Evaluating Histologic Endpoints in MASH Patients: A Systematic Literature Review of Associations with Patient-Relevant Outcomes

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Background

- MASH is a chronic liver disease associated with long-term clinical consequences (e.g., liver cirrhosis, decompensation and/or failure, HCC) which may lead to death
- Clinical trials investigating treatments for MASH require long follow-up times to observe these serious, late-stage clinical events
  - In other disease areas, surrogate endpoints, which are short-term markers that reliably predict more serious or patient-relevant outcomes, are commonly used to accelerate drug development and treatment access,
- Both the FDA[1] and EMA[2] have acknowledged the utility of surrogate endpoints in MASH, with proposed surrogates including:
  - Histologic fibrosis
  - NASH resolution
- A summary of contemporary evidence of the relationship between histologic surrogates of disease progression and patient-relevant outcomes will inform the appropriateness of surrogate endpoints in MASH

Objectives:

1. Review the existing literature on surrogate endpoints (i.e., fibrosis stage, NASH resolution) used for MASH by identifying studies assessing the association between histologic surrogates and patient-relevant outcomes, and,
2. Synthesize the data to describe the relationship between these surrogate endpoints and patient-relevant outcomes, including clinical and HRQoL outcomes

Methods

- **Search strategy**
  - Search period: 2014 to date last searched (November 13, 2024)
  - Databases: MEDLINE and Embase
  - Clinical trial registries: clinicaltrials.gov, WHO-ICTRP, EU platform
  - Manual search of the reference lists of previous reviews
- **Study selection**
  - Title-abstract screening, followed by full-text publication screening, both conducted in duplicate with reconciliation
  - Based on PECOS criteria summarized below

Population
- Adult patients with a diagnosis of MASH

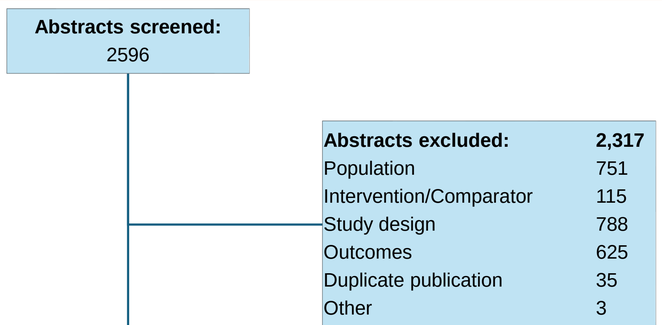
Exposure/Comparator
- Histologic fibrosis stage
- NAS
- NITs (any type)

Outcomes
- Clinical liver-related outcomes (mortality, LRE, etc.)
- HRQoL
- Safety: CV-related events (CV-related mortality, MACE, etc.)

Study design
- Clinical trials
- Observational studies

Other
- Results published/available
- English language
- Publication date 2014-2024

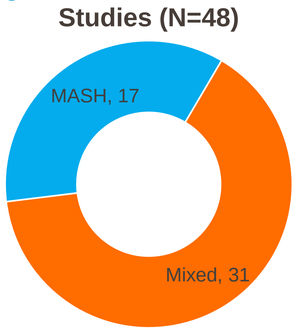
Included studies (PRISMA diagram)



Results

Who were the patients included in the studies assessing associations between surrogate endpoints and outcomes?

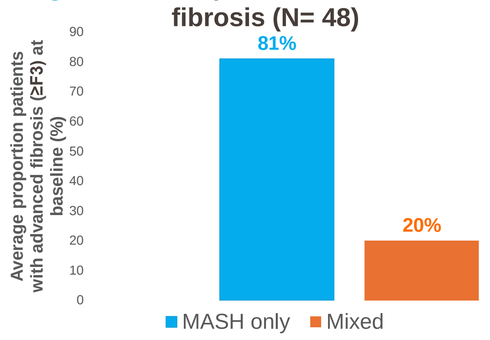
Fig 1. Overview of Included Studies (N=48)



In MASH only studies:
- The average **proportion of patients with advanced fibrosis (≥F3)** at baseline was 81% (Figure 2)
- With most studies reporting 100%

In mixed (MASH/MASLD) studies:
- The average **proportion of MASH patients** was 59%, with most studies including between 55-75%
- The average **proportion of patients with advanced fibrosis (≥F3)** at baseline was 20% (Figure 2)
- With most studies reporting between 15-25%

Fig 2. Baseline prevalence of advanced fibrosis (N= 48)



✓ This underscores the need to interpret associations between surrogate endpoints and outcomes in the context of baseline disease severity
✓ To address this, results are reported separately for MASH-only and mixed studies throughout the analysis

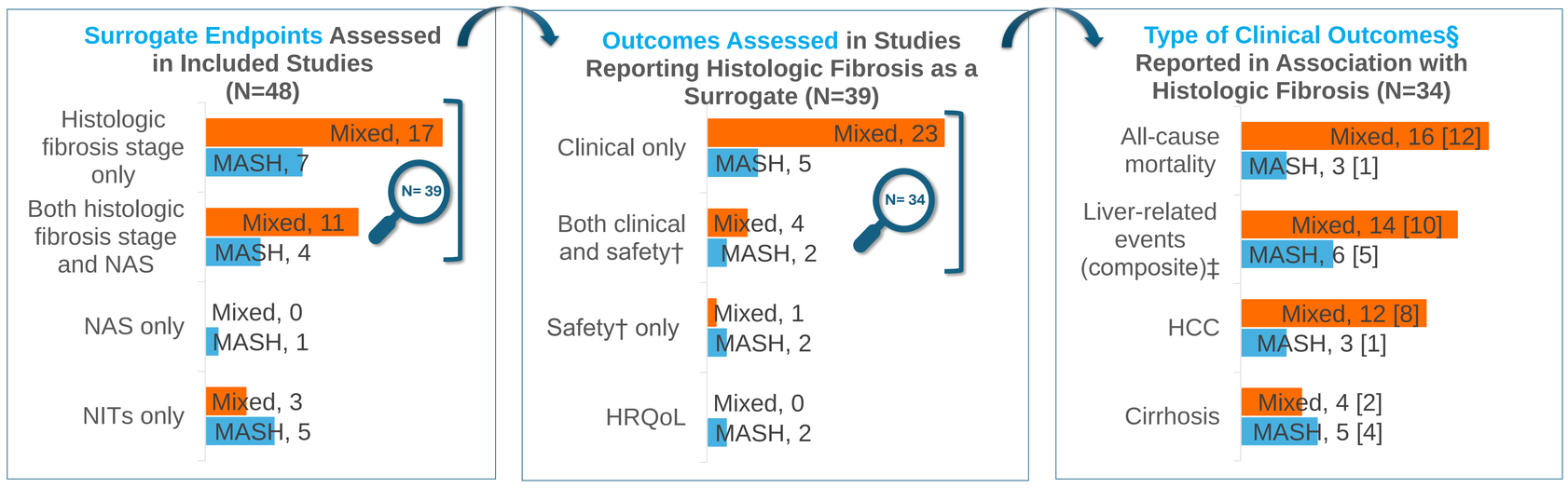
What were the most commonly reported associations between surrogate endpoints and patient-relevant outcomes in the identified literature?

- A funnel approach was used to progressively narrow down from all included studies to those most relevant for characterizing associations between histologic fibrosis and clinical outcomes
- The three figures below reflect this stepwise analysis from broader patterns to more focused insights

Fig 3. Distribution of surrogate endpoints evaluated in association with any outcome across the 48 included studies

Fig 4. Among the 39 studies reporting associations with histologic fibrosis (alone or with NAS), the types of outcomes assessed were documented

Fig 5. Focused on the 34 studies assessing an association between histologic fibrosis and at least one clinical outcome



Notes: †CV-related events, including CV-related death. ‡Studies may report data for both composite outcomes of the occurrence of one of multiple possible liver-related clinical events (e.g., hepatic decompensation, transplant, end-stage liver disease) as well as the individual events. §Studies reporting a quantitative association through an HR.

- Across the 48 included studies, histologic fibrosis emerged as the most frequently assessed surrogate, highlighting its central role in evaluating disease progression in this population (Figure 3)
- Building on Figure 3, clinical outcomes were the most frequently assessed in association with histologic fibrosis (Figure 4)
- Among the 34 studies that evaluated an association between histologic fibrosis stage and at least one clinical outcome, the most commonly reported outcomes were mortality, LRE, HCC, and cirrhosis (Figure 5)

What was the direction and significance of the association between histologic fibrosis and key clinical outcomes?

- While Figure 5 maps what outcomes are assessed, it does not provide information about how strong or consistent the associations with fibrosis stage are
- To evaluate the robustness of the relationship between fibrosis stage and key clinical outcomes, the approach was to focus on studies that quantified the association, i.e., studies reporting HRs
- While mortality and HCC were among the most frequently reported outcomes overall (Figure 5), only one MASH study reported an HR for each, which was insufficient to assess trends

Liver-related events (composite)

MASH population

Mixed MASH/MASLD population

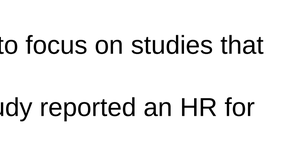
Progression to cirrhosis

MASH population

Mixed MASH/MASLD population

Conclusions

- **This SLR reflects increasing research efforts aimed at understanding the relationship between surrogate endpoints (such as histologic fibrosis) and patient-relevant clinical outcomes in MASH**
- **Despite variations among included studies, findings consistently indicated that more severe fibrosis is associated with worse clinical outcomes**
- **A meta-analysis could help quantify this association and reinforce the evidence base, but heterogeneity in study populations and outcome definitions must be carefully evaluated through a feasibility assessment before proceeding**
- **Such quantitative analyses are planned for future publications**



Abbreviations: CV, Cardiovascular; EMA, European Medicines Agency; EU, European Union; FDA, Food and Drug Administration; HCC, Hepatocellular carcinoma; HR, Hazard ratio; HRQoL, Health-related quality of life; LRE, Liver-related events; MACE, Major adverse cardiovascular events; MASH, Metabolic dysfunction-associated steatohepatitis; MASLD, Metabolic dysfunction-associated steatotic liver disease; NAS, NAFLD activity score; NASH, Non-alcoholic steatohepatitis; NITs, Noninvasive tests; PRISMA, Preferred Reporting Items for Systematic Reviews and

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