

Nomogram for individualized prediction of recurrence after postoperative adjuvant TACE for hepatitis B virus-related hepatocellular carcinoma

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Abstract

This study sought to develop an effective and reliable nomogram for predictions of recurrence for postoperative adjuvant transarterial chemoembolization (PA-TACE) in patients with hepatitis B virus-related (HBV) hepatocellular carcinoma (HCC).

The nomogram was established based on data obtained from a retrospective study on 235 consecutive patients with HBV HCC who received PA-TACE as an initial therapy from 2006 to 2010 in our center. Eighty-four patients who were collected at another institution between 01/2008 and 12/2010 served as an external validation set. Recurrence-free survival (RFS) was collected. The nomogram for tumor recurrence was developed based on the data obtained before the PA-TACE procedure. Predictive accuracy and discriminative ability of the nomogram were assessed by concordance index (C-index), calibration curves, and validation set.

The 1, 2, 3-year RFS rates were 55.5%, 27.0%, and 14.1%, respectively, in the patients from the derivation set and 60.7%, 33.2%, and 23.8% in those from the validation set. Four risk factors (HBV-DNA level, vascular invasion, change of Child–Pugh score, and tumor diameter) in the multivariate analysis were significantly associated with RFS. The statistical nomogram incorporated these 4 factors achieved good calibration and discriminatory abilities with the c-index of 0.74 (95% CI 0.66–0.82). The findings were supported by the independent external validation set (c-index, 0.70; 95% CI 0.58–0.83). The area under the receiver operating characteristic curve in our model was greater than those of conventional staging systems in the validation patients (corresponding c-indices, 0.56–0.64).

The novel nomogram may achieve an optimal prediction for recurrence outcome in HBV-related HCC with PA-TACE.

Abbreviations: AFP = alpha-fetoprotein, EASL = European Association for the Study of the Liver, HBeAg = hepatitis B e antigen, HBsAg = hepatitis B surface antigen, HBV = hepatitis B virus-related, HBV-DNA = hepatitis B virus deoxyribonucleic acid, HCC = hepatocellular carcinoma, MVI = microvascular invasion, PA-TACE = postoperative adjuvant transarterial chemoembolization, RCT = randomized controlled study, RFS = recurrence-free survival, TACE = transarterial chemoembolization.

Keywords: hepatocellular carcinoma, nomogram, recurrence, TACE

1. Introduction

Hepatocellular carcinoma (HCC) is the most prevalent primary malignant hepatic tumor with a dismal prognosis.^[1] Nearly 70% to 90% of HCC cases develop in patients with chronic cirrhosis

of the liver, which is often caused by hepatitis B virus (HBV) persistent infection.^[2]

Curative hepatic resection is the recommended treatment modality for early HCC with a single nodule and normal liver function but without clinically significant portal hypertension (very early or early HCC, BCLC stage A).^[3] Nevertheless, the long-term prognosis of hepatic resection has been disappointing because of the high recurrence rates in the remnant liver.^[4] Recurrent HCC occurs in more than half of all patients within 5 years after resection, with most occurring within the first 2 years and 78% to 96% occurring in the remnant liver.^[4,5]

Transarterial chemoembolization (TACE) is the treatment approach most commonly used for unresectable HCC. Current guidelines including the BCLC staging system recommend TACE as the standard treatment of intermediate-stage HCC.^[6] By arterial injection of chemotherapeutic drugs and embolizing agents, TACE decreases blood flow to the tumor and induces tumor ischemic necrosis.^[7] The effectiveness of TACE as an adjuvant therapy for HCC has been documented in clinical studies.^[8,9] A randomized controlled study (RCT) showed postoperative adjuvant (PA) TACE to be beneficial for patients with HCC larger than 5 cm in diameter, multiple nodules, or macroscopic vascular invasion.^[10] However, in a retrospective propensity score analysis based on an HCC cohort without satellite nodules and vascular invasion, adjuvant TACE showed

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no superiority in terms of the survival rate and the recurrence rate.^[11] Although no large-scale, multicentered RCTs were available to address the issue, several studies based on HCC patients with more tumor numbers, larger tumor size, and vascular invasion were in favor of adjuvant TACE.^[12] Therefore, adjuvant TACE is widely used in postoperative HCC patients with a range of recurrence risk factors such as large tumor size, microvascular invasion, multiple tumor nodules, and satellite lesions.^[13] Therefore, it is reasonable to establish a reliable and easy-to-use model for preoperative selection which kind of patients can benefit from PA-TACE.

Several factors for predicting the treatment effect of adjuvant chemotherapy after resection. Baseline tumor characteristics before hepatectomy have a significant impact on patient recurrence-free survival (RFS), including serum alpha-fetoprotein (AFP) and platelet count have been associated with tumor recurrence in HCC patients.^[14,15] Meanwhile, relevant studies have shown that postoperative pathological tumor factors, such as tumor number/diameter and the presence of vascular invasion or capsule, are associated with the prognosis of HCC patients.^[14–17] Furthermore, postoperative persistent high HBV viral load was associated with HCC recurrence and resulted in poor prognosis.^[16] Finally, as most patients with HCC have extensive liver cirrhosis, postoperative liver function may further worsen after adjuvant TACE and may negatively impact patient RFS time. However, the factors noted above varied to some extent due to the heterogeneity of the study populations; therefore, comprehensive predictions of recurrence outcome have been difficult to make.

Due to the lack of a reliable and pragmatic statistical prediction measures, development of a predictive system for recurrence that incorporates parameters associated with PA-TACE based on preoperative data becomes urgently needed. Currently, nomogram has been considered to be evidence-based, individualized, and accurate in prognostic estimation and can widely be developed to many tumors.^[18–20] In this study, we construct a clinically novel and reliable nomogram for RFS in patients with hepatitis B-related HCC treated with PA-TACE. Performance of the nomogram was further verified in independently external validation of patients.

2. Methods

2.1. Patients

Consecutive patients, more than 18 years old at the time of the hepatic resection, diagnosed with HBV-related HCC by histopathology or radiological imaging (CT/MRI scans) according to European Association for the Study of the Liver (EASL) criteria^[17] who underwent curative hepatectomy in the Department of Hepatology and PA-TACE in the Interventional Radiology at the Affiliated Zhongshan Hospital of Fudan University between January 2005 and December 2009 (n=530) were screened for eligibility. These patients formed the derivation set of this study. From January 2006 to December 2008, another cohort of 84 patients treated in Sun Yat-sen University Cancer Center by PA-TACE after hepatectomy with the same selection criteria was analyzed as an independent external validation set.

Patients with HBV-related HCC at BCLC-stage A, B, or C, and preoperative liver function status (Child–Pugh stage A or selected B) who received PA-TACE after hepatic resection within 4 weeks were included and formed the initial set for all further analysis.

Patients were excluded if they received liver transplantation or previous treatment for HCC. Additionally, patients who received

hepatic resection despite poor liver function (Child–Pugh C) and whose blood tests were negative for hepatitis B surface antigen (HBsAg) or seropositive with one or more of the human immunodeficiency virus, HCV, or hepatitis D virus were ruled out. Once patients have been found to exist active viral replication, they were given with oral antiviral drugs immediately.

All the patients were rechecked in our center 4 weeks after resection. If no recurrence was found, the PA-TACE treatment strategy was recommended. If the patients were found to have single/multiple tumors during the first evaluation 4 weeks after hepatectomy, they were regarded as tumor recurrence and excluded from this study.

Ethical approval for study protocol was provided by the Institutional review board of the Zhongshan Hospital and Sun Yat-sen University Cancer Center, and informed consent was obtained from all patients for their data to be used for research.

2.2. Collection of data

All laboratory values were determined 1 day before the hepatectomy and 1 day before the PA-TACE session. Viral tests, including hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg), and hepatitis B virus deoxyribonucleic acid (HBV-DNA) load, were performed. Routine pre-operative imaging (chest x-ray, abdominal ultrasound, liver protocol dynamic contrast-enhanced CT and/or MRI, chest computed tomography, and bone scans) was performed 5 to 7 days before the liver resection.

Additionally, the dynamic change in the Child–Pugh score (here after referred to as Child–Pugh score increase) between the time points pre-hepatectomy and pre-PA-TACE was recorded. The histopathological evaluations of the resected specimens were recorded by experienced pathologists as well as intraoperative blood/loss transfusion and portal clamping time.

All patients received regular evaluations, including serum biochemistry, liver function test, level of AFP value, and contrast-enhanced dynamic CT/MRI, every 3 to 4 months after PA-TACE until tumor recurrence or dropout from the follow-up program.

Recurrence was diagnosed based on the combined findings by measurement of their serum AFP level and CT/MRI scan. When recurrent tumor was confirmed during the study phase, the patients were actively treated with percutaneous ethanol injection, radiofrequency ablation, repeat liver resection, or TACE, according to the liver function status, tumor number, and location HCC recurrence. RFS was defined as the time from the PA-TACE until the diagnosis of HCC recurrence using either intrahepatic recurrence or extrahepatic metastasis as end points.

3. Treatment procedures

3.1. Surgical procedure

Surgery was performed through a right bilateral subcostal incision. If necessary, the incision was extended to the left subcostal region. Surgeons carefully searched the abdominal cavity for the extent of local disease, extrahepatic metastases, and peritoneal seeding. The corresponding hepatic pedicle, hepatic vein, and short hepatic veins were ligated and divided. Pringle's maneuver was applied to occlude the blood inflow of the liver with cycles of 15 minutes clamp time/5 minutes unclamped time. Liver resection was carried out using a clamp-crushing method.^[21] Major/minor hepatic resection has been used in all surgery.

3.2. PA-TACE

When the liver function of the patient had recovered at 4 weeks after resection, TACE procedure was performed for the remnant liver. A vascular catheter was inserted through the femoral artery using the Seldinger technique and hepatic angiography was performed. The catheter’s tip was inserted selectively into the proper hepatic artery. An emulsion of 2 to 10mL of Lipiodol Ultra-Fluide (Guerbet, France) mixed with 30 to 50 mg of EADM (Pfizer) was then infused through a microcatheter (Progreat, TERUMO, Japan). The dosages of the chemotherapy drugs and lipiodol depended on the underlying state of liver function and body surface area.^[22] The criteria for liver treatment used in both institutions were similar.

3.3. Study design and statistical analyses

Numeric data are expressed as means and SDs, and categorical data are shown as frequency and proportion.

Patient’s characteristics in the derivation and validation set are presented with descriptive statistics. Survival curves were calculated using the Kaplan–Meier method. Variables that were significantly associated with recurrence-free survival in the univariate analysis ($P < .05$) entered a stepwise Cox regression

model (conditional backward selection). Multivariate Cox regression analysis with stepwise selection was used to detect independent predictors used in a nomogram. The nomogram was formulated using the rms package in R version 3.2.0.

The predictive performance of the nomograms was measured using the concordance index (C-index) and plotting the Kaplan–Meier curves of the quartiles of predictions, and was illustrated by drawing calibration plots. Model validation was performed using bootstraps with 1000 resamples to quantify the overfitting of modeling strategy and predict future performance of the model. Statistical analyses were performed using the R software version 3.2.0 (<http://www.rproject.org/>). Comparisons between the nomogram and other predictive models were performed using R package pROC. The larger the C index, the more accurate the prognostic prediction was. All statistical tests were 2-tailed and a P value $< .05$ was considered statistically significant.

4. Results

4.1. Patient characteristics

A flow chart for derivation and validation sets is shown in Fig. 1. In the derivation cohort ($n = 235$), the mean age of patients was

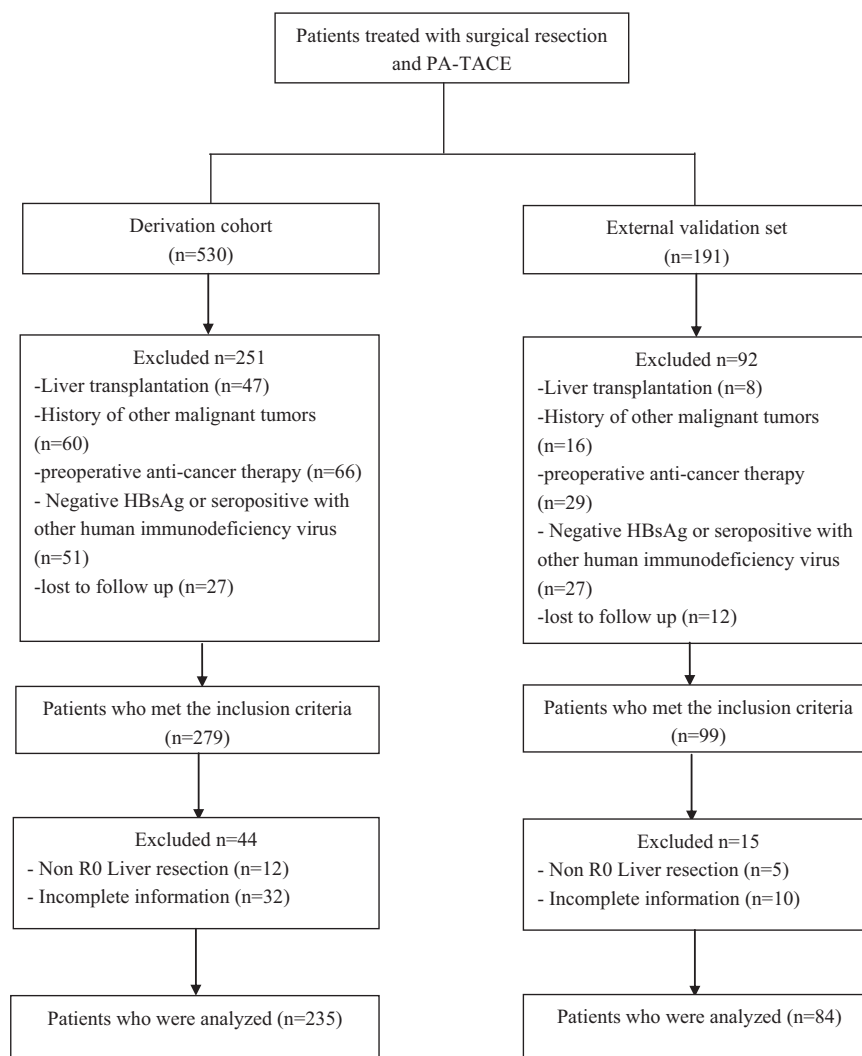


Figure 1. Flowchart of patient selection.

52.1 years (SD, 10.2 years), 86.8% of whom were male. Hepatitis B infection (100%) is the most common cause of chronic liver disease and approximately 28.5% of enrolled patients were detected as positive HBeAg. A total of 27.7%, 60.9%, and 11.4% of patients were diagnosed at BCLC stage A, B, and C, respectively (n=65, 143, and 27, respectively). The Child–Pugh grade prior to PA-TACE (n=168) increased by at least 1 point compared to that before surgical resection, whereas 67 were unchanged or decreased at least 1 point. In terms of tumor factors, most patients had single tumors (59.1%), and the average diameter of the tumors was 6.5 cm (SD, 4.0 cm). Vascular invasion and capsular infiltration were histologically observed in 125 (53.2%) and 49 (20.9%) patients, respectively. Edmondson grade III or IV tumors were noted in 91 (38.7%) patients. Regarding operation factors, 32 (13.6%) required blood transfusion during the perioperative period. No clamping time was observed in 132 (56.2%) patients. Pathological examination revealed cirrhotic livers in most patients. HBV-DNA level reactivation (>10⁴ IU/mL) prior to PA-TACE occurred in 79 (33.6%) patients.

The clinical, histopathological, and surgical factors of the derivation (n=235) and external (n=84) validation sets prior the hepatectomy and PA-TACE are summarized in Table 1. There were no significant differences in baseline characteristics between the derivation and validation set.

4.2. Tumor recurrence in the derivation and validation sets

The median follow-up was 13.4 months (range, 0.7 to 47.0 months) for the derivation set and 14.0 months (range, 1.5 to 41 months) for the validation set. In the derivation set, for patients with PA-TACE, the median RFS was 13.5 months (inter-quartile range 12–16) the 1-, 2-, and 3-year RFS rates were 55.6%, 27%, and 14.1%, respectively. In the validation set, for patients with PA-TACE, the median RFS was 14.0 months (inter-quartile range 12–20), the 1-, 2-, and 3-year RFS rates were 60.7%, 33.2%, and 23.8%, respectively.

4.3. Development of the nomogram from the derivation set

Baseline demographics were used for univariate analysis. Six risk factors provided a significant influence on RFS, prior hepatectomy: BCLC stage, and tumor factor: vascular invasion, tumor diameter, and before PA-TACE: HBV-DNA level, AFP level and Child–Pugh score change. These 6 risk factors were accepted in the multivariate Cox regression analysis. After a stepwise removal of variables, 4 risk factors remained significant predictive value of prognosis (Table 2): HBV-DNA level prior PA-TACE procedure, presence of vascular invasion, tumor diameter, and Child–Pugh change.

These significant independently risk factors were integrated to form RFS estimation nomogram in the derivation set (Fig. 2). The nomogram demonstrated good accuracy for recurrence prediction, with a C index of 0.74 (95% CI, 0.66–0.82). The calibration plot for probability of RFS at 1, 2, 3 year after TACE showed a fair agreement between the prediction by nomogram and actual observation (Fig. 3A–C).

4.4. Validation of the nomogram

For the purpose of externally validating this nomogram, we collected data among a second set of patients (n=84) undergoing

Table 1
Baseline characteristics in patients with postoperative adjuvant TACE.

Variable	Derivation set (N=235)	Validation set (N=84)	P
Pre-SR			
Age, years	52.1±10.2	52.6±10.7	.702
Gender			.762
Male	204 (86.8)	74 (88.1)	
Female	31 (13.2)	10 (11.9)	
HBeAg			.407
Positive	67 (28.5)	28 (33.4)	
Negative	168 (71.5)	56 (66.6)	
Child–Pugh stage			.951
A	232 (98.7)	83 (98.8)	
B	3 (1.3)	1 (1.2)	
BCLC-stage			.977
A	65 (27.7)	24 (28.6)	
B	143 (60.9)	50 (59.5)	
C	27 (11.4)	10 (11.9)	
Aspartate aminotransferase, IU/L	41.1±24.4	41.2±30.4	.974
Creatinine, μmol/L	73.6±15.5	73.9±16.3	.875
Neutrophil, 10 ⁹ /L	3.3±1.5	3.5±1.6	.456
Lymphocyte, 10 ⁹ /L	1.8±0.7 ^a	1.9±0.8	.321
Pathology			
Cirrhosis			.941
Yes	195 (83.0)	70 (83.3)	
No	40 (17.0)	14 (16.7)	
Tumor factors			
Vascular invasion			.708
No	110 (46.8)	35 (41.7)	
Microvascular invasion	98 (41.7)	39 (46.4)	
Macrovascular invasion	27 (11.5)	10 (11.9)	
Tumor diameter, cm	6.5±4.0	6.6±4.2	.881
Tumor number			.375
single nodule	139 (59.1)	45 (53.6)	
Multiple nodules	96 (40.9)	39 (46.4)	
Capsule			.905
Complete	186 (79.1)	67 (79.8)	
Incomplete	49 (20.9)	17 (20.2)	
Edmonson–Steiner classification			.636
I/II	144 (61.3)	54 (64.3)	
III/IV	91 (38.7)	30 (35.7)	
Lymph nodemetastasis			.442
Yes	7 (3.0)	4 (4.8)	
No	228 (97.0)	80 (95.2)	
Surgical factors			
Portal vein tumor thrombus			.719
Yes	22 (9.4)	9 (10.7)	
No	213 (90.6)	75 (89.3)	
Clamping time, min			.549
Yes	103 (43.8)	44 (52.4)	
No	132 (56.2)	40 (47.6)	
Blood transfusion			.69
Yes	32 (13.6)	10 (11.9)	
No	203 (86.4)	74 (88.1)	
Pre-pTACE			
Alphae-fetoprotein, ng/mL			.762
<200	191 (81.3)	67 (79.8)	
≥200	44 (18.7)	17 (20.2)	
Child–Pugh stage			.362
A	199 (83.8)	74 (88.1)	
B	38 (16.2)	10 (11.9)	
HBV-DNA level, IU/mL			.656
≤10 ⁴	156 (66.4)	58 (69.0)	
>10 ⁴	79 (33.6)	26 (31.0)	
Aspartate aminotransferase, IU/L	49.0±40.2	50.1±42.9	.834
Creatinine, μmol/L	69.4±17.2	71.3±21.2	.396
neutrophil, 10 ⁹ /L	3.8±6.7	4.7±10.9	.383
lymphocyte, 10 ⁹ /L	1.5±0.7	1.5±0.6	.51
Platelets, 10 ⁹ /L	146.3±60.1	139.6±50.3	.36

HBeAg=hepatitis B e antigen, HBV-DNA=hepatitis B virus deoxyribonucleic acid, p-TACE=postoperative transarterial chemoembolization.

Table 2
Multivariate stepwise backward Cox regression analysis for recurrent factors in the derivation set.

Variable	Recurrence-free survival		P (Cox)
	Hazard ratio	95% CI	
Child-Pugh increase	1.244	1.048–1.476	.012
HBV-DNA level, IU/mL	1.622	1.194–2.203	.002
Tumor diameter, cm	1.641	1.089–2.474	.018
Vascular invasion	1.403	1.070–1.838	.014

CI = confidence interval, HBV-DNA=hepatitis B virus deoxyribonucleic acid.

PA-TACE at the Cancer Center of Sun Yat-sen University (Table 1). In this validation set, the c-index of the nomogram for predicting RFS was 0.70 (95% CI, 0.58–0.83). The calibration plot for probability of RFS at 1, 2, 3 year after PA-TACE showed a fair agreement between the prediction by nomogram and actual observation (Fig. 3D–F).

4.5. Comparison of predictive accuracy between the nomogram and the conventional models by the validation set

The predictive power of the nomograms and conventional staging systems were compared by ROC curve analysis (Fig. 4).

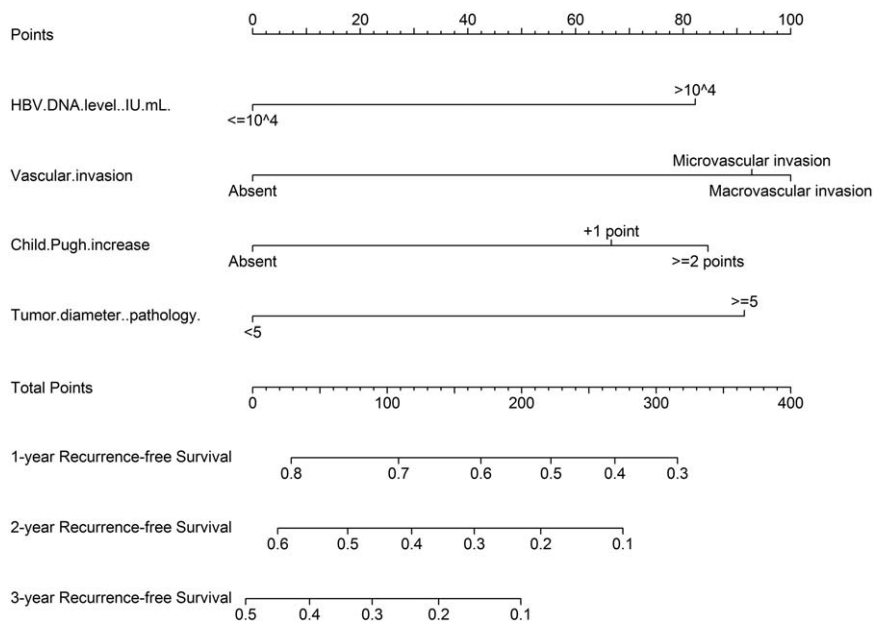


Figure 2. Nomograms for predicting recurrence-free survival after PA-TACE. To use the nomogram, an individual patient's value is located on each variable axis, and a line is drawn upward to determine the number of points received for each variable value. The sum of these numbers is located on the total points axis, and a line is drawn downward to the axes to determine the likelihood of 1-, 2-, and 3-year recurrence-free survival. HBsAg = hepatitis B surface antigen, PA-TACE = postoperative adjuvant transarterial chemoembolization.

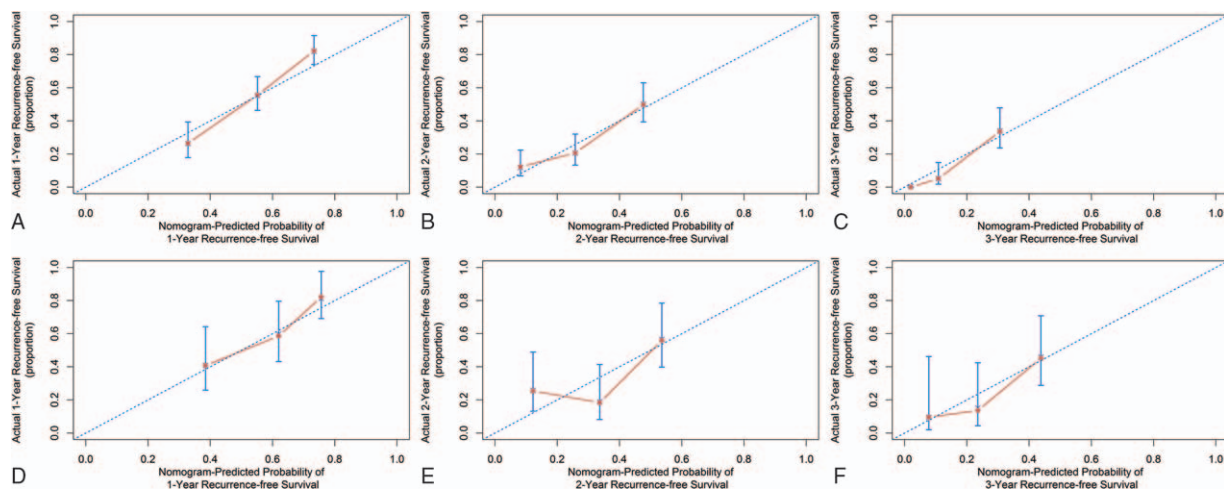


Figure 3. Calibration curve for predicting patient recurrence at (a) 1 years, (b) 2 years, and (c) 3 years in the derivation set and at (d) 1 year, (e) 2 years, and (f) 3 years in the external validation set.

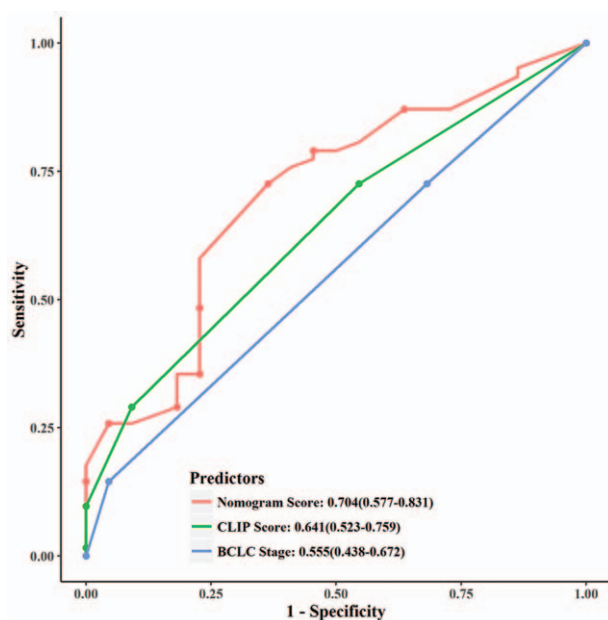


Figure 4. Comparison of predictive accuracy for recurrence-free survival after PA-TACE between the nomogram and the conventional system by the validation set. PA-TACE = postoperative adjuvant transarterial chemoembolization.

The C-index of our nomogram for predicting 2-year recurrence was 0.70 (95% CI, 0.58–0.83). The C-index of the nomogram was significantly higher than BCLC (0.56, 95% CI, 0.44–0.67, $P < .001$) and CLIP (0.64, 95% CI, 0.52–0.76, $P < .001$).

5. Discussion

It is still controversial as to which kind of patients can benefit from the PA-TACE, because of the heterogeneity of the patients covered in the various studies, the clinical elements influencing prognosis importance were quite diverse and have some limitations, whereas there has been no reliable system to predict RFS. We have created statistically predictive nomograms based on the predictive Cox regression model tailored to the individual patient and give accurate recurrence information in these patients. The model is simple and easy-to-use, integrating 4 predictors that constitute the essentials of preoperative clinical evaluation. The predictive performance of the model was further certified by external validation set. This nomogram was more reliable than the traditional staging systems commonly used (c-indices, 0.56–0.64).

A high HBV viral load is known to be a major risk factor for the development of HCC in patients with chronic HBV infection and for HCC recurrence after resection. Huang et al^[16] conducted a large comparative study of 1609 HCC patients with the different serum HBV-DNA level. They concluded that there was significant relationship between HBV reactivation and HCC recurrence after partial hepatectomy, and postoperative high HBV-DNA level (≥ 200 IU/mL) was associated with a high HCC recurrence rate. Likewise, a Taiwanese cohort study conducted by Wu et al^[14] confirmed that high viral loads (HBV-DNA levels $> 10^6$ copies/mL) and hepatic inflammatory activity was correlated with the late recurrence in hepatitis B-related HCC patients. As expected, it is a crucial variable in our nomogram system.

The presence of microvascular invasion (MVI) is a histopathologic feature that indicates aggressive behavior of the HCC, which is a powerful validated risk factor of tumor recurrence following surgical treatment. Currently, the diagnosis of MVI can only reliably be determined by pathologic histology of explanted tissue. Li et al^[10] have proposed a prognostic nomogram for prediction of recurrence after HCC resection. Their results showed that MVI had high relative importance in recurrence-free survival on the basis of the Cox model. Our result is consistent with previous findings showing that the indicator in the nomogram system is of great importance for tumor recurrence.

Recent studies have demonstrated that the deterioration of liver function (defined as an increase of Child–Pugh score) before and after radical hepatectomy is known to be an important risk factor of tumor recurrence. A study from Korean has found that liver function was an independent risk factor of PFS identified by multivariate analyses and the result was confirmed by the 2 validation cohorts.^[8] On the other hand, because most patients with HCC suffer from liver cirrhosis, and surgical postoperative liver function could not be fully recovered in a relatively short time, TACE may aggravate deterioration of liver function and bring a worsen prognosis. Sieghart et al^[23] analyzed the variation of the data before the first and second TACE in 2 sets, and Child–Pugh score change was considered as a significant predictor of tumor recurrence. In keeping with previous findings, the Child–Pugh score increase reflecting liver dysfunction is included in our proposed model.

Tumor diameter is a predictive covariate related to tumor recurrence in our model. Compared with patients only after hepatectomy, Sun et al^[24] performed a cohort study involving 322 patients to assess the effectiveness of PA-TACE for HCC patients with MVI. The maximum tumor diameter and PA-TACE were deemed as independently risk factors for RFS. However, the study has not further analyzed what kind of patient groups is suitable for PA-TACE, and it also has not built related model based on the multivariable regression results. Our model provided a more comprehensive and powerful standard and basis for predicting RFS of PA-TACE in HBV-related HCC.

The major limitation of this study is that our data were acquired retrospectively and the population was restricted to HBV-related HCC. They could not be generalizable to prediction in all patients with HCC etiology other than HBV. It will certainly be necessary to further verify our results among patients with HCC of various etiologies. Second, a prospective study is required to further confirm the reliability of the nomogram. Third, individual single factor variable, which contains a variety of confounding factors, may cause potential bias.

6. Conclusion

By combining 4 risk factors of PA-TACE, a novel, validated nomogram was constructed for predicting the tumor recurrence of PA-TACE in patients with HBV-related HCC. The results showed that the nomogram had good predictive performance. It is warranted that the nomogram should be tested in prospective clinical trials.

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