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A nomogram to predict early postoperative recurrence of hepatocellular carcinoma with portal vein tumour thrombus after R0 liver resection: A large-scale, multicenter study

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ABSTRACT

Background: Portal vein tumour thrombus (PVTT) is a significant poor prognostic factor for hepatocellular carcinoma (HCC). Patients with PVTT limited to a first-order branch or above of the main portal vein (MPV) could benefit from R0 liver resection (LR). A nomogram is needed to predict early postoperative recurrence (ER) in HCC patients with PVTT and to guide selection of these patients for adjuvant therapy to reduce postoperative recurrence risks.

Methods: HCC patients with PVTT limited to a first-order branch or above of the MPV after R0 LR as an initial therapy were included. A nomogram using data from a retrospective training cohort was developed with the Cox regression model. The model was tested in a prospective internal validation cohort and three external validation cohorts.

Results: Of 979 patients, 657 developed postoperative ER (67.1%). ER occurred in 165 of 264 patients (62.5%) in the training cohort, 146 of 218 patients (70.0%) in the internal validation cohort, and 204 of 284 patients (71.8%), 77 of 113 patients (68.1%), and 65 of 100 patients (65%) in the three external validation cohorts, respectively. The nomogram included the following variables: hepatitis B surface antigen (HBsAg), PVTT, HBV DNA, satellite nodules, α-fetoprotein, and tumour diameter. The ROC were 0.836, 0.763, 0.802, 0.837, and 0.846 in predicting ER in the five respective cohorts.

Conclusion: A nomogram was developed and validated to predict postoperative ER in patients with HCC with PVTT after R0 LR. This nomogram could select appropriate patients with high ER risks for postoperative adjuvant therapy.

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the third leading cause of cancer death in the world [1]. HCC often invades portal venous branches, and the incidence of portal vein tumour thrombus (PVTT) has been reported in 44–62.2% of patients with HCC [2,3]. PVTT is a poor prognostic factor for HCC patients [2–5]. If left untreated, the median survival time (MST) in

Abbreviations: HCC, hepatocellular carcinoma; PVTT, portal vein tumour thrombus; LR, liver resection; ER, early recurrence..

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patients with HCC associated with PVTT ranged from 2.7 to 4.0 months [6]. Although the BCLC staging system recommends sorafenib as the standard therapy for patients with HCC associated with PVTT, several studies have demonstrated that in selected patients, R0 liver resection (LR) resulted in better long-term survival outcomes than non-surgical treatments, especially in patients with PVTT limited to a first-order branch or above of the main portal vein (MPV) [7–11]. Recent advances in surgical techniques and perioperative management have also made R0 LR safe.

The long-term overall survival (OS) after LR for patients with resectable HCC remains poor, with high postoperative recurrence rates of around 60–70% within five years of surgery [12–14]. Patients with HCC associated with PVTT are especially prone to develop early recurrence (ER) after liver resection [15–17]. Postoperative adjuvant therapy, such as transcatheter arterial chemoembolization (TACE) and radiotherapy (RT), have been reported to reduce the risks of ER and to improve the long-term OS outcomes in these patients[18]. Thus, there is a need to identify the subgroup of patients with HCC associated with PVTT after R0 LR to undergo adjuvant therapy.

Postoperative HCC recurrences have been divided into early and late recurrences. Many studies [19, 20], like in our study, defined ER as HCC recurrence within 1 year of surgery. While early HCC recurrences are likely to originate from intrahepatic metastases of the initial tumours, late recurrent tumours are more likely to develop from de novo primary HCC in the remnant liver [21–23]. ER has poorer long-term OS outcomes than late tumour recurrence [20, 24]. ER [22,25,26] and PVTT [27,28] are known poor prognostic factors for patients with HCC after LR. A specific and reliable nomogram needs to be developed for these patients with high risks of ER to undergo postoperative adjuvant therapy, such as TACE, radiotherapy, and sorafenib.

In this study, such a nomogram was established using a retrospective internal cohort and validated using a prospective internal validation and three external validation cohorts, with the aim to identify patients who are likely to benefit from postoperative adjuvant therapies with improvements in long-term survival outcomes.

Materials and methods

Study population

The training cohort was conducted retrospectively at the Eastern Hepatobiliary Surgery Hospital (EHBH) from January 2006 to December 2009. The internal validation cohort was conducted prospectively at the same hospital from January 2011 to December 2013. The three external validation cohorts were conducted prospectively at the Affiliated Tumour Hospital of Guangxi Medical University (ATHGMU) from 2013 to 2017, the Sun Yat-sen University Cancer Centre (SYUCC) from 2013 to 2016, and the West China Hospital (WCHSCU) from 2014 to 2016. The study was approved by the Institutional Ethics Committees of the four respective hospitals. All included patient identities were anonymized before analysis. Therefore, the requirement for informed consent was waived.

The diagnostic criteria for patients with HCC associated with PVTT was the same in the four hospitals: PVTT was diagnosed using both imaging examinations (ultrasound, CT and MRI) and intraoperative and postoperative histopathology[29]. Based on the Cheng's classification[30], PVTT was divided into 4 types according to the extent of PVTT in the portal vein: Type I, tumour thrombus in the segmental branches of the portal vein or above; Type II, tumour thrombus extending to the right or the left portal vein; Type III, tumour thrombus extending to the main portal vein (MPV); and Type IV, tumour thrombus extending to the superior mesenteric vein. Type I and II PVTT were defined as PVTT limited to a first-order branch or above of the MPV.

In all these patients, the clinicopathological factors including age, gender (male or female), serum hepatitis B surface antigen (HBsAg) status (positive or negative), cirrhosis (present or absent), AFP level ($\leq$400 or >400 μg/l), hepatitis B virus (HBV)-DNA ($\leq$4 or >4 log IU/ml), lymph node metastases (yes or no), tumour encapsulation (no, incomplete, or complete), capsular invasion (yes or no), satellite nodules (yes or no), and PVTT (type I and II), were prospectively collected.

Inclusion and exclusion criteria

The same inclusion and exclusion criteria were used for all the five cohorts of patients in this study. The inclusion criteria were [1]: HCC with type I and type II PVTT diagnosed by the criteria as mentioned above [2]; HCC with PVTT treated with R0 LR with Child–Pugh class A or selected B liver function (score $\leq$7) [3]; postoperative HCC recurrence [4]; absence of macroscopic hepatic vein tumour thrombus, macroscopic bile duct tumour thrombus, extrahepatic spread or distant metastases; and [5] no history of any other anti-cancer treatments. The exclusion criteria were [1]: Child–Pugh class C liver function [2]; palliative tumour resection; or [3] incomplete data.

The results obtained from the training cohort were then validated in an independent internal validation and three external validation cohorts.

Surgical procedures

The surgical procedures have been described in a previous report[31]. Only HCC patients with Cheng's type I or II PVTT with Child–Pugh A or selected B liver function (score $\leq$7) were offered R0 LR[32–34]. Surgery was performed through a right subcostal incision with a midline extension. During surgery, we carefully searched the abdominal cavity for extent of local disease, extrahepatic metastases, and peritoneal seeding. After mobilization of the liver, intraoperative ultrasound was performed to assess the number, size of the lesions, and to assess the relation of the tumour to vascular structures. Pringle maneuver was applied to occlude the blood inflow of the liver. Anatomic hepatectomy was carried out by a clamp crushing method. Thrombectomy was performed according to the location and extent of PVTT. For patients with type I or II PVTT located within the resected area, the PVTT was resected en bloc with the tumour. After flushing with normal saline and confirming that no PVTT remained, the stump was closed by a continuous suture.

Follow-up

In addition to history-taking and physical examinations, follow-ups were conducted using laboratory tests, abdominal ultrasonography, and contrast-enhanced CT or MRI. Patients who underwent R0 LR were followed-up once every 2–3 months until death or dropout from the follow-up program. Once HCC recurrence was confirmed, based on the combined results of clinical, laboratory and/or radiological examinations, patients were treated with re-resection, radiofrequency ablation (RFA) or percutaneous ethanol injection (PEI) when the recurrence was localized, or with transcatheter arterial chemoembolization (TACE) or sorafenib when the recurrence had spread intrahepatically or systemically. A diagnosis of HCC recurrence or metastasis was based on computed tomography and/or magnetic resonance imaging with or without a raised serum α-fetoprotein (AFP) level. HCC recurrence was defined as a new lesion in the remnant liver or distant metastasis with typical

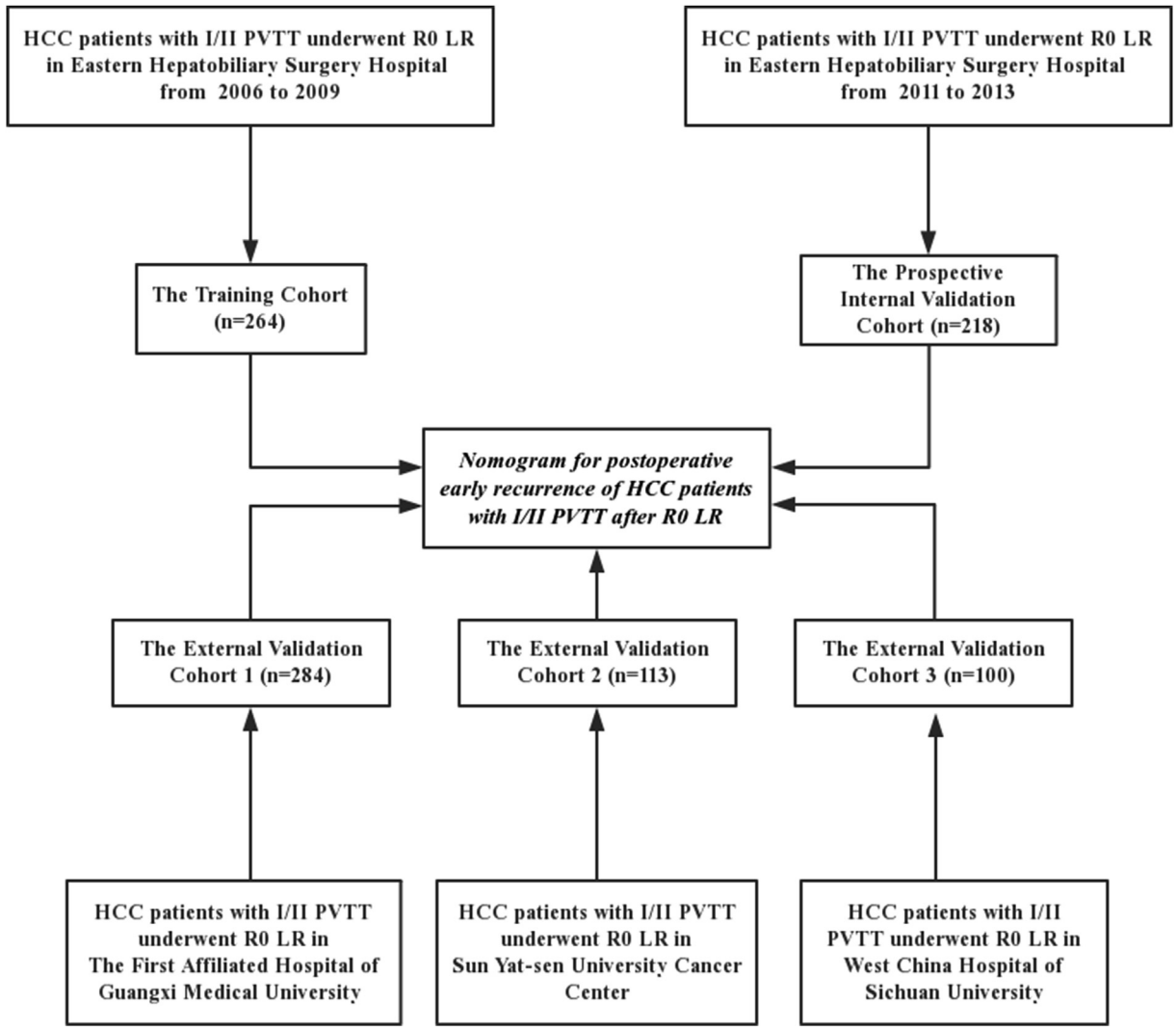

Fig. 1. Flow chart showing the process of selection of recurrent HCC patients with PVTT who underwent LR in the training cohort (n = 264), the prospective internal validation cohort (n = 218), and the three external validation cohorts (n = 284, 113, and 100).

imaging appearances. In our study, HCC recurrences were further divided into early or late recurrences by using 1 year from surgery as the cut-off point.

Statistical analysis

Early recurrence was defined from the date of surgery to the date HCC recurrence was first diagnosed which was within one year of surgery. Continuous variables were reported as means and standard deviations or as medians and interquartile ranges (IQR). Appropriate statistical tests (the independent samples *t*-test or the Mann-Whitney *U* test) were used. Categorical data were reported as counts and percentages and compared using the chi-squared test or the Kruskal-Wallis test. Correlations between clinicopathological parameters and early recurrence in patients with HCC associated with PVTT were done using the chi-square or the Fisher's exact test. Univariate and multivariate logistic regression methods were used to determine the independent risk factors related to early recurrence in patients with HCC associated with PVTT in the training cohort. Variables significantly related to survival in the univariate logistic regression models ($p < .05$) were subsequently included in the multivariate model. The nomogram is based on proportionally converting each regression coefficient in multivariate logistic regression to a 0- to 100-point scale. The effect of the variable with the highest β coefficient (absolute value) is assigned 100 points. The points are added across independent variables to derive total points, which are converted to predicted probabilities. A nomogram was finally constructed to predict early recurrence in the patients in the training cohort. Validation of the model performance was done in the internal and external cohorts. The calibration curves and ROC curves were constructed to estimate the value of the nomogram in the training cohort, the prospective internal validation cohort and the three external validation cohorts.

For clinical use of the model, the total scores of each patient were calculated based on the nomogram. Receiver operating characteristic curve analysis was used to calculate the optimal cut off values that were determined by maximizing the Youden index (sensitivity + specificity - 1). Accuracy of the optimal cut off value was assessed by the sensitivity, specificity, predictive values, and likelihood ratios. P values less than 0.05 were considered statistically significant. All tests were two-tailed. The main R packages of “readxl”, "glm", "rms" and “pROC” were sourced in our study (R version 3.4.2; R Foundation for Statistical Computing, Vienna, Austria).

Table 1
The Clinical pathological Characteristics in HCC patients with PVTT in the Training and Validation cohorts (n = 979).

Clinical Variables	Training Cohort (n = 264)	Prospective Internal Validation Cohort (n = 218)	External Validation Cohort 1 (n = 284)	External Validation Cohort 2 (n = 113)	External Validation Cohort 3 (n = 100)
Age, year	48.24(±9.97)	48.93(±10.00)	48.60 (±9.88)	48.60(±9.97)	50.17(±11.91)
Sex					
male	231(87.5%)	204(93.57%)	262(92.25%)	102(90.26%)	90(90.00%)
female	33(12.5%)	14(6.42%)	22(7.74%)	11(9.73%)	10(10.00%)
HBsAg, positive	234(88.63%)	154(70.64%)	200(70.42%)	99(87.61%)	93(93.00%)
Liver Cirrhosis, Yes	117(44.31%)	161(73.85%)	209(73.59%)	51(45.13%)	94(94.00%)
HBV DNA, $>10^4$ IU/ml	117(44.31%)	100(45.87%)	131(46.12%)	51(45.13%)	41(41.00%)
Lymph node invasion, Yes	40(15.15%)	14(6.42%)	20(7.04%)	17(15.04%)	4(4.00%)
Satellite nodules, Yes	99(37.5%)	105(48.16%)	131(46.12%)	44(38.93%)	50(50.00%)
Tumour encapsulation					
No	165(62.5%)	138(63.30%)	184(64.78%)	77(68.14%)	63(63.00%)
Incomplete	42(15.90%)	28(12.84%)	37(13.02%)	16(14.15%)	11(11.00%)
Complete	57(21.59%)	52(23.85%)	63(22.18%)	20(17.69%)	26(26.00%)
Tumour number					
Single	96(36.36%)	204(93.57%)	265(93.30%)	37(32.74%)	46(46.00%)
Multiple	168(63.63%)	14(6.42%)	19(6.69%)	76(67.25%)	54(54.00%)
Ascites, Yes	21(7.95%)	9(4.12%)	10(3.52%)	8(7.07%)	17(17.00%)
AFP					
<400 ng/ml	84(31.81%)	85(38.99%)	104(36.61%)	34(30.08%)	33(33.00%)
>400 ng/ml	180(68.18%)	133(61.00%)	180(63.38%)	79(69.91%)	67(67.00%)
PVTT					
Type I	99(37.5%)	69(31.65%)	91(32.04%)	39(34.51%)	30(30.00%)
Type II	165(62.5%)	149(68.34%)	193(67.95%)	74(65.48%)	70(70.00%)
Tumour size, cm	9.35(6.90–11.00)	8.88(6.10–11.10)	9.00(6.30–11.28)	9.40(7.00–11.00)	8.65(5.95–11.10)
PT, s	12.20(11.40–12.90)	12.20(11.50–13.00)	12.20(11.60–13.00)	12.10(11.40–12.90)	12.40(11.75–13.30)
TB, μmol/L	15.40(11.30–20.10)	14.00(11.00–18.00)	14.00(11.00–18.00)	15.50(11.40–19.80)	13.40(10.40–17.95)
ALB, g/l	42.40(38.20–44.05)	42.00(38.00–44.00)	42.00(38.95–44.00)	42.30(39.40–44.40)	41.90(39.00–45.00)

Abbreviation: HBsAgHepatitis B surface antigen; PVTT: Portal vein tumour thrombus; AFP: α-fetoprotein; PT: Prothrombin time; TB: Total Bilirubin; ALB: Albumin.

Results

Patient characteristics

264 patients underwent R0 LR from January 2006 to December 2009 at the EHBH for HCC associated with Cheng's type I and II PVTT (Fig. 1). They were assigned to the training cohort. An independent cohort of consecutive patients with HCC associated with Cheng's type I and II PVTT underwent R0 LR from January 2011 to December 2013 as an initial therapy was prospectively studied at the EHBH. These patients formed the internal validation cohort. There were three external validation cohorts. The external validation cohort 1 consisted of 284 patients operated at the ATHGMU between 2013 and 2017. The external validation cohort 2 consisted of 113 patients operated at the SYUCC between 2013 and 2016. The external validation cohort 3 consisted of 100 patients operated at the WCHSCU between 2014 and 2016.

The clinical and pathological characteristics of the patients in the training cohort, the prospective internal validation cohort, and the prospective external validation cohorts 1, 2 and 3 are summarized in Table 1. And the details of recurrence in five cohorts were summarized in Table S1.

Relationship between the clinicopathological characteristics and ER in the patients with HCC associated with PVTT.

The baseline characteristics of the training cohort, the prospective internal validation cohort and the three external validation cohorts are shown in Table 2-6. Some of the baseline clinicopathologic data were similar, but some variables, including the level of HBV DNA, the level of AFP, and the type of PVTT were significantly different between the ER group and the non-ER group in the five cohorts. All the patients had compensated liver functions. Most patients were male and had large tumours (>5 cm), and HBV was the most common aetiological cause of HCC.

Identification of independent prognostic factors in the training cohort

In the training cohort, 16 clinical basic indicators were included in the univariate regression analysis for ER which showed sex, type of PVTT, HBV DNA, tumour encapsulation, AFP, and tumour size to be associated with ER (Table S7). Multivariate logistic analysis showed HBsAg, type of PVTT, HBV DNA, satellite nodules, AFP, and tumour size to be independent risk factors of ER (Table 2).

Development of the postoperative ER-Predicting nomogram

A nomogram was developed to predict ER for patients with HCC associated with PVTT after LR based on the significant prognostic

Table 2
Multivariate logistic analyses on clinical variables in predicting early recurrence in the training cohort.

Clinical Variables	β	OR	95% CI	P
HBsAg, positive vs negative	1.292	3.641	(1.020–12.980)	<.001
PVTT, type II vs type I	2.261	9.592	(3.126–29.430)	0.047
HBV DNA, $>10^4$ vs $\leq 10^4$ IU/ml	2.747	15.587	(5.292–45.910)	<.001
Satellite nodules, yes vs no	1.639	5.147	(1.905–13.900)	<.001
AFP, >400 vs ≤ 400 ng/ml	3.981	53.581	(13.930–206.000)	<.001
Tumour size, cm	0.376	1.457	(1.243–1.707)	<.001

Abbreviation: HBsAgHepatitis B surface antigen; PVTT: Portal vein tumour thrombus; AFP: α-fetoprotein.

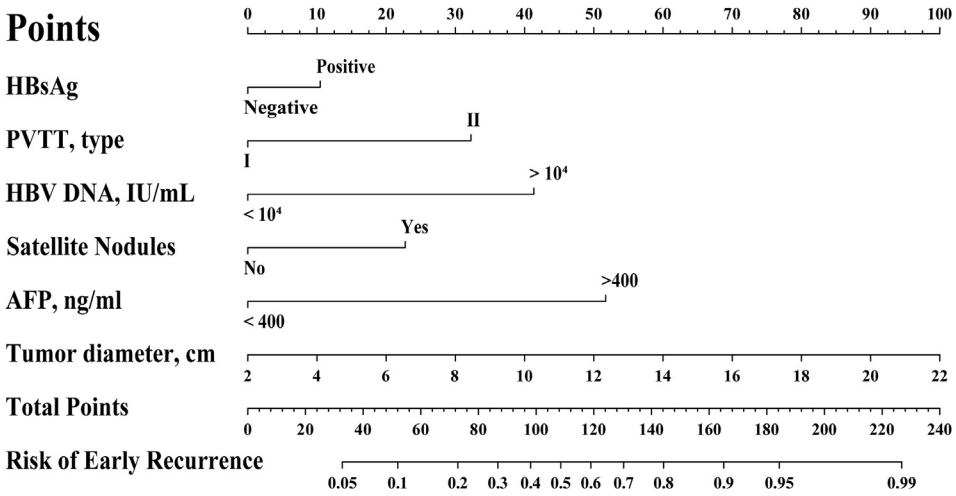

Fig. 2. Nomogram for predicting ER in HCC patients with PVTT who underwent LR.

factors identified in the Cox model (Fig. 2). The nomogram assesses the probability of ER by summing the scores on the point scales for the variables. The tumour diameter had the highest score (100 points). The scores for the other variables were: HBsAg (10 points), HBsAg positivity (32 points), HBV DNA level (42 points), satellite nodules (23 points), and AFP level (52 points).

Validation of the prognostic nomogram

The C-indexes for ER prediction were 0.836 (0.784–0.887) and 0.763 (0.694–0.832) for the training and the prospective internal validation cohorts, respectively (Fig. 3). The receiver operating characteristic (ROC) analyses for the training and the prospective internal validation cohorts showed similar results to those obtained in the calibration curves.

The C-indexes for ER prediction were 0.802 (0.742–0.861), 0.837 (0.753–0.921), and 0.846 (0.767–0.926) for the external validation cohorts 1, 2, and 3, respectively (Fig. 4). The ROC analyses for the three external validation cohorts showed similar results to those obtained in the calibration curves.

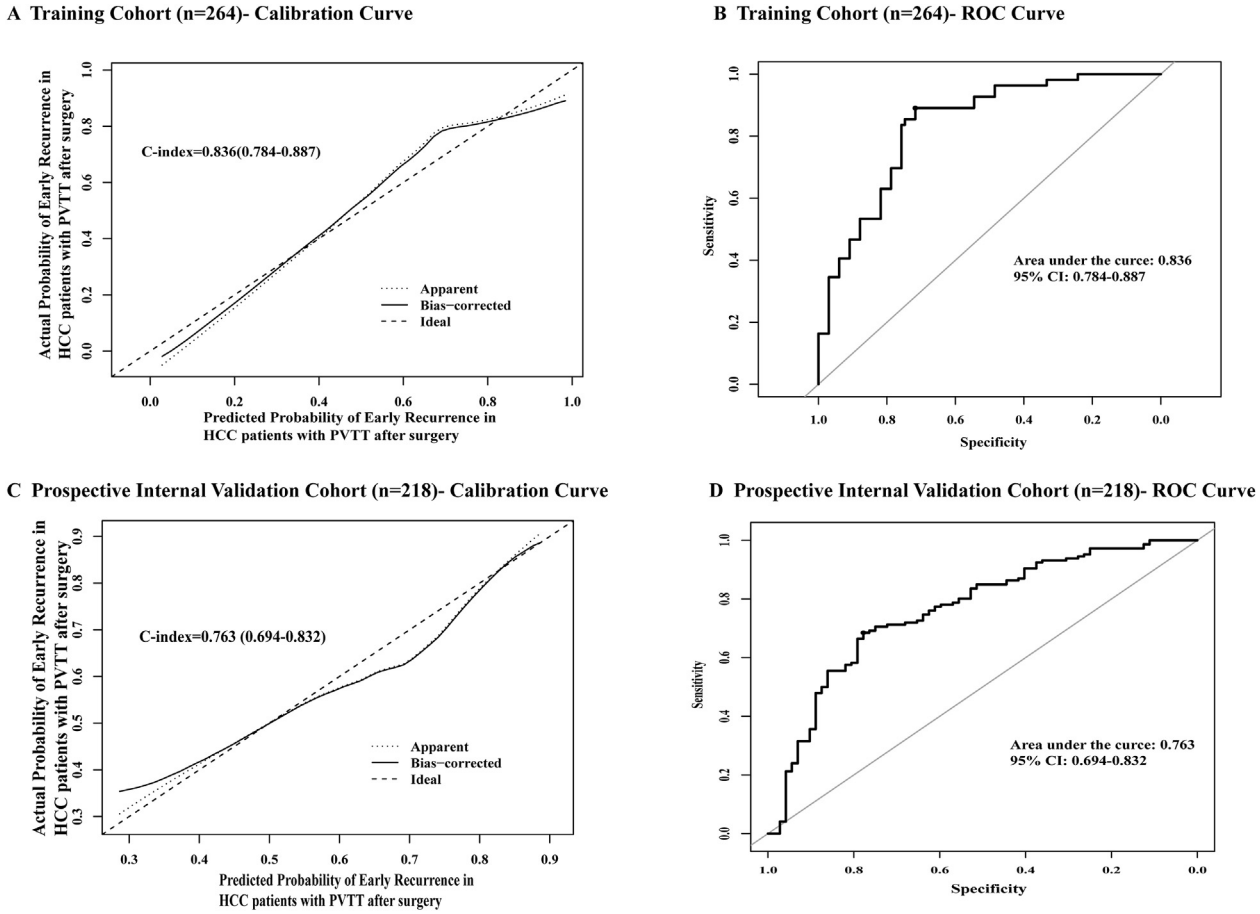

Fig. 3. Calibration and ROC curves for predicting ER in HCC patients with PVTT who underwent LR in the training (A and B) and prospective internal validation (C and D) cohorts.

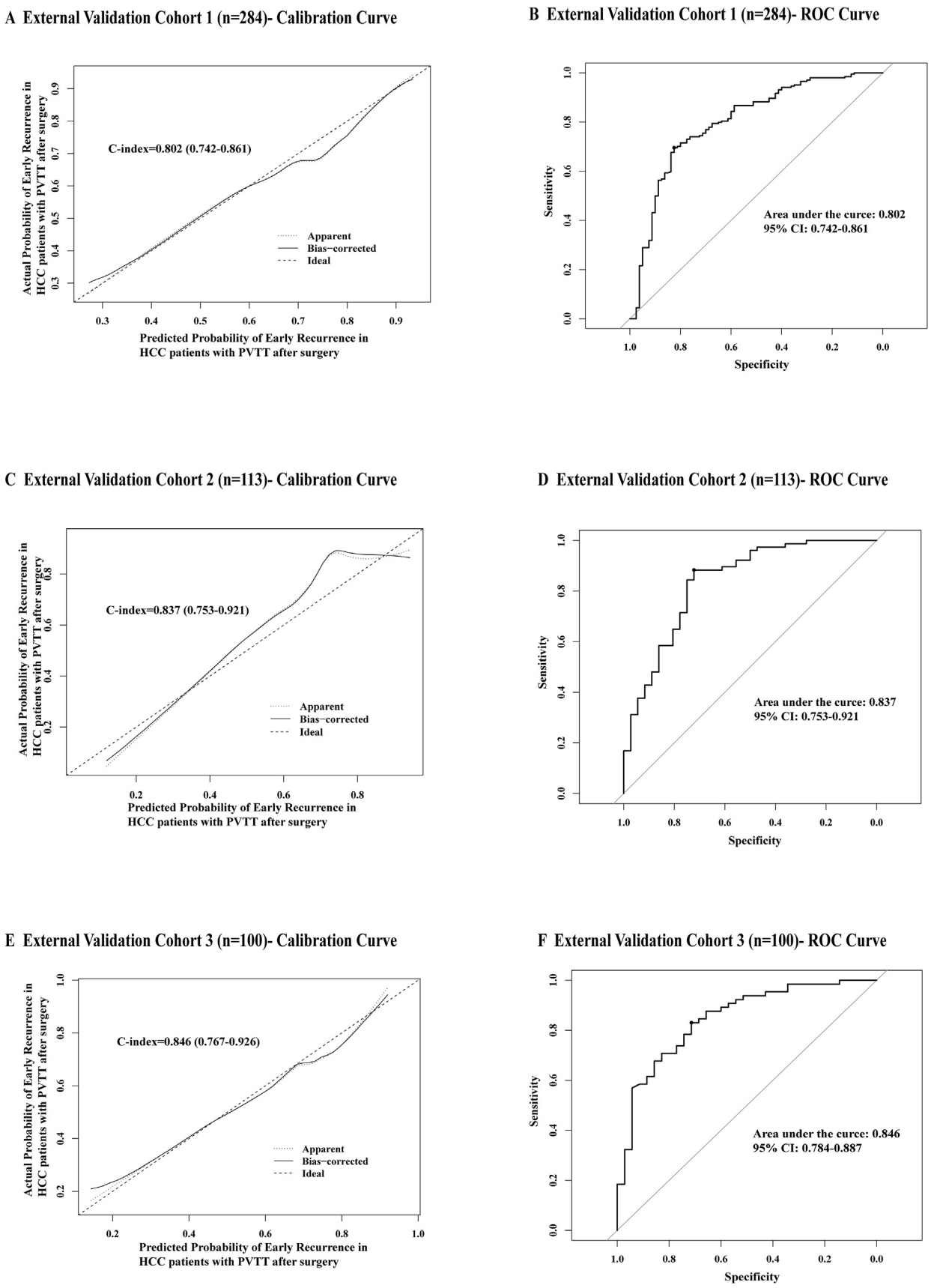

Fig. 4. Calibration and ROC curves for predicting ER in HCC patients with PVTT who underwent LR in external validation cohort 1 (A and B), external validation cohort 2 (C and D), and external validation cohort 3 (E and F).

Risk of postoperative ER based on the nomogram scores

The optimal cut-off value of the total nomogram score was 108. The sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio in differentiating between the presence and absence of ER were 0.891, 0.717, 3.148, and 0.152 in the training cohort; 0.685, 0.778, 3.086, and 0.405 in the prospective internal validation cohort; 0.696, 0.825, 3.977, and 0.368 in the external validation cohort 1; 0.883, 0.722, 3.176, and 0.162 in the external validation cohort 2; and 0.831, 0.714, 2.906, and 0.237 in the external validation cohort 3, respectively (Table S8).

Discussion

PVTT is one of the most significant poor prognostic factors of long-term survival outcomes for patients with HCC[16, 35]. Although many therapeutic modalities have been proposed to treat these patients, the treatment effectiveness remains poor. With advances in surgical technique, R0 LR for patients with HCC associated with PVTT limited to a first-order branch or above of the MPV (type I and II PVTT) becomes safe[16]. However, the postoperative long-term survival outcomes of these patients are poor because of high HCC recurrence rates, especially for ER within 1 year of surgery [39].

To our knowledge, this study is the first to report and validate a nomogram based on data from multiple liver centres to predict postoperative ER in patients with HCC associated with PVTT treated with R0 LR. The detection of patients with high risks of developing ER would allow studies using adjuvant therapy to be carried out on these patients.

Early HCC recurrence is usually associated with intrahepatic metastases of cells in the portal vein, especially in patients with PVTT[36]. Patients with ER of HCC had significantly poorer survival outcomes than those with late recurrence[20]. There is still no scoring system in predicting postoperative ER in HCC patients with PVTT after R0 LR.

This study showed ER to be significantly associated with HBsAg positivity, type of PVTT, HBV DNA load, satellite nodules, AFP level, and tumour diameter. All these data are commonly and easily available in clinical practice. Previous studies[37, 38] have supported our findings that HBsAg positivity predicted recurrence after LR and radiofrequency ablation in patients with hepatitis B virus related HCC; a high HBV DNA load was an independent risk factor of microvascular invasion and early tumour recurrence after partial hepatectomy for HBV-related HCC [39]; PVTT and satellite nodules were related to postoperative ER [4,15]; serum AFP was a significant prognostic factor of RFS and OS in HCC patients [40], and a longer tumour diameter was associated with ER [3,41]. All these variables were integrated in our study to construct the nomogram to predict ER in patients with HCC associated with PVTT.

For simple and easy use of the model, a score with a cut-off value of 108 or more was determined in this study to suggest a high-risk subgroup of patients to develop ER. These high risk patients should be considered for postoperative adjuvant therapy with the hope to improve long-term survival outcomes of these patients[20, 42]. A meta-analysis including six RCT and 659 participants concluded that postoperative adjuvant TACE seems promising for participants with HCC with risk factors (multiple nodules of >5 cm or vascular invasion) [43]. In addition, several well-designed retrospective studies have demonstrated the efficacy of postoperative adjuvant TACE for HCC patients with microvascular invasion, portal vein tumour thrombus, or hepatic vein tumour thrombus[18, 42, 44].

This study had limitations. First, this is a retrospective study with its inherent defects. However, the data in the internal and external validation cohorts were collected prospectively. Second, this study was conducted in China, and most patients had HBV infection. Validation from study groups is required for HCV− or alcoholism-related HCC.

In conclusion, the nomogram was established to predict postoperative ER in patients with HCC associated with PVTT limited to a first-order branch or above of the MPV after R0 LR. This nomogram could identify patients with a high risk of developing ER after surgery. Postoperative adjuvant therapy could be considered for the patients with a high ER risk with a score of 108 or higher. The internal and external validation cohorts demonstrated good performance of the nomogram.

Conflicts of interest

No potential conflicts of interest are disclosed.

Authors contributions

Conception and design: Shu-Qun Cheng, Wan Yee Lau, Xiu-Ping Zhang.

Financial support: Shu-Qun Cheng.

Provision of study materials or patients: Le-Qun Li, Min-Shan Chen, Tian-Fu Wen, Jie Shi, Wei-Xing Guo, Meng-Chao Wu; Collection and assembly of data: Xiu-Ping Zhang, Zhen-Hua Chen, Teng-Fei Zhou.

Data analysis and interpretation: Xiu-Ping Zhang, Zhen-Hua Chen, Teng-Fei Zhou.

Manuscript writing: Xiu-Ping Zhang, Wan Yee Lau.

Final approval of the manuscript: All authors.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ejso.2019.03.043.

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