Relationship between non-invasive tests, clinical outcomes and liver biopsy among people with MASH under real-world conditions

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Background

- Liver biopsy has been the reference standard for assessing disease severity in metabolic dysfunction-associated steatohepatitis (MASH), yet biopsies are rarely conducted in clinical practice.
- Advanced fibrosis has been shown to be a key risk factor for liver decompensation and liver-related events[1].
- There is a lack of data that demonstrates the relationship between histologic changes and incidence of clinical events such as progression to cirrhosis and end-stage liver disease.

Objective

To characterize the relationship between histology, non-invasive test (NIT) values, and incidence of clinical outcomes.

Methods

- This analysis included US adults enrolled in TARGET-NASH, a longitudinal observational study containing >6,000 participants with MASH/MASLD.
- Eligible participants had at least 1 liver biopsy and 2 FIB-4 measurements (at least one year apart).
- Index date was defined as the date of the first eligible NIT around the biopsy selected for the analysis.
- Participants were classified into two subgroups based on longitudinal changes in FIB-4 category (<1.3, 1.3-2.67, >2.67) between the first and second assessment:
  - Stable/Improved – no change/decrease in FIB-4 category
  - Worsened – Increase in FIB-4 category
- Fine-Gray multivariable subdistribution hazard models with time-varying covariates assessed the association between FIB-4 categorical changes and time to clinical events.

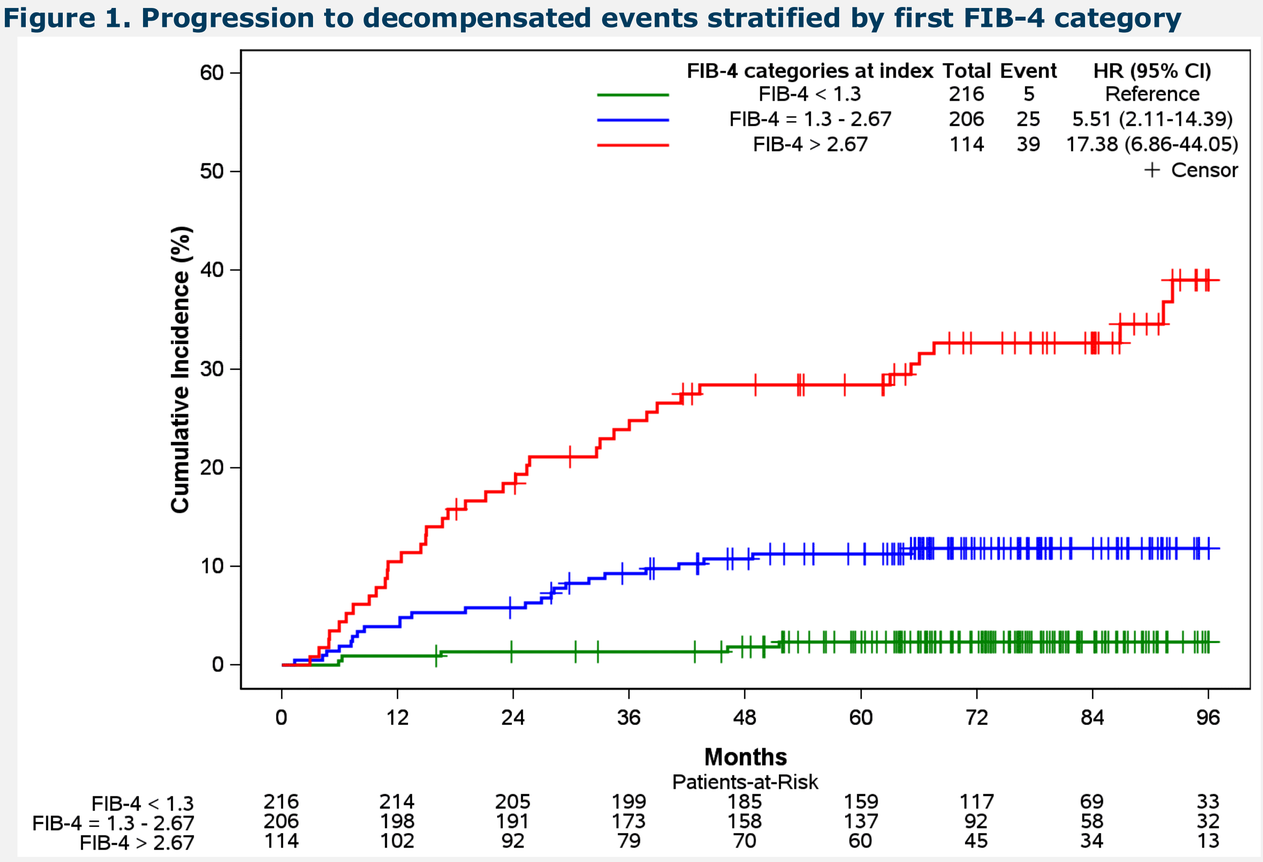
Results

Table 1. Participant Demographics at Index

	FIB4 < 1.3 (n=227)	FIB-4 ≥1.3 and ≤2.67 (n=230)	FIB-4 >2.67 (n=168)	Overall (n=625)
Age				
Median, years (Q1 – Q3)	48 (38 - 56)	60 (52 - 65)	60 (56 - 66)	56 (47 - 64)
Female, n (%)	157 (69)	140 (61)	123 (73)	420 (67)
Race: Non-Hispanic White, n (%)	157 (69)	180 (78)	128 (76)	465 (74)
Ethnicity: Hispanic/Latino, n (%)	25 (11)	29 (13)	22 (13)	76 (12)
BMI (kg/m^2) Median (Q1 – Q3)	33 (29 – 39)	33 (28 – 38)	33 (28-39)	33 (29 – 38)
Comorbidities, n (%)				
Hypertension	140 (62)	180 (78)	155 (92)	475 (76)
Type 2 Diabetes	135 (60)	151 (65)	126 (75)	412 (66)
Cirrhosis[2]	33 (15)	103 (45)	147 (88)	283 (45)

Note: Cirrhosis is defined by the previously validated Target RWE definition for MASH[2]: Liver biopsy with fibrosis stage = 4 OR liver biopsy with fibrosis stage=3 and 1 or more secondary indicators OR 2 or more secondary indicators OR FibroScan stiffness result 12.5-15.9 kPa AND one or more secondary indicators OR FibroScan stiffness result ≥16 kPa

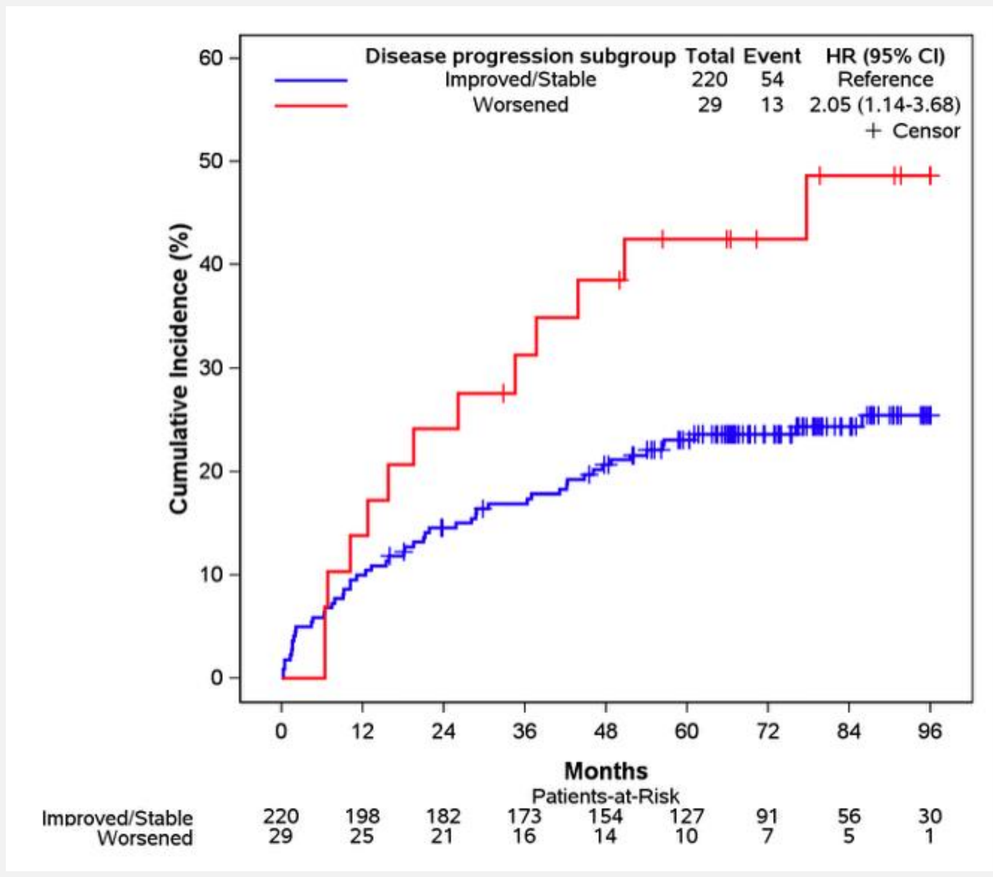
Figure 1. Progression to decompensated events stratified by first FIB-4 category



Note: In the analysis of progression to decompensated events, the index date was the earliest date of compensated cirrhosis diagnosis.

Results

Figure 2. Progression to composite events from index data by disease progression categories



Note: Composite events for MASL and MASH include all-cause mortality, cirrhosis, ascites, hepatic encephalopathy, gastroesophageal variceal hemorrhage, HCC, liver transplant, all-cause cancer excluding HCC and skin cancer, and cardiovascular events.

Results (cont.)

- Of 625 eligible participants (median age: 56 years, 74% Non-Hispanic White, 67% female, median BMI: kg/m^2), 14.2% (n=89) and 85.8% (n=536) were classified in the worsened and stable/improved FIB-4 subgroups, respectively (Table 1).
- The mean (SD) of the first FIB-4 for each FIB-4 category was: 0.85 (0.26) for FIB-4 <1.3 (n=227), 1.92 (0.40) for FIB-4 1.3-2.67 (n=230) and 4.90 (2.43) for FIB-4 >2.67 (n=168).
- Participants with index FIB-4 >2.67 had a higher incidence of decompensated events (34.2%, HR: 17.38, 95% CI: 6.86–44.05) (Figure 1)
- The FIB-4 worsened subgroup had a higher incidence of cirrhosis (25.6%, incidence rate = 5.4/100 person-years) compared with the improved/stable subgroup (13.4%, 2.4 /100 person-years; p=0.044).
- Among those with non-cirrhotic MASH at index, a higher proportion experienced a composite of clinical events in the worsened group (44.8%) than the improved/stable group (24.5%, p=0.021) (Figure 2).
- Participants with FIB-4 >2.67 at index had a higher risk of all-cause mortality (HR: 6.02, 95% CI: 2.86-12.68) and 5.5 times the risk of progressing to cirrhosis (HR: 5.48, 95% CI: 2.39-12.57) compared with those who had FIB-4 <1.3 at index.

Conclusions

- Given the limitations of liver biopsy, NITs like FIB-4 may be used to assess disease severity and disease progression.
- Changes into higher FIB-4 categories were associated with a higher incidence of cirrhosis and a composite of clinical events.
- These findings reinforce the use of noninvasive tools to help assess risk of clinical events for people in MASH management.

Limitations

- Real-world databases are subject to potential missingness, limited generalizability and surveillance bias.
- Selection bias is inherent as liver biopsies are often not conducted as part of standard of care.
- This analysis is designed to maximize data available from participants with at least one biopsy and 2 FIB-4 measurements enrolled in the TARGET-NASH study.
- FIB-4 does not have the best predictive value compared to other NITs that could be used; however, give the dearth of data on those other NITs, FIB-4 was selected due to sample size and data availability.

References: [1]Lam et al. (2024). Advanced liver fibrosis predicts liver outcomes in biopsy-proven metabolic dysfunction-associated steatotic liver disease: A US-based single-center retrospective cohort study. *Journal of Clinical and Translational Hepatology,* 12 (12), 988. [2]Barritt et al. (2017). Design and rationale for a real-world observational cohort of patients with nonalcoholic fatty liver disease: the TARGET-NASH study. *Contemporary Clinical Trials*, 61, 33-38.

Acknowledgements and Disclosures: Target RWE communities are collaborations among academic & community investigators, the pharmaceutical industry and patient community advocates. Target RWE communities are sponsored by TARGET PharmaSolutions Inc (d.b.a., Target RWE). The authors would like to thank all the investigators, participants, and research staff associated with TARGET-NASH. ClinicalTrials.gov Identifier: NCT02815891. This analysis was funded by Madrigal Pharmaceuticals.