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ORIGINAL RESEARCH

Establishment and Validation of a Nomogram Based on Inflammation-Immunity-Nutrition Biomarker Scores to Predict Postoperative Early Recurrence in Patients with Hepatocellular Carcinoma: A Multicenter Study

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Purpose: Early postoperative recurrence of hepatocellular carcinoma (HCC) significantly impairs patient quality of life and shortens survival. However, existing models rely on single-center or single-dimensional data, making accurate detection of early postoperative HCC recurrence challenging. Thus, designing/evaluating a reliable, non-invasive, comprehensive tool to predict HCC recurrence risk is crucial for guiding postoperative individualized antitumor treatment and improving prognosis.

Patients and methods: We retrospectively enrolled patients with HCC (n=1424) receiving curative-intent hepatectomy at the First Affiliated Hospital of Army Medical University of China between December 2012 and December 2022. Patients were randomly stratified into training and testing cohorts in a 7:3 ratio. Using least absolute shrinkage and selection operator (LASSO) logistic and multivariate logistic regression, we screened optimal predictors and subsequently developed a nomogram alongside an online calculator. The prediction model was externally validated at two other medical institutions (n = 218). The area under the curve (AUC) of the receiver operating characteristic, calibration, and decision curves were used to evaluate model performance.

Results: The nomogram intuitively showed nine independent risk factors in the prediction model for short-term recurrence in patients with HCC: Edmondson Steiner III–IV, tumor satellite nodules, vascular invasion, largest tumor > 5 cm, alpha-fetoprotein (AFP) level ≥ 400 μg/L, DeRitis ratio ≥ 1.49, gamma-glutamyl transferase (GGT) level ≥ 63.5 U/L, prognostic nutritional index (PNI) < 46.18, and neutrophil-to-lymphocyte ratio (NLR) ≥ 1.91. The AUCs of the training, testing, and validation cohorts were 0.760 (95% CI: 0.731–0.790), 0.784 (95% CI: 0.741–0.828), and 0.787 (95% CI: 0.728–0.846), respectively, indicating good predictive performance. The calibration and decision curves indicated that the model could be translated into tangible clinical benefits.

Conclusion: We constructed and evaluated a nomogram based on inflammation-immunity-nutrition biomarker scores to predict early postoperative recurrence of HCC, offering a free, user-friendly online calculator for quick access to results. This calculator empowers clinicians to convert complex clinical data into actionable insights, enabling the design of risk-stratified postoperative management strategies.

Keywords: HCC, postoperative early recurrence, prediction model, nomogram, inflammation-immunity-nutrition biomarker scores

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Introduction

Hepatocellular carcinoma (HCC) is a highly recurrent and metastatic malignancy, posing a significant global health burden. HCC is currently the sixth most common cancer and the third leading cause of cancer-related deaths globally.[1,2] HCC treatment is based on surgical resection; however, even after surgery, an alarmingly high risk (70%) of tumor recurrence within five years remains.[3–6] This high recurrence remains among the main bottlenecks that limit long-term treatment efficacy in patients with HCC.

Clinically, early and late recurrences generally manifest within a 2-year window following surgical resection.[7,8] In contrast to late recurrence, early recurrence can lead to a worse quality of life and lower survival rate, severely challenging the prognostic management of patients with HCC.[7,9] Most of the existing prediction models have limited predictive value for postoperative early recurrence owing to small sample size, single-center design, or single-dimensional variables.[10–12] Thus, identifying and developing a trustworthy and comprehensive tool for predicting risk of recurrence in HCC for guiding individualized postoperative medical care is warranted.

Recent research has confirmed that nutritional status, immune defense, and inflammatory response are closely related to tumor recurrence. Several existing clinical prediction models aim to combine preoperative inflammation and nutrition or immune-related indicators of patients with HCC, including albumin, platelet-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio (NLR), prognostic nutritional index (PNI), and preoperative alpha-fetoprotein (AFP) values, which are more innovative and practical than traditional models.[10,13,14] However, these models often ignore the correlations, interactions, and inseparability between nutrition, immunity, and inflammatory states. Previous studies have used the inflammation-immunity-nutrition score nomogram to predict the prognosis of different tumours[15–18] but have rarely forecasted the likelihood of early postoperative recurrence for HCC patients.

This research aimed to formulate a novel inflammation-immunity-nutrition biomarker score, providing a practical tool for predicting early postoperative risk in HCC. Furthermore, the nomogram transforms a complex regression equation into a visual graph, enhancing prediction readability and substantially improving ease of use in clinical practice and the operability of personalized assessment and intervention.

Methods

Patients

In this study, we employed a retrospective case-control design to retrieve HCC data from the First Affiliated Hospital of Army Medical University, the 958th Hospital of the Chinese People's Liberation Army, and Guang'an People's Hospital. Overall, 2651 HCC patients meeting the eligibility criteria were subjected to screening. The criteria for inclusion were as follows: (1) between 18 and 75 years of age; (2) previous radical hepatectomy performed by the same surgical team; (3) HCC confirmed by postoperative pathological examination; and (4) histologically confirmed R0 resection. The exclusion criteria included: (1) preoperative liver function classification Child-Pugh C; (2) prior preoperative anticancer treatment; (3) combination with other or secondary malignant tumors; and (4) incomplete clinical records or lack of follow-up post-surgery within a 24-month period. Patient data were collated by three investigators, two of whom were responsible for data extraction, while the other investigator performed accuracy checks.

The study was conducted in accordance with the principles of the Declaration of Helsinki (as revised in 2013) and approved by the ethical committee of each participating hospital: the First Affiliated Hospital of Army Medical University [Approval No. (B)KY2025011], Guang'an People's Hospital [Approval No. 2025022], and the 958th Hospital of the Chinese People's Liberation Army [Approval No. ER2025KY088]. Informed consent was waived by the Ethics Committees due to the use of de-identified, historical medical records in this retrospective study.

Data

Input variables were divided into the following groups: (1) basic demographic features: sex, body mass index (BMI), age, smoking behavior, drinking behavior, and history of hepatitis B virus infection; (2) pathological tumor features: maximum tumor diameter, vascular invasion, tumor satellite nodules, and Edmondson Steiner grade; (3) preoperative hematological indicators: inflammatory-immune markers, such as neutrophil (NEUT), lymphocyte (LYMPH), and white

blood cell counts, hepatitis B surface antigen, AFP level and NLR; (4) nutrition-related markers: hemoglobin, albumin (ALB), fasting blood glucose, blood creatinine, and PNI; and (5) hepatic function indicators: alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), and alkaline phosphatase (ALP) levels, platelet count, prothrombin activity (PTA), and DeRitis ratio.

The formulas employed to determine the clinical indicators included: BMI = weight (kg)/height^2 (m^2); PNI = ALB (g/L) + 5 * Lymph; DeRitis ratio = AST (U/L) / ALT (U/L); and NLR = NEUT / LYMPH.

Follow-up

Patients were monitored monthly for the initial three months following surgery and every 3 months up to the 2-year mark postoperatively. Follow-up was conducted to evaluate whether tumor recurrence occurred within 2 years post-surgery in patients with HCC. Follow-up evaluation included routine liver function tests, serum AFP measurement, liver contrast-enhanced ultrasound, abdominal enhanced computed tomography, and tumor-specific magnetic resonance imaging. Diagnosis of HCC recurrence adhered to the criteria outlined in the 2022 Chinese guidelines for primary liver cancer therapy and diagnosis.[19]

Construction and Verification of the Nomogram

Based on the training dataset, significant differences between the recurrence and non-recurrence groups were analyzed using univariate logistic regression. Furthermore, we optimized variable selection, reduced multicollinearity, and controlled model overfitting using least absolute shrinkage and selection operator (LASSO) regression. Predictors identified via LASSO were included in the multivariate logistic regression model and a nomogram established thereafter. Finally, a practical online calculator was created based on the nomogram.

The performance of a prediction model is typically verified via multiple validations of three dimensions: discrimination, accuracy, and clinical validity. Receiver operating characteristic (ROC) curve analysis was performed to assess model discrimination, with an area under the curve (AUC) $\geq$0.75 indicating good discrimination. A calibration curve was used to assess consistency between the predicted probability and the observed results. Additionally, clinical applicability was examined using decision curve analysis (DCA).

Statistical Analysis

Statistical analyses were performed using SPSS (version 26.0) and the R software (version 4.3.2). Normally distributed quantitative variables are presented as the mean ± standard deviation and were compared using independent *t*-tests, whereas non-normally distributed quantitative variables are presented as median (Q1, Q3) quartiles and were analyzed using the Mann–Whitney *U*-test. Categorical variables are described as frequencies and were compared using chi-square tests. All tests were two-tailed, with $P < 0.05$ considered statistically significant.

Results

Patient Characteristics

Relevant clinical data entered into the database were retrospectively reviewed and screened in strict accordance with the inclusion and exclusion criteria. Finally, 1424 eligible patients from the First Affiliated Hospital of Army Medical University between 2012 and 2022 were included and randomly allocated to the training (n = 996) and testing (n = 428) cohorts in a 7:3 ratio. Additionally, 218 eligible patients with HCC from two tertiary hospitals between 2015 and 2022 were enrolled in the external validation cohort (Figure 1). Baseline characteristics were not significantly different between the training and testing groups (Table 1). For most factors, significant differences were observed between the training and validation cohorts, warranting further discussion. In the training cohort, early HCC recurrence risk was 44.6%; moreover, smoking behavior, drinking behavior, NEUT and LYMPH counts, AST, ALT, GGT, ALP, and AFP levels, PTA, PNI, and NLR, along with some pathological features, differed significantly between the recurrence and non-recurrence groups (Table 2).

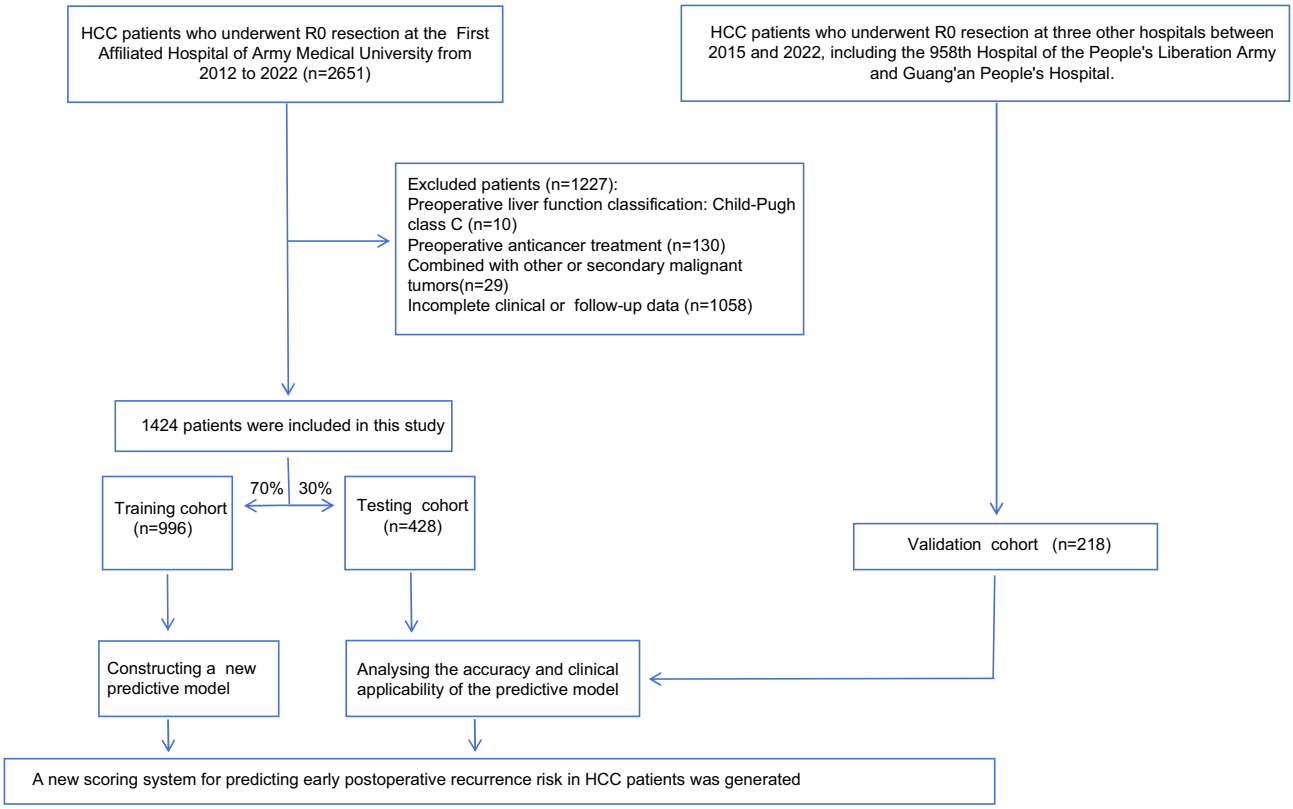

Figure 1 Patient selection flowchart.
Abbreviations: HCC, hepatocellular carcinoma; R0, complete tumor resection with negative margins.

LASSO, Univariate, and Multivariate Logistic Regression Analyses

Univariate logistic analysis identified 13 risk factors associated with early HCC recurrence, including smoking behavior, drinking behavior, LYMPH count, and PTA, PNI, NLR, GGT, and AFP levels, DeRitis ratio, Edmondson-Steiner, vascular invasion, tumor satellite nodules, and largest tumor diameter (Table 3). Through LASSO regression, 10 potential predictors

Table 1 Characteristics in the Training, Testing, and Validation Cohorts

Variables	Training Set (n = 996)	Testing Set (n = 428)	*P*	Validation Set (n = 218)	*P*
WBC, M (Q_1, Q_3)	5.76 (4.46, 8.11)	5.66 (4.37, 7.78)	0.103	5.46 (4.18, 7.16)	**0.012**
NEUT, M (Q_1, Q_3)	3.56 (2.58, 5.93)	3.54 (2.50, 5.67)	0.381	3.58 (2.51, 5.03)	0.441
Lymph, M (Q_1, Q_3)	1.29 (0.93, 1.71)	1.26 (0.93, 1.61)	0.244	1.13 (0.78, 1.49)	**<0.001**
Hb, M (Q_1, Q_3)	142.00 (130.00, 152.25)	141.00 (126.00, 151.00)	0.082	136.00 (123.00, 148.00)	**<0.001**
PLT, M (Q_1, Q_3)	142.00 (100.75, 182.00)	136.00 (93.00, 180.00)	0.050	140.00 (103.25, 182.50)	0.722
AST, M (Q_1, Q_3)	44.35 (31.00, 94.78)	43.00 (30.17, 91.95)	0.482	64.50 (29.00, 161.75)	**0.025**
ALT, M (Q_1, Q_3)	46.00 (28.00, 93.28)	42.05 (27.67, 92.20)	0.399	68.00 (33.25, 196.75)	**<0.001**
DeRitis ratio, M (Q_1, Q_3)	0.96 (0.74, 1.18)	0.95 (0.72, 1.17)	0.602	0.85 (0.64, 1.11)	**0.001**
GGT, M (Q_1, Q_3)	53.00 (33.00, 102.00)	52.50 (32.00, 98.25)	0.978	58.00 (33.25, 120.50)	0.074
ALP, M (Q_1, Q_3)	91.00 (73.00, 118.00)	93.00 (74.00, 120.25)	0.365	90.00 (72.25, 118.75)	0.819
ALB, M (Q_1, Q_3)	40.50 (36.30, 43.80)	40.65 (36.10, 43.60)	0.603	36.90 (30.13, 41.88)	**<0.001**
Cr, M (Q_1, Q_3)	73.00 (65.00, 82.35)	72.45 (63.90, 81.00)	0.121	67.05 (58.62, 80.00)	**<0.001**
Glu, M (Q_1, Q_3)	5.21 (4.75, 6.17)	5.36 (4.80, 6.29)	0.098	5.20 (4.72, 6.21)	0.846

(*Continued*)

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Table 1 (Continued).

Variables	Training Set (n = 996)	Testing Set (n = 428)	*P*	Validation Set (n = 218)	*P*
PTA, M (Q_1, Q_3)	85.20 (75.68, 95.00)	85.65 (74.70, 93.40)	0.541	93.01 (85.00, 103.45)	**<0.001**
PNI, M (Q_1, Q_3)	46.90 (41.49, 51.16)	46.55 (41.30, 50.75)	0.332	42.10 (35.51, 49.00)	**<0.001**
NLR, M (Q_1, Q_3)	2.61 (1.78, 5.34)	2.75 (1.83, 5.27)	0.301	3.21 (1.94, 5.18)	0.085
AFP, n(%)			0.819		0.097
<400	664 (66.67)	288 (67.29)		158 (72.48)	
≥400	332 (33.33)	140 (32.71)		60 (27.52)	
Age, M (Q_1, Q_3)	50.00 (44.00, 58.00)	50.00 (44.00, 58.00)	0.339	55.00 (49.00, 61.50)	**<0.001**
Sex, n(%)			0.652		**0.021**
Male	872 (87.55)	371 (86.68)		178 (81.65)	
Female	124 (12.45)	57 (13.32)		40 (18.35)	
Smoking behaviour, n(%)			0.459		**<0.001**
No	493 (49.50)	221 (51.64)		137 (62.84)	
Yes	503 (50.50)	207 (48.36)		81 (37.16)	
Drinking behaviour, n(%)			0.976		**<0.001**
No	553 (55.52)	238 (55.61)		155 (71.10)	
Yes	443 (44.48)	190 (44.39)		63 (28.90)	
BMI, n(%)			0.850		
< 18.5	49 (4.92)	21 (4.91)			
18.5 ≤BMI< 24	552 (55.42)	244 (57.01)			
≥24	395 (39.66)	163 (38.08)			
HBV Hepatitis, n(%)			0.880		**<0.001**
No	98 (9.84)	41 (9.58)		83 (38.07)	
Yes	898 (90.16)	387 (90.42)		135 (61.93)	
Edmondson Steiner, n(%)			0.100		**<0.001**
I–II	801 (80.42)	360 (84.11)		152 (69.72)	
III–IV	195 (19.58)	68 (15.89)		66 (30.28)	
Tumour satellite nodules, n(%)			0.739		**<0.001**
No	871 (87.45)	377 (88.08)		167 (76.61)	
Yes	125 (12.55)	51 (11.92)		51 (23.39)	
Vascular invasion, n(%)			0.269		0.842
No	583 (58.53)	237 (55.37)		126 (57.80)	
Yes	413 (41.47)	191 (44.63)		92 (42.20)	
Largest tumour, n(%)			0.628		**<0.001**
≤5	697 (69.98)	294 (68.69)		93 (42.66)	
>5	299 (30.02)	134 (31.31)		125 (57.34)	
Group, n(%)			0.614		**0.010**
Recurrence(+)	552 (55.42)	231 (53.97)		100 (45.87)	
Recurrence(-)	444 (44.58)	197 (46.03)		118 (54.13)	

Notes: Data are expressed as number (percentage) or median [IQR]; M: Median, Q_1: 1st Quartile, Q_3: 3st Quartile; Bold values indicate statistically significant differences ($p < 0.05$).

Abbreviations: WBC, White Blood Cell; NEUT, Neutrophil; Hb, Hemoglobin; PLT, Platelet; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; ALP, Alkaline phosphatase; GGT, Gamma-Glutamyl Transferase; ALB, albumin; Cr, Creatinine; Glu, Glucose; PTA, Prothrombin Activity; NLR, Neutrophil-to-Lymphocyte Ratio; PNI, Prognostic Nutritional Index; AFP, Alpha-fetoprotein; BMI, Body mass index; HBV, Hepatitis B virus.

were selected from 13 candidates to enhance the robustness of the model and avoid overfitting (Figure 2A and B). Finally, multivariate logistic regression analysis was performed to further screen nine independent risk-associated variables for postoperative early HCC recurrence (Table 4): Edmondson Steiner III–IV (odds ratio [OR] = 2.584, 95% confidence interval [CI]: 1.804–3.700, P <0.001), tumor satellite nodules (OR = 2.133, 95% CI: 1.383–3.291, $P < 0.001$), vascular invasion (OR = 1.768, 95% CI: 1.328–2.354, $P < 0.001$), largest tumor ≤5 cm (OR = 0.483; 95% CI: 0.351–0.665; $P <$

Table 2 Characteristics of the Patients Presenting with and Without Early Recurrence in the Training Set

Variables	Total (n = 996)	Recurrence(+) (n = 552)	Recurrence(-) (n = 444)	Statistic	*P*
WBC, M (Q_1, Q_3)	5.76 (4.46, 8.11)	5.53 (4.32, 7.98)	5.97 (4.60, 8.13)	Z=−1.60	0.109
NEUT, M (Q_1, Q_3)	3.56 (2.58, 5.93)	3.38 (2.51, 5.71)	3.79 (2.73, 6.01)	Z=−2.37	**0.018**
Lymph, M (Q_1, Q_3)	1.29 (0.93, 1.71)	1.33 (0.97, 1.77)	1.27 (0.89, 1.65)	Z=−2.08	**0.037**
Hb, M (Q_1, Q_3)	142.00 (130.00, 152.25)	143.00 (130.00, 153.00)	141.00 (129.00, 152.00)	Z=−0.98	0.327
PLT, M (Q_1, Q_3)	142.00 (100.75, 182.00)	140.00 (101.00, 180.00)	143.50 (98.00, 185.00)	Z=−0.74	0.458
AST, M (Q_1, Q_3)	44.35 (31.00, 94.78)	39.90 (29.00, 86.10)	48.85 (33.22, 104.55)	Z=−3.79	**<0.001**
ALT, M (Q_1, Q_3)	46.00 (28.00, 93.28)	42.90 (27.40, 89.25)	49.60 (28.98, 100.93)	Z=−2.02	**0.044**
DeRitis ratio, M (Q_1, Q_3)	0.96 (0.74, 1.18)	0.95 (0.75, 1.17)	0.96 (0.73, 1.19)	Z=−0.41	0.683
GGT, M (Q_1, Q_3)	53.00 (33.00, 102.00)	47.00 (30.00, 83.08)	65.00 (37.90, 122.00)	Z=−5.92	**<0.001**
ALP, M (Q_1, Q_3)	91.00 (73.00, 118.00)	88.00 (71.00, 110.00)	96.00 (75.88, 124.00)	Z=−3.42	**<0.001**
ALB, M (Q_1, Q_3)	40.50 (36.30, 43.80)	40.45 (36.68, 44.00)	40.50 (35.68, 43.52)	Z=−1.17	0.241
Cr, M (Q_1, Q_3)	73.00 (65.00, 82.35)	73.50 (65.68, 82.93)	72.95 (64.18, 82.12)	Z=−1.03	0.302
Glu, M (Q_1, Q_3)	5.21 (4.75, 6.17)	5.21 (4.76, 6.13)	5.21 (4.72, 6.21)	Z=−0.30	0.766
PTA, M (Q_1, Q_3)	85.20 (75.68, 95.00)	85.70 (77.15, 96.15)	84.50 (73.85, 93.62)	Z=−2.62	**0.009**
PNI, M (Q_1, Q_3)	46.90 (41.49, 51.16)	47.67 (42.90, 51.86)	45.70 (39.52, 50.12)	Z=−4.95	**<0.001**
NLR, M (Q_1, Q_3)	2.61 (1.78, 5.34)	2.38 (1.60, 4.37)	2.92 (2.00, 7.14)	Z=−5.23	**<0.001**
AFP, n(%)				χ^2=68.05	**<0.001**
<400	664 (66.67)	429 (77.72)	235 (52.93)		
≥400	332 (33.33)	123 (22.28)	209 (47.07)		
Age, M (Q_1, Q_3)	50.00 (44.00, 58.00)	49.00 (43.00, 57.00)	50.00 (44.00, 59.00)	Z=−1.08	0.278
Sex, n(%)				χ^2=0.19	0.660
Male	872 (87.55)	481 (87.14)	391 (88.06)		
Female	124 (12.45)	71 (12.86)	53 (11.94)		
Smoking behavior, n(%)				χ^2=4.04	**0.044**
No	493 (49.50)	289 (52.36)	204 (45.95)		
Yes	503 (50.50)	263 (47.64)	240 (54.05)		
Drinking behavior, n(%)				χ^2=4.49	**0.034**
No	553 (55.52)	323 (58.51)	230 (51.80)		
Yes	443 (44.48)	229 (41.49)	214 (48.20)		
BMI, n(%)				χ^2=5.85	0.054
< 18.5	49 (4.92)	35 (6.34)	14 (3.15)		
18.5 ≤BMI< 24	552 (55.42)	296 (53.62)	256 (57.66)		
≥24	395 (39.66)	221 (40.04)	174 (39.19)		
HBV Hepatitis, n(%)				χ^2=1.01	0.316
No	98 (9.84)	59 (10.69)	39 (8.78)		
Yes	898 (90.16)	493 (89.31)	405 (91.22)		
Edmondson Steiner, n(%)				χ^2=35.47	**<0.001**
I–II	801 (80.42)	481 (87.14)	320 (72.07)		
III–IV	195 (19.58)	71 (12.86)	124 (27.93)		
Tumor satellite nodules, n(%)				χ^2=21.82	**<0.001**
No	871 (87.45)	507 (91.85)	364 (81.98)		
Yes	125 (12.55)	45 (8.15)	80 (18.02)		
Vascular invasion, n(%)				χ^2=36.82	**<0.001**
No	583 (58.53)	370 (67.03)	213 (47.97)		
Yes	413 (41.47)	182 (32.97)	231 (52.03)		
Largest tumor, n(%)				χ^2=55.81	**<0.001**
≤5	697 (69.98)	440 (79.71)	257 (57.88)		
>5	299 (30.02)	112 (20.29)	187 (42.12)		

Notes: Data are expressed as number (percentage) or median [IQR]; Z: Mann–Whitney test, χ^2: Chi-square test; M: Median, Q_1: 1st Quartile, Q_3: 3st Quartile; Bold values indicate statistically significant differences ($p < 0.05$).

Abbreviations: WBC, White Blood Cell; NEUT, Neutrophil; Hb, Hemoglobin; PLT, Platelet; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; ALP, Alkaline phosphatase; GGT, Gamma-Glutamyl Transferase; ALB, albumin; Cr, Creatinine; Glu, Glucose; PTA, Prothrombin Activity; NLR, Neutrophil-to-Lymphocyte Ratio; PNI, Prognostic Nutritional Index; AFP, Alpha-fetoprotein; BMI, Body mass index; HBV, Hepatitis B virus.

Table 3 Univariable Logistic Regression Analyses of Risk Factors for Postoperative Early Recurrence in Patients with HCC

Variables	β	S.E	Z	*P*	OR (95% CI)
Age	0.008	0.006	1.251	0.211	1.008 (0.996–1.019)
Sex					
Male					1.000 (Reference)
Female	−0.085	0.194	−0.440	0.660	0.918 (0.628–1.343)
Smoking behavior					
No					1.000 (Reference)
Yes	0.257	0.128	2.009	**0.044**	1.293 (1.006–1.661)
Drinking behavior					
No					1.000 (Reference)
Yes	0.272	0.128	2.117	**0.034**	1.312 (1.020–1.688)
BMI					
18.5 ≤BMI< 24					1.000 (Reference)
≥24	−0.094	0.133	−0.709	0.478	0.910 (0.702–1.180)
< 18.5	−0.771	0.328	−2.354	**0.019**	0.463 (0.243–0.879)
HBV Hepatitis					
No					1.000 (Reference)
Yes	0.217	0.217	1.002	0.317	1.243 (0.812–1.902)
Edmondson Steiner					
I–II					1.000 (Reference)
III–IV	0.965	0.165	5.836	**<0.001**	2.625 (1.898–3.630)
Tumor satellite nodules					
No					1.000 (Reference)
Yes	0.907	0.199	4.566	**<0.001**	2.476 (1.678–3.655)
Vascular invasion					
No					1.000 (Reference)
Yes	0.791	0.131	6.025	**<0.001**	2.205 (1.705–2.851)
Largest tumor					
>5					1.000 (Reference)
≤5	−1.050	0.143	−7.346	**<0.001**	0.350 (0.264–0.463)
WBC	0.013	0.016	0.759	0.448	1.013 (0.980–1.046)
NEUT	0.018	0.017	1.093	0.274	1.018 (0.986–1.052)
Lymph	−0.280	0.105	−2.654	**0.008**	0.756 (0.615–0.930)
Hb	−0.003	0.003	−0.786	0.432	0.997 (0.991–1.004)
PLT	0.001	0.001	0.871	0.384	1.001 (0.999–1.003)
AST	0.001	0.000	1.250	0.211	1.001 (1.000–1.001)
ALT	0.000	0.000	0.890	0.373	1.000 (1.000–1.001)
DeRitis ratio	0.345	0.176	1.963	**0.049**	1.412 (1.001–1.993)
GGT	0.003	0.001	4.095	**<0.001**	1.003 (1.002–1.004)
ALP	0.002	0.001	1.696	0.090	1.002 (1.000–1.004)
ALB	−0.012	0.011	−1.070	0.285	0.988 (0.967–1.010)
Cr	−0.006	0.004	−1.444	0.149	0.994 (0.985–1.002)
Glu	0.062	0.032	1.929	0.054	1.064 (0.999–1.133)
PTA	−0.010	0.004	−2.736	**0.006**	0.990 (0.982–0.997)
PNI	−0.047	0.009	−5.381	**<0.001**	0.954 (0.938–0.971)
NLR	0.042	0.010	4.058	**<0.001**	1.043 (1.022–1.064)
AFP					
<400					1.000 (Reference)
≥400	1.132	0.140	8.106	**<0.001**	3.102 (2.359–4.078)

Notes: Bold values indicate statistically significant differences. ($p < 0.05$).

Abbreviations: BMI, Body mass index; HBV, Hepatitis B virus; WBC, White Blood Cell; NEUT, Neutrophil; Hb, Hemoglobin; PLT, Platelet; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; ALP, Alkaline phosphatase; GGT, Gamma-Glutamyl Transferase; ALB, albumin; Cr, Creatinine; Glu, Glucose; PTA, Prothrombin Activity; PNI, Prognostic Nutritional Index; NLR, Neutrophil-to-Lymphocyte Ratio; AFP, Alpha-fetoprotein; CI, Confidence Interval; OR, Odds Ratio; S.E, Standard Error.

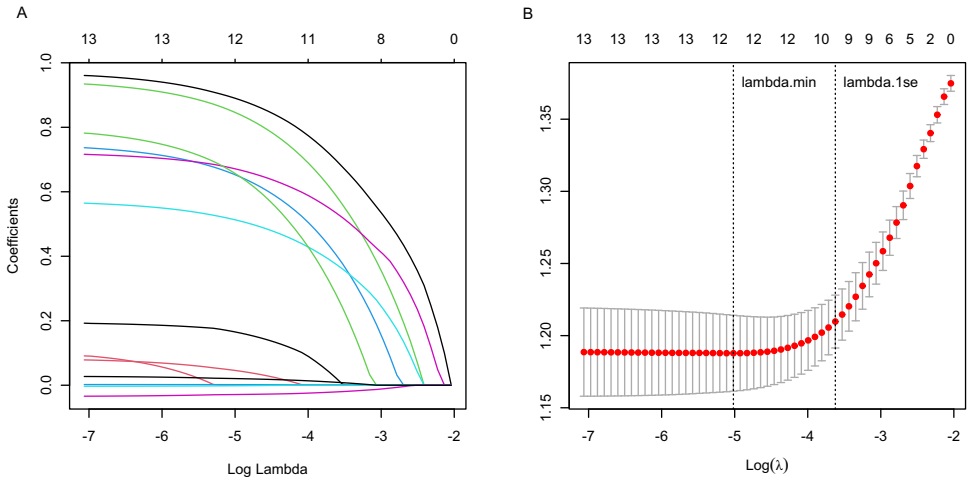

Figure 2 LASSO coefficient profiles for postoperative early recurrence in patients with HCC. (**A**) Each curve presents the change in the coefficient. The ordinate is the coefficient value, the lower abscissa is log(λ), and the upper abscissa is the number of non-zero coefficients in the model. (**B**) Ten-fold cross-validation was performed to fit and select the model.
Abbreviations: LASSO, least absolute shrinkage and selection operator; HCC, hepatocellular carcinoma.

0.001), AFP level ≥ 400 ng/μL (OR = 2.645; 95% CI: 1.953–3.581; $P < 0.001$), DeRitis ratio (OR = 2.232, 95% CI: 1.482–3.363, $P < 0.001$), GGT level (OR = 1.002, 95% CI: 1.001–1.004, $P = 0.003$), PNI (OR = 0.967, 95% CI: 0.946–0.988, $P = 0.002$), and NLR (OR = 1.026, 95% CI: 1.002–1.051, $P = 0.036$).

Table 4 Multivariate Logistic Regression Analysis of Predictors Selected by the LASSO Regression Procedure in the Training Set

Variables	β	S.E	Z	*P*	OR (95% CI)
Smoking behaviour					
No					1.000 (Reference)
Yes	0.252	0.145	1.744	0.081	1.287 (0.969–1.708)
Edmondson Steiner					
I–II					1.000 (Reference)
III–IV	0.949	0.183	5.180	**<0.001**	2.584 (1.804–3.700)
Tumour satellite nodules					
No					1.000 (Reference)
Yes	0.758	0.221	3.427	**<0.001**	2.133 (1.383–3.291)
Vascular invasion					
No					1.000 (Reference)
Yes	0.570	0.146	3.899	**<0.001**	1.768 (1.328–2.354)
Largest tumour					
>5					1.000 (Reference)
≤5	−0.728	0.163	−4.464	**<0.001**	0.483 (0.351–0.665)
AFP					
<400					1.000 (Reference)
≥400	0.972	0.155	6.287	**<0.001**	2.645 (1.953–3.581)
DeRitis ratio	0.803	0.209	3.841	**<0.001**	2.232 (1.482–3.363)
GGT	0.002	0.001	2.957	**0.003**	1.002 (1.001–1.004)
PNI	−0.034	0.011	−3.047	**0.002**	0.967 (0.946–0.988)
NLR	0.026	0.012	2.094	**0.036**	1.026 (1.002–1.051)

Notes: Bold values indicate statistically significant differences (p < 0.05).
Abbreviations: AFP, Alpha-fetoprotein; CI, Confidence Interval; GGT, Gamma-Glutamyl Transferase; LASSO, Least Absolute Shrinkage and Selection Operator; NLR, Neutrophil-to-Lymphocyte Ratio; PNI, Prognostic Nutritional Index; OR, Odds Ratio; S.E, Standard Error.

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Nomogram Construction

To simplify the model, we used DeRitis ratio, GGT level, PNI, and NLR to select the best threshold point on the ROC curve and calculated the critical values as follows: 1.49, 63.50 U/L, 46.18, and 1.91, respectively. This method transforms continuous variables into categorical variables and reintroduces them into the constructed model, improving its clinical applicability to a certain extent. Based on the nine risk factors screened, a nomogram was developed to quantify the risk of early postoperative HCC recurrence.

As shown in Figure 3, Edmondson Steiner III–IV, tumor satellite nodules, vascular invasion, largest tumor > 5 cm, AFP level ≥ 400 ng/μL, DeRitis ratio ≥ 1.49, GGT level ≥ 63.5 U/L, PNI < 46.18, and NLR ≥ 1.91 were independent risk factors for short-term HCC recurrence, with scores of 100, 78, 67, 72, 93, 98, 54, 38, and 59, respectively. Indicator scores were summed to obtain a total score, and a corresponding risk scale is presented in the nomogram (Figure 3).

Evaluation and Verification of the Prediction Model

In the training set, the ROC curve exhibited strong discriminative ability (AUC, 0.760; 95% CI: 0.731–0.790; Figure 4A). The discriminative ability in the test (AUC, 0.784; 95% CI: 0.741–0.828) and validation (AUC, 0.787;

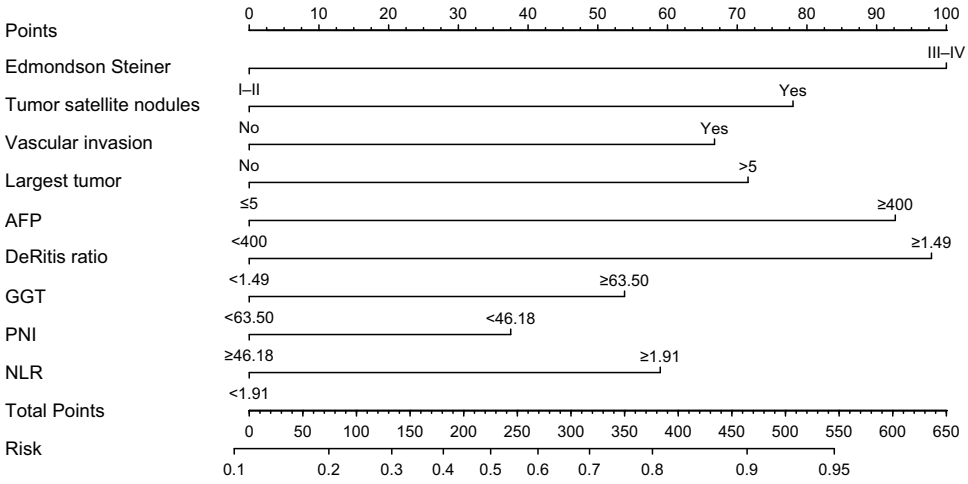

Figure 3 Nomogram for predicting early HCC recurrence risk after surgery. The predictive indicators on each level represent a certain score. The total score corresponds to the early recurrence risk and is generated by summing the scores of each predictor.

Abbreviations: AFP, alpha-fetoprotein; GGT, gamma-glutamyl transferase; HCC, hepatocellular carcinoma; NLR, neutrophil-to-lymphocyte ratio; PNI, prognostic nutritional index.

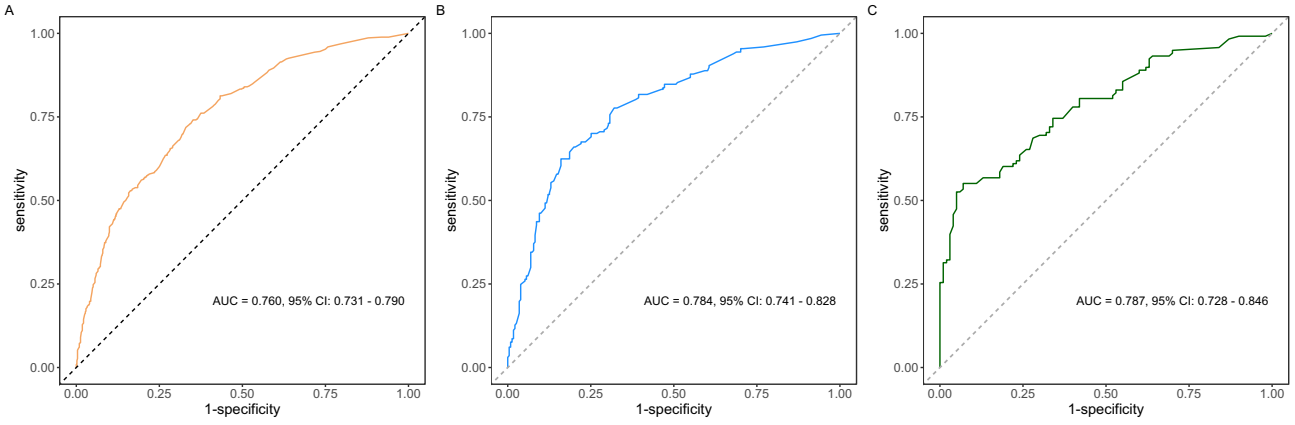

Figure 4 ROC curve and AUC of the prediction model. (**A**) ROC curve in the training cohort. (**B**) ROC curve in the testing cohort. (**C**) ROC curve in the validation cohort.

Abbreviations: ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval.

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95% CI: 0.728–0.846) sets was verified (Figure 4B and C). In the Hosmer–Lemeshow test, χ^2 values of 14.78 (P = 0.063), 10.91 (P= 0.207), and 13.97 (P = 0.083) were obtained in the training, test, and validation sets, respectively. Therefore, the model displayed good goodness-of-fit, and the calibration curve analysis showed that the predicted probability of short-term postoperative recurrence in patients with HCC was highly consistent with the actual risk in both internal and external validations (Figure 5). Furthermore, the DCA method was applied to evaluate the transferability of the model to clinical contexts. The model demonstrated significantly higher net benefit in internal/external validation sets than the two extremes, indicating good clinical utility (Figure 6).

Web-Based Calculator

Using the above nomogram, we created a web-based calculator to predict short-term recurrence risk in patients with HCC post-hepatectomy (Figure 7). The clinician enters the variable in the left option box, upon which the right-hand section presents the predicted likelihood of early recurrence in patients with HCC. The excellent performance of the web-based calculator in terms of accuracy, convenience, and speed can assist clinical decision makers in personalized medicine implementation. The calculator has been published online and is available at this URL: https://zhangxiaosong520.shinyapps.io/Prediction_model/.

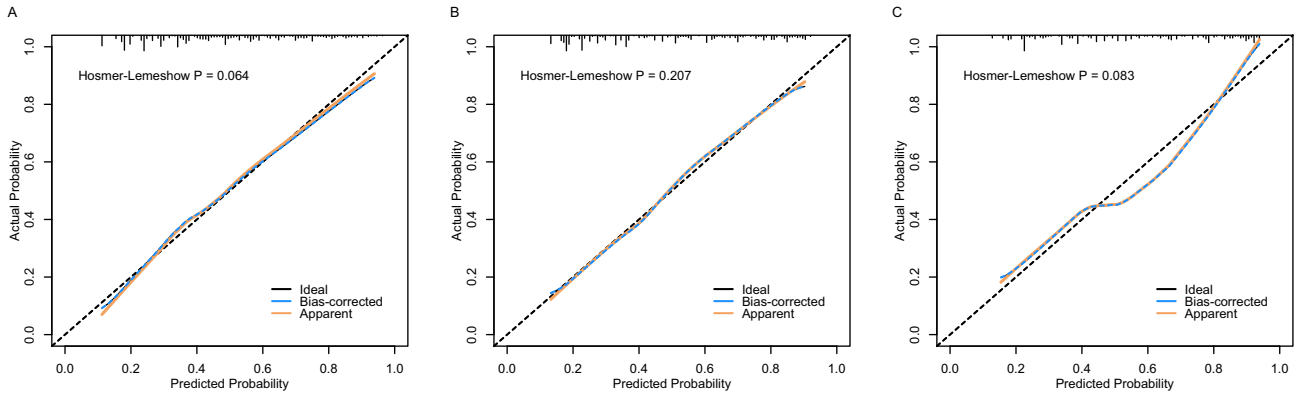

Figure 5 Nomogram calibration plots in the training (**A**), testing (**B**), and validation (**C**) cohorts.

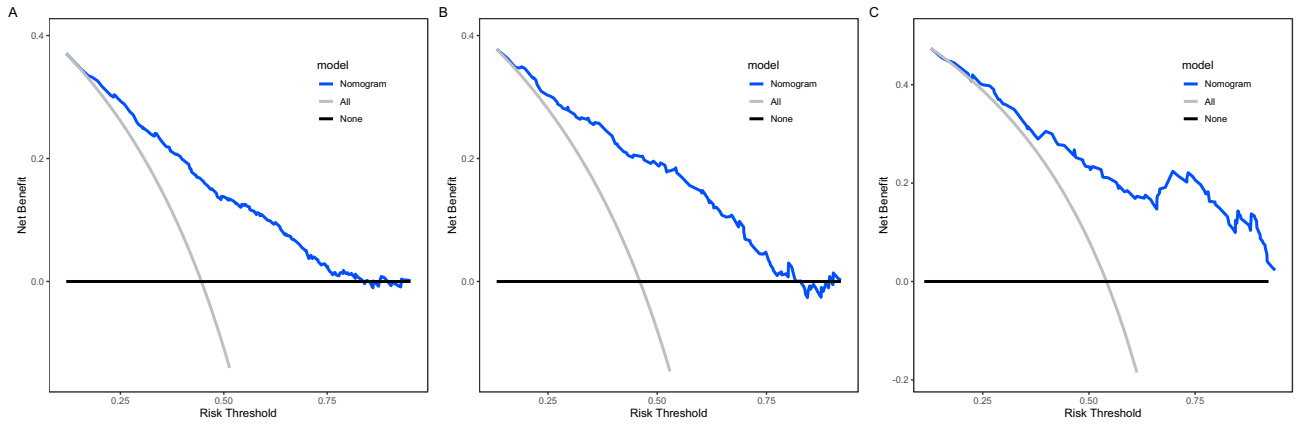

Figure 6 Decision clinical analysis curves of the nomogram in the training (**A**), testing (**B**), and validation (**C**) cohorts.

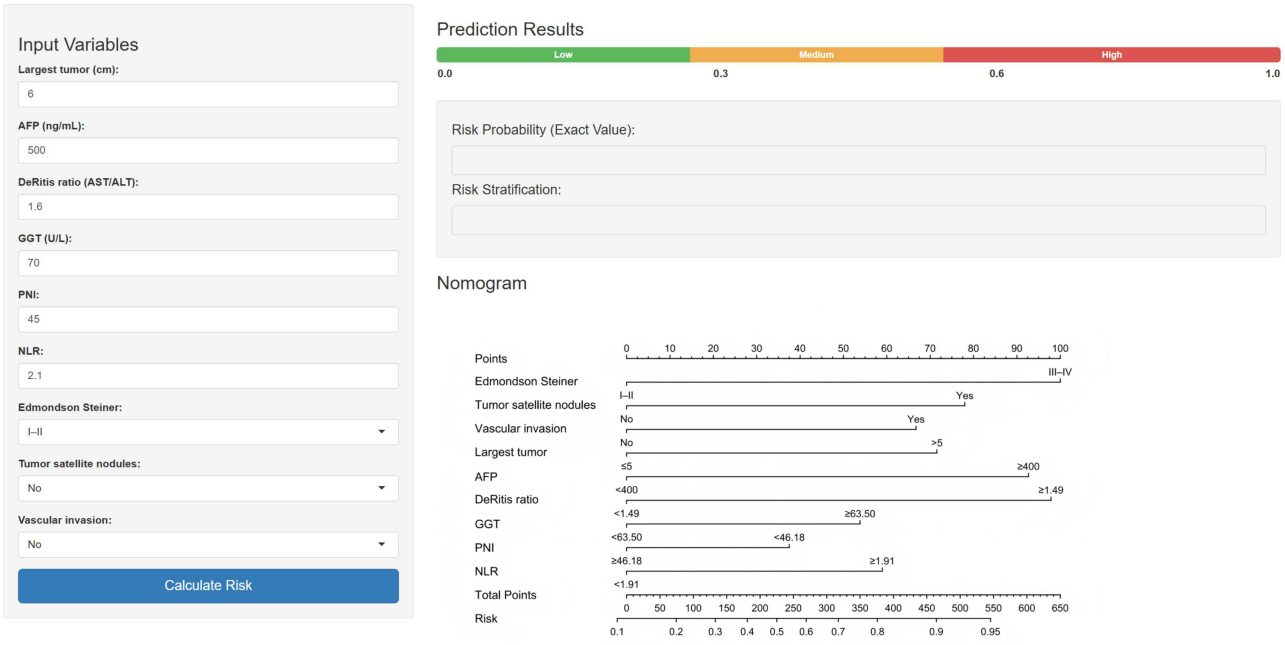

Figure 7 Multicenter validation of a web-based tool for early HCC recurrence risk assessment.
Abbreviations: AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; HCC, hepatocellular carcinoma; NLR, neutrophil-to-lymphocyte ratio; PNI, prognostic nutritional index.

Discussion

This study formulated and validated a novel multidimensional model that, for the first time, integrates clinical indicators across four critical dimensions, namely tumor characteristics, nutritional status, immunity, and inflammation, thereby providing a more com; prehensive risk assessment framework compared with those based on traditional single-dimensional indicators (eg, AFP level, microvascular invasion [MVI], and NLR).[10–12,14,20] Notably, this model demonstrated enhanced predictive ability compared with conventional metrics. Moreover, based on conventional laboratory test indicators, no special molecular markers (eg, AFP-L3 or PIVKA-II) are required.[21,22]

Although surgical resection is the main HCC treatment, the postoperative recurrence rate remains high.[2,3] Early recurrence of HCC is linked to lower quality of life and reduced survival rates, presenting substantial challenges in effective prognostic management.[2,7] Studies have aimed to develop models to predict early HCC recurrence risk. For instance, a multicenter study found that a tumor diameter > 5 cm, AFP level > 400 μg/L, satellite nodules, and MVI served as independent risk markers for postoperative early recurrence (≤ 2 years).[23] Additionally, the Chinese Guidelines for the Diagnosis and Treatment of Primary Liver Cancer (2024 Edition) define AFP ≥ 400 ng/mL as a core threshold for the diagnosis and prognosis evaluation of HCC.[24] Moreover, Liu et al indicated that the GGT level is an aggravating parameter for such a risk.[25] The joint application of GGT levels and the DeRitis ratio exhibited strong predictive ability for MVI occurrence in patients with HCC, which aids in the timely identification of poor prognosis.[26] However, the predictive value of existing models in estimating outcomes is limited, highlighting the urgent need for novel, accurate, and comprehensive predictive models for personalized diagnostic and therapeutic approaches for patients with HCC.

Consistent with the findings of previous research regarding the incidence of early recurrence among patients with HCC, 46% of the 1642 cases included in this study experienced early recurrence after surgery.[4–6] Our nomogram model was based on the following nine variables: Edmondson Steiner III–IV, tumor satellite nodules, vascular invasion, largest tumor, AFP level, DeRitis ratio, GGT level, PNI, and NLR. Among these, the first seven variables have been widely included in previous risk models of postoperative early HCC recurrence. However, the predictive capability of NLR and PNI, when integrated with the above variables, remains unknown. An elevated NLR reflects either increased neutrophil infiltration or decreased lymphocytes in the tumor microenvironment, which may promote tumor immune escape and accelerate recurrence.[27,28] Wong et al reported that NLR is a valuable biomarker for

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predicting postoperative early recurrence in patients with HCC, with NLR ≥ 3 being associated with shortened overall survival;[14] our findings corroborate these results. Furthermore, the PNI calculated from serum albumin and circulating blood lymphocyte counts has frequently been used to assess the nutritional-immune profile of patients with diverse tumors. Zhao et al confirmed that PNI, a nutritional indicator, exhibits an independent association with the overall survival of patients with nasopharyngeal carcinoma.[29] In several studies, PNI has been recognized as a practical prognostic indicator for HCC.[10,30] Specifically, Chan et al confirmed that PNI serves as an independent predictor of early-stage HCC recurrence.[10] Therefore, of the nine independent risk factors for early postoperative HCC recurrence that were screened in this investigation, NLR and PNI served as critical factors in the inflammatory-immune-nutrition biomarker score.

The predictive performance of the model in forecasting postoperative HCC early recurrence in the training, testing, and verification sets was 0.760, 0.784, and 0.787, respectively, suggesting the effectiveness of the model's predictive performance. The model's clinical applicability and application value underwent further evaluation using calibration and DCA curve analysis. Additionally, our nomogram was based on datasets from three clinical institutions, which were internally and externally validated using the test and validation sets, respectively. Compared with that of a previous single-center model, the predictive efficacy of the current multicenter model was high and the reliability was strong.[11,25] Despite baseline disparities between the training and validation sets, the excellent real-world applicability of the model in external validation indirectly highlights its replicability and generalizability. The model results were visualized in a nomogram, and clinicians can objectively evaluate various HCC-related clinical indicators in patients.

This study has several strengths. First, all data are from real-world settings, and the large sample size together with internal and external validation ensures high credibility and authenticity. Second, we developed a multidimensional model based on nutrition–immunity–inflammation status, which complements existing models for predicting HCC recurrence. Finally, the web-based calculator enables clinicians to turn complex clinical data into actionable decisions, allowing risk-stratified postoperative strategies—avoiding unnecessary tests in low-risk patients and focusing resources on high-risk groups—while empowering patients and achieving both precision medicine and humanistic care.

Nevertheless, the study also had certain limitations. First, retrospective data inevitably introduce selection or information bias, leading to insufficient representation of high-risk recurrence groups. Second, although reliability was enhanced through multicenter internal validation, the model has not yet been validated in major HCC-endemic regions outside East Asia (eg, Africa, Southeast Asia), and its generalizability requires further exploration. In future work, we plan to conduct prospective validation in patients with different risk strata of HCC and establish international multicenter collaborations.

Recurrence risk can be rapidly and conveniently estimated using the online calculator derived from the nomogram, which aids in preliminary risk stratification in clinical practice and assists surgeons in implementing accurate monitoring and early intervention.

Conclusions

We established and verified an integrated nomogram formulated on inflammation, immunity, and nutrition biomarker scores, which may assist clinicians in predicting early recurrence after HCC resection and in providing appropriate actions to ameliorate survival outcomes. Moreover, this study provides a free and available online calculator for clinicians to quickly obtain results and customize individualized antitumor strategies.

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Disclosure

The authors report no conflicts of interest in this work.

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