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ORIGINAL RESEARCH

Construction and Validation of a Predictive Model for Post-TACE Recurrence Risk in Hepatocellular Carcinoma: A Retrospective Cohort Study

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Background: Transarterial chemoembolization (TACE) is widely used for unresectable hepatocellular carcinoma (HCC) and as adjuvant therapy to prevent postoperative recurrence. However, accurate prognostic models for HCC patients undergoing TACE remain underutilized clinically.

Methods: This retrospective study included 265 HCC patients who underwent TACE, randomly assigned to training and validation sets (6:4 ratio). Recurrence-related risk factors were identified using Cox regression and further screened by Least Absolute Shrinkage and Selection Operator (LASSO) regression. A prognostic nomogram was constructed, with decision curve analysis (DCA) assessing its clinical utility.

Results: Univariate Cox regression identified sex, vascular invasion, ascites, modified albumin–bilirubin grade (mALBI), China Liver Cancer (CNLC) staging, white blood cell count, neutrophils, fibrinogen (Fib), and neutrophil-to-lymphocyte ratio as significant risk factors (all HR > 1, $P < 0.05$). Albumin (ALB), prognostic nutritional index, and alkaline phosphatase-to-albumin ratio (AAPR) were protective factors (all HR < 1, $P < 0.05$). Multivariate analysis identified elevated Fib and higher CNLC stage as independent predictors (all $P < 0.05$). LASSO extracted vascular invasion, neutrophils, ALB, activated partial thromboplastin time, Fib, and AAPR as prognostic variables. Areas under the ROC curve at 6 months, 1 year, and 2 years were 0.717, 0.794, and 0.884, respectively. DCA demonstrated greater net clinical benefit than Barcelona Clinic Liver Cancer and CNLC staging systems. Risk stratification by nomogram tertiles showed significantly earlier recurrence in high-risk patients (all $P < 0.05$).

Conclusion: This TACE-based prognostic nomogram integrating clinical and laboratory parameters accurately predicts postoperative recurrence and enables individualized risk stratification, assisting clinicians in tailoring interventions and delivering personalized therapy.

Keywords: hepatocellular carcinoma, nomogram, transarterial chemoembolization, retrospective, recurrence

Introduction

Hepatocellular carcinoma (HCC) represents a major global health burden and remains one of the leading causes of cancer-related mortality worldwide.[1–3] Even after initially successful locoregional or surgical treatment, early intrahepatic recurrence frequently limits long-term survival.[4–6] Despite improvements in surveillance, diagnosis, and multimodal therapeutic strategies, a substantial proportion of patients remain ineligible for curative resection or transplantation, and recurrence following locoregional therapy continues to constitute a significant clinical challenge.[7] Transarterial chemoembolization (TACE) occupies a central role in the treatment of intermediate-stage and many unresectable HCCs and is widely applied as a bridging or downstaging procedure before potentially curative therapies.[8,9] However, clinical outcomes after TACE vary markedly among individuals.[10] Conventional staging systems, such as the Barcelona Clinic Liver Cancer (BCLC) classification and the China Liver Cancer (CNLC) staging system,

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provide general guidance for post-TACE risk prediction, but their clinical net benefit and prognostic accuracy remain limited. Several studies have shown that incorporating quantitative liver function markers may enhance risk stratification, particularly when treatment decisions require balancing antitumor efficacy with preservation of liver function.[11,12] Recent integrative bioinformatics analyses have identified hub genes and molecular targets in HCC progression, underscoring the complexity of tumor biology and the need for refined prognostic approaches.[13]

Beyond anatomical and hepatic reserve indicators, systemic inflammatory and nutritional markers have emerged as reliable and readily accessible predictors of HCC prognosis. Across multiple HCC cohorts and meta-analyses, elevated neutrophil-to-lymphocyte ratio (NLR), reduced prognostic nutritional index (PNI), and decreased albumin-to-alkaline phosphatase ratio (AAPR) have consistently been associated with higher recurrence rates and poorer survival outcomes.[14,15] These biomarkers are thought to reflect the interplay between tumor-promoting inflammation in the tumor microenvironment, immunosuppression, and the nutritional and hepatic synthetic capacity of the patient, all of which significantly influence prognosis after TACE. Incorporating such markers into predictive models may improve discriminative ability and better identify biological phenotypes at high risk for early recurrence.[16]

Recently, coagulation-related biomarkers, including plasma fibrinogen and composite measures such as fibrinogen to albumin ratio (FAR) or fibrinogen to lymphocyte ratio, have been recognized as independent prognostic indicators of HCC.[17] Preclinical and translational studies indicate that elevated fibrinogen is associated with tumor aggressiveness, angiogenesis, and immune evasion, and has been linked to adverse outcomes following resection or locoregional therapies.[18] These findings provide a mechanistic rationale for integrating coagulation parameters with inflammatory and hepatic markers when constructing prognostic tools for patients undergoing TACE.[19] Beyond circulating markers, specific molecular proteins have shown prognostic value in HCC. For example, elevated Vav1 expression correlates with unfavorable clinicopathological features and reduced 5-year overall survival.[20] Similarly, KIF5B has been identified as a prognostic signature involved in metabolic reprogramming, with upregulation associated with poor outcomes.[21]

Although a growing number of prognostic models and nomograms have been published in recent years, few specifically target early recurrence after TACE, and their concordance indices often remain suboptimal.[22] Thus, there is a lack of a user-friendly nomogram that incorporates clinical, imaging, and routine laboratory measures and that requires rigorous internal validation. Decision curve analysis (DCA) and time-dependent AUC evaluations are increasingly used to demonstrate not only statistical improvement but also net clinical benefit compared with conventional staging systems.[23] Furthermore, preclinical studies of novel therapeutic combinations, such as SHR6390 with cabozantinib, demonstrate efficacy in suppressing HCC progression, highlighting the evolving treatment landscape and the necessity for precise patient stratification.[24]

In this retrospective cohort of 265 patients with hepatocellular carcinoma treated with TACE, we developed and internally validated a prognostic nomogram to predict early post-TACE recurrence. The model incorporates tumor burden, liver function, systemic inflammatory and nutritional indices (NLR, PNI, AAPR), and coagulation parameters. Independent predictors were identified using univariate Cox analysis and LASSO regression to reduce overfitting, and model performance was evaluated by time-dependent ROC curves, calibration, and decision curve analysis, with comparison to established staging systems. The nomogram enables individualized estimation of early recurrence risk at clinically relevant time points, supporting risk-adapted surveillance and personalized post-TACE management.

Methods

Patient Characteristics

This retrospective study included patients with HCC who underwent TACE in the Department of Hepatobiliary and Pancreatic Surgery at Shenzhen People's Hospital between January 1, 2020, and January 1, 2025 (n = 312). All patients had a confirmed diagnosis of HCC. The inclusion criteria were: (a) age ≥18 years; (b) diagnosis of HCC based on pathology or imaging; (c) Child–Pugh stage A or B; and (d) receipt of TACE as the first-line treatment during the index admission. The exclusion criteria were: (a) incomplete clinical or follow-up data, (b) death from non–HCC-related causes, (c) unclear treatment modality, (d) presence of multiple concurrent malignancies, and (e) severe cardiac disease. After applying these criteria, 265 eligible patients were included in the final analysis. All patients were randomly assigned to a training set (n = 156) and a validation set (n = 109) in a 6:4 ratio. A total sample size of 265 provides sufficient statistical stability and degrees of freedom for robust analysis.[25] The study was conducted in accordance with the ethical principles of the Declaration of Helsinki (2013) and was approved by the Ethics Committee of Shenzhen People's Hospital (Approval No. LL-KY-2025247-01). As a retrospective study using anonymized electronic medical record data, informed consent was waived by the Ethics Committee of Shenzhen People's Hospital. The study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[26]

Data Collection

Data collected in this study included demographic characteristics such as age, sex, body mass index (BMI), presence of liver cirrhosis, ascites, performance status (PS), and nutritional risk screening (NRS2002), as well as prior treatment history, including surgery, interventional therapy, ablation, and systemic therapy. Laboratory parameters comprised complete blood count, liver and renal function tests, coagulation profiles, and hepatitis B virus deoxyribonucleic acid (HBV-DNA) levels. Tumor-related information encompassed tumor size, tumor number, vascular invasion, lymph node metastasis, and multiple staging systems, including the China Liver Cancer (CNLC) staging, Barcelona Clinic Liver Cancer (BCLC) staging, modified albumin–bilirubin (mALBI) grade, and Child–Pugh grade. In addition, several nutritional and immune-inflammatory indices were calculated, including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), prognostic nutritional index (PNI), and albumin-to-alkaline phosphatase ratio (AAPR), using the following formulas: NLR = neutrophil count / lymphocyte count; PLR = platelet count / lymphocyte count; PNI = serum albumin (g/L) + 0.005 × lymphocyte count (per mm^3); and AAPR = serum albumin (g/L) / alkaline phosphatase (U/L).

Follow-Up and Outcome Definition

In this study, disease-free survival (DFS) was used as the primary endpoint, defined as the time from TACE treatment to either HCC recurrence or tumor-related death, with the event determined by whichever occurred first.[27] Recurrence was defined as the appearance of a new tumor during follow-up, confirmed by imaging studies, including CT, contrast-enhanced CT, or magnetic resonance imaging (MRI), or by pathological biopsy. Patients were followed according to established guidelines, with routine follow-up every three months during the first two years after TACE and every six months thereafter. Postoperative monitoring was conducted through outpatient visits, telephone interviews, or electronic medical record (HIS) review. Within the first year after TACE, CT or MRI and serum tumor marker assessments were performed every three months. The last follow-up for this study was conducted on October 17, 2025.

Statistical Analysis

All statistical analyses were performed using R software (version 4.5.1). Continuous variables were expressed as mean ± standard deviation (mean ± SD) and compared using the Student's *t*-test or Mann–Whitney *U*-test, as appropriate. Categorical variables were presented as counts and percentages and compared using the chi-square test or Fisher's exact test. Univariate Cox regression analysis was used to identify factors associated with DFS. Variables with $P < 0.1$ were further selected using least absolute shrinkage and selection operator (LASSO) regression to reduce collinearity, followed by multivariate Cox regression to determine independent prognostic factors. Hazard ratios (HRs) and 95% confidence intervals (CIs) were reported. A prognostic nomogram was constructed based on the independent predictors. Model performance was assessed using time-dependent receiver operating characteristic (ROC) curves at 6 months, 1 year, and 2 years, calibration curves with 1000 bootstrap resamples, and decision curve analysis (DCA) to compare the clinical net benefit with that of the BCLC and CNLC staging systems. Patients were stratified into low-, intermediate-, and high-risk groups according to the tertiles of the nomogram score, and survival differences were evaluated using Kaplan–Meier curves and the Log rank test. A two-sided P value < 0.05 was considered statistically significant.

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Results

Demographic Characteristics and Baseline Data

After rigorous screening, a total of 265 HCC patients who underwent TACE were included in this study, and the detailed inclusion process is shown in Figure 1. Patients were randomly assigned to a training set (n = 156) and a validation set (n = 109). No significant differences were observed for any variables between the two datasets (all P > 0.05). The mean age of the overall cohort was 58.4±13.2 years, and the majority were male (86.8%). According to BCLC staging, most patients were classified as stage B (27.9%) or stage C (59.2%), while CNLC staging was predominantly stage II or III, accounting for approximately 81.5% of the cohort. Nearly all patients had mALBI grade 1 or 2 (98.1%). The mean BMI was 23.2±3.52, which falls within the normal range. Regarding nutritional status, 81.1% of patients had an NRS 2002 score of 0 or 1. Additionally, 83.8% of patients had an ECOG PS of 0 or 1. Most patients had not received prior surgery (83.4%), systemic therapy (86.0%), interventional therapy (85.3%), radiotherapy (98.1%), or ablation (93.6%). Tumor-related characteristics showed a mean maximal tumor diameter of 54.38±42.12 mm, with most tumors lacking vascular invasion (65.7%), and approximately half of the patients presenting with lymph node metastasis (47.9%). All baseline demographic and clinical data are summarized in Table 1.

Screening of Risk Variables

To further identify risk factors for recurrence in HCC patients undergoing TACE, univariate and multivariate Cox regression analyses were performed in the training set (Table 2). The results indicated that sex, vascular invasion, ascites, mALBI grade, CNLC stage, white blood cell count, neutrophil count, fibrinogen (Fib), and neutrophil-to-lymphocyte ratio (NLR) were associated with increased risk of post-TACE recurrence (all HR > 1, P < 0.05), whereas ALB, PNI, and AAPR were protective factors (all HR < 1, P < 0.05; Figure 2A). Furthermore, multivariate Cox regression analysis revealed that CNLC stage and Fib were independent predictors of recurrence after TACE (Figure 2B). To reduce

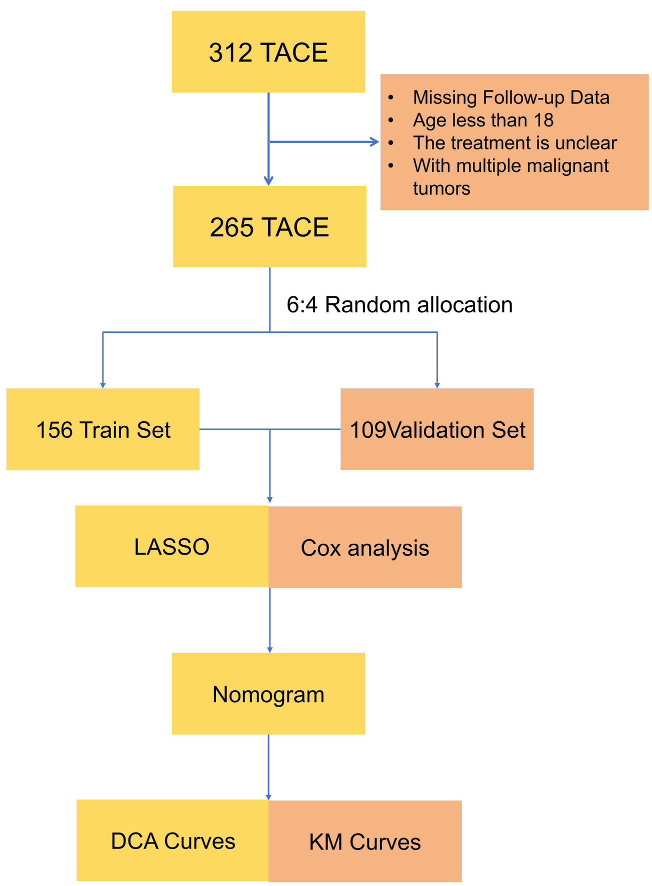

Figure 1 Study flow chart.

Table 1 Baseline Characteristics

Variable	Level	Total	Train Set	Validation Set	p	SMD
n		265	156	109		
Age (mean SD)		58.4 (13.2)	57.70 (12.92)	59.40 (13.61)	0.302	0.128
Sex	Female	85 (32.1%)	26 (16.7)	9 (8.3)	0.071	0.257
	Male	230 (86.8%)	130 (83.3)	100 (91.7)		
BMI (mean SD)		23.2 (3.52)	23.20 (3.62)	23.21 (3.40)	0.976	0.004
Cirrhosis	No	85 (32.1%)	49 (31.4)	36 (33.0)	0.886	0.035
	Yes	180 (67.9%)	107 (68.6)	73 (67.0)		
Ascites	No	257 (97.0%)	150 (96.2)	107 (98.2)	0.564	0.121
	Yes	8 (3.0%)	6 (3.8)	2 (1.8)		
Tumor size (mean SD)		54.38 (42.12)	51.54 (42.59)	58.44 (41.30)	0.190	0.164
Vascular invasion	No	174 (65.7%)	103 (66.0)	71 (65.1)	0.985	0.019
	Yes	91 (34.3%)	53 (34.0)	38 (34.9)		
Lymph node metastasis	No	127 (47.9%)	77 (49.4)	50 (45.9)	0.664	0.070
	Yes	138 (52.1%)	79 (50.6)	59 (54.1)		
Child Pugh	A	209 (78.9%)	123 (78.8)	86 (78.9)	1.000	0.001
	B	56 (21.1%)	33 (21.2)	23 (21.1)		
Surgery	No	221 (83.4%)	133 (85.3)	88 (80.7)	0.420	0.121
	Yes	44 (16.6%)	23 (14.7)	21 (19.3)		
Drug	No	228 (86.0%)	137 (87.8)	91 (83.5)	0.411	0.124
	Yes	37 (14.0%)	19 (12.2)	18 (16.5)		
Intervention	No	226 (85.3%)	135 (86.5)	91 (83.5)	0.607	0.086
	Yes	39 (14.7%)	21 (13.5)	18 (16.5)		
Radiotherapy	No	260 (98.1%)	154 (98.7)	106 (97.2)	0.684	0.105
	Yes	5 (1.9%)	2 (1.3)	3 (2.8)		
Ablation	No	248 (93.6%)	145 (92.9)	103 (94.5)	0.802	0.064
	Yes	17 (6.4%)	11 (7.1)	6 (5.5)		
mALBI	1	92 (34.7%)	55 (35.3)	37 (33.9)	0.594	0.132
	2	168 (63.4%)	97 (62.2)	71 (65.1)		
	3	5 (1.9%)	4 (2.6)	1 (0.9)		
BCLC	A	18 (6.8%)	10 (6.4)	8 (7.3)	0.978	0.055
	B	74 (27.9%)	43 (27.6)	31 (28.4)		
	C	157 (59.2%)	93 (59.6)	64 (58.7)		
	D	16 (6.0%)	10 (6.4)	6 (5.5)		
CNLC	I	38 (14.3%)	20 (12.8)	18 (16.5)	0.424	0.211
	II	69 (26.0%)	46 (29.5)	23 (21.1)		
	III	147 (55.5%)	83 (53.2)	64 (58.7)		
	IV	11 (4.2%)	7 (4.5)	4 (3.7)		
NRS 2002	0	168 (63.4%)	98 (62.8)	70 (64.2)	0.644	0.202
	1	47 (17.7%)	25 (16.0)	22 (20.2)		
	2	29 (10.9%)	19 (12.2)	10 (9.2)		
	3	9 (3.4%)	5 (3.2)	4 (3.7)		
	4	12 (4.5%)	9 (5.8)	3 (2.8)		
ECOG PS	0	174 (65.7%)	103 (66.0)	71 (65.1)	0.998	0.046
	1	48 (18.1%)	28 (17.9)	20 (18.3)		
	2	25 (9.4%)	15 (9.6)	10 (9.2)		
	3	16 (6.0%)	9 (5.8)	7 (6.4)		
	4	2 (0.8%)	1 (0.6)	1 (0.9)		
HCV-RNA (mean SD)		0.96 (3.34)	0.89 (3.32)	1.07 (3.37)	0.674	0.052
HBV-DNA (mean SD)		1.51 (0.50)	1.51 (0.50)	1.50 (0.50)	0.896	0.016
WBC (mean SD)		5.66 (2.61)	5.65 (2.40)	5.66 (2.89)	0.966	0.005
Neu (mean SD)		3.5 (2.23)	3.48 (2.07)	3.53 (2.44)	0.860	0.022

(*Continued*)

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Table 1 (Continued).

Variable	Level	Total	Train Set	Validation Set	p	SMD
Lym (mean SD)		1.74 (0.44)	1.73 (0.44)	1.76 (0.43)	0.575	0.070
HGB (mean SD)		1.67 (0.47)	1.66 (0.48)	1.68 (0.47)	0.752	0.039
PLT (mean SD)		1.78 (0.42)	1.78 (0.42)	1.78 (0.42)	0.936	0.010
ALT (mean SD)		58.59 (78.57)	52.91 (86.59)	54.56 (65.78)	0.866	0.022
AST (mean SD)		73.00 (81.08)	75.39 (94.87)	69.59 (55.97)	0.568	0.074
TBIL (mean SD)		21.00 (15.73)	22.09 (19.11)	19.36 (8.73)	0.165	0.184
DBIL (mean SD)		8.37 (10.55)	8.99 (13.05)	7.49 (5.13)	0.254	0.152
ALB (mean SD)		37.08 (5.02)	37.27 (5.02)	36.82 (5.03)	0.473	0.090
GGT (mean SD)		160.92 (148.79)	159.36 (161.52)	163.16 (129.09)	0.838	0.026
ALP (mean SD)		149.00 (131.30)	149.51 (121.19)	148.25 (145.14)	0.939	0.009
PT (mean SD)		13.33 (1.36)	13.32 (1.31)	13.35 (1.44)	0.862	0.022
INR (mean SD)		1.09 (0.15)	1.10 (0.15)	1.09 (0.13)	0.821	0.029
APTT (mean SD)		33.80 (5.25)	33.99 (5.18)	33.53 (5.35)	0.478	0.088
Fib (mean SD)		3.13 (1.09)	3.19 (1.11)	3.05 (1.06)	0.277	0.136
AFP (mean SD)		8391.93 (33,787.2)	8351.91 (29,688.58)	8449.21 (39,057.93)	0.982	0.003

Notes: Surgery, prior history of surgical treatment; Drug, prior history of drug therapy; Intervention, prior history of interventional therapy; Radiotherapy, prior history of radiotherapy; Ablation, prior history of ablation therapy; mALBI, modified albumin–bilirubin grade, calculated as $0.66 \times \log_{10}$(total bilirubin [μmol/L]) − 0.085 × albumin [g/L].

Abbreviations:; HCV-RNA, hepatitis C virus ribonucleic acid; BCLC, Barcelona Clinic Liver Cancer staging system; CNLC, China Liver Cancer staging system; NRS 2002, Nutritional Risk Screening 2002; ECOG PS, Eastern Cooperative Oncology Group performance status; HBV-DNA, hepatitis B virus deoxyribonucleic acid; WBC, white blood cell count; Neu, neutrophil count; Age, patient age; BMI, body mass index; Tumor size, maximum tumor diameter; Lym, lymphocyte count; HGB, hemoglobin; PLT, platelet count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; DBIL, direct bilirubin; ALB, albumin; GGT, gamma-glutamyl transferase; ALP, alkaline phosphatase; PT, prothrombin time; INR, international normalized ratio; APTT, activated partial thromboplastin time; Fib, fibrinogen; AFP, alpha-fetoprotein; SMD, Standardized Mean Difference.

Table 2 Univariate and Multivariate Cox Regression Analyses

Variable	Level	All	HR (Univariable)	HR (Multivariable)
Sex	Female	21 (13.5%)		
	Male	135 (86.5%)	1.99 (1.05–3.79, p=0.036)	1.96 (0.94–4.07, p=0.072)
Vascular invasion	No	104 (66.7%)		
	Yes	52 (33.3%)	1.80 (1.16–2.79, p=0.009)	1.43 (0.86–2.36, p=0.165)
Ascites	No	153 (98.1%)		
	Yes	3 (1.9%)	4.93 (1.16–20.86, p=0.030)	2.90 (0.51–16.47, p=0.229)
Child Pugh	A	122 (78.2%)		
	B	34 (21.8%)	1.66 (1.00–2.78, p=0.052)	1.35 (0.70–2.59, p=0.370)
mALBI	1	48 (30.8%)		
	2	106 (67.9%)	1.40 (0.88–2.23, p=0.157)	0.86 (0.44–1.68, p=0.656)
	3	2 (1.3%)	5.96 (1.38–25.83, p=0.017)	3.11 (0.24–39.63, p=0.383)
CNLC	I	27 (17.3%)		
	II	43 (27.6%)	0.85 (0.44–1.64, p=0.636)	1.17 (0.57–2.40, p=0.675)
	III	81 (51.9%)	1.22 (0.69–2.17, p=0.497)	1.25 (0.64–2.43, p=0.514)
	IV	5 (3.2%)	3.59 (1.01–12.77, p=0.048)	4.33 (1.03–18.12, p=0.045)
WBC	Mean ± SD	5.6 ± 2.8	1.10 (1.02–1.18, p=0.011)	1.40 (0.58–3.39, p=0.454)
Neu	Mean ± SD	3.5 ± 2.5	1.13 (1.05–1.21, p=0.001)	0.80 (0.31–2.09, p=0.655)
ALB	Mean ± SD	36.9 ± 5.1	0.93 (0.89–0.98, p=0.004)	1.04 (0.83–1.32, p=0.713)
ALP	Mean ± SD	155.1 ± 151.6	1.00 (1.00–1.00, p=0.079)	1.00 (0.99–1.00, p=0.089)
APTT	Mean ± SD	33.7 ± 5.2	1.04 (0.99–1.08, p=0.089)	1.03 (0.97–1.09, p=0.323)
Fib	Mean ± SD	3.2 ± 1.1	1.60 (1.32–1.92, p<0.001)	1.62 (1.29–2.04, p<0.001)

(*Continued*)

Table 2 (Continued).

Variable	Level	All	HR (Univariable)	HR (Multivariable)
NLR	Mean ± SD	3.1 ± 3.1	1.12 (1.04–1.19, p=0.001)	0.95 (0.75–1.20, p=0.648)
PNI	Mean ± SD	43.9 ± 7.1	0.96 (0.93–0.99, p=0.015)	0.88 (0.70–1.11, p=0.293)
AAPR	Mean ± SD	0.4 ± 0.2	0.31 (0.12–0.79, p=0.015)	0.90 (0.22–3.72, p=0.885)

Abbreviations: HBV DNA, hepatitis B virus deoxyribonucleic acid; CNLC, China Liver Cancer staging system; WBC, white blood cell count; Neu, neutrophil count; PLT, platelet count; AST, aspartate aminotransferase; TBIL, total bilirubin; DBIL, direct bilirubin; GGT, gamma-glutamyl transferase; ALP, alkaline phosphatase; APTT, activated partial thromboplastin time; Fib, fibrinogen; AFP, alpha-fetoprotein; NLR, neutrophil-to-lymphocyte ratio; AAPR, albumin-to-alkaline phosphatase ratio. HR, Hazard Ratio.

multicollinearity, LASSO regression was applied to variables with a univariate P value < 0.1, and six variables including vascular invasion, neutrophil count (Neu), ALB, activated partial thromboplastin time (APTT), Fib, and AAPR were identified as risk factors for post-TACE recurrence (Supplementary Figure S1). Partial likelihood deviance and coefficient plots from the LASSO analysis were visualized in the training set (Figures 3A and B).

Construction of the Prognostic Model

Based on the results of the LASSO analysis, a prognostic model was constructed to assess the risk of post-TACE recurrence. Eight variables including age, sex, neutrophil count (Neu), albumin (ALB), fibrinogen (Fib), vascular invasion, albumin-to-alkaline phosphatase ratio (AAPR), and activated partial thromboplastin time (APTT) were incorporated into the nomogram (Figure 3C). The concordance index (C-index) of the model in the training set, evaluated using the "Hmisc" package, was 0.694, indicating good discriminatory ability. Similarly, the C-index in the validation set was 0.657. Calibration curves demonstrated good predictive performance of the model in both the training and validation cohorts (Supplementary Figure S2A and S2B). In addition, receiver operating characteristic (ROC) curves were used to evaluate the model's accuracy. In the training set, the area under the curve (AUC) for 6-month, 1-year, and 2-year DFS were 0.717, 0.794, and 0.884, respectively (Figure 3D). In the validation set, the corresponding AUC values at 6 months, 1 year, and 2 years were 0.653, 0.749, and 0.841 (Figure 3E). These results indicate that the nomogram exhibits good predictive accuracy for post-TACE recurrence.

Clinical Utility of the Prognostic Model

To evaluate the clinical applicability of the prognostic model, nomogram-based risk scores were calculated for each patient and compared with the clinical net benefits of conventional BCLC and CNLC staging systems. Decision curve analysis (DCA) demonstrated that, in the training set, the nomogram-derived risk scores provided higher clinical net benefit at 6 months, 1 year, 18 months, and 2 years compared with BCLC and CNLC staging (Figures 4A–D). Similar results were observed in the validation set (Supplementary Figures S3A-D), indicating that the nomogram-based risk scoring system has substantial clinical utility. Furthermore, the head-to-head C-index data of the training set indicated that the nomogram risk score was significantly affected by the BCLC and CNLC classifications ($p < 0.05$) (Table S1). However, in the validation set, although the nomogram risk score had a relatively high C-index, there was no significant statistical difference ($p > 0.05$). This might be due to the insufficient sample size (Table S2).

Furthermore, patients were stratified into low-, intermediate-, and high-risk subgroups according to the tertiles of the nomogram scores. Kaplan-Meier analysis revealed that the time to recurrence (TTR) was significantly shorter in the high-risk group compared with the intermediate- and low-risk groups (Figure 4E). Consistent findings were observed in the validation cohort (Figure 4F).

Discussion

In this retrospective study of 265 HCC patients undergoing postoperative TACE, we developed and internally validated an integrated prognostic nomogram to assess the risk of early recurrence. The model incorporated tumor-related variables, liver function parameters, inflammatory and nutritional indices, and coagulation biomarkers, demonstrating

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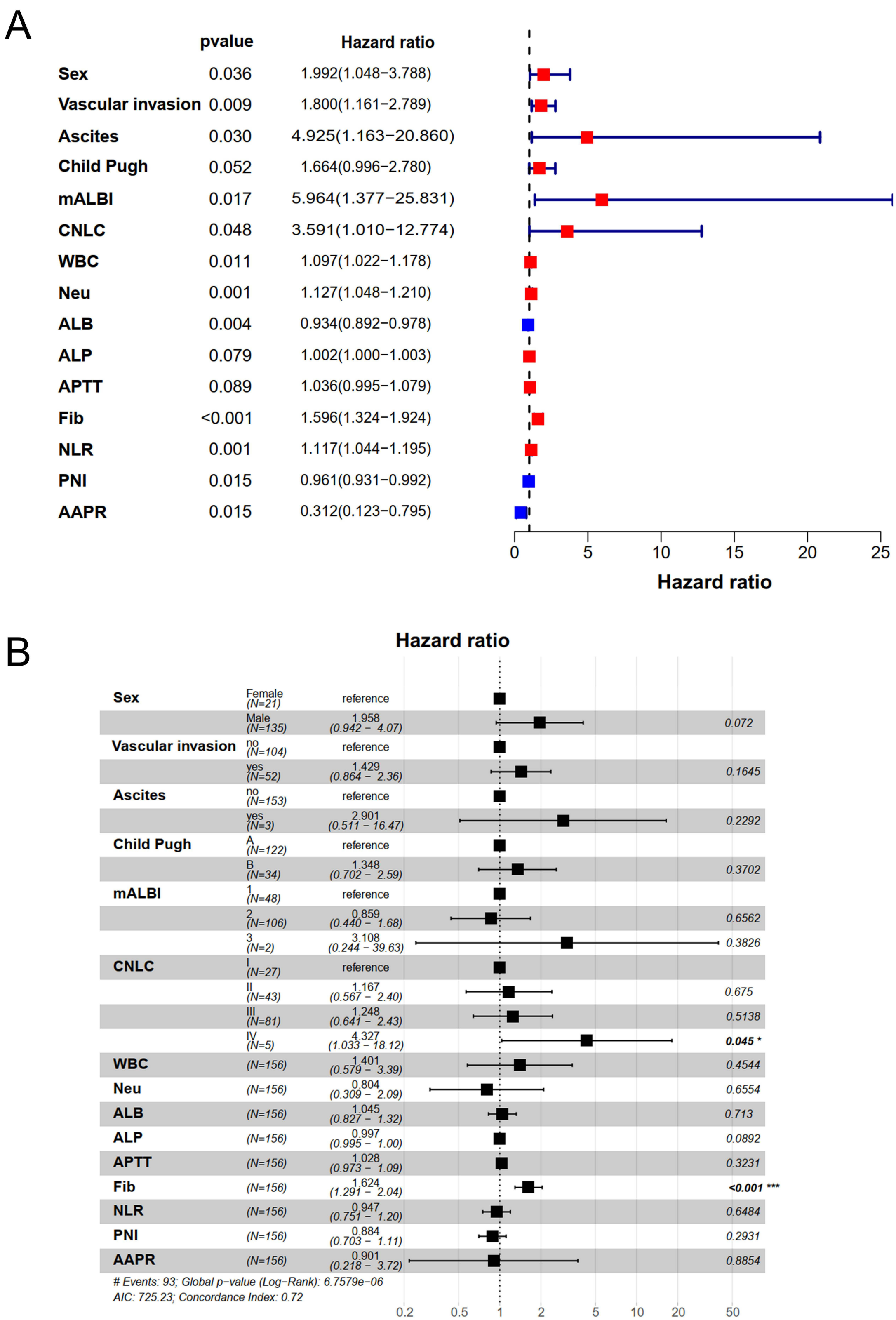

Figure 2 Univariate and multivariate Cox regression analysis of clinical variables. (**A**) univariate Cox regression analysis of the training set (**B**) multivariate Cox regression analysis of the training set. *P < 0.05; **P < 0.01; ***P < 0.001.

Abbreviations: mALBI, modified albumin-bilirubin grade; CNLC, China Liver Cancer staging system; WBC, white blood cell count; Neu, neutrophil count; ALB, albumin; ALP, alkaline phosphatase; APTT, activated partial thromboplastin time; Fib, fibrinogen; NLR, neutrophil-to-lymphocyte ratio; PNI, prognostic nutritional index; AAPR, albumin-to-alkaline phosphatase ratio.

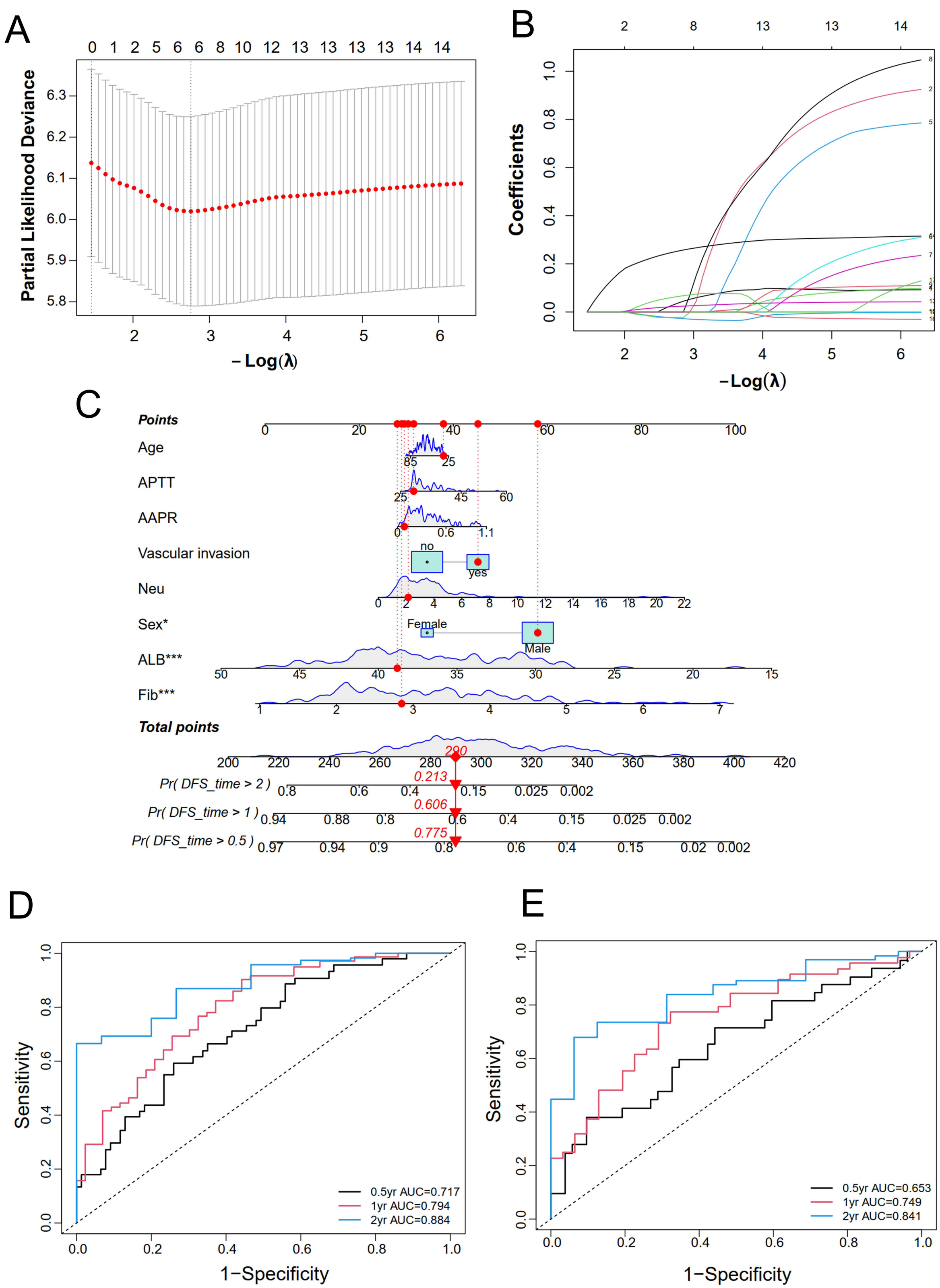

Figure 3 Construction of recurrence prediction model. (**A**) Partial Likelihood Deviance plot of LASSO analysis (**B**) Coefficients plot of LASSO analysis (**C**) Nomogram of training set (**D** and **E**) ROC curves of training set and validation set. *P < 0.05; ***P < 0.001.

Abbreviations: Neu, neutrophil count; ALB, albumin; APTT, activated partial thromboplastin time; Fib, fibrinogen; AAPR, albumin-to-alkaline phosphatase ratio.

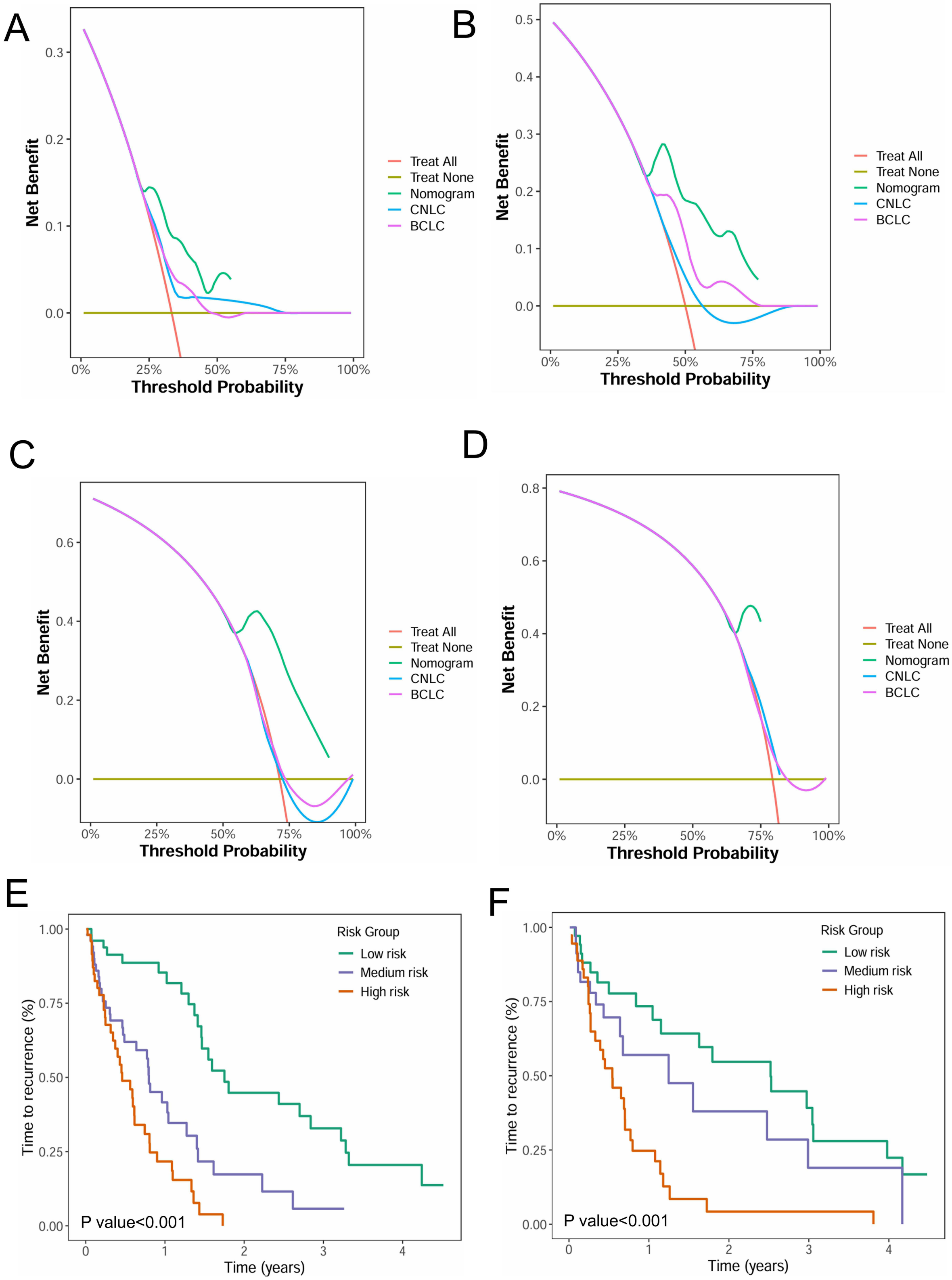

Figure 4 Clinical value of prognostic model. (**A-D**) DCA curves of the training set at 6 months, 1 year, 18 months, and 2 years (**E** and **F**) KM survival curves of the training set and validation set cohorts in the high, medium, and low risk groups.

superior predictive performance compared with conventional staging systems. Early recurrence after TACE remains a major clinical challenge, with recent studies reporting recurrence rates approaching 50% within two years,[6,28] highlighting the urgent need for individualized, data-driven risk assessment tools to guide surveillance and therapeutic strategies.[6] Laboratory-based systemic biomarkers reflect the complex interplay among tumor aggressiveness, hepatic functional reserve, and patient-level inflammatory status,[29] and incorporating these markers into predictive models has been shown to enhance prognostic discrimination and better capture the biological behavior of the disease.

Our findings support accumulating evidence that systemic inflammation and nutrition-related indices play critical roles in HCC progression and treatment outcomes.[30,31] In recent cohort studies, neutrophil-based markers, such as NLR and absolute neutrophil count, have been associated with pro-tumor inflammation, immune dysregulation, and poor response to locoregional therapy.[14,32] Similarly, nutritional parameters including albumin, PNI, and derived indices such as AAPR have been validated as surrogate markers of hepatic synthetic function and systemic immunonutritional status, closely linked to recurrence and survival following TACE or resection.[33,34] The inclusion of neutrophil count, albumin, and AAPR in our LASSO-selected variable set is consistent with these findings, underscoring the importance of patient-related nutritional and inflammatory indices in post-TACE prognosis.

Beyond inflammatory and nutritional markers, our study highlights the prognostic significance of coagulation-related variables, particularly fibrinogen and APTT. Recent evidence suggests that fibrinogen promotes tumor progression within the tumor microenvironment by facilitating angiogenesis, tumor cell adhesion, and immune evasion.[35] Elevated fibrinogen is increasingly recognized as a marker of a pro-tumor inflammatory state and predicts higher recurrence rates following locoregional therapy. Alterations in APTT may reflect advanced hepatic dysfunction or systemic inflammation, both of which can impair liver regeneration after TACE and enhance residual tumor activity. In our multivariate Cox analysis, the identification of fibrinogen as an independent predictor of recurrence reinforces its mechanistic relevance and potential clinical utility.

The nomogram constructed from these variables demonstrated good discrimination and calibration, with time-dependent AUCs of 0.717, 0.794, and 0.884 at 6 months, 1 year, and 2 years, respectively. Importantly, decision curve analysis indicated greater net clinical benefit over a wide range of threshold probabilities compared with BCLC and CNLC staging, suggesting that the model more effectively captures clinically actionable risk stratification. As precision monitoring and multimodal therapeutic strategies gain increasing attention, particularly with the growing use of TACE in combination with immune checkpoint inhibitors or targeted therapies, accurate risk assessment tools are essential for optimizing treatment planning and improving long-term outcomes.[35,36]

The clinical implications of our findings are significant. High-risk patients identified by the nomogram may benefit from intensified surveillance, early consideration of combination therapy, or more aggressive reintervention, whereas low-risk patients may avoid unnecessary procedures, reducing treatment-related morbidity and healthcare burden. The biological plausibility of the selected variables, including vascular invasion, fibrinogen, albumin-related index, APTT, and neutrophil count, strengthens the clinical relevance of the model, as each reflects known promoters of HCC progression, systemic dysregulation, or liver stress after TACE. Vascular invasion, in particular, has long been recognized as a marker of early metastatic dissemination and aggressive tumor biology, explaining its close association with early recurrence even after embolization.[37–40]

Despite the strengths of this study, including variable integration, robust statistical methodology, and internal validation, several limitations should be acknowledged. First, this study was conducted using a retrospective design at a single center, which may limit the generalizability of the findings and introduce selection bias. Although LASSO selected only six variables, age and sex are well-established prognostic factors and are routinely included in clinical nomograms. Automatic selection methods like LASSO may exclude clinically relevant covariates due to shrinkage or collinearity, but this does not negate their prognostic value. Prior studies, including SEER-based models for extremity liposarcoma and lung cancer nomograms, retain age and sex to adjust for baseline risk, improve interpretability, and enhance generalizability.[41,42] To reduce this risk, consecutive patient enrollment and uniform inclusion criteria were applied, and multivariable modeling with penalized regression was used to improve model stability and reduce confounding. Internal validation further supported the consistency of model performance. However, these approaches cannot fully address center-specific practice patterns or population characteristics. Therefore, external validation in independent multicenter cohorts is essential and represents an important priority for future research before routine clinical application. Imaging-based biomarkers, which have shown promise in improving post-TACE recurrence prediction, were not incorporated in this study and may represent a direction for future investigation.[43,44] Genomic, transcriptomic, and circulating biomarkers recently associated with early recurrence were also not included.[45,46] Additionally, mALBI grade 3 included only several patients in the training set, leading to insufficient statistical power to reliably assess outcomes in this subgroup. Future studies may consider merging small subgroups or expanding the sample size to achieve more robust analysis. Lastly, although the study focused on early recurrence with clear clinical significance, heterogeneity in prior treatments among patients may introduce some bias in prognostic estimates.

In summary, this study presents a clinically practical and statistically robust nomogram capable of accurately predicting early recurrence in HCC patients undergoing postoperative TACE. The model outperforms conventional staging systems in prognostic performance, and the nomogram-derived risk scores allow stratification of patients according to recurrence risk. Prospective multicenter validation studies, together with the incorporation of imaging and molecular biomarkers, are warranted to further improve generalizability and support translation into routine clinical practice.

Conclusions

This study developed and validated a practical nomogram capable of accurately predicting early recurrence in HCC patients after postoperative TACE. By integrating clinical, inflammatory, nutritional, and coagulation biomarkers, the model outperformed conventional staging systems and effectively stratified patients into distinct risk groups. This tool may support individualized surveillance and treatment planning, although further external validation is required to confirm its broader clinical applicability.

Data Sharing Statement

Data supporting the findings of this study are not publicly available because they contain information that could potentially compromise the privacy of research participants. Access to anonymized patient-level data is restricted to on-site study personnel who are registered with and approved by the Institutional Review Board, and such data are available only in encrypted file formats or through secure, encrypted systems. However, upon reasonable request and subject to approval by the institutional data review committee, the authors may provide access to de-identified data for research purposes that are consistent with the original study objectives and ethical approvals. Requests should include a detailed research proposal, intended data use, and proof of relevant ethical approval, and should be directed to the corresponding author, Liping Liu (email: liuliping@mail.sustech.edu.cn).

Ethics Approval and Consent to Participate

This study was a retrospective observational investigation in which all patient data were anonymized, and the study was conducted in strict accordance with the STROBE guidelines; therefore, informed consent was waived by the Ethics Committee of Shenzhen People's Hospital.

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Disclosure

All authors declare no conflicts of interest in this study.

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