Characterizing the real-world clinical outcomes of patients with NASH without cirrhosis versus with cirrhosis

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Background

- Nonalcoholic steatohepatitis (NASH), also known as metabolic dysfunction-associated steatohepatitis (MASH), is characterized by fat accumulation and inflammation of the liver. This can result in scarring, development of cirrhosis and progression to other advanced liver diseases (including decompensated cirrhosis [DCC], hepatocellular carcinoma [HCC], and liver transplantation [LT]).[1]
- Data from clinical trials suggest approximately 20% of MASH patients progress to cirrhosis within two years of diagnosis and of those, it is estimated another 20% progress to more advanced liver diseases.[1,2]
- However, there is limited real-world evidence of the risk and clinical outcomes of progression to advanced liver diseases.

Objective

- **This analysis aimed to assess the risk of progression to advanced liver diseases or mortality among those with NASH and with versus without cirrhosis at baseline.**

Methods

- Eligible adults with ≥1 inpatient claim for NASH (ICD-10-CM K75.81) or ≥2 outpatient claims for NASH were identified from Optum's de-identified Clinformatics® Data Mart Database (CDM) (01Oct2015-31Dec2022). Patients with other causes of liver diseases, HIV, or exposure to heavy metals at any point were excluded.
- Index date was defined as 30 days following first diagnosis of NASH, to allow for delays in cirrhosis reporting at baseline. Two cohorts of patients were defined based on the presence of cirrhosis, classified by ≥1 code for cirrhosis, DCC, LT, or HCC, in the baseline period (6 months before and 1 month after index date).
  - This additional one-month window beyond index date was used to account for cirrhosis reporting delays at the time of NASH diagnosis.
- Patients were followed for ≥12 months (death was exempted), until end of follow-up defined by the first of: death, loss of follow-up, or study end.
- Patient demographics and baseline comorbidity burden were summarized categorically and continuously using summary statistics.
- Among those without cirrhosis at baseline, time to event analyses were performed using Kaplan Meier (KM) curves, as well as Cox proportional hazard (CoxPH) models adjusting for baseline characteristics, to estimate the risk of progressing to a composite clinical outcome.
  - Consistent with previous clinical trials, composite clinical outcome was defined by all-cause death or a significant hepatic event (cirrhosis, DCC, or LT).[3]
- Time to event analyses and the risk of all-cause death were estimated using similar methods, to quantify the risk associated with having cirrhosis at baseline; overall and stratified by risk of advanced liver disease (low risk= fibrosis-4(FIB-4) <1.0; intermediate risk= FIB-4 ≥1.0 to ≤3.25; high risk= FIB-4>3.25).
  - Mortality data in CDM are sourced from the Social Security Administration Death Master File, the Center for Medicare and Medicaid Services, obituary data, discharge data, electronic health records, and insurance enrollment data.
- All statistical analyses were performed within Optum's De-identified Data Workspace using the Jupyter Notebook.

Results

Cohort characteristics

- A total of 28,576 patients with NASH were included; 68.0% were free from cirrhosis and 32.0% had cirrhosis at baseline.
- Those without cirrhosis at baseline had longer mean follow-up (3.2 vs. 2.5 years), were younger (mean 59.8 vs. 67.1 years), and had a lower comorbidity burden than those with cirrhosis (**Table 1**).

Table 1. Characteristics of NASH patients with versus without cirrhosis

	Without cirrhosis (n=19,419)	With cirrhosis (n=9,157)
Follow-up per person, years, mean (SD)	3.2 (1.5)*	2.5 (1.6)
Age at index, years, mean (SD)	59.8 (13.4)*	67.1 (10.8)
Categorical age at index, years, n (%)		
≤44 years	2,815 (14.5)^	350 (3.8)
45-64 years	7,813 (40.2)	2,616 (28.6)
≥65 years	8,791 (45.3)	6,191 (67.6)
Sex, n (%)	-	-
Female	11,431 (58.9)^	5,999 (65.5)
Race, n (%)	-	-
Asian	871 (4.5)^	171 (1.9)
Black	1,380 (7.1)	654 (7.1)
Hispanic	3,648 (18.8)	1,376 (15.0)
White	12,647 (65.1)	6,447 (70.4)
Region, n (%)		
Northeast	2,180 (11.2)	787 (8.6)
Midwest	4,018 (20.7)	2,163 (23.6)
South	9,287 (47.8)	4,479 (48.9)
West	3,902 (20.1)	1,715 (18.7)
Comorbidities of interest, n (%)		
CVD	13,108 (67.5)*	7,790 (85.1)
T2DM	5,899 (30.4)*	5,209 (56.9)
Obesity	9,734 (50.1)*	4,820 (52.6)
Categorical FIB-4, n (%)		
Low risk (FIB-4 < 1.0)	2,210 (11.4)	291 (3.2)
Intermediate risk (1.0 ≤ FIB-4 ≤3.25)	4,391 (22.6)	1,579 (17.2)
High risk (FIB-4 > 3.25)	447 (2.3)	1,487 (16.2)
Unavailable	12,371 (63.7)	5,800 (63.3)

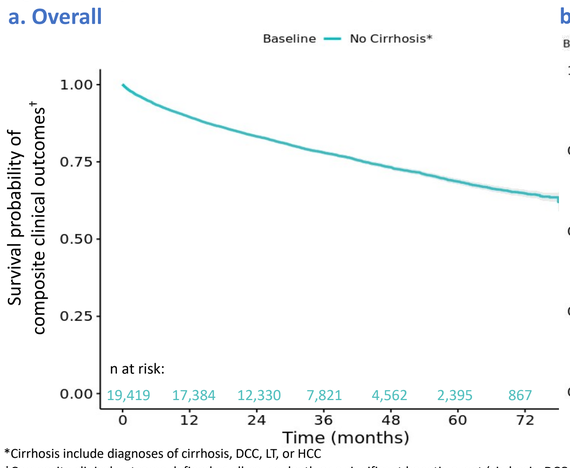
CVD, cardiovascular disease; SD, standard deviation; T2DM, type 2 diabetes mellitus. *P<0.01 when using two-tailed Student's T-Test to compare the means between cohorts with vs without cirrhosis. ^P<0.01 when using chi-squared test to compare the distribution categorical characteristics between the cohorts with vs. without cirrhosis.

Risk of composite clinical outcome

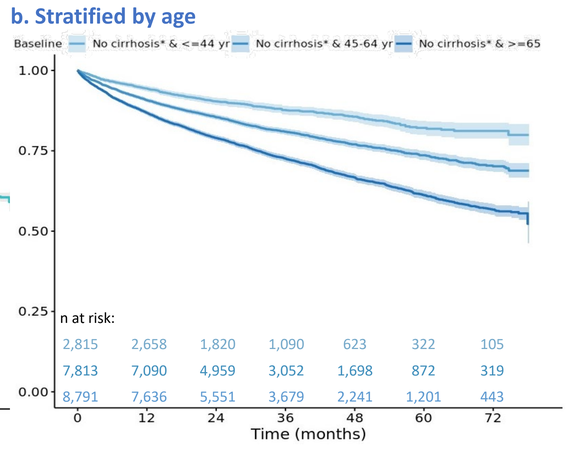
- Among those without cirrhosis at baseline, 23.1% (n=4,489) experienced the composite clinical outcome over follow-up. The risk (95% confidence interval, CI) of the composite outcome increased from 10.5% (10.1-10.9%) in year one to 31.4% (30.5-32.3%) by year five (**Figure 1**).
  - The risk of progressing to the composite outcome increased with increasing age.

Figure 1. Kaplan Meier curve for composite clinical outcomes in NASH patients without baseline cirrhosis

a. Overall



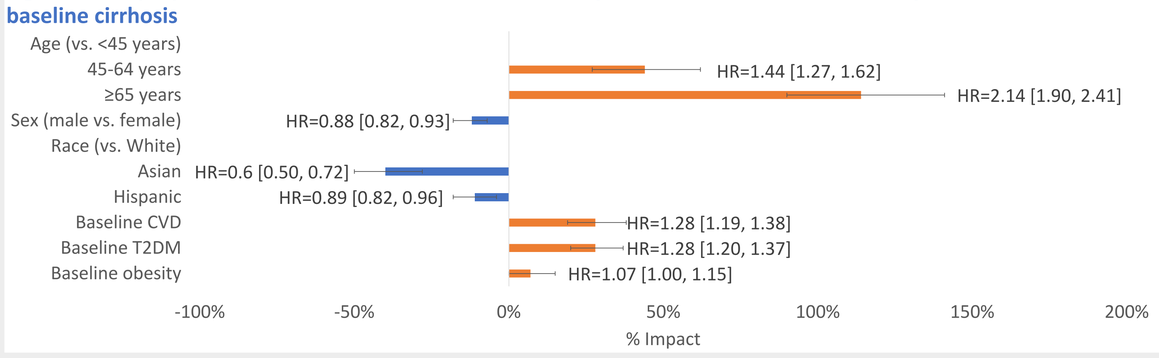
b. Stratified by age



*Cirrhosis include diagnoses of cirrhosis, DCC, LT, or HCC
†Composite clinical outcome defined as all-cause death or a significant hepatic event (cirrhosis, DCC, or LT)
DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LT, and liver transplantation.

- Among those without baseline cirrhosis, the risk of progressing to the composite outcome increased with age, baseline cardiovascular disease (CVD), or type-II diabetes mellitus (T2DM), or obesity (**Figure 2**).

Figure 2. Cox proportional hazards model estimates for composite clinical outcome in NASH patients without baseline cirrhosis



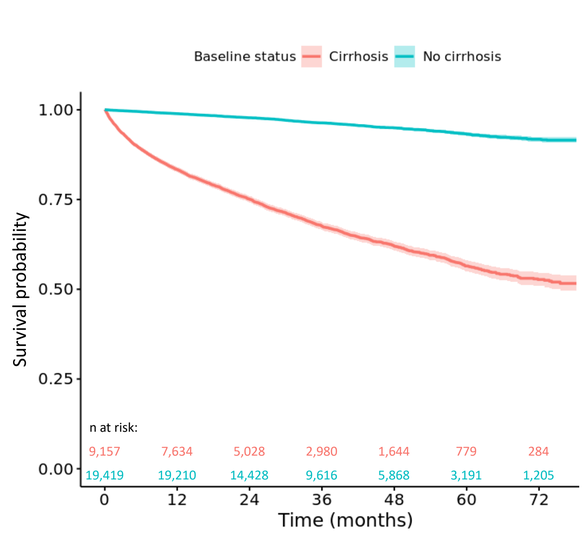
CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; T2DM, type 2 diabetes mellitus.
Note: region and Black race was also adjusted in the model, but not presented here due to lack of significance (P≥0.05) and space limitations

Risk of all-cause deaths

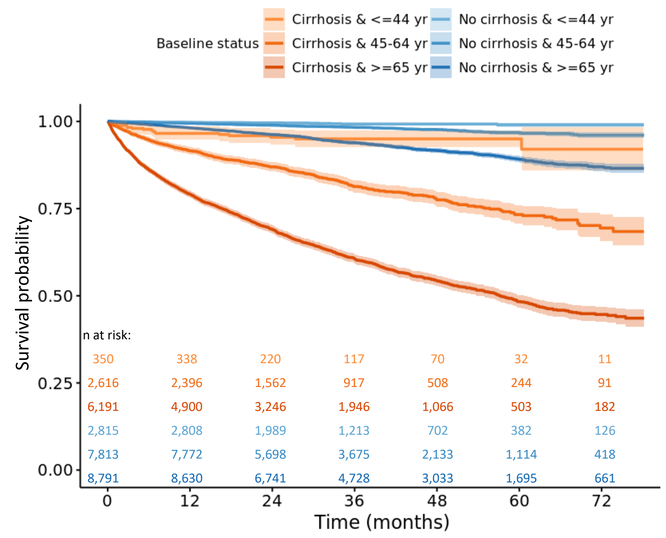
- Those with cirrhosis had a significantly higher risk of all-cause death over follow-up than those without cirrhosis, and this was consistently increasing with age in both those with and without baseline cirrhosis (**Figure 3**).

Figure 3. Kaplan Meier curve for all-cause death in NASH patients with vs. without baseline cirrhosis

a. Overall



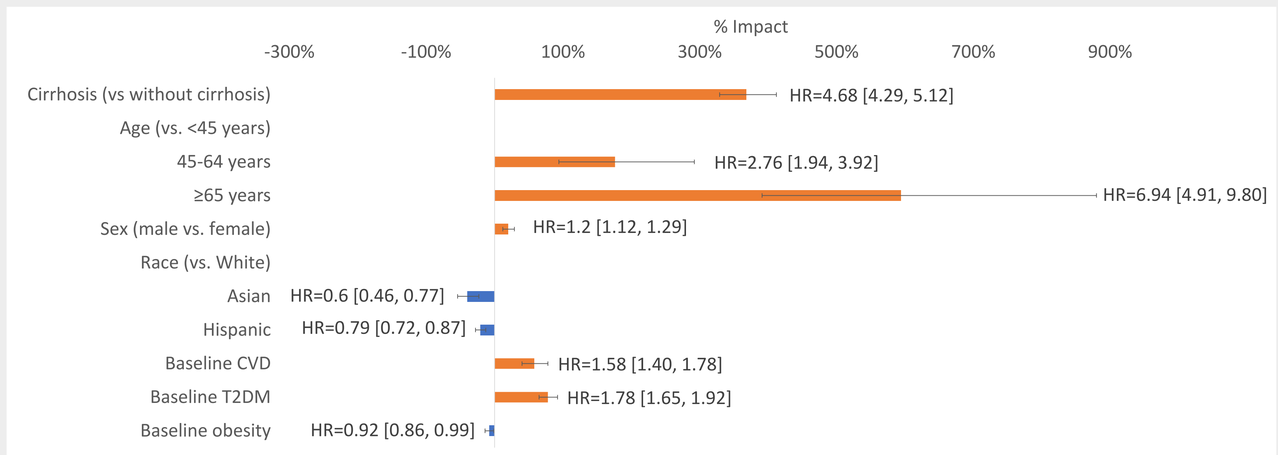
b. Stratified by age



DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LT, and liver transplantation.
*Cirrhosis include diagnoses of cirrhosis, DCC, LT, or HCC

- After adjusting for baseline covariates, the risk of all-cause death remained significantly higher among those with cirrhosis vs. without cirrhosis, with an overall HR (95% CI) of 4.7 (4.3-5.1), suggesting a close to five times higher risk of all-cause deaths (**Figure 4**).
  - Older age, male sex, and baseline CVD or T2DM were all associated with a significantly higher risk of all-cause death.

Figure 4. Cox proportional hazards model estimates for all-cause death in the entire NASH study population



CVD, cardiovascular disease; T2DM, type 2 diabetes mellitus.
Note: region and Black race was also adjusted for in the model, but not presented here due to lack of significance (P≥0.05) and space limitations

- Consistent with the overall study population, after adjusting for age, sex, race, region, and baseline CVD, T2DM, obesity, the risk of all-cause death was significantly higher for patients with cirrhosis, vs. those without cirrhosis, across stratifications by risk of advanced liver disease (**Table 2**).
  - The risk of all-cause death for patients with cirrhosis (vs. without) was greatest among those with intermediate risk of advanced liver disease (HR=3.7), followed by high risk (HR=3.2) and low risk (HR=2.7).

Table 2. Cox proportional hazards model estimates for all-cause death by FIB-4 risk level for NASH patients with vs. without cirrhosis

FIB-4 risk grouping	HR	95% CI	p value
Low risk (FIB-4 < 1.0)	2.71	[1.43, 5.14]	<0.01
Intermediate risk (FIB-4 ≥1.0 to ≤ 3.25)	3.73	[3.03, 4.58]	<0.01
High risk (FIB-4 > 3.25)	3.19	[2.40, 4.24]	<0.01

CI, confidence interval; FIB-4, fibrosis-4; HR, hazard ratio. Note: models adjusted for age, sex, race, region, and baseline CVD, T2DM, and obesity.

Discussion

- Findings from this retrospective claims analysis demonstrated the substantial clinical burden associated with MASH, especially among those with baseline cirrhosis or those who progress to cirrhosis.
- In the overall MASH study population, the risk of all-cause death was nearly five times higher for patients with cirrhosis than patients without cirrhosis. Risk of all-cause death also increased with time and was higher among older patients and those with baseline T2DM or CVD.
- Across categories of risk levels for advanced liver disease (defined by FIB-4), those with cirrhosis had a higher risk of death than those without. Risk was highest among those with intermediate risk of liver disease. While a lower magnitude was observed in the high-risk category, this may be driven by the relatively few non-cirrhosis patients captured within this category (6.3%).
- For patients with MASH and without cirrhosis at baseline, the risk of experiencing a significant hepatic event increased with time and was higher among older patients, and those with baseline T2DM or CVD.
- This study relied on a large, well validated database that has been used extensively for studies of clinical outcomes. [4,5]
- This retrospective database study relied on routinely collected claims data and is subject to data entry errors, missing data, and coding specificity limitations. Additionally, this study relied on the use of ICD-10-CM codes for identifying MASH patients and while this method is consistent with previous research, the diagnostic reference standard for NASH is liver biopsy.
- Nonetheless, therapies that slow MASH progression may help reduce risks for all-cause death and progression to other advanced liver diseases.

References

1.Sheka AC, Adeyi O, Thompson J, et al. *JAMA*. 2020;323(12):1175-1183. 2. Loomba R, Adams LA. *Hepatology*. 2019;70(6):1885-1888. 3. Karim G, Bansal MB. *touchREV Endocrinol*. 2023;19(1):60-70 4. Chen X, Affinati AH, Lee Y, et al. *Diabetes Care*. 2022;45(5):1170-1176. 5. Schulman IH, Chan K, Der JS, et al. *Am J Kidney Dis*. 2023;82(1):63-74.e61.

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