Comparison of prognoses between cirrhotic and noncirrhotic patients with hepatocellular carcinoma and esophageal varices undergoing surgical resection

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Abstract

Background: Esophageal varices (EV) is common and is a poor prognostic factor for patients with hepatocellular carcinoma (HCC). However, the outcomes between cirrhotic and noncirrhotic HCC patients with EV is not well studied. The present study aimed to investigate the clinical manifestations and prognoses of HCC patients after surgical resection stratified by the cirrhosis status.

Methods: A total of 111 patients with HCC and EV, who underwent surgical resection, were retrospectively enrolled between July 2003 and July 2019. The diagnosis of liver cirrhosis was established using the Ishak fibrosis score F5 or F6 in the nontumor part of liver specimens. Prognostic factors were analyzed using the Cox proportional hazards model.

Results: There were 85 (76.6%) and 26 (23.4%) patients with and without cirrhosis, respectively. Compared with those without cirrhosis, there were more females, less seropositive rate of hepatitis B surface antigen (HBsAg), more seropositive rate of antibody against to hepatitis C virus (HCV), less albumin-bilirubin (ALBI) grade 1, lower platelet count, and more had tumor burden within the Milan criteria in cirrhotic patients. Cirrhotic patients had a higher risk of posthepatectomy decompensation compared to noncirrhotic patients (hazard ratio 9.577, $p = 0.017$). No difference was observed in overall survival and recurrence-free survival between patients with or without cirrhosis.

Conclusion: Compared with patients without cirrhosis, cirrhotic patients with HCC and EV are vulnerable to posthepatectomy decompensation. However, cirrhosis is not a poor prognostic factor of overall survival and recurrence for HCC patients after surgical resection.

Keywords: Esophageal varices; Noncirrhotic hepatocellular carcinoma; Posthepatectomy decompensation

1. INTRODUCTION

Hepatocellular carcinoma (HCC) is the major cause of the primary liver cancers, and it is the second leading cause of cancer mortality in the world.[1] The global incidence and mortality rate of liver cancer per 100,000 person-years in 2018 were 9.3 and 8.5, respectively.[2] This indicates that the patients' prognosis are suboptimal owing to a high mortality to incidence ratio of 0.91. Most of the patients with HCC had underlying advanced chronic liver diseases, such as hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, nonalcoholic fatty liver disease, or alcoholic hepatitis. With the progression of liver fibrosis, esophageal varices (EV) might occur in patients with clinically significant portal hypertension (CSPH), defined as a hepatic venous pressure gradient (HVPG) >10 mm Hg.[3] Mass application of HVPG is unrealistic in most hospitals duo to the high cost and relatively invasiveness. Therefore, the existence of EV is regarded as a surrogate of CSPH for clinical practice.[4]

Previous studies showed that EV were found in 43.1% to 63.3% of patients with HCC.[5,6] Moreover, the presence of EV was associated with a poor prognosis for patients with HCC, including those who underwent surgical resection.[6–11]

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Consequently, patients with HCC and with EV were not recommended to undergo surgical resection previously.[12] Instead, local ablation therapy, such as radiofrequency ablation (RFA), was recommended in this clinical setting.

Nevertheless, with the advance in patient selection, surgical techniques, and perioperative care, the outcomes of HCC patients with CSPH or EV have been improved. Several studies confirmed that CSPH or EV was not an independent risk factor of poor prognosis for HCC patients after surgical resection.[13–15] Our recent study demonstrated that surgical resection could provide a better outcome than RFA for patients with HCC and with EV.[16] Therefore, according to the current guidelines of the European Association for the Study of the Liver and American Association for the Study of Liver Diseases, the presence of CSPH or EV is no longer contraindicated to liver resection in HCC patients.[17,18]

Recent evidence also suggests that CSPH does not indicate to cirrhosis necessarily,[19] implying that EV could occur in the absence of cirrhosis. However, the long-term outcomes of patients with HCC and EV stratified by the status of cirrhosis are not fully elucidated.

This study aimed to compare the clinical manifestations and outcomes between cirrhotic and noncirrhotic patients with HCC accompanying with EV after surgical resection.

2. METHODS

2.1. Patients

We retrospectively reviewed clinical record of 1346 consecutive treatment-naïve patients with pathology-confirmed HCC who underwent surgical resection as the primary treatment modality from July 2003 to July 2019 at Taipei Veterans General Hospital. Of these patients, 673 (50.0%) received esophagogastroduodenoscopy (EGD) within 3 months of HCC diagnosis; 547 of them did not have EV; 15 of them received liver transplantation subsequently. The remaining 111 patients were enrolled for the final analysis (Fig. 1).

The study was executed in accordance with the Declaration of Helsinki and had been approved by the Institutional Review Board of Taipei Veterans General Hospital (VGHIRB No. 2021-05-015CC). Consent waivers were obtained, and patient information and records were anonymized and deidentified before analysis.

Major hepatectomy was defined as the removal of three or more Couinaud segments.[20] After surgery, the macroscopic and microscopic features including tumor size, the number of tumors, macrovascular, and microvascular invasion were recorded. In addition, the stage of fibrosis (score 0–6) in the nontumor part of liver specimens was graded according to the Ishak staging system, liver cirrhosis was defined as an Ishak score ≥F5.[21]

Patients were followed up regularly every 3 months after surgery and were assessed by serum biochemistry tests, α-fetoprotein (AFP) levels, and ultrasonography. Tumor recurrence was suspected if serum AFP levels were elevated (>20 ng/mL) or new lesions were detected by surveillance ultrasonography, which was confirmed by dynamic computed tomography scan or magnetic resonance imaging.

Posthepatectomy decompensation was defined by the occurrence of any of the following liver-related complications are identified during hospitalization: (1) refractory ascites causing a delay in the removal of surgical drains or requiring paracentesis; (2) increase of bilirubin levels to >3 mg/dL; (3) alteration of coagulation factors requiring fresh-frozen plasma infusion with an international normalized ratio of >1.50; and (4)

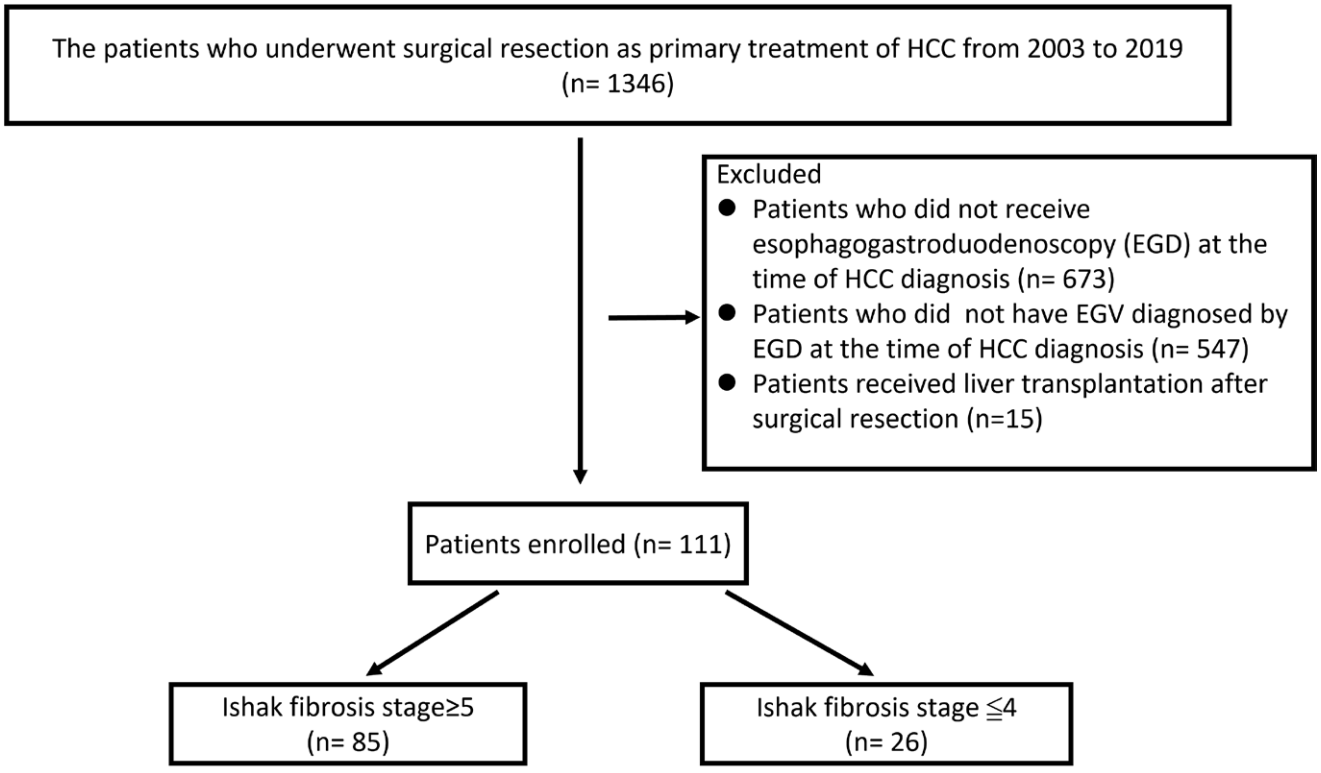

Fig. 1 Patient inclusion flow chart.

renal impairment, defined as a serum urea nitrogen level of >20.0 mg/dL or increase of serum creatinine level to >2 mg/dL requiring dopamine hydrochloride or terlipressin therapy or dialysis.[22]

2.2. EV and EV bleeding

The presence of EV was assessed by EGD and classified as F1, small and straight varices; F2, moderately sized, tortuous varices; and F3, large, tumorous varices. EV size of F2 and F3, or F1 with red coloring, was defined as high-risk EV.[23] Variceal bleeding was defined by active bleeding, white nipple sign, and large varices without other potential bleeders during follow-up period. Admission due to gastrointestinal bleeding was defined by a major presentation of melena or hematemesis. Blood transfusion before and after endoscopic treatment was recorded during each variceal bleeding episode. Rebleeding of varices was defined according to the Baveno V consensus by the presence of hematemesis or melaena, which required hospital admission, blood transfusion, or a drop in hemoglobulin by >3 g/dL if no transfusion is administrated.[3] Bleeding-free survival (BFS) was calculated from the initial date of endoscopic evidence of EV to the date of bleeding or death. EV bleeding prophylaxis was defined as primary prevention with nonselective beta blockers (NSBBs) or prophylactic EV ligation for high-risk varices according to Baveno IV consensus.[24]

2.3. Statistical analysis

The primary endpoint was overall survival (OS), which was calculated from the HCC diagnosis to the patient's death, the patient's last visit, or 30 June 2020. The albumin-bilirubin (ALBI) score was calculated as: (log10 bilirubin [μmol/L] × 0.66) + (albumin [g/L] × −0.0852). ALBI grade 1, 2, and 3 were stratified as follows: ALBI score ≤ −2.60 (ALBI grade 1), > −2.60 to ≤ −1.39 (ALBI grade 2), and > −1.39 (ALBI grade 3). The Fisher exact test or a χ^2-test with Yates' correction was used to compare categorical variables when appropriate, and the Mann-Whitney *U* test was used to compare continuous variables. The cumulative rates of OS, recurrence-free survival (RFS), BFS were estimated using the Kaplan-Meier method and compared using Cox's proportional hazards model.

The variables with statistical significance ($p < 0.05$) or approximate significance ($p < 0.1$) by univariate analysis were subjected to a multivariate analysis using a forward stepwise logistic regression model. A two-tailed value of $p < 0.05$ was considered statistically significant. All statistical analyses were conduct using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, New York).

3. RESULTS

3.1. Baseline clinical characteristics

Of the 111 patients with EV and resectable HCC, there were 85 (76.6%) patients with cirrhosis and the remaining 26 (23.4%)

Table 1

Demographic data of cirrhotic and noncirrhotic patients with hepatocellular carcinoma and esophageal varices undergo surgical resection

Patient demographic	All (N = 111)	Cirrhosis (N = 85)	Noncirrhosis (N = 26)	*p*
Age (y)	65 (55–75)	66 (55–72)	64 (51–69)	0.999
Sex (M/F) (%)	87/24 (78.4%/21.6%)	62/23 (72.9%/27.1%)	25/1 (96.2%/3.8%)	0.013
HBsAg (±) (%)	71/40 (64%/36%)	49/36 (51.4%/45.9%)	22/4 (84.6%/15.4%)	0.018
Anti-HCV (±) (%)	35/76 (31.5%/68.5%)	33/52 (38.8%/61.2%)	2/24 (7.7%/92.3%)	0.003
MELD score	8.08 (7.18–9.28)	8.09 (7.18–9.18)	8.0 (7.16–9.66)	0.552
Child Pughs class (A/B) (%)	110/1 (99.1%/0.9%)	85 (100%)	25/1 (96.1%/3.9%)	0.234
ALBI grade (1/2 + 3) (%)	43/68 (38.7%/61.3%)	28/57 (32.9%/67.1%)	15/11 (57.7%/42.3%)	0.023
Splenomegaly (Y/N) (%)	60/51 (54.1%/45.9%)	52/33 (61.2%/38.8%)	8/18 (30.8%/69.2%)	0.012
Ascites (Y/N) (%)	16/95 (14.4%/85.6%)	13/72 (15.3%/84.7%)	3/25 (11.5%/88.5%)	0.666
Albumin (g/dL)	3.8 (3.5–4.1)	3.8 (3.5–4.05)	4.05 (3.6–4.2)	0.493
ALT (IU/L)	45 (28–94)	46 (28–110)	41.5 (26.5–68.75)	0.324
AST (IU/L)	54.5 (34–83)	54 (36.5–89)	39.5 (33.5–65.5)	0.29
ALKP (IU/L)	90.5 (67.5–121.5)	96 (70–122.5)	79 (61.75–122.75)	0.039
T-Bil (mg/dL)	0.83 (0.68–1.2)	0.88 (0.69–1.205)	0.765 (0.67–1.17)	0.349
Creatinine (mg/dL)	0.83 (0.72–1.0)	0.82 (0.715–0.99)	0.875 (0.72–1.09)	0.369
INR	1.09 (1.04–1.16)	1.1 (1.05–1.17)	1.075 (1.017–1.112)	0.002
PLT ($\times 10^9$/L)	106 (84–160)	99 (77–140.5)	175 (104.5–215.7)	<0.001
Tumor numbers	1 (1–1)	1 (1–1)	1 (1–1)	0.449
Tumor size	3.7 (2.1–5.7)	3.2 (1.9–4.7)	6.3 (2.8–10.5)	0.002
Within Milan criteria (Y/N) (%)	64/47 (57.7%/42.3%)	54/31 (63.5%/36.5%)	12/14 (46.2%/53.8%)	0.024
AFP (ng/mL)	31 (7–220)	23 (6.5–168)	182 (7.75–4257.25)	0.132
Macrovascular invasion (Y/N) (%)	14/87 (12.6%/87.4%)	10/75 (11.8%/88.2%)	4/22 (15.4%/84.6%)	0.736
Microvascular invasion (Y/N) (%)	69/42 (62.7%/37.3%)	48/37 (56.5%/43.5%)	21/5 (80.8%/19.2%)	0.036
BCLC stage (0-A/B-C) (%)	82/29 (73.9%/26.1%)	65/20 (76.5%/23.5%)	17/9 (65.4%/35.6%)	0.26
Major hepatectomy (Y/N) (%)	25/86 (22.5%/77.5%)	14/71 (16.5%/83.5%)	11/15 (42.3%/57.7%)	0.006
R0 Resection (Y/N) (%)	101/10 (91.0%/9.0%)	80/5 (94.1%/5.9%)	21/5 (80.8%/19.2%)	0.037
Posthepatectomy decompensation (Y/N) (%)	25/86 (22.5%/77.5%)	23/62 (27.1%/82.9%)	2/24 (7.7%/92.3%)	0.039
High-risk EV (Y/N) (%)	45/66 (40.6%/59.4%)	38/47 (44.7%/55.3%)	7/19 (26.9%/73.1%)	0.106
EV bleeding (Y/N) (%)	28/83 (26.1%/73.9%)	24/61 (28.2%/71.8%)	4/22 (15.4%/84.6%)	0.301
Variceal bleeding-free survivals (months)	52.2 (0–191.9)	52.2 (0–191.9)	63.2 (0.3–163.7)	0.949
Tumor recurrence-free survivals	15.4 (0.4–112.8)	18.4 (0.4–112.8)	7.0 (0.9–94.1)	0.803
Overall survivals	60.4 (0.4–191.9)	56.3 (0.4–191.9)	60.4 (2.2–164.0)	0.974

ALBI = albumin-bilirubin; AFP = alpha fetal protein; ALKP, alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BCLC = Barcelona Clinic Liver Cancer classification; EV = esophageal varices; HCV = hepatitis C virus; INR = international normalized ratio; MELD, model for end-stage liver disease; PLT = platelet; R0 resection = microscopically margin-negative resection; T-Bil = total bilirubin.

Table 2

The univariate and multivariate with posthepatectomy decompensation rate

		Univariate analysis		Multivariate analysis	
Variable	**N (%)**	**Hazard ratio (95% CI)**	***p***	**Hazard ratio (95% CI)**	***P***
Age (y/o) >65/ ≦ 65	56/55	2.561 (0.999–6.566)	0.050	4.347 (1.344–14.064)	0.014
Sex M/F	87/24	0.838 (0.292–2.407)	0.743		
HBsAg Y/N	71/40	0.648 (0.261–1.605)	0.348		
Anti-HCV Y/N	35/76	1.627 (0.645–4.105)	0.303		
Albumin (g/dL) ≦ 4/>4	35/76	2.959 (0.931–9.405)	0.066		
T-Bil (mg/dL) ≥1.0/<1.0	47/64	0.883 (0.356–2.187)	0.788		
BCLC stage B-C/0-A	82/29	1.856 (0.712–4.837)	0.206		
ALBI grade 2/1	68/43	1.851 (0.700–4.896)	0.214		
Plt ($mL^{-}1$) ≦ 100 K/>100 K	49/62	1.505 (0.615–3.678)	0.370		
MELD score >8/ ≦ 8	58/53	0.803 (0.329–1.958)	0.629		
ALT (IU/L) ≥40/<40	62/49	1.546 (0.616–3.879)	0.353		
AST (IU/L) ≥40/<40	70/41	1.323 (0.514–3.408)	0.562		
AFP (ng/mL) ≥20/<20	68/43	1.162 (0.461–2.928)	0.750		
Macrovascular invasion Y/N	14/87	3.079 (0.954–9.933)	0.060		
Microvascular invasion Y/N	69/42	1.107 (0.439–2.792)	0.830		
R0 resection N/Y	10/101	0.650 (0.155–2.722)	0.555		
Major hepatectomy Y/N	25/86	3.156 (1.190–8.365)	0.021	6.012 (1.646–21.961)	0.007
Within Milan Criteria N/Y	47/64	1.345 (0.550–3.291)	0.516		
Cirrhosis Y/N	85/26	4.452 (0.974–20.350)	0.054	9.577 (1.497–61.272)	0.017
Splenomegaly Y/N	60/51	1.028 (0.415–2.548)	0.953		
Ascites Y/N	16/95	1.705 (0.531–5.473)	0.370		
High-risk EV Y/N	45/66	2.800 (1.122–6.990)	0.027		
Variceal bleeding Y/N	28/83	4.038 (1.555–10.487)	0.004	4.664 (1.484–14.663)	0.004

AFP = alpha fetal protein; ALBI = albumin-bilirubin; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BCLC = Barcelona Clinic Liver Cancer classification; CI = confidence intervals; EV = esophageal varices; HCV = hepatitis C virus; INR = international normalized ratio; MELD, model for end-stage liver disease; PLT = platelet; R0 resection = microscopically margin-negative resection; T-Bil = total bilirubin.

patients without cirrhosis in the nontumor part of liver specimens (Table 1). Compared with cirrhotic patients, the noncirrhotic patients were more males, had more positive hepatitis B surface antigen (HBsAg) in serum, more with ALBI grade 1, lower serum alkaline phosphatase (ALKP) level, shorter prothrombin time, less HCV infection, lesser thrombocytopenia, and lesser splenomegaly. Regarding the tumor factors, noncirrhotic patients had larger tumor size, more tumor beyond the Milan criteria, more with microvascular invasion, received more major hepatectomy, had lesser R0 resection, and a lower rate of posthepatectomy decompensation.

Stratified by the degree of EV, 45 (40.5%) patients were identified with high-risk varices and 66 (59.5%) patients with low-risk varices. As shown in Supplementary Table 1 (http://links.lww.com/JCMA/A149), compared with those with low-risk varices, more with high-risk varices had splenomegaly, thrombocytopenia, higher serum ALKP level, longer prothrombin time, EV bleeding, and posthepatectomy decompensation.

3.2 Factors associated with EV bleeding and posthepatectomy decompensation

No patients died during the operation. Beside, 25 (22.5%) patients experienced posthepatectomy decompensation. On multivariable analysis, age >65 years, major hepatectomy, cirrhosis, and EV bleeding were the independent risk factors associated with posthepatectomy decompensation (Table 2). Moreover, 28 (25.8%) patients experienced EV bleeding during follow-up. BFS was not different between patients with and without cirrhosis (Fig. 2A). However, the BFS was longer in patients with low-risk varices than in those with high-risk varices (median 94.4 months versus 33.1 months) (Fig. 2B). Macrovascular invasion, microvascular invasion, emergence of posthepatectomy decompensation, ascites, and high-risk varices were the independent risk factors associated with EV bleeding based on the outcomes of a multivariate analysis (Supplementary Table S2, http://links.lww.com/JCMA/A149).

3.3 Factors associated with poor RFS and OS

After a median follow-up of 28.2 (11.9–60.8) months, 77(69.4%) patients had tumor recurrence after the operation. There was no difference in RFS rates between patients with or without liver cirrhosis (Fig. 2C), nor between patients with high or low risk of varices (Fig. 2D). On multivariable analysis, presence of macrovascular invasion, microvascular invasion, R1 resection, ascites, posthepatectomy decompensation, and EV bleeding were associated with poor RFS (Table 3).

Fifty-one patients were certified dead, and the other 60 patients were still alive at the last visit. Among them, 32 (62.7%) patients died due to tumor progression, 9 (17.6%) due to liver failure, 4 (7.8%) due to sepsis, 3 (5.9%) due to EV bleeding, the remaining 3 (5.9%) patients died by other reasons.

The OS was not different between patients with or without liver cirrhosis (median 56.3 months versus 60.4 months, p = 0.974) (Fig. 2E). Whereas the 5-year OS rates were higher in patients with low-risk varices than patients with high-risk varices (median 99.9 months versus 47.5 months, p = 0.023) (Fig. 2F).

On multivariable analysis, the presence of macrovascular invasion, microvascular invasion, R1 resection, ascites, posthepatectomy decompensation, and EV bleeding were associated with poor OS rates (Table 4).

4. DISCUSSION

There were several major findings of this study. First, not all of the HCC patients with EV had underlying liver cirrhosis. Noncirrhotic patients were less likely to experience

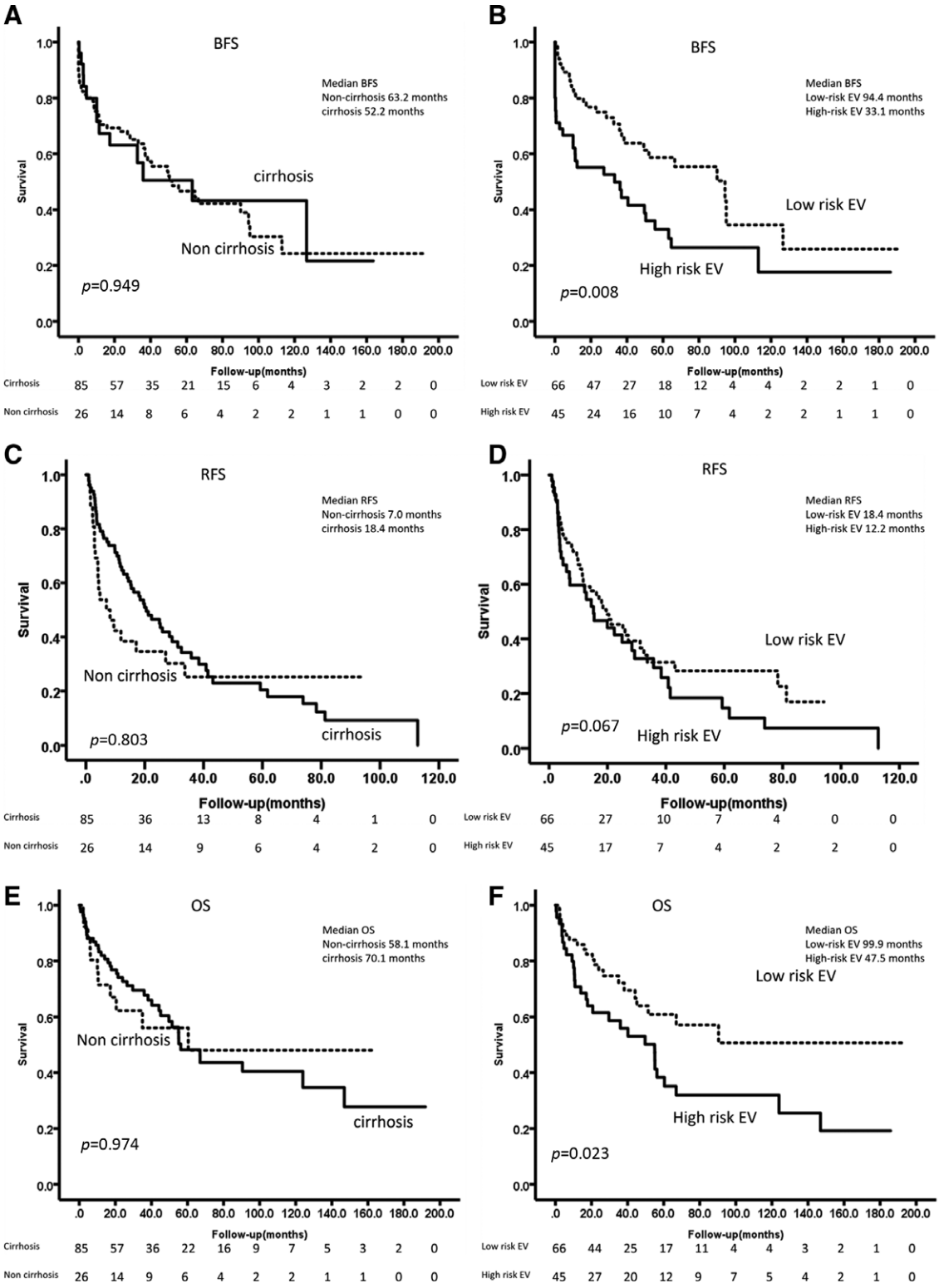

Fig. 2 Kaplan-Meier curves of BFS, RFS, and OS in patients with/without liver cirrhosis and with/without high-risk varices. BFS = bleeding-free survivals; OS = overall survivals; RFS = recurrence-free survivals.

posthepatectomy decompensation but did not have better long-term outcomes, both in terms of OS and RFS, than cirrhotic patients. Second, tumor factors such as vascular invasion and signs of portal hypertension such as ascites, but not the status of cirrhosis, were independent important prognostic factors of OS. Third, among HCC patients with EV who underwent surgical resection, posthepatectomy decompensation and EV bleeding were associated with poor outcomes.

There were little literature discussing noncirrhotic HCC patients with CSPH. In our cohort, 26 of 111 (23.4%) HCC

Table 3

The univariate and multivariate with poor recurrence-free survival rate

		Univariate analysis		Multivariate analysis	
Variable	**N (%)**	**Hazard ratio (95% CI)**	***p***	**Hazard ratio (95% CI)**	***p***
Age (y/o) >65/ ≦ 65	56/55	1.396 (0.907–2.147)	0.129		
Sex M/F	87/24	1.217 (0.715–2.073)	0.469		
HBsAg Y/N	71/40	0.947 (0.608–1.477)	0.811		
Anti-HCV Y/N	35/76	1.088 (0.689–1.718)	0.718		
Albumin (g/dL) ≦ 4/>4	35/76	1.288 (0.803–2.065)	0.294		
T-Bil (mg/dL) ≥1.0/<1.0	47/64	1.084 (0.704–1.671)	0.713		
BCLC stage B-C/0-A	82/29	1.800 (1.122–2.886)	0.015		
ALBI grade 2/1	68/43	1.216 (0.784–1.886)	0.382		
Plt (mL^{-1}) ≦ 100K/>100K	49/62	1.243 (0.807–1.916)	0.323		
MELD score >8/ ≦ 8	58/53	1.047 (0.685–1.601)	0.832		
ALT (IU/L) ≥40/<40	62/49	1.170 (0.760–1.803)	0.475		
AST (IU/L) ≥40/<40	70/41	1.652 (1.042–2.619)	0.033		
AFP (ng/mL) ≥20/<20	68/43	1.584 (1.022–2.456)	0.040		
Macrovascular invasion Y/N	14/87	3.671 (2.015–6.687)	<0.001	3.491 (1.822–6.691)	<0.001
Microvascular invasion Y/N	69/42	2.222 (1.402–3.520)	0.001	2.336 (1.388–3.934)	0.001
R0 resection N/Y	10/101	3.411 (1.736–6.704)	<0.001	3.666 (1.816–7.400)	<0.001
Major hepatectomy Y/N	25/86	1.983 (1.205–3.264)	0.007		
Within Milan Criteria N/Y	47/64	1.376 (0.900–2.105)	0.141		
Cirrhosis Y/N	85/26	0.937 (0.562–1.562)	0.803		
Splenomegaly Y/N	60/51	1.240 (0.807–1.907)	0.326		
Ascites Y/N	16/95	2.011 (1.160–3.485)	0.013	1.851 (1.005–3.409)	0.048
High-risk EV Y/N	45/66	1.482 (0.970–2.265)	0.069		
Posthepatectomy decompensation Y/N	25/86	2.079 (1.272–3.398)	0.003	2.080 (1.221–3.545)	0.007
Variceal bleeding Y/N	28/83	2.182 (1.382–3.446)	0.001	2.213 (1.283–3.514)	0.003

AFP = alpha fetal protein; ALBI = albumin-bilirubin; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BCLC = Barcelona Clinic Liver Cancer classification; CI = confidence intervals; EV = esophageal varices; HCV = hepatitis C virus; INR = international normalized ratio; MELD, model for end-stage liver disease; PLT = platelet; R0 resection = microscopically margin-negative resection; T-Bil = total bilirubin.

Table 4

The univariate and multivariate with poor overall survival rate

		Univariate analysis		Multivariate analysis	
Variable	**N (%)**	**Hazard ratio (95% CI)**	***p***	**Hazard ratio (95% CI)**	***p***
Age (y/o) >65/ ≦ 65	56/55	1.240 (0.710–2.166)	0.450		
Sex M/F	87/24	1.219 (0.592–2.513)	0.591		
HBsAg Y/N	71/40	0.734 (0.416–1.295)	0.285		
Anti-HCV Y/N	35/76	0.887 (0.485–1.623)	0.698		
Albumin (g/dL) >4/ ≦ 4	35/76	1.631 (0.853–3.119)	0.139		
T-Bil (mg/dL) ≥1.0/<1.0	47/64	1.060 (0.599–1.877)	0.842		
BCLC stage B-C/0-A	82/29	1.797 (1.001–3.227)	0.050		
ALBI grade 2/1	68/43	0.739 (0.415–1.314)	0.303		
Plt (mL^{-1}) ≦ 100K/>100K	49/62	1.135 (0.653–1.973)	0.654		
MELD score >8/ ≦ 8	58/53	1.309 (0.753–2.276)	0.340		
ALT (IU/L) ≥40/<40	62/49	0.813 (0.466–1.419)	0.466		
AST (IU/L) ≥40/<40	70/41	1.876 (0.998–3.529)	0.051		
AFP (ng/mL) ≥20/<20	68/43	2.014 (1.106–3.666)	0.022		
Macrovascular invasion Y/N	14/87	5.901 (2.945–11.823)	<0.001	4.607 (1.811–11.723)	0.001
Microvascular invasion Y/N	69/42	3.452 (1.701–7.004)	0.001	3.797 (1.658–8.698)	0.002
R0 resection N/Y	10/101	2.206 (0.989–4.920)	0.053		
Major hepatectomy Y/N	25/86	2.593 (1.427–4.712)	0.002		
Within Milan Criteria N/Y	47/64	0.682 (0.393–1.183)	0.173		
Cirrhosis Y/N	85/26	1.011 (0.518–1.973)	0.974		
Splenomegaly Y/N	60/51	1.553 (0.882–2.734)	0.127		
Ascites Y/N	16/95	2.905 (1.578–5.345)	0.001	2.933 (1.416–6.074)	0.004
High-risk EV Y/N	45/66	1.891 (1.084–3.299)	0.025		
Posthepatectomy decompensation Y/N	25/86	2.722 (1.495–4.955)	0.001	2.350 (1.133–4.874)	0.022
Variceal bleeding Y/N	28/83	3.191 (1.839–5.538)	<0.001	2.570 (1.379–4.791)	0.003

AFP = alpha fetal protein; ALBI = albumin-bilirubin; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BCLC = Barcelona Clinic Liver Cancer classification; CI = confidence intervals; EV = esophageal varices; HCV = hepatitis C virus; INR = international normalized ratio; MELD, model for end-stage liver disease; PLT = platelet; R0 resection = microscopically margin-negative resection; T-Bil = total bilirubin.

patients with EV were noncirrhotic, which was a considerable proportion. The possible reason of CSPH in these patients may be due to vascular invasion or compression by HCC (21 patients, 80.8%), formation of arterioportal shunt due to angiogenesis effect of HCC (6 patients, 23.1%), or chronic liver disease (10 patients, 38.5%, with Ishak fibrosis stage 3 or 4) itself. According to our study, the severity of portal hypertension such as EV bleeding and ascites, but not the status of cirrhosis, is independently associated with the prognosis of patients with HCC.

There were more males (25 patients) than female (1 patient) had noncirrhotic HCC and EV. Among the male noncirrhotic patients, 21 (84.0%) had positive HBsAg in serum. According to the previous study, around 30% of HBV-related HCC occurred in noncirrhotic patients, higher than that in HCV-related HCC patients (around 4.4%–10.6%).[25] The results might be due to the HBV DNA integration into the host cells, the oncogenic effects of HBx and pre-S deletion mutants of HBV.[25–28] These factors lead to the chromosomal rearrangement, increase the rate of genomic instability, dysregulate cell cycle control, promote endoplasmic reticulum stress, and cause mitochondrial dysfunction and hepatocarcinogenesis in the absence of significant liver fibrosis.[26,29] Besides, patients with HBV-associated HCC had a significantly higher male-to-female ratio when compared to those with HCV-related HCC.[30,31] According to the original cohort study,[14] the proportion of female was 24% (42/175) in cirrhotic patients which was slightly higher than 18.5% (50/271) of noncirrhotic patients ($p = 0.098$), which was also compatible to another study.[32] In current study, it is interesting to find the proportion of female in noncirrhotic patients was 3.8% (1/26), which is much lower than 27.1% (23/85) of cirrhotic patients. It cannot be well-explained. However, our previous study found female patients with HCC and EV tended to choose radiofrequency ablation rather than surgical resection (11/68, 16.2% vs. 73/183, 39.9%; $p = 0.001$).[16] Moreover, tumor was usually larger and higher percentage of major hepatectomy was performed in noncirrhotic patients. It is believed that the selection bias of fewer noncirrhotic female with HCC and EV was due to their reluctance to receive major hepatectomy and preference of nonsurgical treatment due to portal hypertension. The above findings might explain the reasons more males developed noncirrhotic HCC than females.

This study discovered that a higher percentage of microvascular invasion, tumor burden beyond the Milan criteria, a lower percentage of splenomegaly, thrombocytopenia, and R0 resection in noncirrhotic HCC patients with EV, which implied more advanced tumor invasion and less severity of portal hypertension in these patients. These results may contribute to the selection bias of surgeon, who tend to avoid hepatectomy in patients with a large tumor and clinical signs of liver cirrhosis such as thrombocytopenia and splenomegaly. The larger tumor burden (beyond Milan criteria) may contribute to higher portal pressure and cause EV, leading to a poor prognosis.

In current study, 25 patients developed posthepatectomy decompensation, only 2 of them expired in 30 days. They all had liver cirrhosis, and both were expired due to EV bleeding. Although cirrhosis is one of the predictors determining posthepatectomy decompensation (Table 2), major hepatectomy and EV bleeding also determined the posthepatectomy decompensation, which was consistent with other study.[4] It is not surprising to find liver cirrhosis per se was not the determinant of RFS or OS, because liver cirrhosis is confounded by posthepatic decompensation.[33] For determining the OS, posthepatic decompensation is much more important than liver cirrhosis per se. It is noteworthy of multivariate analysis of RFS and OS (Tables 3 and 4), posthepatectomy decompensation, ascites, EV bleeding, micro- and macrovascular invasion were all associated with poor prognosis. It is believed that patient's poor outcome affected by ascites and EV bleeding were mediated via severity of portal hypertension instead of cirrhosis.

There were more cirrhotic patients with high-risk varices than noncirrhotic patients, but no significance (44.7% vs. 26.9%, $p = 0.106$). High-risk varices, posthepatectomy decompensation, and ascites were independent factors associated with shorter BFS. According to a previous review article,[34] these finding indicated higher portal pressure in these patients. Macro- and microvascular invasion were also associated with shorter BFS, which might be related to their negative impact to OS. Our previous study demonstrated that EV was not associated with a poor prognosis for HCC patients after resection surger.[14] But in this study, EV bleeding, which indicating more severe portal hypertension, was associated with poor prognosis in HCC patients who underwent liver resection, which was consistent with another previous study.[35] The severity of portal hypertension, but not the status of liver cirrhosis, determined the outcomes for HCC patients with EV after resection surgery.

There were several limitations of this study. First, a limited number of noncirrhotic HCC patients with EV were selected. Second, some patients did not receive EGD at the time of HCC diagnosed and were excluded in this study, which might lead to selection bias. Third, some patients might experience EV bleeding and receive treatment at other hospital without official record.

In conclusion, this is the first study to comprehensively evaluate the impact of cirrhosis in HCC patients with EV. The grade of portal hypertension, but not the status of liver cirrhosis, determined the outcomes of HCC patients with EV after resection surgery. Beside, posthepatectomy liver decompensation was more frequent in patients with liver cirrhosis and perioperative care should be awarded. Further larger cohort study is required for more pathophysiological mechanisms of noncirrhotic HCC patients with CSPH.

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REFERENCES

1. McGlynn KA, Petrick JL, El-Serag HB. Epidemiology of hepatocellular carcinoma. *Hepatology* 2021;**73**(Suppl 1):4–13.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;**68**:394–424.
3. de Franchis R; Baveno VI Faculty. Expanding consensus in portal hypertension: report of the Baveno VI Consensus Workshop: stratifying risk and individualizing care for portal hypertension. *J Hepatol* 2015;**63**:743–52.
4. Bruix J, Sherman M; American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. *Hepatology* 2011;**53**:1020–2.
5. Giannini EG, Risso D, Testa R, Trevisani F, Di Nolfo MA, Del Poggio P, et al.; Italian Liver Cancer (ITA.LI.CA.) Group. Prevalence and prognostic significance of the presence of esophageal varices in patients with hepatocellular carcinoma. *Clin Gastroenterol Hepatol* 2006;**4**:1378–84.
6. Hsieh WY, Chen PH, Lin IY, Su CW, Chao Y, Huo TI, et al. The impact of esophagogastric varices on the prognosis of patients with hepatocellular carcinoma. *Sci Rep* 2017;**7**:42577.

7. Bruix J, Castells A, Bosch J, Feu F, Fuster J, Garcia-Pagan JC, et al. Surgical resection of hepatocellular carcinoma in cirrhotic patients: prognostic value of preoperative portal pressure. *Gastroenterology* 1996;**111**:1018–22.
8. Su CW, Fang KC, Lee RC, Liu CA, Chen PH, Lee PC, et al. Association between esophagogastric varices in hepatocellular carcinoma and poor prognosis after transarterial chemoembolization: a propensity score matching analysis. *J Formos Med Assoc* 2020;**119**:610–20.
9. Berzigotti A, Reig M, Abraldes JG, Bosch J, Bruix J. Portal hypertension and the outcome of surgery for hepatocellular carcinoma in compensated cirrhosis: a systematic review and meta-analysis. *Hepatology* 2015;**61**:526–36.
10. Torzilli G, Belghiti J, Kokudo N, Takayama T, Capussotti L, Nuzzo G, et al. A snapshot of the effective indications and results of surgery for hepatocellular carcinoma in tertiary referral centers: is it adherent to the EASL/AASLD recommendations?: an observational study of the HCC East-West study group. *Ann Surg* 2013;**257**:929–37.
11. Cucchetti A, Cescon M, Golfieri R, Piscaglia F, Renzulli M, Neri F, et al. Hepatic venous pressure gradient in the preoperative assessment of patients with resectable hepatocellular carcinoma. *J Hepatol* 2016;**64**:79–86.
12. Bruix J, Reig M, Sherman M. Evidence-based diagnosis, staging, and treatment of patients with hepatocellular carcinoma. *Gastroenterology* 2016;**150**:835–53.
13. Ishizawa T, Hasegawa K, Aoki T, Takahashi M, Inoue Y, Sano K, et al. Neither multiple tumors nor portal hypertension are surgical contraindications for hepatocellular carcinoma. *Gastroenterology* 2008;**134**:1908–16.
14. Chang CY, Hsieh WY, Chau GY, Chen PH, Su CW, Hou MC, et al. Esophageal varices are not predictive of patient prognosis after surgical resection of hepatocellular carcinoma. *Eur J Gastroenterol Hepatol* 2018;**30**:1368–77.
15. Roayaie S, Jibara G, Tabrizian P, Park JW, Yang J, Yan L, et al. The role of hepatic resection in the treatment of hepatocellular cancer. *Hepatology* 2015;**62**:440–51.
16. Wei CY, Chau GY, Chen PH, Liu CA, Huang YH, Huo TI, et al. A comparison of prognoses between surgical resection and radiofrequency ablation therapy for patients with hepatocellular carcinoma and esophagogastric varices. *Sci Rep* 2020;**10**:17259.
17. European Association for the Study of the Liver. Electronic address eee, European Association for the Study of the L. EASL Clinical Practice Guidelines: management of hepatocellular carcinoma. *J Hepatol* 2018;**69**:182–236.
18. Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abecassis MM, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American Association for the study of liver diseases. *Hepatology* 2018;**68**:723–50.
19. Rodrigues SG, Montani M, Guixé-Muntet S, De Gottardi A, Berzigotti A, Bosch J. Patients with signs of advanced liver disease and clinically significant portal hypertension do not necessarily have cirrhosis. *Clin Gastroenterol Hepatol* 2019;**17**:2101–9.e1.
20. Su CW, Lei HJ, Chau GY, Hung HH, Wu JC, Hsia CY, et al. The effect of age on the long-term prognosis of patients with hepatocellular carcinoma after resection surgery: a propensity score matching analysis. *Arch Surg* 2012;**147**:137–44.
21. Ishak K, Baptista A, Bianchi L, Callea F, De Groote J, Gudat F, et al. Histological grading and staging of chronic hepatitis. *J Hepatol* 1995;**22**:696–9.
22. Cescon M, Vetrone G, Grazi GL, Ramacciato G, Ercolani G, Ravaioli M, et al. Trends in perioperative outcome after hepatic resection: analysis of 1500 consecutive unselected cases over 20 years. *Ann Surg* 2009;**249**:995–1002.
23. Beppu K, Inokuchi K, Koyanagi N, Nakayama S, Sakata H, Kitano S, et al. Prediction of variceal hemorrhage by esophageal endoscopy. *Gastrointest Endosc* 1981;**27**:213–8.
24. de Franchis R. Evolving consensus in portal hypertension. Report of the Baveno IV consensus workshop on methodology of diagnosis and therapy in portal hypertension. *J Hepatol* 2005;**43**:167–76.
25. Desai A, Sandhu S, Lai JP, Sandhu DS. Hepatocellular carcinoma in non-cirrhotic liver: a comprehensive review. *World J Hepatol* 2019;**11**:1–18.
26. Liang YJ, Teng W, Chen CL, Sun CP, Teng RD, Huang YH, et al. Clinical implications of HBV PreS/S mutations and the effects of PreS2 deletion on mitochondria, liver fibrosis, and cancer development. *Hepatology* 2021;**74**:641–55.
27. Xu R, Zhang X, Zhang W, Fang Y, Zheng S, Yu XF. Association of human APOBEC3 cytidine deaminases with the generation of hepatitis virus B x antigen mutants and hepatocellular carcinoma. *Hepatology* 2007;**46**:1810–20.
28. Murata M, Matsuzaki K, Yoshida K, Sekimoto G, Tahashi Y, Mori S, et al. Hepatitis B virus X protein shifts human hepatic transforming growth factor (TGF)-beta signaling from tumor suppression to oncogenesis in early chronic hepatitis B. *Hepatology* 2009;**49**:1203–17.
29. Craig AJ, von Felden J, Garcia-Lezana T, Sarcognato S, Villanueva A. Tumour evolution in hepatocellular carcinoma. *Nat Rev Gastroenterol Hepatol* 2020;**17**:139–52.
30. Kao WY, Su CW, Chau GY, Lui WY, Wu CW, Wu JC. A comparison of prognosis between patients with hepatitis B and C virus-related hepatocellular carcinoma undergoing resection surgery. *World J Surg* 2011;**35**:858–67.
31. Chen PH, Kao WY, Chiou YY, Hung HH, Su CW, Chou YH, et al. Comparison of prognosis by viral etiology in patients with hepatocellular carcinoma after radiofrequency ablation. *Ann Hepatol* 2013;**12**:263–73.
32. Lai MW, Chu YD, Lin CL, Chien RN, Yeh TS, Pan TL, et al. Is there a sex difference in postoperative prognosis of hepatocellular carcinoma? *BMC Cancer* 2019;**19**:250.
33. Citterio D, Facciorusso A, Sposito C, Rota R, Bhoori S, Mazzaferro V. Hierarchic interaction of factors associated with liver decompensation after resection for hepatocellular carcinoma. *JAMA Surg* 2016;**151**:846–53.
34. Bosch J, Abraldes JG, Berzigotti A, García-Pagan JC. The clinical use of HVPG measurements in chronic liver disease. *Nat Rev Gastroenterol Hepatol* 2009;**6**:573–82.
35. Liu HT, Cheng SB, Wu CC, Yeh HZ, Chang CS, Wang J. Impact of severe oesophagogastric varices on liver resection for hepatocellular carcinoma in cirrhotic patients. *World J Surg* 2015;**39**:461–8.