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Prevalence, Awareness & Disease Burden

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Prevalence, Awareness & Disease Burden

1. ACT on MASH: Multi-country cross-sectional online survey Evaluating Awareness, Understanding, Screening Perceptions, and Stigma Related to MASLD/MASH Among Healthcare Professionals Across Five Countries.

Aim:

- To assess healthcare professionals' (HCPs) awareness, knowledge, confidence, and perceptions regarding metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH).
- To evaluate HCPs' understanding of the relationship between MASLD/MASH and cardiometabolic comorbidities, as well as their screening practices and perceived barriers to diagnosis.

Methods:

- Online cross-sectional survey conducted in 2025 across Canada, France, Germany, Japan, and the United States.
- 774 HCPs included with 20 years of clinical experience: gastroenterologists, hepatologists, endocrinologists, cardiologists, obesity specialists, primary care physicians, radiologists, and nurse practitioners/physician assistants (US only).
- Survey assessed knowledge, awareness, confidence in identifying at-risk patients, perceptions of disease burden, screening practices, and barriers to screening.

Results:

- Most participants worked in outpatient clinics (49%) or hospital settings (42%).

Table 1. Clinical Outcomes

Criteria	Outcome
">Very" or "extremely" knowledgeable about MASLD and MASH	62% and 63% respectively
Aware of the distinction between MASLD and MASH	82%
• Highest among hepatologists	98%
• Lowest among cardiologists	72%
"Very" or "extremely" confident in identifying patients at risk of MASH	48%
Agreement that MASLD/MASH increase cardiovascular risk	87% Agreed
Early diagnosis and management improve health outcomes	89% Believed

- Nearly half of MASLD (45%) and MASH (42%) diagnoses were reported to result from incidental findings.
- Radiologists reported incidental findings of MASLD and MASH in 21% and 14% of scans reviewed in a typical month, respectively.
- The perceived importance of screening patients with cardiometabolic conditions for MASH varied considerably, ranging from 42% for chronic kidney disease to 86% for persistently elevated liver enzymes.
- 30% of HCPs identified concerns about stigmatizing patients with obesity as a barrier to screening.

Conclusion

- **Despite generally high awareness and knowledge of MASLD and MASH, significant gaps remain in HCPs' confidence to identify patients at risk.**
- **A substantial proportion of MASLD and MASH cases continue to be detected incidentally rather than through proactive screening.**
- **Variability in screening priorities and concerns about obesity-related stigma may contribute to underdiagnosis.**
- **Targeted educational initiatives are needed to improve risk identification, screening practices, and multidisciplinary management of patients with MASLD/MASH.**

2. ACT on MASH: A Multinational Survey Evaluating Awareness, Disease Perceptions, and Cardiometabolic Comorbidities Among Individuals at Risk for or Living with MASLD and MASH.

Aim:

- To evaluate awareness, knowledge, and perceptions of MASLD and MASH among individuals diagnosed with MASLD/MASH and those at risk for MASH across multiple countries.

Methods:

- Cross-sectional online survey conducted in 2025 across Canada, France, Germany, Japan, and the United States.
- Included adults diagnosed with MASLD/MASH or at risk for MASH (defined as having ≥1 cardiometabolic risk factor or elevated liver enzymes).
- Survey developed by a multidisciplinary team, including a patient advocacy representative.
- Participants were recruited through online panels, databases, outreach initiatives, and social media.

Results:

- A total of 516 respondents completed the survey including MASH (n = 252), MASLD (n=132) and at risk for MASH (n=132)
- Median age: 48 years; 50% female; 49% had a university degree or higher.
- Cardiometabolic comorbidities were highly prevalent in:
  - Obesity: 67–72%
  - Hypertension: 42–47%
  - Type 2 diabetes: 25–35%

Table 2. Patient outcomes

Crietria	Results
Diagnosed respondents reported receiving a timely diagnosis	MASLD: 62%; MASH: 60%
Disease knowledge with Very/extremely familiar with disease progression	MASLD: 15%; MASH: 37%
Among at-risk individuals	
Risk of developing MASLD/MASH recognized	58%
Very/extremely concerned about developing the disease	58%
Very/extremely familiar with MASH	9%
Perceived stigma	
Agreed or strongly agreed that liver disease is associated with stigma.	55% people with MASH

Conclusion

- **Awareness and understanding of MASLD and MASH remain suboptimal among both diagnosed and at-risk populations.**
- **High rates of obesity, hypertension, and type 2 diabetes highlight the substantial cardiometabolic burden associated with these conditions.**
- **Limited knowledge of disease progression and widespread perceptions of stigma underscore the need for:**
  - **Enhanced patient education**
  - **Stigma-reduction initiatives**
  - **Improved patient–provider communication**
- **Greater awareness efforts may facilitate earlier recognition, engagement, and management of MASLD and MASH.**

3. Re-evaluating MASH: Time to explore a multisystem treatment approach.

Aim:

- Despite its growing burden, MASH continues to be underrecognized and underdiagnosed globally, with prevalence expected to rise by 56% from 2016 to 2030.
- Treatment options remain limited, with semaglutide 2.4 mg and resmetirom currently the only approved therapies for MASH.

Methods:

- Cross-sectional online survey conducted in 2025 across Canada, France, Germany, Japan, and the United States.
- Included adults diagnosed with MASLD/MASH or at risk for MASH (defined as having ≥1 cardiometabolic risk factor or elevated liver enzymes).
- Survey developed by a multidisciplinary team, including a patient advocacy representative.
- Participants were recruited through online panels, databases, outreach initiatives, and social media.

Results:

- After 72 weeks, semaglutide 2.4 mg led to:
  - Resolution of steatohepatitis with no worsening ofliver fibrosis in 62.9% of participants (vs 34.3% with placebo)
  - Improvernent in liver fibrosis with no worsening of steatohepatitis in 36.8% of participants (vs 22.4% with placebo)
  - The effect of semaglutide on MASH-related outcomes maybe only partially mediated by weight reduction
- After 52 weeks, resmetirom led to:
  - MASH resolution with no worsening of fibrosis in 29.9% of participants (vs 9.7% with placebo)
  - Fibrosis improvement by ≥1 stage with no worsening of MASLD activity score in 25.9% of participants (vs 14.2% with placebo)
- MASH is highly interconnected with other cardiometabolic diseases, particularly CVD and obesity, with obesity being a key driver of MASH

Conclusion

- **Incretin-based therapies (semaglutide up to 7.2 mg and tirzepatide up to 15 mg) provide up to -21% weight loss in people with obesity.**
- **Semaglutide 2.4 mg and resmetirom improved various lipid parameters and cardiometabolic risk factors in people with MASH**
- **Additionally, semaglutide 2.4 mg reduced MACE by 21% in people with overweight or obesity and CVD, including those with a FIB-4score ≥1.3.**

4. Prevalence, predictors, and population impact in a large screening cohort showing binge drinking as a key driver of steatotic liver disease.

Aim:

- To investigate the association between self-reported frequent binge drinking and increased liver stiffness.
- To evaluate the relationship between binge drinking, phosphatidylethanol (PEth) levels, and socio-demographic and cardiometabolic risk factors.

Methods:

- Prospective cohort study including participants from the general population and individuals at risk of steatotic liver disease.
- Liver stiffness was assessed using vibration-controlled transient elastography (VCTE).
- Significant liver fibrosis was defined as VCTE ≥8 kPa.

- Alcohol consumption patterns were assessed using the AUDIT-C questionnaire.
- Definitions:
  - Frequent binge drinking: ≥5 alcohol units per occasion at least once weekly.
  - Alcohol overuse: ≥14 units/week (women) or ≥21 units/week (men) for ≥5 years.
  - High alcohol intake: PEth ≥200 ng/mL.
- Multivariable logistic regression adjusted for socio-demographic factors, cardiometabolic risk factors, alcohol overuse, and PEth levels.

Results:

- A total of 6,400 participants were included with mean age of 57 years with 52% of female, 37% of obese patients and 9% with type 2 diabetes
- Overall:
  - 5.9% had VCTE ≥8 kPa
  - 17% had PEth ≥200 ng/mL
- Frequent binge drinking was reported by 1,092 participants:
  - 71% were male
  - 81% reported alcohol overuse

Table 3. Comparison of parameters for frequent binge drinkers vs non-binge drinkers

Parameter	Frequent Binge Drinkers	Non-Binge Drinkers	p-value / Interpretation
Elevated Liver Stiffness (VCTE ≥8kPa)	10.3%	4.7%	$p < 0.001$; significantly higher prevalence among binge drinkers
High Alcohol Intake (PEth≥200ng/mL)	60%	8%	Markedly more common among binge drinkers
Median Peth Level, ng/mL (IQR)	253 (118–494)	21 (6–65)	Indicates substantially higher recent alcohol consumption in binge drinkers

- After adjustment for confounders, frequent binge drinking remained independently associated with increased liver stiffness with OR of 1.41 (95% CI: 1.03–1.93; p=0.031)
- Other associated factors:
  - Male sex was strongly associated with binge drinking.
  - Partnership and parenthood were associated with lower odds of binge drinking.
  - Hypertension remained independently associated with binge drinking with OR of 1.70 (95% CI: 1.40–2.06)

Conclusion

- **Frequent binge drinking is independently associated with increased liver stiffness and a higher risk of significant liver fibrosis.**
- **The association persists even after accounting for overall alcohol consumption and objective alcohol intake measured by PEth.**
- **Binge drinking represents an important and independent determinant of liver disease risk beyond cumulative alcohol exposure.**
- **Assessment of drinking patterns should be incorporated into liver disease risk evaluation and prevention strategies.**

5. Real-world evidence from over 11.7 million individuals in the UK shows increased diagnosis and risk stratification for MASLD in primary care over the last 20 years.

Aim:

- To evaluate temporal trends in:
  - Recorded prevalence and incidence of MASLD in UK primary care.
  - Associated cardiometabolic comorbidities.
  - Availability and utilization of FIB-4 risk stratification over the last decade.
- To identify potential gaps in fibrosis risk assessment across patient subgroups.

Methods:

- Real-world evidence study using the UK Clinical Practice Research Datalink (CPRD) from 2003–2022.
- MASLD cases were identified using NAFLD diagnostic codes as a proxy.
- Exclusion criteria are patients with age <18 years; <1 year follow-up, pre-existing autoimmune liver disease and viral hepatitis
- Controls were matched 1:4 based on basis of age (±5 years); sex and general practice
- Assessed:
  - Point prevalence and incidence of MASLD
  - Comorbidities
  - Availability of laboratory components required to calculate FIB-4

Results:

- Among 11.7 million individuals in CPRD (2022) includes 365,797 MASLD patients and 1,460,288 matched controls
- Recorded MASLD prevalence increased approximately 5-fold over the last decade:
  - 0.52% in 2013
  - 2.42% in 2023 ($p<0.001$)
- Annual MASLD incidence doubled:
  - 1.60 per 1,000 person-years (2012)
  - 3.31 per 1,000 person-years (2022) ($p<0.001$)
- Compared with controls, MASLD patients with the median age of 53 years; 51.8% of male
  - Had higher prevalence of:
  - Type 2 diabetes: 21.0% vs 7.7% ($p<0.001$)
  - Hypertension: 35.3% vs 18.7% ($p<0.001$)
- Availability of FIB-4 components improved significantly:
  - 4.3% before 2015
  - 22.8% during 2015–2022 ($p<0.001$)
- Proportion of patients with high-risk FIB-4 scores decreased slightly:
  - 7.6% pre-2015
  - 6.4% post-2015
- South Asians were overrepresented among MASLD patients, 11.0% vs 7.2% in controls ($p<0.001$)
- However, South Asians were less likely to have FIB-4 data available, with adjusted OR: 0.67 (95% CI: 0.65–0.70; $p<0.001$)

Conclusion

- **Recorded MASLD prevalence in UK primary care increased fivefold over the past decade, reflecting improved recognition but also highlighting a substantial remaining diagnostic gap.**
- **Availability of fibrosis risk stratification using FIB-4 has improved but remains suboptimal in routine practice.**
- **MASLD is strongly associated with cardiometabolic comorbidities, particularly type 2 diabetes and hypertension.**
- **A potential care gap exists among South Asian patients, who are at higher risk for MASLD but are less likely to undergo fibrosis risk assessment.**

6. Global burden of disease study of 2023 shows cirrhosis burden dynamics in the Asia-Pacific region from 1990 to 2023 and forecasting to 2050.

Aim:

- To assess trends in the burden of cirrhosis across the Asia-Pacific region from 1990 to 2023.
- To identify key drivers of disease burden, evaluate regional disparities and healthcare efficiency, and project future cirrhosis burden through 2050.

Methods:

- Analysis of data from the Global Burden of Disease (GBD) Study 2023.
- Study evaluated, incidence, prevalence, mortality and disability-adjusted life years (DALYs)
- Analyses were stratified by age, sex and socio-demographic Index (SDI)
- Statistical approaches included:
  - Estimated Annual Percentage Change (EAPC) for trend analysis
  - Slope Index of Inequality (SII) for disparity assessment
  - Decomposition analysis to identify burden drivers
  - Frontier analysis to assess healthcare efficiency
  - Projections of cirrhosis burden through 2050

Results:

- Between 1990 and 2023:
  - Prevalent cirrhosis cases increased by 57%, reaching 624.7 million (95% UI: 584.4–671.8 million).
  - Total deaths increased by 7%, reaching 354,279 (95% UI: 309,789–401,481).
- Mortality burden was substantially higher in men:
  - Men: 246,656 deaths
  - Women: 107,623 deaths
- Despite increasing absolute burden, age-standardized rates declined:
  - Incidence: EAPC −0.56%
  - Mortality: EAPC −2.53%
  - DALYs: EAPC −2.33%
- Countries with the highest burden:
  - India: 188,370 deaths
  - China: 121,033 deaths
- Highest age-standardized mortality rate was in solomon Islands, 37.4 per 100,000 population
- Incidence among individuals aged ≥95 years increased dramatically to 657% increase
- Decomposition analysis showed that:
  - Population growth and aging were the primary contributors to the rising absolute burden.
  - These demographic changes offset improvements in disease prevention and managernent.
- Health inequality improved over time calculated with DALY SII improved from −426.9 to −308.1
- Mortality-related healthcare efficiency gaps narrowed across the region.
- By 2050:
  - Age-standardized rates are projected to continue declining.
  - Absolute deaths are projected to increase to 391,317 annually.

Conclusion

- **Although age-standardized incidence, mortality, and DALY rates have declined across the Asia-Pacific region, the absolute burden of cirrhosis continues to rise.**
- **Population aging and growth are the main drivers of this increasing burden, particularly in India and China.**
- **Improvements in healthcare efficiency and reductions in inequality have occurred, but are insufficient to offset demographic pressures.**
- **Future healthcare policies should prioritize integrated cirrhosis care, prevention strategies, and resource allocation tailored to an aging population to address the projected increase in disease burden.**

7. International, multicenter cohort study with cardiovascular health metrics (Life's Essential 8) and the risk and trajectories in MASLD, type 2 diabetes, and comorbid disease.

Aim:

- To evaluate the impact of the American Heart Association's Life's Essential 8 (LE8) cardiovascular health metrics on:
  - The development of MASLD and type 2 diabetes (T2D).
  - Progression from a healthy state to MASLD, T2D, comorbid MASLD-T2D, and mortality.
- To assess the role of cardiovascular health in the prevention and progression of metabolic disorders.

Methods:

- Data were analyzed from three large population-based cohorts including nationwide community survey in China, NHANES and UK Biobank
- Total study population: 246,723 participants.
- LE8 scores were calculated using:
  - Behavioral health metrics
  - Clinical health metrics
  - Physical examination findings
  - Structured questionnaire data
- Multinomial logistic regression assessed associations between LE8 scores and four health states:
  - Healthy (reference)
  - MASLD only
  - T2D only
  - Comorbid MASLD-T2D
- Multi-state models and restricted cubic spline (RCS) analyses evaluated the impact of LE8 scores on transitions between disease states and mortality.

Results:

- Across all three cohorts, higher LE8 scores were consistently associated with lower risks of (all $P < 0.001$) :
  - MASLD
  - T2D
  - MASLD-T2D comorbidity
- In UK Biobank prospective analyses, participants with high versus low cardiovascular health (CVH) scores had significantly lower risks of:
  - Incident MASLD: HR 0.27 (95% CI: 0.18–0.39)
  - Incident T2D: HR 0.10 (95% CI: 0.09–0.12)
- Among individuals with either MASLD or T2D alone, higher CVH scores significantly reduced progression to MASLD-T2D comorbidity.
- Each 10-point increase in LE8 score was associated with:
  - 24% lower mortality risk following MASLD onset
  - 11% lower mortality risk following T2D onset
- Both behavioral and biological LE8 domains contributed significant protective effects.
- Restricted cubic spline analysis demonstrated significant non-linear dose-response relationships between LE8 scores and disease transitions ($P_{non\text{-}linear} < 0.05$).

Conclusion

- **LE8 scores are strong predictors of the risk and progression of MASLD and T2D.**
- **Better cardiovascular health substantially reduces the likelihood of developing MASLD, T2D, their coexistence, and associated mortality.**
- **Improvements in both lifestyle behaviors and biological risk factors contribute to these protective effects.**
- **The LE8 framework may serve as a valuable tool for integrated prevention, risk stratification, and management of MASLD, T2D, and related cardiometabolic diseases.**

8. Prevalence and development of a simple score to detect advanced fibrosis in dysmetabolic patients with MASLD in the WHO Africa region.

Aim:

- To evaluate the prevalence, severity, and clinical correlates of MASLD and advanced liver fibrosis (ALF) among patients with metabolic dysfunction in Africa.
- To develop and validate a simple, non-invasive score for identifying advanced liver fibrosis in settings with limited access to FibroScan.

Methods:

- Prospective cohort study conducted as part of the MetLive Study.
- Consecutive patients with hypertension (HBP); obesity (BMI ≥30 kg/m²), type 2 diabetes mellitus (T2DM) were enrolled the Gambia (training cohort) and South Africa (validation cohort)
- All participants underwent comprehensive clinical assessment, including FibroScan-CAP.
- Definitions:
  - MASLD: CAP ≥248 dB/m or hyperechoic liver on ultrasound
  - Advanced liver fibrosis (ALF): LSM ≥8 kPa
  - Cirrhosis: LSM ≥12 kPa
- A simplified fibrosis score was developed using receiver operating characteristic (ROC)-derived cut-offs and validated in the South African cohort.

Results:

- Training Cohort (The Gambia) enrolled 315 participants with 76% of female; median age of 55 years; 33% had obesity; 61% T2DM; 56% hypertension and 46% had steatosis
- Disease burden in Gambia is:
  - MASLD: 43% (n=130)
  - Advanced liver fibrosis: 8.3% (n=26)
  - Cirrhosis: 2.2% (n=7)
- Validation Cohort (South Africa) enrolled 127 participants with 58% of female; median age of 53 years; 54% had obesity; 21% T2DM; 79% hypertension and 67% had steatosis
- Disease burden:
  - MASLD: 65%
  - Advanced liver fibrosis: 24.5%
  - Cirrhosis: 10% (n=12)

Predictors of Disease

- Independent predictors of MASLD:
  - BMI
  - Waist-to-hip ratio (WHR)
  - Gamma-glutamyl transferase (GGT)
- Independent predictors of advanced liver fibrosis:
  - Elevated GGT
  - Lower platelet count

Simplified Fibrosis Score

- Based on ≥2 of the following:
  - BMI ≥26 kg/m²
  - WHR ≥0.92
  - GGT ≥41 IU/L

- Diagnostic performance for detecting ALF:
  - Sensitivity: 89%
  - Negative Predictive Value (NPV): 93%
  - Outperformed FIB-4 in sensitivity
  - Specificity: 50%

Conclusion

- **MASLD and advanced liver fibrosis are common among individuals with metabolic dysfunction in both The Gambia and South Africa.**
- **A simple score incorporating BMI, waist-to-hip ratio, and GGT effectively identifies patients at risk for advanced fibrosis.**
- **The tool demonstrated high sensitivity and NPV, making it useful for ruling out advanced fibrosis in resource-limited settings.**
- **This approach may facilitate earlier identification and referral of high-risk patients in African regions where access to FibroScan remains limited.**

9. In people living with HIV and pre-diabetes in Tanzania, estimation of liver fibrosis risk using non-invasive biomarker tests.

Aim:

- To estimate the risk of liver fibrosis and the 10-year risk of cirrhosis among people living with HIV (PLHIV) and pre-diabetes in Tanzania.
- To evaluate the performance of multiple non-invasive tests (NITs) for fibrosis risk stratification in this population.

Methods:

- Cross-sectional analysis of baseline data from the META Trial, a Phase III randomized controlled trial of metformin conducted in Tanzania.
- Included 1,691 PLHIV with pre-diabetes.
- Liver fibrosis risk was assessed using:
  - Fibrosis-4 Index (FIB-4)
  - Metabolic Dysfunction-Associated Fibrosis-5 (MAF-5)
  - NAFLD Fibrosis Score (NFS)
  - LiverRisk Score
- Ten-year cirrhosis risk was estimated using the Cirrhosis Outcome Risk Estimator (CORE).
- Risk categories were assigned using validated and age-adjusted cut-offs.

Results:

- Patient Characteristics include total participants of 1,691 with mean age of 49.4 ± 9.4 years; 75.0% females and 99.2% of Black ethnicity:
- Fibrosis Risk Assessment showed the following:
  - FIB-4 (age-adjusted thresholds):
    - Low risk: 65.2%
    - Indeterminate risk: 31.8%
    - High risk: 3.0%
  - NAFLD Fibrosis Score (NFS):
    - Indeterminate risk: 50.9%
    - High risk: 8.3%

- MAF-5 Score: High risk was 59.9% of participants
- LiverRisk Score: <1% classified as medium or high risk

- Cirrhosis Risk (CORE) 5.8% of participants had a ≥1% estimated 10-year risk of developing cirrhosis or a cirrhosis-related outcome.
- Sex-Based Differences
- Females were more frequently classified as low risk than males by FIB-4, 70% vs 50%, p<0.001
- Males showed higher-risk classifications according to:
  - MAF-5
  - LiverRisk
  - CORE
- No significant sex differences were observed using NFS.

Conclusion

- **Non-invasive fibrosis tests produced markedly different estimates of liver fibrosis risk among PLHIV with pre-diabetes in Tanzania.**
- **FIB-4 and NFS classified most participants as low risk, whereas MAF-5 identified a substantial proportion as high risk.**
- **Approximately 6% of participants were estimated to be at risk of cirrhosis-related outcomes within 10 years.**
- **These findings highlight the need for:**
  - **Local validation of non-invasive fibrosis assessment tools.**
  - **Integration of liver disease screening into HIV care programs in Africa.**
  - **Improved strategies to address the growing burden of MASLD/MASH and metabolic comorbidities among PLHIV.**

10. A 20-year study in 204 countries study the global trends and disparities in preventable premature liver deaths due to MASLD.

Aim:

- To quantify the global burden of premature deaths (PDs) attributable to MASLD-related liver disease.
- To estimate the proportion of premature deaths that are potentially preventable across countries.
- To identify socioeconomic and demographic factors associated with preventable MASLD-related mortality.

Methods:

- Global ecological analysis including 204 countries from 2004–2023.
- Data sources:
  - Global Burden of Disease (GBD) database
  - United Nations (UN) and WHO covariates
- Premature death (PD) defined as death occurring before 70 years of age.
- Countries were categorized into four groups:
  - Group A: High MASLD prevalence and low mortality-to-prevalence ratio (MPR) (benchmark performers)
  - Group B: High SDI countries
  - Group C: Middle SDI countries
  - Group D: Low SDI countries

- The 10th percentile of MPR in 2004 was used as the benchmark within each group.
- Preventable premature deaths were calculated as the excess of observed over expected PD rates.
- Determinants of preventability were assessed using linear mixed-effects models with country-specific random intercepts.

Results:

- Global Burden
- 1,262,126 MASLD-related premature liver deaths occurred worldwide between 2004 and 2023.
- 49.3% (622,459 deaths) were estimated to be potentially preventable.

Table 4. Distribution and trends of Preventable Deaths over time

Country Group	Share of Global Preventable Deaths	Base value	Trends over time
Group A (Benchmark countries)	6.0%	23.5%	21.3%
Group B (High SDI)	41.0%	57.4%	52.7%
Group C (Middle SDI)	41.1%	57.8%	61.3%
Group D (Low SDI)	11.9%	50.5%	53.0%

- Significant temporal trends observed ($p < 0.002$).
- Factors Associated with Preventability

Group A (Benchmark Countries)

- Lower preventability associated with:
  - Higher SDI ($\beta = -0.789$)
  - Larger male population ($\beta = -0.016$)
- Higher preventability associated with:
  - Diabetes prevalence ($\beta = 0.009$)
  - Older age ($\beta = 0.016$)
  - Urbanization ($\beta = 0.004$)

Group B (High SDI Countries)

- Higher preventability associated with, obesity prevalence ($\beta = 0.011$)
- Lower preventability associated with:
  - Older age ($\beta = -0.021$)
  - Greater Universal Health Coverage ($\beta = -0.003$)

Group C (Middle SDI Countries)

- Higher preventability associated with:
  - Obesity ($\beta = 0.006$)
  - Older age ($\beta = 0.008$)

Group D (Low SDI Countries)

- Higher preventability associated with:
  - Older age ($\beta = 0.010$)
  - Urbanization ($\beta = 0.002$)
- Lower preventability associated with:
  - Larger male population ($\beta = -0.022$)

Conclusion

- **Nearly half of all premature MASLD-related liver deaths globally are potentially preventable.**
- **Significant disparities exist across countries and socioeconomic groups.**
- **Obesity, diabetes, aging populations, urbanization, and healthcare access influence preventable mortality rates.**
- **These findings highlight the urgent need for targeted public health policies, improved prevention strategies, and equitable healthcare access to reduce the growing global burden of MASLD-related premature mortality.**

Diagnosis, Screening & Risk Stratification

1. Automated MASLD Screening Within the iDiabetes Platform Improves FIB-4 Screening and Identification of Advanced Fibrosis and Cirrhosis New cases.

Aim:

- To evaluate the implementation of an automated MASLD fibrosis screening algorithm integrated into the iDiabetesPlus precision diabetes care platform in primary care.
- To assess its effectiveness in facilitating universal FIB-4 screening, risk stratification, automated referral pathways, and detection of advanced fibrosis/cirrhosis in patients with diabetes.

Methods:

- iDiabetesPlus was piloted in October 2024 and implemented as standard diabetes care from January 2025 across 16 primary care practices in Scotland.
- All patients with diabetes were automatically enrolled during annual diabetes reviews.
- The platform performed automated FIB-4 screening for all patients.
- Patients with ALT >30 U/L underwent reflex liver aetiology testing and NAFLD Fibrosis Score (NFS) calculation.
- Enhanced Liver Fibrosis (ELF) testing was automatically triggered for patients with indeterminate or high-risk FIB-4/NFS results.
- Automated referral to secondary care was generated for patients meeting predefined high-risk criteria (ELF ≥9.8, FIB-4 >2.67, NFS >0.675, or positive aetiology results).

Results:

- A total of 4,533 patients with diabetes were enrolled; 91% had type 2 diabetes.
- FIB-4 screening was completed in 4,499 patients (99.3%).
- FIB-4 results:
  - 63.1% had low-risk scores (<1.30)
  - 33.0% had intermediate-risk scores (1.30–2.67)
  - 3.9% had high-risk scores (>2.67)
- Second-line ELF testing was performed in 973 patients (21.5%); 53.5% had ELF <9.8.
- Automated secondary care referrals were generated for 614 patients (13.6%).
- Among 435 FibroScan assessments:
  - 52.0% had LSM <8 kPa
  - 24.8% had LSM 8–11.9 kPa
  - 23.2% had LSM ≥12 kPa
- The screening pathway identified previously undiagnosed advanced fibrosis or cirrhosis in 2.2% of the screened diabetes population.

Conclusion

- **Integration of MASLD screening into the iDiabetesPlus platform achieved near-universal FIB-4 screening in a real-world primary care diabetes population.**
- **Selective second-line ELF testing reduced unnecessary secondary care referrals by more than 50%.**
- **The automated screening pathway effectively identified new cases of advanced fibrosis and cirrhosis, supporting scalable early detection of MASLD-related liver disease in patients with diabetes.**

2. Diabetes MASH Index for non-invasive identification of at-risk metabolic dysfunction-associated steatohepatitis in patients with type 2 diabetes.

Aim:

- To develop and validate a simple, non-invasive model (DiabetesMASH Index [DMI]) for identifying at-risk MASH (MASH with fibrosis stages F2–F4) in patients with type 2 diabetes (T2D).
- To compare its diagnostic performance with established non-invasive fibrosis scores, including FIB-4, NFS, and AST/ALT ratio (AAR).

Methods:

- Prospective multicenter study involving a derivation cohort of 525 adults with T2D who underwent liver biopsy across 10 centers.
- External validation was performed in three independent multinational cohorts:
  - DiabetesLiver Integrated Management cohort (n=3,711)
  - Singapore cohort (n=422)
  - NHANES cohort (n=1,674)
- At-risk MASH was defined histologically in the derivation cohort and by the FAST score in validation cohorts.
- Model performance was assessed using AUROC, calibration analysis, and decision curve analysis.

Results:

- The DiabetesMASH Index (DMI) was developed using four routinely available variables including age, waist circumference, ALT and HbA1c
- DMI demonstrated strong diagnostic performance (Table)

Table 5. Clinical results for DMI

Parameters	AUROC Results
Derivation cohort	0.79 (95% CI: 0.75–0.83)
DiabetesLiver cohort	0.91 (95% CI: 0.89–0.94)
Singapore cohort	0.88 (95% CI: 0.80–0.96)
NHANES cohort	0.90 (95% CI: 0.86–0.94)

- DMI consistently outperformed FIB-4, NFS, and AAR across all cohorts.
- Calibration analyses demonstrated good agreement between predicted and observed risk.
- Diagnostic thresholds:
  - Rule-out threshold: 0.184 (Sensitivity 85%, NPV 92%)
  - Rule-in threshold: 0.452 (Specificity 90%, PPV 57%)
- The indeterminate zone included:
  - 35.8% of patients in the derivation cohort
  - 19.9%, 24.8%, and 19.1% in the validation cohorts

Conclusion

- **The DiabetesMASH Index is a validated, affordable, and non-invasive tool for identifying at-risk MASH in patients with T2D.**
- **Using readily available clinical and laboratory parameters, DMI provides superior diagnostic performance compared with commonly used fibrosis scores.**
- **DMI may facilitate large-scale screening and early identification of patients who could benefit from targeted MASH therapies.**

3. ActiMASH: In patients with MASLD, a novel blood-based score to measure liver activity.

Aim:

- To develop and validate ActiMASH, a non-invasive blood-based test for assessing MASLD activity and identifying MASH in patients with type 2 diabetes.
- To evaluate its ability to predict fibrosis progression and improve screening for at-risk MASH.

Methods:

- Nested study within the multicenter prospective QUID-NASH trial involving 407 patients with type 2 diabetes and available liver biopsy data.
- Participants were divided into:
  - Derivation cohort (n=273)
  - Validation cohort (n=134)
- Liver RNA sequencing was performed to identify molecular pathways associated with disease activity.
- Proteomic analysis of circulating extracellular vesicles (EVs) was conducted in 23 patients (8 with steatosis and 15 with MASH) to identify potential biomarkers.
- Liver stiffness measurement (LSM) by vibration-controlled transient elastography was performed at baseline and during follow-up.
- A logistic regression model was developed and validated to generate the ActiMASH score.

Results:

- Proteomic analysis identified transferrin receptor carried by large extracellular vesicles (TFRC-lEVs) as a novel biomarker associated with:
  - MASH ($p<0.001$ in derivation cohort; $p=0.02$ in validation cohort)
  - Hepatocyte ballooning ($p=0.002$ and $p=0.02$, respectively)
- Transcriptomic analysis linked elevated TFRC-lEV levels with activation of the heme metabolism pathway.
- Experimental studies demonstrated increased TFRC-lEV release under MASH-like conditions.
- Independent predictors of MASH included TFRC-lEV levels, Sex, AST, Triglycerides
- These variables were combined to create the ActiMASH score.
- Diagnostic performance:
  - AUROC for MASH: 0.81 in both derivation and validation cohorts.
  - ActiMASH scores increased significantly with higher NAFLD Activity Score (NAS) ($p<0.0001$).
- Using a cut-off value of ≥45:
  - Sensitivity for identifying at-risk MASH improved from 36% to 68% compared with the current EASL strategy.
  - Specificity remained high (83% vs. 87%).
- After a median follow-up of 4 years:
  - All patients with LSM progression (>5 kPa increase) had baseline ActiMASH ≥45.
  - No patient with ActiMASH <45 showed fibrosis progression ($p=0.007$).

Conclusion

- **ActiMASH is a novel, validated blood-based test incorporating circulating extracellular vesicle biomarkers to assess MASLD activity non-invasively.**
- **The score accurately identifies MASH, correlates with histological disease activity, and predicts future fibrosis progression.**
- **ActiMASH may substantially improve screening and risk stratification of at-risk MASH in patients with type 2 diabetes while reducing reliance on liver biopsy.**

4. Predicting adverse liver outcomes in MASLD by comparing non-invasive risk scores.

Aim:

- To compare the predictive performance of established risk scores for identifying incident major adverse liver outcomes (MALO) in patients with confirmed MASLD.
- To evaluate the discrimination and calibration of the following models:
  - Cirrhosis Outcome Risk Estimator (CORE)
  - Fibrosis-4 (FIB-4)
  - Metabolic Dysfunction–Associated Fibrosis-5 (MAF-5)
  - Liver Risk Score (LRS)
  - Anticipate-NASH

Methods:

- Individual participant data meta-analysis (IPD-MA) of well-characterized MASLD cohorts with longitudinal follow-up.
- Complete-case analysis included 927 participants from 14 independent studies.
- Median age: 49 years; 53.0% male.
- Type 2 diabetes prevalence: 41.8%; median BMI: 28 kg/m².
- Median follow-up duration: 4.8 years.
- Model performance was assessed using:
  - Area under the curve (AUC) for discrimination
  - Observed-to-expected (O) ratios for calibration
- Subgroup analyses were performed using the maximum available sample size for each model.

Results:

- During follow-up, 2.1% of participants developed MALO.
- At 10 years, discrimination (AUC) in the complete-case cohort was:
  - FIB-4: 0.823
  - MAF-5: 0.733
  - CORE: 0.713
  - Anticipate-NASH: 0.703
  - LRS: 0.610
- Analysis using all available data showed similar findings:
  - FIB-4 (n=2,326): AUC 0.821
  - Anticipate-NASH (n=2,315): AUC 0.770
  - MAF-5 (n=1,403): AUC 0.758
  - CORE (n=1,970): AUC 0.738
  - LRS (n=1,586): AUC 0.684
- FIB-4 consistently demonstrated the strongest discriminatory performance across analyses.
- Calibration varied substantially:
  - CORE underpredicted MALO incidence (O 2.567)
  - LRS markedly overpredicted risk (O 0.007)
  - MAF-5 also overpredicted risk (O 0.020)

Conclusion

- **Risk prediction models for MASLD demonstrate significant heterogeneity in both discrimination and calibration.**
- **FIB-4 showed the most consistent and robust performance for predicting major adverse liver outcomes.**
- **Existing risk scores are not interchangeable across different MASLD populations.**
- **Population-specific validation and recalibration are essential before widespread clinical implementation of these models.**

5. Measurement of waist circumference might make the difference in real-life evaluation of the FIB-4 two-step fibrosis screening strategy in MASLD.

Aim:

- To evaluate the real-world performance of the guideline-recommended FIB-4–based screening strategy for detecting advanced fibrosis in patients with MASLD referred to hepatology clinics.
- To identify factors associated with FIB-4 misclassification and assess whether waist circumference (WC) improves fibrosis risk stratification.

Methods:

- Multicenter study including 1,484 patients with MASLD referred to hepatology clinics in Milan and Verona.
- Participants met criteria for fibrosis screening, including:
  - Type 2 diabetes
  - Obesity with metabolic comorbidities
  - Elevated liver transaminases
- Fibrosis assessment followed current guideline recommendations:
  - FIB-4 cut-off of 1.3 (or 2.0 for patients >65 years)
  - Liver stiffness measurement (LSM) ≥8 kPa used to define significant fibrosis
- Factors associated with false-negative and false-positive FIB-4 results were analyzed using multivariable regression.

Results:

- Mean age was 53 ± 13 years; 61% were male.
- Significant fibrosis (LSM ≥8 kPa) was present in 29% of patients.
- FIB-4 results:
  - Low risk (FIB-4 <1.3/2.0): 1,049 patients (71%)
  - High risk (FIB-4 ≥1.3/2.0): 435 patients (29%)
- Diagnostic performance of FIB-4:
  - Sensitivity: 48%
  - Specificity: 79%
  - Negative Predictive Value (NPV): 79%
  - Accuracy: 70%
  - AUROC: 0.70 (95% CI: 0.68–0.74)
- Misclassification rates:
  - False negatives: 224/1,049 (21%)
  - False positives: 224/435 (51%)
- Patients with false-negative results were more likely to have older age; hypertension, diabetes, higher BMI, larger waist circumference, higher HOMA index, triglycerides, and fasting glucose
- Waist circumference was the only independent predictor of missed fibrosis with OR of 1.07 (95% CI: 1.02–1.12)
- Incorporating waist circumference into the low-risk FIB-4 group:
  - Increased sensitivity from 48% to 82%
  - Increased NPV to 82%
  - Reduced the number of missed patients with significant fibrosis
  - At the expense of lower specificity (34%)

Conclusion

- **In routine hepatology practice, FIB-4 alone may lead to substantial misclassification of fibrosis risk in MASLD patients.**
- **Waist circumference, a simple marker of visceral adiposity, independently identifies patients with significant fibrosis who may be missed by FIB-4.**
- **Incorporating waist circumference into a stepwise screening algorithm improves sensitivity and reduces missed referrals for advanced fibrosis.**
- **Combined assessment may enhance real-world fibrosis risk stratification in MASLD.**

6. In patients with MASLD including patients with T2D, LIVERFAST outperforms FIB-4, in sequential combination with VCTE for identifying ≥F3 Stages.

Aim:

- To compare the performance of the blood-based LIVERFASt test with FIB-4, both used sequentially with vibration-controlled transient elastography (VCTE), for identifying advanced fibrosis (≥F3) in patients with MASLD.
- To assess the utility of LIVERFASt in patients with type 2 diabetes mellitus (T2DM).

Methods:

- Retrospective study conducted at a tertiary hepatology center.
- Included patients with MASLD who underwent:
  - LIVERFASt testing
  - FIB-4 assessment
  - VCTE
  - Liver biopsy within 6 months
- Diagnostic performance was evaluated using:
  - Sensitivity
  - Specificity
  - Positive predictive value (PPV)
  - Negative predictive value (NPV)
  - Number needed to diagnose (NND)
- Subgroup analyses were performed in patients with T2DM.

Results:

- LIVERFASt outperformed FIB-4 for detecting advanced fibrosis (≥F3).
- Compared with the high FIB-4 cut-off (>2.67), LIVERFASt demonstrated nearly twofold higher sensitivity and higher NPV
- Compared with the guideline-recommended FIB-4 cut-off (≥1.3 [≥2.0 if >65 years]), LIVERFASt showed higher specificity and higher PPV
- Sequential testing with LIVERFASt and VCTE achieved:
  - PPV of 90.4%
  - Compared with 76.0% for FIB-4 plus VCTE
  - Similar NPV between strategies

Table 6. Results for outcome for LIVERFASt vs FIB-4

Outcome Measure	LIVERFASt	FIB-4	Comparison/Impact
Detection of ≥ F3 Fibrosis (High-Risk Threshold)	NND=4.56	NND = 7.98	LIVERFASt identified nearly twice as many advanced fibrosis cases with fewer patients needing evaluation
VCTE Referrals Required (Guideline-Recommended Cut-offs)	187/447 patients	243/447 patients	Significantly fewer VCTE referrals with LIVERFASt (p<0.001)
VCTE Referrals in T2DM Subgroup	118/228 patients	146/228 patients	Reduced VCTE referrals in high-risk T2DM patients (p<0.01)
True Negatives (Correctly Ruled Out Fibrosis at First Step)	42.7%	35.6%	Higher proportion of patients correctly excluded from further testing (p<0.05)

Conclusion

- **LIVERFASt demonstrated superior performance compared with FIB-4 for identifying advanced fibrosis in MASLD.**
- **Integration of LIVERFASt into MASLD screening pathways may improve diagnostic efficiency, reduce unnecessary VCTE referrals, and enhance detection of advanced fibrosis.**
- **The test was particularly effective in ruling out fibrosis, allowing more patients to avoid second-line testing.**
- **Similar benefits were observed in high-risk patients with T2DM, supporting its potential role in routine fibrosis risk stratification.**

7. Liver Fibrosis as the Sole Predictor of Adverse Outcomes in MASH: Reconsidering MASH Resolution as a Clinical Trial Endpoint.

Aim:

- To evaluate the association between histological features of metabolic dysfunction-associated steatohepatitis (MASH), fibrosis stage, and long-term clinical outcomes in patients with MASLD.
- To determine whether MASH resolution or fibrosis is a better predictor of mortality and liver-related clinical events.

Methods:

- Analysis of 9,712 adults with MASLD from 41 countries enrolled in the global G-MASLD cohort.
- Inclusion criteria: Liver biopsy with assessment of Steatosis (0–3); Lobular inflammation (0–3); Hepatocyte ballooning (0–2) and Fibrosis stage (F0–F4)
- Outcomes assessed:
  - All-cause mortality
  - Hepatic decompensation
  - Hepatocellular carcinoma (HCC)
  - Liver transplantation
  - Composite clinical events

Results:

- Study population with mean age of 51 ± 13 years, included 49% male; 66% obesity, 51% type 2 diabetes and 54% hypertension
- Advanced fibrosis (AF; F3–F4) was present in 42% and significant fibrosis (SF; F2) in 15%.
- Patients with AF were older and had a higher prevalence of diabetes and hypertension (all $p<0.001$).
- Histological activity was significantly greater in patients with AF:
  - Higher NAS scores (4.9 vs 3.8)
  - More frequent NAS ≥5 (64% vs 35%)
  - Greater lobular inflammation and hepatocyte ballooning (all $p<0.0001$).
- Higher NAS scores were strongly associated with advanced fibrosis:
  - OR per 1-point increase: 1.64
  - NAS ≥5 vs <5: OR 3.32 (both $p<0.0001$).
- Lobular inflammation and hepatocyte ballooning independently predicted advanced fibrosis.
- Long-term outcomes showed Advanced fibrosis independently predicted:
  - All-cause mortality (aHR 2.10; $p<0.0001$)
  - Clinical events (aHR 3.73; $p<0.0001$)
- After adjustment for fibrosis:
  - NAS score was not associated with adverse outcomes.
  - Lobular inflammation was not associated with adverse outcomes.
  - Hepatocyte ballooning was not associated with adverse outcomes.
- Findings remained consistent across fibrosis subgroups and after adjustment for liver stiffness ≥10 kPa.

Conclusion

- **Histological features of MASH are strongly associated with advanced fibrosis but do not independently predict adverse clinical outcomes.**
- **Advanced fibrosis is the primary determinant of mortality and liver-related events in MASLD.**
- **The variability and limited prognostic value of MASH histology make MASH resolution a suboptimal primary clinical trial endpoint.**
- **Fibrosis-focused non-invasive tests and fibrosis improvement should be prioritized as clinically meaningful endpoints in future MASLD/MASH trials.**

8. Prognostic Value of Liver Stiffness Changes in Patients with Biopsy-Confirmed MASH-Related Cirrhosis.

Aim:

- To evaluate whether changes in liver stiffness measurement (LSM) assessed by vibration-controlled transient elastography (VCTE) reflect disease progression or regression in patients with biopsy-proven compensated MASH cirrhosis.
- To determine the association between longitudinal LSM changes and the risk of liver-related events (LREs).

Methods:

- Multicenter cohort study involving 248 adults with biopsy-proven compensated MASH cirrhosis across 16 centers in the US, Europe, and Asia.
- Patients underwent at least two VCTE assessments performed 6 months to 5 years apart.
- Median interval between LSM measurements was 1.4 years.
- Incidence of LREs was evaluated according to absolute and relative changes in LSM, with non–liver-related death treated as a competing event.

Results:

- Mean age was 60 years; 48.8% were male.
- Baseline median LSM was 19.1 kPa, decreasing to 16.8 kPa at the second assessment.
- Over a median follow-up of 3.2 years after the second LSM, 29 patients (11.7%) developed LREs; 5-year cumulative incidence was 18.7%.
- Patients with a relative LSM increase ≥30% had a significantly higher risk of LREs (adjusted SHR 1.69; 95% CI 1.04–2.77; p=0.035).
- Relative LSM decreases of ≥10%, ≥20%, or ≥30% were not associated with a significant reduction in LRE risk.
- Absolute LSM increases were associated with higher event rates, whereas decreases did not consistently translate into improved outcomes.

Conclusion

- **A relative increase in LSM of ≥30% is an independent predictor of disease progression and liver-related events in patients with MASH cirrhosis.**
- **Conversely, a relative decrease in LSM of ≥30% does not confer a significant reduction in LRE risk.**
- **Serial LSM monitoring may serve as a valuable non-invasive tool for identifying patients at increased risk of clinical deterioration.**

9. Spatial Metabolic Profiling Reveals Lipid and Fibrotic Remodeling in MASLD.

Aim:

- To characterize spatial metabolic alterations associated with fibrosis progression in MASLD using a high-resolution, multimodal molecular imaging approach.
- To develop a comprehensive spatial metabolic atlas of the human liver and identify zone-specific metabolic signatures linked to MASH progression.

Methods:

- Liver biopsies from 36 patients with MASLD spanning fibrosis stages F0–F4 were analyzed.
- Desorption electrospray ionization mass spectrometry imaging (DESI-MSI) was performed at 20 × 20 µm spatial resolution to map metabolic signatures associated with:
  - Steatosis
  - Lobular inflammation
  - Hepatocyte ballooning
  - Fibrosis

- Histology-guided regions of interest were used to evaluate zone-specific lipid metabolism and fibrosis-related changes.
- SHG/TPEF microscopy was employed to quantify collagen architecture and correlate molecular profiles with fibrosis patterns and liver zonation.
- Statistical significance was assessed using Benjamini-Hochberg False Discovery Rate (FDR ≤5%).

Results:

- Distinct metabolic signatures comprising hundreds of metabolites were identified across:
  - Microvesicular and macrovesicular steatosis
  - Lobular inflammation
  - Hepatocyte ballooning
- MASH was associated with marked zone-specific disruption of hepatic lipid metabolism.
- The greatest metabolic differences were observed between fibrotic and non-fibrotic regions, highlighting substantial metabolic heterogeneity within fibrotic tissue.
- Fibrotic septa exhibited unique molecular signatures that differentiated:
  - Progressive septa from regressive septa
  - Male from female metabolic patterns
- Spatial metabolic mapping revealed previously unrecognized fibrosis-associated molecular heterogeneity.

Conclusion

- **A high-resolution spatial metabolic atlas of MASLD was successfully established, revealing zone-specific alterations in lipid metabolism associated with fibrosis and disease progression.**
- **Significant metabolic heterogeneity exists within fibrotic tissue, including distinct profiles of progressive versus regressive septa.**
- **Novel sex-specific metabolic signatures were identified.**
- **These findings enhance understanding of fibrosis architecture and metabolic remodeling in MASH and may facilitate the development of spatially targeted diagnostic biomarkers and therapeutic strategies.**

10. Predictive Value of CRP-TyG Index and Fasting C-Peptide/HDL-C Ratio for Advanced Fibrosis in Patients with MASLD and Type 2 Diabetes.

Aim:

- To evaluate the predictive value of the C-reactive protein–triglyceride-glucose index (CTI) and the fasting C-peptide-to-HDL cholesterol ratio (FCP/HDL) for identifying advanced steatosis and liver fibrosis in patients with type 2 diabetes mellitus (T2DM) and MASLD.
- To assess the utility of these metabolic and inflammatory indices as non-invasive screening tools for liver disease progression.

Methods:

- Baseline analysis from a prospective doctoral study conducted at a tertiary diabetes, nutrition, and metabolic diseases center.
- Included patients with T2DM and MASLD who were not optimally controlled.
- Assessments performed:
  - Anthropometric measurements
  - Biochemical investigations
  - Transient elastography (FibroScan)
- Metabolic and inflammatory markers, including CTI and FCP/HDL, were calculated using validated formulas.
- Associations with liver steatosis and fibrosis were evaluated using correlation and ROC analyses.

Results:

- A total of 72 patients were enrolled were 48.6% male; mean age of 59.1 ± 9.0 years; mean BMI of 33.9 ± 5.9 kg/m² and obesity prevalence: 70.8%
- Mean FibroScan parameters:
  - Controlled Attenuation Parameter (CAP): 296.5 ± 61.1 dB/m
  - Liver Stiffness Measurement (LSM): 7.05 ± 2.52 kPa
- Moderate-to-severe steatosis was present in 62.5% of patients.
- Fibrosis was observed in 72.2% of patients, with 18 patients classified as F2–F4.

Table 7. Clinical outcomes showing significant and moderate predictors

Parameters	Outcomes
Significant positive correlations	
LSM and CTI	r=0.335; p=0.004
LSM and FCP/HDL	r=0.270; p=0.024
CAP and CTI	r=0.417; p<0.001
CAP and FCP/HDL	r=0.278; p=0.020
Predictors of moderate-to-severe steatosis	
CTI	AUROC 0.677 (p=0.048)
FCP/HDL	AUROC 0.655 (p=0.030)
Predictors of advanced fibrosis	
CTI	AUROC 0.656 (p=0.048)
FCP/HDL	AUROC 0.697 (p=0.015)

Conclusion

- **CTI and FCP/HDL are significantly associated with liver steatosis and fibrosis severity in patients with T2DM and MASLD.**
- **Both indices demonstrated modest but significant ability to identify advanced hepatic fibrosis and moderate-to-severe steatosis.**
- **These easily obtainable metabolic and inflammatory markers may serve as practical, non-invasive tools for large-scale risk stratification and screening of patients at risk for progressive liver disease.**

11. In patients with MASLD, low vitamin D levels are independently associated with increased fibrosis risk.

Aim:

- To investigate the association between low vitamin D levels and increased liver fibrosis risk in patients with metabolic dysfunction–associated steatotic liver disease (MASLD).
- To assess whether vitamin D status could serve as a simple biomarker for fibrosis risk stratification.

Methods:

- Retrospective single-center study including 56 patients with MASLD followed between January 2020 and December 2024.
- Serum vitamin D levels and clinical, metabolic, and biochemical parameters were collected.
- Increased fibrosis risk was defined as FIB-4 ≥1.3.
- Vitamin D status was categorized as:
  - Insufficiency: <30 ng/mL
  - Severe deficiency: <10 ng/mL
- Associations between vitamin D levels and fibrosis risk were evaluated using univariate and multivariable analyses adjusted for age, sex, BMI, and metabolic factors.

Results:

- Median age was 52 years; 56% were male.
- Median BMI was 30 kg/m².
- Increased fibrosis risk (FIB-4 ≥1.3) was identified in 34% of patients.
- Vitamin D insufficiency was present in 62% of patients, including 18% with severe deficiency.
- Patients with increased fibrosis risk had significantly lower vitamin D levels:
  - 18 ng/mL (IQR 12–25) vs. 25 ng/mL (IQR 19–32); p=0.03
- Vitamin D insufficiency was more common among patients at increased fibrosis risk:
  - 71% vs. 54%; p=0.04
- After adjustment for confounding factors, vitamin D <30 ng/mL remained independently associated with increased fibrosis risk:
  - Adjusted OR: 2.1
  - 95% CI: 1.0–4.5
  - p=0.046

Conclusion

- **Low vitamin D levels are highly prevalent in patients with MASLD and are independently associated with an increased risk of liver fibrosis.**
- **Vitamin D assessment may represent a simple, inexpensive, and widely accessible adjunctive tool for fibrosis risk stratification.**

12. A non-invasive risk stratification study showing prediabetes as a high-risk subgroup for advanced liver fibrosis in non-diabetic MASLD.

Aim:

- To determine the prevalence of significant and advanced liver fibrosis among non-diabetic MASLD patients with prediabetes.
- To evaluate the utility of non-invasive tools, including FIB-4 and ARFI elastography, for fibrosis risk stratification in this population.

Methods:

- Cross-sectional study of consecutive non-diabetic MASLD patients evaluated at a tertiary referral center between 2024 and 2025.
- Prediabetes was defined using standard glycemic criteria.
- Liver fibrosis was assessed using:
  - Fibrosis-4 Index (FIB-4)
  - Acoustic Radiation Force Impulse (ARFI) elastography
- Prevalence of:
  - Significant fibrosis (F≥2)
  - Advanced fibrosis (F≥3) was determined.
- Factors associated with advanced fibrosis were analyzed, and the diagnostic performance of FIB-4 was assessed using ROC analysis.

Results:

- A total of 107 non-diabetic MASLD patients were included with mean age of 47.3 ± 12.6 years and 56.1% of male.
- Significant fibrosis (F≥2) was present in 15.0% of patients.

- Advanced fibrosis (F≥3) was identified in 11.3% of patients.
- Among patients with prediabetes, 41.7% had advanced fibrosis despite the absence of overt diabetes.
- Independent predictors of advanced fibrosis:
  - Older age
  - Higher AST levels
- FIB-4 demonstrated excellent diagnostic performance for advanced fibrosis with AUROC of 0.949

Conclusion

- **Prediabetes is associated with a substantial burden of advanced liver fibrosis in non-diabetic patients with MASLD.**
- **Reliance solely on diabetes status for fibrosis screening may delay identification of clinically significant liver disease.**
- **Non-invasive tools such as FIB-4 and ARFI elastography can effectively identify patients at risk and support earlier fibrosis risk stratification in individuals with prediabetes.**

13. A cohort study of 63,587 persons showing lower predictive performance of FIB-4 with lower eGFR categories.

Aim:

- To evaluate the association between kidney function (eGFR), FIB-4 score, and the risk of major adverse liver outcomes (MALO) in individuals with or at high risk of MASLD.
- To assess the predictive performance of FIB-4 across different levels of renal function.

Methods:

- Population-based cohort study using the Stockholm Creatinine Measurements (SCREAM) cohort.
- Included 63,587 individuals with or at high risk of MASLD, defined by:
  - MASLD diagnosis
  - Type 2 diabetes
  - Obesity
- Participants were stratified by eGFR as ≥90 mL/min/1.73m²; 60–89 mL/min/1.73m²; 30–59 mL/min/1.73m² and <30 mL/min/1.73m²
- Age-adjusted FIB-4 scores were categorized as low, indeterminate, or high risk.
- Cox regression analysis evaluated associations between FIB-4 and MALO.
- Harrell's C-index was used to assess discriminatory performance.

Results:

- Median follow-up duration was 4.9 years (IQR: 2.0–9.2 years).
- Across all eGFR categories, high FIB-4 scores were associated with a higher incidence of MALO compared with low FIB-4 scores.
- FIB-4 demonstrated varying predictive performance according to kidney function:
  - eGFR ≥90 mL/min/1.73m²: C-index 0.77
  - eGFR 60–89 mL/min/1.73m²: Intermediate performance

- eGFR 30–59 mL/min/1.73m²: C-index 0.64
- eGFR <30 mL/min/1.73m²: C-index 0.69

- Predictive accuracy declined as renal function worsened.

Conclusion

- **Elevated FIB-4 scores were consistently associated with an increased risk of major adverse liver outcomes across all levels of kidney function.**
- **FIB-4 showed the strongest discriminative performance in individuals with preserved renal function (eGFR ≥90 mL/min/1.73m²).**
- **Reduced predictive accuracy in patients with CKD suggests that alternative or complementary fibrosis assessment tools may be needed in individuals with impaired kidney function.**

14. In patients with type 2 diabetes, external validation and recalibration of the CORE risk score to predict 10-year risk of liver cirrhosis.

Aim:

- To evaluate the performance of the Cirrhosis Outcome Risk Estimator (CORE) for predicting major adverse liver outcomes (MALO) in patients with type 2 diabetes (T2D).
- To recalibrate CORE for a T2D population and compare its predictive accuracy and clinical utility with the FIB-4 score.

Methods:

- Population-based study using data from the Swedish National Diabetes Register.
- Included individuals with T2D diagnosed between January 1998 and December 2022.
- Incident MALO events were identified through national health registers.
- Model performance was assessed using:
  - Time-dependent area under the curve (tAUC)
  - Calibration plots
  - Decision curve analysis
- CORE was recalibrated using cause-specific flexible parametric models to account for the higher baseline liver risk in the T2D population.
- Performance was compared with FIB-4.

Results:

- A total of 37,015 patients with T2D were included.
- During a median follow-up of 6.2 years, 784 patients developed MALO.
- The 10-year cumulative incidence of MALO was 2.7%.
- CORE demonstrated superior discrimination compared with FIB-4:
  - CORE: 10-year AUC = 0.86
  - FIB-4: 10-year AUC = 0.81
- Initial CORE predictions underestimated observed risk and required recalibration.
- The recalibrated CORE model showed:
  - Improved calibration
  - Better alignment between predicted and observed risk

- Greater clinical utility than FIB-4

- Decision curve analysis demonstrated a higher net benefit for CORE at risk thresholds up to 30%.

Conclusion

- **CORE outperformed FIB-4 in predicting major adverse liver outcomes among patients with T2D.**
- **Recalibration improved the accuracy of risk estimation in this higher-risk population.**
- **CORE more effectively identifies individuals at elevated risk of cirrhosis-related outcomes and may reduce unnecessary referrals compared with FIB-4.**
- **The findings support the use of CORE as a risk stratification tool for long-term liver outcome prediction in patients with T2D.**

15. A systematic review and meta-analysis analyzing young adults with MASLD showing anthropometric indices and body composition as predictors of liver fibrosis.

Aim:

- To evaluate anthropometric indices and body composition parameters as predictors of liver fibrosis in young adults (18–40 years) with MASLD.
- To identify non-invasive risk factors associated with fibrosis progression through a systematic review and meta-analysis.

Methods:

- Systematic review of studies identified through PubMed, Embase, Web of Science, and Scopus.
- Included studies assessed anthropometric and body composition measures in young adults with MASLD.
- Meta-analyses were performed using fixed- or random-effects models based on heterogeneity (I^2).
- Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to estimate associations with liver fibrosis.

Results:

- Nine studies involving 15,370 patients were included.

Table 8. Outcomes showing relation of the parameters and association with liver fibrosis

Parameter	Association with Liver Fibrosis	Odds Ratio (OR)	Interpretation
Waist-to-Height Ratio ≥0.5	Increased risk	10.73	Strongest predictor of liver fibrosis
Waist-to-Hip Ratio	Increased risk	1.53	Significant association with fibrosis
Waist Circumference	Increased risk	1.10	Higher waist circumference linked to fibrosis
General Obesity	Increased risk	7.63	Major risk factor for liver fibrosis
Overweight Status	Increased risk	1.30	Modestly increased fibrosis risk
Muscle Mass Percentage	Decreased risk	0.71	Protective against liver fibrosis
Muscle Mass-to-Fat Mass Ratio	Decreased risk	0.13	Strong protective effect against fibrosis

Conclusion

- **Waist-to-height ratio may be a superior predictor of liver fibrosis compared with traditional obesity measures in young adults with MASLD.**
- **Central adiposity is strongly associated with fibrosis risk, while greater muscle mass and favorable muscle-to-fat ratios appear protective.**
- **Assessment of abdominal fat distribution should complement BMI in clinical practice.**
- **Management strategies should focus on reducing visceral adiposity while preserving or enhancing skeletal muscle mass to mitigate fibrosis progression.**

Treatment, Therapeutic Interventions & Clinical Outcomes

1. Prospective Evaluation of SGLT2 Inhibitors on Liver Histology and Metabolic Biomarkers in Type 2 Diabetes and MASLD

Aim:

- To evaluate the effects of sodium–glucose cotransporter 2 inhibitors (SGLT2i) on liver fibrosis, steatosis, and metabolic biomarkers in patients with type 2 diabetes mellitus (T2DM) and metabolic dysfunction-associated steatotic liver disease (MASLD) in a real-world clinical setting.

Methods:

- Prospective study involving 67 patients with T2DM and MASLD (age range: 37–89 years) and followed for 6 months after initiation of SGLT2i therapy.
- Serum levels of PPARα, PPARγ, SREBP1, and MTTP were measured using ELISA.
- Liver fibrosis and steatosis were assessed using:
  - Two-dimensional shear wave elastography (2D-SWE)
  - Ultrasound-guided attenuation parameter (UGAP)
- Biochemical and anthropometric parameters were also evaluated.

Results:

Table 9. Liver Serum and fibrosis study outcomes

Parameters	Baseline value	6 months value	P value
MTTP levels	198.4 ng/L	428.9 ng/L	p<0.001 (Increased significantly)
PPARγ levels	895.0 ng/L	565.4 ng/L	p<0.001 (Decreased significantly)
Liver stiffness (2D-SWE values)	6.22 kPa	6.10 kPa	p=0.001 (Improved)

- 2D-SWE values showed an inverse correlation with MTTP levels (ρ=−0.268; p=0.03).
- UGAP values positively correlated with:
  - Liver stiffness (2D-SWE) (ρ=0.365; p=0.002)
  - Leukocyte count, triglycerides, and liver enzyme levels
- UGAP values were inversely associated with HDL cholesterol (p≤0.01).
- Significant improvements were observed in:
  - Fasting plasma glucose
  - HbA1c
  - INR
  - Waist circumference
  - BMI (all p≤0.04)

Conclusion

- **SGLT2i therapy was associated with early improvements in hepatic steatosis, liver fibrosis, and glycemic control in patients with T2DM-related MASLD.**
- **Favorable modulation of PPARγ and MTTP suggests improved hepatic lipid metabolism.**
- **These findings support the potential role of SGLT2i in slowing MASLD progression.**

2. A nested case-control study using LIFE study data to analyze effects of SGLT-2 inhibitors on clinical outcomes in patients with MASLD and type 2 diabetes mellitus

Aim:

- To evaluate whether SGLT-2 inhibitors and DPP-4 inhibitors reduce the risk of liver-related and extrahepatic clinical events in patients with metabolic dysfunction-associated steatotic liver disease (MASLD) and type 2 diabetes mellitus (T2DM).
- To assess their association with hepatocellular carcinoma (HCC), extrahepatic malignancies, major adverse cardiovascular events (MACE), and mortality.

Methods:

- Nested case-control study using Japanese administrative claims data covering 2.56 million individuals, A total of 10,338 patients were included.
- Included patients newly diagnosed with steatotic liver disease (SLD/MASLD) and T2DM within the first three years of database availability.
- Excluded patients without SLD and those already receiving antidiabetic therapy.
- Cases were patients who developed at least one major outcome:
  - Hepatocellular carcinoma (HCC)
  - Extrahepatic malignancy
  - Major adverse cardiovascular events (MACE)
  - Death
- Associations between new prescriptions and outcomes were analyzed using conditional logistic regression.

Results:

- During 25–42 months of follow-up:
  - 65 developed HCC
  - 1,082 developed extrahepatic malignancies
  - 753 experienced MACE
  - 219 died
- SGLT-2 inhibitor use was significantly less frequent among patients who developed HCC (P=0.037).
- SGLT-2 inhibitor use was associated with a lower risk of extrahepatic malignancies:
  - Adjusted OR: 0.588 (95% CI: 0.374–0.925; P=0.022)
- DPP-4 inhibitors showed no significant association with extrahepatic malignancy risk (P=0.29).
- Neither SGLT-2 inhibitors nor DPP-4 inhibitors demonstrated significant associations with:
  - Major adverse cardiovascular events (MACE)
  - All-cause mortality

Conclusion

- **In patients with MASLD and T2DM, SGLT-2 inhibitor therapy may reduce the risk of hepatocellular carcinoma and extrahepatic malignancies.**
- **The potential benefits of SGLT-2 inhibitors may extend beyond glycemic control to event prevention.**
- **No significant effects were observed on cardiovascular events or mortality.**

3. COMBAT_T2_NASH trial: Analyzing the effect of empagliflozin alone or combined with low-dose semaglutide on metabolic dysfunction-associated steatohepatitis and type 2 diabetes

Aim:

- To evaluate whether empagliflozin alone or in combination with semaglutide improves histological and metabolic outcomes in patients with biopsy-confirmed metabolic dysfunction-associated steatohepatitis (MASH) and type 2 diabetes mellitus (T2DM).
- To assess the effect of treatment on MASH resolution, fibrosis progression, liver histology, glycemic control, and body weight.

Methods:

- Randomized, placebo-controlled trial involving 61 patients with biopsy-confirmed MASH and F1–F3 fibrosis.
- Participants were assigned to:
  - Empagliflozin + semaglutide (COMBI; n=23)
  - Empagliflozin alone (EMPA; n=17)
  - Placebo (PLAC; n=21)
- Treatment duration: 48 weeks.
- Primary endpoint: MASH resolution without fibrosis progression.
- Secondary endpoints:
  - Changes in NAFLD Activity Score (NAS)
  - Steatosis
  - Activity component (lobular inflammation + ballooning)
  - Metabolic and biochemical parameters

Results:

- Fifty-four participants had paired liver biopsies available for analysis.

Table 10. Clinical outcomes of the study

Parameter	Placebo	Empagliflozin alone	Empagliflozin+ Semaglutide	Significance
Body weight reduction	+0.1 ± 3.4 kg	−0.4 ± 7.4 kg	−8.6 ± 5.4 kg	Significant improvement with COMBI vs placebo (p<0.0001)
HbA1c reduction	−0.1 ± 0.9%	−0.4 ± 0.7%	−1.3 ± 0.9%	Significant improvement with COMBI only (p=0.0002)
MASH resolution without fibrosis progression	5.6%	0%	9.5%	Numerically higher with COMBI
NAFLD Activity Score (NAS)	−0.1 ± 1.1	−0.1 ± 0.7	−1.3 ± 1.0	Significant improvement with COMBI (p=0.0002)

- **Histologist improvements with COMBI:**
  - Greater reduction in steatosis (p<0.0001)
  - Greater reduction in inflammatory activity (p=0.0078)
- **Biomarkers:**
  - Significant reductions in liver transaminases and cytokeratin-18 fragments (M30/M65) with COMBI only (all p<0.01).
- Empagliflozin monotherapy did not demonstrate significant improvements versus placebo.

Conclusion

- **Combined empagliflozin and low-dose semaglutide therapy resulted in greater improvements in MASH-related steatosis, inflammation, body weight, and glycemic control compared with placebo.**
- **The proportion of patients achieving MASH resolution without fibrosis progression was numerically higher with combination therapy.**
- **Empagliflozin monotherapy showed limited histological benefit.**
- **The observed improvements were likely driven by semaglutide-associated weight loss and improved glycemic control.**

4. Impact of concomitant UDCA therapy with norucholic acid leads to biochemical and histologic improvement in PSC.

Aim:

- To evaluate the efficacy of norucholic acid (NCA) in patients with primary sclerosing cholangitis (PSC) receiving:
  - NCA with background ursodeoxycholic acid (UDCA)
  - NCA as monotherapy
- To compare histological, biochemical, and safety outcomes between these subgroups.

Methods:

- Subgroup analysis of the NUC-5 Phase 3, randomized, double-blind, placebo-controlled trial.
- Adult PSC patients with ALP ≥1.5 × upper limit of normal (ULN)
- Treatment:
  - NCA 1,500 mg once daily or placebo
  - Stable background UDCA (≤20 mg/kg/day) permitted throughout the study
- Study duration: 192 weeks
- Primary analysis performed at 96 weeks
- Primary endpoint:
  - No worsening in histological disease stage (Ludwig classification)
  - Plus partial normalization of ALP to <1.5 × ULN
- Secondary endpoints:
  - Histological improvement
  - Biochemical response
  - Safety outcomes

Results:

- Patient Distribution
- NCA + UDCA: 158 patients
- Placebo + UDCA: 78 patients
- NCA alone: 47 patients
- Placebo alone: 18 patients

Table 11. Primary Composite and secondary Endpoint Achievement

Criteria	NCA+ UDCA	Placebo + UDCA	NCA alone	Placebo alone
Primary Endpoint Achieved	12.7%	5.1%	23.4%	0%
Histological Improvement (Ludwig Stage)	23.4%	11.9%	30.3%	6.7%
Partial ALP Normalization (<1.5× ULN)	18.4%	15.4%	25.5%	5.6%
≥40% Reduction in ALP from Baseline	14.6%	11.5%	31.9%	0%

Safety:

- Adverse events were generally comparable between:
  - NCA monotherapy
  - NCA plus UDCA combination therapy
- No new safety concerns were identified.

Conclusion

- **NCA improved both histological and biochemical outcomes in patients with PSC.**
- **Clinical benefits were observed whether NCA was used:**
  - **As monotherapy**
  - **In combination with UDCA**
- **The combination of NCA + UDCA was well tolerated and showed a safety profile comparable to NCA alone.**
- **Greater improvements across efficacy endpoints were observed in patients receiving NCA without concomitant UDCA, suggesting a potentially stronger treatment effect with NCA monotherapy.**

5. A reduced risk of hepatic decompensation and mortality observed with statin use in liver cirrhosis.

Aim:

- To evaluate the association between statin use and the risks of hepatic decompensation and all-cause mortality in patients with compensated liver cirrhosis.
- To explore the potential disease-modifying role of statins beyond lipid-lowering effects.

Methods:

- Retrospective, multinational, longitudinal cohort study conducted within the Cirrhosis Outcome and Research Endeavour (CORE) Consortium.
- Included consecutive adults with compensated cirrhosis from 13 tertiary centers across 8 countries.
- Compensated cirrhosis was defined as:
  - Liver stiffness measurement (LSM) ≥10 kPa
  - No prior hepatic decompensation
- Statin exposure was assessed at baseline.
- Primary outcomes:
  - Hepatic decompensation
  - All-cause mortality
- Statistical analyses performed by fine–Gray competing-risk regression, multivariable adjustment for demographic, metabolic, and liver disease-related factors and inverse Probability of Treatment Weighting (IPTW) to strengthen causal inference

Results:

Study Population

- Total participants: 2,564
- Median follow-up: 3.09 years
- Statin users: 901 patients (35.1%)

Hepatic Decompensation

- Statin use was associated with a significantly lower risk of hepatic decompensation:
  - Adjusted SHR: 0.70
  - 95% CI: 0.57–0.86
- Protective effect was consistent across:
  - Moderate-risk cirrhosis
  - High-risk cirrhosis

All-Cause Mortality

- Statin use was associated with lower mortality in partially adjusted analyses.
- The association was attenuated after full multivariable adjustment.

IPTW Analysis

- Statin use remained significantly associated with:
  - Reduced hepatic decompensation risk, SHR: 0.55
  - Reduced all-cause mortality, SHR: 0.65

Conclusion

- **In this large multinational cohort, statin therapy was associated with:**
  - **Lower risk of hepatic decompensation**
  - **Improved overall survival in compensated cirrhosis**
- **Findings support a potential disease-modifying effect of statins in cirrhosis beyond cholesterol reduction.**

6. One-Year ALP and Bilirubin Levels Predict Long-Term Outcomes in PBC Patients on Second-Line Fibrate Therapy.

Aim:

- To validate whether biochemical response at 1 year of fibrate therapy predicts transplant-free survival in patients with primary biliary cholangitis (PBC) receiving fibrates as second-line treatment.

Methods:

- Nationwide retrospective cohort study conducted in Japan (2001–2024).
- Included patients with PBC treated with bezafibrate (BZF) or pemafibrate (PMF) due to inadequate response or intolerance to UDCA.
- Assessed biochemical response at 1 year using:
  - ALP <1.67×ULN, ≥15% ALP reduction, and normalized total bilirubin (T-Bil)
  - Normalization of both ALP and T-Bil
  - ALP normalization with T-Bil <0.6×ULN
- Associations with transplant-free survival were evaluated using Kaplan–Meier and Cox proportional hazards analyses.

Results:

- Total patients: 558 (BZF: 344; PMF: 214); 82% female; median age 60 years.
- At 1 year:
  - 57.3% achieved ALP <1.67×ULN, ≥15% ALP reduction, and T-Bil normalization.
  - 59.3% achieved normalization of both ALP and T-Bil.
  - 47.5% achieved ALP normalization with T-Bil <0.6×ULN.
- Over a median follow-up of 4.9 years, 27 patients (4.8%) died or underwent liver transplantation.
- All three criteria were associated with improved outcomes in univariate analysis.
- After adjustment, only ALP <1.67×ULN, ≥15% ALP reduction, and T-Bil normalization remained an independent predictor of transplant-free survival (HR 0.31; 95% CI 0.11–0.83), corresponding to a 69% lower risk of death or transplantation.

Conclusion

- **ALP and T-Bil levels after 1 year of fibrate therapy are valuable prognostic markers in PBC patients receiving second-line fibrate treatment.**
- **Achieving ALP <1.67×ULN with ≥15% reduction and normalized T-Bil independently predicts superior transplant-free survival.**

7. Real-world outcomes in patients with MASH/MASLD stratified by fibrosis severity.

Aim:

- To assess the incidence of major adverse cardiovascular events (MACE) and major adverse liver outcomes (MALO) among patients with biopsy-confirmed MASH across different stages of liver fibrosis (F-stage).
- To evaluate the risk of MACE and MALO among patients with MASLD according to liver stiffness measurements (LSM) obtained using vibration-controlled transient elastography (VCTE).

Methods:

- This retrospective study analyzed de-identified patient EHR data with following study groups:
- MASH Cohort (Cohort 1): Patients with biopsy-confirmed MASH with F-stage (F0-F4) at baseline; F0/1: No or mild fibrosis; F2/3: Moderate or advanced fibrosis; F4: Cirrhosis
- MASLD Cohort (Cohort 2): Patients with MASLD, ≥1 cardiometabolic risk factor, and ≥1 LSM (stratified as mild, moderate, or severe); Mild: <8 VCTE; Moderate: 8-15 VCTE; Severe: >15 VCTE

Study Outcomes:

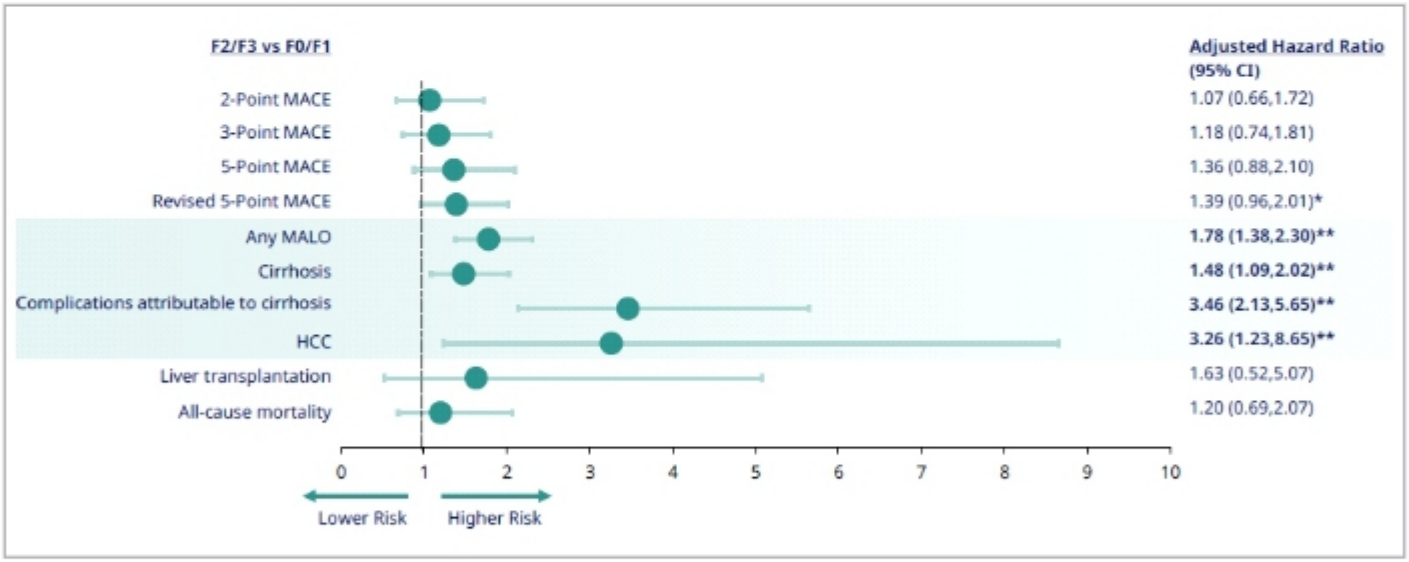
- 2-point MACE (nonfatal myocardial infarction, ischemic stroke);
- 3-point MACE (2-point and CV-related mortality);
- 5-point MACE (3-point, heart failure hospitalization [HFH], unstable angina [UA]);
- Revised 5 (r5)-point MACE (2-point MACE, all-cause mortality, HFH, UA);
- Any MALO or its components, including cirrhosis, cirrhosis-related complications, hepatocellular carcinoma (HCC), liver transplantation, or all-cause mortality

Results:

Outcomes among patients with biopsy-confirmed MASH and F-stage 2/3 vs F-stage 0/1 (Figure)

- Patients with baseline fibrosis stage F2/F3 showed a numerically higher risk of 2-point, 3-point, 5-point, and recurrent 5-point major adverse cardiovascular events (MACE) compared with those with F0/F1 fibrosis (p>0.05).
- In contrast, patients with F2/F3 fibrosis had a significantly greater risk of major adverse liver outcomes (MALO) than those with F0/F1 fibrosis, including:
  - Any MALO: HR 1.78 (95% CI: 1.38–2.30)
  - Cirrhosis: HR 1.48 (95% CI: 1.09–2.02)
  - Cirrhosis-related complications: HR 3.46 (95% CI: 2.13–5.65)
  - Hepatocellular carcinoma (HCC): HR 3.26 (95% CI: 1.23–8.65)
- All liver-related outcomes were significantly increased among patients with F2/F3 fibrosis compared with F0/F1 fibrosis (p<0.05).

Figure 1. Forest plots with adjusted hazard ratios comparing outcomes among patients with biopsy-confirmed MASH and F-stage 2/3 (n=502) vs F-stage 0/1 (n=293)

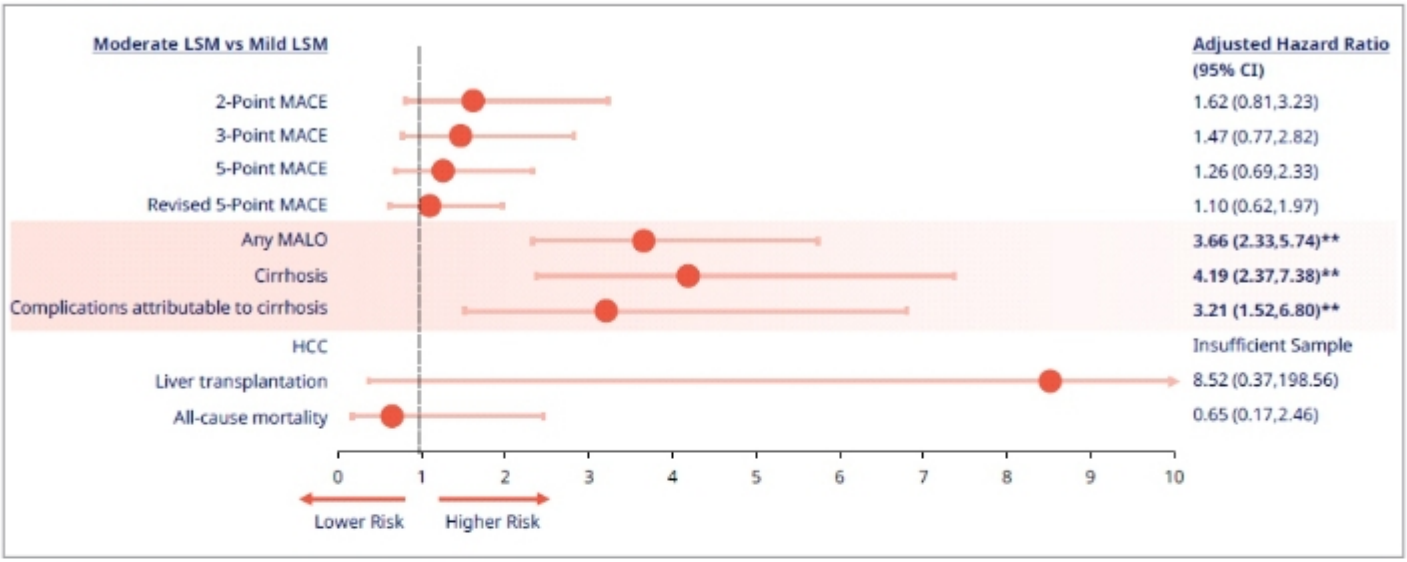


Outcomes among patients with MASLD and moderate LSM vs mild LSM

- Compared with patients with mild baseline LSM, those with moderate LSM demonstrated a numerically higher risk of 2-point, 3-point, 5-point, and recurrent 5-point major adverse cardiovascular events (MACE) (p>0.05).
- Patients with moderate LSM had a significantly increased risk of major adverse liver outcomes (MALO) compared with those with mild LSM, including:
  - Any MALO: HR 3.66 (95% CI: 2.33–5.74)
  - Cirrhosis: HR 4.19 (95% CI: 2.37–7.38)
  - Cirrhosis-related complications: HR 3.21 (95% CI: 1.52–6.80)

- All liver-related outcomes were significantly more frequent among patients with moderate versus mild LSM ($p<0.05$), highlighting the association between increased liver stiffness and adverse hepatic outcomes.

Figure 2. Forest plots with adjusted hazard ratios comparing outcomes among patients with MASLD and moderate LSM (n=189) vs mild LSM (n=359)



Conclusion

- **Patients with MASH or MASLD and significant fibrosis (F2/F3 or liver stiffness measurement of 8–15 kPa) were at a significantly greater risk of major adverse liver outcomes (MALO) and showed a trend toward a higher risk of major adverse cardiovascular events (MACE) compared with those with mild or no fibrosis (F0/F1 or mild LSM) at baseline.**
- **These real-world findings highlight the clinical importance of identifying and treating patients early in the disease course, with the potential to reduce liver-related complications and potentially improve cardiovascular outcomes.**

8. Long-Term Histologic Outcomes of Recurrent MASH After Liver Transplantation: Evidence from a 35-Year Cohort Study.

Aim:

- To determine the incidence, timing, and histologic progression of recurrent and de novo MASH after liver transplantation (LT) using centrally reviewed liver biopsy specimens.

Methods:

- Retrospective cohort study of adult LT recipients at Cleveland Clinic (1984–2020).
- All available post-transplant liver biopsies were centrally re-reviewed by expert hepatopathologists using NASH-CRN criteria.
- Post-transplant MASLD/MASH was classified as:
  - **Recurrent:** MASH was the indication for LT.
  - **De novo:** LT performed for non-MASH etiologies.
- Outcomes assessed:
  - Incidence of post-transplant MASLD/MASH.
  - Time from LT to first biopsy-confirmed MASH.
  - Fibrosis progression, advanced fibrosis (F3), and cirrhosis (F4).

Results:

- Included 2,567 LT recipients; 35% were female and 17.3% underwent LT for MASH.
- **Recurrent disease:**
  - MASLD: 13.9%
  - Histologic MASH: 6.3%
- **De novo disease:**
  - MASLD: 13.1%
  - Histologic MASH: 4.2%
- Recurrent MASLD and MASH occurred significantly more frequently than de novo disease ($p<0.001$).
- Development of graft MASH was independently associated with reduced overall survival ($p<0.001$).
- Among 118 patients with post-transplant histologic MASH:
  - Median time to diagnosis: 1.8 years after LT.
  - Fibrosis progressed by ≥1 stage in 50% of patients over a median 3-year follow-up.
  - Advanced fibrosis (F3) developed in 30%.
  - Cirrhosis (F4) developed in 5.5%.
  - Median fibrosis progression rate: 0.54 stages/year (~1 stage every 1.85 years).

Conclusion

- **MASLD and MASH are common complications after liver transplantation, with recurrent disease occurring more frequently than de novo disease.**
- **Histologic MASH develops early after LT and is associated with reduced survival.**
- **Fibrosis progresses rapidly, advancing by approximately one stage every two years, highlighting the need for early detection and management.**

9. In patients undergoing TIPS placement, diabetes found to be an independent risk factor for hepatic encephalopathy and death.

Aim:

- To evaluate the impact of type 2 diabetes mellitus (T2DM) on clinical outcomes following transjugular intrahepatic portosystemic shunt (TIPS) placement in patients with portal hypertension.
- To determine whether T2DM independently influences the risk of hepatic encephalopathy (HE) and mortality after TIPS.

Methods:

- Multicenter retrospective cohort study involving patients who underwent covered TIPS placement:
  - Hannover Medical School (2009–2021)
  - Two Vienna centers (2000–2025)
- Included patients treated for portal hypertension-related complications with available diabetes and outcome data.
- Exclusion criteria included malignancy, non-T2DM diabetes types, rescue TIPS placement and incomplete datasets
- Outcomes assessed:
  - Overt hepatic encephalopathy (HE)
  - All-cause mortality
- Multivariable competing-risk regression analyses were adjusted for age and MELD score.

Results:

- A total of 650 patients were included, vienna cohort (366 patients) and hannover cohort (284 patients)
- Baseline characteristics were median age of 57 years, 65.7% of male, 66.3% had alcohol-related liver disease, 75.4% underwent TIPS for recurrent/refractory ascites and Median MELD score of 12
- T2DM was present in 185 patients (28.5%).
- Patients with T2DM were older (60 vs. 56 years; p<0.001) but had similar:
  - MELD scores
  - Pre-TIPS portal pressure gradient
  - Post-TIPS portal pressure gradient
- Median follow-up duration: 20.2 months.

Table 12. Comparison of diabetic and non-diabetic patients

Clinical Outcome After TIPS	T2DM Patients	Non-T2DM Patients	Statistical Significance
Cumulative Incidence of Hepatic Encephalopathy (HE)	Higher	Lower	p < 0.001
Overt HE at 6 Months	43.4%	24.2%	p < 0.001
Cumulative Incidence of Death	Higher	Lower	p < 0.001
One-Year Mortality	29.0%	15.9%	p < 0.001

- Multivariable analysis identified T2DM as an independent risk factor for:
  - Hepatic encephalopathy: aSHR 1.59 (95% CI: 1.21–2.08; p<0.001)
  - Mortality: aSHR 1.34 (95% CI: 1.03–1.75; p=0.028)

Conclusion

- **T2DM is an independent predictor of both hepatic encephalopathy and mortality following TIPS placement.**
- **Patients with T2DM experienced significantly higher rates of overt HE and nearly double the one-year mortality compared with non-diabetic patients.**
- **These findings highlight the importance of careful risk assessment, monitoring, and management of T2DM in patients undergoing TIPS.**