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ORIGINAL RESEARCH

Nomogram Based on Tumor Burden Score and Inflammation-Nutritional Indicators to Predict the Prognosis of Hepatocellular Carcinoma Patients Undergoing TACE Combined with Targeted and Immunotherapy

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Purpose: This study aimed to develop and validate a prognostic model integrating the tumor burden score (TBS) with inflammation-nutritional indicators for patients with intermediate-to-advanced hepatocellular carcinoma (HCC). The model was designed to predict outcomes in patients undergoing triple therapy with transarterial chemoembolization (TACE), targeted therapy, and immunotherapy. Its predictive performance was subsequently assessed.

Patients and Methods: The training cohort comprised 112 eligible patients treated at Ganzhou People's Hospital between September 2021 and June 2024, while an external validation cohort included 84 patients from the First Affiliated Hospital of Gannan Medical University. Cox regression analysis identified independent prognostic factors for overall survival (OS), and a nomogram was constructed from these predictors. We assessed the model's performance using the concordance index (C-index), time-dependent receiver operating characteristic (ROC) curves, calibration curves, and decision curve analysis (DCA). Based on the nomogram-derived risk scores, patients were stratified into low- and high-risk groups. Differences in OS between these groups were compared with Kaplan-Meier curves and the Log rank test.

Results: Multivariate Cox analysis identified TBS, the prognostic nutritional index (PNI), the systemic immune-inflammation index (SII), and extrahepatic metastasis as independent predictors of OS ($P < 0.05$). The nomogram achieved a C-index of 0.778 (95% CI: 0.719–0.838) in the training cohort and 0.689 (95% CI: 0.606–0.772) in the external validation cohort. After bootstrap correction, the C-index was 0.793 (95% CI: 0.738–0.848). This model consistently outperformed conventional clinical staging systems in both C-index and AUC values, while calibration curves and decision curve analysis affirmed its predictive accuracy and clinical utility. Kaplan-Meier analysis confirmed a significant difference in overall survival between the low- and high-risk groups.

Conclusion: The nomogram incorporating TBS and inflammation-nutritional indicators exhibits acceptable prognostic performance and effectively identifies high-risk patients, providing valuable guidance for clinicians in risk stratification and individualized treatment planning.

Keywords: hepatocellular carcinoma, inflammatory indicators, nomogram, prognostic nutritional index, tumor burden score

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Introduction

Liver cancer is the sixth most common malignancy globally and the third leading cause of cancer death. Hepatocellular carcinoma (HCC), the predominant histological subtype, comprises roughly 75–85% of cases.[1] Its insidious onset means over 80% of patients are diagnosed at intermediate or advanced stages, when curative interventions like surgical resection or ablation are typically no longer viable.[2] Research has established that triple therapy-combining transarterial chemoembolization (TACE), targeted therapy, and immunotherapy-can extend survival in patients with intermediate-to-advanced HCC,[3–6] and this approach has gained considerable clinical traction. Nevertheless, substantial tumor heterogeneity leads to unsatisfactory outcomes in a proportion of patients,[7] which continues to challenge the optimal selection of triple therapy in practice.

The tumor burden score (TBS), which integrates tumor size and number, offers superior prognostic discrimination compared to either parameter alone.[8] Nutritional status and systemic inflammation are also critical determinants of cancer outcomes. The prognostic nutritional index (PNI) has been established as a predictor for patients with HCC undergoing TACE.[9] Furthermore, inflammatory biomarkers such as the neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII) are widely used to forecast prognosis, disease progression, and recurrence in HCC.[10–14] Prognostic tools for patients with intermediate-to-advanced HCC receiving TACE combined with targeted therapy and immunotherapy, however, are still lacking. Consequently, we aimed to develop and validate a novel prognostic model that incorporates TBS with inflammation-nutritional indicators to enable more reliable risk stratification and inform individualized treatment decisions.

Materials and Methods

Patients

This retrospective study screened 479 patients with hepatocellular carcinoma (HCC) who received transarterial chemoembolization (TACE) combined with targeted therapy and immunotherapy between September 2021 and June 2024 at Ganzhou People's Hospital (Hospital 1, n=271) and the First Affiliated Hospital of Gannan Medical University (Hospital 2, n=208). Inclusion criteria comprised: (1) age ≥18 years; (2) HCC diagnosis confirmed by clinical or histopathological criteria; (3) initial diagnosis of intermediate-to-advanced HCC deemed unsuitable for curative treatments like surgery or ablation; (4) Child-Pugh class A or B liver function. Patients were excluded if they: (1) had received other antitumor therapies before starting the triple therapy; (2) underwent additional antitumor modalities during follow-up; (3) had incomplete or indeterminable records of maximum tumor diameter or tumor number; (4) presented with severe comorbidities; (5) had other concurrent malignancies; or (6) lacked complete clinical data or were lost to follow-up. The final analysis included 112 patients from Hospital 1 as the training cohort and 84 patients from Hospital 2 as the external validation cohort.

This study was conducted in accordance with the Declaration of Helsinki and received approval from the institutional ethics committee (Ethical Approval No. PJB2025-354-01). Informed consent was waived due to the retrospective design. Patient data were anonymized and subject to access controls to protect confidentiality and privacy. The patient enrollment process is summarized in Figure 1.

Data Collection

Clinical information, including sex, age, hepatitis history, cirrhosis, Child-Pugh grade, BCLC stage, CNLC stage, TNM stage, AFP, total bilirubin, albumin, ALT, AST, neutrophil count, monocyte count, lymphocyte count, platelet count, tumor number, tumor diameter, vascular invasion, and extrahepatic metastasis, was obtained from the electronic medical record system. These variables were collected within one week before treatment began. Vascular invasion was defined as radiological evidence of tumor invasion into intrahepatic vessels, the main portal vein, or major abdominal vessels.[15]

Definitions and Calculations of Relevant Indicators

The indicators were calculated as follows: TBS^2 = (maximum tumor diameter)^2 + (tumor number)^2; PNI = albumin + 5×lymphocyte count; SII = platelet count ×neutrophil count/lymphocyte count; LMR = lymphocyte count/monocyte count;

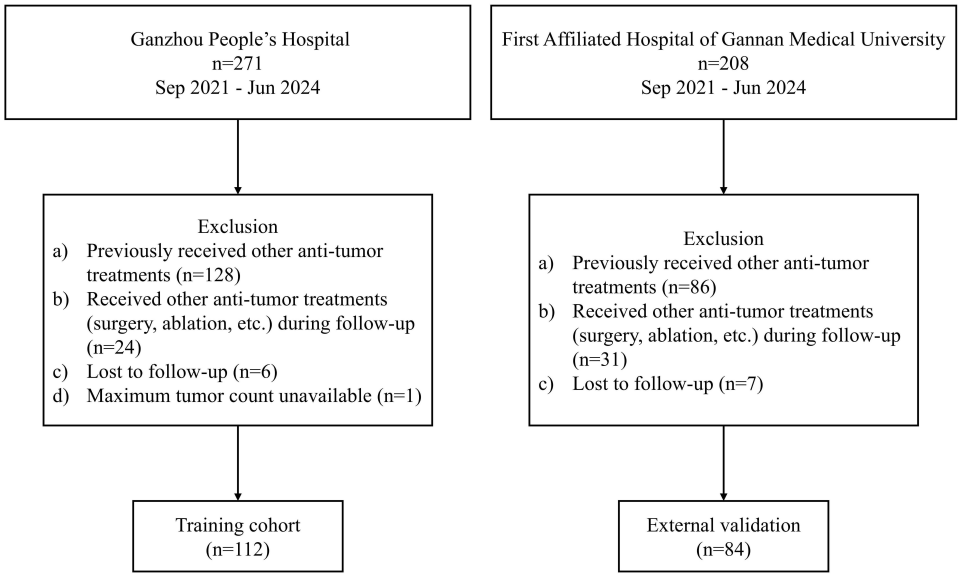

Figure 1 Patient enrollment flowchart.

PLR = platelet count/lymphocyte count; NLR = neutrophil count/lymphocyte count. Optimal cutoff values for all indicators were determined using X-tile software.[16] Maximum tumor diameter and tumor number were assessed by contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) prior to treatment. Data were independently interpreted by two radiologists with at least five years of experience. In case of disagreement, a senior radiologist with ten years of experience provided the final assessment.

Treatment Procedures

TACE Procedure

Under local anesthesia, the Seldinger technique was used to catheterize the femoral artery, followed by angiography of the celiac artery or common hepatic artery. Superselective catheterization of the tumor-feeding arteries was then performed. According to tumor size, an appropriate dose of chemotherapeutic agents (20–40 mg lobaplatin and 20–40 mg epirubicin) mixed with 10 mL of iodized oil was administered to embolize the tumor vasculature. After saturation of the tumor vessels and stasis of portal venous branches surrounding the lesion, 300–500 μm PVA particles were slowly injected until complete vascular occlusion was achieved. A repeat angiogram was performed to evaluate residual tumor staining. The interval between TACE sessions was determined based on imaging results.

Targeted and Immunotherapy

Within one month after the initial TACE procedure, patients received targeted therapy and immunotherapy depending on their overall health condition and liver function recovery. The molecularly targeted therapy regimens were as follows: sorafenib, 400 mg twice daily; lenvatinib, 8 mg once daily for patients weighing <60 kg and 12 mg once daily for those weighing ≥60 kg; regorafenib, 160 mg once daily; apatinib, 750 mg once daily; and bevacizumab, 15 mg/kg per administration. The immune checkpoint inhibitor regimens were as follows: camrelizumab, 200 mg every 3 weeks via intravenous infusion; pembrolizumab, 200 mg every 3 weeks via intravenous infusion; tislelizumab, 200 mg every 3 weeks via intravenous infusion; and sintilimab, 200 mg every 3 weeks via intravenous infusion.

Outcomes and Follow-Up

Follow-up was conducted via outpatient visits and telephone interviews. Contrast-enhanced CT or MRI was repeated every 3–6 months to evaluate patient status. The final follow-up date was December 31, 2024. The primary endpoint was overall survival (OS), defined as the interval from the date of initial TACE to death from any cause or the last follow-up.

Statistical Analysis

Statistical analyses and visualization were performed using SPSS 26.0, R software (version 4.4.2), and X-tile (version 3.6.1). The Shapiro–Wilk test was used to assess the normality of continuous variables. Normally distributed variables were expressed as mean ± standard deviation (SD), whereas non-normally distributed variables were presented as median and interquartile range (IQR). Categorical variables were expressed as frequencies and percentages and compared using the chi-square test. Continuous variables were compared using the *t*-test or Wilcoxon rank-sum test, while categorical variables were compared using the chi-square test or Fisher's exact test. Survival curves were generated using the Kaplan-Meier method and compared with the Log rank test.

Multicollinearity among variables was evaluated using Pearson correlation coefficients and the variance inflation factor (VIF). A Pearson correlation coefficient >0.8 or a VIF >10 indicated significant collinearity. Cox proportional hazards models were employed for univariate and multivariate analyses. Variables were selected using a bidirectional stepwise regression approach based on the minimum Akaike information criterion (AIC). A nomogram was constructed using the final set of predictors. Internal validation was performed using bootstrap resampling with 1,000 iterations. Model discrimination was evaluated by calculating the concordance index (C-index) and time-dependent ROC curves in both cohorts. Calibration was assessed using calibration plots and Brier scores. Decision curve analysis (DCA) was used to assess clinical utility across a range of threshold probabilities. Total risk scores were derived from the nomogram, and the optimal cutoff value was determined using X-tile software. A P-value <0.05 was considered statistically significant.

Results

Baseline Characteristics of Patients

A total of 196 eligible patients with intermediate-to-advanced HCC were ultimately included in this study, with 112 patients from Hospital 1 assigned to the training cohort and 84 patients from Hospital 2 assigned to the external validation cohort. In the training cohort, there were 97 males (86.6%) and 15 females (13.4%); 97 patients (86.6%) had hepatitis B virus infection; and 16 patients (14.3%) were classified as Child-Pugh B. Regarding BCLC staging, 44 patients (39.3%) were stage B and 68 (60.7%) were stage C. In the external validation cohort, there were 74 males (88.1%) and 10 females (11.9%); 67 patients (79.8%) had hepatitis B infection; and 13 patients (15.5%) were classified as Child-Pugh B. The distribution of BCLC stage included 26 patients (31.0%) in stage B and 58 (69.0%) in stage C. Except for age, no significant differences were observed in baseline characteristics between the two cohorts, indicating good comparability (Table 1).

Table 1 Baseline Characteristics of Patients

Variables	Training (n=112)	External Validation (n=84)	Statistic	P
Gender, n (%)			χ^2=0.10	0.757
Female	15 (13.4)	10 (11.9)		
Male	97 (86.6)	74 (88.1)		
Age (years), median (IQR)	59.5 (50.8–67.0)	55.5 (48.5–62.0)	Z=−2.12	**0.034**
HBV infection, n (%)			χ^2=1.65	0.199
No	15 (13.4)	17 (20.2)		
Yes	97 (86.6)	67 (79.8)		

(*Continued*)

Table 1 (Continued).

Variables	Training (n=112)	External Validation (n=84)	Statistic	P
Cirrhosis, n (%)			χ^2=0.79	0.375
No	47 (42.0)	30 (35.7)		
Yes	65 (58.0)	54 (64.3)		
Child-Pugh class, n (%)			χ^2=0.05	0.816
A	96 (85.7)	71 (84.5)		
B	16 (14.3)	13 (15.5)		
BCLC stage, n (%)			χ^2=1.45	0.228
B	44 (39.3)	26 (31.0)		
C	68 (60.7)	58 (69.0)		
TBS, n (%)			χ^2=0.19	0.666
<15	74 (66.1)	53 (63.1)		
≥15	38 (33.9)	31 (36.9)		
PNI, n (%)			χ^2=0.02	0.902
<44.1	55 (49.1)	42 (50.0)		
≥44.1	57 (50.9)	42 (50.0)		
SII, n (%)			χ^2=1.83	0.176
<555.5	48 (42.9)	28 (33.3)		
≥555.5	64 (57.1)	56 (66.7)		
LMR, n (%)			χ^2=0.01	0.931
<2.7	74 (66.1)	55 (65.5)		
≥2.7	38 (33.9)	29 (34.5)		
PLR, n (%)			χ^2=0.12	0.731
<268.4	94 (83.9)	72 (85.7)		
≥268.4	18 (16.1)	12 (14.3)		
NLR, n (%)			χ^2=0.25	0.617
<5.1	81 (72.3)	58 (69.1)		
≥5.1	31 (27.7)	26 (30.9)		
AFP (ng/mL), n (%)			χ^2=0.06	0.803
<400	50 (44.6)	36 (42.9)		
≥400	62 (55.4)	48 (57.1)		

(*Continued*)

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Table 1 (Continued).

Variables	Training (n=112)	External Validation (n=84)	Statistic	P
TB (μmol/L), n (%)			χ^2=3.77	0.052
<17.1	33 (29.5)	36 (42.9)		
≥17.1	79 (70.5)	48 (57.1)		
ALB (g/L), n (%)			χ^2=0.01	0.930
<35	38 (33.9)	28 (33.3)		
≥35	74 (66.1)	56 (66.7)		
ALT (U/L), n (%)			χ^2=2.60	0.107
<40	55 (49.1)	51 (60.7)		
≥40	57 (50.9)	33 (39.3)		
AST (U/L), n (%)			χ^2=1.14	0.286
<40	27 (24.1)	26 (30.9)		
≥40	85 (75.9)	58 (69.1)		
Tumor number, n (%)			χ^2=0.64	0.425
<3	38 (33.9)	24 (28.6)		
≥3	74 (66.1)	60 (71.4)		
Tumor size (cm), n (%)			χ^2=2.39	0.122
<5	21 (18.7)	9 (10.7)		
≥5	91 (81.3)	75 (89.3)		
Macrovascular invasion, n (%)			χ^2=0.75	0.385
No	55 (49.1)	36 (43.9)		
Yes	57 (50.9)	48 (57.1)		
Extrahepatic metastasis, n (%)			χ^2=0.02	0.886
No	85 (75.9)	63 (75.0)		
Yes	27 (24.1)	21 (25.0)		

Notes: Data are expressed as number (percentage) or median [IQR]; Bold values are values with statistical differences (P value<0.05).

Abbreviations: HBV, hepatitis B virus; BCLC, Barcelona clinic liver cancer; TBS, tumor burden score; PNI, prognostic nutritional index; SII, systemic immune-inflammation index; LMR, lymphocyte-to-monocyte ratio; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; AFP, alpha-fetoprotein; TB, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Univariate and Multivariate Regression Analyses

In the training cohort, collinearity analysis showed that the absolute values of Pearson correlation coefficients between variables were all <0.8 (Supplementary Table 1), and all VIF values were <10 (Supplementary Table 2), indicating the absence of multicollinearity. Cox regression analysis was conducted in the training cohort. Univariate Cox analysis identified BCLC stage, TBS, PNI, SII, LMR, PLR, NLR, AST, tumor size, vascular invasion, and extrahepatic metastasis as significant predictors of OS ($P < 0.05$). Because TBS is derived from tumor size and tumor number, tumor size was excluded from the multivariate Cox analysis to prevent collinearity. Remaining variables were entered into the multivariate Cox model, and the

optimal model was selected based on the minimum Akaike information criterion (AIC) using bidirectional stepwise regression. Multivariate Cox analysis further confirmed that TBS, PNI, SII, and extrahepatic metastasis were independent prognostic factors for OS. Detailed results of univariate and multivariate analyses are presented in Table 2. In the multivariate analysis, elevated TBS and SII, as well as the presence of extrahepatic metastasis, were identified as independent risk factors for poorer overall survival, whereas a higher PNI was identified as an independent protective factor.

Construction of the Nomogram

A prognostic nomogram predicting 12-, 18-, and 24-month survival probabilities was constructed based on the independent risk factors identified in the Cox analyses. As shown in Figure 2, SII contributed the most to prognosis, followed by TBS, extrahepatic metastasis, and PNI.

Table 2 Univariate and Multivariate Cox Regression Analysis for OS

Variables	Univariable		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P
Gender, (female/male)	0.65 (0.37~1.15)	0.140		
Age(y), (</≥60)	0.82 (0.37~1.82)	0.623		
HBV infection, (no/yes)	0.74 (0.33~1.64)	0.455		
Cirrhosis, (no/yes)	1.38 (0.77~2.47)	0.279		
Child-Pugh class, (A/B)	2.12 (0.95~4.73)	0.065		
BCLC stage, (B/C)	2.79 (1.43~5.44)	**0.003**		
TBS, (</≥15)	3.46 (1.98~6.06)	**<0.001**	2.44 (1.37~4.37)	**0.003**
PNI, (</≥44.1)	2.97 (1.63~5.41)	**<0.001**	2.08 (1.12~3.83)	**0.020**
SII, (</≥555.5)	4.10 (2.05~8.23)	**<0.001**	2.59 (1.24~5.40)	**0.011**
LMR, (</≥2.7)	0.30 (0.15~0.62)	**0.001**		
PLR, (</≥268.4)	2.72 (1.43~5.15)	**0.002**		
NLR, (</≥5.1)	2.76 (1.57~4.87)	**<0.001**		
AFP (ng/mL), (</≥400)	1.44 (0.82~2.51)	0.206		
TB (μmol/L), (</≥17.1)	0.88 (0.49~1.58)	0.663		
ALB (g/L), (</≥35)	0.60 (0.34~1.05)	0.075		
ALT (U/L), (</≥40)	0.86 (0.49~1.49)	0.582		
AST (U/L), (</≥40)	2.53 (1.14~5.64)	**0.023**		
Tumor number,(</≥3)	1.78 (0.95~3.36)	0.074		
Size (cm), (</≥5)	4.78 (1.48~15.4)	**0.009**		
Macrovascular invasion, (no/yes)	2.20 (1.23~3.94)	**0.008**		
Extrahepatic metastasis, (no/yes)	3.52 (1.97~6.28)	**<0.001**	2.34 (1.30~4.23)	**0.005**

Notes: Bold values are values with statistical differences (P value<0.05).

Abbreviations: HBV, hepatitis B virus; BCLC, Barcelona clinic liver cancer; TBS, tumor burden score; PNI, prognostic nutritional index; SII, systemic immune-inflammation index; LMR, lymphocyte-to-monocyte ratio; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; AFP, alpha-fetoprotein; TB, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

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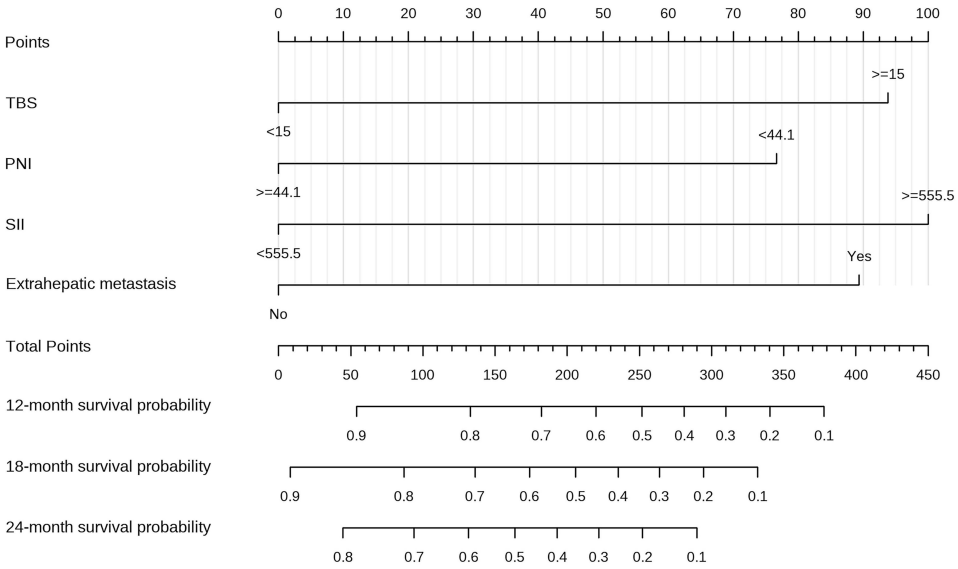

Figure 2 Nomogram for survival prediction of HCC patients with intermediate-to-advanced HCC undergoing triple therapy.

Evaluation and Validation of the Nomogram

Internal validation was performed using the bootstrap method. The C-index of the nomogram was 0.778 (95% CI: 0.719–0.838) in the training cohort, and the bootstrap-corrected C-index was 0.793 (95% CI: 0.738–0.848). In the external validation cohort, the C-index was 0.689 (95% CI: 0.606–0.772). In the training cohort, the ROC curves of the nomogram are shown in Figure 3A, with AUC values of 0.866 (0.795–0.938), 0.798 (0.701–0.894), and 0.838 (0.740–0.937) for predicting 12-, 18-, and 24-month OS, respectively. In the external validation cohort, the ROC curves are shown in Figure 3B, with corresponding AUC values of 0.696 (0.563–0.829), 0.732 (0.608–0.856), and 0.770 (0.620–0.921). Collectively, these results indicate that the model has acceptable predictive accuracy. Moreover, in both the training and external validation cohorts, the nomogram demonstrated significantly higher C-index and AUC values compared with CNLC, BCLC, and TNM staging systems (Tables 3 and 4), suggesting superior prognostic performance.

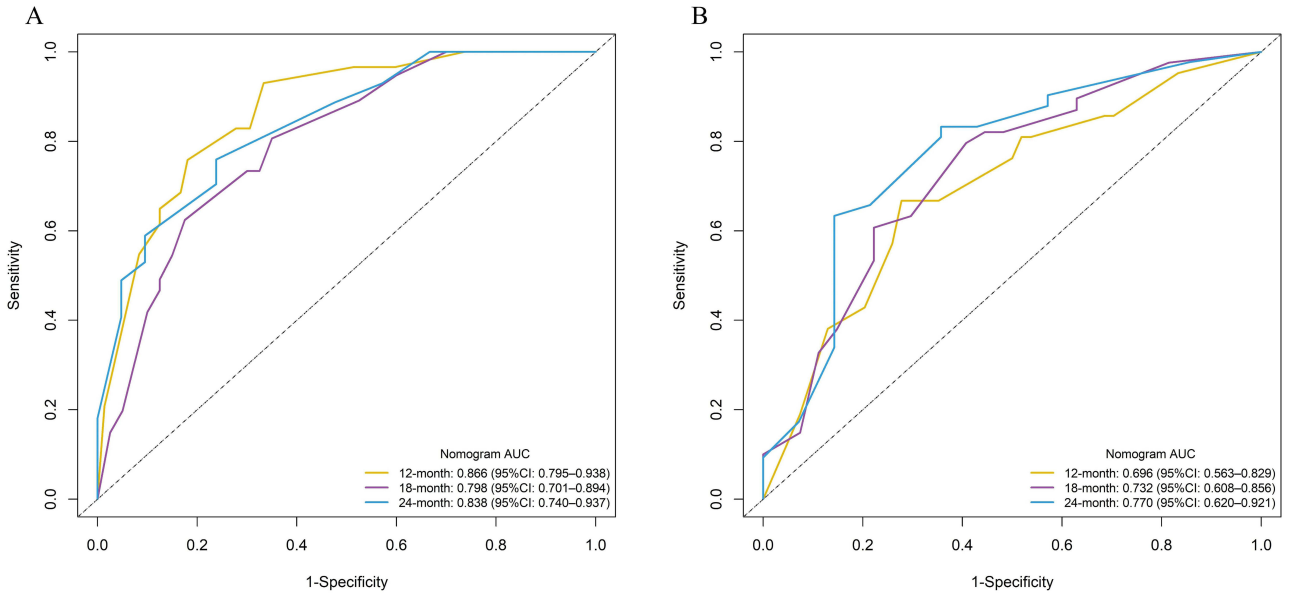

Figure 3 Time-dependent ROC curves of the nomogram. (**A**) The training cohort. (**B**) The external validation cohort.

Table 3 C-Index and AUC of Prognostic Staging Systems in the Training Cohort

Models	C-Index (95% CI)	AUC (95% CI) at 12 Months	AUC (95% CI) at 18 Months	AUC (95% CI) at 24 Months
Nomogram	0.778 (0.719–0.838)	0.866 (0.795–0.938)	0.798 (0.701–0.894)	0.838 (0.740–0.937)
CNLC	0.691 (0.613–0.769)	0.763 (0.663–0.864)	0.709 (0.602–0.815)	0.760 (0.657–0.863)
BCLC	0.620 (0.553–0.688)	0.661 (0.576–0.746)	0.619 (0.518–0.720)	0.643 (0.521–0.764)
TNM	0.687 (0.610–0.765)	0.772 (0.674–0.871)	0.696 (0.586–0.805)	0.734 (0.627–0.841)

Abbreviations: AUC, area under curve; CI, confidence interval.

Table 4 C-Index and AUC of Prognostic Staging Systems in the External Validation

Models	C-Index (95% CI)	AUC (95% CI) at 12 Months	AUC (95% CI) at 18 Months	AUC (95% CI) at 24 Months
Nomogram	0.689 (0.606–0.772)	0.696 (0.563–0.829)	0.732 (0.608–0.856)	0.770 (0.620–0.921)
CNLC	0.553 (0.471–0.635)	0.556 (0.419–0.694)	0.524 (0.391–0.657)	0.553 (0.394–0.712)
BCLC	0.535 (0.465–0.606)	0.548 (0.436–0.659)	0.499 (0.385–0.613)	0.504 (0.366–0.642)
TNM	0.543 (0.456–0.630)	0.566 (0.426–0.706)	0.481 (0.345–0.617)	0.516 (0.351–0.681)

Abbreviations: AUC, area under curve; CI, confidence interval.

Calibration plots showed excellent agreement between predicted and observed OS probabilities. In the training cohort, the Brier scores for the 12-, 18-, and 24-month predictions were 0.139, 0.185, and 0.158, respectively (0 = perfect; 1 = worst). In the external validation cohort, the corresponding scores were 0.195, 0.209, and 0.182 (Figure 4).

DCA demonstrated that, in both cohorts, the nomogram provided greater clinical net benefit across a wide range of threshold probabilities at 12-, 18-, and 24-months compared with the "treat-all" and "treat-none" strategies, confirming its excellent clinical utility (Figure 5).

Risk Stratification Based on the Nomogram

To further evaluate the predictive capability of the model, total risk scores for each patient were calculated using the nomogram. The optimal cutoff value was determined using X-tile software. Patients were then stratified into high-risk and low-risk groups accordingly. Kaplan-Meier curves revealed significant differences in OS between the two groups in both the training and external validation cohorts ($P<0.0001$) (Figure 6), indicating that the risk stratification system effectively distinguishes patients with different prognoses and provides reliable guidance for clinical assessment.

Discussion

Most patients with hepatocellular carcinoma (HCC) are diagnosed at intermediate or advanced stages, precluding curative interventions like surgical resection. For this population, the combination of transarterial chemoembolization (TACE), targeted therapy, and immunotherapy has demonstrated efficacy in controlling tumor progression and conferring significant clinical benefit. Nevertheless, heterogeneous factors including tumor burden, nutritional status, and systemic immune-inflammatory responses contribute to suboptimal outcomes in a subset of patients. Consequently, the pre-treatment identification of patients most likely to respond is critically important.

This study aimed to establish and validate a prognostic prediction model for patients with intermediate-to-advanced HCC undergoing triple therapy. Our findings demonstrated that elevated TBS and SII, along with the presence of extrahepatic metastasis, were independent risk factors for poorer OS, whereas a higher PNI served as an independent protective factor. Based on these four variables, a nomogram predicting 12-, 18-, and 24-month OS was developed and validated. The results demonstrated that the C-index of the nomogram model was 0.778 in the training cohort and 0.689

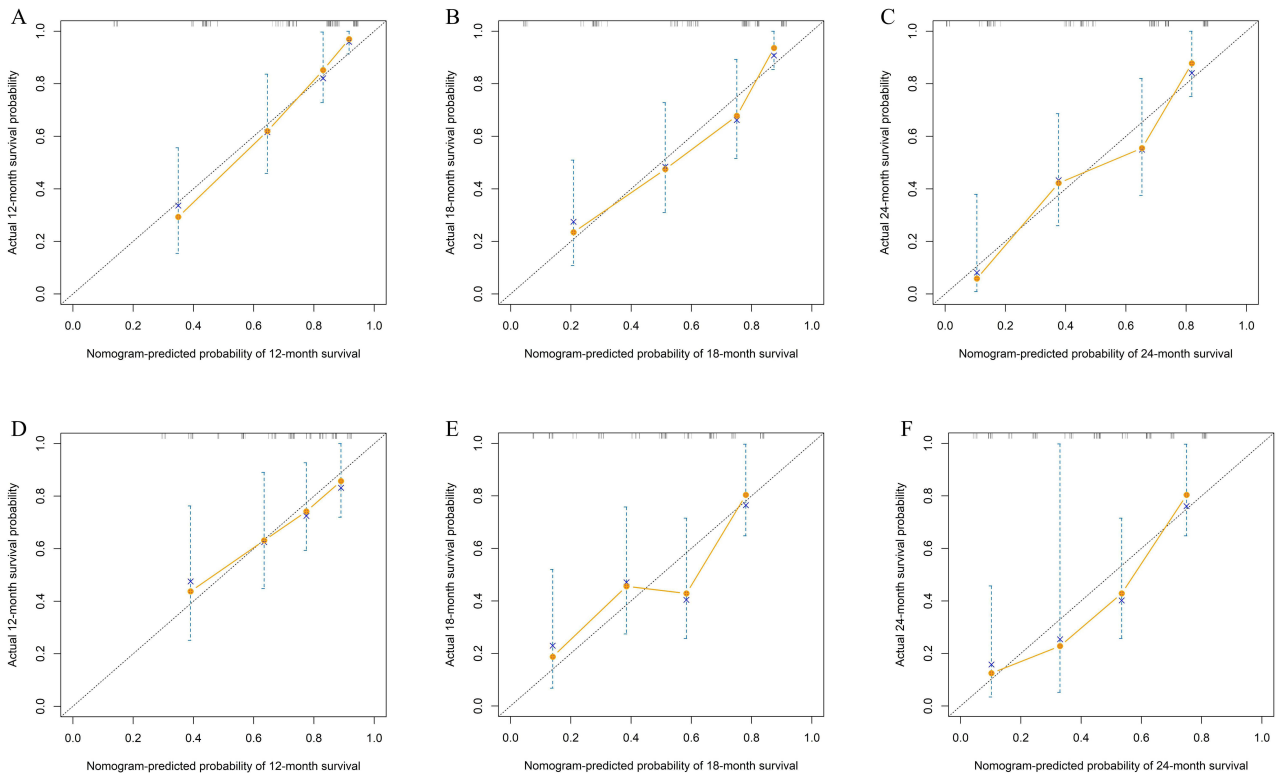

Figure 4 Calibration plots of the nomogram. (**A–C**) The training cohort. (**D–F**) The external validation cohort.

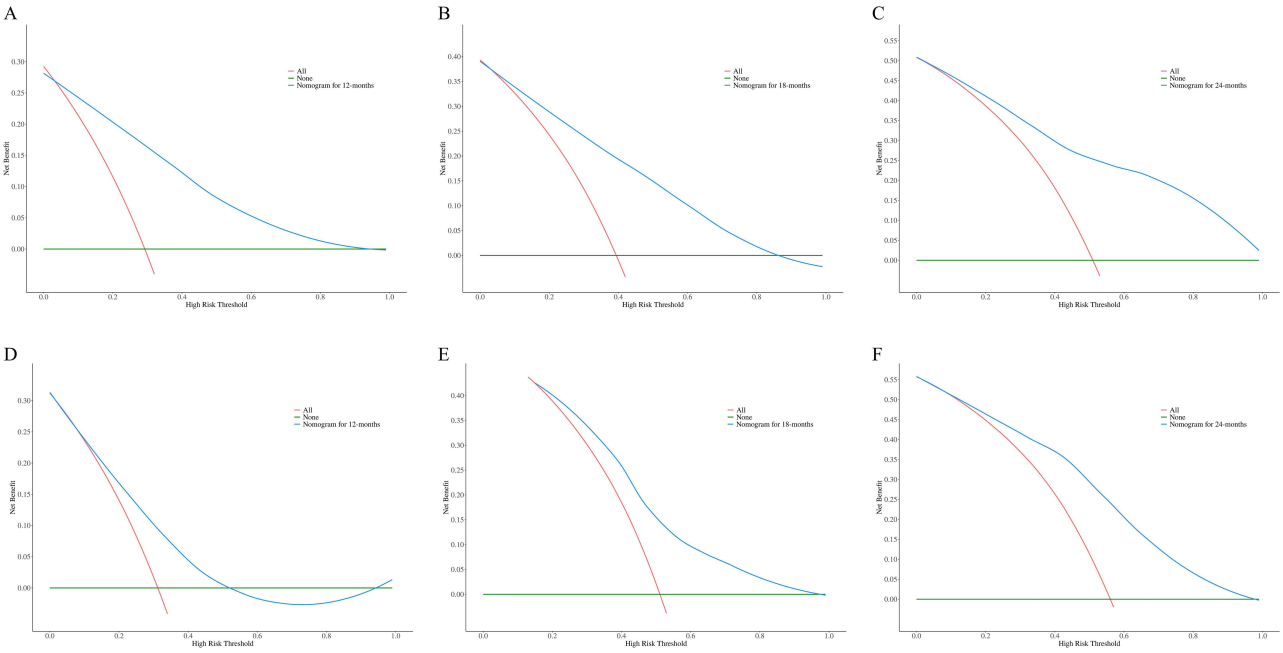

Figure 5 DCA curves of the nomogram. (**A–C**) The training cohort. (**D–F**) The external validation cohort.

in the external validation cohort. Although the C-index decreased in the validation cohort due to differences in sample size and the heterogeneity inherent to retrospective data, both cohorts still exhibited acceptable predictive performance. Furthermore, calibration curves confirmed excellent predictive accuracy, and DCA curves demonstrated substantial

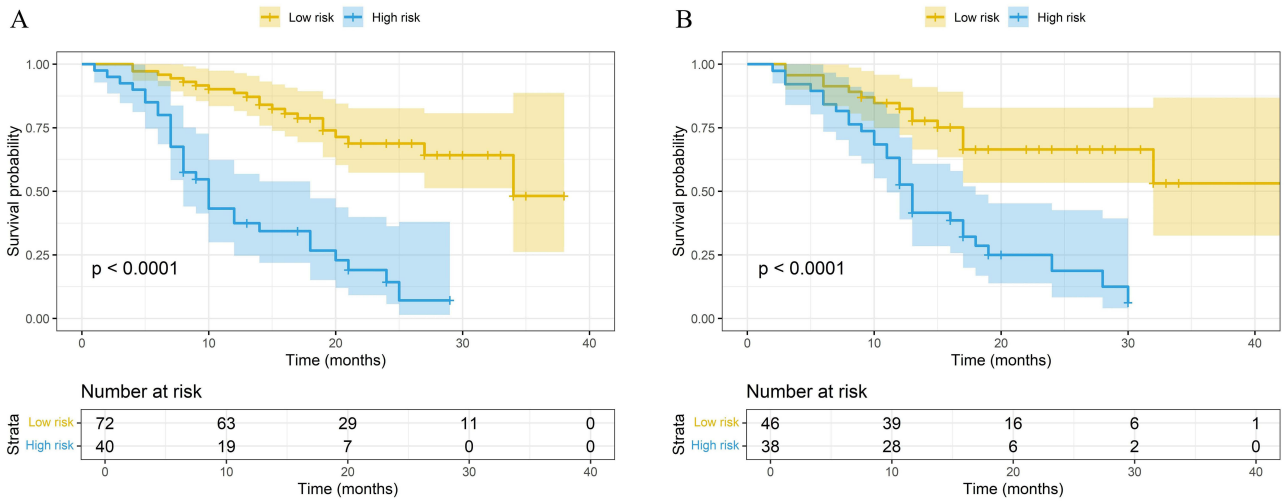

Figure 6 Kaplan-Meier survival curves of high- and low-risk groups based on the nomogram risk stratification. (**A**) The training cohort. (**B**) The external validation cohort.

clinical utility. Compared with traditional staging systems such as CNLC and BCLC, the nomogram integrates tumor burden, nutritional status, and immune-inflammatory conditions, thereby providing a more comprehensive and accurate prognostic assessment. By stratifying patients into low- and high-risk groups, the model revealed significant survival differences in both cohorts, further supporting its practical value. Thus, the nomogram provides a quantitative tool to assess survival risk prior to treatment and may help guide subsequent clinical management.

In particular, the prognostic information provided by the nomogram may help inform several aspects of clinical decision-making. For patients predicted to have a higher risk of poor survival, clinicians may consider closer follow-up, earlier assessment of treatment response, or timely adjustment of therapeutic strategies. In contrast, patients classified as lower risk may continue the current treatment strategy with greater confidence. In this way, the model may assist clinicians in tailoring treatment intensity and surveillance strategies according to individual risk profiles.

Tumor burden is one of the most critical determinants of prognosis in HCC and is typically evaluated using tumor size and number, which are incorporated into various staging systems. However, analyzing continuous (tumor diameter) or ordinal (tumor number) variables with arbitrary cutoff values not only reduces statistical power but may also lead to inaccurate causal interpretations.[17] Unlike the dichotomous Milan or up-to-seven criteria, TBS is a simple continuous parameter that represents the extent of tumor involvement in the liver. Notably, Ho et al[18] showed that TBS has the highest homogeneity and the lowest AICc compared to these two criteria. Sasaki et al[8] showed that TBS could accurately predict outcomes in patients undergoing liver resection for colorectal liver metastases Although TBS calculated from pathology and imaging may differ slightly, another study by the same group demonstrated that imaging- and pathology-based TBS showed no significant differences in prognostic performance and remained superior to tumor size and number alone.[19] Multiple subsequent studies likewise confirmed that TBS enables precise prognostic stratification in HCC patients undergoing surgical resection, liver transplantation, or TACE.[18,20–22] Our findings further support TBS as a reliable independent predictor reflecting tumor burden and prognosis.

Malnutrition is common throughout the disease course of cancer patients and is closely linked to clinical outcomes. The PNI, first proposed by Buzby et al,[23] incorporates serum albumin and lymphocyte count and was initially used to predict surgical risk in gastrointestinal procedures Lymphocytes play a crucial role in tumor immune surveillance and immune escape,[24] reflecting the host immune status, whereas serum albumin is a key indicator of nutritional reserve. Consequently, PNI is strongly associated with prognosis. Mei et al[25] analyzed 442 HCC patients receiving immunotherapy and reported that PNI was an independent predictor of OS and outperformed other inflammation-based scores. A meta-analysis[26] similarly found that higher PNI was significantly associated with improved OS and RFS in patients undergoing curative resection, with survival increasing proportionally to PNI levels.

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Cancer-related inflammation promotes tumor cell differentiation, proliferation, and metastasis, and elevated systemic inflammation indicates a poor prognosis.[27–30] The systemic immune-inflammation index (SII), which integrates platelet, neutrophil, and lymphocyte counts, provides a comprehensive reflection of systemic inflammatory status. Chen et al[31] found that a high SII was associated with poorer overall and progression-free survival and served as an independent prognostic factor in hepatocellular carcinoma (HCC) patients with bone metastases undergoing radiotherapy. A meta-analysis of SII in HCC patients treated with transarterial chemoembolization (TACE) likewise demonstrated that an elevated SII significantly predicted a worse prognosis.[32] These collective findings align with the results of the present study.

In the univariate Cox analysis, we also evaluated other common inflammatory markers—the NLR, PLR, and LMR. None of these retained independent prognostic significance in the subsequent multivariate model. This likely reflects the fact that the SII, by integrating neutrophil, platelet, and lymphocyte counts simultaneously, captures more comprehensive prognostic information that may overlap with or surpass the predictive value of the individual ratios. Consequently, the SII was selected as the more representative systemic inflammation marker during variable selection.

In addition, the results of this study should be interpreted with caution in light of potential competing risk bias and unmeasured confounding. Patients with intermediate-to-advanced HCC often have complex clinical conditions, and some deaths may be related not only to tumor progression but also to liver failure, comorbidities, or other causes. Moreover, as a retrospective study, certain factors that may influence prognosis were not fully captured. These issues may have affected the estimated associations between predictors and survival outcomes to some extent, and therefore warrant further evaluation in prospective studies with more comprehensive data collection.

This study has several limitations. First, the exclusion of patients with any prior antitumor therapy may introduce selection bias. Second, treatment heterogeneity was increased because patients received various targeted agents and immunotherapies in addition to TACE. Finally, although the nomogram showed favorable predictive performance during external validation, the sample size was relatively small and verification was confined to a single external center. Future large-scale, multicenter prospective studies are needed to further validate these findings.

Conclusion

In summary, we developed a nomogram incorporating tumor burden score and inflammation-nutritional indicators to predict 12-, 18-, and 24-month prognosis in patients with intermediate-to-advanced HCC undergoing triple therapy. The model exhibits satisfactory discrimination and calibration and clinical applicability and effectively stratifies patients into high- and low-risk categories. This tool may assist clinicians in identifying patients most likely to benefit from triple therapy and provide valuable guidance for personalized initial treatment decision-making.

Ethical Statement

This study has received ethical approval from the Institutional Review Board (IRB) of Ganzhou People's Hospital (Ethical Approval Number: PJB2025-354-01). For the other participating hospital, we obtained formal institutional data access and collaboration agreements from its administrative or research departments and adhered strictly to the principles outlined in the Declaration of Helsinki. Given that this is a retrospective study, the IRB granted a waiver of informed consent. All patient-related data used in this study complies with privacy protection regulations.

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Author Contributions

All authors have made significant contributions to the reported work, including the conception, study design, execution, data acquisition, analysis, and interpretation; involvement in drafting, revising, or critically reviewing the manuscript; final approval of the published version; agreement on the journal for submission; and consent to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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