Prognostic value of liver fibrosis in steatotic liver disease: a systematic literature review and meta-analysis

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POSTER #50

INTRODUCTION

Background

- MASLD and its progressive form MASH are among the most common liver disorders worldwide
- MASH is associated with long-term clinical consequences (e.g., liver cirrhosis, decompensation and/or failure, HCC) which may lead to death
- Clinical trials in this population require long follow-up times and large sample sizes to observe sufficient clinical events for statistical comparison
  - Surrogate endpoints (short-term markers that reliably predict clinical outcomes) are commonly used to accelerate drug development and treatment access
- Surrogate endpoints in MASH, such as histologic fibrosis stage and NASH resolution, have been accepted by the FDA[1] and EMA[2] to provide conditional approvals for medications targeted to treat this condition

Rationale

- Synthesis of the association between histologic fibrosis stage and long-term clinical consequences will inform the appropriateness of surrogate endpoints in MASH

OBJECTIVES

1. Review the existing literature on surrogate endpoints (histologic fibrosis stage) used for MASH
2. Examine the relationship between fibrosis stage and clinical outcomes such as mortality and/or liver-related events in patients with MASH

METHODS

Search strategy

- **Search period:** 2014 to November 13, 2024
- **Data sources:** MEDLINE, Embase, clinical trial registries (clinicaltrials.gov, WHO-ICTRP, EU platform), manual search of the reference lists of previous reviews

Study selection

TABLE 1. PECOS criteria for identifying relevant studies

	Inclusion criteria
Population	Adults with a diagnosis of MASH
Exposure	Fibrosis stage based on histological assessment
Comparators	• F2-3 vs F4 • Other comparators in which F2 and/or F3 are compared to F4
Outcomes	Primary: • Liver transplant • Hepatic decompensation events • Progression to cirrhosis • ESLD • HCC • Composite outcomes of the above liver-related events • Mortality Secondary: • HRQoL Exploratory: • CV-related events • CV-related mortality • MACE • Other HRQoL outcomes
Study design	• Clinical trials • Observational studies • Correlational or prognostic studies

Evidence synthesis

- If n≥3 studies were available for an endpoint, meta-analysis conducted
  - If n<5 studies estimating an endpoint, only fixed-effect (FE) model was used
  - If n≥5 studies estimating an endpoint, both random-effects (RE) models (HKSJ method with Paule-Mandel estimator and DL method) and FE model were used
- If n<3 studies were available for endpoint, narrative synthesis conducted only

RESULTS

Thirty-three unique studies examined the relationship between fibrosis stage and clinical outcomes (**Figures 1 and 2**).

FIGURE 1. PRISMA diagram.

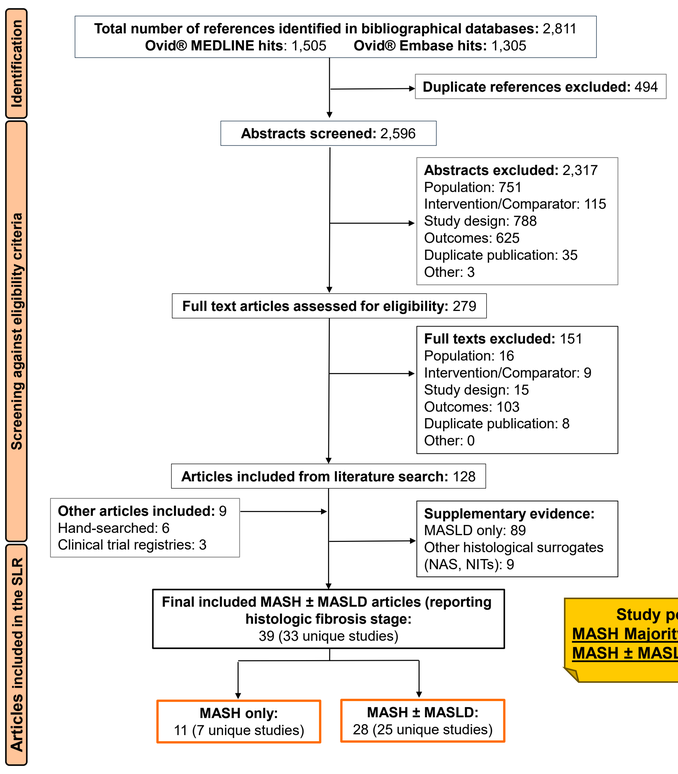
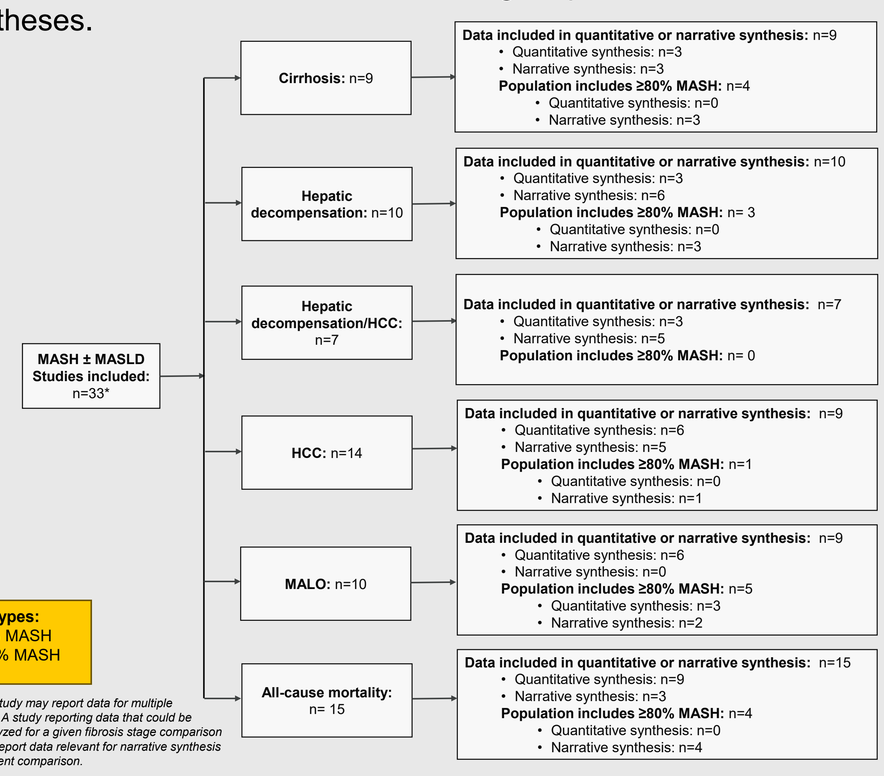
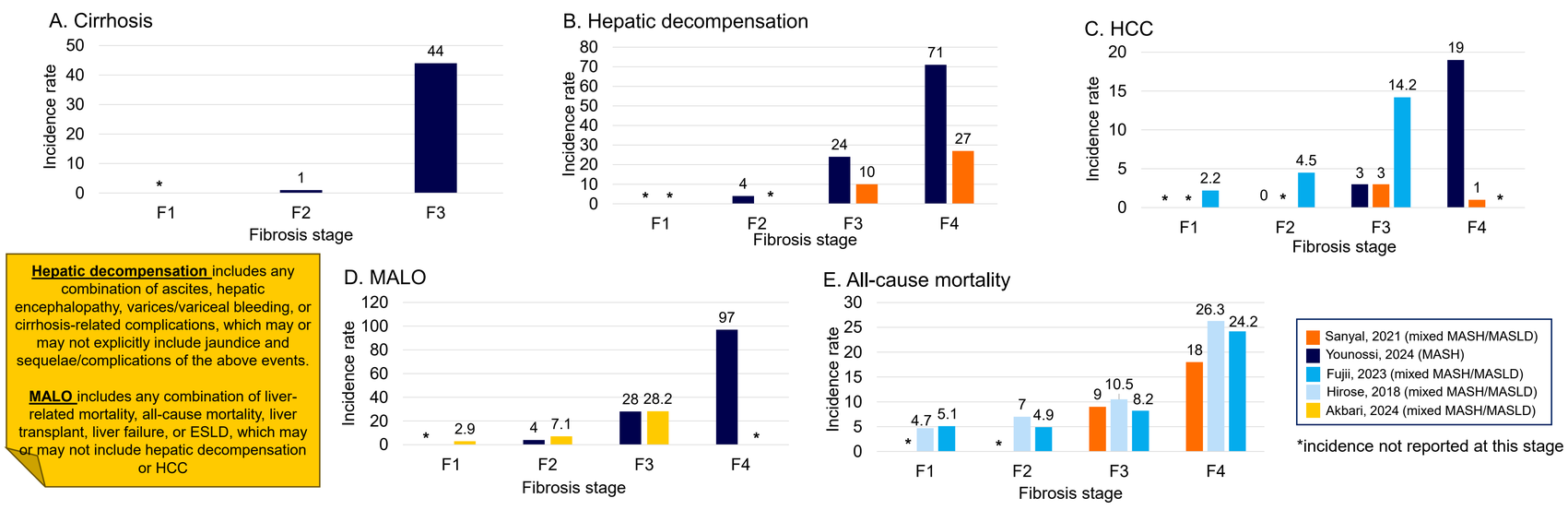


FIGURE 2. Number of studies contributing to quantitative and narrative syntheses.



In individual studies, patients at higher F-stages had higher incidence of adverse clinical outcomes compared to those at lower F-stages (**Figure 3**).

FIGURE 3. Incidence rate of outcomes per fibrosis stage (per 1000 patient years) in MASH ± MASLD patients



*incidence not reported at this stage

Hepatic decompensation includes any combination of ascites, hepatic encephalopathy, varices/variceal bleeding, or cirrhosis-related complications, which may or may not explicitly include jaundice and sequelae/complications of the above events.

MALO includes any combination of liver-related mortality, all-cause mortality, liver transplant, liver failure, or ESLD, which may or may not include hepatic decompensation or HCC

Patients at higher F-stages had greater risk of adverse clinical outcomes versus those at lower F-stages when pooling data across studies (**Table 2**).

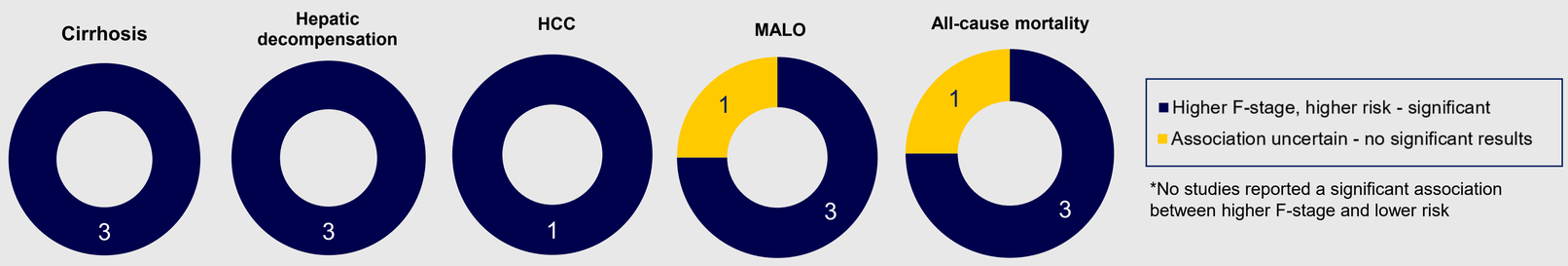
TABLE 3. Results of quantitative synthesis in MASH ± MASLD studies

Outcome	Available comparisons	Adjusted estimates: Final selected model (number of studies)	Adjusted estimates: pooled aHR (95% CI)	Adjusted estimates: I^2 (%)	Unadjusted estimates: Final selected model (number of studies)	Unadjusted estimates: pooled uHR (95% CI)	Unadjusted estimates: I^2 (%)
Cirrhosis, decompensated	F3 vs F2	Fixed effects (n=3)	2.05 (1.45, 2.90)*,†	77.6	-	-	-
Hepatic decompensation	F3-4 vs F0-2	Fixed effects (n=3)	10.93 (6.31, 18.92)*	47.8	-	-	-
Hepatic decompensation/ HCC	F3-4 vs F0-2	Fixed effects (n=3)	20.50 (8.25, 50.93)*	59.9	Fixed effects (n=3)	32.37 (13.51, 77.59)*	60.6
HCC	F4 vs F3	Fixed effects (n=3)	1.52 (0.33, 7.10)†	2.7	-	-	-
	F3-4 vs F0-2	PM-HKSJ (n=5)	5.57 (1.87, 16.60)*	17.0	-	-	-
MALO	F4 vs F3	Fixed effects (n=3)	3.27 (1.98, 5.41)*,†	45.9	Fixed effects (n=5)	2.43 (1.70, 3.46)*,†	64.6
	F4 vs F2	Fixed effects (n=3)	6.31 (3.38, 11.79)*,†	72.3	Fixed effects (n=3)	6.62 (3.72, 11.78)*,†	71.2
	F3-4 vs F0-2	PM-HKSJ (n=6)	6.66 (4.04, 10.99)*	34.1	-	-	-
All-cause mortality	F4 vs F3	Fixed effects (n=3)	2.13 (1.10, 4.10)*,†	0.0	Fixed effects (n=4)	2.30 (1.35, 3.94)*,†,‡	0.0
	F4 vs F0-2	-	-	-	Fixed effects (n=3)	5.63 (3.15-10.06)*,†,‡	0.0
	F3-4 vs F0-2	PM-HKSJ (n=9)	3.36 (2.37-4.75)*	0.0	-	-	-

Notes: *p<0.05, sufficient quantitative data was not available for MASH only studies to estimate unadjusted or adjusted pooled hazard ratios

Data from studies conducted in MASH majority populations are consistent with trends observed in MASH ± MASLD populations (**Figure 4**).

FIGURE 4. Number of MASH majority studies showing consistency with MASH ± MASLD results



*No studies reported a significant association between higher F-stage and lower risk

CONCLUSION

- Patients with histologically defined advanced fibrosis and cirrhosis are at increased risk of adverse clinical outcomes compared to patients with earlier stages of fibrosis, including a two- to three-fold increased risk of all-cause mortality, a three- to six-fold increased risk of MALO, and over ten-fold risk of hepatic decompensation.
- These findings support the prognostic relevance of histologic fibrosis stage and its use as a surrogate marker for long-term clinical outcomes in patients with MASH
- Additional longitudinal studies, using either clinical trial or observational designs, are required to support future quantitative analysis in the MASH population

ABBREVIATIONS

CV, cardiovascular; EMA, European Medicines Agency; ESLD, end stage liver disease; EU, European Union; FDA, Food and Drug Administration; FE, fixed-effect; HCC, hepatocellular carcinoma; HKSJ, Hartung-Knapp- Sidik-Jonkman; HRQoL, health-related quality of life; major adverse cariovascular event; MALO; major adverse liver outcome; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; NASH, non-alcoholic steatohepatitis; PECOS, population, population, exposure, comparison, outcome, and study design; PY, person year; RE, random effect.

DISCLOSURES AND ACKNOWLEDGEMENTS

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1. Food and Drug Administration. *Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment Guidance for Industry (Draft guidance).* 2018. **2.** European Medicines Agency. *Reflection paper on regulatory requirements for the development of medicinal products for non-alcoholic steatohepatitis (NASH).* 2023.

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