Original Article

A new staging system for hepatocellular carcinoma associated with portal vein tumor thrombus

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Background: A new staging system for patients with hepatocellular carcinoma (HCC) associated with portal vein tumor thrombus (PVTT) was developed by incorporating the good points of the BCLC classification of HCC, and by improving on the currently existing classifications of HCC associated with PVTT.

Methods: Univariate and multivariate analysis with Wald χ^2 test were used to determinate the clinical prognostic factors for overall survival (OS) in patients with HCC and PVTT in the training cohort**.** Then the conditional inference trees analysis was applied to establish a new staging system.

Results: A training cohort of 2,179 patients from the Eastern Hepatobiliary Surgery Hospital and a validation cohort of 1,550 patients from four major liver centers in China were enrolled into establishing and validating a new staging system. The system was established by incorporating liver function, general health status, tumor resectability, extrahepatic metastasis and extent of PVTT. This staging system had a good discriminatory ability to separate patients into different stages and substages. The median OS for the two cohorts were 57.1 (37.2–76.9), 12.1 (11.0–13.2), 5.7 (5.1–6.2), 4.0 (3.3–4.6) and 2.5 (1.7–3.3) months for the stages 0 to IV, respectively (P<0.001) in the training cohort. The corresponding figures for the validation cohort were 6.4 (4.9–7.9), 2.8 (1.3–4.4), 10.8 (9.3–12.4), and 1.5 (1.3–1.7) months for the stages II to IV, respectively (P<0.001). The mean survival for stage 0 to 1 were 37.6 (35.9–39.2) and 30.4 (27.4–33.4), respectively (P<0.001).

Conclusions: A new staging system was established which provided a good discriminatory ability to separate patients into different stages and substages after treatment. It can be used to supplement the other HCC staging systems.

Keywords: Hepatocellular carcinoma (HCC); portal vein tumor thrombus (PVTT); staging system; overall survival (OS)

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Introduction

Hepatocellular carcinoma (HCC) ranks as the sixth most common neoplasm and the third leading cause of cancer death (1). Portal vein tumor thrombosis is an important prognostic factor of long-term overall survival (2-4), occurring in 12.5% to 39.7% of patients with HCC at diagnosis, and up to 64.7% at autopsy. If left untreated, a median survival time (MST) of 2.7 to 4.0 months was reported (5,6). It has been considered as the bottleneck in the treatment of HCC (7).

Several clinical classifications of HCC has been proposed. The Barcelona Clinic Liver Cancer (BCLC) system is most commonly used (8), and is endorsed by the EASL-EORTC GP guidelines (9-11). However, the BCLC staging system classifies all patients with HCC associated with PVTT into stage C and recommends sorafenib as the only treatment (12,13). Such a classification is too rough and refinement is needed. A refinement can help clinicians and patients to appreciate the extent of HCC, to guide treatment, to predict prognosis, to compare treatment results and diagnostic accuracies of the various options at a comparable tumor staging.

There are currently two available systems to classify the extent of HCC associated with PVTT: the Cheng's Classification for PVTT (Type I–IV) and the Japanese staging system (Vp1–Vp4) (14-16). The Cheng's Classification comprises of 4 categories (14,15) (Type I, II, III, IV) based on the extent of PVTT invasion into the portal vein. This classification is very similar to the Japanese classification with the exception that it combines Vp1 and Vp2 as Type I, and it subdivides Vp4 into Type III and IV (17). However, these two systems do not have the key prognostic predictors which include liver function, resectability of tumor, overall health status and recommended treatment modalities. Thus, a new staging system which incorporates these factors and recommends treatment options in different stages of HCC associated with PVTT is needed.

This study aimed to set up a new staging system by incorporating liver function, resectability of tumor, extent of PVTT, overall health status and extrahepatic metastasis. Patients with HCC associated with PVTT were separated into different stages and substages, and their long-term overall survival (OS) outcomes were analyzed. We present the following article in accordance with the TRIPOD reporting checklist (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-19-810/rc).

Methods

Patients and study design

The demographic, clinical and pathological data of consecutive patients with HCC associated with PVTT who were treated in five centers in China were retrospectively reviewed. The data from the Eastern Hepatobiliary Surgery Hospital in Shanghai from January 2002 to January 2017 were used as a training cohort to establish the new staging system. Data on patients who were treated in four other major liver centers in China from 2012 to 2017 were used as a validation cohort to assess the performance of this newly established system. The names of the four participating hospitals are Affiliated Tumor Hospital of Guangxi Medical University, West China Hospital of Sichuan University, Sun Yat-sen University Cancer Center and Affiliated Provincial Hospital of Anhui Medical University. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committees of all the five hospitals (Permit Number: EHBHKY-2019-001-017). Informed consent was obtained from all the patients prior to treatment. All the patients who were regularly followed-up as we have described previously (18). All the patients who entered into this study were re-examined in their hospital within a month after surgery. Follow-up was performed on the outpatient bases and/or by telephone calls at 1 to 3-month intervals according to the standard epidemiologic procedure. During follow-up, serum levels of alpha-fetoprotein (AFP) and HBV DNA, liver function, and ultrasonic examination of the liver were carried out. For patients who were suspected to develop recurrence or progressive diseases, abdominal computed tomography and/or magnetic resonance imaging were used to confirm the diagnosis. RFA, PEI, TACE or multi-disciplinary treatment (MDT) was selected for treatment of HCC recurrence according to the liver function, location and number

of recurrence nodules, and intra- and/or extra-hepatic metastases.

Extrahepatic metastasis was defined as multiple extrahepatic metastases in a single organ, or extrahepatic metastases in multiple organs. Tumor resectability was defined as a single tumor or multiple tumors which was (were) confined to a single hemiliver, a sector or a segment, and the volume of the liver remnant after liver resection was predicted to be more than 30% (19).The patients enrolled into this study all died of HCC progression or recurrence. Death due to other causes were excluded from this study. Patients who had bile duct and hepatic venous tumor thrombus were excluded. The median survival time was used for the training cohort, while the median or mean time was used for the validation cohort due to limited follow-up time for the patients (mean time for stage 0 to I and median time for stage II to IV, respectively).

Treatments of patients

All patients who entered into this study were reviewed at the multi-disciplinary HCC boards of the respective hospitals when the diagnosis of HCC was first made. Information on the therapeutic risks and benefits was provided to the patients. A shared-decision was made between the clinicians and the patients. All patients who had adequate liver function and radiologically resectable tumor were initially evaluated for partial hepatectomy. If the patient was not a surgical candidate, transarterial chemoembolization (TACE), TACE combined with sorafenib (TACE-Sor), TACE combined with external radiotherapy (TACE-RT), sorafenib or local ablative procedures such as percutaneous ethanol injection or radiofrequency ablation were offered, depending on the size, number and position of the tumor. Patients with advanced diseases were offered systemic therapy. The treatment was performed under standard procedures as previously described (20). A written informed consent was obtained from all the patients.

Statistical analysis

Survival was analyzed by the Kaplan-Meier method and survival curves were compared by the log-rank test. The overall survival (OS) was defined as the time from the date of first diagnosis of HCC associated with PVTT to death, the last follow-up or the date of data censoring (1st Jan. 2017). To check the similarity between the Training Cohort and the Validation Cohort, the demographic, clinical, and laboratory characteristics of patients on presentation in the two sets were compared using the Pearson's chi-square test for categorical variables, and the Wilcoxon rank sum test for continuous variables. Categorical variables were shown as number (percentage). Univariate and multivariate cox regression was used to identify significant variables related with OS. Partial Wald χ^2 test (21) and conditional inference trees (22) were used to determinate the last variables to establish the new staging system. The Schoenfeld residual plots of each prognostic factors were observed and transformed into the time-dependent relative coefficients. A value of $P<0.05$ was statistically significant. The analysis was performed with the SPSS software (IBM SPSS Statistics, USA, version 24.0) and the R-project (R Foundation for Statistical Computing, Vienna, Austria, version 3.4.4).

Results

Patient characteristics

Of the 3,729 patients with HCC associated with PVTT in this study, 2,179 patients formed the training cohort and 1550 patients the validation cohort. The characteristics of the patients in the two cohorts are shown in *Table 1*. There were no significant differences in age, albumin, HBsAg, and AFP level between the two cohorts. In the Training Cohort, there were significantly more patients with abnormal ALT levels, cirrhosis and tumor size >5 cm than the Validation Cohort (52.7% *vs.* 41.9%, P<0.001; 70.5% *vs.* 61.5%, P<0.001 and 80.3% *vs.* 74.9%, P<0.001, respectively). There were also significantly less patients with multiple tumors than in the validation cohort (25.1% *vs.* 51.5%, P<0.001). The characteristics of all the patients who were enrolled into this study are shown in Table S1.

Patients treatments

The first treatments are shown in *Table 2*. In the training cohorts, there were 1,067 (49.1%) patients who underwent liver resection, 706 (32.4%) TACE, 34 (1.6%) molecular targeting drugs or chemotherapy, 177 (8.1%) TACE-SUR, 107 (4.9%) RT-TACE and 88 (4.0%) the best supportive care (BSC), respectively. The median OS time was 17.6 (95% CI: 15.7–19.6) for liver resection, 3.7 (CI: 3.4–4.0) for TACE, 5.6 (CI: 5.4–5.9) for MDT or Chemotherapy, 8.1 (CI: 7.3–9.0) for TACE-SUR, 9.5 (CI: 6.8–12.3) for RT-TACE and 2.5 (CI: 1.7–3.3) for BSC, respectively in the Training Cohort. In the validation cohort, there were

Table 1 Patient's characteristics of all the enrolled patients

Variables	Training cohort (n=2,179)	Validation cohort (n=1,550)	P
Gender, n (%)			
Male	1,961 (90.4)	1,362 (87.9)	0.015
Female	210 (9.6)	188 (12.1)	
Age, years, n (%)			0.95
≤50	1,128 (51.8)	804 (51.9)	
>50	1,051 (48.2)	746 (48.1)	
Biochemistries, n (%)			
Total bilirubin (mmol/L)			0.001
≤18.8	1,374 (63.1)	1,074 (69.3)	
>18.8	805 (36.9)	476 (30.7)	
Albumin (g/L)			0.497
≤34	295 (13.5)	198 (12.8)	
>34	1,884 (86.5)	1,352 (87.2)	
ALT (μL/L)			<0.001
≤44	1,031 (47.3)	901 (58.1)	
>44	1,148 (52.7)	649 (41.9)	
HbsAg			0.447
Positive	1,908 (87.6)	1,370 (88.4)	
Negative	271 (12.4)	180 (11.6)	
Cirrhosis			<0.001
Yes	1,536 (70.5)	953 (61.5)	
No	643 (29.5)	597 (38.5)	
Tumor characteristics, n (%)			
AFP (ng/mL)			0.071
≤400	851 (39.1)	651 (42.0)	
>400	1,328 (60.9)	899 (58.0)	
Tumor size (cm)			<0.001
≤5	429 (19.7)	389 (25.1)	
>5	1,750 (80.3)	1,161 (74.9)	
Tumor number			<0.001
Single	1,632 (74.9)	752 (48.5)	
Multiple	547 (25.1)	798 (51.5)	
Local tumor resectability			<0.001
Yes	1,067 (49.0)	1,054 (68.0)	
No	1,112 (51.0)	496 (32.0)	

Table 1 (*continued*)

Table 1 (*continued*)

Variables	Training cohort (n=2,179)	Validation cohort (n=1,550)	P
Extrahepatic metastasis			0.02
No	1,895 (87.0)	1,387 (89.5)	
Yes	284 (13.0)	163 (10.5)	
Cheng's classification for PVTT, n (%)			<0.001
0	322 (14.8)	785 (50.6)	
I	319 (14.6)	276 (17.8)	
II	716 (32.9)	249 (16.1)	
III	647 (29.7)	216 (13.9)	
IV	175 (8.0)	24 (1.5)	
Japan's VP classification for PVTT, n (%)			<0.001
0	0	0	
1 and 2	319 (14.6)	276 (17.8)	
3	716 (32.9)	249 (16.1)	
4	822 (37.7)	240 (15.4)	
EOCG-PS, n (%)			0.070
0	1,067 (49.0)	785 (50.6)	
1–2	1,024 (47.0)	683 (44.1)	
3–4	88 (4.0)	82 (5.3)	
Child-Pugh, n (%)			0.071
A–B	2,091 (96.0)	1,468 (94.7)	
C	88 (4.0)	82 (5.3)	

PVTT, portal vein tumor thrombus.

1,054 (68.0%) patients who underwent liver resection, 249 (16.1%) TACE, 24 (1.5%) molecular targeting drugs or chemotherapy, 132 (8.5%) TAI, 5 (4.9%) RFA, and 82 (5.3%) BSC, respectively. The mean OS time was 35.8 (CI: 34.3–37.3) for liver resection, the median OS time was 4.0 (CI: 2.9–5.1) for TACE, 2.5 (CI: 1.1–3.9) for MDT or chemotherapy, 7.7 (CI: 6.3–9.1) for TAI, 4.0 (CI: 0–10.4) for RF and 1.5 (CI: 1.3–1.7) for BSC, respectively (Table S2).

Importance of the clinical prognostic factors

Through univariate and multivariate cox regression analyses, the extent of PVTT (HR with 95% CI: 3.023; 2.537–3.602), the Eastern Cooperative Oncology Group performance status 0–1 (ECOG PS) (3.451; 2.919-4.082) and 8.703; 6.813–11.118), the Pugh-Child grading (8.703; 6.813-11.118), extrahepatic metastasis (1.711; 1.475–1.985), local tumor resectability (1.312; 1.163–1.481) and whether the main PV was involved by PVTT (1.599; 1.443–1.773) were independently associated with OS (*Figure 1A,1B*). As patients with Child-Pugh C were in tune with patients with ECOG PS 3–4, these two models were respectively established in the multivariate analysis. For further analysis, the above six indicators with a high Wald χ^2 value [209.6 (299.9), 299.9, 152.8, 79.8, 50.3 and 19.5] were filled into the process of the conditional inference trees by the permutation tests in *Figure 2A,2B*. Table S3 shows the conditions of each variable in each node by the conditional inference trees. The scaled Schoenfeld residual plots showed that the coefficient estimates varied early in time and quickly stabilized by approximately two months. The pooled two months coefficients were obtained and

Table 2 Number of patients who underwent the first treatment in training cohort and validation cohort

The new staging system	First treatment, n (%)							
	Resection	TACE	MDT or Che	TACE-Sor	RT-TACE	TAI	RF	BSC
Training cohort (n=2,179)	1,067 (49.1)	706 (32.4)	34 (1.6)	177 (8.1)	107 (4.9)			88 (4.0)
0	322 (14.8)	0	0	0	0	0	0	0
I	745 (34.2)	0	0	0	0	0	0	0
II	0	586 (26.9)	0	100 (4.6)	107 (4.9)	0	0	0
III	0	120 (5.5)	34 (1.6)	77 (3.5)	0	0	0	0
IV	0	0	0	0	0	0	0	88 (4.0)
Validation cohort (n=1,550)	1,054 (68.0)	249 (16.1)	24 (1.5)			132 (8.5)	5 (0.4)	82 (5.3)
0	785 (50.6)	0	0	0	0	0	0	0
I	269 (17.4)	0	0	0	0	0	0	0
II	0	182 (11.7)	12 (0.8)	0	0	90 (5.8)	4 (0.3)	0
III	0	67 (4.3)	12 (0.8)	0	0	42 (2.7)	1 (0.1)	0
IV	0	0	0	0	0	0	0	82 (5.3)

MDT, multimodality treatment; Che, systemic chemotherapy; Sor, sorafenib; RT, radiotherapy; TAI, transhepatic arterial infusion; RF, radiofrequency ablation; BSC, best supportive care; TACE, transcatheter arterial chemoembolization.

transformed into the relative coefficient for use in this study. The reference category of each prognostic factor was assigned a value of zero (Table S4).

Establishment of the new staging system

Figure 3 shows the new staging system for patients with HCC associated with PVTT. In brief, patients with either poor general performance function (ECOG PS 3–4) or decompensated liver function (Pugh-Child grade C) were classified into stage IV (the terminal stage). The presence of extrahepatic metastasis was used to stratify patients into stage III (the advanced stage). The remaining patients were stratified into stage II with unresectable HCC (the intermediate stage) and stage 1 with resectable HCC (the early stage). Patients with microvascular invasion diagnosed on microscopic examination for resected specimens obtained after liver resection were stratified as stage 0 (the very early stage). Patients in stages I to III were further classified into A (without main portal vein invasion) and B (with main portal vein invasion).

Validation of the new staging system

The survival profiles of the patients for the new staging system are shown in Table S5 and *Figure 4*. The new staging system stratified patients well into distinct groups and sub-groups. There were significantly less patients who were classified into the new classification stage 0 (P<0.001) in the training cohort than the validation cohort. In the training cohort, the median survival for stage 0 to IV were 57.1 (37.2–76.9), 12.1 (11.0–13.2), 5.7 (5.1–6.2), 4.0 (3.3–4.6) and 2.5 (1.7–3.3) months for the stages 0 to IV, respectively (P<0.001). The cumulative 1-, 3- and 5-year OS rates were 86.3%, 69.7% and 61.9% for stage 0 patients, 50.2%, 28.9% and 19.3% for stage I, 26.8%, 8.7% and 2.9% for stage II, 10.6%, 0%, 0% for stage III, respectively, P<0.001. For patients in stage IV, the 1-year survival rate was 0% (*Figure 4*). In the Validation Cohort, the mean survival for stage 0 to I were 37.6 (35.9–39.2) and 30.4 (27.4–33.4), respectively (P<0.001). The median survival for stage II to IV were 6.4 (4.9–7.9), 2.8 (1.3–4.4), 10.8 (9.3–12.4), and 1.5 (1.3–1.7) months, respectively

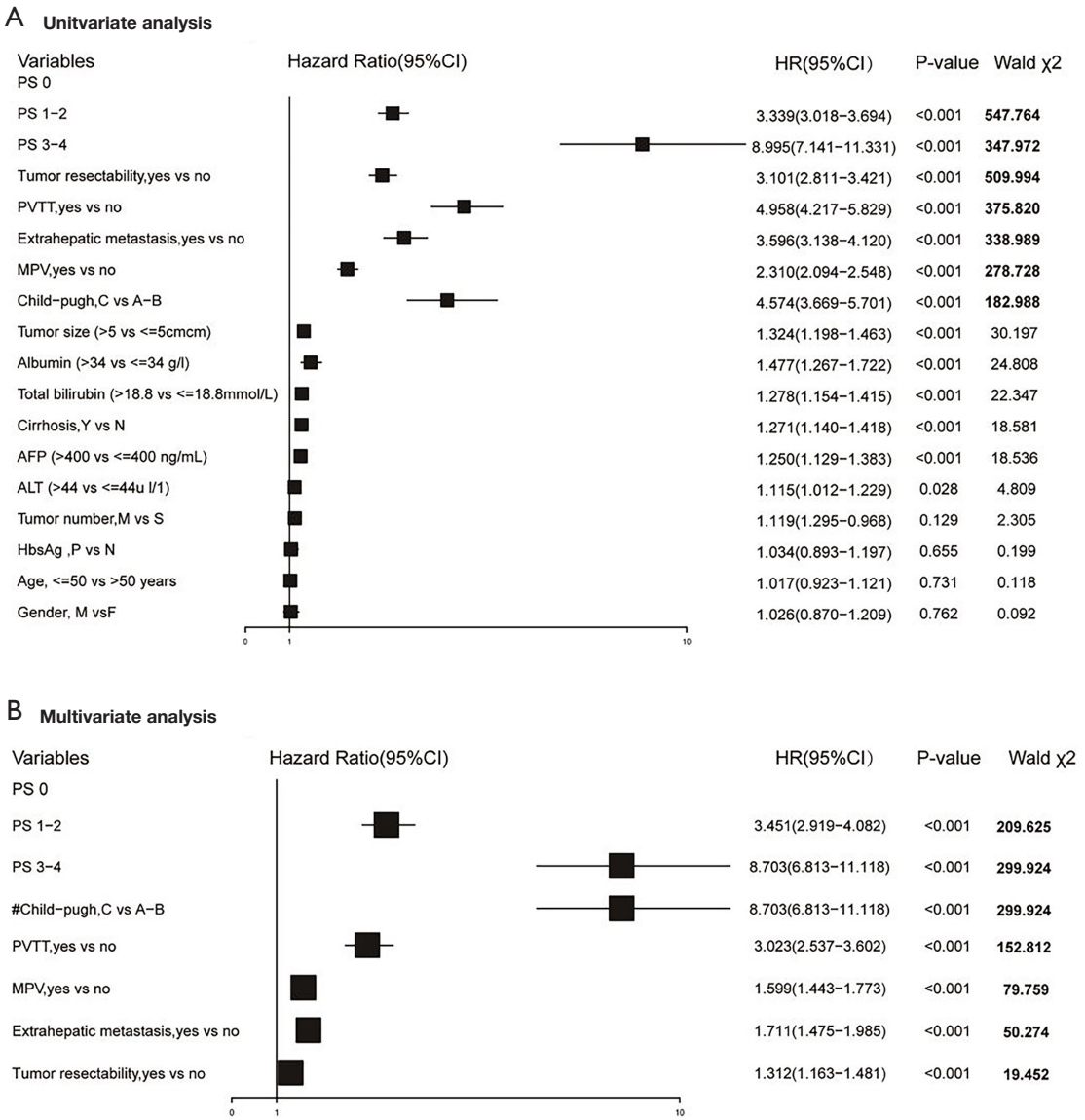


Figure 1 Univariate (A) and multivariate analysis (B) with Wald χ^2 test for OS in the patients with hepatocellular carcinoma associated with portal vein tumor thrombus. Two models were established by serval variables with or without the Child-Pugh.

(P<0.001). The cumulative 1-, 3- and 5-year OS rates were 78.1%, 67.5% and 61.4% for stage 0, 65.6%, 56.2% and 48.6% for stage I, 29.6%, 18.7% and 12.8% for stage II, 12.5%, 0%, 0% for stage III, 1.2%, 0%, 0% for stage IV, respectively (P<0.001) (*Figure 4C*). The survival analyses for patients in the new staging system are shown in *Figure 4B,4D*. The patients were also well stratified into the distinct sub-groups (P<0.005).

Comparison of predictive accuracy and clinical usefulness of the new staging system to other common staging systems

In comparison to other commonly used staging systems, the time-dependent-ROC curve area analysis was used to determine which staging systems were good at predicting the OS. As shown in *Figure 5A,5B*, the predicting capacity of the new staging system was better than any of the other staging systems, including the CLIP, Okuda, BCLC, TNM, JIS,

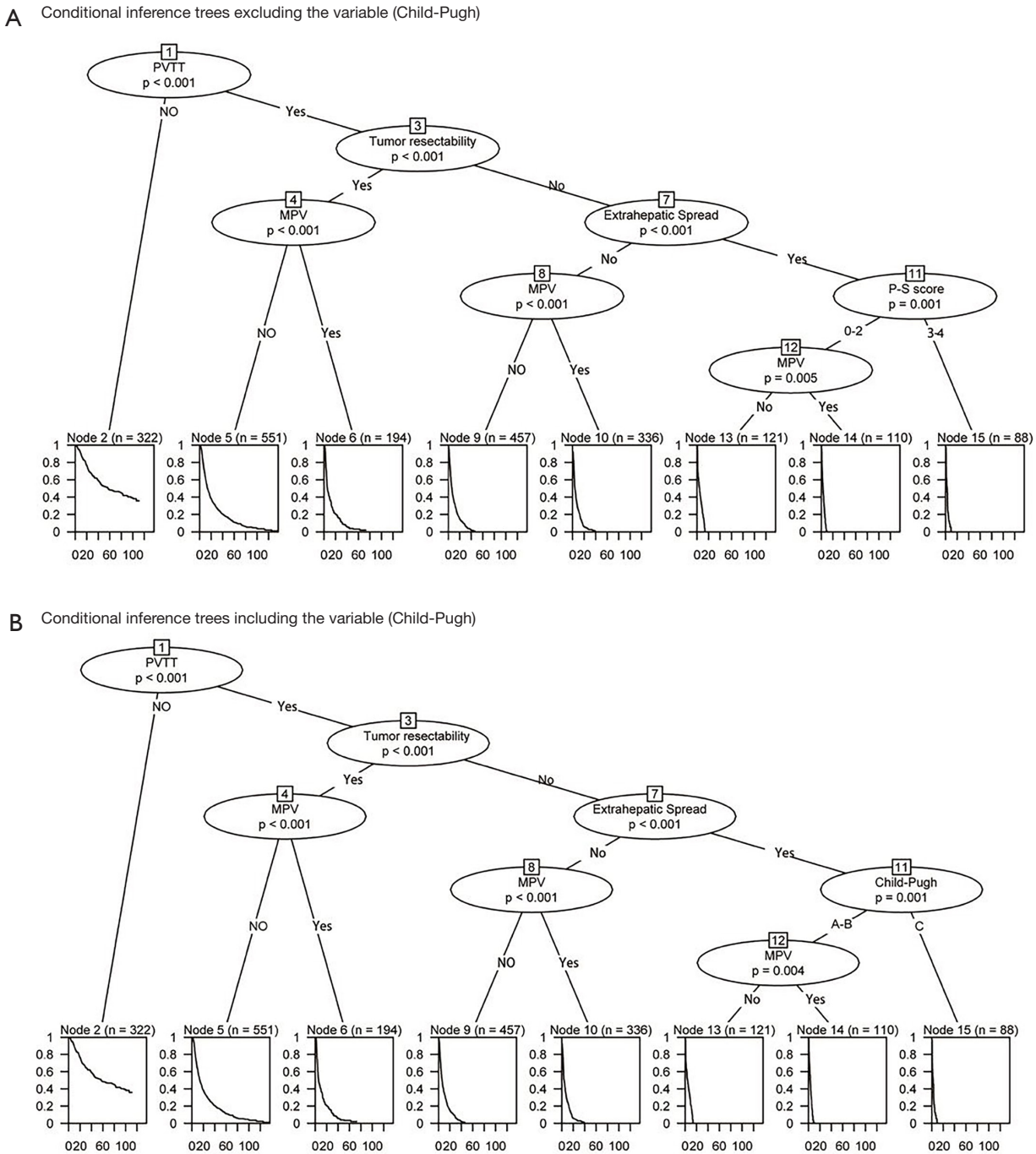
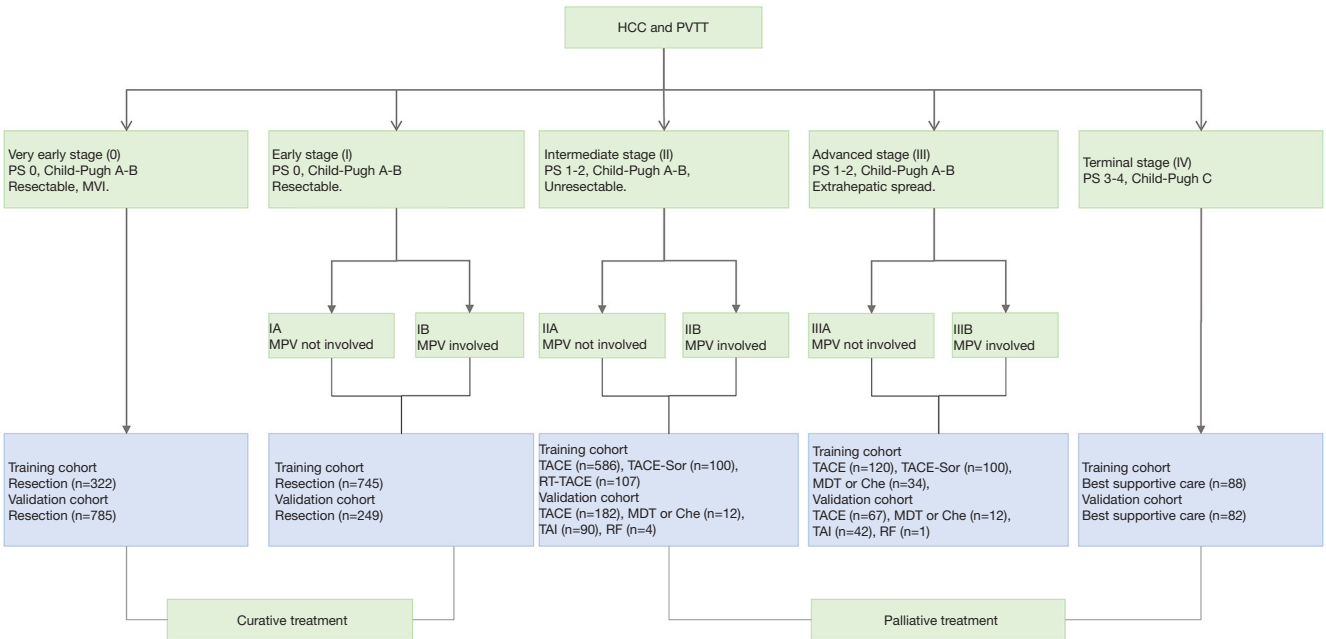


Figure 2 Conditional inference trees by serval variables without (A) or with (B) the Child-Pugh for overall survival in the patients with hepatocellular carcinoma associated with portal vein tumor thrombus.

CUPI, and Child-Pugh staging systems both in the training cohort and validation cohort. In addition, the decision curve analysis (DCA) was used to facilitate the comparison of clinical usefulness between the new staging system and the other staging systems. As shown in *Figure 5C,5D*, DCA showed that the new staging system provided superior net benefit when compared to those of the other staging systems both in the training cohort and validation cohort.



HCC, hepatoellular carcinoma; MVI, microvascular invasion; PVTT, portal vein tumor thrombus; PS, ECOG, performance status; MPV, main portal vein; MDT, multimodality treatment; Che, systemic chemotherapy; Sor, sorafenib; RT, radiotherapy; TAI, transhepatic arterial infusion; RF, radiofrequency ablation; BSC, best supportive care; TACE, transcatheter arterial chemoembolization.

Figure 3 The new staging system for hepatocellular carcinoma associated with portal vein tumor thrombus.

Discussion

PVTT has been considered as a bottleneck in the treatment of HCC, and effective treatment of PVTT may improve treatment results for HCC (7). This study established a staging system in conjunction with a treatment algorithm which is applicable to patients with HCC associated with PVTT. It improves on the stage C classification of the widely accepted BCLC staging for HCC, and the Cheng's and the Japanese Classifications for HCC associated with PVTT, by incorporating liver function, general health status, tumor resectability, extrahepatic metastasis and extent of PVTT. This new staging system divides patients into five stages and with three substages for stages I, II and III. In the validation cohort which had significantly different patient characteristics, it still had good discriminatory power in stratifying patients with HCC associated with PVTT into different prognostic groups. This staging system may improve management of patients with HCC associated with PVTT by guiding clinical studies to compare the effectiveness of different treatment options for the different stages of disease.

The most common used HCC classification and scoring systems are the tumor-node-metastasis (TNM) staging, Okuda staging, Cancer of the Liver Italian Program (CLIP) scoring system, Barcelona Clinic Liver Cancer (BCLC) staging, French, Chinese University Prognostic Index (CUPI), Japanese Integrated Scoring (JIS), and Tokyo scoring system. The TNM system is based only on tumor characteristics and extent of invasion. It does not include hepatic function (23). According to the TNM staging, HCC patients with PVTT are defined as T3b, which could not be used to predict prognosis or survival outcomes of these patients. The BCLC system stratifies HCC patients into five categories (0, very-early stage; A, early-stage; B, intermediate-stage; C, advanced-stage; or D, end-stage disease) using tumor-related parameters (tumor size, number of nodules, vascular invasion, and extrahepatic spread) and patient characteristics, including Child-Pugh liver function class and performance status (9). According to the BCLC staging, HCC patients with PVTT are defined as BCLC C stage. The only proposed treatment option for this group of patients is sorafenib. The CLIP scoring system combines four tumor-related features-tumor extent and morphological features, serum alpha-fetoprotein levels, and portal vein thrombosis, with a cirrhosis severity index and the Child-Pugh score, to stratify HCC patients into groups (24). According to the CLIP system, PVTT is an independent risk factor to stratify HCC patients. The CUPI

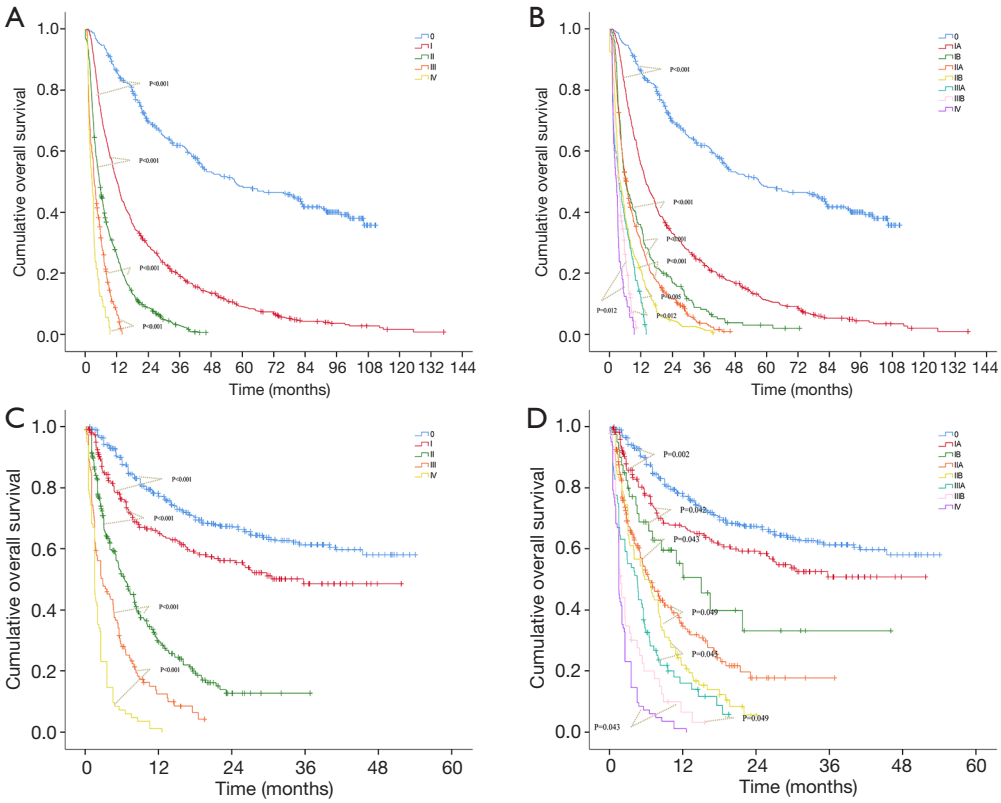


Figure 4 Overall survival of the different stagings and substagings for the new staging system for hepatocellular carcinoma associated with portal vein tumor thrombosis. (A,B) Training cohort; (C,D) validation cohort.

staging combines the conventional TNM system with factors relating to liver function and tumor load (25). The six prognostic factors are: the TNM stage, asymptomatic disease at presentation, total bilirubin level, ascites, alkaline phosphatase level, and alfa-fetoprotein level. The serological variables, liver function variables and PVTT (T3b of TNM) are combined to predict prognosis of HCC patients with PVTT. The JIS is based on the modified TNM system by the Liver Cancer Study Group of Japan and the Child-Pugh score (26). Vascular invasion (PVTT) is acknowledged a staging index to stratify HCC patients. The CLIP, CUPI and JIS staging systems include PVTT as a staging index, and can therefore distinguish different prognosis of HCC patients with PVTT. However, all these scoring and staging systems have limitations because they could not be used to make a preoperative decision on liver resection (LR) for HCC patients with PVTT. This new PVTT system was established to provide a good discriminatory ability to separate patients into different stages and substages with treatments. It can be used to supplement the other HCC staging systems.

This new staging system divides treatment into: potentially curative treatment for patients in stage 0 and I, and palliative treatment for patients in stage II to IV. With this system, new and promising treatments can be compared stage-by-stage with the conventional treatment. The data from this study showed that in selected patients, long-term survival can be achieved with liver resection, and some patients with more advanced HCC can still derive substantial survival benefits from multi-modality treatments.

There is still no worldwide consensus on the management of patients with HCC associated with PVTT (27). Sorafenib is the only recommended treatment by BCLC for these patients. However, the reported median survival time is only 6.5 months in the Asian-Pacific study (28) and 10.5 months in the SHARP study (29). With recent advances, there have been increasing attempts to use more aggressive multi-modality treatments for advanced HCC in selected patients, such as surgical resection, TACE, or TACE plus RT (30-34). The National Comprehensive Cancer Network (NCCN)

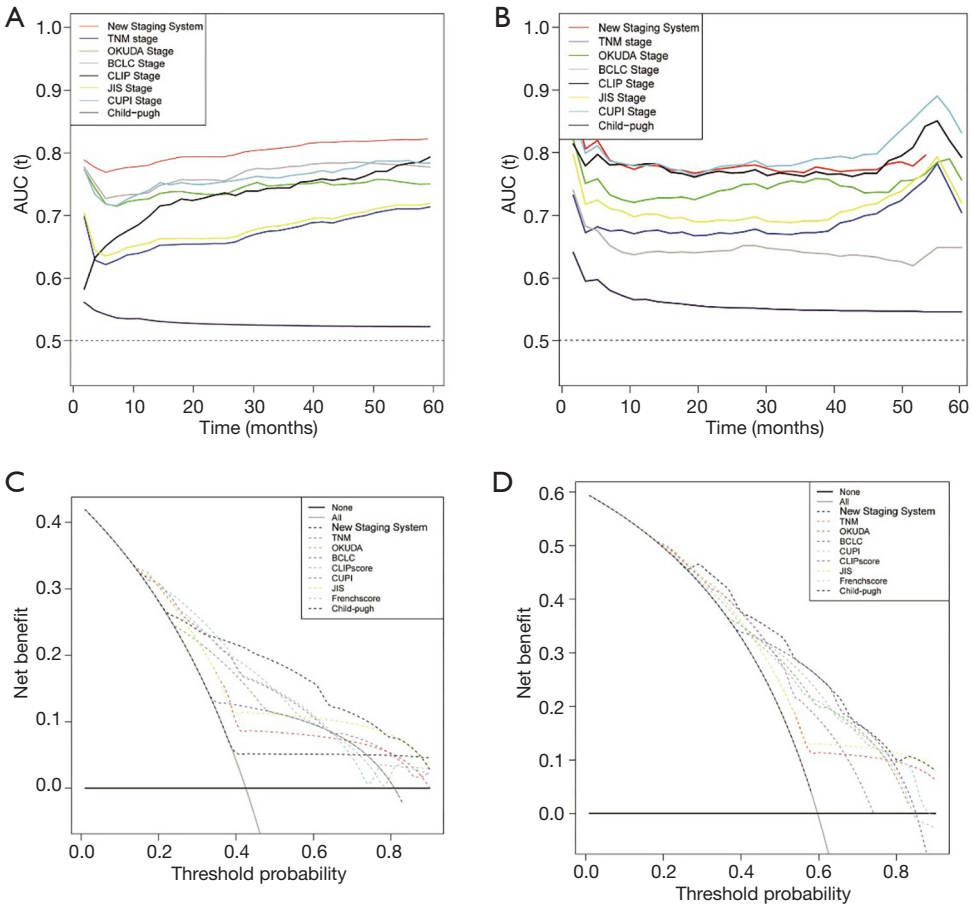


Figure 5 Comparison of the new staging system to other common standing systems. Time-dependent ROC analysis for different staging systems in the training cohort (A) and validation cohort (B); the DCA curves of different staging systems in the training cohort (C) and validation cohort (D). ROC, receiver operating characteristic curve; DCA, decision curve analysis.

Guidelines version 2.2018 for hepatocellular carcinoma suggested that hepatic resection can be considered for patients with major vascular invasion (35). A recent study with a large sample from Japan showed liver resection to result in better survival outcomes than non-surgical treatments, as long as the PVTT was confined to the first-order branch, but not involved the main portal vein (36). The median survival time in the surgery group was 1.77 years longer than the non-surgery group (2.87 *vs.* 1.10 years; P<0.001), and 0.88 years longer than the non-surgery group in the propensity score-matched cohorts (2.45 *vs.* 1.57 years; P<0.001). Similar results from a large-scale, multicenter, propensity score matching analysis reported by us showed surgical treatment to be better than non-surgical treatment in patients with HCC associated with PVTT which had not involved the main portal vein and with Pugh-Child A and selected B liver function (20). A recently published meta-analysis suggested that surgical resection provided survival benefits in patients with advanced HCC when compared with TACE (37). Another recently published randomized clinical trial showed that TACE plus external radiotherapy was well-tolerated and provided good progression-free survival in patients with advanced HCC with macroscopic vascular invasion (38). An EHBH-PVTT scoring system was established as an aid to decision-making on hepatectomy for HCC patients with PVTT in our team (39). It could select appropriate HCC patients with PVTT limited to a first-order branch of the main portal vein or above for liver resection. These results indicated that careful patient selection is important in the treatment of HCC associated with PVTT. The new system refines selection of patients with HCC associated with PVTT for treatments which can

vary from the best supportive care to liver resection.

The limitations of this study are: First, our study did not include patients with HCC associated with PVTT which coexisted with tumor thrombosis of the hepatic and inferior venous systems. Second, the majority of patients had HBV-related HCC and all the enrolled patients came from China. Whether this new staging system can be used in patients with non-HBV-related HCC is uncertain. Third, this is a retrospective study with its inherent defects. Fourth, the grades of evidence used in this study were IIb to III only. Fifth, this study did not look into treatment mortalities, morbidities and side-effects.

In conclusion, a new staging system was proposed to provide better discriminatory ability and prognostic value for patients with HCC associated with PVTT. This system can also serve as a guide to compare the effectiveness of different treatment options for these patients.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-19-810/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-19-810/coif). Dr. WYL serves as an unpaid editorial board member of *Hepatobiliary Surgery and Nutrition*. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committees of all the five hospitals (Permit Number: EHBHKY-2019-001-017). Informed consent was obtained from all the patients prior to treatment.

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Supplementary

Table S1 Patient's other characteristics of all the enrolled patients

Variables	Validation cohort 1 (n=2,179)					Validation cohort 2 (N=1,550)				
	Stage 0 (n=322)	Stage I (n=745)	Stage II (n=793)	Stage III (n=231)	Stage IV (n=88)	Stage 0 (n=785)	Stage I (n=269)	Stage II (n=292)	Stage III (n=122)	Stage IV (n=82)
Gender, n (%)										
Male	287 (89.1)	679 (91.1)	711 (89.7)	210 (91.0)	82 (93.2)	685 (87.3)	227 (84.4)	263 (90.1)	113 (92.6)	74 (90.2)
Female	35 (10.9)	66 (8.9)	82 (10.3)	21 (9.0)	6 (6.8)	100 (12.7)	42 (15.6)	29 (9.9)	9 (7.4)	8 (9.8)
Age, years, n (%)										
≤50	159 (49.4)	440 (59.1)	374 (47.2)	110 (47.7)	45 (51.1)	398 (50.7)	136 (50.6)	160 (54.8)	70 (57.4)	40 (48.8)
>50	163 (50.6)	305 (40.9)	419 (52.8)	121 (52.3)	43 (48.9)	387 (49.3)	133 (49.4)	132 (49.2)	52 (42.6)	42 (51.2)
Biochemistries, n (%)										
Total bilirubin (mmol/L)										
≤18.8	228 (70.8)	543 (72.9)	448 (56.5)	130 (56.3)	25 (28.4)	603 (76.8)	197 (73.2)	179 (61.3)	69 (56.6)	26 (31.7)
>18.8	94 (29.2)	202 (27.1)	345 (43.5)	101 (43.7)	63 (71.6)	182 (23.2)	72 (26.8)	113 (38.7)	53 (43.4)	56 (68.3)
Albumin (g/L)										
≤34	10 (3.1)	47 (6.3)	154 (19.4)	35 (15.2)	49 (55.7)	76 (9.7)	22 (8.2)	36 (12.3)	20 (16.4)	44 (53.7)
>34	312 (96.9)	698 (93.7)	639 (80.6)	196 (84.8)	39 (44.3)	709 (90.3)	247 (91.8)	256 (87.7)	102 (83.6)	38 (46.3)
ALT (μL/L)										
≤44	185 (57.5)	348 (46.7)	350 (44.1)	108 (46.8)	40 (45.5)	505 (64.3)	164 (61.0)	124 (42.5)	58 (47.5)	38 (46.3)
>44	137 (42.5)	397 (53.3)	443 (55.9)	123 (53.2)	48 (54.5)	280 (35.7)	105 (39.0)	168 (57.5)	64 (52.5)	44 (53.7)
HbsAg										
Positive	284 (88.2)	670 (89.9)	668 (84.2)	208 (90.0)	78 (88.7)	682 (86.9)	245 (91.1)	262 (89.7)	109 (89.3)	72 (87.8)
Negative	38 (11.8)	75 (10.1)	125 (15.8)	23 (10.0)	10 (11.3)	103 (13.1)	24 (8.9)	30 (10.3)	13 (10.3)	10 (12.2)
Cirrhosis										
Yes	197 (61.2)	513 (68.9)	587 (74.0)	171 (74.0)	67 (76.1)	465 (59.2)	194 (72.1)	159 (54.5)	77 (63.1)	58 (70.7)
No	125 (38.8)	232 (31.1)	206 (26.0)	60 (26.0)	21 (23.9)	320 (40.8)	75 (27.9)	133 (45.5)	45 (36.9)	24 (29.3)
Tumor characteristics, n (%)										
AFP (ng/mL)										
≤400	173 (53.7)	274 (36.8)	306 (38.6)	79 (34.2)	20 (22.7)	382 (48.7)	110 (40.9)	95 (32.5)	44 (36.1)	20 (24.4)
>400	149 (46.3)	471 (63.2)	487 (61.4)	152 (65.8)	68 (87.3)	403 (51.3)	159 (59.1)	197 (67.5)	78 (63.9)	62 (75.6)
Tumor size (cm)										
≤5	149 (46.3)	138 (18.5)	119 (15.0)	17 (7.4)	6 (6.8)	287 (36.6)	62 (23.0)	25 (8.6)	9 (7.4)	6 (7.3)
>5	173 (53.7)	607 (81.5)	674 (85.0)	214 (92.6)	82 (93.2)	498 (63.4)	207 (77.0)	267 (91.4)	113 (92.6)	76 (92.7)
Tumor number										
Single	294 (91.3)	693 (93.0)	604 (76.2)	28 (12.1)	13 (24.8)	539 (68.7)	114 (42.4)	68 (23.3)	16 (13.1)	15 (18.3)
Multiple	28 (8.7)	52 (7.0)	189 (23.8)	203 (87.9)	75 (85.2)	246 (31.3)	155 (57.6)	224 (76.7)	106 (86.9)	67 (81.7)

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Table S2 Median survival time of all the enrolled patients who underwent different treatments in training cohort and validation cohort

First treatment	Median survival time (95% CI)	
	Training cohort	Validation cohort
Resection	17.6 (15.7–19.6)	*35.8 (34.3–37.3)
TACE	3.7 (3.4–4.0)	4.0 (2.9–5.0)
MTD or Che	5.6 (5.4–5.9)	2.5 (1.1–3.9)
TACE-SUR	8.1 (7.3–9.0)	NA
RT-TACE	9.5 (6.8–12.3)	NA
TAI	NA	7.7 (6.3–9.1)
RF	NA	4.0 (0–10.4)
BSC	2.5 (1.7–3.3)	1.5 (1.3–1.7)

*, mean survival time. CI, confidence interval; MTD, multidisciplinary therapy; Che, systemic chemotherapy; SUR, surgery; RT, external radiotherapy; TAI, transhepatic arterial infusion; RF, radiofrequency ablation; BSC, best support care.

Table S3 Patient's variables of all the nodes by the conditional inference trees in training cohort

Tree nodes in two models	Variables in each node in the cohort 1	Training cohort (n=2,179)
Node1 and Node2	MVI; PS =0; Child-Pugh = A-B; resectability	322 (14.8)
Node4	PVTT; PS =1–2; Child-Pugh = A–B; resectable; extrahepatic spread =0	745 (34.2)
Node5	PVTT; PS =1–2; Child-Pugh = A–B; resectability; extrahepatic spread =0; MPV =0	551 (25.3)
Node6	PVTT; PS =1–2; Child-Pugh = A–B; resectable; extrahepatic spread =0; MPV =1	194 (8.9)
Node8	PVTT; PS =1–2; Child-Pugh = A–B; unresectable; extrahepatic spread =0	793 (36.4)
Node9	PVTT; PS =1–2; Child-Pugh = A–B; unresectable; extrahepatic spread =0; MPV =0	457 (21.0)
Node10	PVTT; PS =1–2; Child-Pugh = A–B; unresectable; extrahepatic spread =0; MPV =1	336 (15.4)
Node12	PVTT; PS =1–2; Child-Pugh = A–B; extrahepatic spread =1	231 (10.6)
Node13	PVTT; PS =1–2; Child-Pugh = A–B; extrahepatic spread =1; MPV =0	121 (5.6)
Node14	PVTT; PS =1–2; Child-Pugh = A–B; extrahepatic spread =1; MPV =1	110 (5.1)
Node15	Child-Pugh = C or PS =3–4; no matter other status	88 (4.0)

Table S4 The scaled Schoenfeld residual plots

	Relative coefficient				
	0	1	2	3	4
Child-Pugh	A–B				C
PVTT	No		Yes		
ECOG -PS	0		1-2		3-4
Extrahepatic Metastasis	No	Yes			
Tumor resectability	No	Yes			
MPV	No	Yes			

MPV, main portal vein.

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Table S5 The 1-, 2- and 3-year overall and median survival outcomes of all the enrolled patients in the new staging system

	1-year		2-year		3-year		Median survival time (95% CI)	
	Training cohort	Validation cohort	Training cohort	Validation cohort	Training cohort	Validation cohort	Training cohort	Validation cohort
Stage								
0	86.3	78.1	69.7	67.5	61.9	61.4	57.1 (37.2-76.9)	*37.6 (35.9-39.2)
I	50.2	65.6	28.9	56.2	19.3	48.6	12.1 (11.0-13.2)	*30.4 (27.4-33.4)
II	26.8	29.6	8.7	12.8	2.9	12.8	5.7 (5.1-6.2)	6.4 (4.9-7.9)
III	10.6	12.5	NA				4.0 (3.3-4.6)	2.8 (1.3-4.4)
IV	0	1.2	NA				2.5 (1.7-3.3)	1.5 (1.3-1.7)
Sub-stage								
IA	55.5	67.3	33.2	59.3	23.1	50.9	13.9 (12.1-15.7)	*31.5 (28.4-34.7)
IB	35.1	55.4	16.9	33.3	8.3	33.3	6.0 (4.4-7.7)	15.0 (8.3-21.7)
IIA	29.7	34.8	11.8	17.8	3.8	17.8	6.4 (5.6-7.2)	6.4 (4.5-8.3)
IIB	20.8	22	4.7	5.6	1.7	NA	4.0 (3.0-4.9)	5.7 (3.2-8.3)
IIIA	10.4	16.1	NA				3.4 (2.1-4.6)	4.5 (2.6-6.4)
IIIB	0	6.7	NA				3.3 (2.6-4.0)	1.8 (1.2-2.4)

*, mean survival time. CI, confidence interval.

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