild and moderate-to-severe steatosis (S01 vs S23) with an AUC of 0.85 (sensitivity 86.7%, specificity 80.0%) at a 0.79 dB/cm/MHz cut-off. A machine learning model combining USAT and E with AST, ALT and GGT improved detection of significant inflammatory activity ($A \geq 2$) compared to biochemical markers alone (AUC of 0.89, accuracy of 85.0%).

Conclusion: USAT showed strong correlation with histological fat content, confirming its reliability as non-invasive marker of steatosis in MASLD. Its progressive increase with inflammatory grades suggests a link between fat accumulation and inflammation. Combining MPUS parameters with biochemical markers improved prediction of steatohepatitis, supporting their use in multiparametric models for comprehensive, non-invasive MASLD assessment.

PO1-15-YI

Oleoylethanolamide as adjunct therapy for metabolic dysfunction-associated steatotic liver disease: A meta-analysis of randomized controlled trials with meta regression and trial sequential analysis

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Background and aims: Adjunct therapies for metabolic dysfunction associated steatotic liver disease are needed beyond lifestyle advice. Small randomized trials suggest oleoylethanolamide may improve biochemical and imaging outcomes, but the size of benefit, safety, and effect modifiers remain uncertain. This meta analysis evaluates the efficacy and safety of oleoylethanolamide (OEA) 250 mg/day, an endogenous ppar-alpha agonist, in improving clinical, biochemical, and molecular outcomes in adults with metabolic dysfunction–associated steatotic liver disease.

Method: We systematically searched online databases for randomized controlled trials comparing oleoylethanolamide plus hypocaloric diet versus placebo plus hypocaloric diet. We used RevMan 5.4 software with Random effects model to synthesize mean differences for alanine aminotransferase and aspartate aminotransferase and odds ratios for imaging based steatosis response and adverse events. Prespecified mixed effects meta regression tested baseline body mass index, intervention duration, sex distribution, and achieved weight loss. Trial sequential analysis assessed certainty and required information size. Molecular outcomes included gene expression of SIRT1, AMPK, PGC-1 alpha , PPAR-alpha, UCP1, UCP2, and circulating NRG4 measured by quantitative polymerase chain reaction and enzyme-linked immunoassay in included trials.

Results: Four RCTs with a total of 244 patients showed that OEA vs placebo lowered ALT (MD −12.1 IU/L, 95% CI −17.5 to −6.8; $p < 0.001$) and AST (MD −8.5 IU/L, 95% CI −13.2 to −3.9; $p = 0.001$) and improved imaging-based steatosis response (OR 1.61, 95% CI 1.06–2.45; $p = 0.026$). Lipids also improved: triglycerides (MD −16.8 mg/dL, 95% CI −27.9 to −5.7; $p = 0.003$), and HDL-C (MD +3.0 mg/dL, 95% CI 0.6–5.4; $p = 0.014$). Adverse events were non-significant. Meta-regression suggested partial mediation by weight loss for ALT (17% attenuation per kg; $p = 0.03$); other moderators were non-significant (all $p > 0.10$). TSA indicated conclusiveness for ALT and AST but not for steatosis or lipid endpoints. OEA activated fat-metabolism pathways: it increased PPAR-alpha, UCP1, and UCP2 expression (all $p \leq 0.025$), raised SIRT1 ($p = 0.001$), PGC-1 alpha ($p = 0.011$), AMPK ($p = 0.019$), and boosted NRG4 ($p = 0.027$).

Conclusion: OEA plus calorie restriction improves liver enzymes and imaging response in MASLD with neutral safety. Molecular signals such as SIRT1 and AMPK support the mechanism. Larger, longer trials are needed to confirm these findings.

PO1-16
Barriers and operational challenges in implementing a multidisciplinary and multicentre clinical study involving laboratories, primary care physicians, and hepatologists: Insights from the CARPA study

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Background and aims: Multidisciplinary and multicentre clinical studies are essential for generating high-quality evidence in the definition of clinical pathways in MASLD. However, studies involving multiple stakeholders—such as primary care, laboratories, and Liver units—face substantial operational challenges that can compromise data quality, timelines, and feasibility. The main aim was to identify and characterise key barriers during the implementation of a clinical study (CARPA) requiring multidisciplinary approach and to propose strategies to enhance coordination and data quality.

Method: CARPA is a multicenter study carried out in Spanish Centers. Patients identified in primary care showing FIB-4≥1.3 were randomised to Arm A: patients underwent an ELF test, or Arm B: patients underwent Vibration Controlled Transient Elastography (VCTE), and were referred to liver unit when VCTE ≥ 8kPa or ELF≥9.8. Barriers identified were categorised into thematic domains: (1) coordination and communication, (2) operational and logistical, (3) data management and quality, (4) regulatory and ethical, (5) financial and administrative, and (6) methodological aspects. For each domain, mitigation strategies were identified based on best practices in multicentre multistakeholder trial management.

Results: 13 centers from 10 autonomous communities in Spain were invited and 4 failed to get green card, mainly due to inability to build a multidisciplinary team. Selection of patients in primary care, lab circuits training and patient referral were the key bottlenecks in the clinical pathway. During the first 12 months, a 21% of target patients (1,633/7,866) were included. Major barriers were lack of interoperability between laboratory systems (n=5), poor communication pathways in multidisciplinary teams, ethics approvals and contracting causing delays (n=4), and variability in resources and staff engagement across sites (n=4).
Recommended strategies included using standardised operating procedures and improving shared digital data capture systems, harmonising regulatory submissions, and implementing continuous training and quality assurance frameworks.

Conclusion: Successful implementation of multicenter clinical studies involving laboratories, primary care, and liver units requires proactive planning, standardised workflows, and strong communication frameworks. Early identification of operational barriers and coordinated governance structures can substantially improve study efficiency, data integrity, and stakeholder engagement.

PO2-03-YI

Monocyte PLIN2 expression is a metabolic marker of obesity and metabolic dysfunction-associated steatohepatitis (MASH), independent of type 2 diabetes, reflecting an altered metabolomic profile

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Background and aims: Metabolic dysfunction-associated steatohepatitis (MASH), obesity and type 2 diabetes (T2D) are characterized by metabolic dysfunction and inflammation. Perilipin 2 (PLIN2) has a key role in lipid metabolism and its expression in monocytes has been associated with the severity of MASLD/MASH. The hypothesis is that circulating PLIN2 could reflect metabolic/inflammatory status of the liver. The aim was to elucidate whether PLIN2 expression in monocytes is associated with a metabolic signature of metabolic syndrome.

Method: We included 190 individuals (114 with and 76 without MASH) and stratified by obesity and/or T2D. Insulin resistance indexes (HOMA-IR and Adipo-IR) were calculated, and PLIN2 expression was measured in monocytes isolated from PBMCs. Mass spectrometry-derived metabolomic and lipidomic data were assessed in all participants.

Results: PLIN2 expression in monocytes was higher in obese subjects without T2D or MASH compared to non-obese ($p = 0.031$), and significantly elevated in individuals with MASH, independently of T2D status. PLIN2 showed strong positive correlation with age, BMI, glycemia, HbA1c, insulin, free fatty acids (FFA), HOMA-IR and Adipo-IR ($rho > 0.35$, $p < 0.001$). Furthermore, it was associated with histological features of liver damage including lobular inflammation, hepatocytes ballooning, steatosis severity and presence of fibrosis. Metabolomic and lipidomic profiling revealed positive correlation between PLIN2 and metabolites such as lactate, branched-chain amino acids (BCAAs), lysine, leucine, Cer(d18:1/22:0), glutamic acid, PC42:1, PC42:2, Cer(d18:0/22:0) and DAG34:1, which remained significant after adjusting for HOMA-IR, BMI, sex, age and NAS. In contrast, some metabolites and lipids indexes showed negative correlations with PLIN2, but lost significance after adjustment.

Conclusion: Elevated PLIN2 expression in circulating monocytes characterizes individuals with obesity and MASH, independent of T2D, and reflects underlying hepatic injury. Its association with insulin resistance and specific metabolomic and lipidomic profiles further supports a functional link between adipose tissue metabolism and liver pathology. These findings position monocyte PLIN2 as a promising noninvasive biomarker for assessing hepatic damage and metabolic risk, and as a potential tool for liquid biopsy–based monitoring of MASH progression.

PO2-04

Repeatability and reproducibility of hepatic steatosis quantification by controlled attenuation parameter across different stages of steatotic liver disease

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Background and aims: Assessment of hepatic steatosis is key for diagnosis and monitoring of steatotic liver disease (SLD), especially in the era of etiologic treatments. While guidelines recommend imaging methods such as the controlled attenuation parameter (CAP), concerns regarding its precision and reproducibility question its use as monitoring tool.

Method: We assessed the repeatability (same day, same operator), and reproducibility (different day) of CAP and FibroScan–AST (FAST) score in subjects with (suspected) SLD of different severity. Repeatability was tested in individuals with suspected SLD in secondary care (Cohort I, n=40) and tertiary care (Cohort II, n = 58). Reproducibility within 28 days was assessed in four cohorts including subjects with suspected SLD (Cohort III, n=37), suspected fibrosis (Cohort IV, n=163), compensated advanced SLD (Cohort V, n=32) and clinically significant portal hypertension (Cohort VI, n=28). Agreement was analyzed using intraclass correlation coefficient (ICC), Bland–Altman analysis, minimal detectable change (MDC), and Cohen's Kappa (k) for steatosis category (S) based on CAP thresholds at ≥248 (≥S1) and ≥275 (≥S2) dB/m.

Results: Same-day CAP repeatability was moderate to good (ICC 0.64–0.80). Bland-Altman analysis showed no proportional bias, but second measurements were systematically lower; 95% limits of agreement were −61-51 dB/m (Cohort I) and −73-65 dB/m (Cohort II). Corresponding MDC was 56-69 dB/m (relative: 18-24%). Categorical agreement at ≥248/≥275 dB/m was moderate to strong (k=0.33-0.65).

Between-day reproducibility declined with disease severity (more advanced fibrosis stage and lower steatosis) and was moderate to poor (ICC −0.10-0.56). In line, MDC increased with disease severity (more fibrosis, less steatosis) ranging from 81-174 dB/m (relative: 34-95.6%). FAST agreement and reproducibility were high (ICC >0.70 in Cohorts III-V) with MDC ~19-32.9%. Bland-Altman revealed no fixed/proportional bias except near upper scale limits.

Conclusion: Although agreement of CAP is moderate to good, an MDC of ~60 dB/m (20-25%) impairs its use for monitoring hepatic steatosis. MDC of CAP cannot be averaged across different settings of use.

PO2-07-YI
MetALD prevalence and screening discrepancy: Evidence from a Russian real-world cohort

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Background and aims: Metabolic dysfunction and alcohol-associated liver disease (MetALD) is a newly defined subtype of steatotic liver disease. The assessment of MetALD prevalence is complicated by the condition's diagnostic reliance on patient self-reported alcohol intake, a method with known limitations. The RUS-AUDIT-S is a validated short questionnaire for the Russian Federation to identify individuals at risk of alcohol misuse. The aim of this study was to evaluate the prevalence and diagnostic challenges of MetALD in a nationwide Russian cohort.

Method: This was a real-world, investigator-initiated prospective study conducted across 27 outpatient centers in Russia between March and June 2025. A total of 3748 consecutive patients were assessed for inclusion. Patients aged between 18 and 90 years who provided written informed consent were included in the study. Data on cardiometabolic risk factors and ultrasound results were either extracted from medical records within a 1-year period or obtained during the study. Alcohol consumption was evaluated using both a self-reported weekly intake and the RUS-AUDIT-S questionnaire.

Results: A total of 953 patients were enrolled. US-confirmed hepatic steatosis was present in 541 patients, 526 of whom met the 2023 MASLD criteria. Only 13 patients (2.5%) self-reported consuming ≥10 alcohol units per week, and none met the formal MetALD criteria. However, among 436 patients who completed the RUS-AUDIT-S, 41 were identified as being at risk for alcohol misuse. This subgroup of 41 patients was predominantly male (53.7%, n=22) and more frequently comprised of smokers (41.5%, n=17), with significantly higher serum ALT levels compared to both the general MASLD group and controls without steatosis ($p<0.005$), although no strong association was observed in a logistic regression analysis. A significant correlation was found between RUS-AUDIT-S scores and self-reported drinks (rho=0.66, ($p<0.001$). Median weekly drinks were significantly higher in the at-risk group compared to the general MASLD group: 3.0 (IQR 1.00–7.00) vs. 0.00 (IQR 0.00–1.00) ($p<0.001$).

Conclusion: Our results shows a notably low prevalence of MetALD when defined by patient self-report. The use of screening tools like the RUS-AUDIT-S indicates that the problem of occult alcohol misuse in patients with hepatic steatosis may be underestimated, pointing to a risk of MetALD underdiagnosis in real-world practice.

PO2-08-YI

Correlation between serum chitinase-3-like protein 1 levels and liver fibrosis severity in patients with metabolic dysfunction–associated steatotic liver disease

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Background and aims: CHI3L1 (chitinase-3-like protein 1, also known as YKL-40) is a glycoprotein involved in hepatic inflammation, remodeling, and fibrosis. It functions as an upstream regulator of fibrogenesis and has been shown to correlate with the rate of fibrotic progression. This study aimed to evaluate the correlation between serum CHI3L1 levels and liver stiffness measurements in patients with MASLD.

Method: A cross-sectional analysis was conducted in 40 patients diagnosed with MASLD, defined by hepatic steatosis based on a controlled attenuation parameter (CAP) value of ≥ 288 dB/m on FibroScan® and a presence of at least one cardiometabolic risk factor. None of the participants had other causes of steatotic liver disease, including viral hepatitis, HIV infection, and significant alcohol consumption. Baseline characteristics and laboratory data were recorded. Serum CHI3L1 was measured by ELISA, with levels < 79 ng/mL indicating non-significant fibrosis. Liver stiffness was assessed using FibroScan® and categorized as low (< 8 kPa), intermediate (8 – 12 kPa), or high (> 12 kPa) fibrosis risk. Correlation between CHI3L1 and fibrosis severity was analyzed using linear regression.

Results: The mean age was 50.3 ± 13.1 years; 55% were male. Mean BMI was 31.1 ± 4.6 kg/m², 95% had dyslipidemia, 70% hypertension, and 48% diabetes. The mean CAP was 337.3 ± 27 dB/m, liver stiffness (E) 7.5 ± 6.3 kPa. The median CHI3L1 level was 101.4 ng/mL (IQR 69 – 135.7), suggesting that more than 50% of patients had significant fibrosis (≥ F2). Based on FibroScan®, 32 (80%) had low, 5 (12.5%) intermediate, and 3 (7.5%) high fibrosis risk, with CHI3L1 levels tending to increase across fibrosis categories. CHI3L1 levels varied widely in the low fibrotic risk group. Those low-risk individuals identified by FibroScan® but exhibiting high CHI3L1 levels could possess a faster fibrogenesis speed, warranting further longitudinal follow-up and assessment. Linear regression demonstrated a positive correlation between CHI3L1 and liver stiffness ($R^2 = 0.173$), suggesting that elevated CHI3L1 may reflect progressive fibrotic remodeling in MASLD.

Conclusion: Serum CHI3L1 levels were elevated in most patients with MASLD and correlated positively, though moderately, with liver stiffness. Elevated CHI3L1 levels despite low fibrosis risk on FibroScan® may indicate a higher risk of hepatic fibrosis progression. CHI3L1 may serve as a promising noninvasive biomarker for fibrosis assessment in MASLD, warranting validation in larger cohorts.

PO2-09-YI

Severity of liver fibrosis and risk of heart failure with preserved ejection fraction in high-metabolic-risk patients with metabolic dysfunction–associated steatotic liver disease

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Background and aims: An association between metabolic dysfunction–associated steatotic liver disease (MASLD) and cardiovascular diseases (CVD) has been reported, but the relationship between MASLD severity and CVD or the risk of heart failure with preserved ejection fraction (HFpEF) remains limited in patients at high metabolic risk.

Method: Cross-sectional analysis of 799 patients with type 2 diabetes (T2D) and/or obesity (BMI 30–40 kg/m², age 40–80 years) with MASLD, prospectively recruited in four diabetology departments in France (2020–2024). Advanced hepatic fibrosis (HF) was defined using a composite criterion (biopsy, MRE ≥3.62 kPa, imaging signs of cirrhosis, or transient elastography [TE] ≥12 kPa) [1]. Liver disease severity was assessed using FIB-4, ELF™, and TE. Cardiovascular diseases (CVD) included a history of stroke, coronary artery disease, carotid atherosclerosis, or peripheral artery disease (PAD). The risk of HFpEF was estimated using the HFpEF-ABA score, which includes age, BMI, and a history of atrial fibrillation.

Results: Participants (median age 60 years, BMI 32.7 kg/m², T2D 86%, obesity 74%) had a 27.8% prevalence of CVD (including stroke 4.1%, coronary artery disease 16%, carotid atherosclerosis 11%, and PAD 6.5%). No significant association was observed between advanced hepatic fibrosis and history of CVD: the proportion of CVD in patients with advanced hepatic fibrosis was: 25% versus 27% and 33% in patients with low and intermediate risk of advanced fibrosis, respectively, p=0.75. However, the proportion of patients at high risk of HFpEF increased with fibrosis severity: 25.6% (low), 35.9% (intermediate), and 41.6% (advanced), p = 0.017. Non-invasive fibrosis markers were higher in patients with a high HFpEF-ABA score > 70% compared to low HFpEF ≤ 70% (TE: 6.1 vs 5.5 kPa; ELF™: 9.67 vs 9.10; FIB-4: 1.50 vs 1.14; all p-values < 0.001).

Conclusion: In patients with T2D and/or obesity with MASLD, no association was found between CVD and the severity of hepatic fibrosis. However, an increased risk of HFpEF was observed in the presence of advanced hepatic fibrosis. These findings require confirmation using NT-proBNP and echocardiography.

PO2-10-YI
Circulating Mir-122, Mir-34a, and Mir-99a as potential predictive biomarkers of Metabolic Dysfunction-Associated Steatotic Liver Disease

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Background and aims: The development of reliable non-invasive diagnostic biomarkers for metabolic dysfunction-associated steatotic liver disease (MASLD) remains essential to enhance patient safety and reduce the need for liver biopsy. Circulating microRNAs (miRNAs) have recently emerged as promising molecular indicators reflecting hepatic injury and metabolic dysfunction. This case–control study aimed to assess the diagnostic potential of circulating miR-122, miR-34a, and miR-99a as non-invasive biomarkers for the detection and progression monitoring of MASLD.

Method: A total of 210 patients with histologically confirmed MASLD were enrolled, including 124 with simple steatosis (SS) and 86 with metabolic dysfunction–associated steatohepatitis (MASH). Ninety age- and sex-matched healthy individuals served as controls. All participants underwent full clinical and laboratory evaluation, anthropometric assessment, and histopathological confirmation. Serum levels of miR-122, miR-34a, and miR-99a were quantified using real-time PCR. Subjects with viral hepatitis (B or C), autoimmune hepatitis, alcohol consumption, hepatocellular carcinoma, liver cirrhosis, portal hypertension, diabetes mellitus, or ischemic heart disease were excluded.

Results: Histological assessment classified 124 patients as SS and 86 as MASH, with an age range of 38–56 years. Both miR-122 and miR-34a were significantly elevated in MASLD patients compared with healthy controls ($p < 0.001$). At a cut-off value of 1.261, miR-122 yielded 92% sensitivity and 85% specificity in distinguishing MASLD from controls. Conversely, miR-99a expression was significantly reduced in MASLD, with a further decline in MASH. Using a cut-off of 0.46, miR-99a demonstrated 94% sensitivity and 96% specificity in differentiating SS from MASH. Moreover, miR-122 levels correlated positively with serum lipids, HOMA-IR, AST, ALT, and histological indicators of steatohepatitis and fibrosis, independent of gender differences.

Conclusion: Upregulation of circulating miR-122 may serve as a sensitive non-invasive marker for MASLD diagnosis and an indicator of hepatic fibrosis, while downregulation of miR-99a may aid in distinguishing MASH from simple steatosis. Combining multiple circulating miRNAs could enhance diagnostic precision and predictive performance. Further large-scale studies are recommended to explore broader miRNA profiles and their potential roles in the pathogenesis, prognosis, and therapeutic targeting of MASLD.

PO2-11-YI

Depression, anxiety, and comorbidities as key factors associated with fatigue in MASLD: Insights from a nationwide study

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Background and aims: Fatigue is one of the most frequent and disabling symptoms in chronic liver diseases, significantly affecting quality of life and clinical outcomes. Its underlying mechanisms are multifactorial and may involve both metabolic and psychosocial factors. Data on the prevalence and determinants of fatigue in metabolic dysfunction-associated steatotic liver disease (MASLD) remain limited, especially in large, unselected cohorts. The present study aimed to identify clinical, metabolic, and psychosocial factors associated with clinically meaningful fatigue in patients with MASLD in a real-world clinical setting.

Method: This cross-sectional, multicenter study was conducted in outpatient centers across 45 regions of Russia. MASLD was diagnosed according to the 2023 criteria. Comorbidities were determined from medical history and records. Anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS), with scores ≥8 on the HADS-A or HADS-D subscales indicating clinically relevant symptoms. Fatigue was evaluated with the Fatigue Assessment Scale (FAS), with scores ≥22 denoting clinically significant fatigue (CSF).

Results: Of 524 MASLD patients enrolled, 445 completed the FAS. CSF was present in 224 patients (50.3%). It showed a strong association with depression and anxiety ($p < 0.0001$) and was more prevalent in patients with hypothyroidism ($p = 0.0101$), coronary heart disease (CHD) ($p = 0.0026$), type 2 diabetes mellitus (T2D) ($p = 0.0012$), and hyperuricemia ($p = 0.0178$). Female sex ($p = 0.0002$) and higher body mass index ($p = 0.0372$) were also significantly associated with fatigue. Logistic regression analysis revealed that anxiety (odds ratio [OR] 1.29; 95% confidence interval [CI], 1.18–1.41; $p < 0.001$), depression (OR 1.14; 95% CI, 1.06–1.24; $p = 0.001$), CHD (OR 2.47; 95% CI, 1.19–5.11; $p = 0.015$), and hypothyroidism (OR 1.16; 95% CI, 1.01–1.35; $p = 0.042$) were independently associated with CSF in patients with MASLD.

Conclusion: Fatigue is highly prevalent in patients with MASLD and is strongly associated with depression, anxiety, and several comorbid conditions, including hypothyroidism, CHD, T2D, and hyperuricemia. These findings highlight the multifactorial nature of fatigue in MASLD and underscore the need for its comprehensive assessment and management. Further research is warranted to elucidate the underlying mechanisms linking MASLD with fatigue and to develop targeted interventions aimed at improving patient-reported outcomes.

PO2-12-YI
Measures of comorbid cardiometabolic burden and cardiovascular disease risk in SLD

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Background and aims: Steatotic liver disease (SLD) is commonly associated with higher burden of cardiometabolic risk factors (CMRFs). This study was aimed to examine the associations between CMRF count, patterns and risk of cardiovascular disease (CVD).

Method: We included 10121 UK Biobank participants (39% women) with MRI-confirmed liver steatosis. Latent class analysis was used to derive CMRF patterns based on 5 CMRFs (obesity, diabetes, hypertension, high triglycerides and low HDL). Cox models were used to estimate associations between CMRF count and patterns with incidence and mortality of cardiovascular disease (CVD), and all-cause mortality.

Results: Approximately 95% of SLD participants had ≥ 2 CMRFs. During a median follow-up of 4.9 years, 268 CVD events and 212 deaths were recorded. Higher CMRF count was independently associated with elevated risk of CVD (HR per each additional CMRF: 1.22 (1.08, 1.38)), CVD mortality (1.47 (1.08, 1.99)), and all-cause mortality (1.16 (1.01, 1.33)). Three distinct CMRF patterns were identified, reflecting varying levels of CMRF burden and demographic characteristics. While certain patterns with high CMRF burden were associated with increased CVD risk, the associations were substantially attenuated after adjusting for CMRF count.

Conclusion: CMRF burden is a key determinant of cardiovascular risk in people with SLD, but data-driven CMRF patterns do not improve risk prediction beyond simple counts. CMRF count remains a practical measure of cardiometabolic burden.

PO2-14-YI

Evaluating alanine aminotransferase as a screening marker for steatotic liver disease in HIV-positive and general populations: A cross-sectional study from Egypt

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Background and aims: Alanine aminotransferase (ALT) is widely used to screen for liver disease, but its performance in detecting steatoticliver disease (SLD) across different populations remains uncertain.

Method: We conducted a cross-sectional study of 1,022 participants (767 consecutive HIV positive individuals, and 255individuals recruited from general population(controls)) who underwent transient elastography with controlled attenuation parameter (CAP) measurement at Kasr Alaini Viral hepatitis centere, Cairo,Egypt, over the period between August 2024 and Sebtemper 2025. Hepatic steatosis was defined as CAP ≥248 dB/m. Participants with significant alcohol consumption, viral hepatitis, or other chronic liver diseases were excluded. ALT values were standardized with an upper limit of normal (ULN) of 50 U/L. We calculated sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for various ALT cutoffs. Optimal thresholds were determined using receiver operating characteristic (ROC) curve analysis. We assessed performance at standard ALT cutoffs (30, 40, and 50 U/L) and examined risk-stratified subgroups based on metabolic factors (diabetes, obesity), age, and sex. Continuous variables were compared using the Mann-Whitney U test, and categorical variables using the chi-square test.

Results: Steatosis prevalence was 28.0% in HIV patients versus 74.1% in controls ($p<0.001$). Otimal ALT cutoffs were 17.0 U/L (HIV) and 23.3 U/L (controls), both below traditional normal ranges, yet yielded poor discrimination (AUROC 0.559 and 0.625, respectively). At the conventional 40 U/L cutoff, sensitivity was only 14.0% in HIV and 39.2% in controls, missing 86.0% and 60.8% of steatosis cases, respectively. Even at 30 U/L, 71.2% of HIV and 44.4% of control cases were undetected. Risk stratification revealed steatosis prevalence ranging from 14.0% (no diabetes, BMI ≤25) to 92.5% (diabetes plus obesity), yet AUROC remained below 0.67 across all subgroups, including those with dual metabolic risk factors.

Conclusion: ALT demonstrates poor discriminatory capacity for detecting hepatic steatosis regardless of population or metabolic risk profile. Traditional ALT thresholds miss the majority of steatosis cases, particularly in HIV populations. These findings challenge ALT's utility as a screening tool for SLD and suggest direct imaging assessment should be considered for at-risk populations rather than relying on transaminase-based screening strategies.

PO2-15
Diagnostic accuracy of blood-based non-invasive tests for advanced fibrosis in patients with MASLD

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Background and aims: Metabolic dysfunction–associated steatotic liver disease (MASLD) is a leading cause of chronic liver disease worldwide. Accurate and early identification of advanced fibrosis and compensated advanced chronic liver disease (cACLD) is crucial for risk stratification and management. Non-invasive tests (NITs) offer an alternative approach to liver biopsy but their diagnostic accuracy in overweight MASLD populations requires further validation. This study aimed to evaluate and compare the diagnostic performance of several blood-based NITs in a tertiary care center.

Method: We included 124 overweight and obese patients (mean BMI 32.9 ± 5.8 kg/m²; mean age 57.2 ± 9.9 years; 42.7% male) who underwent liver stiffness measurement (LSM) by transient elastography. The following NITs were assessed: LiverRisk, FIB-4, APRI, NAFLD Fibrosis Score (NFS), BARD, and Rittis ratio. Diagnostic accuracy for cACLD was evaluated using ROC curve analysis, and pairwise comparisons of AUROCs were performed with DeLong's test.

Results: All NITs showed a positive correlation with LSM, reflecting their ability to detect fibrosis progression. The strongest correlations were observed for APRI ($r = 0.37$, $p < 0.001$), FIB-4 ($r = 0.33$, $p < 0.001$), and LiverRisk ($r = 0.33$, $p < 0.001$). The ROC analysis for identifying patients with cACLD showed excellent diagnostic accuracy for FIB-4 (AUC = 0.855; 95% CI 0.780–0.912) and APRI (AUC = 0.843; 95% CI 0.767–0.902), good accuracy for NFS (AUC = 0.786) and LiverRisk (AUC = 0.774), and poor performance for Rittis (AUC = 0.629) and BARD (AUC = 0.524). FIB-4 significantly outperformed LiverRisk ($p = 0.0207$), NFS ($p = 0.0116$), Rittis ($p = 0.0001$), and BARD ($p < 0.0001$), while showing comparable accuracy to APRI ($p = 0.65$). These results support FIB-4 and APRI as reliable first-line diagnostic tools to identify MASLD patients with significant fibrosis more effectively than other models ($p < 0.05$), with no significant difference between these two ($p = 0.65$).

Conclusion: Blood-based NITs demonstrate excellent diagnostic accuracy and strong correlation with elastography findings, supporting their use as reliable, first-line non-invasive tools for identifying MASLD patients at risk of advanced fibrosis and cACLD. Their use in clinical practice could facilitate earlier diagnosis, better risk stratification, and improved clinical management while reducing the need for invasive liver biopsy.

PO3-03-YI
Evaluating non-invasive screening strategies for identifying treatment-eligible fibrotic MASH in MASLD patients

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Background and aims: Non-invasive tests (NITs), particularly FIB-4, are increasingly used to detect advanced chronic liver disease. However, FIB-4 shows suboptimal performance as a stand-alone screening tool in the general population. We therefore evaluated the ability of FIB-4–based strategies to identify individuals with fibrotic MASH eligible for pharmacologic treatment.

Method: We analysed two cohorts: patients with biopsy-proven MASLD from a German tertiary care cohort, and participants with MASLD defined by VCTE and CAP from US representative adults from NHANES 2017–2020. Individuals with presumed cirrhosis (F4 on biopsy or LSM ≥15 kPa) were excluded from the main analyses, consistent with AASLD resmetirom treatment criteria. We assessed the sensitivity and specificity of FIB-4 and LSM in the German cohort and extended this with newer NITs in NHANES.

Results: Among 365 patients with biopsy-proven MASLD (mean age 51 years; 53.2% male), 58.4% had F2–F3 fibrosis, indicating treatment eligibility. Using the EASL–EASD–EASO two-step screening strategy (FIB-4 ≥1.3, or ≥2.0 for those aged ≥65 years, followed by VCTE), only 31% of patients with biopsy-confirmed F2–F3 fibrosis would have been identified. FIB-4 alone resulted in a 50% loss in sensitivity, and the addition of LSM caused a further 20% loss. Findings were consistent when including individuals with cirrhosis. In NHANES, among 2,785 community-dwelling individuals with MASLD (mean age 55 years; 53.5% male), 369 (13.3%) had an LSM between 8–15 kPa, meeting AASLD non-invasive criteria for resmetirom eligibility. Using age-specific cut-offs, FIB-4 demonstrated low sensitivity (19%) but high specificity (86%). Newer NITs outperformed FIB-4: LiverPRO (F2 model, threshold 0.25) had a sensitivity of 56% and specificity of 61%; SAFE (threshold 0), 77% and 45%; and MAF-5 (threshold 0), 86% and 45%. There were no meaningful changes including individuals with LSM ≥ 15 kPa. A two-step strategy using MAF-5 as the high-sensitivity screening test followed by FIB-4 confirmation yielded a sensitivity of 17% (69% points lower than MAF-5 alone) and a specificity of 91% (46% points higher), indicating that most true positives were excluded in the second step.

Conclusion: Detecting patients eligible for pharmacologic treatment due to fibrotic MASH remains challenging in both clinical and population-based settings. FIB-4–based screening strategies miss the majority of individuals who may benefit from resmetirom, highlighting the need for improved non-invasive algorithms.

PO3-05-YI

Commonly associated MASLD-related genetic variants do not confer an increased risk of mortality in older adults with MASLD – a post-hoc analysis of the ASPREE trial

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Background and aims: There is an increasing focus on personalised genetic risk assessment in modern medicine. In metabolic dysfunction-associated steatotic liver disease (MASLD), multiple gene variants have been implicated in disease pathogenesis and increased rates of adverse outcomes – however, these have not been well studied in older people. We aimed to evaluate the impact of previously associated MASLD-related genetic variants (*PNPLA3* (rs738409 C > G), *MBOAT7* (rs641738 C > T), *TM6SF2* (rs58542926 C > T), *HSD17B13* (rs72613567 T > TA), *GCKR* (rs1260326 C > T), and *LYPLAL1* (rs12137855 C > T)) on the presence of MASLD in older persons. We also sought to determine whether these variants conferred an increased risk of all-cause mortality or major adverse cardiovascular events (MACE) within the MASLD group.

Method: The ASPirin in Reducing Events in the Elderly (ASPREE) trial examined the utility of aspirin in relatively healthy adults aged ≥ 70 years. Key exclusion criteria at baseline included prior cardiovascular disease events, physical disability, or dementia. Additional sub-studies were performed, including gathering biochemistry, and DNA genotyping. This analysis was performed on participants with a calculable Fatty Liver Index (FLI) score to stratify participants as MASLD (FLI ≥ 60 with a cardiometabolic criterion and no secondary steatosis) vs no-MASLD (FLI < 30) in those with DNA genotyping. Key previously identified MASLD genetic variants were evaluated. Cox proportional hazard models (adjusted for known contributors to death/MACE in this cohort as well as aspirin/placebo) were applied.

Results: Of the ASPREE participants classifiable by the FLI (32.5% MASLD, 32.8% no-MASLD, and 34.7% indeterminate), 8,065 had DNA genotyping. There were higher rates of *GCKR* (rs1260326 C > T) homozygotes in the MASLD group (17.8% vs 14.6%, p < 0.01), but no differences in other gene variants. There was no increased risk of mortality or MACE for any gene variant within the MASLD group, though there was an association between *MBOAT7* (rs641738 C > T) homozygotes and a reduced risk of MACE (aHR 0.59 [0.38 – 0.90], p = 0.01) even after adjustment for other risk factors.

Conclusion: Previously identified genetic variants do not confer an increased risk of mortality or MACE in older adults with MASLD, though *MBOAT7* is associated with reduced MACE. Further mechanistic work may provide novel insights into potential therapies for older persons with MASLD.

PO3-06
ADAPT and VCTE show comparable performance for identifying patients living with MASH having F2-F3 or F4 histological proven fibrosis: Implications for selecting patients eligible for therapy

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Background and aims: Following the recent approval of pharmacological therapies for metabolic dysfunction–associated steatohepatitis (MASH) in patients with moderate fibrosis (F2–F3) without cirrhosis (F4), there is an urgent need for reliable non-invasive tests (NITs) to identify patients eligible for therapy. We evaluated the diagnostic performance of two well-established NITs for fibrosis assessment—the PRO-C3–based ADAPT algorithm and vibration-controlled transient elastography (VCTE)—in a Danish prospective outpatient cohort.

Method: This single-centre, prospective study included 259 patients with histologically confirmed F0–F4 MASLD from the Copenhagen Cohort of MASLD (CoCoMASLD; >1,000 participants), recruited at Hvidovre Hospital between 2017 and 2022. Among participants, 91 (35.1%) had F2–F3 fibrosis and 48 (18.5%) had cirrhosis (F4). ADAPT was calculated using Elecsys® (Roche) PRO-C3, platelet count, age, and diabetes status, and VCTE by FibroScan® (Echosens). FIB-4 and standard biochemical parameters were collected. Cut-offs for F4 were >11 for ADAPT and >15 kPa for VCTE; and for F2–F3, 9–11 for ADAPT and 8–15 kPa for VCTE. Diagnostic performance was assessed by calculating AUROC, sensitivity, specificity, PPV, and NPV.

Results: The cohort had a median age of 56 years (Q1–Q3: 43–64), 56.4% male, BMI 33.2 (29.4–38.1), and 41.3% had diabetes. Median AST was 48 U/L (34–63.2), ALT 69 U/L (40–98), PRO-C3 39.4 ng/mL (33–51), 9 (7.8–10.9), and VCTE 10.3 kPa (7–15.4). For F4 fibrosis, both ADAPT and VCTE demonstrated strong diagnostic accuracy: AUROC 84% (95% CI: 79–90%) for ADAPT (sens 0.65, spec 0.86, PPV 51%, NPV 91%) and 88% (95% CI: 83–93%) for VCTE (sens 0.77, spec 0.84, PPV 52%, NPV 94%), with no statistical significant differences between tests (AUROC p=0.25; sens/spec p=0.18/0.64). While PPV was modest, limiting the ability to rule in cirrhosis (~50%), NPV was high (~91%). For F2–F3 fibrosis, diagnostic performance was lower: ADAPT sensitivity/spec 0.31/0.78, PPV 43%, NPV 68%; VCTE 0.61/0.67, PPV 50%, NPV 75%. Sensitivity was higher for VCTE (p<0.001), whereas specificity was higher for ADAPT (p=0.017). Both tests demonstrated modest rule-in capability, but some capability of ruling out F2–F3 patients (NPV 68-77%).

Conclusion: ADAPT and VCTE performed similarly in detecting F2-F3 or F4 fibrosis, one being blood-based and the other imaging-based. This supports the use of NITs for identifying patients eligible for MASH therapy.

PO3-08-YI

Urinary titin N-fragment level as a marker of both extramyocellular lipid content and hepatic disease severity in steatotic liver disease

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Background and aims: Myosteatosis is an extrahepatic characteristic of metabolic dysfunction-associated steatohepatitis, but biomarkers of muscle quality are lacking. Here, we assessed muscle fat content by a robust magnetic resonance imaging method and urinary titin N-fragment level, a marker of sarcomere degradation, in a cohort of patients with steatotic liver disease (SLD).

Method: Participants with SLD were prospectively recruited. Liver disease severity was assessed by vibration-controlled transient elastography and subsequent Agile3+ calculation. Muscle fat content was measured using single-voxel proton magnetic resonance spectroscopy (^{1}H-MRS) on right soleus and tibialis anterior (TA) using a PRESS-sequence (Three Tesla Signa Premier, GE Healthcare®). AMARES algorithm was used to measure separately intramyocellular lipid content (IMCL) and extramyocellular lipid content (EMCL) on water-suppressed spectra (JMRUI®). Urinary titin N-fragment level was measured by enzyme-linked immunosorbent assay using a commercialized kit (IBL® Japan) and corrected for dilution by the urinary creatinine level.

Results: Forty-two participants with SLD (MASLD, n=17; ALD, n=25) with muscle ^{1}H-MRS data and urinary titin level were recruited. Based on elastography, 27% (12/45) of participants were classified fibrosis grade 0-1 (F0-1), 35% F2 (16/45), 31% F3 (14/45) and 7% F4 (3/45). In the soleus, mean IMCL and EMCL were 7.9 and 34.4 µmol/g. In the TA, mean IMCL and EMCL were 6.3 and 19.6 µmol/g respectively. No significant differences in IMCL or EMCL in either muscle were observed between the MASLD and ALD groups. Mean urinary titin N-fragment level was 51.0 pmol/Cr in the MASLD group and 58.4 pmol/Cr in the ALD group ($p > 0.05$ between groups). Urinary titin N-fragment level significantly correlated in the pooled SLD group with creatine kinase serum level ($r = 0.42$, $p = 0.010$), another marker of muscle mass, with soleus EMCL alone ($r = 0.51$, $p = 0.010$) and with Agile3+ score ($r = 0.39$, $p = 0.013$).

Conclusion: Urinary titin N-fragment level specifically correlated with soleus EMCL in SLD suggesting its potential use as a biomarker of muscle quality in this specific population. The absence of difference in muscle fat content according to SLD subtype supports the use of SLD definition from a non-hepatic perspective. The positive correlation between titin levels and Agile3+ scores once again confirms the hypothesis of a disruption in the muscle-liver axis associated with the severity of SLD.

PO3-10-YI

Ceus in masld: towards a non-invasive marker of histological activity

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Background and aims: Microvascular dysfunction is a critical yet under-investigated aspect of metabolic dysfunction-associated steatotic liver disease (MASLD). Time-intensity curve (TIC) analysis from contrast-enhanced ultrasound (CEUS) offers real-time quantification of hepatic perfusion.

Method: Patients undergoing liver biopsy for suspected MASLD were prospectively included to undergo CEUS with TIC analysis (11 perfusion parameters) on the same day. Associations between TIC parameters and histological features steatosis, ballooning, inflammation, activity, fibrosis, steatohepatitis (MASH), and at-risk MASH (MASH + F2–3) were analysed. ROC analysis assessed diagnostic performance for MASH and significant fibrosis (≥F2).

Results: A total of 63 patients were included: 56 with MASLD (26 non-MASH, 28 MASH) and 7 controls. Risk groups were control (n=7), low-risk MASLD F0–1 (n=14), at-risk MASH F2–3 (n=19), and MASLD cirrhosis F4 (n=13).

Steatosis showed significant negative correlations with Maximum Gradient (ρ = -0.438), Mean Gradient (ρ = -0.255), Area Under the Curve (AUC; ρ = -0.473), and Wash-out AUC (ρ = -0.436). Ballooning correlated positively with Wash-in AUC (ρ = 0.262). Inflammation and activity correlated negatively with Wash-out AUC (ρ = -0.334, -0.302). Fibrosis showed positive correlations with Wash-in AUC (ρ = 0.404), Time-to-Peak (ρ = 0.326), and Time-Washout Ratio (ρ = 0.320).

In MASLD patients, Wash-in AUC was higher in MASH than non-MASH (median 813.7 vs 692.6 AU; p = 0.048). Across progression stages, Wash-in AUC increased from 777 AU in controls to 1,021 AU in cirrhosis (p = 0.002). Wash-out AUC decreased from 3,949 AU in controls to 2,812 AU in at-risk MASH (p = 0.018). Time-to-Peak and Time-Washout Ratio were also prolonged with fibrosis progression.

Diagnostic performance for MASH was fair (Wash-in AUC: AUC 0.657; 82% sensitivity, 39% specificity). For fibrosis ≥F2, Wash-in AUC (AUC 0.732), Time-to-Peak (AUC 0.731), and Time-Washout Ratio (AUC 0.722) showed moderate accuracy.

Conclusion: Although many TIC-derived parameters reached significance, the overall AUC, WIAUC, WOAUC and TTP were the most consistently discriminative. All these parameters capture complementary aspects of hepatic microvascular function. Their behaviour across disease stages supports the concept of progressive vascular impairment in progressive MASH. These findings position CEUS as a promising non-invasive tool for assessing MASLD/MASH severity.

PO3-11-YI

Long-term intake of bicarbonate-sulfate-calcium-magnesium mineral water improves MASLD-related outcomes by modulating intestinal permeability, systemic inflammation, and oxidative stress

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Background and aims: Fonte Essenziale®—a mineral water enriched in bicarbonate, sulfate, calcium, and magnesium—has shown potential in modulating the gut-liver axis and gut microbiota in hepatic steatosis. However, its long-term effects on intestinal permeability (IP), IP-related systemic inflammation (SI), and oxidative stress—key contributors to steatosis—remain unexplored in Metabolic dysfunction-Associated Steatotic Liver Disease (MASLD).

Method: Eighty-seven MASLD patients were randomized into two groups: group A received Fonte Essenziale® (400 ml/day, fasting) plus a controlled nutritional regimen (physical exercise and diet) for 12 months, followed by a 6-month washout; group B received the controlled nutritional regimen alone. IP markers, SI cytokines (IL-1beta, IL-6, TNF-alpha), oxidative stress (dROMs/BAP), and clinical data, including Controlled Attenuation Parameter (CAP), were collected at baseline (T0), 12 months (T12), and post-washout (T18). Baseline in-IP was defined by fecal zonulin > 110 ng/ml and serum LPS-binding protein (LBPp) > 10 µg/ml; im-IP was defined by normalization of both. CAP reduction ≥ 30% indicated a significant steatosis improvement.

Results: Thirty-eight patients in group A and 39 in group B completed the study. At T12, group A showed significant reductions in fecal zonulin (p: 0.0163) and serum LBPp ($p < 0.0001$), with increased occludin and claudin-1 levels (all $p < 0.0001$). im-IP prevalence was higher in group A (p: 0.0037). IL-1beta, TNF-alpha, IL-6, LPS, and dROM/BAP decreased significantly in group A and among those achieving im-IP (all $p < 0.05$). CAP reduction (T0 vs T12, $p < 0.0001$) and improvements in insulin and HDL levels (all $p < 0.0001$) were observed in group A. Multivariate analysis (adjusted for sex, age, smoking, BMI, diabetes, MASLD-related drugs, and baseline CAP) identified water intake (aHR: 2.104, p: 0.001) and im-IP (aHR: 1.214, p: 0.024) as independent predictors of steatosis improvement. All benefits persisted at T18.

Conclusion: Prolonged Fonte Essenziale® intake significantly improved hepatic steatosis and MASLD-related outcomes by modulating IP, SI, and oxidative stress.

PO3-13-YI

Two-tier screening approach for liver fibrosis stratification in outpatients with type 2 diabetes mellitus: A multicenter cross-sectional study

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Background and aims: To examine the prevalence and severity of metabolic dysfunction-associated steatotic liver disease (MASLD) in outpatients with type 2 diabetes mellitus (T2DM), and to assess the effectiveness of the EASL-EASD-EASO algorithm for liver fibrosis screening.

Method: We retrospectively enrolled 1203 Italian older outpatients with T2DM who underwent vibration-controlled transient elastography (VCTE) with liver stiffness measurement (LSM) and controlled attenuation parameter (CAP) assessment. MASLD was defined as CAP ≥248 dB/m. Significant liver fibrosis was defined as LSM ≥8 kPa, compensated advanced chronic liver disease (cACLD) as LSM ≥10 kPa, and clinically significant portal hypertension (CSPH) as LSM ≥25 kPa or LSM ≥20 kPa and platelet count <150 000/mm^3. FIB-4 index was calculated in all participants.

Results: The prevalence rates of MASLD, significant liver fibrosis, cACLD, and CSPH were 71.3%, 21.1%, 11.7% and 1.7%, respectively. A 2-tier screening strategy for liver fibrosis using the FIB-4 index and VCTE showed that among patients with a normal FIB-4 index, 629 (83.3%) had LSM <8 kPa and 126 (16.7%) had LSM≥8 kPa. Sensitivity, specificity, NPV, and PPV of the FIB-4 index for detecting LSM≥8 kPa were 50.4%, 66.3%, 83.3% and 28.6%, respectively. Increased body weight (adjusted-OR 3.34, 95%CI 1.75–6.39) and elevated ALT levels (adjusted-OR 1.54, 95%CI 1.01–2.36) were the strongest predictors of significant liver fibrosis.

Conclusion: MASLD and significant liver fibrosis are common in older patients with T2DM. Fibrosis risk stratification using FIB-4, followed by VCTE, is a good strategy in real-world settings. However, relying solely on FIB-4 may fail to identify some patients with advanced disease, particularly those with increased body weight and elevated serum aminotransferase levels.

PO3-14
Diagnostic patterns and fibrosis risk in MASLD-related hepatocellular carcinoma

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Background and aims: Hepatocellular carcinoma (HCC) due to metabolic dysfunction-associated steatotic liver disease (MASLD) has emerged as a rising global health concern over the past decade. Its prognosis depends on the stage at diagnosis and identifying factors related to late presentation could enhance screening and monitoring strategies. This study aims to examine the circumstances of HCC diagnosis and to describe patients who benefited from screening (ultrasound and AFP) versus those diagnosed incidentally.

Method: We conducted a retrospective cohort study of 60 patients with MASLD-related HCC admitted to our tertiary care hospital between January 2020 and October 2025. Demographic, clinical, biological, and imaging data were extracted from medical records and the Romanian Birth and Death Registry and recorded in an anonymous database.

Results: Our cohort was comprised mainly of males (64%) with a mean (SD) age of 72.78 (9.6) years. Comorbidities included heart failure (51%), diabetes (54%), hypertension (87%), dyslipidemia (35%) and obesity (42%). Liver biopsy was performed in 25% of cases. Of the 60 patients, 13 (21.66%) had liver cirrhosis, of whom 77% were compensated. Using the Barcelona Clinic Liver Cancer (BCLC) staging system, 1 patient had BCLC A, 3 patients had BCLC B, 4 patients BCLC C, and 5 were in BCLC D. HCC was diagnosed through screening in 28 (47%) patients, while 53% were diagnosed incidentally. Both unifocal and multifocal tumors were found at similar rates in screened and non-screened groups (p=0.325), and distant metastases were present in 12 (20%) cases. Only 31.25% of incidentally diagnosed patients survived throughout the study. A Fib-4 ≥ 2.67 in individuals younger than 65 and >2 for those older than 65 suggested a higher risk of severe liver fibrosis. Our results indicate severe liver fibrosis in 71.6% (43) of patients, among whom 44.1% were screen-diagnosed and 55.81% were incidentally diagnosed. Twenty-two percent underwent surgical resection, while one patient received a liver transplant.

Conclusion: The results highlight the importance of actively monitoring high-risk patients. Recognizing factors linked to late tumor presentation in patients with MASLD can aid in developing improved monitoring strategies. The Fib-4 index is a useful tool for identifying patients at risk of advanced liver fibrosis and may improve clinical practice regarding diagnosis and outcomes.

PO3-15-YI

Performance of non-invasive fibrosis scores in assessing liver fibrosis after sleeve gastrectomy in MASLD patients

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Background and aims: Recent studies have shown that bariatric surgery is effective not only in reducing obesity but also in improving hepatic steatosis and associated fibrosis. The primary objective of this study is to assess the progression of liver fibrosis (LF), using non-invasive markers, in patients with *Metabolic-dysfunction Associated Steatotic Liver Disease* (MASLD) who underwent *Laparoscopic Sleeve Gastrectomy* (LSG). The secondary objective is to assess a potential correlation between fibrosis' change and reduction in *Body Mass Index* (BMI) after LSG.

Method: This observational, retrospective study included all patients who completed a 5-year follow-up after undergoing LSG at our center. Anthropometric, clinical, and biochemical data were collected at baseline, at 1 and 5 years after surgery. LF was assessed at each time point using the non-invasive scores *Fibrosis-4* (FIB-4) and *AST to Platet Ratio Index* (APRI).

Results: A total of 41 patients were included (median age 49 years; 73.2% female). There was a progressive reduction in median BMI (baseline vs 1-year and 5-year: 43.7 vs 31.3 vs. 30.5 kg/m², respectively), with at least one BMI class reduction observed in 88% of patients. Fasting glucose normalized in 62.5% of patients, triglycerides decreased significantly by 22%, and HDL cholesterol increased by 33%. A significant reduction in transaminase levels was observed at 1 year after surgery (AST [U/L], baseline vs. 1-year: 23 vs. 17; $p < 0.01$; ALT [U/L]: 26 vs 14; $p < 0.01$), and this improvement was confirmed at 5 years ($p < 0.01$). No significant changes in median FIB-4 were observed at 1 or 5 years compared to baseline. In contrast, median APRI showed a statistically significant reduction at both time points compared to baseline (0.18 vs 0.22; $p < 0.01$: 1y vs baseline; 0.20 vs 0.22; $p = 0.03$: 5y vs baseline), without any modification between the first and fifth year of follow-up. No significant correlation emerged between changes in FIB-4 or APRI and post-surgical BMI reduction. Considering the stratification into FIB-4 and APRI classes, a progressive increase in the risk category at one and five years was observed for FIB-4, while a decrease in the risk category at one year was observed using APRI.

Conclusion: LSG significantly reduces BMI and improves metabolic and hepatic parameters in MASLD patients. The decline in transaminases reflects reduced hepatic inflammation after weight loss. APRI, being age-independent, may better capture long-term hepatic improvement than FIB-4.

PO4-05
Clinical spectrum of children seen in Metabolic Dysfunction Associated Liver Disease (MASLD) clinic in a quaternary UK referral centre

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Background and aims: The clinical spectrum of paediatric MASLD and its associated comorbidities is poorly understood. This study characterises a cohort of children with MASLD, focusing on extrahepatic comorbidities.

Method: Retrospective review of 288 children with MASLD reviewed within the Paediatric Hepatology Service at King's College Hospital over an 18-month period. Inclusion was based on imaging evidence of hepatic steatosis after exclusion of secondary causes of steatotic liver disease. Demographic data, anthropometric measures, transient elastography parameters (controlled attenuation parameter [CAP] and liver stiffness measurement [LSM]), ultrasonographic findings, and metabolic, endocrine, neurodevelopmental and sleep comorbidities were recorded.

Results: Median age was 15 years (interquartile range [IQR] 4), with a high male preponderance (71.2%). Median CAP was 299 dB/m (IQR 73.8), 11.2% compatible with grade ≥S1 steatosis (≥248dB/m), 7.6% grade ≥S2 steatosis (≥268dB/m) and 63.7% grade S3 steatosis (≥280dB/m). Median LSM was 7 kPa (IQR 2.8), with 29.6% showing advanced fibrosis (≥8kPa) and 6% ≥12kPa. Ultrasonography revealed splenomegaly in 32.6%, and steatosis graded as mild (20.5%), mild-to-moderate (58.0%) and severe (12.5%).

Neurodevelopmental and behavioural conditions were common, with ADHD or autism spectrum disorder in 13.8%. Endocrine abnormalities included hypothyroidism (3.8%) and hypogonadism-associated disorders (2.8%). Ten percent were heterozygous for alpha-1-antitrypsin deficiency, and 15.2% had positive autoantibodies without autoimmune liver disease.

Metabolic comorbidities were frequent; acanthosis (19%), elevated HbA1c (16.3%) and pharmacologically managed diabetes mellitus (11.1%). Hypertension occurred in 5.9%. Sleep-related issues were reported in 17.7%, with 10.4% referred for formal sleep study assessment. Among adolescent girls, 60% reported menstrual irregularities.

Conclusion: In our paediatric liver tertiary MASLD clinic, nearly two thirds of children have evidence of grade S3 steatosis (≥280dB/m) and one third of children of possible fibrosis (LSM ≥8kPa). Approximately 1 in 5 children with MASLD had evidence of an extrahepatic comorbidity. Neurodevelopmental and behavioural conditions were common, as were menstrual abnormalities for girls warranting further investigation. The above findings underscore the need for early detection and integrated multidisciplinary care.

PO4-06-YI

Adipose tissue insulin resistance is a marker and a major driver of severe metabolic dysfunction associated steatohepatitis

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Background and aims: Adipose insulin resistance (ADIPO-IR index) and excess free fatty acids (FFA, from impaired lipolysis suppression) are associated with severe fibrosis in MASLD. Whether ADIPO-IR also marks hepatic necro-inflammation and MASH severity is unknown. We aimed to determine if ADIPO-IR independently predicts MASH and fibrosis and explore its links to hepatic inflammation and response to intervention.

Method: The cohort included 375 individuals without diagnosis diabetes at enrollment with liver biopsy categorized: MASH n = 219, No-MASH n = 104 (including MASL n = 64) and CT n = 52 (healthy liver). Participants were also characterized with ADIPO-IR (FFAxInsulin), waist/height, visceral (VAT) and subcutaneous adipose tissue (SAT) by tomography, glucose tolerance by OGTT and PNPLA3 variants. A subgroup underwent liver transcriptomic analysis. An intervention subgroup with severe obesity was followed for 12 months after receiving either bariatric surgery (BS, n = 34) or lifestyle intervention (LS, n = 37), with post-intervention histology to find MASLD responders and non-responders. Logistic regression assessed ADIPO-IR as a predictor of MASH and fibrosis at baseline, adjusted for age, gender and BMI.

Results: Subjects with MASH, No MASH or CT had comparable BMI (38.2 - 39.5 kg/m2) and SAT. But MASH and No-MASH had higher waist/height and VAT compared to CT ($p < 0.05$). ADIPO-IR increased with the severity of steatosis, inflammation and fibrosis. After adjusting for age, sex, and BMI, ADIPO-IR independently predicted the presence of MASH (OR = 1.72, $p = 0.003$) and significant fibrosis (OR = 1.92, $p = 0.004$). PNPLA3 variant carriers had similar ADIPO-IR. Liver transcriptomic analysis revealed that ADIPO-IR was positively correlated with the enrichment of gene sets related to inflammatory and immune responses, including neutrophil degranulation and interferon-gamma signaling. Post-intervention, ADIPO-IR was significantly reduced ($p < 0.0001$) and reduction below the overall median (FU/baseline = 0.4877) was more prevalent in the BS group (67.6 % vs. 32.4 % for LS) and in MASLD responders (60.5 % vs. 32.1 % for non-responders). Regardless of the intervention, the change in waist/height predicted ($p < 0.05$) the change in ADIPO-IR.

Conclusion: ADIPO-IR is an independent predictor of MASH and fibrosis in MASLD. Its correlation with hepatic inflammatory gene expression combined with its significant reduction following histological improvement, highlights ADIPO-IR as a key marker & driver of MASH.

PO4-08

Prospective evaluation of sodium-glucose cotransporter 2 inhibitors on liver steatosis, fibrosis and metabolic biomarkers in patients with type 2 diabetes and steatotic liver disease

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Background and aims: Metabolic dysfunction associated steatotic liver disease (MASLD) is highly prevalent among patients with type 2 diabetes mellitus (T2DM), however, effective therapies remain limited. This prospective observational study evaluated the impact of sodium–glucose cotransporter 2 inhibitors (SGLT2i) on liver steatosis, fibrosis and key metabolic biomarkers in T2DM-associated MASLD.

Method: Sixty-five T2DM patients initiating SGLT2i therapy were prospectively followed for six months. Serum sterol regulatory element-binding protein 1 (SREBP1), peroxisome proliferator-activated receptor (PPAR) α and γ, and microsomal triglyceride transfer protein (MTTP) were measured by ELISA. Liver steatosis and fibrosis were assessed noninvasively using the ultrasound-guided attenuation parameter (UGAP) and two-dimensional shear wave elastography (2D-SWE), respectively alongside with comprehensive biochemical and anthropometric assessments.

Results: After six months of SGLT2i therapy, PPARγ significantly decreased (872.2→565.4 ng/L, $p<0.001$) while MTTP increased (201.3→422.0 ng/L, $p<0.001$). Liver stiffness improved, as reflected by reduced 2D-SWE values (6.17→6.08 kPa, $p<0.001$) and correlated inversely with MTTP ($\rho=-0.287$, $p=0.02$). UGAP correlated significantly with 2D-SWE ($\rho=0.430$, $p<0.001$), increasing with liver enzymes and triglycerides, and decreasing with HDL-cholesterol ($p\leq0.02$). Notable improvements were seen in glucose, HbA1c and INR, with significant reductions in BMI and waist circumference ($p<0.001$).

Conclusion: SGLT2i improved liver steatosis, fibrosis and metabolic regulation in T2DM- associated MASLD, accompanied by favorable modulation of PPARγ and MTTP. These results support the potential of SGLT2i to attenuate hepatic steatosis and fibrosis through metabolic pathways, suggesting their therapeutic potential for MASLD and warranting further controlled studies.

PO4-10-YI

Genetic and endocrine determinants of MASLD phenotypes: insights from the PNPLA3–TSH interaction

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Background and aims: Thyroid hormones influence hepatic lipid metabolism and energy balance, pathways also involved in metabolic dysfunction–associated steatotic liver disease (MASLD). Subtle thyroid-stimulating hormone (TSH) variations may interact with genetic factors such as the PNPLA3 rs738409 polymorphism, a key determinant of hepatic fat accumulation. This study assessed the association between PNPLA3 genotypes and TSH levels, and their combined effect across non-MASLD, lean MASLD, and obese MASLD phenotypes.

Method: A cross-sectional analysis was performed in 381 adults, classified as non-MASLD (n = 170), lean MASLD (n = 32) and obese MASLD (n = 179). Genotyping of PNPLA3 rs738409 (C/C, C/G, G/G) and quantification of serum TSH were performed following standard laboratory protocols. Liver parameters were assessed by transient elastography (CAP, LSM) and serum liver enzymes (AST, ALT, GGT). Associations and interaction effects were explored using multivariate regression models adjusted for age and sex.

Results: 77.7% (n=296) of participants were carriers of at least one G allele of the PNPLA3 gene. Mean TSH concentrations increased progressively in the non-MASLD, lean, and obese MASLD groups, with higher values among G allele carriers. In the adjusted models, carriers without MASLD had higher TSH levels than non-carriers (β = 0.55 mIU/L, 95% CI: 0.05-1.06, p = 0.031). Among lean individuals with MASLD, those with the G/G genotype also tended to show higher TSH concentrations (β = 2.33 mIU/L, 95% CI: −1.16 to 5.83, p = 0.182). A significant interaction was observed between TSH and PNPLA3 in terms of the risk of lean MASLD (OR = 3.02, 95% CI: 1.06–8.57, p = 0.038), indicating that carriers of the G allele with higher TSH levels were more likely to present this phenotype. In obese MASLD, TSH was independently associated with AST levels (β = 0.112, 95% CI: 0.067–0.158, p < 0.001).

Conclusion: In lean MASLD, the association between TSH and liver parameters appears to be influenced by the genetic background PNPLA3, indicating possible genotype-dependent sensitivity within the thyroid-liver axis. In contrast, in obese MASLD, the relationship between TSH and markers of liver damage appears to be determined primarily by metabolic factors independent of genotype. These findings highlight the distinct endocrine and metabolic pathways underlying MASLD phenotypes and support the integration of thyroid and genetic profiles in their clinical characterization.

PO4-11
Real-life evaluation of the FIB-4 two-step fibrosis screening algorithm in MASLD: measurement of waist circumference might make the difference

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Background and aims: Given the global burden of metabolic dysfunction–associated steatotic liver disease (MASLD), accurate fibrosis detection for timely hepatology referral is crucial. International guidelines recommend a two-step screening algorithm using FIB-4 (cut-off 1.3 or 2.0 if >65ys) followed by liver stiffness measurement (LSM, cut-off 8 kPa). Aim: to evaluate FIB4 performance and identify factors influencing accuracy.

Method: Multicenter study enrolling 563 ultrasound MASLD (mean age 50 ± 13 years, 64% males) referred to two hepatology clinics (Milan and Verona) and meeting inclusion criteria for algorithm application (diabetes, obesity or elevated transaminases).

Results: Fibrosis prevalence (LSM ≥ 8 kPa) was 18%. FIB-4 < 1.3 and ≥ 1.3 were in 432 (77%) and 131 (23%) patients. Using the 1.3 cut-off (2.0 if >65 ys), 58/432 (13%) were false negatives and 86/131 (65%) false positives. FIB-4 showed high specificity (81%) and negative predictive value (87%) but low sensitivity (44%), with an accuracy of 74%. Patients misclassified as non-fibrotic (FIB3<1.3; LSM >8kPa) were significantly older (>65ys), hypertensive, with higher HOMA-index, BMI, waist circumference (WC), glucose and prevalence of severe steatosis. In multivariate analysis (adjusted for age, gender, HOMA, hypertension, severe steatosis), WC remained the only independent factor associated with fibrosis (OR 1.055, CI 95%1.005-1.106). Patients misclassifed as fibrotic (FIB3>1.3; LSM <8kPa) had lower WC, BMI and HOMAindex; WC remained inversely associated with the absence of fibrosis (OR 0.92, CI 95% 0.86-0.99).

Conclusion: In this real-life cohort, FIB-4 may lead to misclassification. Incorporating a simple measurement as waist circumference into risk algorithm could improve diagnostic accuracy and reduce missed fibrosis cases requiring hepatology referral.

PO4-14-YI

Association between neck circumference and Steatotic Liver Disease: A systematic review and meta-analysis

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Background and aims: Neck circumference (NC) reflects visceral adiposity, yet is rarely used in clinical practice. BMI fails to capture fat distribution, and waist circumference can be unreliable in contexts such as obesity, pregnancy, abdominal distension, certain ethnicites, and childhood. NC is simple and reproducible, yet the extent to which it correlates with steatotic liver disease (SLD) remains unclear. We conducted a systematic review and meta-analysis to examine this association across studies using imaging, biochemical, and histological assessments.

Method: PubMed, Embase, Scopus, and Web of Science were searched through October 2025 using a librarian-reviewed strategy. Studies reporting NC in participants with and without SLD, or reporting correlations between NC and SLD were included. Two reviewers independently screened and extracted data. Adjusted odds and hazard ratios were pooled as generic relative effects (RE), and mean NC differences were summarized as standardized mean differences (SMD) using random-effects models. Leave-one-out analyses tested robustness.

Results: Of 337 studies, 39 (n=67,395) were included. Studies were comprised of community or national (14; 36%), workplace (8; 21%), and clinical cohorts (17; 44%) across 15 countries in Asia (18, 51%), Europe (9, 23%), the Americas (8, 21%), and the Middle East (4, 10%). Pediatric cohorts accounted for 4 studies (10%). Individuals with SLD had a higher NC than those without (pooled RE = 1.64, 95% CI 1.35–1.99; I^2 = 72%). The association remained significant in subgroup analyses of adults (1.58, 1.30–1.92; I^2 = 69%), children (2.56, 1.74–3.76; I^2 = 61%), women (1.84, 1.42–2.39; I^2 = 66%) and men (1.97, 1.30–2.98; I^2 = 64%). In studies reporting group means, NC was higher in SLD than non-SLD (SMD = 1.08, 95% CI 0.84–1.32; I^2 = 69%). Several studies found NC to be independently associated with SLD after adjustment for BMI and waist measures. Effects were consistent across ultrasound (ORs 1.3–2.5) and CAP-based (AUC 0.65–0.82) assessments. Biopsy-based studies demonstrated clear associations with steatosis but inconsistent findings for fibrosis. No single study altered pooled results.

Conclusion: NC is consistently associated with SLD across populations and SLD diagnostic methods. The magnitude of association is clinically meaningful and often independent of overall adiposity. NC measurement is quick, inexpensive, and reproducible, and may serve as a practical tool for SLD screening and risk-stratification.

PO4-15
Liver steatosis predictors in liver cirrhosis with or without ascites.

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Background and aims: Steatotic liver disease (SLD) affects approximately 1/3 of the European population and progresses to steatohepatitis, cirrhosis and hepatocellular carcinoma (HCC), therefore evaluation of the steatosis is mandatory in any etiology of the cirrhosis.

The primary endpoint was (presentation of a diagnostic algorithm designed to assess hepatic steatosis also in decompensated cirrhosis with ascites) identification of biomarkers that could be predictors of hepatic steatosis above 5% in cirrhotic patients. Secondary outcomes include biomarkers for steatosis evaluation in the ascites presence.

Method: A descriptive, prospective 6-month study was conducted in a single hospital in Bucharest. Patients with cirrhosis of any etiology with and without ascitic decompensation were selected, aged between 20 and 72 years. Of these, 27 did not present ascites and could be evaluated with transient elastography (TE) and controlled attenuation parameters (CAP). Enrollment took place between September 2024 and March 2025.

Results: Of the 135 patients with liver cirrhosis, only 27 could be evaluated with TE and CAP in the absence of ascites. Demographic data of the entire sample (mean age, 52.81 ± 10.57 years, 101 [74.8%] males); demographic data of those with TE assessment (mean age 51.19 ± 11.81 years, 20 [74.1%] males; 8 [29.6%] had values below 262 dB/m [indicating the absence of steatosis] on CAP measurement). A CAP value ≥ 262 dB/m was used to define and select SLD, all patients had advanced fibrosis (cirrhotic stage) with a mean stiffness of 39.24 ± 21.98 kPa. Significant differences were found between the CAP <= 262 and the > 262 dB/m group and positive correlations were found in terms of total cholesterol value p = 0.0128; threshold 150.5 mg/dl and BMI value p = 0.0025; threshold 30.5. In the multivariable analysis, total cholesterol and BMI were significantly associated with the presence of hepatic steatosis. The next step was to calculate the probability threshold value for the presence of steatosis, in order to indirectly evaluate cirrhotic patients with ascites in whom the evaluation with TE and CAP could not be performed. The results showed that the presence of steatosis is also found in 12.5% of patients with present ascites.

Conclusion: Hepatic steatosis is closely associated with increased BMI and total cholesterol, and 12.5% of patients with ascites may have SLD.

PO5-03-YI

Metabolome analysis revealed red flag signatures for the identification of MASLD risk across patients with similar dysmetabolic traits

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Background and aims: Adolescents and adults with dysmetabolic traits can either develop MASLD or show no evidence of fatty liver despite comparable cardiometabolic burden. 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 profile in a dysmetabolic cohort (n=383), including adolescents with MASLD (n=100, A-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: Targeted metabolomics (TM) was performed by UHPLC and analyzed through MetaboAnalyst 6.0.

Results: Serum TM analysis revealed two main hierarchical clusters across dysmetabolic patients, highlighting that A/B-MASLD and NI-MASLD/Dys showed a similar metabolic pattern, respectively. In particular, ~100 species were dysregulated (adjusted $p<0.05$ FDR) in A/B-MASLD *vs* NI-MASLD/ Dys patients. We found that 64 metabolites were shared between the A/B-MASLD groups, suggestive of a conserved signature across pediatric and adult biopsied cases due to a comparable rate 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 (A-, 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 or mild/moderate stages. 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%).

Conclusion: Serum TM 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 complications in pediatric cases. Furthermore, we disclosed 2 compounds specific for MASLD and 5-metabolites highly predictive of severe MASLD.

PO5-05
Metabolic Dysfunction-associated Steatotic Liver Disease as an emerging indication for liver transplantation in Korea

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a major indication for liver transplantation (LT) in Western countries, predicted to become the leading cause soon. In Korea, while Hepatitis B virus (HBV)-related liver disease was historically the leading indication for LT, it is now rapidly decreasing due to vaccination and antiviral treatments. Concurrently, the population with MASLD is markedly growing in Korea. However, the diagnostic criteria for MASLD in end-stage liver disease remain unclear, and no studies have assessed the actual burden of MASLD as an LT indication in Korea.

Method: This study was a retrospective analysis using data from the Korean Network for Organ Sharing. We included adult (≥18 years) patients who underwent LT in Korea between January 2000 and December 2021 (n=20,961). "Suspected MASLD" (sMASLD) was operationally defined as patients with an original disease category of "Others," "Unknown disease," or "Missing data" who also had a Body Mass Index (BMI) ≥ 25 kg/m². Post-LT survival outcomes were compared between the sMASLD group and other indications.

Results: Among the 20,961 total LT recipients, the most common indications were HBV (34.5%), malignancy (15.9%), and alcoholic liver disease (14.8%). Patients in the "Others + Unknown + missing" category, from which the sMASLD cohort was derived, accounted for 26.5% of all LTs. Trend analysis since 2010 revealed a significant increase in the proportion of LTs performed for sMASLD (7.9%, 8.1% and 16.9% at 2010, 2015 and 2020, respectively). Kaplan-Meier survival analysis demonstrated that the post-LT survival outcomes for the sMASLD group were similar or superior to those of other indications.

Conclusion: As metabolic diseases increase globally, MASLD appears to be a rapidly growing indication for LT in Korea. In this study, post-LT outcomes for sMASLD were favorable. To properly understand the clinical significance of MASLD, it is necessary to systemize its diagnosis in patients with end-stage liver disease and include it as a separate category in the Korean LT registration system. Further evaluation based on more accurate diagnosis and classification is warranted.

PO5-06-YI

Longitudinal changes of liver elastography, FIB4 and Agile3+ add prognostic significance to baseline values in patients with Metabolic dysfunction Associated Steatotic Liver Disease (MASLD)

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Background and aims: Liver fibrosis is the key prognostic factor in MASLD. Currently, several non-invasive tests (NITs) are available to stratify the degree of fibrosis. The aim of this study is to compare liver stiffness measurement (LSM) to other NITs (Agile3+ and FIB4) as prognostic factors both at baseline (t_0) and in its variation over time.

Method: This is a retrospective study including 389 patients who underwent at least two NITs measurements (LSM, FIB4, Agile3+) with a minimum 6-month interval, from January 2011 to December 2023. They were stratified into 3 risk groups (low, medium, high) according to t_0-LSM (<10,10-20,>20kPa), FIB4 (<1.3 [2 in >65years]), 1.3 [2 in >65years]-2.67,>2.67) and Agile3+ (<0.45,0.45-0.68,>0.68). Primary outcome was a composite of Liver Related Events (LRE), death or liver transplantation.
Cox regression analysis were generated for time to primary outcome stratified by Baseline NITs and Δ%NITs categories (worsening: NITs increase >20%, stable, improved: NITs decrease >20%).

Results: During a median follow-up of 28 months (IQR14.4-43.4), 29 (7.5%) patients experienced the composite primary endpoint. All three t_0-NITs showed a good predictive performance for the composite endpoint (AUC>0.85). For each NITs, compared to patients at low risk, either patients with medium or high risk had a significant increased risk for the primary outcome (medium vs low risk HR 9.7 [LSM], 5.6 [Agile3+[, 6.36 [FIB4], p ≤0.05) (high vs low risk HR 48.1 [LSM], 39.1 [Agile3+], 56.4 [FIB4], p≤0.05)

Cox analysis revealed significantly lower risk of outcome for LSM high-risk patients who showed longitudinal improvement (HR 0.16,95%CI 0.04–0.68,p=0.01), and a significantly higher risk of outcome in intermediate patients who showed longitudinal worsening (HR 6.66, 95%CI 1.69–26.23,p<0.01). Patients with a high t_0-FIB4 and that showed longitudinal worsening had a higher risk of composite outcome compared with patients who was stable or improved (HR 4.14,95%CI 1.2-14.2,p=0.02). Patients with high t_0-Agile3+ and that showed longitudinal improvement had a lower risk of composite outcome compared with patients who was stable or worsened (HR 0.21,95%CI 0.06-0.70,p=0.01).

Conclusion: Our study strengthens the use of NITs both at baseline and during follow up as reliable prognostic factors in MASLD able to identify the subgroups of patients at risk of LREs. In patients with intermediate or high risk of events at baseline, NITs surveillance should be encouraged.

PO5-09-YI
Arterial stiffness in patients with metabolic dysfunction-associated steatotic liver disease

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a leading cause of chronic liver disease, associated with hepatic inflammation, fibrosis, and increased morbidity and mortality. Growing evidence suggests that MASLD is linked to atherosclerotic vascular disease beyond traditional cardiovascular risk factors. Increased arterial stiffness may represent a shared pathway between metabolic and hepatic injury. This study aimed to evaluate the relationship between MASLD and arterial stiffness and to identify potential overlapping mechanisms.

Method: Over a one-year period, patients presenting to the Sibiu Clinical County Hospital with liver steatosis on conventional ultrasound, altered liver function tests, or cardiometabolic risk factors were prospectively evaluated. All underwent clinical assessment, abdominal ultrasound, vibration-controlled transient elastography (FibroScan), and arterial stiffness measurement using the Arteriograph. Seventy-five patients with MASLD were included. Liver fibrosis and steatosis were assessed by liver stiffness measurement and controlled attenuation parameter (CAP). Arterial stiffness was evaluated by aortic pulse wave velocity (aoPWV) and aortic augmentation index (aoAix).

Results: In the entire cohort (75 patients), fibrosis and steatosis parameters were correlated with Arteriograph measurements, including aortic pulse wave velocity (aoPWV) and aortic augmentation index (aoAix). Using Pearson's correlation coefficient (r), a significant positive linear relationship was observed between the number of metabolic syndrome components and arterial stiffness, expressed by aoPWV (r = 0.35) and aoAix (r = 0.325). Arterial stiffness (aoPWV) also showed a significant linear correlation with liver fibrosis score (r = 0.424), CAP score (r = 0.416), and CAP degree (r = 0.439), assessed using FibroScan.

Conclusion: Significant correlations were identified between hepatic fibrosis, steatosis, and arterial stiffness in patients with MASLD. These findings underscore that cardiometabolic and hepatic alterations tend to intensify with worsening metabolic dysfunction, highlighting the need for early detection and comprehensive cardiovascular risk monitoring in this population.

PO5-10-YI

Performance of clinical criteria to identify candidates for pharmacological treatment in patients with MASLD: impact of the metabolic profile

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Background and aims: Resmetirom and semaglutide have recently obtained conditional approval by FDA/EMA to treat metabolic dysfunction-associated steatotic liver disease (MASLD) and fibrosis. This study aimed to evaluate the diagnostic performance of proposed clinical criteria by an American Expert Panel for identifying candidates for resmetirom treatment and to determine whether their accuracy depends on the patient's metabolic profile.

Method: We conducted a multicenter cross-sectional study including patients with MASLD from three European centers (H. Universitari Vall d'Hebron, Barcelona; H. Pitié-Salpêtrière, Paris; and IRCCS O. Casa Sollievo della Sofferenza, Italy). Eligible patients had available laboratory data, transient elastography (TE), ultrasound, and liver biopsy within ≤6 months. Patients were considered candidates for MASLD drug treatment if they had steatohepatitis (NAS≥4) and stage F2–F3 fibrosis. Assessed clinical criteria according to the Expert Panel (Noureddin et al, CGH 2024) included AST >20 IU/L in men or >17 IU/L in women, CAP >280 dB/m, TE 10–20 kPa, and absence of ultrasound signs of cirrhosis, portal hypertension and/or thrombocytopenia (<140,000/mm³). Sensitivity (Se), specificity (Sp), positive and negative predictive values (PPV, NPV), and overall diagnostic accuracy were assessed in the entire cohort and in subgroups defined by obesity (BMI ≥30 kg/m²) and type 2 diabetes mellitus (T2DM).

Results: 723 patients were included and classified as follows: T2DM without obesity (n=156), obesity without T2DM (n=185), both T2DM and obesity (n=263), and neither condition (n=119). Sensitivity, NPV, and overall accuracy were comparable across subgroups, whereas specificity (76%; 95%CI 72–80) and PPV (41%; 95%CI 35–48) differed significantly among categories (p<0.01 and p=0.01, respectively). Obesity in the absence of T2DM was associated with an increased risk of false positives (OR 1.92; 95%CI 1.24–2.60; p<0.01), while T2DM was associated with a higher likelihood of true positives (OR 1.67; 95% CI 1.25–2.08; p<0.01).

Conclusion: The diagnostic performance of current clinical criteria to identify MASLD patients eligible for available drug therapy depends on the metabolic phenotype. In patients with obesity but without T2DM, specificity decreases due to a higher rate of false positives, whereas diagnostic accuracy is highest in those with T2DM, irrespective of BMI.

PO5-11
Prevalence and risk factors on the appearance and development of ALD, MASLD and MetALD in Catalonia

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Background and aims: Steatotic liver disease (SLD) comprises a spectrum of conditions, including MASLD, ALD and MetALD. Although MASLD is the most prevalent form, ALD and MetALD remain underreported and there is need for more epidemiologic studies. We aimed to evaluate SLD prevalence, estimate underdiagnosis rates, and identify sociodemographic factors associated with disease development and progression.

Method: We constructed a retrospective cohort of adults diagnosed with SLD, between 2018 and 2023 from electronic health records of the Catalan public health system (PADRIS database). MASLD patients were identified by the presence of metabolic risk factors and changes in their hepatic steatosis index (HSI). MetALD patients met MASLD criteria with additional evidence of alcohol. ALD patients were selected based on alcohol consumption and at least one hepatic risk marker.

Results: Excluding 2020 (due to COVID-19), MASLD prevalence increased steadily from 25.28% in 2018 to 51.68% in 2023. In contrast, MetALD and ALD prevalence remained stable (1.29 and 2.47% respectively). Comparing between groups, ALD patients had the lowest mean age (56.1 years, p-value<0.001). Cardiovascular risk factors were more frequent in MASLD and MetALD patients compared to ALD ones. ALD patients had the highest ratio of hepatic events when diagnosed (4.49%, p-value<0.001) and presented the most advanced disease stage(p-value<0.001). After follow-up, MetALD patients had the highest ratio of cardiovascular events (27.63%, p-value<0.001) and ALD patients had the highest progression (8.8%, p-value<0.001) and death rates (3.29%, p-value<0.001). Patients with low annual income were the most frequent across all diagnostics, and their disease progression rate was higher. Progressing patients with SLD showed a reduction of BMI and an increase of FIB4 and MELD-NA, but BMI remained stable when considering only MASLD/MetALD patients. Type 2 diabetes prevalence increased markedly in all progressing groups (p-value<0.001), while dyslipidemia and arterial hypertension increased only among MASLD/MetALD progressing patients (p-value<0.001).

Conclusion: We confirmed a significant gap between SLD prevalence and diagnosis rates for all categories, together with a diagnostic delay. This is the largest SLD study conducted and the first to focus on sociodemographic factors. MetALD patients had greater metabolic dysfunction and greater comorbidity and events than MASLD patients.

PO5-12

Inclusion of the fatty liver-associated variants in the clinical workup of patients: Results of an eight years' experience in a tertiary referral center with genotyping facility

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Background and aims: Genetic testing has become increasingly available in clinical practice. In our department we introduced in year 2013 the genotyping of fatty liver-associated variants in the clinical workup of liver patients. Here we present the results of the genotyping procedures of patients from our department up to 2021.

Method: We analysed a total of 462 patients with fatty liver phenotypes who were referred for the genotyping of the two fatty-liver associated variants, i.e. *PNPLA3* p.I148M and *MBOAT7* p.E17G, by our physicians. In addition, to this panel, we genotyped the newly detected *MTARC1* rs2642438 variant which has been shown to have protective effects on liver health (*Fairfield et al, Hepatol Commun. 2022*). Genotyping was performed using allelic discrimination assays. Liver steatosis and fibrosis were quantified using controlled attenuation parameter (CAP) and transient elastography (TE).

Results: The results of genotyping procedures were provided to the admitting physicians within the average time of 24 days from blood sampling. The minor allele frequency (MAF) of the *PNPLA3*, *MBOAT7* and *MTARC1* variants were 25.2%, 40.8% and 21.5%, respectively and did not significantly differ from the data available for European cohorts. Among tested variants, the *PNPLA3* p.I148M genotype correlated with increased serum ALT and AST activities and transferrin saturation (all $P < 0.01$) as well as iron ($P = 0.02$) in [MM] homozygous carriers. The homozygosity for the [M] allele was also associated with higher CAP (299 ± 62 db/m, $P < 0.01$) as compared to the carriers of the common allele (267 ± 74 db/m). A correlation for *MBOAT7* p.E17G was found with increased levels of leucocytes ($P = 0.02$) but not with liver phenotypes (all $P>0.05$) when tested for an association with either hetero- or homozygosity. Finally, we did not find any relevant associations between the *MTARC1* polymorphism and liver steatosis or fibrosis.

Conclusion: Our data underscore the central role of *PNPLA3* p.I148M variant in the fatty liver phenotype. Genotyping of this variant in clinical practice can be rapidly performed and might help to detect patients with worse liver status.

PO5-13-YI

Low ceruloplasmin levels define a distinct non-obese metabolic dysfunction-associated steatotic liver disease phenotype

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Background and aims: Low ceruloplasmin levels are classically linked to Wilson's disease. Their significance in metabolic dysfunction–associated steatotic liver disease (MASLD), especially in intermediate ranges, remains unclear. We aimed to determine the prevalence and clinical relevance of low ceruloplasmin levels in a well-characterized cohort of MASLD patients.

Method: We conducted a bicentric cross-sectional study on patients aged 18–50 years diagnosed with MASLD. Patients with other causes of acute or chronic liver disease were excluded. Demographic, metabolic, biochemical, and non-invasive fibrosis data were collected. Ceruloplasmin was considered low when ≤0.20 g/L, according to the 2025 EASL guidelines for Wilson's disease (Leipzig criteria).

Results: Of the 233 patients screened, 23 were excluded, resulting in 210 patients for analysis. Ceruloplasmin was measured in 128 patients. Testing was more frequently performed in younger patients (median age 38 [range 18–50] vs. 43 years [20–50]; p = 0.001), with smaller waist circumference (112.1 ± 14.3 vs. 117.3 ± 17.8 cm; p = 0.026) and higher aminotransferase levels (ALT: 64 [13–257] vs. 38 [12–187] IU/L, p < 0.001; AST: 38 [13–169] vs. 30 [12–135] IU/L, p < 0.001). Among the 128 tested, 19 patients (14.8%) exhibited low ceruloplasmin levels (median: 0.18 [0.11 – 0.2] g/L) without any other argument for Wilson's disease. This subgroup was exclusively male (100% vs. 57% male, p < 0.001), and had significantly lower body mass index (BMI: 29.3 ± 4.7 vs. 34.5 ± 6.7 kg/m², p = 0.001) and waist circumference (105 vs. 110 cm, p = 0.030). They also displayed higher ferritin (279 vs. 154 µg/L, p = 0.035) and bilirubin (0.7 vs. 0.5 mg/dL, p < 0.001), and lower CRP (1.3 vs. 3.7 mg/dL, p = 0.006). No significant differences were found in aminotransferase levels or liver stiffness measured by elastography between the low and high ceruloplasmin groups.

Conclusion: In routine clinical practice, ceruloplasmin testing is more often performed in younger patients with elevated aminotransferases. Low ceruloplasmin is observed in 15% of MASLD patients who also have higher ferritin levels and similar disease severity despite lower BMI and adiposity as compared with MASLD patients with normal ceruloplasmin levels. Prospective studies should evaluate its dynamics and prognostic significance.

PO5-14-YI

Diagnostic utility of the MAF-5 score for detecting significant fibrosis in Egyptian metabolic-dysfunction associated steatotic liver disease (MASLD) patients: Comparison with FIB-4 and NFS

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Background and aims: Metabolic Dysfunction–Associated Steatotic Liver Disease (MASLD) is highly prevalent in Egypt. Liver fibrosis remains the major determinant of adverse outcomes. The Metabolic Dysfunction–Associated Fibrosis 5 (MAF-5) score is a novel, non-invasive index that may aid in the early detection and risk stratification of fibrosis. Our objective was to evaluate the diagnostic performance of the MAF-5 score in predicting significant liver fibrosis among Egyptian MASLD patients, compare it with established non-invasive scores (FIB-4 and NFS), explore its correlation with metabolic and hepatic parameters, and determine its role as an independent predictor of fibrosis.

Method: A cross-sectional study was conducted on 125 MASLD patients attending Alexandria University Hospital Clinics. Demographic, clinical, and laboratory data were collected. MAF-5 was calculated using waist circumference, BMI, diabetes status, AST, and platelet count. Liver fibrosis was assessed by Vibration-Controlled Transient Elastography (VCTE) as the reference standard. Comparative performance with FIB-4 and NFS was analyzed, along with correlation and logistic regression analyses.

Results: Significant fibrosis was present in 28% of patients (35/125). MAF-5 demonstrated the highest diagnostic accuracy (AUC = 0.717) compared with NFS and FIB-4. Using a cut-off of ≥ 0, MAF-5 showed high sensitivity (94.3%) and negative predictive value (96%) for excluding significant fibrosis, though specificity was low (20%). The score correlated strongly with metabolic and hepatic markers (ALT, HbA1c, GGT, and triglycerides). In multivariate analysis, MAF-5 was the only independent predictor of significant fibrosis (OR = 1.376, p = 0.007).

Conclusion: MAF-5 is a simple, non-invasive, and reliable tool for predicting significant fibrosis in Egyptian MASLD patients. It outperforms traditional scores, particularly for ruling out fibrosis, and integrates key metabolic components that can mirror disease progression. Given its practicality and low cost, MAF-5 may serve as a valuable screening tool in resource-limited settings. Further large-scale and longitudinal studies are warranted to validate these findings.

PO5-15
Determinants of long-term remnant liver donor fibroprogression

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Background and aims: There have been recent reports on fibroprogression and biopsy proven cirrhosis occurring in the remnant donor liver on long term follow up. Long-term structural evolution of the remnant liver and its potential drivers need to be delineated, specifically, the impact of post-donation duration, evolution of metabolic dysfunction in the donor. We evaluated steatosis, inflammation and fibrosis using multiparametric ultrasonogram and blood markers in a donor cohort to identify the primary drivers of fibrosis in remnant liver. We aim to evaluate steatosis, inflammation, and fibrosis using multiparametric ultrasound and blood markers in a donor cohort, and to identify the primary determinants of fibrosis in the remnant liver.

Method: Cross-sectional observational study of 175 living liver donors using multiparametric ultrasound was carried out: 2-D Shear-Wave Elastography, sound speed plane wave ultrasound, attenuation plane wave ultrasound and viscosity plane wave ultrasound. Donors were stratified by time since donation (≤5 years vs. >5 years) and by the presence of metabolic dysfunction components. Association between fibrosis stage and components of metabolic syndrome, duration after donation were analysed statistically.

Results: The cohort (n=175) was predominantly female (84%) and aged 26–50 years, with a high prevalence (49.7%) of elevated BMI (>25 kg/m²). Unexpectedly, only 33.7% were F0–F1. The majority exhibited significant fibrosis: 41.1% F2, 20.6% F3, and 4.6% (n=8) F4. Steatotic liver disease (SLD) prevalence was 60%, exceeding population norms. Median viscosity (inflammation) was 2.1–2.2 (normal <1.4). Steatosis markers were elevated: Steatosis-A 0.57–0.59 (normal <0.50 dB/cm/MHz) and CAP 256–267 dB/m (normal <248 dB/m). Metabolic dysfunction was the strongest associate of fibroprogression. Hypertension (p<0.001) linked to advanced fibrosis (29.4% F4 vs 1.9% normotensive). Diabetes (p=0.006) showed 30% F4 vs 3% in non-diabetics. Dyslipidaemia (p=0.023) showed 19% F4 vs 2.6% in normal profiles. Hypothyroidism (14.3%) showed no association (p=0.62).

Conclusion: Living liver donors harbor a surprisingly high burden of MASLD and subclinical fibrosis in their remnant liver. This study identifies metabolic comorbidities, specifically hypertension, diabetes, and dyslipidaemia as the critical determinants of advanced stiffness (F3-F4). This underscores the need for mandatory, long-term metabolic surveillance in living donors to prevent steatosis and fibroprogression in the remnant liver.

PO6-02-YI

Hepatic antifibrotic response by fibrogenesis markers in in patients with MASLD undergoing a 6-month randomized dietary trial

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Background and aims: Lifestyle intervention aiming at weight loss (WL) is the cornerstone of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) management, but treatment response by non-invasive tests (NITs) is not yet established. Here, we aim to assess antifibrotic response to WL by collagen and non-collagen fibrogenesis markers.

Method: We included 146 patients with MASLD (median age 52 [46-61] years, 63% male) undergoing 6-month randomized dietary trial (2021-2023): Mediterranean Diet (n=49) or Low-Charb Diet (n=49) or nutritional advice (n=48). Inclusion criteria: MASLD and LSM (VCTE)<10 kPa, Body Mass Index (BMI) of 25-35 kg/m^2, age<65 years. Exclusion criteria: HbA1c>9.5%, type 2 diabetes (T2D) treated with insulin of GLP1-RA. All parameters were assessed at baseline and 6 months. Serum non-collagen (TSP2, CD163 and IGFB7 - Mainz) and collagen (C4M, PRO-C3, PRO-C4, PRO-C6 and PRO-C8 - Nordic Bioscience) markers were measured through in-house standardized ELISA assay. Primary endpoint was changes in NIT levels between patients achieving <5% WL (group A n=91), compared to those achieving 5-10% WL (group B n=38) and ≥10% WL (group C n=17).

Results: Median BMI was 30,4 [28,7–33,4] kg/m^2, T2D and PNPLA3 GG were present in 31% and 21,8% of cases. PRO-C4 levels fell significantly in group B (p=0,041) and C (p=0,015), but not in group A (p=0,147). TSP2 levels fell substantially in group B (p=0,046) and in group C (p=0,004) but not in group A (p=0,714). FIB-4 and VCTE did not show clinically significant changes. Delta PRO-C4 showed a stepwise negative increase across the 3 groups: from mean -71,7 (SD 510,3) ng/ml to mean -228,7 (634,2) ng/ml to mean -695,5 (1735,8) ng/ml (ANOVA p=0,011). Delta TSP2 varied from mean -0,2 (13,5) ng/ml to mean -4,2 (14,5) ng/ml to mean -12,6 (15,8) ng/ml (ANOVA p=0,004). PRO-C4 and TSP2 showed significant association with delta weight changes: R^2 0,05 (p=0,003) and 0,08 (p=0,0002). Delta TSP2> -1,96 ng/ml and delta PRO-C4> -703 ng/ml (both by Youden Index) were associated with WL >5% after adjustment for age, male sex, obesity, T2D and PNPLA3 GG: aOR 0,16 (0,04-0,63, p=0,008) and aOR 0,29 (0,29-0,96, p=0,043) respectively.

Conclusion: In patients with MASLD without advanced fibrosis undergoing dietary intervention, serum TSP2 and PRO-C4 levels fell significantly in correlation to WL and were associated with WL>5%. This evidence suggests their clinical utility to monitor attenuation of hepatic fibrogenesis.

PO6-05-YI

External validation of a machine learning model for liver fibrosis risk assessment in U.S. representative adults

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Background and aims: LiverPRO is a new algorithm to predict liver fibrosis, with distinct formulas for F2, F3, and F4 stages. Unlike traditional scores, LiverPRO does not require all input variables; it automatically selects the best-performing model based on available data. The full model includes age, albumin, AST, bilirubin, sodium, cholesterol, GGT, ALP, platelets, and INR. We performed an external validation of LiverPRO in a nationally representative population.

Method: We used data from U.S. adults participating in NHANES (2017-2023), with LSM and LiverPRO components except for INR. Participants with heart failure or alcohol intake >50/60 g/day (female/male) were excluded. Diagnostic performance was assessed for LSM ≥8 and ≥12 kPa (commonly interpreted as compatible with significant and advanced fibrosis) using AUCs and detection rates at the proposed LiverPRO thresholds. Performance was evaluated in the overall population and relevant subgroups.

Results: The study included 10,852 adults (48.6% male, mean age 50 yr) of whom 60% had at least one indicator for screening, 10.5% had LSM ≥8 kPa and 3.6% had LSM ≥12 kPa. Using the LiverPRO F2 algorithm, 4.6% were classified high, 26.1% intermediate, and 69.3% low risk, with LSM ≥8 kPa prevalences of 37.5%, 16.1%, and 6.6%, respectively. At the 0.25 threshold, sensitivity and specificity for LSM ≥8 kPa were 57% and 72% and for LSM ≥12 kPa 69% and 71%. Among those meeting screening criteria, sensitivity and specificity remained largely unchanged (LSM ≥8 kPa: 59% and 63%; LSM ≥12 kPa: 69% and 61%). The F3 and F4 LiverPRO algorithms with their specific cut-offs did not improve performance for both LSM thresholds. The LiverPRO F2 algorithm achieved the highest AUC for LSM ≥8 kPa (0.71 vs 0.67/0.66 for F3/F4 model) and ≥ 12 kPa (0.76 vs 0.72/0.71). LiverPRO outperformed FIB-4 (AUC 0.61 and 0.67 for LSM ≥8 and 12kPa). For LSM ≥8 kPa, AUCs were higher in females (0.73) than males (0.68), stable across age groups (18–35: 0.66; 35–65: 0.70; 65–80: 0.70), higher with at-risk alcohol consumption (0.74), and lower when meeting EASL–EASD–EASO screening criteria (0.66).

Conclusion: The LiverPRO algorithm was externally validated in a representative U.S. general population, where the F2 algorithm demonstrated the best performance for detecting LSM ≥8 and ≥12 kPa, producing a clear risk gradient across strata. Performance was highest among adults with at-risk alcohol consumption, indicating potential in a group where non-invasive tests often perform less consistently.

PO6-11

Lysosomal acid lipase (LAL) activity is inversely associated with histological progression of metabolic dysfunction-associated steatotic liver disease (MASLD): a single-centre prospective study

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Background and aims: Lysosomal acid lipase (LAL) hydrolyzes lipids in the lysosomal compartment. Patients with genetic LAL deficiency (LAL-D) display liver steatosis and hypercholesterolemia and biopsy-proven metabolic dysfunction-associated steatotic liver disease (MASLD) may develop an acquired LAL-D. Aim: to investigate whether low LAL activity could predict MASLD progression.

Method: 144 MASLD patients were enrolled, tested for LAL activity (expressed as LAL/platelets) and for the severity of steatosis and fibrosis by Fibroscan (Controlled Attenuation Parameter-CAP; Liver Stiffness Measurement-LSM) and were followed up for a mean of 8.1years. Ninety-four patients underwent liver biopsy which was repeated at the end of follow-up.

Results: In biopsied patients 10% developed metabolic dysfunction-associated steatohepatitis (MASH), 10% had worsening of NAFLD activity score (NAS) and 10% had worsening of fibrosis. Overall, 26% of patients had a composite histological endpoint (i.e development of MASH and/or worsening of NAS and/or worsening of fibrosis). Lower baseline LAL/platelet ratio was associated with worsening of NAS, fibrosis and with the composite histological endpoint and remained independently associated with the composite histological endpoint (OR = 0.51, CI 95%0.04-0.60) after adjustment for age, HOMA, gender, CAP and/or LSM. On the other hand, in the whole cohort (n = 144) no statistically significant changes in liver disease assessed non-invasively (median CAP and LSM) was observed.

Conclusion: Measurement of LAL activity could help in identifying patients with a higher risk of MASLD progression towards MASH and fibrosis. In particular, lower LAL activity could be associated with the development of inflammation, a feature not detectable by available non-invasive techniques.

PO6-12
Liver stiffness as a marker of subclinical atherosclerosis in metabolic syndrome

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Background and aims: The aim of this study was to evaluate the correlations between liver fibrosis and arterial stiffness in patients with metabolic syndrome and to determine whether differences exist between patients with and without metabolic syndrome regarding the following parameters: liver stiffness, pulse wave velocity, aortic augmentation index, and common carotid intima-media thickness.

Method: We conducted an observational study including 75 patients (30 men and 45 women) who presented to the Sibiu Clinical County Hospital over one year. All patients underwent clinical, paraclinical, and elastography assessments. Liver stiffness was measured using FibroScan. Arteriograph measurements and carotid ultrasound were performed to assess aortic pulse wave velocity (aoPWV), aortic augmentation index (aoAix), and common carotid intima-media thickness. Patients were divided into two groups: those with metabolic syndrome and those without. Arterial stiffness parameters were compared between groups, and correlations between liver stiffness and arteriograph parameters were analyzed separately for each group.

Results: In patients with metabolic syndrome, correlations between arteriograph measurements and liver fibrosis scores were weak. Conversely, in patients without metabolic syndrome, stronger associations were observed between arterial stiffness and liver fibrosis. In this group, aoPWV correlated with liver stiffness values ($r = 0.149$), while aoAix correlated with liver stiffness ($r = 0.171$) and fibrosis score ($r = 0.213$). A linear correlation was also found between common carotid intima-media thickness and fibrosis score ($r = 0.261$).

Conclusion: Correlations between liver stiffness and arterial stiffness were stronger in patients who did not meet all criteria for metabolic syndrome. In these patients, a significant linear relationship was observed between common carotid intima-media thickness and liver fibrosis score. Arteriograph parameters correlated better with liver stiffness in patients without metabolic syndrome than in those with it. These findings suggest that liver stiffness may serve as a predictor of subclinical atherosclerosis.

PO6-13
Influence of PNPLA3 rs738409 across body mass index categories in metabolic dysfunction–associated steatotic liver disease (MASLD)

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Background and aims: Genetic variants of the patatin-like phospholipase domain-containing 3 (PNPLA3) gene are closely related to hepatic steatosis and fibrosis, but their contribution to the phenotypic heterogeneity of metabolic dysfunction-associated steatotic liver disease (MASLD) remains unclear. Given the metabolic diversity associated with body mass index (BMI), the aim of this study was to evaluate the association between the PNPLA3 rs738409 polymorphism and the risk of MASLD, and to determine whether this effect differs according to BMI category.

Method: A cross-sectional analysis was conducted in 455 categorized according to body mass index (BMI) as individuals with normal weight (n = 161), overweight (n = 217), or obesity (n = 77). The diagnosis of MASLD was based on metabolic and imaging criteria. PNPLA3 rs738409 genotypes (C/C, C/G, G/G) were determined and analyzed under additive and dominant models. Age- and sex-adjusted logistic regression analyses were used.

Results: The 76.7% (n = 349) of individuals were carriers of at least one G allele. Genotype distribution did not differ significantly between BMI categories (p = 0.718). Among normal-weight individuals, PNPLA3 carriers showed a modest and non-significant increase in the risk of MASLD (OR = 1.59, 95% CI: 0.63-4.62, p = 0.356). In the overweight group, carriers showed a trend toward increased risk (OR = 1.86, 95% CI: 0.99-3.52, p = 0.054), with an enrichment of G allele carriers among MASLD cases (80.1% vs. 67.9%, p = 0.042). In the obese group, regression models were unstable due to limited sample size, although descriptive analysis suggested a higher prevalence of the risk genotype among NAFLD cases (74%). In the overall model, BMI remained independently associated with MASLD (OR = 1.86; 95% CI: 1.37-2.43; p < 0.001), while the PNPLA3 × BMI interaction was not significant (OR = 0.83; 95% CI: 0.47-1.09; p = 0.177).

Conclusion: The rs738409 variant of the PNPLA3 gene was highly prevalent in this cohort and was associated with a tendency toward greater susceptibility to MASLD, especially among overweight individuals. The absence of a significant interaction between the gene and BMI suggests that the genetic contribution of PNPLA3 may act additively rather than synergistically with adiposity, while excess body weight remains the dominant factor in metabolic liver injury.

PO6-14-YI

Depression and Anxiety levels are higher in obese women than in men in a cohort of MASLD patients

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Background and aims: Obesity is a major determinant of metabolic dysfunction-associated steatotic liver disease (MASLD) and is closely linked to psychiatric disorders, including depression and anxiety. Increasing evidence highlights the interplay between these conditions with sex and age. We aimed to investigate the prevalence and determinants of depression and anxiety in patients with MASLD.

Method: We prospectively enrolled 277 patients with MASLD (age 54 [20–80] years; 157 males/120 females; BMI 29 [18–46] kg/m²; T2DM: 61 [22.0%]). All patients underwent liver stiffness measurement by FibroScan® 530. Advanced fibrosis was defined according to liver stiffness values ≥8.0 kPa. Depression and anxiety were assessed using the Hospital Anxiety and Depression Scale (HADS), categorized as: 0–7 (normal), 8–10 (borderline), and ≥11 (abnormal).

Results: Overall, 26% of patients showed at least borderline depression (≥8 points) and 28% at least borderline anxiety; notably, 33 patients were already on antidepressant or anxiolytic treatment. Women were more frequently affected than men (depression: 36.7% vs. 17.8%; anxiety: 40.8% vs. 17.9%). In women, depression correlated with BMI (p=0.18, p=0.048), and anxiety correlated inversely with age (ρ= –0.20, p=0.028). The Kruskall-Wallis test, only in women, shows that in females aged ≥50 years, depression levels are higher in patients with a BMI ≥30 (p=0.026). In multivariable logistic regression adjusted for age, BMI, liver stiffness, antidepressants and diabetes, moderate-to-severe depression remained significantly associated with BMI ≥30 (OR=2.2, 95% CI=1.02–4.73, p=0.045).

Conclusion: In patients with MASLD, psychological burden appeared more pronounced among women, with obesity emerging as a key determinant of depression and younger age of anxiety. These findings highlight the importance of systematic psychological assessment, particularly in obese women, to facilitate timely referral and tailored support.

PO6-15
Pbesity - Factor of hepatocarcinogenesis in chronic hepatitis C

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Background and aims: To investigate whether obesity is a risk factor of hepatocarcinogenesis in chronic hepatitis C patients.

Method: We retrospectively analyzed the incidence of hepatocellular carcinoma (HCC) among patients with HCV infection followed up at 5 hospitals. Between 2002 and 2022, a total of 1365 patients who were positive for HCV, negative for HBsAg, and without HCC visited the 5 hospitals and were followed up .They were divided into four groups according to BMI ;BMI <18.5,n=107;18.5< = BMI <25, n=980; 25<=BMI <30,n=251;30<BMI, n=27) and the cumulative incidence rates of HCC were compared , considering age, sex, alcohol intake , and liver function in multivariate analysis.

Results: There were 698 male and 667 female patients with the median age of 60 year (range 15-85). The follow –up period was 16.1+ 3.1 years, amounting to a total observation period of 8326 person-years. HCC developed in 371 patients, showing cumulative incidence rates of 10.8 %, 20.3%, and 38.9% at 3, 5 and 10 years, respectively. The incidence rates differed significantly among the BDI groups (p=0.007 by the long rank test). Univariate analyses showed that older age, male, comorbidity with diabetes mellitus, heavy alcohol intake, low albumin concentration, high AST level, low platelet count, and high AFP concentration were significant risk factors of HCC. Adjusting for these factors, multivariate Cox proportional hazard regression showed that obesity was an independent risk factor of HCC, with a hazard ratio of 1.795 (95% CI:1.074-3.000; p=0.0260) when25<=BMI <30 and 3.210(95%CI:1.469-7.016, p=0.0035) when 30 <BMI as compared to the patients with BMI <18.5.

Conclusion: Obesity is an independent risk factor of hepatocarcinogenesis among chronic hepatitis C patients.

PO7-04
E3 ligase Peli1 promotes both lipid metabolic disorder and inflammation in metabolic dysfunction-associated steatohepatitis

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Background and aims: Metabolic diseases like obesity and fatty liver disease involve disrupted lipid metabolism and chronic inflammation, yet mechanisms linking these processes are unclear. Peli1, an E3 ubiquitin ligase involved in innate immunity, had an undefined role in metabolism. This study investigated whether Peli1 contributes to metabolic dysfunction-associated steatohepatitis (MASH) by regulating the key metabolic transcription factor HNF4α and inflammatory signaling.

Method: Peli1 knockout (Peli1$^{-/-}$) and wild-type (WT) mice were fed a high-fat diet (HFD) or chow for 16 weeks. Metabolic phenotyping included body weight, glucose/insulin tolerance tests, and energy expenditure measurement. Tissues were analyzed for lipid content and gene expression. In vitro studies used primary hepatocytes and other cells from WT and Peli1$^{-/-}$ mice stimulated with free fatty acids (FFA) or poly(I:C). Mechanisms were examined via Western blot, immunoprecipitation (for ubiquitination), and RT-qPCR.

Results: Peli1 deficiency protected mice from HFD-induced obesity and insulin resistance, showing reduced weight gain, improved glucose tolerance, and enhanced insulin signaling (e.g., restored AKT phosphorylation). Peli1$^{-/-}$ mice exhibited less lipid accumulation in liver and adipose tissue. Metabolic chamber analysis revealed higher energy expenditure and increased lipid oxidation in Peli1$^{-/-}$ mice, linked to upregulated hepatic fatty acid oxidation genes (e.g., Cpt1α, Pgc1α). Mechanistically, Peli1 directly bound HNF4α and promoted its Lys48-linked ubiquitination and proteasomal degradation, which was reversed in Peli1$^{-/-}$ mice. Furthermore, Peli1 deficiency suppressed TLR-stimulated pro-inflammatory gene expression (e.g., Il-6, Tnfα) and inhibited activation of NF-κB and MAPK pathways by promoting TRAF3 degradation and c-IAP2 activity.

Conclusion: This study identifies Peli1 as a critical molecular link between nutrient overload, hepatic lipid metabolism, and inflammation in MASH. Its novelty lies in demonstrating that Peli1 directly targets HNF4α for degradation, impairing fatty acid oxidation, while simultaneously activating pro-inflammatory pathways via TLR signaling. Peli1 knockout ameliorates diet-induced metabolic syndrome by stabilizing HNF4α and suppressing inflammation. These findings position Peli1 as a promising therapeutic target for treating metabolic diseases like MASH by simultaneously addressing metabolic dysfunction and inflammation.

PO7-05-YI

The influence of coagulation homeostasis disorders on the development of obstetric complications in pregnant women with metabolic-associated steatohepatitis and dyslipidemia

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Background and aims: Currently, there is growing concern about pregnancy-related, obstetric, and perinatal complications in women affected by MASLD. Our aim: to assess the frequency of obstetric complications and disorders of blood coagulation homeostasis in pregnant women with MASH and obesity.

Method: A prospective randomized clinical study included an examination of 97 pregnants with MASH against the background of obesity. The control group consisted of 40 practically healthy women. All women were divided into 3 groups depending on BMI: Group IA – 31 overweight pregnants, Group IB – 36 pregnants with grade I obesity, Group IC – 30 pregnants with grade II obesity. The assessment of coagulation homeostasis was carried out by studying the overall blood coagulation potential: PT (Prothrombin Time), PTI (Prothrombin Index), potential plasminogen activity (PPA), plasma fibrinogen level and antithrombin III activity.

Results: Pregnant women with MASH on the background of obesity exhibit disturbances in coagulation function with a tendency toward peripheral microthrombosis, DIC syndrome, and macrothrombosis, which may serve as early prognostic criteria for the development of obstetric and perinatal complications. PT was reduced in group IA by 3.5%, in group IB by 14.5%, and in group IC by 17.3% compared to the control group. At the same time, PTI was significantly higher than in the control group: in group IA by 1.12 times, in group IB by 1.20 times, and in pregnant women of group IC by 1.31 times. The fibrinogen level in group IA was elevated 1.29 times, in group IB 1.48 times, and in group IC 1.61 times, while PPA increased 1.06, 1.23, and 1.36 times, respectively, compared to the control group. The detected decrease in antithrombin III activity correlated with the increase in BMI: in the group of pregnant women with NASH and overweight – by 12.9%, with obesity grade I – by 20.6%, and with obesity grade II – by 25.2% compared to the control.

Conclusion: In pregnant women with MASH and obesity, hemostatic disorders were identified, depending on the degree of obesity. The coagulation imbalance is accompanied by a significant increase in obstetric complications such as placental dysfunction (12.3-fold), fetal growth restriction in every 4th pregnants, preeclampsia in every 3rd woman, and hemorrhage in every 7th woman. This necessitates timely correction of the impact of comorbid pathology (MASH with obesity) from the early stages of gestation to enable timely prediction and prevention of obstetric risks.

PO7-08

Associations between glycaemic indices and non-invasive markers of hepatic steatosis and steatohepatitis in Chinese adults with prediabetes

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Background and aims: Metabolic dysfunction–associated steatotic liver disease (MASLD) and steatohepatitis (MASH) are strongly linked with insulin resistance and chronic hyperglycaemia in type 2 diabetes mellitus. However, their associations with dysglycaemia in prediabetes remain insufficiently explored. This study investigated associations between glycaemic indices and non-invasive markers of MASLD and MASH risk in a Chinese cohort with prediabetes.

Method: This cross-sectional study included 173 adults (mean age 60.5 ± 7.5 years, 38.2% male) with prediabetes recruited from a community metabolic screening programme in Hong Kong. Participants underwent an oral glucose tolerance test and transient elastography (FibroScan) to assess glycaemic and hepatic parameters. Glycaemic indices included fasting, 1-hour, and 2-hour glucose and HbA1c. Hepatic steatosis and MASH risk were evaluated using the controlled attenuation parameter (CAP) and FibroScan–AST (FAST) score, respectively. Associations between each glycaemic index-liver parameter pair were evaluated by bivariate correlation and multivariable linear regression. Models were progressively adjusted for age, sex, and alcohol use (Base model), with further adjustment for physical and sedentary activity (Model 1).

Results: MASLD was present in 60.0% of participants, with a mean CAP of 262.9 ± 58.1 dB/m. The median (interquartile range) FAST score was 0.08 (0.09), indicating a low overall MASH risk. For CAP, only 2-hour glucose showed a significant correlation in unadjusted analysis ($r = 0.20$, $p = 0.010$). This correlation persisted as an independent association after adjustment for age, sex, and alcohol use ($\beta = 0.23$, $p = 0.003$) and remained significant after further adjustment for physical and sedentary activity ($\beta = 0.18$, $p = 0.032$). Fasting glucose, 1-hour glucose, and HbA1c were not significantly associated with CAP in any model (all $p > 0.05$). In contrast, none of the glycaemic indices showed significant correlations or adjusted associations with MASH risk assessed by the FAST score.

Conclusion: 2-hour postprandial glucose showed the strongest association with hepatic steatosis, while no glycaemic index was linked to MASH risk. These findings highlight that post-load dysglycaemia, an established driver of steatosis in diabetes, is already associated with hepatic fat accumulation at the prediabetic stage and may represent an early intervention target. Longitudinal studies are necessary to clarify causality and clinical implications for MASLD prevention.

PO7-09-YI

Assessing the enhanced Liver Fibrosis® test for identifying MASLD patients eligible for pharmacological treatment

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Background and aims: Identifying patients with metabolic dysfunction-associated steatotic liver disease (MASLD) who could benefit from approved pharmacological treatments (Resmetirom/Semaglutide) remains a clinical challenge. The Enhanced Liver Fibrosis® (ELF) test has been proposed as a non-invasive diagnostic tool in this setting. The aim of this study was to evaluate the diagnostic performance of ELF test, alone and in combination with transient elastography (TE), in identifying fibrosis stages 2–3 (F2–F3), and to assess the influence of metabolic profile on test performance.

Method: Cross-sectional study incluiding MASLD patients with available liver biopsy, ELF, and TE performed within ≤6 months. Patients with F2–F3 fibrosis by biopsy were considered eligible for treatment. Cut-offs used were as follows: TE 10–19.9kPa, ELF 9.8–11.3 (alone) and ELF 9.2–9.7 (combined with TE). Sensitivity, specificity, predictive values, and diagnostic accuracy were calculated for the overall cohort and for subgroups with type 2 diabetes (T2DM) and obesity (BMI ≥30).

Results: A total of 112 patients were included; 49 (43.7%) had fibrosis stages 2-3, 36 (16.1%) had stages 0-1 and 27 (12.1%) had stage 4 by biopsy. TE was the most sensitive test in the overall cohort (53%; 95% CI 39.4–66.3%; p=0.01) and also in both subgroups, where it showed the same sensitivity (58.6%; 95% CI 40.7–74.5; p=0.06). The TE-ELF combination demonstrated the highest specificity across all scenarios: overall cohort (88.9%; 95% CI 78.8–94.5%; p≤0.001), BMI≥30 (91.8%; 95% CI 80.8–96.8%; p≤0.001) and T2DM (81.1%; 95% CI 65.8–90.5%; p=0.03). In BMI≥30, the TE-ELF combination achieved the highest diagnostic accuracy (67.9%; 95% CI 56.9–77.3%; p=0.22), whereas in diabetic patients, no significant differences in accuracy were observed between the tests.

Conclusion: ELF is comparable to TE in identifying MASLD patients eligible for pharmacological treatment, regardless of metabolic profile. The combination of both methods improves diagnostic accuracy, increases specificity, and reduces false positives, particularly in patients with obesity.

PO7-11
A multidisciplinary care pathway enhances MASLD screening and cardiometabolic management in real-world secondary care.

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Background and aims: Patients with cardiometabolic risk factors are at high risk for Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD), yet screening and management remain inconsistent in secondary care. Following a retrospective audit showing major practice gaps, the prospective phase of the OPTIMA-NASH project evaluated the real-world impact of a structured multidisciplinary care pathway on adherence to diagnostic and therapeutic recommendations.

Method: Outpatients attending cardiology, diabetology, lipidology and hepatology clinics in a large metropolitan hospital were prospectively managed according to an integrated flowchart derived from 2024 EASL-EASD-EASO guidelines. Key indicators included completeness of cardiometabolic profiling, use of non-invasive fibrosis scores, and achievement of guideline-based therapeutic targets for blood pressure, glycaemia, and lipids. Data were compared with the retrospective cohort previously audited in the same setting.

Results: Among 143 prospectively enrolled patients (mean age 67 ± 11 years, 71% male), complete cardiometabolic profiling increased from 76% to 98% ($p<0.001$). Appropriate FIB-4 testing rose from 13% to 99% ($p<0.001$). Achievement of at least one therapeutic target (HbA1c ≤6.5%, triglycerides <150 mg/dL, LDL-C according to ESC/EAS risk class, blood pressure <130/85 mmHg) significantly improved ($p<0.001$). The use of glucose-lowering agents with established cardiovascular and metabolic benefits, such as GLP-1 receptor agonists and SGLT2 inhibitors, increased from 11–13% to 22–25% ($p<0.01$).

Conclusion: The prospective implementation of a standardized multidisciplinary pathway substantially enhanced adherence to MASLD screening and cardiometabolic management in secondary care. Structured cross-specialty collaboration effectively bridged diagnostic and therapeutic gaps, supporting early identification and optimal care of at-risk patients.

PO7-12
Efficacy of luseogliflozin in elderly patients with type 2 diabetes and metabolic dysfunction associated steatotic liver disease

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Background and aims: Metabolic dysfunction associated steatotic liver disease (MASLD) is the most common chronic liver disease. Sodium glucose cotransporter 2 inhibitors (SGLT2i) are widely used in the treatment of type 2 diabetes and have been reported to improve MASLD and metabolic dysfunction-associated steatohepatitis (MASH). Among SGLT2i, luseogliflozin is notable for not causing a significant increase in plasma concentration, even in patients with impaired liver function. We aimed to evaluate the effects of luseogliflozin on MASLD especially in elderly patients with type 2 diabetes.

Method: A total of 34 consecutive patients with type 2 diabetes and MASLD were treated with luseogliflozin for 24 weeks. Patients were divided into two groups based on age: ≥70 years (n=15) and <70 years (n=12). Laboratory data, including alanine aminotransferase (ALT) as a marker of liver function and the fibrosis-4 (FIB-4) index as a marker of liver fibrosis, were assessed at baseline, 12 weeks, and 24 weeks.

Results: Overall, ALT levels significantly decreased [33.6 ± 20.0 U/L at baseline to 27.6 ± 16.9 U/L at 12 weeks ($p < 0.01$)]. Both the elderly and non-elderly groups also showed significant reductions in ALT [24.8 ± 10.2 U/L at baseline to 20.7 ± 6.3 U/L at 12 weeks ($p = 0.03$), and 41.5 ± 23.3 U/L at baseline to 33.7 ± 20.8 U/L at 12 weeks ($p = 0.02$), respectively]. No significant changes in the FIB-4 index were observed during the study period.

Conclusion: Luseogliflozin improved ALT levels in elderly patients as well as in non-elderly patients. These findings suggest that luseogliflozin may represent a therapeutic option for elderly patients with type 2 diabetes and MASLD.

PO7-13-YI

Aldafermin as a promising therapy for metabolic dysfunction–associated steatotic liver disease: evidence from a meta-analysis of randomized trials

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a chronic liver disease marked by liver injury, inflammation and cirrhosis. MASLD is associated with high mortality rate and liver transplantation. Aldafermin, a synthetic version of the human hormone FGF19, is among the emerging therapeutic agents that improve and regulate the liver pathogenesis in MASLD patients. This meta-analysis aimed to assess the therapeutic efficacy and safety profile of aldafermin in patients with MASLD.

Method: We searched on Scopus, Cochrane Library, PubMed and Web of Science till September 2025 to include the randomized controlled trials (RCTs) that met our criteria. We pooled the estimate as risk ratio (RR) with the corresponding 95% confidence intervals for all dichotomous outcomes. We pooled the estimate as Mean Difference (MD) for all continuous outcomes with the corresponding 95% confidence intervals. There were two different doses of aldafermin, 1mg and 3mg, therefore we conducted subgroub analysis to check the efficacy of the two doses.

Results: A total of four RCTs containing 491 patients were analyzed. Aldafermin improved the reduction of aspartate aminotransferase levels (MD: − 11.79, 95 % CI [− 18.06 to − 5.51]) and (MD: − 13.9, 95 % CI [− 18.59 to − 9.21]), alanine aminotransferase levels (MD: − 19.79, 95 % CI [− 30.28 to − 9.3]) and (MD: − 21.91, 95 % CI [− 29.62 to − 14.21]), enhanced liver fibrosis score (ELF) (MD: − 0.13, 95 % CI [− 0.29 to 0.02]) and (MD: − 0.33, 95 % CI [− 0.50 to − 0.17]), and liver fat content by at least 30% in a dose-dependent manner (RR: 2.16, 95 % CI [1.41 to 3.32]) and (RR: 5.00, 95 % CI [1.34 to 18.64]), in the 1 mg and 3 mg subgroups respectively. The aldafermin group did not exhibit any significant differences in histologic endpoints, lipid profile, metabolic parameters, or overall side effects, however, there is exception of the higher incidence of diarrhea in the aldafermin 3 mg group.

Conclusion: Aldafermin significantly decreases liver fat content, serum fibrosis markers, and liver enzyme levels, suggesting that it is a safe and feasible treatment option for MASLD. Despite encouraging numerical trends, its effect on histologic endpoints is still statistically misleading. To confirm these results and demonstrate long term efficacy, Larger and prolonged RCTs are required to enhance the validity of the evidence further.

PO7-14

Weight-adjusted waist index as an anthropometric marker of metabolic- dysfunction associated steatotic liver disease: the role of lipoprotein receptor–related protein 5 gene variants

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Background and aims: Metabolic dysfunction–associated steatotic liver disease (MASLD) is the hepatic manifestation of metabolic syndrome and the most common cause of chronic liver disease worldwide. Closely linked to obesity and metabolic risk, MASLD contributes substantially to morbidity and mortality. Early identification using non-invasive anthropometric markers is crucial. The Weight-Adjusted Waist Index (WWI), combining waist circumference and body weight, has been proposed as a novel indicator of central adiposity. This study investigated the relationship between LRP5 gene variants, WWI, and MASLD risk.

Method: Participants were voluntarily recruited and provided written informed consent. A structured questionnaire included sociodemographic data and anthropometric measurements. Body weight, height, waist and hip circumferences were measured following standard procedures. WWI is calculated by dividing waist circumference (cm) by the square root of body weight (kg) The LRP5 rs4988321 polymorphism was genotyped using the TaqMan SNP Genotyping Assay from venous blood samples.

Results: A total of 106 participants (59 MASLD patients and 47 controls) were included. The median age of the MASLD group was 46 years versus 30 years in controls (Mann–Whitney U = 710.0, $p < 0.001$). Waist circumference was 100.0 cm versus 89.5 cm (U = 507.5, $p < 0.001$). The mean hip circumference was 112.26 ± 9.96 cm and 103.85 ± 8.70 cm, and BMI 31.50 ± 4.96 kg/m² versus 25.21± 4.77 kg/m² (both $p < 0.001$). Waist-to-hip ratio (0.91±0.08 vs 0.86 ± 0.09, $p = 0.002$) and WWI (11.19 ± 0.76 vs 10.55 ± 0.92, $p < 0.001$) were significantly higher in the MASLD group. MASLD prevalence increased across WWI categories: 25.0% (low), 46.2% (medium), and 73.1% (high) ($\chi^2 = 14.120$, $p = 0.001$). The linear-by-linear association test confirmed a significant positive trend ($p < 0.001$). Genotype frequencies for GG and GA+AA were 81.4% and 18.6% in the MASLD group, and 76.6% and 23.4% in controls, showing no significant difference ($\chi^2 = 0.360$, $p = 0.548$; Fisher's Exact $p = 0.632$). The relationship between WWI and LRP5 genotypes was also not significant ($\chi^2 = 3.513$, $p = 0.173$).

Conclusion: Anthropometric parameters including age, BMI, waist circumference, and WWI were significantly higher in individuals with MASLD. Both chi-square and linear-by-linear association analyses demonstrated that MASLD prevalence increased with higher WWI levels, whereas LRP5 rs4988321 genotype variations were not associated with WWI or disease status.

PO8-03-YI

The association between adipose tissue dysfunction and MASH severity is mediated by insulin resistance, regardless of BMI

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Background and aims: In metabolic dysfunction–associated steatohepatitis (MASH), lipotoxicity and insulin resistance are key drivers of disease pathogenesis. Adipose tissue dysfunction contributes primarily through excessive free fatty acid (FFA) release and dysregulated adipokine signaling. However, the relationship between adipose tissue insulin resistance (AT-IR), AT dysfunction, and the histological severity of hepatic inflammation and fibrosis remains unclear, partly due to limited biopsy-based data on inflammation.

Method: Markers of AT dysfunction (MCP-1, TNF-α, leptin, adiponectin), insulin resistance (AT-IR = FFA × insulin and HOMA-IR), hepatic lipid oxidation (β-hydroxybutyrate, BHB), circulating lipids and apolipoproteins were measured in individuals with biopsy-proven metabolic dysfunction-associated steatotic liver disease from the European SLD Registry. Stable isotope fluxomics was used to investigate AT-lipolysis in a subgroup of patients. MASH severity was evaluated in terms of fibrosis stage and activity score. Multivariable regression and mediation analysis were used to elucidate direct and indirect associations.

Results: The cohort included 463 individuals (35% females) with and without type 2 diabetes (T2D, 41% vs 59% respectively) and with a wide range of BMI (20-60 kg/m^2), ranging across the full spectrum of MASLD. MASH severity was found associated with increased AT-IR and altered cytokine profiles, independently of BMI and T2D. In particular, we found an association between fibrosis and increased TNF-α and MCP-1 (also known as CCL2) and between activity score ≥2 and altered MCP1 and adiponectin. On the contrary, FFA and BHB, as well as triglycerides and apoliproteins, were not associated with MASLD severity or BMI, but instead they were increased with T2D. Given the strong correlation between AT-IR and these circulating proteins levels (TNF-α, MCP-1 and Leptin), we used mediation analysis to untangle the observed net of associations. We found that the association between TNF-α and MASH severity is mediated by AT-IR, while MCP-1 showed also a direct effect on both hepatic inflammation and fibrosis, independently of BMI and T2D.

Conclusion: MASH severity is not strictly linked to BMI or T2D alone, but rather to dysfunctional adipose tissue and insulin resistance. Moving toward a holistic phenotyping of individuals with MASLD is essential to improve risk stratification and targeted interventions.

PO8-04-YI

Liver stiffness dynamics in patients with metabolic dysfunction-associated steatotic liver disease: a prospective real-life study

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Background and aims: Static measurements of liver stiffness (LS) assessed by transient elastography are mainly used in routine practice to evaluate metabolic dysfunction-associated steatotic liver disease (MASLD), whereas dynamic data are lacking. We wanted to evaluate longitudinal LS to reflect the evolution of MASLD.

Method: Patients with MASLD assessed with serial LS from baseline diagnostic and at one- and three-year follow-ups (FU) were prospectively included. Patients were classified as progressors (PRO, > 20 % LS increase compared to baseline), stable (STB, between -20 and +20 %) and improvers (IMP, > 20 % LS decrease compared to baseline).

Results: 192 patients diagnosed with MASLD were included. At baseline, 57 % were F0-F1, 38 % were F2-F3 and 5 % were F4. 36 % were treated for type 2 diabetes. Initial management included lifestyle advice (74 %), dietitian support (8 %), inclusion in an interventional clinical trial (7 %), bariatric surgery (BS, 6 %) and glucagon-like peptide-1 receptor agonist (GLP1-RA, 3 %). After one year (n = 192), 30 % were IMP, 47 % were STB and 23 % were PRO. IMP at one-year were characterised at baseline by a higher body mass index (IMP, median, 32.0 vs. STB, 30.5 vs. PRO, 30.9 kg/m²; p = 0.027), a larger waist circumference (115 vs. 107 vs. 107 cm; p = 0.002) and a higher LS (8.9 kPa vs. 6.3 vs. 5.0; p < 0.001). Moreover, IMP had a greater reduction than PRO in body weight (BW, -5 vs. 0 %; p < 0.001), alanine aminotransferase (-34 vs. -8 %; p = 0.004), gamma-glutamyl transferase (-25 vs. -5 %; p = 0.032) and steatosis (-7 vs. -2 %; p = 0.045). BS was present in IMP (14 %) and STB (3 %), while GLP1-RA treatment was present only in STB (6 %). In multivariate logistic regression, a lower baseline LS (OR = 0.686; 95% CI: 0.536 – 0.841; p < 0.001) and an increase in BW (1.082; 1.007 – 1.182; p < 0.031) were independent predictors of being PRO. After three years (n = 134), the proportion of patients in the three groups remained similar (IMP 34 %; STB 42 %; PRO 25 %) with the same characteristics.

Conclusion: We provide the first prospective data on standardised longitudinal LS in real-life conditions within a MASLD cohort. The majority of patients remains stable at one and three years, with normal baseline LS. Screening for advanced fibrosis leads to effective and sustainable lifestyle advice. Patients with low LS and increasing body weight should be monitored.

PO8-05
Clinical relevance of repeating FIB-4 in the screening strategy for identifying MASLD-related advanced fibrosis

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Background and aims: The EASL-EASD-EASO guidelines recently proposed a screening strategy for MASLD-related advanced fibrosis (AF). In patients with intermediate FIB-4 (1.30-2.67), two strategies are proposed: i) the immediate referral to hepatologist for a second-line test, or ii) repeating FIB-4 at 1 year after intensified management of comorbidities. In patients with initial low FIB-4 < 1.30, monitoring FIB-4 every 1-3 years is suggested. However, there are no strong evidence supporting these recommendations. Therefore, we assessed the clinical relevance of these recommendations.

Method: A retrospective cohort including MASLD patients with low or intermediate FIB-4 was conducted in 2 tertiary centers between 2018-2022. Inclusion criteria were the access to a liver stiffness measurement (LSM) concomitantly to the initial FIB-4, and repeated FIB-4 during follow-up.

Results: 625 patients were included. Median BMI was 34.0 kg/m^2 (30.8-39.0) and 70.7% of patients had T2D. Initial median FIB-4 was 1.31 (0.95-1.74) and 35.7% of patients had a high risk for AF. After 3 years of follow-up, median FIB-4 remained stable at 1.32 (1.01-1.92).

Respectively, 21.3% and 22.4% of patients with initial low FIB-4 changed to the intermediate category at 1 and 3y. The negative predictive value for AF detection was not improved by repeating FIB-4 (76.8% at baseline, 71.6% at 1y and 75.3% at 3y).

Factors predicting change in FIB-4 category at 3y were age (OR: 1.16; CI95%: 1.0-1.1; p < 0.001), arterial hypertension (OR: 2.0; CI95%: 1.1-4.0; p = 0.019) and GLP1-RA introduction during the 3y period (OR: 0.2; CI95%: 0.0-0.7; p = 0.015).

In patients with an initial intermediate FIB-4, 77.2% remain stable at 1y and 68.5% at 3y. Decrease from intermediate to low category occurred in 13.3% of patients at 1y and 16.8% at 3y. Factors associated with FIB-4 decrease at 1y were weight loss (OR: 1.1; CI95%: 1.0-1.1; p = 0.029) and introduction of a GLP1-RA during the year (OR: 4.4; CI95%: 1.2-16.6; p = 0.029).

Conclusion: The majority of MASLD patients did not change of FIB-4 category in a 3y time frame. Repeating FIB-4 over time does not seem effective in picking up false negative cases. In case of intermediate FIB-4, weight loss and GLP1-RA treatment are associated with FIB-4 normalization at 1y, but this effect is temporary and observed in few patients. These data suggest that a second-line NIT should be systemically performed in patients with intermediate FIB-4 in order to limit clinical inertia.

PO8-06-YI
Minimal detectable change for non-invasive monitoring of steaotic liver disease

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Background and aims: Non-invasive fibrosis tests (NITs) are frequently used to monitor liver disease in different settings, but their reproducibility/precision is unclear.

Method: We retrospectively studied agreement and the minimal detectable change (MDC; reflecting the smallest difference that likely represents a true change) of blood-based NITs and vibration-controlled transient elastography (VCTE) in clinical scenarios from suspected metabolic dysfunction-associated steatotic liver disease (cohort I, n=61), suspected fibrosis (cohort II, n=384), suspected portal hypertension (cohort III, n=90) and clinically significant portal hypertension (cohort IV, n=67). Same-day repeatability was studied within subgroups.

Results: Patients had a mean age of 45-58 years, ~2/3 were male, the prevalence of obesity was 30-60%. Median LSM and prevalence of advanced fibrosis increased along cohorts I-IV. LSM and LSM-based scores (FIB-4/APRI to a smaller extent) tended to decrease from cohorts II-IV, with increasing variation at higher biomarker values (kPa) and in more advanced cohorts (I-IV). Agreement was good to excellent for all NITs, especially composite lab-based scores. MDC (absolute and relative) was essentially dependent on the setting, and increased for LSM and FIB-4/APRI from cohorts I-IV (for LSM: >2.0kPa [>35%] in cohort I to >9.7-37.6kPa [>68-88%] in cohorts II-IV). Same-day repeatability was >34% for LSM and 10-87% for standard laboratory tests.

Conclusion: The MDC of NITs varies significantly with disease severity and clinical context. This underscores the critical need to account for specific settings and background disease severity when interpretating NIT dynamics over time.

PO8-07-YI
Relationship between thyroid function and the development of liver and cardiovascular events in patients with MASLD

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Background and aims: The impact of thyroid function on liver disease progression in patients with metabolic dysfunction-associated steatotic liver disease (MASLD) remains unclear. We aimed to evaluate its association with the risk of major liver and cardiovascular events.

Method: Single-center retrospective study including MASLD patients with ≥1 year follow-up and repeated thyroid measurements (TSH, T3, T4). Demographic, laboratory, transient elastography (LSM), metabolic, and CV comorbidity data were collected. Major liver outcomes (MALO): hepatocellular carcinoma, liver transplantation, liver-related death, or hepatic decompensation; major CV events (MACE): cardiac death, ischemic heart disease, or stroke. Bivariate and adjusted multivariate analyses were conducted according to event occurrence.

Results: Of the 2310 patients evaluated, 904 met inclusion criteria and were analyzed (mean age 57 years, 55% women; BMI 32.9 ± 6.2 kg/m²), with median follow-up of 4.5 years. Hypertension, diabetes, and dyslipidemia were present in 53.9%, 43.5%, and 57.2%, respectively; 14.9% had prior CV disease and 16.5% thyroid dysfunction, predominantly hypothyroidism.

Patients who developed MALO were older, had lower BMI, worse liver profile, and higher baseline LSM (31 ± 20 vs 12 ± 10 kPa; p<0.001). They exhibited higher mean TSH (3.20 ± 2.96 vs 2.58 ± 1.86 mIU/L; p=0.026) and lower T3 (2.45 ± 0.62 vs 3.22 ± 0.58 ng/dL; p<0.001) and T4 (1.10 ± 0.14 vs 1.17 ± 0.15 ng/dL; p<0.001). In multivariate analysis adjusted for MELD, platelets, LSM, and age, elevated TSH was associated with higher risk of MALO (OR 1.18; 1.02–1.35; p=0.021), whereas T3 was protective (OR 0.13; 0.04–0.40; p < 0.001) and T4 showed a similar trend (OR 0.09; 0.007–1.17; p=0.067).

Patients who developed MACE were older, predominantly male, had worse metabolic profiles, and more CV comorbidities. They presented with higher TSH (3.34 ± 2.17 vs 2.58 ± 1.92 mIU/L; p=0.035) and lower T3 (2.81 ± 0.39 vs 3.20 ± 0.62 ng/dL; p < 0.001), T4 showed no differences. Adjusted models accounting for age, sex, prior cardiovascular disease, and smoking showed TSH increased MACE risk (OR 1.19; 1.02–1.39; p=0.029) and T3 decreased it (OR 0.32; 0.13–0.79; p=0.014).

Conclusion: In MASLD, a profile of reduced thyroid activity characterized by elevated TSH and decreased T3 was associated higher risk of both MALO and MACE, whereas T4 was related only to MALO. These findings suggest a potential role of thyroid function as a relevant prognostic marker in MASLD.

PO8-08
Biomarkers of cardiometabolic risks for disease severity prediction in metabolic dysfunction-associated steatotic liver disease patients

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is associated with cardiometabolic risk factors (CMRFs). We aimed to evaluate the impact of CMRFs and biomarkers on disease severity in MASLD.

Method: We conducted the analysis by using the database from a nationwide SLD registry database in Taiwan.

Results: A total of 2,882 MASLD patients (54.1% males, mean age = 55.6 ± 13.9 years, mean body mass index [BMI]= 28.1 ± 4.9 kg/m^2) were recruited. The proportions of patient carrying CMRFs of overweight/obesity, hypertension, hypertriglyceridemia, low high-density lipoprotein cholesterol (HDL-C) level, and diabetes/prediabetes were 91.2%, 74.5%, 54.8%, 59.6%, and 74.5%, respectively. There was a significant linear trend between advanced fibrosis and the items of CMRFs (5.9%, 25% and 56.6% in patients with one CMRF, 3 CMRFs, and ≥ 4 CMRFs, respectively, P< 0.001). Compared with 4.4% (85/1,925) of advanced fibrosis in patients who had high sensitivity C-reactive protein (hs-CRP) < 1mg/L, the proportions of advanced fibrosis in patients who had hs-CRP 1-3mg/L and >3mg/L were 7.5% (32/425, aOR= 1.76, 95% CI= 1.16-2.68, P= 0.01) and 7.4% (21/285, aOR= 1.72, 95% CI= 1.05-2.82, P= 0.03), respectively. The aOR for advanced fibrosis in patients of hemoglobin A1c (HbA1c) 5.7-6.5%, 6.5-8.0%, and > 8.0% were 1.02 (95% CI= 0.68-1.53, P= 0.93), 1.83 (95% CI= 1.16-2.88, P= 0.01), and 2.78 (95% CI= 1.45-5.34, P= 0.002), respectively.

Conclusion: There was a significant linear association between advanced fibrosis and the items of CMRFs. Biomarkers of CMRFs could serve as the predictive biomarkers for advanced fibrosis.

PO8-09
Statins in cirrhosis and its complications: An umbrella review and meta-analysis of systematic reviews

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Background and aims: Statins have been proposed as hepatoprotective agents in cirrhosis, but evidence from systematic reviews is inconsistent and often overlapping. We conducted an umbrella review to synthesise available data and address study overlap.

Method: We searched PubMed, EMBASE, and the Cochrane Library up to December 2024 for systematic reviews of statin therapy in cirrhosis. Quality was assessed with AMSTAR-2, study overlap was quantified using corrected covered area (CCA) and reduced through hierarchical exclusion prioritising methodological rigour, comprehensiveness, and recency. Random-effects meta-analyses were performed with comprehensive bias assessment.

Results: Of 847 records screened, 13 systematic reviews (168 unique studies; 10.736.270 participants from 34 countries) were included after overlap adjustment (final CCA = 4.41%). Statins were associated with a substantial reduction in hepatocellular carcinoma risk (HR 0.53, 95% CI 0.48–0.59, I^2 = 46.7%) and hepatic decompensation (HR 0.54, 95% CI 0.49–0.59, I^2 = 0.1%). Geographic heterogeneity was significant: Asian populations showed stronger benefits (HCC: HR 0.49, 95% CI 0.45–0.53, I^2 = 0%) compared to Western populations (HR 0.71, 95% CI 0.52–0.96, I^2 = 95.7%, p for subgroup difference = 0.003). All-cause mortality was reduced (HR 0.65, 95% CI 0.52–0.81) but with substantial heterogeneity (I^2 = 80%). Leave-one-out sensitivity analysis confirmed the robustness of HCC findings (HR range 0.51–0.56). Publication bias assessment showed no significant asymmetry.

Conclusion: This umbrella review demonstrates robust associations between statin use and reduced risks of HCC and hepatic decompensation in cirrhosis, with particularly strong effects in Asian populations. These findings support continuing statin therapy in patients with compensated cirrhosis for both cardiovascular and potential hepatoprotective benefits. Future research should explore the mechanisms underlying geographic differences and establish optimal dosing strategies. The development of LDL-cholesterol targets for hepatoprotection represents an important area for future investigation.

PO8-10
Two-step algorithm using FIB-4 followed by M2BPGi for high-risk SLD

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Background and aims: In Japan, the proportion of steatotic liver disease (SLD) within chronic liver disease is increasing. Establishing a practical system to efficiently identify high-risk SLD—patients with F2–F3 fibrosis who may be candidates for therapy—is a clinical priority. With population ageing, the intermediate FIB-4 category becomes relatively large, so re-classification is required in real-world practice. Although guidelines propose stepwise evaluation after FIB-4 using VCTE or serum fibrosis markers, VCTE (FibroScan) is difficult to implement in primary care due to cost and installation. We therefore evaluated a two-step approach: exclude low risk with FIB-4, then apply M2BPGi to the intermediate category.

Method: We retrospectively analyzed adults with suspected SLD who underwent concurrent attenuation imaging (ATT) and point shear-wave elastography (pSWE) using Arietta 850 deepinsight (Fujifilm Medical, Japan) between January 2020 and December 2023. SLD was defined as ATT ≥0.67 dB/cm/MHz. Fibrosis thresholds were F2+ = pSWE ≥7.0 kPa and F3+ = ≥11.0 kPa. After excluding viral hepatitis and autoimmune liver disease, 422 SLD cases were included (of 661 with concurrent ATT/pSWE). M2BPGi was available in 362 and FIB-4 in 414. The primary endpoint was diagnostic performance for F2+ and F3+; the key secondary endpoint was risk re-classification within the intermediate FIB-4 category using M2BPGi (cut-off 1.00 COI).

Results: AUROC for F2+ was 0.710 (95%CI 0.66–0.76) with FIB-4 and 0.689 (0.63–0.74) with M2BPGi; for F3+, 0.765 (0.71–0.83) and 0.728 (0.66–0.80), respectively. The FIB-4 distribution was low 43.0%, intermediate 31.4%, and high 25.7%. Positivity rates were 27.6% / 52.7% / 66.7% for F2+ and 4.4% / 22.1% / 36.3% for F3+ across low/intermediate/high. Within the intermediate FIB-4 category, M2BPGi increased the post-test probability for F2+ from 36.7% to 65.1%, and for F3+ from 10.2% to 30.2%, indicating strengthened capture of advanced cases. As a reference, FIB-4 ≥2.67 yielded PPV 66.7% (F2+) and 36.3% (F3+) with reduced sensitivity, supporting two-step triage in the intermediate category.

Conclusion: A two-step pathway that excludes low risk with FIB-4, applies M2BPGi only to the intermediate FIB-4 category, and refers the high FIB-4 category directly to hepatology raises the post-test probability of F2–F3 high-risk SLD to a practical level and is feasible in primary care.

PO8-11
Homocysteine as a new indicator of cardiovascular risk and fibrosis in paediatric metabolic dysfunction-associated steatotic liver disease

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD), the most prevalent chronic liver disease in the pediatric population, is associated with an elevated risk of progression to steatohepatitis (MASH), hepatic fibrosis, and cardiovascular (CV) events. The early identification of children with MASLD at risk for advanced liver fibrosis and cardiometabolic complications remains a significant clinical challenge. Recent studies elevated homocysteine (Hcy) levels as strong predictors of MASLD severity and CV risk in adults. However, their diagnostic and prognostic utility in pediatric populations remains limited and requires further validation. Our study aimed to evaluate the role of Hcy as an indicator of hepatic and CV risk in pediatric MASLD.

Method: In this observational study, we enrolled 182 children diagnosed with MASLD (mean age 10.89 years). Among them, 93 (51.1%) had mild steatotic liver disease (Mild SLD), while 89 (48.9%), with moderate-to-severe SLD at ultrasound, underwent liver biopsy. Besides the clinical parameters, we analysed CV risk parameters, including systolic and diastolic blood pressure (SBP and DBP), the triglycerides (TGs)/high-density lipoprotein (HDL) ratio by standard laboratory procedures, and serum Hcy levels, by high-performance liquid chromatography with fluorimetric detection.

Results: Our results revealed that the MASH group showed higher ALT, AST, insulin, HOMA-IR, and FIB-4 values, and lower HDL levels than the mild and all SLD. Analysis of CV risk parameters revealed that TG/HDL ratio and Hcy levels were significantly elevated in MASH patients compared with SLD groups. In the MASH group, the correlation analysis with biochemical and histological parameters showed a positive association between Hcy levels with insulin resistance (HOMA-IR: $r=0.31$, $p=0.02$), TGs/HDL ratio ($r=0.43$, $p=0.02$) and the degree of hepatic fibrosis ($r=0.27$, $p=0.032$), respectively. Furthermore, Hcy demonstrated a strong diagnostic performance for detecting significant fibrosis ($F>1$), with an area under the receiver operating characteristic curve (AUC) of 0.809 ($p<0.001$), outperforming conventional non-invasive fibrosis scores such as APRI (AUC =0.50, $p > 0.05$) and FIB-4 (AUC=0.67, $p >0.05$).

Conclusion: Our results support the potential role of Hcy as a robust, non-invasive biomarker for stratifying not only CV risk but also hepatic fibrosis in children with MASLD.

PO8-13-YI
Metformin and mortality in SLD patients with diabetes: A propensity score-matched analysis

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Background and aims: Steatotic liver disease (SLD) affects 65% of patients with type 2 diabetes mellitus (T2DM), creating a substantial mortality burden. Metformin's impact on mortality in SLD patients with diabetes remains inadequately characterized, particularly across different disease severity strata.

Method: We analyzed NHANES data (2007-2018) linked to mortality data, including adults with SLD and T2DM requiring pharmacotherapy. We compared metformin users to patients using other antidiabetic medications through 1:2 propensity score matching (PSM) and inverse probability of treatment weighting (IPTW). The primary outcome was all-cause mortality with prespecified subgroup analyses stratified by insulin use and chronic kidney disease status. Interaction testing was performed using product terms in Cox models.

Results: Among 2,540 participants (1,920 metformin users, 620 controls) followed for a median of 8.3 years, PSM yielded 906 well-balanced participants (343 controls matched to 563 metformin users). Overall, metformin use is associated with significantly lower all-cause mortality (HR 0.64, 95% CI 0.44-0.93, p=0.020), representing a 36% relative risk reduction. In stratified analyses, non-insulin users (n=697, 71.7%) demonstrated significant mortality reduction (HR 0.64, 95% CI 0.45-0.90, p=0.011), which remained consistent across IPTW methods (IPTW-Overlap: HR 0.70, p=0.045). Among insulin users (n=209, 28.3%), results showed similar point estimates but wider confidence intervals (HR 0.61, 95% CI 0.28-1.33, p=0.212). The test for interaction between insulin use and metformin effect was not statistically significant (p=0.182), indicating no evidence of effect modification by insulin use despite differences in precision. Alternative IPTW approaches in insulin users showed heterogeneous results: IPTW-ATC suggested potential harm (HR 1.21, p=0.461), while IPTW-ATT (HR 0.41, p=0.002) and overlap weights (HR 0.58, p=0.034) indicated benefit, suggesting residual confounding by disease severity. Results were also consistent across chronic kidney disease strata with no evidence of effect modification (p-interaction=0.692).

Conclusion: Metformin associated with substantial mortality reduction in SLD patients with diabetes, with consistent benefits across insulin use strata, suggesting benefits may extend across different levels of diabetes severity.

PO8-14-YI

Investigation of metabolic dysfunction associated steatotic liver disease (MASLD) prevalence in a Hungarian autoimmune liver disease (AILD) patient population

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Background and aims: The global prevalence of MASLD is around 25-35% and shows a gradual increase, posing a growing health risk. Its coexistence with other chronic liver diseases is associated with a more progressive disease course. The prevalence and characteristics of MASLD in autoimmune liver disease (AILD) populations from the Central and Eastern European (CEE) region are poorly defined, and routine metabolic screening is not standard practice. We aimed to determine the MASLD prevalence in a Hungarian cohort of patients with autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), and variant syndromes.

Method: A total of 148 patients (AIH: 29, PBC: 38, PSC: 57, AIH-PBC: 9 and AIH-PSC: 15; M/F: 49/99; median time since diagnosis 3 (2-5) years) were enrolled. Liver steatosis was determined by abdominal ultrasound, CAP values from liver elastography, or liver biopsy (>5% steatosis) when available. MASLD was diagnosed according to EASL criteria.

Results: The overall MASLD prevalence was 40.5% (60/148) and differed significantly across AILD subtypes (p=0.030). Prevalence was highest in PBC (57.9%) and lowest in AIH (27.6%); in PSC, prevalence was 36.9%. Significant metabolic and age-related differences were observed. PBC patients were older (median 59.5 years) compared with AIH (45.0 years; $p = 0.003$) and PSC (37.0 years; $p < 0.001$, respectively). Both hypertension (57.9%) and diabetes mellitus (68.4%) were significantly more common in the PBC group (p = 0.001 and p = 0.005, respectively) than in AIH or PSC. In contrast, PSC patients were younger and demonstrated lower HbA1c (5.4%) and fasting glucose levels (4.8 mmol/L), consistent with a metabolically healthier profile. BMI and lipid parameters did not differ significantly between groups. The presence of significant fibrosis (≥F2) was not associated with a MASLD diagnosis in any etiological group.

Conclusion: MASLD prevalence in this Hungarian AILD cohort was notably high, particularly among PBC patients who also carried the greatest cardiometabolic burden. Not PSC, but AIH showed the lowest prevalence. Significant fibrosis was not associated with MASLD in this early disease stage. Our results highlight the importance of systematic metabolic risk assessment in all AILD patients—especially those with PBC—to support the early identification and management of MASLD.

POSTER ABSTRACT PRESENTATIONS

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Public health

PO1-02-YI

High risk of potential resmetirom-drug interactions in older adults with metabolic dysfunction-associated steatotic liver disease – a modelling analysis using data from the ASPREE trial

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Background and aims: Resmetirom is the first approved therapy for at-risk metabolic dysfunction-associated steatohepatitis (MASH), a subtype of metabolic dysfunction-associated steatotic liver disease (MASLD). Resmetirom is a substrate of CYP2C8 and OATB1P1/OATB1P3. Older persons have high rates of MASLD, and are concurrently at risk of harm from polypharmacy and potential drug-drug interactions (DDI). We modelled the incidence of potential resmetirom-drug interactions over time in a cohort of relatively healthy older Australian adults.

Method: The ASPirin in Reducing Events in the Elderly (ASPREE) trial examined the utility of aspirin in relatively healthy adults aged ≥ 70 years. Key exclusion criteria at baseline included prior cardiovascular disease events, physical disability, or dementia. Multiple sub-studies were performed, including collecting biochemical parameters, as well as linkage with the Australian Pharmaceutical Benefits Scheme (PBS) database. The Fatty Liver Index (FLI) was used to identify those in the cohort with/without MASLD (FLI ≥ 60 and a metabolic criterion, vs FLI < 30), and the cumulative rate of prescriptions during follow-up were evaluated in MASLD subjects to model the incidence of potential resmetirom-drug interactions (i.e., CYP2C8, OATP1B1 and/or OATP1B3 inhibitors). Drugs evaluated included statins, gemfibrozil, verapamil, amiodarone, clopidogrel, pioglitazone, rosiglitazone, fluoxetine, olanzapine, and leflunomide.

Results: Data were available in 16703 participants. 7712 could be classified by the FLI and had data linkage to the PBS; 2543 (33.0%) had no MASLD and 2517 (32.6%) had MASLD. At baseline, MASLD subjects had higher rates of statin prescription (26.1% vs 15.9%, p<0.01) as well as non-statin potential DDI prescription (3.3% vs 1.4%, p<0.01). Over median 4.6 years of follow-up, 54.7% of MASLD vs 37.4% of non-MASLD (p<0.01) had at least one statin prescription, and 10.0% MASLD vs 7.0% non-MASLD (p<0.01) had a non-statin potential DDI. Additionally, 7.1% of MASLD patients had both a statin and non-statin potential DDI during follow-up.

Conclusion: MASLD was common in older adults, and when modelling risk of potential DDIs with potential resmetirom prescribing there was a high risk of both statin and non-stain resmetirom-drug interactions. Clinicians should be alert for potential interactions and consider increased monitoring or resmetirom dose adjustment depending on the nature of the interaction(s).

PO2-01
MASLD or MetALD? Unveiling the tole of alcohol in liver disease progression in diabetic patients

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Background and aims: The transition from the term "non-alcoholic fatty liver disease" (NAFLD) to "steatotic liver disease" (SLD), an umbrella term for several related conditions, offers benefits, particularly in identifying cardiometabolic risk factors more effectively. However, the impact of alcohol consumption on liver disease progression remains significant, leading to the recognition of a new entity: MetALD (metabolic dysfunction-associated steatotic liver disease with moderate alcohol intake).

Aim: This study aimed to compare characteristics associated with liver disease progression in diabetic patients diagnosed with metabolic dysfunction-associated steatotic liver disease (MASLD) versus those with MetALD.

Method: In this prospective study, 286 diabetic patients were followed for 12 months. All patients underwent transient elastography (TE) and ultrasound to assess hepatic steatosis. Participants were classified into MASLD and MetALD groups. The performance of the fibrosis-4 index (FIB-4) and NAFLD fibrosis score (NFS) was also evaluated.

Results: MASLD was diagnosed in 58.2% (167 patients), of whom 4.9% (7 patients) had TE values suggestive of liver cirrhosis. Patients with MASLD presented with lower values of mean CAP, at 313.32 ± 32.79 dB/m, and had a prevalence of severe steatosis of 49.7%, compared with subjects with MetALD, who had a mean CAP of 318.51 ± 35.97 dB/m and a prevalence of severe steatosis of 55.5%. Among those with MetALD, 17.6% (21 patients) had TE values compatible with advanced fibrosis. The MASLD subjects presented a slight decrease in liver fibrosis values from 6.58 ± 2.27 kPa to 6.03 ± 1.57 kPa in 12 months. On the contrary, MetALD subjects had an increase of LSM values from 11.83 ± 6.27 kPa to 12.24 ± 8.66 kPa. MASLD participants had higher BMI (27.62 ± 3.83 kg/m²) and WC (97.75 ± 5.82 cm) than MetALD participants (BMI 26.4 ± 4.34 kg/m²; WC 96.2 ± 6.51 cm; $p < 0.05$). Conversely, MetALD patients showed elevated HbA1c levels (6.41 ± 1.15%) compared to MASLD subjects (6.16 ± 1.27%; $p < 0.05$).

Conclusion: In diabetic patients, the coexistence of moderate alcohol intake and cardiometabolic risk factors (MetALD) is associated with more advanced liver fibrosis and impaired long-term glycemic control, compared to MASLD alone.

PO2-02-YI

Novel trends in liver transplantation for MASLD and ALD: Emerging epidemiology, allocation & post-transplant challenges

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Background and aims: The prevalence of metabolic dysfunction–associated steatotic liver disease (MASLD), formerly known as nonalcoholic fatty liver disease (NAFLD), has increased worldwide. By 2019, 38% of adults in North America or Australia had MASLD, and 5% had metabolic dysfunction–associated steatohepatitis (MASH), formerly known as nonalcoholic steatohepatitis (NASH). People with MASLD or MASH are at increased risk of adverse liver-related health outcomes, and MASH is projected to soon become the leading indication for liver transplant (LT) in the US. The new nomenclature of MASLD was adopted to replace NAFLD in 2023. While their definitions differ, approximately 99% of patients with NAFLD would be classified as having MASLD. The aim of the study to review and summarize recent trends and emerging challenges in liver transplants for MASLD (metabolic dysfunction–associated steatotic liver disease) and ALD (alcohol-related liver disease).

Method: A focused narrative synthesis of registry data, epidemiologic modeling, and cohort studies (2013–2025) evaluating LT indication trends, donor/recipient characteristics, and post-LT outcomes in MASLD and ALD.

Results: The proportion of liver transplant candidates with ALD increased from ~23% in 2013 to nearly 50% in 2022, while MASLD rose from 19% to 27%. MASLD recipients frequently present with obesity, diabetes, and cardiovascular comorbidities, contributing to higher peri- and post-transplant metabolic risk. De novo or recurrent steatosis in grafts is increasingly reported, though long-term graft survival appears preserved. Allocation disparities and differing pre-transplant requirements (sobriety for ALD vs metabolic optimization for MASLD) highlight policy gaps. Advances include machine-perfused and marginal graft use, metabolic risk-stratified recipient selection, and early post-LT weight and glycemic interventions.

Conclusion: MASLD and ALD now dominate liver transplant indications. Novel strategies in candidate selection, allocation policy, and metabolic management are critical to improving outcomes. Future research should focus on recurrence of graft steatosis, cardiovascular mortality, and metabolic precision medicine in post-LT care.

PO3-01
The burden of MASH-related liver cancer in Canada in 2021 and its trends from 1990 to 2021 in comparison to global estimates

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Background and aims: Metabolic dysfunction-associated steatohepatitis (MASH) affects over 5% of Canadians and is a leading cause of liver-related morbidity and mortality. The annual progression rate to liver cancer (hepatocellular carcinoma (HCC)) among patients with MASH is reaching 2% per year. Our study aimed to assess the burden of MASH-related liver cancer in Canada in 2021 and its trends from 1990 to 2021.

Method: Data on liver cancer due to MASH were retrieved from the Global Burden of Disease (GBD) 2021 Study results (source: Institute for Health Metrics and Evaluation, used with permission). We evaluated incidence, prevalence, Disability-Adjusted Life Years (DALY), and mortality in Canada and compared them to the global estimates. Data were presented as age-standardized rates with 95% uncertainty intervals (95%UI). The percentage changes between 1990 and 2021 were calculated.

Results: The incidence of MASH-related liver cancer in Canada increased 2.73 times, from 0.26 [95%UI 0.19-0.35] per 100,000 population in 1990 to 0.71 [0.51-0.97] in 2021, while the global incidence increased by 36% (from 0.36 [0.29-0.45] to 0.49 [0.40-0.60]). The prevalence in Canada increased 3.16 times (1.01 [0.74-1.36] vs. 0.32 [0.23-0.42]), while worldwide the increase was 53%. During 1990-2021, the DALY rate in Canada increased 2.43 times compared to a 19% increase globally. There was a 3-fold increase in the mortality rate in Canada (from 0.22 [0.16-0.30] to 0.66 [0.47-0.91]) vs. a 23% global increase.

Conclusion: Tripling the rates of MASH-related liver cancer in Canada over the last three decades poses a substantial public health risk. It requires the development and wide implementation of effective preventive, screening and management strategies.

PO4-01

The benefits of assessing skeletal muscle density rather than muscle mass as an indicator of metabolic disturbances in individuals with overweight: a cross-sectional study

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Background and aims: Changes in skeletal muscle are described in cases of severe metabolic dysfunction-associated steatotic liver disease and cirrhosis. Changes at earlier stages, particularly in cases of simple overweight, are not known. The aim is to investigate body composition and liver status in subjects with overweight but without obesity.

Method: Individuals were assessed prospectively by clinical examination, biological assays, bioimpedance (Tanita®), liver elastometry (Fibroscan®) and abdominal CT of the third lumbar vertebra (L3) for quantifying adipose tissue and skeletal muscle (surface area and density).

Results: Twenty-four individuals were included with a mean BMI of 28.1 kg/m², average age 45.9 years, normal mean blood glucose level at 95.7 mg/dL and mean HOMA-IR at 2.9. Concerning liver status, the mean controlled attenuation parameter was compatible with moderate steatosis (258 dB/m). Four patients had severe steatosis (CAP ≥ 296 dB/m). These patients have more pronounced insulin resistance (mean HOMA-IR 4 vs. 2.7, p=0.04). The mean elasticity was normal at 4.6 kPa. No patient presented with fibrosing disease. The mean skeletal muscle index calculated on CT was 43.2 cm²/m². Five individuals could be classified as myopenic (muscle area < 39 cm²/m² for women and < 50 cm²/m² for men). Interestingly, they were in fact characterised by very tall stature (1.79 m vs. 1.70 m, p = 0.03), with no other clinical features and no sign of severe liver disease. The mean skeletal muscle density based on CT was 43.2 HU. Two patients were identified as myosteatotic (muscle density < 33 HU). Compared with the others, they had the same body weight and the same BMI. The skeletal muscle density index (SMDI), calculated as muscle density divided by muscle surface area, was 0.28 HU/cm². SMDI was inversely correlated with visceral fat assessed by bioimpedancemetry (r = -0.59, p = 0.002) or CT (r = -0.56, p = 0.004) but not with subcutaneous fat. SMDI was not related to the degree of liver stiffness in this population.

Conclusion: The high height of some subjects could lead to the erroneous diagnosis of myopenia in people with no evidence of severe disease. However, characteristics were noted in this apparently "healthy" population, such as moderate hepatic steatosis, insulin resistance and decreased muscle density compatible with myosteatosis in some subjects. Low skeletal muscle density index is linked with visceral adiposity, suggesting a muscle-adipose tissue axis at early stages of metabolic disturbances.

PO4-02-YI

The impact of dietary interventions on liver health biomarkers in individuals with MASLD and MetALD: a systematic literature review and meta-analysis of RCTs

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) and its subtype, metabolic dysfunction-associated alcohol-related liver disease (MetALD), represent the most prevalent chronic liver diseases worldwide, closely linked to unhealthy dietary patterns. Lifestyle modification is considered a first-line therapy; however, the comparative effectiveness of different dietary approaches remains unclear. This systematic review and meta-analysis aimed to evaluate the impact of dietary interventions on liver health biomarkers in individuals with MASLD and MetALD.

Method: A systematic search of Medline, Embase, Web of Science, ClinicalTrials.gov, and International Clinical Trials Registry Platform was conducted for randomized controlled trials (RCTs) published between 2018 and 2024. Eligible trials assessed dietary interventions in MASLD or MetALD and reported changes in alanine aminotransferase (ALT), liver stiffness, MRI-proton density fat fraction (MRI-PDFF), and controlled attenuation parameter (CAP). Data were synthesized using weighted mean differences (MD) with fixed or random effects models.

Results: A total of 68 full-text articles were included in the systematic review, of which 24 met the criteria for the meta-analysis. Since no eligible studies were identified in individuals with MetALD, the findings apply solely to people with MASLD.Fasting significantly reduced ALT (MD = −12.47 IU/L, 95% CI: -22.03, -2.92, p = 0.01, fasting n = 160, control n = 154) and liver stiffness (MD = −0.24 kPa, 95% CI: -0.46, -0.03, p = 0.03, fasting n = 109, control n = 108) compared to the control group. The Mediterranean diet (MedDiet) resulted in modest yet significant differences in ALT (MD = −2.93 IU/L, 95% CI: -5.68, -0.19, p = 0.04, MedDiet n = 291, control n = 295), liver stiffness (MD = −0.35 kPa, 95% CI: -0.54, -0.16, p = 0.00, MedDiet n = 155, control n = 155), and MRI-PDFF (MD = −1.37%, 95% CI: -2.33, -0.40, p = 0.01, MedDiet n = 178, control n = 180). LCHF / ketogenic diets showed a non-significant trend toward ALT reduction (MD = −6.87 IU/L, 95% CI: -19.34, 3.78, p = 0.19, intervention n = 186, control n = 138). Omega-3 fatty acids supplementation did not significantly alter ALT.

Conclusion: Fasting and Mediterranean diet demonstrate consistent positive effects on liver health-related biomarkers in MASLD. Larger, long-term isocaloric RCTs with standardized outcome reporting are warranted to confirm these findings.

PO4-09-YI

Increased diagnosis and risk stratification for MASLD in primary care over the last 20 years: Real-world evidence from over 11.7 million individuals in the UK

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Background and aims: MASLD is a leading cause of chronic liver disease with a rapidly growing prevalence. However, there is significant underdiagnosis in healthcare records, contributing to missed intervention opportunities and late presentation. Tools to stratify MASLD (e.g., Fib-4) exist but are underused. The last decade has seen large educational efforts to promote detection and risk stratification in MASLD. Here we study the changes in prevalence, incidence of recorded MASLD, associated diseases, and availability of Fib-4 score in the UK primary care population.

Method: This real-world evidence (RWE) study used the UK primary care database Clinical Practice Research Datalink (CPRD). We identified individuals with recorded MASLD diagnosis between 2003 and 2022. NAFLD codes were used as a proxy given their near-complete overlap with MASLD. Individuals with <1 year of follow-up, age <18 years, or pre-existing autoimmune liver disease and viral hepatitis were excluded. We calculated point prevalence, incidence, comorbidities and availability of Fib-4 components. Controls were matched 1:4 on sex, age (±5 years), and general practice.

Results: Out of 11.7 million individuals active in CPRD in 2022, we identified 365,797 MASLD patients and 1,460,288 controls. In the last decade, recorded MASLD prevalence rose approximately 5-fold, from 0.52% in 2013 to 2.42% in 2023 ($p<0.001$). Annual incidence doubled from 1.60 in 2012 to 3.31 in 2022 per 1000 person-years ($p<0.001$). Compared to controls, MASLD patients (median age of 53, 51.8% male) had a higher prevalence of type 2 diabetes (21.0% vs 7.7%; $p<0.001$) and hypertension (35.3% vs 18.7%; $p<0.001$). The availability of components to calculate Fib-4 in MASLD group increased from 4.3% pre-2015 to 22.8% 2015 to 2022 ($p<0.001$). The proportion of MASLD patients with high-risk Fib-4 scores modestly decreased from 7.6% to 6.4% (pre- vs post-2015). South Asians were over-represented in the MASLD cohort (11.0% vs 7.2%; $p<0.001$) and had the lowest adjusted odds ratio of having Fib-4 components (0.67, 95% CI: 0.65–0.70; $p<0.001$).

Conclusion: Recorded MASLD prevalence in UK primary care has increased 5-fold in the last decade, although there remains a large diagnostic gap. Fibrosis risk stratification has improved, commensurate with education efforts but overall implementation remains low. There is a potential care gap among South Asians, who are at high risk but less likely to have data collected for risk stratification.

PO5-01
Prevalence of MASLD and fibrosis assessed by transient elastography in U.S. adolescents before and during the COVID-19 pandemic: Insights from NHANES 2017-2023

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a common but understudied disease in adolescents. We aimed to estimate the updated prevalence of MASLD and related fibrosis among US adolescents using transient elastography.

Method: This study analyzed data from the National Health and Nutrition Examination Survey 2017 to March 2020 and August 2021 to August 2023 among adolescents ages 12-19 years. Steatotic liver disease was assessed using the median controlled attenuation parameter (CAP) and fibrosis by median liver stiffness measurement. Variance inflation factors (VIFs) were used to evaluate multicollinearity. Multivariable logistic regression models were used to assess the association between MASLD and risk factors. All data statistical analyses were performed by R software (version 4.4.1). A p-value of less than 0.05 was considered statistically significant.

Results: A total of 2588 participants were included in the analysis (mean [SD] age, 15.4 [2.3] years; 1366 male participants [52.8%]). The overall age-adjusted prevalence of MASLD was 21.0% (95% CI: 19.1–23.0) using a CAP threshold of ≥ 248 dB/m and 16.1% (95% CI: 14.4–17.8) using ≥ 263 dB/m. The prevalence of MASLD-related fibrosis was 9.0% and 9.7% using CAP thresholds of 248 dB/m and 263 dB/m, respectively. Higher prevalence of MASLD and fibrosis was observed among adolescents with overweight, obesity, and prediabetes. Between the two survey cycles, the age-standardized prevalence of MASLD remained stable, with a non-significant decline observed in the prevalence of fibrosis. Multivariable analysis identified male sex, non-Hispanic Asian ethnicity, increased waist circumference, overweight, and obesity as independent risk factors for MASLD, while waist circumference was the only independent factor associated with fibrosis.

Conclusion: In conclusion, this cross-sectional, nationally representative analysis shows that approximately one-fifth affected by MASLD and one in ten exhibiting MASLD-related fibrosis. Significant differences were observed by sex and race and ethnicity, with a higher prevalence in males, and Hispanic adolescents showing the highest prevalence of both MASLD and fibrosis. These findings highlight populations that may benefit from increased clinical vigilance and identify priority groups for future longitudinal studies to determine the natural history of MASLD in adolescents. Furthermore, early detection and prompt intervention should be prioritized to prevent progression to fibrosis.

PO6-07
MAFLD in Vietnam: A neglected public health challenge requiring urgent policy action

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Background and aims: Metabolic dysfunction-associated fatty liver disease (MAFLD) is rapidly becoming a major public health concern in Vietnam, largely driven by rising rates of obesity, type 2 diabetes, and lifestyle transitions. Despite its significant contribution to morbidity, mortality, and healthcare costs, MAFLD remains under-recognized in national health strategies and is poorly integrated into existing non-communicable disease (NCD) frameworks. This narrative review aims to synthesize available evidence on MAFLD in Vietnam, evaluating epidemiological, clinical, and health systems perspectives, and to propose strategies for strengthening national response.

Method: We conducted a narrative review of epidemiological, clinical, and health system data relevant to MAFLD in Vietnam. Sources included peer-reviewed studies published between 2015 and 2024, national reports, and international guidelines. Findings were contextualized within the Vietnamese healthcare system to assess applicability and identify gaps in prevention, diagnosis, and management.

Results: The evidence shows that MAFLD affects more than one-quarter of adults in urban areas and is increasingly prevalent in rural populations. Key barriers to effective management include limited diagnostic capacity, lack of standardized guidelines, insufficient clinician awareness, and underdeveloped multidisciplinary care models. Complications are compounded by the coexistence of hepatitis B virus infection and the increasing burden of cardiovascular comorbidities, which together exacerbate disease severity and accelerate progression to cirrhosis and hepatocellular carcinoma.

Conclusion: MAFLD represents a neglected yet urgent public health issue in Vietnam. Addressing this challenge requires a strategic national roadmap that integrates MAFLD into NCD policy, expands screening in primary care using non-invasive tools, and invests in training to improve early detection and risk stratification. Strengthening multidisciplinary collaboration and leveraging digital health technologies can further enhance patient engagement and access to care. Regional cooperation and active participation in international clinical trials are essential to accelerate innovation and policy responses. Coordinated, proactive strategies are needed to mitigate long-term health and socioeconomic consequences and to establish Vietnam as a regional leader in tackling metabolic liver disease.

PO6-10-YI

Real-world epidemiology and clinical outcomes in MASLD: A 20-year nationwide analysis of over 23 million individuals in Taiwan's National Health Insurance Research Database

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Background and aims: MASLD is associated with increased risk of hepatic and extra-hepatic endpoints. However, most evidence originates from Western cohorts. Its impact on the unselected East Asian general population remains underexplored. We aimed to determine the prevalence and long-term outcomes of MASLD using Taiwan's National Health Insurance Research Database (NHIRD), which represents over 99% of the population, to bridge these knowledge gaps.

Method: This retrospective study used NHIRD data between 2003 and 2022. We identified individuals with MASLD diagnosis using medical codes. Patients with <1 year of follow-up post-NHIRD registration, age <18, or who had pre-existing autoimmune and alcoholic liver disease were excluded. We calculated the point prevalence and analysed time-to-event for cirrhosis, hepatocellular carcinoma (HCC), acute myocardial infarction (AMI), stroke, and chronic kidney disease (CKD). Controls were matched at a 1:4 ratio; those with a prior endpoint were excluded from endpoint analysis.

Results: Over 23 million individuals were active in NHIRD in 2022. We identified 1,304,409 MASLD patients. Patients had a median age of 50, were 54.7% male, and had high rates of type 2 diabetes (26.7%) and hypertension (39.0%). Recorded prevalence increased by more than 3-fold, from 1.9% in 2003 to 6.31% in 2022 ($p<0.001$). Over a median follow-up of 8.4 to 8.8 years, incidence rates (per 1000 person-years) in the MASLD cohort were: 3.8 (95% CI: 3.7–3.8) and 2.2 (95% CI: 2.1–2.2) for cirrhosis and HCC; 2.2 (95% CI: 2.2–2.3), 6.2 (95% CI: 6.1–6.2), and 12.4 (95% CI: 12.3–12.4) for AMI, stroke and CKD. After adjusting for common, known risk factors, MASLD was strongly associated with cirrhosis (aHR 2.68, 95% CI: 2.64–2.71) and HCC (aHR 2.30, 95% CI: 2.25–2.34). Risks for stroke (aHR 1.07, 95% CI: 1.05–1.08) and CKD (aHR 1.13, 95% CI: 1.12–1.14) were also elevated albeit modestly. Notably, MASLD was not associated with an increased risk for AMI (aHR 0.93, 95% CI: 0.92–0.95) after adjustment for comorbidities and deprivation index.

Conclusion: This 20-year study provides a population-level depiction of MASLD in an East Asian population. While the recorded prevalence is rising sharply, significant under-diagnosis likely persists. MASLD is an independent risk factor for cirrhosis, HCC, stroke, and CKD. However, its association with AMI was not observed after adjustment.

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