Distinctive Features and Outcomes of Hepatocellular Carcinoma in Patients With Alcohol-Related Liver Disease: A US Multicenter Study

Andrew deLemos, MD[1], Milin Patel, MD[1], Samer Gawrieh, MD[2], Heather Burney, MS[3], Lara Dakhoul, MD[2], Ethan Miller, MD[4], Andrew Scanga, MD[5], Carla Kettler, BS[3], Hao Liu, PhD[3], Patrick Roche, BS[1], Julia Wattacheril, MD, MPH[6] and Naga Chalasani, MD[2]

INTRODUCTION: **The burden of hepatocellular carcinoma (HCC) occurring in patients with alcoholic liver disease (ALD) is increasing at an alarming rate. The aims of this study were to compare the patient and tumor characteristics of HCC occurring in ALD-alone relative to and in addition to other chronic liver diseases.**

METHODS: **Patients diagnosed with HCC between 2000 and 2014 were identified at 5 US clinical centers. The patients were categorized as ALD-alone, ALD plus viral hepatitis, or a non-ALD etiology. Clinical and tumor characteristics among the 3 groups were compared, and survival probability was estimated by the Kaplan-Meier method. The frequency of noncirrhotic HCC was compared across the 3 groups.**

RESULTS: **A total of 5,327 patients with HCC were analyzed. Six hundred seventy (12.6%) developed HCC due to underlying ALD. Ninety-one percent of ALD-related HCC arose in men, in contrast to non-ALD etiologies where men accounted for 70% of HCCs cases ($P < 0.001$). Patients with ALD-alone-related HCC were older at diagnosis and had tumors less likely to be detected as part of routine surveillance. The ALD-alone cohort was least likely to be within the Milan criteria and to undergo liver transplantation. Overall survival in the ALD-alone HCC cohort was lower than the other 2 groups (1.07 vs 1.31 vs 1.41 years, $P < 0.001$). HCC in the noncirrhotic ALD cohorts occurred in only 3.5% of the patients compared with 15.7% in patients with non-ALD etiologies ($P < 0.001$).**

DISCUSSION: **HCC occurring in patients with ALD occurred mostly in older men and almost exclusively in a cirrhotic background. They present with advanced tumors, and their survival is lower than HCCs occurring in non-ALD.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/CTG/A223

Clinical and Translational Gastroenterology 2020;11:e00139. https://doi.org/10.14309/ctg.0000000000000139

INTRODUCTION

Alcohol use has a universal impact on public health and productivity. The Global Status Report on Alcohol and Health from 2016 reported a prevalence of alcohol consumption in high sociodemographic index areas of 72% in women and 83% in men with average daily consumption of 1.9 and 2.9 standard drinks, respectively (1). This alarming degree of alcohol consumption worldwide translates to an increasing burden of alcoholic liver disease (ALD) and its related complications. In 2016, there were an estimated 1.25 million deaths due to cirrhosis and chronic liver disease (CLD), of which 334,900 (27%) were due to alcohol (2). The age-standardized adult liver transplant waitlist rate for ALD nearly doubled between 2007 and 2016 (3), and ALD has replaced hepatitis C as the leading indication for liver transplantation in the United States (4). A recent population-based study using the US Census and national mortality data from 2007 to 2016 found a 4.5 annual percentage increase in cirrhosis-related mortality from ALD (5).

Mortality in ALD often results from the development of hepatocellular carcinoma (HCC). HCC is now the fourth most common cause of cancer-related death worldwide (6). In 2015, alcohol was responsible for 245,000 or 30% of all HCC deaths (7). The World Health Organization estimates that more than 1 million people will die of HCC in 2030 (8). The confluence of increased alcohol exposure together with the increase in incident HCCs creates an urgent need to better understand the relationship between alcohol use, ALD, and HCC.

[1]Department of Medicine, Atrium Health, Charlotte, North Carolina, USA; [2]Department of Medicine, Indiana University School of Medicine, Indianapolis, Indiana, USA; [3]Department of Biostatistics, Indiana University School of Medicine, Indianapolis, Indiana, USA; [4]Department of Gastroenterology, Hepatology and Nutrition, MD Anderson Cancer Center, Houston, Texas, USA; [5]Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee, USA; [6]Department of Medicine, Columbia University Vagelos College of Physicians and Surgeons, New York, New York, USA. **Correspondence:** Naga Chalasani, MD. E-mail: nchalasa@iu.edu. Andrew deLemos, MD. E-mail: andrew.delemos@atriumhealth.org.

Received October 17, 2019; accepted January 27, 2020; published online March 24, 2020

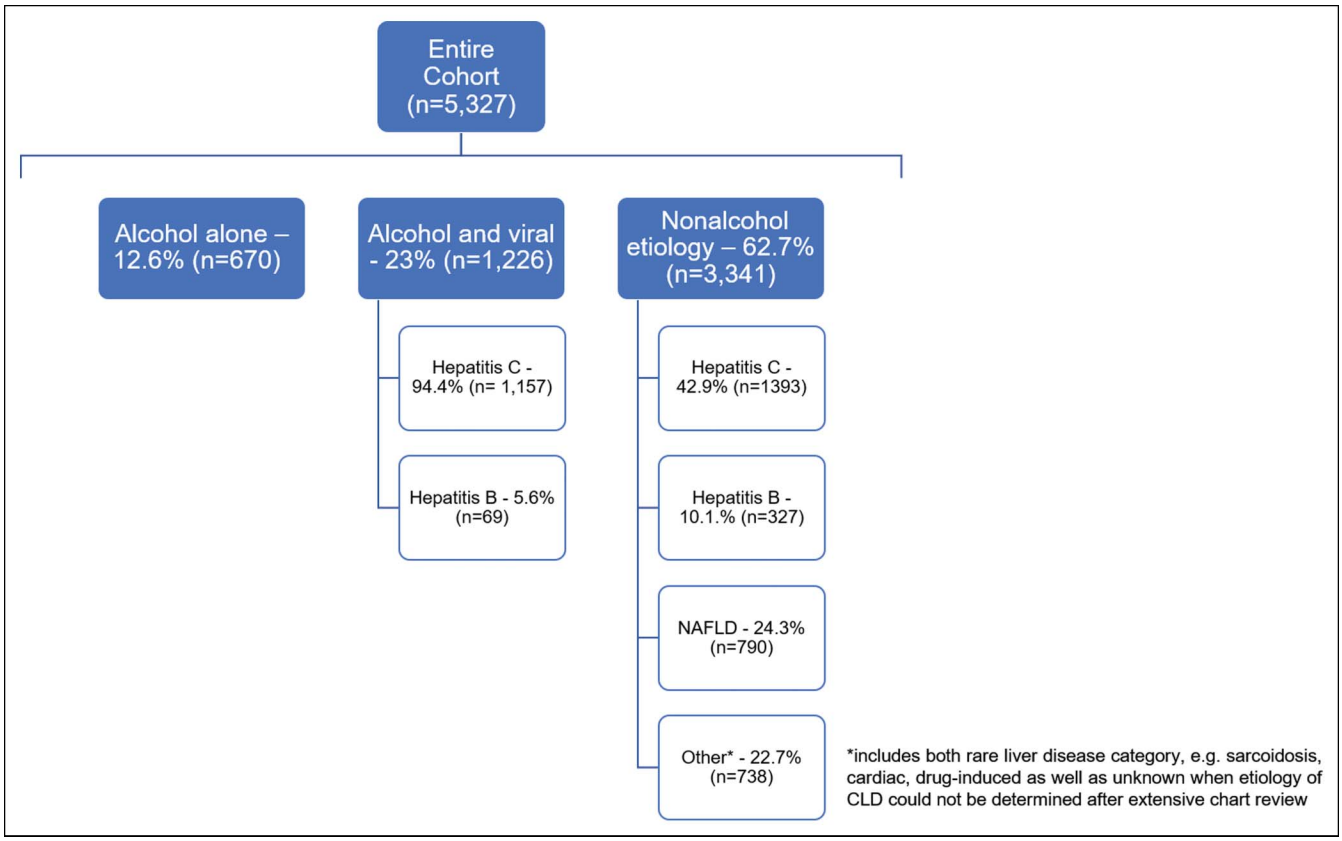


Figure 1. HCC cohort stratified by CLD etiology. CLD, chronic liver disease; HCC, hepatocellular carcinoma; NAFLD, nonalcoholic fatty liver disease.

Patients with ALD-related HCCs present with advanced tumors often due to a delay in diagnosis from a lack of surveillance (9–11). European cohort studies have shown a reduction in the median overall survival of ALD-related HCCs compared with Hepatitis C (HCV)-related HCCs after adjusting for lead time bias, but the prognostic significance of alcohol did not persist after stratifying by Barcelona-Clinic Liver Cancer stage (10,12). Thus, liver function and tumor characteristics at diagnosis seem to affect survival more than the underlying etiology of liver disease (13).

Old age and male gender are established risk factors for HCC in ALD and were recently shown to be independently associated with the development of HCC in a prospective trial of patients with alcohol-related cirrhosis undergoing surveillance in France (13,14). Environmental factors such as diabetes and body mass index (BMI) may also influence the occurrence of HCC and together with age and gender were recently included in an HCC prognostic model that successfully risk stratified patients with alcohol and nonalcoholic fatty liver disease (NAFLD)-related cirrhosis (15). Finally, genetic variants in *PNPLA3* and *TM6SF2* confer increased susceptibility to HCC in patients with ALD. Interestingly, the presence of both risk alleles accounted for half of the attributable risk of HCC in a study of approximately 2,000 patients across Europe (16). Although similar patient, environmental, and genetic factors affect HCC risk, particularly for alcohol and NAFLD-related HCC, the contribution of each variable undoubtedly differs based on liver disease etiology.

Our study aims to characterize distinctive features and outcomes of HCC in patients with ALD. We studied 5,327 patients with HCC seen at 5 major liver centers across the United States over a 14.5-year period between 2000 and 2014. We contrasted HCCs in patients with ALD exclusively and in combination with viral hepatitis to HCC cases that occurred in the absence of documented ALD. In view of the recent trend of younger patients presenting with ALD and the effect of alcohol metabolites in directly promoting hepatic carcinogenesis (17,18), we included in our analysis a substantial subset of HCCs from noncirrhotic patients to determine the frequency of noncirrhotic ALD-related HCC from our cohort as well.

METHODS

Cohort compilation

A detailed description of the ascertainment and characterization of the cohort is available for review in the study by Gawrieh et al. (19). Each participating site had local institutional review board approval to conduct the study. Briefly, we retrospectively identified HCC cases between January 2000 and June 2014 using center-specific cancer registries, manually reviewed the health record to verify the diagnosis, and extracted relevant data into a shared database coordinated at Indiana University. A diagnosis of HCC required histological and/or radiographic evidence consistent with the American Association for Study of Liver Disease guidelines (20). Tumor characteristics including alpha fetoprotein, largest tumor diameter, Tumor, Node, Metastasis stage, and whether the HCC was within the Milan criteria were captured at the time of diagnosis (21,22). All HCC treatment modalities were recorded from the medical record for analysis as well.

Table 1. **Patient and disease characteristics for alcohol alone vs nonalcohol etiology**

Variable	Overall, N = 4,101	Alcohol alone, N = 670	Nonalcohol etiology, N = 3,431	*P* value
Age (yr)	63.0 (56.0, 70.0)	65.0 (59.0, 71.0)	62.0 (56.0, 70.0)	<0.001
Male sex	3,009 (73.4%)	610 (91.0%)	2,399 (69.9%)	<0.001
Race				
White	2,832 (70.1%)	492 (74.1%)	2,340 (69.4%)	
Black	406 (10.1%)	49 (7.4%)	357 (10.6%)	
Hispanic	436 (10.8%)	108 (16.3%)	328 (9.7%)	<0.001
Asian	176 (4.4%)	5 (0.8%)	171 (5.1%)	
Other	188 (4.7%)	10 (1.5%)	178 (5.3%)	
BMI (kg/m^2)	27.8 (24.4, 31.9)	28.6 (24.9, 32.6)	27.6 (24.3, 31.7)	0.009
Obesity	1,232 (35.2%)	238 (40.5%)	994 (34.2%)	0.004
Diabetes	1,681 (41.3%)	295 (44.6%)	1,386 (40.7%)	0.06
Hypertension	2,608 (64.1%)	444 (67.1%)	2,164 (63.5%)	0.08
Dyslipidemia	1,110 (27.3%)	180 (27.4%)	930 (27.3%)	0.98
Coronary artery disease	785 (19.3%)	134 (20.3%)	651 (19.1%)	0.50
Peripheral vascular disease	343 (8.5%)	77 (11.7%)	266 (7.8%)	0.001
ALT (units/L)	47.0 (30.0, 80.0)	39.0 (26.0, 63.0)	49.0 (31.0, 84.0)	<0.001
AST (units/L)	73.0 (45.0, 125.0)	61.0 (41.0, 111.0)	75.0 (46.0, 128.0)	<0.001
Total bilirubin (mg/dL)	1.1 (0.7, 2.0)	1.2 (0.7, 2.1)	1.1 (0.7, 1.9)	0.001
Alkaline phosphatase (units/L)	138.0 (96.0, 211.0)	153.5 (105.0, 230.0)	135.0 (94.0, 207.0)	<0.001
Albumin (g/dL)	3.5 (3.0, 4.0)	3.4 (2.9, 3.9)	3.5 (3.0, 4.0)	0.002
Platelets (K/mm^3)	149.0 (90.0, 236.0)	146.0 (91.0, 221.0)	150.0 (90.0, 238.0)	0.33
Creatinine (mg/dL)	0.9 (0.8, 1.1)	0.9 (0.8, 1.2)	0.9 (0.7, 1.1)	0.009
INR	1.2 (1.1, 1.3)	1.2 (1.1, 1.4)	1.2 (1.1, 1.3)	0.001
MELD score	10.0 (8.0, 14.0)	11.0 (8.0, 14.0)	10.0 (8.0, 14.0)	<0.001
APRI score	1.4 (0.7, 2.7)	1.2 (0.7, 2.2)	1.5 (0.7, 2.8)	0.001
APRI category				
<1.0	1,402 (37.6%)	251 (40.7%)	1,151 (37.0%)	
1.0–2.0	975 (26.1%)	188 (30.5%)	787 (25.3%)	<0.001
>2.0	1,354 (36.3%)	177 (28.7%)	1,177 (37.8%)	
Is cirrhosis present? (Y/N/unclassified)				
No	583 (14.2%)	44 (6.6%)	539 (15.7%)	
Yes	3,349 (81.7%)	611 (91.2%)	2,738 (79.8%)	<0.001
Unclassified	169 (4.1%)	15 (2.2%)	154 (4.5%)	

Table 1. (*continued*)

Variable	Overall, N = 4,101	Alcohol alone, N = 670	Nonalcohol etiology, N = 3,431	*P* value
Complications				
Ascites	2,071 (50.5%)	402 (60.0%)	1,669 (48.6%)	<0.001
Encephalopathy	954 (23.3%)	197 (29.4%)	757 (22.1%)	<0.001
Varices	1,701 (41.5%)	306 (45.7%)	1,395 (40.7%)	0.02
SBP	164 (4.0%)	30 (4.5%)	134 (3.9%)	0.49
No complications occurred	805 (19.6%)	109 (16.3%)	696 (20.3%)	0.02
Portal vein thrombosis	1,085 (26.5%)	195 (29.1%)	890 (25.9%)	0.09
Pugh-Child classification				
Child A	1,749 (48.2%)	241 (39.6%)	1,508 (50.0%)	<0.001
Child A-B	321 (8.9%)	54 (8.9%)	267 (8.8%)	
Child B	1,113 (30.7%)	224 (36.8%)	889 (29.5%)	
Child C	444 (12.2%)	90 (14.8%)	354 (11.7%)	

APRI, AST to Platelet Ratio Index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; INR, international normalized ratio; MELD, model for end-stage liver disease; SBP, spontaneous bacterial peritonitis.

A diagnosis of alcohol-related HCC required evidence by chart review of a physicians' documentation of alcohol use disorder, defined as a history of more than 3 drinks a day, clinical documentation of alcoholism/alcohol use disorder, enrollment in a substance abuse treatment program, or a history of alcoholic hepatitis. Other etiologies of CLD were similarly determined by a chart review of hepatologist's notes and/or confirmatory laboratory testing. We manually extracted liver-related complications, the presence of comorbid metabolic risk factors, and laboratory tests of hepatic function to calculate the model for end-stage liver disease (MELD) and Pugh-Child scores. The patients were classified as either cirrhotic, noncirrhotic, or unclassified according to the criteria published previously by Mittal et al. and externally validated by our consortium (19,23). Patient survival was established from cancer registries and medical records. For patients who are still alive or died with an unknown date of death, the date of the last contact available in the medical record was used to define the time of censoring for the survival analysis.

Statistical analyses

HCC cases were categorized into 3 groups for analysis: (i) alcohol alone, (ii) alcohol plus viral etiology for CLD, or (iii) a nonalcohol etiology. The last cohort was further divided for a subgroup analysis of NAFLD alone vs alcohol alone. We also contrasted the 3 groups by 3 different eras of diagnosis: 2000–2004, 2005–2009, and 2010–2014. Categorical variables were summarized and compared using the χ^2 test. Continuous variables were expressed as median with interquartile range, and the Kruskal-Wallis test was used to assess for significance. The overall survival probability was estimated by the Kaplan-Meier method and compared between the 3 groups using the log-rank test. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Prevalence of alcohol-related HCC in the study cohort

A study flow diagram is depicted in Figure 1. Five thousand three hundred twenty-seven patients with HCC were included in the analysis. 11.4% were classified as noncirrhotic, whereas 85.2% had confirmed cirrhosis. ALD-alone was identified as the CLD in 12.6% (n = 670) of patients, whereas ALD plus viral hepatitis (94.4%—chronic hepatitis C) was the combined liver disease in 23% (n = 1,226). The third cohort (n = 3,431) included the remaining 64.4% of patients with HCC but without an ALD diagnosis, the majority of whom had CLD because of either chronic hepatitis C (42.9%), hepatitis B (10.1%), or NAFLD (24.3%).

Characteristics of patients with HCC from ALD

In comparison to the cohort of patients without ALD, patients with alcohol-alone-related HCC were overwhelmingly men (91% vs 70%, $P < 0.001$) (Table 1). They were also older (65 vs 62 years, $P < 0.001$), had higher BMIs (28.6 vs 27.6, $P = 0.009$), and were more likely to be of white and/or Hispanic ethnicity (90.4% vs 78.5%, $P < 0.001$). The alcohol-alone group had more advanced liver disease, as denoted by a higher median MELD score (11 vs 10, $P < 0.001$), and Child-Pugh class B/C status (51.6% vs 41.2%, $P < 0.001$). Other selected clinical and biochemical features between the 2 groups are summarized in Table 1.

The cohort of patients with ALD plus viral hepatitis in contrast to the group without ALD was diagnosed with HCC at a significantly younger age (57 vs 62 years, $P < 0.001$) and had lower BMI (26.9 vs 27.6, $P = 0.0005$) and lower frequency of obesity (29.1% vs

Table 2. Patient and disease characteristics comparing alcohol plus viral etiology and nonalcohol etiologies

Variable	Overall, N = 4,657	Alcohol plus viral etiology, N = 1,226	Nonalcohol etiology, N = 3,431	*P* value
Age (yr)	60.0 (55.0, 68.0)	57.0 (53.0, 61.0)	62.0 (56.0, 70.0)	<0.001
Male sex	3,514 (75.5%)	1,115 (90.9%)	2,399 (69.9%)	<0.001
Race				
White	3,204 (69.9%)	864 (71.3%)	2,340 (69.4%)	
Black	586 (12.8%)	229 (18.9%)	357 (10.6%)	
Hispanic	413 (9.0%)	85 (7.0%)	328 (9.7%)	<0.001
Asian	189 (4.1%)	18 (1.5%)	171 (5.1%)	
Other	194 (4.2%)	16 (1.3%)	178 (5.3%)	
BMI (kg/m^2)	27.4 (24.2, 31.5)	26.9 (24.0, 30.7)	27.6 (24.3, 31.7)	0.0005
Obesity	1,321 (32.7%)	327 (29.1%)	994 (34.2%)	<0.001
Diabetes	1,714 (37.0%)	328 (26.8%)	1,386 (40.7%)	<0.001
Hypertension	2,849 (61.5%)	685 (56.0%)	2,164 (63.5%)	<0.001
Dyslipidemia	1,098 (23.7%)	168 (13.8%)	930 (27.3%)	<0.001
Coronary artery disease	788 (17.0%)	137 (11.2%)	651 (19.1%)	<0.001
Peripheral vascular disease	343 (8.5%)	77 (11.7%)	266 (7.8%)	0.001
ALT (units/L)	53.0 (33.0, 87.0)	61.0 (39.0, 93.0)	49.0 (31.0, 84.0)	<0.001
AST (units/L)	79.0 (50.0, 131.0)	92.0 (62.0, 138.0)	75.0 (46.0, 128.0)	<0.001
Total bilirubin (mg/dL)	1.1 (0.7, 2.0)	1.4 (0.9, 2.2)	1.1 (0.7, 1.9)	<0.001
Alkaline phosphatase (units/L)	135.0 (96.0, 202.0)	134.0 (100.0, 189.0)	135.0 (94.0, 207.0)	0.71
Albumin (g/dL)	3.4 (2.9, 4.0)	3.2 (2.7, 3.7)	3.5 (3.0, 4.0)	<0.001
Platelets (K/mm^3)	135.0 (84.0, 218.0)	106.0 (72.0, 159.0)	150.0 (90.0, 238.0)	<0.001
Creatinine (mg/dL)	0.9 (0.7, 1.1)	0.9 (0.7, 1.1)	0.9 (0.7, 1.1)	0.02
INR	1.2 (1.1, 1.4)	1.2 (1.1, 1.4)	1.2 (1.1, 1.3)	<0.001
MELD score	10.0 (8.0, 14.0)	11.0 (8.0, 14.0)	10.0 (8.0, 14.0)	<0.001
APRI score	1.7 (0.8, 3.2)	2.3 (1.3, 4.0)	1.5 (0.7, 2.8)	<0.001
APRI category				
<1.0	1,347 (31.6%)	196 (17.0%)	1,151 (37.0%)	
1.0–2.0	1,066 (25.0%)	279 (24.3%)	787 (25.3%)	<0.001
>2.0	1,852 (43.4%)	675 (58.7%)	1,177 (37.8%)	
Is cirrhosis present? (Y/N/unclassified)				
No	561 (12.0%)	22 (1.8%)	539 (15.7%)	
Yes	3,928 (84.3%)	1,190 (97.1%)	2,738 (79.8%)	<0.001
Unclassified	168 (3.6%)	14 (1.1%)	154 (4.5%)	

Table 2. (*continued*)

Variable	Overall, N = 4,657	Alcohol plus viral etiology, N = 1,226	Nonalcohol etiology, N = 3,431	*P* value
Complications				
Ascites	2,494 (53.6%)	825 (67.3%)	1,669 (48.6%)	<0.001
Encephalopathy	1,268 (27.2%)	511 (41.7%)	757 (22.1%)	<0.001
Varices	2,098 (45.1%)	703 (57.3%)	1,395 (40.7%)	<0.001
SBP	229 (4.9%)	95 (7.7%)	134 (3.9%)	<0.001
No complications occurred	833 (17.9%)	137 (11.2%)	696 (20.3%)	<0.001
Portal vein thrombosis	1,249 (26.8%)	359 (29.3%)	890 (25.9%)	0.02
Child-Pugh classification				
Child A	1,943 (46.8%)	435 (38.3%)	1,508 (50.0%)	<0.001
Child A-B	336 (8.1%)	69 (6.1%)	267 (8.8%)	
Child B	1,314 (31.6%)	425 (37.4%)	889 (29.5%)	
Child C	560 (13.5%)	206 (18.1%)	354 (11.7%)	

APRI, AST to Platelet Ratio Index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; INR, international normalized ratio; MELD, model for end-stage liver disease; SBP, spontaneous bacterial peritonitis.

34.2%, $P < 0.001$) and diabetes (26.6% vs 40.7%, $P < 0.001$) (Table 2). Similar to the alcohol-alone group, the ALD and viral cohort were predominantly men (91% vs 70%, $P < 0.001$) and were more decompensated at the time of HCC diagnosis with a higher median MELD score and significantly more portal hypertensive-related complications (Table 2). The combined ALD plus viral cohort of patients also had comparatively more clinical features of decompensated cirrhosis than the ALD-alone cohort (see Table 1, Supplementary Digital Content 1, http://links.lww.com/CTG/A223). Although these 2 groups did not differ in median MELD score at time of HCC diagnosis, the combined ALD and viral cohort had more hepatic synthetic dysfunction, as illustrated by significantly lower albumin (3.2 vs 3.5 g/dL, $P < 0.001$) and higher total bilirubin (1.4 vs 1.1 mg/dL, $P < 0.001$). The features of metabolic syndrome including obesity, diabetes mellitus, hypertension, and dyslipidemia were less frequently encountered in the combined ALD and viral cohort compared with both the alcohol-alone cohort and the nonalcohol cohort ($P < 0.001$ for each risk factor, Table 2 and see Table 1, Supplementary Digital Content 1, http://links.lww.com/CTG/A223).

Tumor characteristics in patients with ALD-related HCC

The ALD-alone and non-ALD cohorts did not differ in largest tumor size (4.7 cm) (Table 3). However, the ALD-alone group was significantly less likely to be diagnosed with HCC as part of screening (21.6% vs 28.4%, $P = 0.001$) and more likely to present incidentally (15.8% vs 12.5%, $P = 0.04$) or as part of symptoms workup (59.9% vs 54.5%, $P = 0.02$) (Table 3). Comparatively, the ALD plus viral cohort presented with smaller tumors than the non-ALD and ALD-alone cohorts (3.7 vs 4.7 cm, $P < 0.001$) (Table 4 and see Table 2, Supplementary Digital Content 1, http://links.lww.com/CTG/A223). A small but significant difference in the rate of routine screening as the diagnostic HCC methodology was seen between the ALD and viral vs alcohol-alone cohort (26.3% vs 21.6%, $P = 0.04$), although the alcohol-alone cohort had a noticeably higher rate for the diagnosis of HCC to occur incidentally (15.8% vs 9%, $P < 0.001$). A histologic HCC diagnosis was statistically less likely to occur in the alcohol plus viral cohort (55%) in comparison to both the nonalcohol group (69.8%, $P < 0.001$, Table 4) and the alcohol-alone group (67.3%, $P < 0.001$, see Table 2, Supplementary Digital Content 1, http://links.lww.com/CTG/A223).

The HCCs diagnosed in the ALD-alone and nonalcohol groups did not differ by anatomic stage or frequency within the Milan criteria at the time of diagnosis. However, both ALD-alone and nonalcohol groups presented with significantly higher stage HCC (stage III or IV) than the ALD and viral group (51.5% and 48.3% vs 41.5%, respectively, P for both ≤ 0.001). Not surprisingly, therefore, the patients in the ALD and viral cohort were more likely to present with HCC within the Milan Criteria (30% and 34.4% vs 42%, respectively, P for both <0.001). Selected differences in tumor characteristics between groups are summarized in Tables 3 and 4, and see Table 2, Supplementary Digital Content 1, http://links.lww.com/CTG/A223).

Alcohol-alone vs NAFLD subgroup analysis

We compared the ALD-alone-related HCC cohort to the subgroup of 790 NAFLD-related HCCs from the overall 3,341 nonalcohol cohort. The NAFLD HCC cases were diagnosed at an older age than the ALD-alone cohort (65 vs 68 years, $P < 0.001$). The male gender disparity in HCC cases was even more pronounced in the subgroup analysis (91% vs 64.6%, $P < 0.001$). The ALD-alone group had a higher total bilirubin (1.2 vs 0.9 mg/dL, $P < 0.001$),

Table 3. Tumor characteristics comparing alcohol-alone with nonalcohol etiology

Variable	Overall, N = 4,101	Alcohol alone, N = 670	Nonalcohol etiology, N = 3,431	*P* value
Tumor size (cm)	4.7 (2.7, 8.7)	4.7 (3.0, 8.1)	4.7 (2.7, 8.9)	0.93
AFP (ng/mL)	37.2 (6.4, 876.1)	25.8 (5.5, 876.1)	41.2 (6.7, 872.3)	0.03
AFP category				
<20	1,553 (43.5%)	284 (47.7%)	1,269 (42.6%)	
20–200	754 (21.1%)	116 (19.5%)	638 (21.4%)	0.07
>200	1,264 (35.4%)	195 (32.8%)	1,069 (35.9%)	
How was HCC diagnosed?				
Part of screening	927 (27.3%)	118 (21.6%)	809 (28.4%)	0.001
Incidental	442 (13.0%)	86 (15.8%)	356 (12.5%)	0.04
Symptoms workup	1,880 (55.3%)	327 (59.9%)	1,553 (54.5%)	0.02
Other	7 (0.2%)	2 (0.4%)	5 (0.2%)	0.37
NA/unknown	169 (5.0%)	19 (3.5%)	150 (5.3%)	0.08
Regular surveillance within 2 yr before HCC?				
Yes	984 (28.9%)	121 (22.0%)	863 (30.2%)	0.0003
Unknown	1,291 (37.9%)	220 (40.0%)	1,071 (37.5%)	
Method of diagnosis				
Histology	2,845 (69.4%)	451 (67.3%)	2,394 (69.8%)	0.21
Imaging	3,842 (93.7%)	633 (94.5%)	3,209 (93.5%)	0.36
Other	24 (0.6%)	4 (0.6%)	20 (0.6%)	0.97
Unknown	4 (0.1%)	0 (0.0%)	4 (0.1%)	0.38
Anatomic stage				
Stage I	1,173 (31.9%)	176 (29.9%)	997 (32.3%)	
Stage II	706 (19.2%)	109 (18.5%)	597 (19.4%)	
Stage IIIA	420 (11.4%)	72 (12.2%)	348 (11.3%)	
Stage IIIB	567 (15.4%)	92 (15.6%)	475 (15.4%)	0.09
Stage IIIC	52 (1.4%)	2 (0.3%)	50 (1.6%)	
Stage IVA	203 (5.5%)	38 (6.5%)	165 (5.4%)	
Stage IVB	551 (15.0%)	99 (16.8%)	452 (14.7%)	
Anatomic stage category				
Stage I or II	1,879 (51.2%)	285 (48.5%)	1,594 (51.7%)	0.09
Stage III or IV	1,793 (48.8%)	303 (51.5%)	1,490 (48.3%)	
Tumor differentiation				
Well	759 (32.6%)	136 (38.0%)	623 (31.6%)	0.006
Moderate	1,066 (45.8%)	159 (44.4%)	907 (46.1%)	
Poor	486 (20.9%)	58 (16.2%)	428 (21.7%)	
Undifferentiated/anaplastic	16 (0.7%)	5 (1.4%)	11 (0.6%)	
Tumor stage				
Single	1,414 (34.9%)	206 (31.2%)	1,208 (35.6%)	
3 tumors <3 cm	328 (8.1%)	47 (7.1%)	281 (8.3%)	
Large multinodular	867 (21.4%)	157 (23.8%)	710 (20.9%)	0.08
Vascular invasion or extrahepatic spread	1,447 (35.7%)	250 (37.9%)	1,197 (35.2%)	
Tumor within the Milan criteria	1,377 (33.7%)	200 (30.0%)	1,177 (34.4%)	0.06

AFP, alpha fetoprotein; HCC, hepatocellular carcinoma; NA, not applicable.

Table 4. Tumor characteristics comparing alcohol plus viral etiology and nonalcohol etiologies

Variable	Overall, N = 4,657	Alcohol plus viral etiology, N = 1,226	Nonalcohol etiology, N = 3,431	*P* value
Tumor size (cm)	4.4 (2.6, 8.0)	3.7 (2.4, 5.9)	4.7 (2.7, 8.9)	<0.001
AFP (ng/mL)	39.6 (7.3, 722.9)	37.5 (9.0, 411.5)	41.2 (6.7, 872.3)	0.59
AFP category				
<20	1,721 (42.1%)	452 (40.7%)	1,269 (42.6%)	
20–200	942 (23.0%)	304 (27.4%)	638 (21.4%)	<0.001
>200	1,424 (34.8%)	355 (32.0%)	1,069 (35.9%)	
How was HCC diagnosed?				
Part of screening	1,054 (27.9%)	245 (26.3%)	809 (28.4%)	<0.001
Incidental	440 (11.6%)	84 (9.0%)	356 (12.5%)	<0.001
Symptoms workup	2,111 (55.8%)	558 (59.9%)	1,553 (54.5%)	<0.001
Other	8 (0.2%)	3 (0.3%)	5 (0.2%)	<0.001
NA/unknown	199 (5.3%)	49 (5.3%)	150 (5.3%)	<0.001
Regular surveillance within 2 yr before HCC?				
Yes	1,175 (31.0%)	312 (33.4%)	863 (30.2%)	<0.001
Unknown	1,448 (38.2%)	377 (40.4%)	1,071 (37.5%)	
Method of diagnosis				
Histology	3,068 (65.9%)	674 (55.0%)	2,394 (69.8%)	<0.001
Imaging	4,350 (93.4%)	1,141 (93.1%)	3,209 (93.5%)	0.58
Other	23 (0.5%)	3 (0.2%)	20 (0.6%)	0.15
Unknown	6 (0.1%)	2 (0.2%)	4 (0.1%)	0.70
Anatomic stage				
Stage I	1,320 (32.0%)	323 (31.0%)	997 (32.3%)	
Stage II	883 (21.4%)	286 (27.5%)	597 (19.4%)	
Stage IIIA	457 (11.1%)	109 (10.5%)	348 (11.3%)	
Stage IIIB	602 (14.6%)	127 (12.2%)	475 (15.4%)	<0.001
Stage IIIC	60 (1.5%)	10 (1.0%)	50 (1.6%)	
Stage IVA	216 (5.2%)	51 (4.9%)	165 (5.4%)	
Stage IVB	587 (14.2%)	135 (13.0%)	452 (14.7%)	
Anatomic stage category				
Stage I or II	2,203 (53.4%)	609 (58.5%)	1,594 (51.7%)	<0.001
Stage III or IV	1,922 (46.6%)	432 (41.5%)	1,490 (48.3%)	
Tumor differentiation				
Well	796 (31.7%)	173 (32.1%)	623 (31.6%)	<0.001
Moderate	1,168 (46.6%)	261 (48.4%)	907 (46.1%)	
Poor	529 (21.1%)	101 (18.7%)	428 (21.7%)	
Undifferentiated/anaplastic	15 (0.6%)	4 (0.7%)	11 (0.6%)	
Tumor stage				
Single	1,610 (34.9%)	402 (33.1%)	1,208 (35.6%)	<0.001
3 tumors < 3 cm	444 (9.6%)	163 (13.4%)	281 (8.3%)	
Large multinodular	995 (21.6%)	285 (23.5%)	710 (20.9%)	
Vascular invasion or extrahepatic spread	1,560 (33.8%)	363 (29.9%)	1,197 (35.2%)	
Tumor within the Milan criteria	1,689 (36.4%)	512 (42.0%)	1,177 (34.4%)	<0.001

AFP, alpha fetoprotein; HCC, hepatocellular carcinoma; NA, not applicable.

Table 5. Selected features of alcohol-alone-related HCC by era of diagnosis

Variable	Overall, N = 670	Diagnosis date			*P* value
		2000–2004, N = 145	2005–2009, N = 156	2010–2014, N = 369	
Age at HCC diagnosis	65.0 (59.0, 71.0)	66.0 (61.0, 71.0)	65.5 (59.0, 70.0)	64.0 (58.0, 71.0)	0.10
Male sex	610 (91.0%)	131 (90.3%)	142 (91.0%)	337 (91.3%)	0.94
Obesity	238 (40.5%)	39 (36.8%)	47 (33.3%)	152 (44.6%)	<0.001
APRI ≥ 1.0	365 (59.3%)	62 (54.9%)	87 (58.4%)	216 (61.0%)	<0.001
MELD score	11.0 (8.0, 14.0)	10.0 (8.0, 13.0)	10.0 (8.0, 14.0)	11.0 (9.0, 15.0)	0.10
Tumor size	4.7 (3.0, 8.1)	6.0 (3.8, 10.0)	4.3 (2.9, 8.1)	4.4 (2.7, 7.1)	0.0004
AFP (ng/mL)	25.8 (5.5, 876.1)	77.2 (7.4, 1,897)	42.2 (5.7, 876.1)	14.9 (4.8, 530.0)	0.007
HCC diagnosed by screening	118 (21.6%)	19 (14.5%)	16 (14.0%)	83 (27.6%)	<0.001
Tumor stage					
Single	206 (31.2%)	27 (19.1%)	48 (32.0%)	131 (35.5%)	<0.001
3 tumors < 3 cm	47 (7.1%)	6 (4.3%)	12 (8.0%)	29 (7.9%)	
Large multinodular	157 (23.8%)	41 (29.1%)	40 (26.7%)	76 (20.6%)	
Vascular invasion or extrahepatic spread	250 (37.9%)	67 (47.5%)	50 (33.3%)	133 (36.0%)	
Tumor within Milan the criteria	200 (30.0%)	23 (16.0%)	48 (31.4%)	129 (35.0%)	<0.001

APRI, AST to Platelet Ratio Index; AFP, alpha fetoprotein; HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease.

MELD score (11 vs 10, $P = 0.004$), and more evidence of clinical decompensation as assessed by Pugh-Child's class B/C status (51.6% vs 39.6%, $P < 0.001$) compared with the NAFLD HCC subgroup. The degree of underlying hepatic dysfunction as appraised biochemically and clinically did not appreciably change in the NAFLD subgroup analysis relative to the overall cohort. The tumor characteristics of the NAFLD subgroup largely mirrored the overall nonalcohol cohort as well. Although there was no significant difference in greatest tumor size between alcohol-alone vs NAFLD-alone HCCs (4.7 vs 5.0 cm, $P = 0.13$), NAFLD associated HCCs were more likely than ALD-alone-related HCCs to present as single tumors (31.2% vs 40.5%) and less likely to present with vascular invasion or extrahepatic spread 37.9% vs 32.1%) ($P = 0.004$ for overall tumor stage).

Trend of ALD-related HCC over the study period

We contrasted the features of ALD-alone-related HCC during 3 diagnostic periods of time (2000–2004, 2005–2009, and 2010–2014) (Table 5). The age at HCC diagnosis did not significantly change during the 3 time periods in the alcohol-alone group ($P = 0.10$), but the maximum tumor size decreased significantly between 2000 and 2004 (6 cm) and the latter 2 eras (4.3 and 4.4 cm, respectively, $P = 0.0004$). Median AFP values at HCC diagnosis also decreased significantly over the 3 time periods (77.2 vs 42.2 vs 14.9, $P = 0.007$). Predictably, the diagnosis of HCC by screening was highest during the most recent era (27.6%) compared with the earlier 2 eras (14.5% and 14%, $P < 0.001$), which accordingly translated to earlier anatomic stage tumors that were more frequently within the Milan criteria (16% vs 31% vs 35%, $P < 0.001$).

Features of noncirrhotic HCC in ALD

Interestingly, noncirrhotic HCC was seldom seen in the ALD-alone group compared with the cohort without documented ALD (6.6% vs 15.7%, $P < 0.001$). Noncirrhotic HCC was also exceptionally rare in the ALD plus viral cohort occurring in only 22 of 1,226 cases (1.8%). The striking male predominance of ALD-related HCC was accentuated in noncirrhotic patients with only 7.6% occurring in women in the combined ALD-alone and ALD plus viral cohorts compared with 37.1% in the nonalcohol group ($P < 0.001$). At diagnosis, the ALD and viral cohorts' largest tumor size was 5.1 cm, which was significantly smaller than the alcohol-alone (8.2 cm) and nonalcohol (8.5 cm) cohorts ($P = 0.03$). However, the differences in tumor sizes did not translate to statistically significant differences in anatomic stage or tumor differentiation.

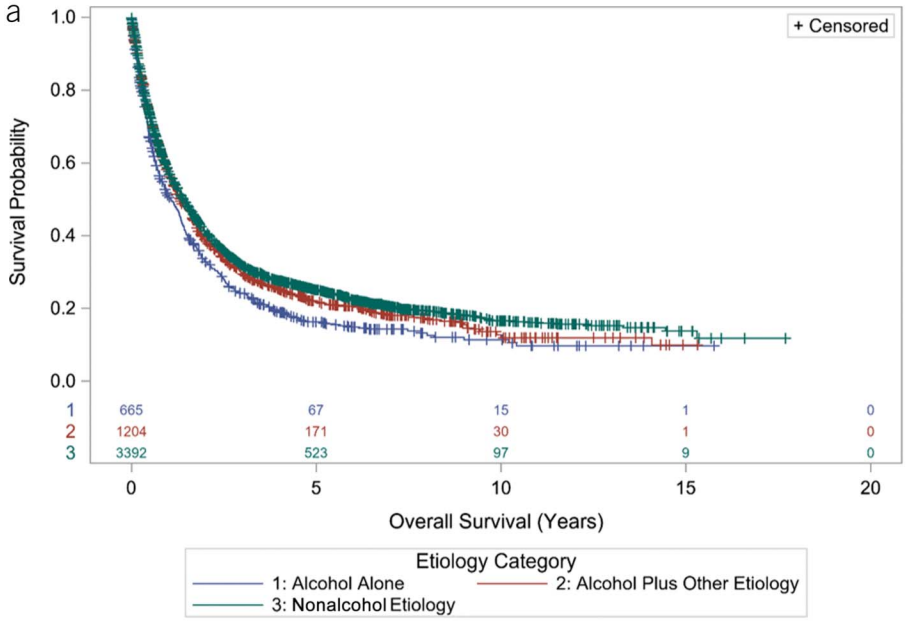
Treatment and survival of patients with ALD-related HCC

Patients with alcohol-alone-related HCC were less likely to undergo surgical resection (8.1% vs 15.4%, $P < 0.001$) and liver transplantation (11.5% vs 16.8%, $P = 0.0005$) but more likely to receive palliative care (29.3% vs 23.4%, $P = 0.001$) than patients in the nonalcohol cohort (see Table 3, Supplementary Digital Content 1, http://links.lww.com/CTG/A223). By contrast, the alcohol and viral cohort had the lowest rate of resection (6.6%, $P < 0.001$) but the highest rate of liver transplantation (19.5%, $P = 0.04$) and exposure to palliative care services (31.5%, $P < 0.001$). Median survival was significantly reduced in patients in the ALD-alone HCC cohort (1.07 years [95% CI: 0.88–1.29]) compared with the ALD plus viral group (1.31 years [95% CI: 1.17–1.46], $P = 0.002$) and the non-ALD cohort group (1.41 years [95% CI: 1.32–1.51], $P < 0.001$) (Figure 2).

DISCUSSION

Our consortium of over 5,000 HCC cases from centers encompassing a wide geographic area of the United States illustrates salient features of ALD-related HCC relative to HCCs occurring in other CLDs. We have reaffirmed in our US-based cohort findings seen in European and North American cohorts that ALD-related HCCs are overly represented in male patients (10,14,24). Male gender was associated with almost 4 times the odds of having HCC irrespective

a



b

Etiology Category	Median	95% Confidence Interval		Log Rank p-value
		Lower	Upper	
Alcohol alone	1.07 years	0.88	1.29	<0.0001
Alcohol and viral	1.31 years	1.17	1.46	
Nonalcohol etiology	1.41 years	1.32	1.51	

Figure 2. (**a**) Survival analysis for 3 cohorts. (**b**) Log-rank test.

of underlying CLD from the US Surveillance, Epidemiology, and End Results-Medicare database (25). Data from the US Census found HCC-related mortality rates in men to be 3.4-fold higher than in woman (5). Patients with alcohol-related HCC from our cohort were diagnosed at an older age than corresponding cases in the alcohol and viral cohort and the nonalcohol cohorts. Our finding contrasts with the Italian Liver Cancer Database in which ALD-related HCCs over a similar time period presented at a younger age than HCV-related HCCs (66.7 vs 70.7, $P < 0.001$) (10). A recent retrospective study from an ethnically diverse population in Dallas found NASH-related HCC to occur at an older age than both ALD and HCV-associated HCC (67.9 vs 59.7 vs 58.2, respectively, $P < 0.001$) (26). Nonetheless, older age has consistently been identified as independently associated with HCC risk in patients with CLD, regardless of etiology (15,24).

The alcohol plus viral hepatitis cohort almost exclusively contained patients with HCV, and while our study period predated the availability of direct-acting antiviral therapy, the analyses validate the synergism between alcohol and HCV-associated HCC (27). These patients developed HCCs at a significantly earlier age and overall were more likely to have cirrhosis complications than the alcohol-alone and nonalcohol cohorts. This finding, however, should be viewed within the context of a higher frequency of surveillance as the HCC diagnostic methodology in the alcohol and viral cohort relative to the alcohol-alone group.

In contrast to Surveillance, Epidemiology, and End Results and US Veterans Affairs data that rely on International Statistical Classification of Diseases-9 and International Statistical Classification of Diseases-10 classification, our cohort characterized patients directly from individual medical records (25,28). To our knowledge, the HCC cases from our consortium represent the largest US cohort with direct ascertainment of tumor variables and treatment modalities. ALD-alone-related HCCs were most likely to present as large and multinodular tumors with evidence of vascular invasion or extrahepatic spread and correspondingly were rarely treated by liver transplantation. Moreover, unadjusted survival in the alcohol-alone cohort was significantly shorter than in the other 2 groups. Across the 3 distinct time periods, 2000–2004, 2004–2009, and 2010–2014, the frequency of HCC surveillance in the alcohol-alone cohort increased, resulting in more tumors diagnosed at an early stage and improved survival.

A strength of our cohort is the sizable proportion of noncirrhotic HCC cases. Remarkably, there were very few cases of noncirrhotic ALD-related HCC (6.6%), far fewer than in the nonalcohol cohort (15.7%), and comparatively less than the US Veterans Affairs cohort of 11.1% noncirrhotic alcohol-related HCCs identified using the same criteria for the absence of cirrhosis (23). Notably, the frequency of noncirrhotic ALD-related HCC did not change over the 3 different time periods. Since the largest burden of noncirrhotic HCC is arising on a background of NAFLD, it is curious that features of metabolic syndrome, common to both alcohol and NAFLD, have not translated to a similar increase in noncirrhotic ALD-related HCC. Given shared genetic and inflammatory underpinnings of toxic-metabolic liver injury, one speculates whether the differences are a result of epigenetic variation.

In summary, our detailed examination of patients with ALD-related HCCs highlights several features. The striking predominance of older male patients with ALD-alone-related HCCs is noteworthy. Moreover, the diagnosis of HCC in this group

often occurred belatedly with a correspondingly negative impact on survival relative to patients with HCC in the absence of ALD. The ALD plus viral HCC cohort contrasts nicely with the ALD-alone cohort. As anticipated, the combined cohort had more advanced cirrhotic features and their HCCs were diagnosed at a younger age. They survived longer than patients in the ALD-alone group and had the highest likelihood of receiving a liver transplant among the 3 groups. Last, noncirrhotic HCC was a truly rare occurrence in patients with ALD.

The results of our study emphasize the need to identify patients at risk for alcohol use disorder, ALD, and alcohol-related cirrhosis for linkage to care. As a preventable disease, it is disturbing that mortality rates from ALD are increasing. Our large data set reinforces the consequences of a delayed diagnosis of HCC in patients with ALD and should prompt renewed attention to addressing the increasing prevalence of alcohol consumption and ALD globally.

CONFLICTS OF INTEREST

Guarantor of the article: Naga Chalasani, MD.

Specific author contributions: All authors contributed to study concept, data analysis, and manuscript preparation.

Financial support: Supported in part by David W. Crabb Professorship Endowment at Indiana University School of Medicine (N.C.)

Potential competing interests: M.P., L.D., A.S., H.L., C.K., H.B., and P.R. declare no conflicts of interest. A.d.L. had paid consulting activities with Gilead in the past 12 months. S.G. consulting: TransMedics, research grant support: Cirius, Galmed, and Zydus. N.C. had paid consulting activities with following companies in past 12 months: Abbvie, Shire, NuSirt, Afimmune, Axovant, Allergan, Madrigal, Coherus, Siemens, and Genentech. He has received research support from Lilly, Galectin, Gilead, Exact Sciences, and Cumberland. E.M. is a minority holder of stock in Amgen. J.W. has paid consulting activities with Astra Zeneca and has received research support from Janssen, Genfit, and Intercept, Galectin, Gilead, Zydus, Conatus, and Shire.

Study Highlights

WHAT IS KNOWN

- ✓ The magnitude of ALD globally is alarming.
- ✓ Mortality in ALD is often because of HCC.

WHAT IS NEW HERE

- ✓ HCC in ALD occurs predominantly in older men.
- ✓ Patients with ALD-related HCCs present with advanced tumors outside the Milan criteria.
- ✓ Survival after HCC diagnosis is lower in ALD relative to other CLDs.

TRANSLATIONAL IMPACT

- ✓ Identifying patients at risk for ALD is critical to prevent the adverse consequences of cirrhosis and HCC.

ACKNOWLEDGMENTS

The following individuals have contributed to the data extraction: Keaton R. Jones, MD and Chelsey McShane, MD (Indiana University School of Medicine), Hamzah Abu-Sbeih, MD, Essam Khalifa, MD (MD Anderson Cancer Center), Emily Mao, MD (Baylor College of Medicine), Barbara Channell, BSN, RN (Vanderbilt University School of Medicine), Krista Bossi, MS, Sarah LeStrange, MS (Atrium Health), Averill Guo, MD, Sydney Pomenti, MD, Meaghan Phipps, MD, Jonathan Yeh, MSPA, MBA, PA-C (Columbia University Irving Medical Center), Alexandra Livanos, MD, PhD (Icahn School of Medicine at Mount Sinai).

REFERENCES

1. GBD 2016 Alcohol Collaborators. Alcohol use and burden for 195 countries and territories, 1990-2016: A systematic analysis for the Global Burden of Disease Study 2016. Lancet 2018;392:1015–35.
2. GBD 2016 Causes of Death Collaborators. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: A systematic analysis for the Global Burden of Disease Study 2016. Lancet 2017;390:1151–210.
3. Cholankeril G, Gadiparthi C, Yoo ER, et al. Temporal trends associated with the rise in alcoholic liver disease-related liver transplantation in the United States. Transplantation 2019;103:131–9.
4. Cholankeril G, Ahmed A. Alcoholic liver disease replaces hepatitis C virus infection as the leading indication for liver transplantation in the United States. Clin Gastroenterol Hepatol 2018;16:1356–8.
5. Kim D, Li AA, Perumpail BJ, et al. Changing trends in etiology-based and ethnicity-based annual mortality rates of cirrhosis and hepatocellular carcinoma in the United States. Hepatology 2019;69:1064–74.
6. International Agency for Research on Cancer, World Health Organization. Cancer Today (https://gco.iarc.fr/today/home). Accessed September 26, 2019.
7. Global Burden of Disease Liver Cancer Collaborators; Akinyemiju T, Abera S, Ahmed M, et al. The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the global, regional, and national level: Results from the Global Burden of Disease Study 2015. JAMA Oncol 2017;3:1683–91.
8. World Health Organization. Projections of Mortality and Causes of Death, 2016 to 2060 (http://www.who.int/healthinfo/global_burden_disease/projections/en/). Accessed September 26, 2019.
9. Schutte K, Bornschein J, Kahl S, et al. Delayed diagnosis of HCC with chronic alcoholic liver disease. Liver Cancer 2012;1:257–66.
10. Bucci L, Garuti F, Camelli V, et al. Comparison between alcohol- and hepatitis C virus-related hepatocellular carcinoma: Clinical presentation, treatment and outcome. Aliment Pharmacol Ther 2016;43:385–99.
11. Singal AG, Yopp AC, Gupta S, et al. Failure rates in the hepatocellular carcinoma surveillance process. Cancer Prev Res (Phila) 2012;5:1124–30.
12. Costentin CE, Mourad A, Lahmek P, et al. Hepatocellular carcinoma is diagnosed at a later stage in alcoholic patients: Results of a prospective, nationwide study. Cancer 2018;124:1964–72.
13. Ganne-Carrie N, Nahon P. Hepatocellular carcinoma in the setting of alcohol-related liver disease. J Hepatol 2019;70:284–93.
14. Ganne-Carrie N, Chaffaut C, Bourcier V, et al. Estimate of hepatocellular carcinoma incidence in patients with alcoholic cirrhosis. J Hepatol 2018;69:1274–83.
15. Ioannou GN, Green P, Kerr KF, et al. Models estimating risk of hepatocellular carcinoma in patients with alcohol or NAFLD-related cirrhosis for risk stratification. J Hepatol 2019;71:523–33.
16. Stickel F, Buch S, Nischalke HD, et al. Genetic variants in PNPLA3 and TM6SF2 predispose to the development of hepatocellular carcinoma in individuals with alcohol-related cirrhosis. Am J Gastroenterol 2018;113:1475–83.
17. Wilson DM, III, Tentler JJ, Carney JP, et al. Acute ethanol exposure suppresses the repair of O6-methylguanine DNA lesions in castrated adult male rats. Alcohol Clin Exp Res 1994;18:1267–71.
18. Mechilli M, Schinoppi A, Kobos K, et al. DNA repair deficiency and acetaldehyde-induced chromosomal alterations in CHO cells. Mutagenesis 2008;23:51–6.
19. Gawrieh S, Dakhoul L, Miller E, et al. Characteristics, aetiologies and trends of hepatocellular carcinoma in patients without cirrhosis: A United States multicentre study. Aliment Pharmacol Ther 2019;50:809–21.
20. Marrero JA, Kulik LM, Sirlin CB, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American Association for the Study of Liver Diseases. Hepatology 2018;68:723–50.

21. Edge SB, Compton CC. The American Joint Committee on Cancer: The 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 2010;17:1471–4.
22. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334:693–9.
23. 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;14:124–31 e1.
24. Sharma SA, Kowgier M, Hansen BE, et al. Toronto HCC risk index: A validated scoring system to predict 10-year risk of HCC in patients with cirrhosis. J Hepatol 2017. [Epub ahead of print August 24, 2017.]
25. 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;62:1723–30.
26. Hester CA, Rich NE, Singal AG, et al. Comparative analysis of nonalcoholic steatohepatitis- versus viral hepatitis- and alcohol-related liver disease-related hepatocellular carcinoma. J Natl Compr Canc Netw 2019;17:322–9.
27. Hassan MM, Hwang LY, Hatten CJ, et al. Risk factors for hepatocellular carcinoma: Synergism of alcohol with viral hepatitis and diabetes mellitus. Hepatology 2002;36:1206–13.
28. Beste LA, Leipertz SL, Green PK, et al. Trends in burden of cirrhosis and hepatocellular carcinoma by underlying liver disease in US veterans, 2001-2013. Gastroenterology 2015;149:1471–82.e5; quiz e17–8.