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ORIGINAL ARTICLE

Gender survival differences in hepatocellular carcinoma: Is it all due to adherence to surveillance? A study of 1716 patients over three decades

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adherence, gender, hepatocellular carcinoma, surveillance, survival.

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Abstract

Background and Aims: Hepatocellular carcinoma (HCC) is one of the commonest causes of cancer-related death worldwide. Whether gender is an independent factor for HCC survival is debatable. We studied the influence of gender on the clinical characteristics of HCC and on survival.
Methods: The study cohort comprised patients with HCC seen in our department from 1988 to 2021. Clinical data were prospectively collected. We studied and compared demography, HCC characteristics, and survival between females and males. Survival analysis was censored on October 31, 2015.
Results: There were 1716 HCC patients. 343 (20.0%) were females. Females were significantly older at diagnosis (median 69 *vs* 62 years, $P < 0.001$). More females were diagnosed via regular HCC surveillance (37.9% *vs* 29.6%, $P = 0.003$). Hence, as expected, females had less-advanced HCC at diagnosis with smaller median tumor diameter (30 *vs* 39.5 mm, $P = 0.038$), lower frequency of portal vein tumor thrombus (19.4% *vs* 33.4%, $P < 0.001$), less distant metastases (7.7% *vs* 11%, $P = 0.043$), and earlier Barcelona Clinic Liver Cancer (BCLC) stages (0/A, 39.7% *vs* 28.4%, $P < 0.001$). On multivariable analysis, HCC diagnosis via surveillance but not female gender was an independent predictor of improved HCC survival.
Conclusions: In this large cohort of multi-ethnic Asian patients, females with HCC were significantly more adherent to surveillance and hence presented with less advanced HCC with correspondingly better overall survival than males. The gender difference in survival is likely due to females having better adherence to HCC surveillance. Surveillance to diagnose early-stage HCC remains crucial in improving outcomes.

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third leading cause of cancer-related mortality worldwide.[1] The incidence of HCC is higher in males than females, with a reported ratio of 4 to 1.[2] Aside from well-known etiological differences in chronic liver disease, the differences in characteristics and prognosis of HCC between males and females remain poorly understood. A previous study reported a better survival rate in female patients with HCC than their male counterparts.[3] Gender-related hormonal effect on the growth of HCC has been hypothesized but it has yet to be proven. Whether gender is an independent factor for HCC survival remains debatable. The aim of this study was to evaluate the influence of gender on clinical characteristics of HCC and on survival and to identify factors that may explain the differences if present.

Patients and methods. We have been prospectively enrolling patients with HCC who are seen in our Department of Gastroenterology and Hepatology Singapore General Hospital, a tertiary hospital in Singapore, into a Research Electronic Data Capture (REDCap) database. Our department also runs a regular program for HCC surveillance in at-risk patients. Patients who

were enrolled in the database between 1988 and August 2021 were included in our study. Clinical data were prospectively collected. We compared demography, clinical and tumor characteristics, and survival between male and female patients with HCC. Survival census was done on October 31, 2015 with input from our National Registry of Deaths.

The study was approved by the institutional review board of Singapore General Hospital in accordance with the Declarations of Helsinki and Istanbul, with a waiver of informed consent.

Data collected included patient demographics, etiology of chronic liver disease, Child-Pugh status, and laboratory studies at the time of HCC diagnosis, mode of HCC diagnosis, HCC-related variables, and treatment modalities.

The etiology was classified as hepatitis B virus (HBV) if the HBV surface antigen was positive, or anti-HBV core total antibody positive in the absence of other risk factors for HCC, as hepatitis C virus (HCV) if anti-HCV IgG antibody or HCV RNA was positive and as alcohol if the consumption of alcohol exceeded 60 g/day for at least 5 years in both male and female patients.

Severity of underlying liver cirrhosis was classified based on Child-Pugh status at the time of HCC diagnosis.

Mode of HCC diagnosis was considered as "surveillance" if the HCC was diagnosed during regular surveillance of at-risk patients for HCC. It is defined as "symptomatic" when the patient was not under HCC surveillance and presented with

Table 1 Clinical characteristics of males and females with HCC

Patient characteristics	Overall ($n = 1716$)	Male ($n = 1373$)	Female ($n = 343$)	*P* value
Age, median (IQR)	63 (55–71)	62 (54–69)	69 (61–76)	<0.001
Ethnicity				
Chinese	1505 (87.7%)	1197 (87.2%)	308 (89.8%)	0.26
Malay	130 (7.6%)	105 (7.6%)	25 (7.3%)	
Indian	45 (2.6%)	41 (3.0%)	4 (1.2%)	
Others	36 (2.1%)	30 (2.2%)	6 (1.7%)	
Eastern cooperative oncology group (ECOG) status				
0	728 (45.7%)	572 (44.7%)	156 (49.8%)	0.10
1	437 (27.4%)	363 (28.4%)	74 (23.6%)	
2	308 (19.3%)	255 (19.9%)	53 (16.9%)	
3	98 (6.2%)	75 (5.9%)	23 (7.3%)	
4	21 (1.3%)	14 (1.1%)	7 (2.2%)	
Etiology of underlying liver disease				
HBV	1137 (66.3%)	930 (67.7%)	207 (60.3%)	
HCV	78 (4.5%)	64 (4.7%)	14 (4.1%)	
HBV/HCV	56 (3.3%)	50 (3.6%)	6 (1.7%)	
Alcohol	83 (4.8%)	80 (5.8%)	3 (0.9%)	
Autoimmune	9 (0.5%)	2 (0.2%)	7 (2%)	
Cryptogenic/NASH	353 (20.5%)	247 (17.9%)	106 (30.9%)	
Viral	1271 (74.1%)	1044 (76%)	227 (66.2%)	<0.001
Non-viral	445 (25.9%)	329 (24.0%)	116 (33.8%)	
HBV related	1193 (69.5%)	980 (71.4%)	213 (62.1%)	<0.001
Non-HBV related	523 (30.5%)	393 (28.6%)	130 (37.9%)	
Autoimmune	9 (0.5%)	2 (0.2%)	7 (2%)	<0.001
Non-autoimmune	1707 (99.5%)	1371 (99.8%)	336 (98%)	
Alcohol	83 (4.8%)	80 (5.8%)	3 (0.9%)	< 0.001
Non-alcohol	1633 (95.2%)	1293 (94.2%)	340 (99.1%)	
HCC diagnosis				
Surveillance	535 (31.3%)	406 (29.6%)	129 (37.9%)	0.003
Symptomatic	1177 (68.7%)	966 (70.4%)	211 (62.1%)	
Ascites				
None	1142 (67.8%)	922 (68.4%)	220 (65.5%)	0.21
Mild/controlled	272 (16.2%)	207 (15.4%)	65 (19.3%)	
Severe/uncontrolled	270 (16%)	219 (16.2%)	51 (15.2%)	
Encephalopathy				
None	1638 (97.2%)	1308 (97%)	330 (97.6%)	0.32
Grade I/II	39 (2.3%)	34 (2.5%)	5 (1.5%)	
Grade III/IV	9 (0.5%)	6 (0.4%)	3 (0.9%)	
Child-Pugh status				
A	899 (54.2%)	720 (54.1%)	179 (54.6%)	0.73
B	567 (34.2%)	452 (34.0%)	115 (35.1%)	
C	192 (11.6%)	158 (11.9%)	34 (10.4%)	

Table 2 Comparison of patient characteristics based on the mode of HCC diagnosis

Patient characteristics	Overall ($n = 1712$)	Surveillance ($n = 535$)	Symptomatic ($n = 1177$)	*P* value
Age, median (IQR)	63 (55–71)	63 (56–70)	63 (55–71)	0.992
Eastern cooperative oncology group (ECOG) status				
0–1	1163 (73.1%)	475 (94.4%)	688 (63.3%)	<0.001
2–4	427 (26.9%)	28 (5.6%)	399 (36.7%)	
Etiology of underlying liver disease				
HBV	1134 (66.2%)	351 (65.6%)	783 (66.5%)	
HCV	77 (4.5%)	31 (5.8%)	46 (3.9%)	
HBV/HCV	56 (3.3%)	7 (1.3%)	49 (4.2%)	
Alcohol	83 (4.8%)	34 (6.4%)	49 (4.2%)	
Autoimmune	9 (0.5%)	5 (0.9%)	4 (0.3%)	
Cryptogenic/NASH	353 (20.6%)	107 (20%)	246 (20.9%)	
HBV related	1190 (69.5%)	358 (66.9%)	832 (70.7%)	0.116
Non-HBV related	522 (30.5%)	177 (33.1%)	345 (29.3%)	
Viral	1267 (74.0%)	389 (72.7%)	878 (74.6%)	0.409
Non-viral	445 (26.0%)	146 (27.3%)	299 (25.4%)	
Ascites				
None	1140 (67.8%)	447 (85.3%)	693 (59.8%)	<0.001
Mild or severe	542 (32.2%)	77 (14.7%)	465 (40.2%)	
Encephalopathy				
None	1636 (97.1%)	510 (97.5%)	1126 (97.0%)	0.784
Grade I/II	39 (2.3%)	11 (2.1%)	28 (2.4%)	
Grade III/IV	9 (0.5%)	2 (0.4%)	7 (0.6%)	
Child-Pugh status				
A	898 (54.2%)	393 (76.3%)	505 (44.2%)	<0.001
B or C	759 (45.8%)	122 (23.7%)	637 (55.8%)	

Table 3 Comparison of HCC characteristics between genders

Tumor characteristic	Overall ($n = 1716$)	Male ($n = 1373$)	Female ($n = 343$)	*P* value
Numbers of lesion				
Single	890 (52.7%)	685 (50.7%)	205 (60.8%)	<0.001
Multiple/diffuse	799 (47.3%)	667 (49.3%)	132 (39.2%)	
Tumor diameters (mm), median (IQR)	36 (20–71)	39.5 (20–78)	30 (17–56.5)	0.038
Portal vein invasion	480 (30.6%)	419 (33.4%)	61 (19.4%)	<0.001
Lymph node involvement	129 (8%)	111 (8.6%)	18 (5.6%)	0.048
Distant metastases	174 (10.4%)	148 (11.0%)	26 (7.7%)	0.043
AFP, median (IQR)	79 (8–4123.5)	82 (8–544)	56 (7–1905.5)	0.57
BCLC				
0/A	468 (30.7%)	348 (28.4%)	120 (39.7%)	<0.001
B/C/D	1058 (69.3%)	876 (71.6%)	182 (60.3%)	
Treatment				
Curative	534 (31.1%)	411 (29.9%)	123 (35.9%)	0.12
Non-curative	390 (22.7%)	321 (23.4%)	69 (20.1%)	
Best supportive care	510 (29.7%)	410 (29.9%)	100 (29.2%)	

symptoms. Barcelona Clinic Liver Cancer (BCLC) system which incorporates a patient's physical functional status and liver functional status, as well as tumor characteristics based on imaging, was used to stage HCC in our study population.

Treatment modalities were classified into three categories, curative, non-curative, and best supportive care. Curative treatment modalities included liver transplantation, surgical resection, and radiofrequency or microwave ablation. Non-curative treatment modalities included transhepatic arterial chemoembolization (TACE), Ytrium-90 selective internal radiation therapy (Y90-SIRT), stereotactic body radiation therapy (SBRT), and systemic therapy. If the patient did not receive any specific HCC treatment, it was deemed as the best supportive care.

A survival census was performed with the National Registry of Death on October 31, 2015. Under the law, all deaths of

Table 4 Comparison of HCC characteristics based on the mode of HCC diagnosis

Tumor characteristic	Overall ($n = 1712$)	Surveillance ($n = 535$)	Symptomatic ($n = 1177$)	P value
Numbers of lesion				
Single	889 (52.7%)	367 (69.5%)	522 (45.0%)	<0.001
Multiple/diffuse	799 (47.3%)	161 (30.5%)	638 (55.0%)	
Tumor diameters (mm), median (IQR)	36 (20–71)	23 (16–38)	56 (29–100)	<0.001
Portal vein invasion	480 (30.6%)	36 (6.9%)	444 (42.4%)	<0.001
Lymph node involvement	129 (8%)	11 (2.1%)	118 (10.8%)	<0.001
Distant metastases	174 (10.4%)	3 (0.5%)	171 (14.9%)	<0.001
AFP, median (IQR)	79 (8–4139)	10.5 (4–46.2)	520 (18–12 000)	<0.001
BCLC				
0/A	467 (30.6%)	341 (69.7%)	126 (12.2%)	<0.001
B/C/D	1058 (69.4%)	148 (30.3%)	910 (87.8%)	
Treatment				
Curative	532 (37.2%)	350 (72.0%)	182 (19.2%)	<0.001
Non-curative	390 (27.2%)	101 (20.8%)	289 (30.6%)	
Best supportive care	510 (35.6%)	35 (7.2%)	475 (50.2%)	

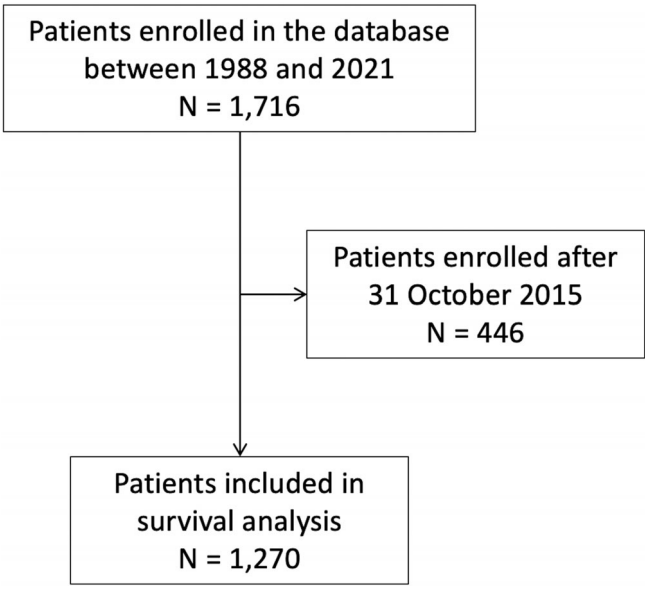

Figure 1 Flowchart of study population with survival census on October 31, 2015.

local residents must be reported to the National Registry of Deaths.

Statistical analysis. Continuous variables were presented as median with interquartile range (IQR) and compared using the Mann–Whitney U test. Categorical variables were presented as frequencies and percentages and compared using the Chi-square test. Survival census was performed on October 31, 2015. Survival duration was defined from the date of HCC diagnosis to the date of death as recorded in the National Registry of Deaths or censored on October 31, 2015 if the patient was still alive. The survival probability was calculated using Kaplan–Meier method and compared using the log-rank test. To factor in the possibility of lead-time bias, which represents the apparently improved survival due to earlier HCC diagnosis in the course of the disease, we subtracted the calculated lead-time from the survival duration for patients in the surveillance group. The lead time was calculated based on the formula, $T = 3 \times$ HCC doubling time $\times \log(d^1/d^0)/\log 2$, which was proposed by Schwartz *et al.*[4] T is the lead time in days, d^0 and d^1 are the median tumor diameters of the surveillance group and the symptomatic group respectively from the survival analysis cohort. We calculated the lead time with an assumption of three different HCC doubling times, 60, 90, and 120 days, in keeping with the ranges used in previous studies.[5–7] Univariate and multivariable Cox proportional hazard regression analyses were performed to identify factors associated with overall survival. A two-tailed P value of 0.05 or less was considered statistically significant. All statistical analyses were performed using SPSS version 28 (IBM).

Results

Patient characteristics. A total of 1716 patients with HCC between 1988 and August 2021 were included in our study, 80% were males. Patients' baseline demography and characteristics are shown in Table 1. Females were significantly older at HCC diagnosis (median age of 69 *vs* 62, $P < 0.001$). Females had a significantly higher frequency of non-viral liver disease (33.8% *vs* 24.0%, $P < 0.001$). In terms of specific etiology, autoimmune liver disease was more common (2.0% *vs* 0.2%, $P < 0.001$), and alcohol was less common (0.9% *vs* 5.8%, $P < 0.001$) in females. There was no difference in the surveillance status for viral and non-viral liver disease (Table 2). There was also no difference in the distribution of Child-Pugh status between the two genders.

Clinical presentation and tumor characteristics. Significantly more females were diagnosed with HCC via surveillance compared to males (37.9% *vs* 29.6%, $P = 0.003$). As a result, females had less advanced HCC at diagnosis. The differences in HCC characteristics between the two genders are shown in Table 3. Females had a higher frequency of solitary HCC (60.8% *vs* 50.7%, $P < 0.001$) as well as smaller median tumor

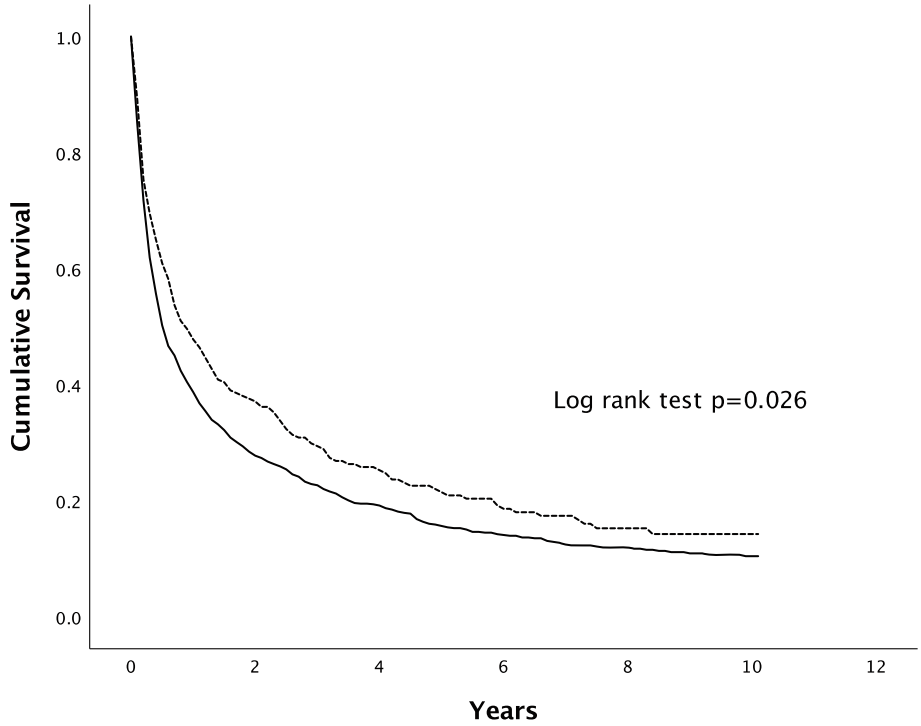

Figure 2 Overall survival of males and females with HCC. The difference in survival was statistically significant ($P = 0.026$ by Kaplan–Meier, log-rank test). ——, Male; -----, Female.

Table 5 1, 3, 5-year survival

	1 year (%)	3 years (%)	5 years (%)	*P* value
Overall				
Male	39	23	16	0.026
Female	48	29	21	
Surveillance group				
Male	53	30	22	0.836
Female	57	34	20	
Symptomatic group				
Male	21	9	5	0.056
Female	27	14	10	

size (30.0 *vs* 39.5 mm, $P < 0.001$) when compared with males. Females also had a lower frequency of portal vein tumor invasion (19.4% *vs* 33.4%, $P < 0.001$) and extrahepatic involvement (5.6% *vs* 8.6%, $P = 0.048$). Similarly, significantly more females were in BCLC stages 0/A (39.7% *vs* 28.4%, $P < 0.001$). Alpha-fetoprotein (AFP) concentration at the time of HCC diagnosis did not differ significantly between the two genders (Table 3).

Comparison of clinical and tumor characteristics of patients with HCC diagnosed via surveillance versus symptomatic presentation. As surveillance was the main factor affecting survival in our study populations, we compared the baseline clinical and HCC characteristics of patients with HCC diagnosed via surveillance *versus* symptomatic presentation. Patients who had HCC diagnosed via surveillance had significantly better Eastern Cooperative Oncology Group (ECOG) status (ECOG 0–1 94.4% *vs* 63.3%, $P < 0.001$) at the time of HCC diagnosis. Surveillance cases also had significantly better Child-Pugh status (Child-Pugh A, 76.3% *vs* 44.2%, $P < 0.001$) and were free of ascites at presentation (85.3% *vs* 59.8%, $P < 0.001$) (Table 2). In terms of tumor characteristics, HCCs in the surveillance group were less advanced at presentation, as evidenced by significantly smaller tumor size (23 *vs* 56 mm, $P < 0.001$), less portal vein invasion (6.9% *vs* 42.4%, $P < 0.001$), and less extrahepatic involvement (0.5% *vs* 14.9%, $P < 0.001$) (Table 4). Patients who had HCC diagnosed via surveillance also had significantly better BCLC stage (BCLC 0/A, 69.7% *vs* 12.2%, $P < 0.001$) and hence were significantly more likely to receive curative treatment (72.0% *vs* 19.2%, $P < 0.001$) (Table 4).

Treatment and survival analysis. More females underwent HCC treatment with curative intent compared with males, but this was not statistically significant (35.9% *vs* 29.9%, $P = 0.053$) (Table 3).

As the survival census was performed on October 31, 2015, patients who were enrolled in the database after this date were excluded from the survival analysis. A total of 1270 patients were included in the survival analysis (Fig. 1).

The overall median survival of HCC was significantly higher in females than in males (10.1 *vs* 6.1 months, $P = 0.03$) (Fig. 2). The 1-, 3- and 5-year survival rates were 48%, 29%, and 21% in females compared to 39%, 23%, and 16% in males respectively (Table 5).

Table 6 Univariate and multivariable Cox regression analysis on overall survival

Variable	Univariate			Multivariable		
	Hazard ratio	Confidence interval	*P* value	Hazard ratio	Confidence interval	*P* value
Female	0.84	0.72–0.98	0.026	0.96	0.79–1.17	0.695
Age	1.01	1.01–1.02	<0.001	1.01	0.99–1.01	0.086
Surveillance	0.73	0.62–0.86	<0.001	0.81	0.67–0.99	0.042
Child-Pugh A	0.36	0.32–0.41	<0.001	0.58	0.49–0.68	<0.001
BCLC 0/A	0.23	0.19–0.27	<0.001	0.40	0.21–0.50	<0.001
Single lesion	0.49	0.43–0.55	<0.001	0.78	0.67–0.91	0.002
Absence of metastasis	0.33	0.27–0.39	<0.001	0.56	0.46–0.69	<0.001
Absence of portal vein tumor thrombosis	0.26	0.22–0.29	<0.001	0.41	0.35–0.49	<0.001
Non-viral etiology	0.93	0.79–1.08	0.327	–	–	–

Table 7 Comparison of survival between males and females stratified by treatment modality

	1 year (%)	3 years (%)	5 years (%)	*P* value
Curative[‡]				
Male	87	67	50	0.310
Female	92	73	57	
Non-curative[†]				
Male	39	13	5	0.178
Female	43	19	16	
Best supportive care				
Male	13	1	0	0.114
Female	17	3	0	

[†]Non-curative: TACE, Y90-SIRT, SBRT, or systemic therapy.
[‡]Curative: Resection, radiofrequency ablation, or liver transplant.

Table 8 Differences in survival after adjustment for lead time

Doubling times (Days)	Estimated lead times (Days)	Median survival (Days)		*P* value
		Male	Female	
60	184	169	260	0.036
90	277	164	251	0.052
120	369	159	248	0.057

In univariate analysis, the female gender was associated with better survival when compared to the male. However, this was not statistically significant in multivariable analysis. Multivariable Cox regression analysis after adjusting for gender and age showed that the main predictors for improved survival were HCC diagnosis via surveillance, Child-Pugh status A, BCLC 0/A, and HCC with less advanced features (Table 6). When survival was analyzed according to the treatment modality, there was no statistically significant difference between the two genders (Table 7).

As HCC diagnosis via surveillance was a predictor for survival, we performed statistical analysis to adjust for possible lead-time bias. The median diameter of HCC from the survival analysis cohort was 57 mm in the symptomatic group, and 28 mm in the surveillance group. Based on these tumor diameters and HCC doubling times of 60, 90, and 120 days, the calculated lead time bias in our populations corresponded to 184, 277, and 369 days respectively. Survival benefit remained significant in females after adjustment of HCC doubling time of 60 days ($P = 0.036$). However, the survival benefit with HCC doubling times of 90 and 120 days decreased to near significance (Table 8).

When the survival was analyzed according to the mode of diagnosis, the median survival was higher in patients with HCC diagnosed through surveillance in comparison to the symptomatic group (14.0 *vs* 5.6 months, $P < 0.001$) (Fig. 3). When females were compared with males according to the mode of HCC diagnosis, there was no significant difference in survival in between the two genders, as shown in Figures 4, 5.

Discussion

This large cohort study of multi-ethnic Asian patients across three decades demonstrated several clinical differences between males and females with HCC. Importantly, females diagnosed with HCC had better survival than their male counterparts. However, this advantage in survival disappeared when the analysis is adjusted according to the mode of HCC diagnosis, that is, via HCC surveillance *versus* symptomatic HCC disease. This suggests that the better survival of females with HCC may be due to more of them being diagnosed via surveillance rather than HCCs in females being less aggressive compared to males.

Our study confirmed the predilection of HCC for males,[8] with a male-to-female ratio of 4 to 1. Studies have hypothesized sex hormones as the potential biological factors in the pathogenesis of HCC, with the protective effect of estrogen against HCC development and increased risk with testosterone.[9,10] Traditional factors driving this male predominance in HCC include higher prevalence of HBV infection in males as well as gender differences in high-risk lifestyle behavior with heavier alcohol consumption and smoking among males.[11] Nevertheless, this male predominance may diminish in the near future with the control of HBV and HCV and the increasing prevalence of NAFLD especially in females.[12]

In this study, females were diagnosed at a significantly older age than males. It is well known that chronic HBV infection confers a higher risk of HCC as the HBV itself is oncogenic,

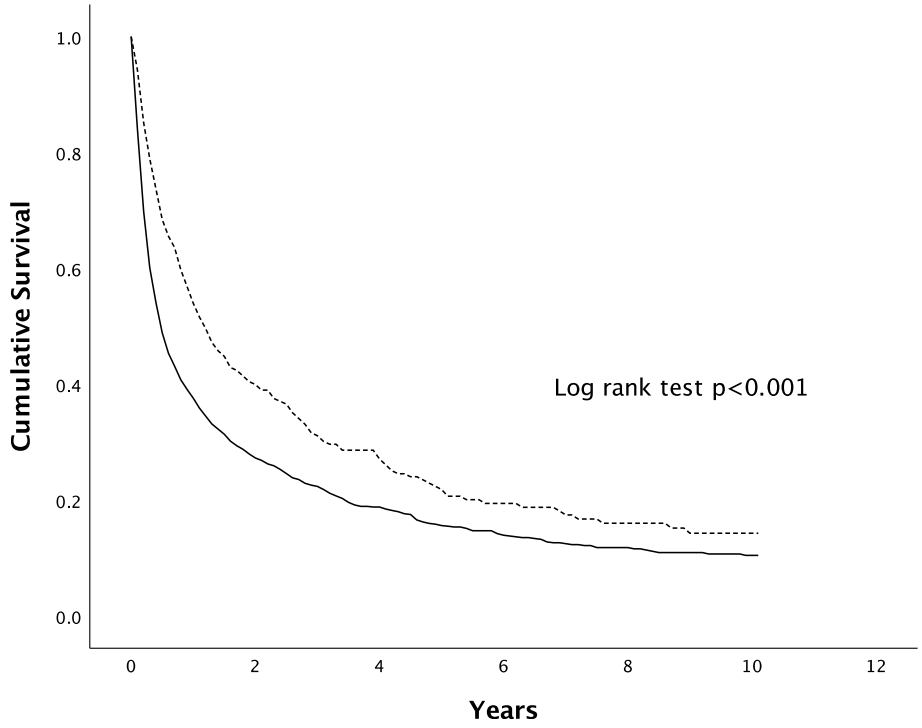

Figure 3 Survival of patients with HCC diagnosed via surveillance versus symptomatic presentation. The difference in survival was statistically significant ($P < 0.001$ by Kaplan–Meier, log-rank test). -----, surveillance; ——, symptomatic.

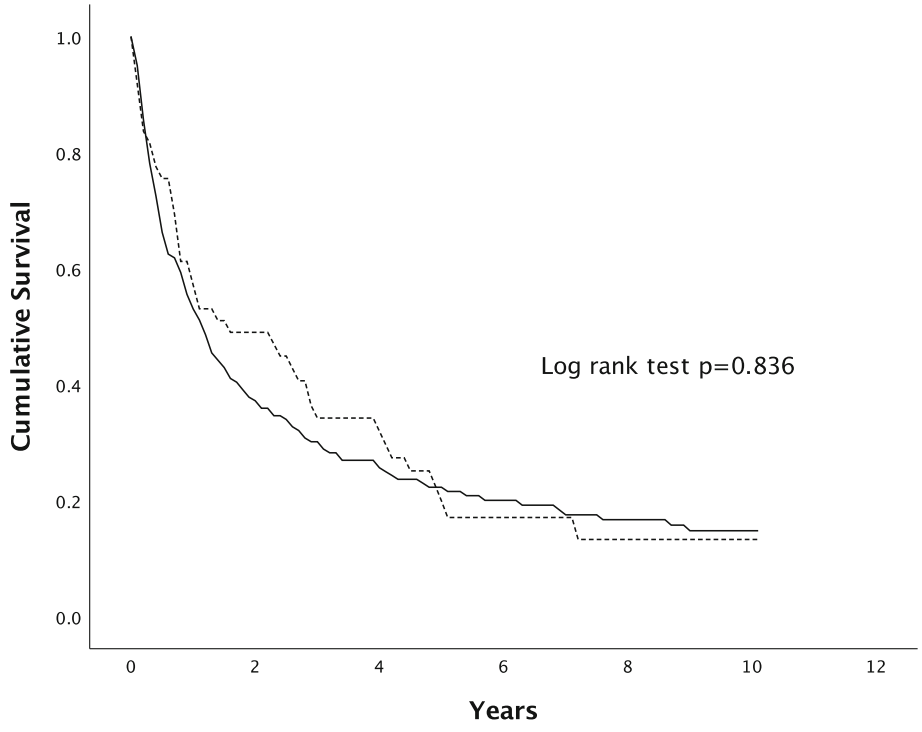

Figure 4 Survival of patients with HCC diagnosed via surveillance. The difference in survival was statistically not significant ($P = 0.836$ by Kaplan–Meier, log-rank test). ——, Male; -----, Female.

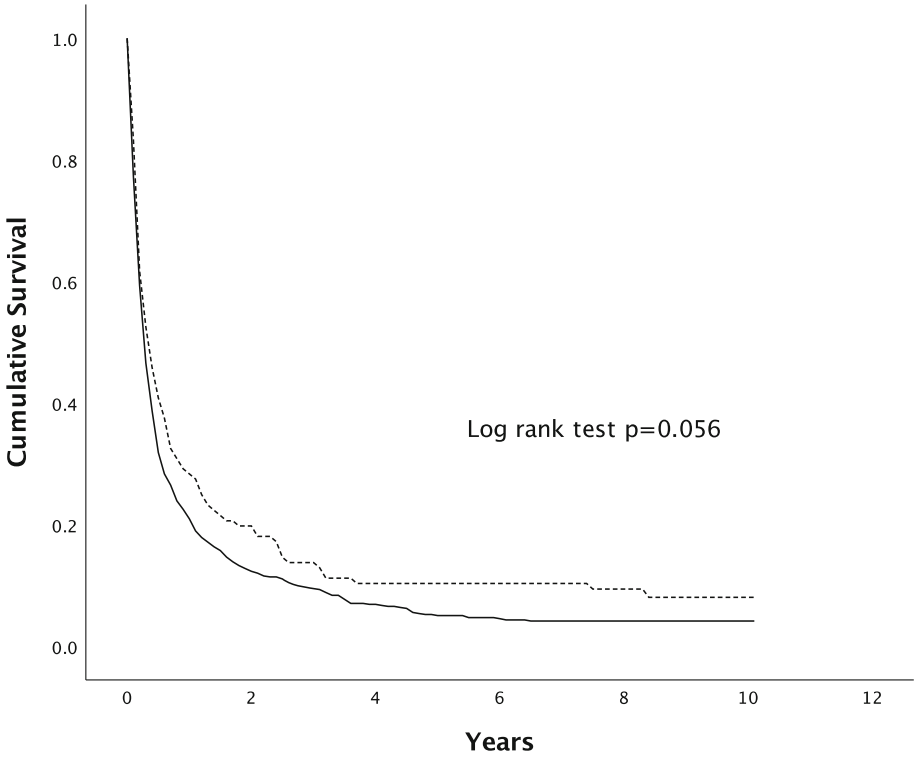

Figure 5 Survival of patients with HCC diagnosed via symptomatic presentation. The difference in survival was statistically not significant ($P = 0.056$ by Kaplan–Meier, log-rank test).——, Male; -----, Female.

and hence HCC may develop at a younger age regardless of underlying cirrhosis status.[13] This age difference may be due to a significantly higher proportion of males with HBV as the underlying etiology of their HCC. Indeed, HCC patients with HBV were significantly younger at diagnosis compared with those with non-HBV causes (data not shown). Notably, other workers have shown that females were also older at diagnosis in both areas with high[14] or low[15–17] prevalence of HBV infection, suggesting there are other additional factors contributing to the age difference.

Our study demonstrated that females with HCC had better overall survival than males. This finding has been reported previously, with the majority of the studies involving Western populations and only two studies being in Asian cohorts.[3,14–18] We have also shown that a significantly higher proportion of females had HCC diagnosed during regular HCC surveillance. However, only two of the aforementioned studies looked at HCC surveillance status.[16,18] Rich *et al*. reported survival superiority in females with HCC, and more HCCs were diagnosed via surveillance in females but this was not statistically significant.[18] In the study by Farinati *et al*. more HCCs were detected through surveillance among females.[16] This is similar to our study where there was no survival advantage in females when a comparison was made based on HCC surveillance status. In the two studies involving Asian populations, both reported better survival in female patients with HCC but did not look at the patients' HCC surveillance status.[3,14] Thus our study is the first to demonstrate that better survival in Asian females with HCC is likely due to better adherence to HCC surveillance. Nevertheless, it should be mentioned that although the Asian study by Tangkijvanich *et al*. did not look at HCC surveillance status, gender was not an independent predictor of survival, and the independent factors, such as tumor stage at initial diagnosis, could have been related to surveillance.[14]

Multivariable analysis confirmed that the detection of HCC at an early stage via surveillance was a predictor of improved survival. As a significantly higher proportion of females had HCC diagnosed during regular HCC surveillance, the tumor was detected at a significantly earlier BCLC stage, with significantly smaller tumor size and significantly lower incidences of portal vein tumor invasion and extrahepatic involvement. Being diagnosed at an earlier stage allows better therapeutic options, as evidenced by the trend of a higher proportion of women receiving curative treatment options in this study. Although Child-Pugh status was also a predictor of better survival, there was no significant difference between the two genders in their Child-Pugh status. Hence Child-Pugh status did not account for the difference in survival between females and males. Although patients with non-viral liver disease were significantly greater in females than in males, there was no difference in the surveillance status for viral and non-viral liver disease. Hence, the discrepancy in the proportion of viral and non-viral liver disease in females and males did not account for females undergoing more regular surveillance.

It can be argued the survival benefit seen in our female patients is due to a long lead-time bias inherent in a surveillance

population as the survival advantage diminished when we factored in the lead-time duration of 90 and 120 days as opposed to a lead-time duration of 60 days. However, surveillance is currently the only way to detect HCC at an early stage. Surgical treatment including resection and liver transplantation, as well as ablation, are the mainstay and only potentially curative treatments for patients with HCC, with 5-year survival exceeding 70%.[19] These options are only possible with early detection of HCC. In other words, in a patient who is destined to develop HCC, being diagnosed at an early stage during HCC surveillance will allow better chances for curative treatment and correspondingly better survival. Indeed, a randomized controlled study by Zhang *et al*. showed that biannual surveillance *versus* non-surveillance improved HCC survival.[20] The role of HCC surveillance has been well established and proven over the years, with improvement in the prognosis of HCC as well as overall survival in patients with cirrhosis.[21–23]

To our knowledge, this is one of the largest studies to examine gender differences in HCC characteristics and prognosis and the only multi-ethnic study in Asia. This is also the first Asian study to show that better survival in females with HCC is likely due to better adherence to a program of HCC surveillance.

One of the limitations of our study is lead-time bias as that is often unavoidable in an observational study. As mentioned earlier, we addressed this by studying the effect of possible lead time bias with various HCC sojourn times as HCC is known to have various tumor doubling times.[24] Another limitation of our study is that we did not explore why females were more adherent to HCC surveillance. A recent study looking at HCC surveillance compliance showed that females were 2.5 times more likely to participate in HCC surveillance programs than males.[25] Female gender was also associated with a higher compliance rate with HCC surveillance in another study.[26] Common factors associated with higher compliance rates in these two studies included a family history of liver cancer, older age, lower household income, and higher education degree. The exact reasons for this healthcare-seeking behavioral difference between females and males remain unclear and may be related to conformity to masculinity.[27] Owing to the retrospective design of our analysis, we were unable to identify the reasons for this gender difference in adherence rate in our population but were likely due to a combination of various socio-economic factors as seen in the other studies.

In conclusion, the gender difference in HCC survival in our study was due to better adherence to a surveillance program among female patients. Thus, our study reinforces the importance of regular HCC surveillance to detect early-stage HCC in patients at risk of developing HCC. More efforts are needed to improve our patients' adherence to a program of regular surveillance for HCC.

References

1 Sung H, Ferlay J, Siegel RL *et al*. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.* 2021; **71**: 209–49.
2 Park J-W, Chen M, Colombo M *et al*. Global patterns of hepatocellular carcinoma management from diagnosis to death: The BRIDGE study. *Liver Int.* 2015; **35**: 2155–66.
3 Lam CM, Yong JL, Chan AO *et al*. Better survival in female patients with hepatocellular carcinoma: oral contraceptive pills related? *J. Clin. Gastroenterol.* 2005; **39**: 533–9.
4 Schwartz M. A biomathematical approach to clinical tumor growth. *Cancer*. 1961; **14**: 1272–94.
5 Wong GL, Wong VW, Tan GM *et al*. Surveillance programme for hepatocellular carcinoma improves the survival of patients with chronic viral hepatitis. *Liver Int.* 2008; **28**: 79–87.
6 Cucchetti A, Trevisani F, Pecorelli A *et al*. Estimation of lead-time bias and its impact on the outcome of surveillance for the early diagnosis of hepatocellular carcinoma. *J. Hepatol.* 2014; **61**: 333–41.
7 van Meer S, de Man RA, Coenraad MJ *et al*. Surveillance for hepatocellular carcinoma is associated with increased survival: results from a large cohort in The Netherlands. *J. Hepatol.* 2015; **63**: 1156–63.
8 El-Serag HB. Hepatocellular carcinoma: an epidemiologic view. *J. Clin. Gastroenterol.* 2002; **35**: S72–8.
9 Mucci LA, Kuper HE, Tamimi R, Lagiou P, Spanos E, Trichopoulos D. Age at menarche and age at menopause in relation to hepatocellular carcinoma in women. *BJOG*. 2001; **108**: 291–4.
10 Tuo JY, Li HL, Wang J, Fang J, Tan YT, Xiang YB. Menstrual factors, reproductive history and liver cancer risk: findings from a prospective cohort study in Chinese women. *Cancer Epidemiol. Biomark. Prev.* 2022:EPI-22-0439; **31**: 2046–53.
11 Jackson SM, Marks MA, Katki HA *et al*. Sex disparities in the incidence of 21 cancer types: quantification of the contribution of risk factors. *Cancer*. 2022; **128**: 3531–40.
12 Goh GB, Li JW, Chang PE, Chow KY, Tan CK. Deciphering the epidemiology of hepatocellular carcinoma through the passage of time: A study of 1,401 patients across 3 decades. *Hepatol Commun.* 2017; **1**: 564–71.
13 Beasley RP. Hepatitis B virus: the major etiology of hepatocellular carcinoma. *Cancer*. 1988; **61**: 1942–56.
14 Tangkijvanich P, Mahachai V, Suwangool P, Poovorawan Y. Gender difference in clinicopathologic features and survival of patients with hepatocellular carcinoma. *World J. Gastroenterol.* 2004; **10**: 1547–50.
15 Phipps M, Livanos A, Guo A *et al*. Gender matters: characteristics of hepatocellular carcinoma in women from a large, multicenter study in the United States. *Am. J. Gastroenterol.* 2020; **115**: 1486–95.
16 Farinati F, Sergio A, Giacomin A *et al*. Is female sex a significant favorable prognostic factor in hepatocellular carcinoma? *Eur. J. Gastroenterol. Hepatol.* 2009; **21**: 1212–18.
17 Dohmen K, Shigematsu H, Irie K, Ishibashi H. Longer survival in female than male with hepatocellular carcinoma. *J. Gastroenterol. Hepatol.* 2003; **18**: 267–72.
18 Rich NE, Murphy CC, Yopp AC *et al*. Sex disparities in presentation and prognosis of 1110 patients with hepatocellular carcinoma. *Aliment. Pharmacol. Ther.* 2020; **52**: 701–9.
19 European Association for the Study of the Liver, Electronic address: easloffice@easloffice.eu; European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma [published correction appears in J Hepatol. 2019 Apr; 70(4):817]. *J. Hepatol.* 2018; **69**: 182–236.
20 Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. *J. Cancer Res. Clin. Oncol.* 2004; **130**: 417–22.
21 Singal AG, Pillai A, Tiro J. Early detection, curative treatment, and survival rates for hepatocellular carcinoma surveillance in patients with cirrhosis: a meta-analysis. *PLoS Med.* 2014; **11**: e1001624.
22 Stravitz RT, Heuman DM, Chand N *et al*. Surveillance for hepatocellular carcinoma in patients with cirrhosis improves outcome. *Am. J. Med.* 2008; **121**: 119–26.
23 Yuen MF, Cheng CC, Lauder IJ, Lam SK, Ooi CG, Lai CL. Early detection of hepatocellular carcinoma increases the chance of treatment: Hong Kong experience. *Hepatology*. 2000; **31**: 330–5.

24 Sheu JC, Sung JL, Chen DS *et al*. Growth rate of asymptomatic hepatocellular carcinoma and its clinical implications. *Gastroenterology*. 1985; **89**: 259–66.
25 Cao M, Li H, Sun D *et al*. Assessment of the compliance, influencing factors, and yielding results of liver cancer screening in a high-risk population: a cross-sectional study. *Cancer*. 2022; **128**: 3653–62.
26 Guo LW, Zhang SK, Liu SZ *et al*. Compliance rate and impact factor analysis of liver cancer screening in urban areas of Henan Province. *Zhonghua Zhong Liu Za Zhi*. 2021; **43**: 233–7.
27 O'Brien R, Hunt K, Hart G. 'It's caveman stuff, but that is to a certain extent how guys still operate': men's accounts of masculinity and help seeking. *Soc. Sci. Med.* 2005; **61**: 503–16.