

VOLUME 29 NUMBER 2 April 2023

pISSN 2287-2728
eISSN 2387-285X

CLINICAL and MOLECULAR HEPATOLOGY

The forum for latest knowledge of hepatobiliary diseases



Asia clinical practice guidelines for HCC

Single-cell phenotypes of immune cells in NAFLD

Global burden of primary liver cancer

Factors of unrecognized cirrhosis in HCC patients

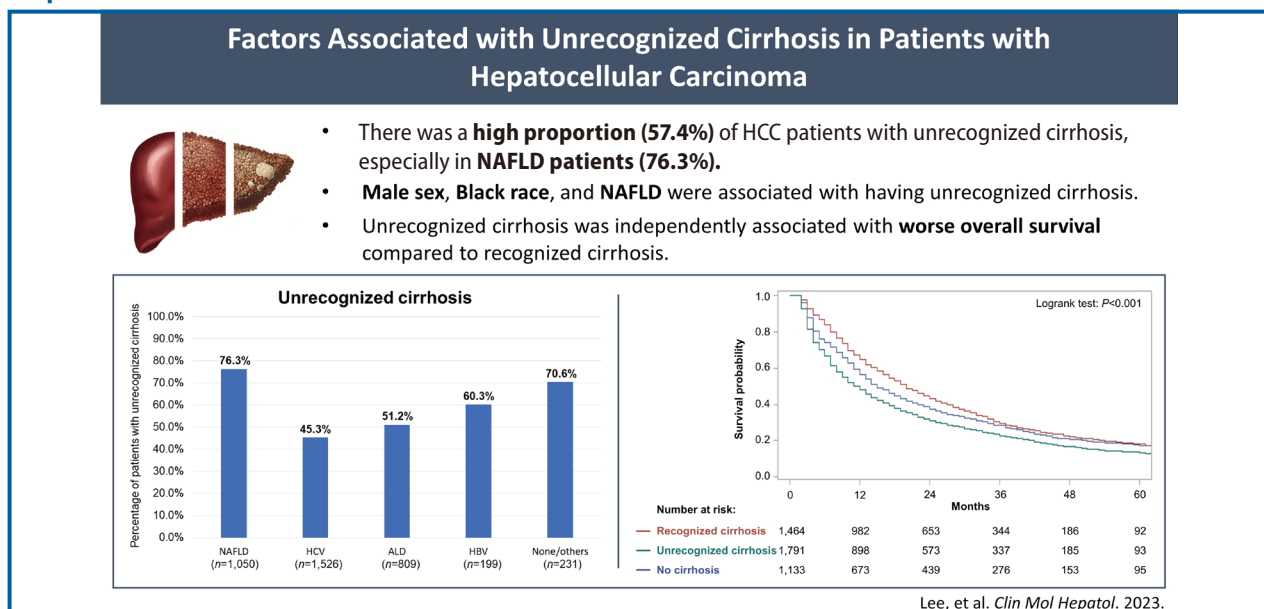
Original Article

Factors associated with unrecognized cirrhosis in patients with hepatocellular carcinoma

Yi-Te Lee¹, Mohammad A. Karim², Hye Chung Kum², Sulki Park², Nicole E. Rich³, Mazen Nouredin^{4,5}, Amit G. Singal³, and Ju Dong Yang^{4,5,6}

¹California NanoSystems Institute, Crump Institute for Molecular Imaging, Department of Molecular and Medical Pharmacology, University of California, Los Angeles, Los Angeles, CA; ²Population Informatics Lab, School of Public Health, Texas A&M University, College Station, TX; ³Division of Digestive and Liver Diseases, University of Texas Southwestern Medical Center, Dallas, TX; ⁴Karsh Division of Gastroenterology and Hepatology, ⁵Comprehensive Transplant Center, ⁶Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA

Graphical Abstract



Study Highlights

- Cirrhosis is the most important risk factor of HCC; however, early cirrhosis is often undiagnosed. We characterized factors associated with unrecognized cirrhosis in a national sample of HCC patients from the United States. Among HCC patients with cirrhosis, 57.4% had unrecognized cirrhosis, with the highest proportion (76.3%) among those with NAFLD-related HCC. Male sex (aOR: 2.12, 95% CI: 1.83–2.46), non-Hispanic Black race (aOR: 1.93, 95% CI: 1.45–2.57), and NAFLD etiology (aOR: 4.46, 95% CI: 3.68–5.41) were associated with having unrecognized cirrhosis. Unrecognized cirrhosis was associated with worse survival (aHR: 1.17, 95% CI: 1.08–1.27) compared to recognized cirrhosis. Our findings suggest these groups as important intervention targets to improve HCC surveillance uptake.

Background/Aims: Cirrhosis is the most important risk factor of hepatocellular carcinoma (HCC), and patients with cirrhosis are recommended to receive semiannual surveillance for early HCC detection. However, early cirrhosis is often asymptomatic and can go undiagnosed for years, leading to underuse of HCC surveillance in clinical practice. We characterized the frequency and associated factors of unrecognized cirrhosis in a national sample of patients with HCC from the United States.

Methods: HCC patients aged 68 years and older, diagnosed during 2011 to 2015 were included from the SEER-Medicare Linked Database. If cirrhosis was diagnosed within 6 months immediately preceding HCC diagnosis or after HCC diagnosis, cases were categorized as unrecognized cirrhosis. Factors associated with unrecognized cirrhosis were identified using logistic regression analyses. Factors associated with overall survival were evaluated using Cox regression analyses.

Results: Among 5,098 HCC patients, 74.8% patients had cirrhosis. Among those with cirrhosis, 57.4% had unrecognized cirrhosis, with the highest proportion (76.3%) among those with NAFLD-related HCC. Male sex (aOR: 2.12, 95% CI: 1.83–2.46), non-Hispanic Black race (aOR: 1.93, 95% CI: 1.45–2.57), and NAFLD etiology (aOR: 4.46, 95% CI: 3.68–5.41) were associated with having unrecognized cirrhosis. Among NAFLD-related HCC patients, male sex (aOR: 2.32, 95% CI: 1.71–3.14) was associated with unrecognized cirrhosis. Unrecognized cirrhosis was independently associated with worse overall survival (aHR: 1.17, 95% CI: 1.08–1.27) compared to recognized cirrhosis.

Conclusions: Unrecognized cirrhosis is common in NAFLD-related HCC, particularly among male and Black patients, highlighting these groups as important intervention targets to improve HCC surveillance uptake and outcomes. (*Clin Mol Hepatol* 2023;29:453-464)

Keywords: Liver cirrhosis; NAFLD; Hepatocellular carcinoma; Cancer screening

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary liver cancer worldwide.^{1,2} Cirrhosis caused by any etiology is the most important risk factor of HCC, and over 90% of patients with HCC in the Western world have underlying cirrhosis.^{1,3} Professional society guidelines recommend patients with cirrhosis undergo semiannual surveillance for HCC.⁴⁻⁶ A systematic review of cohort studies highlighted a consistent association between HCC surveillance and improved clinical outcomes, including early tumor detection and HCC mortality.

ty.⁷

However, HCC surveillance is underused in clinical practice related to patient- and provider-level barriers.⁸ Although there are failures at multiple steps in the cancer screening continuum,⁹⁻¹¹ one common failure is under-recognition of cirrhosis.¹²⁻¹⁵ Early compensated cirrhosis is often asymptomatic and can be undiagnosed for years, particularly given a lack of systematic screening for cirrhosis.¹⁶ Patients with unrecognized cirrhosis are not enrolled in HCC surveillance programs so can experience late-stage HCC detection and worse survival.¹⁷

Corresponding author : Ju Dong Yang

Karsh Division of Gastroenterology and Hepatology, Comprehensive Transplant Center, Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, 8900 Beverly Blvd, Los Angeles, CA 90048, USA
Tel: +1-310-423-1971, Fax: +1-310-423-2356, E-mail: judong.yang@cshs.org
<https://orcid.org/0000-0001-7834-9825>

Editor: Donghee Kim, Stanford University School of Medicine, CA, USA

Received: Dec. 15, 2022 / **Revised:** Jan. 15, 2023 / **Accepted:** Jan. 29, 2023

Abbreviations:

aHR, adjusted hazard ratio; ALD, alcoholic liver disease; aOR, adjusted odds ratio; API, Asian/Pacific Islander; CI, confidence interval; FIB-4, Fibrosis-4; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; ICD-O-3, International Classification of Diseases for Oncology, 3rd edition; Metro, metropolitan; NAFLD, nonalcoholic fatty liver disease; OR, odds ratio; OS, overall survival; SEER, Surveillance, Epidemiology, and End Results; US, United States

Identifying factors associated with under-recognition of cirrhosis can help target intervention strategies, such as increased use of non-invasive markers of fibrosis. A prior retrospective cohort study from the Veterans Administration (VA) reported nonalcoholic fatty liver disease (NAFLD) is associated with a 4.8-fold increased risk of unrecognized cirrhosis.¹⁷ However, it is unclear if these data are generalizable to non-VA populations given differences in patient populations as well as practice patterns.

Herein, we aimed to characterize the frequency and associated factors of unrecognized cirrhosis and its impact on overall survival in a national sample of patients with HCC from the United States.

MATERIALS AND METHODS

Study population

HCC patient data were extracted from the SEER-Medicare Linked Database, which linked data on incident cancer cases from SEER program's 18 cancer registries to data from Medicare, the primary health insurer for individuals aged 65 years and older.¹⁸ The inclusion criteria for HCC cases were (1) International Classification of Diseases (ICD)-Oncology-3 codes, site: C22.0 AND histology: 8170–8175, AND (2) adults ≥ 68 years of age, AND (3) HCC was diagnosed between 2011 and 2015. The reason for limiting the study cohort to adults ≥ 68 years of age is to ensure a 3-year follow-up period after Medicare enrollment for identifying potential risk factors and etiologies for HCC. The exclusion criteria (Supplementary Fig. 1) were (1) HCC cases diagnosed only based on death certificate without microscopic confirmation ($n=437$), OR (2) HCC cases from Medicare Part A and B enrollment with fewer than 3-year follow-up after Medicare enrollment, or HCC cases with fewer than 6-month follow-up after HCC diagnosis ($n=1,886$), OR (3) HCC cases from Medicare health maintenance organizations (HMOs) enrollment ($n=3,487$). We excluded HCC cases from Medicare HMOs because Medicare HMOs plans were not required to submit individual claims information to the Centers for Medicare and Medicaid Services, which might introduce bias to subsequent analyses.

Cirrhosis was defined based on ICD-9 or 10 codes from Medicare claims,¹⁹ or presence of cirrhosis complications including ascites, hepatic encephalopathy, esophageal varices,

etc (Supplementary Table 1).²⁰ If cirrhosis was diagnosed within 6 months immediately preceding HCC diagnosis, or after HCC diagnosis, cases were categorized as "unrecognized cirrhosis." Etiology of HCC was defined based on ICD-9 or 10 codes.²⁰

For overall survival (OS) analyses, we excluded HCC cases without follow-up after diagnosis OR HCC cases who died at the same calendar month of HCC diagnosis (i.e., 0-month follow-up, Supplementary Fig. 1) ($n=710$).

Study variables

Demographic and clinical variables including sex, age, race/ethnicity (categorized as non-Hispanic White, non-Hispanic Black, non-Hispanic Asian/Pacific Islander [API]/Others, and Hispanic), regions stratified by poverty level (as determined by United States Census data), rural-urban regions (level of metropolitan and nonmetropolitan based on the United States Department of Agriculture Economic Research Service definition), National Cancer Institute (NCI) Comorbidity Index, liver disease etiology, and the presence of diabetes, ascites, and hepatic encephalopathy were included in this study.

To calculate the NCI Comorbidity Index for representing the noncancer comorbidity, we applied the ICD diagnosis and procedure codes one year before HCC diagnosis.²¹ To avoid collinearity in the subsequent multivariable analyses, the NCI Comorbidity Index for HCC patients was calculated after excluding liver disease and diabetes.²⁰ To determine the etiology of HCC, Medicare claims ICD-9 or 10 codes for hepatitis C virus (HCV), hepatitis B virus (HBV), alcoholic liver disease (ALD), NAFLD, and others were used. We classified patients with ICD-9 or 10 code for obesity, diabetes, history of bariatric surgery or both dyslipidemia and hypertension in the absence of HBV, HCV, alcohol abuse, and other known liver disease as NAFLD since NAFLD is often under-coded.²⁰ For patients with ≥ 2 etiologies, the etiology was assigned by the following hierarchy: HCV>HBV>ALD>others>NAFLD. The ICD-9 or 10 codes for defining chronic liver diseases, diabetes, and complications related to cirrhosis were provided in Supplementary Table 2 and Supplementary Table 3, respectively.

The variables of tumor stage and treatment type were included in the OS analyses. We defined early-stage HCC as a single tumor, less than or equal to 5 cm in diameter without vascular invasion or extrahepatic metastasis since SEER-Medicare Linked Database only categorizes tumor number as

unifocal or multifocal.²⁰ Treatments were stratified as potentially curative treatments (liver resection, liver transplantation, and tumor ablation) and non-curative treatments (che-

moembolization, radioembolization, other radiation, systemic treatment, and others/best supportive care).²⁰

Table 1. Clinical characteristics of HCC patients with recognized cirrhosis, unrecognized cirrhosis, or no cirrhosis

Characteristics	Recognized cirrhosis (n=1,625)	Unrecognized cirrhosis (n=2,190)	No cirrhosis (n=1,283)	P-value
Male Sex	962 (59.2)	1,569 (71.6)	907 (70.7)	<0.001
Age	75.2±5.67	76.8±6.11	78.6±6.54	<0.001
Race/ethnicity				<0.001
Non-Hispanic White	968 (59.6)	1,378 (63.0)	878 (68.4)	-
Non-Hispanic Black	100 (6.1)	180 (8.2)	110 (8.6)	-
Non-Hispanic API/Others	257 (15.8)	360 (16.4)	193 (15.0)	-
Hispanic	300 (18.5)	272 (12.4)	102 (8.0)	-
Poverty level				0.76
0% to <5% poverty	318 (19.6)	447 (20.4)	246 (19.2)	-
5% to <10% poverty	363 (22.3)	520 (23.7)	309 (24.1)	-
10% to <20% poverty	517 (31.8)	659 (30.1)	384 (29.9)	-
20% to 100% poverty	427 (26.3)	564 (25.8)	344 (26.8)	-
Rural-Urban				0.002
Metro >1 million	986 (60.7)	1,333 (60.9)	710 (55.3)	-
Metro 250k to 1 million	340 (20.9)	408 (18.6)	280 (21.8)	-
Metro <250k	132 (8.1)	162 (7.4)	120 (9.4)	-
Non-Metro/Rural	167 (10.3)	287 (13.1)	173 (13.5)	-
NCI Comorbidity Index				0.67
Low (0 to 2)	1,223 (75.3)	1,660 (75.8)	959 (74.7)	-
Moderate (>2 to 4)	221 (13.6)	312 (14.2)	192 (15.0)	-
High (>4)	181 (11.1)	218 (10.0)	132 (10.3)	-
Etiology				<0.001
HCV	834 (51.3)	692 (31.6)	189 (14.7)	-
NAFLD	249 (15.3)	801 (36.6)	763 (59.5)	-
ALD	395 (24.3)	414 (18.9)	86 (6.7)	-
HBV	79 (4.9)	120 (5.5)	47 (3.7)	-
Other/None	68 (4.2)	163 (7.4)	198 (15.4)	-
Diabetes	1,083 (66.6)	1,408 (64.3)	771 (60.1)	<0.001
Ascites	986 (60.7)	1,227 (56.0)	0 (0)	<0.001
Hepatic encephalopathy	540 (33.2)	335 (15.3)	0 (0)	<0.001
Early stage*	485 (29.9)	301 (13.7)	181 (14.1)	<0.001
Curative treatment†	474 (29.2)	435 (19.9)	258 (20.1)	<0.001

Values are presented as number (%) or mean±standard deviation.

ALD, alcoholic liver disease; API, Asian/Pacific Islander; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; Metro, metropolitan; NAFLD, nonalcoholic fatty liver disease; NCI, National Cancer Institute.

*Early-stage HCC was defined as a single tumor, less than or equal to 5 cm in diameter without vascular invasion or extrahepatic. †Curative treatments were defined as liver resection, liver transplantation, and tumor ablation.

Statistical analysis

Demographic and clinical variables among patients with unrecognized cirrhosis, recognized cirrhosis, and no cirrhosis were compared using chi-square test for categorical variables and one-way analysis of variance test for continuous variable (i.e., age). Factors associated with unrecognized cirrhosis were identified using univariate and multivariable logistic regression analyses. OS probabilities of HCC patients stratified by cirrhosis status were estimated using the Kaplan-Meier method and compared using the log-rank test. Factors associated with OS were evaluated using univariate and multivariable Cox regression analyses.

All statistical analyses were performed using SAS 9.4 (SAS Institute, Inc., Cary, NC, USA) and Stata 16.1 (StataCorp, College Station, TX, USA) software with two-sided tests and a significance level of 0.05.

RESULTS

Clinical characteristics

We identified 5,098 eligible patients with HCC, of whom

NAFLD (35.6%) was the leading underlying etiology, followed by HCV (33.6%), ALD (17.6%), other/no etiologies (8.4%), and HBV (4.8%). A total of 3,815 patients with HCC (74.8%) were diagnosed with underlying cirrhosis, although there was a wide variation between etiologies (89.0% HCV, 80.9% HBV, 90.4% ALD, 57.9% NAFLD, and 53.8% other/no etiologies).

Among patients with cirrhosis, 2,190 patients (57.4%) had unrecognized cirrhosis. The clinical characteristics of HCC patients with recognized cirrhosis, unrecognized cirrhosis, and no cirrhosis were summarized in Table 1. Compared to those with recognized cirrhosis, a higher proportion of patients with unrecognized cirrhosis were older, male, non-Hispanic Black, and had underlying NAFLD. In fact, 76.3% of patients NAFLD and 70.6% of those with other etiologies had unrecognized cirrhosis at HCC diagnosis (Fig. 1).

Factors associated with unrecognized cirrhosis

Among HCC patients with cirrhosis, univariate logistic regression analysis revealed older age, male sex, living in non-metro/rural counties, and NAFLD etiology as being associated with greater odds of having unrecognized cirrhosis, while Hispanic ethnicity and higher NCI comorbidity index were associated with lower odds of unrecognized cirrhosis (Table

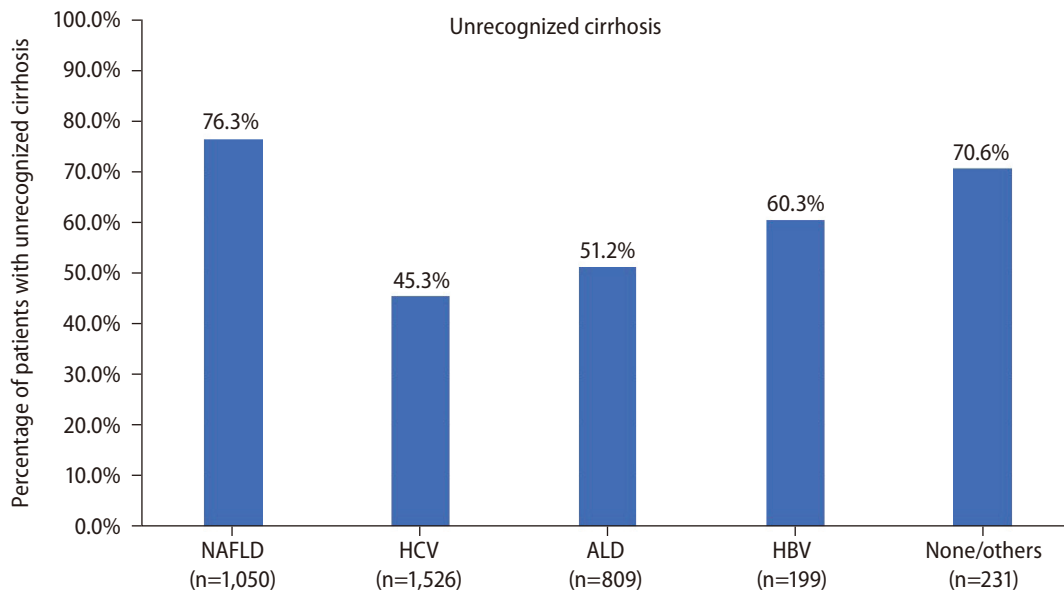


Figure 1. Proportion of HCC patients with unrecognized cirrhosis by etiology. A high proportion of individuals with NAFLD-related HCC had unrecognized cirrhosis. ALD, alcoholic liver disease; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; NAFLD, nonalcoholic fatty liver disease.

Table 2. Factors associated with unrecognized cirrhosis among HCC patients with cirrhosis (n=3,815)

Characteristics	Univariate analysis		Multivariable analysis	
	OR (95% CI)	P-value	aOR (95% CI)	P-value
Male sex (ref. female)	1.74 (1.52 to 1.99)	<0.001	2.12 (1.83 to 2.46)	<0.001
Age	1.05 (1.04 to 1.06)	<0.001	1.04 (1.03 to 1.05)	<0.001
Race/ethnicity				
Non-Hispanic White	Ref	Ref	Ref	Ref
Non-Hispanic Black	1.26 (0.98 to 1.64)	0.08	1.93 (1.45 to 2.57)	<0.001
Non-Hispanic API/Others	0.98 (0.82 to 1.18)	0.86	1.22 (0.99 to 1.50)	0.07
Hispanic	0.64 (0.53 to 0.77)	<0.001	0.79 (0.65 to 0.96)	0.02
Poverty level				
<5%	Ref	Ref	Ref	Ref
5% to <10%	1.02 (0.84 to 1.24)	0.85	1.04 (0.84 to 1.29)	0.70
10% to <20%	0.91 (0.76 to 1.09)	0.30	0.93 (0.77 to 1.14)	0.51
20% to 100%	0.94 (0.78 to 1.14)	0.55	1.05 (0.85 to 1.30)	0.67
Rural-Urban				
Metro >1 million	Ref	Ref	Ref	Ref
Metro 250k to 1 million	0.89 (0.75 to 1.05)	0.16	0.87 (0.73 to 1.04)	0.14
Metro <250k	0.91 (0.71 to 1.16)	0.44	0.85 (0.65 to 1.11)	0.23
Non-Metro/Rural	1.27 (1.03 to 1.56)	0.02	1.08 (0.86 to 1.36)	0.52
NCI Comorbidity Index				
Low (0 to 2)	Ref	Ref	Ref	Ref
Moderate (>2 to 4)	1.04 (0.86 to 1.25)	0.68	0.95 (0.77 to 1.16)	0.59
High (>4)	0.89 (0.72 to 1.10)	0.27	0.72 (0.57 to 0.90)	0.005
Etiology				
HCV	Ref	Ref	Ref	Ref
NAFLD	3.88 (3.26 to 4.62)	<0.001	4.46 (3.68 to 5.41)	<0.001
ALD	1.26 (1.06 to 1.50)	0.007	1.25 (1.04 to 1.50)	0.02
HBV	1.83 (1.35 to 2.47)	<0.001	1.70 (1.23 to 2.33)	0.001
Other/None	2.89 (2.14 to 3.90)	<0.001	2.86 (2.09 to 3.93)	<0.001
Diabetes	0.90 (0.79 to 1.03)	0.13	0.73 (0.63 to 0.85)	<0.001

ALD, alcoholic liver disease; aOR, adjusted odds ratio; API, Asian/Pacific Islander; CI, confidence interval; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; Metro, metropolitan; NAFLD, nonalcoholic fatty liver disease; NCI, National Cancer Institute; OR, odds ratio.

2). In multivariable logistic regression analysis, older age (adjusted odds ratio [aOR]: 1.04, 95% confidence interval [CI]: 1.03–1.05), male sex (aOR: 2.12, 95% CI: 1.83–2.46), non-Hispanic Black race (reference: non-Hispanic White; aOR: 1.93, 95% CI: 1.45–2.57), and NAFLD etiology (reference: HCV; aOR: 4.46, 95% CI: 3.68–5.41) were associated with unrecognized cirrhosis (Table 2). Conversely, Hispanic ethnicity (aOR: 0.79, 95% CI: 0.65–0.96), higher NCI comorbidity index (aOR: 0.72, 95% CI: 0.57–0.90), and diabetes (aOR: 0.73, 95% CI: 0.63–

0.85) were inversely associated with having unrecognized cirrhosis in multivariable analysis (Table 2).

Subgroup analysis was performed to further identify factors associated with unrecognized cirrhosis among cirrhotic patients with NAFLD-related HCC. Male sex (aOR: 2.32, 95% CI: 1.71–3.14) and older age (aOR: 1.03, 95% CI: 1.00–1.05) was associated with unrecognized cirrhosis, while higher NCI comorbidity index (aOR: 0.58, 95% CI: 0.39–0.86) was inversely associated (Table 3).

Table 3. Factors associated with unrecognized cirrhosis among cirrhotic patients with NAFLD-related HCC (n=1,050)

Characteristics	Univariate analysis		Multivariable analysis	
	OR (95% CI)	P-value	aOR (95% CI)	P-value
Male sex (ref. female)	2.38 (1.78 to 3.18)	<0.001	2.32 (1.71 to 3.14)	<0.001
Age	1.03 (1.01 to 1.05)	0.01	1.03 (1.00 to 1.05)	0.02
Race/ethnicity				
Non-Hispanic White	Ref	Ref	Ref	Ref
Non-Hispanic Black	1.61 (0.61 to 4.25)	0.33	1.85 (0.67 to 5.07)	0.23
Non-Hispanic API/Others	1.49 (0.90 to 2.49)	0.12	1.56 (0.92 to 2.64)	0.10
Hispanic	0.56 (0.38 to 0.81)	0.003	0.70 (0.47 to 1.05)	0.08
Census Poverty Level				
<5%	Ref	Ref	Ref	Ref
5% to <10%	0.84 (0.53 to 1.33)	0.45	0.85 (0.53 to 1.37)	0.51
10% to <20%	0.58 (0.38 to 0.88)	0.01	0.65 (0.42 to 1.01)	0.06
20% to 100%	0.66 (0.42 to 1.04)	0.07	0.79 (0.48 to 1.29)	0.34
Rural-Urban				
Metro >1 million	Ref	Ref	Ref	Ref
Metro 250k to 1 million	0.76 (0.53 to 1.09)	0.13	0.73 (0.50 to 1.06)	0.10
Metro <250k	0.92 (0.55 to 1.55)	0.77	1.06 (0.61 to 1.82)	0.85
Non-Metro/Rural	1.08 (0.71 to 1.64)	0.72	1.14 (0.73 to 1.78)	0.56
NCI comorbidity index				
Low (0 to 2)	Ref	Ref	Ref	Ref
Moderate (>2 to 4)	1.24 (0.82 to 1.89)	0.30	1.20 (0.78 to 1.86)	0.41
High (>4)	0.65 (0.45 to 0.96)	0.03	0.58 (0.39 to 0.86)	0.007
Diabetes	0.73 (0.49 to 1.09)	0.12	0.71 (0.47 to 1.08)	0.11

aOR, adjusted odds ratio; API, Asian/Pacific Islander; CI, confidence interval; HCC, hepatocellular carcinoma; Metro, metropolitan; NAFLD, nonalcoholic fatty liver disease; NCI, National Cancer Institute; OR, odds ratio.

Association between unrecognized cirrhosis and overall survival

Compared to patients with recognized cirrhosis, significant lower proportion of patients with unrecognized cirrhosis were presented with early-stage HCC (13.7% vs. 29.9%) and underwent potentially curative treatments (19.9% vs. 29.2%) (Table 1). Median OS were 20 months (interquartile range [IQR]: 9–43 months), 12 months (IQR: 4–33 months), and 15 months (IQR: 6–41 months) for patients with recognized cirrhosis, unrecognized cirrhosis, and no cirrhosis, respectively ($P<0.001$; Fig. 2). In multivariable Cox regression analysis adjusting for the demographic and clinical variables, tumor stage, and treatment type (Table 4), unrecognized cirrhosis was independently associated with worse OS (adjusted HR [aHR]: 1.17, 95% CI: 1.08–1.27) compared to recognized cirrho-

sis, while patients with no cirrhosis had favorable OS (aHR: 0.84, 95% CI: 0.76–0.93).

DISCUSSION

We investigated the frequency and associated factors for unrecognized cirrhosis among patients with cirrhosis and HCC using a large United States Medicare-based database. We found over 50% of HCC patients had unrecognized cirrhosis prior to HCC diagnosis, including three-fourths of those with NAFLD-related HCC. Older age, male sex, Non-Hispanic Black race, and NAFLD etiology were independently associated with greater odds of unrecognized cirrhosis, while Hispanic ethnicity, higher comorbidity, and diabetes were associated with lower odds of having unrecognized cirrhosis.

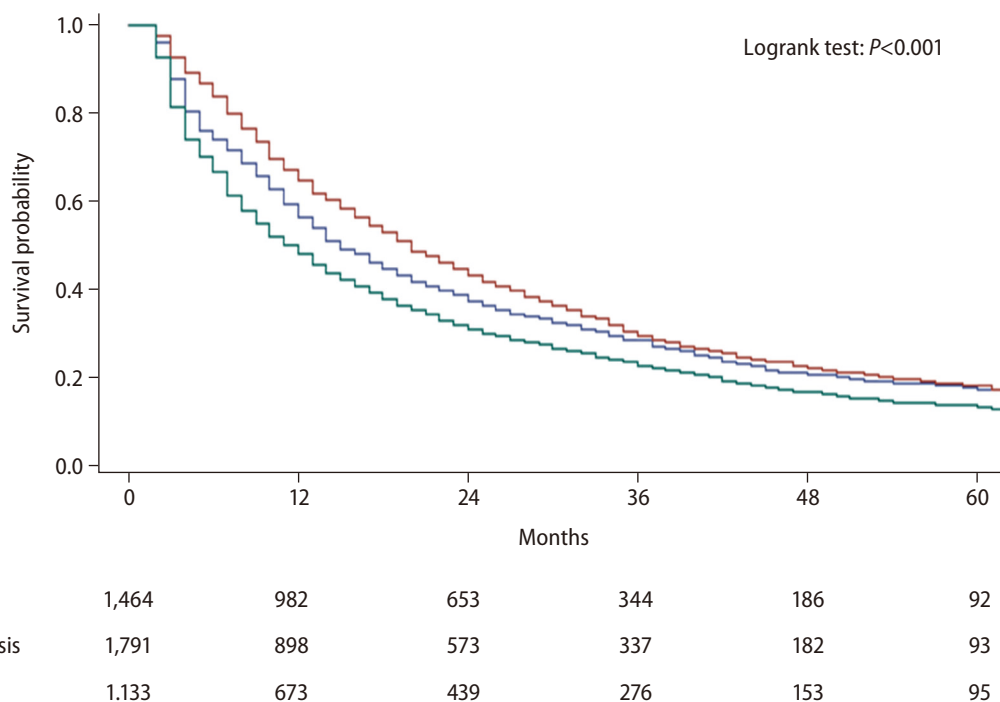


Figure 2. Overall survival estimates of HCC patients stratified by cirrhosis status. HCC, hepatocellular carcinoma.

Lastly, our study confirmed that HCC patients with unrecognized cirrhosis were associated with worse survival than those with recognized cirrhosis.

In line with the findings in the previous VA study,¹⁷ we showed that NAFLD was associated with a more than four-fold increased likelihood of having unrecognized cirrhosis compared to HCV. A recent study showed that only 4.4% of patients with NAFLD in the United States were aware of their liver disease, much lower than the percentages of patients with HCV (42.4%) and HBV (17.2%).²² The low awareness of liver diseases among patients with NAFLD could be attributed to the insufficient understanding of NAFLD for both the general population and non-hepatologist physicians.²³ Considering the increasing burden of NAFLD in the world,^{24,25} American Association of Clinical Endocrinology and American Association for the Study of Liver Diseases recently provided a clinical practice guideline for diagnosis and management of NAFLD to prevent the development of liver cirrhosis and related comorbidities.^{26,27} The guideline suggests using liver fibrosis prediction calculations (e.g., Fibrosis-4) to initially assess the risk of advanced liver fibrosis in NAFLD patients, and triage the high-risk patients for fibrosis/cirrhosis screening by transient elastography. With increased availability of

non-invasive biomarkers of fibrosis and transient elastography, the guideline will potentially increase recognition of NAFLD-related cirrhosis, especially for primary care physicians and endocrinologists who often look after NAFLD patients.

In overall and NAFLD subgroup analyses, we observed sex differences with the male having more than a two-fold increased likelihood of having unrecognized cirrhosis, which could arise from the variance of adherence to regular follow-up with physician and screening test.^{15,28} For example, a United States cohort study demonstrated females were more compliant with HCC surveillance than males.²⁸ More recently, a study exploring potential reasons for HCC screening underuse showed similar results, indicating that men were less likely to stick to regular outpatient care than women.¹⁵ Even patients having regular outpatient care, failure of receiving ultrasound or noninvasive biomarkers for fibrosis might cause unrecognized of cirrhosis.^{15,29} Further investigation is warranted to understand underlying causes of this sex difference.

We noted Non-Hispanic Black race was associated with increased likelihood of having unrecognized cirrhosis. Higher likelihood of having unrecognized cirrhosis in non-Hispanic

Table 4. Factors associated with overall survival among HCC patients (n=4,388)

Characteristics	Univariate analysis		Multivariable analysis	
	HR (95% CI)	P-value	aHR (95% CI)	P-value
Cirrhosis status				
Recognized cirrhosis	Ref	Ref	Ref	Ref
Unrecognized cirrhosis	1.35 (1.25 to 1.46)	<0.001	1.17 (1.08 to 1.27)	<0.001
No cirrhosis	1.11 (1.02 to 1.21)	0.02	0.84 (0.76 to 0.93)	0.001
Male sex (ref. female)				
	1.16 (1.08 to 1.25)	<0.001	1.06 (0.98 to 1.14)	0.14
Age				
	1.03 (1.02 to 1.03)	<0.001	1.01 (1.00 to 1.02)	<0.001
Race/ethnicity				
Non-Hispanic White	Ref	Ref	Ref	Ref
Non-Hispanic Black	1.01 (0.89 to 1.15)	0.86	0.97 (0.85 to 1.12)	0.70
Non-Hispanic API/Others	0.65 (0.59 to 0.72)	<0.001	0.77 (0.69 to 0.86)	<0.001
Hispanic	0.94 (0.85 to 1.04)	0.22	0.92 (0.83 to 1.02)	0.12
Census Poverty Level				
<5%	Ref	Ref	Ref	Ref
5% to <10%	1.14 (1.03 to 1.26)	0.01	1.06 (0.95 to 1.17)	0.30
10% to <20%	1.12 (1.02 to 1.24)	0.02	1.03 (0.93 to 1.14)	0.55
20% to 100%	1.14 (1.03 to 1.26)	0.009	1.08 (0.97 to 1.20)	0.17
Rural-Urban				
Metro >1 million	Ref	Ref	Ref	Ref
Metro 250k to 1 million	1.15 (1.06 to 1.25)	0.001	1.14 (1.05 to 1.24)	0.002
Metro <250k	1.23 (1.09 to 1.39)	0.001	1.07 (0.94 to 1.21)	0.29
Non-Metro/Rural	1.28 (1.15 to 1.42)	<0.001	1.12 (1.00 to 1.25)	0.04
NCI comorbidity index				
Low (0 to 2)	Ref	Ref	Ref	Ref
Moderate (>2 to 4)	1.23 (1.11 to 1.35)	<0.001	1.09 (0.99 to 1.20)	0.09
High (>4)	1.60 (1.43 to 1.78)	<0.001	1.35 (1.21 to 1.51)	<0.001
Etiology				
HCV	Ref	Ref	Ref	Ref
NAFLD	1.37 (1.27 to 1.49)	<0.001	1.19 (1.09 to 1.31)	<0.001
ALD	1.36 (1.24 to 1.50)	<0.001	1.18 (1.06 to 1.30)	0.001
HBV	0.87 (0.73 to 1.03)	0.10	1.08 (0.91 to 1.28)	0.40
Other/None	1.21 (1.06 to 1.38)	0.004	1.13 (0.98 to 1.29)	0.09
Diabetes	1.09 (1.02 to 1.17)	0.01	1.04 (0.97 to 1.12)	0.29
Early stage*	0.46 (0.42 to 0.50)	<0.001	0.54 (0.50 to 0.60)	<0.001
Curative treatment [†]	0.27 (0.25 to 0.30)	<0.001	0.30 (0.28 to 0.33)	<0.001

aHR, adjusted hazard ratio; ALD, alcoholic liver disease; API, Asian/Pacific Islander; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; Metro, metropolitan; NAFLD, nonalcoholic fatty liver disease; NCI, National Cancer Institute.

*Early-stage HCC was defined as a single tumor, less than or equal to 5 cm in diameter without vascular invasion or extrahepatic. [†]Curative treatments were defined as liver resection, liver transplantation, and tumor ablation.

Black patients may partly explain underlying racial ethnic disparity in HCC surveillance, curative treatment, and overall survival as reported in previous studies.^{20,30-33} Consistent with other studies, our previous study using SEER-Medicare Linked Database showed that non-Hispanic Black race is inversely associated with HCC surveillance receipt, early stage HCC detection, and curative treatment receipt.²⁰ A comprehensive approach to monitoring and eliminating racial-ethnic disparities in early recognition of cirrhosis and surveillance implementation is urgently needed to reduce disparities in early HCC detection and prognosis. Other than demographic factors, we found that higher comorbidities and diabetes were associated with lower odds of having unrecognized cirrhosis. This could be explained by higher health-care utilization in patients with comorbid conditions.

While under-recognition of cirrhosis is thought to be related to poor survival due to the lack of HCC surveillance, no study directly interrogates their association. The previous VA study showed HCC patients with unrecognized cirrhosis were 6.5 times more likely to be diagnosed with advanced stage HCC compared to with recognized cirrhosis,¹⁷ implying their unfavorable prognosis. Importantly, our study first confirmed the inferior survival of HCC patients with unrecognized cirrhosis, even after adjusting for tumor stage and treatment type. Therefore, earlier recognition of cirrhosis, particularly in the growing population of NAFLD patients will likely lead to improved overall survival after HCC diagnosis.

We acknowledge the inherent limitations of this retrospective study. First, compared to previous study by Walker et al.¹⁷, where a systematic electronic chart review was performed, use of ICD-9 and ICD-10 codes in our current study to define cirrhosis and the underlying etiology of HCC could have led to misclassification. For example, some cirrhosis cases may have been recognized but could have been undercoded; codes for cirrhosis were not assigned within 6 months preceding HCC diagnosis may not guarantee the unrecognized of cirrhosis. However, consistency of the findings between ours and Walker et al.¹⁷ confirmed the validity of the results. Secondly, Medicare population represents older individuals, and the study results might not be generalizable to younger patients with HCC. In addition, the stringent inclusion and exclusion criteria of this study might introduce selection bias. For instance, since most of the patients with HBV- or HCV-related HCC were diagnosed and deceased before 70 years old,^{34,35} patients with NAFLD-related HCC might have been

overrepresented and burden of unrecognized cirrhosis could have been overestimated in the current study. Lastly, missing data on Child-Pugh score prevent us from performing granular subgroup analyses.

Despite these limitations, our study has the strength of including nationwide population compared to the previous study.¹⁷ We first confirmed the findings (i.e., NAFLD, Black race, and age are associated unrecognized cirrhosis) from the previous study¹⁷ in a larger cohort outside VA system. In addition, the majority of patients in the previous study had HCV-associated HCC,¹⁷ while few HCC patients with NAFLD were included.¹⁷ Our study included more balanced etiologies and 1,813 HCC patients had NAFLD, which could represent the trends of global rise of HCC patients attributed to NAFLD. Lastly, we enrolled the HCC patients diagnosed between 2011–2015, which follows the period (2005–2011) of the previous study,¹⁷ highlighting the issue of unrecognized cirrhosis remains unsolved and requires immediate intervention.

In summary, our results highlight that unrecognized of cirrhosis remains a common barrier to effective HCC surveillance implementation in the United States, particularly among patients with NAFLD-related HCC. We also validated the independent association between unrecognized cirrhosis and poor prognosis. Future studies and efforts are required to evaluate intervention strategies to better recognize cirrhosis at early stages to promote increased uptake of HCC surveillance programs and improve patients' outcomes.

Authors' contribution

Concept and design: Yang JD; Acquisition and Statistical analysis: Karim M; Drafting of the manuscript: Lee Y-T, Singal AG, Yang JD; Interpretation of data, Critical revision of the manuscript for important intellectual content: All authors; Administrative, technical, or material support: Yang JD; Supervision: Yang JD.

Acknowledgements

This study used the SEER-Medicare Linked Database. The authors acknowledge the efforts of the Centers for Disease Control and Prevention; National Program of Cancer Registries; National Cancer Institute; the Surveillance, Epidemiology, and End Results program; and the Medicare program in the creation of the SEER-Medicare Linked Database.

Dr. Singal's research is funded by National Institutes of Health R01 MD012565 and U01 CA230694. Dr. Rich's research is funded by American College of Gastroenterology Junior Faculty Development Award. Dr. Karim's research is funded in part by a fellowship supported by the Cancer Prevention and Research Institute of Texas (CPRIT) grant award RP170259 (to Mohammad A. Karim, PhD; PI: Shine Chang, PhD and Sanjay Shete, PhD). Dr. Karim and Dr. Kum's research is funded in part by the Population Informatics Lab, and the Texas Virtual Data Library (ViDaL) at Texas A&M University. Dr. Yang's research is supported by American College of Gastroenterology Junior Faculty Development Award and Department of Defense Peer Reviewed Cancer Research Program Career Development Award CA191051 and National Institutes of Health K08 CA259534. The American College of Gastroenterology, the CPRIT, Cedars-Sinai Medical Center, Department of Defense, National Institutes of Health, the Population Informatics Lab, and the ViDaL at Texas A&M University had no role in the collection of data; the design and conduct of the study; management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Conflicts of Interest

Dr. Singal has been on advisory boards and served as a consultant for Wako Diagnostics, Glycotest, Exact Sciences, Roche, GRAIL, Genentech, Bayer, Eisai, BMS, Exelixis, AstraZeneca, and TARGET RWE. Dr Rich as served as consultant for AstraZeneca. Dr. Nouredin has been on the advisory board for 89BIO, Gilead, Intercept, Pfizer, Novo Nordisk, Blade, EchoSens, Fractyl, Terns, Siemens and Roche diagnostic; MN has received research support from Allergan, BMS, Gilead, Galmed, Galectin, Genfit, Conatus, Enanta, Madrigal, Novartis, Pfizer, Shire, Viking and Zydus; Dr. Nouredin is a minor shareholder or has stocks in Anaetos, Rivus Pharma and Viking. Dr. Yang provides consulting services for Exact Sciences, Gilead Sciences, Exelixis, and Eisai. Dr. Lee, Dr. Karim, Dr. Kum, and Dr. Park have no conflicts of interest to disclose.

SUPPLEMENTARY MATERIAL

Supplementary material is available at Clinical and Molecular Hepatology website (<http://www.e-cmh.org>).

REFERENCES

1. Yang JD, Hainaut P, Gores GJ, Amadou A, Plymoth A, Roberts LR. A global view of hepatocellular carcinoma: trends, risk, prevention and management. *Nat Rev Gastroenterol Hepatol* 2019;16:589-604.
2. Lee YT, Singal AG, Luu M, Nissen NN, Gores GJ, Yang JD. Increasing incidence of intrahepatic cholangiocarcinoma relative to hepatocellular carcinoma in the United States. *Gastro Hep Advances* 2022;1:121-124.
3. Yang JD, Kim WR, Coelho R, Mettler TA, Benson JT, Sanderson SO, et al. Cirrhosis is present in most patients with hepatitis B and hepatocellular carcinoma. *Clin Gastroenterol Hepatol* 2011;9:64-70.
4. European Association for the Study of the Liver. EASL clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 2018;69:182-236.
5. Omata M, Cheng AL, Kokudo N, Kudo M, Lee JM, Jia J, et al. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. *Hepatol Int* 2017;11:317-370.
6. Singal AG, Llovet J, Yarrow M, Mehta N, Heimbach J, Dawson L. AASLD guidance on prevention, diagnosis and treatment of hepatocellular carcinoma. *Hepatology*. Forthcoming.
7. Singal AG, Zhang E, Narasimman M, Rich NE, Waljee AK, Hoshida Y, et al. HCC surveillance improves early detection, curative treatment receipt, and survival in patients with cirrhosis: a meta-analysis. *J Hepatol* 2022;77:128-139.
8. Hanouneh IA, Alkhouri N, Singal AG. Hepatocellular carcinoma surveillance in the 21st century: saving lives or causing harm? *Clin Mol Hepatol* 2019;25:264-269.
9. Wolf E, Rich NE, Marrero JA, Parikh ND, Singal AG. Use of hepatocellular carcinoma surveillance in patients with cirrhosis: a systematic review and meta-analysis. *Hepatology* 2021;73:713-725.
10. Singal AG, Tiro JA, Murphy CC, Blackwell JM, Kramer JR, Khan A, et al. Patient-reported barriers are associated with receipt of hepatocellular carcinoma surveillance in a multicenter cohort of patients with cirrhosis. *Clin Gastroenterol Hepatol* 2021;19:987-995.e1.
11. Simmons OL, Feng Y, Parikh ND, Singal AG. Primary care provider practice patterns and barriers to hepatocellular carcinoma surveillance. *Clin Gastroenterol Hepatol* 2019;17:766-773.
12. Singal AG, Yopp AC, Gupta S, Skinner CS, Halm EA, Okolo E, et al. Failure rates in the hepatocellular carcinoma surveillance process. *Cancer Prev Res (Phila)* 2012;5:1124-1130.

13. Parikh ND, Tayob N, Al-Jarrah T, Kramer J, Melcher J, Smith D, et al. Barriers to surveillance for hepatocellular carcinoma in a multicenter cohort. *JAMA Netw Open* 2022;5:e2223504.
14. Singal AG, Lok AS, Feng Z, Kanwal F, Parikh ND. Conceptual model for the hepatocellular carcinoma screening continuum: current status and research agenda. *Clin Gastroenterol Hepatol* 2022;20:9-18.
15. Marquardt P, Liu PH, Immergluck J, Olivares J, Arroyo A, Rich NE, et al. Hepatocellular carcinoma screening process failures in patients with cirrhosis. *Hepatol Commun* 2021;5:1481-1489.
16. Schuppan D, Afdhal NH. Liver cirrhosis. *Lancet* 2008;371:838-851.
17. Walker M, El-Serag HB, Sada Y, Mittal S, Ying J, Duan Z, et al. Cirrhosis is under-recognised in patients subsequently diagnosed with hepatocellular cancer. *Aliment Pharmacol Ther* 2016;43:621-630.
18. Warren JL, Klabunde CN, Schrag D, Bach PB, Riley GF. Overview of the SEER-Medicare data: content, research applications, and generalizability to the United States elderly population. *Med Care* 2002;40(8 Suppl):IV-3-18.
19. Kramer JR, Davila JA, Miller ED, Richardson P, Giordano TP, El-Serag HB. The validity of viral hepatitis and chronic liver disease diagnoses in Veterans Affairs administrative databases. *Aliment Pharmacol Ther* 2008;27:274-282.
20. Karim MA, Singal AG, Kum HC, Lee YT, Park S, Rich NE, et al. Clinical characteristics and outcomes of nonalcoholic fatty liver disease-associated hepatocellular carcinoma in the United States. *Clin Gastroenterol Hepatol* 2023;21:670-680.e18.
21. Yang JD, Ahmed Mohammed H, Harmsen WS, Enders F, Gores GJ, Roberts LR. Recent trends in the epidemiology of hepatocellular carcinoma in Olmsted County, Minnesota: a US population-based study. *J Clin Gastroenterol* 2017;51:742-748.
22. Alqahtani SA, Paik JM, Biswas R, Arshad T, Henry L, Younossi ZM. Poor awareness of liver disease among adults with NAFLD in the United States. *Hepatol Commun* 2021;5:1833-1847.
23. Younossi ZM, Ong JP, Takahashi H, Yilmaz Y, Eguc Hi Y, El-Kassas M, et al. A global survey of physicians' knowledge about nonalcoholic fatty liver disease. *Clin Gastroenterol Hepatol* 2022;20:e1456-e1468.
24. Ge X, Zheng L, Wang M, Du Y, Jiang J. Prevalence trends in non-alcoholic fatty liver disease at the global, regional and national levels, 1990-2017: a population-based observational study. *BMJ Open* 2020;10:e036663.
25. Cho Y, Kim BH, Park JW. Preventive strategy for nonalcoholic fatty liver disease-related hepatocellular carcinoma. *Clin Mol Hepatol*. 2022 Nov 10. doi: 10.3350/cmh.2022.0360.
26. Cusi K, Isaacs S, Barb D, Basu R, Caprio S, Garvey WT, et al. American Association of Clinical Endocrinology clinical practice guideline for the diagnosis and management of nonalcoholic fatty liver disease in primary care and endocrinology clinical settings: co-sponsored by the American Association for the Study of Liver Diseases (AASLD). *Endocr Pract* 2022;28:528-562.
27. Seif El Dahan K, Daher D, Singal AG. HCC Surveillance in Patients with NAFLD. *Clin Mol Hepatol Hepatol*. 2022 Sep 14. doi: 10.3350/cmh.2022.0247.
28. Ladenheim MR, Kim NG, Nguyen P, Le A, Stefanick ML, Garcia G, et al. Sex differences in disease presentation, treatment and clinical outcomes of patients with hepatocellular carcinoma: a single-centre cohort study. *BMJ Open Gastroenterol* 2016;3:e000107.
29. Kumar R, Goh BG, Kam JW, Chang PE, Tan CK. Comparisons between non-alcoholic steatohepatitis and alcohol-related hepatocellular carcinoma. *Clin Mol Hepatol* 2020;26:196-208.
30. Rich NE, Hester C, Odewole M, Murphy CC, Parikh ND, Marrero JA, et al. Racial and ethnic differences in presentation and outcomes of hepatocellular carcinoma. *Clin Gastroenterol Hepatol* 2019;17:551-559.e1.
31. Rich NE, Carr C, Yopp AC, Marrero JA, Singal AG. Racial and ethnic disparities in survival among patients with hepatocellular carcinoma in the United States: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2022;20:e267-e288.
32. Barzi A, Zhou K, Wang S, Dodge JL, El-Khoueiry A, Setiawan VW. Etiology and outcomes of hepatocellular carcinoma in an ethnically diverse population: the multiethnic cohort. *Cancers (Basel)* 2021;13:3476.
33. Lee YT, Wang JJ, Luu M, Nouredin M, Kosari K, Agopian VG, et al. The mortality and overall survival trends of primary liver cancer in the United States. *J Natl Cancer Inst* 2021;113:1531-1541.
34. Szpakowski JL, Tucker LY. Causes of death in patients with hepatitis B: a natural history cohort study in the United States. *Hepatology* 2013;58:21-30.
35. Degos F, Christidis C, Ganne-Carrie N, Farmachidi JP, Degott C, Guettier C, et al. Hepatitis C virus related cirrhosis: time to occurrence of hepatocellular carcinoma and death. *Gut* 2000;47:131-136.