Metabolic dysfunction-associated steatohepatitis as a risk factor for hepatocellular carcinoma mortality

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Introduction

- Hepatocellular carcinoma (HCC) is a leading cause of cancer-related deaths worldwide.[1]
- Metabolic dysfunction-associated steatohepatitis (MASH), the most advanced form of metabolic dysfunction-associated steatotic liver disease (MASLD), has become one of the fastest growing risk factors of HCC in the US.[2]
- While studies suggest that patients with MASH who develop HCC may be at a higher risk of HCC mortality, evidence regarding this relationship among older adults (aged 65 and over) is limited.[3-5]

Aim

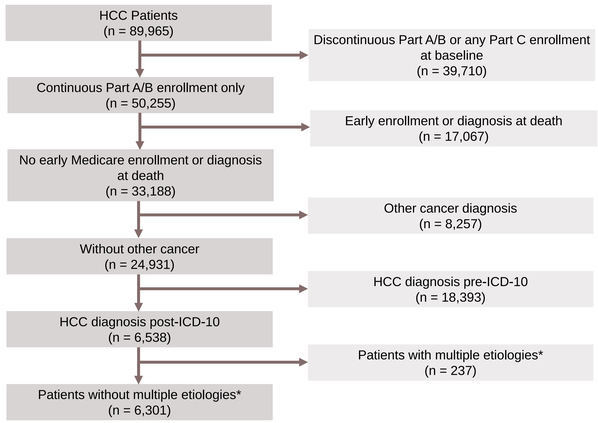
- To assess the differential risk of HCC-related death among patients with and without MASH within a competing risks framework using nationally representative data.

Method

Study Design and Setting

- A retrospective cohort study was conducted using SEER-Medicare linked data from October 1, 2015, through December 31, 2020.
- The study period consisted of the time from a patient's HCC diagnosis (index date) through the first of the following events: HCC death, non-HCC death, end of data availability, another censoring event, or dropout/loss to follow-up.
- The 12-month interval preceding the index date was used for sample selection (Figure 1) and covariate measurement.
- MASH was defined based on the presence of one inpatient or two outpatient claims with an ICD-10 K75.81 code as the primary or secondary diagnosis during the baseline period or within 30 days of the index date.
- Medicare beneficiary death date and SEER cause of death classification were used to establish timing and cause of death, respectively.

Figure 1: Sample Selection Diagram



*Defined as the presence of a confirmatory diagnosis for both MASH and at least one of the following conditions: alcoholism, alcoholic liver disease, toxic liver disease, viral hepatitis, chronic hepatitis unspecified, Wilson's disease, autoimmune hepatitis, Gaucher disease, primary biliary cholangitis, hemochromatosis, Alpha-1-antitrypsin deficiency, lipid storage disorders, or primary sclerosing cholangitis.

Analysis

- Crude cumulative incidence plots were produced using the nonparametric Aalen–Johansen estimator, an extension of the Kaplan-Meier method accounting for competing events.
- Potential bias due to the competing risk of non-HCC death was characterized and accounted for by fitting cause-specific (CS) hazard and Fine-Gray (FG) subdistribution hazard models.
- Due to the different risk sets being considered, the more etiologically relevant hazard ratios (HRs) from the CS models were used for main results, with estimates from the FG model providing insight into the extent to which differential non-HCC death rates may be driving this relationship.
- Proportional hazards and nonlinearity assumptions were assessed via Schoenfeld and Martingale residuals, respectively.

Results

Figure 2: Crude Cumulative Incidence of HCC Death by MASH Status

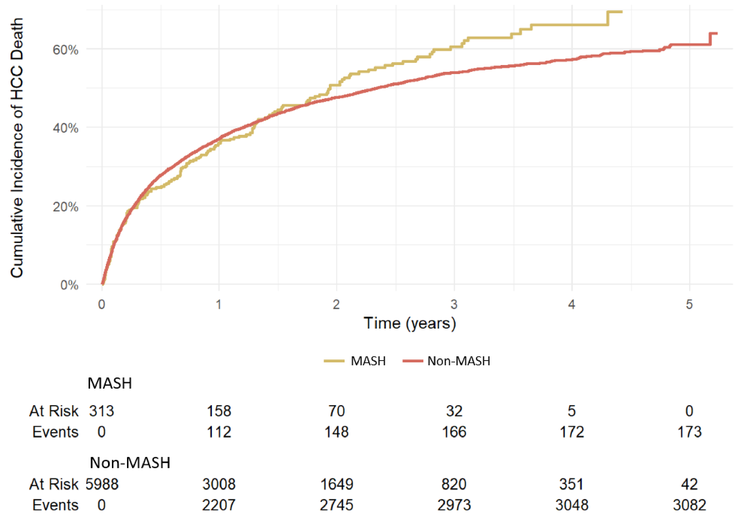


Table 1: Baseline Characteristics

Characteristic	MASH (n = 313)	Non-MASH (n = 5,988)	Overall (n = 6,301)
Age, mean (SD)	74.34 ± 5.65	75.1 ± 6.8	75.0 ± 6.8
Sex, female, n (%)	152 (48.56)	1,740 (29.06)	1,892 (30.0%)
Race, n (%)			
White	221 (70.61)	3,741 (62.47)	3,962 (62.88)
Black	4 (1.28)	492 (8.22)	496 (7.87)
Hispanic	57 (18.21)	929 (15.51)	986 (15.65)
Asian	17 (5.43)	610 (10.19)	627 (9.95)
Other	14 (4.47)	216 (3.61)	230 (3.65)
mCCI*, n (%)			
0	78 (24.92)	2,031 (33.92)	2,109 (33.47)
1	50 (15.97)	1,289 (21.53)	1,339 (21.25)
2+	185 (59.11)	2,668 (44.56)	2,853 (45.28)

*Modified Charlson Comorbidity Index (mCCI) - traditional CCI excluding HCC and cirrhosis

Table 2: HRs for HCC Death with Non-HCC Death as Competing Event

MASH vs Non-MASH*	HR	95% CI	p-value
Cause-Specific Hazard Model for HCC death	1.23	1.05, 1.44	**<0.01**
Cause-Specific Hazard Model for non-HCC death	1.19	0.90, 1.58	0.20
Subdistribution Hazard Model for HCC death	1.17	1.00, 1.38	0.05

*Models were adjusted for year of HCC diagnosis, age at HCC diagnosis, sex, race/ethnicity, cirrhosis status, HCC stage at diagnosis, and Charlson Comorbidity Index.

- The majority of patients (68.1%) died within 5 years of HCC diagnosis, with 76% of these deaths attributable to HCC.
- Median survival was less than one year from HCC diagnosis for both MASH and non-MASH patients.
- Crude HCC mortality rates were higher in patients with vs those without MASH (55.3% vs 51.5%), with the cumulative incidence of HCC death diverging after 2 years (Figure 2).
- MASH was significantly associated with a 23% higher risk of HCC mortality (adjusted CS HR, 1.23; 95% CI, 1.05-1.44) and a non-significant 19% higher risk of non-HCC mortality (adjusted CS HR, 1.19; 95% CI, 0.90-1.58) over the follow-up period (Table 2).
- The non-significant non-HCC death HR and minimal difference between the subdistribution and cause-specific HCC death HRs indicate that the impact of non-HCC death as a competing event appears to be limited in this setting.

Conclusions

- Clinically rich SEER-Medicare data and advanced survival analysis methodology were used to generate novel insight into the relationship between MASH and HCC death.
- The significantly higher risk of HCC death observed in MASH patients relative to other etiologies indicates that underlying liver damage may be more severe at HCC diagnosis, with the lack of effective treatment historically available for MASH compounding this effect over time.
- Main study limitations include limited follow-up post-ICD-10, MASH undercoding, Medicare-only generalizability, inability to identify fibrosis stage, and omitted variable bias. Residual analyses indicate that main model assumptions hold.

References

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