Characteristics of NASH patients who develop hepatocellular carcinoma (HCC) with and without a corresponding cirrhosis diagnosis

EPH 288

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Background

- Primary liver cancer is a leading cause of morbidity and mortality worldwide, with HCC accounting for up to 80% of cases [1].
- Non-alcoholic steatohepatitis (NASH), or MASH, a progressed form of nonalcoholic fatty liver disease (NAFLD), has become one of the fastest growing HCC risk factors in the United States, with a cumulative annual HCC incidence of 2% - 13% in NASH cirrhosis patients [2].
- Although HCC occurs more frequently in cirrhosis patients, it's estimated that up to 50% of NASH HCC patients are non-cirrhotic at HCC diagnosis [3-4].
- Potential drivers of non-cirrhotic HCC identified in previous studies include obesity, type 2 diabetes, hypertension, elevated alanine aminotransferase (AA), age, and sex [3-5].
- Currently, limited evidence exists regarding which NASH patients are more likely to develop HCC without intermediate progression to cirrhosis.

Objective

- To describe the characteristics of NASH patients who are diagnosed with HCC in the absence of cirrhosis

Methods

Study Design and Setting

- We conducted a descriptive analysis using nationally representative SEER-Medicare linked data from Jan. 1, 1999, through Dec. 31, 2020.
- The study period consisted of the time from a patient's incident NAFLD or NASH diagnosis (index date) through their incident HCC diagnosis date.
- The 12-month interval preceding the index date served as the washout and baseline period for confirming incident NAFLD/NASH and the application of inclusion/exclusion criteria.

Exposure and Outcome

- Because a NASH-specific diagnosis code was not introduced until the release of ICD-10 in 2015, separate samples based on three case definitions were assessed to account for the limited follow-up post-ICD-10 and inability to differentiate between NAFLD and NASH patients pre-ICD-10.
  - ICD-10 NASH - presence of a claim/claims containing an ICD-10 NASH code from October 1, 2015, through the end of follow-up.
  - ICD-10 Switchover - presence of a claim/claims containing either an incident ICD-10 NASH code or an incident non-specific ICD-9 code with a subsequent ICD-10 NASH code for validation over the entire study period.
  - ICD-9/10 NAFLD - presence of a claim/claims containing any non-specific ICD-9 or ICD-10 NAFLD and NASH codes, with index date set at first observed claim with any one of these codes over the entire study period.
- Because SEER data only include diagnosis month and year, HCC diagnosis date was based on the first observed HCC Medicare claim within this time frame.
- Index NAFLD, NASH, and cirrhosis dates could occur prior to or within a 30-day window following HCC diagnosis to allow for measurement error in the timing of claims-based diagnoses.

Results

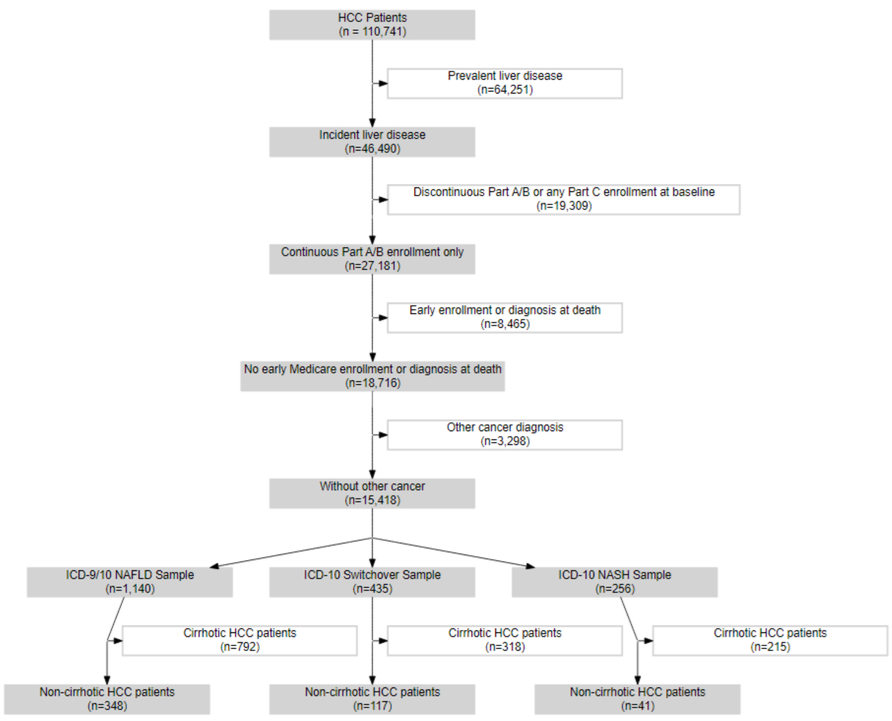

Figure 1. Sample Selection Diagram

- Among the three samples, 31% of NAFLD patients (n=348), 27% of ICD-10 switchover patients (n=117), and 16% of ICD-10 NASH (n=41) patients did not have a cirrhosis diagnosis prior to or within 30 days of their HCC diagnosis.
- Average time-to-HCC diagnosis ranged from 0.06 to 3.3 years in non-cirrhotic NASH and NAFLD patients, respectively. Over 50% of NASH and Switchover patients received their index diagnosis ≤30 days following HCC diagnosis, with both likely a function of delayed detection and, in the NASH sample, the select population being considered.
- Across all three samples, almost all patients had hypertension (≥92%). Patients were also older (average age at NAFLD or NASH diagnosis >73) and more likely to be male (>64%), Non-Hispanic White (>69%), and have type 2 diabetes (>69%) or hyperlipidemia (>75%).
- Non-cirrhotic NASH patients were less likely to have undergone clinical testing prior to HCC diagnosis, potentially due to a shorter time-to-HCC diagnosis, and more likely to have a metabolic disorder (17%), be obese or overweight (97.6%), and to not have elevated AA.

Table 1. Demographic and Clinical Characteristics

	ICD-10 NASH Sample (N=41)	ICD-10 Switchover Sample (N=117)	ICD-9/10 NAFLD Sample (N=348)
Age			
Mean (SD)	73.9 (6.13)	73.4 (5.51)	74.2 (5.80)
Median [Min, Max]	73.0 [66.0, 89.0]	72.0 [66.0, 89.0]	74.0 [66.0, 91.0]
Race/Ethnicity			
Non-Hispanic White	30 (73.2%)	78 (66.7%)	243 (69.8%)
Non-Hispanic Black	0 (0%)	2 (1.7%)	11 (3.2%)
Hispanic	3 (7.3%)	20 (17.1%)	57 (16.4%)
Asian/Pacific Islander	7 (17.1%)	11 (9.4%)	29 (8.3%)
Other/Unknown	1 (2.4%)	6 (5.1%)	8 (2.3%)
Sex			
Male	27 (65.9%)	80 (68.4%)	224 (64.4%)
Female	14 (34.1%)	37 (31.6%)	124 (35.6%)
Modified Charlson Comorbidity Index			
0	12 (29.3%)	50 (42.7%)	157 (45.1%)
1	9 (22.0%)	27 (23.1%)	79 (22.7%)
2+	20 (48.8%)	40 (34.2%)	112 (32.2%)
Time to HCC Diagnosis (years)			
Mean (SD)	0.0628 (0.544)	1.53 (2.90)	3.28 (4.14)
Median [Min, Max]	-0.0422 [-0.0822, 2.90]	-0.0192 [-0.0822, 11.3]	1.15 [-0.0822, 15.7]
Liver transplant			
Yes	0 (0%)	0 (0%)	0 (0%)
No	41 (100%)	117 (100%)	348 (100%)
Alpha Fetoprotein (AFP) Tumor Marker Test			
Yes	4 (9.8%)	31 (26.5%)	160 (46.0%)
No	37 (90.2%)	86 (73.5%)	188 (54.0%)
Des-gamma-carboxy prothrombin Test			
Yes	0 (0%)	2 (1.7%)	2 (0.6%)
No	41 (100%)	115 (98.3%)	346 (99.4%)
Alpha-Fetoprotein L3% Test			
Yes	1 (2.4%)	3 (2.6%)	4 (1.1%)
No	40 (97.6%)	114 (97.4%)	344 (98.9%)

Table 2. Potential Risk Factors Associated with Non-Cirrhotic HCC

	ICD-10 NASH Sample (N=41)	ICD-10 Switchover Sample (N=117)	ICD-9/10 NAFLD Sample (N=348)
Type 2 Diabetes			
Yes	33 (80.5%)	91 (77.8%)	242 (69.5%)
No	8 (19.5%)	26 (22.2%)	106 (30.5%)
Hypertension			
Yes	38 (92.7%)	108 (92.3%)	320 (92.0%)
No	3 (7.3%)	9 (7.7%)	28 (8.0%)
Metabolic Disorder			
Yes	7 (17.1%)	11 (9.4%)	22 (6.3%)
No	34 (82.9%)	106 (90.6%)	326 (93.7%)
Obesity			
Yes	25 (61.0%)	63 (53.8%)	112 (32.2%)
No	16 (39.0%)	54 (46.2%)	236 (67.8%)
Overweight			
Yes	15 (36.6%)	27 (23.1%)	23 (6.6%)
No	26 (63.4%)	90 (76.9%)	325 (93.4%)
Elevated Alanine Aminotransferase			
Yes	4 (9.8%)	25 (21.4%)	81 (23.3%)
No	37 (90.2%)	92 (78.6%)	267 (76.7%)
Hypercholesterolemia			
Yes	17 (41.5%)	44 (37.6%)	170 (48.9%)
No	24 (58.5%)	73 (62.4%)	178 (51.1%)
Hyperlipidemia			
Yes	32 (78.0%)	88 (75.2%)	263 (75.6%)
No	9 (22.0%)	29 (24.8%)	85 (24.4%)

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Conclusions

- **Clinically rich SEER-Medicare data were used to generate novel insight into the characteristics of non-cirrhotic NAFLD and NASH HCC patients.**
- **Results indicate that 16% of NASH and 31% of NAFLD patients present with HCC in the absence of cirrhosis. Hypertension and diabetes were prevalent in both groups, with non-cirrhotic NASH patients more likely to be obese, have a shorter time-to-HCC diagnosis, have an underlying metabolic disorder, and less likely to have elevated Alanine Aminotransferase.**
- **Main study limitations include limited follow-up period in the ICD-10 NASH sample, reliance on claims-based coding, which does not reflect disease onset and may be more indicative of delays in NASH/NAFLD diagnosis among non-cirrhotic HCC patients, Medicare-only generalizability, and omitted variable bias.**