Comparative Analysis of Nonalcoholic Steatohepatitis– Versus Viral Hepatitis– and Alcohol-Related Liver Disease–Related Hepatocellular Carcinoma

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ABSTRACT

Background: Despite an increasing burden of nonalcoholic steatohepatitis (NASH), limited data are available comparing outcomes of NASH-related hepatocellular carcinoma (HCC) versus other etiologies. **Methods:** Patient demographic and tumor characteristics were collected for 1,051 patients diagnosed with NASH-, alcohol-related liver disease (ALD)-, hepatitis C virus (HCV)-, and hepatitis B virus (HBV)-related HCC at 2 large health systems from January 2008 through December 2016. Patient demographics, clinical characteristics, and survival were compared. Risk-adjusted treatment receipt and overall survival (OS) were examined using multivariable analysis. **Results:** A total of 92 patients with NASH-related HCC were compared with 153 patients with ALD-, 719 with HCV-, and 87 with HBV-related HCC. Patients with NASH were older, more likely female, and more likely Hispanic white. Patients with NASH and HBV had more compensated liver disease than those with ALD or HCV, including significantly higher proportions having noncirrhotic HCC. Despite similar surveillance receipt and Barcelona Clinic Liver Cancer (BCLC) tumor stage at diagnosis, patients with NASH had higher rates of curative-intent therapy than those with other diseases. Unadjusted median OS was 16 months for NASH, 15 months for ALD, 14 months for HCV, and 8 months for HBV. In multivariable analysis, NASH was associated with worse OS compared with ALD (hazard ratio, 1.92; 95% CI, 1.3–2.5), but there was no difference between NASH- and HCV- or HBV-related HCC. **Conclusions:** Patients with NASH-related HCC present with more preserved liver function, including a higher proportion having noncirrhotic HCC, than other diseases. Despite patients having similar tumor stage at diagnosis, NASH is independently associated with worse survival compared with ALD, but similar survival compared with HCV and HBV.

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Background

Hepatocellular cancer (HCC) is the seventh most common cancer and the fourth leading cause of cancer-related death worldwide.¹ HCC is the most common type of primary liver cancer and the fastest growing cause of cancer-related deaths in the United States.^{1–4} Typically occurring in a background of chronic liver disease and cirrhosis, the most common risk factors worldwide have traditionally included hepatitis B virus (HBV), hepatitis C virus (HCV), and alcohol-related liver disease (ALD).⁵ However, in the past decade, due to increasing rates of obesity and metabolic syndrome, nonalcoholic steatohepatitis (NASH) has emerged as the fastest growing risk factor for the development of HCC.^{6–12}

Despite the increasing global burden of NASH and causative link to HCC, limited data are available comparing outcomes of NASH-related HCC and viral hepatitis (HBV and HCV) and ALD etiologies. Currently, the largest published outcomes-based report used the SEER data set and demonstrated that NASH-related HCC is associated with worse overall survival (OS) than HCC in patients with cirrhosis from viral hepatitis or ALD.⁶ However, due to the inherent limitations of administrative data sets for studying HCC (eg, lack of granular data regarding tumor stage or underlying liver function), the ability to draw definitive conclusions from this study is limited.¹³ Previous studies using nonadministrative data have attempted to clarify differences in outcomes between HCC etiologies after adjusting for tumor stage and underlying liver function, but are limited by a paucity of patients and lack of racial/ethnic diverse patient cohorts.^{7,11,14}

Therefore, the aim of our study was to compare the clinical presentation, treatment, and survival of NASH-related HCC with HCC in the setting of viral hepatitis and ALD using a prospectively maintained HCC database from 2 large health systems with a diverse patient population.

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Methods

Patient Population

Following Institutional Review Board approval, we retrospectively queried a prospectively maintained HCC database identifying all adult patients newly diagnosed with HCC from January 2008 through December 2016 at 2 health systems: Parkland Memorial Health and Hospital System, a safety-net hospital, and UT Southwestern Medical Center, a tertiary referral center. Both health systems have multidisciplinary clinics and conferences, staffed by UT Southwestern faculty from transplant hepatology, surgical oncology, medical oncology, and interventional radiology.¹⁵ HCC diagnosis was based on the American Association for the Study of Liver Diseases (AASLD) criteria as previously described.^{16,17} Patients were excluded if imaging studies were not available to characterize tumor burden or if they had received prior treatment at an outside institution. HBV and HCV etiologies were confirmed by serologies (HBV surface antigen or DNA positivity; HCV antibody or RNA positivity); ALD by heavy alcohol consumption history (>3 drinks per day for men and >2 drinks per day for women, as best determined per medical record review) and absence of other coexisting chronic liver disease; and NASH by demonstration of hepatic steatosis by imaging or biopsy, exclusion of significant alcohol consumption, and absence of coexisting chronic liver disease.¹⁸ Patients with HCC and other etiologies of chronic liver disease were excluded from the study.

Data Collection

A retrospective review of each patient's medical record was performed to obtain patient demographics, clinical history, laboratory data, and imaging results. Laboratory data included alpha-fetoprotein, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, platelet count, and international normalized ratio (INR). Tumor characteristics of interest included the number of lesions, maximum tumor diameter, lymph node involvement, portal vein invasion, presence of extrahepatic metastases, and tumor stage at diagnosis. The Barcelona Clinic Liver Cancer (BCLC) system was used for tumor staging.¹⁰

Comorbid conditions such as metabolic syndrome, hyperlipidemia, diabetes, hypertension, and obesity were confirmed by vital reports, laboratory tests, and medication review and were in accordance with the National Cholesterol Education Program Adult Treatment Panel III definition of metabolic syndrome.¹⁹ Absence of cirrhosis was defined by Mittal et al²⁰ as: (1) level 1 evidence of noncirrhosis as no evidence of cirrhosis on a resection specimen or liver biopsy within 1 year of HCC diagnosis and no features suggestive of cirrhosis on abdominal imaging within 3 years before HCC diagnosis or (2) level 2

evidence of noncirrhosis as AST to platelet ratio index <1 based on laboratory values within 6 months before and 4 weeks after HCC diagnosis and no features suggestive of cirrhosis on abdominal imaging within 3 years before HCC diagnosis and 2 of 3 test values in the normal range (albumin >3.5 g/L, platelets >200,000/mL, or INR <1.1) within 6 months before and 4 weeks after HCC diagnosis.

Clinical history of interest included HCC-directed treatments and OS. HCC treatment was categorized as none, curative (transplantation, surgical resection, or ablative techniques), locoregional (transarterial embolization [TACE], yttrium 90, or TARE [transarterial radioembolization], or radiation therapy), or systemic (sorafenib, regorafenib, or clinical trial of systemic therapy). If a patient received multiple treatments, they were classified by the most definitive type of therapy received. For example, if a patient received TACE and liver transplantation, they were classified as having received curative-intent therapy.

Statistical Analysis

Chi-square tests and analysis of variance were used to compare categorical and continuous variables of the study population, stratified by etiology. Logistic regression models were used to evaluate the association between etiology and receipt of curative-intent therapy in patients with BCLC stage 0 or A HCC. Survival analysis was performed by Kaplan-Meier method with log-rank univariate analysis. Patients were censored at time of death, last clinic visit, or end of study period (September 2017). All variables significant in the univariate analysis (log-rank $P < .05$) were placed in the multivariable model. Hazard ratios (HRs) and P values for the multivariable model were obtained using Cox proportional hazard regression. All tests were 2-sided and performed at the 5% significance level. Statistical analysis was performed using SPSS, version 22 (SPSS Inc).

Figure 1. Proportion of total HCC cases comprised by each etiology, stratified by time period.

Abbreviations: ALD, alcohol-related liver disease; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; NASH, nonalcoholic steatohepatitis.

Table 1. Clinicopathologic and Treatment Factors

Factor	NASH (n=92)	ALD (n=153)	HCV (n=719)	HBV (n=87)	P Value
Age, y (SD)	67.9 (10.8)	59.7 (9.0)	58.2 (6.8)	54.0 (10.7)	<.001
Sex, n (%)					<.001
Female	51 (55.4)	13 (8.5)	139 (19.3)	12 (13.8)	
Male	41 (44.6)	140 (91.5)	580 (80.7)	75 (86.2)	
Race/Ethnicity, n (%)					<.001
Non-Hispanic white	34 (37.0)	49 (32.0)	247 (34.4)	20 (23.0)	
Non-Hispanic black	5 (5.4)	16 (10.5)	303 (42.1)	33 (37.9)	
Hispanic white	49 (53.3)	87 (56.9)	144 (20.0)	7 (8.0)	
Asian	4 (4.3)	1 (0.7)	25 (3.5)	27 (31.0)	
Insurance, n (%)					<.001
Uninsured	9 (9.8)	17 (11.1)	71 (9.9)	9 (10.3)	
Medicare	6 (6.5)	22 (14.4)	177 (24.6)	18 (20.7)	
Medicaid	42 (45.7)	51 (33.3)	172 (23.9)	18 (20.7)	
Private	11 (12.0)	27 (17.6)	96 (13.4)	15 (17.2)	
Other	24 (26.1)	36 (23.5)	203 (28.2)	27 (31.0)	
Hospital setting, n (%)					<.001
Safety-net	49 (53.3)	101 (66.0)	532 (74.0)	70 (80.5)	
Tertiary care	43 (46.7)	52 (34.0)	187 (26.0)	17 (19.5)	
ECOG performance status, n (%)					.291
0	52 (56.5)	75 (49.0)	375 (52.2)	44 (50.6)	
1	20 (21.7)	52 (34.0)	202 (28.1)	27 (31.0)	
≥2	20 (21.7)	23 (15.0)	138 (19.2)	16 (18.4)	
Unknown	0	3 (2.0)	4 (0.6)	0	
BMI group, n (%)					<.001
<25	12 (13.0)	44 (28.8)	268 (37.3)	45 (51.7)	
25–29	33 (35.9)	57 (37.3)	244 (33.9)	20 (23.0)	
≥30	47 (51.1)	49 (32.0)	195 (27.1)	18 (20.7)	
Unknown	0	3 (2.0)	12 (1.7)	4 (4.6)	
Diabetes mellitus, n (%)					<.001
No	22 (23.9)	96 (62.7)	518 (72.0)	69 (79.3)	
Yes	70 (76.1)	57 (37.3)	201 (28.0)	18 (20.7)	
Hypertension, n (%)					<.001
No	7 (7.6)	59 (38.6)	262 (36.4)	51 (58.6)	
Yes	85 (92.4)	93 (60.8)	456 (63.4)	36 (41.4)	
Hyperlipidemia, n (%)					<.001
No	39 (42.4)	88 (57.5)	438 (60.9)	57 (65.5)	
Yes without statin	19 (20.7)	45 (29.4)	220 (30.6)	24 (27.6)	
Yes with statin	34 (37.0)	20 (13.1)	61 (8.5)	6 (6.9)	
Metabolic syndrome, n (%)					<.001
No	18 (19.6)	95 (62.1)	516 (71.8)	74 (85.1)	
Yes	74 (80.4)	58 (37.9)	203 (28.2)	13 (14.9)	

(continued on next page)

Abbreviations: AFP, alpha-fetoprotein; ALD, alcohol-related liver disease; BCLC, Barcelona Clinic Liver Cancer; BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus; IQR, interquartile range; NASH, nonalcoholic steatohepatitis; SBRT, stereotactic body radiation therapy; TACE, transarterial embolization.

Table 1. Clinicopathologic and Treatment Factors (cont.)

Factor	NASH (n=92)	ALD (n=153)	HCV (n=719)	HBV (n=87)	P Value
Child-Pugh score, n (%)					<.001
A	56 (60.9)	45 (29.4)	341 (47.4)	52 (59.8)	
B	27 (29.3)	71 (46.4)	285 (39.6)	28 (32.2)	
C	9 (9.8)	37 (24.2)	93 (12.9)	7 (8.0)	
Cirrhosis, n (%)					<.001
No	15 (16.3)	8 (5.2)	48 (6.7)	13 (14.9)	
Level 1 noncirrhosis (% of no)	13 (86.7)	4 (50.0)	25 (52.1)	9 (69.2)	
Level 2 noncirrhosis (% of no)	2 (13.3)	4 (50.0)	23 (41.9)	4 (30.8)	
Yes	77 (83.7)	145 (94.8)	671 (93.3)	74 (85.1)	
Platelet count, median (SD)	141.5 (85.2)	102.0 (105.6)	120.0 (84.0)	149.0 (98.7)	<.001
Total bilirubin, median (SD)	0.9 (3.9)	1.8 (3.5)	1.1 (2.9)	0.9 (3.1)	.029
AFP, median (IQR)	6.7 (3–611)	12.3 (4–509)	63.0 (11–939)	336.0 (8–5,824)	<.001
Surveillance within 12 months, n (%)					.916
No	70 (76.1)	113 (73.9)	559 (77.7)	68 (78.2)	
Yes	18 (19.6)	32 (20.9)	133 (18.5)	17 (19.5)	
Unknown	4 (4.3)	8 (5.2)	27 (3.8)	2 (2.3)	
Tumor size, median (SD)	4.1 (4.9)	3.8 (4.3)	3.7 (5.3)	4.7 (5.3)	.049
Number of nodules, median (SD)	1.0 (1.2)	1.0 (1.1)	1.0 (1.1)	1.0 (0.9)	.502
BCLC stage, n (%)					.149
0/A	44 (47.8)	57 (37.3)	299 (41.6)	33 (37.9)	
B	18 (19.6)	21 (13.7)	112 (15.6)	13 (14.9)	
C	17 (18.5)	31 (20.3)	159 (22.1)	26 (29.9)	
D	13 (14.1)	44 (28.8)	149 (20.7)	15 (17.2)	
Definitive treatment, n (%)					.001
None	24 (26.1)	59 (38.6)	236 (32.8)	32 (36.8)	
Curative	40 (43.5)	36 (23.5)	205 (28.5)	24 (27.6)	
Transplantation	9 (9.8)	14 (9.2)	51 (7.1)	1 (1.1)	
Resection	17 (18.5)	6 (3.9)	82 (11.4)	16 (18.4)	
Ablation	14 (15.2)	16 (10.5)	72 (10.0)	7 (8.0)	
Locoregional	20 (21.7)	47 (30.7)	193 (26.8)	21 (24.1)	
TACE	18 (19.6)	46 (30.1)	175 (24.3)	20 (23.0)	
SBRT	2 (2.2)	1 (0.7)	2 (0.3)	1 (1.1)	
Yttrium 90	0	0	16 (2.2)	0	
Systemic	8 (8.7)	11 (7.2)	85 (11.8)	10 (11.5)	

Abbreviations: AFP, alpha-fetoprotein; ALD, alcohol-related liver disease; BCLC, Barcelona Clinic Liver Cancer; BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus; IQR, interquartile range; NASH, nonalcoholic steatohepatitis; SBRT, stereotactic body radiation therapy; TACE, transarterial embolization.

Results

Patient Sample

A total of 1,051 patients were identified as meeting inclusion criteria during the study period: 719 (68.4%) HCV-related HCC, 153 (14.6%) ALD-related HCC, 92 (8.8%) NASH-related HCC, and 87 (8.3%) HBV-related HCC.

No significant change was seen in the proportion of HCC cases related to individual etiologies over time. In

the time period from 2008 to 2010, the proportion of NASH-related HCC nearly doubled from 5.5% of all HCC cases to 9.5% in the most recent time period; however, this was not statistically significant when compared with proportions of all etiologies by time period (Figure 1). When comparing absolute incidence of only NASH cases over time, there was a significant increase of new cases over time (15.2% of all NASH cases were diagnosed

from 2008–2010, 43.5% from 2011–2013, and 41.3% from 2014–2016; $P=.001$).

Clinicopathologic Features

Table 1 describes the differences in clinicopathologic features among included patients. Patients with NASH-related HCC were significantly older and more likely female than those with other etiologies. Patients with ALD and NASH were more likely to be Hispanic white and less likely to be Non-Hispanic black than those with HCV- or HBV-related HCC. As expected, patients with NASH-related HCC had higher rates of metabolic syndrome than those with ALD-, HCV-, and HBV-related etiologies. Patients with NASH and HBV had more preserved liver function as measured by Child-Pugh A score, less portal hypertension as reflected by median platelet count, and higher proportions of noncirrhotic HCC. In a sensitivity analysis only including level 1 evidence for noncirrhosis, NASH-related HCC continued to have the highest proportion of noncirrhosis (16% vs 3% for ALD-, 4% for HCV-, and 11% for HBV-related HCC; $P<.001$). No difference was seen in HCC surveillance rates within 12 months before HCC diagnosis or BCLC tumor staging among all etiologies; however, patients with NASH and HBV had larger median tumor size.

Treatment Patterns

Despite similar tumor stage between HCC etiologies, a higher proportion of patients with NASH-related HCC underwent curative-intent therapy than those with ALD-, HCV-, and HBV-related HCC. Table 2 represents odds of receiving curative-intent therapy. Patients with NASH-related HCC were significantly more likely to receive curative-intent therapy than those with ALD-related HCC (OR, 0.415; 95% CI, 0.21–0.83). Although patients with NASH-related HCC also appeared more likely to receive curative-intent therapy than those with viral hepatitis-related HCC, this difference did not reach statistical significance. As expected, patients with BCLC stage B (OR, 0.109; 95% CI, 0.07–0.18), stage C (OR, 0.027; 95% CI, 0.01–0.06), and stage D HCC (OR, 0.068; 95% CI, 0.04–0.12) were less likely to receive curative-intent therapy compared with those with BCLC stage 0/A HCC. Age, race/ethnicity, insurance status, and surveillance in patients with BCLC stage 0/A HCC were not independently associated with receipt of curative-intent therapy.

Overall Survival

Figure 2A represents unadjusted OS of the entire cohort. Median OS was 16 months for NASH-, 15 months for ALD-, 14 months for HCV-, and 8 months for HBV-related HCC ($P=.030$). Patients with HCV-related HCC who had achieved sustained viral response after direct-acting antiviral therapy had improved OS compared with those with untreated HCV (26 vs 12 months; $P<.001$). Respective

Table 2. Multivariable Analysis of Patient, Tumor, and Treatment Variables Associated With Odds of Curative-Intent Therapy Receipt

Variable	OR	95% CI	P Value
Age	1.002	0.98–1.03	.850
Race/Ethnicity			
Non-Hispanic white	Ref		
Non-Hispanic black	1.107	0.73–1.68	.633
Hispanic white	0.774	0.49–1.22	.270
Asian	1.190	0.53–2.66	.671
Insurance			
Uninsured	Ref		
Medicaid	0.920	0.45–1.88	.819
Medicare	1.680	0.84–3.38	.145
Private	1.395	0.64–3.06	.407
Other	1.666	0.86–3.21	.127
Etiology of HCC			
NASH	Ref		
ALD	0.415	0.21–0.83	.013
HCV	0.603	0.33–1.10	.099
HBV	0.594	0.25–1.40	.235
Surveillance within 12 months			
No	Ref		
Yes	1.360	0.92–2.02	.128
BCLC stage			
0/A	Ref		
B	0.109	0.07–0.18	<.001
C	0.027	0.01–0.06	<.001
D	0.068	0.04–0.12	<.001

Abbreviations: ALD, alcohol-related liver disease; BCLC, Barcelona Clinic Liver Cancer; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; NASH, nonalcoholic steatohepatitis; OR, odds ratio.

1-, 3-, and 5-year survival rates were 57%, 37%, and 21% for NASH-; 56%, 34%, and 24% for ALD-; 52%, 28%, and 18% for HCV-; and 41%, 18%, and 13% for HBV-related HCC. In subgroup analysis, no significant difference in OS between liver disease etiologies was seen among patients with BCLC stage 0/A or B HCC ($P=.352$ and $P=.413$, respectively; Figure 2B and C); however, HCV-related HCC was associated with improved OS compared with ALD-, HBV-, and NASH-related HCC among those with BCLC stage C HCC (5 vs 4, 3, and 3 months, respectively; $P=.005$; Figure 2D).

Table 3 represents a multivariable analysis of clinicopathologic variables associated with OS of the entire cohort. ALD-related HCC was associated with improved OS compared with NASH-related HCC (HR, 0.522; 95% CI, 0.37–0.78), whereas no significant difference was seen in survival between NASH-related and viral hepatitis-related HCC (HR, 0.872; 95% CI, 0.64–1.19 for HCV; HR, 1.419; 95%

Figure 2. Overall survival of (A) all patients, (B) patients with BCLC stage 0/A HCC, (C) patients with BCLC stage B HCC, and (D) patients with BCLC stage C HCC, stratified by etiology.

Abbreviations: ALD, alcohol-related liver disease; BCLC, Barcelona Clinic Liver Cancer; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; NASH, nonalcoholic steatohepatitis.

CI, 0.94–2.15 for HBV). As expected, advanced BCLC stage was associated with worse survival (HR, 1.449; 95% CI, 1.13–1.89 for BCLC stage B; HR, 2.658; 95% CI, 2.07–3.41 for BCLC stage C; and HR, 3.123; 95% CI, 2.45–3.99 for BCLC stage D), while receipt of surveillance within 12 months (HR, 0.739; 95% CI, 0.60–0.92), and receipt of any therapy (HR, 0.104; 95% CI, 0.08–0.14 for curative; HR 0.382, 95% CI, 0.31–0.48 for locoregional; and HR, 0.529; 95% CI, 0.41–0.68 for systemic therapy) were independently associated with improved survival. Results were unchanged when considering transplant-free survival (HR, 0.58; 95% CI, 0.4–0.8 for ALD; HR, 0.90; 95% CI, 0.7–1.2 for HCV; HR, 1.25; 95% CI, 0.8–1.9 for HBV).

Discussion

In our study, patients with NASH-related HCC had significantly higher rates of preserved liver function, including a higher proportion who presented with HCC in the

absence of cirrhosis, compared with ALD- and HCV-related HCC. Despite similar receipt of HCC surveillance and BCLC tumor stage at diagnosis, patients with NASH-related HCC had the highest rate of curative-intent therapy. However, NASH-related HCC was associated with worse OS compared with ALD-related HCC but similar survival to viral hepatitis-related HCC.

This is one of the first studies comparing liver disease etiologies in a racially/ethnically diverse cohort. Similar to racial/ethnic disparities in NASH prevalence, we found that patients with NASH were more likely to be Hispanic white, particularly Hispanic white female, and less likely to be Non-Hispanic black compared with other etiologies.^{21,22} The study by Younossi et al⁶ grouped race/ethnicity as white versus other and did not subdivide white race into Hispanic and non-Hispanic ethnicities. These data are important when considering the increasing Hispanic white population in the United States.²³

Table 3. Cox Multivariable Analysis of Patient, Tumor, and Treatment Variables Associated With Death

Variable	HR	95% CI	P Value
Age	1.007	0.99–1.02	.212
Sex			
Male	Ref		
Female	1.102	0.90–1.35	.349
Race/Ethnicity			
Non-Hispanic white	Ref		
Non-Hispanic black	1.098	0.90–1.34	.350
Hispanic white	1.087	0.88–1.34	.437
Asian	1.124	0.78–1.61	.528
Insurance			
Uninsured	Ref		
Medicaid	0.827	0.62–1.10	.189
Medicare	0.934	0.69–1.26	.656
Private	1.045	0.76–1.45	.791
Other	0.864	0.66–1.14	.302
Etiology of HCC			
NASH	Ref		
ALD	0.522	0.37–0.75	<.001
HCV	0.872	0.64–1.19	.386
HBV	1.419	0.94–2.15	.098
Surveillance within 12 months			
No	Ref		
Yes	0.739	0.60–0.92	.006
BCLC stage			
0/A	Ref		
B	1.449	1.13–1.86	.004
C	2.658	2.07–3.41	<.001
D	3.123	2.45–3.99	<.001
Definitive treatment			
None	Ref		
Curative	0.104	0.08–0.14	<.001
Locoregional	0.382	0.31–0.48	<.001
Systemic	0.529	0.41–0.68	<.001

Abbreviations: ALD, alcohol-related liver disease; BCLC, Barcelona Clinic Liver Cancer; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; NASH, nonalcoholic steatohepatitis.

Furthermore, racial/ethnic disparities in HCC incidence may worsen in the future given the availability of direct-acting antiviral therapy for HCV and its association with lower HCC incidence.²⁴ In contrast, there are minimal effective treatments for NASH and no preventive measures for progression to HCC.

Another notable finding of our study is the high proportion of NASH-related HCC that presented in the

absence of cirrhosis, similar to that seen with HBV-related HCC. This finding has been reported in other studies.^{20,25} The pathogenesis of HCC developing at higher rates in NASH compared with other etiologies is unclear but may support the hypothesis that HCC pathogenesis is triggered by the same initial insult, but otherwise proceeds on a parallel but separate pathway from fibrosis progression. The high rates of noncirrhotic HCC in patients with HBV have resulted in surveillance recommendations for HCC in noncirrhotic subgroups, such as Asian men aged >40 years and Asian women aged >50 years; however, the role of HCC surveillance in patients with noncirrhotic NASH is less clear.^{26–28} Given the large burden of NASH in the United States and globally, it would likely not be feasible to perform surveillance in all patients. Furthermore, the incidence of HCC in these patients is unlikely to be sufficiently high for HCC surveillance to be cost-effective. Development of risk stratification tools may help identify subgroups of patients with NASH in whom HCC surveillance would be cost-effective.

Our study adds important prognostic data for the implication of the clinicopathologic differences seen among etiologies by adding valuable information about treatment receipt and survival. Patients with NASH-related HCC had better unadjusted survival, although these differences were partly mitigated after adjusting for tumor burden, liver dysfunction, and receipt of curative-intent therapy. In multivariable models, NASH-related HCC continued to be associated with worse survival compared with ALD-related HCC, but with similar survival compared with HCV-related HCC. Lack of granular data for these factors in large administrative analyses or in studies using small sample sizes with limited statistical power may partly explain the mixed survival outcomes previously reported.^{6,7} For example, Younossi et al⁶ found worse survival was associated with NASH-related HCC compared with HCV/HBV; however, their analysis was not able to include type of treatment or underlying liver function. As far as we are aware, our study represents the largest NASH-related HCC study to capture tumor stage, liver dysfunction, HCC-directed therapy, and OS. The large size of our cohort also allowed individual comparison with other etiologies, whereas other studies often combine non-NASH etiologies, which may obscure differences in presentation or prognosis.^{6,7,12}

Study findings were interpreted in light of the following limitations. First, due to a relatively small sample size of patients with NASH only, subset analysis of NASH-related HCC was not adequately powered to determine specific prognostic factors associated with survival in this specific cohort. Second, we were unable to evaluate the prognostic importance of genetic factors, such as the *PNPLA3* gene, which may be an individual risk factor for

HCC development and poor prognosis.²⁹ Third, our study was conducted in 2 large health systems, representing safety-net and tertiary care centers, but may not be representative of patients seen in other settings. However, the inclusion of 2 diverse types of health systems is important, particularly given differences between safety-net and non-safety-net systems.³⁰ These limitations are outweighed by our study's strengths, including its large sample size, racially/ethnically diverse cohort, and prospectively collected data.

Conclusions

Our findings show that patients with NASH-related HCC present with more preserved liver function, including 15% presenting without evidence of cirrhosis. Despite similar tumor stage, patients with NASH-related HCC are more likely to undergo curative-intent therapy. However, NASH etiology is associated with worse survival

compared with ALD, and similar survival compared with viral hepatitis-related HCC.

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References

- Global Burden of Disease Cancer Collaboration, Fitzmaurice C, Akinyemiju TF, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 cancer groups, 1990 to 2016: a systematic analysis for the Global Burden of Disease study. *JAMA Oncol* 2018; 4:1553–1568.
- American Cancer Society. Cancer Facts & Figures 2018. Atlanta, GA: American Cancer Society; 2018.
- Mittal S, El-Serag HB. Epidemiology of hepatocellular carcinoma: consider the population. *J Clin Gastroenterol* 2013;47(Suppl):S2–6.
- Ryerson AB, Ehemann CR, Altekruse SF, et al. Annual Report to the Nation on the Status of Cancer, 1975–2012, featuring the increasing incidence of liver cancer. *Cancer* 2016;122:1312–1337.
- Chayanupatkul M, Omino R, Mittal S, et al. Hepatocellular carcinoma in the absence of cirrhosis in patients with chronic hepatitis B virus infection. *J Hepatol* 2017;66:355–362.
- Younossi ZM, Otgonsuren M, Henry L, et al. Association of nonalcoholic fatty liver disease (NAFLD) with hepatocellular carcinoma (HCC) in the United States from 2004 to 2009. *Hepatology* 2015;62:1723–1730.
- Reddy SK, Steel JL, Chen HW, et al. Outcomes of curative treatment for hepatocellular cancer in nonalcoholic steatohepatitis versus hepatitis C and alcoholic liver disease. *Hepatology* 2012;55:1809–1819.
- Marrero JA, Fontana RJ, Su GL, et al. NAFLD may be a common underlying liver disease in patients with hepatocellular carcinoma in the United States. *Hepatology* 2002;36:1349–1354.
- Starley BQ, Calcagno CJ, Harrison SA. Nonalcoholic fatty liver disease and hepatocellular carcinoma: a weighty connection. *Hepatology* 2010; 51:1820–1832.
- Michitaka K, Nishiguchi S, Aoyagi Y, et al. Etiology of liver cirrhosis in Japan: a nationwide survey. *J Gastroenterol* 2010;45:86–94.
- Tokushige K, Hashimoto E, Yatsuji S, et al. Prospective study of hepatocellular carcinoma in nonalcoholic steatohepatitis in comparison with hepatocellular carcinoma caused by chronic hepatitis C. *J Gastroenterol* 2010;45:960–967.
- Kim NG, Nguyen PP, Dang H, et al. Temporal trends in disease presentation and survival of patients with hepatocellular carcinoma: a real-world experience from 1998 to 2015. *Cancer* 2018;124:2588–2598.
- Llovet JM, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. *Semin Liver Dis* 1999;19:329–338.
- Giannini EG, Marabotto E, Savarino V, et al. Hepatocellular carcinoma in patients with cryptogenic cirrhosis. *Clin Gastroenterol Hepatol* 2009; 7:580–585.
- Yopp AC, Mansour JC, Beg MS, et al. Establishment of a multidisciplinary hepatocellular carcinoma clinic is associated with improved clinical outcome. *Ann Surg Oncol* 2014;21:1287–1295.
- Merriman RB, Tran TT. AASLD practice guidelines: the past, the present, and the future. *Hepatology* 2016;63:31–34.
- Heimbach JK, Kulik LM, Finn RS, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. *Hepatology* 2018;67:358–380.
- Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. *Hepatology* 2018;67:328–357.
- Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement: executive summary. *Crit Pathw Cardiol* 2005;4:198–203.
- Mittal S, El-Serag HB, Sada YH, et al. Hepatocellular carcinoma in the absence of cirrhosis in United States veterans is associated with nonalcoholic fatty liver disease. *Clin Gastroenterol Hepatol* 2016;14:124–131.e1.
- Rich NE, Oji S, Mufti AR, et al. Racial and ethnic disparities in nonalcoholic fatty liver disease prevalence, severity, and outcomes in the united states: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2018;16:198–210.e2.
- Rich NE, Hester C, Odewole M, et al. Racial and ethnic differences in presentation and outcomes of hepatocellular carcinoma. *Clin Gastroenterol Hepatol* 2019;17:551–559.e1.
- Vespa J, Armstrong DM, Medina L. Demographic Turning Points for the United States: Population Projections for 2020 to 2060. United States Census Bureau, 2018. Available at: https://www.census.gov/content/dam/Census/library/publications/2018/demo/P25_1144.pdf. Accessed August 8, 2018.
- Konjeti VR, John BV. Interaction between hepatocellular carcinoma and hepatitis C eradication with direct-acting antiviral therapy. *Curr Treat Options Gastroenterol* 2018;16:203–214.
- Trevisani F, Frigerio M, Santi V, et al. Hepatocellular carcinoma in non-cirrhotic liver: a reappraisal. *Dig Liver Dis* 2010;42:341–347.
- European Association for the Study of the Liver, European Organisation for Research and Treatment of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 2012;56:908–943.
- Kew MC. Epidemiology of chronic hepatitis B virus infection, hepatocellular carcinoma, and hepatitis B virus-induced hepatocellular carcinoma. *Pathol Biol (Paris)* 2010;58:273–277.
- Sakuma K, Saitoh N, Kasai M, et al. Relative risks of death due to liver disease among Japanese male adults having various statuses for hepatitis B s and e antigen/antibody in serum: a prospective study. *Hepatology* 1988;8:1642–1646.
- Singal AG, Manjunath H, Yopp AC, et al. The effect of PNPLA3 on fibrosis progression and development of hepatocellular carcinoma: a meta-analysis. *Am J Gastroenterol* 2014;109:325–334.
- Mokdad AA, Murphy CC, Pruitt SL, et al. Effect of hospital safety net designation on treatment use and survival in hepatocellular carcinoma. *Cancer* 2018;124:743–751.