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RESEARCH

Development and validation of a model for predicting who can benefit from multiple TACE in HCC patients

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Abstract

This study was to develop and validate a model for predicting who can benefit from multiple transcatheter arterial chemoembolization (TACE) in hepatocellular carcinoma (HCC) patients.

228 and 98 patients were included in the development and validation sets, respectively. The primary clinical endpoint was benefiting from consecutive multiple TACE treatments. Logistic regression analysis was used to screen the independent risk factors for the clinical endpoint. The independent risk factors were then used to construct the predictive model. The area under receiver operating characteristic (ROC) curves, calibration curves, and clinical decision curves were used to evaluate the predictive ability of the model.

Multivariate Logistic regression analysis showed that complete envelope, hepatic lopes, tumor number, and alpha-fetoprotein (AFP) were independent risk factors for benefiting from multiple TACE in HCC patients. The area under the curve (AUC) of the model constructed by using independent risk factors in the development and validation sets was 0.843 (95% confidence interval [CI]: 0.784–0.902) and 0.828 (95%CI: 0.739–0.916), respectively. The calibration curves and clinical decision curves showed that the model had good predictive ability.

The model established in this study has a good predictive effect on HCC patients who can benefit from multiple TACE.

Keywords Benefit · Hepatocellular carcinoma (HCC) · Nomogram · Predictive model · Transcatheter arterial chemoembolization (TACE)

Introduction

HCC is one of the most common cancers in the world. Viral hepatitis is the most common cause in Asia, and alcoholic fatty liver is the main cause in Europe and America [1, 2]. For early-stage HCC, radical treatment measures are mainly used, including liver transplantation and hepatectomy. For advanced hepatocellular carcinoma, TACE is the main local treatment [3, 4]. Some HCC patients need to receive repeated TACE treatment due to the large tumor burden, but TACE treatment is not effective for all HCC due to the biological characteristics of the tumor, and even some HCC patients develop resistance to multiple TACE treatments [5, 6]. When HCC patients who are not suitable for multiple TACE treatment receive TACE treatment, the tumor progression may not only be uncontrolled but also affect the quality of life due to the complications caused by the treatment [7]. Therefore, there is a clinical need for a tool to predict whether patients with HCC will benefit from multiple TACE treatments. Many studies are focusing on the risk factors of poor prognosis of HCC, such as tumor characteristics and basic conditions of patients [8–11]. However, studies to predict which patients with HCC will benefit from multiple TACE treatments are lacking.

This study aimed to investigate the impact of benefiting from multiple TACE on the prognosis of HCC patients. This study also aimed to select independent risk factors for benefiting from multiple TACE, and then to construct a nomogram to predict HCC patients who can benefit from multiple TACE.

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Materials and methods

Patient selection

The inclusion criteria for patients in this study are as follows: 1) had a definite diagnosis of HCC confirmed either by clinical diagnosis or liver biopsy; 2) had received two or more TACE treatments; 3) age between 18 and 80; 4) Eastern Cooperative Oncology Group (ECOG) score standard ≤ 2; 5) no history of other malignancies or serious underlying diseases; 6) get regular follow-up. The exclusion criteria for this study included: 1) had undergone radical surgery (liver transplantation, hepatectomy); 2) incomplete clinical baseline data; 3) did not agree to participate in this study. Conventional TACE was used in this study [12]. In addition, all HCC patients in this study were treated with immune and targeted systemic therapy after TACE.

This retrospective study included 326 eligible patients seen at our center between 2018 and 2023. Based on a ratio of 7:3, 228 and 98 patients were included in the development and validation sets, respectively.

Data collection and follow-up

In this study, the clinical baseline data of the patients included age, sex, nutrient artery, complete envelope, hepatic lobes, chronic liver disease, tumor number, tumor max size, portal hypertension, AFP, alanine aminotransferase (ALT), aspartate transferase (AST), total bilirubin (TBIL), albumin (ALB), platelet (PLT), benefit, survival status, overall survival (OS).

The primary clinical endpoint was benefiting from consecutive multiple TACE treatments, and the secondary endpoint was OS. Benefiting from consecutive multiple TACE was defined as the treatment effect after two consecutive TACE treatments, each of which was assessed as stable disease (SD) or better by the Response Evaluation Criteria in Solid Tumors (RECIST) [13]. OS was defined as the time between the first TACE and death, or the time between the first TACE and the follow-up deadline if death did not occur. The tumor was evaluated by contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) 3–4 weeks after each TACE. All patients were followed up through inpatient medical records, outpatient examination, or telephone.

Statistical analysis

SPSS 26.0 software was used for statistical analysis. Continuous numerical variables with a normal distribution were analyzed using mean (standard deviations (SD)), and comparisons between the two groups were performed using the independent sample t-test. The continuous variables that did not meet the normal distribution were analyzed by the median (interquartile (IQR)), and the Mann–Whitney U test was used to compare them between the two groups. Categorical variables were analyzed by count (percentage), and the Chi-square test was used to compare them between the two groups. P values less than 0.05 were deemed statistically significant.

The following steps were used for the development and validation of a nomogram for benefiting from multiple TACE. Firstly, univariate logistic regression analysis was used to detect potential risk factors, and P values less than 0.05 were included in the multivariate analysis. Secondly, multivariate Logistic regression analysis was used to screen out the independent risk factors. Thirdly, a new nomogram was constructed using the screened independent risk factors. Finally, the AUC of the ROC curve, calibration curves, and clinical decision curves were used to evaluate the predictive power of the nomogram. Kaplan-Meier curves were used to compare the median OS between the benefit and no-benefit groups.

Results

Patient characteristics

A total of 326 patients were enrolled in this study, including 228 patients in the development set and 98 patients in the validation set. The flowchart for including patients in this study is shown in Fig. 1. The clinical characteristics of the patients in the development and validation sets are shown in Table 1. The patients who achieved multiple TACE benefit outcomes in the development and validation sets were 166 (72.8%) and 65 (66.3%), respectively. As shown in Fig. 2, the comparison of median OS between the benefit group and the non-benefit group in both the development (Fig. 2A; p value < 0.0001) and validation (Fig. 2B; p value = 0.0081) sets showed statistically significant differences.

Univariate and multivariate logistic analysis

The results of univariate and multivariate logistic regression analyses of benefiting from multiple TACE in HCC patients of development set are shown in Table 2. After univariate analysis, age, complete envelope, hepatic lobes, tumor number, tumor max size, AFP, and PLT were the influencing factors for benefiting from multiple TACE. After multivariate analysis, complete envelope (HR = 2.386; 95%CI: 1.141, 4.987; p = 0.021), hepatic lobes (HR = 0.274; 95%CI: 0.132, 0.567; p < 0.001), tumor number (HR = 0.177; 95%CI: 0.084, 0.372; p < 0.001), and AFP (HR = 0.414; 95%CI:

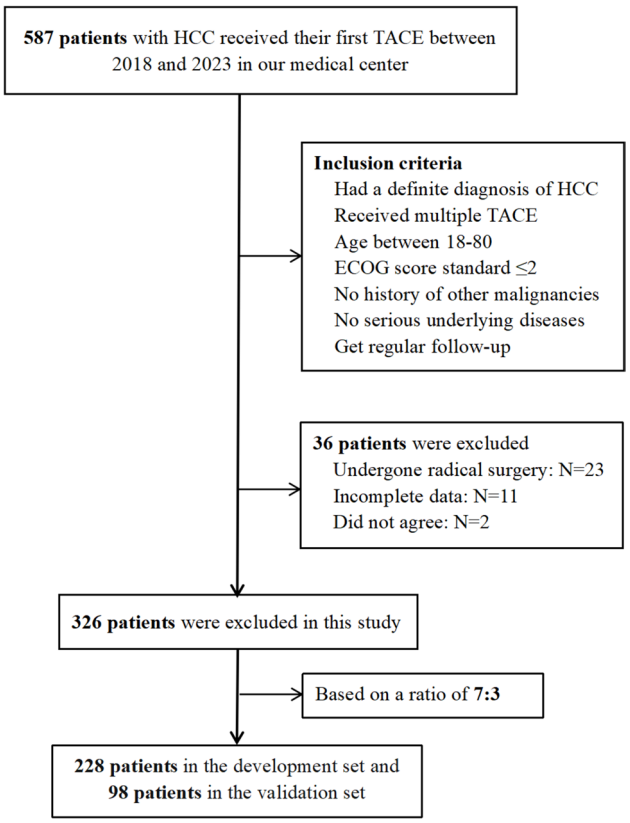

Fig. 1 Flowchart for including HCC patients in this study. HCC, hepatocellular carcinoma; TACE, transcatheter arterial chemoembolization; ECOG, Eastern Cooperative Oncology Group

0.199, 0.862; $p = 0.018$) were independent risk factors for benefiting from multiple TACE.

Development, validation, and evaluation of the nomogram

As shown in Fig. 3, a nomogram was constructed based on the four independent risk factors screened by logistic regression analysis. The predictive power of the nomogram was evaluated using the AUC of the ROC curve, calibration curves, and clinical decision curves in the development and validation sets.

As shown in Fig. 4, the AUC of the model predicting benefit from multiple TACE was 0.843 (95%CI: 0.784–0.902) in the development set (Fig. 4A) and 0.828 (95%CI: 0.739–0.916) in the validation set (Fig. 4B). As shown in Fig. 5, calibration curves in the development (Fig. 5A) and validation (Fig. 5B) sets showed good agreement between the predicted rate of benefiting from multiple TACE and the actual rate. As shown in Fig. 6, the clinical decision curves in both the development (Fig. 6A) and validation (Fig. 6B) sets indicated that the predictive model had a clear clinical benefit.

Discussion

The main goal of treatment for advanced HCC is to prolong the survival time of patients [14]. As a local treatment to control tumor progression, TACE plays an important role in clinical practice [12, 15]. Because of the individual differences between patients with HCC, not all patients can benefit from TACE [16]. Many studies have focused on prognostic risk factors after TACE in patients with advanced HCC. Several studies have found that tumor characteristics are important prognostic factors for HCC. Several studies have suggested that the immune and nutritional status of patients is prognostic factors for HCC. Many studies have constructed many nomograms to predict the prognosis of HCC patients based on these risk factors [9–11]. However, there is a lack of studies to predict whether patients with advanced HCC will benefit from multiple TACE treatments. This study aimed to develop and validate a model for predicting who can benefit from multiple TACE in HCC patients.

After setting the clinical endpoint of benefiting from multiple TACE, univariate and multivariate logistic regression analyses were performed, and four independent risk factors were screened out in this study, including complete envelope, hepatic lobes, tumor number, and AFP. The integrity of the HCC envelope reflects the invasiveness of the tumor, which will affect the sensitivity of the tumor to receive treatment, thus affecting the prognosis of patients. Therefore, the integrity of the envelope is an important prognostic factor in patients with HCC receiving TACE treatment [17]. The extent of HCC invasion in the hepatic lobes reflects the degree of tumor differentiation, and the larger the extent of invasion, the worse the degree of tumor differentiation may be. Poor differentiation may lead to poor prognosis [18, 19]. Tumor number and AFP level represent the level of tumor burden. A large number of tumors and a high AFP level reflect a high tumor burden, which may not only affect the nutritional status of patients, but also further affect the acceptance of HCC patients in TACE treatment [20–22]. All these risk factors may lead to poor prognosis. Based on these factors, a nomogram was constructed to predict patients who would benefit from multiple TACE. This study also used the K-M curves to compare the overall survival between the benefit group and the no-benefit group in the development set and the validation set, and the differences were statistically significant. This indicates that benefiting from multiple TACE can affect the prognosis of HCC patients.

The nomogram constructed in the development set showed good predictive ability in both the development set and the validation set. Satisfactory AUCs were obtained in both the development and validation sets, which indicated

Table 1 Clinical characteristics of development set and validation set

Variables		Development set (n = 228)	Validation set (n = 98)	*p* value
Age		54.7 (11.7)	54.5 (11.4)	0.862
Sex	Male	188(82.5%)	72(73.5%)	0.064
	Female	40(17.5%)	26(26.5%)	
Nutrient artery	No	125(54.8%)	67(68.4%)	0.023
	Yes	103(45.2%)	31(31.6%)	
Complete envelope	No	77(33.8%)	36(36.7%)	0.606
	Yes	151(66.2%0	62(63.3%)	
Hepatic lobes	Single	147(64.5%)	72(73.5%)	0.113
	Double	81(35.5%)	26(26.5%)	
Chronic liver disease	No	28(12.3%)	9(9.2%)	0.419
	Yes	200(87.7%)	89(90.8%)	
Tumor number	Single	135(59.2%)	57(58.2%)	0.860
	Multiple	93(40.8%)	41(41.8%)	
Tumor max size (mm)		78(39–112)	74(42–107)	0.932
Portal hypertension	No	147(64.5%)	57(58.2%)	0.701
	Yes	81(35.5%)	41(41.8%)	
AFP (≥ 400ug/L)	No	145(63.6%)	62(63.3%)	0.955
	Yes	83(36.4%)	36(36.7%)	
ALT (U/L)		37(27–56)	51(29–77)	0.005
AST (U/L)		49(35–78)	68(41–110)	0.001
TBIL (umol/L)		13.2(9.3–20.2)	13.3(9.6–24.1)	0.501
ALB (g/L)		37.7(34.3–40.7)	37.7(34.3–41.4)	0.850
PLT (10^9/L)		139(88–190)	140(89–200)	0.837
Benefit	No	62(27.2%)	33(33.7%)	0.238
	Yes	166(72.8%)	65(66.3%)	
Status	Alive	43(18.9%)	26(26.5%)	0.120
	Dead	185(81.1%)	72(73.5%)	
OS (months)		22(16–34)	18(14–25)	0.007

AFP, alpha-fetoprotein; *ALT*, alanine aminotransferase; *AST*, aspartate transferase; *TBIL*, total bilirubin; *ALB*, albumin; *PLT*, platelet; *OS*, overall survival

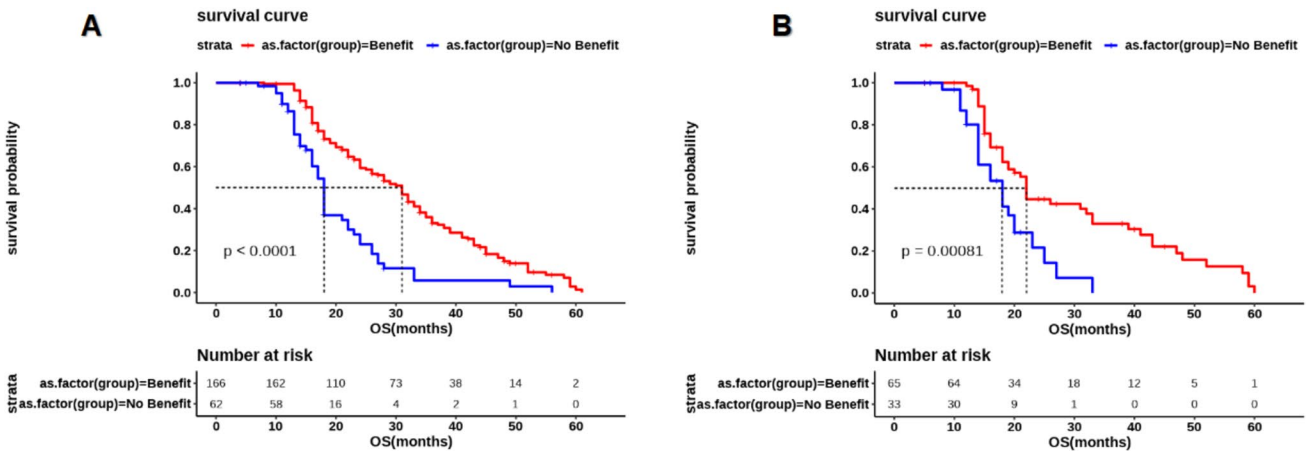

Fig. 2 Kaplan-Meier curves of OS between benefit and no-benefit groups in the development (**A**) and validation (**B**) sets. OS, overall survival

Table 2 Univariable and multivariable logistic regression analysis of benefit from multiple TACE in development set

Variables	Univariate analysis		Multivariate analysis	
	OR (95%CI)	*p* value	OR (95%CI)	*p* value
Age	1.026 (1.000,1.052)	0.049	1.023 (0.991,1.056)	0.157
Sex (Female)	0.740 (0.330,1.658)	0.464		
Nutrient artery (Yes)	1.095 (0.608,1.970)	0.763		
Complete envelope (Yes)	2.160 (1.184,3.941)	0.012	2.386 (1.141,4.987)	0.021
Hepatic lobes (Double)	0.180 (0.096,0.338)	< 0.001	0.274 (0.132,0.567)	< 0.001
Chronic liver disease (Yes)	0.879 (0.354,2.183)	0.781		
Tumor number (Multiple)	0.137 (0.071,0.266)	< 0.001	0.177 (0.084,0.372)	< 0.001
Tumor max size	0.991 (0.984,0.998)	0.015	1.001 (0.991,1.011)	0.913
Portal Hypertension (Yes)	0.828 (0.453,1.513)	0.540		
AFP (≥ 400ug/L)	0.259 (0.141,0.477)	< 0.001	0.414 (0.199,0.862)	0.018
ALT	1.002 (0.997,1.007)	0.483		
AST	1.001 (0.999,1.003)	0.569		
TBIL	1.005 (0.983,1.027)	0.678		
ALB	1.002 (0.947,1.060)	0.950		
PLT	0.997 (0.993,1.000)	**0.041**	1.000 (0.995,1.004)	0.886

TACE, transcatheter arterial chemoembolization; *OR*, odds ratio; *AFP*, alpha-fetoprotein; *ALT*, alanine aminotransferase; *AST*, aspartate transferase; *TBIL*, total bilirubin; *ALB*, albumin; *PLT*, platelet

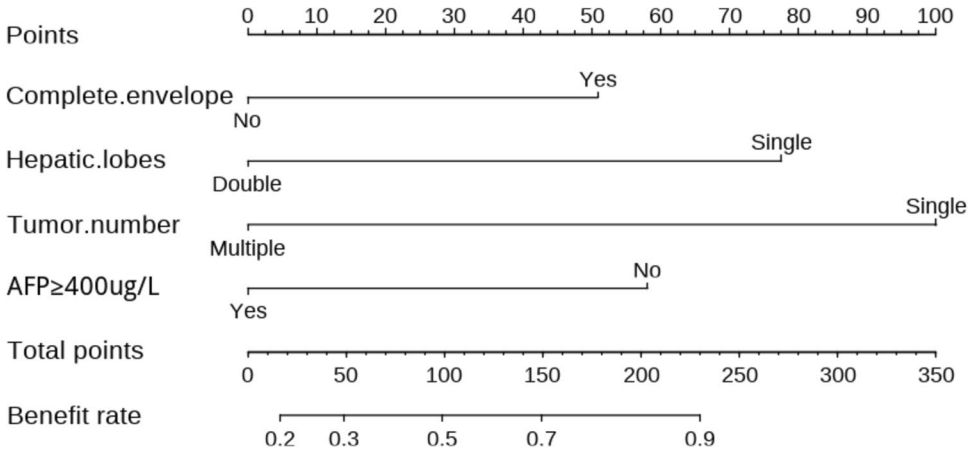

Fig. 3 Nomogram to predict the probability of benefiting from multiple TACE in HCC patients. AFP, alpha-fetoprotein; TACE, transcatheter arterial chemoembolization; HCC, hepatocellular carcinoma

that the prediction ability of the model was good. The calibration curves and clinical decision curves in the development set and validation set showed that the nomogram constructed in this study could achieve high prediction accuracy and get good clinical benefits. Through this model, HCC patients who are suitable for multiple TACE treatments can be found clinically, while for HCC patients

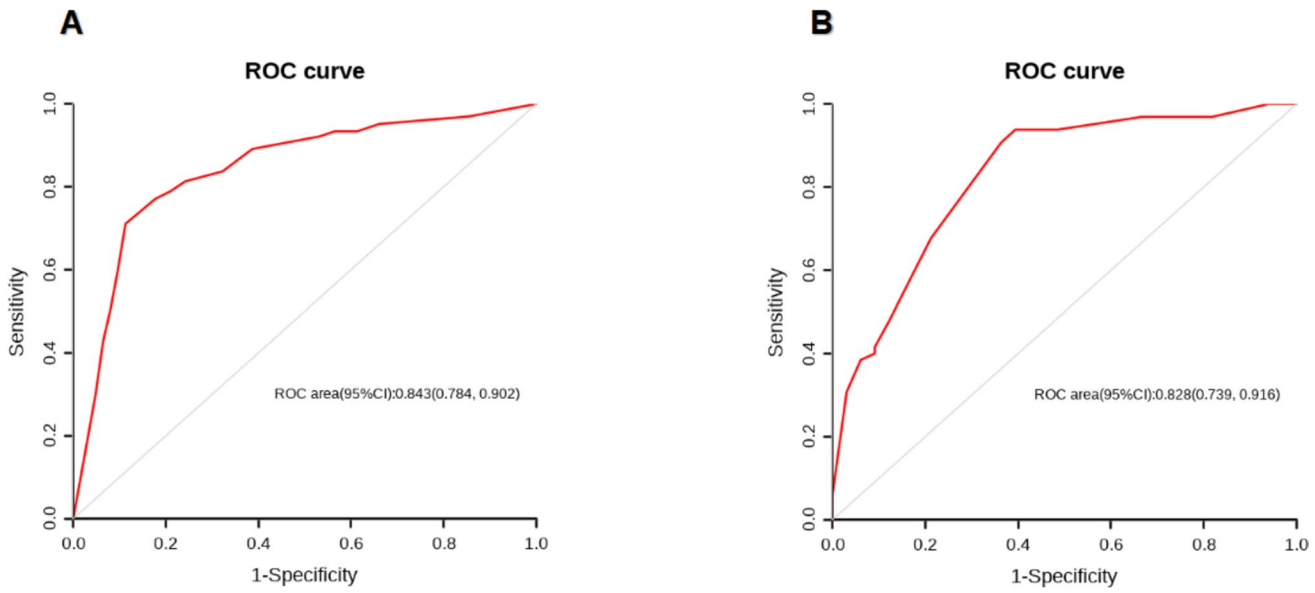

Fig. 4 The AUC of the nomogram in the development (**A**) and validation (**B**) sets. ROC, receiver operating characteristic; AUC, the area under the curve

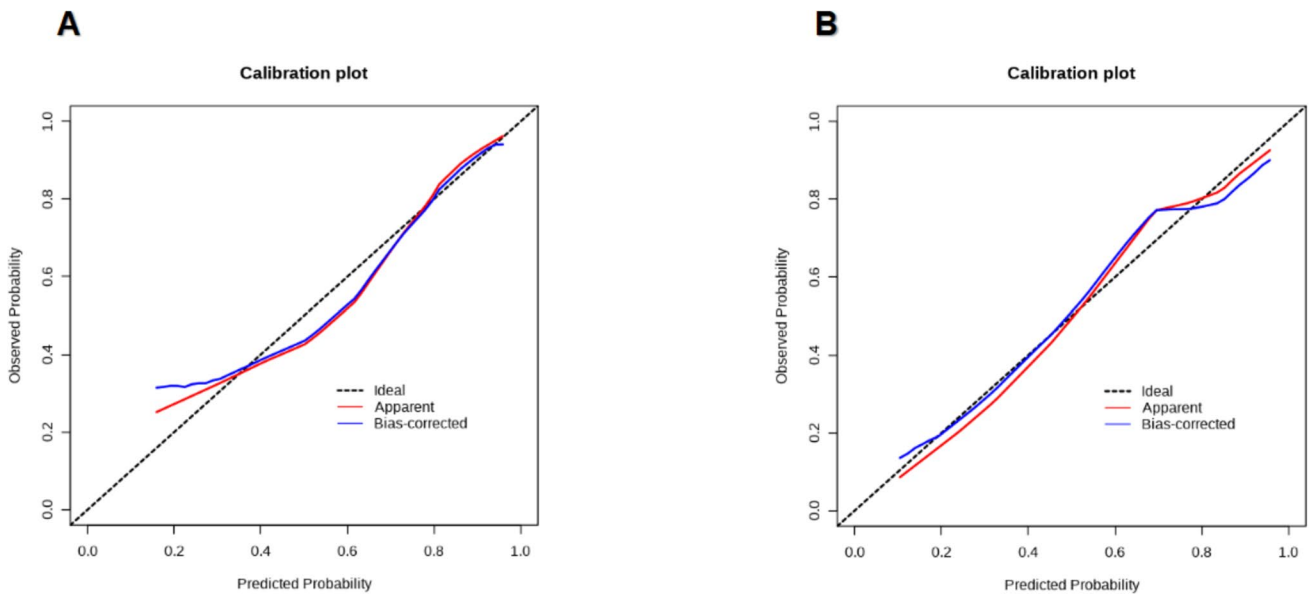

Fig. 5 Calibration curves of the nomogram in the development (**A**) and validation (**B**) sets

who are not suitable, clinicians can add some necessary systemic therapies, such as [23, 24].

The nomogram constructed in this study also has the following strengths. The variables required in this study were tumor characteristics that were readily available in clinical practice. Compared with genetic testing, which is an expensive indicator, this model has high economic practicability. It is suitable for application in all levels of cancer treatment centers. More importantly, there are no studies addressing what kind of HCC patients would benefit from multiple TACE. This study achieved this goal.

However, this study has some limitations. First of all, this study is a single-center study, and its conclusions still need to be supported by multi-center and large sample size data. Secondly, this study is retrospective, and the constructed nomogram still needs to be further tested by prospective studies. Moreover, the nomogram constructed in this study is suitable for predicting whether HCC patients can benefit

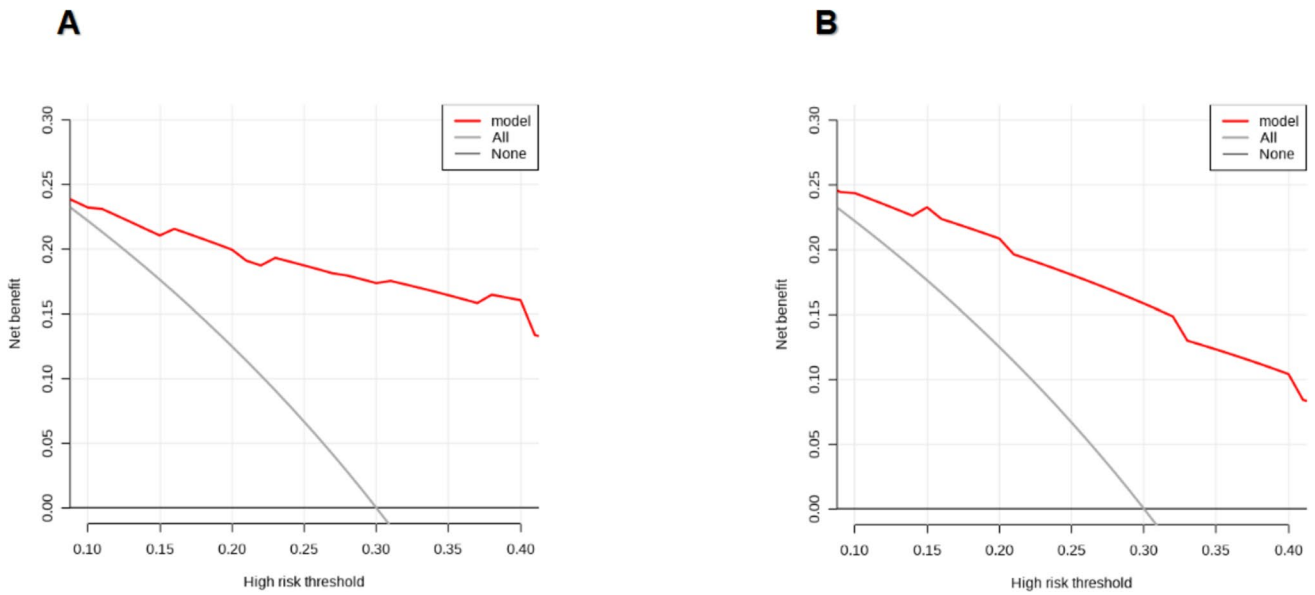

Fig. 6 Clinical decision curves of the nomogram in the development (**A**) and validation (**B**) sets

from multiple TACE treatments, and its role in predicting the benefit of other treatments or predicting the prognosis of HCC patients is not clear at present, which needs further research to confirm.

Conclusions

The model established in this study has a good predictive effect on HCC patients who can benefit from multiple TACE.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Huizhi Zhang, Xingxing Wang, Hongxiang Wang, Junchi Li, Kai Lei, Run Hu, and Zuojin Liu. The first draft of the manuscript was written by Huizhi Zhang and Xingxing Wang. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability No datasets were generated or analyzed during the current study.

Declarations

Conflict of interest All authors declare no conflict of interest.

Ethical approval This study was reviewed and approved by the Ethics Committee of the Second Affiliated Hospital of Chongqing Medical University.

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