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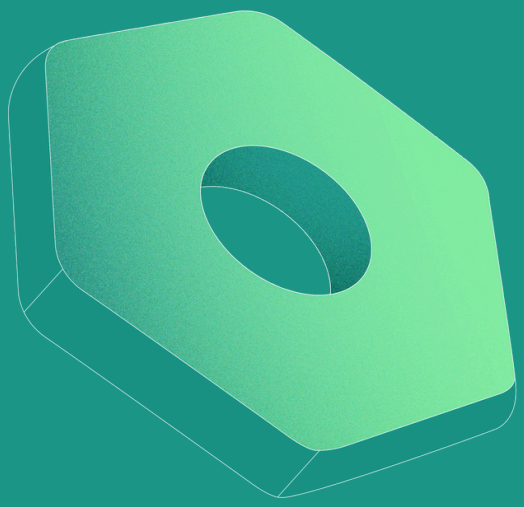

ABSTRACT BOOK

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ORAL ABSTRACT PRESENTATIONS

OS-1-YI
Spatial transcriptomics maps the metabolic zonation of hepatocytes in MASLD I148M-PNPLA3 carriers

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Background and Aims: The I148M polymorphism in *PNPLA3* gene is the main genetic predictor of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD). Few data showed that I148M overexpression in hepatocytes correlated with metabolic switching and mitochondrial (mt)-dysfunction. Thus, this study aims to: 1) deepen the impact of *PNPLA3* variation on (mt)-function by overexpressing the I148M protein in HepG2 and Hep3B cells, to force the effect or introduce the mutation, respectively; 2) dissect hepatocytes metabolic zonation in liver biopsies of MASLD patients who are wild-type (WT) and homozygous for the PNPLA3 I148M variant sharing a similar disease severity (NAFLD activity score (NAS) =4) through a spatial transcriptomic approach.

Method: PNPLA3-I148M protein was upregulated in hepatoma cells by lentiviral transfection. Spatial transcriptomics was performed by Visium CytAssist (10X Genomics) in frozen liver biopsies. Data were analyzed by Loupe Browser.

Results: The I148M protein upregulation in hepatoma cells fostered lipid accumulation, resulting in increased PGC1a activity as responsive strategy to clear fat overload. Both I148M overexpressed models showed lower OXPHOS capacity and ATP production. The I148M-mediated mt-dysfunction was furtherly corroborated by high ROS content and release of mtDNA fragments in cells supernatant (adjusted ***p<0.001, **p<0.01 and *p<0.05). To translate the *in vitro* findings into clinic, we spatially mapped pericentral (PC) and periportal (PP) hepatocytes in hepatic biopsies of WT and I148M MASLD patients by using the *CYP3A4/CYP2E1* and *HAL/SDS* genes as zonation markers, respectively. Among Differentially expressed genes (DEGs), we found increased mitobiogenesis (*PGC1a)* as responsive strategy to fat accumulation (*SREPF1, DGAT2, HSD17B, ACACA, FABP1)* in PP areas of both WT and I148M MASLD patiens. In WT PP zones we also observed a high expression of DEGs related to physiologic fusion-mitophagy processes (Mfn1, Mfn2, Opa1, BnipL, Bnip3), mitochondrial $\boldsymbol{\beta}$-oxidation (PPAR*a)* and respiration (SDHA, ATP5MF), that on the opposite were reduced in I148M PP areas, thus demonstrating a mt-impairment. Finally, according to the canonical PC-PP axis, WT PC zones revealed an enrichment of pathways related to glycolysis, biosynthesis of unsaturated fatty acids, fatty acid degradation/elongation, autophagy/mitophagy, PPAR and Wnt signaling. Conversely, these pathways were enhanced in PP areas of I148M MASLD individual (KEGG Pathway database enrichment analysis, *p<0.05; *p<0.001).

Conclusion: The I148M overexpression in *in vitro* hepatocytes unveiled its involvement in mt-maladaptation, resulting in progressive damage. The I148M mutation in MASLD patients is associated with an unbalanced metabolic zonation among PC and PP areas compared to WT, thus providing new insights about the impact of genetic in MASLD.

OS-2-YI
Alcohol-driven steatotic liver disease carries the highest cirrhosis risk in U.S. veterans

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Background and Aims: Steatotic liver disease (SLD), which includes metabolic dysfunction-associated (MASLD) and alcohol-related liver disease (ALD), continues to be the leading cause of chronic liver disease in the U.S. Veterans are particularly at high risk for SLD due to the high prevalence of metabolic comorbidities and unhealthy alcohol use. We aim to evaluate risks of cirrhosis across the spectrum of SLD among U.S. Veterans.

Method: Veterans with SLD (defined by the presence of hepatic steatosis) between 01/01/2010 and 12/31/2018 (followed through 12/31/2023) were identified from the national Veterans Affairs (VA) database. Patients with other chronic liver diseases, baseline cirrhosis, or hepatocellular carcinoma were excluded. Alcohol use was assessed using AUDIT-C scores. SLD was categorized into three groups: MASLD (SLD with ≥1 cardiometabolic risk factor (CMRF) and no AU [AUDIT-C=0]), MetALD (SLD with ≥1 CMRF and low-level AU [AUDIT-C 1-2 for women, 1-3 for men]), and ALD (SLD with high-level AU [AUDIT-C >2 for women, >3 for men]). We performed sensitivity analyses to evaluate patients with ALD without any CMRF. The incidence of cirrhosis (per 100 person-years) was analyzed using competing risks models (censored for death) and adjusted Cox proportional hazards models.

Results: Overall, we identified 682,274 patients with MASLD, 517,464 with MetALD, 305,692 with ALD, and 60,461 with ALD without CMRF. The cohort was predominantly male (93%) and non-Hispanic White (68-71%). Patients with MASLD were slightly older (63.3 ± 12.38 years) compared to those with ALD (61 ± 12.38) and MetALD (60.0 ± 12.85 years) ($p<0.001$). The incidence of cirrhosis was significantly higher in patients with ALD (0.66 per 100 person-years) compared to patients with MetALD (0.39 per 100 person-years, $p<0.001$) or MASLD (0.43 per 100-person years, $p<0.001$). In adjusted multivariable Cox regression models, the risk of cirrhosis was significantly higher in ALD compared to MASLD (HR 1.76, 95% CI 1.61-19.91, $p<0.001$) whereas MetALD did not show a statistically significant difference in cirrhosis risk compared to MASLD (HR 0.99, 95% CI 0.96-1.01, $p=0.36$). On sensitivity analyses of patients with ALD without CMRF, the risk of cirrhosis was similarly higher compared to patients with MASLD.

Conclusion: Among a national cohort of U.S. Veterans with SLD, those with predominantly alcohol-driven disease—both with and without CMRF—had the highest long-term risks of cirrhosis, 68 – 76% higher than patients with MASLD. These findings along with existing studies demonstrating higher prevalence of alcohol use disorder among Veterans compared to the general population, emphasize the urgent need for implementing effective assessment of alcohol use with timely linkage to resources and treatment for those with high-risk alcohol use in addition to optimizing concurrent CMRF.

OS-3

Liver stiffness measurement by vibration-controlled transient elastography versus histology in predicting major adverse liver outcomes due to metabolic dysfunction-associated steatotic liver disease

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Background and Aims: Commonly used non-invasive tests might be as good as histological fibrosis staging in predicting major adverse liver outcomes (MALOs), but the studies are typically limited by a small number of patients and events. We aimed to compare the prognostic performance of Liver stiffness measurement (LSM) by vibration-controlled transient elastography (VCTE) and fibrosis stage by histology in patients with metabolic dysfunction-associated steatotic liver disease (MASLD).

Method: This secondary analysis of the multicentre VCTE-Prognosis cohort included 3 532 patients who had undergone both LSM by VCTE and liver biopsy for MASLD (mean age 51.9 years, 57.3% male, 41.7% diabetes, body mass index 29.7 kg/m^2). The patients were followed for MALOs, defined as hepatocellular carcinoma (HCC), hepatic decompensation, liver transplantation or liver-related deaths.

Results: The median baseline LSM by VCTE was 8.8 (interquartile range 6.1-13.3) kPa, and 33.5% of patients had F3-F4 fibrosis on histology. At a median follow-up of 55.8 months, 148 (4.2%) patients developed MALOs, including 47 HCC and 123 patients with hepatic decompensation. Pairwise comparison showed that LSM and histology had a similar area under the receiver-operating characteristic curve (AUROC 0.857 vs 0.846 at 3 years; 0.859 vs 0.860 at 5 years), area under the precision-recall curve (0.162 vs 0.096 at 3 years; 0.218 vs 0.156 at 5 years) and integrated time-dependent AUROC (iAUROC 0.861 vs 0.841) for MALOs. Similarly, the discrimination for HCC (AUROC 0.816 vs 0.829 at 3 years; 0.826 vs 0.842 at 5 years; iAUROC 0.821 vs 0.813) and hepatic decompensation (AUROC 0.867 vs 0.859 at 3 years; 0.862 vs 0.868 at 5 years; iAUROC 0.864 vs 0.856) was comparable between LSM and histology. The 5-year integrated Brier scores of LSM and histology were also similar, which were 0.0170 and 0.0168 for MALOs, 0.0146 and 0.0143 for HCC, and 0.0146 and 0.0143 for hepatic decompensation, respectively.

Conclusion: In a large multicentre longitudinal cohort of patients with MASLD, LSM by VCTE and histological fibrosis staging had similar prognostic performance for MALOs.

OS-4-YI

Lipid droplet size explains discordances between histology and magnetic resonance proton density fat fraction in steatotic liver disease

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Background and Aims: Hepatic steatosis grades derived from magnetic resonance imaging (MRI) proton density fat fraction (PDFF) can disagree with those derived from histology. We evaluated with digital image analysis (DIA) whether the size distribution of lipid droplets (LDs) was associated with disagreements between histology and MRI-PDFF.

Method: Prospective, multicentric study of 355 patients with chronic liver disease, having paired liver biopsy and MRI. Using conventional microscopy, steatosis was graded by pathologists (S0-S3), based on the proportion of hepatocytes containing large LDs. DIA automatically segmented and quantified LDs as the proportionate area of tiny (<1 micrometer^2), small (1-90 micrometer^2), large (>90 micrometer^2), and total droplets. MRI-PDFF graded steatosis as PDFF-S0 <5.75%; PDFF-S1 ≥5.75%; PDFF-S2 ≥15.5%; PDFF-S3 ≥21.35%. Multivariable modelling was performed to identify predictors of discordance between histology- and PDFF-derived steatosis grade.

Results: DIA showed that as steatosis accumulates in the liver, the size of LDs progressively increases. Histology- and PDFF-derived steatosis grades were discordant in 50% (n=178). The independent predictors of discordances included greater proportionate areas of tiny and small LDs, and lower proportionate area of total LDs. Within histology-derived S0, disagreements were due to higher MRI grading having higher proportionate areas of tiny and small LDs. Within histology-derived S2 and S3, disagreements were due to lower MRI grading having lower proportionate areas of large and total LDs.

Conclusion: LDs size distribution explains the discordances between histology and MRI-PDFF. While PDFF captures the whole spectrum of LDs size, pathologists underestimate steatosis grade in patients with abundant tiny and small LDs, as these are disregarded in their scoring system. Conversely, conventional histology overestimates steatosis grade in patients with abundant large LDs, indicating a bias in subjective visual assessment.

OS-5
Best buys to diagnose and treat metabolic dysfunction-associated steatohepatitis: A multi-country generalized cost-effectiveness analysis

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Background and Aims: Metabolic dysfunction-associated steatohepatitis (MASH) is a highly prevalent disease among people with type 2 diabetes (T2D). MASH is also a major risk factor for more severe stages of liver disease, such as cirrhosis and hepatocellular carcinoma, resulting in a high economic burden. We aimed to identify the most cost-effective management approaches to detect, prevent and treat MASH and liver fibrosis in people with T2D.

Method: A generalized cost-effectiveness analysis was conducted from a health system perspective in Germany, Italy, Spain and Sweden, using a 95% coverage level for each approach. Seven multifaceted approaches in addition to the standard of care (SoC), defined as the absence of any systematic intervention, were considered: 1) Fibrosis-4 (FIB-4) test at the primary health care level; 2) FIB-4 and the Enhanced Liver Fibrosis (ELF) test or vibration-controlled transient elastography (VCTE); 3) adding hepatologist visits and intensive lifestyle intervention (ILI) to 2); 4) replaced ILI with resmetirom (RES) in 3); 5) adding ILI to 4); 6) replaced ILI with semaglutide (SEM) in 3); 7) adding ILI to 6). A cohort state-transition model simulated liver fibrosis progression or regression and the different approaches impact over the cohort's lifetime. Transition probabilities, health outcomes, prevalent cases and cost inputs were sourced from the literature and health system fee schedules or estimated. Conservatively, we considered the impacts of each approach only on transition probabilities F2 and F3 within a 1-5% progression/regression range, and on their related health outcomes within a 0.03-0.08 range. Health outcomes were measured as quality-adjusted life years. Outcomes of interest were the incremental cost-effectiveness ratios (ICERs), where the intervention with the estimated lowest ICERs served as the comparator and from there an expansion path was built, and the average cost-effectiveness ratios (ACERs).

Results: For Germany, approaches with ELF, 3 and 6, and approaches with VCTE, 6 and 7, were found to be the most cost-effective, with ICERs of up to 7.4 and 4,437.6K international dollars (I$) 2023, respectively, and ACERs around 2.1 and 2.9–10.0K I$2023, respectively. For Italy, approaches 3 and 6 resulted in ICERs up to 182.2K, and ACERs of 3.8–6.7K. For Spain, SoC and approach 2 had ICERs of up to 27.3K, and ACERs in the 2.9–3.9K range. For Sweden, SoC and approach 2 had the most cost-effective profile, with ICERs of up to 133.4K, and ACERs in the 4.6–6.1K range.

Conclusion: Several screening approaches that included lifestyle and pharmacological treatments aimed at tackling liver fibrosis in patients with T2D and MASH were found to be cost-effective based on the reported and assumed costs in each country. These "best buys", evaluated in relation to the willingness to pay threshold of each country, can inform the health policy decision process.

OS-6
Distinct genetic signatures linking MASH in liver, subcutaneous and visceral adipose tissue

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Background and Aims: Metabolic Dysfunction Associated Steatotic Liver Disease (MASLD) presents with a wide range of clinical features. Adipose tissue distribution plays an important role in the development and progression of MASLD/MASH, with visceral obesity being an individual risk factor. However, the underlying mechanisms in the liver, visceral and subcutaneous adipose tissue are not fully understood. Therefore, this study aims to investigate gene expression profiles across these tissue types, identifying distinct molecular characteristics that correlate with disease severity.

Method: Liver (L), subcutaneous (SC) and visceral (VI) adipose tissue samples were obtained from patients undergoing bariatric surgery and healthy controls (n=10 per group) and classified according to the histological presence of steatotic liver disease. The tissue samples were then subjected to RNA sequencing.

Results: Significant differences in gene expression were observed between all four groups (control, healthy obese, simple steatosis and steatohepatitis (MASH)) and in all tissues analyzed (L, SC, VI). With increasing disease severity, the number of upregulated genes increased in all tissue types compared to the control group. Unlike tissues from patients with healthy or steatotic livers, MASH was associated with the upregulation of specific genes related to inflammatory pathways in both the liver and SC adipose tissue. In VI adipose tissue, 65% of the genes upregulated in MASH were already elevated in simple steatosis, primarily affecting glucose and lipid metabolism. Additionally, there were 18 genes uniquely and consistently upregulated across all tissue types in MASH.

Conclusion: The transcriptomic profiles of liver, visceral and subcutaneous adipose tissue in obese patients reflect the liver phenotype, confirming an important role in the development and progression of MASLD. In particular, the adipose tissue profiles show a clear separation of the three groups, suggesting a potential pathophysiological role in the progression of MASLD/MASH and may ultimately be of diagnostic value in the future.

OS-7
The ubiquitin-like modifier FAT10 regulates the senescence of hepatocytes during metabolic dysfunction-associated steatohepatitis progression

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Background and Aims: The accumulation of senescent hepatocytes has been identified as a key factor in Metabolic dysfunction-Associated Steatotic Liver Disease (MASLD) progression, from simple steatosis to Metabolic dysfunction-Associated Steatohepatitis (MASH), up to the development of cirrhosis and Hepatocellular Carcinoma (HCC). But the mechanisms and actors participating to this phenomenon are still poorly described. Here, we identify the ubiquitin like modifier, the human leukocyte antigen-F Adjacent Transcript 10 (FAT10), also called Ubiquitin D (UBD), as a regulator of the senescence in hepatocytes.

Method: The impact of FAT10 on the senescent phenotype was studied *in vitro* in a model of human hepatocyte cell line made senescent after irradiation, through its downregulation by a siRNA or its stable overexpression by a lentiviral infection and the phenotype was characterized using molecular, immunostaining and functional approaches. The association between FAT10 and senescence markers was studied in humans using transcriptomic data from a MASH/no-MASH cohort and validated using immunostaining. The potential partner of FAT10 was identified using proximity ligation assay (PLA). The impact of FAT10 overexpression on hepatocyte senescence status during MASH development was studied *in vivo* in mice fed a MASH diet after an AAV infection.

Results: *In vitro*, FAT10 downregulation modulates the senescent transcriptome of hepatocytes and leads to greater induction of the senescent phenotype, through the increase of SA-β-Galactosidase activity, the acceleration of proliferation arrest, the activation of DNA damage response and the accumulation of lipid droplets. A potential mechanism shows that FAT10 interacts with P21 in senescent hepatocytes to modulate its degradation. Interestingly, FAT10 chronic overexpression in hepatocytes leads ultimately to loss of senescence phenotype and induces colony formation, suggesting senescence escape towards cancerization. In human MASH livers, FAT10 expression correlates with senescence markers and interacts with P21 in nuclei of MASH hepatocytes. Finally, specific FAT10 overexpression in hepatocytes of MASH mice decreases senescence markers.

Conclusion: In summary, we demonstrate that the increase of FAT10 expression in hepatocytes during MASH progression induces the loss of hepatocyte senescent phenotype which may be one of the key mechanisms involved in the progression of MASH to HCC.

OS-8
Investigating the liver microenvironment by spatial transcriptomics in MASH and MetALD HCCs

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Background and Aims: MASH accounts for 20% of HCCs in the Western world and is the leading cause of HCC in patients without cirrhosis. The higher propensity for HCC development without cirrhosis in MASH compared with other etiologies underscores the unique metabolic and inflammatory micro-environment that cooperate with extrahepatic cancer drivers associated with metabolic syndrome and, when present, alcohol consumption. Here we investigate the metabolic and inflammatory microenvironment of MASH HCC using Digital Spatial Profiling (DSP) technology in multiple tumour (T) and non-tumour (NT) regions of interest (ROIs) from surgical resection samples of cirrhotic and non-cirrhotic patients with HCC related to MASH and MetALD.

Methods: The study population comprised 5 cirrhotic (K) and 4 non cirrhotic (F1/F2/F2/F3) SLD HCC patients. Six had no alcohol consumption (F1/F2/K/K/K) and 3 were MASLD predominant Met-ALD (F2/F3/K). Spatial resolution of RNA expression from >1,800 genes was assessed using the GeoMx® Cancer Transcriptome Atlas in T and NT ROIs of FFPE (Formalin-Fixed Paraffin-Embedded) tissue samples. A masking approach was used to define homogeneous areas of interest (AOI) containing PanCK or CD45 labelled cells in each ROI. All cells present in each AOI in the tumor or in the non-tumoral liver were analyzed separately as a mini-bulk RNA-Seq,

Results: 95 ROIs (range 9-17 ROIs per sample) have been analyzed. After QC 82 ROIs were retained for a total number of 38938 PanCK positive cells (hepatocytes, cholangiocytes and tumor cells) and of 4239 CD45 positive cells. Principal Component Analysis of all ROIs showed a clear separation between PanCK AOIs and CD45 AOIs in T vs NT. Focusing on CD45 ROIs, we found that the inflammatory infiltrate, richer in NT liver, displays distinct transcriptional profiles in T vs NT; with 13 down-regulated and 26 up-regulated differentially expressed genes. CD45 AOIs enrich oxidative phosphorylation and integrins signaling pathways, and downregulate lymphocyte effector pathways in T tissues. WGCNA (weighted gene co-expression network analysis) of all CD45 ROIs identified 5 modules of highly connected and co-expressed genes (hub genes) associated with the tumor status. Additional modules were specific for CD45 AOIs stratified according to the presence of cirrhosis, MASH or Met-ALD. Cell type deconvolution analysis of CD45 and PanCK AOIs stratified according to tumor status show an enrichment of Tregs, central venous LSECs and stellate cells in tumor vs non-tumor tissue.

Conclusion: Our DSP analysis allowed to obtain a highly granular spatial resolution of the transcriptome and the microenvironment in specific subgroups of MASH HCCs.

OS-9
Deciphering the Gut-to-Kupffer cell communication network mediated by gut-derived extracellular vesicles

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Background and Aims: Extracellular vesicles (EVs) mediate inter-organ communication in metabolic disorders such as MAFLD. We previously found that EVs from prediabetic gut tissue induce diabetogenic hallmarks, including liver steatosis, when injected in healthy mice [unpublished]. Moreover, gut EVs are preferentially captured by Kupffer cells (KC) [unpublished], despite the fact that hepatocytes comprise approximately 80% of liver cells. We hypothesize that this EV-mediated gut-KC interaction modulates hepatic metabolism and aim to build a Gut-to-Kupffer cell communication network to investigate this connection.

Method: We adapted the NicheNet tool (Browaeys et al., 2020), originally designed for inter-cell communication analysis, to specifically assess how omics data derived from EVs impact recipient cells. We applied the modified tool to in-house proteomics data of gut-derived EVs from healthy and prediabetic mouse models (Ferreira et al., 2022) and incorporated liver single-cell RNA-seq data from the Tabula Muris Atlas (The Tabula Muris Consortium, 2018); focusing specifically on the annotated KC as the recipient cells of the gut EVs. Given that hepatocytes comprise the majority of liver cells, we used the Seurat Wilkinson test to identify genes upregulated in KC relative to hepatocytes. Additionally, we conducted differential abundance analysis of the gut EVs proteome between prediabetic and healthy states using the limma R package.

Results: The modified NicheNet tool yielded a ranked list of EVs proteins for each condition based on their regulatory potential in KCs. Analysis of the top 30 proteins revealed previously unreported gut-EVs to KC communication pathways. In the prediabetic state, selenocysteine lyase (SCLY)—a key player in redox homeostasis—showed communication links with several upregulated genes in KC. This suggests that elevated redox stress in KC signals the gut to increase SCLY transfer via EVs, potentially helping to restore hepatic redox balance. In the healthy state, Apolipoprotein E (APOE) exhibited a strong regulatory potential on the KC gene Interleukin 1 beta (ILB1), a primary inflammatory cytokine. If APOE modulates ILB1 inhibition, it may contribute to counteracting hepatic inflammation.

Conclusion: Our modified tool allowed a detailed mapping of gut-EVs communication with KC, revealing how gut-liver interactions through EVs could influence hepatic metabolism in prediabetes. Further exploration could reveal novel signalling pathways that, once validated, would enhance our understanding of EVs in diabetes pathophysiology and associated liver disease.

OS-10

The combination of lanifibranor with empagliflozin further enhances metabolic improvement in patients with metabolic dysfunction-associated steatohepatitis (MASH) and type-2 diabetes (T2D)

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Background and Aims: The broad disease biology of MASH, from upstream insulin resistance to progressive liver fibrosis, underlies the concept that many patients may benefit from tailored combination therapy with complementary efficacy. We compared the therapeutic effects of lanifibranor alone and the combination of lanifibranor with an SGLT2 inhibitor versus placebo in the prospective proof-of-concept study 'LEGEND'.

Method: The LEGEND trial enrolled 39 patients (33 completers) with MASH and T2D, randomized 1:1:1 to lanifibranor (L), lanifibranor with empagliflozin (L+E) and placebo (P) for a treatment duration of 24 weeks. MASH was diagnosed per historical liver biopsy or MRI imaging (cT1 or cT1+PDFF). Change in HbA1c from baseline (BL) to treatment week (TW) 24 was the primary efficacy endpoint. Circulating biomarkers included liver enzymes, inflammation and fibrosis markers, lipid and glucose metabolism; MRI-based imaging included hepatic steatosis (PDFF), MASH composite disease activity and fibrosis (cT1), visceral (VAT) and subcutaneous (SAT) adipose tissue, spleen and liver volume; vital signs and safety were evaluated.

Results: Both L and L+E met the primary endpoint of HbA1c improvement versus P (both $p<0.001$, FAS); 50% in both active arms reached HbA1c < 6.5% at TW24, with 58% and 80% HbA1c decrease ≥1% for L and L+E versus 0% for P, respectively. Liver tests (ALT, AST, GGT), fibrosis markers (TIMP-1, P3NP, Pro-C3), insulin, HOMA-IR, hs-CRP, ferritin, glycemia, lipid profile (HDL-C, Triglycerides) improved and adiponectin increased by a mean of 3-fold in both L ($p=0.009$) and L+E ($p=0.004$) arms compared to no increase for P. Patients had a mean weight increase of 3.6% with L at TW24, while mean weight remained unchanged in the L+E and placebo arms. The ratio VAT/SAT shifted favorably toward SAT for both L and L+E compared to placebo (-18% and -5% vs +2%, respectively). Significant improvements of hepatic steatosis and composite MASH activity + fibrosis were observed for both L and L+E with mean relative MRI-PDFF changes of -49 and -41% and mean absolute cT1 changes of -82 and -85 ms respectively. Spleen and liver volumes decreased with L and L+E compared to placebo. L and L+E were safe and well tolerated.

Conclusion: The combination of lanifibranor with an SGLT2 inhibitor is well tolerated and has comparable beneficial effects on noninvasive hepatic and cardiometabolic markers of MASH as lanifibranor monotherapy, including a shift toward SAT, without observed weight gain. The combination is well tolerated.

OS-11
Association between metabolic dysfunction policies and the global burden of metabolic dysfunction-associated steatotic liver disease

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Background and Aims: Although metabolic dysfunction-associated steatotic liver disease (MASLD) is intrinsically associated with cardiometabolic risk factors, evidence assessing the potential impact of MASLD-related public health policies (PHP) on reducing the burden of MASLD remains unknown. We aimed to determine the relationship between establishing MASLD-related PHP and the global burden of MASLD over time.

Method: We conducted a multinational ecological study. Data on policies were obtained from the World Health Organization between 2013 – 2021, while age-standardized disability-adjusted life years (DALYs) due to MASLD were obtained from the Global Burden of Disease study between 2017 – 2021. We classified PHP into two categories: 1. Countries with the policies established by 2013 and 2. Countries with PHP after 2013 (or no policies). We estimated an incidence rate ratio (IRR) using multilevel generalized linear models with a Poisson family distribution adjusted by population structure, healthcare access and quality index, human development index, alcohol use per capita, smoking, body mass index, and physical activity.

Results: A total of 110 countries were included. The median age-standardized MASLD-related DALYs were 47.8 [IQR: 33 – 74.3] per 100,000 inhabitants. Fifty-three percent of countries had national policies on diabetes by 2013, while 46.4% had cardiovascular disease (CVD) policies, 60.9% had nutritional policies, and 57.3% had policies on physical activity. In adjusted models, the establishment of PHP in diabetes by 2013 was associated with a significant reduction in MASLD-related DALYs (IRR 0.49, 95% CI: 0.27 – 0.90, p = 0.021). Similar associations were observed in the establishment of national policies on nutrition (IRR 0.46, 95%CI: 0.23 – 0.94, p = 0.034) and policies on CVD (IRR 0.43, 95% CI: 0.21 – 0.88, p = 0.020) by 2013. However, the PHPs on physical inactivity were not significantly associated with lower MASLD-related DALYs (IRR 0.60, 95% CI: 0.29 – 1.25, p = 0.177). In all the multivariable models, higher alcohol use was significantly associated with an increase in MASLD-related DALYs.

Conclusion: Establishing national PHP targeting diabetes, CVD, and nutrition may significantly reduce the burden of MASLD. Additionally, alcohol use remains a critical modifiable risk factor contributing to the global burden of MASLD, underscoring the need for integrated approaches in public health strategies and better methods to quantify alcohol use in clinical practice.

POSTER ABSTRACT PRESENTATIONS

Basic Science

PO1-04-YI
FLAME model: validation of a tool incorporating alpha-glutathione-s-transferase serum levels for predicting advanced fibrosis and cardiovascular events in MASLD

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Background and Aims: Acute cardiovascular events (ACE), in parallel with hepatic fibrosis (HF) worsening, severely burden the prognosis of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) patients.
Alpha-glutathione-s-transferase (alphaGST) represents a liver enzyme whose serum levels progressively increase with the HF progression in alcoholic and viral chronic hepatitis. However, its usefulness in MASLD remains unexplored.
We aimed to evaluate the accuracy of the alphaGST serum levels and the FLAME index in predicting advanced fibrosis (AF), as well as the performance of the FLAME index in predicting the 5-year first ACE occurrence in ACE-naïve MASLD individuals, in comparison to the other non-invasive tools (NITs).

Method: Between January 2016 and December 2017, we consecutively enrolled 200 patients presenting the recently proposed MASLD diagnostic criteria (training cohort) (TrC), receiving a percutaneous liver biopsy (pLB). AlphaGST serum levels (pg/ml) were assessed in all subjects.
Principal component analysis (PCA) selected the variables associated with AF for each specifically identified domain and receiving operator curve (ROC) analysis estimated the relative best cut-off (BCO). Liver stiffness measurement (LSM), NAFLD fibrosis (NFS), Fibrosis-4 (FIB-4), and BMI-AST/ALT Ratio-Diabetes (BARD) were determined as NITs. During a 5 years follow-up, the first ACE was recorded in ACE-naïve subjects.
A validation cohort (VlC) of 60 MASLD pLB-receiving patients was enrolled (January 2018 - May 2019) and 5 years followed up.

Results: AlphaGST levels increased with the worsening of the fibrosis stage ($p < 0.0001$) both in the TrC and VlC, showing an elevated accuracy in predicting AF [TrC: AUC: 0.89, VlC: AUC:0.89, both $p<0.0001$]. The PCA-selected variables glycosylated hemoglobin (HbA1c) (domain: “Free plasma glucose/Insulin resistance-related abnormalities”), HDL (domain: “Lipid-Associated Metabolic alterations”), and alphaGST (domain: “Excretion of liver-injuring toxic metabolites/anti-oxidative stress mechanisms - impairment”) (BCO: HbA1c > 5.5 %; HDL $\leq$ 43.5 mg/dL; alphaGST > 3917 pg/ml) defined the specific system scoring of “FLAME”.
FLAME [AUC-TrC: 0.95, VlC: 0.94, $p < 0.0001$] showed better performance in the prediction of AF compared to alphaGST [TrC:0.89; VlC:0.89], NFS [Trc:0.80; VlC: 0.79], FIB-4 [TrC: 0.88; VlC: 0.85], BARD [TrC 0.83; VlC: 0.81], and LSM [0.88; VlC: 0.83], as well as [AUC-TrC: 0.92, VlC: 0.91, $p < 0.0001$] to NFS [TrC: 0.76; VlC: 0.86], FIB-4 [TrC: 0.79; VlC: 0.89], BARD [TrC: 0.80; VlC: 0.82], and LSM [TrC: 0.80; VlC: 0.80] in predicting ACEs [FLAME >6; HR: 2.62, $p < 0.0001$].
MASLD patients presenting a baseline FLAME index > 6 showed a higher risk of the 5-year ACE occurrence [TrC - HR: 2.624, $p <0.0001$].

Conclusion: FLAME is a novel alphaGST-incorporating tool that accurately predicts AF and ACEs in MASLD.

PO1-05-YI
Cholesterol exacerbates the pathophysiology of metabolic dysfunction-associated steatohepatitis by upregulating Hypoxia-Inducible Factor 1 and modulating microcirculatory dysfunction

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Background and Aims: Cholesterol is a pivotal lipotoxic molecule that contributes to the progression of metabolic dysfunction-associated steatohepatitis (MASH). Additionally, microcirculatory changes are critical components of metabolic dysfunction-associated steatotic liver disease (MASLD) pathogenesis. This study aimed to investigate the role of cholesterol as an insult that modulates microcirculatory damage in MASLD and the underlying mechanisms.

Method: An experimental MASLD/MASH model was established in 20 male C57BL/6 mice fed a high-fat, high-carbohydrate (HFHC) diet for 39 weeks. At weeks 31-39, 2% cholesterol was added to the diet of 10 mice (HFHC + CHOL) (CEUA L-012/2018 A2). Leukocyte recruitment and hepatic stellate cell (HSC) activation were assessed by intravital microscopy, and hepatic microvascular blood flow (HMBF) was measured by laser speckle flowmetry. Comparisons between groups were made using one-way ANOVA with Tukey's post hoc test. Significance was set at $p < 0.05$.

Results: Mice fed the HFHC + CHOL diet showed increased hepatomegaly, steatosis, liver inflammation, hepatocellular damage and fibrosis compared to the other groups. The group receiving cholesterol showed greater labeling for alpha-smooth muscle actin, increased transcription of COL1A1 in the liver (both $p < 0.001$), and greater activation of HSC (both $p < 0.001$) compared to the other groups. Cholesterol supplementation resulted in greater recruitment of leukocytes into the liver microcirculation, with a greater reduction in the number of rolling (HFHC + CHOL vs. CTL and HFHC; $p < 0.001$ and $p = 0.002$, respectively) and adherence of leukocytes (HFHC + CHOL vs. CTL and HFHC; $p < 0.001$ and $p = 0.023$, respectively), in addition to increased mRNA transcripts for ICAM-1 (HFHC + CHOL vs CTL and HFHC; $p < 0.001$ and $p = 0.012$, respectively). Flow cytometry showed that the IFN-γ/IL -4 ratio, indicative of a Th1-type pattern, was higher in mice fed cholesterol than in those fed a CTL diet ($p = 0.022$). The HFHC and HFHC + CHOL groups showed a 56% and 71% reduction in HMBF, respectively (both $p < 0.001$), with the HFHC + CHOL group showing greater impairment ($p = 0.045$) with increased mRNA transcripts for HIF1A (HFHC + CHOL vs CTL and HFHC; $p < 0.001$ and $p = 0.044$, respectively) compared to the other groups. The hepatic transcripts for HIF1A and basal HMBF had strong negative Pearson correlation coefficients, suggesting that these variables were inversely proportional.

Conclusion: These findings suggest cholesterol exacerbates MASLD progression through microcirculatory dysfunction and HIF1A upregulation through hypoxia and inflammation. This study highlights the importance of cholesterol-induced lipotoxicity, which causes microcirculatory dysfunction associated with MASLD pathology, thus reinforcing the potential of lipotoxicity and microcirculation as therapeutic targets for MASLD.

PO1-08
HK3, a novel MASH drug with profound anti-obesity action

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Background and Aims: Obesity is a major risk factor for metabolic dysfunction-associated steatohepatitis (MASH), showing an increasing prevalence. We have previously demonstrated promising anti-fibrotic and hepatoprotective effects in various preclinical models in the presence of a positive allosteric modulator of the GABA-A receptor, HK3. While HK3 has been primarily investigated for its liver-protective properties, its potential impact on obesity and related metabolic disorders has not been fully explored. Therefore, this study aims to evaluate the *in vivo* efficacy of HK3 in treating obesity using the DIO mouse model, potentially offering a dual benefit in addressing both obesity and MASH.

Method: 6-week-old C57BL/6J mice received a high-fat diet (HFD; D12492) for 12 weeks, followed by 30 days treatment period of HFD together with 25 mg/kg HK3 (DIO + HK3) or vehicle (DIO + CMC). Control Group (STD + CMC) received the standard rodent diet and vehicle. Body weight and food intake was recorded each day or twice a week, respectively. At the end of the study the body composition of the mice was measured using an MRI device to assess the total body fat and the lean mass. Further, blood was collected and serum was separated to analyse blood chemistry biomarkers (ALT, AST, TG, TC, HDL-C, LDL-C).

Results: During the study, HK3 significantly reduced body weight and body weight gain in DIO mice compared to vehicle-treated animals ($p<0.0001$ both), whereas no significant differences in food intake between DIO + HK3 and DIO+CMC were observed. After the 30-day treatment period, the total body weight of DIO+CMC reached 48.7 ± 0.8 g, whereas the body weight of DIO + HK3 mice was significantly lower at 43.5±0.9 g ($p < 0.01$). Fat mass was reduced by more than 20% (21.1 ± 0.8 g vs. 16.6 ± 0.7 g), whereas the lean mass did not change by HK3-treatment (22.1 ± 0.3 g vs. 21.6 ± 0.5 g). In addition, HK3 was able to reduce elevated ALT as well as AST concentration (in U/L) in the DIO mouse group (203.0 ± 23.53 vs. 289.2 ± 12.9 and 81.34 ± 15.18 vs 174.8 ± 27.59 U/L, $p < 0.01$, $p < 0.05$, respectively). Triglyceride levels were significantly reduced by 33 %, and total cholesterol by 36 % in presence of HK3 ($p < 0.001$ and $p < 0.0001$).

Conclusion: These results provide strong evidence for beneficial effects of HK3 for the treatment of obesity besides its prominent anti-fibrotic liver action. Consequently, this compound might represent an innovative pharmacological approach to treat MASH and in parallel obesity as a *first-in-class* drug.

PO1-12
Hormetic effects of 7-Ketocholesterol in preventing ferroptosis-induced hepatocyte death

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Background and Aims: Ferroptosis is an iron-dependent form of cell death characterized by lipid peroxidation which plays a significant role in liver and neurodegenerative disease progression. 7-ketocholesterol (7KC)is the most common product of the reaction between cholesterol and oxygen radicals and is the predominant concentrated oxysterol found in the blood. The toxic effect of 7KC is known partially due to its pro-apoptotic properties. At elevated concentrations, 7KC is a powerful inducer of oxidative stress, inflammation, and cellular degeneration that are common features of many chronic diseases. 7-dehydrocholesterol (7DHC) was suggested to function as an anti-ferroptosis molecule (the immediate precursor of cholesterol). 7KC is a naturally occurring metabolite of 7DHC as it can be generated following the oxidization of 7DHC by cytochrome P4507A1. Currently, the role of 7KC in ferroptosis is yet to be elucidated. This study aimed to investigate the impact of 7KC on hepatocytes ferroptosis.

Method: AML12 hepatocytes were exposed to 20µM Erastin or 5µM RSL3 for induction of ferroptosis. To assess the effect of 7KC, cells in both conditions were also treated with 20µM or more of 7KC, and cell death was evaluated. Gene expression of Erastin, 7KC, and combination treatments was evacuated by RNA sequencing.

Results: 7KC at low concentration protected cells from ferroptosis induced by Erastin and RSL3, 7KC reduced malondialdehyde (levels in Erastin-treated cells and prevented the loss of polyunsaturated fatty acids that was observed after Erastin induction alone. Additionally, 7KC inhibited the cholesterol synthesis pathway, while Erastin enhances it. This inhibition by 7KC also led to the suppression of the enzyme 7-dehydrocholesterol reductase (DHCR7), which metabolizes 7-DHC to cholesterol. Finally, erastin also increased hepatocytes steatosis while 7KC prevented this lipid accumulation.
Conclusion: These results suggest that 7KC at low nontoxic concentrations may reduce lipid peroxidation and ferroptosis. results presented here demonstrate for the first time that a low concentration of 7KC protects, rather than augments, hepatocytes ferroptosisas, diminish lipid peroxidation and steatosis under ferroptosis setting. Additionally, the inhibition of DHCR7 may have led to an increase in the metabolite 7DHC, which is known to inhibit ferroptosis. Future research is needed to understand the metabolic mechanism of such projection.

PO1-15-YI

Impact of using healthy versus cancer in vitro models on the outcome of nutraceuticals and pharmaceuticals in metabolic-associated steatotic liver disease

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Background and Aims: Metabolic-associated steatotic liver disease (MASLD) affects 30% of the global population and is associated with an obesogenic diet and sedentary lifestyle. Changes in lifestyle, such as a balanced diet and increased physical activity, remain the first therapeutic approach. Nutrient-derived molecules (nutraceuticals) may drive various molecular mechanisms such as the upregulation of mitochondrial oxidation and/or pose antioxidant properties that improve the MASLD phenotype. However, the exact mechanisms remain poorly understood, partly because of the different outcomes in various MASLD models. Here, we aim to investigate the molecular effects of nutraceuticals and pharmaceuticals in MASLD using a systematic screen in two hepatic cell lines. Traditionally, cancer cell lines are used to evaluate therapeutics; here, we explore using a healthy tissue-immortalized cell line.

Method: We used HepG2 (hepatoma-derived hepatocytes) and Fa2N4 (immortalized hepatocytes) in this study. Steatosis was induced by exposure of cells to 600 uM free fatty acid (FFA) mix of oleic acid and palmitic acid (2:1) and 1mM fructose for 48h. To test the effect of nutraceuticals on the development of steatosis, cells were treated for 24h with nutraceuticals (butyrate, acetate, propionate, resveratrol, berberine, curcumin, chlorogenic acid, vitamin E) and pharmaceuticals (semaglutide, resmetirom, obeticholic acid and DGAT2 inhibitor) simultaneously with FFA mix or after 24h FFA mix. Intracellular triglycerides were visualized with Oil Red O staining and subsequently quantified. To study the effect of nutraceuticals and pharmaceuticals on gene expression levels, transcriptome analysis was performed.

Results: HepG2 cells had increased intracellular triglyceride levels at basal level and upon FFA stimulation compared to Fa2N4 cells with Oil Red O staining indicating macrosteatosis in HepG2 cells versus microsteatosis in Fa2N4 cells upon FFA stimulation. Treatment with butyrate, acetate or propionate significantly increased intracellular lipids, whereas berberine and vitamin E treatment decreased lipid content dependent on cell line origin and/or concentration. Treatment with resmetirom dramatically decreased intracellular lipids in Fa2N4 cells, showing a mild reduction in HepG2 cells. On the other hand, inhibitor of DGAT2 reduced lipids more drastically in HepG2 compared to in Fa2N4 cells.

Conclusion: This is the first study utilizing immortalized Fa2N-4 cells as a model for steatotic liver disease. When comparing our model to HepG2, the *in vitro* standard for liver cells, our first results indicate nutrient and receptor specificity differences between the two cell lines. Further characterization of this model should reveal more insight into the underlying mechanisms contributing to the improved intracellular triglyceride content in the different cell lines.

PO1-16-YI

Distinct genetic signatures linking MASH in liver, subcutaneous and visceral adipose tissue

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Background and Aims: Metabolic Dysfunction Associated Steatotic Liver Disease (MASLD) presents with a wide range of clinical features. Adipose tissue distribution plays an important role in the development and progression of MASLD/MASH, with visceral obesity being an individual risk factor. However, the underlying mechanisms in the liver, visceral and subcutaneous adipose tissue are not fully understood. Therefore, this study aims to investigate gene expression profiles across these tissue types, identifying distinct molecular characteristics that correlate with disease severity.

Method: Liver (L), subcutaneous (SC) and visceral (VI) adipose tissue samples were obtained from patients undergoing bariatric surgery and healthy controls (n=10 per group) and classified according to the histological presence of steatotic liver disease. The tissue samples were then subjected to RNA sequencing.

Results: Significant differences in gene expression were observed between all four groups (control, healthy obese, simple steatosis and steatohepatitis (MASH)) and in all tissues analyzed (L, SC, VI). With increasing disease severity, the number of upregulated genes increased in all tissue types compared to the control group. Unlike tissues from patients with healthy or steatotic livers, MASH was associated with the upregulation of specific genes related to inflammatory pathways in both the liver and SC adipose tissue. In VI adipose tissue, 65% of the genes upregulated in MASH were already elevated in simple steatosis, primarily affecting glucose and lipid metabolism. Additionally, there were 18 genes uniquely and consistently upregulated across all tissue types in MASH.

Conclusion: The transcriptomic profiles of liver, visceral and subcutaneous adipose tissue in obese patients reflect the liver phenotype, confirming an important role in the development and progression of MASLD. In particular, the adipose tissue profiles show a clear separation of the three groups, suggesting a potential pathophysiological role in the progression of MASLD/MASH and may ultimately be of diagnostic value in the future.

PO1-19-YI

Combined mGluR5 inhibition and AMPK activation by MPEP: dual approach to reducing lipid accumulation in hepatic steatosis

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Background and Aims: Recent research indicates that hyperactivation of the metabotropic glutamate receptor type 5 (mGluR5) in hepatic stellate cells (HSC) promotes fat accumulation in hepatocytes (Choi et al., 2019). We previously demonstrated that 2-methyl-6-(phenylethynyl) pyridine (MPEP), an mGluR5 negative allosteric modulator, reduces lipid deposition in HepG2 cells, in an oleate/palmitate-induced steatosis model (Ferrigno et al., 2020). Aim of the present study is to investigate the role of mGluR5 in reducing steatosis in HepG2 cells. We utilized two mGluR5 negative allosteric modulators (MPEP and Fenobam), an orthosteric antagonist (carboxyphenylglycine, CPG), and an orthosteric agonist ((S)-3,5-dihydroxyphenylglycine, DHPG). Additionally, given our previous findings that MPEP depletes ATP in hepatocytes (Ferrigno et al., 2018), we also evaluated whether MPEP modulates AMP-activated protein kinase (AMPK), a key regulator of lipid metabolism, in this *in vitro* steatosis model.

Method: Lipid accumulation was induced in HepG2 cells by administering 2 mM oleate/palmitate (O/P) for 24h. Cells were pre-incubated with 0.3-3-30 µM MPEP, 1-25-50 µM Fenobam, 100-150-200 µM CPG, alone or in combination with 0.1-1-10 µM of the AMPK inhibitor Compound C. Non-steatotic cells were treated with 100-200-300 µM DHPG, alone or in combination with 30 µM MPEP. Lipid accumulation was assessed by Nile Red dye and quantified with ImageJ, while cell viability was measured by MTT. The ATP content was evaluated by luciferine-luciferase method and the p-AMPK/AMPK ratio was analyzed by Western blot.

Results: In O/P-treated steatotic HepG2 cells, MPEP, Fenobam and CPG reduced lipid accumulation in a dose-dependent manner. In non-steatotic cells, DHPG treatment induced lipid accumulation; the co-administration of MPEP neutralized this effect, confirming the direct role of mGluR5. Moreover, MPEP, and not Fenobam or CPG, depleted ATP in lean HepG2 cells. AMPK is a key regulator of lipid metabolism activated by ATP depletion; so, we hypothesized that MPEP's defatting effect was mediated by AMPK activation. To verify this hypothesis, O/P-administered HepG2 cells were co-treated with MPEP alone and with Compound C, an AMPK inhibitor. The administration of Compound C neutralized MPEP effect. In addition, Western blot analysis showed that p-AMPK/AMPK ratio is increased in steatotic HepG2 cells treated with MPEP.

Conclusion: mGluR5 negative allosteric modulators and antagonists reduce fatty acid accumulation in an *in vitro* benign steatosis model. This effect is mediated by selective mGluR5 receptor inhibition. Moreover, only MPEP showed an additional AMPK-mediated mechanism, suggesting an alternate lipid-lowering pathway beyond receptor targeting, contributing to the observed lipid-lowering effect.

PO1-21
Minibioreactor arrays (MBRAs) to model microbiome response to tryptophan and alcohol in the context of alcohol-associated liver disease (ALD)

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Background and Aims: Intestinal microbiota (IM) plays a causal role in the severity of alcohol-associated liver disease (ALD). Using IM transplantation in mice, we proved that the dysbiosis of alcohol use disorder (AUD) patients with severe alcohol-associated hepatitis (sAH) could be modified, leading to an improvement in alcohol-induced liver injury by increasing tryptophan metabolites to activate aryl hydrocarbon receptor (AhR) signaling pathway. However, the effect of tryptophan on IM in AUD patients, as well as its interactions with alcohol, remain to be elucidated. For this purpose, we used an in vitro approach with Minibioreactor arrays (MBRAs) that allows for the study of IM in a continuous-flow culture with well-controlled factors.

Method: Fecal samples from AUD patients with sAH (n=2) or with noAH (n=2) were transferred to MBRAs chambers and treated with different tryptophan concentrations were initiated for 48 hours. Subsequently, alcohol was introduced in the system for 5 days. Finally, alcohol was removed and the cultures were maintained for an additional 5 days. IM analysis was conducted by 16s sequencing. AhR activity of tryptophan derivatives in supernatants was determined.

Results: After 24h of stabilization, MBRA effectively maintains each fecal community. Tryptophan had no effect on the alpha and beta diversity of the IM from sAH and noAH patients. However, normal tryptophan level decreased the relative abundances of *Escherichia – Shigella* and increased *Bacteroides* in noAH IM, decreased *Proteobacteria* in sAH IM. In the absence of alcohol, tryptophan changed more number of bacteria in noAH IM (14 genus, 2 phylum) than in sAH IM (4 genus). However, with alcohol conditions, tryptophan had minimal effect on the noAH IM. Compared to low tryptophan, normal and high tryptophan levels increased the AhR activity.

Conclusion: AUD IM's is the more dynamic in terms of changes as compared to sAH. Therefore, with the advantage of MBRA our study suggests that tryptophan supplementation to restore the recommended nutritional intake in AUD and AH patients may be beneficial.

PO1-24-YI
Computational electrophysiology highlights cardiac toxicity risks of Pentoxifylline, a key therapy for fatty liver disease, via sodium current inhibition

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Background and Aims: Pentoxifylline, also known as oxpentifylline, is a xanthine derivative often prescribed for treating fatty liver disease (steatosis). Clinical and experimental studies indicate that Pentoxifylline can lead to sinus bradycardia, affecting patients' quality of life. However, its potential cardiotoxic effects are still being actively researched. This study aims to assess how varying concentrations of Pentoxifylline influence cardiac electrophysiology.

Method: The sinoatrial node (SAN) model includes inward rectifier ion channels, sodium channels, potassium channels, calcium channels, and mechanisms for calcium diffusion. A concentration range of Pentoxifylline (0.1 µmol/L to 10 µmol/L) over 200 ms is applied to alter the conductance of the Nav1.5 voltage-gated sodium ion channel within SAN electrophysiology. Both current-clamp and voltage-clamp techniques are used to document electrophysiological responses.

Results: Introducing a current stimulus (Istim) with varying intensities (0.1–0.10 nA) and durations (10–50 ms) triggered action potentials (AP) in the SAN. Pentoxifylline's effects on SAN electrophysiology were evaluated in two steps. First, dose-dependent changes in the Nav1.5 channel's current-voltage (I-V) profile under the voltage clamp revealed a sustained inward current reduction, reaching a 26% decrease at 10 µmol/L. Additionally, the I-V curve shifted 20% more positive, and half-activation potential increased by 28%. Incorporating these changes into the whole-cell model showed that at 10 µmol/L, AP repolarization was prolonged, and AP firing frequency decreased.

Conclusion: This study indicates that higher Pentoxifylline concentrations reduce spontaneous AP firing frequency by inhibiting Nav1.5 currents. Therefore, dose management of Pentoxifylline is essential to mitigate cardiac toxicity risks, and further trials are recommended to explore its underlying cellular mechanisms.

PO2-10
A serial investigation to develop herbal-derived therapeutics targeting MASLD and metabolic syndrome using Amomum Xanthioides

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Background and Aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic syndrome (MS) are significant medical concerns due to their rapidly increasing prevalence and the absence of effective therapeutics. This study aims to investigate the therapeutic potential of amomum xanthioides (AX) and AX-derived candidates, including the ethyl acetate fraction of AX (EFAX) and Bacillus subtilis- or Lactobacillus casei-fermented AX (BAX and LAX), based on a series of preclinical experiments employing high-fat diet (HFD) mouse models.

Method: We performed four animal experiments to examine the efficacy of AX and AX-derived herbal medications in ameliorating MASLD and MS. We specifically evaluated: 1) the effects of AX, 2) the effects of EFAX, 3) a comparative study of the effects of EFAX and BAX, and 4) a comparative analysis of the effects of AX and LAX. We fed the HFD (60% kcal fat) to all 6-week-old male C57BL/6j mice for 10 weeks, with the exception of the normal chow diet group. Starting from the 4th week, we administered AX, EFAX, BAX, LAX, or metformin (200 mg/kg/day for all drugs) orally to the treatment groups for 6 weeks. The primary assessments encompassed the evaluation of hepatic lipid accumulation (triglycerides and total cholesterol) and insulin resistance (fasting blood glucose and serum insulin). Secondary assessments encompassed alterations in body weight, dietary consumption, and hepatic inflammatory cytokine levels.

Results: AX and AX-derived herbal medicines including EFAX, BAX and LAX in HFD-fed mice significantly reduced body weight, fat mass, and hepatic lipid accumulation compared to metformin-treated and HFD-only groups without affecting appetite. Especially, LAX improved key metabolic markers such as fasting blood glucose, insulin levels, and insulin sensitivity by upregulating glucose transporters (GLUT2 and GLUT4) and insulin receptor expression in the pancreas and liver. Additionally, BAX and LAX exhibited strong anti-inflammatory effects by reducing serum IL-6 levels and suppressing hepatic inflammation via the downregulation of pro-inflammatory cytokines (TNF-α and IL-1β) and oxidative stress markers (ROS and MDA). LAX also restored hepatic lipid balance by decreasing lipogenic proteins (SREBP-1 and GPAM) and promoting lipolytic pathways (PPAR-α and AMPK-α). Normalization in serum lipid profiles, including reductions in triglycerides, total cholesterol, and LDL cholesterol, further demonstrated the therapeutic potential of BAX and LAX.

Conclusion: The results of this study show that fermentation with Bacillus subtilis or Lactobacillus casei makes AX work better as a medicine. This means that BAX and LAX could be useful for treating both MASLD and MS.

PO2-12
Metabolic associated steatotic liver disease and mental illness: role of fibroblast growth factor-21

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Background and Aims: Incidence of metabolic associated steatotic liver disease (MASLD) is increased in mental illness, with and without obesity. Myriad contributing factors include psychiatric drugs. The mechanisms of antipsychotic (AA) associated MASLD are poorly understood. We reported clinically relevant doses of AA induced MASLD, altered hepatic iron (Fe) metabolism and impaired immune response in a preclinical model, in the absence of obesity. Fibroblast Growth Factor–21 (FGF-21) modulates lipid and glucose metabolism, sympathetic nervous system activity, and inflammation, and is an emerging therapeutic target for MASLD. We hypothesize that AA alter FGF-21 signaling, which may impact drug associated effects on MASLD. Our aim was to examine the role of FGF-21 in the development of AA induced MASLD using bioanalytical and proteomic methodologies in a pre-clinical model.

Method: C57BL/6J mice (8 wk) were treated with risperidone (RIS, 1 mg/kg PO) or drug vehicle (VEH, 0.1% acetic acid PO) for 14 or 28 d. Acute immune challenge: RIS and VEH mice were injected with lipopolysaccharide (LPS, 500 ng/kg) or VEH (PBS) on d14. Two hr post LPS, blood was collected. Adaptive immune challenge: RIS and VEH mice were immunized by injection with Pneumovax23® or VEH on d5 of AA treatment; blood was collected on d14. Hepatic proteomes were analyzed by mass spectrometry and profiled by sequential window acquisition of all theoretical spectra (SWATH) analysis in mice treated for 28 d with RIS or VEH. Differentially expressed (DE) proteins were identified (significance $p < 0.05$) and mapped to disease pathways (KEGG). MASLD was histologically confirmed. FGF-21 was quantified by ELISA (Millipore EZRMFGF-21-26K).

Results: Mouse model of lean/non-obese MASLD. There was no effect of RIS (14 or 28 d) on bodyweight ($p > 0.05$), however RIS caused histopathology confirmed MASLD in the absence of obesity. Proteomic analysis revealed AA-associated changes in known MASLD pathways. Pathways included mitochondrial function, energy metabolism, Fe metabolism, ferroptosis and reactive oxidation species (ROS) pathways. Adaptive and acquired immune responses were altered with AA treatment. RIS treatment resulted in a blunted cytokine response to LPS challenge and inability to mount an antibody titer response to vaccination vs VEH ($p < 0.01$). FGF-21 concentrations in plasma were significantly elevated by RIS vs. VEH in both immune challenge studies (14 d; $p < 0.05$) but were unchanged by LPS or vaccination treatments.

Conclusion: MASLD is increased in mental illness and with AA treatment. AA associated MASLD occurs in the presence and absence of obesity and is linked to altered FGF21 signaling and DE traits pivotal to metabolic dysfunction and SNS activity. These data support the hypothesis that AA drugs act, at least in part, by altering FGF-21 associated pathways, consistent with FGF21 as a therapeutic target for MASLD.

PO2-14
Effect of constitutive androstane receptor activation on hepatic unsaturated triglyceride levels

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Background and Aims: Constitutive androstane receptor (CAR) and pregnane X receptor (PXR) are nuclear receptors that play critical roles in xenobiotic clearance and lipid metabolism. Their activation significantly influences lipogenesis and beta-oxidation in the liver, both under normal conditions and during nutritional stress. While ligands (drugs and environmental contaminants) for both receptors are thought to promote steatosis under normal nutritional conditions, they may reduce steatosis by inhibiting lipogenesis during nutritional stress in high-fat diet-fed mice.

Method: In our recent study utilizing lipidomic analysis, we found that CAR activation significantly downregulates triglyceride (TG) content and modifies the hepatic lipidome in mice administered the CAR ligand TCPOBOP, favoring triglycerides enriched with unsaturated fatty acids. Here, we extend these findings to newly developed human CAR agonists in humanized PXR/CAR/CYP3A4/7 mice.

Results: We observed a significant intra-class effect within the TG class, marked by increased levels of TG containing long-chain highly unsaturated fatty acids (TG 60:12, TG 60:13). Additionally, we identified a statistically significant decrease in total lysophosphatidylcholine (LPC) levels as well as some individual LPC species.

Conclusion: These results suggest promising implications for the use of these receptor ligands in the treatment of hepatic steatosis. Funded by NETPHARM grant by EU.

PO2-15
Arsenic as a risk factor for metabolic-associated steatotic liver disease (MASLD): A mechanistic study

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Background and Aims: Metabolic associated steatotic liver disease (MASLD) impacts approximately 25% of the adult Americans and now is the leading cause of end stage liver disease and hepatocellular carcinoma (HCC). While obesity is a major driver, it clearly is not the only factor and many other potential factors including in lean MASLD patients may be involved. There is emerging evidence that the exposome, especially heavy metals such as arsenic may play a role. We, therefore, assessed the possible role and mechanisms of arsenic in steatotic liver disease.

Method: We performed geo-spatial mapping studies on arsenic and HCC to extrapolate impact on MASLD. Spatial Poisson regression modeling was conducted to estimate the risk ratios (RR) of incident liver cancers by tertiles of population-weighted arsenic levels (0.54 -1.41, 1.41 - 2.50, and 2.53 - 30.8 ppb) at a county level. For mechanistic studies, we used the human hepatic cell line, HepG2 which we exposed to low dose arsenic (0.1 - 0.2 micromolar) for 3 - 6 weeks. We used standard cell biology/molecular techniques to identify the impact of arsenic (As) on HepG2 physiology and gene expression.

Results: The high arsenic group had relative risks (RRs) of 1.064 (95% CI 1.010 - 1.122) for liver cancer compared to the low arsenic group, after adjusting for all covariates. Additionally, every unit increase in natural log water arsenic was associated with a 4.9% increase in liver cancer incidence (RR 1.049, 95% CI 1.013 - 1.086) after adjusting for all covariates. Furthermore, we performed HepG2 studies. When we assessed fat accumulation by oil-red staining we say that As resulted in a 45 and 80% induction in basal conditions with As 0.1 and 0.25 mcg/L which was accentuated with palmitate supplementation. There was concomitant induction of lipid droplet structural proteins PLIN2 and PLIN5 by 20 - 30%, $p < 0.05$. As induced extracellular acidification rate (ECAR) by 23 - 35% ($p < 0.001$) and candidate metabolic markers such as ACACA, FASN and SREBP1 by 1.5 - 3 folds (all $p < 0.05$). This was further supported by findings on RNAseq from As treated HepG2 where molecules with metabolic pathways (e.g. nynrin) were some of the top dysregulated genes.

Conclusion: We demonstrate a correlational link between As and MASLD using HCC as a surrogate marker. Mechanistically. We provide support that As may play an impact in the steatotic liver disease by changing the metabolic function of the hepatocyte. Future studies will focus on extrapolating these mechanistic alterations to MASLD patients.

PO2-17
A human stem cell-based hepatic model as a tool for metabolic dysfunction-associated steatotic liver disease modeling and drug screening

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Background and Aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the leading cause of liver disease mortality and morbidity, being associated with sedentary lifestyles and unhealthy diets. Thus, research is focused on the development of effective therapies. Hepatocytes are the first responders to lipid oversupply, dictating disease progression. Therefore, human-based in vitro hepatic models are a key tool for evaluating effective drug candidates. Stem cell-derived hepatocyte-like cells (HLCs) offer significant advantages over primary hepatocytes or hepatic cell lines as a platform for disease modelling. Here, we established a human neonatal mesenchymal stem cell-derived HLC model able to recapitulate the pathophysiology of MASLD, occurring at the hepatocyte level. After characterizing the therapeutic effects of NRF2 induction, the model was validated for drug screening.

Method: HLCs were obtained using a differentiation and maturation protocol previously established, lasting 34 days. On day 31 (D31), cells were treated with 25 µM - 250 µM of oleic acid (OA) and palmitic acid (PA) in a 2:1 ratio, respectively, for 72h. During the last 24h of fatty acid exposure, HLCs were treated with the NRF2 inducer dimethyl fumarate (DMF). The disease model was characterized by lipid droplet formation (Bodipy staining); expression of genes involved in energy metabolism and antioxidant response, insulin resistance markers and inflammation signaling (qPCR); mitochondrial function (cellular respirometry) and production of glucose, reactive oxide species (ROS) and ceramides.

Results: Upon OA and PA exposure, HLCs presented lipid accumulation in a dose-dependent fashion, induction of gluconeogenesis, lipogenesis, ER stress, antioxidant response and inflammation. These alterations were accompanied by increased production of glucose ($p < 0.001$) and ROS ($p < 0.01$) and synthesis of ceramides, which are characteristics of the MASLD setting. Additionally, signs of mitochondrial dysfunction were also present, namely a decrease in spare respiration and an increase in proton leak-linked respiration ($p < 0.05$). Noteworthy, DMF treatment led to decreased glucose ($p < 0.001$) and ROS production ($p < 0.05$) along with induction of fatty acid oxidation, activation of the bile acid synthesis pathway ($p < 0.01$) and increased ceramide secretion ($p < 0.05$).

Conclusion: Stem cell-derived HLCs of human origin were competent for MASLD modeling drug screening. The potential of NRF2 inducers should be further explored as a therapeutic alternative. The work was financially supported by Fundação para a Ciência e a Tecnologia (FCT) through SFRH/BD/144130/2019 to J.S.R., UIDB/04138/2020 and UIDP/04138/2020. This research was also funded by HORIZON-HLTH-2022-STAYHLTH-02, grant number 101095679.

PO2-23

Novel point-of-care, rapid breath test to identify patients with metabolic-dysfunction associated steatotic liver disease with advanced fibrosis - a pilot study

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Background and Aims: There is a clear need for cost-effective, easy-to-use Point of Care (PoC) screening technologies for diagnosing metabolic-dysfunction associated steatotic liver disease (MASLD) and steatohepatitis (MASH), particularly those identifying advanced fibrosis, a key predictor of liver-related mortality. Volatile organic compounds (VOCs) biomarkers in exhaled breath, which reflect altered hepatic metabolism, are promising but current VOC analysis technologies are labor-intensive. NaNose Medical Ltd. is developing a unique nanotechnology-based sensing device, DiaNose, which uses semi-selective chemiresistor sensor array and machine learning to detect “breath fingerprints” without complex VOC concentrations analysis. Sensors’ signals data from clinical studies is used to train models to classify disease stages.

Method: The sensor array consists of functionalized metal nanoparticle films over electrodes, detecting VOCs through electric response. DiaNose includes a single-use breath collection unit, a replaceable sensor, and a measurement system. In clinical studies, it collects data from MASLD patients with different fibrosis stages, verified through biopsy or FibroScan tests.

Results: Data from 30 MASLD patients (13 with no/early fibrosis, 17 with advanced fibrosis) were used to develop a classification model. Cross-validation produced accuracies of 85.5% sensitivity, 79% specificity, and 82.3% overall accuracy. Data collection is ongoing to enhance stability and generalization.

Conclusion: Preliminary results indicate DiaNose’s potential for non-invasive PoC screening, accurately distinguishing MASLD with early versus advanced fibrosis. This tool could facilitate patient referral, optimize primary care management, and support trial stratification to advance treatment development.

PO3-03-YI
The mechanisms of metabolic dysfunction-associated steatotic liver disease (MASLD) development: what can we learn from a MASLD-resistant porcine model?

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Background and Aims: Steatotic liver disease is very common in people with obesity but the causal and temporal relationship between these pathological entities is difficult to study in humans or rodents. Inevitably, there are people who become obese and yet do not develop MASLD. In this study we used a porcine model of diet-induced obesity which is commercially bred for a high lean-to-fat mass ratio. Through longitudinal monitoring of parameters of metabolic fitness, we aim to characterise this relative protection from MASLD. We hypothesised that this pig breed would remain insulin-sensitive, preserve adipose tissue energy buffering capacity, and be protected from MASLD despite a hypercaloric diet (HCD).

Method: Six adult female commercial pigs were studied on a normal diet and then during HCD consisting of 8400kcal/day (45% fat content, 1:1 soybean and palm oil) for 12 weeks. Weekly fed and fasted blood samples were obtained and glucose, insulin, non-esterified fatty acids (NEFA), triglycerides, and total cholesterol were measured. Insulin response to oral glucose (OGT) was quantified and liver biopsies obtained. A subset of animals (n=3) also underwent a euglycaemic-hyperinsulinaemic clamp (EHC) at baseline and 12 weeks. Fat distribution and liver fat fraction were measured by MRI at baseline and 6 and 12 weeks.

Results: HCD resulted in significant weight gain (5±0.5kg/week), with fat being predominantly stored subcutaneously. Fasted insulin and insulin response to OGT were unchanged throughout the trial, but there was a reduction in M value (10.17±2.90 vs 5.49±0.82 mg/min·kg) during the EHC at 12 weeks, implying a degree of insulin resistance had developed. NEFA suppression during EHC was maintained. Fasted triglycerides (0.30±0.05 vs 0.34±0.05mmol/l, $p<0.05$) and post prandial NEFA (72.42±74.84 vs 151.42±66.97µmol $p>0.05$), increased throughout the study. Fasted NEFA, however, did not increase. On the contrary, a moderate albeit non-significant reduction was observed (314.67±191.92 to 189.33±132.20 µmol/l). Total cholesterol remained unaltered. Histological steatosis was not seen as <5% of hepatocytes contained lipid droplets and fat liver fraction increased by only 1%.

Conclusion: HCD resulted in obesity and altered insulin sensitivity but were protected from steatosis in this model. Moreover, the pigs developed only some of the alterations of lipid profile reported in humans and other animal models of diet-induced obesity. The NEFA response implies that NEFA disposal was markedly increased to adapt to HCD. This potentially protective mechanism warrants further investigation.

PO3-05
Advanced unbiased proteomics reveals new molecular mechanisms in steatotic liver disease

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Background and Aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a chronic inflammatory disease linked with obesity and a high-fat diet (HFD). Its molecular mechanisms are still being studied, especially the role of protein post-translational modifications (PTMs). Traditionally, PTMs have been studied by mass spectrometry (MS) using closed searches (CS). However, open searches (OS-PTM) and advanced ways of integrating quantitative information allow the hypothesis-free unveiling of whole proteome PTMs, proteins and pathways involved in the development of MASLD.

Method: The raw MS data (Project PXD007653) obtained by Krahmer et al. (2018) (doi: 10.1016/j.devcel.2018.09.017), in total liver lysate, were reanalyzed by open search (OS-PTM) in a mouse model of MASLD development over time. In this model, mice were induced MASLD by HFD for 3 (HFD3, n=3) or 12 (HFD12, n=3) weeks. The control group (Control, n=3) was fed a low-fat diet. A novel approach was implemented to accumulate quantitative information and capture specific and global alterations across the proteome.

Results: OS-PTM revealed a complex PTM picture in mouse liver and allowed a reliable protein quantitation. New MASLD-linked pathways were identified, but the biggest effect was the decrease in the labile protein-bound iron, directly correlated with the decrease in ferritin, Rab12, which regulates lysosomal trafficking of the transferrin receptor, and other lysosomal trafficking proteins or iron-dependent chromatin structure regulators; and inversely correlated with the increase in mitochondrial and endoplasmic reticulum hemoprotein oxidases, such as those involved in choline catabolism, the Cyp450 family and a group of alcohol dehydrogenases involved in fatty acid oxidation and in the second phase of branched-chain amino acid degradation.

Conclusion: OS-PTM, together with an advanced way of integrating quantitative information, makes it possible to delve deeper into the proteome and automatically detect global and specific changes. This technology enables unbiased exploration of the molecular mechanisms underlying MASLD development. The results suggest that altered iron homeostasis plays a crucial role in disease progression, which could be a key therapeutic target to reduce the pathology and improve clinical outcomes.

PO3-07-YI

Immune landscaping in a mouse model unveils an immunosuppressive cell composition in hepatic crown-like structures involved in metabolic dysfunction-associated steatohepatitis

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Background and Aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) and its progression to steatohepatitis (MASH) are highly prevalent in the global population. Hallmarks of MASH are steatosis, inflammation, hepatocyte ballooning and fibrosis, all of which together increase the risk of developing end-stage liver disease and hepatocellular carcinoma (HCC). Treatment availability for MASH patients is limited, underscoring the need to develop effective therapies. To ensure preclinical findings are translatable to human conditions, the use of well-characterized animal models is essential. In our study, we characterized the melanocortin-4-receptor knockout (Mc4rKO) mouse model fed a western diet (WD) and compared its progression to human data. Additionally, we explored the liver's immune landscape to better understand its role in disease progression.

Method: We used age-matched male BL6, Mc4rKO on normal diet (ND) and Mc4rKO on WD mice to study control, MASLD and MASH, respectively. Liver histology was used to define the macroscopic landscape, alongside bulk RNAseq analysis to describe the transcriptomic signatures involved in progression. To specify the metabolic similarity of the model, transcriptomic-driven metabolic pathway analysis of Mc4rKO mice was compared to patient data. The immune landscape of mouse livers was analysed by solution (sMC) and imaging mass cytometry (IMC) focusing on macrophage and T cell populations.

Results: The Mc4rKO mouse model closely mirrors the human transition from healthy liver to MASLD and ultimately HCC, displaying features of advanced MASH histopathology along with obesity, type 2 diabetes and metabolic syndrome. The transcriptomic signature of MASH livers strongly indicated inflammation and fibrosis, along with an upregulation of HCC-related genes. The metabolic comparison revealed significant similarities between mouse and human MASH. The immune landscape in MASH livers is characterized by a marked infiltration of lipid-associated macrophages, monocyte-derived Kupffer cells and CXCR6+ CD8 T cells. Furthermore, an immune community was found within hepatic crown-like structures (hCLS) and consisted of macrophages, T cells, neutrophils and B cells. Notably, CXCR6+ CD8 T cells, associated with auto-aggression and exhaustion, were located within these structures.

Conclusion: Our data demonstrates that the Mc4rKO mouse model shares characteristics of human MASH, validating its translatability for future studies. Most importantly, we reveal a complex community of immune cells within hCLS, locating CXCR6+ CD8 T cells to this specific environment. The exhaustion of these T cells suggests an immune-suppressive function of hCLS within the MASH liver, potentially supporting the progression from MASH to HCC.

PO3-08-YI
Liver adrenoceptor alpha-1b plays a protective role in MASLD progression

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Background and Aims: The brain plays a central role in regulating many physiological functions, including the metabolism of organs like the liver. This regulation happens through neuroendocrine and autonomic mechanisms, which together maintain homeostasis. Unfortunately, in metabolic diseases such as metabolic dysfunction-associated steatotic liver disease (MASLD), these sophisticated processes can be severely impaired leading to autonomic dysfunction and alterations in liver innervation. Recent tissue clearing studies convincingly showed that neural innervations within the liver are of sympathetic nature, suggesting that adrenergic receptors, responsible for sympathetic signaling in the liver, may play a crucial role in regulating liver metabolism. The liver mainly expresses the adrenoceptor alpha 1b (ADRA1B) and studies have demonstrated decreased expression of this receptor in the livers of both obese and MASLD mouse models. This study aims to investigate whether the loss of liver *Adra1b* exacerbates the liver's response to metabolic stress, such as MASLD.

Method: We developed a conditional liver-specific knockout model for *Adra1b* (KO) using CRISPR-Cas9 technology, with KO mice and wild-type (WT) littermates fed a GAN Nash diet for 32 weeks to induce MASLD. We evaluated liver damage via plasma ALT/AST levels and gene expression analysis of inflammatory and fibrotic markers. Liver steatosis, fibrosis, and inflammation were quantified using automated image analysis software, MorphoQuant. Additionally, TNF-alpha levels in both plasma and liver were measured to assess inflammation.

Results: While KO mice did not exhibit differences in ALT/AST, they had elevated bilirubin levels and a higher bilirubin-to-albumin ratio, indicating more advanced liver damage. Histological analysis showed increased fibrosis and inflammation in KO mice, with significantly higher collagen deposition and macrophage infiltration. Notably, we observed a significant accumulation of TNF-alpha in the liver of KO mice compared to WT littermates, while no such difference was found in the plasma.

Conclusion: Our data suggests that ADRA1B plays a protective role in MASLD progression by mitigating liver inflammation and fibrosis. The absence of liver *Adra1b* exacerbates these pathological processes, likely through TNF-alpha accumulation in the liver. These findings provide insight into the sympathetic regulation of liver function in MASLD and highlight a potential therapeutic target for the progression of this disease.

PO3-13-YI
JAK2 inhibitor ruxolitinib ameliorates portal hypertension associated with metabolic dysfunction-associated liver disease

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Background and Aims: Portal hypertension (PHT) commonly arises from cirrhosis, but non-cirrhotic portal hypertension (NCPH) related to metabolic dysfunction, specifically in metabolic dysfunction-associated steatotic liver disease (MASLD), presents unique challenges. This study explores the therapeutic potential of the JAK2 inhibitor, ruxolitinib, to reduce MASLD-associated PHT, focusing on its impact on endothelial-to-mesenchymal transition (EndMT).

Method: A methionine-choline-deficient (MCD) diet was used to induce MASLD-associated PHT in mouse model. Ruxolitinib was administered to evaluate its effects on portal pressure and endothelial function. Serological analysis and histopathological assessments were conducted alongside RT-PCR and Western blot to measure EndMT-related protein expression.

Results: Mice treated with ruxolitinib demonstrated a reduction in spleen weight-to-body weight ratio, indicating a decrease in portal pressure. H&E and Masson staining showed that the treatment group had less portal vein occlusion, reduced luminal narrowing, and decreased perivascular fibrosis compared to the control group. Additionally, ruxolitinib treatment led to lower serum TC levels and reduced expression of endothelial damage markers (ICAM1, Vimentin, Fibronectin, N-cadherin, TGF-β, SNAI1), suggesting an alleviation of EndMT and endothelial dysfunction.

Conclusion: Ruxolitinib is potential in alleviating metabolic-associated PHT by mitigating endothelial dysfunction and EndMT, providing a promising therapeutic avenue for managing non-cirrhotic, MASLD-assouciated PHT.

PO3-14
Arsenic as a risk factor for hepatocellular carcinoma (HCC) risk among patients with metabolic associated liver disease (MASLD)

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Background and Aims: MASLD is a major public health challenge in Western countries impacting a quarter of the adult population. The most feared consequence is HCC. The drivers of the transition of MASLD à HCC remain unclear. We have recently demonstrated via geo-spatial mapping that arsenic (As) exposure correlates with HCC risk (PMID: 37926230). We investigated whether arsenic could be co-factor in HCC development in MASLD.

Method: Patients. We used the Texas Hepatocellular Carcinoma Consortium which follows more than 4000 patients with cirrhosis (predominantly MASLD). We measured toenail clippings by mass spectroscopy from 80 patients with cirrhosis who remained cancer free over a median of 1.5 years and 20 patients who developed HCC over that time period. Mechanistic Studies. We used the human hepatic cell line, HepG2 which we exposed to low dose arsenic (0.1 - 0.2 micromolar) for 3 - 6 weeks. We used standard cell biology/molecular techniques to identify the impact of arsenic on HepG2 physiology and gene expression.

Results: Of the 18 heavy metals assayed, only arsenic (As) was elevated (mean or median level with SD if mean and IQR for median) in toenails of those who later progressed to HCC compared to those who did not progress (p value).
From a mechanistic perspective, we assess cancer stem cell (CSCs) markers as a manifestation of malignant transformation. HepG2 cells had an increase in CD44 positive stem cells by FACS analysis 30% ($p < 0.01$). The physiological consequences include increased organoid growth by 50% ($p < 0.05$). Since CSCs are associated with chemoresistance, we also noted that As pretreatment decreased efficacy of oxaliplatin (39% decrease in Annexin V measured apoptosis, $p < 0.05$). We went upstream to assess chromatin status. Using the Click-IT assay of uracil incorporation, we noted that arsenic increased nascent mRNA by 47% ($p = 0.0001$) and this was by changed histone mark H3K9 including increase in stimulatory aceylation and suppression of inhibitory trimethylation (64 and 79%, respectively, $p < 0.05$).

Conclusion: We present evidence for a possible role for As in the malignant degeneration of MASLD. The mechanisms may include induction of CSCs with concomitant activation in chromatin.

PO3-15
Low doses of bacterial D-lactate modulate liver steatosis and ameliorate experimental MASLD

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Background and Aims: The gut microbiota plays a significant role in MASLD progression, particularly through bacterial metabolites that enter the liver via the portal vein, influencing hepatic metabolic processes. Supplementation with probiotics, especially *Lactobacillaceae* strains, has shown liver health benefits, such as reducing serum liver enzyme levels and liver fat accumulation. Recent studies on *L. reuteri* showed that its D-lactate production may contribute to liver protection. Unlike L-lactate, D-lactate is largely produced by bacteria, with only minimal amounts synthesized by eukaryotic cells. This study aims to investigate the effects of low-dose D-lactate in reducing lipid accumulation and protecting against MASLD progression, potentially establishing D-lactate-producing probiotics as a novel therapeutic avenue for liver disease management.

Method: We employed two experimental mice models: a methionine choline-deficient (MCD) diet model supplemented with *L. reuteri* DSM17938 and a 20-week High-Fat High-Fructose Diet (HFHFD) model supplemented with either *L. reuteri* DSM17938 *or* 1 mM D-lactate. Lliver histology and mRNA expression levels related to inflammation, lipid metabolism, and fatty acid transport were assessed. D-lactate role was evaluated *in vitro* by examining its effects on palmitic acid (PA) accumulation and mRNA expression associated with hepatic lipid metabolism.

Results: Mice on a MCD diet, supplemented with *L. reuteri*, showed reduced hepatocellular vacuolization and inflammation compared to controls, though serum ALT and AST levels remained unaffected. Supplementation lowered liver fibrosis markers, and decreased expression of lipid metabolism genes and inflammatory markers. *In vitro* supplementation with 1 mM D-lactate specifically reduced lipid accumulation in hepatocytes exposed to PA, lowered lipid metabolism marker expression. In the 20-week HFHFD model, 1 mM D-lactate reduced body weight gain, liver-to-body weight ratio, and steatosis. It also lowered serum ALT, decreased hepatic inflammation markers, and prevented fibrosis markers upregulation. Moreover, D-lactate supplementation altered gut microbiota composition, showing significant effects on beneficial bacterial populations in both normal and HFHFD conditions, suggesting an additional role in gut-liver axis modulation.

Conclusion: Our findings demonstrate that *L. reuteri* DSM17938 effectively mitigates experimental MASLD, in part through the production of intestinal D-lactate. This study highlights D-lactate potential to reduce MASLD by modulating liver metabolism, decreasing inflammation, and influencing gut microbiota, presenting low-dose D-lactate as a promising new therapeutic strategy for MASLD management.

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PO3-19
Preliminary data analysis on bone fracture risk assessment in patients with metabolic dysfunction-associated steatotic liver disease

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Background and Aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) and type 2 diabetes (T2D) share several risk factors for the development of bone fragility. However, there is insufficient evidence of the qualitative changes in bone tissue when these conditions coexist. This study aims to evaluate the relationship between the Trabecular Bone Score (TBS), an index of bone quality, and the risk of fragility fractures in patients with MASLD.

Method: All patients with MASLD who consecutively attended the Medicine and Hepatology Unit of the University Hospital of Messina from February 1st, 2024, to July 31st, 2024, were enrolled. Patients with decompensated cirrhosis, indirect signs of portal hypertension, history of hepatitis B or C infection, thyroid or parathyroid diseases with gland dysfunction, chronic kidney failure, heart failure, active malignant neoplasia, or those who had received treatments affecting bone metabolism for more than three months were excluded. All patients underwent liver stiffness elastography with evaluation of the Controlled Attenuation Parameter (CAP). Dual-energy X-ray Absorptiometry (DEXA) was performed to evaluate fracture risk assessment using the FRAX algorithm and TBS evaluation for each patient. Glycemic decompensation was defined as glycated hemoglobin (HbA1c) values higher than 7.0%. A digital dataset was created to record patients' demographic, clinical, biochemical data and instrumental exam results. All statistical analyses were performed by using SPSS version 25 software.
Results: Thirty-one patients [58% males, median age 67 (83 – 48)] with a median follow-up of 321 weeks (48 – 864) have been included in the analysis. All patients had T2D and were treated with glycemic lowering therapies. Eleven of the 31 patients (33%) had a diagnosis of compensated cirrhosis with CAP values > 238 dB/m (compatible with hepatic steatosis), 14 (42.4%) were obese (body mass index > 30 kg/m^2), and 28 (84.4%) had dyslipidemia. Nine patients (27%) had glycemic decompensation. After stratifying patients by TBS (cut-off value = 1 .350), a significant association between altered TBS and the presence of cirrhosis was observed (p = 0.02). No significant associations were identified for CAP values > 238 dB/m (p = 0.48), obesity (p = 0.27) and glycemic decompensation (p = 0.41). Stratifying patients by femoral T-score also produced statistically significant results, with a notable association with cirrhosis (p = 0.008).

Conclusion: Preliminary data analysis indicated an increased fracture risk due to alterations in trabecular bone microarchitecture and reduced bone mineral density in patients with advanced chronic liver disease and T2D. Expanding the sample size may provide further insights regarding CAP levels, glycemic control, and the influence of therapeutic regimens, which will require additional analyses.

PO4-02
Distinct roles of hepatic S100A10 and S100A11 in metabolic dysfunction-associated steatotic liver disease and hepatocellular carcinoma

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Background and Aims: Obesity and metabolic syndrome are major etiological factors associated with the development of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD). MASLD initiates with the aberrant accumulation of fat in hepatocytes and can progress towards inflammation and fibrosis, priming the liver for Hepatocellular Carcinoma (HCC) development, the 3rd cause of cancer-related death. We and others identified S100 calcium binding proteins as promising mediators of MASLD and HCC development. In this regard, we compared the impact of the hepatic downregulation of two closely related members, i.e. S100A10 and S100A11, in genetic and diet-induced MASLD mouse models, as well as in mouse models of HCC development.

Method: Hepatotropic AAV8-encoding shRNAs targeting S100A10 or S100A11 were used to downregulate these proteins specifically in hepatocytes of mice fed with a diet inducing steatosis, inflammation and fibrosis (FPC diet) or in a genetic model of MASLD bearing hepatocyte-specific deletion of PTEN (LPTENKO). The impact of S100A10 or S100A11 downregulation on HCC development was further investigated in different models with or without fatty liver disease. Aged LPTENKO mice spontaneously developing MASLD-driven HCC, diethylnitrosamine (DEN)-injected mice fed or not with high fat diet and mice harbouring two of the main mutations found in human HCC have been investigated.

Results: Our data indicate that downregulation of S100A10 or S100A11, before or after disease induction, reduced steatosis and fibrosis development, with a preponderant action of S100A11. Unexpectedly, we uncovered an opposite role of S100A10 and S100A11 in hepatic carcinogenesis. Downregulation of S100A10 significantly fostered carcinogenesis in a fatty liver setting, whereas overall, the knock-down of S100A11 does not slow down liver cancer initiation, except in LPTENKO mice. Supporting these results, the knock-down of S100A10 enhanced tumour growth, while the opposite outcome was observed following S100A11 downregulation. Those distinct effects on tumoral growth are observed either with or without a MASLD / obesity context.

Conclusion: S100A10 and S100A11 expression in hepatocytes promote MASLD development and represent suitable therapeutic targets. However, for the first time, we identified a tumour suppressive role of S100A10 in restraining hepatic carcinogenesis, while targeting S100A11 is beneficial to restrain liver tumour growth. Our study pinpoints the singularity of S100 family members in tumoral processes and lipid metabolism. Those results would pave the way to highlight S100A10 and S100A11 proteins as key therapeutic targets to implement to the therapeutic arsenal of liver diseases clinical management.

PO4-07-YI
Circulating EV-miRs for the diagnosis and staging of MASLD and hepatocellular carcinoma

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Background and Aims: Non-invasive biomarker-driven algorithms are urgently needed for classifying Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) and monitoring its progression to Steatohepatitis (MASH) and Hepatocellular Carcinoma (HCC). In this study, we investigated microRNAs (miRs) present in serum extracellular vesicles (EVs) that may serve as diagnostic and prognostic biomarkers.

Method: A total of 71 individuals were clinically categorized into five study groups: no steatosis (n=9), simple steatosis (n=18), MASH F0/F1 (n=18), MASH F2/F3 (n=18), and MASLD-HCC (n=8). EV-miRs were isolated using exoRNeasy Midi kit (Qiagen) and small RNA transcriptome was sequenced using QIAseq miRNA Library kit (Qiagen). The best transcripts were selected and area under the curve (AUC), univariable and multivariable analysis were performed. Afterwards, logistic regression models (LM) were designed to improve accuracy.

Results: In total, 1,461 EV-miRs were identified. Notably, the EV levels of 29 miRs were found to be dysregulated in MASH compared to simple steatosis, irrespective of the degree of liver fibrosis and BMI. A LM combining only 2 of these could reach an AUC of more than 0.93. Additionally, 9 miRs were associated with fibrosis grade (F0-F1 vs. F2-F3) regardless of BMI, with AUC up to 0.95 when combined in LM. Finally, a total of 78 miRs were found to be dysregulated in MASLD-HCC compared to MASLD, regardless of age, sex, BMI and fibrosis grade, with 3 exhibiting great accuracy with AUC>0.93, sensitivity>87% and specificity>92%. Furthermore, the LMs combining 2 or 3 miRs reached AUC of 1.0 for MASLD-HCC diagnosis.

Conclusion: EV-miRs present a high potential as diagnostic and staging tool for MASLD and MASLD-HCC. Future validation in a larger sample of patients is necessary to confirm these findings.

PO4-10
Hepatoprotective effects of fatty acid synthase inhibitor TVB-3664 in the GAN diet-induced obese and biopsy-confirmed mouse model of MASH

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Background and Aims: Denifanstat, an oral fatty acid synthase (FASN) inhibitor, have recently been demonstrated to improve NAFLD Activity Score (NAS) and fibrosis stage in a phase 2b clinical trial (FASCINATE-2) in patients with metabolic dysfunction-associated steatohepatitis (MASH). The present study aimed to investigate metabolic, biochemical, histopathological and transcriptomic effects of TVB-3664, a FASN inhibitor analogue, in the translational Gubra Amylin NASH (GAN) diet-induced obese and biopsy-confirmed mouse model of MASH with liver fibrosis.

Method: Male C57BL/6 mice were fed the GAN diet high in fat, fructose and cholesterol for 39 weeks prior to study start. A liver pre-biopsy was collected 4 weeks before treatment start. Only GAN DIO-MASH mice with biopsy-confirmed NAFLD Activity Score (NAS≥5) and moderate/advanced fibrosis (stage F2-F3) were included and stratified into treatment groups (n=16-17 per group). Mice were administered once daily oral vehicle or TVB-3664 (10mg/kg) for 12 weeks. Histopathological pre-to-post individual assessment of NAS and fibrosis stage was performed. Other terminal endpoints included quantitative liver histology, blood and liver biochemistry in addition to RNAsequencing-Bioinformatic analysis.

Results: GAN DIO-MASH mice demonstrated robust vehicle-corrected weight loss of 12% after 12 weeks of TVB-3664 treatment in conjunction with reduced adiposity and preserved lean tissue mass. Furthermore, TVB-3664 treatment improved hepatomegaly, plasma transaminases in addition to reduced plasma cholesterol and triglyceride levels. TVB-3664 treatment promoted a ≥2-point significant improvement in NAS, predominantly driven by reduction in steatosis score. Benefits on NAS were supported by quantitative liver histology on steatosis (hepatocytes with lipids, liver lipids) and marker of inflammation (galectin-3). TVB-3664 treatment did not improve fibrosis stage, however reduced fibrogenesis (α-SMA). Finally, TVB-3664 treatment induced significant gene regulation and suppressed genes involved in extracellular matrix and inflammation pathways.

Conclusion: TVB-3664 improved metabolic, biochemical, and histopathological parameters of MASH including NAFLD Activity Score in the GAN DIO-MASH mouse model. Longer treatment intervention might be required for observing anti-fibrotic action.

PO4-14
Role of kupffer cells in maintaining liver health during metabolic associated fatty liver disease (MAFLD)

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Background and Aims: Kupffer cells, the resident macrophages of the liver, play a critical role in maintaining hepatic homeostasis. During lipotoxic challenges, such as high-fat diets, Kupffer cell died, and liver is repopulated by infiltrated monocytes that undergo a transformation to monocyte derived Kupffer cells.

Method: Using conditional knockout models and high-fat diet-induced steatosis, we investigate how the turnover and differentiation from monocyte to Kupffer cells during lipotoxic stress contribute to liver health. In addition, we explore how p38 signaling in Kupffer cells regulates their differentiation and function during lipotoxic challenges and how this adaptation could prevent or attenuate hepatic steatosis.

Results: We show that the depletion of resident Kupffer cells triggers monocyte recruitment and differentiation into Kupffer-like cells in the liver. This monocyte-derived repopulation exhibits a distinct transcriptional profile when differentiated under lipotoxic or homeostasis condition, in terms of anti-inflammatory and lipid-handling pathways, suggesting that the differentiation under lipotoxic stress represents an adaptive mechanism that protects against hepatic lipid overload. Our data indicate that p38 MAPK signaling plays a critical role in this process, controlling the differentiation and lipid-processing capacity of repopulated Kupffer cells.

Conclusion: The adaptive replacement of Kupffer cells with bone marrow-derived monocytes under lipotoxic conditions represents a protective mechanism against hepatic steatosis. p38 signaling in Kupffer cells emerges as a central regulator of this differentiation process, influencing their function in lipid metabolism and potentially opening new avenues for therapeutic interventions targeting Kupffer cell dynamics in metabolic liver diseases.

PO4-16-YI

Purified low-fat dietary intervention does not reverse MASLD-associated cerebral hypoxia and neuroinflammation in a MASLD mouse model

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Background and Aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) has increasingly been associated with cognitive deficit, cerebral hypoperfusion, and increased risk of neurodegenerative disease. Here, we further assessed MASLD-associated cerebrovascular dysfunction and trialled a low-fat diet (LFD) as an intervention in aged MASLD mice.

Method: 6-week-old male C57BL/6NTac mice were fed control diet (CD) or high-fat high-cholesterol diet (HFD) for 26 weeks to induce MASLD. Half the mice in each group were then placed on the LFD and aged to 18-months. Behavioural tests were performed on all mice. Steatosis and fibrosis were assessed by histology. Cortical oxygenation at baseline and in response to systemic hypercapnia (10% CO_2) was measured *in vivo*. Cerebrovascular structure, pericytes, and microglia were characterised by immunofluorescent staining. Cortical metabolites were measured by nuclear magnetic resonance.

Results: Unexpectedly, the LFD drove steatosis in CD-LFD mice and fibrosis in HFD-LFD mice. Both HFD and HFD-LFD mice exhibited anxiety-like behaviours, whilst aged CD-LFD and HFD-LFD mice showed impaired memory. Interestingly, HFD, HFD-LFD, and CD-LFD mice all exhibited lower baseline cortical oxygenation but preserved cerebrovascular reactivity. No changes were observed in vascular structure. However, HFD mice had lower cortical nicotinamide and NAD+ compared to CD, indicative of oxidative stress. HFD and HFD-LFD also showed increased microglia density and cell volume, indicating reactive microglia.

Conclusion: The LFD exacerbated the liver disease and was unable to rescue brain dysfunction. HFD-induced steatosis is associated with brain hypoxia, oxidative stress, and neuroinflammation, which may contribute to the increased risk of neurodegeneration in MASLD.

PO4-18
RIPK3 inhibition boosts hepatocyte energy and glucose metabolism while reducing inflammation and fibrosis under metabolic stress

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Background and Aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is strongly associated with metabolic syndrome (MetS). Receptor-interacting protein kinase 3 (RIPK3) is a key player in execution of necroptosis, a regulated necrotic cell death. RIPK3 has also emerged as a modulator of metabolism, but its therapeutic potential remains uncertain due to unclear cell-specific roles in MASLD pathogenesis. This study aimed to investigate the role of RIPK3 inhibition in MASLD, focusing on its effects on hepatic lipid and glucose metabolism, inflammation, and fibrosis.

Method: Both 2D and 3D models, including immortalized murine and human monocultures and co-cultures of hepatocytes and non-parenchymal cells (NPCs), were used to simulate metabolically healthy and diseased conditions. MetS conditions were induced by exposing the cells to elevated glucose, insulin, and free fatty acid (FFA) concentrations. Phenotypic assays evaluated cell viability, neutral lipid accumulation, glucose uptake, and collagen deposition, and paralleled targeted molecular profiling.

Results: Under MetS mimicking conditions, hepatocyte viability was not compromised; instead, ATP production was higher in MetS mimic-loaded Ripk3-/- immortalized murine hepatocytes and in primary human hepatocyte (PHH) spheroids treated with GSK'872, a RIPK3 pharmacological inhibitor. While fat accumulation was not altered in MetS-loaded Ripk3-/- immortalized murine hepatocytes, RIPK3 silencing and chemical inhibition reduced intracellular neutral lipid content after 1 week of FFA incubation in PHH spheroids. Immortalized murine Ripk3-deficient hepatocytes also showed improved glucose uptake and expression of enzymes implicated in glucose metabolism in response to MetS stimulus, although these effects were mitigated in the presence of activated macrophages. Exposing macrophages to the secretome of Ripk3-deficient murine hepatocytes did not impact pro-inflammatory markers but increased arginase 1 (Arg1) expression, suggesting a potential anti-inflammatory role. Indeed, in human co-culture spheroids, RIPK3 inhibition decreased the secretion of cytokines and chemokines under metabolic stress, along with decreased pro-collagen1α1 secretion.

Conclusion: RIPK3 inhibition improves energetic metabolism, reduces inflammation, and reduces pro-fibrogenic marker under metabolic stress *in vitro* conditions, highlighting its potential as a metabolic target in MetS/MASLD. (Support by PTDC/MED-FAR/3492/2021, FCT, Portugal, and La Caixa LCF/PR/HR21/52410028)

PO4-19-YI
Hepatic miRNA expression in experimental models 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 diseases, ranging from simple steatosis to metabolic dysfunction-associated steatohepatitis (MASH). It is the primary cause of liver-related mortality when progressing to cirrhosis and/or hepatocellular carcinoma (HCC). microRNAs (miRNAs) play a key role in MASLD progression and hold great potential as targeted therapies. On this regard, different animal models have been used to gain insight into the molecular mechanisms and drivers of MASLD progression and pathophysiology.
The aim of this reverse translation study was to evaluate the expression of extracellular vesicle (EV)-miRNAs - previously identified as differentially expressed in MASLD patients -, in the livers of established MASLD mouse models; and to determine the signalling networks governed by these miRNAs.

Method: C57BL/6 mice were fed three different MASLD-induced diets, namely a high-fat (HF), high-calorie diet with fructose/glucose in drinking water for 10 and 20 weeks; a methionine and choline-deficient HF diet supplemented with 0.1% L-methionine in drinking water for 3 weeks; and a HF choline-deficient diet for 14 weeks. The levels of the top-five most differentially expressed EV-miRNAs during human MASLD progression, previously identified by us (hsa-miR-10a-5p, -miR-125a-5p, -miR-361-5p, -miR-423-5p and -miR-99a-5p), were assessed from total RNA liver samples using TaqMan Small RNA Assay Kits. Enriched KEGG pathways analysis was performed for each candidate miRNA, through over-representation analysis using DIANA-miRPath v4.0 tool.

Results: Despite some small changes, expression of hsa-miR-10a-5p, -miR-125a-5p, and -miR-423-5p did not change significantly in the livers of mice fed the three different diets comparing with respective controls. In turn, hsa-miR-99a-5p and -miR-361-5p expression was significantly increased in mice fed the HF choline deficient MASH-inducing diet. KEGG pathway enrichment analysis revealed that these miRNAs, along with three well-known MASH-upregulated miRNAs (hsa-miR-21, -miR-34a and -miR-222-3p), associate with metabolic pathways involved in MASLD progression to advanced stages of liver disease, including TGF-β and stem cell pluripotency signalling pathways.

Conclusion: Overall, our findings suggest that hsa-miR-99a-5p and -miR-361-5p may play a significant role in MASLD progression and serve as potential therapeutic targets. Further investigation into the expression of these miRNAs in the human liver and exploration of its cellular signalling networks could provide valuable insights into MASLD treatment strategies (Supported by 2022.08837.PTDC, FCT).

PO4-23

Targeted lipidomics and fatty acids profiles reveal ω-oxidation as a rescue pathway of inhibited β-oxidation in a rat model of drug-associated microvesicular liver steatosis

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Background and Aims: Significant alterations on mitochondrial metabolism are associated with valproate (VPA) therapy, including impairment of fatty acid β-oxidation (FAO) by CPT1A inhibition, depletion of essential cofactors, NAD^+ or CoA, and modifications of enzyme acylation. VPA is a branched-chain fatty acid and mild deacetylase inhibitor, well recognized as an important anticonvulsive drug with potential hepatotoxicity or teratogenicity. We hypothesize that the pleiotropic effects of VPA on mitochondrial energy metabolism, unequivocally linked with liver toxicity, may significantly alter free fatty acid (FFA) homeostasis. This work aims to clarify the mechanisms of microvesicular steatosis and VPA-induced liver injury (DILI).

Method: The analysis of FFA was performed through a validated analytical method, using stable isotope dilution (SID)-gas chromatography-mass spectrometry (GC-MS) in single-ion-monitoring mode (SIM).

Results: The effects of drug administration *in vivo* were evaluated by assessing Wistar rats subjected to single or repeated administration of VPA. Metabolite profiling in rat plasma revealed quantitative ratios of ca. 30 FFAs among saturated, unsaturated or hydroxylated derivatives. Levels of FFA in the plasma of animals subjected to VPA administration revealed a significant accumulation of dicarboxylic acids (pentanedioic and hexanedioic) (versus controls) and some hydroxylated derivatives of hexanoic and octanoic acids. No statistically significant changes were observed for the majority of saturated and unsaturated FFA.

Conclusion: Mass spectrometry-based targeted lipidomics are crucial tools to assess FAO-related metabolites and to investigate the mechanisms of VPA-associated mitochondrial dysfunction. The observed accumulation of dicarboxylic acids in rat plasma is suggestive of a fatty acid loading of microsomal ω-oxidation pathway. These biomarkers reveal the drug-induced inhibition of flux through mitochondrial FAO.

PO5-01-YI
PDE4 inhibition mitigates metabolic-associated steatotic liver disease by reducing lipogenesis and enhancing triglyceride secretion in obese mice

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Background and Aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is characterized by abnormal lipid droplet accumulation, inflammation, and disrupted lipid metabolism in hepatocytes. Phosphodiesterase 4 (PDE4) plays a key role in regulating inflammatory responses, and its inhibition significantly reduces TNF-α release, thereby mitigating inflammation. Additionally, PDE4 is upregulated in alcohol-related liver disease in rodents, and PDE4 knockout mice show resistance to diet-induced obesity (DIO) and diabetes. However, the effects of PDE4 on liver function and metabolism remain poorly understood. This study aimed to explore the impact of pharmacological PDE4 inhibition on the MASLD phenotype in DIO.

Method: Male C57Bl6 mice were divided into four groups and fed either a standard chow diet or a high-fat diet (HFD; 60% fat) for 12 weeks. In the 10th week, mice were administered daily subcutaneous injections of either vehicle (VEH) or the pan PDE4 inhibitor rolipram (2 mg/kg). Food intake and body weight were monitored. At the conclusion of the experiment, liver and adipose tissue were collected for further analysis. All experimental procedures were approved by the Ethics Committee for Animal Use of the Ribeirão Preto Medical School.

Results: We confirmed that PDE4 expression is upregulated in response to obesity in the liver, but not in the hypothalamus or brown adipose tissue. Rolipram treatment resulted in decreased body weight and energy intake in the HFD group, accompanied by increased energy expenditure, reduced weight of epididymal and retroperitoneal fat pads, with no significant effect observed in the chow group. Notably, PDE4 inhibition reduced liver triglycerides in obese animals, which correlated with elevated noradrenaline content. Histological examination revealed decreased lipid accumulation in hepatocytes following rolipram treatment. In accordance, we also found that the treatment induced upregulation of PGC1-a and PPARa, and downregulation of Elov3 and MCP-1 expression. To verify if these effects persisted irrespective of changes in body weight, animals were fed an HFD for 3 days, and in vivo triglyceride (TG) liver secretion was evaluated by inhibiting lipoprotein lipase enzyme in animals receiving acute rolipram injection. PDE4 inhibition increased VLDL secretion in HFD-treated animals, accompanied by elevated CD36 and EPAC levels in the liver. This suggests that the reversal of MASLD may be due to enhanced VLDL secretion.

Conclusion: These findings suggest that PDE4 activity may contribute to the development of MASLD in obese animals and underscore its potential as a therapeutic target for obesity-associated liver disease.

PO5-03-YI

Exposure to the environmental Bisphenol A influences trained immunity-related pathways in metabolic dysfunction-associated steatotic liver disease (MASLD): A preliminary observation

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Background and Aims: Dysregulation of innate immunity, contributing to low-grade inflammation, promotes Metabolic dysfunction-associated steatohepatitis (MASH) progression. Trained Immunity (TI) represents a novel concept of the immunological response involving the innate immune cells, triggered by a second antigenic contact, gaining a long-term reversible pro-inflammatory phenotype. Bisphenol A (BPA) is a well-known endocrine disrupter compound (EDC), widely produced worldwide and cumulated in the human body. Recently, our group revealed BPA as an alternative antigen able to activate TI in healthy subjects, suggesting implications in the immunometabolic switch potentially inducing a different immune reactivity. However, the role of this EDC exposure on TI pathways in MASH individuals remains unexplored. We investigated the influence of BPA on TI reactivity in MASH patients via activation of specific pro-inflammatory pathways.

Method: We enrolled healthy individuals (n:26) and patients with histological diagnosis of MASH (n:30). A 10 ml serum sample was collected to extract and quantify BPA, as well as to isolate and stimulate monocytes with predefined TI protocol. In detail, a liquid-liquid extraction of BPA from serum with methanol (1:1, v/v), followed by a solid-phase extraction cartridge for clean-up and concentration was performed. High-Performance Liquid Chromatography (HPLC) system coupled to a triple quadrupole mass spectrometer was used for BPA quantification. Monocytes of healthy individuals and MASH patients were isolated through a density gradient centrifugation and then stimulated with BPA for 24 h (1 nM, 10 nM, 20 nM) and lipopolysaccharide (LPS) (10 ng/mL) for 24 h (at day 0 and 6, respectively).

Results: BPA serum levels were more elevated in MASH compared with healthy individuals (7.79 ± 2.34 vs 0.139 ± 0.049 ng/mL, $p < 0.0001$).
The induction of TI mediated by BPA (1 nM, 10, nM, and 20 nM) was enhanced in MASH patients compared to healthy individuals, as higher levels of proinflammatory cytokines (both TNF-alpha and IL-6) were detected for each BPA concentration chosen for the stimulation (all $p < 0.05$). Finally, an increased concentration of IL-10 levels in MASH patients was also reported for each BPA concentration ($p < 0.05$), probably as a compensative phenomenon.

Conclusion: BPA appears as an antigen and strong stimulator of innate immune training in MASH patients., representing the fuel of a pro-inflammatory phenotype, potentially involved in the onset, worsening, and perpetuation of the disease.

PO5-05
The pan-PPAR agonist lanifibranor improves liver inflammation, ballooning, and fibrosis in a diet-induced obese MASH hamster model of binge drinking

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Background and Aims: We aimed to setup an animal model to evaluate the efficacy of drugs targeting MASH in a context of moderate to heavy alcohol use, which may aggravate liver lesions in patients with MASH. Because mouse and rat are not convenient models to study the effects of alcohol, our objective was to validate a diet-induced obese MASH hamster model of binge drinking, as this species spontaneously shows a high preference for alcohol. Therefore, we tested the effects of lanifibranor (LANI), a pan-PPAR agonist currently evaluated in phase III trial for the treatment of MASH.

Method: Diet-induced obese MASH hamsters were gavaged with saline (control) or with alcohol binge drinking (40% alcohol at 10mL/kg p.o., 3 times per week), and were simultaneously treated with vehicle or LANI 30mg/kg p.o. QD for 5 weeks.

Results: Compared to control, binge drinking in obese MASH hamsters led to higher plasma triglycerides levels, hepatic inflammation and ballooning scores and greater liver fibrosis, as measured with % Sirius Red labelling (all $p<0.05$). Binge drinking significantly raised the expression of genes involved in lipogenesis (ACC and SCD1), inflammation (IL-1b, IL-6, and MCP-1), cell death (caspase 3) and fibrosis (a-SMA, Col1a1 and TIMP1). Compared to hamsters treated with both binge drinking and vehicle, LANI significantly lowered total cholesterol, LDL-cholesterol, and triglycerides plasma levels. Liver triglycerides content, hepatic inflammation and ballooning scores, as well as liver fibrosis were all reduced with LANI (all $p<0.05$ vs. vehicle).

Conclusion: LANI significantly improved dyslipidemia and liver lesions in our obese MASH hamster model of binge drinking, which should help evaluating drugs targeting MASH in a context of moderate to heavy alcohol use.

PO5-10-YI
Hepatocyte-derived extracellular vesicles carrying miR-21 trigger muscle cell dysfunction

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Background and Aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a multifactorial disease characterized by homeostasis dysregulation, not only in the liver but also in distant organs. Recent evidence has highlighted the role the muscle-liver-axis in the pathogenesis of MASLD. In fact, sarcopenia and myosteatosis associate with an increased risk of metabolic-associated steatohepatitis (MASH). In addition, we have previously shown that microRNA-21 (miR-21) is increased in the liver and skeletal muscle of MASH patients, with its abrogation ameliorating disease progression in vivo. In this work, we aimed to evaluate whether liver cell-derived extracellular vesicles (EVs) may transduce signalling events to muscle cells in the context of MASLD.

Method: AML-12 liver cells were transfected with either a precursor of miR-21 or a control oligo for 48 hours. EVs were isolated from the cell culture medium by polymer-based precipitation and characterized by nanoparticle tracking analysis. C2C12 differentiated muscle cells were then incubated with EVs for 24 hours. Gene expression was evaluated by qRT-PCR and cell viability was assessed by MST and LDH. The AdipoRed assay was used to measure lipid content.

Results: miR-21 overexpression in AML-12 cells lead to the release of miR-21-loaded EVs. Further, incubation of C2C12 muscle cells with such EVs lead to a significant increased expression of miR-21; lipid metabolism- and energy-related genes, such as *Srebf1* and *Cpt1*; and inflammatory marker *Nlrp3*. In addition, atrophy regulator *Fbxo32* and myotube differentiation regulator *Pax7* were also up-regulated, while expression levels of muscle growth inhibitor *Myostatin* were significantly decreased, suggesting the presence of a regenerative muscle response mechanism to damage. Despite these transcriptional changes, hepatocyte-derived miR-21-loaded EVs did not significantly affect cell death and viability, nor lipid accumulation.

Conclusion: Overall, increased miR-21 expression in hepatocytes - which is observed in MASH patients – is able to transduce negative metabolic effects to myotubes functionality through miR-21-loaded EVs, influencing muscle regeneration and inhibiting degradation, thereby mimicking the transcriptional profiles observed in sarcopenic muscle of MASH patients.

PO5-14
10 year progression of metabolic risk factors - correlation with steatosis and fibrosis degree in a general population cohort

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Background and Aims: There is evidence that aging is associated with an increase in the number of metabolic risk factors potentially increasing prevalence and degree of hepatic steatosis. Aiming to evaluate which factors could predominantly be associated, we studied a group of individuals from the general population that had been previously evaluated, comparing risk factors, as well as hepatic steatosis and fibrosis grade after a 10-year interval.

Method: From 220 participants initially included, it was possible to re-evaluate 92 with a similar methodology, single visit to a multidisciplinary consultation: hepatologist, dietitian and nurse. A physical examination, blood panel and liver elastography (Fibroscan®) with assessment of CAP (for steatosis), LSM (for liver stiffness) and a nutritional evaluation (BMI, waist circumference-WC, dietary intake) were carried out.

Results: 53.3% of the participants were male, with an average baseline age of 47.5±16.2years. Steatosis prevalence increased from 29.3% to 47.8% (p=0.014). Prevalence of moderate fibrosis increased from 3.3% to 5.6% (NS), but none of the current fibrotic patients presented fibrosis at baseline. Eighty percent of those with steatosis at baseline, now had moderate fibrosis. Average weight was 73.7±14.1kg at baseline vs. 77.6±15.9kg (p<0.001) currently, implicating an increase in the average BMI from 26.7±3.6 at baseline to 28.2±4.4kg/m2 (p<0.001). Average WC also increased: (89.1±12.5 vs. 93.92±14.1cm: p<0.001). The proportion of overweight participants has risen from 69.7% to 81.4% (p=0.035), obese prevalence increased from 15.7% to 27.9% (p=0.001). Mean systolic blood pressure increased from 122.9±18.6mmHg to 130.9±20.7mmHg (p<0.001). Participants with steatosis, had higher BMI: 28.1±3.2 vs. 25.6±3.4kg/m2 (p=0.001) and WC: 94.8±10.6 vs. 84.4±11.8cm (p<0.001) compared to baseline. From univariate analysis, the BMI (p=0.002), ALT (p=0.012), GGT (p<0.001) and HDL (p=0.010), at baseline significantly correlate with the presence of steatosis 10 years later. However, in multivariate analysis only GGT remained significantly associated (OR: 1.043 [1.002-1.086]: p=0.038).

Conclusion: We confirmed aging to associate with increased prevalence of overweight/obesity as well as waist circumference, with potential increase in visceral fat, a significant risk factor for metabolic diseases. As expected, the prevalence of steatosis and moderate fibrosis also increased. These findings highlight the need for interventions with an emphasis on preventing weight gain, that besides promoting cardiovascular and metabolic health, can mitigate the progression of liver diseases. Interestingly, elevation of GGT in the baseline was the best predictor of steatosis development.

PO5-20
Endoscopic ultrasonography-guided liver biopsy: A good alternative from an endohepatologist point of view

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Background and Aims: Comparative studies have demonstrated endoscopic ultrasound-guided liver biopsy (EUS-LB) is an effective and safe alternative to traditional techniques (percutaneous-PC, transjugular-TJ). However, many of them are retrospective, unicentric and without cost-effective analysis. Our aim was to confirm the efficacy, safety and cost-utility of EUS-LB, by comparing it with traditional routes. We also considered the pathologist's satisfaction with the specimen and the impact on the hepatologist's clinical management.

Method: Observational, prospective and multicentric study including patients who underwent EUS-LB in tertiary centers (N = 52), compared with an equivalent number of PC-LB (N = 50) and TJ-LB (N = 37) selected aleatory and retrospectively. Results were expressed in terms of standard deviation, range or percentage, and compared with Pearson Chi-Square. Bonferroni's method was used for pairwise multiple comparisons. Significance value $p < 0.05$. Cost-efficacy analysis was presented as incremental cost-effectiveness ratio (ICER).,

Results: Diagnostic yield was similar between the three groups (EUS-LB 87%, PC-LB 92%, TJ-LB 76%, $p = 0.097$), as well as the rate of adverse events (EUS-LB 4%, PC-LB 10%, TJ-LB 8%, $p = 0.252$), all of them mild and conservatively treated in EUS-LB group. Despite the tissue fragmentation was higher in EUS-LB (EUS-LB 9 ± 2 fragments; PC-LB 2 ± 1; TJ-LB 4 ± 3), and the longest specimen length lower in mm (EUS-LB 10 ± 8 , PC-LB 15 ± 7, TJ-LB 14 ± 8, $p < 0.0001$), no differences were found in the number of complete portal tracts (EUS-LB 9 ± 8, PC-LB 7 ± 3, TJ-LB 8 ± 5, $p = 0.571$) nor in tissue adequacy (EUS-LB 19%, PC-LB 30%, TJ-LB 36%, $p = 0.164$). Pathologist's satisfaction was good-acceptable in 83% of EUS-LB, with no differences from traditional LB techniques. Histological diagnoses of EUS-LB had a similar clinical impact to PC-LB and higher than TJ (EUS-LB 88%, PC-LB 94%, TJ-LB 73%, $p = 0.016$). Metabolic dysfunction-associated steatotic liver disease (MASLD) was the most frequent diagnosis in EUS-LB group (34%) with adequate fibrosis stage assesment. EUS-LB was more cost-effective in patients that need both LB and EUS (average saving of 112.20 euros for every 15% of additional histologic diagnosis), in case of cholestasis when Magnetic Resonance Cholangiopancreatography (MRCP) can`t be done, and if PC-LB was contraindicated (average saving of 234.75 euros for every 15% of additional histologic diagnosis).

Conclusion: EUS-LB is a useful alternative for the study of liver diseases, including the staging of MASLD. In spite of specimen fragmentation, it is as effective as traditional LB techniques, satisfactory for the pathologist and the hepatologist in clinical practice, with better safety profile. EUS-LB is an attractive choice, because of its cost-effectiveness, when EUS and LB are both needed, when PC-LB can`t be performed and in the study of cholestasis.

PO5-22-YI
RIPK3 modulates the liver immune microenvironment during MASLD progression towards hepatocellular carcinoma

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Background and Aims: The receptor-interacting protein kinase 3 (RIPK3) is critical in, at least, two lytic and inflammatory types of regulated cell death triggered in metabolic dysfunction-associated steatotic liver disease (MASLD), namely necroptosis and inflammasome-mediated pyroptosis. We have previously shown that blocking RIPK3 arrests steatotic liver disease progression *in vivo* and ameliorates the hepatic metabolic dysfunction. Still, the precise role of RIPK3 in MASLD-driven hepatocarcinogenesis remains elusive.

Method: Two-week-old male C57BL/6 wild-type mice (WT) or *Ripk3*-deficient (*Ripk3*$^{-/-}$) pups were injected with diethylnitrosamine (DEN; 25 mg/kg i.p.), followed by feeding with a choline deficient–high fat diet (CD-HFD) or a standard diet (SD) from 4 to 42-weeks-old. In parallel, mice were fed from 4 to 57-weeks-old with CD-HFD. Macroscopic tumours were counted and measured for phenotypic characterization. Gene expression and protein production were evaluated through qRT-PCR and immunoblotting, respectively. Liver samples were freshly processed for immunophenotyping by flow cytometry.

Results: Macroscopically discernible tumours were only detected in mice exposed to DEN and DEN+CD-HFD. Ablation of *Ripk3* abrogated tumour frequency in both models and reduced tumour size in the DEN model. Tumour development was accompanied by increased hepatic expression of *Alb*, *α-Sma* and *Ki67*, markers of hepatocytes, fibrosis and cell proliferation, respectively, which were downregulated in tumour lesions of *Ripk3*$^{-/-}$ mice. Furthermore, *Ripk3* deficiency reduced hepatic macrophage infiltration in both DEN-exposed and CD-HFD-fed mice, accompanied by a general decrease in the expression of *Nlrp3* and its downstream effectors in pyroptosis, caspase-1 and *Il1β.* In line, mice lacking *Ripk3* displayed decreased expression of *Mhc-ii* and *Tlr4* in DEN+CD-HFD tumours. Finally, blocking RIPK3 did not impact the hepatic infiltration of CD4^{+}T or CD8^{+}T cells. Still, *Pd-l1 and Pd-1* levels were reduced in tumour nodules from mice lacking RIPK3.

Conclusion: *Ripk3* deficiency ameliorated hepatic inflammation in experimental MASLD, while reducing the hepatic tumour burden in both toxic and dietary models of hepatocellular carcinoma. Further, our results indicate that *Ripk3* deletion impacts on PD-L1/PD-1 axis, which could dampen T cell exhaustion in tumour microenvironment and eventually improve patient response to immunotherapy. Future studies will elucidate the cell-specific role of RIPK3 during MASLD progression.
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PO6-17
Alteration feature of VCAM1 in liver tissue of MASLD condition

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Background and Aims: The overexpression of VCAM1 is a key factor of Monocyte migration to the liver in hepatic sinusoidal endothelial cells (LSECs) in metabolic dysfunction-associated steatotic liver disease (MASLD). However, the relationship between the inflammation levels and VCAM1 expression at different stages of progression in MASLD is not well understood. In this study, we examined the correlation between liver inflammation and VCAM1 expression.

Method: C57BL/6 Mice fed with a high-fat, high-fructose diet (HFHFD) for 10 weeks or 20 weeks presented a typical model of MASLD. Furthermore, the level of VCAM1 in serum was evaluated in each of 10 fatty liver patients.

Results: In serum, AST and ALT levels did not show a significant difference in the 10-week model compared to the Naive group; however, they were found to have increased approximately 2.5 and 7-fold, respectively, in the 20-week model. However, both TG and TC increased 1.5-fold compared to the naive group, there was no difference between the 10-week and 20-week models in the serum levels. In liver tissue, only TC increased 3-fold in the 10-week model compared to the naive group, while TG did not show any increase. In contrast, both TG and TC increased by 2-fold and 12-fold, respectively, in the 20-week model. The expression of VCAM1 was noticeably increased in the 20-week model compared to the 10-week model, and it was also confirmed that TGF-beta levels had risen further. Moreover, in human NASH, VCAM-1 expression within serums was significantly increased compared to the Normal group.

Conclusion: As fatty liver progresses, we propose that VCAM1 overexpression plays a major role in exacerbating the inflammatory environment in the liver, and we aim to develop a treatment strategy against MASLD targeting VCAM1.

PO6-19-YI
Alcohol-induced immune-metabolic deregulation exacerbates aortic lesion progression in a novel murine model for MetALD

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Background and Aims: The recent re-classification of steatotic liver disease (SLD) distinguishes metabolic dysfunction-associated steatotic liver disease (MASLD) from the newly termed MetALD, combining MASLD and significant alcohol consumption. Yet, the underlying mechanisms specifically contributing to liver dysfunction during MASLD and MetALD, and their impact on cardiovascular diseases—the major cause of mortality in patients with SLD—remain to be elucidated. Hence, we aimed to investigate the effects of alcohol intake on liver disease progression during dyslipidemia and its subsequent impact on atherosclerosis development.

Method: Hyperlipidemic low-density lipoprotein receptor-deficient (*Ldlr*$^{-/-}$) mice were fed a Western diet (WD) for 8 weeks combined with either regular or ethanol-containing drinking water (alternating 10-20% v/v) to induce MASLD and MetALD, respectively.

Results: While ethanol intake in WD-fed *Ldlr*$^{-/-}$ mice resulted in only a mild elevation in systemic ethanol levels, liver weights and hepatic lipid content were increased compared to mice receiving regular drinking water. Bulk transcriptomics revealed that *Ldlr*$^{-/-}$ mice developing MetALD exhibited increased inflammation and alterations in genes related to lipid metabolism in the liver. In line, ethanol-consuming WD-fed *Ldlr*$^{-/-}$ mice displayed higher hepatic mRNA levels of various pro-inflammatory markers and more Ly6C^{high} monocytes in the liver. In addition to more pronounced hepatic inflammation, mice developing MetALD showed increased monocyte numbers in circulation and elevated gene expression levels of pro-inflammatory markers in the aorta. Moreover, altered hepatic lipid metabolism was also reflected in elevated cholesterol and triglyceride levels in circulation in mice consuming ethanol. Importantly, WD-fed *Ldlr*$^{-/-}$ mice receiving ethanol displayed enlarged aortic root lesion size, which occurred independently of the enhanced dyslipidemia, indicating a direct immunomodulatory effect of ethanol on atherosclerosis.

Conclusion: Our study demonstrates that moderate alcohol consumption in dyslipidemic mice significantly accelerates liver disease and atherosclerosis, thereby identifying alcohol as immunomodulatory lifestyle factor that increases the risk of cardiovascular events in patients with MetALD.

PO6-21
Communication through gut-derived extracellular vesicles: Implications for liver disease progression

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Background and Aims: Metabolic homeostasis depends on organ interactions, with extracellular vesicles playing a key role as mediators in communication and in the pathogenesis of metabolic disorders such as fatty liver pathogenesis. Our findings revealed that the protein content of gut-derived extracellular vesicles (GDEs) reflects the organism's metabolic state. We aim to test the hypothesis that GDEs mediate communication in the gut-liver axis during T2D progression. We will examine how GDEs' protein and lipid content contribute to diabetogenic effects and whether treatment with metformin and pioglitazone modifies GDEs' cargo.

Method: C57Bl/6J mice were fed either a normal chow diet (NCD) or a high-fat diet (HFD) for 12 weeks, followed by 6 weeks of daily treatment with either pioglitazone or metformin. GDEs were isolated, and their lipid and protein content analyzed. To evaluate the biological impact of GDEs, fluorescently labeled GDEs from both NCD- and HFD-fed mice were injected retro-orbitally into normoglycemic mice every other day for six weeks.

Results: Both drugs shifted GDEs protein composition towards a pattern typical of NCD-fed animals. Prediabetic GDEs were enriched in lipid metabolism proteins and ceramides, known to be proinflammatory and linked to diabetes. Chronic exposure of healthy mice to GDEs resulted in their preferential accumulation in the resident hepatic macrophages, Kupffer cells (KCs). Mice receiving HFD-GDEs had higher hepatic triglyceride and greater weight gain than controls.

Conclusion: GDEs facilitate the transfer of key lipids and proteins between the gut and liver, potentially detoxifying harmful lipids by directing them to KCs. In prediabetes, impaired KC detoxification may increase the risk of hepatic metabolic disturbances. Additionally, our findings suggest that treatment with metformin and pioglitazone improves metabolic health by modifying GDEs' content, highlighting their potential as early biomarkers and underscoring their role in evaluating the effectiveness of antidiabetic therapies.

PO7-03-YI
Association of cardiometabolic risk and phenotypic age with the course of metabolic dysfunction-associated steatotic liver disease

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Background and Aims: Increased phenotypic age (PA) is linked to the progression of metabolic dysfunction-associated steatotic liver disease (MASLD) and its cardio-metabolic risk factors (CMRFs), and recent studies position PA as a mortality predictor in MASLD patients. While various laboratory metrics assess cardiometabolic risk in MASLD, their connection to aging is unclear. Sirtuin 1 (SIRT1) has emerged as a critical regulator in MASLD pathogenesis, influencing both metabolic processes and cellular aging. Our study aims to explore the association between PA, aging rate (AR), SIRT1, CMRFs of MASLD, and established indices in MASLD patients.

Method: The study group included patients with MASLD (n = 48) with at least one CMRF, aged 51.8 [42.3; 59.6] years (37.5 % female), none of whom had a high (FIB-4 > 2.67) fibrosis risk. The control group (n = 17) consisted of gender-matched healthy adults aged 25.0 [23.7; 27.1] years, thus free from age-related pathological changes. PA and AR were calculated according to the method by M. Levine et al. (2018). The calculated indices included non-HDL cholesterol (non-HDL-C), triglyceride-glucose (TyG) index, atherogenic index of plasma (AIP), metabolic score for insulin resistance (METS-IR), FIB-4, lipid accumulation product (LAP), cardiometabolic index (CMI), and AST to platelet ratio index (APRI).

Results: MASLD patients had higher calendar age (CA) and PA compared to controls ($p < 0.05$). Significant differences were observed in all calculated indices ($p < 0.05$), but not in AR and SIRT1 levels. Patients with MASLD and accelerated aging (20.8 %) had higher TyG index values ($p = 0.037$) than those with normal AR. In the study group, AR was associated with TyG index ($p = 0.014$) and AIP ($p = 0.022$), CA and PA ($p = 0.0001$) were both directly linked to FIB-4, SIRT1 was inversely correlated with APRI ($p = 0.013$). 95.8 % of MASLD patients were on antihypertension therapy; 91.7 % were at risk based on anthropometric measurements; 64.6 % had prediabetes or type 2 diabetes mellitus (DM); 50.0 % had increased triglyceride levels; and 33.3 % had reduced HDL-C levels. The presence of any single CMRF was associated with significant differences in ARs. However, patients with 4 - 5 CMRFs (n = 20) had higher PA compared to those with 1 - 3 CMRFs ($p = 0.045$), despite no differences in CA, and showed differences ($p < 0.05$) in non HDL C, TyG index, AIP, METS-IR, LAP, and CMI. SIRT1 levels differed based on prediabetes/DM status ($p = 0.043$).

Conclusion: In MASLD patients, both CA and PA are linked to higher fibrosis risk, as indicated by FIB-4. Patients with 4 - 5 CMRFs show higher PA than those with 1 - 3, suggesting that early detection of accelerated aging can help identify MASLD patients at high cardiometabolic and fibrosis risk. The TyG index and AIP may serve as indicators of increased ARs, while APRI could assist in evaluating SIRT1-targeted therapies, particularly in patients with MASLD and DM.

PO7-07-YI
Modeling metabolic-dysfunction associated steatotic liver disease in juvenile zebrafish: a novel platform for disease study and drug discovery

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Background and Aims: The zebrafish (*Danio rerio*) has proven to be a powerful model organism for human diseases, showing advantageous traits such as large progeny and up to 80% homology to human disease-related genes. Among others, zebrafish is a remarkable model for studying liver and metabolic diseases, such as metabolic dysfunction-associated steatotic liver disease (MASLD). MASLD is nowadays a public health challenge, with increasing prevalence and limited therapeutic options. We aim to leverage zebrafish's unique characteristics to generate a MASLD model, facilitating a deeper understanding of the disease and discovering novel therapeutic strategies.

Method: 20 days post fertilization (dpf) juvenile zebrafish were fed with a control diet (CD) or a high-fat/high-carbohydrate diet (HFC) for 30 days. Samples were collected at 30, 40, and 50 dpf to monitor disease progression. The model was characterized by measuring abdominal fat accumulation, hepatic steatosis, liver inflammation, and liver fibrosis. Phenotypic outcomes were further validated through liver time-series RNA sequencing analysis. Differentially expressed genes were identified by DESeq2 and functional enrichment analysis performed using Gene Set Enrichment Analysis (GSEA), with all genes ranked according to fold-change for each timepoint. Finally, the ability of the model to respond to rescue treatments was assessed. Fish were exposed to a 10-day treatment period after 15 days of HFC feeding and then evaluated for the disease-related phenotypes.

Results: By 30 dpf, a significant increase associated with the HFC diet was observed in abdominal fat accumulation and hepatic steatosis. These changes persisted throughout the experimental period. The onset of inflammation assessed by neutrophil recruitment in the liver was not significantly detectable until 40dpf, indicating a putative transition to MASH. Moreover, a significant increase in Sirius Red staining intensity, indicative of fibrosis, was detected in the HFC group compared to the CD group, however, no liver fibrotic scarring was observed. The time-series transcriptomic analysis identified 2953 genes being differentially expressed in at least one of the timepoints. GSEA results showed enriched genesets involved in lipid metabolism, inflammation, and cellular repair. Additionally, diseased fish reverted several MASLD-related phenotypes to control conditions after the 10-day rescue treatment.

Conclusion: The zebrafish model successfully replicated, critical features of MASLD in humans in a cost-effective manner, including early lipid accumulation, onset of inflammation, and markers of liver fibrosis. The model was also responsive to MASLD rescue treatment, suggesting its feasibility for preclinical drug discovery. Overall, the model holds great potential for advancing the understanding of MASLD and the development of effective treatments.

PO7-13
Role of genetic variants in association with the severity of liver fibrosis and steatosis in patients with steatotic liver disease

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Background and Aims: The pathogenesis of steatotic liver disease (SLD) development involves several factors, including genetic variations. This study evaluated the association between several genetic polymorphisms and the severity of liver fibrosis and steatosis in Thai patients with SLD.

Method: The extent of fibrosis and steatosis were assessed by magnetic resonance elastography (MRE) and magnetic resonance imaging–proton density fat fraction (MRI-PDFF), respectively. The polymorphisms in the patatin-like phospholipase domain containing 3 (*PNPLA3*), transmembrane 6 superfamily member 2 (*TM6SF2*), Hydroxysteroid 17-β Dehydrogenase 13 (*HSD17B13*), and sirtuin 5 (*SIRT5*) genes were determined by allelic discrimination in blood samples.

Results: 204 patients aged 57.0 ± 13.5 years were included. Sixty-two (30.4%) patients had significant fibrosis (≥F2). Among F2-F4 fibrosis, the *PNPLA3* rs738409 GG genotype was significantly higher than the CC + CG genotypes (44.9% vs. 21.4%, p = 0.001). The *SIRT5* rs12216101 GG vs. TT + TG genotypes also exhibited a similar trend (64.3% vs. 27.9%, p = 0.012). However, the distributions of *TM6SF2* rs58542926 and *HSD17B13* rs6834314 were not different. In multivariate analysis, the *PNPLA3* GG genotype (OR = 3.48, 95%CI: 1.50–8.06; p = 0.004) and *SIRT5* rs12216101 GG genotype (OR = 5.43, 95%CI: 1.32–22.33; p = 0.019) were independently associated with F2-F4 fibrosis. Additionally, the proportion of patients with F2-F4 fibrosis significantly increased with the number of combined risk genotypes of these two polymorphisms. Among S2-S3 steatosis, the prevalence of *HSD17B13* AG + GG genotypes was higher than that of the AA genotype (37.5% vs. 23.9%, p = 0.048) and independently associated with moderate/severe steatosis in multivariate analysis (OR = 2.26, 95%CI: 1.14–4.49; p = 0.020). However, other genetic variants were not associated with the severity of steatosis.

Conclusion: Our data indicate that the *PNPLA3* and *SIRT5* polymorphisms were independently and additively linked to significant fibrosis, while the *HSD17B13* polymorphism was associated with increased steatosis in Thai populations. These data might emphasize the importance of genetic variants in progressive SLD and could support the clinical utility of genetic genotyping in identifying patients with SLD who are at increased risk of unfavorable outcomes.

PO7-16
Physics-based modeling of cholesterol and bile acids metabolism: Insights into the enterohepatic circulation and implications for metabolic dysfunction-associated steatotic liver disease (MASLD)

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Background and Aims: Liver is a central organ in cholesterol and bile acid metabolism. It synthesizes cholesterol, produces bile for digestion, regulates cholesterol balance, and plays a key role in bile acid signaling pathways. Studies show that disruption or impairment in bile acid enterohepatic circulation may contribute to development of MASLD and its progression to metabolic dysfunction-associated steatohepatitis (MASH), cirrhosis, and hepatocellular carcinoma [1] [2]. Thus, understanding the regulation of cholesterol and bile acid metabolism in progression of MASLD could facilitate targeting these pathways, mitigating disease progression and reducing liver-related complications. In order to explore the impact of bile acid enterohepatic circulation on MASLD, we developed a physics-based model to monitor the concentration and transfer of bile acid species across different organs.

Method: A physiology-based compartmental modeling was implemented in this study to evaluate the concentration of bile acid species across the virtual human body. To this end, a system of coupled ordinary differential equations (ODEs) were implemented to take to account cholesterol uptake, de novo synthesis and metabolism to bile acid as well as their release and reabsorption via blood circulation system.

Results: The model successfully captures hepatic cholesterol biosynthesis and metabolism to bile acids. In addition, the level of cholesterol in hepatocytes, the concentration of bile acid species in liver bile duct, gall bladder, intestine, portal vein, sinusoid and overall circulation system was predicted. Experimental data from healthy volunteers were used to validate the concentration of bile species in plasma and intestine. These results establish a reliable foundation for further adaptations to simulate altered metabolic conditions within the model.

Conclusion: The physics-based approach developed in this study provides a novel and validated model to monitor and predict the cholesterol and bile acid states for healthy virtual humans. Further adaptations to the model could provide insight on the impact of MASLD on cholesterol concentration, metabolism and bile acid enterohepatic circulation. Additionally, the model can simulate the impact of impairment in cholesterol and bile acid state to evaluate the risk of development of MASH. Furthermore, different treatment strategies can be incorporated in the model to explore the impact of possible treatments on metabolic.

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PO7-19-YI
Cell-specific functions of RIPK3 in hepatocyte-macrophage communication in metabolic-dysfunction associated steatotic liver disease

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Background and Aims: Metabolic-dysfunction associated steatotic liver disease (MASLD) is the leading chronic liver disease worldwide and is the fastest-growing cause of liver mortality and morbidity. Still, there is a lack of pharmacologic therapies, which calls for a better understanding of the underlying mechanisms to identify potential therapeutic targets. Receptor-interacting protein kinase 3 (RIPK3) is a key executor of necroptosis, an immunogenic form of regulated cell death activated in MASLD that has been implicated in disease pathogenesis. However, the potential therapeutic benefit resulting from RIPK3 inhibition remains a subject of debate, fueled partly by a lack of studies focusing on the cell-dependent contribution of RIPK3. Here, we aimed to understand the cell-specific role of RIPK3 and the crosstalk between hepatocytes and macrophages in the context of MASLD.

Method: *In vitro* monolayer and transwell co-cultures were performed using wild-type (WT) and *Ripk3*-deficient AML12 hepatocytes and J774A.1 macrophages exposed to palmitic acid (PA). Cell death and inflammatory markers were evaluated through cytotoxicity assays, qRT-PCR, and immunoblotting.

Results: Our data showed RIPK3 cell-specific functions. In monolayer co-cultures, PA-pretreated WT hepatocytes failed to activate macrophages, while *Ripk3* ablation in hepatocytes induced an inflammatory response, evidenced by increased pro-inflammatory markers in macrophages. Simultaneously, *Ripk3* ablation in hepatocytes markedly increased anti-inflammatory arginase-1 (*Arg1*) expression, suggesting a role for RIPK3 in mediating macrophage polarization towards healing responses, while possibly linking the pro-inflammatory response to tissue repair processes. In agreement, *Ripk3* deletion in hepatocytes conferred protection against PA-induced cell death, and co-cultures with macrophages further contributed to hepatocyte repair. Intriguingly, *Ripk3* knockdown in macrophages promoted a pro-inflammatory phenotype in basal conditions, which was exacerbated in macrophages primed with lipopolysaccharide (LPS) plus interferon-gamma (IFN-gamma). However, in macrophages co-cultured with PA-pretreated *Ripk3*$^{-/-}$ hepatocytes, *Ripk3* knockdown significantly upregulated *Arg1* expression. Finally, our results uncovered a macrophage-specific role of RIPK3 in modulating hepatocyte metabolism, namely through the upregulation of enzymes involved in triglyceride synthesis and downregulation of those linked to peroxisomal β-oxidation.

Conclusion: These findings provide novel information about the unexpected roles of RIPK3 that could modulate the interplay between macrophages and hepatocytes in MASLD. These intricacies should be considered when evaluating RIPK3 as a therapeutic target for MASLD. (Supported by PTDC/MED-FAR/3492/2021, FCT; and LCF/PR/HR21/52410028, “la Caixa” Foundation)

PO7-20
Bile acids as potential metabolic markers to differentiate progression and resolution of metabolic dysfunction-associated steatohepatitis

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Background and Aims: Metabolic dysfunction-associated steatohepatitis (MASH), associated with obesity, insulin resistance and dyslipidemia, is a highly prevalent liver disease. Despite this, there are currently no approved biomarkers to readily assess disease progression and regression in MASH. There has been growing interest in the potential role of bile acids in the development of MASH. FXR agonists, such as the bile acid derivative 6-ethylchenodeoxycholic acid (obeticholic acid), have been investigated as therapeutic agents in clinical trials in humans. The importance of dysregulation of bile acid metabolism in progression of MASH has been reported. However, the significance of bile acid restoration in the reversal/regression of MASH remains unclear, as does the potential of circulating bile acids, its precursors and metabolites to serve as markers for treatment response or disease progression.

Method: We assessed circulating bile acids and cholesterol metabolites in plasma using state-of-the-art high-resolution mass spectrometry in a cohort (n=38) of well-characterized MASH patients with paired liver biopsies. Based on histology, patients were classified into two groups: progressors (progression of fibrosis of at least ≥1 stage) or regressors (resolution of steatohepatitis or fibrosis regression ≥1 stage). All detected bile acids were quantified using 5 points calibration curve. The predictive model used a logistic regression with the outcome as dependent variable and the level of lipids at the baseline as independent variables. To account for multiple-testing, Benjamini-Hochberg False Discovery Rate (FDR) was estimated and markers with FDR ≤ 5% were considered for analysis.

Results: We fitted three models including (i) a predictive model to estimate the potential of baseline levels in predicting the outcome, (ii) a time-course model to associate the changes between baseline and progression/regression in each individual, and (iii) a post-hoc model to estimate the association of the bile acids with the clinical outcome. We observed that bile acids and biosynthesis precursors were reduced upon the regression of fibrosis in MASH patients compared to progressors. We identified six bile acids including chenodeoxycholic acid, glycochenodeoxycholic acid, glycocholic acid, taurochenodeoxycholic acid, taurocholic acid, and taurodeoxycholic acid, as well as one peroxisomal bile intermediate, which were significantly lower in patients with disease regression and can differentiate fibrosis progression from regression.

Conclusion: Our study identifies specific bile acid markers that differentiate between fibrosis progression and fibrosis regression/resolution of steatohepatitis in MASH. These markers hold potential for assessment of disease evolution and may provide novel insights into MASH pathogenesis.

PO7-22
Non-invasive assessment of liver fat fraction utilizing the electrical properties of tissue

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Background and Aims: The dielectric properties of tissue (permittivity and conductivity) are derived from its chemical composition and are altered in disease states such as Liver cancer, cirrhosis, fibrosis, and steatotic liver disease (SLD). A novel thermoacoustic technology has been developed to noninvasively measure the electrical properties of the human liver in order to assess the liver fat fraction. To that end, liver models with precisely controlled triglycerides were developed and verified by magnetic resonance imaging proton density fat fraction (MRI-PDFF). The dielectric properties of healthy and steatotic liver tissues were thoroughly characterized. These outcomes are later utilized to develop the TAEUS FLIP device and used in a clinical study to assess liver fat fraction in subjects ranging from S0 to S3.

Method: The electrical properties of ex vivo Bovine and Porcine liver tissues (which were shown to have similar dielectric properties to human liver tissue) were characterized using a calibrated dielectric measurement device (SPEAG DAK). Steatotic liver tissue phantoms were made using bovine liver mixed with mass balance quantified amounts of triglycerides (shortening) and measured for dielectric properties. The ground liver and shortening mixtures were investigated by both dielectric measurements and MRI-PDFF, simulating steatotic liver with fat fraction ranging from 1% to 30% by weight. This data was used to determine the permittivity and conductivity of steatotic liver tissue with quantified fat fractions at body temperature.

Results: Porcine livers were found to have relative permittivity of 47+-1 (1% fat fraction) and conductivity of 0.8+-0.03 S/m. Those dropped to 24+-2 and 0.4+0.01 S/m at 30% fat fraction. Both the relative permittivity and conductivity were shown to follow the Brugmann mixing model over a wide range of fat fractions. In phantom studies of materials mimicking human steatotic liver disease ranging from 2 - 40% fat fraction, the TAEUS FLIP system demonstrated an error of less than 2% in estimating fat fraction in all cases. Clinical assessment of human subjects, with the TAEUS FLIP has successfully obtained fat fraction measurements in healthy, MASLD, and obese subjects ranging in BMI from 21 - 47.5, with liver fat fraction as low as 1.3% and as high as 38.1%.

Conclusion: This study develops fatty liver models and applies quantitative methods in a point-of-care device to characterize fatty liver tissue phantoms, as well as human subjects ranging from healthy to those with severe steatotic liver disease.

POSTER ABSTRACT PRESENTATIONS

Clinical Science

PO1-01
Comparison of transient elastography and shear wave elastography in patients with MAFLD: A single-center experience

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Background and Aims: Metabolic-associated fatty liver disease and liver fibrosis are intimately linked to insulin resistance, type 2 diabetes, obesity, and metabolic syndrome. Transient elastography (TE) and point shear wave elastography (pSWE) were used to measure liver stiffness in patients who met the ultrasound criteria for steatotic liver diseases (SLD). This study compared two methods for estimating liver stiffness in patients with SLD, which in turn correlated with liver fibrosis.

Method: Ultrasound B-mode imaging was used to identify SLD. In total, 250 MAFLD patients were recruited. Patient characteristics, laboratory investigations, and liver stiffness measurements using TE and pSWE were assessed on the same day

Results: The correlation between TE and pSWE was significant (Spearman's r = 0.867*, p < .001). The Bland-Altman Plot analysis confirmed this, with 97.5% of variations in LSM falling within 95% agreement ranges. Cohen's κ was used to assess the agreement between TE and pSWE fibrosis stages, showing almost perfect agreement (83.5% kappa agreement) and a strong association between pSWE and TE in the assessment fibrosis stages

Conclusion: In patients with MAFLD, TE, and SWE are reliable methods for measuring liver stiffness and can be used as non-invasive screening tools for assessing fibrosis in SLD.

PO1-02-YI
Fibrinolytic activity of blood plasma in pregnant women with MASH against various degrees of obesity

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Background and Aims: Today, the problem of diagnosis and treatment of MASLD, which is causally related to obesity and hyperlipidaemia, has received special attention in medicine. In Ukraine there has been an increase in the frequency of functional and metabolic liver lesions in women of reproductive age and during pregnancy. Abdominal obesity and disorders of lipid metabolism are important factors in the development of MASLD, and BMI is an independent predictor of the development of steatosis and steatohepatitis and is often associated with the development of obstetric and perinatal complications during pregnancy. Our aim was to conduct an analysis of the state of fibrinolytic activity of blood plasma in pregnant women with NAFLD against the background of obesity of various degrees.

Method: In our study, 69 pregnant women with MASLD at the stage of MASH and obesity were examined at 27-32 weeks of pregnancy, in whom signs of steatosis were detected during ultrasound of the liver. The control group consisted of 30 healthy women. All pregnant women with MASLD and abdominal obesity were divided into 3 groups: IA group – 23 pregnant women with overweight, IB group – 25 women with obesity I degree, IC group – 24 pregnant women with obesity II degree. To evaluate the fibrinolysis system, we studied total (TFA), enzymatic (EFA) and non-enzymatic (NFA) fibrinolytic activity of plasma.

Results: The analysis of the results of the studies showed that pregnant women with NASH on the background of obesity are characterized by a significant decrease in TFA due to a decrease in the functioning of its enzymatic link. Thus, the TFA indicator in pregnant women of the IA group was 14.8% lower than the indicator of the control group, in patients of the IB group - by 18.6% and in IC - by 22,8%. EFA in pregnant women with MASH and Overweight was 27.5% lower than the control group, in IB – by 43.4%, and in IC - by 54.2%. At the same time, a compensatory increase in NFA was observed: in the IA group - by 1.21 times, in the IB group - by 1.52 times, in IC group - by 1.66 times compared to the control group. During pregnancy, with MASLD combined with obesity, a marked suppression of the TFA and EFA of the blood plasma was established against the background of a probable increase in NFA of the blood. These changes can serve as a prerequisite for the occurrence of microthrombosis with the subsequent development of IUGR, fetal distress and placental dysfunction.

Conclusion: Established disorders of the fibrinolysis system are directly correlated with BMI growth and may be caused by the presence of MASLD and lipid disorders in the liver and indicate the need to develop individual programs for the prediction and treatment.

PO1-06
Normal fibrosis-4 values do not exclude advanced fibrosis in 15% of patients with metabolic dysfunction-associated steatotic liver disease

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Background and Aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) represents the leading cause of chronic liver disease globally. Identifying patients with MASLD who are at risk of advanced liver disease and require further evaluation in a specialist setting is paramount. Guidelines recommend screening for MASLD in high risk-groups following a 2-tier system: FIB-4 and/or NAFLD fibrosis score in primary care, followed by ELF and/or transient elastography in a specialist setting. However, both FIB-4 and ELF were historically derived by tertiary care cohorts and may underestimate the disease burden in a low-prevalence disease setting, such as primary care. In this study, we aimed to examine the performance of low FIB-4 in patients with MASLD when compared to transient elastography, histology at baseline and document the clinical outcomes of these patients.

Method: Consecutive patients diagnosed with MASLD from 2012 to 2015 (before the implementation of the two-tier system), were included. Patients' clinical and anthropometric characteristics as well as clinical outcomes at the end of follow-up were collected retrospectively. Clinical outcomes were defined as death, cardiovascular events, extrahepatic cancers and liver-related outcomes (new diagnosis of cirrhosis, HCC and decompensation (hepatic encephalopathy, variceal bleeding or ascites). Baseline FIB-4 values were compared against liver stiffness measurements (LSM) (FibroScan®), fibrosis stage in liver biopsies and clinical outcomes. SPSS was used for data analysis.

Results: 563 patients were included in the study: 66% male, median age 51 years and BMI 29.6, 36% Caucasian, 36% Arabs, 27% Asians. 302 (54%) patients had a low FIB-4 score (<1.3) and normal LSM (<8 kPa) (true negatives), and 52 patients (9%) had normal fib-4 (FIB-4 <1.3) but increased liver LSM (>8kPa). 77 patients with FIB-4<1.3 were biopsied. Interestingly, 15% had fibrosis stage ≥3. From those included in the false negative group (52 patients), 4 (7.7%) developed cirrhosis (median 8 years), 4 (7.7%) had cardiovascular events (median time 6.5 years) and 1 patient developed extrahepatic cancer. Hypertension was significantly associated with false negative results in the multivariate analysis, with either LSM or fibrosis stage as the reference standard.

Conclusion: The high prevalence of false negatives in this study highlights a vulnerable cohort of patients that would be missed following the current guidelines. Better referral pathways are required with the results validated in prospective studies.

PO1-09
The vitamin E conundrum: Should you still be using it for metabolic dysfunction-associated steatotic liver disease (MASLD)

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Background and Aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a leading cause of chronic liver disease worldwide representing significant clinical burden. With limited therapeutic options available, and some concern with long term use of vitamin E, the role of vitamin E in treatment of MASLD remains to be clarified. This study aims to evaluate the impact of Vitamin E on long term outcomes and survival in MASLD patients.

Method: Data on 289 patients with biopsy proven MASLD recruited from a tertiary care hospital were analyzed. Binary logistic regression analysis was performed to examine the association between usage of vitamin E and long term outcomes of liver related events (LRE) and mortality.

Results: 155 patients (52.5% of cohort) received Vitamin E therapy. Demographic characteristic of patients in both groups were similar for gender, Body Mass Index, history of diabetes mellitus, hypertension, statin use and fibrosis staging. For patients who received Vitamin E, the median follow-up duration was 66 months with a median vitamin E use of 26 months while follow-up in non Vit E group was 41 months. There were a total of 33 LRE in the cohort. Vitamin E use was not associated with LRE for HCC OR 1.13; (0.34-3.79,p=0.84), ascites: OR 0.80 (0.02-2.43,p=0.69), variceal hemorrhage OR 2.85 (0.29-27.79,p=0.34) hepatic encephalopathy OR 0.94 (0.19-4.73,p=0.94), liver transplant OR 1.01 (0.99-1.02,p=0.33), mortality OR 0.75 (0.19-2.83,p=0.66) and overall combined outcome OR 1.45 (0.69-3.03,p=0.32).

Conclusion: Vitamin E supplementation may not be associated with significant improvement in long-term outcomes in patients with MASLD.

PO1-10
Clinical superior applicability and repeatability of Hepatoscope 2DTE thanks to imaging-related criteria

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Background and Aims: Hepatoscope® is an ultraportable ultrasound system providing 50 Hz transient elastography for the non-invasive assessment of liver fibrosis. It uses imaging-based features to evaluate a quality index (QI) for individual stiffness values. We investigated the contribution of this imaging-based QI on the intra- and inter-user repeatability of liver stiffness measurement (LSM) in patients with steatotic liver diseases (SLD).

Method: DIACEPA study (NCT04782050) was a prospective cross-sectional monocentric study for the non-invasive ultrasound diagnosis of chronic liver diseases. This retrospective subanalysis focused on patients with SLD. Patients were seen on a routine visit, underwent LSM with FibroScan® VCTE™ and shear wave elastography (SWE) with Aixplorer®. Additionally, they were tested with Hepatoscope 2DTE (prototype), twice by an expert user and a novice user (4 reads in total). Both operators were blinded to 2DTE results. The software used was a prototype. For each stiffness value, a QI was calculated on a continuous scale (0-100%), based on ultrasound image brightness, shear wave amplitude, and uniformity of the stiffness map. If QI>85%, the value was considered as valid to be included in the calculation of a median. The prototype was set to collect the first 15 values with QI>85% and up to 40 could be saved. Three different medians were calculated to simulate various levels of quality control: LSM10/30 (median of the first 10 values with an IQR/M < 30%); LSM10/85 (first 10 values with QI>85%); and LSM4/90 (first 4 values with a QI>90%). Intra-class and Spearman's correlations were calculated and compared.

Results: Sixty-six patients were analyzed, including 56 (84.6%) with MASLD/MASH. The age was 59.4 ± 13.6 years, 25 (37.9%) patients were female, the BMI was 31.2 ± 6.3 kg/m², FIB-4 was 2.1 ± 1.5, and 92.4% of patients were diabetic. The median LSM were 6.4 and 6.6 kPa for VCTE and SWE, respectively.
For LSM10/30, expert and novice repeatability as well as inter-user repeatability were calculated at 0.78, 0.70 and 0.63, respectively, on 38 patients. For LSM10/85, the ICCs assessed on 64 patients for expert and novice repeatability were 0.72, and the inter-user repeatability increased significantly to 0.82, compared to LSM10/30. Lastly, when using 4 values with a QI>90%, 66 patients were eligible, the intra-user repeatability was good for expert and novice at 0.77 and 0.79, respectively, and the inter-user repeatability was significantly higher than LSM10/30, at 0.81. For both LSM10/85 and LSM4/90, their correlations with VCTE were 0.58 and 0.59, respectively, and 0.55 and 0.61 for SWE.

Conclusion: Hepatoscope 2DTE (prototype version) allows the measurement of liver stiffness in SLD patients. Implementing imaging-based QI on LSM jointly provides a higher applicability than conventional IQR/M criterion, and an improved inter-user repeatability

PO1-13-YI
Alcohol and metabolic factors influence steatotic liver disease clinical outcomes

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Background and Aims: The prevalence of steatotic liver disease (SLD) is increasing worldwide and it has become the leading cause for chronic liver diseases. Increase in alcohol consumption/prevalence of metabolic risk factors and aging population is linked to increased liver mortality and morbidity. It is also well known that alcohol use and metabolic factors frequently coexist, however there is limited data on their synergetic effect on the liver diseases and their outcomes. We aimed to describe the effect of cardiometabolic risk factors (CMRF) and alcohol intake on fibrosis and clinical outcomes in three SLD subgroups.

Method: Patients who underwent a liver biopsy between 1993 and 2024 at a single tertiary centre and who had histological confirmation of SLD were included. All patients were reclassified into three SLD subgroups. SLD subgroup outcomes were tabulated for ordinal groups of CMRF and alcohol intake. Alcohol thresholds taken from multisociety Delphi consensus statement and alcohol use was categorized into four levels. We looked at major adverse liver outcomes (MALO) (decompensation, transplantation, hepatocellular carcinoma) and liver related deaths. Statistical analysis was done in R.

Results: In total 726 patients were included with median of 60.5 months (IQR 29 – 84.5). 516 (71%) had metabolic dysfunction associated steatotic liver disease (MASLD), 85 (12%) MASLD with increased alcohol intake (MetALD) and 125 (17%) – alcohol related liver disease (ALD). The median age was 53 (IQR 43 - 61) years. Death occurred in 64 (8.8%) patients and 24 deaths were liver related. MALO occurred in 51 (7%) patients where some patients had more than one MALO. At five years, the cumulative incidence of MALO was 1.8% (0.80%, 3.6%) in MASLD, 7.1% (2.6%, 15%) in MetALD and 25% (17%, 33%) in ALD.

We showed a joint effect of CMRF and alcohol in increasing the risk of significant fibrosis: the prevalence of fibrosis was 18% in patients with one CMRF and very low alcohol consumption (MASLD), 40% in patients with two CMRF and low alcohol consumption (MASLD) and 71% in patients with four CMRF and MetALD. Multivariable analysis showed that alcohol consumption consistent with MetALD (OR 3.77, 95% CI 0.95-12.69, p=0.040) or ALD (OR 15.87, 95% CI 6.94-39.50, p<0.001) was independently associated with MALO/liver related death. The accumulation of CMRF were not linked to an increased risk of MALO/liver related deaths.

Conclusion: We have demonstrated that SLD subgroups have distinct clinical phenotypes. CMRF and alcohol synergise to increase the risk of significant fibrosis but clinical outcomes are dominated mainly by alcohol consumption. Clinicians should perform an accurate assessment of alcohol consumption in SLD groups and advise patients to become completely abstinent.

PO1-14
Diagnostic performance of serum mac-2-binding protein glycosylation isomer as a fibrosis biomarker in non-obese and obese patients with steatotic liver disease

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Background and Aims: An accurate assessment of disease severity, particularly the extent of liver fibrosis, is essential for the management of patients with steatotic liver disease (SLD). Serum mac-2-binding protein glycosylation isomer (M2BPGi) is a new biomarker for liver fibrosis. However, its performance in SLD, particularly in obese patients, remains to be explored.

Method: This study evaluated the role of M2BPGi in predicting liver fibrosis in 205 patients with SLD using magnetic resonance elastography (MRE) as a reference. The performance of M2BPGi was compared to vibration-controlled transient elastography (VCTE), fibrosis-4 (FIB-4) index, APRI, and aspartate aminotransferase (AST)/platelet ratio index (APRI), and NAFLD fibrosis score (NFS).

Results: The mean age of the patients was 57.0 ± 13.4 years, and 105(51.2%) were men. There were 65 (31.7%), 89 (43.4%), and 72 (35.1%) patients with a history of type 2 diabetes (T2DM), hypertension, and dyslipidemia, respectively. There were 150 (73.2%) patients classified as obese, and the average BMI of all patients was 27.8±4.6 kg/m2. The mean values of MRE and MRI-PDFF were 2.9±1.2 kPa and 12.2±7.5%. Sixty-two (30.2%) patients had significant fibrosis (F2) or more, defined as MRE ≥3.0 kPa. There were significant differences in the mean levels of M2BPGi between the F0-F1 and F2-F4 stages (0.66±0.40 vs 1.31±0.76 COI, P<0.001), between F0-F2 and F3-F4 (0.69±0.44 vs 1.52±0.73 COI, P<0.001) and between F0-F3 and F4 (0.73±0.45 vs 1.84±0.82 COI, P<0.001). The area under the ROC curves for VCTE, M2BPGi FIB-4, APRI, and NFS in differentiating significant fibrosis were 0.95 (95% CI; 0.91-0.98), 0.85 (0.79-0.92), 0.81 (0.74-0.89), 0.79 (0.71-0.87) and 0.80 (0.72-0.87) (all P<0.001), respectively. The optimal cut-off values of M2BPGi in predicting significant fibrosis, advanced fibrosis, and cirrhosis were 0.82, 0.95, and 1.23 cut-off index (COI, yielding satisfactory sensitivity, specificity, and diagnostic accuracy. The performance of M2BPGi was consistent among subgroups according to BMI, while the AUROCs of FIB-4, APRI, and NFS were remarkably declined in patients with BMI ≥30 kg/m2. In multivariate analysis, the independent factors associated with significant liver fibrosis were VCTE and M2BPGi.

Conclusion: Although fibrosis stages based on simple serum algorithms are practical and not expensive, their results could be negatively affected by obesity. Our data demonstrated that measuring serum M2BPGi levels could accurately assess liver fibrosis in patients with SLD, particularly in patients with F2-F4 fibrosis independently of BMI. Since obesity and metabolic disturbance are closely related to SLD development, serum M2BPGi could be used as a promising fibrosis biomarker for SLD in clinical settings.

PO1-17
Measuring hepatic steatosis with proton density fat fraction quantification at 0.55T: Pilot study and comparison with 3.0T MRI

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Background and Aims: Magnetic resonance imaging (MRI)-based body composition metrics are highly valued for studying metabolic-associated steatotic liver disease (MASLD). Proton density fat fraction (PDFF) is the ratio of unconfounded fat signal to the sum of the unconfounded fat and water signals. PDFF of the liver is commonly measured using 1.5 T or 3T MRI systems. However, low-field systems are increasingly favored due to lower cost, improved safety profile, minimized artifacts around metallic implants, and enhanced patient comfort. In this pilot study, we adapted and evaluated a liver fat quantification protocol at 0.55T compared to a clinical 3T protocol to measure liver fat in patients with MASLD.

Method: In this prospective pilot study, nine adult patients (average age 56.7 ± 13.6 years, 6 females) with ≥5% hepatic steatosis on 3T MRI underwent a novel 0.55T MRI PDFF protocol within 90 days. Liver fat quantification was reported using PDFF.

Results: Presenting comorbidities of the nine patients included prediabetes/diabetes (40%), hypertension (60%), and hyperlipidemia (50%). Mean aspartate aminotransferase was 52.6 ± 30.8 U/L, mean alanine transaminase was 65.7 ± 51.6 U/L, and mean Fibrosis-4 score was 1.9 ± 1.4. Mean liver stiffness was 13.9 ± 18.5 kPa on vibration-controlled transient elastography. Mean 3T MRI-PDFF was 17.18%, compared to 14.39% 0.55T MRI-PDFF (correlation coefficient r = 0.98). In dividing the subjects into three groups, 5-10% PDFF, 10-20% PDFF and above 20% PDFF, 0.55T MRI-PDFF was more similar to 3T MRI-PDFF results in the 5-10% liver fat cohort (mean 3T MRI-PDFF 6.66% vs 5.56% on 0.55T MRI-PDFF, 1.10% difference). In contrast, in >20% liver fat patients, a larger discrepancy was observed (mean 3T MRI-PDFF 25.68% vs. 20.91% 0.55T).

Conclusion: Our data demonstrates that 0.55T MRI is feasible and comparable to 3T MRI in quantifying liver fat among patients with MASLD. This novel low-field PDFF MRI approach has potential for many future translational applications, including screening the general population for high metabolic risk profiles at high risk for developing steatotic liver disease, or monitoring allograft health in post-transplant liver patients. Further protocol optimization is needed to achieve more robust measurements in moderate and severe hepatic steatosis.

PO1-18-YI
Mapping the hepatic mtDNA genomic landscape in patients with MASLD: The era of GPT-4 artificial intelligence

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Background and Aims: Artificial intelligence (AI) is enabling big data mining. We took advantage from generative AI tool (GPT-4) to assist in analyzing -omics data from a small, completely anonymized dataset of 39 liver biopsies of patients with MASLD, who underwent mtDNA whole-genome sequencing (WGS cohort) to identify potential pathogenic mutations. We then investigated the correlation among mtDNA variants and: a) hepatic mitochondrial respiration assessed in 80 MASLD patients (Seahorse cohort); b) histological damage and serum cell-free circulating (ccf-) mtDNA fragments in biopsied MASLD patients (Hepatology service cohort, n=555).

Method: A customized GPT-4 model with coding skills was used for genomic data analysis (mtGPT-4).

Results: In the WGS cohort, 520 mtDNA nonsynonymous variants were detected. The unbiased analysis run by mtGPT-4 revealed that ten mtDNA mutations significantly correlated with NAS≥5 and nine with advanced fibrosis (F3-4). Most of the mtDNA SNPs associated with NAS≥5 affected the mitochondrial tRNAs while those positively correlated with F3-F4 stages located in the respiratory complexes' genes, supporting that mitochondrial respiration fails as much as the disease severity increases. To assess the impact of a group of mtDNA mutations on MASLD progression, we asked mtGPT-4 to perform a phylogenetic cluster analysis. The H haplotype was the most common (36%), followed by T (23%), K, and J (7.6%). Patients belonging to T cluster exhibited a higher rate of steatosis (55% vs 31%, p=0.02), NAS≥5 (OR: 4.35, 95% CI: 2.11-9.5) and severe fibrosis (OR: 7.02, 95% CI: 2.11-9.5) compared to non-T subjects. Among the T patients, seven T haplotypes (T1b, T1a1b, T2b, T2b1*, T2b2b, T2b3+151) were recorded, each including a specific mtDNA mutation panel. Aiming to identify key mtDNA mutations driving disease severity, we requested mtGPT-4 to extract a list of mtDNA variants which were shared across the T haplotypes. A total of 8 mtDNA variants were found of which two, the chrM.4216 T>C (p.Y304H) in the MT-ND1 gene and the chrM.10463 T>C MT-TR (tRNAArg), significantly correlated with steatosis, NAS and fibrosis. Both mutations not only individually emerged from the unbiased analysis but also occurred in combination in phylocluster T, driving its association with the MASLD pathology. A preliminary validation in the Seahorse cohort revealed that carriers of the chrM.4216 variant had lower hepatic complex I activity and oxygen consumption rate compared to TT patients ($p<0.05$). In the Hepatology service cohort, the chrM.4216 variant associated with elevated ccf-ND1 serum release, severe NAS and fibrosis at multivariate analysis adjusted for sex, age, BMI, T2M and genetic mutations in PNPLA3/TM6SF2/MBOAT7 genes.

Conclusion: GPT-4 facilitated the analysis of -omic dataset, aiding in the identification of novel mutations of mitochondrial origin involved in MASLD pathogenesis.

PO1-22-YI

MetALD is diagnosed at more advanced stages of fibrosis as compared to MASLD but at earlier stages as compared to ALD in the general population

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Background and Aims: The 2023 Delphi Consensus definition of steatotic liver disease (SLD) introduced the term metabolic and alcohol associated liver disease (MetALD). Studies on MetALD have focused on disease prevalence and prognosis. The aim of this study was to assess the stage of liver disease at diagnosis of MetALD compared to other SLD subtypes.

Method: Cross-sectional analysis of two prospective cohorts included in screening programs for liver disease with transient elastography (TE) in the general population in Spain, between 2012 and 2016 (cohort 1), and during 2022 (cohort 2). SLD was determined by FLI≥60, Controlled Attenuation Parameter (CAP)≥263 dB/m or liver stiffness measurement (LSM) by TE≥10kPa. Patients were categorized into: 1) metabolic dysfunction-associated steatotic liver disease (MASLD); 2) MetALD; 3) alcohol-associated liver disease (ALD); 4) Others. The stage of liver disease was based on LSM by TE: Stage1(S1) (<10kPa), S2 (10-25kPa), S3 (>25kPa).

Results: Out of 4,198 participants included in the study, 1,930 (46%) had SLD: 1,639 (85%) MASLD, 216 (11%) MetALD, 64 (3%) ALD, and 11 (1%) others. The proportion of females was significantly different between groups: 47% vs 26% vs 17% in MASLD, MetALD and ALD (p<0.001); while median age was similar. Median LSM of the different SLD subtypes were 5.3 vs 5.6 vs 7.1 kPa in MASLD, MetALD and ALD (p<0.001)(Figure). The proportion of the different stages among SLD subtypes (MASLD vs MetALD vs ALD) were: S1) 92.9% vs 92.1% vs 70.3%; S2) 6.4% vs 7.0% vs 23.4%; S3) 0.7% vs 0.9% vs 6.3% (p<0.001). Both median CAP and FLI were higher in MetALD compared to MASLD (CAP: 299 vs 288 dB/m [p=0.029]; FLI: 83 vs 78 [p<0.001]), and similar in MetALD as compared to ALD.

Conclusion: In a general population-based setting, patients with MetALD are diagnosed at a more advanced stage than patients with MASLD, but at an earlier stage compared to patients with ALD.

PO1-23-YI
Impact of a multidisciplinary clinic for metabolic dysfunction-associated steatotic liver disease on cardiovascular risk and liver health

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Background and Aims: Cardiovascular disease (CVD) is the leading cause of mortality in metabolic dysfunction-associated steatotic liver disease (MASLD) patients. Guidelines recommend a multidisciplinary approach, but real-world data are limited. This study aimed to assess the efficacy of a multidisciplinary MASLD clinic in optimising control of metabolic comorbidities and liver injury markers.

Method: We conducted a retrospective analysis of 465 patients seen in a multidisciplinary MASLD clinic from June 2014 to June 2024. All participants were evaluated by both a hepatologist and an expert in cardiovascular disease. Patients were referred directly from primary care or through the Camden and Islington MASLD Pathway (London, UK), which involved a FIB-4 and, if needed, an ELF score. Each patient received a comprehensive hepatological assessment, cardiovascular risk assessment and management, and, where required, dietary counselling by a dietician. Diagnostic criteria for comorbidities, including hypertension, type II diabetes, dyslipidaemia, and obesity, were based on recognised clinical guidelines. Cardiovascular risk was assessed using the QRISK-3 Score, with statins recommended for patients with a ≥10% 10-year CVD risk or a history of cardiovascular events. Baseline and follow-up data on anthropometry, blood pressure, and laboratory values were collected. Primary endpoints were changes in liver injury markers (transaminases, LSM) and metabolic comorbidities (e.g., blood pressure, HbA1c, lipid profile, and QRISK-3 Score).

Results: The mean age of 465 patients was 57 ± 12 years, 56% were males, and 54% Caucasian. Hypertension, diabetes, and dyslipidaemia were present in 66%, 56%, and 84% of patients, respectively. At baseline, 65% had abnormal ALT, while LSM, measured in 95% of patients, had a median of 7.9 kPa. Of 190 liver biopsies ,79% showed steatohepatitis, with bridging fibrosis in 29% and cirrhosis in 14%. At a 15-month median follow-up, 61% of patients remained under secondary care, with significant improvements observed in ALT ($p<0.001$), AST ($p<0.001$), GGT ($p<0.001$), total cholesterol ($p<0.001$), LDL-c ($p<0.001$), TG ($p=0.007$), systolic and diastolic blood pressure ($p<0.001$ and $p=0.001$), weight ($p<0.001$), BMI ($p<0.001$), LSM ($p=0.020$), and QRISK-3 Score ($p=0.002$). Waist circumference decreased significantly in obese patients, with 12% achieving ≥10% weight loss. Therapy adjustments improved metabolic markers, notably HbA1c, blood pressure, and lipid profile in patients with diabetes, hypertension, and dyslipidaemia, respectively.

Conclusion: A multidisciplinary approach to MASLD effectively improves liver and CV risk markers. Long-term collaboration between primary and secondary care is crucial to achieve and maintain these health improvements.

PO2-01

Microvascular complications of type 2 diabetes mellitus in patients with concomitant metabolic dysfunction-associated steatotic liver disease in primary care, a prospective cohort study

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Background and Aims: Study results are heterogenic regarding the risk for the diabetic microvascular complications retinopathy and neuropathy among patients with type 2 diabetes mellitus (T2DM) and concomitant metabolic dysfunction-associated steatotic liver disease (MASLD) with or without advanced fibrosis (AF). The risk for diabetic foot ulcers is scarcely studied among these patients. We aimed to explore the association between MASLD, with and without AF, and retinopathy, neuropathy and foot ulcers in a Swedish primary care setting.

Method: Study participants with T2DM were recruited in connection with routine control in primary care. Liver fat content was assessed using magnetic resonance imaging with liver proton density fat fraction (MASLD ≥ 5 %) or vibration-controlled transient elastography (VCTE) with controlled attenuation parameter (MASLD ≥ 248 dB/m) and hepatic fibrosis using VCTE (AF ≥ 10 kPa). Data on retinopathy, neuropathy and foot ulcers was collected from medical health records. The diagnosis of retinopathy was based on routine fundus photography. Findings of neuropathy on electromyography/nerve conduction test or a diagnosis based on clinical signs/medical history was noted. Ongoing or previous foot ulcers, with longer healing time than 6 weeks, were noted as diabetic foot ulcers.

Results: A total of 299 participants were included in the study. 153 (51 %) participants were classified as MASLD, 19 (6 %) as MASLD with AF and 127 (42 %) as non-MASLD. There were significant differences between the groups regarding BMI ($p < 0.001$) and HbA1c ($p = 0.028$). 59 participants had retinopathy, 65 neuropathy, 11 foot ulcers and in total 115 one or more of these complications. There were no significant differences, regarding the risk for these complications, between the participants having MASLD, MASLD with AF or non-MASLD.

Conclusion: This is one of few studies regarding the presence of AF in MASLD in patients with T2DM in primary care. Our study suggests that the prevalence of MASLD, with or without advanced liver disease, in the general T2DM population could be overstated. The results regarding neuropathy and retinopathy are in line with other studies showing unchanged risk and could support that there are geographical differences. Foot ulcers were very uncommon in all the groups, making these results uncertain, but this is the first study of the subject from primary care.

PO2-02
Relationship between endothelial dysfunction and metabolic dysfunction-associated steatotic liver disease

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Background and Aims: It is currently considered that metabolic dysfunction-associated steatotic liver disease (MASLD) is a risk factor for liver cirrhosis, liver cancer, diabetes and cardiovascular disease. The presence of cardiovascular complications of MASLD worsens its course and prognosis for patients. In recent years, researchers have focused on the features of intercellular interaction and endothelial dysfunction (ED) as a factor in vascular damage in patients with MASLD, but endothelial dysfunction has not been studied enough. The aim - to evaluate the relationship between markers of systemic inflammation, degree of liver fibrosis and endothelial dysfunction in patients with MASLD.

Method: We examined 241 patients and determined the level of inflammatory mediators, endothelin (ET-1), the activity of the Willebrand's factor (vWF), the thickness of the intima-media complex, presence atherosclerotic plaque and stenosis of the carotid arteries, index HOMA-IR. The ratio between the content of adiponectin and leptin was represented as log A / L. The anthropometric survey, measured levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), the degree of liver fibrosis using elastography (FibroScan), ECG and echocardiography were conducted.

Results: Correlation analysis revealed a direct correlation between HOMA-IR and leptin ($r = 0.8$; $p = 0.00166$) and inverse correlation between HOMA-IR and adiponectin ($r = -0.66$; $p = 0.0033$) and index log A / L ($r = -0.71$; $p = 0.0000$) It is evident that the decrease in the concentration of adiponectin with a parallel increase in the content of leptin increases IP. A comparative analysis of the level of CRP inflammation marker in obese patients showed a direct relationship with HOMA-IR ($r = 0.58$; $p = 0.05$), glucose ($r = 0.44$; $p = 0.0045$) and insulin ($r = 0.66$; $p = 0.0001$) in the blood. The patients with MASLD by obesity showed a reduction in endothelium-dependent vasodilation, indicating the presence of endothelial dysfunction. The concentration of proinflammatory cytokines such as TNF-α and IL-6 in patients with MASLD was 3-7 times higher than the similar parameters of patients with a similar degree of obesity but without evidence MASLD. The concentration of ET-1 in the blood plasma of patients with MASLD has a strong direct correlation with the degree of cardiovascular risk and cognitive deficit in surveyed patients. It is found that many inflammatory mediators (TNF-α, IL-1, IL-6) and markers (C-reactive protein, fibrinogen) highly correlate with the degree of obesity, the concentration of ET-1, vWF and markers of insulin resistance a predictor for cardiovascular risk.

Conclusion: The development of MASLD is associated with the development of endothelial dysfunction, increasing levels of leptin and markers of systemic inflammation, decreasing levels of adiponectin in patients with MASLD.

PO2-03
Digital communication intervention and weight loss in patients with metabolic dysfunction-associated steatotic liver disease: A randomised controlled Study

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Background and Aims: Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) is the most prevalent liver disease globally. The primary therapy for MASLD is lifestyle modification, aiming for a 7-10% reduction in body weight. This study evaluates the effectiveness of digital communication interventions in promoting and sustaining lifestyle changes in patients with MASLD outside of clinical settings. The primary objective was to assess the effectiveness of digital communication interventions in reducing weight in MASLD patients. Secondary outcomes included changes in liver enzymes and lipid profiles between the intervention and control groups.

Method: A randomized controlled trial was conducted involving 120 well-characterized MASLD patients from Phramongkutklao Hospital. Participants were randomized into three groups: one-way communication group (A), interactive communication group (B), and control group (C). Measurements of body weight, height, waist circumference, blood pressure, liver function, lipid profile, fasting plasma glucose, and HbA1C were recorded before and after the intervention.

Results: The intervention group experienced an average weight loss of 0.86 kg (P = .03), compared to a loss of 0.42 kg in the control group (P = .81). Additionally, the intervention group showed reductions in waist circumference (-2.06 cm, P = 0.003), cholesterol levels (-13.8 mg/dL, P = .002), and LDL (-21 mg/dL, P = .026). No significant changes were observed in the control group regarding serum ALT (3.3 IU/L, P = .31) and triglycerides (5.8 mg/dL, P = .08). The differences between the intervention and control groups were statistically significant for weight (P = .02), waist circumference (P = .003), and BMI (P = .02).

Conclusion: Digital communication interventions promoting a healthy lifestyle were associated with significant reductions in weight, waist circumference, and improvements in cardiometabolic profiles in MASLD patients. Larger studies are needed to evaluate the long-term benefits of this approach and its potential impact on liver histology.

PO2-05
Differences in gut microbiome diversity in patients with metabolic dysfunction-associated steatotic liver disease associate with response to faecal microbiota transplant

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Background and Aims: The gut microbiome influences the pathogenesis and progression of metabolic dysfunction-associated steatotic liver disease (MASLD), at least partly via circulating gut microbial metabolites. Faecal microbiota transplant (FMT) from selected donors may restore pre-morbid microbiome-metabolome interactions in patients with MASLD. Our aim was to assess microbiome engraftment after FMT and its impact on MASLD patients' metabolism.

Method: Fifteen MASLD patients with liver stiffness of > 8 kPa were recruited from a specialist MASLD clinic (St Mary's Hospital, London, UK), and each received three healthy donor capsulised FMTs, each six weeks apart (ClinicalTrials.gov ID: NCT06024681). We designed a plasma poly-metabolic scoring model (PMRS) based on 1H-NMR data that distinguished MASLD from healthy individuals, and stool donors (n=11). Plasma, stool samples and clinical parameters were collected fortnightly (week 0-24) during this longitudinal study. Fasted plasma samples were analysed by 1H-NMR spectroscopy and scored based on their full metabolic profiles. A decrease in the poly-metabolic risk scores of MASLD FMT recipients by week 24, was used to determine their response status to FMT. 16S rRNA gene sequencing was performed on stool samples to profile changes in gut microbial composition, primarily assessed by alpha and beta diversity, comparing responders and non-responders.

Results: 11/15 FMT recipients demonstrated metabolic profile shifts towards those of the healthy donors after receiving three FMTs and were deemed responders. Non-responders had higher baseline ALT levels (p=0.03) compared to responders and exhibited higher levels of triglycerides (p=0.001), HOMA-IR (p=0.026), and ALT (p=0.049) levels at the trial endpoint. Responders displayed greater gut microbial alpha diversity (Inverse Simpson, p=0.0007) at baseline, as well as increased beta diversity (p=0.028) after their first FMT.

Conclusion: 1H-NMR plasma PMRS could effectively differentiate MASLD FMT recipients to responders and non-responders, and this associated with gut microbiome diversity changes. These findings provide insight into the gut microbiome's contribution to metabolic perturbations in MASLD, highlighting the potential for personalised risk assessment and treatment options.

PO2-08
Advanced metabolic-dysfunction associated steatotic liver disease fibrosis: Low number-needed-to screen in multiple lines of care

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Background and Aims: Non-invasive liver tests (NITs) can detect advanced fibrotic MASLD and reduce unnecessary referrals. Yet data comparing numbers-needed-to-screen (NNS) in multiple lines of care are scarce. Therefore we introduced NLA2, the first Dutch MASLD care path, encompassing primary, secondary and tertiary clinics.

Method: Patients at cardiometabolic risk for MASLD were recruited from GPs, regional clinics and a UMC, whilst excluding other liver diseases. Simultaneous FIB4, MAF5, Enhanced Liver Fibrosis (ELF)-test and vibration-controlled transient elastography (VCTE/FibroScan®) allowed testing of NIT combinations. FIB4 ≥3.25 and/or Liver Stiffness Measurement (LSM) ≥8.0 kPa indicated potential advanced fibrosis, prompting referral to hepatology. Referral patterns were compared to regular care between 2016-2024 using a predefined evaluation standard.

Results: 655 participants entered NLA2, 270 from primary, 156 from secondary and 229 from tertiary care. After excluding patients with MetALD or other liver diseases, 597 were analyzed. Median age was 60 years (51-68), 45.9% were women, 51.4% had obesity and 45.2% had T2DM. 73.9% of participants had CAP ≥248 dB/m, suggesting ≥S1 steatosis. 15.5% had LSM ≥8.0 kPa, yielding a NNS of 6.7. NNS decreased across lines of care: 12.1, 5.1 and 5.2 for primary, secondary and tertiary care respectively, inversely related to cardiometabolic comorbidities (mean number 2.1, 2.3, 2.9). ELF was available for 535 participants. 20.0% had ELF ≥9.8, yielding NNS of 5.0. FIB4 stratifies 64% as low risk for advanced fibrosis and 36% as intermediate/high risk. MAF5 stratifies 40% as low risk for advanced fibrosis and 60% as high risk.
In a 2-tiered algorithm in case of MAF5 ≥1, VCTE as second test would refer 6.4%; using ELF would refer 11.7%. In a 2-tiered algorithm in case of intermediate FIB4 (1.3-3.25), VCTE as second test would refer 13.1%; using ELF would refer 13.5%. Of 96 patients at risk for advanced fibrosis, 72 were referred to hepatology. 465 patients were referred to hepatology via regular care between 2016 and 2024. Compared to regular care, NLA2 improved correct referrals 4-fold (RR 4.03; 95% CI 2.53-6.41). Unnecessary referrals were reduced 2-fold (RR 0.44; 95% CI 0.27-0.69).

Conclusion: The first Dutch MASLD care path study shows incrementally lower NNS for potential advanced fibrosis detection across multiple lines of care and a significantly improved referral pattern for fibrotic MASLD. We found a marked difference in referral-rate between different NIT combinations.

PO2-09
Association of newly-onset dyslipidemia and metabolic dysfunction-associated steatotic liver disease (MASLD) among chronic hepatitis B patients with antivirus treatment in China

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Background and Aims: Dyslipidemia has been associated with MASLD, however, its impact on the MASLD among chronic hepatitis B (CHB) patients has not been well studied. This study evaluated the effect of newly-onset dyslipidemia, in terms of triglycerides (TG) change, on emerge of MASLD among Chinese CHB patients.

Method: This retrospective cohort study included adult(18-65y) CHB patients who initiated nucleos(t)ide analogues (NAs) treatment during 2010-2020 with lipid test. Patients with normal level of TG (<1.7 mmol/L according to Chinese guideline for dyslipidemia) at baseline were included. The earliest identified NAs prescription date was defined as the cohort entry date and prior one-year was set as baseline. TG level was evaluated in one-year post treatment initiation. Patients with at least one abnormal test were considered as having newly-onset dyslipidemia and the date of the highest level was defined as the index date. For patients maintained normal, the date of the highest one of normal level was defined as the index date. Patients were followed from the index date until emerge of MASLD, last visit date or end of study, whichever occurred first. MASLD was identified by diagnosis and medical procedure (ultrasonography, CT, MR).

Results: In overall, 1015 eligible patients were included in the study cohort. Males accounted for 65.9% with median age of 51.0 (IQR: 40-60). Regarding other metabolism comorbidities, 14.2% of the patients had diabetes and 17.6% had hypertension. After NA treatment, patients received 1(IQR: 1-2) TG test per year on average and 15.9% patients had newly-onset dyslipidemia with TG increased to abnormal level. Among these patients, 18.5% had MASLD (incidence rate 0.09/person-year) identified during follow up, while only 8.1% developed MASLD (incidence rate 0.04/person-year) among patients maintained normal TG level. After adjustment for age, gender, baseline liver disease, metabolic diseases (diabetes and hypertension), and NA drug at cohort entry, the aHR of newly-onset dyslipidemia on MASLD was 2.14 (95% CI: 1.29-3.57) compared with maintained normal level. Moreover, patients had newly-onset dyslipidemia developed MASLD more quickly compared to those maintained normal, with median time to emerge of MASLD of 257 days and 609 days, respectively.

Conclusion: Among CHB patients with antiviral treatment, newly-onset dyslipidemia of high TG level increases the risk of MASLD, and accelerates the onset of MASLD. Lipid metabolism plays a role in disease progression while is infrequently tested in practice, thus monitor on lipid profile is warranted in treatment of CHB patients.

PO2-13
Assessing the impact of glucagon-like peptide-1 receptor agonists in metabolic dysfunction associated steatosis liver disease

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Background and Aims: Glucagon-like peptide-1 receptor agonists (GLP-1RA) are an effective treatment for Type 2 diabetes (T2D) and obesity and have shown promise in improving metabolic dysfunction-associated steatotic liver disease (MASLD). The aim of this study is to describe the real-world experience (RWE) of prescription of GLP-1RA on liver health in patients with T2D and MASLD.

Method: In this retrospective study, adult patients with a diagnosis of T2D and MASLD with at least 12 months of treatment with GLP-1RA were identified at a tertiary care hospital from 01/2015-10/2022. Other causes of liver diseases were excluded. Demographics, medical comorbidities, markers of liver inflammation and function, metabolic parameters (glycosylated hemoglobin [HbA1c]m lipids) and medications were recorded at baseline and 12 months post-initiation of GLP-1RA. The primary outcome of interest was change in ALT from baseline (baseline ALT values defined as ± 3 months of initiating GLP-1RA) to 12 months. Secondary outcomes include the change in FIB-4 score, weight, HbA1c, LDL, HDL, TG, and other medications prescriptions using the same time points as the primary outcome. Wilcoxon signed rank test, were used to test for significant differences between baseline and 12 months for continuous outcomes.

Results: A total of 4742 patients with T2D and NAFLD were prescribed GLP-1RA in this dataset. At the time of this analysis, 898 patients had complete data for baseline and 12 months. The mean age was 59 years (SD 10.4), 63% were female, 66.4% of patients identify as White and 27.5% as Black, 4.4% identify as Hispanic or Latino and 52.7% have private insurance, and 63% are married.
A significant decrease in ALT by 3.0 IU/L ($p < 0.001$) from baseline to 12 months. There was no significant change in FIB-4 from baseline to 12 months (0.03, $p = 0.31$). Significant decreases were observed in AST (median Δ = -2.0 IU/L, $p < 0.001$), HbA1c (median Δ = -0.7 %, $p < 0.001$), BMI (median Δ = -1.0 kg/m^2, $p < 0.001$), and TG (median Δ = -10 mmol/L; $p = 0.002$). HDL significantly increased by 1.0 mg/dL ($p = 0.001$). There was a noteworthy decrease in LDL by 1.0 mg/dL ($p = 0.054$). Hispanic patients had a higher baseline ALT (78 IU/L; 95% CI: 53, 103) than non-Hispanic patients. There is no significant difference in change in ALT over time by race ($p = 0.057$) or ethnicity ($p = 0.66$).

Conclusion: In this analysis, prescription of GLP-1RA illustrates early improvement in markers of liver inflammation and liver cardiometabolic parameters in individuals with DM2 and MASLD. The lack of change in FIB-4 is likely influenced by age and early analysis at 12 months. With longer follow up and analysis of the entire cohort we hope to assess the impact of GLP-1RA on liver cardiometabolic health and liver fibrosis. We will also be able to assess the role of ethnicity and race on the longitudinal effect on FIB-4.

PO2-16
Circulating CEACAM1 as a biomarker for hepatic steatosis in a metabolic context: Insights from the Portuguese PREVADIAB2 study

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Background and Aims: Hepatic insulin clearance (IC) plays a key role in the development of type 2 diabetes (T2DM) and Metabolic-Associated Steatotic Liver Disease (MASLD), alongside with insulin secretion and insulin resistance. It is also well-established that increased hepatic steatosis is linked to reduced IC. Carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1), a transmembrane glycoprotein, becomes phosphorylated in hepatocytes in response to insulin and contributes to IC by enhancing receptor-mediated endocytosis. We hypothesize that circulating CEACAM1 in humans serves as a biomarker for MASLD, particularly in relation to impaired insulin metabolism.

Method: In the PREVADIAB2 cohort (n=1019), diabetes status was assessed using a 75g-OGTT. Circulating CEACAM1 were measured via ELISA, and hepatic steatosis indices and insulin metabolism parameters were calculated. Hierarchical clustering was applied to insulin metabolic indices (HOMA-IR for systemic insulin resistance, fasting ISR for insulin secretion, fasting IC for insulin clearance, IGI for first-phase insulin secretion) and circulating CEACAM1.

Results: BMI, insulin resistance (HOMA-IR), and hepatic steatosis progressively increased in prediabetes and T2DM, while insulin secretion rose and its clearance declined in parallel with circulating CEACAM1, indicating compensatory hyperinsulinemia. The prevalence of hepatic steatosis increased significantly with disease progression associated with steadily decreased circulating CEACAM1 as the disease advanced. Multidimensional stratification of PREVADIAB2 population used insulin metabolic indices and circulating CEACAM1. Hierarchical clustering analysis revealed four distinct clusters, highlighting a positive correlation between IC and circulating CEACAM1 in clusters with high prevalence of individuals with normoglycemia, lower obesity, high IC and reduced hepatic steatosis. In contrast, the cluster analysis also revealed that as BMI and hepatic steatosis increased, insulin resistance and hyperinsulinemia became more pronounced, and this hyperinsulinemia resulted from increased insulin secretion and reduced IC, with lower circulating CEACAM1 and loss of correlation between IC and CEACAM1.

Conclusion: This study reveals a progressive increase in insulin resistance, hyperinsulinemia, BMI, and hepatic steatosis, accompanied by a decline in circulating CEACAM1. Cluster analysis further demonstrates reduced IC associated with lower circulating CEACAM1 in cases of advanced steatosis, underscoring CEACAM1's potential as a non-invasive biomarker for monitoring metabolic disease progression. These findings suggest that CEACAM1 may be particularly useful for tracking metabolic risk in individuals with obesity or those at high risk for type 2 diabetes with concurrent steatotic liver disease.

PO2-18
Impact of hepatitis C eradication with direct-acting antivirals on metabolic and liver-related outcomes in diabetic patients: A long-term prospective analysis

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Background and Aims: Data on the long-term impact of hepatitis C virus (HCV) eradication on metabolic and liver-related outcomes in patients with type 2 diabetes (T2D) and chronic liver disease (CLD) after direct-acting antiviral (DAAs) therapy remain scarce. This study aimed to evaluate these outcomes (primary endpoint) over an extended follow-up period and their impact on overall survival (OS).

Method: All patients with T2D and HCV-related CLD treated with DAAs from April 1st, 2014, to December 31st, 2016, followed up until September 31st, 2024 at the Medicine and Hepatology Unit of the University Hospital of Messina were enrolled in the study. Demographic, biochemical and clinical features were collected for each patient at baseline and during follow-up. Regression models were applied to identify predictors independently associated with metabolic and liver-related outcomes.

Results: One-hundred eighty-two patients [53.3% males; median age 71 years (41 – 97); 55.5% with cirrhosis] followed for a median of 56.5 months were included in the study. Forty-six of 182 patients (25.3%) maintained clinical stability over time, 31 (17%) died and 38 (20.9%) had liver disease progression [Liver decompensation (LD) and hepatocellular carcinoma (HCC)]. One-hundred-fifty patients (82.4%) developed T2D-related complications (89 macrovascular/61 microvascular). Significant improvements in liver stiffness ($p < 0.001$), glycated hemoglobin (HbA1c) ($p = 0.004$), serum gamma-globulins ($p < 0.001$), and aminotransferase ($p < 0.001$) levels were noted at the end of follow-up. LD was associated with higher liver stiffness ($p = 0.003$), bilirubin values ($p = 0.002$) and lower LDL-cholesterol (LDL-c) levels ($p = 0.017$), while HCC with higher liver stiffness ($p = 0.003$). Kaplan-Meier analysis revealed a significant difference in HCC onset between cirrhotic and non-cirrhotic ($p < 0.001$). Major cardiovascular events were related to higher BMI ($p = 0.024$) and low LDL-c ($p = 0.043$), while peripheral artery disease to higher HbA1c ($p = 0.036$), total cholesterol (TC) ($p = 0.006$) and triglycerides (TG) ($p = 0.045$) levels. Diabetic neuropathy was associated with higher fasting glucose levels ($p = 0.03$), T2D retinopathy with lipid-lowering therapy ($p = 0.036$) and higher TC ($p = 0.04$), while diabetic nephropathy to elder age ($p < 0.001$), higher serum creatinine and HbA1c values ($p < 0.001$; $p = 0.023$). Lipid-lowering therapy showed a protective role against T2D nephropathy ($p = 0.039$). Cox regression analysis showed that higher liver stiffness ($p < 0.001$), creatinine levels ($p = 0.007$) and lower TG levels ($p = 0.03$) were independent predictors of death.

Conclusion: DAA treatment of HCV infection significantly improves liver disease and the natural course of T2D. Early intervention is crucial, as the severity of hepatic disease before starting DAA therapy could impact liver-related outcomes and OS.

PO2-19
Prevalence of steatotic liver disease in people living with HIV and high prevalence of cardiovascular risk factors

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Background and Aims: Due to the current effectiveness of antiretroviral therapy (ART), people living with human immunodeficiency virus (PLWH) have an increasing average life expectancy, with growing rates of cardiometabolic disease in general and metabolic dysfunction-associated steatotic liver disease (MASLD) in particular. Concurrent factors such as alcohol use and chronic viral hepatitis frequently contribute to liver damage. The authors aimed to study the prevalence and characteristics of steatotic liver disease (SLD) in a population of PLWH and high prevalence of cardiovascular disease (CVD) risk factors.

Method: The authors retrospectively studied all patients followed in a CVD risk clinic directed at PLWH from October 2021 until June 2024. Data was collected from computer hospital records and analyzed with Excel® software.

Results: Study population consisted of 72 patients, of which 58.3% were male. The median age was 61 years. All patients presented CVD risk factors: 94.4% had hypertension, 80.6% dyslipidemia, 48.6% smoking habits, 42% obesity and 36.1% diabetes. Established atherosclerotic CVD was present in 19.4%. Regarding human immunodeficiency virus-specific factors, 44.4% presented CD4 nadir <200 cells/mm3, 48.6% had been exposed to protease inhibitors and 79.2% were currently taking integrase inhibitors. CVD risk was predicted to be high or very high in 77.8% using Systematic COronary Risk Evaluation 2 (SCORE2). Regarding SLD, 38.9% (n=28) of patients presented with ultrasound evidence of steatosis, of which 50% could be defined as MASLD, 28.6% as alcohol-associated and 21.4% as metabolic disfunction and alcohol-associated liver disease; one patient had a previous hepatitis C virus genotype 3 infection with cure criteria. Fibrosis-4 (FIB-4) score was higher than 1.30 in 32.1% (n=9) of patients, of which only one presented with a degree of fibrosis >=F2 on transient elastography (TE). The observed agreement between FIB-4 and TE was low (44.4%).

Conclusion: Study population showed a high prevalence of SLD, with probable multifactorial etiologies, but of which 71.4% could be at least partially attributed to metabolic disfunction. FIB-4 estimated an overall low risk of predicted fibrosis but showed poor agreement with TE. In the advent of advancing therapeutic options for metabolic dysfunction-associated steatohepatitis, while strict metabolic risk factors control remains essential, early identification and staging of MASLD in PLWH is of uttermost importance.

PO2-20
Screening of advanced liver fibrosis and metabolic dysfunction-associated steatotic liver disease assessed by transient elastography in Roma population

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Background and Aims: The most common cause of liver disease-related death globally is cirrhosis, which is thought to be the last stage of liver fibrosis. The development of cirrhosis has been discovered to be significantly influenced by viral hepatitis B (VHB) and C (VHC), alcohol-related liver disease (ALD), and metabolic dysfunction-associated steatotic liver disease (MASLD). Our study objective was to determine the prevalence of MASLD and advanced liver fibrosis in individuals of the Roma group living in Northeastern Romania.

Method: Four hundred and fifty-six adult asymptomatic participants of a Roma County from Northeastern region of Romania, were selected for this study. Following the acquisition of informed consent, each participant's demographic, clinical, and physiological details were recorded. Every participant completed the AUDIT-C questionnaire. Liver fibrosis was measured using transient elastography (TE), and fast blood tests were utilized to screen for the presence of the VHB and VHC.

Results: We found that 60.9% of the screened participants were males, 56.5% had a smoking habit, and 14.4% had a history of blood transfusions, tattooing, drug use or imprisonment over the years. Moreover, 68.2% of the patients had a body mass index above the normal limit, 8.6% of the participants were positive for the presence of HBs antigen, while 6.1% exhibited HCV antibody positive titer. In addition, approximately two-thirds of the subjects (65.1%) were diagnosed with metabolic syndrome and according to Audit-C questionnaire we found that 33.1% of the individuals had a history of alcohol consumption. Advanced liver fibrosis was found in 11.6% of the participants, and liver cirrhosis in 8.3% of the cohort. Furthermore, we observed that more than half of the participants (51.1%) from Roma county had the criteria for MASLD.

Conclusion: By screening a cohort of apparently clinically healthy Roma subjects residing in the North-Eastern Romania and having important risk factors such as blood transfusions, tattooing habits, and increased alcohol consumption, we observed that the frequency of advanced fibrosis and MASLD is more increased in Roma individuals, as compared to available data.

PO2-21
Lifestyle modification and cognitive behavioral therapy in the treatment of MASLD

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Background and Aims: Treatment options of MASLD are limited due to lack of effective pharmacotherapy. The question is also their price and the possibility of their use on a large population of patients with MASLD. Therefore, our armamentarium should also include other approved options. Weight reduction is recommended in the treatment of MASLD, but no long-term controlled prospective study assessing the detailed course of MASLD during lifestyle modification has been available so far. We hypothesize that professionally tailored life-style counselling using professional lifestyle modification based on cognitive behavioral therapy (CBT) and mindfulness, especially mindful eating in patient with metabolic syndrome and MASLD will improve liver fat content and other non-invasive parameters of liver disease.

Method: Patients will be randomly assigned to a standard care or a professional lifestyle modification counselling during a 12-months follow-up. Fifty patients will receive professional lifestyle intervention using CBT and the so-called third wave of CBT, especially mindfulness. The patients will be guided by certified experts to increase motivation and to change eating and exercise habits, which will be mapped before and after the intervention. Fifty control subjects will have standard care with regular visits at an outpatient department of hepatology where only standard recommendations of lifestyle change and weight reduction will be given. During one year follow-up were patients periodically examined (anthropometry, bioimpedance, biochemistry, liver stiffness measurement using transient elastography, nuclear magnetic resonance spectroscopy. ClinicalTrials.gov ID: NCT05816915.

Results: We present preliminary results. Even with a small number of patients who had already completed the 12-month intervention (25%), there was a statistically significant reduction in liver fat ($p < 0.05$), liver function tests (ALT 45.2 ± 16 vs. 33.1 ± 10; $p = 0.02$) and parameters of glucose metabolism (glycemia 6.48 ± 1.5 vs. 5.23 ± 0.45; $p = 0.05$; insulinemia 17.5 ± 5.9 vs. 12.37 ± 6.4; $p = 0.009$) in the active group. In contrast, we observed no significant difference in ALT, parameters of glucose metabolism, or liver fat in the control group. Moreover, our results in the active group are supported by the fact that we obtained very similar results if we analyzed all patients in the active group already after 3 months of follow-up compared to controls.

Conclusion: We conclude that lifestyle modification based on cognitive behavioral therapy and mindfulness (especially mindful eating) is a suitable part of the armamentarium in the treatment of MASLD.

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PO2-22
Natural history of metabolic dysfunction-associated steatotic liver disease: A 5-year community-based follow-up study

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Background and Aims: Most of the studies of metabolic dysfunction-associated steatotic liver disease (MASLD) are based on clinically diagnosed patients; there is lack of studies documenting the burden of MASLD in the community.
The aim of this study was to document the prevalence, natural history and the incidence of MASLD in community-based Manitobans over 5 years of follow-up.

Method: A cohort of 1867 individuals enrolled at community-based MASLD screening clinics, was followed for 5 years. The prevalence of MASLD, liver biochemistry and non-invasive markers of hepatic fibrosis were measured at baseline and at the end of the 5-yr period. Incidence of MASLD among those free of the condition at baseline, was documented. Currently, 45% of the participants completed the 5-year follow-ups; their results are presented here.

Results: The overall prevalence of hepatic steatosis, detected by the portable ultrasound, was 54.5%. Among 854 participants who completed follow-up, 11% reversed their condition and had no detectable steatosis at the end of a 5-yr. period. Conversely, 33% of non-steatotic participants at baseline had detectable hepatic steatosis at 5-yr. examination.
Overall, at the end of follow-up, several important markers decreased compared to baseline: median weight of the participants decreased 3.5% (from 195 to 188 lbs., p 0.02), median BMI decreased from 31.2 to 30 (p 0.014), the proportion of obese individuals (BMI>=30) decreased from 57% to 50% ($p < 0.01$) of the cohort. Mean ALT decreased from 30.3 to 27.4 (p 0.04), and the proportion of those with ALT twice above normal (TAN) was 7.4% vs 4.4% at baseline vs 5-yr. respectively, p 0.05. Similarly, mean AST was 26.6 vs.24.2 and those with AST TAN was 3.2% vs. 1.7% respectively.
Mean fibrosis markers (liver stiffness and FIB-4) at baseline vs. 5-yr. were 6.4 vs. 6.6 kPa and 0.9 vs. 1.0 respectively. The proportion of participants with the liver stiffness <=7 kPa increased from 76% to 87%, $p < 0.0001$. The proportion of individuals with low FIB-4 (FIB-4<1.45) decreased from 85% to 79% (p 0.04), however, those with FIB-4>3.25 remained low at 1.2%.

Conclusion: Despite a decrease in some biomarkers, only 11% were successful in reversing their MASLD, while 33% developed MASLD in 5 years. This trend underlies the need for a better clinical management and public education.

PO3-01
Association between sarcopenia and coronary atherosclerosis in metabolic dysfunction-associated steatotic liver disease

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Background and Aims: This study aimed to assess the association between sarcopenia and incident coronary atherosclerosis in patients with metabolic dysfunction-associated steatotic liver disease (MASLD).

Method: Among individuals who underwent abdominal ultrasound during a health check-up between 2012 and 2016, those with MASLD were selected. Appendicular skeletal muscle mass (ASM), adjusted for body mass index (BMI), was used to define sarcopenia. Coronary atherosclerosis was defined as > 100 calcium score or 50% diameter stenosis on coronary computed tomography. Associations were estimated using a multivariable Cox model and confirmed using propensity score matching for covariates, including baseline fibrosis and cardiovascular risk burden. Sensitivity analyses were conducted.

Results: Among the 1,872 patients with MASLD, 149 (8.0%) and 1,723 (92.0%) were sarcopenic and non-sarcopenic, respectively. At baseline, sarcopenic MASLD patients were significantly older (57 vs. 47 years) and had a higher atherosclerotic cardiovascular disease (ASCVD) risk score (9.19 vs. 3.75) than those in the non-sarcopenic group (*P*s<0.05). During the median follow-up of 5.6 years, 373 patients (19.9%) developed coronary atherosclerosis. Sarcopenia was significantly associated with the risk of coronary atherosclerosis (hazard ratio [HR], 1.73, 95% confidence interval [CI], 1.28–2.34; *P*<0.001), together with age, hypertension, and cigarette use. The results from the sensitivity analysis (HR, 1.96; 95% CI, 1.23–3.11; *P*=0.004) and propensity score matching (HR, 2.00; 95% CI, 1.10–3.65; *P*=0.008) confirmed the significant association.

Conclusion: Sarcopenia was associated with the incidence of coronary atherosclerosis in patients with MASLD, independent of baseline fibrosis or the ASCVD risk burden.

PO3-02
Evaluation of long-term changes in liver function and structure in patients exposed to SARS-CoV-2 infection: a prospective study

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Background and Aims: Severe Acute Respiratory Syndrome – Coronavirus – 2 (SARS-CoV-2) binds to Angiotensin Converting Enzyme – 2 (ACE-2) receptor targeting various organs including liver. Liver involvement is a common feature of SARS-CoV-2 acute infection. A few studies have also described chronic hepatic alterations in patients with previous COVID-19 syndrome. We hypothesize that steatosis seen in COVID-19 patients reflects their metabolic profile and is not due to a persistent inflammation sustained by SARS-CoV-2 virus.

Method: We conducted a prospective study to evaluate long-term changes in liver function and structure in patients hospitalized for COVID-19. Patients without a prior known liver disease with mild to moderate COVID-19 were enrolled during hospitalization and reevaluated during follow-up visit at a medium 16 months. Complete blood panel with metabolic profile, body mass index (BMI), alcohol consumption and physical activity were compared between baseline and follow-up. Specific ultrasound scans were obtained during hospital stay and at follow-up to quantify steatosis using Steatoscore2.0.

Results: Among 55 eligible patients, 33 were included in the analysis and only 3 (9 %) had a new diagnosis of steatosis at follow-up. Steatoscore2.0 did not change significantly from baseline (1.7 versus 1.73, $p = 0.348$). At follow-up BMI raised and physical activity estimated by International Physical Activity Questionnaire reduced (26.3 vs 26.6, $p = 0.005$; 540 vs 480, $p = 0.015$ respectively). There was a statistically significant increase in total cholesterol (144.5 vs 187 $p = 0.003$) and Low-Density Lipoprotein (LDL) cholesterol (73.8 vs 141.8 $p = 0.003$). Inflammatory markers normalized at follow-up (C-Reactive Protein 41.1 [11.4 - 56.7] vs 0.8 [0.4 -1.9], $p < 0.001$); a similar pattern was also observed for ferritin levels: from 410.0 [235.0 - 974.0] to 91.0 [37.9 - 154.0], $p < 0.001$). Four patients (12%) had a 3-times rise in liver transaminase levels at baseline, and this was not confirmed at follow-up. Variation in Steatoscore2.0 correlated significantly with that of Triglyceride-glucose index (TyG index) as a surrogate of insulin resistance.

Conclusion: Functional and structural changes in liver might be a result of the altered metabolic profile in patients with previous SARS-CoV-2 infection.

PO3-04-YI

From MAFLD to MASLD: a real-life head-to-head comparison of MAFLD and MASLD criteria in estimating liver disease progression risk in not-lean and lean patients

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Background and Aims: The potential benefits of adopting Metabolic dysfunction-associated steatotic liver disease (MASLD) rather than Metabolic dysfunction-associated fatty liver disease (MAFLD) diagnostic criteria in defining the disease progression risk of steatotic (SLD) patients have never been systematically evaluated in real-life.
We aimed to compare the MASLD and MAFLD criteria in estimating the 3-year risk of advanced fibrosis (AF) progression and hepatocellular carcinoma (HCC) occurrence in not-lean (NL) and lean (L) SLD patients.

Method: We retrospectively analyzed the data stored in the University Hospital (UH)-official Health Documents Digitization Archive of 931 SLD patients admitted to UH “Luigi Vanvitelli” between January 2016 and May 2021, and followed up for 3 years. Based on baseline Body Mass Index (BMI), patients were subdivided into “L” (BMI <25 kg/m^2) (n:134) and “NL” (n:797) and, subsequently, by separately applying MAFLD and MASLD criteria, in NL-MASLD (n:206), NL-MASLD/MAFLD (n:481), NL-MAFLD (n:110), and L-MASLD (n:39), L-MASLD/MAFLD (n:68), L-MAFLD (n:27).

Results: MASLD and MAFLD criteria similarly estimated [MASLD: OR: 2.334, C.I.95%: 1.878 - 3.028, MAFLD: OR: 2.469, C.I.95%: 1.892 - 3.668, p < 0.0001; positive predictive value (PPV), MASLD: 0.800, C.I. 95%: 0.641-0.89 vs MAFLD: 0.785, C.I. 95%: 0.604-0.897, p: 0.076)] the overall 3-year risk of AF progression in NL-SLD, whereas in L-SLD, MAFLD criteria better estimated the overall 3-year risk of AF progression [PPV, MASLD: 0.571, C.I. 95%: 0.405-0.841 vs MAFLD: 0.714, C.I. 95%: 0.558-0.794, p: 0.006].
Multivariate competing risk analysis (adjusted for sex, age, diabetes, steatosis, and fibrosis severity) revealed diabetes (aHR: 2.113, C.I. 95%: 1.981-2.434, p:0.001), high-sensitivity-C-reactive protein (aHR: 1.441; C.I. 95%: 1.232-1.775; p:0.02) and Homeostatic-model-assessment-for-insulin-resistance (aHR: 1.228; C.I. 95%: 1.152-1.893; p:0.03) as associated with AF-progression in L-MAFLD.
Compared to MAFLD, MASLD diagnostic criteria similarly estimated the 3-year risk of HCC occurrence both in NL [HR: 1.104, C.I..95%: 0.824-1.593, p:0.741] and L [HR: 1.260, C.I.95%: 0.768-2.104, p:0.701] patients.

Conclusion: MASLD criteria better estimate the AF progression risk limitedly to L-SLD patients.

PO3-06-YI

The impact of diabetes mellitus and glucagon-like peptide-1 agonists on frailty for patients with advanced chronic liver disease

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Background and Aims: Glucagon-like peptide-1 agonists have beneficial anti-hyperglycaemic, cardiovascular, renal and weight loss effects for patients with type 2 diabetes mellitus (DM). Caution is recommended when using these medications in patients with severe advanced chronic liver disease (ACLD).
Frailty is a major determinant of adverse outcomes for patients with ACLD increasing the risk of ascites, hepatic encephalopathy, hospitalisation and infections. GLP-1 agonists have been shown to effect skeletal muscle loss. Given the risk of sarcopenia with these medications the authors reviewed the enrolment frailty measurements of a controlled single centre interventional study for patients with ACLD undergoing branched-chain amino acid (BCAA) supplementation. Patients taking GLP-1 agonists were compared against patients with DM who were not taking GLP-1 agonists and patients who did not have DM.

Method: The electronic record for all patients with ACLD taking part in a controlled single centre interventional study assessing BCAA supplementation were retrospectively reviewed to assess if they were taking GLP-1 agonists and if they had a diagnosis of DM at time of enrolment. Patient demographics, hand grip strength (HGS) and liver frailty index were recorded in descriptive statistics. The inclusion criteria for this trial were diagnosis of advanced chronic liver disease. Exclusion criteria were Barcelona Clinic Liver Cancer stage c or greater hepatocellular carcinoma, active non-hepatic cancer, breastfeeding, pregnancy or the use of anabolic steroids.

Results: 90 patients were recruited between 15/2/2024 and 2/10/2024. 7(7.78%) patients were taking GLP-1 agonists at enrolment. 13(14.44%) patients had DM but were not taking GLP-1 agonists at enrolment.
The median body mass index (BMI) for patients taking GLP-1 agonists was 37.4 (inter quartile range 31.28-40.34), 28.13 (26.13-30.51) for patients with DM not taking GLP-1 agonists and 27.2 (23.39-32.52) for patients without DM.
The median LFI for patients taking GLP-1 agonists was 3.89 (3.63-3.94), 4.10 (3.86-4.41) for patients with DM not taking GLP-1 agonists and 3.89 (3.72-4.52) for patients without DM. No patients taking GLP-1 agonists had low HGS (<16kg for female participants, <25 kg for male participants) compared to 7 (53.85%) for patients with DM not taking GLP-1 agonists and 27 (38.56%) for patients without DM.

Conclusion: The enrolment data for a controlled interventional study of patients with advanced chronic liver disease demonstrates similar median frailty metrics for patients taking GLP-1 agonists to patients with DM not taking GLP-1 agonists and patients without DM. Given their indication median BMI was, as expected, higher for patients taking GLP-1 agonists. Further work should aim to capture the progression of frailty metrics over time in patients with ACLD taking GLP-1 agonists.

PO3-09
Validation of PNPLA3 polymorphisms as risk factor for MASLD and MASH in Southeast Asian populations with MASLD

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Background and Aims: PNPLA3 rs738409 has been associated with an increased risk of liver-related events in patients with metabolic dysfunction-associated steatotic liver disease (MASLD). Information about the PNPLA3 rs738409 variant in Southeast Asia is relatively scarce compared to other regions. In this study, we investigated the prevalence of PNPLA3 rs738409 polymorphism in Thai patients with MASLD.

Method: This was a cross-sectional study in 30 patients with biopsy-proven MASLD from a tertiary center in Bangkok, Thailand. PNPLA3 (rs738409 c.444C>G) polymorphisms were evaluated.

Results: In patients with MASLD, the frequencies of PNPLA3 rs738409 CC and CG+GG were 44% and 56%, respectively. In patients with MASLD who has c>g variant, the frequencies of CG was 45% and GG was 11%. In patients with metabolic dysfunction-associated steatohepatitis (MASH), PNPLA3 CG+GG compared to CC was associated with higher AST level, ALT level, hepatic steatosis and liver stiffness by vibration controlled transient elastography.

Conclusion: We demonstrated that PNPLA3 CG+GG increase the risk of MASH progression among Thai patients. Moreover, prevalence of PNPLA3 CG+GG was not uncommon in Southeast Asian populations with MASLD.$

PO3-10
Determining the prevalence and characterizing the associated factors & health outcomes related to metabolic dysfunction associated steatotic liver disease in patient with type2 diabetes mellitus at SQUH

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Background and Aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) encompasses a spectrum of liver conditions, ranging from simple steatosis to cirrhosis, with potential progression to hepatocellular carcinoma. Its prevalence among patients with type 2 diabetes mellitus (T2DM) globally is estimated at 30%, with a notable burden in the Middle East. This study aimed to investigate the prevalence of MASLD and metabolic dysfunction-associated steatohepatitis (MASH) in patients with T2DM and assess associated metabolic and health outcomes, particularly diabetic complications such as retinopathy, neuropathy, and nephropathy.

Method: A prospective cohort study was conducted at Sultan Qaboos University Hospital, enrolling 245 patients aged 18 and above diagnosed with T2DM based on ADA criteria from September 2022 to December 2024. Data collection included demographic details, body mass index (BMI), duration of diabetes, HbA1c, liver enzymes (ALT, AST), lipid profile, albumin/creatinine ratio, diabetic complications (neuropathy, retinopathy), and liver stiffness measured via transient elastography. Multivariate regression analysis was performed to identify independent risk factors for liver steatosis and fibrosis.

Results: Of the 245 participants (mean age 57.96 ±11.62 years, 39.2% male), the prevalence of MASLD was 89.8%, while 41.6% exhibited significant fibrosis. Higher BMI (29.01 kg/m²) was strongly correlated with both steatosis and fibrosis ($p < 0.01$). Elevated levels of triglycerides, ALT, total cholesterol, and LDL were significantly associated with liver steatosis ($p < 0.01$). Fibrosis was more prevalent in patients with higher ALT and longer duration of diabetes. Diabetic complications, such as retinopathy and nephropathy, were identified as independent risk factors for MASLD progression. Multivariate analysis revealed that BMI (OR 1.15, 95% CI: 1.09-1.22), duration of T2DM, and hypertensive status were key predictors of advanced liver disease.

Conclusion: The study highlights a high prevalence of MASLD among patients with T2DM, with significant associations between metabolic dysregulation and liver health. BMI, lipid profile, and diabetic complications serve as important predictors of disease progression, underscoring the need for integrated management strategies in diabetic care to mitigate liver related morbidity.

PO3-11
Prevalence of multifactorial steatotic liver disease: Why it should be included in the international classification of steatotic liver disease

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Background and Aims: The recent introduction of the terms Metabolic dysfunction-Associated Steatotic Liver Disease (MASLD) and Steatotic Liver Disease (SLD) has provided a new way of approaching patients with fatty liver. The new terminology has been associated with more specific criteria for the definition of each subgroup of SLD individually. However, in clinical practice hepatologists often encounter patients with more complex phenotypes satisfying criteria for the inclusion in more than one subgroup (e.g. obese/overweight patients having at the same time chronic HCV infection or hypothyroidism or drug-related steatosis). The prevalence of these complex phenotypes and the clinical relevance of them is unknown.

Method: We analyzed data from clinical records of consecutive outpatients who underwent ultrasound examination at the Liver Unit of the University of Foggia (Italy) between January 2023 and September 2024. Inclusion criteria were: 1) detection of liver steatosis by liver ultrasound (any grade) 2) age ³18 years. Data on medical history and medication were recorded and physical examination was also performed. All patients were classified according to the definition provided by the current guidelines as MASLD, ALD (alcoholic liver disease), MetALD, secondary liver steatosis or cryptogenic. Patients with secondary causes of liver steatosis were subclassified according to the number of factors potentially causing secondary liver steatosis (simple secondary liver steatosis or complex secondary liver steatosis when more than one cause of secondary hepatic steatosis were recorded). Patients were categorized as fitting to current classification when they satisfied criteria for only one class of SLD. Steatosis in patients with criteria for inclusion in more than one subgroup of SLD were considered “multifactorial” and analyzed separately.

Results: We included in our final analysis 1,121 patients who referred to our Liver Unit. 28% of patients had pure MASLD; 20% of patients satisfied criteria for MetALD; 2% had ALD and 1% had cryptogenic steatosis. 553 patients (49%) had inclusion criteria for more than one subgroup. They were considered multifactorial because they were not classified appropriately by current guidelines. Multifactorial SLD showed a different distribution by age, gender and comorbidities in comparison with the other classes of SLD.

Conclusion: A new entity called multifactorial steatotic liver disease should be included in international guidelines. Patients with multifactorial SLD could require specific indications for long-term management based on specific risk of morbidity or mortality which is currently unknown.

PO3-12-YI
The pattern of liver enzymes enhances the prognostic value of the Fibrosis-4 index for patients with metabolic dysfunction–associated steatotic liver disease

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Background and Aims: The Fibrosis-4 index (Fib-4) is a simple, non-invasive tool to screen for severe liver fibrosis and has prognostic value in metabolic dysfunction-associated steatotic liver disease (MASLD) patients. Recent studies suggest that a cholestatic pattern of liver enzymes is associated with higher rates of liver-related outcomes and poorer patient prognosis in MASLD. We sought to evaluate the predictive effectiveness of Fib-4, the pattern of liver enzymes, or their combination in determining liver-related outcomes, major adverse cardiac events (MACE), and total mortality in MASLD.

Method: This longitudinal study analyzed a large dataset of 200,000 individuals diagnosed with MASLD and/or obesity with cardiovascular risk factors. Liver-related events, MACE, and all-cause mortality were recorded over a 15-year follow-up period.

Results: Patients with a cholestatic pattern of liver enzymes had higher incidence of ascites (1.6% vs 0.6%, p<0.0001), myocardial infarction (MI) (6.2% vs 4.4%, p<0.0001), heart failure (HF) (14.6% vs 6.1%, p<0.0001), and a higher overall mortality in 15-years. Stratifying patients by Fib-4 score (Fib-4<1.3 low; 1.3< Fib-4<2.67 medium; Fib-4>2.67 high) revealed higher incidence of liver-related outcomes and MACE with higher Fib-4 scores. Incidence of ascites was 13.7%, 1.1%, and 0.2% for high, medium, and low Fib-4, respectively (p<0.0001). Incidence of HF was 34.9%, 14.4%, and 3.3%, respectively (p<0.0001). All-cause mortality in 15 years was significantly higher with higher Fib-4 scores (p<0.0001). Combining both parameters, cholestatic patients had worse outcomes than hepatocellular patients within each Fib-4 group. Importantly, within each Fib-4 category (i.e low, medium or high) cholestatic patients had a long-term survival that was comparable to patients with a higher Fib-4 category but with a non-cholestatic pattern.

Conclusion: Fib-4 is a strong prognostic indicator for MASLD patients. Combining Fib-4 with the pattern of liver enzymes enhances stratification into risk groups. This combined scoring approach can be a valuable tool to better define high-risk MASLD patients.

PO3-16-YI
Gaps in MAFLD screening and management: a retrospective audit of patients at cardiometabolic risk in secondary care

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Background and Aims: Significant gaps exist between cross-specialty guidelines and the management of cardiometabolic patients at high risk for MAFLD, particularly those referred to secondary specialist settings. A siloed approach and inadequate communication in secondary care hinder effective disease management and efforts to reduce the MASLD burden. The OPTIMA-NASH (Optimizing Management of Comorbid NASH through Multidisciplinary Integration and Artificial Intelligence Alliance) study aims to identify and address these practice gaps.

Method: This single-center, retrospective, longitudinal practice improvement initiative, based on a clinical audit, includes patients with at least one cardiometabolic risk (CMR) factor (prediabetes, type 2 diabetes, obesity, dyslipidemia, arterial hypertension, atherosclerotic cardiovascular disease) evaluated at Niguarda outpatient clinics. Over 24 months, we classified patients based on their CMR into high (1 criterion) or very high (2 or more criteria). We assessed the availability of data needed to calculate MAFLD screening and progression risk scores.

Results: A total of 854 patients were reviewed, with a mean age of 65.8 ± 15 years and 485 (56.8%) were male. Notably, 41.3% had diabetes, 27.5% were obese (mean BMI 27.9 ± 4.9), 29.6% had mixed dyslipidemia and 59.3% were hypertensive. Additionally, 15.6% had ischemic heart disease, 25.1% had atrial fibrillation, 2.8% heart failure, 4.8% had a history of TIA/stroke, and 10.2% had chronic kidney dysfunction (eGFR < 60 ml/min/1.73 m²). Overall, 692 (81.0%) patients had 2 or more risk factors, reflecting very high CMR. Data to calculate the FIB-4 score were available for 311 records. Mean FIB-4 was 1.7 ± 1.67; 159 patients (51%) had a FIB-4 > 1.3, indicating a need for transient elastography (TE) measurement. NAFLD-Fibrosis score (NFS) data were available for 162 patients. Mean NFS was -1.224 ± 1.733; 85 (52%) had an NFS > -1.455. TE was documented for 153 patients and mean TE was 8 kPa ± 6.9. Both FIB-4 and NFS demonstrated moderate accuracy for predicting fibrosis stages ≥ F3. AUROCs were 0.768 (95%CI 0.617-0.919) for FIB4 and 0.739 (95%CI 0.568-0.909) for NFS, respectively, consistent with literature on MASLD. Controlled attenuation parameter (CAP) measurements were available for only 80 patients, yielding a mean value of 306.5 dB/m ± 49.9; 62 patients (77.5%) had a CAP > 275 dB/m.

Conclusion: In this secondary care setting, a minority of patients with cardiometabolic risk factors were screened for MASLD, highlighting critical areas for improvement in practice. This gap underscores the need for improved protocols and enhanced communication between specialties to facilitate timely screenings and interventions. By addressing these pitfalls, we can better manage MASLD and reduce its associated burden in at-risk populations.

PO3-17
Liver fibrosis, based on Fibrosis-4 Index, is associated with coronary stent failure and cardiovascular outcomes in patients after coronary stenting

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Background and Aims: Advanced liver fibrosis is associated with adverse cardiovascular outcomes and highly prevalent in patients with coronary artery disease (CAD). However, assessment of liver fibrosis is frequently neglected in clinical practice. This large prospective cohort study aims to explore the association between liver fibrosis and adverse clinical outcomes in patients with CAD undergoing coronary artery stenting.

Method: The study included patients who underwent drug-eluting stent (DES) implantation. These patients were categorized into three groups based on their FIB-4 scores: FIB-4 ≤ 1.3 (low probability of advanced fibrosis), FIB-4 between 1.3 and 2.67 (intermediate probability of advanced fibrosis), and FIB-4 > 2.67 (high probability of advanced fibrosis). The primary outcome was stent failure, defined as either in-stent restenosis or stent thrombosis. The secondary outcome was major adverse cardiovascular events (MACE), including all-cause mortality, myocardial infarction, heart failure or ischemic stroke. Cox proportional hazard models were used to examine the association between the FIB-4 score and these outcomes.

Results: Of 13,987 enrolled CAD patients, 3,173 (22.7%) had a FIB-4 score >2.67. During a median of 3.0 (IQR: 1.0–6.4) years, 1,046 patients experienced stent failure and 7,302 developed MACE. Patients with FIB-4 >2.67 had the highest incidence rate of stent failure per 100 persons-years [2.38 (95%CI: 2.08-2.67)] and MACE [21.82 (95% CI: 21.02-22.60]. After multivariate adjustment, FIB-4 >2.67 was significantly associated with an increased risk of developing stent failure [HR 1.27 (95%CI: 1.06-1.52); P =0.010] and MACE [HR 1.79 (95% CI: 1.67-1.91); P <0.010]. Subgroups and sensitivity analyses confirmed these findings.

Conclusion: A FIB-4 score >2.67 is present in approximately 1/4 of CAD patients after coronary stenting. These patients have an increased risk of stent failure and adverse cardiovascular outcomes.

PO3-18-YI

Metabolic dysfunction-associated steatotic liver disease (MASLD) in patients with inflammatory bowel disease (IBD): A single-center prospective study.

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Background and Aims: Patients with inflammatory bowel disease (IBD) have an increased risk of developing metabolic dysfunction-associated steatotic liver disease (MASLD). This study aims to assess the prevalence of MASLD in patients with IBD and evaluate the association of MASLD with demographic, laboratory, and clinical characteristics.

Method: A total of 101 adult IBD patients were enrolled in the current study [Crohn's disease (CD) / Ulcerative colitis (UC) / unclassified colitis: 57/ 42/ 2, male/female: 60/41, mean age: 43.5 years (range: 15-86) mean age of IBD diagnosis: 35.9 years (range: 9-85)]. Fifty-nine patients underwent abdominal ultrasound, clinical examination, and laboratory testing to diagnose MASLD.

Results: Of the 59 patients evaluated, 23 (39%) were diagnosed with MASLD [CD/UC: 15/7; male/female: 14/9, mean age: 46 years (range: 22-72), mean age of IBD diagnosis: 37.4 years (range: 9-72)]. Patients with MASLD had significantly increased rates of central obesity ($p = 0.026$, OR = 3.545) and overall obesity ($p = 0.002$, OR = 16.0) compared to non-MASLD patients. Additionally, MASLD patients exhibited significantly higher BMI ($p = 0.013$) and fasting plasma glucose levels ($p = 0.027$). No significant differences were observed between groups regarding age ($p = 0.236$), age at IBD diagnosis ($p = 0.403$), sex ratio ($p = 0.847$), disease type ($p = 0.248$), smoking status ($p = 0.529$), or liver function markers, including SGOT ($p = 0.168$), SGPT ($p = 0.139$), γ-GT ($p = 0.825$), ALP ($p = 0.615$), urea ($p = 0.772$), platelets ($p = 0.080$), total bilirubin ($p = 0.075$), direct bilirubin ($p = 0.121$), INR ($p = 0.825$), creatinine ($p = 0.766$) and albumin ($p = 0.917$). Lastly, no significant differences were found regarding diabetes mellitus ($p = 0.275$), portal hypertension ($p = 0.831$), hypothyroidism ($p = 0.294$), hyperlipidemia ($p = 0.700$), history of anti-TNF treatment ($p = 0.629$), or clinical activity markers of IBD (CDAI, $p = 0.481$; Trulove-Witts, $p = 0.344$).

Conclusion: MASLD is prevalent among IBD patients and is significantly associated with central and overall obesity, as well as increased fasting plasma glucose levels. These findings suggest that steatotic liver, along with potential diabetes mellitus, may be early manifestations of metabolic syndrome in IBD patients, preceding other cardiometabolic disorders.

PO3-20-YI

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

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Background and Aims: Hepatocellular carcinoma (HCC) commonly develops in patients with liver cirrhosis; however, non-cirrhotic metabolic dysfunction-associated steatotic liver disease (MASLD) also presents a significant HCC risk. Developing effective screening protocols for MASLD-HCC necessitates identifying “at-risk” patients for targeted surveillance. Liver stiffness measurement (LSM) using two-dimensional shear wave elastography (2D-SWE), together with clinical and demographic parameters could enhance MASLD-HCC risk stratification. The utility of LSM performed with the SuperSonic Imagine (SSI) ultrasound machine was evaluated to predict HCC risk in MASLD patients.

Method: Retrospective study conducted on a consecutive prospective cohort of MASLD patients from a tertiary liver disease center in Bologna. All patients underwent baseline LSM-SSI and attended follow-up visits every 6-12 months. Patients with less than 6 months follow-up, unavailable baseline 2D-SWE, or prior HCC were excluded. LSM-SSI cut-offs based on recent meta-analysis data were applied. Primary endpoint was the incidence of de novo HCC, with hepatic decompensation and portal vein thrombosis (PVT) as competing risks. Univariate competing-risks regression (CRR), using Fine and Gray’s proportional subhazards method, identified HCC risk predictors.

Results: Among 352 patients (mean follow-up: 38 ± 26 months), the average age was 56.4 ± 13.4 years, and the BMI was 29.6 ± 4.4 kg/m². At baseline, 73% of patients had LSM-SSI <7.37 kPa, 27% ≥7.37 kPa, and 8% >15.59 kPa. All patients with liver events had baseline LSM-SSI ≥7.37 kPa. Among these, 9.5% developed HCC, 6.3% experienced the first liver decompensation, and 2.1% developed PVT. For non-cirrhotic patients (LSM-SSI ≤15.6 kPa), baseline LSM-SSI was significantly associated with HCC risk (HR 1.542, 95% CI 1.269-1.875, p<0.0001). Using a significant fibrosis cut-off of 8.28 kPa, LSM-SSI demonstrated 66.7% sensitivity, 88.1% specificity, and 99.6% negative predictive value for HCC (AUC: 0.770) and a number needed to diagnose of 25.2. Multivariate analysis identified LSM-SSI (HR 1.052, 95% CI 1.030-1.075, p<0.001), type 2 diabetes mellitus (HR 4.555, p=0.038), and gamma-glutamyl transferase (HR 1.004, p=0.003) as independent predictors of MASLD-HCC.

Conclusion: For non-cirrhotic MASLD, an LSM-SSI <7.37 kPa effectively rules-out the need for HCC screening, whereas patients with significant fibrosis may benefit from HCC surveillance based on elevated LSM-SSI and other identified risk factors.

PO3-22-YI
Determinants of liver stiffness improvements and worsening in metabolic dysfunction associated steatotic liver disease: Insights from two cohorts

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Background and Aims: Liver stiffness measurement (LSM) is key for monitoring disease progression in patients with Metabolic dysfunction-Associated Steatotic Liver Disease (MASLD). Identifying predictors of LSM change could enhance prognosis and guide management. This study assessed metabolic and clinical factors that impact LSM changes over time in two large cohorts of MASLD patients.

Method: We included MASLD patients with ≥ 2 outpatient visits from 2014 to 2022. Follow-up LSM was > 6 months from baseline. LSM worsening was defined as >30% increase if baseline LSM was ≥ 5 kPa, or as follow-up LSM > 6 kPa if baseline was < 5 kPa. LSM improvement was defined as > 30% LSM decrease (if baseline > 6 kPa). Alternate analyses used a > 40% change cut-off.
Significant weight and HbA1c changes were defined as > 5% and > 10%, respectively.
We calculated the difference between actual and “expected” FIB-4 at follow-up (based on the patient’s age at the follow-up visit, but using the blood tests performed at the first visit), and we defined “expected” Fibroscan improvement or worsening based on changes in weight, HbA1c, ALT, and FIB-4, where at least one variable showed a corresponding improvement or worsening while the others remained stable.

Results: Among 400 enrolled (mean age 54, 70% male), median follow-up was 20 months.
LSM improved by > 30% in 13.5% of patients and worsened > 30% in 11.3%; using a > 40% cut-off, 6.5% showed improvement and 6.0% showed worsening. Only about one-third of patients with LSM > 30% or > 40% changes showed corresponding shifts in FIB-4.
In multivariate logistic regression analysis, LSM worsening > 30% was independently associated with increased HbA1c (OR 1.03), longer follow-up (OR 1.07) and total cholesterol change (OR 0.97, indicating a lower likelihood of LSM worsening), while LSM improvement > 30% correlated with weight reduction (OR 0.89). Similarly, in multivariate logistic regression analysis, LSM worsening > 40% was independently associated with an increase in HbA1c (OR 1.04), while LSM improvement > 40% was independently associated with weight reduction (OR 0.89).
“Expected” Fibroscan improvement was linked with actual Fibroscan reduction (p=0.002), showing high negative predictive values (NPV: 92-96%), but expected worsening did not predict actual LSM increase (NPV: 72-89%).

Conclusion: About 20% of MASLD patients experienced significant LSM changes over 20 months. Weight reduction improved LSM, while increased HbA1c predicted worsening LSM, supporting a focus on metabolic management. The variables contributing to “expected” Fibroscan changes may aid in guiding diagnostic pathways but require a comprehensive, multidisciplinary model of care.

PO3-23-YI
Prognostic significance of ELF test compared to liver elastography and liver biopsy in patients with metabolic dysfunction-associated steatotic liver disease (MASLD)

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Background and Aims: Liver fibrosis stands out as the main prognostic risk factor in MASLD. The enhanced liver fibrosis (ELF) score is a composite of direct fibrosis biomarkers that reflect extracellular matrix turnover. While the ELF test exhibits high diagnostic accuracy for advanced liver fibrosis in MASLD patients, its role as a prognostic biomarker remains uncertain. Our aim is to compare the prognostic effectiveness of ELF, liver stiffness measurement (LSM), FIB4, and liver histology in patients with MASLD.

Method: We retrospectively enrolled patients with MASLD who underwent liver biopsy between 2013 and 2023. The ELF score was automatically using a serum sample collected at baseline. FIB4 computation, LSM with Fibroscan and liver biopsy were performed at baseline. Liver fibrosis stage was assessed according to the NASH CRN Scoring System. The primary outcome was a composite endpoint including all-cause mortality, hepatocellular carcinoma, liver transplantation or complications related to cirrhosis (ascites, variceal bleeding, hepatic encephalopathy, MELD≥15). Subjects were stratified based on existing literature cut-offs for ELF (<9.8, 9.8-11.2, >11.2), LSM (<10, 10-15, >15 kPa), FIB-4 (<1.3, 1.3-2.67, >2.67), and histology (F≤2, F3, F4) to assess the risk of occurrence of the primary outcome.

Results: We included data of 289 patients (30.4% female, median age 50y [IQR 39-58]). Over a median follow-up time of 41 months (IQR 21-68), the composite endpoint occurred in 34 (11.8%) patients. The frequency of the primary outcome exhibited a stepwise increase with ELF scores <9.8 (0.5%), 9.8 to 11.2 (14.5%) and >11.2 (69.7%). Survival curves for comparisons between groups revealed significant differences for all index tests based on pre-defined histological and non-invasive test stratification (Log Rank test p <0.05). At multivariate Cox regression analysis, ELF and liver histology were significant predictors of the primary outcome after adjusting for gender, diabetes, age and BMI. (ELF > 11.2 vs < 9.8 HR 132.7 [95%CI 15.6-1127.4 p<0.01], 9.8-11.2 vs <9.8 HR 22.5 [95%CI 2.8-184.3 p=0.04]) (F4 vs F≤2 HR 92.0 [95%CI 20.1-421.9 p<0.01], F3 vs F≤2 HR 10.2 [95%CI 2.3-45.5 p=0.05]). Furthermore, the intermediate and high risk group defined by LSM had a significantly higher risk of developing the composite outcome compared to the low-risk group (LSM 10-15kPa vs <10kPa HR 5.51 [95%CI 1.25 – 24.18 p=0.02], LSM >15kPa vs <15 kPa HR 22.89 [95%CI 6.17 – 84.94 p<0.01]). Intermediate risk group according to FIB4 displayed no significant higher risk of composite outcome compared to low-risk group (HR 2.87 [95%CI 0.53 – 15.55 p=0.22]).

Conclusion: The ELF test demonstrated comparable performance to histologically evaluated fibrosis in forecasting clinical outcomes. It should be regarded as a viable alternative to liver biopsy for conducting prognostic assessments in patients with MASLD.

PO3-24
Dynamic change in the enhanced liver fibrosis test to predict adverse outcomes in chronic liver disease

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Background and Aims: The use of non-invasive markers to predict adverse outcomes in chronic liver disease is essential for patient management and risk stratification. Serial liver stiffness measurements have shown predictive value for hepatic decompensation, and a single Enhanced Liver Fibrosis (ELF) score has also demonstrated prognostic utility. In this study, we aimed to evaluate the performance of serial ELF scores in predicting adverse liver outcomes.

Method: In this single-centre, retrospective study (June 2018 to July 2024), we used a Concordance index (c-index) analysis within a Cox proportional hazards model to evaluate the impact of single ELF scores and time-related serial ELF changes on major adverse liver outcomes (MALO). Age, sex, body mass index (BMI), metabolic-associated liver disease (MASLD), alcohol-related liver disease and smoking history, were assessed. Serial ELF scores were also categorized according to National institute for health and care excellence (NICE) guidelines with a cutoff of 10.51, assigning participants to categories of "Stay low," "Go low," "Go high," or "Stay high." C-index was calculated to test the discriminative ability of serial or categorical ELF tests.

Results: Our cohort of 398 participants had a median follow-up time after an initial ELF test of 2.4 ± 1.4 years, during which time 24 (6 %) patients experienced MALO. In multivariate Cox proportional hazards model, changes in the ELF test over time were significantly associated with MALO: hazard ratio (HR) 1.44 ($p = 0.0013$). BMI showed a protective effect with an HR of 0.90 ($p = 0.013$). Participants with MASLD or an alcohol related liver disease showed an elevated risk (HRs of 1.44 and 1.55 , respectively), though neither reached statistical significance. The model's overall c-index of 0.712 indicates acceptable predictive accuracy. The single, initial, ELF score showed stronger predictive power for with a HR of 3.05 per unit increase ($p < 0.001$) and a c-index of 0.889. The NICE-categorized ELF changes (e.g., "Go low," "Go high," and "Stay high") were significantly associated with MALO, with HRs of 35.9 , 38.6 , and 242.0 , respectively, compared to "Stay low." This model yielded a c-index of 0.922 , underscoring the strong predictive accuracy of serial ELF measurements for liver-related outcomes.

Conclusion: Serial ELF measurements demonstrated high predictive accuracy for liver-related outcomes, with changes categorized by NICE cutoff showing substantial HRs, particularly for patients where the ELF remained above 10.51. Serial use of ELF can support identification of patients at high risk of adverse clinical outcomes.

PO4-01-YI
The impact of cardiopulmonary fitness on steatotic liver disease in a combined lifestyle intervention for adolescents with obesity

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Background and Aims: The interplay between liver and muscle health is incompletely understood, especially in adolescents. Cardiopulmonary exercise testing (CPET) evaluates cardiopulmonary fitness. Its association with metabolic-dysfunction associated steatotic liver disease (MASLD) is poorly characterized. In this work, patients' initial cardiopulmonary fitness and its association with MASLD at baseline and at 6 months during lifestyle intervention was assessed.

Method: Adolescents with (severe) obesity were prospectively followed-up at a residential care center in the context of a structured, combined lifestyle intervention. CPET was performed at the start using a step-wise load increasing protocol. Raw data were analyzed by 2 independent assessors, and the maximal parameters were obtained. Lean mass was obtained by DEXA scanning. MASLD was defined as the presence of liver steatosis on ultrasound, and it was categorized into 3 severity degrees by an experienced assessor. Adolescents were grouped based on the presence or absence of MASLD, and improvement was defined as at least one category amelioration on ultrasound.

Results: 86 adolescents with obesity, 45 boys and 41 girls, with a mean age of 15.8 years, were included. The mean BMI z-score was 2.84. 62 adolescents (72.1 %) had MASLD, predominantly males (58.1 %). Between the steatosis groups, the maximal cardiopulmonary fitness (expressed as VO2max/kg and percentage of the predicted VO2max ; VO2max%) was equally distributed. However, VO2max on lean mass was significantly lower in patients with MASLD: 38.1 (34.1 – 42.4) vs. 33.9 (30.3 – 40.3) ml/kg/min (p = 0.033). This highlights the importance of fat-free mass on cardiopulmonary fitness and MASLD. Next, data on improvement of MASLD after 6 months were available for 55 patients, of which 41 (74.5 %) improved. Strikingly, a higher VO2max/kg and VO2max% at baseline were associated with steatosis improvement, with a median (IQR) of improvement vs. no improvement of respectively 18.1 (15.1 – 21.9) vs. 15.4 (13.7 – 18.4) ml/kg/min (p = 0.020) and 59 (49 – 71) vs. 50 (44 – 59) % (p = 0.023). Moreover, this was also observed for VO2max on lean mass: 36.5 (30.4 – 41.5) vs. 32.4 (28.0 – 34.1) ml/kg/min (p = 0.048). This raises the hypothesis that baseline cardiopulmonary fitness, independent from (fat) mass, is an important contributor to MASLD improvement during lifestyle intervention in adolescents with obesity. As a sensitivity analysis, we alternatively defined MASLD resolution as CAP < 248dB/m when baseline CAP values were > 248dB/m. Confirming our findings, VO2max/kg (p = 0.002), VO2max% (p = 0.003) and VO2max on lean mass (p = 0.006) were lower in the non-resolution group.

Conclusion: Cardiopulmonary fitness is linked with liver health. Baseline cardiopulmonary fitness in adolescents with obesity is a possible predictor for MASLD improvement in a combined lifestyle intervention.

PO4-03
The effect of obesity and hepatic steatosis on the course and outcomes of COVID 19-associated pneumonia in patients with metabolic dysfunction-associated steatotic liver disease

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Background and Aims: Obesity is a recognized risk factor for the development of metabolic dysfunction-associated steatotic liver disease (MASLD). Excess fat accumulation leading to innate and acquired dysimmunity may be responsible for increased adverse outcomes in patients with COVID-19 and MASLD. The aim of the study is to compare the effects of obesity and HS on the course and outcomes of COVID-19-associated pneumonia (COVID-19 AP).

Method: The prospective cohort study included 100 patients (>18 years old) admitted to the hospital with COVID-19 AP. The presence of obesity was defined as a body mass index (BMI) of more than 30 kg/m^2. Waist circumference (WC) more than 80 cm in women and more than 94 cm in men was regarded as a abdominal type of obesity. Liver density < 40 HU according to computed tomography (CT) data was used as a criterion for HS. The laboratory markers, severity of lung damage, need for biological therapy (BT), duration of hospitalization, and deaths were evaluated.

Results: 2 groups were identified: 39 obese patients and 60 control groups, 1 patient was excluded due to alcohol abuse (AUDIT 17), comparable in age (55.03 ± 14.38 and 58.22 ± 16.66, p = 0.32), the presence of hypertension (p = 0.90) and type 2 diabetes mellitus (T2DM) (p = 0.42). In the obese group there were more women (74.4% and 51.7%, p = 0.024), significantly higher BMI (34.08 ± 4.34 and 25.7 ± 3.29, p < 0.001) and WC (102.13 ± 12.09 and 88.77 ± 10.56, p < 0.001), HS (43.6% and 13.3%, p=0.001). Groups were comparable in the volume of lung lesions (p = 0.09), but a more severe course was observed in patients with HS (p = 0.04). Patients of the HS and obesity were significantly more often prescribed biological and antibacterial therapy. We assessed the components of the metabolic syndrome as independent risk factors. The relationship between the need for BT with HS (OR–11.4, 95% CI [3.1 – 41.5], p<0.001) and obesity (OR – 2.3, 95% CI [1.02 – 5.4], p = 0.04) has been established. To eliminate the possible interfering effect of HS, the Mantel-Hensel test was used, the adjusted OR was 1.39 95% CI [0.54 - 3.5], p = 0.49. Associations with T2DM (p = 0.61) and hypertension were not revealed (p = 0.76). An assessment of in-hospital outcomes showed that the presence of obesity did not significantly affect the duration of hospitalization (14.97 and 15.47, p = 0.72) and mortality (p = 0.32), the presence of HS significantly increased it (p = 0.014).

Conclusion: The established relationship between the need for BT and obesity is associated with a higher prevalence of liver steatosis in the study group. The presence of HS had a significant impact on the course and outcomes of COVID-19 AP. As an independent risk factor, it requires timely diagnosis and closer monitoring. Detection of HS using CT data during the study of the underlying disease can become an important diagnostic step that determines the prognosis of the disease, risk stratification tool in patients with MASLD.

PO4-05
A prove-of-concept study of pioglitazone low dose vs standard dose for the treatment of metabolic dysfunction-associated steatohepatitis

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Background and Aims: Pioglitazone provides benefit for metabolic dysfunction-associated steatohepatitis (MASH) treatment but can also have side effects. This study aims to compare efficacy of low dose pioglitazone (15mg) versus standard dose (30mg) among type 2 diabetes mellitus patients with MASH focus on decrement of steatosis, improvement of liver enzyme defined by normalized ALT and compare side effect in both arms in short-term regimen.

Method: This study was prove-of-concept study conducted with double blinded randomized controlled trial, including patients with MASH and type 2 diabetes mellitus. Subjects were assigned to pioglitazone low dose (15 mg/day) and standard dose (30 mg/day) for 12 weeks, their hepatic fat content was measured by computed tomography via hepatic attenuation index calculation and controlled attenuation parameter by fibroscan, compared before prescribe pioglitazone and after take a drug for 12 weeks.

Results: Pioglitazone, both low dose and standard dose regimens significantly improve hepatic steatosis resolution (50% vs 30%, p value 0.003) and improvement of liver enzyme (60% vs 50%, p-value 0.04). Changes in hepatic steatosis and improvement of liver enzyme were similar with different doses of pioglitazone (15 or 30 mg/day) and were independent of blood glucose control. Adverse events were markedly found more in the pioglitazone 30 mg/day group (30% vs 7.7%).

Conclusion: Short term treatment with pioglitazone even at low dosage significantly improved liver steatosis and inflammation. The beneficial effects of pioglitazone on MASH were independent of blood glucose control.

PO4-06-YI
Multidisciplinary management combining hepatologist counseling, cognitive/behavioral therapy, and nutritional support (the “CoCoNut” protocol) improves the clinical outcomes of MASLD patients

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Background and Aims: Metabolic dysfunction-associated Steatotic Liver disease (MASLD) is a systemic disorder severely burdened by various extra-hepatic complications. In this context, acute cardiovascular events (ACE) represent a real plague dramatically affecting mortality, suggesting the cruciality of holistic approaches.
Although several drugs have been tested to target dysmetabolic comorbidities, lifestyle modifications remain the cornerstone intervention. Unfortunately, the dietary-behavioral prescription is constantly limited by poor compliance, and, despite emerging evidence supporting behavioral therapy's relevance, the real benefits of offering motivational support to MASLD individuals remain unexplored in real life.
Considering this, we aimed to evaluate the effectiveness of a multidisciplinary (hepatologist-nutritionist-psychologist- “CoCoNut”) management in improving clinical outcomes in MASLD, via ameliorating adherence to specialistic tailored indications.

Method: MASLD patients (n.286) were consecutively enrolled and randomized in three cohorts: 72 followed generic hepatologist-provided advice (“H”), 71 also received a nutritionists-prescribed individualized intervention (“HN”) (H+N= “standard of care”), and 143 were treated with an approach additionally involving cognitive/behavioral-based psychological support (“HNP”) (“experimental-group”). Baseline anthropometric, biochemical, clinical, liver stiffness (LSM), controlled attenuation parameter (CAP), lifestyle habits, and body composition values were recorded. Along 18 months, semestral hepatological (for all), nutritional (H and HN), and psychological (HNP) follow-ups reassessed parameters and evaluated compliance.

Results: After 18 months, the prevalence of patients achieving a $\geq$10% decrease in body weight was significantly higher in HNP (HNP:62.09%; HN:44.9%; H:35.8%; HNP vs HN, p:0.01; HNP vs H, p:0.0002). In HNP, a significant improvement in Homeostatic-model-assessment-for-insulin-resistance (p:0.001), HDL ($p < 0.0001$), LSM (p:0.007), CAP (p:0.002), and fat-mass ($p < 0.0001$) was observed. Loss of compliance rate was significantly lower in HNP (HNP:12.08%; HN:34.7%; H:45.8%; HNP vs HN, HNP vs H, p:0.001) Relevantly, HNP patients presented a significantly lower risk of ACEs [HR: 0.497, IC (0.236-0.751) 95%, p:0.04)]. Logistic regression analysis (adjusted for sex, age, drug administration, and cardiovascular risk factors) revealed that HNP adherence was significantly associated with lower ACE occurrence (aOR: 0.81; C.I. 95%: 0.55-0.97; p:0.02). Large family, dynamic work, and city life emerged as social factors influencing compliance (OR: 2.11, 1.78, 1.12) (all $p < 0.05$).

Conclusion: Integrating standard hepatological-nutritional with psychological support significantly improves the metabolic and clinical outcomes of MASLD patients.

PO4-08-YI
Effect of diabetes treatment and antilipidemic drugs on metabolic dysfunction-associated steatotic liver disease in type 2 diabetic patients

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Background and Aims: It was aimed to investigate the effects of antidiabetic and antilipidemic drugs on liver steatosis and fibrosis in patients with type 2 diabetes mellitus (T2DM).

Method: In a single-center study conducted at a tertiary university hospital, liver steatosis, and fibrosis were prospectively evaluated with FibroScan® in adults with T2DM and without other causes of liver disease. In FibroScan® measurements, a CAP score of ≥ 275 dB/m was considered metabolic dysfunction–associated steatotic liver disease (MASLD) (≥ 302 dB/m was grade III (S3)), F ≥ 8 kPa (F2-4) was considered clinically significant fibrosis, and F ≥ 9.6 kPa (F3,4) was considered advanced fibrosis. The effects of antidiabetic (secretagogues, insulin sensitizers, incretin mimetics, SGLT2 inhibitors, and insulin) and antilipidemic drugs (statin and fenofibrate) used by T2DM patients on liver steatosis and fibrosis were tested by Kaplan-Meier and multivariate Cox regression analysis.

Results: 504 patients with T2DM (272 (54%) female, mean age 60.5 ± 10.6 years, 228 (45.2%) obese, mean duration of T2DM was 153.2 ± 104.3 months) participated in the study.

247 (49%) patients used only oral antidiabetic drugs (OAD), 48 (9.5%) used only insulin, and 209 (41.5%) used both OAD and insulin. 252 (50%) patients had MASLD. 346 (68.7%) had no fibrosis, 158 (31.3%) had clinically significant fibrosis, and 111 (22%) had advanced fibrosis.

In multivariate analysis, MASLD was found to be less in those with advanced age (≥ 65 years old) and insulin users, and more in those with body mass index (BMI) ≥ 30 kg/m^2 ($p < 0.05$), however, antilipidemic drugs were not found related to MASLD frequency. There was more S3 steatosis in those using only OAD than in those using combination and obese patients ($p = 0.000$, and $p = 0.010$, respectively).

In multivariate analyses, insulin use, antilipidemic drugs, and advanced age were associated with less clinically significant fibrosis ($p = 0.000$, $p = 0.007$, and $p = 0.001$, respectively), and BMI ≥ 30 kg/m^2 was associated with more clinically significant fibrosis ($p = 0.004$). Insulin use, antilipidemic drugs, and advanced age were associated with less advanced fibrosis ($p = 0.000$, $p = 0.003$, and $p = 0.024$, respectively), and BMI ≥ 30 kg/m^2 was associated with more advanced fibrosis ($p = 0.005$) in multivariate analyses.

Conclusion: In the type 2 diabetic population while MASLD and clinically significant fibrosis were more commonly seen in those using OAD, less was seen in those using insulin. Clinically significant fibrosis was less common in those using antilipidemic drugs.

PO4-09-YI
Degree of adherence to the mediterranean diet is highly predictive of prognosis in patients with MASLD: Findings from NHANES 2011-2018

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Background and Aims: Nutrition plays crucial roles in metabolic and liver health, with the Mediterranean diet (MD) being widely recommended. Although higher Mediterranean Diet Scores (MDS), a measure of adherence to the MD, are associated with improved hepatic steatosis and fibrosis, limited research has evaluated the impact of MDS on long-term prognosis, particularly in liver fibrosis. To address this gap, we utilized data from NHANES 2011-2018 and linked mortality data to evaluate the impact of MDS and estimated liver fibrosis on the prognosis of patients with metabolic-associated fatty liver disease (MASLD).

Method: From 39,156 participants, the final sample consisted of 4,550 individuals after excluding those younger than 40 or older than 80 years, and those with missing dietary, physical, or biochemical data. Hepatic steatosis was approximated using the United States Fatty Liver Index (US-FLI) with a threshold of 60 or higher. MDS was calculated from two-day interview results across nine food groups, with scores ranging from -1 to 8, and participants classified into tertiles based on MDS distribution. Liver fibrosis was evaluated using the FIB-4 index. For participants under 65 years, fibrosis grades were classified as low (<1.3), intermediate (1.3–2.67), and high (≥2.67). For those aged 65 and older, low and intermediate thresholds were set to 2.0. A Cox proportional hazards model was used to evaluate overall mortality in MASLD patients, incorporating interaction terms between FIB-4 index and MDS. Statistical analyses followed CDC sample weighting guidelines.

Results: MASLD patients had significantly higher adjusted mortality compared to non-MASLD groups in the Kaplan-Meier analysis (Log-rank: $p = 0.0258$). Among MASLD patients, a higher MDS was associated with a reduced mortality risk (HR: 0.78, $p < .0001$). Compared to the reference low group with FIB-4, the intermediate group had an increased mortality risk (HR: 1.25, $p < .0001$), and those with high group had a significantly higher mortality risk (HR: 2.64, $p < .0001$). Age (HR: 1.06, $p < .0001$) and male gender (HR: 1.62, $p < .0001$) were also significant predictors of mortality risk. In addition, interaction analysis between MDS and FIB-4 based on the Cox model showed that higher MDS was predictive of better prognosis in patients with intermediate and high FIB-4 scores. These results persisted after adjusting for ethnicity, income, and smoking status.

Conclusion: Adherence to a MD is associated with improved prognosis in MASLD patients in a dose-dependent fashion. The predictivity of MDS for mortality increases with FIB-4 estimated risk of advanced fibrosis. These findings suggest that dietary interventions focused on the MD may be particularly impactful in patients with advanced fibrosis. Future studies should explore long-term dietary adherence and other potential therapeutic strategies for improving MASLD patient outcomes.

PO4-11-YI
High burden of MASLD and metALD in People with HIV: A call for liver fibrosis screening prioritization

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Background and Aims: Evidence suggests that metabolic dysfunction-associated steatotic liver disease (MASLD) has heightened severity in people with HIV (PWH). However, hepatology guidelines do not recognize HIV as a risk factor for MASLD and fibrosis. Most data rely on the outdated NAFLD nomenclature, emphasizing the need for research within the MASLD framework. We aimed to assess the prevalence and factors associated with steatotic liver disease (SLD), its subcategories, and significant liver fibrosis in PWH.

Method: We analyzed data from clinical centers in Canada, Italy and Germany on consecutive PWH undergoing unselected screening for SLD and liver fibrosis. SLD was defined as controlled attenuation parameter ≥248 dB/m. MASLD was defined as SLD plus ≥1 cardiometabolic factor without alcohol intake >20-30g/day. Metabolic dysfunction- and alcohol-associated liver disease (MetALD) was defined as SLD with ≥1 cardiometabolic factor and alcohol intake 20-60g/day. Alcohol-associated liver disease (ALD) was defined as SLD with alcohol intake >60g/day. Cryptogenic SLD (cSLD) was defined as SLD without cardiometabolic risk factors or other causes of SLD. Significant liver fibrosis and cirrhosis were diagnosed by liver stiffness measurement ≥8 kPa and ≥13 kPa, respectively. Logistic regression was used to investigate factors associated with MASLD and fibrosis.

Results: Among 3,006 PWH (median age 53, 25% female, all on ART, 85% with undetectable HIV viral load), 14% had HCV coinfection and 3% had HBV coinfection. SLD, MASLD, MetALD, cSLD, and ALD prevalence were 43.4%, 26.2%, 9.8%, 5.2%, and 2.2%, respectively. Overall, 11.2% had significant fibrosis, and 3.5% had cirrhosis. PWH with MASLD and MetALD had a significantly higher prevalence of significant fibrosis (17.9% and 15.2%) and cirrhosis (5.3% and 5.9%) compared to those without SLD (7.8% significant fibrosis, 3.0% cirrhosis; p<0.001 and p=0.04, respectively). In multivariable analysis, body mass index (OR 1.28, 95% CI: 1.21–1.32) and age >50 (OR 1.47, 95% CI: 1.07–2.08) were independently associated with MASLD after adjusting for sex, duration of HIV infection, ALT, GGT, nadir CD4 <200 cells/uL, and use of integrase inhibitors. Significant fibrosis was associated with age (OR 1.01, 95% CI: 1.00–1.06), male sex (OR 1.53, 95% CI: 1.13–2.25), MASLD (OR 2.55, 95% CI: 1.70–3.25), MetALD (OR 1.89, 95% CI: 1.17–2.99), integrase inhibitor use (OR 1.65, 95% CI: 1.17–2.24), nadir CD4 <200 cells/uL (OR 1.45, 95% CI: 1.06–1.98), and HCV coinfection (OR 3.41, 95% CI: 2.46–4.71), while HBV coinfection was not.

Conclusion: The updated SLD definition reveals a high prevalence of significant liver fibrosis in PWH, driven by hepatic steatosis with metabolic alterations (MASLD and MetALD), HIV-related factors, and HCV coinfection. PWH should be globally recognized as a high-risk population for MASLD and prioritized for liver fibrosis screening.

PO4-12-YI
Exploring the interplay between sarcopenia, liver and cardiovascular damage in non-cirrhotic MASLD patients: a genetic perspective

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Background and Aims: Sarcopenia is associated with advanced liver fibrosis, and bioelectrical impedance analysis (BIA) reliably assesses muscle mass. Both metabolic-dysfunction associated steatotic liver disease (MASLD) and sarcopenia increase cardiovascular (CV) risk. Genetic variants like PNPLA3, TM6SF2, and HSD17B13 influence MASLD risk, but their roles in sarcopenia and CV damage are unexplored.

Aim: To assess the impact of sarcopenia and genetic variants on liver and CV damage in non-cirrhotic MASLD patients.

Method: We enrolled 841 MASLD patients from three Liver Units. Fibrosis was assessed by liver stiffness measurement (LSM) (LSM≥8 kPa for advanced fibrosis) and steatosis by controlled attenuation parameter (CAP) at Fibroscan (CAP>280 dB/m for severe steatosis). Sarcopenia was defined by the lowest tertile of skeletal muscle index (SMI = skeletal muscle mass/height^2) at BIA. CV risk was assessed using SCORE2 and SCORE-OP; CV damage markers included carotid intima-media thickness (cIMT)≥0.9 mm, carotid plaques, epicardial fat thickness (EFT) ≥5.2 mm. Increased waist circumference (WC) >102/88 cm in men/women. Genetic polymorphisms in PNPLA3, TM6SF2, and HSD17B13 were assessed in 424 patients.

Results: Mean age was 51 ys, 63% male. 43% were obese, 65% had increased WC. 50% were dyslipidemic, 25% diabetic. 24% had advanced fibrosis, 71% severe steatosis. 71% had higher high CV risk, 22% had increased cIMT, 35% had carotid plaques, 83% had increased EFT. Sarcopenia (SMI<10.35/7.75 kg/m2 in men/women) was linked to older age (54 vs 48 ys, p<0.001), lower BMI (27 vs 33.4 kg/m2, p<0.001), WC (99 vs 110 cm, p<0.001), CAP (293 vs 317 dB/m, p<0.001), and LSM (4.9 vs 6.4 kPa, p<0.001) compared to non-sarcopenic. Sarcopenic also had higher dyslipidemia (56% vs 46%, p=0.03), increased cIMT (28% vs 18%, p=0.01), and EFT (85% vs 77%, p=0.05). At adjusted multivariate analysis, sarcopenia remained associated with low BMI (OR 0.61; 95% CI 0.5-0.7, p<0.001), WC (OR 0.92; 95% CI 0.8-0.97, p=0.001), female sex (OR 2.21; 95% CI 1.2-4.0, p=0.008), and increased cIMT (OR 2.1; 95% CI 1.1-3.97).
In sarcopenic, PNPLA3 CG/GG variant was linked to increased LSM (OR 1.82, 95% CI 1.1-3.1, p=0.03) but lower cIMT (OR 0.39, 95% CI 0.15-0.96, p=0.04). TM6SF2 wild-type allele was associated with increased cIMT (OR 3.4, 95% CI 1.3-5.8, p=0.004), and WC (OR 2.3, 95% CI 1.4-3.6, p=0.001). No differences were seen in HSD17B13 variant.

Conclusion: Sarcopenia independently correlates with atherosclerosis markers in non-cirrhotic MASLD, though liver damage is less common, possibly due to lower visceral fat. In sarcopenic patients, the PNPLA3 variant correlated with increased liver damage but lower subclinical atherosclerosis, while TM6SF2 polymorphism showed a protective role against CV damage. Combining imaging and genetic data is required to clarify the role of sarcopenia in liver and CV damage in non-cirrhotic MASLD.

PO4-17-YI
Role of neck circumference as a screening modality in metabolic dysfunction-associated steatotic liver disease in rural area

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Background and Aims: Metabolic Dysfunction-Associated Liver Disease (MASLD) is a significant health concern with increasing prevalence. Identifying simple and reliable screening tools is crucial, especially in resource-limited rural settings. Neck circumference (NC) and waist circumference (WC) have emerged as potential anthropometric indicators for MASLD. This study aims to evaluate the effectiveness of NC and WC, individually and in combination with Body Mass Index (BMI), as screening tools for MASLD in a rural population.

Method: The study included 207 participants from a rural community, stratified by sex. Abdominal ultrasounds were used to diagnose steatosis and were confirmed with two radiologists. We performed pairwise correlation analysis and Receiver Operating Characteristic (ROC) curve analysis to determine the sensitivity and specificity of NC and WC in predicting MASLD. Logistic regression models were used to assess the predictive value of NC and WC in combination with BMI. Optimal cut-points for NC were determined using the Youden Index.

Results: The correlation between NC and MASLD was significant, with r=0.2175 and p=0.0016. Optimal cut-points for NC were identified as 41 cm for males and 34.5 cm for females. ROC analysis revealed an area under the curve (AUC) of 0.65 for the overall population, 0.75 for males, and 0.68 for females. WC showed a little stronger correlation with MASLD (r=0.3412, p<0.001) than NC. ROC analysis indicated an AUC of 0.75 for the overall population, 0.78 for males, and 0.75 for females. Logistic regression models incorporating NC and BMI yielded an AUC of 0.75 for the overall population, 0.79 for males, and 0.74 for females. Models with WC and BMI showed slightly higher predictive value with an AUC of 0.76 for the overall population, 0.78 for males, and 0.76 for females.

Conclusion: Both NC and WC are effective screening tools for MASLD in a rural population, with WC demonstrating a slightly higher predictive value. Combining NC or WC with BMI improves the accuracy of MASLD prediction. Optimal cut-points for NC were identified as 41 cm for males and 34 cm for females, supporting its utility in gender-specific screening strategies. Further research is needed to validate these findings in larger and more diverse populations.

PO4-20-YI

The liver frailty index is a good reflection of muscle function and identifies increased frailty in patients with non-cirrhotic steatotic liver disease compared with healthy controls

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Background and Aims: Muscle function decay and frailty are prevalent in cirrhosis whatever the cause. However, muscle function evaluation in non-cirrhotic patients are lacking, as well as data by etiology, including steatotic liver diseases (SLD). Our aim is to determine if muscle function already decays in non-cirrhotic SLD and if the SLD subtype impacts muscle function.

Method: SLD patients were prospectively recruited and classified according to the recent SLD subtype categories. Liver disease was assessed by transient elastography (Fibroscan®). Cirrhotic patients were excluded. Controls were defined by the absence of liver steatosis on controlled attenuation parameter (< 215 dB/m). Muscle function was assessed by isokinetic dynamometer (Cybex®). All patients and controls also underwent the three tests used to calculate the liver frailty index (LFI): handgrip strength, sit-to-stand test and balance test. SLD patients and controls were classified based on the LFI as robust (LFI < 3) or pre-frail/frail (LFI ≥ 3). Results are expressed as means ± SD.

Results: One-hundred and thirty-seven patients with SLD were included: 69 with alcohol-related liver disease (ALD) and 66 with metabolic dysfunction-associated steatotic liver disease (MASLD). Thirty healthy participants matched for sex and age (controls: 47.8 years ± 14.1, ALD: 50.2 ± 10.8, MASLD: 52.5 ± 10.4; p = 0.16) were used as controls. However, the groups differed for several parameters, such as alanine aminotransferase (controls: 18.4 IU/L ± 10.2, ALD: 74.8 ± 53.2, MASLD: 48.3 ± 29.5; p < 0.0001), liver stiffness (controls: 4.4 kPa ± 1, ALD: 8.9 ± 3.5, MASLD: 9 ± 3.9; p < 0.0001) and body mass index (controls: 22.1 kg/m² ± 2, ALD: 26.3 ± 5, MASLD: 33.3 ± 6.4; p < 0.0001). LFI was higher in all SLD subgroups compared to controls (controls: 2.2 ± 0.8, ALD: 3.2 ± 0.8, MASLD 3.1 ± 0.7; p < 0.0001) without any difference between MASLD and ALD patients (p = 0.67). 56.5 of ALD patients and 58.5 % of MASLD patients were considered pre-frail or frail (p = 0.81) compared to only 10 % of control patients (p < 0.0001). LFI negatively correlated with right knee extension evaluated by isokinetic dynamometer in all SLD patients (N = 137, r = -0.53; p < 0.0001).

Conclusion: LFI is an accurate method to assess muscle function in non-cirrhotic SLD patients. Muscle function assessed by the LFI decays compared to age-matched non-SLD controls. Frailty is not influenced by the SLD subtype. This reinforces the concept of a muscle-liver axis already in the early stages of SLD.

PO4-21
Is tissue copper level associated with macrosteatosis in Wilson's disease?

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Background and Aims: Wilson's disease (WD) is a hereditary metabolic disorder characterized by the accumulation of copper in the liver and other organs, particularly in the brain, due to a defect in intrahepatic copper transport. Clinical manifestations of WD can vary, presenting as hepatic, neurological, or mixed involvement. Histological abnormalities in the liver in WD can include megamitochondrial steatosis and inflammation. The pathogenesis of hepatic steatosis in WD is not fully understood, and the role of tissue copper in this context remains a subject of debate. This study aimed to elucidate the relationship between tissue copper levels and steatosis in patients who underwent liver biopsy at diagnosis.

Method: Liver biopsies were obtained using the Menghini technique. Patients diagnosed with WD and who had a Leipzig score of 4 or higher were included. The liver biopsies performed for diagnosis were evaluated retrospectively. Patients were compared based on the presence or absence of steatosis in relation to tissue copper levels and clinical parameters.

Results: A total of 115 patients with WD were included, with a mean diagnostic age of 22.12 ± 12.34 years. Among these, 78 were male (67.8%), and 26 patients (25.5%) were screening cases. According to the pattern of involvement, 63.8% presented with hepatic symptoms, 9.5% with neurological symptoms, and 26.7% with a mixed presentation. Kayser-Fleischer (KF) rings were observed in 25.5% of the patients. The mean Leipzig score was 4.77 ± 1.94. Steatosis was detected in 32 (27.8%) patients who underwent liver biopsy.The mean tissue copper level was found to be 796.88 ± 758.98 mcg, the mean 24-hour urinary copper excretion was 466.27 ± 737.11 µg, and the mean ceruloplasmin level was 16.54 ± 9.24 mg/dl. Liver tissue copper was 813.00 mcg ± 850.477 and 790.87± 1003.11 mcg in biopsy with and without steatosis, respectively (p=0.92); 24 h urine Cu excretion was 291.58 ± 367.319 µg and 535.71 ± 832.072 µg in biopsy with and without steatosis, respectively (p=0.03). No significant correlation was observed between the presence of steatosis and liver tissue copper or ceruloplasmin levels, whereas a statistically significant inverse correlation was found between 24-hour urinary copper levels and fatty liver (p = 0.03) . Among patients with KF rings, 18% had liver steatosis, although 30% of those without KF rings had liver steatosis (p = 0.15). When evaluating hepatic steatosis by pattern of involvement, steatosis was found in 38.8% of patients with hepatic involvement, 10% of those with neurological involvement, and 11% of those with mixed involvement (p = 0.02).

Conclusion: Hepatic steatosis in WD is not associated with tissue copper levels; however, an inverse correlation was observed between 24-hour urinary copper and hepatic steatosis.

PO4-22
Severe metabolic dysfunction-associated steatotic liver disease is associated with gut dysbiosis and shift in the metabolic function of the gut microbiota in people with HIV

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Background and Aims: The progression of metabolic dysfunction-associated steatotic liver disease (MASLD) to its severe forms, including metabolic dysfunction-associated steatohepatitis (MASH) and liver fibrosis, is influenced by a combination of lifestyle and genetic factors. Recently, several studies have emphasized gut microbial dysbiosis as a key driver in this process. However, the role of gut dysbiosis in people with HIV (PWH), a population with a complex MASLD pathogenesis and at risk for severe liver disease, is not known.

Method: Consecutive PWH from a prospective Cohort in Montreal, Canada (LIVEr disease in HIV, LIVEHIV), underwent liver stiffness measurement (LSM) with controlled attenuation parameter (CAP) by Fibroscan and the measurement of serum cytokeratin-18, a biomarker of hepatocyte apoptosis used to diagnose MASH. We included patients with a diagnosis of MASLD, defined as CAP >238 dB/m without viral hepatitis coinfection or alcohol abuse. Severe MASLD was defined as presence of MASH (cytokeratin-18 >130.5 U/L) and/or significant liver fibrosis (LSM >7.1 kPa). Taxonomic composition of gut microbiota was determined using 16S ribosomal RNA gene sequencing of stool samples. PICRUSt-based functional prediction was employed. Bacterial and functional differences were assessed using a generalized linear model, with adjustment for age and sex as confounding factors, using a negative binomial distribution.

Results: 34 patients with MASLD were enrolled (mean age 52 years, 15% females, mean LSM 6.7 kPa, mean cytokeratin-18 184 U/L). Among them, 32% had severe MASLD. After adjusting for age and sex, liver health status (severe MASLD yes vs. no) explained seven percentage of the overall variation (r2 = 0.07, p = 0.09) in bacterial composition. Several genera were found to be significantly different between PWH with severe MASLD. Notably, participants with severe MASLD had increases of genera Eubacterium, Bacteroides, Roseburia, Ruminococcus, Slackia, Holdemanella, Bilophila and decreases of Alloprevotella, Paraprevotella, Prevotella, Olsenella, Oribacterium, Romboutsia, Desulfovibrio, Dialister. In severe MASLD, functional analysis revealed increases in fatty acid degradation and flavonoid biosynthesis, and decreases in pyrimidine metabolism, steroid biosynthesis, folate biosynthesis, and alanine, aspartate, glutamate metabolism.

Conclusion: In PWH, MASLD severity is associated with gut dysbiosis and a shift in metabolic function of the gut microbiota. Some of these taxa are similar to those associated with MASLD in populations without HIV. Thus, gut microbiota analysis adds information to classical predictors of MASLD severity and suggests novel metabolic targets for pre-/probiotics therapies. Larger, longitudinal studies are needed to define the role of the gut microbiota in the pathogenesis of liver disease in this high-risk population.

PO4-24
Bariatric surgical interventions in steatotic liver disease (SLD): Mapping global research trends of the last two decades (2005-2024)

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Background and Aims: Steatotic liver disease (SLD) has risen alongside global obesity rates, now posing a significant health burden. Bariatric surgery has emerged as a promising intervention for managing SLD in morbidly obese patients, showing potential benefits for weight reduction, and liver histological and metabolic improvements. However, there remains limited clarity on which surgical procedures are the most effective and safe, along with an expanding interest in less invasive alternatives like endoscopic interventions. This analytical study aims to map global research trends on bariatric surgery for SLD, identifying key publication trends, institutions, and research gaps.

Method: We searched the Scopus database for publications related to bariatric surgery and SLD within the year range 2005 to 2024, the retrieved publications were reviewed in terms of the type of study, country, institutions, journals, keywords, and citations. The bibliometric data were visualized using VOSviewer software version 1.6.20 for collaboration network and co-occurrence analysis.

Results: Our search strategy yielded 1,355 publications from the year 2005 to 2024. The majority were original research articles [55.64%, n=754], followed by review articles [34.17%, n=463]. In terms of country of origin, the United States (US) was on the top with 405 publications (29.89%), followed by Italy (10.70%, n=145), and the United Kingdom (10.03%, n=136). The top three institutions were Inserm, France (0.03%,n=48), Harvard Medical School, US (0.03%, n=42), and Instituto de Salud Carlos III, Spain (0.02%, n=27). 1,206 articles were finally included in the citation analysis with 67,566 citations and an h-index of 110. The most cited article (n=4,974) was by Chalasani *et al.* (2018) published in the journal '*Hepatology*' which describes the practice guidelines by the American Association for the Study of Liver Diseases (AASLD). The guideline recommends foregut bariatric surgery in otherwise eligible obese individuals with SLD. There has been an increasing global focus on exploring bariatric surgery in morbidly obese patients with SLD in the last two decades. Bariatric surgery has demonstrated effectiveness in ameliorating SLD; however, an ongoing question remains whether Roux-en-Y gastric bypass (RYGB) or laparoscopic sleeve gastrectomy (LSG) offers superior outcomes. Besides, recent years (2018–2024) have shown increased interest in endoscopic sleeve gastroplasty and intragastric balloon, with 42 related publications.

Conclusion: The number of bariatric surgery publications on SLD has gradually grown over the last two decades, particularly since 2015. However, there is still a gap necessitating a large number of clinical trials and original studies. This study highlights key research trends, institutions, and emerging areas to support focused research in bariatric surgical interventions for SLD.

PO5-02
Morphological changes in liver cirrhosis on imaging and associations to clinical parameters, liver stiffness, steatosis and etiology

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Background and Aims: The characteristic appearance of liver cirrhosis on imaging correlates to pathology, but it is not well-investigated to what extent it correlates to other parameters and to the severity of the liver disease, or if it differs depending on etiology.

Method: 150 patients with cirrhosis undergoing hepatocellular carcinoma surveillance, are followed biannually with clinical examination, blood panels, vibration controlled transient elastogarphy (VCTE) and magnetic resonance imaging (MRI) in an ongoing prospective multi-center cohort study. Baseline abbreviated MRI examinations (T1W dynamic contrast series) were evaluated for changes of liver morphology and an overall imaging diagnostic impression of cirrhosis was registered for each patient based on a 5-point grading scale (1 = none, 2 = subtle, 3 = moderate, 4 = evident, 5 = severe) considering anatomic features of chronic liver disease and signs of portal hypertension. Patients were classified into two groups based on their imaging-score, none-moderate changes (n = 73) and evident-severe changes (n = 74). Data are presented as mean ± standard deviation or median (min-max).

Results: Mean age was 64 ± 11 years with a male predominance (56 %). The most common causes of cirrhosis were alcohol-related liver disease (ALD, 33 %) and metabolic dysfunction-associated steatotic liver disease without excessive alcohol consumption (MASLD, 25 %), and with excessive alcohol consumption (MetALD, 10 %). The morphologic changes on imaging were: none 7 %, subtle 15 %, moderate 27 %, evident 36 %, and severe 13 %. Patients with cirrhosis caused by ALD had the highest imaging-score and patients with MASLD the lowest, with evident-severe changes in 71 % vs 24 % of the cases, p < .001. Higher median levels of MELD-score were seen at baseline and 6-month follow-up in patients with evident-severe changes as compared to none-moderate changes 8 (6 - 18) *vs.* 7 (6 - 16), p = .001, and 8 (6 - 20) *vs.* 7 (6 - 15), *p* = .001, respectively. Similarly, in patients with evident-severe changes as compared to patients with none-moderate changes, MELD-score > 10 was seen in 26 % *vs.* 8 % (p = .002) at baseline, and 28 % *vs.* 8 % (p < .001) at follow-up. Similar differences were seen in Child Pugh score > 5 (36 % *vs.* 11 %, p = .001, and 39 % *vs.* 22 %, p = .043, respectively). Furthermore, liver stiffness was higher (31.8 ± 21.1 kPa *vs.* 21.3 ± 17.5 kPa p = .004) and hepatic fat content lower with increasing imaging scores (3.9 ± 3.2 % *vs.* 6.2 ± 5.1 %, p = .004). Similar patterns were observed in subgroup analysis of hepatic fat content in MASLD patients (5.2 ± 4.2 % *vs.* 8.7 ± 5.7 %, p = .102).

Conclusion: Morphological changes in liver cirrhosis differ depending on the etiology of cirrhosis and correlate to some extent with clinical parameters.

PO5-06-YI

A targeted steroidomic approach to investigate the impact of sexual dimorphism on liver damage 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 sexual dimorphic disease with a prevalence that is higher in men than in pre-menopausal women while the reverse is true after menopause. Steroid hormones, including sex hormones, may exert an important role on the metabolic profile and the degree of liver damage. The aim of this study was to to shed light on sexual dimorphism in patients with MASLD by using a targeted steroidomic approach.

Method: We enrolled 463 consecutive patients (males n = 275 [59%]; females n = 188 [41%]) with a histological diagnosis of MASLD and 112 healthy controls (males n = 55 [49%]; females n = 57 [51%]). A panel of 26 steroids and their metabolites (including glucocorticoids and androgen as well as their representative glucuro- and sulphoconjugated metabolites) were measured on plasma samples by liquid chromatography coupled to mass spectrometry (LC-MS/MS). Severe fibrosis was defined by F ≥ 3 according to Kleiner classification

Results: The prevalence of F ≥ 3 was 36% (men/women 31% / 45%, p = 0.061). Patients with MASLD showed different levels of steroids metabolites compared to healthy controls both in men and women. Overall, 56 % of the patients were aged ≥ 50 years (y) (men/women 47% / 69%, p < 0.001). In men younger than 50y, the severity of hepatic fibrosis did not correlate with steroids levels. Conversely, in males aged ≥ 50y, several androgens metabolites were significantly reduced in those with F ≥ 3 compared to those without severe fibrosis. In women with MASLD aged < 50y, progesterone levels were 5 -fold lower in the group with F ≥ 3 compared to those without severe fibrosis (p = 0.018). Notably, in women aged ≥ 50y and with F ≥ 3, testosterone levels were increased about 1.5 -fold compared to those without severe fibrosis (p = 0.046).

Conclusion: In patients with MASLD, we identified different steroids profiles according to gender and age that varied according to the severity of hepatic fibrosis. Further studies are needed to understand the complex interplay between steroids metabolism and sexual dimorphism in the onset and progression of MASLD.

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PO5-08-YI

Statin use is inversely associated with steatotic liver disease and liver fibrosis, whereas aspirin use is not: Results from two large population based studies

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Background and Aims: Liver fibrosis is a growing public health concern, largely due to the increasing prevalence of steatotic liver disease (SLD). Therapeutic options that target steatosis and fibrosis are scarce. Here we investigate the potential hepatoprotective effects of aspirin and statins in the general population.

Method: Data were used from two population-based cohorts: the Rotterdam Study (RS) and NHANES (2017–2020 cycle). Participants aged ≥40 years with reliable liver stiffness measurements (LSM) and data on aspirin and statin use were included. Those with excessive alcohol consumption (≥50g/day for females, ≥60g/day for males), viral hepatitis or heart failure were excluded. Liver fibrosis was defined as LSM ≥8.0 kPa, and SLD by ultrasound or a CAP value >275 dB/m. We used logistic regression models to evaluate associations between aspirin and statin use and liver outcomes, adjusted for age, sex, ethnicity, serum triglycerides, total cholesterol, waist-circumference, diabetes, hypertension and the number of metabolic risk factors. Interaction and multicollinearity between aspirin and statin use were tested via interaction terms and VIF values. Non-linearity was assessed amongst the pooled cohort using restricted cubic splines for the duration of statin use.

Results: 11.197 participants were included. Of these, 6.055 from the RS (median age 64 years [IQR 56–71],44% male) and 5.142 from NHANES (median age 60 years [IQR 50–69],50% male). The prevalence of SLD was 33% in the RS and 48% in the NHANES, liver fibrosis was present in 4.7% of RS and 11.4% in NHANES. In RS, 15% were on aspirin and 22% on statin therapy, compared to 29% and 30% in NHANES. Statin was independently and inversely associated with SLD in the RS (aOR0.47;95%CI:0.38–0.58) and liver fibrosis the RS (aOR0.57;95%CI0.38–0.86) and NHANES (aOR0.60;95%CI0.47–0.78). Non-linear effects were observed for SLD (p=0.033) and fibrosis (p=0.002). During the initial three years of statin treatment, the risk reduction increased to 20% for steatosis and 40% for fibrosis, stabilizing thereafter and remaining consistent for up to 20 years. Aspirin was not significantly associated with steatosis (RS:aOR1.05;95%CI0.87–1.28; NHANES:aOR1.19;95%CI0.95–1.49) or fibrosis (RS:aOR0.94;95%CI0.65–1.36; NHANES:aOR0.94;95%CI0.69–1.26). There were no interactions observed between statin and aspirin use, and no multicollinearity between the two. The inverse association of statin with SLD and fibrosis was also observed among subgroups with metabolic dysfunction.

Conclusion: Statin use, but not aspirin, was independently inversely associated with both SLD and fibrosis in a population-based setting, also among important subgroups. The risk reduction increased up to three years of treatment and remained stable thereafter. Therefore, statin treatment may be considered as part of SLD disease management

PO5-09-YI
Prevalence of low ceruloplasmin in patients with alcohol use disorder

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Background and Aims: Ceruloplasmin is commonly ordered in evaluation of abnormal liver associated enzymes, with a low ceruloplasmin suggestive of a diagnosis of Wilson Disease (WD). However, ceruloplasmin can be low for other reasons. Little is known about the effects of heavy alcohol use on ceruloplasmin. We examined ceruloplasmin levels in patients with alcohol use disorder (AUD).

Method: Patients with AUD were enrolled in a 4-week multidisciplinary inpatient treatment program. Laboratory values were collected at admission, weeks 1 and 3, and vibration controlled transient elastography (VCTE) with controlled attenuation parameter (CAP) was performed at weeks 1, 2, and 4 per protocol. Low ceruloplasmin was defined by a serum ceruloplasmin level of less than 20 mg/dL. Statistical analysis was performed using Graphpad Prism.

Results: 244 patients were included, with a mean age of 46.1 years, with 84 (34.4%) female. Mean ceruloplasmin was 28.13 mg/dL (SD 6.7). 21 (8.6%) patients had low ceruloplasmin, with only one female patient with low ceruloplasmin (p=0.0015). There were significant differences between patients with low and normal ceruloplasmin, with mean thiamine level of 152.4 nmol/L and 182.4 nmol/L (p=0.021), ESR 5.5 mm/hr and 12 mm/hr (p=0.015), week 4 CAP of 208 dB/m and 237.7 dB/m (p=0.028), respectively. There was no difference in ceruloplasmin levels between patients with normal serum transaminases and those with elevated transaminases or those with normal vs. elevated liver stiffness measurements on VCTE.

Conclusion: Low ceruloplasmin is common in patients with AUD and associated with lower thiamine levels, ESR, triglycerides, and hepatic steatosis when compared to patients with normal ceruloplasmin levels. Furthermore, low ceruloplasmin was not associated with evidence of liver disease or injury.

PO5-12-YI
Unveiling the hidden link: Psoriasis and liver disease risk

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Background and Aims: Psoriasis is a chronic immune-mediated skin disorder affecting 1-5% of the global population, characterized by erythematous-desquamative plaques, often found on extensor surfaces. Recent studies have highlighted a notable association between psoriasis and metabolic dysfunction-associated steatotic liver disease (MASLD). Metabolic abnormalities, such as insulin resistance, obesity, and dyslipidemia, are prevalent in both psoriasis and NAFLD, suggesting possible shared pathophysiological pathways. This study aimed to investigate the relationship between psoriasis and MASLD.

Method: Liver fibrosis and steatosis were assessed by FibroScan and controlled attenuation parameter (CAP) measurements.

Results: Three participant groups were analyzed: (1) patients with moderate-to-severe psoriasis, (2) healthy controls, and (3) patients with MASLD. The psoriasis group included 35 individuals (24 males, 11 females), mean age 42.46 ± 10.09 years. Healthy controls included 49 individuals (14 males, 35 females), mean age 37.12 ± 15.31 years. MASLD patients included 43 individuals (24 males, 19 females), mean age 59.91 ± 11.56 years. Mean BMI was 29.58 ± 5.76 for psoriasis, 24.71 ± 6.94 for controls, and 29.15 ± 4.61 for MASLD.
Significant differences in LSM and CAP values were observed among groups ($p < 0.01$). Multivariate analysis revealed significant associations between LSM and age ($p = 0.046$), and between CAP and factors such as gender ($p = 0.014$), age ($p = 0.04$), BMI ($p < 0.01$), psoriasis presence ($p = 0.003$), and hypercholesterolemia ($p = 0.03$).

Conclusion: Psoriasis is significantly associated with liver fibrosis and steatosis, highlighting the importance of liver monitoring in these patients.

PO5-15-YI
Does cardiovascular risk differ with age-specific body composition in women with in metabolic dysfunction-associated steatotic liver disease?

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Background and Aims: Body composition is crucial to metabolic health and plays a key role in the development of chronic diseases, including metabolic dysfunction-associated steatotic liver disease (MASLD). Factors such as visceral fat influence liver health due to its relationship to inflammation, insulin resistance, and susceptibility to metabolic and cardiovascular disease. Despite its importance, most studies on MASLD have focused on men. Women, especially postmenopausal women, experience changes in body composition that affect their risk of MASLD. Hormonal changes influence fat distribution and disease progression, but research on women and body composition in MASLD is limited. This study explores the relationship between body composition and the prevalence of MASLD in women, also examining associations with cardiovascular risk.

Method: A retrospective analysis of women undergoing routine screening was conducted, evaluating clinical, anthropometrical and biochemical variables. Body composition was measured by bioelectrical impedance; hepatic steatosis was assessed with vibration-controlled transient elastography, and the diagnosis of MASLD followed the 2023 multi-society consensus criteria. Participants were grouped by age and were further stratified by body composition percentiles.

Results: The study included 1,003 women, of whom 59.2% were younger than 50 years of age. The prevalence of MASLD was 50%, higher in older women (56.9%) than in younger women (45.1%) ($p<0.001$). Among women with MASLD, 63.2% of younger and 66.6% of older women had overweight or obesity. MASLD was associated with higher levels of visceral fat, total fat mass and lower lean mass. Positive correlations were found between MASLD and waist circumference ($r=0.246$), waist-to-hip ratio ($r=0.252$) and visceral fat ($r=0.122$), while lean mass and muscle mass were inversely related. Women in the highest tertiles of fat mass and visceral fat had significantly higher prevalence of MASLD and cardiovascular risk (Framingham and PREVENT scores). Conversely, higher lean mass was related to lower prevalence of MASLD and better cardiovascular risk profiles. ROC curve analysis showed that variables such as fat mass percentage (AUC=0.877 and 0.837), visceral fat (AUC=0.873 and 0.850), and fat mass (AUC=0.858 and 0.845) demonstrated strong predictive ability for MASLD, with high discriminative power ($p<0.001$). In contrast, lean mass (AUC=0.672 and 0.721) and muscle mass (AUC=0.668 and 0.714) showed moderate predictive capacity.

Conclusion: These findings highlight the role of body composition in MASLD risk, especially in postmenopausal women. The results highlight the variability of cardiovascular and MASLD risk as a function of body composition and age, supporting age-specific approaches to risk assessment and intervention in women.

PO5-18
NT-proBNP levels correlate with liver fibrosis in MASLD patients

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Background and Aims: The main group of causes of death in patients with metabolic dysfunction-associated steatotic liver disease (MASLD) are cardiovascular diseases. N-terminal pro-B-type natriuretic peptide (NT-proBNP) is one of the early markers of disorders of the cardiovascular system. There is uncertainty as to whether there is a relationship between liver fibrosis, as the degree of MASLD progression, and NT-proBNP, and the possible effect of dapagliflozin on these parameters.

Method: twenty-eight patients, aged 25-67 years, both sexes, with confirmed MASLD, type 2 diabetes and without cardiovascular diseases were studied. They were divided into two groups: Group A (n = 17) – no fibrosis or minimal fibrosis (F0-F1 according to the METAVIR score) and Group B (n = 11) – moderate or severe fibrosis (F2-F3 according to the METAVIR score). During the first visit, baseline levels of NT-proBNP were assessed, and liver elastography was performed. Both groups received dapagliflozin 10 mg once a day for 3 months, after these parameters were reassessed and compared between the groups. For statistical analysis, the following methods were used: descriptive statistics (mean, standard deviation), independent t-test for comparisons between groups, paired t-test for within-group changes before and after treatment.

Results: NT-proBNP levels differed depending on the group ($p < 0.05$): in group A NT-proBNP was less than 125 pg/ml (41 ± 39 pg/ml), and in group B it was more than 125 pg/ml (211 ± 187 pg/ml). After 3 months of taking dapagliflozin, a decrease in the average index of liver stiffness was noted, but this did not reach statistical significance in group A (6.5 ± 1.2 kPa vs 6.4 ± 1.0 kPa; $p = 0.12$) and group B (10.8 ± 2.1 kPa vs 10.7 ± 2.0 kPa; $p = 0.31$). NT-proBNP under the influence of dapagliflozin in group A did not increase statistically significantly (57 ± 54 pg/ml; $p = 0.25$). In group B, NT-proBNP decreased by 10% (192 ± 131 pg/ml; $p < 0.05$).

Conclusion: the level of NT-proBNP increases with the progression of liver fibrosis in patients with MASLD. When taking dapagliflozin for 3 months, a decrease in the level of NT-proBNP was noted in patients with higher degrees of liver fibrosis, and with minimal fibrosis or its absence, no statistically significant changes were recorded. A non-statistically significant decrease in the average liver stiffness index is noted, which may require further, longer-term studies.

PO5-19
Non-invasive parameters compared to FibroScan for the assessment of liver stiffness and controlled attenuation parameters in patients with fatty liver disease

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Background and Aims: Fibroscan technology evaluating liver stiffness measurement (LSM) signifying fibrosis and Controlled Attenuation Parameter (CAP) signifying steatosis are well validated. CAP serves as a numerical parameter for monitoring diet and lifestyle modifications in MASLD. Blood based markers which would tally with LSM and CAP are more cost effective for follow up especially at primary care. NLR (Neutrophil-Lymphocyte Ratio), PLR (Platelet Lymphocyte Ratio) and NPAR (Neutrophil Percentage-to-Albumin Ratio) were associated with MASLD, while neither NLR,PLR or NPAR were significantly associated with fibrosis; whether these correlate with steatosis or CAP remains unanswered.

Method: This cross-sectional study subjected 350 MASLD patients to non-invasive blood tests namely FIB-4 (Fibrosis-4), APRI (AST Platelet Ratio Index) NLR, NPAR and PLR along with LSM and CAP. The LSM cutoffs were F0: 1–6 kPa, F1: 6.1–7 kPa, F2: 7.1–9 kPa, F3: 9.1–10.3 kPa and F4: ≥ 10.4 kPa and CAP cutoffs were S0: 100-250 dB/m, S1: 251-288 dB/m, S2: 287-330 dB/m and S3: >330 dB/m.Patients were grouped into two - Less fibro progressed (F0,F1,F2) and Fibro Progressed group (F3 and F4) and according to CAP Values to S1,S2 and S3. Sensitivity, Specificity, Positive Predictive Value, Negative predictive value along with ROC Curves for each blood-based tests were obtained

Results: In case of LSM, FIB-4 demonstrated sensitivity -0.692, Specificity - 0.804, Positive predictive value (PPV) - 72.97 Negative Predictive Value (NPV) -77.36, Diagnostic Accuracy (DA) - 75.63 and APRI (Sensitivity -0.820, Specificity - 0.627, PPV -62.75, NPV -82.05, DA - 71.21) correlated better with LSM values. However, PLR and NLR did not correlate well with LSM values; but PLR has a very high specificity (Specificity -0.980 and PPV-66.6) well above the time-honoured FIB-4 and APRI and comparable PPV as that of FIB-4 and APRI. Regarding CAP, NPAR showed the highest specificity (97.67%) as well as PPV of 91.31%, followed by NLR (Specificity - 92.77% and PPV - 92.31%) in contrast APRI revealed a very low specificity of 32.5%

Conclusion: APRI and FIB-4 which are time honoured fibrosis markers revealed good specificity and sensitivity with LSM. Regarding CAP correlation the newer blood markers NPAR and NLR revealed high specificity. Further studies with these newer markers being used as direct comparators to CAP or as part of combination scores to be explored.

PO5-21
Serological biomarkers of the extracellular matrix reflecting fibroblast activity and endothelial damage are elevated in patients at risk of MASH with significant liver stiffness

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Background and Aims: In metabolic dysfunction-associated steatohepatitis (MASH), inflammation of the hepatic tissue leads to an increased formation and deposition of extracellular matrix proteins, such as collagens. Over time accumulation of collagens causes hepatic fibrosis, which is associated with increased liver stiffness. Type III, IV, and VI collagen formation may be assessed non-invasively using PRO-C3, PRO-C4, and PRO-C6 assessing the pro-peptide of type III and VI collagen, and the 7S domain of type IV collagen to understand fibroblast activation (PRO-C3 & PRO-C6) and endothelial damage (PRO-C4). We aimed to investigate how such features may be affected in patients with increased liver stiffness measure (LSM), in patients identified as at risk of MASH, due to obesity and presence of type 2 diabetes (T2D).

Method: 958 patients from the NASH-PASS study, were identified as at risk of MASH due to obesity and presence of T2D. All had LSM assessed using vibration-controlled transient elastography (VCTE) by Fibroscan. Blood samples were collected at the time of LSM. PRO-C3, PRO-C6, and PRO-C4 were assessed using fully validated competitive immunoassays. Between groups comparisons of biomarker levels were performed using Mann-Whitney or Kruskal-Wallis test.

Results: The median (Q1, Q3) age and BMI of the 958 included patients were 56.4 (48.3, 63.7) years and 35.1 (31.7, 38.9) kg/m^2, respectively, and 473 patients had T2D. 22% of the patients had significant LS (VCTE > 8 kPa). While weak Spearman correlation between LS and our biomarkers was observed, the levels of PRO-C3, PRO-C4, and PRO-C6 were significantly elevated in patients with significant LS, compared to those without (VCTE < 8 kPa), ($p < 0.0001$, $p < 0.05$, and $p < 0.0001$), (AUROC = 0.672, 0.546, and 0.623).

Conclusion: MASH patients with increased LSM (VCTE > 8 kPa) had significantly increased fibroblasts activity (PRO-C3 & PRO-C6) and ECM remodelling of the basement membrane reflecting endothelial damage (PRO-C4), compared to patients without increased LSM (VCTE < 8 kPa).

PO5-23
Prevalence of liver fibrosis in vulnerable individuals from North-Eastern Romania using Transient Elastography

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Background and Aims: Liver cirrhosis is considered the final stage of liver fibrosis progression and the leading cause of worldwide mortality due to liver diseases. Certain liver infections, such as viral hepatitis B (VHB) and C (VHC), alcohol-related liver disease (ALD), and metabolic dysfunction-associated steatotic liver disease (MASLD) were found to be significant contributors to liver cirrhosis development. The aim of our study was to assess the prevalence of liver steatosis and fibrosis in individuals with vulnerable conditions.

Method: Five hundred and seventy-one adult asymptomatic participants, all living in a rural county from Romania were selected for this study. After informed consent was obtained, the demographical, clinical, and physiological description was made for each participant. AUDIT-C questionnaire was applied to each participant. Transient Elastography (TE) was used to measure liver fibrosis, and hepatitis virus B and C presence was screened using rapid blood tests.

Results: Of the screened participants, we discovered that 31.2% had less than a high school diploma and 56.85% were men. In our study, just 1.9% of participants had previously received blood transfusions, while 35.6% reported having a history of smoking. The metabolic syndrome was also detected in 61% of the patients, 70% of the subjects had a body mass index of ≥25 kg/m2, 8.5% of the participants tested positive for HBs antigen, and 13.1% had an HCV antibody-positive titer. Additionally, 5.71% of the participants in our study had MASLD, and 7.3% had MetALD according to the AUDIT-C questionnaire. On TE exams, we found that 9.9% of the participants had advanced liver fibrosis, 16.1% of the group had liver cirrhosis, and 24.6% of the subjects had severe steatosis.

Conclusion: By screening a cohort of apparently clinically healthy individuals residing in vulnerable conditions from the North-Eastern part of Romania and having different socioeconomic profiles, we observed that the frequency of advanced fibrosis and cirrhosis is more increased, as compared to available data.

PO5-24
Liver fibrosis in T2DM, prevalence and feasibility of screening with AI in primary care

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Background and Aims: Metabolic dysfunction-associated liver disease (MASLD), the global commonest cause of chronic liver disease, progresses to liver cirrhosis. Prevalence of MASLD in type 2 diabetes mellitus(T2DM) is ~65% (95% CI [62%-68%]). American and European Clinical guidelines recommend screening for liver fibrosis in patients with T2DM: current UK guidelines, are incongruent because of perceived difficulties. A recent Lancet Viewpoint agrees that screening in T2DM would provide opportunities to detect advanced liver fibrosis. The aims are to confirm extent of liver fibrosis in T2DM in a Primary Care setting and determine the feasibility of liver fibrosis screening in T2DM (Diabetic Liver Disease) in primary care.

Method: Blood samples of anonymised demographic details, in a socially-ethnically diverse area of London, with T2DM, being analysed for routine 6-monthly HbA1c, were interrogated through artificial intelligence by recording, age, AST, ALT and platelet count to calculate fibrosis-4(FIB-4) score.

Results: 581 patients - 273 males and 308 females with 2 thresholds: i) 50% had FIB-4 ≤1.3(F0/F1, low risk), 39% at 1.3-2.67(F2/F3, moderate risk) and 10% >2.67(F4, advanced fibrosis) ii) a higher cut off for confounders 58% had FIB-4 <1.45(F0/F1), 36% as ≥1.45-3.25(F2/F3) and 6% with >3.25(F4). FIB-4 scores at F0/F1 vs F2/F3 and F2/F3 vs (F4) or F0/F1 vs F4 were statistically significant($p<0.05$).

Conclusion: High prevalence of liver fibrosis confirms importance of screening for MASLD in T2DM (Diabetic Liver Disease) as suggested by recent Guidelines. Automated assay of FIB-4 with bloods at HbA1c, in primary care, indicates ease of adopting MASLD screening, in patients with T2DM (Diabetic Liver Disease) and steer pathways change.

PO6-01-YI
Muscle composition predicts adverse outcomes in chronic liver disease: A 5-year follow-up study

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Background and Aims: Sarcopenia and muscle fat infiltration (MFI) are common in advanced liver disease, but their prognostic role in early-stage liver disease is unclear. This study investigated muscle factors for predicting adverse outcomes in chronic liver disease.

Method: Patients investigated for suspected liver disease underwent liver biopsy, transient elastography (TE) and neck-to-knee magnetic resonance imaging, used to calculate a muscle assessment score, consisting of a z-score of fat-free muscle volume (MVZ) and anterior thigh MFI, adjusted for sex and BMI, using AMRA® Researcher. Follow-up included a retrospective review of patient records for major liver or cardiovascular adverse events (MALO/MACE) or mortality. MALO included liver disease progression (e.g., cirrhosis, ESLD, HCC or liver transplant). MACE included myocardial infarction, ischemic stroke, unstable angina, coronary revascularization, or congestive heart failure requiring hospitalization. Hazard ratios were calculated using Cox regression using univariable (cHR) and multivariable analyses (aHR, adjusted for sex, age, BMI, type 2 diabetes, hypertension, and dyslipidaemia).

Results: Of the 77 patients studied, 31 (40%) were women. Mean age at baseline were 58 ± 13 years and mean BMI 30.9 ± 5.2 kg/m^2. Type 2 diabetes prevalence was 35%, and MASLD was the most common etiology (61%). Mean TE was 10.3 ± 5.7 kPa. Median fibrosis stage at biopsy was 2 (0-4) and 28 (36%) patients had advanced fibrosis. Mean MFI and MVZ were 0.58 ± 2.79 pp and 0.34 ± 1.30 SD, respectively.
Over a median follow-up of 4.9 yrs (IQR: 3.0–6.1), 15 patients had major adverse events or death. Six patients experienced MALOs (2 cirrhosis, 3 ESLD, 1 HCC) and 6 experienced MACEs (2 ischaemic stroke, 2 unstable angina, 1 myocardial infarction, 1 congestive heart failure). Three deaths occurred, unrelated to MALO or MACE.
Baseline fibrosis stage was not significantly linked to major adverse events (cHR 1.67, 95% CI: 0.99–2.81). Higher TE values increased risk, with a cHR of 1.08 per unit increase in kPa (95% CI: 1.01–1.15), though this association weakened in the adjusted model (aHR 1.07, 95% CI: 0.98–1.17). Increased MVZ (SD) was associated with a reduced risk of adverse events (cHR 0.48, 95% CI: 0.30–0.77), confirmed in the adjusted analysis (aHR 0.58, 95% CI: 0.35–0.96). Higher MFI (pp) increased risk of adverse events (cHR 1.27, 95% CI: 1.12–1.45), confirmed in the adjusted analysis (aHR 1.27, 95% CI: 1.02–1.58).

Conclusion: Higher MFI and lower MVZ were associated with an increased risk of future adverse events in patients investigated for chronic liver disease, even when adjusting for traditional risk factors. These findings suggest that incorporating muscle health assessments, alongside TE, in early management and risk stratification of chronic liver disease could enhance prognostic accuracy.

PO6-02
Insulin resistance and sarcopenia in patients with MASLD: Is there a relationship?

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Background and Aims: Recent studies have shown that sarcopenia often accompanies MASLD. Sarcopenic obesity in combination with the progressive loss of skeletal muscle mass negatively affects the metabolic status of a person, which leads to a decrease in the quality of life and the development of cardiovascular diseases.
The aim was to determine the relationship between inflammatory markers, insulin resistance and sarcopenia in patients with MASLD.

Method: The study included 226 normal, overweight, and obese MASLD patients and 114 non-MASLD patients. Anthropometric examination and MRI were performed, AST, ALT, GGT levels, degree of liver fibrosis using elastography (FibroScan), ECG were measured. Cardiovascular risk stratification was assessed using the SCORE version for high-risk countries. The level of inflammatory mediators (TNF-α, IL-1, IL-6), markers (CRP, fibrinogen), myostatin, endothelin-1, the thickness of the intima-media complex, the presence of atherosclerotic plaque and carotid artery stenosis, HOMA-IR insulin resistance index were determined for all patients.

Results: Thus, the body weight of men with MASLD was 1.3 times greater than in the group of healthy men. The body weight of women with MASLD was 1.5 times higher compared to the group of healthy women. There were no significant differences or trends in body length between healthy and MASLD males and MASLD females. The BMI of men with MASLD was 1.4 times higher than that of healthy men. The BMI of women with MASLD was also 1.4 times higher than that of healthy women. The muscle mass of men and women with MASLD was statistically significantly lower ($p < 0.05$) than that of sexually healthy men and women. Moreover, muscle mass in healthy men was statistically significantly higher ($p<0.05$) than in the corresponding groups of women. Thus, healthy men's muscle mass increased by 20.5% compared to healthy women. Higher levels of inflammation, HOMA index, and decreased adiponectin levels were found in patients with MASLD, and sarcopenia compared to patients with preserved muscle mass. According to the results of the study, the component composition of body weight changes in MASLD. Compared with healthy men with MASLD, body fat mass was 35.2% higher, while muscle mass and bone mass in men were 29.1% and 32.0% lower, respectively. Compared to healthy women with MASLD., body fat mass was 30.2% higher, while muscle mass and bone mass in women were 17.4% and 22.7% lower, respectively. Strong inverse correlations ($r = 0.71$, $p < 0.001$) were found between muscle mass and hsCRP levels in men and women with MASLD.

Conclusion: The mechanisms of pathogenesis of sarcopenia and MASLD are common: insulin resistance, increased inflammation, secretion of myokines by skeletal muscles, myostatin, and decrease in adiponectin level.

PO6-04
Modest alcohol consumption influences on the spectrum of bile acids in individuals with intact liver function, resembling the changes in patients with MASLD

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Background and Aims: Modest alcohol consumption appears to have controversial influence on health outcomes. Nowadays, increased level of stress among Ukrainians, may prompt more regular alcohol consumption within “one drink” – limits, particularly for relaxation. Our aim was to assess the effect of modest but regular alcohol consumption (MrAC) on the spectrum of bile acids (BA) in individuals with intact liver function.

Method: MrAC was considered as no more than one drink per day for women and no more than two drinks per day for men, four and more days per week (one drink = 10 grams of pure alcohol). None of the patients that were included into the study, did fulfil the diagnostic criteria of MASLD/MASH or ALD. None of the patients did receive long-term medicaments or special dietary supplements. The parameters of liver function tests as well as CBC were within normal ranges. To compare the spectrum of BA, the results of bile examination of healthy individuals that did not drink any alcohol for three weeks before the examination. The bile was obtained after intubation of the duodenum under the ultrasound control. The spectrum of BA was assessed using photocalorimetry. The data were analysed using parametric and non-parametric methods of evaluating the results through Statistica program (StatSoft Inc, USA).

Results: 27 adult patients were included into the study, of those 14 confirmed MrAC. The other 13 patients formed the control group. The groups were statistically comparable in age and sex. The levels of primary unconjugated BA were significantly increased in the study group (MrAC), while taurine-conjugated BA were significantly decreased compared to healthy controls ($p>0.01$). Glycine-conjugated BA were also slightly increased in the study group, but without statistical significance ($p<0.05$). The levels of secondary BA were decreased in patients who were exposed to alcohol ($p>0.01$). We also registered increased free bile cholesterol levels in patients of the main group ($p>0.05$).

Conclusion: 1. MrAC may lead to the shift in the pool of BA that may be considered as first pre-clinical changes, that occur before other manifestations inherent in ALD. That is why, no dose of alcohol can be considered safe for the liver.
2. Similar changes in BA-spectrum were previously registered in our study of BA in patients with MASLD [1].
3. The decrease of secondary BA may possibly be explained through the influence of low doses of alcohol on gut microbiome, leading to the shift in BA axis. But more studies should be done.
4. We hypothesize, that the decrease of tauroconjugates under the constant (even low) doses of alcohol may be due to the possible involvement of the amino acid taurine in the other processes. In particular, taurine influences the ethanol-induced elevation of dopamine in the brain reward system after alcohol consumption [2].

PO6-05
Predictive factors for hepatocellular carcinoma development in patients with metabolic-dysfunction-associated steatotic liver disease with or without cirrhosis

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Background and Aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) represents the fastest growing cause of hepatocellular carcinoma (HCC) worldwide. Despite 20-50% of MASLD HCC cases occurring in non-cirrhotic individuals, surveillance in this cohort is not routinely recommended. Risk stratification is needed to guide screening recommendations and selection of individuals for HCC surveillance. We aimed to determine predictive factors for HCC development in a diverse population with MASLD and to derive HCC risk prediction models in a cirrhotic and non-cirrhotic background.

Method: This study involved MASLD patients with a long follow-up. Baseline characteristics, independently predictive of HCC development on multivariate cox regression analysis, were incorporated into risk prediction models. The study population was further divided into derivation and validation groups in a 70:30 ratio and two further models (cirrhotic and non-cirrhotic) for internal validation. Harrell's c-index values were used to assess model discrimination.

Results: 524 non-HCC and 99 HCC patients with MASLD were included. We identified age, presence of cirrhosis, moderate alcohol consumption (MAC), Fibrosis-4 (FIB-4) index, alkaline phosphatase (ALP) and glycated haemoglobin (HbA1c) as independent predictors of HCC in MASLD patients. In non-cirrhotics, age, MAC, FIB-4, gamma-glutamyl transferase (GGT) and HbA1c were independently predictive of HCC. In MASLD and non-cirrhotic MASLD cohorts, models displayed good discrimination with Harrell's c-index values of 0.89 and 0.85 respectively for predicting HCC. In the validation cohort, Harrell's c-index value was 0.86 for both models.

Conclusion: We identified predictors of HCC development and derived novel HCC risk prediction scores in an ethnically diverse cohort of patients with MASLD. These models have the potential to support risk stratification and guide patient selection for HCC surveillance. External validation and cost effectiveness studies will allow assessment of generalisability to broader populations.

PO6-06-YI
Inter-observer variability of liver biopsy reading in clinical trials for metabolic dysfunction-associated steatohepatitis: A monocentric experience

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Background and Aims: Liver histology plays a crucial role in clinical trials concerning metabolic dysfunction-associated steatohepatitis (MASH). Despite the issues associated with invasive liver biopsies—including complications, related costs, and variability in interpretation—they remain essential for defining inclusion/exclusion criteria and surrogate endpoints. The variability in results can lead to screening failures in clinical trials and may misrepresent study outcomes.
Method: We assessed the reliability of liver biopsy readings conducted in the context of nine different clinical trials for MASH at our center. Fifty-nine samples were analyzed by both central hepatopathologists and our hospital's pathology unit. We compared internal and central MASH-validated scores, including the MASH CRN scores (steatosis, inflammation, ballooning, and fibrosis), MASH diagnosis, MASH+F>1 diagnosis, and MASH+F>2 diagnosis. Inter-reader reliability was assessed by overall percentage agreement observed and by unweighted kappa coefficients. The kappa coefficient represents the degree that agreement between 2 observations differs from that expected by chance.

Results: Inter-reader percentage agreement (and unweighted kappa coefficients) observed were 60% (0.383), 64% (0.216), 68% (0.0), 26% (-0.199), and 48% (0.190) for steatosis, ballooning, lobular inflammation, NAS score, and fibrosis respectively. Inter-reader percentage agreement (and unweighted kappa coefficients) observed were 66% (0.088), 60% (0.211), and 87% (0.585) for MASH, MASH+F>1, and MASH+F>2 diagnoses respectively. According to study-specific inclusion criteria, inter-reader percentage agreement (and unweighted kappa coefficients) observed was 67% (0.289).

Conclusion: The reliability of hepatopathologists' liver biopsy evaluation using currently accepted criteria is suboptimal. This lack of reliability may affect MASH clinical trials by misclassifying fibrosis subgroups and MASH diagnosis leading to patients who do not meet MASH study entry criteria. Therefore, the decision to require liver biopsy to grade MASH for the prescription of future approved drugs should be carefully considered.

PO6-08-YI
MASLD and FIB4 are independent predictors of major adverse liver outcomes and cardiovascular events in type 2 diabetes: findings from a single-center cohort using AI-driven machine learning

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Background and Aims: MASLD and liver fibrosis are common in type 2 diabetes (T2D), and the FIB-4 index is a widely used non-invasive marker of liver fibrosis. However, data on the specific predictive role of FIB-4 in identifying the risk of major adverse liver outcomes (MALOs) in T2D remain limited.
The primary objective of this study was to evaluate whether the presence of MASLD and elevated FIB-4 predict an increased incidence of MALO in a cohort of patients with T2D, utilizing AI-driven data extraction for analysis. Secondary objectives included assessing whether MASLD and FIB-4 serve as predictors of MACE, and identifying any additional variables associated with MALO and MACE.

Method: This was an observational retrospective cohort study conducted at the outpatient diabetes clinic of the Gemelli Polyclinic in Rome, Italy, from Jan-2016 to Jan-2022. Data were extracted using an AI driven system, which collected comprehensive clinical information. The cohort consisted of adult patients with T2D. MASLD was identified by imaging or the Hepatic Steatosis Index (HSI) and the FIB-4 was calculated. A FIB-4 greater than 2.67 was considered indicative of a high probability of advanced liver fibrosis.
The primary outcome was the occurrence of MALO, while a secondary outcome was MACE. To evaluate the predictive role of MASLD and FIB-4 for MALO and MACE, multivariable logistic regression models were developed. Each model was adjusted for clinically relevant covariates, with statistical significance defined as $p < 0.05$.

Results: A total of 1,711 patients were included, of whom 67 (3.9%) experienced a MALO and 203 (11.86%) a MACE. Patients with MASLD had significantly higher odds of experiencing MALO (OR 2.03, 95% CI 1.10–3.77, p=0.024) and MACE (OR 1.40, 95% CI 1.01–1.95, p=0.042). A FIB-4 >2.67 was strongly associated with an increased risk of both MALO (OR 6.92, 95% CI 4.01–11.96, p<0.001) and MACE (OR 2.39, 95% CI 1.67–3.42 p<0.001). In the second multivariable model, which excluded patients with cirrhosis at baseline, MASLD remained a significant predictor of MALO (OR 2.51, 95% CI 1.04–6.04, p=0.040), and a FIB-4 >2.67 continued to be associated with an increased risk of MALO (OR 3.02, CI 1.34–6.77, p=0.007). Additionally, HbA1c was a significant predictor in both models (OR 1.02, 95% CI 1.01–1.04, p=0.009).

Conclusion: This study demonstrated that MASLD and elevated FIB-4 are independent predictors of MALOs and MACE in patients with T2D. The findings underscore the importance of routine non-invasive screening for liver fibrosis and MASLD in diabetic populations, as well as the role of HbA1c in predicting adverse outcomes. Early detection and optimal glycemic control could help reduce the risk of both liver and cardiovascular complications. Furthermore, the use of AI-driven data extraction demonstrates the potential for enhancing clinical research and improving patient management in real-world settings.

PO6-09-YI
Distinct postprandial metabolic and inflammatory responses in healthy individuals versus patients with metabolic dysfunction-associated steatotic liver disease

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Background and Aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a spectrum of conditions from simple steatosis to metabolic dysfunction-associated steatohepatitis (MASH), characterized by inflammation and fibrosis. Low-grade systemic inflammation, possibly driven by crosstalk between immune and metabolic pathways, may play a crucial role in the progression to MASH, wherein dietary responses and/or microbiome metabolites may contribute to this inflammatory-fibrotic state. This research aimed to explore whether postprandial metabolic and inflammatory responses to dietary triggers, e.g. saturated fat or fructose, may provide insights into the mechanisms driving the MASLD-MASH transition. Or indeed, better define MASLD vs MASH phenotypes.

Method: 34 patients with obesity and MASLD and 10 non-obese healthy controls were recruited. Patients with MASLD were stratified according to liver fibrosis score (FibroScan; F0/1 MASLD, n = 18; F2/3 MASH, n = 16). MASLD, MASH, and healthy completed a high-fat mixed meal test (46g fat (33g saturated fat), 50g carbohydrates, 10g protein). MASLD and MASH also completed a high-fructose / glucose challenge (75g fructose, 25g glucose). Blood samples were drawn over 6-hours to evaluate metabolic (glucose, insulin, triglycerides (TAG), non-esterified fatty acids (NEFA)), inflammatory (IL-6) and metabolite responses. Ex vivo cytokine (IL-1β, IL-6, CCL3) responses to bacterial (TLR2/4) and viral (TLR7/8) ligands were determined in whole blood.

Results: Insulin resistance, determined by HOMA-IR, was greater in MASLD and MASH vs healthy. Postprandial increases in glucose, insulin and TAG were significantly greater in patients with MASLD and MASH compared to healthy but were similar between MASLD and MASH. Plasma IL-6 responses were also similar between MASLD and MASH. Interestingly whole blood inflammatory profiles were distinctly different. MASLD, but not MASH, exhibited greater whole blood cytokine responses to bacterial and viral ligands compared to healthy. The IL-1β response to viral ligands was higher in MASLD versus MASH.

Conclusion: The preliminary data suggests that whilst a continuum of postprandial metabolic dysfunction presents in MASLD vs MASH, there are nuances with respect to inflammatory responses which may/may not explain fibrotic disease progression

PO6-10
Prevalence of steatosis and steatohepatitis in patients undergoing bariatric surgery: A biopsy-based study

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Background and Aims: Obesity and its complications are considered a major health problem worldwide. Many patients with morbid obesity and steatosis may require bariatric surgery. Liver biopsy is still considered the gold standard for diagnosing steatosis and can be done during bariatric surgery.
The aim is to study the prevalence of steatosis, steatohepatitis, and the associated risk factors in obese patients undergoing bariatric surgery.

Method: A prospective, single-center, biopsy-based study was conducted involving 162 patients who underwent sleeve gastrectomy. The study assessed various patient characteristics including age, sex, diabetes mellitus (DM) status, body mass index (BMI), liver function tests, lipid profiles, and insulin resistance (measured by the homeostatic model assessment of insulin resistance, HOMA-IR). Steatosis was assessed using both liver biopsy and the Controlled Attenuation Parameter (CAP). During the surgery, liver biopsies were collected and subsequently analysed by two expert pathologists to determine the presence of steatosis and steatohepatitis.

Results: The prevalence of steatosis in the study population, as determined by liver biopsy, was 63.6%. Among these cases, 37.7% were classified as mild steatosis (S1), 22.8% as moderate steatosis (S2), and 3.1% as severe steatosis (S3). Additionally, only 14.2% of the patients with steatosis were found to have steatohepatitis. Notably, 36.4% had no steatosis (S0). The absence of steatosis was significantly associated with younger age ($p = 0.041$), female sex ($p = 0.007$), low prevalence of DM ($p = 0.036$), lower HOMA-IR ($p= 0.038$), lower hemoglobin ($p= 0.008$), and lower albumin levels ($p = 0.008$). However, there was no significant association between steatosis and BMI, liver enzymes, or lipid profile, about 40% of patient without steatosis (S0) were diagnosed by CAP as sever steatosis (S3).

Conclusion: The prevalence of steatosis and steatohepatitis in obese patients undergoing bariatric surgery was 63.6%. Female sex, younger age, lower prevalence of diabetes, and lower HOMA-IR are associated with absence of steatosis and steatohepatitis. The current cutoff values of CAP for hepatic steatosis led to over diagnosis in obese patients and should be reevaluated.

PO6-11-YI
ASAP score for hepatocellular carcinoma risk stratification in patients with metabolic dysfunction-associated steatotic liver disease on long-term follow-up

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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) worldwide. The identification of novel tools able to stratify the risk of HCC is an unmet medical need. We aimed to investigate the performance of alpha-fetoprotein (AFP), protein induced by vitamin K absence or antagonist II (PIVKA-II), and age-sex-AFP-PIVKA-II (ASAP) score for HCC risk stratification in MASLD patients on long-term follow-up (FU).

Method: We retrospectively enrolled 515 MASLD patients (age: 58, 49–66 years; males: 285 [55.3 %]; T2DM: 251, [48.7 %]) with advanced liver fibrosis (liver stiffness measurement [LSM] ≥ 8.0 kPa or F ≥ 2 at liver biopsy); 374 / 515 (72.6 %) had compensated advanced chronic liver disease (cACLD) (LSM ≥ 10.0 kPa or F ≥ 3 at liver biopsy). All patients had at least 6 months of FU. AFP and PIVKA-II were measured by CLEIA (Lumipulse®G600II, Fujirebio, Japan) in baseline serum samples. Performance for HCC prediction was assessed by C statistic.

Results: During a median of 2.8 (IQR 1.0 – 4.6) years of FU, 26 / 515 (5.1 %) patients developed HCC (BCLC 0/A, n = 18 [69.2 %) vs. BCLC B/C, n = 8 [30.8 %]). HCC incidence rate was 1.39 per 100 person/years in the overall study cohort (n = 515) and 2.02 per 100 person/years among cACLD patients (n = 374). In the entire study cohort, ASAP score showed a moderate accuracy for HCC prediction (C-index = 0.77, 0.68 – 0.86), that was significant superior to each biomarker used alone (AFP, C-index = 0.71, 0.60 – 0.83; PIVKA-II, C-index = 0.72, 0.61 – 0.84). Furthermore, ASAP score allowed to stratify patients into 3 risk categories with different HCC incidence: low-risk (ASAP score ≤ -0.75; incident HCC: 2 / 148; 1.4 %), medium-risk (ASAP score -0.75 –0.75; incident HCC: 13 / 302; 4.2 %), and high-risk (ASAP score > 0.75; incident HCC: 11 / 64; 16.9 %) (log-rank test, p < 0.001). Notably, no HCC occurred in the low-risk group in the first 4 years of FU.

Conclusion: In MASLD patients with significant fibrosis, ASAP score showed appropriate performance for HCC prediction and may be useful to tailor a personalized surveillance strategy according to patients' individual risk of HCC development.

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PO6-12-YI

Association between polycystic ovary syndrome, steatotic liver disease in pregnancy, and adverse pregnancy outcomes: results from the prospective Fatty Liver in Pregnancy cohort

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Background and Aims: Polycystic Ovary Syndrome (PCOS), often associated with insulin resistance (IR), is one of the strongest predictors of steatotic liver disease (SLD) in women, which in turn has been associated with adverse pregnancy outcomes (APOs). We evaluated the relationship between PCOS and SLD in pregnancy, the role of IR, and its influence on APOs.

Method: We leveraged the prospective "Fatty Liver in Pregnancy" cohort to evaluate the prevalence of PCOS by medical record and SLD by liver ultrasound performed between 18-26 weeks gestation. PCOS patients were stratified by evidence of IR, defined as history of diabetes mellitus (DM) or gestational diabetes (GDM) in a prior pregnancy. History of pre-pregnancy SLD, SLD during pregnancy, and prevalence of APOs were compared between the groups and to a control population without SLD/PCOS.

Results: Of 1,148 patients enrolled from 2019-2024, 73 (6%) had PCOS; 211 (18%) had evidence of SLD. Patients with PCOS were more likely to be Hispanic (60% vs 54%, p= 0.04), have hypertension (20% vs 8%, p = 0.00), have taken Metformin previously (4% vs 0.3%, p = 0.00) or Aspirin during pregnancy (50% vs 35% p = 0.02), and were on average older (31% vs 29%, p = 0.01) with higher pre-pregnancy BMIs (31% vs 28%, p = 0.00). The PCOS group had higher rates of prior GDM as well as DM (17% vs 5%, p = 0.01; 9% vs 3%, p = 0.01), as did those with SLD (13% vs 6%, p = 0.00; 8% vs 3%, p = 0.00). In those with both SLD and PCOS, rates were higher than in either group alone compared to controls (36% p = 0.00; 19% p = 0.00). PCOS patients had a higher incidence of preeclampsia (21% vs 13%, p = 0.05), which more than doubled in those with PCOS and IR (47% vs 13%, p = 0.00). There was an increased incidence of preterm birth and current GDM in those with PCOS and IR (33% vs 14%, p = 0.03; 29% vs 11%, p = 0.04). The PCOS cohort had a higher prevalence of diagnosed pre-pregnancy SLD (4% vs 1% p = 0.01), which was increased in those with PCOS and IR (13% vs 1%, p = 0.00). Those with PCOS and IR also had an increased incidence of SLD in pregnancy (43% vs 20%, p = 0.03). In a multivariate analysis adjusted for age and BMI, PCOS with IR was associated with SLD in pregnancy (OR 3.11, CI: 1.02-9.45; p = 0.05).

Conclusion: SLD was seen in 26% of pregnant patients with PCOS. Although PCOS is a known risk factor for SLD, only PCOS with IR was associated with SLD in pregnancy. PCOS with IR also plays an important role in the development of some APOs, necessitating the consideration of PCOS phenotypes when evaluating risk of both SLD in pregnancy and pregnancy outcomes.

PO6-13-YI
Diagnosis, prognosis and sequential use of non-invasive tests in patients with MetALD

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Background and Aims: Non-invasive tests (NITs) play a central role in the early detection and risk stratification of steatotic liver disease (SLD). However, whether the recommended NIT cut-offs are applicable in metabolic and alcohol-related liver disease (MetALD) remains unclear. We evaluated the diagnostic, prognostic and sequential use of five NITs in patients with MetALD.

Method: Single-center cohort study with patients classified by histological or ultrasonic hepatic steatosis and self-reported alcohol intake. We used diagnostic low rule-out/high rule-in cut-offs for advanced fibrosis (≥F3) with FIB-4 (<1.30/≥2.67), ELF (<9.8/≥11.3), ADAPT (<6.3/≥7.2), LiverRisk score (<10/≥15) and TE (<10 kPa/≥15 kPa). Liver biopsies were the diagnostic reference and we evaluated prognostic performance for hepatic decompensation and mortality with Harrel's C.

Results: We identified 291 patients with SLD of which 73 had MetALD. Sensitivity to rule-out ≥F3 and specificity to rule-in was ≥75% for all NITs in MetALD patients. Applying both rule-out and rule-in cut-offs, FIB-4 (47%) had the largest indeterminate zone, while it was lowest with ADAPT (11%) and TE (11%). Blood-based NITs and TE rule-out concordance was highest with LiverRisk score (81%) and lowest with FIB-4 (56%). For clinical outcomes, patients were followed for a median of 62 months (IQR: 50-89 months). Among MetALD patients, 18 died and 13 developed hepatic decompensation during follow-up. All NITs were prognostic for decompensation-free survival in MetALD, with the highest Harrel's C for ADAPT ≥7.15 (C-statistic=0.794) and lowest for FIB-4 <1.30 (C-statistic=0.619). A sequential testing strategy with FIB-4 as the first-tier, ELF or ADAPT as the second tier, and TE as the third tier, showed similar prognostic performance for hepatic decompensation between the only ELF (HR=21.1, 95% CI: 4.6-96.6) or ADAPT (HR=23.1, 95% CI: 5.2-108.0) strategy.

Conclusion: Widely available NITs are applicable for MetALD, where cut-offs can diagnose advanced fibrosis and predict clinical outcomes.

PO6-14
Fast and robust MRI assessment of abdominal obesity and liver tissue characteristics – a population-scale analysis

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Background and Aims: Accurate body composition tools have become increasingly important for assessing adipose and muscle tissue in clinical and research settings, including obesity management and sarcopenia assessment. While volumetric MRI offers a comprehensive assessment, single-slice MRI has emerged as a useful alternative due to lower costs and reduced data processing requirements, making it practical for use in conjunction with MRI sequences used for monitoring liver and cardiometabolic risk factors. This study aimed to evaluate the correlations between single-slice and volumetric assessments of visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), and skeletal muscle tissue, and their associations with liver and cardiometabolic risk factors.

Method: We analyzed data from a subset of 4,604 individuals in the UK Biobank (50% male, mean age 62 years [SD 7], BMI 27 [4] kg/m2). A single axial slice at L3 was extracted from Dixon MRI to measure VAT, SAT, and skeletal muscle areas using semi-automatic segmentations, while VAT and SAT volumes were obtained through automated segmentation techniques. Liver MRI scans were analysed using LiverMultiScan. Correlation coefficients were used to assess the relationship between single-slice measurements and volumetric VAT, SAT, and skeletal muscle, as well as their associations with cardiometabolic risk factors.

Results: Single-slice L3 measurements of SAT and VAT demonstrated very strong correlations with VAT volumes (rho = 0.97, $p < 0.001$) and SAT (rho = 0.94, $p < 0.001$), independent of sex, age, BMI, waist circumference, diabetes status, and liver tissue characteristics (SAT: median rho 0.93, VAT: median rho 0.96, all $p < 0.001$). Both single-slice and volumetric VAT/SAT measurements showed similar correlations with liver and cardiometabolic risk factors (all $p < 0.01$ for liver cT1, liver fat content, HbA1c, triglycerides, high-density lipoprotein, systolic blood pressure). Single-slice skeletal muscle measurements correlated strongly with abdominal skeletal muscle volumes ($r = 0.90$, $p < 0.001$).

Conclusion: Single-slice L3 measurements of VAT, SAT, and abdominal skeletal muscle show robust correlations with volumetric assessments across individuals with diverse cardiometabolic profiles, while exhibiting comparable associations with liver and cardiometabolic risk factors. The brief scan time (approx.1 min, or under 15 min when combined with LiverMultiScan) provides a practical and efficient solution for clinical applications, including the monitoring of treatment responses in MASLD and obesity clinical trials.

PO6-15
Cardiovascular risk from metabolic dysfunction-associated steatotic liver disease, cardiometabolic risk factor count, and their longitudinal changes

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Background and Aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is known to be associated with incident cardiovascular disease (CVD). However, CVD risk could vary across individuals with MASLD depending on their cardiometabolic burden. The presence of MASLD, as well as its risk burden, may also change over time. We investigated the cardiovascular implications of MASLD, cardiometabolic risk factor count, and their longitudinal changes.

Method: From nationwide health screening data, we included adults aged 20-79 without increased/excessive alcohol intake or concomitant liver diseases at baseline examination in 2009 (N=7,292,497). Participants were classified according to MASLD status; those with MASLD were further categorized based on their count of qualifying cardiometabolic risk factors (1-5). The subgroup of participants who underwent follow-up examinations in 2011 (N=4,198,672) were additionally classified according to their baseline and follow-up MASLD status; those with persistent MASLD were further categorized based on the combination of baseline and follow-up cardiometabolic risk factor counts. The risk of CVD event, defined as a composite of myocardial infarction, ischemic stroke, heart failure, or cardiovascular death, was assessed using multivariable-adjusted Cox model.

Results: Over a median follow-up of 12.3 years, 220,088 new CVD events occurred. The presence of MASLD was associated with higher CVD risk than its absence (HR, 1.44 [95% CI, 1.43-1.46]). Among participants with MASLD, the CVD risk increased gradually with higher cardiometabolic risk factor count (per 1-higher; HR, 1.18 [95% CI, 1.18-1.19]). The development of MASLD during follow-up was associated with higher CVD risk than its sustained absence (HR, 1.28 [95% CI, 1.25-1.31]), whereas the regression of MASLD was associated with lower CVD risk than its sustained presence (HR, 0.84 [95% CI, 0.82-0.86]). Among individuals with persistent MASLD, gaining cardiometabolic risk factor counts during follow-up was associated with elevated CVD risk (per +1 change; HR, 1.12 [95% CI, 1.11-1.13]), whereas losing risk factor counts was associated with reduced CVD risk (per -1 change; HR, 0.89 [95% CI, 0.88-0.90]).

Conclusion: MASLD status, cardiometabolic risk factor count, and their longitudinal changes were all associated with CVD risk. Accurate identification of these factors may facilitate personalized assessment and management of CVD risk related to MASLD.

PO6-20-YI

Baseline liver elastography and its longitudinal changes predict liver related outcomes in patients with metabolic dysfunction-associated steatotic liver disease (MASLD)

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Background and Aims: Liver fibrosis is the primary prognostic factor in MASLD. Liver biopsy is the gold standard for staging fibrosis, although it is invasive and expensive procedure. Currently, non-invasive methods are available to stratify the degree of fibrosis.
The aim of this study is to validate liver stiffness as a prognostic factor both at baseline and in its variation over time during follow-up.

Method: This is a retrospective single-center cohort study including 389 patients who underwent at least two Fibroscan liver stiffness measurements, with a minimum 6-month interval between scans, from January 2011 to December 2023. They were stratified into 3 risk groups according to Baseline liver stiffness measurements (LSM) (<10, 10-20, >20 kPa). Primary outcome was a composite of Liver Related Events (LRE), death or liver transplantation.
Kaplan-Meier curves were generated for time to primary outcome stratified by Baseline LSM and Δ% Fibroscan categories (worsening: LSM increase >20%, stable, improved: LSM decrease >20%). Multivariable Cox regression analysis, adjusted for age, gender, BMI and type 2 diabetes, was used to assess the association of baseline LSM and Δ% fibroscan with primary outcome event. Cumulative incidence curves and incidence rates have been assessed and compared for each risk subgroup.

Results: During a median follow-up of 28 months (IQR 14.4 – 43.4), 29 (7.5%) patients experienced the composite primary endpoint. These patients were older and had a higher LSM at baseline (median 23.3 vs 6.2 kPa, p <0.01) and higher Δ% fibroscan (16.9% vs -3.5%, p <0.01) than patients who did not experienced a liver related event (LRE).
Baseline LSM show a good predictive performance for the composite endpoint events with an AUC of 0.897 (95% CI 0.845 – 0.948). Compared to patients with an LSM <10, patients with LSM between 10 and 20 kPa had a 9.7 fold higher risk for the primary outcome (HR 9.7 [2.05 – 45.79], p ≤0.01) and those with LSM>20 had a 55.6-fold higher risk (HR 55.63 [12.15 – 254.74], p ≤0.01).
Multivariate Cox regression analysis also revealed significantly lower risk of developing LRE for high-risk patients (>20 kPa) who showed longitudinal improvements (Δ%LSM > -20%) on fibroscan results (HR 0.16, 95%CI 0.04 – 0.68, p=0.01), and a significantly higher risk of developing LRE in intermediate patients (10-20 kPa) who showed worsening longitudinal changes (Δ%LSM > 20%) on fibroscan results (HR 6.66, 95%CI 1.69 – 26.23, p<0.01). Incidence rate of composite outcome per 1000 person-year was 15.5, 19.7, 81.4 for LSM improved, stable or worsened groups respectively.

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

PO6-22
Multi-parametric MRI of the liver and heart are associated with major liver and cardiovascular events: A prospective cohort study

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Background and Aims: Individuals with steatotic liver disease (SLD) and cardiovascular disease (CVD) experience higher rates of mortality and morbidity globally. Our aim was to investigate the prognostic value of MRI-derived biomarkers in assessing the risk of experiencing liver or cardiovascular events, both at the population level and in individuals with SLD.

Method: UK biobank participants aged 40-70 years were scanned between 2016 and 2020. LiverMultiscan was used alongside cardiac MR (CMR) to estimate cT1 (ms), liver fat content (%) and left ventricular ejection fraction (LVEF, %) in a multiorgan assessment. Outcomes were new-onset major liver events, major CVD events, related hospitalization, and all-cause mortality from hospital and death registry records. Hazard ratios were reported, adjusted for age, sex and body mass index (BMI) and repeated in steatotic liver disease (SLD: liver fat > 5% and one cardiometabolic risk factor)

Results: 28,841 had available LiverMultiScan and CMR data (mean age 64 years, 53 % female, 17% BMI ≥ 30 kg/m^2) with a median follow-up time of 4 years (2-6). 7761 people met the diagnostic criteria for SLD (mean age 64 years, 40% female, 40% BMI ≥ 30 kg/m^2). The median time to liver events was 32 months (18-44), and to CVD events was 28 months (14-41). Overall incidence rates per 1000 person-years were 0.4 for liver events and 2.4 for liver hospitalization; 11 for CV events and 14 for CVD hospitalization; and 3.2 for all-cause mortality.
As a continuous variable, liver cT1 was associated with liver and CVD events and all-cause mortality while liver fat was only associated with liver-related hospitalization. The risk of CVD event was significantly elevated with cT1 ≥ 800ms (HR: 1.3, [1.1,1.6]). There was no further increase in CVD risk with increasing cT1, there was, however, a highly significant risk of liver related events with higher cT1 (≥ 875ms; 13.1 [4,7,37]). These results were maintained in the SLD group. In those with repeat LiverMultiScans (n=2,325, mean follow-up time = 3 years (2.9-3.1)), increasing cT1 was associated with increased CVD events and hospitalizations (combined: HR 2.0, 1.1-3.7, $p < 0.01$), compared with stable cT1, with no corresponding association for increasing PDFF.
Reduced LVEF was associated with cardiovascular events and hospitalization. Concurrent LVEF ≤ 50% and elevated cT1 (≥ 800ms) was associated elevated risk of all-cause mortality (HR: 2.6, [1.1,6.4]) and with a shorter time to having a CVD event (median time to event 0.8 vs, 2.4 years; $p < 0.05$).

Conclusion: In a population level study, elevated cT1 was associated with an increased risk of both liver and cardiovascular events. The risk of mortality is greatly increased in those with evidence of both liver and cardiac impairment suggesting a role for integrated prevention pathways.

PO6-23-YI
Reference ranges and determinants of hepatic steatosis and increased liver stiffness in the third trimester of pregnancy using transient elastography

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Background and Aims: Steatotic liver disease (SLD) poses a significant public health challenge, increasingly affecting younger individuals and reproductive age women. Pregnancy is a valuable opportunity to identify maternal disease predispositions and to apply preventative interventions; however, most efforts to date have focused on investigating gestational risk factors for cardiovascular disease and type 2 diabetes mellitus, with limited attention given to maternal liver health. This study aimed to better understand the relationship between SLD and pregnancy, and to establish gestation-specific reference ranges for transient elastography in the third trimester.

Method: Three thousand pregnant women were prospectively recruited between 35+0- and 36+6-weeks' gestation at the Harris Birthright Research Centre (King's College Hospital, London, United Kingdom). Exclusion criteria were chronic liver disease, alcohol intake > 14 units/week pre-pregnancy, multifetal gestation and major fetal abnormalities. Hepatic steatosis and liver stiffness were assessed using FibroScan®, with exams considered suitable if at least 10 consecutive measurements were recorded, and the IQR/Median for stiffness measurement was ≤ 30%. The 90th percentile of Controlled Attenuation Parameter (CAP) and Liver Stiffness Measurements (LSM) was calculated to establish gestational cutoffs. Determinants of steatosis and increased liver stiffness were investigated with multiple logistic regression.

Results: Among participants, 70.2% were White, 15.9% Black, 7.4% South Asian, 1.9% East Asian, and 4.5% of mixed ethnicity. Median age was 34 years (interquartile range [IQR] 31-37) and median BMI in early gestation was 24.4 kg/m^2 (IQR 21.9-28.3). Gestational cutoffs were 246 dB/m for CAP values and 7.1 kPa for LSM. Steatosis was associated with obesity (odds ratio [OR] 11.7, 95% CI 8.01-17.2), overweight (OR 2.71, 95% CI 1.85-3.99) and weight gain during pregnancy (OR 1.03, 95% CI 1.01-1.06). Increased liver stiffness was associated with type 1 diabetes mellitus (OR 19.5, 95% CI 4.06-104), obesity (OR 1.94, 95% CI 1.3-2.87), a history of fetal growth restriction (OR 2.43, 95% CI 1.19 – 4.62), previous gestational diabetes (OR 1.98, 95% CI 1.10-3.74), pre-eclampsia (OR 1.8, 95% CI 1.04-2.97), and nulliparity (OR 1.56, 95% CI 1.11-2.20).

Conclusion: Overweight and obese women, those with pre-eclampsia and women with a history of fetal growth restriction or gestational diabetes may face a higher risk of long-term liver disease after pregnancy. By identifying at-risk groups, these results highlight pregnancy as an opportunity for early intervention, contributing to a multidisciplinary approach to managing SLD. Future longitudinal studies should focus on these subgroups to better understand the natural course of disease.

PO6-24
The impact of COVID - 19 on liver fibrosis progression in mexican patients with metabolic dysfunction associated steatotic liver disease: a case - control study

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Background and Aims: Chronic liver diseases rank as the fourth leading cause of death in Mexico. Covid-19 was the leading cause of death in 2020. Cardiovascular disease and diabetes are directly linked to metabolic dysfunction-associated steatotic liver disease (MASLD). Liver fibrosis can be assessed using FIB-4 index. Mortality from COVID-19 was directly linked to obesity, diabetes mellitus, cardiovascular diseases, and elevated FIB-4 levels, which were associated with a worse prognosis. Both liver fibrosis and the SARS-CoV-2 virus share profibrogenic pathways and could play a role in the progression of liver fibrosis. Therefore, it is crucial to determine the impact of COVID-19 on the progression of MASLD. To evaluate the differential impact of COVID-19 severity on fibrosis progression in patients with MASLD.

Method: We conducted a case-control study at the Centro Médico Nacional 20 de Noviembre in Mexico City. We employed ultrasound and FIB-4 index, to assess liver fibrosis. Cases were patients with MASLD who had a history of SARS-CoV-2 infection within the past 24 months, stratified into moderate and severe categories. Controls were patients with MASLD without serological or clinical evidence of previous infection. Demographic, clinical, and laboratory data were collected from medical records. We calculated adjusted odds ratios for age, sex, BMI, and FIB-4 to assess the association between COVID-19 severity and fibrosis progression in MASLD patients.

Results: A total of 160 patients were included in the study: 84 cases and 76 controls. The majority of patients were female (77.4 %, n = 65), and males (22.6 %, n = 19). Obesity class I was the most prevalent (40%), followed by overweight (36.3%), obesity class II (15%), and normal weight (7.5 %). The primary comorbidities were type 2 diabetes (35.6 %) and systemic hypertension (33.8%). Among the cases, 40.6% had mild COVID-19, 11.3 % moderate COVID-19, and 1 % had severe COVID-19. The distribution of FIB-4 index showed that 57.4% were in the mild risk category, 28.1 % in the moderate risk category, and 12.5 % in the severe risk category. There were no statistically significant differences ($p > 0.05$) between cases and controls for variables such as HOMA-IR, glucose, HbA1c, insulin, triglycerides, cholesterol, LDL, HDL, ALT, AST, albumin, GGT, C-reactive protein, and ferritin. In the groups with mild, moderate, or severe COVID-19, there were no statistically significant differences in FIB-4 values ($p > 0.05$). The odds ratio for FIB-4 in advanced fibrosis was 1.9 (95 % CI: 0.439 - 8.240).

Conclusion: Our study did not find a significant association between COVID-19 infection and the progression of liver fibrosis in patients with MASLD. While comorbidities influenced the outcomes, their interaction with COVID-19 regarding fibrosis was not statistically significant. Further research is needed to confirm these findings.

PO7-01
Efficacy of essential phospholipids in reducing hepatic steatosis in patients with different stages of metabolic dysfunction-associated steatotic liver disease – A phase IV study

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Background and Aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is strongly linked with obesity, type-2 diabetes, and dyslipidaemia. Essential phospholipids (EPLs) are used as adjunctive therapy for managing liver disorders. This study assessed the efficacy of EPL in reducing hepatic steatosis in patients with MASLD and metabolic diseases.

Method: Patients (aged 18-70) with MASLD, baseline steatosis (CAP score > 248 dB/m), liver fibrosis F1-F3 (liver stiffness measurement: 5-13 kPa) and at least one metabolic disease were randomized 1:1 to receive EPL (1800 mg/day/EPL Os + standard of care [SOC]) or placebo + SOC. Primary outcome: Reduction in steatosis (CAP score) from baseline to 6 months. Secondary outcomes: CAP score subgroup analysis by baseline CAP, HbA1c, TG, country, gender; efficacy results on HbA1c and lipid parameters (TG, LDL-C and HDL-C) over study period.

Results: Among 193 patients, modified intention-to-treat set included 82 (EPL; mean age: 53.7 yrs) and 83 (placebo; mean age: 52 yrs) patients. Most had obesity (EPL: 78%, placebo: 85.5%) and CAP scores ≥ 280 dB/m (EPL: 82.9%, placebo: 81.9%). A statistically significant reduction in CAP score at month 6 was seen in EPL vs placebo (p=0.0269). Subgroup analysis showed reduction in CAP score with EPL vs placebo across different stages of liver and metabolic diseases: CAP subgroups: < 288 dB/m, (least square mean difference (LSMD) [95%CI], p-value) (-16.69 [-39.54 – 6.16], p=0.1474); ≥ 288 dB/m, (-12.97 [-28.65 – 2.71], p=0.104). HbA1c subgroup: < 8%, (-15.39 [-30.02 – -0.77], p=0.0392); ≥ 8%, (-18.84 [-50.12 – 12.44], p=0.2222). TG subgroup: ≤ 1.6935 mmol/L, (- 9.67 [-29.23 – 9.89], p=0.3265); >1.6935 mmol/L, (-16.49 [-34.62 – 1.65], p=0.0742). Country: Germany (-15.01 [-31.93 – 1.9], p=0.0812); Poland, (-14.85 [-35.64 – 5.95], p=0.1591). Gender: female, (-13.09 [-32.62 – 6.44], p=0.1857); male, (-17.12 [-35.27 – 1.04], p=0.0643). EPL significantly reduced HbA1c levels (LSMD, -0.55; 95%CI, -0.95 – -0.15; p=0.0069), while changes in lipid parameters were not statistically significant (LDL-C: -0.03 [-0.45 – 0.39], p=0.9051; HDL-C: 0.22 [-0.52 – 0.96], p=0.5617; TG: 0.06 [-0.22 – 0.34], p=0.6789; total cholesterol: 0.16 [-0.33 – 0.65], p=0.5281).

Conclusion: Treatment with EPLs significantly reduced hepatic steatosis and improved glycemic control in patients with MASLD, with varying disease severity, indicating its potential role as an early intervention alongside SOC.

PO7-02
Assessing the predictive accuracy of the aMAP Risk Score for hepatocellular carcinoma

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Background and Aims: Hepatocellular carcinoma (HCC) is a significant complication of cirrhosis, associated with high morbidity and mortality rates. Various scoring systems have been developed to predict the risk of HCC development, including the aMAP score, which was developed and validated in 2020. This study aims to evaluate the efficacy of the aMAP score in predicting the onset of hepatocellular carcinoma.

Method: We conducted a retrospective analysis of 62 cirrhotic patients monitored in our department between 2006 and 2022. We collected data on demographics, clinical parameters, cirrhosis status, HCC imaging results, and alpha-fetoprotein levels. The aMAP score (ranging from 0 to 100) was calculated based on age, sex, albumin-bilirubin levels, and platelet count. Data were analyzed using SPSS software version 26.

Results: A total of 62 patients were analyzed, with a male-to-female ratio of 1.36. The mean age was 64 ± 12.7 years. The primary causes of cirrhosis included hepatitis C virus (35.5%), hepatitis B virus (30.6%), metabolic dysfunction-associated steatotic liver disease (6.5%), and indeterminate origins (27.4%). During follow-up, 45.2% (n=28) of patients developed HCC, with a mean time to onset of 12 months. Imaging revealed a single nodule in 64.7% (n=11) of cases. The mean aMAP score was 64.54 ± 9.08. The aMAP score was significantly higher in the HCC group compared to the non-HCC group. The predictive performance of the aMAP score for HCC development was significant, with an area under the receiver operating characteristic curve (AUROC) of 0.754 ($p < 0.001$). The optimal cut-off score was determined to be 57.5, yielding a sensitivity of 89% and a specificity of 56%.

Conclusion: The aMAP score is an accurate and user-friendly tool for predicting hepatocellular carcinoma in patients with cirrhosis. Its application in clinical practice may enhance surveillance, improve early detection of HCC, and potentially reduce mortality rates associated with this malignancy.

PO7-04
Advanced fibrosis affects quality of life and muscle function in patients with metabolic-dysfunction associated steatotic liver disease

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Background and Aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is an increasing global public health challenge that affects more than 30% of adults globally. The mainstay of treatment are lifestyle interventions, including exercise and healthy diet. Evidence on the direct impact of MASLD on quality of life (QoL) is limited. Also, emerging research highlights the role of muscle function in disease severity. This study aimed to explore the association between QoL, exercise, diet, muscle function, and MASLD severity defined by liver stiffness.

Method: Consecutive patients were prospectively enrolled from MASLD clinics at St. Mary's Hospital, London. Patients underwent anthropometric evaluation, and blood tests. Liver severity was assessed using transient elastography (TE). Muscle function was assessed via handgrip strength (HST) and the five-time sit-to-stand test (FTSST). Questionnaires evaluated adherence to the Mediterranean diet (MD), physical activity (PA), and QoL.

Results: One hundred twenty patients were included. Univariate analysis revealed a significant association between increased liver severity and worse QoL outcomes in physical and social functioning ($p<0.001$, $p=0.042$). Increased adherence to MD and PA was associated with significantly improved QoL domain scores in physical functioning and general health for MD ($p=0.040$, $p=0.022$) and emotional well-being and general health for PA ($p=0.010$, $p=0.037$). Multivariate analysis showed significant associations between body mass index (BMI) and seven QoL domains ($p<0.05$ in all). Independent T-testing revealed significant associations between fibrosis and weaker handgrip strength ($p=0.023$).

Conclusion: There was significant association between MASLD severity and reduced physical and social functioning. Furthermore, adherence to MD and PA, significantly improved physical functioning and emotional well-being. Clinical practice requires comprehensive management strategies and evaluation of muscle function, which is easily reproducible in practice, for MASLD patients.

PO7-05-YI
Therapeutic potential and safety profiles of resmetirom in the treatment of non-alcoholic steatohepatitis: a systematic review and meta-analysis

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Background and Aims: Non-alcoholic steatohepatitis (NASH) is a significant cause of liver-related morbidity and mortality, with limited treatment options. Resmetirom, a liver-specific thyroid hormone receptor-β agonist, has shown promise in reducing liver fat and improving fibrosis. This systematic review and meta-analysis aimed to evaluate the therapeutic potential and safety profiles of Resmetirom (MGL-3196) in the treatment of NASH.

Method: Patients with NASH were included in the analysis, with Resmetirom treatment compared to placebo. The primary outcomes assessed were NASH resolution, fibrosis improvement, hepatic fat reduction, changes in LDL, ALT, and adiponectin levels, and safety profiles including treatment-emergent adverse events (TEAEs). Randomized Controlled Trials (RCTs) were included, while non-RCTs, RCT Phase 1 studies, and animal studies were excluded. Data sources included PubMed, Cochrane, Web of Science, and Google Scholar.

Results: Resmetirom significantly increased the odds of achieving NASH resolution (OR = 2.40, 95% CI: 1.07 to 5.39) and fibrosis improvement (OR = 2.40, 95% CI: 1.07 to 5.39). It also significantly reduced hepatic fat content (mean difference = -21.42, 95% CI: -32.81 to -10.03) and ALT levels (mean difference = -15.94, 95% CI: -24.24 to -7.65), while increasing adiponectin levels (mean difference = 0.66, 95% CI: 0.13 to 1.18). However, no significant effect on weight loss was observed. Safety profiles indicated a higher incidence of TEAEs in patients treated with Resmetirom (OR = 1.55 for 80 mg and 1.99 for 100 mg), including an increased risk of drug-related adverse events (OR = 1.67, 95% CI: 1.31 to 2.12), diarrhea (OR = 2.17, 95% CI: 1.47 to 3.19), and nausea (OR = 1.87, 95% CI: 1.35 to 2.58).

Conclusion: Resmetirom (MGL-3196) shows promise in the treatment of NASH, demonstrating significant improvements in NASH resolution, fibrosis, MRI-PDFF, ALT levels, and adiponectin levels. However, it is associated with an increased risk of certain adverse events, particularly diarrhea and nausea. Further research is necessary to confirm these findings and explore the broader applicability of Resmetirom in diverse patient populations, including those with early-stage disease and cirrhosis.

PO7-06
Enhancing trial recruitment in MetALD and ALD with LiverPRO to detect fibrosis

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Background and Aims: Alcohol-related liver damage presents a clinical challenge due to a high risk of fibrosis progression, which is associated with high mortality and limited treatment options. Clinical trials often encounter high screen failure rates, primarily due to the difficulty in identifying candidates with significant liver fibrosis (defined as TE ≥8 kPa) in at-risk populations. This study introduces an improved method for identifying MetALD and ALD trial candidates using LiverPRO, a CE-marked diagnostic tool that employs machine learning to estimate the risk of liver fibrosis based on routine blood tests.

Method: This prospective, population-based cohort study included individuals from Southern Denmark with a history of self-reported excess alcohol use. Participants without a known history of liver disease were assessed using the new SLD nomenclature, and only those meeting the ALD and MetALD criteria were included in the analysis. In the definition of SLD, steatosis was defined as CAP >248 dB/m. We compared four non-invasive diagnostic tests: ELF, MELD-Na, FIB-4, and LiverPRO to evaluate their effectiveness in identifying suitable candidates with liver fibrosis for ALD clinical trials. The area under the receiver operating characteristic curve (AUC) was calculated for each test, with comparisons made using the DeLong method. Additionally, we report the number of correctly classified cases, false positive rates (FPR), and false negative rates (FNR). We applied a cut off of 9.8 for the ELF test, 9 for MELD-Na, 1.3 for FIB-4, and 65% for LiverPRO.

Results: A total of 1,855 participants with self-reported alcohol overuse were invited, of which 461 (25%) met the MetALD criteria and 198 (11%) met the ALD criteria. The median age was 61 years (IQR 54–66), and 68% were male. In the MetALD group, 12% had a TE >8 kPa, whereas in the ALD group, 29% had TE >8 kPa. The AUC for detecting elevated liver stiffness (TE ≥8 kPa) was for the ELF test 0.72 (95% CI 0.64-0.80), for MELD-Na 0.64 (95% CI 0.56-0.71), for FIB-4 0.77 (95% CI 0.70-0.84), and for LiverPRO 0.87 (95% CI 0.83-0.91). Pairwise comparisons using the DeLong method showed p-values <0.005 in all cases, indicating that LiverPRO was significantly better at identifying participants with elevated liver stiffness in a low-prevalence population. The correct classification rates for LiverPRO, ELF, MELD-Na, and FIB-4 were 85%, 82%, 74%, and 60%, respectively. The FPR were 8%, 14%, 20%, and 44%, and the FNR were 50%, 46%, 55%, and 19%, respectively, for LiverPRO, ELF, MELD-Na, and FIB-4.

Conclusion: LiverPRO demonstrated superior accuracy in detecting elevated liver stiffness among MetALD and ALD participants, making it an effective tool for improving recruitment in clinical trials.

PO7-08
Impact of type 2 diabetes on hepatic fibrosis in patients with MASLD

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Background and Aims: In Europe, the prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) is 30.9% in the general population and 68% among patients with type 2 diabetes (T2D). In Portugal, hepatic steatosis is found in 37.8% of the population, MASLD in 17%, and the estimated prevalence of T2D is 13.6%. T2D is considered a predictor of hepatic fibrosis and a risk factor for hepatocellular carcinoma (HCC). The main objective is to assess the impact of T2D on hepatic fibrosis in patients with MASLD.

Method: This retrospective study included MASLD patients who underwent hepatic elastography between July 2022 and February 2024. Criteria included: Controlled Attenuation Parameter (CAP) ≥ 248 dB/m for the diagnosis of steatosis; elasticity (kPa) of 8.5–10.2 kPa for F3 and >10.2 kPa for F4. Clinical, demographic, laboratory, elasticity, and CAP data were collected, excluding other causes of liver disease. Patients were divided into two groups: Group 1 (with T2D) and Group 2 (without T2D). Statistical analysis was conducted using SPSS.

Results: A total of 252 individuals (123 men), with a median age of 57 years and mean BMI of 31.98 kg/m², were included in the study; 96 patients in Group 1 and 156 in Group 2. No significant difference was found in BMI between groups, but significant differences were observed in age (higher in Group 1), male sex, dyslipidemia, and hypertension (both more prevalent in Group 1). A positive correlation was observed between the degree of steatosis and fibrosis stage ($p < 0.05$). Steatosis grade S3 was present in 83.3% of Group 1 versus 70.5% of Group 2 ($p < 0.05$); fibrosis F3/F4 in 47.9% of Group 1 versus 11.5% of Group 2 ($p < 0.001$); and cirrhosis in 29.2% of Group 1 versus 6.4% of Group 2.

Conclusion: T2D was associated with a higher degree of steatosis and more severe hepatic fibrosis in patients with MASLD, with cirrhosis observed in approximately one-third of diabetic patients. While BMI was similar between groups, diabetic patients had higher rates of hypertension, dyslipidemia, and were older. Early diagnosis of MASLD in T2D patients and screening for complications (cirrhosis and HCC) are essential.

PO7-09
Higher cut off values of CAP is needed to avoid over diagnosis of steatosis in obese patients

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Background and Aims: Obesity is a major risk for hepatic steatosis may lead to fibrosis and cirrhosis. Non-invasive methods can diagnose steatosis; however, biopsy is still the gold standard. Controlled attenuation parameter (CAP) is one of these non-invasive methods. The aim was to validate the cut off value for CAP and detect anew accurate cut-off value for diagnosis of steatosis in obese patients

Method: This is a prospective single-center biopsy-based study that included 636 obese patients who underwent liver biopsy during different surgical procedures. Steatosis was assessed using both liver biopsy and the Controlled Attenuation Parameter by fibro scan. Intraoperative wedge liver biopsies were analyzed by two hepato-pathologists. CAP examination with the XL probe performed with two expert operators

Results: For S1 steatosis we proposed a new cutoff value of 290 dB/m with sensitivity of 58.2% and specificity of 73.1%, and for S2 and S3 the cutoff value was 317 dB/m with sensitivity of 66.7% and specificity of 83.2%. CAP cut-off values were higher with increased BMI; for patients with BMI≥35 kg/m2 proposed CAP for S1 was 302 dB/m, and for S2& S3 was 317 dB/m. However, for patients with BMI< 35 kg/m2 proposed CAP was 273 dB/m for S1, and 345 dB/m for S2 and S3.

Conclusion: New cut-off values of CAP should be considered in obese patients. Precisely, higher cut-off values were closely associated with a higher BMI

PO7-11-YI
Risk-stratification of patients with metabolic dysfunction-associated steatotic liver disease and indeterminate vibration-controlled transient elastography

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Background and Aims: A noteworthy proportion of patients with metabolic dysfunction-associated steatotic liver disease (MASLD) have an indeterminate vibration-controlled transient elastography (VCTE). Among these patients, we aimed to identify candidates for MASLD treatment by diagnosing significant fibrosis.

Method: Real-world prospective study including a large dataset of MASLD patients with paired VCTE and liver biopsy from 6 centers. A total of n=1196 patients were recruited and divided in training (3 centers, Spain), internal validation (2 centers, Spain), and external validation (1 center, United States) cohorts. In patients with indeterminate liver stiffness measurements (LSM:8-12 kPa), a diagnostic algorithm was developed to identify significant fibrosis, defined as histological stage ≥F2. Statistical analysis was performed using gaussian mixture model (GMM) and k-means unsupervised clusterization.

Results: From the eligible population, 33%, 29%, and 31% had indeterminate VCTE in the training, internal and external validation samples, respectively. Controlled attenuation parameter (CAP) allowed the differentiation of GMM clusters with a cut-off of 280 dB/m (AUC:0.89 [95%CI:0.86-0.97]). Within patients with <280 dB/m, a LSM between 8.0-9.0 kPa showed a 93% sensitivity and a 91% negative predictive value to exclude significant fibrosis. Among patients with ≥280 dB/m, a LSM between 10.3-12.0 kPa diagnosed significant fibrosis with a 91% specificity. Applying this algorithm to the validation cohorts, 36% of the indeterminate VCTE were re-allocated. The re-allocated high-risk group showed a prevalence of 86% significant fibrosis, opening the therapeutic window for MASLD patients.

Conclusion: To identify candidates for MASLD treatment among indeterminate VCTE, an algorithm-based on the sequential combination of LSM and CAP thresholds can optimize the diagnosis of moderate-to-advanced fibrosis.

PO7-12-YI
Use of Glucagon-like peptide-1 receptor agonist is associated with reduced risk of major liver-related events: A meta-analysis

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Background and Aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) represents a leading cause of chronic liver disease worldwide. While glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have shown promise in managing both metabolic and liver-related outcomes, evidence regarding their impact on major liver-related outcomes (MALOs) remains heterogeneous. This meta-analysis aimed to systematically evaluate the incidence of MALOs, specifically hepatocellular carcinoma and hepatic decompensation, in patients using GLP-1 RAs compared to non-users or users of other antidiabetic therapies.

Method: We conducted a meta-analysis following PRISMA guidelines, searching the main medical databases through November 2024. Eligible studies included adult patients with type 2 diabetes treated with GLP-1 RAs, reporting MALOs incidence, with appropriate adjustment for confounding factors. The incidence rates of MALOs (defined as diagnosis of cirrhosis, decompensated cirrhosis, hepatic failure or hepatocellular carcinoma) and relevant MALOs incidence effect measures, were extracted as number of events per person-year from intention-to-treat analyses of populations after adjustment for confounding factors and they were pooled by random effect model. When compared with different control arms in the same study, the population of GLP-1 RA users was included in the analysis for each comparison.

Results: Nine observational studies, including 554996 GLP-1 RA users and 712052 non-users, were included in the meta-analysis for MALOs. Use of GLP-1 RA was associated with a significant reduction of 47% in the risk of MALOs compared to non-users, with a pooled incidence rate ratio (IRR) of 0.53 (95%CI 0.32-0.88). Seven studies, including 436504 GLP-1 RA users and 440984 non-users, were included in the meta-analysis for hepatic decompensation. Use of GLP-1 RA was associated with a significant reduction of 34% in the risk of hepatic decompensation, with a pooled IRR of 0.66 (0.49-0.88). Nine studies, including 643496 GLP-1 RA users and 800413 non-users, were included in the meta-analysis for HCC. Use of GLP-1 RA was associated with a non-significant decrease of 20% in the risk of HCC, with a pooled IRR of 0.80 (95% 0.60-1.05).

Conclusion: This meta-analysis demonstrates that GLP-1 RA use is associated with significant reductions in major liver-related outcomes and hepatic decompensation in patients with type 2 diabetes, while showing a non-significant trend toward reduced HCC risk. These findings support the potential therapeutic value of GLP-1 RAs in preventing progression of liver disease towards complications.

PO7-14-YI
A comparison of the prognostic value of 10 body composition markers for steatosis, MASH and fibrosis in a general population setting

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Background and Aims: Excess abdominal fat is the cornerstone of metabolic dysfunction steatotic liver disease (MASLD), development of metabolic dysfunction associated steatohepatitis (MASH) and fibrosis. Although body mass index (BMI) is used primarily, it might not be the body composition marker that has the most prognostic value for impaired liver health. Here we compare 10 different body composition parameters and how they relate to steatosis, MASH and fibrosis.

Method: We used data from the NHANES 2017-2020 cycle, a United States population-based cohort with data on controlled attenuation parameter (CAP) and liver stiffness measurements (LSM). We selected participants with complete data on weight, height, waist circumference and hip circumference (HC). Exclusion criteria were excessive alcohol consumption, viral hepatitis and ALT > 100 U/L. Steatosis was defined as CAP ≥ 275 dB/m, MASH as FibroScan AST (FAST) score ≥ 0.35, and fibrosis as LSM ≥ 8 kPa. The prognostic value by area under curve (AUC)-analysis of a body shape index (ABSI), body adiposity index (BAI), BMI, body roundness index (BRI), hip circumference, waist circumference, waist to height ratio (WHtR), waist adjusted BMI (wBMI), and weight was determined for MASLD, MASH, and fibrosis. Statistically significant differences were assessed by DeLong test. Next, the correlation between the body composition parameters with CAP and LSM were assessed continuously. Analysis were stratified for sex.

Results: The cohort comprised 6867 participants (age 48 [32-62], 49% male) among them 41.6% had steatosis, 5.8% MASH and 8.7% fibrosis. Waist circumference obtained the highest AUC levels in the overall population for steatosis, MASH and fibrosis (AUC 0.81, 0.74 and 0.76, respectively). WHtR and BRI yielded both identical results in AUC analysis and obtained the highest results in male (AUC 0.83, 0.76 and 0.73, respectively) and in female (AUC 0.79, 0.73 and 0.81, respectively). WC was not significantly inferior compared to WHtR or BRI in the sex-stratified analysis for all investigated outcomes. Diagnostic accuracy for body composition markers for steatosis was lower in female compared to male (best AUC 0.79 vs 0.83), whereas the diagnostic accuracy of body composition markers for fibrosis was higher in female compared to male (best AUC 0.81 vs 0.76).

Conclusion: Waist circumference was the body composition parameter with highest prognostic value and strongest correlations with steatosis, MASH, and fibrosis in the overall population. Waist-circumference based body composition markers such as BRI or WHtR did not have significantly additional predictive value compared to waist circumference. Waist circumference should be considered as the preferred body composition parameter in individuals at risk of steatosis, MASH or fibrosis.

PO7-15
Lower plasma lipoprotein(a) threshold in MASLD patients with advanced fibrosis

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Background and Aims: Whether Lp(a) is associated with increased cardiovascular risk in metabolic dysfunction-associated steatotic liver disease (MASLD) patients is unknown. We aimed to investigate the association between plasma Lp(a) levels and major adverse cardiovascular events (MACE) in MASLD patients.

Method: In this retrospective study, we enrolled 55,357 Chinese patients with ultrasound-defined MASLD from Wenzhou and 4,130 patients with MASLD from Beijing. MACEs were defined as incident nonfatal myocardial infarction, nonfatal ischemic stroke and all-cause mortality. Lp(a) percentile groups were generated with the reference group set at the 1st to 50th Lp(a) percentiles. Cox proportional hazards modeling was used to assess the association between the Lp(a) percentile groups and MACE. Advanced liver fibrosis was defined as fibrosis (FIB)-4 index >2.67.

Results: Overall, 59,487 patients with MASLD (mean age 60.9, SD 12.3; 44.8% female) were analyzed with a median follow-up of 4.8 years (IQR: 2.0-8.3 years), and 8,631 patients had incident MACE morbidity or mortality. There was a significant inverse association between Lp(a) percentiles and advanced liver fibrosis. In patients with advanced liver fibrosis, there was a lower proportion (3.2% lower) in the 91st-100th percentile group of Lp(a) concentration (chi-squared test P <0.001), although the incidence of MACE remained high. MASLD patients with advanced liver fibrosis and high Lp(a) levels (71st to 90th percentile) had a significantly higher risk of MACEs (adjusted HR: 1.37, 95%CI 1.20-1.57; *P* <0.001) than those with low Lp(a) levels (1st to 50th percentile). In MASLD patients without advanced liver fibrosis, those with high Lp(a) levels (71st to 90th percentile) had a significantly higher risk of MACEs (adjusted HR: 1.25, 95%CI 1.18-1.32; *P* <0.001) than those with low Lp(a) levels (1st to 50th percentile). when considering the same HR, patients with advanced liver fibrosis had lower Lp(a) levels. These results were also found in sensitivity analysis.

Conclusion: The plasma Lp(a) levels associated with increased CVD risk were lower for MASLD patients according to the presence of advanced liver fibrosis.

PO7-17-YI
Missense variations in FADS1 and SCD1 genes oppositely affect lipid profile and cardiovascular risk in Italian children with MASLD: A possible monitoring tool also in adults?

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Background and Aims: Dyslipidemia is a hallmark of Metabolic dysfunction-associated steatotic liver disease (MASLD) and lipidomic studies highlighted that changes in hepatic and circulating lipids are related to cardiovascular (CV) complications. Although lipidomic data in children are scant, it has been postulated that alterations in lipid metabolism in pediatric MASLD are similar to that of adults with cardiometabolic disease. Genetics concurs to MASLD pathogenesis and polymorphisms in *FADS1* and *SCD1* genes, mediating fatty acids desaturation and elongation, may contribute in altering lipid profile. Thus, we aimed to assess the impact of variants in these genes on circulating lipids and cardiovascular parameters in 95 pediatric patients with MASLD.

Method: The pediatric cohort was genotyped for rs174537 G>T, rs174556 C>T in *FADS1*, and rs1502593 G>A, rs522951 G>C and the rs3071 A>C in *SCD1* by using Taqman assays. The presence of steatosis was evaluated through abdominal ultrasound and transient elastography.

Results: The pediatric cohort included mainly males (72%) with a mean age of 13±2.2 and BMI of 25±3.9. Hepatic steatosis (CAP>241dB/m) and liver stiffness were diagnosed in 74/80 (92% of which 77% moderate/severe) and 44/80 (55%) children, respectively. At bivariate analysis, variants in *FADS1* gene were associated with lower total cholesterol, LDL and APOB levels ($p<0.05$). These results were confirmed at generalized linear model adjusted by gender, age, BMI, HOMA-IR and TM6SF2 E167K mutation ($p<0.05$). Moreover, carriers of the *FADS1* SNPs showed a significant enhancement of omega-3 PUFAs (18:3n3; 20:5n3), which inversely correlated with arterial blood pressure thus supporting a protective role of these polymorphisms against CV risk. Accordingly, at multivariate analysis adjusted as above, lower epicardial fat thickness and left ventricular mass were detected in carriers of the rs174537 and rs174556 variants ($p<0.05$). Conversely, patients carrying the rs1502593, rs522951 and rs3071 in *SCD1* showed higher circulating cholesterol, LDL and APOB levels at bivariate analysis ($p<0.05$) and the effect remained significant at generalized linear model adjusted as before ($p<0.05$). In these patients, higher circulating saturated fatty acids (18:0, 18:1n7) were found, thus supporting that *SCD1* genetic variants raised the CV risk. In keeping with these findings, the presence of these mutations correlated with increased epicardial fat and blood pressure at multivariate analysis.

Conclusion: As in adult population, genetic screening of variations involved in lipid handling may aid for the identification of MASLD-related comorbidities in children. Specifically, *FADS1* and *SCD1* variants exert opposite effects on lipid profile thus resulting useful for the early stratification of subjects at low or high CV risk.

PO7-18-YI
Prevalence and predictors of steatotic liver disease and significant liver fibrosis in an integrated multidisciplinary healthcare pathway model

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Background and Aims: An integrated healthcare pathway model for metabolic-dysfunction associated steatotic liver disease (MASLD) is recommended for a comprehensive evaluation of the metabolic health. In this prospective study we aimed to assess prevalence and predictors of steatotic liver disease (SLD) and significant liver fibrosis (SLF) in consecutive patients first referred for type 2 diabetes mellitus (T2DM) or SLD in two different settings (diabetology and hepatology clinics) of the “AOU Città della Salute e della Scienza di Torino” University Hospital.

Method: All patients underwent vibration-controlled transient elastography for liver stiffness measurement (LSM) and controlled attenuation parameter (CAP), and echocardiography with speckle tracking analysis. SLD was defined by CAP>247 dB/m. SLF was defined by LSM>7 kPa. Diastolic dysfunction was defined by mitral E/E’ ratio>9 and systolic dysfunction by left ventricular global longitudinal strain (GLS)>-18.

Results: 544 patients (59% in the liver clinic group [LCG] and 41% in the diabetes clinic group [DCG]) were enrolled. In the LCG, all patients fulfilled the criteria for MASLD; prevalence of T2DM and obesity were 21.8% and 42.7%; 4.7% were referred to the DCG for first diagnosed or decompensated T2DM. Median LSM was 5.1 [4.6 – 6.3] kPa and SLF was detected in 17.8% of cases. In the DCG, prevalence of obesity was 52.0% and median LSM was 4.9 [4.1 – 5.9] kPa. SLD was present in 67.7% of cases, of which 59.6% MASLD, 1.3% ALD (alcohol-related liver disease) and 6.7% metALD. SLF was detected in 13.5% of cases, which were referred to the LCG for hepatological evaluation. A history of cardiovascular disease (CVD) was found in 9.7% and 50.2% of patients in the LCG and DCG, respectively. A high Framingham risk score (>20% of 10-year CVD-related mortality) was detected in 12.9% in the LCG and 1.3% in the DCG. Prevalence of diastolic and systolic dysfunctions in those without CVD were 27.4% and 18.2% in the LCG and 8.9% and 3.6% in the DCG. In the LCG, Body Mass Index (BMI) and T2DM were the strongest predictors of SLF (aOR 1.13[95%CI 1.06-1.21], p=0.0002 and 5.66 [95%CI 2.64-12.07], p<0.001). In the DCG, only transaminases were independent predictors of SLF (aOR 1.11 [95%CI 1.04-1.19], p=0.001), while BMI was the only predictor of SLD (aOR 1.09 [95%CI 1.03-1.16], p=0.001).

Conclusion: Two thirds of SLD in the diabetology setting are due to MASLD and associated with BMI. Prevalence of SLF is similar in hepatology and non-hepatology settings. A higher prevalence of pre-clinical CVD is detected in the hepatology setting by advanced echocardiography, consistent with a higher Framingham risk score.

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PO7-21
The major importance of a multidisciplinary team to manage patients with a multifactorial disease such as steatotic liver disease

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Background and Aims: A recent international consensus has introduced a new classification for steatotic liver disease (SLD) based on metabolic risk factors and alcohol consumption history, categorizing it into three subgroups: Metabolic dysfunction-associated steatotic liver disease (MASLD), defined by liver steatosis in the presence of at least one cardiometabolic risk factor; Metabolic and alcohol-related liver disease (MetALD) for those patients with cardiometabolic risk factors who consume moderate-to-high levels of alcohol (140–350 g/week for females and 210–420 g/week for males) and Alcohol-related liver disease (ALD) where alcohol consumption exceeds the previously mentioned alcohol thresholds for MetALD. While this classification is less stigmatizing, it remains unclear if these subgroups reflect distinct disease severity or outcomes. This study aims to analyze the impact of excessive alcohol consumption on SLD severity and assesses the impact of nutritional intervention in clinical outcomes and fibrosis-related metrics across the subgroups.

Method: We conducted a retrospective study of 296 patients with SLD from our outpatient hepatology clinic from February 2021 to May 2024 receiving nutritional consultations. Statistical analyses included Pearson's chi-squared test, the Kruskal–Wallis test, and paired samples t-test, with significance set at $p < 0.05$.

Results: Comparing with MASLD patients, MetALD and ALD patients are predominantly males with present or past smoking habits ($p < 0.01$). ALD patients exhibited a significantly higher Fibrosis-4 (FIB-4) score compared to MASLD patients ($p = 0.06$). Considering the overall population, after the first consultation, BMI significantly decreased from baseline to 12 months ($p = 0.018$) and further at 24 months ($p = 0.005$). Reported alcohol consumption significantly decreased from baseline to 12 months ($p < 0.001$) and 24 months ($p = 0.022$). However, specific fibrosis-related metrics, such as liver stiffness measurement and FIB-4 did not show significant longitudinal changes. Considering the subgroup analysis: MASLD patients decreased the BMI at 12 months ($p = 0.018$) and at 24 months ($p = 0.005$), the controlled attenuation parameter (CAP) at 12 months ($p = 0.007$) and at 24 months ($p = 0.006$) and the NAFLD score at 12 months ($p = 0.008$). MetALD patients significantly improve at 24 months the BMI ($p = 0.021$) and the liver stiffness ($p = 0.047$). ALD patients significantly decrease the alcohol consumption at 12 ($p < 0.01$) and at 24 months ($p = 0.006$) and improve the liver stiffness ($p = 0.009$) at 12 months.

Conclusion: A multidisciplinary approach in SLD patients showed positive impact in clinical and/or fibrosis-related metrics in all subgroups, reinforcing the importance of these strategies in metabolic and alcohol related patients.

PO7-23-YI
Dynamic changes in liver stiffness independently predict liver-related event risk in metabolic dysfunction-associated steatotic liver disease

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Background and Aims: The rising prevalence of cirrhosis and hepatocellular carcinoma (HCC) due to metabolic dysfunction-associated steatotic liver disease (MASLD) underscores the importance of early intervention to mitigate risks associated with liver disease progression. Non-invasive tools like liver stiffness measurement (LSM) via vibration-controlled transient elastography (VCTE) are increasingly used as alternatives to liver biopsy, aiding in diagnosing advanced fibrosis and tracking disease dynamics, thus improving patient management and enabling timely therapeutic actions. This study investigates the relationship between changes in LSM intervals and liver-related complications in MASLD patients.

Method: This retrospective cohort study included 180 patients over 18 years old with at least two LSM measurements and a minimum follow-up of three years. An interval-censored Cox model, following the approach by Gawrieh et al. (2024), was used to evaluate the impact of non-invasive tests (LSM, FAST, Fib-4) on liver-related event (LRE) risk. Patients were categorized based on LSM into low risk (<10 Kpa), cACLD (≥10 Kpa and <15 Kpa), and advanced cACLD (≥15 Kpa). LREs included severe liver complications: portal hypertension, hepatic decompensation, HCC, and liver-related mortality.

Results: The median age was 56 years (range: 16–71), with 72% female and 28% male participants, and a median BMI of 31 (range: 22–61). Median levels of liver enzymes were 33 U/L for AST and 44 U/L for ALT. The median of total cholesterol of 185.5 mg/dL, LDL of 106 mg/dL, HDL of 43 mg/dL, triglycerides of 147 mg/dL, fasting glucose of 111 mg/dL, and HbA1c of 6.3%. A total of 34 LREs were observed: portal hypertension (85.3%, n = 29), cirrhosis decompensation (8.8%, n = 3), and HCC (5.9%, n = 2). In Model 1, advanced ACLD significantly increased the risk of LREs (HR = 10.28, $p < 0.001$). Model 2 demonstrated a similar effect for LSM, with each unit increasing risk by 5% (HR = 1.05, $p < 0.001$). Model 3 indicated the FAST score strongly predicted LREs (HR = 15.43, $p < 0.001$), while Model 4 showed that higher Fib-4 values were significantly associated with increased risk (HR = 1.39, $p < 0.001$), along with the fibrosis stage.

Conclusion: Advanced ACLD indicators, including LSM, FAST, and Fib-4 scores, provide substantial predictive value for LREs in MASLD patients. The high concordance values (>0.78) across all models emphasize the utility of these metrics in assessing liver disease progression, underscoring the importance of regular monitoring for timely interventions.

PO7-24-YI
Enhancing detection of significant fibrosis in people living with HIV: revisiting the conventional ALT cut-off

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Background and Aims: Serum alanine aminotransferase (ALT) is commonly used as a biomarker for liver disease detection. However, the conventional upper limit of normal (ULN) for ALT, typically set at 40–55 U/L, has been questioned in its ability to accurately reflect liver pathology, particularly in cases of significant fibrosis. Recent studies indicate that many patients with significant liver disease, such as metabolic dysfunction-associated Steatotic liver disease (MASLD), exhibit ALT levels within this traditional range, leading to underdiagnosis. The study aimed to evaluate the performance of Alanine Aminotransferase (ALT) as a predictor of significant fibrosis in People Living with HIV (PLHIV).

Method: This cross-sectional study included PLHIV who attended the HIV Clinic at Cairo University Hospitals between January 2022 to March 2024. ROC analysis was conducted to evaluate the diagnostic performance of ALT for detecting significant fibrosis defined as liver stiffness measurement(LSM) reading of ≥8.0kPa using Transient Elastography (TE). Youden's index was used to establish the threshold for ALT that best balanced sensitivity and specificity. Different ALT cut-offs were analyzed to assess the trade-off between sensitivity and specificity, with further stratification by hepatitis C virus (HCV) antibody status.

Results: A total of 726 PLHIV (mean age 36.92 ± 9.81 years, 79.2% males) were included in the analysis with 16.8% having positive antibodies for HCV. Based on Youden’s index, the identified cut-off point (28 U/L) had a good discriminatory ability for detecting significant fibrosis (AUC of 0.67, sensitivity 0.54, and specificity 0.71). The regular cut-off of 50 U/L resulted in reduced sensitivity (0.23) but higher specificity (0.89). Stratification by HCV status showed that for HCV-positive individuals, the optimal cut-off of 33 U/L yielded a sensitivity and specificity of 0.69. while that for HCV-negative individuals was 21 U/L (sensitivity of 0.79 and specificity of 0.48). Applying the regular threshold of 50 U/L in both groups substantially reduced sensitivity (0.38 and 0.16, respectively) without significant change in specificity. In addition, 31% and 53% of HCV negative (N = 13) and HCV positive (N = 38) PLHIV had ALT levels below 30 U/.

Conclusion: The findings suggest that the conventional ALT upper limit may not be sufficient for detecting significant fibrosis in PLHIV. Lower ALT cut-offs, especially when stratified by HCV status, provide a better balance between sensitivity and specificity. The study highlights the importance of adopting lower ALT thresholds in clinical practice to enhance the early detection of significant fibrosis.

POSTER ABSTRACT PRESENTATIONS

Nurses & AHPs

PO1-03-YI
The dietitian's role in the pre-operative workup for patients undergoing laparoscopi surgery of the upper git

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Background and Aims: Hepatomegaly and visceral adiposity can complicate laparoscopic surgery of the upper gastrointestinal tract (GIT) with increased risk of visceral organ injury, longer operating times and unnecessarily technically challenging situations which can be averted by introducing a preoperative two-week very low-calorie diet (VLCD).
The study is designed to describe the volumetric changes in left hepatic lobe volume (LHLV) and body composition following a preoperative two-week VLCD as indicators of visceral adiposity and its effect on aversion of challenging operative difficulties.

Method: A cross-sectional study was conducted on 47 patients scheduled for a laparoscopic Nissen and Redo Nissen Fundoplication. Ethical approval was granted by the Faculty of Health Sciences of the University of the Free State (UFS-HSD2021/1664/2202-0006). Sonographic assessment of the liver volume left of the falciform ligament and an InBody assessment was obtained at baseline and on day of surgery, following the VLCD (1000kcal or 800kcal per day meal plan).

Results: Statistically significant ($p<0.05$) changes in weight, BMI, waist circumference, body fat mass, body fat percentage, abdominal fat, muscle mass and LHLV. A median weight loss of 3.5 kgs, 2.2 kgs body fat loss and 2.5cm decrease in waist circumference was observed. LHLV was reduced by 33% ($p<0.05$). A questionnaire on the surgeon's subjective assessments reported an 86.4% improvement of ease of access to the EG junction.

Conclusion: A dietitian led two-week VLCD will improve access to the upper GIT in laparoscopic surgery by significantly reducing liver volume, visceral adiposity, and can avert technically challenging situations and the need for pre-op LHLV measurement. Due to the findings, the current upper GIT unit has amended its preoperative workup to include a VLCD on all patients scheduled for laparoscopic upper GIT surgery.

POSTER ABSTRACT PRESENTATIONS

Public Health

PO1-07-YI
A randomized controlled study of daily aspirin to reduce fibrosis progression in metabolic dysfunction-associated steatotic liver disease

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Background and Aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is associated with obesity, diabetes and increased risk of cardiovascular disease, cerebrovascular disease, cirrhosis and liver cancer, which ultimately lead to death. From the recent study found that use of aspirin is another strategy to reduce liver fibrosis. When followed up for 1 year, it was found that patients who took aspirin had a statistically significant reduction in the risk of liver fibrosis compared to those who did not take aspirin regularly. This study aims to compare the results of using aspirin to reduce the risk of liver fibrosis in patients with metabolic dysfunction-associated steatotic liver disease (MASLD).

Method: 58 patients with metabolic dysfunction-associated steatotic liver disease from Phramongkutklao Hospital were randomized into two groups (aspirin and placebo). Liver enzyme levels were compared. Fibrosis was assessed by Transient Elastography (Fibroscan) by measuring liver stiffness, NAFLD fibrosis score, FIB-4, APRI index and questionnaire at baseline, 3 months and 6 months. Adverse events were recorded.

Results: Baseline patient characteristics were similar between two groups. Among the group receiving aspirin, at the 6-month follow-up, there was a statistically significant reduction in ALT liver enzyme levels (17.96 ± 11.50 IU/L VS -2.63 ± 9.08 IU/L, P-value 0.045), as well as a significant decrease in liver stiffness measured by Fibroscan (1.13 ± 0.65 kPa vs. 0.60 ± 1.58 kPa, P-value 0.009). Additionally, there was a statistically significant reduction in the FIB-4 score difference (0.11 ± 0.32 vs. -0.16 ± 0.56, P-value 0.014). Weight change did not differ between two groups (0.07 ± 1.51 kg VS 0.55 ± 1.45 kg, P-value 0.939) including the reduction in weight by more than 3%, which also showed no significant difference (10.71% VS 13.33%, P-value 0.201). However, no statistically significant difference was found in the reduction of liver fibrosis at the 3-month follow-up, based on Fibroscan or the FIB-4, NAFLD fibrosis score and APRI index. Two adverse events occurred in the aspirin group, one participant experienced nausea, and another had upper gastrointestinal bleeding which led to discontinuation from the study.

Conclusion: Taking aspirin may help reduce liver fibrosis in people with metabolic dysfunction-associated steatotic liver disease (MASLD) after 6 months of treatment. However, the collected data was a small population. A larger sample group with a longer duration may yield different results.

PO1-11
Applying the SAFE score as the first screening test for MASLD with fibrosis is more cost-effective than the current guideline based on FIB-4

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Background and Aims: For screening for MASLD, current guidelines recommend the FIB4 score first followed by vibration-controlled transient elastography (VCTE). The Steatosis-Associated Fibrosis Estimator (SAFE) score, developed for diagnosing fibrotic MASH, incorporates additional variables (i.e., BMI, diabetes and globulin) to FIB4. Here, we conduct a health economic analysis to compare a screening strategy employing the SAFE score as the first-tier test followed by VCTE against the current approach of using FIB4.

Method: With the analytic framework for incremental cost-effectiveness in diagnosing a case of MASH with fibrosis, we emulated population screening scenarios based on the National Health and Nutrition Examination Survey (NHANES) 2017-20, in which a sample representative of US civilians underwent VCTE.

In the NHANES sample, subjects with abnormal aminotransferases or cardiometabolic risk factors were identified. FIB4 was calculated and the rule-out (<1.3) and rule-in (≥2.67) thresholds for *advanced* (stage 3-4) fibrosis were applied. The SAFE score classified subjects to low (SAFE<0), intermediate (0-100) and high (≥100) risk for fibrotic MASH (stage 2+).

The base case analysis compared the guideline strategy of VCTE for FIB4≥1.3 (including ≥2.67) versus a proposed approach of using SAFE≥100. Outcome parameters included the number of VCTE, the total cost of VCTE and the number diagnosed with LSM≥8kPa and those with LSM≥12kPa. In a sensitivity analysis, we considered screening to subjects with SAFE≥0.

Results: There were 2691 NHANES subjects with MASLD, projecting to 75.8 million (M) US adults, of whom 11% had LSM≥8kPa and 6% LSM≥12kPa.

When the current guidelines using FIB4 were followed, 25% (projected to be 18M adults) would undergo VCTE, yielding 1.7M adults with LSM≥12 kPa and 3.5M with LSM≥8 kPa, while missing 9.1M with LSM≥8kPa, including 3.0M subjects with LSM≥12 kPa.

When SAFE was used, 13M VCTE (27% reduction compared to FIB4) would be needed, which would diagnose 4.8M (35% increase) with LSM≥8kPa including 2.5M with LSM≥12kPa (45% increase).

From the health economics standpoint, the SAFE approach was a dominant strategy, as it led to diagnosing more fibrotic MASH while expending fewer resources. The cost saved by switching from FIB4 to SAFE is estimated at US$ 680M for the entire US adult population.

In a sensitivity analysis utilizing SAFE≥0, the total number of VCTE increased to 39.6M at a cost of $2.95 billion, whereas it would diagnose 9.6M subjects with fibrotic MASH, including 4.0M with LSM≥12kPa. The incremental cost effectiveness is $491 per a case of fibrotic MASH and $1,319 per case with LSM ≥12 kPa.

Conclusion: The new stratification approach using SAFE≥100 to select candidates for VCTE is health economically dominant, with a larger number of subjects diagnosed with fibrotic MASH while reducing costs, in comparison to the current FIB-4-based recommendation.

PO1-20-YI
Liver fibrosis in the elderly: Prevalence and association with cognitive function in the Whitehall II study

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Background and Aims: Emerging research suggests links between steatotic liver disease (SLD) and cognitive function (Petta et al. 2016; Weinstein et al. 2018; Weinstein et al. 2019), yet few studies have explored these associations using direct measures of liver fibrosis (Weinstein et al. 2024). This study aimed to investigate the prevalence of liver fibrosis in a cohort of older adults and examine its association with cognitive performance.

Method: This cross-sectional study drew on data from phase 11 (2012-13) of the Whitehall II study. Liver fibrosis was assessed using FibroTest. SLD subtypes, including metabolic dysfunction-associated SLD (MASLD), metabolic dysfunction and alcohol-associated SLD (MetALD), and alcohol-associated liver disease (ALD), were categorised based on significant liver fibrosis (≥ F2) and presence of cardiometabolic risk factors or excessive alcohol use. Cognitive function was measured using standardised scores: immediate memory (20-word free recall test), phonemic fluency (S words), semantic fluency (animal naming), executive function (Alice Heim 4-I test), and global cognition (Mini-Mental State Examination [MMSE]). Linear regression models were applied to examine the associations between liver fibrosis and cognitive function, adjusting for sociodemographic and lifestyle factors, body mass index, and waist-to-hip ratio.

Results: Of the 6308 Whitehall II participants at phase 11, 4091 had valid FibroTest results (mean age = 69.3 years, standard deviation [SD] = 5.7 years; 71.7% male). Significant fibrosis (≥ F2) was present in 580 (14.2%) participants. Of these, cardiometabolic risk factors for SLD (at least one of obesity, elevated glucose, low HDL cholesterol, hypertension, and hypertriglyceridemia) were present in 565 participants, while 87 exhibited high alcohol use (>20/30 grams per day for females/males; 11 had missing alcohol data). Applying SLD nomenclature, 468 were classified as MASLD, 67 as MetALD, and 20 as ALD. Among all participants with valid FibroTest results, adjusted models showed that a one SD increase in FibroTest score was associated with poorer immediate recall (beta = -0.043, 95% confidence interval [CI] = -0.076 to -0.009; p = 0.012), but not with fluency (beta = -0.002, 95% CI = -0.034 to 0.031; p = 0.917), executive function (beta = 0.0001, 95% CI = -0.030 to 0.030; p = 0.993), or global cognition by MMSE (beta = 0.028, 95% CI = -0.026 to 0.082; p = 0.305).

Conclusion: Around one in seven adults in their late 60s to early 70s exhibited significant liver fibrosis. Greater fibrosis was associated with poorer performance on immediate memory.

PO2-04
MASLD and fibrosis status in patients with type 2 diabetes treated at internal medicine clinics: Türkiye DAHUDER awareness of steatotic liver disease (TR-DASLD) study

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Background and Aims: This awareness study aimed to determine the ultrasound (US) examination rates in relation to US-confirmed metabolic dysfunction-associated steatotic liver disease (MASLD) diagnosis in internal medicine outpatients with type 2 diabetes (T2D) across Türkiye.

Method: A total of 6283 T2D patients were included in this multicenter retrospective cohort study conducted at 17 internal medicine clinics across Türkiye. The presence and indications for US performed within the last 3 years were recorded along with US-confirmed MASLD rates, laboratory findings on the day of US, and referral rates. Fibrosis-4 (FIB-4) index was calculated to estimate the risk of advanced liver fibrosis (FIB-4 index ≥1.3).

Results: Overall, 1731 (27.6%) of 6283 patients had US examination, which revealed MASLD diagnosis in 69.9% of cases. In addition, 24.4% of patients with US-confirmed MASLD were at risk of advanced fibrosis (FIB-4 index ≥ 1.3), and the referral rate was 15.5%.

Conclusion: In conclusion, our findings emphasize an insufficient MASLD awareness among clinicians and the likelihood of most of T2D patients to be at risk of living with an unknown status regarding their MASLD and advanced fibrosis risk.

PO2-06
High prevalence of MAFLD in 33,255 residents in Delhi NCR and accuracy of MAF6, a new MAFLD risk score in the community

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Background and Aims: Despite its prevalence and potential progression to severe liver complications, MAFLD often remains undiagnosed due to its asymptomatic nature. This study aims to demonstrate the prevalence of MAFLD in Delhi NCR's general population, develop MAFLD risk score for early identification of MAFLD, and compare and validate non-invasive risk scores in the community.

Method: A cross-sectional survey was conducted in Delhi from 2017 to 2023 using two-stage sampling of Mohalla Clinics. Data was collected for anthropometry, biomedical tests, and a fibro scan to measure the Controlled Attenuation Parameter (CAP) for steatosis and the Liver Stiffness Measurement (LSM) for fibrosis. Logistic regression was used to identify parameters associated with MAFLD. MAF6 score was developed and tested on two cohorts. Comparative assessment and validation of established non-invasive risk scores, including Fibrosis 4 (FIB 4), Hepatic Steatosis Index (HSI), AST to Platelet Ratio Index (APRI), and AST/ALT ratio, was done within a substantial community cohort.

Results: The study analyzed 33,255 residents across 161 campsites in 11 districts of Delhi. The prevalence of MAFLD was 57.65% (95% CI: 57.1-58.1%), hypertension 66.76% (95% CI: 66.2-67.2%), dyslipidemia 26.24% (95% CI: 25.76-26.71%), obesity 62.74% (95% CI: 62.21 - 63.26), overweight 13.92% (95% CI: 13.55 – 14.3), lean MAFLD 4.39% (95% CI: 4.16 – 4.61) and pre-diabetes/diabetes in 54.23% of participants. Individuals with MAFLD were significantly older (48.34±13.18 vs 37.32±12.97 years) and had higher levels of GGT, cholesterol, ALT, fasting blood sugar, LSM, and CAP values ($p<0.05$). Multivariate analysis identified gender, age, log (GGT), log (platelet), and ALT/AST ratio as significant predictors of MAFLD. Based on these six variables, a novel MAFLD risk score (MAF6) was developed, demonstrating superior performance (AUROC 0.84, 95% CI: 0.844-0.852) compared to existing non-invasive scores like FIB-4 (63.5), APRI (60), HSI (74.5), and ALT/AST ratio (61). Both derivative and validation cohorts had significant p-values (<0.05), and AUROC values were comparable (AUROC 84.7 and 84.8, respectively).

Conclusion: The prevalence of MAFLD in Delhi NCR is 57.65%. These subjects have significant metabolic disorders. A novel MAF6 risk score surpassed existing non-invasive scores (AUROC 0.84) for early MAFLD detection in community settings and can be incorporated into national guidelines for NCD prevention and control, including NAFLD. The data offers insights into public health strategies and highlights the importance of early MAFLD detection and management.

PO2-07
Fibrosis stage vs fibrosis-4 score for predicting clinical outcomes in metabolic dysfunction-associated steatotic liver disease, and evaluation of healthcare resource utilization and associated costs

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Background and Aims: Fibrosis stage is a key prognostic factor in metabolic dysfunction-associated steatotic liver disease (MASLD), but biopsies are invasive and may have complications. The non-invasive Fibrosis-4 (FIB-4) index is a simple, well-validated tool, which could predict fibrosis severity and the occurrence of MASLD outcomes. We compared the utility of biopsy and FIB-4 to predict long-term clinical outcomes and evaluated their relationship with healthcare resource utilization (HCRU) and costs.

Method: This longitudinal observational cohort study included data from adults with biopsy-defined MASLD in Swedish medical records linked to national registers (study period 1973–2020). All patients had a documented fibrosis stage (F0–F4) and age-stratified FIB-4 score (low, intermediate, and high) at baseline (date of first biopsy + 30 days). The discriminative value of fibrosis stage and FIB-4 for all-cause, liver- and cardiovascular (CV)-related outcomes were evaluated using Harrell's concordance index (C-index). HCRU comprised the number of outpatient visits (from 2001) and hospitalization events per-person per-year (PPPY) and length of stay (LoS). Mean PPPY HCRU and cost estimates were derived using negative binomial and generalized linear models, respectively, adjusted for age, sex, body mass index (BMI), presence of type 2 diabetes, calendar time and, for CV-related HCRU, also adjusted for CV history, hypertension and hyperlipidaemia.

Results: Of 959 patients, median age at diagnosis was 52 years (interquartile range 39–60), 38.4% were women and mean (standard deviation) BMI 29.1 (5.9) kg/m^2. Fibrosis stage and FIB-4 were equally discriminative for clinical outcomes: liver-related (n=959) C-index values (95% confidence interval) 0.79 (0.71–0.85); 0.75 (0.66–0.81) and CV-related (n=867) C-index values 0.74 (0.71–0.77); 0.75 (0.71–0.78) for fibrosis staging and FIB-4, respectively. Mean outpatient visits were higher with higher FIB-4 score in the all-cause (low 6.29; intermediate 9.34; high 13.65) and liver-related (low 0.17; intermediate 0.30; high 1.28) cohorts. Liver-related hospitalizations were rare, but mean hospitalisations (0.06 vs 0.01) and total costs (€2500 vs €1500) were greater in those with high vs low FIB-4 score, respectively. Similar trends were observed for biopsy-based fibrosis staging. No correlations were noted for liver-related LoS or any CV-related HCRU for either method.

Conclusion: In patients with biopsy-confirmed MASLD, FIB-4 was equivalent to biopsy for predicting clinical outcomes. Patients with higher FIB-4 scores had more outpatient visits and liver-related hospitalizations, with an associated increasing cost burden. HCRU and costs had a similar association to biopsy-based fibrosis staging, supporting FIB-4 as a non-invasive tool for identifying patients at the highest risk of increased clinical and cost burden.

PO2-11
Paving the way for MASH screening of high-risk patients in primary and secondary care

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Background and Aims: Suboptimal awareness and knowledge about MASLD and its progressive stages (MASH and fibrosis) still lead to significant underdiagnosis. The 'Global Research Initiative for Patient Screening on MASH (GRIPonMASH) consortium aims to facilitate and investigate care path implementation for primary care physicians and cardiometabolic physicians, as recommended by multiple scientific societies, to enhance identification of individuals at risk of MASH and advanced fibrosis, simultaneously raising awareness.

Method: This is a prospective multicenter observational study. We aim to screen 10.000 high risk individuals in 10 European countries. High-risk is defined as having type 2 diabetes mellitus (T2DM), metabolic syndrome (MetS), obesity or arterial hypertension. Patients will enter a patient care pathway, starting with 2 non-invasive measurements: FIB-4 and VCTE (FibroScan). In this preliminary analysis only descriptive statistics are described, continuous variables are reported as mean (± SD) and categorical variables as proportion (%).

Results: Thus far, 306 individuals from 5 countries have been screened, 175 (57%) originating from GP practices and 133 (43%) from outpatient clinics (internal medicine/diabetology/endocrinology).
The mean age was 57 (± 12) years, 46% was female, mean BMI was 32.5 (± 6). The primary diagnosis for inclusion was T2DM (40%), followed by hypertension (31%), obesity (27%) and MetS (3%). Regarding steatosis, controlled attenuation parameter (CAP) cutoff for was 275 dB/M, with 60% prevalence of MASLD and mean CAP of 289 (±68) dB/M. Regarding fibrosis evaluation, FIB-4 was

available in 238 patients, 131 patients had FIB-4 < 1.3 (55.1%), 97 patients FIB-4 >1.3 <2.67 (40.7%), 10 patients FIB-4 >2.67 (4.2 %). Mean FIB-4 was 1.3 (± 0.8). Mean liver stiffness measurement (LSM) was 6.3 (±3.8) kPa. In total 82% had a low risk of fibrosis (< 8.0 kPa), 12% were at risk for significant fibrosis (8.0-12.0 kPa) and 6.0% had advanced fibrosis (> 12.0 kPa). Among patients with FIB-4> 2.67, 4/10 (32%) patients had LSM > 8, and among those with FIB-4>1.3, 21/107 (20%) had LSM >8.

Conclusion: Most screenings were performed in individuals presenting with a primary diagnosis of T2DM and the least in those with MetS. In the 306 at risk individuals screened so far, 60% had MASLD. Importantly, altogether 18% of this risk population had significant fibrosis.

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PO3-21-YI
Comparative analysis of prevalence, metabolic profiles, and socio-demographic characteristics of MetALD, MASLD, and ALD in a rural area

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Background and Aims: Metabolic Alcohol-Associated Liver Disease (MetALD) is a condition characterized by the coexistence of metabolic dysfunction and elevated alcohol consumption, distinguishing it from both Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) and Alcohol-Related Liver Disease (ALD). In rural populations, where metabolic dysfunction and alcohol use are prevalent, accurate identification and differentiation of MetALD are critical. This study aimed to investigate the prevalence, metabolic profiles, and socio-demographic characteristics of MetALD, MASLD, and ALD to improve diagnostic accuracy in these settings.

Method: A total of 282 participants aged 20 and above from a rural area in Thailand were recruited. Socio-demographic data and associated factors were collected through structured interviews. Anthropometric measurements and abdominal ultrasound imaging were performed to determine the prevalence of MetALD, MASLD, and ALD. Bonferroni correction was applied for multiple comparisons, and Receiver Operating Characteristic (ROC) curve analysis was utilized to assess the diagnostic performance of metabolic parameters in differentiating MetALD from other conditions.

Results: The prevalence rates of MetALD, MASLD, and ALD were 4.3%, 14.5%, and 4.3%, respectively. ROC analysis indicated that alcohol consumption and metabolic parameters, particularly waist circumference and BMI, were the most effective indicators for identifying MetALD, with AUC values ranging from 0.70 to 0.85, suggesting moderate to high diagnostic accuracy. Elevated waist circumference, BMI, neck circumference, and age ≥ 50 years were significant predictors of MASLD, presenting higher odds compared to MetALD and ALD (Bonferroni-corrected p-value < 0.0056).

Conclusion: This study underscores the combined impact of metabolic dysfunction and increased alcohol intake in the pathogenesis of MetALD. Significant predictors such as waist circumference, BMI, and alcohol consumption demonstrated moderate to high diagnostic accuracy. The findings suggest that current diagnostic frameworks may underestimate MetALD if they fail to address its complex etiology, particularly in rural settings where this condition may be more prevalent. A comprehensive diagnostic approach that evaluates both metabolic and alcohol-related factors is essential for improved accuracy. Future research should explore the interplay between metabolic factors and alcohol consumption, with a focus on clinical trials and integrated care pathways to enhance diagnostic precision and treatment outcomes.

PO4-04-YI
Prevalence of MASLD and its association with the consumption of sugar sweetened beverages among a non-communicable disease cohort in the rural district of Iringa, Tanzania

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Background and Aims: The global health community has increasingly shifted its focus toward non-communicable diseases (NCDs), recognizing them as a critical public health emergency, particularly pronounced in low and lower middle-income countries. The prevalence, associated factors, and consequences of MASLD in the African continent, particularly in Sub-Saharan Africa (SSA), remain poorly understood. Indeed, no SSA studies were included in the latest major literature review and meta-analysis on the global epidemiology of MASLD.
Tanzania, like many other SSA countries, is undergoing a demographic and epidemiological transition, leading to a marked increase in the burden of NCDs.
The primary aim of this study was to estimate the prevalence of MASLD among an NCDs population in rural Tanzania. The secondary objective was to investigate whether the consumption of sugar sweetened beverages (SSB) is associated with MASLD.

Method: This study entailed a retrospective analysis of a prospectively collected cohort of consecutive patients attending the NCDs outpatient clinic of Tosamaganga Hospital, from August 2022 to March 2023. Detailed sociodemographic, clinical, laboratory, and abdominal ultrasound data were collected for all participants. The Beverage Intake Questionnaire (BEVQ-15) was administered to evaluate their everyday drinking behaviors; and for each item, the average daily intake in fluid ounces (fl-oz), and calories (kcal) were calculated.

Results: Of 183 patients enrolled in the cohort, 128/183 (70%) were female. The mean age was 58±13.7 years and mean BMI was 28±6.67 Kg/m2. Hypertension affected 141 individuals (77.0%), diabetes affected 77 (42.1%), and both conditions co-occurred in 35 patients (19.1%). SLD was found in 88/183 (48%) patients; with 39/88 (44.3%) of moderate or severe steatosis. MASLD was identified in all steatotic patients. Overall, on average the participants drank a mean of 12.6 fl-oz of SSB (throght sodas). MASLD patients drank an average of 22.4 fl-oz of SSB per day. Multivariable analysis revealed that BMI and daily SSB consumption (fl-oz) exhibited significant associations with MASLD, with respective OR of 1.16 (95% CI: 1.06 – 1.28, p = 0.002) and 1.19 (95% CI: 1.12 – 1.27, p < 0.001).

Conclusion: This study unveils a considerable prevalence of MASLD among the rural Tanzanian NCDs population, affecting nearly half (48%) of all patients studied. Timely identification of MASLD, facilitated by straightforward diagnostic means, holds pivotal importance for patient management and the dissemination of vital lifestyle modification guidance. Furthermore, our study, one of the pioneering efforts to demonstrate a significant association between SSB consumption and MASLD in an African context, underscores the imperative to heighten awareness regarding the risks posed by SSB consumption among NCDs patients and potentially the wider population.

PO4-13
Risk factor awareness for liver disease in four United States cities

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Background and Aims: Liver diseases pose a significant public health burden, yet awareness of risk factors for liver disease remains limited. This study evaluates awareness of key risk factors for liver disease, including high-calorie diets, ultra-processed foods, sedentary lifestyles, and alcohol consumption, among the general population in the four most populous U.S. cities: Chicago, Houston, Los Angeles, and New York City.

Method: An online survey was conducted 5-13 September 2024 in Chicago, Houston, Los Angeles, and New York City to assess knowledge of liver disease risk factors in a sample of 5,408 adults, including 1,000 individuals with diabetes and 800 PCPs, weighted to 4,000 adults (1,000 per city) reflective of the cities' populations in terms of age, gender, ethnicity, and educational background. A risk factor awareness index was created based on responses to questions about the association of five specific dietary and lifestyle factors (i.e., high-calorie diets, high-cholesterol foods, ultra-processed foods, sedentary lifestyle, and alcohol consumption) with liver disease. Each factor was assigned a score of 1 if the respondent was aware of the association, resulting in a total score ranging from 0 to 5, which was then transformed to a 0 to 100 scale. Ordered logistic regression analysis was performed on the index with five factors (age, education, ethnicity, self-reporting diabetes, and primary care provider status) to estimate their associations with awareness level.

Results: Chicago had the highest awareness of risk factors score (47.0), followed by Houston (43.9), Los Angeles (43.3), and New York City (42.0). Primary care providers were over twice (odds ratio (OR) = 2.09, p <0.001) as likely to demonstrate higher awareness of the five risk factors. Higher educational attainment strongly correlated with increased awareness (OR = 1.50, p <0.001). A significant positive association was observed between age and awareness (OR = 1.07, p=0.026), with older respondents demonstrating greater awareness.

Conclusion: This study highlights an overall low awareness of risk factors for liver disease in major U.S. cities, underscoring the importance of raising awareness to support preventive health measures. Age and education were key determinants of awareness, with older and more educated individuals demonstrating greater knowledge of liver disease risk factors. These findings emphasize the need for targeted educational interventions to bridge awareness gaps, particularly among younger and less-educated populations, and as part of preventive care training.

PO4-15
From alcohol to metabolic dysfunction: a new leading cause of cirrhosis in Mexico

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Background and Aims: Liver cirrhosis is a major cause of morbidity and mortality worldwide. Historically, alcohol excess consumption and viral infections, particularly hepatitis B (HBV) and hepatitis C (HCV), have been the main causes. In Mexico, previous studies have highlighted alcohol-related liver disease (ALD) and HCV as leading causes, with a 2012-2017 study reporting HCV, ALD, and nonalcoholic steatohepatitis (NASH) as leading etiologies. Recently, changes in etiology have emerged; vaccination and antiviral programs reduced viral hepatitis-related cirrhosis, and the increasing prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) due to obesity, type 2 diabetes, and metabolic syndrome now drives cirrhosis cases. A 2019 cohort study identified MASLD as the leading cause, followed by ALD and HCV. This study examines the evolving etiology of cirrhosis in Mexico, focusing on regional differences in causes and outcomes.

Method: A multicenter retrospective study across 12 Mexican health centers (2018-June 2024) reviewed cases of liver cirrhosis in adults to identify etiologies. Data collected included sociodemographic, clinical, imaging, and biochemical variables, and prevalence and regional distribution were analyzed.

Results: The study included a total of 2,182 patients diagnosed with liver cirrhosis, with a mean age of 61 ± 12 years. Of these, 53.8% (n=1,175) were women and 46.1% (n=1,007) were men. The most frequent etiology was MASLD, which accounted for 34.4% (n=725) of the cases. ALD related cirrhosis was the second most prevalent cause, affecting 23.6% (n=514) of patients, followed by HCV, responsible for 12.6% (n=265) of cases. Significant regional differences in etiology were observed, MASLD was the most frequent cause in the central and southeastern regions, representing 32.6% (n=541) and 38.6% (n=103) of cases, respectively. In contrast, alcohol-related cirrhosis was the leading cause in the northern region, contributing to 48.2% (n=123) of cases. Regarding health outcomes, notable differences were observed between etiologies. The development of hepatocellular carcinoma

(HCC) occurred in 7% of patients with MASLD, 23.8% of those with HCV, and 7.2% of those with alcohol-related cirrhosis ($p<0.001$). 0.8% of alcohol-related cases, 1.9% of HCV cases and 0.6% of MASLD cases received a liver transplant ($p=0.025$). In addition, portal hypertension was diagnosed in 64.8% of alcohol-related cirrhosis cases, 79.2% of HCV cases and 64.4% of MASLD cases ($p<0.001$).

Conclusion: The study highlights a change in the etiology of cirrhosis in Mexico, with MASLD now being the main cause, especially in the central and southeastern areas. These regional and outcome differences highlight the need for targeted public health measures to address different risk factors in different regions.

PO5-04-YI
Prevalence and health literacy of metabolic dysfunction-associated steatotic liver disease and its associated factors in a rural area: a cross-sectional study

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Background and Aims: Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) is a growing global health burden, particularly in rural areas where health literacy and early detection are often limited. This study aims to assess the prevalence of MASLD, associated risk factors, and health literacy within a rural population in Thailand, highlighting the importance of early detection and lifestyle interventions.

Method: A cross-sectional study was conducted in Sanam Chai Khet district, Thailand, including 207 participants aged 20 and above in the final analyses. Demographic, anthropometric, and cardiometabolic risk factors were recorded. Abdominal ultrasounds were used to diagnose steatosis and were confirmed with two radiologists, and participants' awareness and knowledge of MASLD were assessed using a validated questionnaire. Multiple logistic regression was used to identify associations between MASLD and cardiometabolic risk parameters.

Results: The overall prevalence of MASLD was 14.5%. Neck circumference was significantly associated with MASLD (OR: 1.30, CI: 1.13-1.49, p-value < 0.001), particularly among males with larger neck circumferences (OR: 9.16, CI: 1.45-57.88, p-value = 0.019). It is important to note that this association is stronger than that of the waist circumference (OR: 1.10, CI: 1.06-1.15, p-value < 0.001). A family history of type 2 diabetes also showed a strong association with MASLD (OR: 2.32, CI: 1.12-4.82, p-value = 0.024). Health literacy on MASLD was low, with over 70% of participants unaware of the disease and a significant portion holding misconceptions about its reversibility and asymptomatic nature.

Conclusion: MASLD is prevalent in rural populations. There is a significant gap in health literacy regarding MASLD, with many misconceptions among the rural population. Factors such as neck circumference and family history of type 2 diabetes were positively associated with MASLD, while outdoor occupations appeared protective. There is a clear need for improved health education and early detection strategies to prevent progression and reduce the socioeconomic burden of MASLD in rural areas.

PO5-07-YI
Relationships between fibrosis status, multimorbidity, and all-cause mortality in people with metabolic-dysfunction associated steatotic liver disease in UK Biobank

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Background and Aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common chronic liver condition. People with MASLD are more likely to have multimorbidity. Fibrosis status is the most important prognostic factor in MASLD. This study aimed to investigate the relationship between fibrosis status, multimorbidity and all-cause mortality in people with MASLD.

Method: We analysed data from the UK Biobank. MASLD was defined as a fatty liver index ≥ 60, absence of excessive drinking, and presence of ≥ 1 cardiometabolic risk factor (obesity, diabetes, hypertension, high triglyceride and/or low HDL). Multimorbidity was defined as having ≥ 2 of the long-term conditions in a pre-specified list of 48 extrahepatic conditions. FIB-4 score was used as a surrogate for liver fibrosis status. The associations between FIB-4 scores and multimorbidity prevalence were estimated using logistic regression models. Cox proportional hazards models were used to assess the prospective association between FIB-4 scores, multimorbidity and mortality, adjusting for age, sex, socioeconomic status and lifestyle factors. The mediation effect of multimorbidity on the association between FIB-4 scores and mortality was also assessed.

Results: Of the 345198 UK Biobank participants, 115502 (34.4%) had MASLD at baseline (mean age 57.5 ± 7.9 years, men 56.2%), 2.2% of which had high FIB-4 scores (≥2.67). High FIB-4 scores were positively associated with increased prevalence of multimorbidity (OR 1.48 (95%CI: 1.36-1.60), $p < 0.01$). During a median follow-up of 13.0 years, high FIB-4 scores were associated with 78% higher risk of all-cause mortality (HR 1.78 (1.64, 1.93), $p < 0.01$). Multimorbidity was associated with higher mortality (HR 2.23 (2.12, 2.34), $p < 0.01$), with stronger associations in women than in men. Each additional condition at baseline was associated with 29% higher all-cause mortality (HR 1.29 (1.27, 1.30), $p < 0.01$). Multimorbidity mediated approximately 15% of the association between FIB-4 scores and all-cause mortality, mainly via diabetes, cardiovascular diseases, cancers and chronic kidney disease.

Conclusion: FIB-4 scores were associated with higher multimorbidity and mortality in people with MASLD. Multimorbidity mediated the positive association between fibrosis and mortality, with diabetes, cardiovascular diseases, cancers, and chronic kidney disease contributing notably to this mediation. These findings underscore the importance of managing both fibrosis and multimorbidity in MASLD patients.

PO5-11
Awareness of metabolic dysfunction-associated steatotic liver disease (MASLD) in four cities in the United States, including among people with diabetes and primary care providers

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Background and Aims: Despite an estimated metabolic dysfunction-associated steatotic liver disease (MASLD) prevalence of 38.2% (33.72 – 42.89) in the global population aged above 20 years and an estimated prevalence of 7-14% among children, public awareness remains low. This study evaluates MASLD awareness among adults in the general population, a leading at-risk population (people with diabetes), and primary care providers (PCPs) in the four most populous cities in the United States.

Method: An online survey was conducted 5-13 September 2024 in Chicago, Houston, Los Angeles, and New York City. Respondents included a sample of 5,408 adults, including 1,000 adults with diabetes and 800 PCPs, weighted to n=4,000 (1,000 per city) reflective of the cities' populations in terms of age, gender, ethnicity, and educational background. Awareness of MASLD was assessed with the item "Have you ever heard of metabolic dysfunction-associated steatotic liver disease (MASLD)?," reported as descriptive statistics evaluated with Chi-square tests. A regression model assessed awareness of MASLD with age, gender, ethnicity, education and health utilization factors (reporting ever had a blood test to assess liver enzymes and annual primary care visits). Odds ratios were reported along with 95% confidence intervals (CI) at alpha=0.05.

Results: Among the general population, 18.7% had heard of MASLD, ranging from 16.2% in Houston to 20.2% in Chicago. Among adults with diabetes, 37.8% were aware of MASLD. Of PCPs 54.7% reported having heard of MASLD. Age was negatively associated with MASLD awareness, with only 9.7% of those aged ≥60 aware. Individuals with higher education levels were significantly more likely to have heard of MASLD, with 45.7% of those holding post-graduate degrees reporting awareness ($p<0.001$). Those who had ever had a blood test to assess liver enzymes were 4.4 [CI: 3.39–5.65] times more likely, and those who reported annual primary care visits were 2.0 [CI: 1.26–3.03] times more likely, to have heard of MASLD ($p<0.005$). Ethnicity and city of residency were not significant factors for awareness.

Conclusion: In the four U.S. cities studied, awareness of MASLD was low overall as well as among people with diabetes and PCPs, highlighting the need for targeted health literacy initiatives, including at the city level, to raise MASLD awareness and prevention efforts. Focused initiatives can support individuals in making informed health decisions, reinforcing the importance of prevention among at-risk populations and their caregivers.

PO5-13
Non-invasive pathway for advanced fibrosis and liver-related outcomes in the general population from China, UK, and USA: results from four prospective cohorts

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Background and Aims: Population-based management of chronic diseases is of paramount importance, as this could identify undiagnosed cases at early disease stages, allowing for proper interventions to avoid complications related to end-stage liver disease. Recently, EASL-EASD-EASO proposed a non-invasive pathway for case finding of advanced fibrosis in at-risk individuals with (suspected) metabolic dysfunction-associated steatotic liver disease (MASLD). This study aims to evaluate the diagnostic accuracy of this pathway for fibrosis detection and its association with long-term prognosis in the general population.

Method: We included 468999 participants (age ≥ 18 years) from four prospective cohorts: China cross-sectional cohort (n = 8943), US cross-sectional cohort (n = 6756), UK prognosis cohort (n = 411120), and US prognosis cohort (n = 42180). Individuals were categorized into minimal-, low-, medium-, and high-risk groups according to the MASLD guideline. Advanced fibrosis was defined by liver stiffness measurements ≥ 10 kPa. Associations with liver-related events (LREs, comprising liver-related hospitalisation, cirrhosis, liver cancer, and liver-related death), cardiovascular-related death, and all-cause death were investigated.

Results: The prevalence of advanced fibrosis in minimal-, low-, medium-, and high-risk groups was 1.1%, 2.9%, 6.4%, and 20.9% in the China cross-sectional cohort, and 0.8%, 6.9%, 9.8%, and 37.1% in the US cross-sectional cohort. In the UK prognosis cohort, hazard ratios (HRs) for LREs compared to the minimal-risk group were 2.25 (95% CI 2.14-2.36), 2.95 (95% CI 2.79-3.10), and 11.15 (95% CI 10.29-12.08) for the low-, medium-, and high-risk groups, respectively. Compared with the minimal-risk group, HRs for liver-related hospitalisation, cirrhosis, liver cancer, and liver-related death in the high-risk group were 11.1 (95% CI 10.23-12.04), 50.75 (95% CI 43.73-58.91), 20.72 (95% CI 16.3-26.34), and 42.39 (95% CI 35.47-50.67), respectively. The risk groups within the pathway were associated with a progressively increasing risk of cardiovascular-related death, with HRs of high-risk group reaching 6.43 (95% CI 5.86-7.06) in the UK prognosis cohort and 11.89 (95% CI 9.67-14.61) in the US prognosis cohort. Similarly, all-cause mortality significantly increased across the ascending risk groups in both prognosis cohorts. Notably, subgroup analysis indicated that among participants with and without high

alcohol consumption, increased risk stratification was associated with a higher prevalence of advanced fibrosis and a higher incidence of LREs, cardiovascular-related death and all-cause death.

Conclusion: The stepwise non-invasive pathway from the MASLD guideline appears suitable for identifying individuals at risk for advanced fibrosis and future LREs in the general population.

PO5-16
Prevalence and its associated risk factors of metabolic dysfunction-associated steatotic liver disease among information technology employees in India: A cross-sectional study

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Background and Aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) has emerged as a significant public health concern worldwide, particularly affecting populations with sedentary lifestyles. Among Indian information technology (IT) employees, who often experience prolonged sedentary work hours, high stress levels, shift work and irregular dietary patterns, the risk factors associated with metabolic syndrome and MASLD are pronounced. Despite this, there is limited research examining the prevalence and drivers of MASLD within this occupational group in India. This study aims to fill this gap by assessing the prevalence of MASLD and exploring its associations with specific behavioural and metabolic risk factors among IT employees in Hyderabad, India.

Method: A cross-sectional study was conducted among 345 IT employees aged 30 – 60 years using a modified WHO STEPS questionnaire between July 2023 - July 2024. Anthropometric, biochemical parameters, and liver scans (FibroScan) were assessed and the data was analysed using MS Excel and GraphPad. Associations between liver steatosis, and metabolic and behavioural risk factors were analysed using the chi-square test.

Results: Among the 345 IT employees, 294 (85.2%) were men and 51 (14.8%) were women. The median age was 38 years, with an average of 13.64 ± 5.77 years spent in the IT industry. The overall prevalence of MASLD was 284 (82.31%), with 117 (33.91%) exhibiting severe liver steatosis (Controlled attenuation parameter (CAP) score > 290 dB/m). Significant associations were observed between liver steatosis and body mass index (BMI) ($p < 0.001$), waist circumference (WC) ($p < 0.001$), homeostatic model assessment for insulin resistance (HOMA-IR) ($p < 0.001$), fasting blood glucose (FBG) ($p < 0.001$), waist-hip ratio (W/H) ($p < 0.001$) and smoking ($p = 0.012$). Liver steatosis is positively correlated with BMI ($r = 0.65$, $p < 0.001$), WC ($r = 0.66$, $p < 0.001$), fasting insulin ($r = 0.52$, $p < 0.001$), HOMA-IR ($r = 0.52$, $p < 0.001$), FBG ($r = 0.18$, $p < 0.001$), triglycerides ($r = 0.27$, $p < 0.001$), and total cholesterol ($r = 0.14$, $p = 0.006$). Liver steatosis is negatively correlated with high-density lipoprotein cholesterol (HDL-C) ($r = -0.11$, $p = 0.03$).

Conclusion: IT employees are at an elevated risk of metabolic risk factors and MASLD. Health promotion strategies at the workplace must be in place to address this growing public health concern among the working population of IT companies.

PO5-17-YI

Comparison of diagnostic accuracy and utility of non-invasive tests for clinically significant liver disease among a general population with metabolic dysfunction

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Background and Aims: Screening for liver health in the general population requires accurate non-invasive tests (NITs). A head-to-head comparison of NITs for early detection of clinically relevant liver disease among large general population cohorts with metabolic dysfunction – the target population for screening - has not yet been performed.

Method: Among a pooled population from the Rotterdam Study and NHANES with metabolic dysfunction aged 18-80 years, 10 NITs were investigated: AST to platelet ratio (APRI), Cirrhosis Outcome Risk Estimator (CORE), fibrosis-4 index (FIB-4), Fibrotic NASH index (FNI), FORNS, Hepamet Fibrosis Score (HFS), LiverRisk score (LRS), Metabolic dysfunction associated fibrosis score-5 (MAF-5), NAFLD fibrosis score (NFS) and steatosis associated fibrosis estimated (SAFE). The diagnostic accuracy (area under curve, AUC) was assessed for the detection of increased liver stiffness measurement (LSM ≥8 kPa, LSM ≥12 kPa), MASH (FibroScan AST score ≥0.35), advanced fibrosis (Agile 3+ ≥0.679) or cirrhosis (Agile 4 ≥0.565). Subgroup analysis included stratification by age group, level of obesity and diabetes mellitus status. Sensitivity analysis included an assessment of (1) test characteristics at the threshold corresponding with 80% sensitivity and (2) diagnostic yield when 20% of the at-risk population with the highest NIT score was selected for further work-up.

Results: We analysed 11,404 participants. MAF-5 had the highest AUC for increased LSM (LSM ≥ 8/12 kPa, AUC 0.80/0.87) and advanced fibrosis (AUC 0.90). FNI and MAF-5 were most suited for MASH (AUC 0.93 and 0.92). SAFE and NFS performed best for cirrhosis (AUC 0.92 and 0.91). At the NIT cut-off to obtain at least 80% sensitivity for LSM ≥ 8 kPa, the corresponding MAF-5 cut-off resulted in fewer referrals compared to FIB-4 (42% vs 77%) and had higher specificity (62% vs 24%); the MAF-5 was also superior for detecting LSM ≥ 12 kPa and advanced fibrosis. Age-dependent scores yielded lower sensitivity amongst younger individuals e.g., by referring 20% of the population with the highest NIT-scores, the FIB-4, SAFE, NFS, FORNS and HFS yielded < 10% sensitivity for LSM ≥ 8 kPa amongst individuals aged 18-35y while the FNI and MAF-5 obtained 40% and 71%, respectively.

Conclusion: Of the 10 investigated NITs, the MAF-5 was most suited for ruling in and ruling out all conditions except cirrhosis, for which SAFE yielded the highest accuracy. The performance of FIB-4 was overall low, implying that referral pathways for significant liver disease in low prevalence populations can be improved when more accurate NITs such as MAF-5 are employed.

PO6-03-YI
Rural-urban differentials in health literacy of metabolic dysfunction-associated steatotic liver disease

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Background and Aims: Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) is a highly prevalent condition with major public health implications. Disparities in health literacy between urban and rural populations can significantly impact disease prevalence, management, and outcomes. This study aims to assess and compare the health literacy of MASLD between rural and urban populations, focusing on awareness, knowledge of symptoms, risk factors, and understanding of diagnostic methods.

Method: A cross-sectional, comparative analysis was conducted using survey data from 282 participants in a rural area and 124 participants from an urban setting. The survey assessed awareness of MASLD, understanding of risk factors (such as diabetes and alcohol consumption), knowledge of MASLD symptoms, awareness of diagnostic methods, and familiarity with the potential consequences of the disease. Statistical analyses, including chi-squared tests for categorical variables, t-tests for normally distributed, and Mann-Whitney U tests for non-normally distributed continuous variables, were performed to identify differences in health literacy between the two populations.

Results: The urban population exhibited significantly higher awareness of MASLD (88% vs. 30%, $p<0.001$) and better knowledge of key risk factors, such as diabetes (96%, $p<0.001$) and excessive alcohol consumption (81%, $p=0.008$). However, misconceptions were more prevalent in the urban population, including beliefs that MASLD is contagious (88% vs. 11%, $p<0.001$) and limited understanding of diagnostic tools like biopsy (55% vs. 14%, $p<0.001$). The rural population, while having lower overall awareness, demonstrated a better understanding of the severe consequences of MASLD, such as cirrhosis ($p=0.021$), and had fewer misconceptions. Both populations shared confusion regarding symptoms such as abdominal pain (urban: 24%, rural: 21%, $p=0.515$) and yellow pigmentation (urban: 21%, rural: 14%, $p=0.088$). Both groups also had a high understanding of the importance of physical activity in reducing liver damage (urban: 94%, rural: 97%, $p=0.242$).

Conclusion: There are significant disparities in MASLD health literacy between urban and rural populations. Although urban areas show higher awareness, they also suffer from a higher prevalence of misconceptions that could negatively impact disease management. In contrast, rural populations, despite lower overall awareness, possess a more accurate understanding of severe MASLD consequences. These findings highlight the need for targeted, population-specific educational interventions to address health literacy gaps and improve MASLD management outcomes.

PO6-07
Steatotic liver disease (SLD) in the adult population attending a health check-up program in Thailand: Prevalence and fibrosis status

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Background and Aims: Steatotic liver disease (SLD) presents a major public health challenge. Guidelines advise primary care physicians to use noninvasive tests to assess the risk of advanced fibrosis in SLD patients and to promptly refer at-risk individuals to hepatology specialists. This study examines the prevalence of SLD in Thailand, including fibrosis status, and referral rates, aiming to enhance the regional care system and provide a population-level reference.

Method: This retrospective study analyzed adults who participated in a health check-up program at a university hospital in Southern Thailand from 2019 to 2023. We included adults (≥18 years) who selected packages with abdominal ultrasound. Exclusions were made for those with pre-existing liver diseases, positive HBsAg, or missing essential variables for FIB-4 calculation. Demographics, clinical variables, and referral information were recorded. SLD was defined based on hepatic steatosis identified in ultrasonography reports. Cardiometabolic risk factors including diabetes mellitus (DM), body mass index (BMI), waist circumference (WC), blood pressure, plasma triglycerides, HDL cholesterol, and fasting glucose levels. The BMI and WC cutoffs for Asians were used. Liver fibrosis was assessed using the FIB-4 index, categorizing risk as low (<1.3), indeterminate (1.3-2.67), or high (>2.67) for advanced fibrosis.

Results: During the study period, 6,183 individuals underwent health check-ups with ultrasonography. A total of 5,995 were eligible. SLD was detected in 2,708 individuals (45.2%), with a higher prevalence in males. Among those with SLD, 98.6% had ≥1 cardiometabolic risk. However, incomplete alcohol consumption data precluded the subclassification of SLD into MASLD, MetALD, and ALD. Among the 2,669 SLD patients with cardiometabolic risk, 76.6% were at low risk for advanced fibrosis, 21.8% were at indeterminate risk, and 1.6% were at high risk. The prevalence of DM, hypertension, coronary artery disease (CAD), and chronic kidney disease (CKD) was higher in the indeterminate and high-risk groups compared with those at low risk. The degree of steatosis did not significantly correlate with the severity of fibrosis. Referral rates to specialists were significantly higher for patients at high risk (20.45%) compared to those at intermediate (8.45%) and low risk (7.82%).

Conclusion: The prevalence of SLD among patients residing in southern Thailand was 45.2%, with 98.6% having at least one cardiometabolic risk factor. In primary care, the proportion of patients with advanced fibrosis, ascertained by FIB-4, was 1.6%. Patients with advanced stages of liver fibrosis exhibited a higher prevalence of CAD and CKD. Notably, only 20% of patients requiring specialized care were referred to hepatologists, highlighting an opportunity to improve the clinical care pathway for this commonly encountered liver disease.

PO6-16-YI
Volatile organic compound metabolites in urine are associated with MASLD and fibrosis: an environmental health study

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Background and Aims: Exposure to volatile organic compounds (VOCs) through inhalation, ingestion, and dermal contact has increased over the past decades, raising concerns about their impact on environmental health. VOCs are mostly metabolized by the liver into various compounds which are subsequently excreted in urine. While VOC exposure has been linked to impaired metabolic health, the associations between VOCs and metabolic dysfunction-associated steatotic liver disease (MASLD) as well as fibrosis remain unclear.

Method: We used data from the NHANES 2017-2020 cycle, a United States population-based cohort with data on controlled attenuation parameter (CAP) and liver stiffness measurements (LSM). Participants with viral hepatitis, excessive alcohol consumption or missing data on urine creatinine were excluded. MASLD was defined as CAP ≥ 275 dB/m together with metabolic dysfunction and fibrosis as LSM ≥ 8 kPa. To account for co-linearity between the 15 individual urine VOC metabolites, least absolute shrinkage and selection operator (LASSO) analysis was used to identify urine VOC metabolites that were most associated with MASLD and fibrosis. Weighted quantile sum (WQS) analysis was performed to quantify the associations of the LASSO-selected parameters. Analyses were adjusted for age, sex, smoking and alcohol consumption.

Results: The cohort included 2,279 participants (median age 51 [34–64], 48% male), with 41.4% having MASLD and 9.6% fibrosis. LASSO identified CEMA, MA, 3HPMA and DHBMA as a predictor of increased steatosis and/or fibrosis risk, while PGA, SBMA, CYMA, 2-HPMA and ACTA were linked to reduced steatosis and/or fibrosis risk. WQS analysis generated weighted quantile mixtures of the LASSO-selected VOCs both in positive and negative directions of effect. For steatosis, a non-significant increased risk was observed (aOR 1.13 per quartile, 95%CI 0.97–1.32; 75% accounted for by CEMA), while a significant decreased risk was found (aOR 0.66 per quartile, 95%CI 0.53–0.83; 38% by PGA, 33% by CYMA). For fibrosis, a non-significant increased risk (aOR 1.37 per quartile, 95%CI 0.86–2.17; 31% by MA, 25% by DHBMA, 24% by 3-HPMA) and a significant decreased risk (aOR 0.61 per quartile, 95%CI 0.40–0.93; 48% by PGA, 21% by 2-HPMA) were found.

Conclusion: Urinary metabolites of VOCs are associated with MASLD and fibrosis in the general population. Both positive and negative associations were observed. Notably, MA, a metabolite of styrene and ethylbenzene, is further metabolized by alcohol dehydrogenase into PGA. In this study, higher levels of MA were linked to an increased risk of fibrosis, while higher levels of PGA were associated with a decreased risk of fibrosis. These contrasting associations raise the possibility that impaired metabolism of ethylbenzene and styrene could lead to intra-organic accumulation, potentially contributing to fibrosis risk.

PO6-18
Integrating multidisciplinary screening for HCV micro-elimination in populations with metabolic disorders: Findings from the LIVE(RO)2 Project in Romania

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Background and Aims: The LIVE(RO)2 project in South and East Romania addressed the urgent need for targeted HCV and HBV screening in socio-economically vulnerable populations. Given the high prevalence of metabolic syndrome components, including diabetes and hypertension, in HCV-positive patients, this project highlights the need for a comprehensive approach to screening and staging, which is crucial for achieving micro-elimination in this high-risk cohort. **Aim**: To implement a multidisciplinary screening strategy that prioritizes HCV detection in patients with metabolic syndrome and MASLD. By acknowledging the multisystemic impact of HCV, particularly among those with comorbidities such as diabetes and cardiovascular disease, this approach aims to enhance micro-elimination efforts and improve outcomes within this vulnerable group.

Method: A cohort of 2,704 HCV-positive patients was evaluated for liver stiffness and steatosis using FibroScan, with additional screenings for comorbidities including diabetes, hypertension, and cardiovascular disease.

Results: Among the HCV-positive cohort, females had a significantly higher prevalence of HCV antibodies compared to males. Remarkably, 87% of antibody-positive patients were over 50 years old, and 28.6% had diabetes, with 54.5% of diabetic patients showing advanced fibrosis (F2-F4). Significant fibrosis (F3-F4) was notably associated with advanced age, male gender, psychiatric disorders, diabetes, cardiovascular disease and higher degree of steatosis evaluated by FibroScan-CAP. The study highlights significant gaps in micro-elimination due to under-diagnosis and insufficient cross-specialty coordination, particularly in those with metabolic syndrome components.

Conclusion: Targeted HCV screening within MASLD and metabolic syndrome populations is essential to closing gaps in micro-elimination efforts. Integrating a multidisciplinary approach that involves high-risk groups with metabolic comorbidities could significantly enhance HCV detection and management, leading to improved patient outcomes. This strategy underscores the critical role of viral infection screening in patients with metabolic disorders and supports more effective resource allocation in the pursuit of comprehensive HCV elimination.

PO7-10
Nationwide comparison of the epidemiology of metabolic dysfunction-associated and alcoholic liver disease in the entire korean population from 2010 to 2022

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Background and Aims: Both alcohol overuse and metabolic dysfunction are major contributors to liver disease. The rapid increase in cases of metabolic dysfunction-associated steatotic liver disease (MASLD) is well recognized globally; however, comparative epidemiologic studies with alcoholic liver disease (ALD) are lacking. This study aims to analyze the prevalence of MASLD and ALD in the entire Korean population over the past 12 years (2010 to 2022).

Method: We utilized nationwide registry data from the Health Insurance Review and Assessment Service (HIRA), which includes diagnoses and treatments provided by physicians in Korean clinics and hospitals. We focused on the prevalence of MASLD and ALD-related fatty liver and hepatitis, stratified by year (2010 to 2022), age, and gender, within a population of approximately 50.86 million.

Results: The annual prevalence of MASLD and metabolic-associated steatohepatitis (MASH) increased by 2.2 times (from 15.6 to 34.3 per 1,000 people) and nearly 20 times (from 0.49 to 9.79 per 1,000 people), respectively. In contrast, the prevalence of alcohol-associated liver diseases remained stable (2.8 per 1,000 for alcoholic fatty liver) or slightly decreased (from 2.4 to 2.1 per 1,000 for steatohepatitis). Notably, there was a male predominance among individuals under 50 years old, while females aged 50 and older exhibited a higher prevalence of MASLD and MASH. Conversely, both alcoholic fatty liver and steatohepatitis consistently showed a male predominance over the 12-year period.

Conclusion: The prevalence of MASLD and alcoholic fatty liver may be underreported due to low clinical awareness. Meanwhile, MASH prevalence is rapidly increasing in clinical practice, contrasting with the decline in alcoholic hepatitis cases. These findings reflect the evolving liver-related health landscape in South Korea and provide valuable reference data for future research.

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