Relationship between liver biopsy fibrosis stage and clinical outcomes among persons with MASLD/MASH in a real-world setting

Michael Roden[1], A. Sidney Barritt IV[2], Yestle Kim[3], John O'Donnell[3], Breda Munoz[4], Feng Yu[4], Andrea R. Mospan[4], Heather L. Morris[4], Vincent Wai-Sun Wong[5], Arun J. Sanyal[6] on behalf of the TARGET-NASH Investigators

[1]Henriich Heine University, Dusseldorf, DE; [2]University of Chapel Hill, Chapel Hill, NC, USA; [3]Madrigal Pharmaceuticals, In. Pennsylvania, USA; [4]Target RWE, Durham, NC, USA; [5]The Chinese University of Hong Cong, Hong Kong, CN; [6]Virginia Commonwealth University, Richmond, VA, USA

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Background

- Metabolic dysfunction-associated steatohepatitis (MASH) is a common cause of liver-related morbidity and mortality.
- MASH includes increasing degrees of fibrosis with increasing levels of worsening from fibrosis stage 0 to 4.
- Liver biopsy is the reference standard for the diagnosis of MASH and a patient's disease status often relies on surrogate endpoints such as histologic markers.[1-2]

Objective

To investigate the relationship between change in liver fibrosis stage over time and incidence of clinical outcomes among patients with MASH in a real-world setting.

Methods

Study Design & Data Source

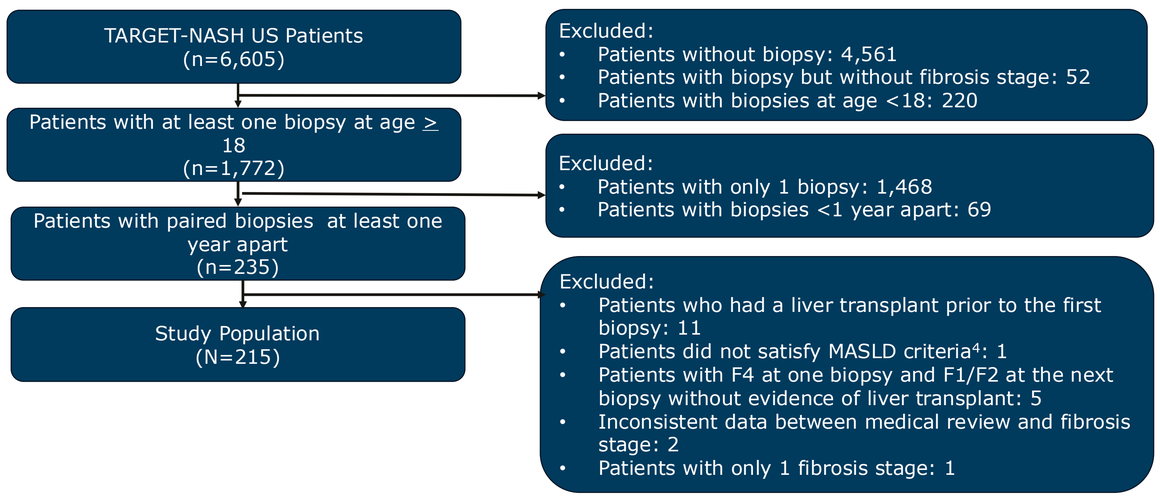
- This analysis includes adults with at least 2 liver biopsies (at least 1 year apart) who previously enrolled in TARGET-NASH (NCT02815891), an ongoing longitudinal observational study with >6,000 people with MASLD receiving usual standard of care in the US.
- Patients were classified into one of the following subgroups based on changes between the first and second biopsy:
  - Stabilized/Improved (S/I) – no change or a reduction in fibrosis stage
  - Worsened (W) – Increase in fibrosis stage
- Incidence of clinical outcomes (where time variables are tied to the incidence of clinical outcomes representing the duration from index date until the clinical event occurs) were stratified by index fibrosis stage and subgroups. Clinical outcomes included clinical evidence of progression between the first (index/baseline) and second biopsy to:
  - Cirrhosis (for patients with MASL or MASH at index and identified using the TARGET-NASH MASH definition[3])
  - Decompensation
  - Hepatocellular carcinoma (HCC)
  - MELD score change from <12 to ≥15
  - Liver transplantation (LT)
  - Cardiovascular (CV) event
  - All-cause mortality
  - Cancer (excluding HCC, skin cancer)

Statistical Analysis:

- Hazard ratios were estimated using modified Fine-Gray sub-distribution hazard models to analyze the time-to-event data in the presence of competing risks and time-dependent covariates

Results

Figure 1. Study Population



- 215 adults: median age 52 years, median BMI 33 kg/m^2, 77% non-Hispanic White, 65% female, and 62% with type 2 diabetes (T2DM) were included (Figure 1 and Table 1).
- Presence of T2DM was greater with index fibrosis stages of F2 or more (F0/F1=49%, F4=72%, p=0.02).
- Associations were noted between fibrosis stage and age at index (F0/F1=49, F4=56; p=0.01); no association was found between demographics, behavioral/lifestyle characteristics by disease progression subgroup.
- Participants within the stable/improving (S/I) fibrosis stage had a lower prevalence of progression to cirrhosis compared to those with worsening of fibrosis stage (S/I=34%, W=72%, p<0.0001) (Figure 3b).
- LT occurred during follow up among those with F3 (n=3, 5%) or F4 (n=14, 39%) at index (median time to LT: 7.5 and 3.3 years) (Figure 3a).
- F3 fibrosis stage and an indication of T2D at any time increased the risk of progression to cirrhosis compared to F0-1 and those with no indication of T2D, respectively (F3 vs. F0-1 HR: 2.0, 95% CI 1.3-3.1; T2D yes vs. no (HR: 2.1, 95% CI 1.4-3.2) (Figure 2).
- Higher fibrosis stage at any time had higher probability of developing decompensation during follow up (F2=0.5, F3=1.4, F4=4.1, vs. F0/F1).
- Older persons were more likely to have a CV event (HR=1.2, 95% CI 1.08, 1.41).
- Fibrosis worsening at any time was associated with higher incidence of cancer (Figure 3a, p-value=0.0672; Figure 3b, not significant).
- Among F0-F3, incidence rate of a composite event (all cause mortality, cirrhosis, hepatic encephalopathy, gastroesophageal variceal hemorrhage, HCC, liver transplant, MELD score change, all cause cancer excluding HCC and skin cancer, and cardiovascular events) after index was highest among index F3 followed by index F2 (incidence rate per 100 person years=13.4 and 9.67, respectively) (Figure 3a).

References: [1]Neuberger J, Patel J, Caldwell H, et al. (2020). Guidelines on the use of liver biopsy in clinical practice from the British Society of Gastroenterology, the Royal College of Radiologists and the Royal College of Pathology. *Gut,* 69 (8), 1382—1403. [2]Rinella ME, et al. (2023). Practice guidance on the clinical assessment and management of nonalcoholic fatty liver disease. *Hepatology*, 77 (5), 1797-1835. [3]Barritt AS 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*, 67, 33-38. [4]Barritt AS et al. (2024). High concordance between nonalcoholic fatty liver disease and metabolic dysfunction associated steatotic liver disease in the TARGET-NASH real world cohort. *ACG,* 10-14309.

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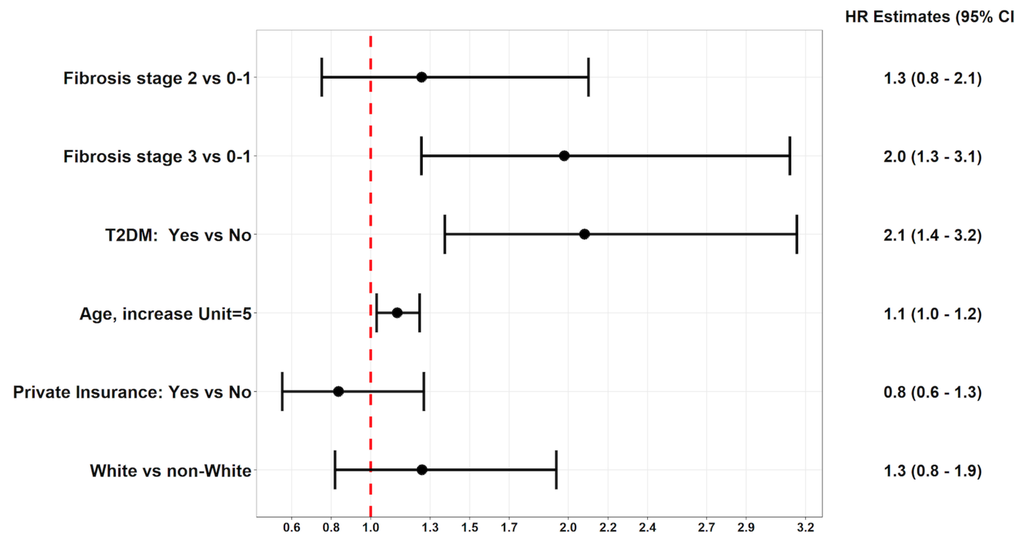
Results

Table 1. Demographics at Index Date

	Fibrosis stage per index histology				
	F0-F1 (N=80)	F2 (N=41)	F3 (N=58)	F4 (N=36)	Total (N=215)
Age at index date (years)					
Median	49	54	53	56	52
Q1-Q3 (IQR)	40-55 (15)	45-60 (15)	44-59 (15)	49-61 (13)	43-57 (14)
Female	59%	63%	79%	56%	65%
Race-Ethnicity, n (%)					
Hispanic/Latino	7 (9%)	6 (15%)	6 (10%)	5 (14%)	24 (11%)
Non-Hispanic White	67 (84%)	26 (63%)	47 (81%)	25 (70%)	165 (77%)
Non-Hispanic Black	4 (5%)	4 (10%)	1 (2%)	2 (6%)	11 (5%)
Non-Hispanic Asian	1 (1%)	3 (7%)	0 (0%)	0 (0%)	4 (2%)
Other/Not Reported	1 (1%)	2 (5%)	4 (7%)	4 (11%)	11 (5%)
BMI (kg/m^2)					
Median (n)	32 (79)	35 (38)	34 (56)	34 (35)	33 (208)
Q1-Q3 (IQR)	29-36 (7)	30-40 (10)	28-39 (11)	29-40 (11)	29-38 (9)
Type 2 Diabetes, n (%)	39 (49%)	29 (71%)	39 (67%)	26 (72%)	145 (67%)

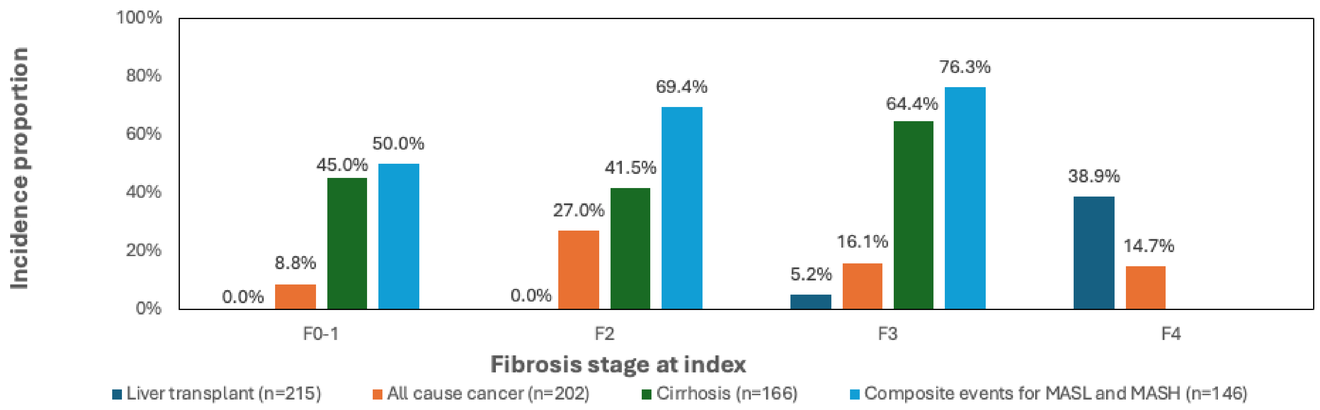
Figure 2. Progression from MASH without cirrhosis to MASH with cirrhosis



Note: Model was adjusted by fibrosis (time varying), age (time varying), type 2 diabetes (time varying), sex, private insurance and Non-Hispanic (NH) White vs. non-NH-White.

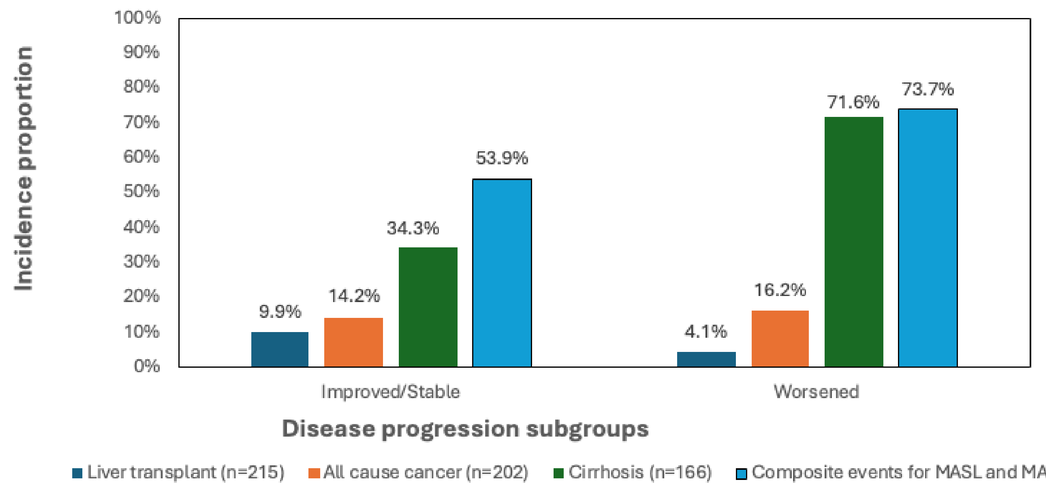
Figure 3. Incidence of Clinical Outcomes by Fibrosis Stage and Disease Progression Subgroups

a. Clinical incidence proportions by fibrosis stage



Note: Composite events includes progression to cirrhosis, decompensation, HCC, MELD score change, LT, CV event, all-cause mortality, or cancer.

b. Clinical incidence proportions by disease progression



Conclusions

- Higher fibrosis stage at index and fibrosis worsening over time were associated with higher risk of clinical outcomes: progression to cirrhosis, decompensation, and cancer.
- People with T2DM had an increased risk of progression to cirrhosis.
- These results, consistent with previous literature, demonstrate the association between fibrosis surrogate endpoints and clinical events in a real-world setting.

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, and multiple biopsies are infrequently conducted for a particular patient.
- This analysis is designed to maximize data available from participants with at least two biopsies enrolled in the TARGET-NASH study.