Clinical Burden of Compensated Cirrhosis due to Metabolic Dysfunction-Associated Steatohepatitis (MASH): A Systematic Literature Review

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Introduction

- Compensated cirrhosis due to metabolic dysfunction-associated steatohepatitis (MASH) represents **a substantial increase in clinical risk vs. earlier disease**, yet data on this population have not been comprehensively synthesized[1]
- **Clinical risk is driven by fibrosis severity, portal hypertension, hepatic reserve, frailty, and cardiometabolic comorbidities**. Mortality risks progressively increase over time and are driven by both liver and non liver related diseases, particularly cardiovascular disease (CVD)[2–5]
- **Evidence on outcomes in compensated cirrhosis due to MASH remains limited**. Disease progression is largely monitored by surrogate markers (liver enzymes, imaging markers) or selected clinical outcomes (hospitalization, cardiovascular [CV] outcomes, fibrosis progression, decompensation events, progression to liver transplantation [LT])[6,7]

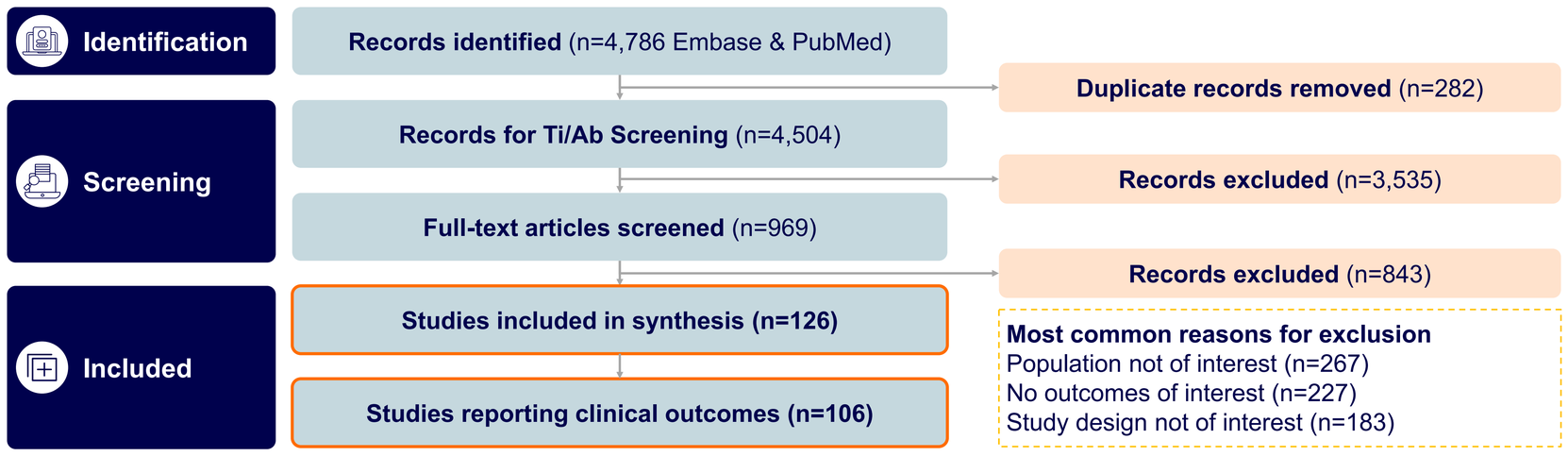
Objectives

This systematic literature review (SLR) was conducted to characterize clinical progression of compensated cirrhosis due to MASH, highlighting progression from compensated to decompensated cirrhosis, hepatocellular carcinoma (HCC), LT, and mortality as identifiable risk factors for disease progression.

Methods

- Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-driven searches following Cochrane guidelines were conducted in Embase and PubMed (2017–February 2026 for articles; 2021–February 2026 for conference abstracts)[8,9]
- Studies with adults with compensated cirrhosis due to MASH in the US, UK, France, Germany, Italy and Spain were included if they reported epidemiological, clinical, economic, or humanistic outcomes
- Title/abstract and full-text screening were performed in duplicate, and all extractions were conducted by one reviewer and independently validated by another
- Study findings were synthesized narratively across natural-history cohorts and interventional trials

Figure 1: PRISMA flow chart for study criteria.



Results

Baseline Characteristics

- A total of 126 studies reporting aforementioned outcomes were identified, **of which 86% reported clinical outcomes**
- Demographic characteristics for the overall compensated cirrhosis population were reported in 13 studies; patients ≥65 (61.07%) predominated the studies **(median age 59–61) (Table 1)**

Table 1: Baseline characteristics across included patient cohorts.

Parameter	Category	Value
Mean Age (years)	Range of age	Mean: 60-73 Median: 59-61
Age distribution	18–64	38.93%
	65–69	15.33%
	70–74	13.63%
	75–79	17.76%
	≥80	14.36%
Race	White	72–96%
	Black/African American	2–8%

Progression and Mortality Risk

- **Long-term mortality (72.2% over 20 years)** was driven by both **liver (37.0%)** and **non-liver (27.2%)** causes (cardiovascular disease or hepatic malignant neoplasm)
- Survival declined markedly over time, with patients having a **~51.3% 10-year survival, ~27.8% 20-year survival**, and an estimated **life expectancy of ~13.8 years for patients with compensated cirrhosis at time of diagnosis**

Table 2: Progression and mortality risk factors in compensated cirrhosis due to MASH.

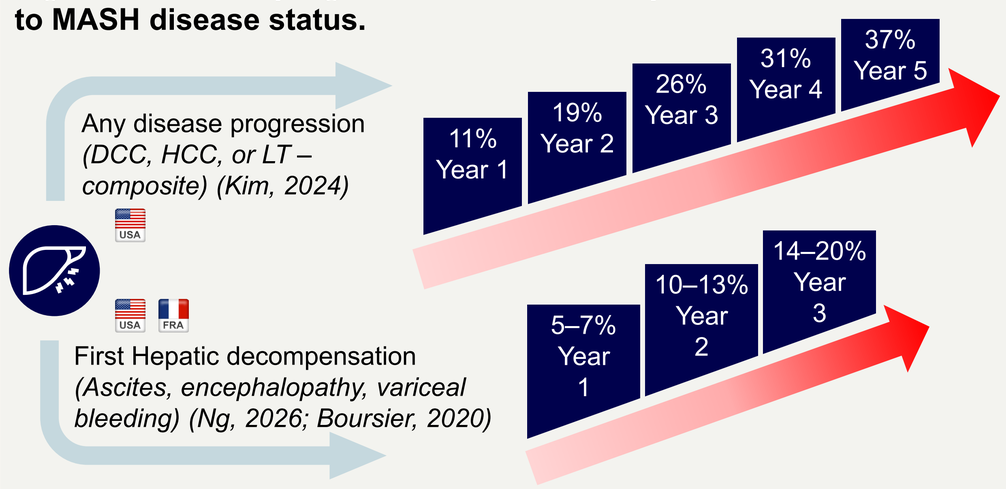
Predictors of Liver-Related Events & Decompensation

Advanced fibrosis severity	Ishak stage 6 vs ≤5 Higher ELF, FIB-4, MASLD Fibrosis Score Increased liver stiffness (VCTE)
Portal hypertension	CSPH (HVPG ≥10 mmHg) Rising HVPG over time
Worsening hepatic function	↑ Bilirubin, INR ↓ Albumin, platelets Higher MELD / Child–Pugh score
Older age	Especially ≥75 years
Frailty / dependency	Nursing-home use, functional dependence
Cardiometabolic comorbidities	Ischemic heart disease Diabetes mellitus
Overall disease severity	Higher MELD and fibrosis burden (MASLD & FIB-4)

Disease Progression

- Across real-world and trial cohorts, compensated cirrhosis due to MASH showed rapid, predictable progression from compensated to decompensated cirrhosis, HCC, and LT (**11% in Year 1 to 37% in Year 5** across all outcomes) **(Fig. 2)**
- Real-world data consistently show that patients with compensated cirrhosis due to MASH experience progressive clinical deterioration over time, with increasing rates of decompensation and downstream liver outcomes

Figure 2: Disease progression rates for compensated cirrhosis due to MASH disease status.



Advanced outcomes

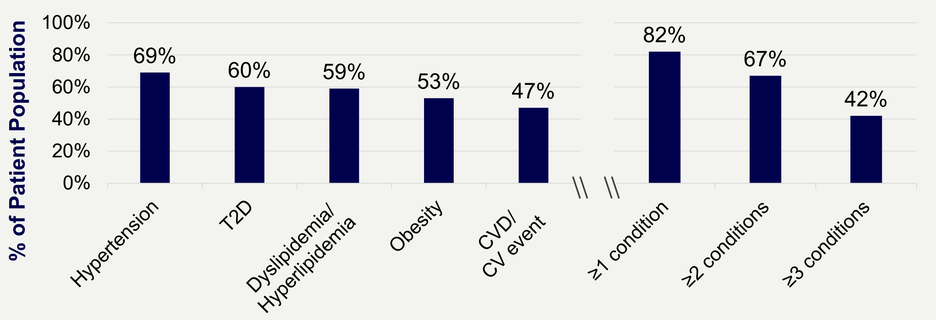
HCC
- **10-year CI: 7.9 per 100 PY** (Chhatwal, 2022)
- **IR: 0.24 per 100 PM** (Luthra, 2025)

LT
- **4% at 2 years** (Bassegoda, 2022)
- **IR: 0.24 per 100 PM** (Luthra, 2025)

Comorbidities

- Patients with compensated cirrhosis due to MASH presented with a high prevalence of comorbidities and other clinical characteristics **(82% of patients with at least one condition)**, including **portal hypertension (69%), type-2 diabetes (60%), dyslipidemia/hyperlipidemia (59%), obesity (53%), and cardiovascular disease (CVD) (47%)**
- The high frequency of metabolic and cardiovascular comorbidities may contribute to the disease complexity and morbidity of compensated cirrhosis due to MASH; however, **such comorbidities are insufficient to explain the risk of liver and non-liver related disease progression**

Figure 3: Comorbidities of compensated cirrhosis due to MASH



Discussion

- Real-world and modeling data consistently show that **compensated cirrhosis due to MASH patients experience progressive clinical deterioration over time**, with increasing rates of decompensation and downstream liver outcomes, including HCC and LT, **that pose a substantial effect on patient mortality**
- **Therapeutic options are** primarily focused on the **management of sequelae and mitigation of disease progression**. Currently, **no Food and Drug Administration (FDA) approved interventions are available** for the treatment of compensated cirrhosis due to MASH
- This study demonstrates an **unmet need for novel therapeutic options to mitigate disease progression** for compensated cirrhosis due to MASH patients, in addition to directly comparable clinical outcomes data for current standard of care approaches

Limitations

- Clinical outcomes data were derived from predominately retrospective studies
- Low representation of European data sources
- Only 57% of the 126 studies being specific to compensated cirrhosis due to MASH, with the remainder inclusive of populations with eventual LT
- Interventions data was predominately Phase 2/2b trials with heterogeneous endpoints
- Inclusion of non-peer reviewed conference abstract and posters.

Conclusion

Evidence demonstrates **rapid progression, high mortality and risk of undergoing LT**, underscoring an unmet need in treatment of disease, and ultimately prevent progression and/or outcomes in compensated cirrhosis due to MASH. **Additional studies are needed to understand the burden of disease**.

Abbreviations

CSPH, clinically significant portal hypertension; CV, cardiovascular; CVD, cardiovascular disease; DCC, decompensated cirrhosis; ELF, Enhanced Liver Fibrosis; F4c, compensated cirrhosis (fibrosis stage 4); FDA, Food and Drug Administration; FIB-4, Fibrosis-4 index; HCC, hepatocellular carcinoma; HVPG, hepatic venous pressure gradient; INR, international normalized ratio; IR, incidence rate; LT, liver transplantation; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; MELD, Model for End-Stage Liver Disease; PM, person-months; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PY, person-years; SLR, systematic literature review; Ti/Ab, title/abstract; UK, United Kingdom; US, United States; VCTE, vibration-controlled transient elastography.

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SLR References

Disclosures

YK, NA, KP and DZ are employees and shareholders of Madrigal Pharmaceuticals, Inc. **LG, AD,** and **NH** are employees of Trinity Life Sciences, LLC, and have provided consulting services to Madrigal Pharmaceuticals, Inc., through their employment with Trinity. Trinity received funding from Madrigal Pharmaceuticals, Inc., for this study.

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