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Differential prognoses among male and female patients with hepatocellular carcinoma

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Abstract

Background: The incidence of hepatocellular carcinoma (HCC) is significantly higher in men than women. Nonetheless, the impact of sex disparities on HCC outcomes remains unclear. We aimed to compare the clinical manifestations and prognoses between male and female patients with HCC.

Methods: This retrospective study enrolled 5337 consecutive patients (3976 men, 1361 women) who were diagnosed with HCC from 2007 to 2020. The prognostic factors were identified by the Cox proportional hazards model.

Results: Male patients were younger upon HCC diagnosis (median age 64 vs 69 years; $p < 0.001$) with more favorable hepatic functional reserves (39.0% vs 35.1% albumin-bilirubin grade 1; $p = 0.025$) but had greater tumor burdens than the female patients. Furthermore, fewer male patients underwent curative therapies for HCC compared with the female patients (49.0% vs 57.0%; $p < 0.001$). After a median follow-up of 20.1 months (interquartile range, 5.8-47.3 months), 3133 patients died. The cumulative 5-year overall survival rates were 37.1% and 41.9% for male and female patients, respectively ($p < 0.001$). From the multivariate analysis, male sex was not an independent factor predictive of poor overall survival in all patients and in the subgroup analysis stratified by treatment modalities. When stratified by age, the female sex was an independent factor associated with lower mortality in younger (≤50 years) patients but not in older patients with HCC.

Conclusion: Sex was not an independent predictor of the outcome of patients with HCC, especially for those aged more than 50 years.

Keywords: Albumin-bilirubin; Liver cancer; Outcomes; Sex differences; Staging

1. INTRODUCTION

Liver cancer is the sixth most prevalent cancer worldwide, with approximately 841 000 new cases diagnosed annually.[1] The incidence rate of primary liver cancer increased more rapidly than any other cancer, by 2% to 3% annually from 2007 to 2016.[2] Its mortality rate also rose by 43% from 2000 to 2016, making it the second most lethal malignant disease with a 5-year survival rate of only 18.1% and over 782 000 deaths worldwide in 2018.[1–3]

Hepatocellular carcinoma (HCC) is the most common type of primary liver malignancy, comprising over 75% of all liver cancers.[1] The main risk factors for HCC are chronic infection with the hepatitis B virus (HBV) or hepatitis C virus (HCV), aflatoxin exposure, excessive alcohol consumption, obesity, cigarette smoking, metabolic dysfunction-associated fatty liver disease, type 2 diabetes mellitus, and male sex.[1,2] Interestingly, sex disparities exist in liver cancers; liver cancer ranks the fifth and ninth most common cancer in men and women, respectively.[4] HCC is a male predominant disease with an estimated ratio of 2:1 to 4:1 compared to women.[5] Hence, sex is an important component of risk scores and nomograms that predict the development of HCC for patients with chronic viral hepatitis.[6,7]

The different features of sex hormones may underlie the differential risk of developing HCC between men and women. Androgens and androgen receptor signaling facilitate tumorigenesis, whereas estrogen plays a protective role against hepatocarcinogenesis.[8–10] Although sex differences in HCC development risk are well recognized, whether the prognosis of patients who have been diagnosed with HCC varies according to sex remains controversial.[11–18] One recent population-based study from the United States reported that long-term rapid increases in liver cancer mortality have attenuated in women but stabilized in men.[2] Several studies further revealed that the female sex was an independent factor associated with lower mortality rates

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in patients with HCC.[17,18] However, some studies showed that there were no significant differences in long-term survival outcomes between the sexes.[13–15,19] Another study in Austria demonstrated that among patients with HCC who underwent surgical resection, women had a shorter median overall survival (OS) than men (35 vs 66 months; $p = 0.029$).[16]

To clarify this issue, this retrospective study was conducted to evaluate the prognostic predictors of HCC focusing on sex differences.

2. METHODS

2.1. Patients and follow-up

A total of 5337 consecutive patients diagnosed with HCC at Taipei Veterans General Hospital from 2007 to 2020 were retrospectively enrolled in this cohort study (Fig. 1A). The HCC diagnosis was established according to the American Association for the Study of Liver Disease diagnostic criteria.[20] All patients with newly diagnosed HCC were consulted about treatment strategies at a weekly multidisciplinary expert meeting and enrolled in the HCC registration system at Taipei Veterans General Hospital since 2007.[21,22] After the multidisciplinary expert meeting, the chosen therapeutic course is shared by the patient with HCC and the physicians after discussing the treatment's efficacy, benefits, risks, and complications and the recommendations from the meeting.

The HCC registration system at Taipei Veterans General Hospital is a prospectively maintained database that records the demographic characteristics, baseline laboratory data, tumor factors, treatments, and outcomes of the enrolled patients. Orthotopic liver transplantation, surgical resection, as well as local ablation therapy (including radiofrequency ablation and percutaneous ethanol injection therapy), are considered curative treatments; other therapies, such as transarterial chemoembolization, radiotherapy, systemic therapy, radiotherapy, and best supportive treatment are defined as noncurative treatments.[23]

The study protocol was conducted in accordance with the Declaration of Helsinki and current ethical guidelines. It was also approved by the Institutional Review Board of the Taipei Veterans General Hospital, Taiwan (VGHIRB No. 2021-05-007AC). As a retrospective cohort study, informed consent was waived by the Institutional Review Board. Patient information was de-identified before the initiation of this study.

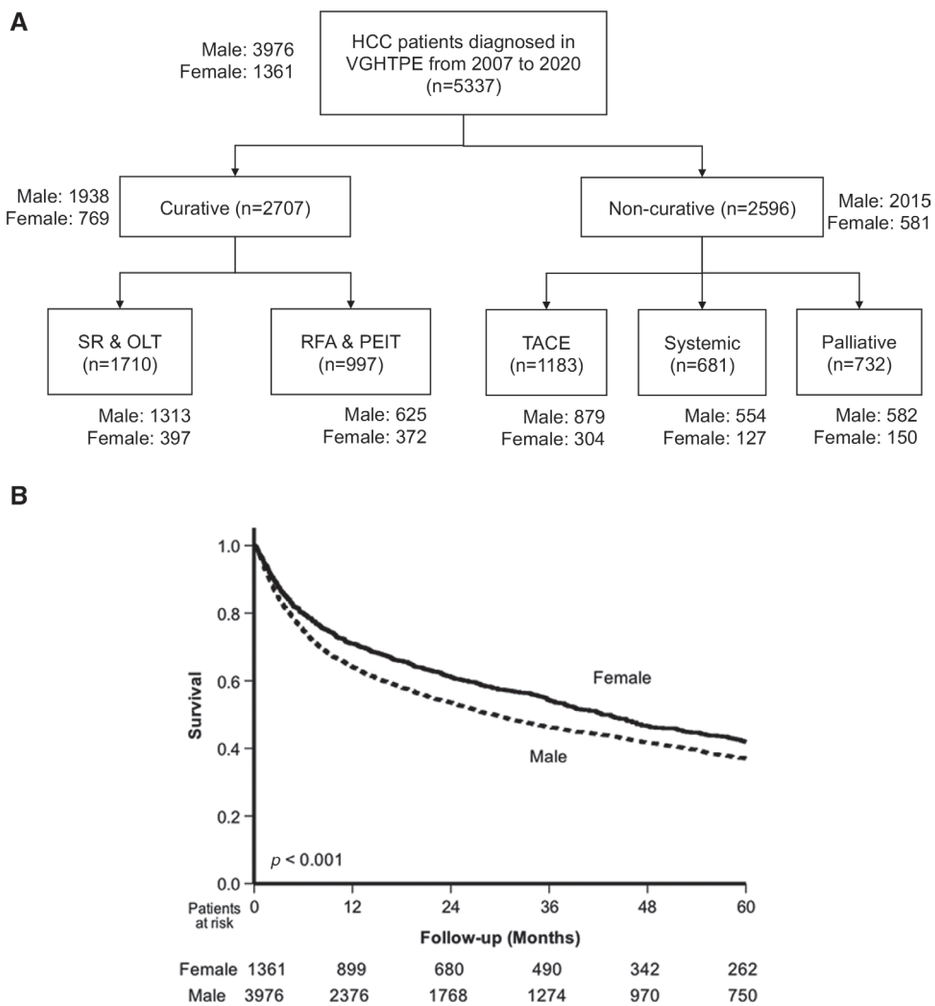

Fig. 1 Study flow chart and comparison of the OS rates between male and female HCC patients in all patients. A, Study flow chart. B, Comparison of the OS rates between male and female patients with HCC. HCC = hepatocellular carcinoma; OLT = orthotopic liver transplantation; OS = overall survival; PEIT = percutaneous ethanol injection therapy; RFA = radiofrequency ablation; SR = surgical resection; TACE = transarterial chemoembolization; VGHTPE = Taipei Veterans General Hospital.

2.2. Biochemical and serologic markers

Serum biochemistry and liver function were quantified using the Roche/Hitachi Modular Analytics System (Roche Diagnostics GmbH, Mannheim, Germany). Serum hepatitis B surface antigen and alpha-fetoprotein (AFP) levels were tested using radioimmunoassays (Abbott Laboratories, North Chicago, IL, USA; Serono Diagnostic SA, Coinsins/VD, Switzerland, respectively). HCV antibody testing was performed using a second-generation enzyme immunoassay (Abbott Laboratories). The albumin-bilirubin (ALBI) score was calculated using the following formula: -0.085 (albumin g/L + 0.66 × log [bilirubin mmol/L]).[24] ALBI grades were defined as grade 1 (score ≤ -2.60), grade 2 (score > -2.60 and ≤ -1.39), and grade 3 (score > -1.39).

2.3. Statistical analysis

The primary endpoint of this study was OS, which was calculated from the date of HCC diagnosis until either death, the last visit, or loss of follow-up; survival was censored on October 31, 2020. Categorical variables were compared using Pearson's chi-square analysis or Fisher's exact test, whereas continuous variables were compared with the Mann-Whitney *U* test. The cumulative OS rates were estimated with the Kaplan-Meier method and compared using the Cox proportional hazards model.

Variables with statistical significance ($p < 0.05$) in the univariate analysis were included in the multivariate analysis using a forward stepwise Cox regression model. The ALBI scores were derived from the serum albumin and bilirubin levels. Accordingly, ALBI grade was used instead of serum albumin and bilirubin levels in the multivariate analysis. A two-tailed $p < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY, USA).

3. RESULTS

3.1. Demographic and clinical characteristics

This study included 3976 (74.5%) male and 1361 (25.5%) female patients with HCC. The demographic characteristics of the enrolled patients are listed in Table 1. Male patients were younger than their female counterparts (median age 64 vs 69 years; $p < 0.001$). Concerning HCC etiology, chronic HBV infection was dominant in the male group, whereas HCV infection was more prevalent in the female group. Male patients had better liver functional reserves than female patients, presenting with higher serum albumin levels, a higher proportion of ALBI grade 1, and higher platelet counts upon HCC diagnosis. However, male patients with HCC had larger tumor sizes, more multiple tumors, more vascular invasion, and more advanced disease according to the Barcelona Clinical Liver Cancer (BCLC) stages than the female patients, indicating that the male patients had more aggressive tumor factors. Furthermore, fewer male patients underwent curative therapies for HCC compared with the female patients (49.0% vs 57.0%; $p < 0.001$).

3.2. Long-term OS and factors associated with poor OS

After a median follow-up of 20.1 months (interquartile range [IQR], 5.8-47.3 months), 3133 patients died, and the remaining

Table 1

Demographics of the study cohort

Characteristics	All (n = 5337)	Male (n = 3976)	Female (n = 1361)	*p*
Age	64 (52-74)	64 (55-75)	69 (61-77)	<0.001
HBsAg (+/-) (%)	2568/1971 (56.6%/43.4%)	2118/1359 (60.9%/39.1%)	450/612 (42.4%/57.6%)	<0.001
Anti-HCV (+/-) (%)	1325/2969 (30.9%/69.1%)	793/2384 (40.0%/60.0%)	532/585 (47.6%/52.4%)	<0.001
ALBI grade (1/2/3) (%)	1992/2680/565 (38.0%/51.2%/10.8%)	1522/1954/423 (39.0%/50.1%/10.8%)	470/726/142 (35.1%/54.3%/10.6%)	0.025
BCLC (0/A/B/C/D) (%)	554/1799/1306/1269/370 (10.5%/34.0%/24.7%/24.0%/7.0%)	356/1279/1003/1030/276 (9.0%/32.4%/25.4%/26.1%/7.0%)	198/520/303/239/94 (14.6%/38.4%/22.4%/17.7%/6.9%)	<0.001
Child-Pugh class (A/B/C) (%)	3775/1050/209 (75.0%/20.9%/4.2%)	2816/783/167 (74.8%/20.8%/4.4%)	959/267/42 (75.6%/21.1%/3.3%)	0.223
Albumin (g/dL)	3.7 (3.2-4.1)	3.7 (3.2-4.1)	3.6 (3.2-4.0)	<0.001
ALT (U/L)	41 (26-69)	42 (27-41)	37.5 (25-65)	<0.001
AST (U/L)	51 (32-94)	50 (31-94)	54 (33-93)	0.563
ALK-P (U/L)	101 (72-152)	101 (72-157)	99 (72-139)	0.002
γGT (U/L)	70 (35-159.5)	78 (36-175)	56 (30-119)	0.322
Bilirubin (mg/dL)	0.83 (0.57-1.34)	0.86 (0.59-1.38)	0.79 (0.53-1.22)	<0.001
PT/INR	1.08 (1.03-1.17)	1.08 (1.03-1.18)	1.08 (1.02-1.17)	0.437
Platelets (×1000/mm^3)	154 (105.25-214)	159 (111-219)	139 (91.5-199)	<0.001
Tumor size (cm)	4.3 (2.5-9.0)	4.7 (2.6-10)	3.5 (2.1-7.1)	<0.001
Number of tumors (1/>1) (%)	3166/2119 (59.9%/40.1%)	2305/1629 (58.6%/41.4%)	861/490 (63.7%/36.3%)	0.001
Vascular invasion (+/-) (%)	1252/3976 (23.9%/76.1%)	1017/2879 (26.1%/73.9%)	235/1097 (17.6%/82.4%)	<0.001
AFP (ng/mL)	42.04 (6.47-914.54)	40.69 (6.19-992.50)	47.7 (7.87-685.22)	0.418
Treatment modality				
SR and OLT	1710 (32.0%)	1313 (33.1%)	397 (29.1%)	
RFA and PEIT	997 (18.7%)	625 (15.7%)	372 (27.3%)	
TACE	1183 (22.2%)	879 (22.1%)	304 (22.5%)	<0.001
Systemic therapy	681 (12.8%)	554 (13.9%)	127 (9.3%)	
Best supportive treatment	732 (13.7%)	582 (14.6%)	150 (11.0%)	
Missing data of treatment	34 (0.6%)	23 (0.6%)	11 (0.8%)	
Curative	2707 (51.0%)	1938 (49.0%)	769 (57.0%)	<0.001
Noncurative	2596 (49.0%)	2015 (51.0%)	581 (43.0%)	

Continuous variables are expressed as the median with 25th and 75th percentiles.

AFP = alpha-fetoprotein; ALBI = albumin-bilirubin; ALK-P = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BCLC = the Barcelona Clinic Liver Cancer; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; OLT = orthotopic liver transplantation; PEIT = percutaneous ethanol injection therapy; PT/INR = prothrombin time/international normalized ratio; RFA = radiofrequency ablation; SR = surgical resection; TACE = transarterial chemoembolization; γGT = γ-glutamyl transpeptidase.

2204 patients were alive at their last visit. The median OS of male and female patients were 29.3 months (IQR, 26.5-32.1 months) and 43.5 months (IQR, 37.5-47.5 months), respectively. The cumulative OS rates of male and female patients with HCC at 1, 3, and 5 years were 64.1% vs 71.0%, 46.3% vs 54.3%, and 37.1% vs 41.9%, respectively (Fig. 1B). However, as shown in Table 2, the multivariate analysis showed that sex was not an independent factor associated with OS. The male and female patients had similar prognostic factors for OS including age, treatment modalities, ALBI grade, serum AFP levels, tumor size, and vascular invasion (Supplementary Table 1, http://links.lww.com/JCMA/A144).

3.3. Comparison of OS between male and female stratified by ALBI grade and treatment modality

As the treatment modality and ALBI grade were crucial in determining HCC outcome (Table 2), we compared the OS between male and female patients stratified by these two factors. Among those who underwent curative therapies, there was no significant difference in OS between male and female patients (Fig. 2A; $p = 0.491$). Moreover, the impact of sex on HCC prognosis was not apparent among patients who underwent curative therapy across all of the three ALBI grades (Fig. 2B–D). The results of this multivariate analysis are shown in Supplementary Table 2 (http://links.lww.com/JCMA/A144).

Among the patients who received noncurative treatments, the men had a shorter OS than the women (median [IQR], 7.1 months [6.48-7.72 months] vs 9.0 months [7.28-10.72 months]; Fig. 3A; $p = 0.002$). Among those receiving noncurative treatments with ALBI grade 1, the OS of female patients was not significantly longer than the male patients statistically ($p = 0.088$; Fig. 3B). In contrast, female patients who received noncurative treatments with ALBI grades 2 ($p = 0.002$; Fig. 3C) and 3 ($p = 0.019$; Fig. 3D) had a longer OS than male patients. As shown in Supplementary Table 3 (http://links.lww.com/JCMA/A144), the multivariate analysis revealed that sex was not an independent risk factor predictive of OS in patients who received noncurative therapies for HCC.

Table 2

Analysis of factors associated with poor OS

Parameters	Univariate HR (95% CI)	*p*	Multivariate HR (95% CI)	*p*
Age (y)				
>65 vs ≤65	1.177 (1.097-1.263)	<0.001	1.407 (1.281-1.545)	<0.001
Sex				
Male vs female	1.179 (1.085-1.280)	<0.001		
Treatment				
Noncurative vs curative	5.181 (4.793-5.600)	<0.001	2.783 (2.473-3.132)	<0.001
HBsAg (+)				
No vs yes	1.061 (0.984-1.145)	0.122		
Anti-HCV (+)				
No vs yes	1.095 (1.008-1.190)	0.031	1.190 (1.074-1.318)	0.001
Albumin (g/dL)				
<3.5 vs ≥3.5	2.765 (2.574-2.970)	<0.001		
Bilirubin (mg/dL)				
>1.0 vs ≤1.0	2.085 (1.943-2.238)	<0.001		
ALT (U/L)				
>40 vs ≤40	1.426 (1.329-1.531)	<0.001	1.127 (1.025-1.240)	0.013
ALK-P (U/L)				
>100 vs ≤100	2.965 (2.727-3.223)	<0.001	1.271 (1.145-1.412)	<0.001
PT/INR				
>1.1 vs ≤1.1	2.010 (1.872-2.157)	<0.001	1.109 (1.003-1.226)	0.044
AFP (ng/mL)				
>20 vs ≤20	2.306 (2.135-2.490)	<0.001	1.521 (1.372-1.685)	<0.001
Numbers of tumor				
>1 vs 1	2.185 (2.036-2.346)	<0.001	1.204 (1.094-1.325)	<0.001
Tumor sizes (cm)				
≥5 vs <5	3.233 (3.007-3.477)	<0.001	1.762 (1.581-1.963)	<0.001
PLT (×1000/mm^3)				
≤100 vs >100	1.012 (0.932-1.098)	0.779		
Vascular invasion				
Yes vs no	4.985 (4.611-5.389)	<0.001	1.992 (1.784-2.223)	<0.001
ALBI grade				
2 vs 1	2.649 (2.432-2.884)	<0.001	1.711 (1.527-1.917)	<0.001
3 vs 1	6.622 (5.900-7.433)	<0.001	3.430 (2.909-4.045)	<0.001

AFP = alpha-fetoprotein; ALBI = albumin-bilirubin; ALK-P = alkaline phosphatase; ALT = alanine aminotransferase; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HR = hazard ratio; OS = overall survival; PLT = platelet; PT/INR = prothrombin time/international normalized ratio.

3.4. Comparison of OS between male and female patients stratified by age

In Taiwan, the mean age at menopause is approximately 50 years.[25] The women in the younger patient group (age ≤50 years) had a longer OS than their male counterparts (Fig. 3E; median [IQR], 43.6 months [11.2-76.0 months] vs 18.7 months [12.3-25.1 months]; $p = 0.020$). Multivariate analysis confirmed that the male sex correlated with poorer prognosis (Table 3; hazard ratio [HR], 1.558; 95% CI, 1.095-2.219; $p = 0.014$). Among those aged more than 50 years, female patients had a longer OS than male patients (Fig. 3F; median [IQR], 43.5 months [38.5-48.5 months] vs 30.8 months [27.7-33.9 months]; $p = 0.001$); however, sex was not an independent risk factor associated with OS according to the multivariate analysis (Table 3).

3.5. Comparison of OS between male and female patients stratified by viral etiology and age

Among the patients with HBV-related HCC, male patients had a shorter OS than women (Fig. 4A; $p = 0.029$). However, no statistically significant difference of OS was shown in both younger (age ≤50 years) and elder patients (age >50 years) (Fig. 4B, C). As the multivariate analysis shown in Table 4, the male sex was not an independent predictor for poor OS in patients with HBV-related HCC.

Regarding the patients with HCV-related HCC, females have significant better OS compared to males (median [IQR], 46.1 months [38.5-53.7 months] vs 31.4 months [26.4-36.4 months]; Fig. 4D, $p = 0.002$). Moreover, the significant difference of OS was observed in elder patients (median [IQR], 46.1 months [38.5-53.7 months] vs 31.1 months [26.3-35.9 months]; $p = 0.001$) but not in younger patients (Fig. 4E, F). By the multivariate analysis, female sex was an independent factor for better prognosis in HCV-related HCC groups of all ages (Table 5; HR, 1.289; 95% CI, 1.081-1.537; $p = 0.005$) and age >50 years (HR, 1.279; 95% CI, 1.069-1.529; $p = 0.007$).

For patients with nonviral HCC, the OS were similar between male and female patients (Fig. 4G). In addition, no apparent difference of OS was exhibited in either younger or elder populations (Fig. 4H, I). Sex was not an independent risk factor related to OS for patients with nonviral HCC by the multivariate analysis (Table 6).

4. DISCUSSION

There are several major findings from our study. First, the female patients were older, had less chronic HBV infection, and poorer liver functional reserve upon HCC diagnosis than the male patients. However, the female patients had less aggressive tumor factors (more single tumors, smaller tumor size, and less vascular invasion), which, in turn, led to more

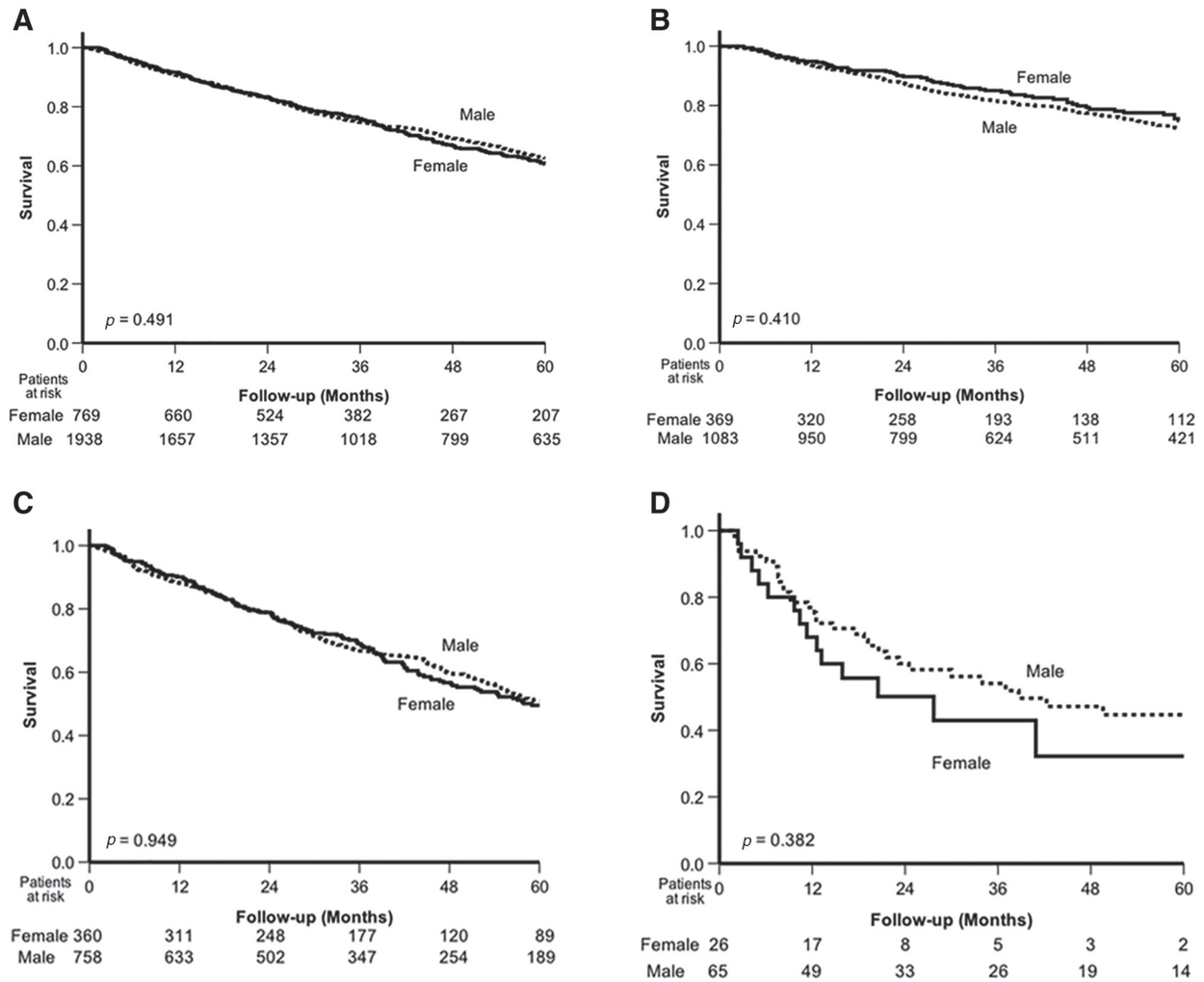

Fig. 2 Comparison of OS between male and female patients with HCC who underwent curative treatment stratified by the ALBI grade. A, All patients (B) ALBI grade 1 (C) ALBI grade 2 (D) ALBI grade 3. ALBI = albumin-bilirubin; HCC = hepatocellular carcinoma; OS = overall survival.

female patients undergoing curative treatments than males. Second, although the female patients had a longer median OS than the male patients, the multivariate analysis and most of the subgroup analyses failed to confirm that sex was an independent factor predictive of the long-term outcome of patients with HCC after adjusting for confounding factors such as liver functional reserve, tumor factors, and treatment modality. Third, among the patients with HCC aged younger than 50 years, the female ones had a longer OS than their male counterparts according to the multivariate analysis. Fourth, females had a better prognosis than males in patients with HCV-related HCC, especially in those who were older than 50 years.

It is well established that male patients have a markedly higher incidence than females in developing HCC.[5] The current study also revealed that 74.5% of patients with HCC are male. Nonetheless, results from evaluating the impact of sex disparities on disease outcomes are inconclusive.[11–18] This might be due to differences in the ethnicities, HCC etiologies, liver functional reserves, tumor characteristics, and treatments included in these studies. For example, a large population-based study of the Surveillance, Epidemiology, and End Results database showed that women had a longer OS than men among both White and Black patients.[18] However, this survival difference between the sexes was not observed among the Asian and Hispanic populations. Moreover, most of these studies showed that the clinical manifestations and treatment modalities were quite different between male and female patients with HCC. These potential confounding factors render investigating the impact of sex on HCC outcome particularly challenging. A large-scale evaluation of comprehensive patient data is needed to elucidate this issue. In this study, we enrolled 5337 consecutive, treatment-naive patients with HCC with detailed data on demographic characteristics, liver function, tumor factors, treatment modalities as well as outcomes. Therefore, the results from the multivariate and subgroup analyses performed in the present study represent a robust and reliable contribution to the field.

In our cohort, male patients with HCC were younger and had a higher rate of chronic HBV infection. Previous studies showed that males have more active HBV viral replication, both in humans and animal models.[26,27] The androgen pathway could enhance the transcription of HBV messenger RNAs through directly binding to the androgen-responsive elements in HBV enhancer I.[26] On the other hand, the estrogen pathway can repress the transcription of HBV genes by altering

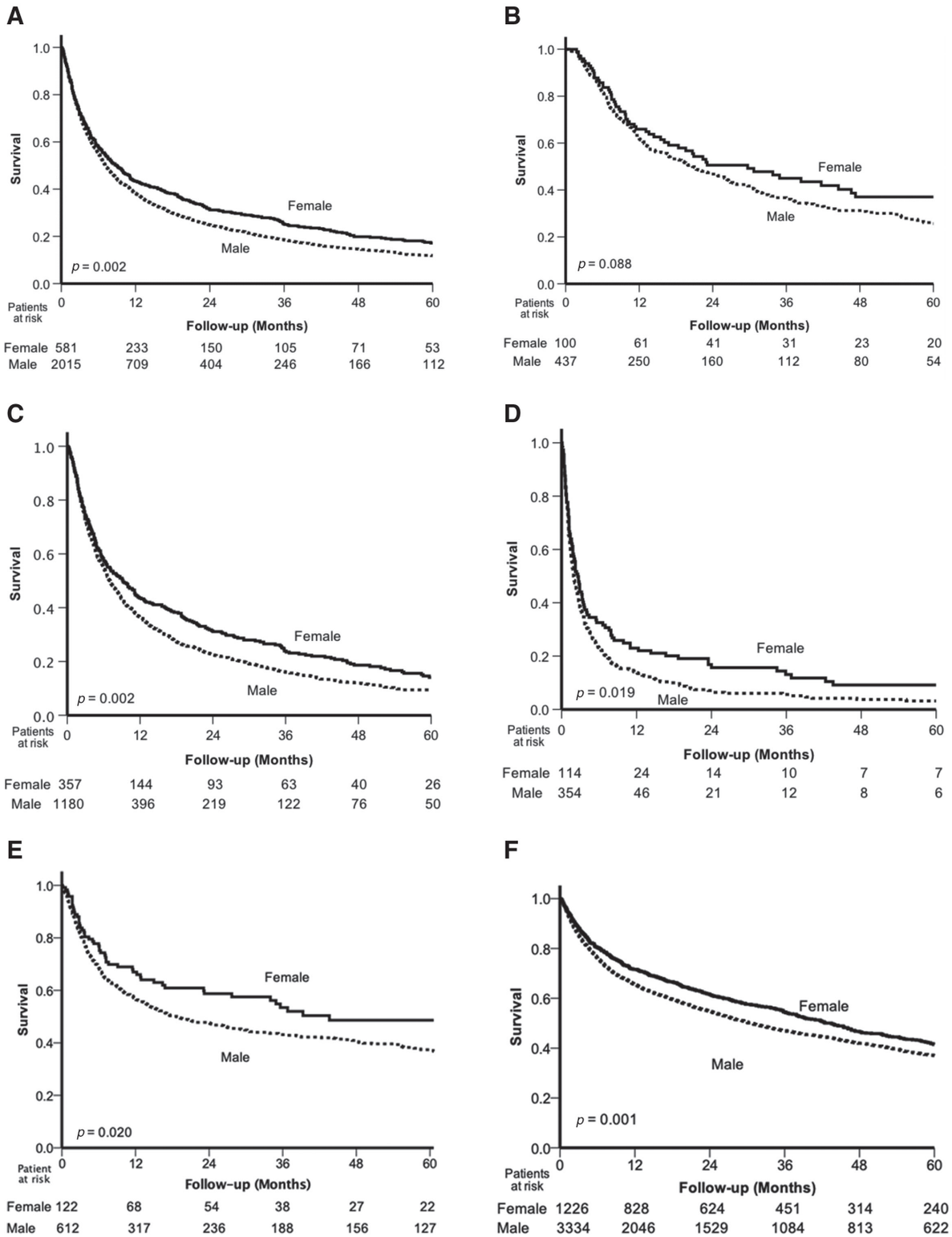

Fig. 3 Comparison of OS between male and female patients with HCC stratified by ALBI grade and age. A, All patients who received noncurative treatment. B, Patients who received noncurative treatment and with ALBI grade 1. C, Patients who received noncurative treatment and with ALBI grade 2. D, Patients who received noncurative treatment and with ALBI grade 3. Comparison of OS between male and female patients with HCC aged (E) ≤50 y (F) >50 y. ALBI = albumin-bilirubin; HCC = hepatocellular carcinoma; OS = overall survival.

Table 3

Multivariate analysis of factors associated with poor OS in HCC patients aged ≤50 years and >50 years

Parameters	HR (95% CI)	*p*
Age ≤50 y		
Sex		
Male vs female	1.558 (1.095-2.219)	0.014
Treatment		
Noncurative vs curative	3.099 (2.241-4.285)	<0.001
HBsAg (+)		
Yes vs no	1.655 (1.165-2.353)	0.005
AFP (ng/mL)		
>20 vs ≤20	1.655 (1.180-2.321)	0.004
Tumor sizes (cm)		
≥5 vs <5	1.574 (1.141-2.173)	0.006
Vascular invasion		
Yes vs no	2.020 (1.510-2.704)	<0.001
ALBI grade		
2 vs 1	1.770 (1.341-2.334)	<0.001
3 vs 1	4.021 (2.685-6.020)	<0.001
Age >50 y		
Treatment		
Noncurative vs curative	3.314 (2.752-3.569)	<0.001
Anti-HCV (+)		
No vs yes	1.134 (1.013-1.269)	0.028
ALK-P (U/L)		
>100 vs ≤100	1.269 (1.133-1.420)	<0.001
AFP (ng/mL)		
>20 vs ≤20	1.490 (1.331-1.668)	<0.001
Numbers of tumor		
>1 vs 1	1.171 (1.054-1.302)	0.003
Tumor sizes (cm)		
≥5 vs <5	1.850 (1.643-2.083)	<0.001
Vascular invasion		
Yes vs no	1.849 (1.637-2.089)	<0.001
ALBI grade		
2 vs 1	1.848 (1.631-2.095)	<0.001
3 vs 1	3.422 (2.874-4.076)	<0.001

AFP = alpha-fetoprotein; ALBI = albumin-bilirubin; ALK-P = alkaline phosphatase; HBsAg = hepatitis B surface antigen; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HR = hazard ratio; OS = overall survival.

the binding of hepatocyte nuclear factor-4α to HBV enhancer I.[28] Therefore, as high HBV viral load is an important driver for hepatic carcinogenesis, it is reasonable that among those with chronic HBV infection, male patients had a higher rate of developing HCC than females.[29] Moreover, the older age of women at diagnosis implicates either the female sex in general or estrogen specifically as playing a protective role in HCC development among women, which is consistent with other studies.[13,15,17]

In our cohort, men presented with a higher tumor burden but had retained better liver function reserve at the time of HCC diagnosis than women. The pathology among male patients was characterized by larger tumor size, as well as a greater proportion of multiple tumors, more vascular invasion, and more advanced BCLC stage. This may result from the nature of HBV-related HCC, which was more frequently found among male patients. In the molecular classification, HBV-related HCC was more commonly categorized as the proliferation class by its genomic and clinical phenotypes, which had more aggressive clinical characteristics and worse disease outcomes.[23,30] However, due to the direct oncogenic effects of HBV infections, HCC can develop in patients with HBV even in the absence of significant liver fibrosis.[31,32] Hence, younger age, less liver cirrhosis, and more preserved liver function were observed in patients with HCC and an underlying HBV infection despite their greater tumor burden.

The aggressive tumor characteristics and advanced HCC staging of male patients resulted in fewer curative therapies being performed in this group despite their preserved liver function and younger age at diagnosis. In our study, only 49% of male patients received curative therapy, compared with 57% of female patients. Therefore, the median OS was significantly longer for female patients than male ones. However, the multivariate analysis showed that liver functional reserve, tumor factors, and treatment modalities were the independent risk factors that contributed to the long-term prognosis of patients with HCC. Sex, however, was not associated with OS after adjusting for these confounding factors.

Several studies have examined the impact of sex disparities on HCC prognosis. Ladenheim et al[15] and Wu et al[19] demonstrated that there were no significant differences in the long-term outcomes of male and female patients. In contrast, Rich et al[17] reported that being female was an independent factor predictive of longer OS (HR, 0.82; 95% CI, 0.68-0.98); however, the statistical significance of the sex effect on OS seems to be marginal. Moreover, the male and female patients had similar liver function, but a higher proportion of early-stage HCC was found in women in this study. Besides, the OS advantage from being female was only observed in patients younger than 65 years and not in older patients with HCC. Above all, HCV infection was the major liver disease etiology (64.6%) in this cohort. Our current study further investigated the impact of sex on HCC outcomes stratified by the different viral etiologies. It revealed that the female sex was an independent predictor for better OS only in HCV-related HCC patients but not in HBV-related HCC patients nor nonviral HCC patients. However, the mechanism of gender factor in determining the outcomes of patients with HCV-related HCC is not yet well been studied. It needs more prospective studies to elucidate this issue.

We also highlight that the survival benefit of the female sex is more prominent among the young patients with HCC, suggesting that the high serum estrogen levels of premenopausal women contribute to their improved prognosis.[17,18,33] Given that the estimated mean age of menopause in Taiwan is approximately 50.2 years old,[25] the patient population in the present study was stratified into those over and under 50 years old for all analyses. This approach revealed that female sex was an independent factor associated with lower mortality in younger but not older patients with HCC, consistent with previous reports. Nevertheless, information on menopausal age was not obtained in these retrospective studies; therefore, future large-scale, retrospective studies are required to elucidate the association between menopause and HCC prognosis.

The Child-Pugh classification system, a traditional assessment of hepatic function reserve in patients with cirrhosis, is not sufficiently accurate due to two subjective parameters (ascites and encephalopathy grading) included in this scoring system.[20,23] Although Child-Pugh classification is widely used for HCC staging, it is not an effective tool for predicting the prognosis of patients with HCC.[20,34] In contrast, the ALBI grading system proposed by Johnson to assess liver function reserve in patients with HCC merely consists of two objective variables (serum albumin and bilirubin levels).[24] The ALBI grade has been widely validated to predict the prognosis of patients with HCC across all BCLC stages and treatment modalities.[35–39] The excellent predictive ability of ALBI grading for the prognosis of patients with HCC was confirmed in our cohort. A high ALBI grade was an independent risk factor associated with poor OS in all patients

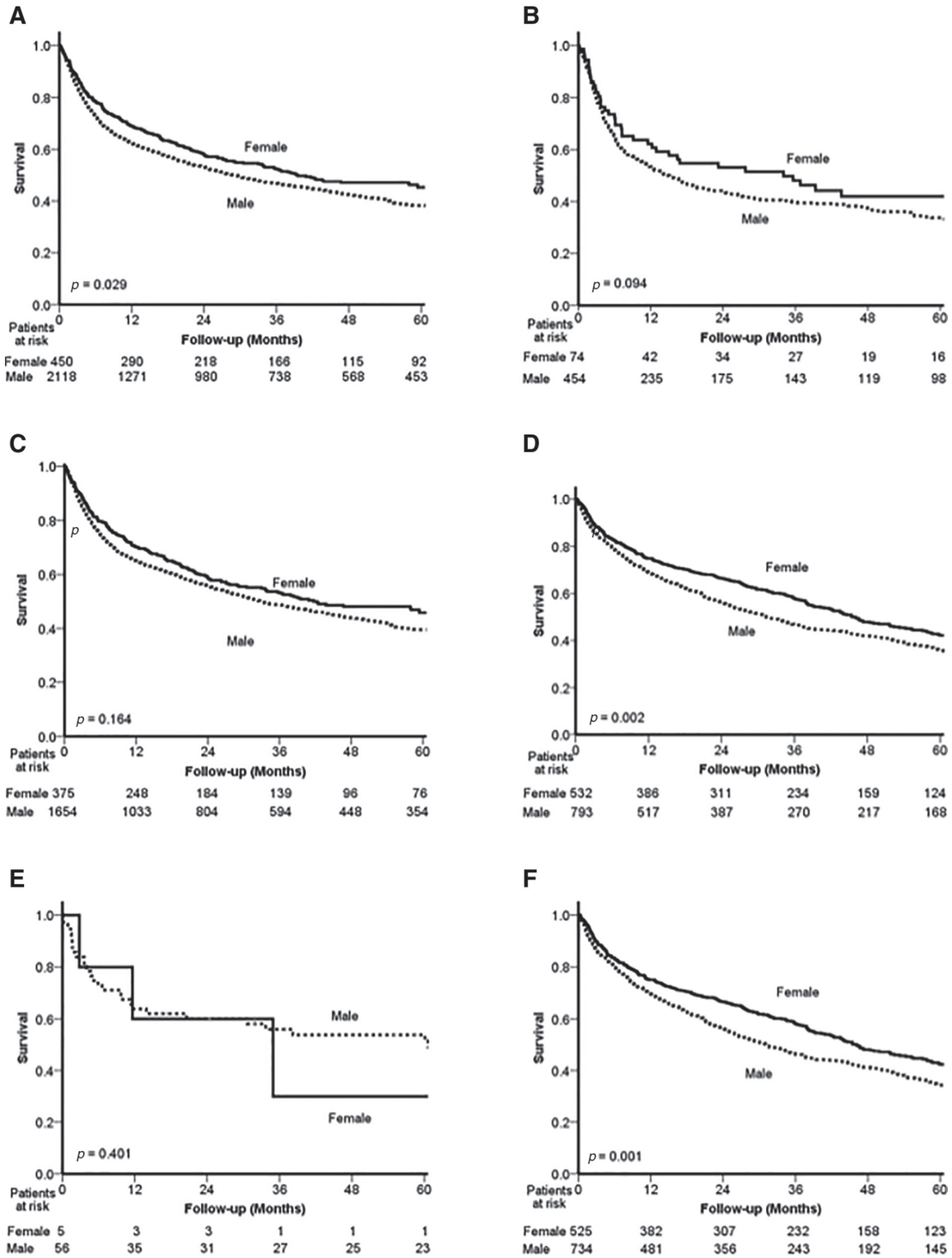

Fig. 4 Comparison of OS between male and female patients stratified by etiology and age. A, All patients with HBV-related HCC (B) patients with HBV-related HCC and age ≤50 y (C) patients with HBV-related HCC and age >50 y (D) all patients with HCV-related HCC (E) patients with HBV-related HCC and age ≤50 y (F) patients with HBV-related HCC and age >50 y (G) all patients with nonviral HCC (H) patients with nonviral HCC and age ≤50 y (I) patients with nonviral HCC and age >50 y. HBV = hepatitis B virus; HCC = hepatocellular carcinoma; OS = overall survival.

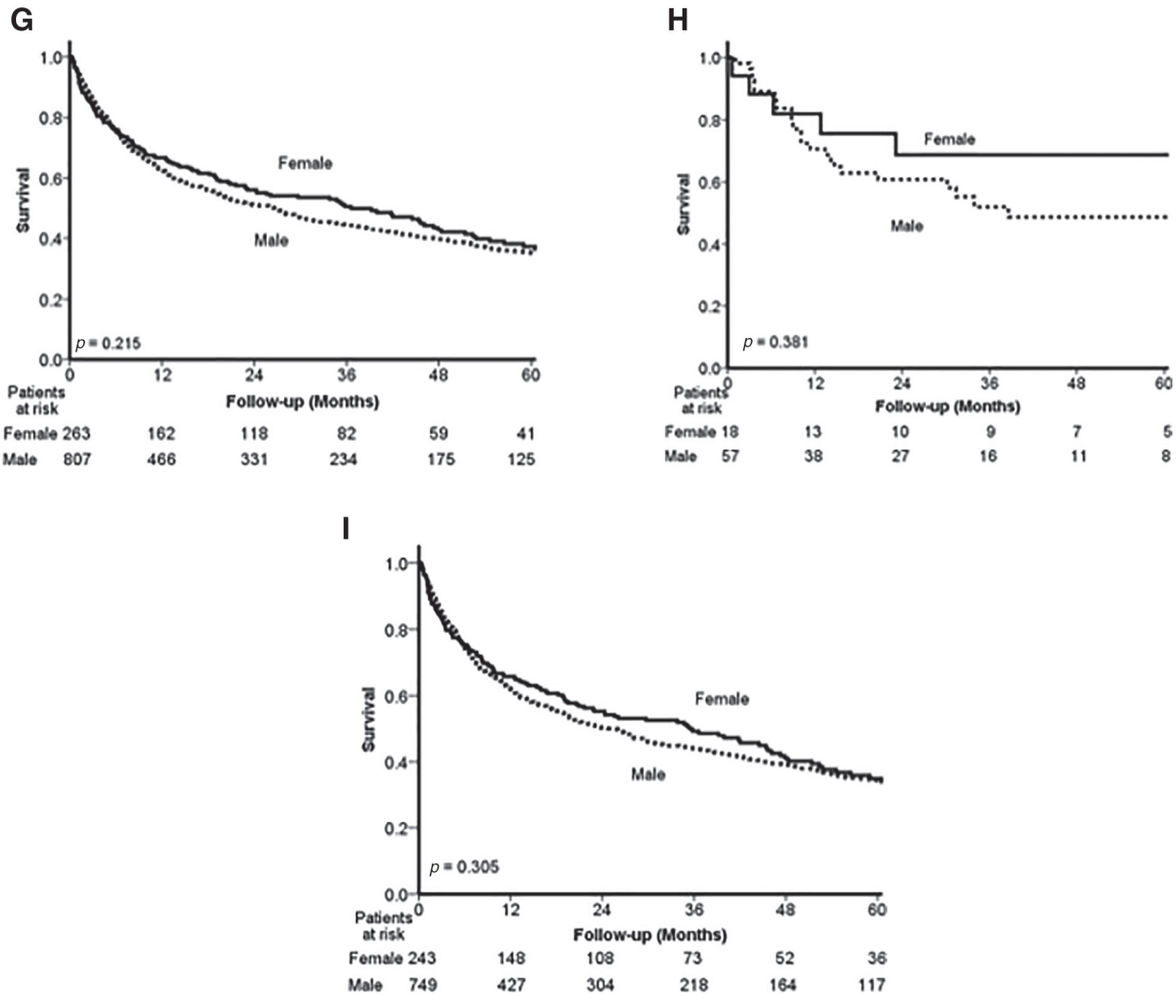

Fig. 4 Continued.

regardless of treatment, sex, and age group in the multivariate analyses.

Since treatment modalities and ALBI grades were crucial in determining the outcomes of patients with HCC, we further stratified our analysis by these two factors. Among patients who underwent curative treatments, the men and women had similar tumor burdens with no noticeable distinctions in tumor number, vascular invasion, and serum AFP levels (Supplementary Table 4, http://links.lww.com/JCMA/A144) and, therefore, similar survival outcomes across the three ALBI grades. As for the noncurative treatment group, larger tumor size and more vascular invasion were observed in male patients (Supplementary Table 5, http://links.lww.com/JCMA/A144). These diversities in tumor features led to significantly worse OS among the men compared with the women in the univariate analysis, especially for those with ALBI grades 2 and 3. Nonetheless, in the multivariate analysis of the noncurative therapy group, being female was not an independent factor predictive of longer OS.

There were several limitations in this study. First, this was a retrospective cohort study in a single, tertiary, referral medical center. Potential selection bias and missing data could exist. Second, our study population was mainly composed of Asians, most of whom had viral hepatitis-induced HCC. Further studies recruiting different ethnic, demographic, and nonviral hepatitis etiology of patients with HCC are needed before generalizing our study findings. Third, the data recorded in our electronic patient health database was limited and did not include menopause status and the history of hormone replacement therapy, which may be associated with the sex disparities in HCC prognosis. Fourth, with the recent advances of systemic therapy for the treatment of HCC, more and more patients now receive molecular target therapy or immune check point inhibitors with acceptable outcomes. However, we could not investigate the impact of gender on the outcomes of patients with HCC receiving systemic therapy due to the relatively small number of patients in each regimen in our cohort. Further prospective studies are warranted to clarify the role of gender in determining the prognosis of HCC patients who received systemic therapy.

In conclusion, although men with HCC had worse OS than women, the male sex was not an independent factor predictive of poor HCC prognosis according to our multivariate analysis, especially for those aged over 50 years.

Table 4

Multivariate analysis of factors associated with poor OS in HBV-related HCC patients of all ages, aged ≤50 years and >50 years

Parameters	HR (95% CI)	*p*
All ages		
Treatment		
Noncurative vs curative	3.148 (2.705-3.663)	<0.001
AFP (ng/mL)		
>20 vs ≤20	1.559 (1.354-1.795)	<0.001
ALT (U/L)		
>40 vs ≤40	1.144 (1.011-1.293)	0.033
ALK-P (U/L)		
>100 vs ≤100	1.200 (1.045-1.378)	0.010
Tumor sizes (cm)		
≥5 vs <5	1.877 (1.622-2.172)	<0.001
Vascular invasion		
Yes vs no	1.874 (1.623-2.164)	<0.001
ALBI grade		
2 vs 1	1.714 (1.486-1.973)	<0.001
3 vs 1	3.585 (2.948-4.358)	<0.001
Age ≤50 y		
Treatment		
Noncurative vs curative	2.557 (1.794-3.644)	<0.001
AFP (ng/mL)		
>20 vs ≤20	1.479 (1.054-2.074)	0.023
Numbers of tumor		
>1 vs 1	1.373 (1.054-1.789)	0.019
Tumor sizes (cm)		
≥5 vs <5	1.755 (1.276-2.414)	0.001
Vascular invasion		
Yes vs no	2.047 (1.537-2.727)	<0.001
ALBI grade		
2 vs 1	1.872 (1.411-2.485)	<0.001
3 vs 1	5.134 (3.495-7.543)	<0.001
Age >50 y		
Age (y)		
>65 vs ≤65	1.290 (1.123-1.481)	<0.001
Treatment		
Noncurative vs curative	3.134 (2.641-3.718)	<0.001
AFP (ng/mL)		
>20 vs ≤20	1.608 (1.374-1.883)	<0.001
ALT (U/L)		
>40 vs ≤40	1.157 (1.006-1.331)	0.041
ALK-P (U/L)		
>100 vs ≤100	1.200 (1.029-1.400)	0.020
Tumor sizes (cm)		
≥5 vs <5	1.954 (1.659-2.303)	<0.001
Vascular invasion		
Yes vs no	1.924 (1.627-2.275)	<0.001
ALBI grade		
2 vs 1	1.676 (1.423-1.974)	<0.001
3 vs 1	3.435 (2.739-4.307)	<0.001

AFP = alpha-fetoprotein; ALBI = albumin-bilirubin; ALK-P = alkaline phosphatase; ALT = alanine aminotransferase; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HR = hazard ratio; OS = overall survival.

Table 5

Multivariate analysis of factors associated with poor OS in HCV-related HCC patients of all ages, aged ≤50 years and >50 years

Parameters	HR (95% CI)	*p*
All ages		
Age (y)		
>65 vs ≤65	1.555 (1.300-1.860)	<0.001
Sex		
Male vs female	1.289 (1.081-1.537)	0.005
Treatment		
Noncurative vs curative	2.306 (1.893-2.809)	<0.001
AFP (ng/mL)		
>20 vs ≤20	1.428 (1.183-1.723)	<0.001
Tumor sizes (cm)		
≥5 vs <5	1.839 (1.516-2.230)	<0.001
Vascular invasion		
Yes vs no	2.182 (1.757-2.709)	<0.001
ALBI grade		
2 vs 1	2.138 (1.729-2.645)	<0.001
3 vs 1	3.478 (2.578-4.691)	<0.001
Age ≤50 y		
Treatment		
Noncurative vs curative	5.044 (2.547-9.989)	0.031
PT/INR		
>1.1 vs ≤1.1	2.120 (1.002-4.484)	0.049
Vascular invasion		
Yes vs no	3.618 (1.401-9.347)	0.008
Age >50 y		
Age (y)		
>65 vs ≤65	1.583 (1.313-1.908)	<0.001
Sex		
Male vs female	1.279 (1.069-1.529)	0.007
Treatment		
Noncurative vs curative	2.270 (1.853-2.780)	<0.001
AFP (ng/mL)		
>20 vs ≤20	1.406 (1.159-1.705)	0.001
Tumor sizes (cm)		
≥5 vs <5	1.828 (1.501-2.227)	<0.001
Vascular invasion		
Yes vs no	2.133 (1.708-2.664)	<0.001
ALBI grade		
2 vs 1	2.178 (1.745-2.717)	<0.001
3 vs 1	3.879 (2.828-5.320)	<0.001

AFP = alpha-fetoprotein; ALBI = albumin-bilirubin; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HR = hazard ratio; OS = overall survival; PT/INR = prothrombin time/international normalized ratio.

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Supplementary data related to this article can be found at http://links.lww.com/JCMA/A144.

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Table 6

Multivariate analysis of factors associated with poor OS in non-HCV non-HBV HCC patients of all ages, aged ≤50 years and >50 years

Parameters	HR (95% CI)	*p*
All ages		
Age (y)		
>65 vs ≤65	1.783 (1.447-2.198)	<0.001
Treatment		
Noncurative vs curative	3.093 (2.452-3.903)	<0.001
AFP (ng/mL)		
>20 vs ≤20	1.554 (1.281-1.885)	<0.001
ALK-P (U/L)		
>100 vs ≤100	1.648 (1.333-2.038)	<0.001
Numbers of tumor		
>1 vs 1	1.347 (1.109-1.637)	0.003
Tumor sizes (cm)		
≥5 vs <5	1.583 (1.278-1.962)	<0.001
Vascular invasion		
Yes vs no	1.873 (1.516-2.314)	<0.001
ALBI grade		
2 vs 1	1.951 (1.568-2.427)	<0.001
3 vs 1	4.871 (3.542-6.698)	<0.001
Age ≤50 y		
Vascular invasion		
Yes vs no	4.598 (2.229-9.488)	<0.001
Age >50 y		
Age (y)		
>65 vs ≤65	1.525 (1.222-1.902)	<0.001
Treatment		
Noncurative vs curative	3.115 (2.455-3.953)	<0.001
AFP (ng/mL)		
>20 vs ≤20	1.489 (1.222-1.814)	<0.001
ALK-P (U/L)		
>100 vs ≤100	1.742 (1.404-2.162)	<0.001
Numbers of tumor		
>1 vs 1	1.420 (1.165-1.731)	0.001
Tumor sizes (cm)		
≥5 vs <5	1.606 (1.289-2.002)	<0.001
Vascular invasion		
Yes vs no	1.843 (1.483-2.291)	<0.001
ALBI grade		
2 vs 1	2.113 (1.882-2.655)	<0.001
3 vs 1	4.721 (3.408-6.541)	<0.001

AFP = alpha-fetoprotein; ALBI = albumin-bilirubin; ALK-P = alkaline phosphatase; HBV = hepatitis B virus; HCV = hepatitis C virus; HR = hazard ratio; OS = overall survival.

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