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Role of Metabolic Dysfunction-associated Steatohepatitis (MASH) as a Risk Factor for Hepatocellular Carcinoma (HCC) Development

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INTRODUCTION

- Primary liver cancer is a leading cause of morbidity and mortality worldwide, with HCC accounting for up to 80% of cases.[1]
- MASH, the progressive form of metabolic dysfunction-associated steatotic liver disease (MASLD), has become one of the fastest growing risk factors for HCC in the US.[2]
- While clinical evidence indicates that MASH predisposes an individual to HCC development in patients with cirrhosis as well as other stages of disease, the strength and nature of this relationship overall and with respect to other etiologies is less well understood.[3]

AIM

- To evaluate the role of MASH as a risk factor for HCC development in the US using nationally representative data.

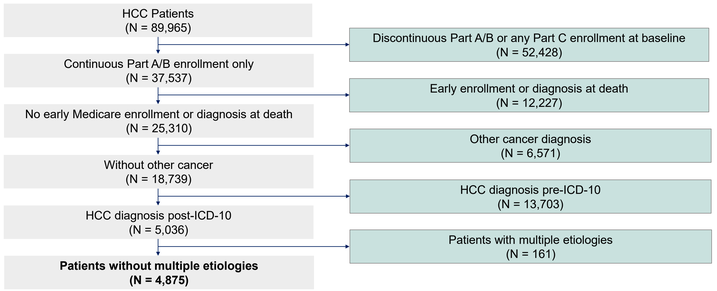
METHOD

- A matched case-control study was conducted using Surveillance, Epidemiology and End Results (SEER)-Medicare linked data from October 1, 2015, through December 31, 2020.
- Eligible controls (non-HCC cases) were matched to cases using k:1 exact matching without replacement based on birth year, race/ethnicity, and sex.
- The index date for cases was set at HCC diagnosis, with controls assigned the same index date of their matched case.
- The 36-month period preceding each patient's index date was used for sample selection, covariate measurement, and ascertainment of MASH status, defined by the ICD-10 code K75.81.
- Liver disease and cirrhosis diagnoses could occur within 30 days following a patient's index date to account for imprecision in claims-based timing.

METHOD

- Logistic regression with robust standard errors was used to calculate adjusted odds ratios (OR) and construct 95% confidence intervals (CI) controlling for matching factors (race/ethnicity, sex, birth year) and obesity, diabetes, cirrhosis, and index year.

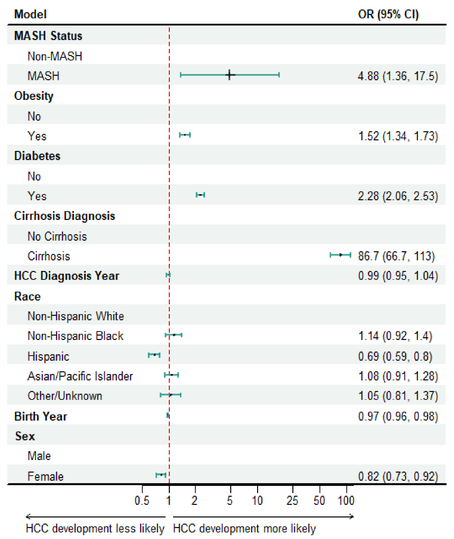
Figure 1: Sample Selection Diagram



RESULTS

- A total of 4,875 HCC cases were matched to 5,030 controls.
- Exposure status was highly skewed, with MASH identified in 5% of HCC cases compared to only 0.1% of controls.
- Among patients with MASH, 60% of controls and 94.6% of cases were diagnosed with cirrhosis as of their index date.
- MASH was significantly associated with a 4.88-fold increase in the odds of HCC development (95% CI: 1.36–17.5, p < 0.001).

Figure 2: Adjusted ORs and 95% CI for HCC development



Note: The x-axis is log-scaled to better incorporate the range of ORs. While the axis is transformed, the plotted ORs and CIs represent untransformed model estimates

Table 1: Characteristics of HCC cases and controls by MASH status

Characteristic	Non-HCC Controls (N = 5,030)		HCC Cases (N = 4,875)	
	Non-MASH (N = 5,025)	MASH (N = 5)	Non-MASH (N = 4,636)	MASH (N = 239)
Age				
Mean ± SD	76.8 ± 6.3	81.4 ± 7.6	77.0 ± 6.4	75.1 ± 5.3
Median [Min, Max]	76.0 [67.0, 100.0]	82.0 [69.0, 89.0]	76.0 [68.0, 100.0]	74.0 [68.0, 89.0]
Race				
Non-Hispanic White	3,295 (65.6%)	3 (60.0%)	2,997 (64.6%)	181 (75.7%)
Non-Hispanic Black	326 (6.5%)	1 (20.0%)	323 (7.0%)	2 (0.8%)
Hispanic	739 (14.7%)	1 (20.0%)	684 (14.8%)	37 (15.5%)
Asian/Pacific Islander	478 (9.5%)	0 (0.0%)	466 (10.1%)	9 (3.8%)
Other/Unknown	187 (3.7%)	0 (0.0%)	166 (3.6%)	10 (4.2%)
Sex				
Male	3,407 (67.8%)	4 (80.0%)	3,193 (68.9%)	121 (50.6%)
Female	1,618 (32.2%)	1 (20.0%)	1,443 (31.1%)	118 (49.4%)
mCCI				
0	2,268 (45.1%)	2 (40.0%)	1,631 (35.2%)	67 (28.0%)
1	1,016 (20.2%)	0 (0%)	898 (19.4%)	49 (20.5%)
2+	1,741 (34.6%)	3 (60.0%)	2,107 (45.4%)	123 (51.5%)
Cirrhosis Diagnosis				
Cirrhosis	170 (3.4%)	3 (60.0%)	3,385 (73.0%)	226 (94.6%)
No Cirrhosis	4,855 (96.6%)	2 (40.0%)	1,251 (27.0%)	13 (5.4%)
AFP Tumor Marker Test				
Yes	30 (0.6%)	2 (40.0%)	1,477 (31.9%)	134 (56.1%)
No	4,995 (99.4%)	3 (60.0%)	3,398 (68.1%)	105 (43.9%)
Diabetes				
Yes	1,600 (31.8%)	5 (100.0%)	2,505 (54.0%)	197 (82.4%)
No	3,425 (68.2%)	0 (0.0%)	2,131 (46.0%)	42 (17.6%)
Hypertension				
Yes	3,618 (72.0%)	5 (100.0%)	3,963 (85.5%)	221 (92.5%)
No	1,407 (28.0%)	0 (0.0%)	673 (14.5%)	18 (7.5%)
Obesity				
Yes	742 (14.8%)	3 (60.0%)	1,184 (25.5%)	131 (54.8%)
No	4,283 (85.2%)	2 (40.0%)	3,452 (74.5%)	108 (45.2%)
Hypercholesterolemia				
Yes	415 (8.3%)	2 (40.0%)	447 (9.6%)	20 (8.4%)
No	4,610 (91.7%)	3 (60.0%)	4,189 (90.4%)	219 (91.6%)
Hyperlipidemia				
Yes	3,173 (63.1%)	3 (60.0%)	2,965 (64.0%)	177 (74.1%)
No	1,852 (36.9%)	2 (40.0%)	1,671 (36.0%)	62 (25.9%)
Dyslipidemia				
Yes	2,000 (39.8%)	2 (40.0%)	2,206 (47.6%)	156 (65.3%)
No	3,025 (60.2%)	3 (60.0%)	2,430 (52.4%)	83 (34.7%)

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CONCLUSIONS

- In this analysis, clinically rich SEER-Medicare data were used to generate additional insight into the relationship between MASH and HCC development.
- Cirrhosis was found to be highly associated with HCC development, reflecting both the imbalance in cirrhosis status between cases and controls (74% vs 3%, respectively) and the often linear nature of liver disease progression.
- Results suggesting that MASH patients are at a higher risk of HCC relative to non-MASH patients highlight the importance of expanded surveillance and effective treatment in reducing the clinical burden of HCC in the MASH population.

DISCLOSURES/ACKNOWLEDGEMENTS

- YK is an employee of Madrigal Pharmaceuticals, Inc.
- SC, EZ, and AC are employees of Medicus Economics, LLC.
- RG performs as Consultant and/or Advisor to Madrigal Pharmaceuticals, Inc.

LIMITATIONS

- Main limitations include less stable estimates for MASH and cirrhosis status due to imbalance between cases and controls; limited generalizability to Medicare beneficiaries residing within SEER surveillance areas; potential omitted variable bias; and an inability to establish causality, capture fibrosis stage, or determine the method of HCC detection (e.g., screening).

CONTACT INFORMATION

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