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ORIGINAL RESEARCH

Development of a Nomogram for Prognostic Prediction of Large Hepatocellular Carcinoma With HBV After TACE Combined Conversion Therapy

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Background: Surgical resection (SR) following transarterial chemoembolization (TACE) is a promising option for large hepatocellular carcinoma (LHCC) with HBV, and identification of these patients at high-risk of prognosis may help individualized treatment.

Purpose: To develop and validate pre- and postoperative prognostic nomograms integrating clinico-therapeutic-pathological features for predicting overall survival (OS) after TACE combined therapy.

Materials and Methods: Between May 2010 and October 2021, 255 consecutive patients with LHCC receiving conversion therapy of TACE combined with Lenvatinib plus PD-1 inhibitors were included from three tertiary-care hospitals. In the derivation cohort (n=201), the Cox regression analysis for developing nomograms for OS (time from initial TACE to death). In the testing cohort (n = 54), two models' performance was compared with five major staging systems.

Results: The preoperative nomogram included alpha–fetoprotein (AFP, HR: 0.486; 95% CI: 0.266–0.886; P = 0.019) and albumin-bilirubin (ALBI) grade (HR: 0.323; 95% CI: 0.181–0.578; P < 0.001) and the postoperative nomogram, included AFP (HR: 0.501; 95% CI: 0.271–0.925; P = 0.027), ALBI grade (HR: 0.356; 95% CI: 0.192–0.659; P = 0.001), MVI (HR: 0.086; 95% CI: 0.024–0.192; P < 0.001), and response to TACE combined therapy (HR: 3.367; 95% CI: 1.479–7.721; P = 0.004). The testing dataset C-indexes of the pre- (0.715) and postoperative (0.912) nomograms were higher than all five staging systems (0.589–0.483; all P < 0.001). Two prognostically distinct risk strata were identified according to these nomograms (all P < 0.001).

Conclusion: Based on 255 patients receiving TACE combined conversion therapy for LHCC, we developed and validated two nomograms for predicting OS, with superior performances than five major staging systems and effective survival stratification.

Keywords: hepatocellular carcinoma, transarterial chemoembolization, conversion therapy, surgical resection, nomogram

Introduction

Hepatocellular carcinoma (HCC), constituting 75–80% of initial liver cancers, stands as a principal cause of cancer–related mortality globally.[1,2] China exhibits a high incidence of HCC, primarily due to viral hepatitis B infections. Due to the latent nature of HCC symptoms and the infrequent individualized physical examinations in China, over 80% of individuals with HCC miss the opportunity for surgical resection (SR) at the initial diagnosis.[3,4] In the past decade, the rapid development of targeted immunotherapy has offered new hope to these individuals with HCC deprived of SR options.[5–7] Early intervention for large HCC (with a maximum diameter exceeding 5 centimeters) can be administered via intra–arterial therapy (IAT), which includes transarterial chemoembolization (TACE), hepatic arterial infusion chemotherapy (HAIC), and radioembolization,[8–12]

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among others, or through a combined regimen of IAT and targeted immunotherapy.[12,13] Following a period of comprehensive treatment, these individuals with unresectable HCC (uHCC) may become eligible for SR if the tumor reduces in size and liver function remains stable along with good overall physical health.

TACE combined with targeted immunotherapy has been validated as a safe and efficacious approach for treating large HCC, demonstrating superior objective response rates (ORR) and survival benefits compared to TACE monotherapy, as evidenced by numerous studies.[14,15] For instance, Zheng et al reported a median overall survival (OS) of 19.5 months and an ORR of 66.7% in individuals with unresectable HCC undergoing TACE combined with Donafenib and Toripalimab.[16] Similarly, individuals receiving TACE in conjunction with Lenvatinib and Camrelizumab for unresectable, multiple nodular, and large HCC (> 5 cm) had a median OS of 16.4 months and an ORR of 51.5%, according to Huang et al.[17]

SR following successful TACE–based therapy is increasingly recognized as a safe and effective strategy for managing large HCC.[18,19] However, its long–term survival benefits exhibit significant individual variability due to extensive tumor heterogeneity. Individuals at high risk of mortality following SR after conversion therapy are prime candidates for postoperative adjuvant therapies and personalized surveillance with shorter intervals. Hence, identifying these high–risk individuals with HCC is crucial for tailoring individualized TACE–based treatments to extend survival and enhance quality of life.

Emerging evidence indicates that microvascular invasion (MVI) and initial response to TACE are correlated with the prognosis of individuals with unresectable HCC (uHCC) after IAT combined with targeted immunotherapy.[20–22] Although individual biological markers provide clear risk warnings for TACE combined with targeted immunotherapy and subsequent resection, their predictive capabilities remain inadequate. Therefore, an accurate and user–friendly prognostic tool is imperative for clinical application. The objective of this investigation is to establish and validate prognostic models based on preoperative and postoperative clinico–therapeutic–pathological variables to predict OS in individuals with large HCC undergoing TACE–based therapy followed by curative–intent SR.

Materials and Methodologies

For this retrospective investigation, the institutional review boards of Qingdao Central Hospital granted approval and waived the requirement for obtaining written informed consent from participants. All patient data was confidential, and the reporting of this study adheres to the Strengthening the Reporting of Cohort Studies in Surgery criteria.[23]

Patients

The diagnosis of HCC was confirmed either pathologically or by adhering to the diagnostic guidelines set forth by the American Association for the Study of Liver Diseases.[24] Between May 2010 and October 2021, three tertiary–care hospitals identified 1126 successive individuals who met the eligibility criteria, presenting with large HCC tumors exceeding 5 cm in maximum diameter, classified as Barcelona Clinic Liver Cancer (BCLC) stage A. The enrollment flowchart for these individuals is presented in Figure 1.

Participants were required to fulfill the following conditions for inclusion: (a) age ≥ 18 years; (b) Eastern Cooperative Oncology Group performance status below 2; (c) Child–Pugh class A liver function; (d) treatment with TACE combined with targeted immunotherapy followed by curative–intent SR. Exclusion criteria included: (a) previous antitumoral treatment prior to TACE; (b) current or prior malignancies other than HCC; (c) inadequate image quality for reliable assessment; (d) lack of follow–up information. All individuals with HCC meeting the Chinese Society of Hepatology guidelines for hepatitis B virus received anti–HBV treatment as clinically indicated.

Clinical data (eg, demographics, etiologies of chronic liver diseases) and laboratory results (eg, alpha–fetoprotein [AFP] and platelet count) were collected at baseline and within two weeks prior to TACE.

Treatment

TACE procedures were performed by three interventional radiologists, each with 5 to 10 years of experience, in a standardized manner following institutional protocols. The equipment used for TACE included: i) digital subtraction angiography (Philips, FD201250mA, Amsterdam, Netherlands); ii) the modified Seldinger technique for inserting an

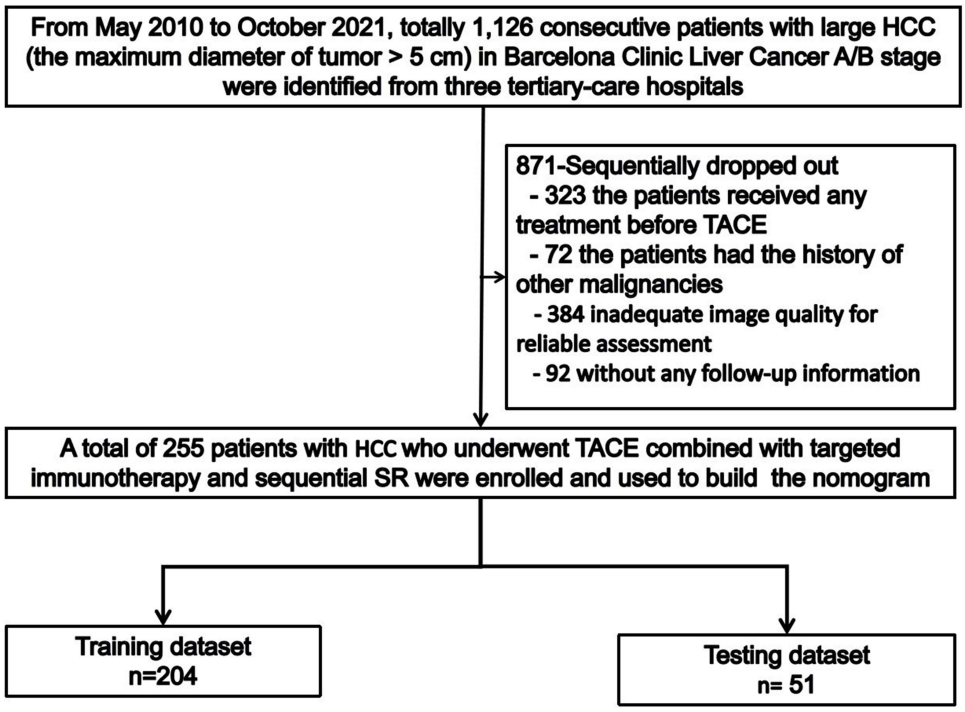

Figure 1 The study flowchart of development of the nomogram for prediction of overall survival.

arterial sheath catheter into the femoral artery; iii) a 5–Fr Yashiro catheter (Terumo, Tokyo, Japan) guided into the celiac trunk and superior mesenteric artery to evaluate the hepatic artery; and iv) a 2.7–Fr micro–catheter (Terumo, Tokyo, Japan) placed into the feeding artery, which was selected or super–selected when feasible. A mixture of 10–20 mL of lipiodol, 30–50 mg of platinum–based drugs, and 20–40 mg of epirubicin was gradually injected until the target vessel was blocked. If needed, gel foam mixed with contrast medium was utilized for embolization to decrease the residual blood flow, and the intervention was repeated until subsequent angiographic imaging confirmed the elimination of tumor staining.

Systemic therapy was combined with treatment regimens determined through multidisciplinary tumor board discussions, personalized based on perceived success probabilities and individual preferences. Oral first–line targeted chemotherapy, including lenvatinib, commenced 1–5 days following the initial TACE session and was continuously administered. Upon disease progression or the occurrence of 3–4 adverse events (AEs), second–line treatments such as regorafenib or apatinib were introduced. Oral lenvatinib (Lenvimafi; Eisai Co., Ltd.) was given to individuals with advanced HCC (Ad–HCC). The starting dosage depends on the individual's body weight and hepatic function. Individuals weighing more than 60 kg with Child–Pugh A liver function started at a dose of 12 mg daily, whereas those weighing less than 60 kg with the same liver function began at 8 mg daily. Upon discovering AEs, the researchers either reduced the dose or temporarily stopped the treatment. Immunotherapy was initiated 1–3 days post–TACE and administered intravenously every three weeks. Fixed–dose programmed death receptor 1(PD–1) inhibitors were used until disease progression or unexpected toxicity occurred. The dosage and interval of lenvatinib were adjusted based on toxicity and disease conditions.

Responses to TACE combined therapy were evaluated every 2–3 months post–treatment initiation using the same imaging methods as at baseline, following the modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria.[25] Treatment responses were categorized as either objective response (OR) (complete response or partial response) or non–objective response (stable disease or progressive disease). SR was recommended if tumor resectability was confirmed by liver surgery expert panels and an objective response to TACE combined therapy was maintained for at least four weeks. Lenvatinib and anti–PD–1 antibodies were halted within one week prior to SR, which was performed by two surgeons each with 5–10 years of experience. Intraoperative ultrasonography was routinely employed to assess minute intrahepatic tumors and ensure the possibility of a negative resection margin. R0 resections were defined as having a tumor–free margin of $\geq$ 1 mm for all detected tumors.

Follow–up and Outcome

Following the first TACE treatment, all subjects underwent routine surveillance at one–month post–procedure and then at intervals of three to six months until the final follow–up date (October 31, 2023) or individual demise. Surveillance included monitoring of serum AFP concentrations and imaging modalities such as contrast–enhanced ultrasound, computed tomography, or magnetic resonance imaging. The primary outcome that was tracked was OS, and its definition is the time interval between the start of TACE and death from any cause.

Statistical Analysis

The RMS package of R software version 3.5.1 (http://www.r–project.org/) was utilized in conjunction with the IBM Corp., NY, USA, SPSS program version 23.0 for statistical analysis. Individuals from center 1 [*BLINDED FOR REVIEW*] were designated as the derivation cohort, while those from the remaining centers [*BLINDED FOR REVIEW*] formed the test cohort. Although no formal sample size calculation was performed beforehand, the large number of death events in the derivation cohort relative to the number of variables analyzed in the multivariable Cox regression analysis ensured adherence to the "ten events per variable" rule of thumb, indicating sufficient accuracy of the regression estimates. Multivariable stepwise Cox regression analyses were utilized to develop two prognostic nomograms based on preoperative and postoperative variables.

Model discrimination for the test cohort was determined using the concordance index (C–index) and time–dependent area under the curve (td–AUC) from 12 to 36 months. Model calibration was evaluated using calibration plots, and the clinical utility of the nomograms was determined through decision curve analysis (DCA). The prognostic performance of the nomograms was compared with major clinical staging systems, including the BCLC,[5] European Association for the Study of Liver (EASL),[26] China Liver Cancer (CNLC),[27] Japan Society of Hepatology (JSH),[28] and Hong Kong Liver Cancer systems (HKLC),[29] using the Z test.

To stratify individuals into high– and low–risk groups, optimal thresholds for the nomograms were identified utilizing X–tile software (version 3.6.1, Yale University School of Medicine, New Haven, Conn). Cumulative survival outcomes for various risk groups were estimated utilizing the Kaplan–Meier method and compared via the log–rank test, with subgroup analyses performed to adjust for known prognostic factors.

The researchers employed two–sided tests for all statistical analyses, considering results with *a* P–value < 0.05 as statistically significant.

Results

Baseline Characteristics of Individuals With HCC

In this study, 255 individuals with large HCC (mean age, 50.3 ± 10.2 years; 211 males; mean tumor diameter, 9.1 ± 1.2 cm) received initial TACE combined with lenvatinib, PD–1 inhibitors, and sequential SR. The fundamental characteristics of individuals with HCC at baseline in the two cohorts are summarized and presented in Table 1. Specifically, the derivation cohort included 204 individuals (mean age, 52.8 ± 11.2 years; 170 male), while the test cohort consisted of 51 individuals (mean age, 49.0 ± 12.0 years; 41 male). The predominant etiology of chronic liver disease in all individuals with HCC was chronic HBV infection, with cirrhosis detected in 230 (90.2%) individuals.

For conversion therapy, the median interval between TACE and SR was 4.5 months (interquartile range [IQR], 1.8–7.2 months) for both the derivation and test cohorts ($P = 0.912$). The median sessions of TACE procedure per individual was 2 for the derivation cohort and 2 for the testing cohort ($P = 1.000$). Following conversion therapy, the mean maximum tumor diameter decreased from 9.2 cm to 3.2 cm ($P < 0.001$) for the derivation cohort and from 9.0 cm to 3.3 cm ($P < 0.001$) for the test cohort.

During a median follow–up time of 20.5 months (IQR, 7.8–44.8 months), the median OS time was 21.8 months, with cumulative 1–, 3–, and 5–year OS rates of 87.6%, 77.2%, and 67.5%, respectively, for the derivation cohort. For the test cohort, the median OS time was 24.2 months, with cumulative 1–, 3–, and 5–year OS rates of 91.4%, 84.2%, and 76.6%, respectively. No marked change was observed ($P = 0.272$).

Table 1 The Baseline Characteristics of Large HCC Patients Who Underwent TACE Combined Therapy in Two Cohorts

Variables	Derivation Cohort (n= 204)	Test Cohort (n=51)	*P* value
Age (years)[a]	52.8 ± 11.2	49.0 ± 12.0	0.0.87
BMI (kg/m^2)	23.2 ± 5.5	24.1 ± 5.2	0.617
Gender[b]			0.619
Male	170 (83.3%)	41 (80.4%)	
Female	34 (16.7%)	10 (19.6%)	
ECOG[b]			1.000
PS 0	199 (97.5%)	50 (98.0%)	
PS 1	5 (2.5%)	1 (2.0%)	
Comorbidities[b]			0.609
Absence	170 (83.3%)	44 (86.3%)	
Presence	34 (16.7%)	7 (13.7%)	
Cirrhosis[b]			0.292
Absence	18 (8.8%)	7 (13.7%)	
Presence	186 (91.2%)	44 (86.3%)	
Ascites[b]			0.226
Absence	194(95.1%)	51 (100%)	
Presence	10(4.9%)	0 (0%)	
Child-Pugh class[b]			0.262
A	201(98.5%)	49 (96.1%)	
B	3(1.5%)	2(3.9%)	
ALBI score[a]	−2.80 ± 0.23	−2.74 ± 0.26	0.337
Maximum diameter of tumors (cm)[b]	9.2 (5.6, 13.8)	9.0 (5.2, 14.2)	0.682
AFP (ug/mL)[b]			0.754
<400	97 (47.5%)	23 (45.1%)	
>400	107 (52.5%)	28 (54.9%)	
DCP (ug/mL)[b]			0.822
<400	45 (22.1%)	12 (23.5%)	
>400	159 (77.9%)	39 (76.5%)	
ALT (U/L)[b]	45.8 (22.4,119.0)	48.2 (22.8, 90.3)	0.258
AST(U/L)[b]	86.2 (43.3, 157.7)	87.7 (32.8,185.2)	0.289
ALB (g/L)[a]	39.5 ± 5.5	39.6 ± 5.0	0.948
TBIL (μmol/L)[a]	18.6 (5.5, 65.3)	19.2 (6.5, 78.2)	0.357
PT(s)[a]	12.6 ± 1.4	12.4 ± 1.3	0.280
INR[a]	1.02 ± 0.12	1.04 ± 0.13	0.892
PLT (×10^9)[a]	195 (67, 262)	212 (78, 243)	0.303
Cre (μmol/L)[a]	71.0 ± 9.2	71.9 ± 10.2	0.664
CRP (μmol/L)[a]	21.4 (5.8, 46.5)	22.2 (6.2, 51.7)	0.209
Ly[a] (×10^9/L)	1.5 ± 0.4	1.6 ± 0.3	0.802
Neu[a] (×10^9/L)	4.3 ± 0.2	4.5 ± 0.4	0.699
TACE sessions[a]	2 (1, 4)	2 (1, 4)	0.985
The interval time between TACE and SR(days)[a]	42 (22, 78)	38 (21, 69)	0.451
MVI[b]			0.007
Absence	124 (60.8%)	34 (82.9%)	
Presence	80(39.2%)	17 (17.1%)	
Response to TACE combined therapy[b]			0.616
OR	108 (52.9%)	25 (49%)	
Non-OR	96 (47.1%)	26 (51%)	

Notes: —Data are number of patients; data in parentheses are percentage unless otherwise indicated. Normally distributed data is represented by mean ± SD and non-normally is median with IQR. P-value < 0.05 indicated a significant difference. [a]Continuous variables were compared using the two samples *t* test or Wilcoxon rank-sum test; [b]Categorical variables were compared by using the Chi square test.
Abbreviations: TACE, transarterial chemoembolization; SR, surgical resection; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; PLT, platelet; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AFP, α-fetoprotein; DCP, des-γ-carboxy prothrombin; ALB, albumin; TBIL, total bilirubin; ALBI, albumin- bilirubin; Cre, creatinine; PLT, Ly, lymphocyte; Neu, neutrophils; PT, prothrombin time; INR, international normalized ratio; MVI, microvascular invasion; OR, objective response.

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Table 2 Multivariable Cox Regression Analysis of Predictors for Overall Survival TACE Combined Therapy Based on Pre- and Postoperative Variables in the Derivation Cohort

Variables	Preoperative Nomogram			Postoperative Nomogram		
	β	Hazard Ratio	*P* value	β	Hazard Ratio	*P* value
AFP level (ng/mL)(> 400 vs ≤ 400)	−0.711	0.486 (0.266–0.886)	0.019	−0.699	0.501(0.271–0.925)	0.013
ALBI grade (1 vs 2)	−1.122	0.323 (0.181–0.578)	<0.001	−1.032	0.356 (0.192–0.659)	0.001
Objective response to TACE combined therapy (no vs yes)				−0.525	0.086 (0.024–0.192)	<0.001
Microvascular invasion (present vs absent)				1.214	3.367(1.479–7.721)	0.004

Note: —Numbers in parentheses are the 95% confidence interval.
Abbreviations: TACE, transarterial chemoembolization; AFP, α-fetoprotein; ALBI, albumin- bilirubin.

Development of the Prognostic Nomograms in the Derivation Cohort

Multivariate analyses of preoperative variables identified that AFP (HR: 0.486; 95% CI: 0.266–0.886; $P = 0.019$) and ALBI grade (HR: 0.323; 95% CI: 0.181–0.578; $P < 0.001$) markedly influenced the OS rate. Further multivariate analyses using postoperative variables indicated that factors markedly impacting OS included AFP (HR: 0.501; 95% CI: 0.271–0.925; $P = 0.027$), ALBI grade (HR: 0.356; 95% CI: 0.192–0.659; $P = 0.001$), MVI (HR: 0.086; 95% CI: 0.024–0.192; $P < 0.001$), and response to TACE combined therapy (HR: 3.367; 95% CI: 1.479–7.721; $P = 0.004$) (Table 2).

Two nomograms were developed using these independent risk factors to predict OS in individuals with large HCC treated with initial TACE, lenvatinib, PD–1 inhibitors, and sequential SR. Nomogram 1 was described by the formula: Y = –7.902 + 1.886 × AFP (0: ≤ 400 ng/mL; 1: > 400 ng/mL) + 3.872 × ALBI grade (0: grade 1; 1: grade 2), where Y indicates the probability of death (Figure 2A). Figure 2B and C display the calibration curves of nomogram 1 in both

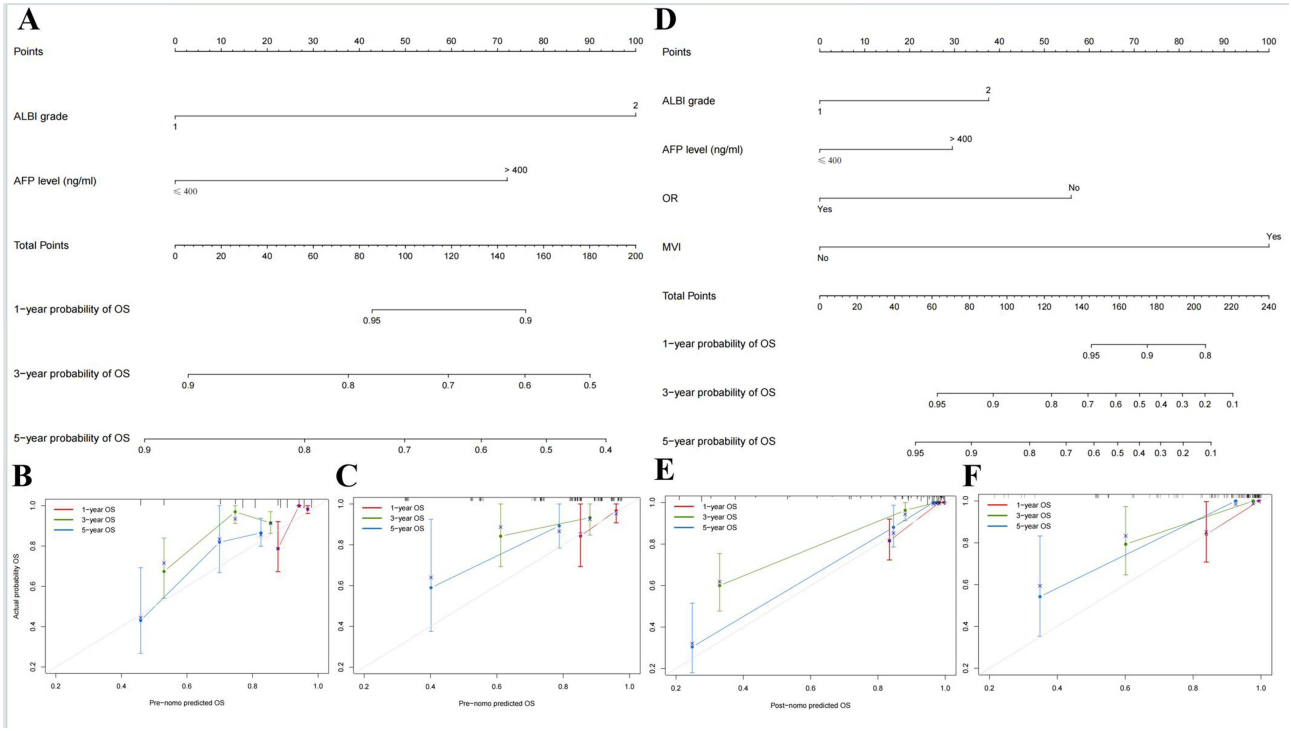

Figure 2 Development of the preoperative nomogram (**A**), and the calibration curves of nomogram 1 in both the derivation (**B**) and test cohorts (**C**) and postoperative (**D**) nomogram and the calibration curves of nomogram 2 in both the derivation (**E**) and test cohorts (**F**).

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the derivation and test cohorts, demonstrating optimal agreement between the predicted 1–, 2–, and 3–year probabilities and the actual 1–, 2–, and 3–year OS probabilities for TACE combined therapy in the two cohorts.

Nomogram 2 was characterized by the formula: Y = –5.893 + 1.437 × AFP (0: ≤ 400 ng/mL; 1: > 400 ng/mL) + 3.067 × ALBI grade (0: grade 1; 1: grade 2) + 9.672 × response (0: non–OR; 1: OR) + 7.114 × MVI (0: Presence; 1: Absence), where Y indicates the probability of death (Figure 2D). Figure 2E and F show the calibration curves of nomogram 2 in the training and test cohorts, indicating optimal agreement between the predicted 1–, 3–, and 5–year probabilities and the actual 1–, 3–, and 5–year OS probabilities for TACE combined therapy in the two cohorts.

Validation of the Prognostic Nomograms and Comparisons With Major Staging Systems

The discriminative ability, including 1–, 3–, and 5–year AUC and C–index of the two nomograms and major staging systems, are summarized in Table 3. The C–index of nomogram 1 was 0.672, while that of nomogram 2 was 0.872, indicating markedly superior performance of nomogram 2 compared to nomogram 1 and all five staging systems (C–index: 0.672–0.542; all $P < 0.001$) in the derivation cohort. Similarly, in the test cohort, the C–index of nomogram 1 was 0.715, and that of nomogram 2 was 0.912, again showing that nomogram 2 outperformed nomogram 1 and all five staging systems (C–index: 0.715–0.483; $P = 0.016$–<0.001). The td–AUC of nomogram 2 was also markedly higher than those of the other staging systems at various time points in both cohorts ($P < 0.05$) (Figure 3A and B). Additionally, DCA demonstrated that nomogram 2 provided greater net benefit across a range of reasonable threshold probabilities compared to the staging systems in both the derivation and test cohorts ($P < 0.05$) (Figure 3C and D).

Survival Risk Stratification

Based on nomogram 1, individuals with HCC were stratified into three risk subgroups with cutoff values of 33.78 and 72.89 points. The cumulative 1–, 3–, and 5–year OS rates were 76.7%, 48.5%, and 31.7% in the high–risk group; 98.7%, 76.2%, and 76.2% in the middle–risk group; and 100%, 92.7%, and 76.2% in the low–risk group. Marked statistical differences were observed ($P < 0.001$) in the derivation cohort (Figure 4A). In the test cohort, the cumulative 1–, 3–, and 5–year OS rates were 72.3%, 72.3%, and 40.5% in the high–risk group; 100%, 77.9%, and 52.1% in the middle–risk group; and 100%, 84.7%, and 74.7% in the low–risk group, with marked statistical differences ($P = 0.032$) (Figure 4B).

Table 3 Comparison of the Performance and Discriminative Ability Between the Current Model and Other Models

Cohorts	Models	1-Years AUC	3-Years AUC	5-Years AUC	C-Index (SE)	P value
DC	Post-nomo	0.926(0.875, 0.978)	0.939(0.896, 0.982)	0.880(0.757, 1.004)	0.878(0.022)	*Ref*
	Pre-nomo	0.803(0.658, 0.948)	0.722(0.611, 0.833)	0.665(0.502, 0.828)	0.672(0.051)	*<0.001*
	BCLC	0.641(0.504, 0.778)	0.526(0.424, 0.629)	0.556(0.379, 0.734)	0.541(0.043)	*<0.001*
	JHS	0.655(0.518, 0.792)	0.527(0.425, 0.630)	0.534(0.358, 0.711)	0.526(0.044)	*<0.001*
	CNLC	0.605(0.458, 0.752)	0.483(0.382, 0.585)	0.508(0.333, 0.684)	0.523(0.044)	*<0.001*
	EASL	0.394(0.247, 0.541)	0.535(0.433, 0.636)	0.496(0.320, 0.671)	0.502(0.044)	*<0.001*
	HKCL	0.647(0.510, 0.783)	0.528(0.426, 0.630)	0.546(0.369, 0.723)	0.530(0.044)	*<0.001*
TC	Post-nomo	0.961(0.902, 1.019)	0.986(0.961, 1.013)	0.729(0.333, 1.124)	0.912(0.028)	*Ref*
	Pre-nomo	0.801(0.619, 0.983)	0.739(0.565, 0.913)	0.521(0.185, 0.857)	0.715(0.079)	*0.016*
	BCLC	0.594(0.338, 0.851)	0.553(0.367, 0.739)	0.504(0.256, 0.753)	0.566(0.083)	*<0.001*
	JHS	0.583(0.326, 0.840)	0.553(0.367, 0.739)	0.504(0.256, 0.753)	0.556(0.082)	*<0.001*
	CNLC	0.617(0.361, 0.872)	0.509(0.342, 0.676)	0.465(0.227, 0.702)	0.547(0.082)	*<0.001*
	EASL	0.583(0.326, 0.840)	0.553(0.367, 0.739)	0.504(0.256, 0.753)	0.559(0.082)	*<0.001*
	HKCL	0.520(0.295, 0.744)	0.474(0.298, 0.651)	0.525(0.283, 0.767)	0.483(0.077)	*0.002*

Abbreviations: DC, derivation cohort; TC, test cohort; ALBI, albumin-bilirubin, AUC, area under receiver operating characteristic curve; BCLC, Barcelona Clinic Liver Cancer, CNLC, China Liver Cancer; HKLC, Hong Kong Liver Cancer; JSH, Japan Society of Hepatology; EASL, European Association for the Study of the Liver.

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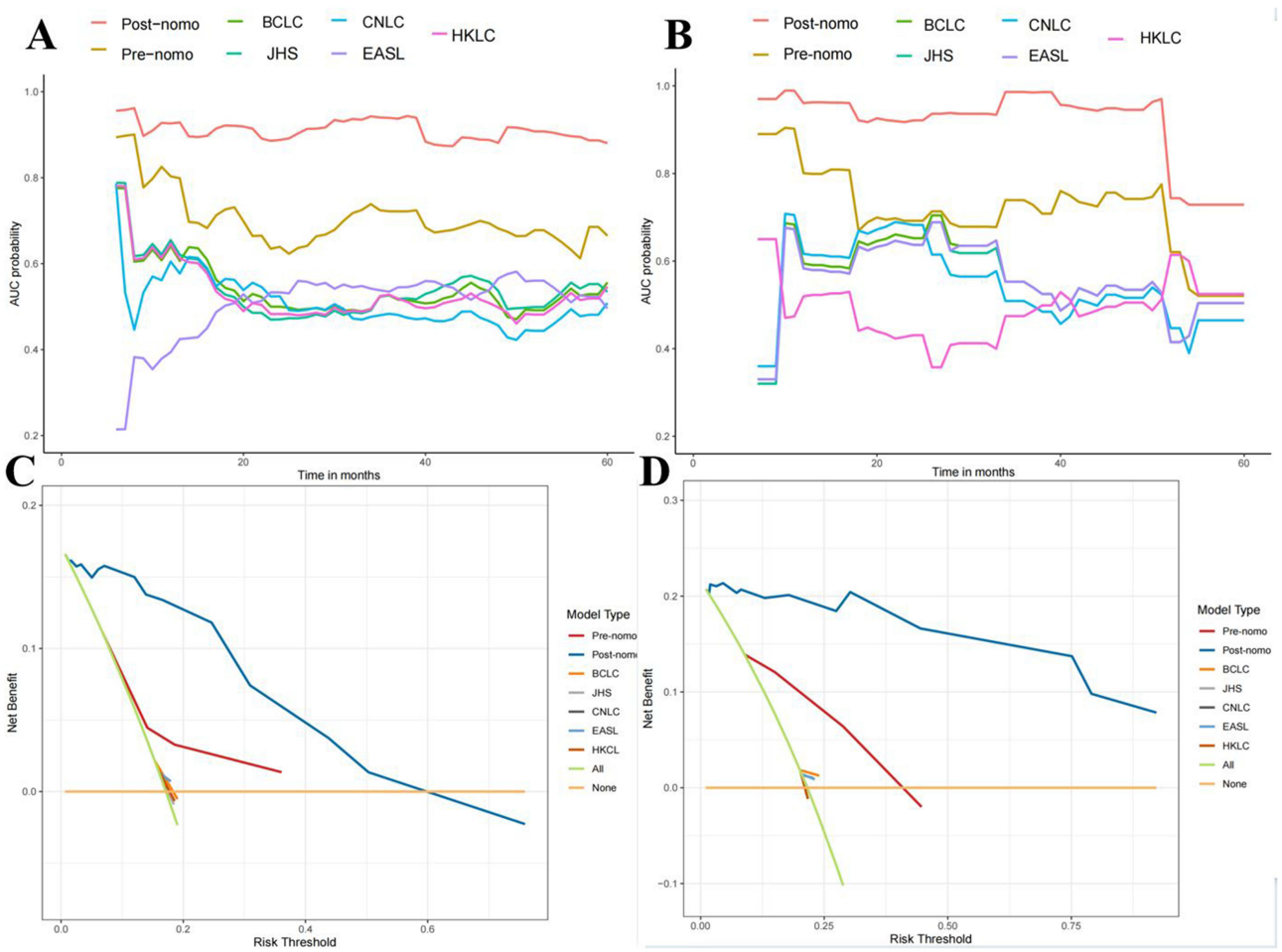

Figure 3 Performances of the preoperative and postoperative nomograms as well as five major staging systems for predicting overall survival. Model discrimination measured with time-dependent areas under the receiver operating characteristic curves at various time points for the derivation (**A**) and testing (**B**) cohorts. Model clinical usefulness measured by decision curves for the derivation (**C**) and testing (**D**) cohorts.

Using nomogram 2, individuals were similarly stratified into three risk subgroups with cutoff values of 25.74 and 81.90 points. The cumulative 1–, 3–, and 5–year OS rates were 73.2%, 28.7%, and 22.6% in the high–risk group; 100%, 80.4%, and 80.4% in the middle–risk group; and 100%, 100%, and 87.7% in the low–risk group, showing marked statistical differences ($P < 0.001$) in the derivation cohort (Figure 4C). In the test cohort, the cumulative 1–, 3–, and 5–year OS rates were 77.8%, 48.5%, and 26.4% in the high–risk group; 100%, 100%, and 82.8% in the middle–risk group; and 100%, 100%, and 63.2% in the low–risk group, with marked statistical differences ($P < 0.001$) (Figure 4D).

Discussion

The prognosis for individuals with large HCC is poor, primarily due to the failure to achieve successful SR, with a median OS time of less than two years. Conversion therapy, previously defined as converting uHCC into resectable HCC, has introduced new hope for managing large HCC.[30] The Chinese Expert Consensus on Conversion Therapy for Hepatocellular Carcinoma also reports that conversion therapy is an intermediate goal in treating large HCC,[31] while long–term survival remains the ultimate objective. Traditional methods of conversion therapy, such as TACE and HAIC, have historically struggled to meet SR requirements. However, many HCC patients with high tumor burden occurred commonly refractoriness to TACE.[32] The rapid advancements in molecular targeted therapy and immunotherapy in recent years have demonstrated that combining targeted immunotherapy with TACE yields a highly synergistic effect,[31] making it an ideal treatment for unresectable large HCC, with an ORR of 56–79%. For instance, Wu et al demonstrated that the combination of TACE, lenvatinib, and anti–PD–1 antibodies (a three–pronged approach) yielded promising

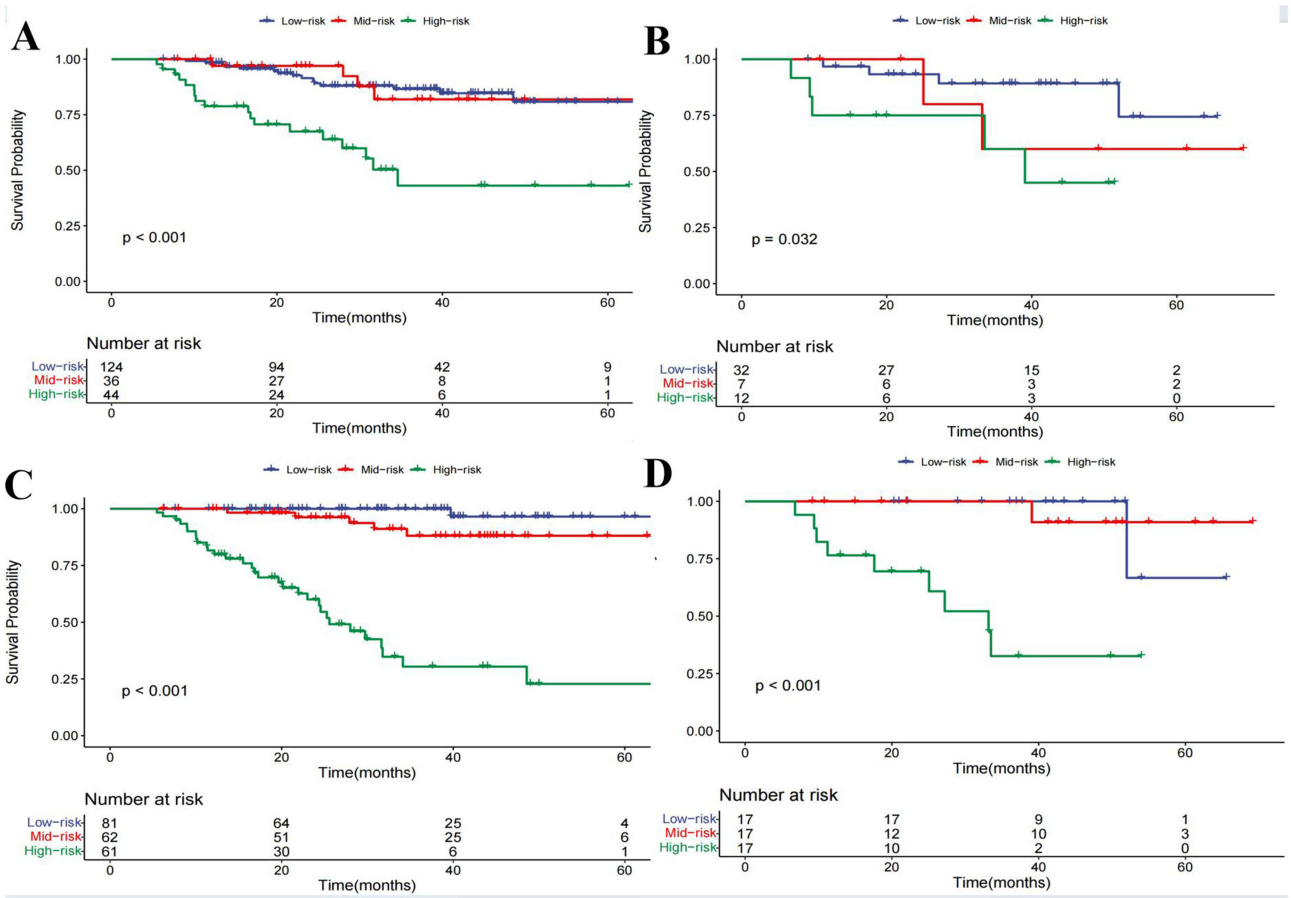

Figure 4 Kaplan-Meier curves for overall survival (OS) outcomes for different risk groups. OS outcomes for risk groups defined by the preoperative nomogram for the derivation (**A**) and testing cohorts (**B**). OS outcomes for risk groups defined by the postoperative nomogram for the derivation (**C**) and testing (**D**) cohorts.

outcomes for individuals with uHCC (77.4% ORR and a 46.8% conversion resection rate).[33] Furthermore, Teng et al found that in a real–world setting, TACE combined with camrelizumab and apatinib for individuals with intermediate and Ad–HCC resulted in a median OS of 24.1 months and a 59.5% ORR.[34]

SR following the combination of TACE, lenvatinib, and anti–PD–1 antibodies is a highly effective conversion therapy option, with potential synergistic antitumor effects observed in previous studies.[35,36] However, the prognosis for this population with large HCC varies markedly. Due to SR being an invasive treatment that can easily cause postoperative complications, it is crucial for individuals to make informed decisions regarding sequential SR before treating large HCC. Identifying high–risk individuals with HCC can assist physicians in making individualized treatment decisions. Consequently, two nomograms were developed and validated based on pre– and postoperative clinical variables to predict OS after TACE combined therapy.

In this study, TACE combined with lenvatinib, PD–1 inhibitors, and sequential SR was performed on 255 individuals with a single large HCC, with a follow–up period exceeding ten years. Several major findings were demonstrated: first, individuals with large HCC who underwent TACE combined conversion therapy had markedly better survival outcomes, with a median OS time of 22.6 months, compared to those who received TACE alone or SR alone. Second, ALBI grade and AFP level were identified as crucial variables associated with OS and used to develop a preoperative nomogram, consistent with previous reports.[37,38] Third, AFP, ALBI grade, MVI, and objective response to conversion therapy were used to develop the postoperative nomogram, which showed markedly improved performance and discrimination (C–index of 0.872 in the derivation cohort and 0.912 in the test cohort) compared to the preoperative nomogram and other staging systems. Fourth, the response to TACE combined with lenvatinib and PD–1 inhibitors should be closely monitored before SR. Better long–term survival may be associated with easier

performance of R0 curative SR, based on the effective reduction of large tumors. Notably, the ALBI score, as an objective and convenient assessment of liver function, has gained increasing value among clinical physicians, replacing the traditional CTP grading method. To date, there has been no research has developed a nomogram based on the ALBI grade to provide personalized survival information for individuals with large HCC who have undergone TACE conversion therapy.

A nomogram is a visual statistical model incorporating novel prognostic risk factors, allowing for quantitative assessment of prognostic risks and estimation of personalized survival. By integrating analyses of liver function, tumor markers, therapeutic response, and histopathologic features such as MVI, our nomograms demonstrated superior prognostic performance compared to major staging systems in the test cohorts, highlighting their incremental value to existing prognostic systems. Additionally, the nomograms enabled effective stratification of OS following conversion therapy, maintaining stability across subgroup analyses when adjusting for known prognostic factors. These findings are clinically relevant. First, the objective response according to mRECIST was associated with better OS in the post-operative nomogram, suggesting that treatment response might indicate the optimal timing for SR after successfully downstaging large HCC to meet resectability criteria. For instance, ongoing downstaging therapy could benefit individuals with resectable tumors exhibiting an mRECIST–defined response of stable disease. Second, the preoperative nomogram can serve as a valuable decision–making tool for personalized surgical planning. High–risk individuals, for instance, might benefit from more intensive surgical approaches such as a wider resection margin. Third, the post-operative nomogram can identify high–risk individuals who may profit from postoperative adjuvant therapies and more intensive surveillance (eg, shorter intervals and more sensitive techniques).

This study had several limitations. First, its retrospective design constituted an intrinsic limitation. Second, all individuals had chronic HBV infection, which might limit the generalizability of our findings to non–HBV cohorts. Third, although data were collected from four tertiary–care hospitals, the number of individuals in the external testing cohort was relatively small. Additionally, due to the retrospective nature and differences in routine practices, the TACE combined therapy regimens varied across participating centers, potentially introducing confounding factors. Lastly, imaging features, which are pivotal risk prediction factors, were not included in our study. Future research should incorporate imaging features into our model to improve its predictive ability. Therefore, large–scale prospective studies, ideally clinical trials, enrolling individuals with more diverse chronic liver disease etiologies and standardized treatment regimens are warranted to validate and refine our findings.

In conclusion, based on data from 255 individuals receiving TACE combined therapy and subsequent curative–intent SR for large HCC from three tertiary–care hospitals, we developed and validated two nomograms integrating clinical, therapeutic, and histopathologic features for predicting OS. The postoperative nomogram demonstrated markedly higher performance than five major staging systems and allowed effective stratification of cumulative OS risk, potentially aiding in individualized treatment decision–making and surveillance strategy selection.

Ethics Approval

The Qingdao Central Hospital's Institutional Review Board approved this retrospective study, which was carried out in accordance with the Declaration of Helsinki rules of conduct from 1975.

Medical Database Availability

The in-house developed medical database of this study is publicly accessible at http://www.yunedc.cn/#/login.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

No conflicts of interest.

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