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Hepatobiliary

Novel Models Predict Postsurgical Recurrence and Overall Survival for Patients with Hepatitis B Virus-Related Solitary Hepatocellular Carcinoma ≤10 cm and Without Portal Venous Tumor Thrombus

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Hepatocellular carcinoma • Early stage • Prognosis • Nomogram

Abstract

Background. The predictive model of postsurgical recurrence for solitary early hepatocellular carcinoma (SE-HCC) is not well established. The aim of this study was to develop a novel model for prediction of postsurgical recurrence and survival for patients with hepatitis B virus (HBV)-related SE-HCC ≤10 cm.

Patients and Methods. Data from 1,081 patients with HBV-related SE-HCC ≤10 cm who underwent curative liver resection from 2003 to 2016 in our center were collected retrospectively and randomly divided into the derivation cohort (n = 811) and the internal validation cohort (n = 270). Eight hundred twenty-three patients selected from another four tertiary hospitals served as the external validation cohort. Postsurgical recurrence-free survival (RFS) and overall survival (OS) predictive nomograms were generated. The discriminatory accuracies of the nomograms were compared with six conventional hepatocellular carcinoma (HCC) staging systems.

Results. Tumor size, differentiation, microscopic vascular invasion, preoperative α-fetoprotein, neutrophil-to-lymphocyte ratio, albumin-to-bilirubin ratio, and blood transfusion were identified as the risk factors associated with RFS and OS. RFS and OS predictive nomograms based on these seven variables were generated. The C-index was 0.83 (95% confidence interval [CI], 0.79–0.87) for the RFS-nomogram and 0.87 (95% CI, 0.83–0.91) for the OS-nomogram. Calibration curves showed good agreement between actual observation and nomogram prediction. Both C-indices of the two nomograms were substantially higher than those of the six conventional HCC staging systems (0.54–0.74 for RFS; 0.58–0.76 for OS) and those of HCC nomograms reported in literature.

Conclusion. The novel nomograms were shown to be accurate at predicting postoperative recurrence and OS for patients with HBV-related SE-HCC ≤10 cm after curative liver resection. ***The Oncologist*** 2020;25:e1552–e1561

Implications for Practice: This multicenter study proposed recurrence or mortality predictive nomograms for patients with hepatitis B virus-related solitary early hepatocellular carcinoma ≤10 cm after curative liver resection. A close postsurgical surveillance protocol and adjuvant therapy should be considered for patients at high risk of recurrence.

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide and is the second leading cause of cancer-related death in China because of endemic hepatitis B virus (HBV) infection [1]. Liver resection is the first-line treatment option for solitary HCC without portal venous tumor thrombus (solitary early HCC [SE-HCC]) in patients with well-preserved liver function [2]. However, the high postsurgical recurrence rate has compromised long-term survival. The postsurgical 5-year recurrence rate based on previously published studies ranged from 57.7% to 70% for SE-HCC [3–5]. Conventional tumor staging systems are currently incapable of accurately predicting the likelihood of recurrence of SE-HCC after surgery [6]. Patients with same tumor stage who underwent surgical resection displayed diverse postoperative outcomes, largely because of the heterogeneity that exists among patients and tumors [7, 8]. Furthermore, there are few distinctive prognostic factors that can be identified from conventional clinicopathological data for SE-HCC.

Recently, molecular signatures such as mRNA [9], DNA methylation [10], and proteogenomic profiles [11] were shown to be good predictors for recurrence of early HCC. However, there are some major issues of molecular signature–based predictors: (a) These profiles were diverse among different studies. Studies based on identical HCC populations with different etiologies may have different aberrant profiles [12]. (b) Different sequencing platforms and software analytic packages are also assuredly contributing to these different profiles. (c) These molecular signature–based biomarkers demand a high level of technology and are expensive, which impedes their application in the current clinical setting.

The development of postsurgical recurrence of HCC is influenced by multiple factors. Tumor clinicopathologic traits, the patient's inflammatory or immune status, underlying liver disease (i.e., cirrhosis related to HBV or HCV), and operative factors are all potential factors contributing to tumor recurrence. Therefore, an ideal postsurgical recurrence predictive model would be generated based on the risk variables selected from the four aspects described above. A nomogram that integrates diverse prognostic and determinant factors is able to generate the individual probability of tumor recurrence or overall survival (OS) in patients with cancer [13].

Considering that nearly 90% of resected HCCs were less than 10 cm [14–16] and there was no prognostic model for patients with HBV-related SE-HCC ≤10 cm after curative hepatectomy, the generation of new models for predicting postsurgical recurrence and survival for this subgroup of patients is urgently required. In this study, we aimed to generate novel prognostic models that integrated tumor pathological features, patient's inflammatory variables, underlying liver diseases, and surgical factors to predict the likelihood of recurrence and OS of patients with HBV-related SE-HCC ≤10 cm after curative liver resection.

Materials, Subjects, and Methods

Study Population

From January 2003 to December 2016, 2,462 consecutive patients with preserved liver function (Child-Pugh A or B class) who underwent liver resection for HCC as their initial treatment in the Department of Liver Surgery, First Affiliated Hospital of Sun Yat-sen University, were evaluated for this study. Clinical data were entered prospectively in a resectable HCC database in our department and were reviewed retrospectively. Patients with HBV-related SE-HCC ≤10 cm were recruited in this study. HCC with etiologies other than HBV (n = 349), tumor size larger than 10 cm (n = 121), multiple tumors (n = 385), macroscopic portal venous tumor thrombus (n = 483), death within 30 days of surgery (n = 6), and R1 resection (n = 37) were excluded. Finally, 1,081 patients were included and randomly allocated to a derivation cohort (n = 811) and an internal validation cohort (n = 270) with a ratio of 3 to 1 based on the data splitting approach [17]. Patient selection is shown in supplemental online Figure 1.

In addition, 823 patients with HBV-related SE-HCC ≤10 cm underwent curative liver resection at another four tertiary hospitals. Among them, 455 were from the Tumor Hospital of Sun Yat-sen University, Guangzhou (January 2004 to June 2006); 138 from the Hunan Provincial People's Hospital, Changsha (March 2009 to December 2010); 215 from the Xiehe Hospital of Huazhong University of Science and Technology, Wuhan (January 2012 to April 2013); and 105 from the Gansu Provincial People's Hospital, Lanzhou (January 2008 to December 2009). These data were collected retrospectively and served as the external validation cohort (supplemental online Fig. 1).

This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee boards of the five hospitals.

Definition

Liver function reserve was evaluated by the albumin-to-bilirubin ratio (ALBI grade) [18]. Although the Child-Pugh score was applied to evaluate liver function in all patients in clinical practice, we used the ALBI score in data analysis in this study because the ALBI score is more accurate and objective than the conventional Child-Pugh score [18]. Neutrophil-to-lymphocyte ratio (NLR) was obtained by neutrophil count divided by lymphocyte count. Platelet-to-lymphocyte ratio (PLR) was obtained by platelet count divided by lymphocyte count. The cutoff value of NLR or PLR that defined a high or low level was determined by the Youden index of NLR or PLR calculated by the receiver operating characteristic (ROC) curves in the derivation cohort. Anatomical resection referred to resection of the tumor-involved segment/section, together with its portal vein branch, resected en bloc [19]. Major resection was defined as a resection extent of more than three segments. Intraoperative blood transfusion referred to transfusion of packed red blood cells during the operation owing to excessive bleeding that resulted in unstable hemodynamic status or hemoglobin <70 g/L.

Follow-Up

The patients were followed postoperatively. The follow-up protocol and management of recurrent HCC was described in our previous study [19]. The end of follow-up was June 30, 2017. The median follow-up period was 37.0 months (4–147 months) for the cohort patients from our center and 29.3 months (4–107 months) for the external validation cohort.

Table 1. Baseline characteristics of the three cohorts of patients

Characteristics	Derivation cohort (*n* = 811)	Internal validation cohort (*n* = 270)	External validation cohort (*n* = 823)	*p* value
Demographic data				
Age, years	51.9 ± 11.4	50.6 ± 12.7	51.3 ± 11.9	.245
Sex, male	700 (86.3)	240 (88.9)	699 (84.9)	.257
Antiviral therapy	749 (92.4)	245 (90.7)	766 (93.1)	.450
Cirrhosis	608 (75.0)	203(75.2)	644 (78.2)	
ALT, median (IQR), U/L	35.0 (23.0–54.0)	33.0 (23.0–50.0)	37.0 (24–48.0)	.132
Child-Pugh score				
5 score	713 (87.9)	239 (88.5)	740 (90.0)	.713
6 score	82 (10.1)	27 (10.0)	68 (8.2)	
7 score	16(2.0)	4 (1.5)	15 (1.8)	
ALBI grade				
Grade 1	410 (50.5)	145 (53.7)	416 (50.6)	.105
Grade 2	393 (48.5)	125 (46.3)	396 (48.1)	
Grade 3	8(0.1)	0 (0)	11 (1.3)	
Hemoglobin (g/L)	138.2 ± 20.9	139.4 ± 18.3	138.3 ± 19.0	.644
Platelet ($\times 10^9$/L)	188.1 ± 74.6	190.0 ± 72.0	175.8 ± 73.2	.714
Inflammatory factors				
NLR, median (IQR)	1.9 (1.32–2.63)	1.9 (1.51–2.72)	2.0 (1.48–2.79)	.216
PLR, median (IQR)	94.6 (70.6–123.9)	95.2 (76.9–138.1)	96.1 (70.9–135.7)	.423
Tumor factors				
Size, median (IQR), cm	5.2 (3.8–8.1)	5.0 (3.6–8.2)	5.0 (3.7–8.0)	.183
AFP, μg/L				
≤20	350 (43.2)	109 (40.4)	341 (41.4)	.221
>20, ≤400	220 (27.1)	63 (23.3)	235 (28.6)	
>400	241 (29.7)	98 (36.3)	247 (30.0)	
Tumor capsule				
Complete	623 (76.8)	219 (81.1)	633 (76.9)	.553
Incomplete	148 (18.2)	38 (14.1)	144 (17.5)	
Noncapsule	40(5.0)	13 (4.8)	46 (5.6)	
MVI				
Yes	210 (25.9)	72 (26.7)	184 (22.4)	.167
No	601 (74.1)	198 (73.3)	639 (77.6)	
Tumor differentiation[a]				
Level 1	157 (19.4)	54 (20.0)	153 (18.6)	.961
Level 2	371 (45.7)	121 (44.8)	370 (44.9)	
Level 3	283 (34.9)	95 (35.2)	300 (36.5)	
Surgical factors				
Extent of resection				
Major	265 (32.7)	86 (31.8)	252 (30.6)	.669
Minor	546 (67.3)	184 (68.2)	571 (69.4)	
Resection type				
Nonanatomic	554 (68.3)	193 (71.5)	543 (66.0)	.221
Anatomic	257 (31.7)	77 (28.5)	280 (34.0)	
Resection margin				
≤1 cm	251 (30.9)	89 (33.0)	275 (33.4)	.549
>1 cm	560 (69.1)	181 (67.0)	548 (66.6)	
Blood loss, median (IQR), mL	200.0 (150–500)	200.0 (100–500)	225.0 (150–600)	.570
No. of blood transfusion	181 (22.3)	55 (20.4)	172 (20.9)	.705

Values in parentheses are percentages unless indicated otherwise.
[a]Tumor differentiation: level 1, high + high to moderate; level 2,= moderate + moderate to low; level 3, low + undifferentiation.
Abbreviations: AFP, α-fetoprotein; ALBI grade, albumin-to-bilirubin ratio; ALT, alanine transaminase; IQR, interquartile range; MVI, microscopic vascular invasion; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

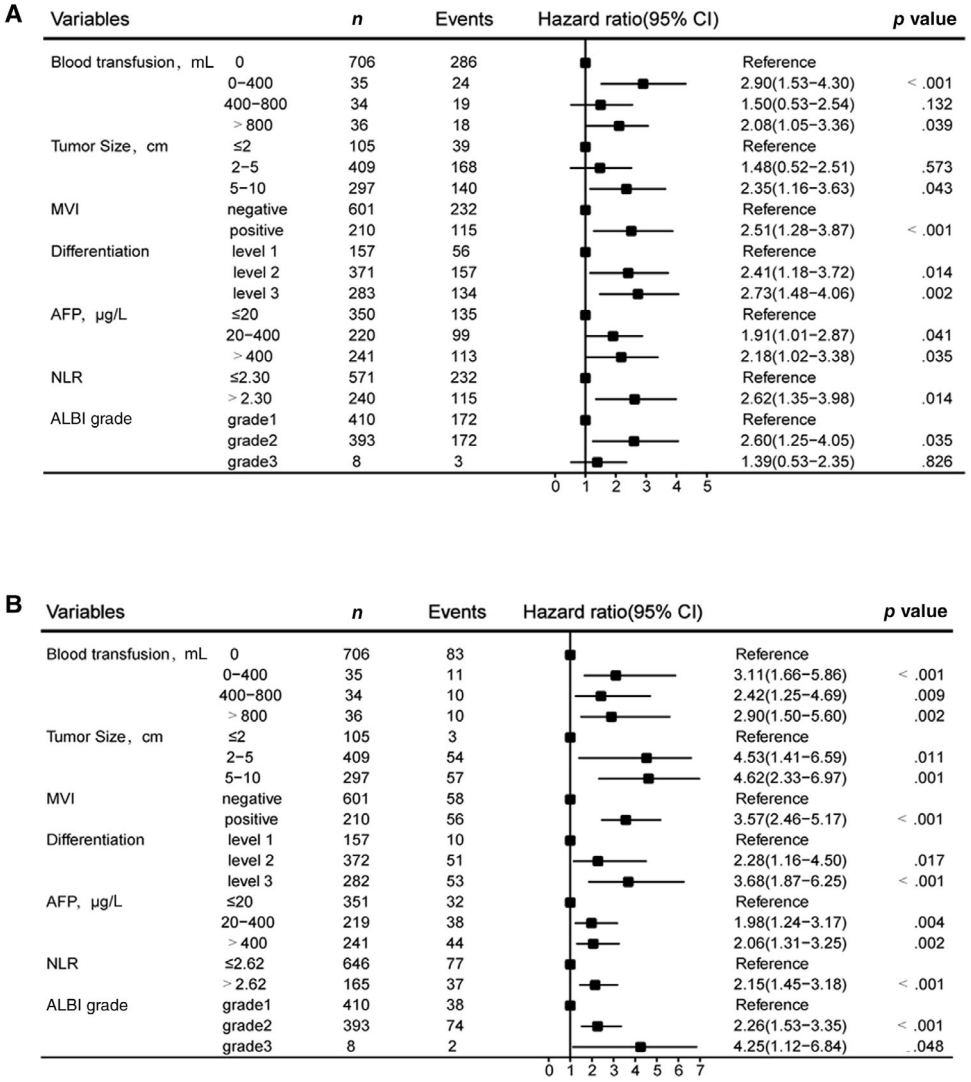

Figure 1. Forest plot to decipher the risk factors associated with recurrence-free survival and overall survival identified by multivariable Cox regression analysis. **(A):** Recurrence-free survival factors. **(B):** Overall survival factors. Tumor differentiation level 1, high + high to moderate; level 2, moderate + moderate to -low; level 3, low + undifferentiation.
Abbreviations: AFP, α-fetoprotein; ALBI grade, albumin-to-bilirubin ratio; MVI, microscopic vascular invasion; NLR, neutrophil-to-lymphocyte ratio.

Statistical Analysis

The clinical database was established with SPSS for Windows (version 22.0, IBM, Armonk, NY). Continuous data are expressed as means ± SD or median (IQR). The Kruskal-Wallis analysis of variance (ANOVA) test or ANOVA *t* test was used to compare continuous data between groups and the χ^2 test for discrete data. Cumulative rates of survival were calculated by the Kaplan-Meier method and compared between groups by means of the log-rank test. A Cox regression model was used to identify risk factors associated with recurrence-free survival (RFS) and OS by univariate and multivariate analysis.

The predictive nomograms were constructed based on the results of risk variables associated with RFS and OS identified by Cox multivariate analysis in the derivation cohort using R software for Windows (version 3.3.3, http://www.r-project.org). A final model selection was performed by a backward stepdown process with the Akaike information criterion [20]. The predictive performance of the nomograms was measured by concordance index (C-index) and assessed by calibration curve comparing nomogram-predicted versus actually observed Kaplan-Meier estimates of probability of RFS and OS. Bootstraps with 1,000 resamples were used for calculations [21]. The predictive performance of the nomograms was validated in the internal validation and external validation cohort by calculating C-indices and assessed by calibration curves.

The discriminatory powers of nomograms were also compared with six conventional HCC staging systems: Barcelona Clinic Liver Cancer staging system (BCLC) [22], American Joint Committee on Cancer Staging (TNM) [23], Japan integrated staging (JIS) [24], Cancer of the Liver Italian Program score (CLIP) [25], Chinese University Prognostic Index (CUPI) [26], and Okuda staging system [27] by

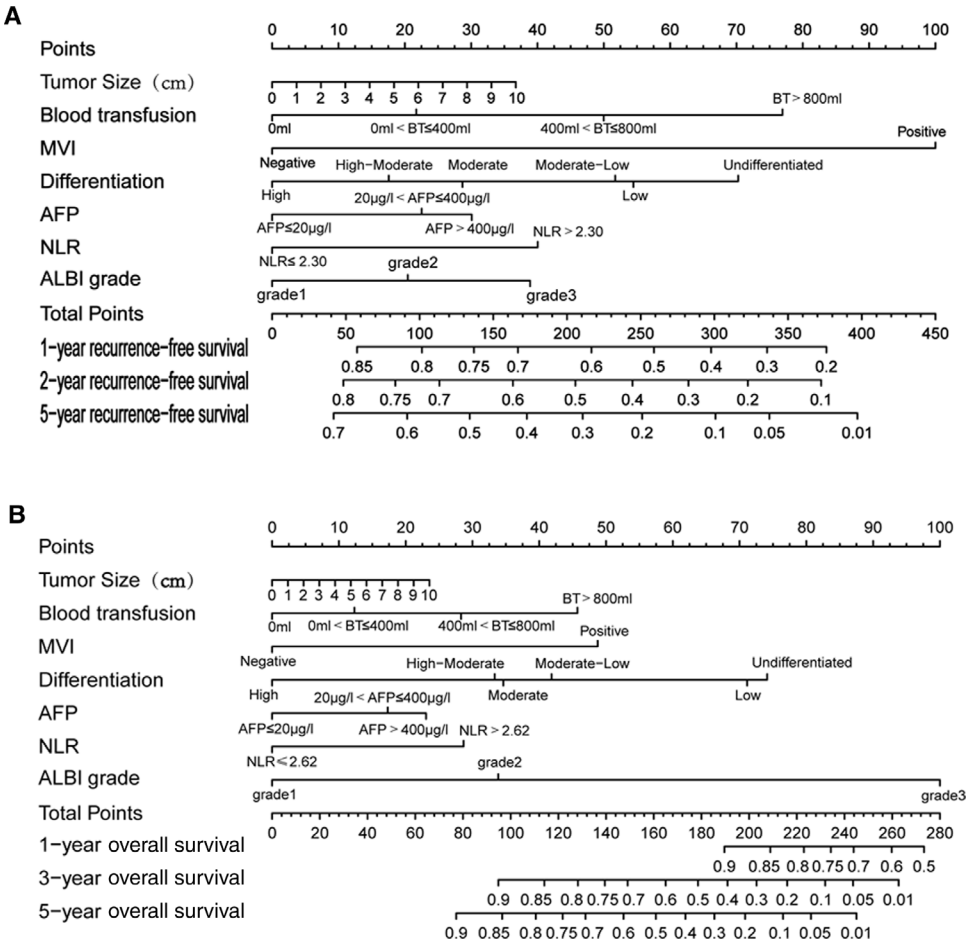

Figure 2. Prognostic nomograms for prediction of postoperative recurrence-free survival (RFS) and overall survival (OS) for hepatitis B virus-related solitary early hepatocellular carcinoma ≤10 cm after curative liver resection. **(A):** RFS predictive nomogram. **(B):** OS predictive nomogram. To use the nomogram, the value of an individual patient is located on each variable axis, and a line is drawn upward to determine the number of points received for each variable value. The sum of these numbers that is the total score of the patient is located on the Total Points axis, and a line is drawn downward to the survival axes to determine the probabilities of survival rate.

Abbreviations: AFP, α-fetoprotein; ALBI grade, albumin-to-bilirubin ratio; BT, blood transfusion; MVI, microscopic vascular invasion; NLR, neutrophil-to-lymphocyte ratio.

analyzing the ROC curves. Values of $p < .05$ were considered statistically significant.

Results

Baseline Characteristics of Patients

This multicenter study recruited 1,904 patients in total with a median age of 52.0 (IQR, 43.0–60.0) years. Among them, 86.1% (1,639/1,094) were male. Microscopic vascular invasion (MVI) occurred in 24.5% (466/1,904) of patients. Over 90% of patients received regular anti-HBV therapy postoperatively using nucleotide antiviral drugs. The clinicopathological data, including demographic factors, inflammatory factors, tumor factors and surgical factors of patients, in the derivation, internal validation, and external validation cohorts were summarized in Table 1. The variables among these three cohorts had no significant difference (all $p > .05$).

Construction of RFS and OS Predictive Nomograms

To identify the variables that were applied to build RFS and OS predictive nomograms, Cox univariable and multivariable regression analyses were performed in the derivation cohort ($n = 811$). Variables selected included age, sex, cirrhosis, antiviral therapy, preoperative alanine transaminase level, Child-Pugh score, ALBI grade, platelet count, NLR, PLR, tumor size, tumor capsule status, preoperative α-fetoprotein (AFP) level, tumor differentiation, MVI, type of resection, extent of resection, resection margin, intraoperative blood loss, and intraoperative blood transfusion (supplemental online Table 1). Significant risk factors ($p < .05$) identified by univariate analysis were entered into the Cox multivariate analysis. The results showed that tumor size, MVI, tumor differentiation, preoperative AFP level, NLR, ALBI grade, and intraoperative blood transfusion were independent risk factors associated with both RFS (Fig. 1A) and OS (Fig. 1B).

We used these seven variables to build a predictive RFS-nomogram (Fig. 2A) and OS-nomogram (Fig. 2B). The C-

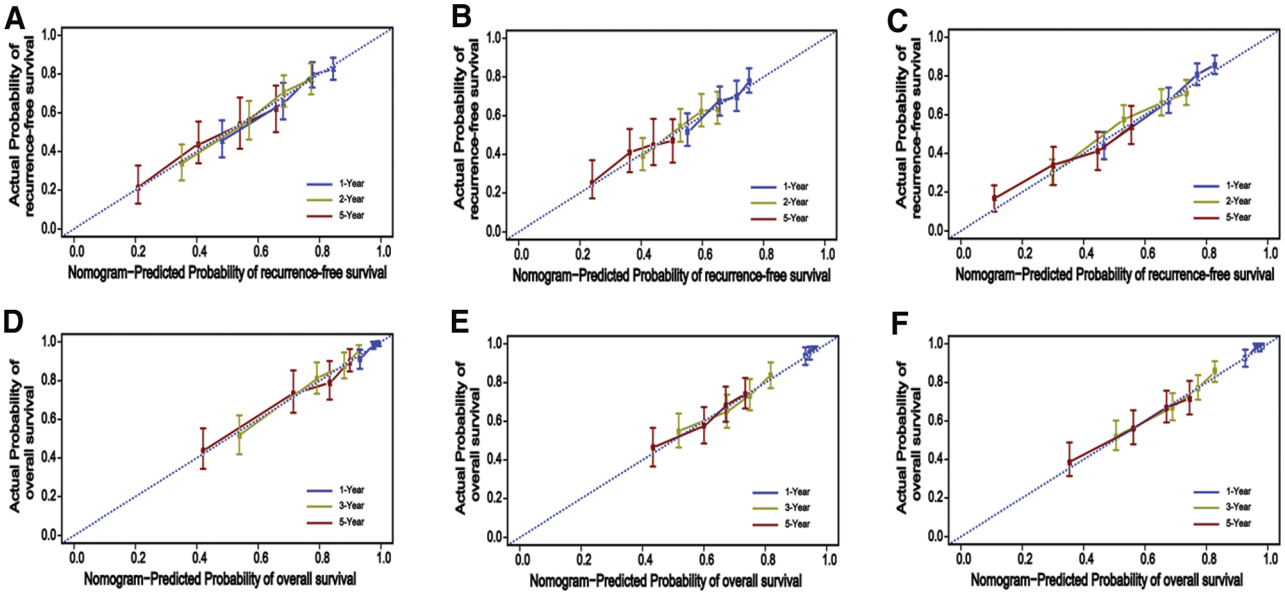

Figure 3. The calibration curves of postoperative recurrence-free survival (RFS) and overall survival (OS) based on nomogram prediction and actual observation in the derivation, internal validation, and external validation cohort. **(A):** The 1-, 2-, and 5-year RFS rates in the derivation cohort. **(B):** The 1-, 2-, and 5-year RFS rates in the internal validation cohort. **(C):** The 1-, 2-, and 5-year RFS rates in the external validation cohort. **(D):** The 1-, 3-, and 5-year OS rates in derivation cohort. **(E):** The 1-, 3-, and 5-year OS rates in the internal validation cohort. **(F):** The 1-, 3-, and 5-year OS rates in the external validation cohort.

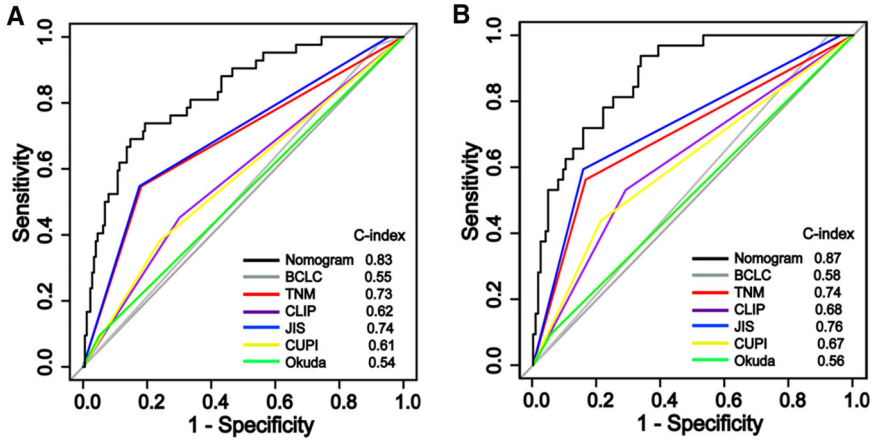

Figure 4. Comparison of predictive accuracy between nomograms and the six conventional hepatocellular carcinoma staging systems. **(A):** The RFS-nomogram. **(B):** The OS-nomogram.
Abbreviations: BCLC, Barcelona Clinic Liver Cancer staging system; CLIP, Cancer of the Liver Italian Program score; CUPI, Chinese University Prognostic Index; JIS, Japanese Integrated Staging; TNM, American Joint Committee on Cancer staging.

indices of the RFS-nomogram and OS-nomogram were 0.83 (95% confidence interval [CI], 0.79–0.87) and 0.87 (95% CI, 0.83–0.91), respectively. Calibration curves based on the seven variables are shown in Figure 3A and D. There was good agreement between actual and nomogram-predicted probabilities for 1-, 2-, and 5-year RFS and 1-, 3-, and 5-year OS, respectively, in the derivation cohort.

Internal and External Validation of Predictive Accuracy

To validate the accuracy of the predictive performance of the RFS-nomogram and OS-nomogram, the probabilities of outcomes were predicted for the internal validation cohort and the external validation cohort. In validation of the RFS-nomogram, the C-indices for the internal validation cohort and the external cohort were 0.80 (95% CI, 0.75–0.83) and 0.85 (95% CI, 0.82–0.87), respectively. Calibration plots showed good agreement of actual and nomogram-predicted probabilities for 1-, 2- and 5-year RFS in the internal (Fig. 3B) and external cohort (Fig. 3C), respectively. In validation of the OS-nomogram, the C-indices for the internal validation cohort and external cohort were 0.85 (95% CI, 0.81–0.89) and 0.89 (95% CI, 0.85–0.92), respectively. Calibration plots also showed good agreement of actual and nomogram-predicted probabilities for 1-, 3- and 5-year OS in the internal validation cohort (Fig. 3E) and external cohort (Fig. 3F), respectively.

Table 2. Typical postsurgical outcome-predictive nomograms for HCC reported in recent literature

Author, year	Region	Patients, n[a]	Patient criteria	Variables recruited in nomogram				C-index	External validation
				Tumor factor	Liver/patient factor	Inflammatory factor	Surgical factor		
Cho [28] 2008	U.S.	184	BCLC 0-C	Size, satellites, AFP, vascular invasion	Age	No	Margin, estimated blood loss	0.67 (RFS) 0.74 (OS)	No
Shim [29] 2015	Korea	760	BCLC 0-B	Tumor volume, MVI	Age, platelet, albumin	No	No	0.69 (RFS) 0.66 (OS)	No
Li [30] 2015	China	310	≥10 cm, single or multiple, or with PVTT	Size, number, differentiation, vascular invasion, capsule	HBV-DNA level	No	No	0.78 (OS)	Yes, single center
Yang [31] 2016	China	540	Multiple HCC	Size, number, MVI, capsule, local invasion, AFP	HBV-DNA load, MELD score	No	Anatomic resection	0.80 (OS)	Yes, single center
Li [32] 2016	China	1,328	Within Milan criteria	Tumor number, size, capsule, AFP, MVI	HBeAg, HBV-DNA	No	Surgical margin	0.76 (RFS) 0.79 (OS)	Yes, single center
Shen [33] 2016	China	618	Single or multiple tumor, PVTT	Tumor number, size, PVTT, AFP, MVI	No	NLR	No	0.75 (RFS) 0.75 (OS)	No
Torzilli [34] 2016	Eastern & Western Network	2,046	BCLC 0-C	Number, size, macrovascular invasion	Cirrhosis, esophageal varices, total bilirubin	No	No	0.61 (RFS) 0.62 (OS)	No
Fu [35] 2017	China	734	BCLC 0-B	Size, number, MVI, AFP	GGT	No	No	0.65 (RFS) 0.7 (OS)	No
Ma [36] 2019	Hong Kong	291	Within Milan criteria	Number, MVI, AFP	Prothrombin time	No	Magnitude of hepatectomy	0.67 (RFS) 0.67 (OS)	No
Kim [37] 2019	Korea	420	HBV-related, BCLC 0-C	Number, PVTT, PIVK-II, satellites, hemorrhage	Albumin, ALP	No	Resection margin	0.71 (RFS) 0.82 (OS)	No
The present study	China	811	HBV-related, solitary, ≤10 cm, no PVTT	Size, MVI, AFP, differentiation	ALBI grade	NLR	Blood transfusion	0.83 (RFS) 0.87 (OS)	Yes, four centers

[a]Number of patients in the derivation cohort.

Abbreviations: AFP, α-fetoprotein; ALBI grade, albumin-to-bilirubin ratio; ALP, alkaline phosphatase; BCLC, Barcelona Clinic Liver Cancer staging system; GGT, γ-glutamyl transpeptidase; HBeAg, hepatitis B-virus E antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease; MVI, microscopic vascular invasion; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; PIVK-II, protein induced by Vitamin K absence-II; PVTT, portal venous tumor thrombus; RFS, recurrence-free survival.

Comparison of Predictive Powers of Nomograms with Conventional HCC Staging Systems and Other Nomograms Reported in Literature

We compared the predictive powers of the RFS-nomogram and OS-nomogram with six conventional HCC staging systems—BCLC, TNM, JIS, CLIP, CUPI, and Okuda—by ROC curve analysis. Our nomograms displayed better discriminatory powers in predicting postoperative RFS and OS in the derivation cohort than those competing models. For the RFS-nomogram, the C-index was 0.83 (95% CI, 0.79–0.87), substantially higher than those of BCLC, TNM, JIS, CLIP, CUPI, and Okuda (Fig. 4A; supplemental online Table 2). For the OS-nomogram, the C-index was 0.87 (95% CI, 0.83–0.91), significantly higher than those of BCLC, TNM, JIS, CLIP, CUPI, and Okuda (Fig. 4B; supplemental online Table 2). Furthermore, our proposed nomograms had the highest C-index for RFS and OS compared with those of prognostic nomograms for resectable HCC reported recently in the literature (Table 2).

The Nomogram Score Could Clearly Classify the Patients into Subgroups with Different Risk of Recurrence or Postoperative Mortality

Based on the RFS-nomogram's score, patients could be divided into low risk (score ≤ 100), intermediate risk (100.1–200), and high risk (>200) of recurrence. The 2-year RFS rates of the three subgroups from the derivation cohort could be markedly discriminated (Fig. 5A). Similar results were obtained from the internal validation cohort (Fig. 5B) and the external validation cohort (Fig. 5C).

As to the OS-nomogram, patients could also be classified into low risk (score ≤ 75), intermediate risk (75.1–150), and high risk (>150) of postsurgical mortality. The 5-year OS rates of these three subgroups were 91.7%, 77.4%, and 52.0%, respectively, in the derivation cohort ($p < .001$; Fig. 5D). Similar results were observed in the internal validation cohort (Fig. 5E) and the external validation cohort (Fig. 5F).

Discussion

To date, the postsurgical prognostic model for HBV-related SE-HCC ≤10 cm is not established. In the present study, we constructed a RFS-nomogram and OS-nomogram to predict postoperative recurrence and OS for these patients based on seven conventional clinicopathological and surgical variables that are easily obtained, allowing for the nomograms to be conveniently used in the real clinical world. The nomograms showed excellent performance to predict postoperative RFS and OS for an individual who had undergone curative liver resection for HBV-related early HCC. Compared with the six conventional HCC staging systems, the two nomograms displayed better discriminatory power in prediction of outcomes.

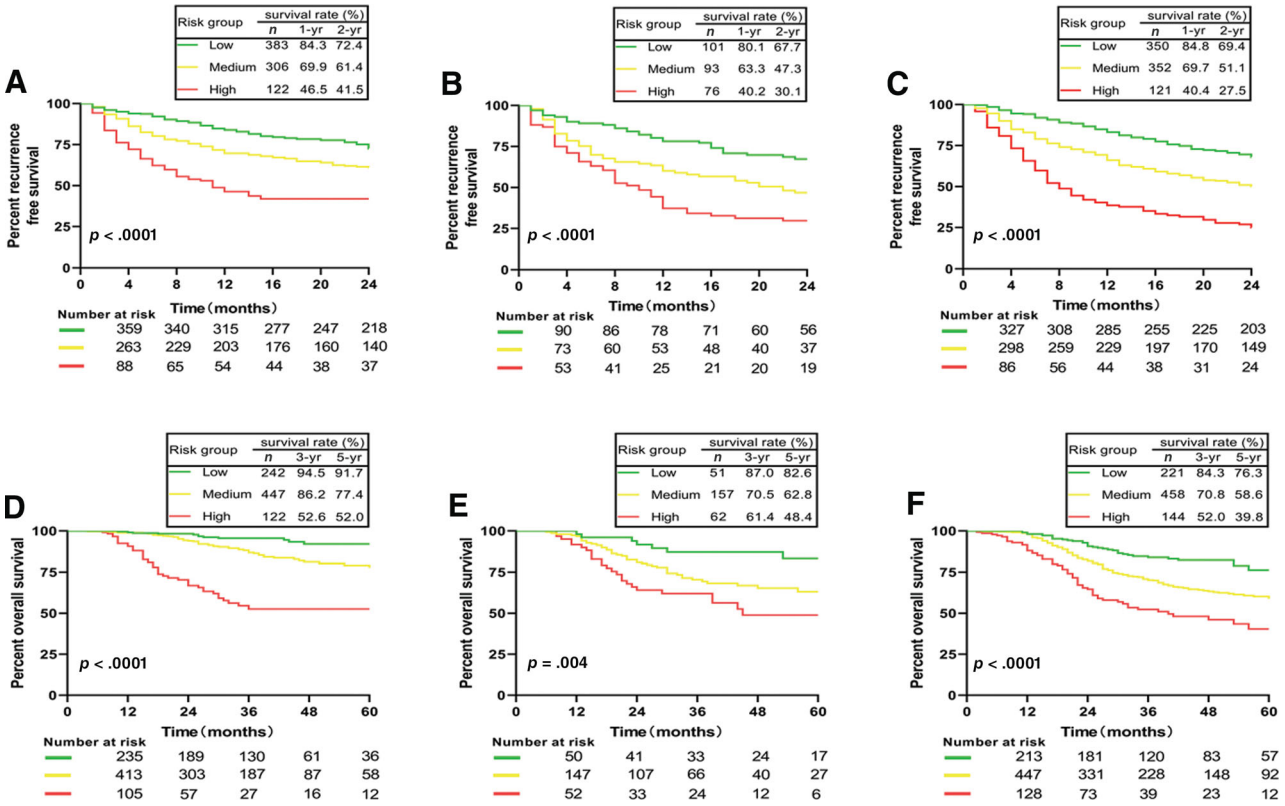

Figure 5. Survival curves for subgroup of patients with different risk of postsurgical recurrence or mortality stratified by nomogram score. **(A):** Recurrence-free survival (RFS) curves in derivation cohort. **(B):** RFS curves in the internal validation cohort. **(C):** RFS curves in the external validation cohort. **(D):** Overall survival (OS) curves in the derivation cohort. **(E):** OS curves in the internal validation cohort. **(F):** OS curves in the external validation cohort.

The postsurgical recurrence of HCC is multifactorial. The full coverage of survival-related risk factors may potentially increase the predictive accuracy of nomogram. Our nomograms were generated by seven significant risk variables that derived from tumor traits (tumor size, MVI, differentiation, AFP), underlying liver function (ALBI grade), patient's inflammatory factor (NLR), and surgical factors (intraoperative blood transfusion), thereby yielding higher C-indices compared with those previously published nomograms (Table 2).

Of the tumor clinicopathologic traits, tumor size, MVI, differentiation, and AFP were identified as independent risk factors associated with RFS and OS by multivariable Cox regression analysis (Fig. 1). These factors are well-known potential risk factors related to postsurgical recurrence of HCC and affect long-term survival of the patient [5, 38–41]. Tumor size is a critical survival predictor for HCC [5, 38]. Current staging systems do not depict this stepwise increment with respect to tumor size. Notably, we did not categorize the tumor size by a cutoff value (i.e., 5 cm) but used the continuous increment of a 1-cm interval in our nomograms. This could make the nomogram's score for each patient more accurate. Another pivotal prognostic factor for HCC is MVI [39, 41]. In the derivation cohort of the present study, the recurrent risk of patient with MVI was 2.5-fold higher than that without MVI (Fig. 1A). As shown in the RFS-nomogram, MVI was the prominent factor contributing to recurrence (Fig. 2A). The occurrence of MVI ranged from 15% to 57.1% [41]. It was 24.5% in the present cohort of 1,904 patients (Table 1). There is a positive relationship between tumor size and the likelihood of MVI [5, 41].

The patient's inflammatory or immune status is one of the critical factors contributing to tumor recurrence [42]. Peripheral blood NLR is a simple index reflecting the systemic inflammation status of the tumor host [43, 44]. Numerous pieces of evidence show that high level of the NLR is a risk factor of HCC recurrence after curative resection [45, 46]. Therefore, inclusion of NLR might improve the predictive performance of a nomogram for HCC.

The two nomograms contained one liver function variable: ALBI grade. The ALBI grade was equally applicable in patients with HCC with underlying HBV-related or HCV-related cirrhosis or without cirrhosis and gave clear discrimination of survival in each grade [47]. In the Cox univariable analysis, the Child-Pugh score was a risk factor that affected OS (supplemental online Table 1); however, in multivariable analysis, it was ALBI grade but not Child-Pugh score that was the risk factor associated with RFS and OS (Fig. 1). Therefore, the ALBI grade was more reliable than the Child-Pugh score in the outcome prediction for HCC patients.

Intraoperative blood transfusion was the only surgical variable entered in the models. Surgical factors are lacking in the currently available HCC staging systems. Many studies showed that intraoperative blood transfusion was a risk factor that negatively influenced long-term survival of patients with HCC after curative liver resection [48, 49]. In the Cox

multivariable analysis, we demonstrated that intraoperative blood transfusion was a significant risk factor associated with both RFS and OS in patients with SE-HCC ≤10 cm (Fig. 1). Liver resection for HCC carries a high risk of intraoperative bleeding because of underlying cirrhosis. In the U.S., the nationwide blood transfusion rate in HCC resections performed from 2005 to 2007 was 28.7% [50]. The blood transfusion rates were 22.3%, 20.4%, and 20.9% in the derivation cohort, internal validation cohort, and external cohort, respectively (Table 1). Reducing intraoperative blood transfusion by minimizing intraoperative blood loss may improve outcomes of patients with HCC.

The two nomograms were validated by an internal validation cohort of separate patients from our center and the external validation cohort of patients from another four tertiary hospitals in different geographic areas in mainland China. The C-indices were 0.80 and 0.85 of the two validation cohorts for predicting RFS and were 0.85 and 0.89 for predicting OS. The calibration plots showed good agreement of actual and nomogram-predicted probabilities for RFS and OS in the internal validation cohort and external validation cohort, respectively (Fig. 3). To date, most of the reported nomograms for HCC lack external validation, especially multicenter validation (Table 2). Our multicenter external validation data showed that the proposed nomograms display good predictive performance for patients from different areas of China. Thus, they are suitable for national application in actual clinical practice.

The proposed nomograms could clearly divide patients into three subgroups with different risk of recurrence or mortality (Fig. 5). Thus, it may help surgeons to adopt close surveillance protocol and design postoperative therapeutic clinical trials for those with high risk of recurrence.

There are some limitations of this study. First, only patients with HBV-related HCC were recruited in this study. Whether the nomograms can be used for those with non–HBV-related HCC needs further validation. Second, the nomograms were generated to predict postoperative RFS and OS based on the data of patients with SE-HCC ≤10 cm undergoing curative liver resection; they may not be suitable for those with intermediate or advanced stage HCC after hepatectomy or those with early stage HCC receiving nonsurgical treatment. Third, this is a retrospective study. Patient selection bias was unavoidable.

Conclusion

We generated two conveniently available nomograms that could accurately and objectively predict postoperative recurrence and OS for patients with HBV-related SE-HCC ≤10 cm after curative liver resection. We could discriminate patients from different risk of recurrence by the nomogram's score. A close surveillance protocol and postsurgical adjuvant therapy is considered for those patients with high risk of recurrence.

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Disclosures

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