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Original Investigation | Gastroenterology and Hepatology

Sex Differences in Mortality Among Patients With Hepatocellular Carcinoma

Taotao Yan, MD, PhD; Ming-Lun Yeh, MD; Jennifer Leong, MD; Hidenori Toyoda, MD; Hiroshi Abe, MD; Dae Won Jun, MD, PhD; Lewis Roberts, MD; Yasuhito Tanaka, MD; Myron Schwartz, MD; Yao-Chun Hsu, MD; Charles Landis, MD; Phillip Vutien, MD; Haruki Uojima, MD; Takashi Honda, MD; Maria Buti, MD; Huy Trinh, MD; Eiichi Ogawa, MD; Satoshi Yasuda, MD; Cheng-Hao Tseng, MD; Mayumi Maeda, MD; Elsa Sola, MD; Takanori Suzuki, MD, PhD; Chung-Feng Huang, MD; Pei-Chien Tsai, MD; Chia-Yen Dai, MD; Jee-Fu Huang, MD, PhD; Wan-Long Chuang, MD, PhD; Ramsey Cheung, MD; Ming-Lung Yu, MD, PhD; Mindie H. Nguyen, MD

Abstract

IMPORTANCE Sex is a well-recognized factor associated with hepatocellular carcinoma (HCC) incidence, but its association with mortality is unclear.

OBJECTIVE To assess the association between sex and the risk of overall, liver-related, and non–liver-related mortality among patients with HCC.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study was conducted among patients with HCC in 17 centers from 5 countries and regions (2000-2023). Male and female patients with HCC who had balanced baseline characteristics via inverse probability of treatment weighting (IPTW) were included, with a propensity score–matched cohort included for sensitivity analyses. Data were analyzed between July 10 and September 8, 2025.

EXPOSURES Male vs female sex.

MAIN OUTCOMES AND MEASURES Overall, liver-related, and non–liver-related mortality.

RESULTS Among 8594 patients with HCC (mean [SD] age, 63.3 [10.9] years; 6214 male [72.3%]; 5644 Asian [65.7%], 458 Black [5.3%], 615 Hispanic [7.2%], and 1784 White [20.8%]), 4567 were from Asia (53.1%), 6327 had cirrhosis (73.6%), and 6617 had viral etiology (77.0%). In the unmatched cohort, males had a higher overall mortality rate per 100 person-years than females in the total cohort (15.9 [95% CI, 15.3-16.4] vs 13.3 [95% CI, 12.5-14.1]; $P < .001$) and in Asian (14.1 [95% CI, 13.5-14.7] vs 11.1 [95% CI, 10.3-12.0]; $P < .001$), Asia region (14.4 [95% CI, 13.6-15.2] vs 10.8 [95% CI, 9.9-11.8]; $P < .001$), cirrhosis (17.6 [95% CI, 16.9-18.3] vs 14.4 [95% CI, 13.5-15.4]; $P < .001$), and hepatitis B (13.6 [95% CI, 12.7-14.5] vs 10.0 [95% CI, 8.6-11.5]; $P < .001$) and C (15.8 [95% CI, 15.0-16.6] vs 13.4 [95% CI, 12.4-14.6]; $P < .001$) subgroups. In the IPTW-matched cohort, male sex was associated with increased overall mortality in the full cohort (adjusted hazard ratio [aHR], 1.14 [95% CI, 1.05-1.23]; $P = .002$) and in Asian (aHR, 1.22 [95% CI, 1.10-1.36]; $P < .001$), Asia region (aHR, 1.23 [95% CI, 1.09-1.39]; $P < .001$), cirrhosis (aHR, 1.18 [95% CI, 1.08-1.29]; $P < .001$), and viral (aHR, 1.15 [95% CI, 1.05-1.26]; $P = .004$) subgroups. Additionally, sex differences varied by liver disease etiology, with male sex having the highest aHR in the association with overall mortality among individuals with alcohol-associated liver disease (aHR, 1.90 [95% CI, 1.02-3.54]; $P = .04$), followed by those with hepatitis B (aHR, 1.22 [95% CI, 1.01-1.47]; $P = .04$) or C (aHR, 1.13 [95% CI, 1.02-1.26]; $P = .03$), but there was no association in patients with metabolic dysfunction–associated steatotic liver disease. There was no significant sex difference for non–liver-related mortality.

(continued)

Key Points

Question Do sex differences exist in mortality in hepatocellular carcinoma (HCC)?

Findings In this cohort study of 8594 patients with HCC, male sex was independently associated with an increased risk of overall mortality only in certain subgroups (Asian, Asia region, cirrhosis, and viral-related HCC subgroups). Within the nonviral subgroup, male vs female patients with alcohol-associated liver disease had increased mortality risk, while no difference was observed for those with metabolic dysfunction–associated steatotic liver disease.

Meaning These findings support incorporation of sex-based considerations in HCC management while also accounting for differences in patient ethnicity and disease etiology.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

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Abstract (continued)

CONCLUSIONS AND RELEVANCE In this study, sex disparities in HCC mortality existed but were heterogeneous across ethnic background and liver disease etiologies. These findings support incorporation of sex-based considerations in HCC management.

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Introduction

Liver cancer, predominantly hepatocellular carcinoma (HCC), is the sixth most common cancer and the third leading cause of cancer-related deaths worldwide.[1] The global burden of liver cancer is projected to nearly double by 2050, with an estimated 1.52 million new cases and 1.37 million deaths.[2]

Sex is an important factor associated with HCC development, progression, and treatment outcomes.[3-11] Males have a disproportionate incidence of HCC compared with females, at a 2:1 to 3:1 ratio across most regions.[3-5] Prior studies also reported significant sex disparities in liver disease etiologies, tumor characteristics, treatment receipt, and clinical outcomes in HCC.[6-11] However, evidence regarding the association of sex with HCC mortality is sparse and inconsistent, likely due to single-center, -country, or -region design and lack of adequate adjustment for background differences between males and females.[8,11-14] For example, a US study of 1110 patients with HCC from 2 medical centers reported a better survival outcome in females compared with males, with female sex independently associated with lower mortality (adjusted hazard ratio [aHR], 0.82; 95% CI, 0.68-0.98),[8] while another study of a single-center US cohort of 1886 patients found no association between sex and overall survival (aHR, 1.01; 95% CI, 0.82-1.24).[12] Among studies in other regions, a cohort study of 694 patients with HCC from a tertiary French liver center reported an association between female sex and improved survival outcome (aHR, 1.39; 95% CI, 1.07-1.81),[13] while another single-center study of 1716 patients from Singapore prospectively enrolled over 3 decades found no significant survival differences by sex (aHR for females compared with males, 0.96; 95% CI, 0.79-1.17).[14] In another study of 4175 patients with HCC who underwent curative-intent hepatectomy or ablation from 12 centers in China, female sex was associated with better cancer-specific survival but only among patients who were middle aged (ages 45-59 years) and not among younger or older age groups.[11]

To address current knowledge gaps, we comprehensively investigated the association of sex with overall, liver-related, and non–liver-related mortality in a large, multinational, clinical practice cohort of patients with HCC and long-term follow-up. We balanced baseline characteristics of male and female groups using inverse probability of treatment weighting (IPTW) in main analyses and propensity score matching (PSM) in a sensitivity analysis. These data may help identify disparities for targeted intervention and inform future treatment of patients with HCC.

Methods

Study Design and Population

This is a retrospective cohort study of adult (aged ≥18 years) patients with HCC between January 1, 2000, and December 31, 2023, in 17 centers from Japan, South Korea, Spain, Taiwan, and the US within the Real-World Evidence From the Global Alliance for the Study of HCC consortium (REAL-HCC). Details regarding HCC diagnosis, study population enrollment, and data collection are described in the eMethods in Supplement 1. Data analyses were conducted between July 10 and September 8, 2025. This study was approved by the Institutional Review Board at Stanford University and each participating study center and is reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline. Formal written

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informed consent from individual patients was waived by the Institutional Review Board at Stanford University due to the retrospective design and retrospective data collection of the study and because all data were fully anonymized prior to analysis.

Study Outcomes and Variables

Primary study outcomes were incidence of overall, liver-related, and non–liver-related mortality. Further details are described in the eMethods in Supplement 1. Race and ethnicity were self-reported by patients during clinical encounters and recorded in the electronic health record (EHR). The EHR recorded the following race and ethnicity options: Asian, Black, Chinese, Filipino, Hispanic, Japanese, Korean, Malaysian, Middle Eastern, Native American, Pacific Islander, South Asian, Southeast Asian, Taiwanese, Vietnamese, White, and mixed race. For analysis, Asian subgroups (Chinese, Korean, Japanese, Taiwanese, Vietnamese, Malaysian, Filipino, South Asian, Southeast Asian, and other Asian) were combined into a single Asian category. Remaining groups with small numbers, including Middle Eastern, Native American, Pacific Islander, and mixed race, were combined into an other category. Patients with missing race and ethnicity data were classified as unknown. Race and ethnicity were included to account for known racial and ethnic disparities in HCC mortality.[15]

Statistical Analysis

Primary analyses were performed in unmatched and IPTW-matched cohorts. First, baseline characteristics were described and compared by sex in the unmatched cohort. Then, IPTW was applied to balance baseline characteristics between female and male patients. Next, mortality analyses were performed in unmatched and IPTW-matched cohorts. Finally, Cox regression analyses were used to assess the association between sex and mortality. Additionally, sensitivity analyses were performed in the PSM-matched cohort. Relevant methodological details are described in the eMethods in Supplement 1. Statistical significance was defined as a 2-tailed $P < .05$. All analyses were conducted using R statistical software version 4.4.2 (R Project for Statistical Computing).

Results

Baseline Characteristics

In the initial cohort of 10 178 patients with HCC, we excluded 1584 patients (1150 who lacked Albumin-Bilirubin and 434 who lacked Barcelona Clinic Liver Cancer [BCLC] data), and 8594 patients (mean [SD] age, 63.3 [10.9] years; 6214 male [72.3%] and 2380 female [27.7%]; 5644 Asian [65.7%], 458 Black [5.3%], 615 Hispanic [7.2%], and 1784 White [20.8%]) met inclusion criteria and were included in the analysis (**Figure 1**). Among the overall population, there were 4567 patients (53.1%) from Asia (53.1%), 6327 patients (73.6%) with cirrhosis and 2267 patients without cirrhosis [26.4%], and 6617 patients with viral etiology (77.0%) and 1977 patients with nonviral etiology [23.0%]. Most HCC was viral related among Asian patients (4568 cases [80.9%]) and those who lived in the Asia region (3678 cases [80.5%]). There was substantial nonviral HCC among White (591 patients [33.1%]) and Hispanic (264 patients [43.0%]) populations. There were differences in baseline characteristics of patients in the included cohort vs those in the excluded cohort and between male and female patients of the included cohort (**Table 1**; eResults in Supplement 1). IPTW yielded a weighted (matched) cohort of 5898 males and 2350 females with HCC with generally balanced background (Table 1; eResults in Supplement 1).

Mortality Analyses

In the total unmatched cohort, 3315 deaths (2522 liver related, 196 not liver related, and 597 of unknown cause) occurred in males after a total of 20 901.8 person-years follow-up and 1134 deaths (877 liver related, 75 not liver related, and 182 of unknown cause) occurred in females after a total of 8534.8 person-years follow-up. Males had a significantly higher overall mortality rate per 100 person-years than females (15.9 [95% CI, 15.3-16.4] vs 13.3 [95% CI, 12.5-14.1]; $P < .001$) (eTable 1 in

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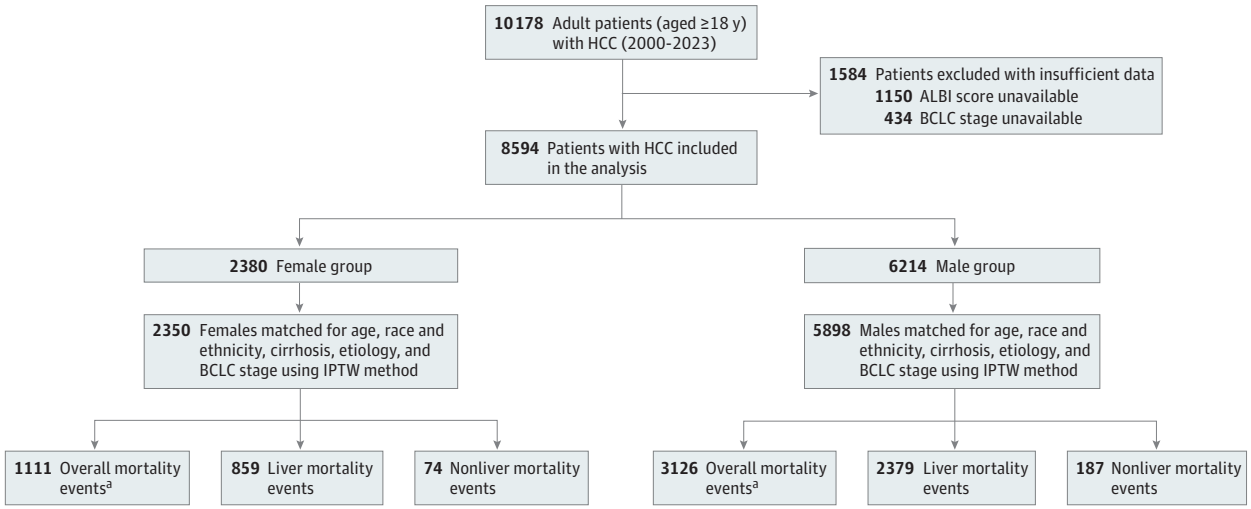
Supplement 1). The 1-, 5-, and 10-year cumulative overall survival rates were lower in males compared with females (79.6% [95% CI, 78.5%-80.6%] vs 84.2% [95% CI, 82.7%-85.7%], 42.8% [95% CI, 41.4%-44.3%] vs 49.7% [95% CI, 47.4%-52.1%], and 29.5% [95% CI, 27.9%-31.2%] vs 34.5% [95% CI, 31.8%-37.5%], respectively; all $P < .001$) (**Figure 2**A), with consistent findings of a higher overall mortality rate in males compared with females by age group, presence of cirrhosis (17.6 [95% CI, 16.9-18.3] vs 14.4 [95% CI, 13.5-15.4]; $P < .001$), hepatitis B virus (HBV; 13.6 [95% CI, 12.7-14.5] vs 10.0 [95% CI, 8.6-11.5]; $P < .001$) and hepatitis C virus (HCV; 15.8 [95% CI, 15.0-16.6] vs 13.4 [95% CI, 12.4-14.6]; $P < .001$), and in viral and nonviral subgroups (eTable 1 and eFigures 1-3 in Supplement 1). Consistent findings for males compared with females were also observed in Asian (14.1 [95% CI, 13.5-14.7] vs 11.1 [95% CI, 10.3-12.0];, $P < .001$) and Asia region (14.4 [95% CI, 13.6-15.2] vs 10.8 [95% CI, 9.9-11.8];, $P < .001$) subgroups (**Figure 3**A-B; eTable 1 and eFigures 4-5 in Supplement 1). Additionally, similar disparities with higher mortality rates in males were observed for liver-related mortality rate, but no significant sex difference was observed for non–liver-related mortality rate (eTable 1 in Supplement 1; Figure 2A and Figure 3A-B). Mortality analyses data in the total IPTW-matched cohort and relevant subgroups are provided in the eResults and eTable 2 in Supplement 1 and Figure 2B.

Association Between Sex and Mortality

In the IPTW-matched cohort, multivariable Cox regression analyses (model 1) adjusted for age, region, diabetes, etiology, and BCLC stage showed that male sex was independently associated with increased risks of overall (aHR, 1.14 [95% CI, 1.05-1.23]; $P = .002$) and liver-related (aHR, 1.14 [95% CI, 1.04-1.24]; $P = .01$) mortality, while no association was observed for non–liver-related mortality (**Table 2**; eTable 3 and eFigure 6 in Supplement 1). However, associations between sex and mortality differed across subgroups. In younger (aged <65 years), Asian (aHR, 1.22 [95% CI, 1.10-1.36]; $P < .001$), Asia region (aHR, 1.23 [95% CI, 1.09-1.39]; $P < .001$), cirrhotic (aHR, 1.18 [95% CI, 1.08-1.29]; $P < .001$), and viral-related HCC (aHR, 1.15 [95% CI, 1.05-1.26]; $P = .004$) subgroups, male sex was independently associated with increased risk of overall mortality (aHRs ranged from 1.15 for viral etiology to 1.23 for Aisa region subgroups). Male sex was also associated with increased risk of liver-related mortality in these subgroups (aHRs ranged from 1.14 [95% CI, 1.03-1.27] for viral etiology to 1.24 [95% CI, 1.10-1.39] for Asian subgroups). No sex association was observed for either mortality outcome in older (aged ≥65 years), non-Asian, non–Asia region, noncirrhotic, and nonviral HCC subgroups. In etiology-specific subgroups, aHRs in the association between male sex and increased

Figure 1. Study Flowchart



ABLI indicates Albumin-Bilirubin; BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma; IPTW, inverse probability of treatment weighting.

[a] Of 1111 all-cause deaths in the female group, 178 died from unknown cause. Of 3126 all-cause deaths in the male group, 560 died from unknown cause.

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Table 1. Baseline Characteristics of Patients

Characteristic	Patients, No. (%)								
	Unmatched cohort					IPTW-matched cohort[a]			
	Overall (N = 8594)	Female (n = 2380)	Male (n = 6214)	SMD	*P* value	Female (n = 2349.7)	Male (n = 5897.8)	SMD	*P* value
Age, mean (SD), y	63.3 (10.9)	66.4 (10.7)	62.1 (10.8)	0.40	<.001	63.6 (10.9)	63.9 (10.4)	0.02	.45
Race and ethnicity									
Asian	5644 (65.7)	1623 (68.2)	4021 (64.7)	0.11	.001	1554.2 (66.1)	3934.7 (66.7)	.02	.98
Black	458 (5.3)	137 (5.8)	321 (5.2)			131.8 (5.6)	321.8 (5.5)		
Hispanic	615 (7.2)	174 (7.3)	441 (7.1)			156.9 (6.7)	399.2 (6.8)		
White	1784 (20.8)	418 (17.6)	1366 (22.0)			477.5 (20.3)	1174.8 (19.9)		
Other or unknown	93 (1.1)	28 (1.2)	65 (1.0)			29.3 (1.2)	67.4 (1.1)		
Geographic region									
Non-Asia	4027 (46.9)	1034 (43.4)	2993 (48.2)	0.10	<.001			0.03	.28
Asia	4567 (53.1)	1346 (56.6)	3221 (51.8)			1287.2 (54.8)	3146.2 (53.3)		
Diabetes	2577 (30.1)	679 (28.6)	1898 (30.6)	0.04	.08	635.1 (27.2)	1834.5 (31.2)	0.09	.001
Cirrhosis	6327 (73.6)	1797 (75.5)	4530 (72.9)	0.06	.02	1687.7 (71.8)	4332.4 (73.5)	0.04	.18
CTP score, mean (SD)[b]	7.32 (1.69)	7.25 (1.64)	7.35 (1.71)	0.06	.05	7.38 (1.67)	7.24 (1.68)	0.08	.01
Child class[b]									
A	1975 (33.7)	557 (33.5)	1418 (33.7)	0.07	.09			0.13	<.001
B	2671 (45.5)	789 (47.4)	1882 (44.8)			749.8 (48.2)	1766.2 (44.0)		
C	1222 (20.8)	319 (19.2)	903 (21.5)			336.5 (21.6)	797.0 (19.8)		
Liver disease etiology									
HBV	2425 (28.2)	483 (20.3)	1942 (31.3)	0.41	<.001	671.9 (28.6)	1653.4 (28.0)	0.03	.96
HCV	4017 (46.7)	1298 (54.5)	2719 (43.8)			1117.0 (47.5)	2869.6 (48.7)		
HBV and HCV	175 (2.0)	44 (1.8)	131 (2.1)			42.7 (1.8)	120.9 (2.1)		
ALD	529 (6.2)	62 (2.6)	467 (7.5)			92.9 (4.0)	224.1 (3.8)		
MASLD	388 (4.5)	178 (7.5)	210 (3.4)			112.1 (4.8)	277.6 (4.7)		
Other[c]	139 (1.6)	67 (2.8)	72 (1.2)			42.1 (1.8)	99.4 (1.7)		
Cryptogenic	921 (10.7)	248 (10.4)	673 (10.8)			271.0 (11.5)	652.9 (11.1)		
BCLC stage									
0/A	4789 (55.7)	1536 (64.5)	3253 (52.3)	0.25	<.001			0.01	1.00
B	1736 (20.2)	389 (16.3)	1347 (21.7)			457.4 (19.5)	1148.8 (19.5)		
C	1367 (15.9)	289 (12.1)	1078 (17.3)			354.7 (15.1)	902.1 (15.3)		
D	702 (8.2)	166 (7.0)	536 (8.6)			183.9 (7.8)	463.1 (7.9)		
ALBI score, mean (SD)	−2.24 (0.68)	−2.23 (0.65)	−2.25 (0.69)	0.04	.15	−2.22 (0.67)	−2.27 (0.68)	0.07	.01
ALBI grade									
1	2870 (33.4)	733 (30.8)	2137 (34.4)	0.11	<.001			0.07	.03
2	4721 (54.9)	1399 (58.8)	3322 (53.5)			1334.6 (56.8)	3171.7 (53.8)		
3	1003 (11.7)	248 (10.4)	755 (12.1)			269.0 (11.4)	658.1 (11.2)		
ALT, median (IQR), U/L	45.0 (29.0-75.0)	40.0 (27.0-67.0)	47.0 (30.0-78.0)	0.17	<.001	41.0 (27.0-67.0)	46.0 (30.0-78.0)	0.15	<.001
AST, median (IQR), U/L	55.0 (36.0-89.0)	56.0 (36.0-87.0)	55.0 (36.0-90.8)	0.08	.58	55.0 (36.0-88.0)	54.0 (36.0-89.0)	0.05	.95
TB, median (IQR), mg/dL	0.90 (0.64-1.39)	0.90 (0.60-1.30)	0.90 (0.66-1.40)	0.04	<.001	0.90 (0.60-1.30)	0.90 (0.64-1.35)	0.01	.04
Albumin, mean (SD), g/dL	3.59 (0.69)	3.55 (0.65)	3.60 (0.71)	0.07	.003	3.55 (0.67)	3.62 (0.69)	0.097	<.001
Creatinine, median (IQR), mg/dL	1.10 (1.02-1.20)	1.10 (1.01-1.20)	1.10 (1.02-1.20)	0.03	.35	1.10 (1.01-1.20)	1.10 (1.01-1.20)	0.04	.15
Platelet count, mean (SD), $\times 10^3/\mu L$	147.5 (89.1)	136.2 (81.6)	151.8 (91.4)	0.18	<.001	140.9 (85.6)	150.5 (90.5)	0.096	.001

(continued)

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Table 1. Baseline Characteristics of Patients (continued)

Characteristic	Patients, No. (%)								
	Unmatched cohort					IPTW-matched cohort[a]			
	Overall (N = 8594)	Female (n = 2380)	Male (n = 6214)	SMD	*P* value	Female (n = 2349.7)	Male (n = 5897.8)	SMD	*P* value
Primary HCC therapy									
No treatment	897 (10.4)	250 (10.5)	647 (10.4)						
Liver transplant	107 (1.2)	33 (1.4)	74 (1.2)			424.1 (18.1)	993.4 (16.8)		
Resection	2083 (24.2)	549 (23.1)	1534 (24.7)			562.9 (24.0)	1510.7 (25.6)		
Local ablation	1477 (17.2)	509 (21.4)	968 (15.6)	0.16	<.001	47.0 (2.0)	98.3 (1.7)	0.09	.10
TACE/Y90	3699 (43.0)	965 (40.5)	2734 (44.0)			987.1 (42.0)	2514.7 (42.6)		
Systemic therapy	157 (1.8)	37 (1.6)	120 (1.9)			37.1 (1.6)	64.7 (1.1)		
Other or unknown	174 (2.0)	37 (1.6)	137 (2.2)			32.5 (1.4)	120.2 (2.0)		

Abbreviations: ALBI, Albumin-Bilirubin; ALD, alcohol-associated liver disease; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; CTP, Child-Turcotte-Pugh; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IPTW, inverse probability of treatment weighting; MASLD, metabolic dysfunction–associated steatotic liver disease; SMD, standardized mean difference; TACE/Y90, transarterial chemoembolization (with or without yttrium-90 radioembolization); TB, total bilirubin.

SI conversion factors: To convert albumin to grams per liter, multiply by 10; ALT and AST to microkatals per liter, multiply by 0.0167; creatinine to micromoles per liter, multiply by 88.4; platelet count to $\times 10^9$ per liter, multiply by 1.0; TB to micromoles per liter, multiply by 17.104.

[a] Weights were derived using age, race and ethnicity, cirrhosis, etiology, and BCLC stage as covariates.

[b] Among patients with cirrhosis.

[c] Includes autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, hemochromatosis, Wilson disease, and others.

risk of overall mortality were highest in alcohol-associated liver disease (ALD)–related HCC (aHR, 1.90 [95% CI, 1.02-3.54]; *P* = .04), followed by HBV-related HCC (aHR, 1.22 [95% CI, 1.01-1.47]; *P* = .04) and HCV-related HCC (aHR, 1.13 [95% CI, 1.02-1.26]; *P* = .03). No sex association was observed in HCC related to metabolic dysfunction–associated steatotic liver disease (MASLD). Male sex was also associated with increased risk of liver-related mortality in HBV-related HCC. The overall mortality risk in males compared with females increased progressively with advancing BCLC stage, with aHRs of 1.12 (95% CI, 1.01-1.24) in stage 0/A, 1.21 (95% CI, 1.02-1.44) in stage B, and 1.31 (95% CI, 1.04-1.66) in stage D. No sex association was observed for non–liver-related mortality risk in any subgroup, except for subgroups of older patients and those with HCV-related HCC. In multivariable model 2, which was further adjusted for HCC therapy, similar findings were observed in the total cohort and across most subgroups (Table 2; eTable 3 and eFigure 6 in Supplement 1).

Sensitivity analyses for association between sex and mortality were conducted in the PSM-matched cohort. Largely consistent findings were observed (eResults, eTable 4, and eTable 5 in Supplement 1).

Discussion

This large, multinational, clinical practice longitudinal cohort study examined more than 8500 patients with HCC in a population with diverse ethnic backgrounds and liver disease etiologies from both the East and West. We observed increased overall and liver-related mortality in males and no significant difference in non–liver-related morality between sexes, a finding that was consistent in matched analyses via IPTW and PSM methods. We also found heterogeneous patterns among various subgroups, with associations between male sex and increased overall and liver-related mortality among Asian, Asia region, cirrhosis, and viral etiology subgroups but not among non-Asian, non–Asia region, noncirrhosis, or nonviral etiology subgroups. The heterogeneity was also pronounced among the specific liver disease etiology subgroup, with males having an aHR of 1.90 for increased overall mortality risk among patients with ALD but only 1.22 and 1.13 among patients with HBV and HCV, respectively, and no significant difference among those with MASLD. Together, these findings highlight the importance of incorporating sex-specific considerations into individualized

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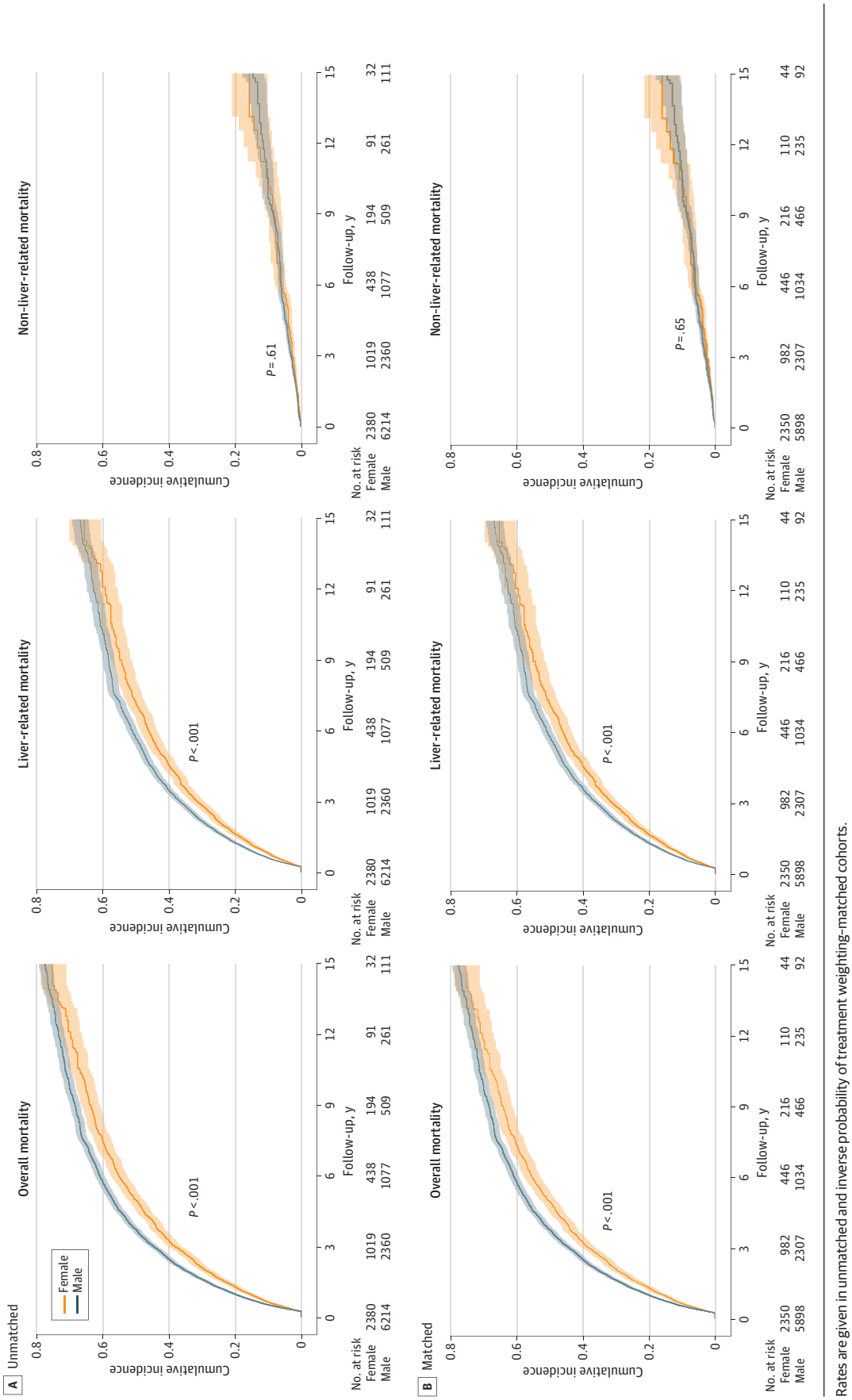
Figure 2. Survival Curves of Cumulative Mortality Rates



Rates are given in unmatched and inverse probability of treatment weighting–matched cohorts.

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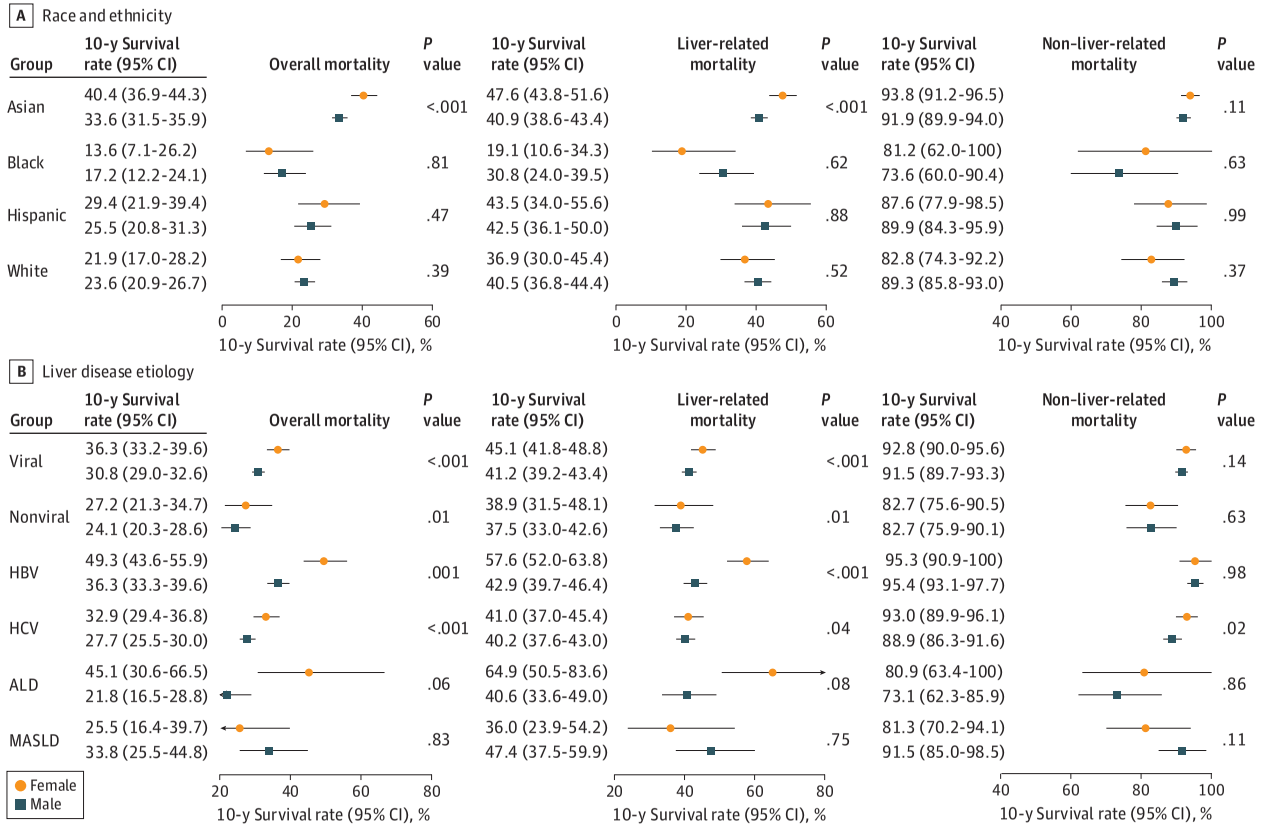
Figure 3. Forest Plots of 10-y Survival Rates in Unmatched Cohort



ALD indicates alcohol-associated liver disease; HBV, hepatitis B virus; HCV, hepatitis C virus; MASLD, metabolic dysfunction-associated steatotic liver disease.

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Table 2. Associations Between Sex and Overall Mortality in Matched Cohort

Population	Group	Event, No.	Univariable HR (95% CI)	*P* value	Multivariable model 1, aHR (95% CI)[a]	*P* value	Multivariable model 2, aHR (95% CI)[b]	*P* value
Total	Female	1111	1 [Reference]	<.001	1 [Reference]	.002	1 [Reference]	<.001
	Male	3126	1.16 (1.08-1.26)		1.14 (1.05-1.23)		1.16 (1.07-1.25)	
Age, y								
<65	Female	408	1 [Reference]	.001	1 [Reference]	.01	1 [Reference]	.01
	Male	1749	1.21 (1.08-1.36)		1.18 (1.04-1.34)		1.17 (1.03-1.32)	
≥65	Female	703	1 [Reference]	.03	1 [Reference]		1 [Reference]	.01
	Male	1377	1.11 (1.01-1.22)		1.11 (1.00-1.22)	.05	1.16 (1.04-1.28)	
Race and ethnicity								
Asian	Female	657	1 [Reference]	<.001	1 [Reference]	<.001	1 [Reference]	<.001
	Male	1818	1.24 (1.12-1.37)		1.22 (1.10-1.36)		1.21 (1.09-1.35)	
Black	Female	92	1 [Reference]	.48	1 [Reference]	.50	1 [Reference]	.33
	Male	213	1.11 (0.83-1.48)		0.91 (0.68-1.21)		0.87 (0.65-1.16)	
Hispanic	Female	104	1 [Reference]	.69	1 [Reference]	.25	1 [Reference]	.23
	Male	252	1.05 (0.82-1.36)		1.17 (0.90-1.52)		1.17 (0.91-1.52)	
White	Female	252	1 [Reference]	.76	1 [Reference]	.41	1 [Reference]	.14
	Male	811	1.02 (0.88-1.19)		1.07 (0.91-1.25)		1.13 (0.96-1.32)	
Geographic region								
Non-Asia	Female	610	1 [Reference]	.18	1 [Reference]		1 [Reference]	.10
	Male	1779	1.07 (0.97-1.19)		1.07 (0.96-1.19)	.21	1.09 (0.98-1.22)	
Asia	Female	501	1 [Reference]	<.001	1 [Reference]	<.001	1 [Reference]	.001
	Male	1347	1.26 (1.13-1.41)		1.23 (1.09-1.39)		1.23 (1.09-1.39)	
Cirrhosis								
No	Female	197	1 [Reference]	.58	1 [Reference]	.61	1 [Reference]	.18
	Male	622	1.05 (0.88-1.26)		1.05 (0.87-1.26)		1.14 (0.94-1.37)	
Yes	Female	914	1 [Reference]	<.001	1 [Reference]	<.001	1 [Reference]	<.001
	Male	2504	1.20 (1.10-1.30)		1.18 (1.08-1.29)		1.18 (1.08-1.29)	
Viral etiology								
Yes	Female	255	1 [Reference]	<.001	1 [Reference]	.004	1 [Reference]	.002
	Male	635	1.17 (1.07-1.27)		1.15 (1.05-1.26)		1.16 (1.05-1.27)	
No	Female	856	1 [Reference]	.05	1 [Reference]	.12	1 [Reference]	.02
	Male	2491	1.18 (1.00-1.39)		1.14 (0.97-1.34)		1.21 (1.03-1.42)	
Liver disease etiology								
HBV	Female	182	1 [Reference]	.02	1 [Reference]	.04	1 [Reference]	.19
	Male	839	1.24 (1.04-1.49)		1.22 (1.01-1.47)		1.13 (0.94-1.36)	
HCV	Female	652	1 [Reference]	.01	1 [Reference]	.03	1 [Reference]	.003
	Male	1579	1.13 (1.02-1.24)		1.13 (1.02-1.26)		1.18 (1.06-1.32)	
ALD	Female	12	1 [Reference]	.02	1 [Reference]	.04	1 [Reference]	.01
	Male	140	2.02 (1.13-3.59)		1.90 (1.02-3.54)		2.35 (1.29-4.30)	
MASLD	Female	84	1 [Reference]	.86	1 [Reference]	.95	1 [Reference]	.57
	Male	105	0.97 (0.72-1.31)		0.99 (0.72-1.36)		1.10 (0.79-1.53)	
Other[c]	Female	39	1 [Reference]	.96	1 [Reference]	.35	1 [Reference]	.67
	Male	39	1.01 (0.64-1.58)		0.81 (0.52-1.26)		0.90 (0.55-1.47)	
Cryptogenic	Female	120	1 [Reference]	.39	1 [Reference]		1 [Reference]	.49
	Male	351	1.10 (0.88-1.37)		1.05 (0.84-1.30)	.68	1.08 (0.87-1.34)	
BCLC stage								
0/A	Female	617	1 [Reference]	.01	1 [Reference]	.01	1 [Reference]	.004
	Male	1309	1.16 (1.05-1.29)		1.12 (1.01-1.24)		1.16 (1.05-1.28)	
B	Female	203	1 [Reference]	.05	1 [Reference]	.03	1 [Reference]	.01
	Male	709	1.20 (1.00-1.44)		1.21 (1.02-1.44)		1.25 (1.05-1.49)	

(continued)

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Table 2. Associations Between Sex and Overall Mortality in Matched Cohort (continued)

Population	Group	Event, No.	Univariable HR (95% CI)	*P* value	Multivariable model 1, aHR (95% CI)[a]	*P* value	Multivariable model 2, aHR (95% CI)[b]	*P* value
C	Female	184	1 [Reference]	.90	1 [Reference]	.68	1 [Reference]	.60
	Male	730	0.99 (0.83-1.18)		0.96 (0.80-1.15)		0.95 (0.79-1.14)	
D	Female	107	1 [Reference]	.02	1 [Reference]	.02	1 [Reference]	.09
	Male	378	1.34 (1.06-1.70)		1.31 (1.04-1.66)		1.23 (0.97-1.56)	

Abbreviations: aHR, adjusted hazard ratio; ALD, alcohol-associated liver disease; BCLC, Barcelona Clinic Liver Cancer; HBV, hepatitis B virus; HCV, hepatitis C virus; MASLD, metabolic dysfunction–associated steatotic liver disease.

[a] Adjusted for age, region, diabetes, etiology, and BCLC stage.

[b] Adjusted for age, region, diabetes, etiology, BCLC stage, and hepatocellular carcinoma therapy.

[c] Includes autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, hemochromatosis, Wilson disease, and others.

HCC management in addition to other factors, such as age, race and ethnicity, cirrhosis, and liver disease etiology.

Aligning with prior studies,[8,11,13,14] we also found better overall survival outcomes in female patients with HCC in unmatched and IPTW-matched cohorts. Some prior studies reported that the better survival in females was likely due to their higher adherence to HCC surveillance programs, earlier-stage diagnosis, or more favorable treatment responses.[8,9,14,16,17] In addition to evidence for behavioral and clinical factors, accumulating evidence suggests that intrinsic sex-specific mechanisms (eg, the protective effects of estrogen, function of the sex-determining region Y gene promoting an immunosuppressive microenvironment and facilitating metastasis, and sex-distinct cancer immune responses) also contribute to sex disparities in HCC prognosis.[18-20] In our study, associations between male sex and an increased risk of overall mortality in HCC were consistently observed in IPTW- and PS-matched cohorts after multivariable adjustment for age, region, diabetes, etiology, and BCLC stage. Compared with prior cohort studies characterized by smaller sample sizes, single-center or single-region designs, or insufficient covariate adjustment,[8,11,13] our findings based on a larger, multinational HCC cohort with rigorous covariate balancing and comprehensive multivariable adjustment expand on prior knowledge by providing robust evidence of association between sex and overall and liver-specific mortality but not non–liver-related mortality.

We also provide detailed data for several relevant subgroups, which highlight substantial variations that may be critical in informing prognosis and management of HCC. In stratified analyses of patients with and without cirrhosis, males compared with females had an aHR of 1.18 for increased risk of overall mortality among patients with cirrhotic HCC and 1.15 among those with viral-related HCC. On the other hand, approximately 25% of our cohort developed HCC on noncirrhotic or nonviral liver disease background (2267 patients without cirrhosis [26.4%] and 1977 patients with nonviral etiology [23.0%]), among whom no sex association with overall mortality was observed. Our findings of sex associations in cirrhotic HCC are partly supported by a prior study of 20 045 patients with cirrhosis without HCC, which reported a 16% higher risk of overall mortality in males.[21] The lack of sex differences in noncirrhotic HCC may be due to preserved liver function and a relatively favorable prognosis, potentially reducing the association of sex with mortality. The higher proportions of nonviral and noncirrhotic HCC in our cohort of 23.0% and 26.4% as compared with approximately 20% by some prior reports are in line with a 2021 global study, in which nonviral HCC accounted for 32% of all HCC cases (19% ALD, 8% MASLD, and 4% other causes).[22,23] These higher proportions are likely associated with the increasing prevalence of nonviral liver diseases (ALD and MASLD) in recent years, high prevalence of noncirrhotic HCC with MASLD, and effective antiviral therapies reducing HCV-related cirrhotic HCC incidence.[24,25]

By specific etiology, the greatest sex differences in overall mortality and the most pronounced sex association were observed in alcohol-associated HCC, followed by HBV- and HCV-related HCC, while no significant sex difference was seen in MASLD-related HCC. The differential magnitude of sex associations across HCC etiologies may be attributed to multiple factors. Clinically, the lack of effective interventions for ALD and the higher alcohol exposure but lower abstinence rates in

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males[26-28] may partly explain the higher aHR in the sex association observed in alcohol-associated HCC. For viral-related HCC, antiviral therapies can substantially improve survival outcomes[29,30] which may attenuate sex-related contributions, while MASLD is associated with noncirrhotic HCC,[31,32] in which associations of sex with mortality appear minimal, as reported previoulsy.[33] Biologically, sex hormones or sex-linked genes differentially influence mechanisms of tumorigenesis, tumor behavior, and immune responses in alcohol-, virus-, and metabolism-related liver diseases,[34-38] which may also contribute to etiology-dependent sex disparities.

In addition to liver disease–dependent sex associations with HCC mortality, we observed distinct patterns of sex disparities across ethnic and geographical backgrounds (Asian vs non-Asian and Asia vs non–Asia region subgroups). Male vs female patients of Asian ethnicity or from the Asia region consistently had aHRs of 1.22 to 1.23 for increased risk of overall mortality, whereas no significant sex differences were observed among non-Asian patients or those from non-Asia regions. In our study, viral-related HCC accounted for most cases among Asian (4568 of 5644 cases [80.9%]) or Asia region (3678 of 4567 cases [80.5%]) patients, while nonviral etiologies accounted for a substantial proportion of HCC cases among non-Asian or non–Asia region patients, particularly among White (591 patients [33.1%]) and Hispanic (264 patients [43.0%]) patients. These differential distributions of etiologies, reflecting regional epidemiological characteristics of HCC,[39] may partly explain observed ethnic or geographical sex disparities given that the association of sex with mortality differs by HCC etiology. For Asian patients or those from the Asia region, certain factors may additionally contribute to the disparities in HCC mortality. These factors may include males having higher alcohol or tobacco consumption[40,41] and females having greater health awareness and knowledge on liver diseases (particularly viral hepatitis).[42] Moreover, the development, progression, and treatment of HCC are inherently complex and are further influenced by multiple factors, including genetic differences among racial groups,[43-45] making it challenging to disentangle the association between sex and mortality in HCC. Nevertheless, our findings provide valuable insights on ethnic and geographical-specific sex disparities in HCC mortality, enhancing our understanding of the association of sex with HCC, particularly in clinical settings, supported by rigorous matching and comprehensive multivariable adjustments to minimize confounding.

Strengths and Limitations

Our study has several strengths. First, we included more than 8500 patients with HCC in clinical settings with multiethnic backgrounds and diverse etiologies from Eastern and Western regions. These patients had detailed clinical data and long-term follow-up (2000-2023), enhancing the generalizability of our findings. Second, we applied 2 approaches, IPTW and PSM, to balance baseline characteristics between study groups and minimize the influence of potential confounders, with further multivariable adjustment to strengthen the validity of observed associations. Third, we expanded the sex differences in HCC mortality, previously reported mainly for overall or viral-related HCC, across all specific major etiologies (HBV, HCV, ALD, and MASLD). Given that the underlying etiology of HCC is rapidly changing from viral to nonviral liver diseases with the successful use of curative antiviral treatment for HCV, our findings of increased mortality risk in males with ALD-related HCC and no significant sex difference in patients with MASLD-related HCC are particularly valuable. With the worse prognosis for male patients with HCC, especially those with ALD, additional clinical interventions should be considered. Male patients with viral-related HCC and ALD-associated HCC should be counseled regarding their increased mortality risk to encourage better adherence to HCC surveillance, clinical monitoring, and treatment of HCC and the underlying liver disease. Care professionals should also be well informed of the poorer prognosis in male patients with HCC to counsel and monitor their male patients accordingly. Because HCC prognosis is highly dependent on HCC treatment types, which are in turn dependent on liver function and tumor staging, early HCC diagnosis is paramount. However, only 52.3% of males in this study had early HCC (BCLC 0/A) at diagnosis compared with 64.5% of females. This findings suggest that more efforts are needed by clinicians and patients to adhere to HCC surveillance to detect new HCC

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cases, as well as HCC recurrences in established HCC cases in all patients, especially male patients. Additionally, clinicians and female patients with MASLD-related HCC should be aware of the lack of significant sex differences in the mortality of patients with MASLD-related to avoid potential bias against female patients with MASLD-related HCC due to perceived higher risk in their male counterparts.

We also acknowledge several limitations. First, despite rigorous matching and multivariable adjustments, residual confounding from certain unmeasured factors (eg, adherence of cancer recurrence surveillance after HCC therapies, background differences between patients included in study analyses and those excluded due to missing data, type of health care delivery system, management practices, socioeconomic status, patient preference, and availability of therapies at different centers and their changes over time) still exist. Second, given the relatively smaller sample size of patients who were not Asian, were not cirrhotic, or had nonviral HCC compared with Asian patients, those who were cirrhotic, or those with viral-related HCC, further studies are needed to validate our findings for these smaller subgroups. Nevertheless, we had more than 2000 patients with noncirrhotic or nonviral HCC in our cohort, and their proportions are consistent with previous reports,[23,31,32] reflecting typical clinical characteristics of HCC, in which cirrhotic or viral-related HCC remains the predominant form. The predominance of Asian patients in our study was likely due to the large number of participating centers from Asian regions, as well as the location of many US centers in the Western US, where there are large Asian populations, an ethnicity disproportionately affected by HCC. Third, due to the relatively small sample size of patients receiving systemic therapy, we did not perform further stratified analyses for this subgroup or different systemic regimens (eg, sorafenib and immune checkpoint inhibitors). Additional studies are therefore needed to fill this data gap. Fourth, potential heterogeneity and selection bias are inherent in the retrospective multicenter design. However, we attempted to mitigate for these by using a standardized study variable definition and data-collection form via individual patient record review at each participating center.

Conclusions

In this cohort study of multinational HCC with longitudinal data, our findings provided robust clinical evidence for notable sex disparities in mortality risk among patients with HCC, driven mainly by differences in liver-related mortality. Male sex was independently associated with an increased risk of overall mortality (aHR, 1.14); however, this sex association remained only in certain subgroups, including Asian, Asia region, cirrhotic, and viral-related HCC subgroups. Additionally, male patients within the nonviral subgroup with ALD had an increased mortality risk compared with females (aHR, 1.90), while no significant difference was observed for patients with MASLD. These findings of sex disparities in HCC mortality support the incorporation of sex-based considerations in HCC management while also accounting for differences in patient ethnicity and disease etiology.

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Corresponding Author: Mindie H. Nguyen, MD Division of Gastroenterology and Hepatology, Stanford University Medical Center, 780 Welch Rd, CJ250K, Palo Alto, CA 94304 (mindiehn@stanford.edu).

Author Affiliations: Division of Gastroenterology and Hepatology, Stanford University Medical Center, Palo Alto, California (Yan, Maeda, Sola, Cheung, Nguyen); Department of Infectious Diseases, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China (Yan); National Regional Infectious Diseases Center, Clinical Research Center

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for Infectious Diseases of Shaanxi, Xi'an, China (Yan); Hepatobiliary Division, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan (Yeh, C.-F. Huang, Tsai, Dai, J.-F. Huang, Chuang, Yu); Hepatitis Research Center, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan (Yeh, C.-F. Huang, Dai, J.-F. Huang, Chuang, Yu); Center for Metabolic Disorders and Obesity, Kaohsiung Medical University, Kaohsiung, Taiwan (Yeh, C.-F. Huang, Dai, J.-F. Huang, Chuang, Yu); Henry D. Janowitz Division of Gastroenterology, Mount Sinai Health System, New York, New York (Leong, Schwartz); Department of Gastroenterology, Ogaki Municipal Hospital, Ogaki, Gifu, Japan (Toyoda, Yasuda); Division of Gastroenterology and Hepatology, Shinmatsudo Central General Hospital, Chiba, Japan (Abe); Department of Internal Medicine, Hanyang University Hospital, Hanyang University College of Medicine, Seoul, South Korea (Jun); Department of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota (Roberts); Department of Gastroenterology and Hepatology, Faculty of Life Sciences, Kumamoto University, Kumamoto, Japan (Tanaka); Virology and Liver Unit, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan (Tanaka); Division of Gastroenterology of Hepatology, E-Da Cancer Hospital/I-Shou University, Kaohsiung, Taiwan (Hsu, Tseng); Kaiser Permanente Central Hospital, Seattle, Washington (Landis); Division of Gastroenterology, University of Washington School of Medicine, Seattle (Vutien); Department of Gastroenterology, Internal Medicine, Kitasato University School of Medicine, Sagamihara, Japan (Uojima); Department of Gastroenterology and Hepatology, Nagoya University Graduate School of Medicine, Nagoya, Japan (Honda); Liver Unit, Department of Internal Medicine, Hospital Universitari Vall d'Hebron and Universitat Autònoma de Barcelona, Barcelona and Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas del Instituto Carlos III, Barcelona, Spain (Buti); Liver Diseases Group, Vall d'Hebron Research Institute, Barcelona, Spain (Buti); San Jose Gastroenterology, San Jose, California (Trinh); Department of General Internal Medicine, Kyushu University Hospital, Fukuoka, Japan (Ogawa); Department of Gastroenterology and Metabolism, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan (Suzuki); Division of Gastroenterology and Hepatology, Veterans Affairs Palo Alto Health Care System, Palo Alto, California (Cheung); Department of Epidemiology and Population Health, Stanford University, Palo Alto, California (Nguyen).

Author Contributions: Dr Yan and Prof Nguyen had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Yan, Schwartz, Buti, Tsai, Dai, Yu, Nguyen.

Acquisition, analysis, or interpretation of data: Yan, Yeh, Leong, Toyoda, Abe, Jun, Roberts, Tanaka, Hsu, Landis, Vutien, Uojima, Honda, Buti, Trinh, Ogawa, Yasuda, Tseng, Maeda, Sola, Suzuki, C. Huang, J. Huang, Chuang, Cheung, Nguyen.

Drafting of the manuscript: Yan, Buti, Maeda, Nguyen.

Critical review of the manuscript for important intellectual content: All authors.

Statistical analysis: Yan, Chuang, Nguyen.

Obtained funding: Roberts.

Administrative, technical, or material support: Yeh, Toyoda, Abe, Roberts, Tanaka, Hsu, Landis, Honda, Trinh, Maeda, Tsai, Chuang, Cheung, Nguyen.

Supervision: Jun, Dai, Yu, Nguyen.

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Data Sharing Statement: See Supplement 2.

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SUPPLEMENT 1.

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SUPPLEMENT 2.

Data Sharing Statement

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