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Prognostic nomogram based on coagulation for individualized prediction after radical resection of hepatocellular carcinoma

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Abstract

Background The prognosis of patients with hepatocellular carcinoma (HCC) following radical resection remains suboptimal. This study aimed to create a nomogram integrating clinicopathological parameters and coagulation indices to predict the recurrence-free survival (RFS) of these individuals.

Methods A total of 863 patients with hepatocellular carcinoma after radical resection were included (504 patients in the training cohort, 216 patients in the internal verification cohort and 142 patients in the external verification cohort). Cox regression analysis was used to determine the independent risk factors in the training cohort, and it was used to construct a prognostic nomogram. Calibration curves, decision curve analysis (DCA), the C index and the time-dependent area under the curve (td-AUC) were used to evaluate the performance of the nomogram, and the internal and external validation cohorts were used for verification. We also calculated total risk points to divide patients into high-, medium- and low-risk groups. The Kaplan–Meier methodology was used to analyze RFS, and differences were compared using the log-rank test.

Results Age, tumor size, tumor differentiation, microvascular invasion, INR and FIB for RFS were integrated into the nomogram. The calibration curves revealed a strong correlation between the predicted and actual results, and the nomogram's C-index and DCA demonstrated superior predictive performance compared with TNM, BCLC, CNLC, and CLIP. Additionally, the td-AUC revealed that the nomogram effectively predicted recurrence-free survival (RFS) at 1, 3, and 5 years. Moreover, significant differences in RFS were observed between the high-, medium-, and low-risk groups ($P < 0.0001$) after the effective cutoff values of the risk points were identified using the nomogram.

Conclusions A nomogram model that is based on coagulation indices has high predictive efficacy for the recurrence of hepatocellular carcinoma in patients and significant clinical application value.

Keywords Hepatocellular carcinoma, Coagulation, Nomogram, Recurrence-free survival

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Introduction

Primary liver cancer is a prevalent malignancy of the digestive tract system. According to GLOBOCAN 2022 statistics, the annual incidence of liver cancer worldwide is approximately 865,000, positioning it as the sixth most common cancer type. The annual death rate is as high as 757,948, ranking third in the world in terms of cancer mortality [1]. According to data released by the China National Cancer Center, primary liver cancer was the fourth most common type of cancer in 2022, with an incidence rate of 367,700, accounting for 15.4% of all new cancer cases (following lung, colorectal, and thyroid gland cancers). The number of deaths due to primary liver cancer in 2022 was 316,500, ranking it as the second leading cause of cancer-related mortality (after lung cancer) [2]. Hepatocellular carcinoma (HCC) represents the most common form of primary liver cancer, constituting 85% to 90% of all liver cancer diagnoses. In recent years, advancements in diagnostic and surgical techniques have led to the adoption of a comprehensive treatment model for hepatocellular carcinoma, which is primarily based on surgical resection. This approach has significantly enhanced the treatment efficacy. However, the postresection recurrence rate remains high, with approximately 60-70% of cases recurring within five years, resulting in an unsatisfactory overall survival rate [3]. Effective prevention and prompt treatment of postoperative recurrence are crucial for reducing mortality and improving the overall survival rate.

The high rate of postoperative recurrence in patients with hepatocellular carcinoma presents a significant clinical challenge. Numerous prognostic staging systems have been introduced to address this issue, such as the Italian Cancer Program (CLIP staging), the Barcelona Clinical Liver Cancer (BCLC staging), the Tumor Node Metastasis (TNM staging), and the China Liver Cancer Staging (CNLC staging). However, these systems often fail to deliver precise individualized assessments. The recurrence of hepatocellular carcinoma is influenced by various factors, including the patient's general condition, tumor aggressiveness, systemic inflammation, nutritional status, and coagulation status.

Coagulation factors are synthesized primarily in the liver. In patients without concurrent hematological disorders, the coagulation profile serves as a surrogate marker of hepatic function. Hepatic injury compromises both the synthetic and reserve capacities of the liver, leading to diminished production of coagulation factors and consequent impairment of systemic coagulation. Hence, metrics of coagulation function offer valuable insights into the extent of hepatic damage and can effectively predict clinical outcomes. In patients with digestive tract tumors, hypercoagulability frequently occurs. Fibrinogen levels are notably elevated in individuals with hepatocellular carcinoma compared with both healthy individuals and those with liver cirrhosis. Current research suggests that coagulation function indicators, including the prothrombin time, INR, and fibrinogen level, can serve as potential markers for the onset of hepatocellular carcinoma and can aid in predicting the prognosis of patients [4–6].

Despite ongoing research into the predictive indicators and risk factors for postoperative recurrence of hepatocellular carcinoma, a comprehensive consensus remains elusive, and the findings are often contentious. Consequently, this study aims to develop a nomogram prediction model that assesses the recurrence-free survival rate of patients with hepatocellular carcinoma following radical resection. This model incorporates general patient information, clinicopathological parameters, and platelet and coagulation indices. The model will be validated using multicenter data to facilitate the formulation of more rational, individualized, and holistic treatment plans and follow-up strategies for clinical application.

Materials and methods

Patients and methods

From January 2015 to December 2019, 720 patients with hepatocellular carcinoma were hospitalized at the First Affiliated Hospital of China University of Science and Technology. After the collection of blood indices and clinical data, these patients were randomly divided at a 7:3 ratio into a training group and an internal validation group. Additionally, 142 patients with hepatocellular carcinoma who underwent curative surgery at Anhui Provincial Cancer Hospital between January 2015 and December 2021 were included for external validation of the model. The study was approved by the Ethics Committee and Institutional Review Board. The data for the patients were retrospectively analyzed for this study. The inclusion criteria were as follows: (1) initial curative liver resection treatment; (2) postoperative pathological diagnosis of primary hepatocellular carcinoma; (3) no extrahepatic metastasis; and (4) complete medical records and follow-up of related information. The exclusion criteria were as follows: (1) preoperative TACE, radiofrequency ablation, or other antitumor treatments; (2) combined cholangiocarcinoma and mixed hepatocellular cholangiocarcinoma; (3) history of malignant tumors; and (4) blood system diseases.

Clinicopathologic variables and follow-up

The clinical data and laboratory test results for patients admitted to the hospital for the first time for HCC treatment were collected. These data included basic patient information, such as sex, age, drug use, and hepatitis history. Pathological examination results, including

pathological types and stages, were independently assessed by two pathologists. Imaging tests, such as abdominal ultrasound, CT, and MRI, were also conducted. Serological examinations, including a complete blood count, comprehensive biochemical panel, coagulation function tests, tumor markers, and viral hepatitis indices (including hepatitis B and hepatitis C), were performed within the first week of admission. Based on these indicators, the staging of HCC was determined using the CNLC, BCLC, TNM, and CLIP classification systems.

The follow-up methods included telephone calls, outpatient visits, and hospitalization. The start time was defined as the surgical resection date of hepatocellular carcinoma, whereas the end time was determined by either postoperative recurrence or the follow-up deadline, which was set for December 2023. The recurrence-free survival time of patients was measured in months. The postoperative follow-up involved enhanced CT examinations, enhanced MRI or contrast-enhanced ultrasound, and tumor marker determination. These tests were conducted once in the first postoperative month, followed by every three months thereafter and every six months after one year.

Statistical analysis

The cutoff values for the platelet (PLT), plateletcrit (PCT), platelet distribution width (PDW), mean platelet volume(MPV), platelet large cell ratio (P-LCR), prothrombin pime(PT), international normalized ratio (INR), activated partial thromboplastin time(APTT), thrombin time(TT), and fibrinogen (FIB) were determined using X-tile software based on PFS. On the basis of these cutoff values, the indicators were categorized into low and high groups. Statistical analysis was conducted using SPSS 22.0 and R software. Categorical outcomes were evaluated using Pearson's chi-square test or Fisher's exact test, whereas continuous variables across cohorts were compared using the Student's t test or the Mann–Whitney U test. Hazard ratios and 95% confidence intervals were computed using univariable and multivariable Cox proportional hazards models. Variables with $P < 0.05$ in the univariable analysis were included in the multivariable analysis. From the Cox regression, variables that were significant at $P < 0.01$ as independent prognostic factors were selected, and RFS nomograms predicting outcomes at postoperative years 1, 3, and 5 were constructed via R. The C index was used to assess the discriminatory power of the nomogram; calibration plots were used to evaluate the alignment between the predictions and observations; and DCA was used to compare the predictive performance of the nomogram against alternative systems. Additionally, total risk scores were calculated, and X-tile software was used to classify patients into high-, medium-, and low-risk groups. Kaplan–Meier analysis was employed to assess RFS, and differences were compared using the log-rank test.

Results

Baseline characteristics

During the study, 1210 patients with liver cancer underwent radical resection. Of these, 852 patients met the inclusion criteria and were divided into three cohorts: training, internal validation, and external validation. The remaining 358 patients were excluded for various reasons, including hepatobiliary cell carcinoma diagnosed postoperatively (121 patients), nonfirst hepatectomy (32 patients), prior anticancer treatment (69 patients), a history of other malignant tumors (35 patients), incomplete clinical or follow-up data (95 patients), perioperative death (5 patients), and blood system diseases (1 patient). The optimal cutoff values for PLT, PCT, PDW, MPV, P-LCR, PT, INR, APTT, TT, and FIB were calculated using X-tile software. The results indicated that the optimal cutoff values were $224*10^9$/L, 0.24%, 12.5 fL, 11.6 fL, 33%, 10.2 s, 1.01, 26.5 s, 19.3 s, and 3.44 g/L, respectively. A baseline characteristic analysis was conducted on the 853 patients (504 from the training cohort, 216 from the internal validation cohort, and 143 from the external validation cohort). There were no statistically significant differences in any of the variables between the training cohort and the validation cohort ($P < 0.05$) (Table 1).

Univariate and multivariate analysis of recurrence in patients with hepatocellular carcinoma

Through univariate Cox regression analysis, 11 risk factors influencing the postoperative recurrence of hepatocellular carcinoma were identified from 21 clinicopathological variables and coagulation indicators. These factors were age, tumor size, degree of differentiation, microvascular invasion, tumor number, PLT, PCT, INR, APTT, FIB, and AFP. Multivariate Cox regression analysis revealed that age (HR = 0.664; 95% CI 0.506–0.872; $P = 0.003$), tumor size (HR = 1.831; 95% CI 1.440–2.328; $P < 0.001$), degree of differentiation (HR = 1.467; 95% CI 1.192–1.805; $P < 0.001$), microvascular invasion (HR = 1.767; 95% CI 1.405–2.221; $P < 0.001$), tumor number (HR = 1.472; 95% CI 1.061–2.043; $P = 0.021$), INR (HR = 1.454; 95% CI 1.145–1.847; $P = 0.002$), FIB (HR = 1.482; 95% CI 1.121–1.959; $P = 0.006$), and AFP (HR = 1.330; 95% CI 1.057–1.673; $P = 0.015$) were independent risk factors for the recurrence of hepatocellular carcinoma following radical surgery ($P < 0.05$) (Table 2).

Table 1 Baseline demographics and clinical characteristics of patients in the training and validation cohorts

Variables	Training cohort	Internal validation cohort	P value*	External validation cohort	P value#
Age (years) (≤ 65/ > 65)	378/126	158/58	0.602	101/41	0.352
Sex (Male/Female)	420/84	179/37	0.879	117/25	0.792
Hepatitis (No/Yes)	92/412	36/180	0.610	21/121	0.337
Tumor size (cm) (≤ 5/ > 5)	270/234	113/103	0.757	70/72	0.367
Differentiation degree (High/medium/low)	26/340/138	11/141/64	0.826	6/84/52	0.102
Microvascular invasion (Yes/No)	268/236	106/110	0.313	69/73	0.334
Tumor number (Single/Multiple)	455/49	193/23	0.704	122/20	0.137
Cirrhosis (No/Yes)	206/298	100/116	0.177	55/87	0.646
PLT(10^9/L) (≤ 224/ > 224)	424/80	183/33	0.841	116/27	0.374
PCT(%) (≤ 0.24/ > 0.24)	412/92	182/34	0.416	118/24	0.711
PDW(fL) (≤ 12.5/ > 12.5)	81/423	36/180	0.843	30/112	0.158
MPV(fL) (≤ 11.6/ > 11.6)	249/255	107/109	0.947	82/60	0.079
P-LCR(%) (≤ 33/ > 33)	152/352	60/156	0.521	50/92	0.251
PT(s) (≤ 10.2/ > 10.2)	101/403	51/165	0.282	33/109	0.406
INR (≤ 1.01/ > 1.01)	360/144	163/53	0.266	90/52	0.065
APTT(s) (≤ 26.5/ > 26.5)	90/414	34/182	0.491	31/111	0.284
TT(s) (≤ 19.3/ > 19.3)	397/107	169/47	0.874	121/21	0.089
FIB(g/L) (≤ 3.44/ > 3.44)	390/114	167/49	0.984	100/42	0.087
AFP(ng/mL) (≤ 400/ > 400)	328/176	133/83	0.369	96/46	0.576
CEA(ng/mL) (≤ 5/ > 5)	400/104	182/34	0.126	119/23	0.311
CA199(U/mL) (≤ 37/ > 37)	439/65	190/26	0.750	108/34	0.395

* Represents the internal validation cohort vs. the training cohort

Represents the external validation cohort vs. the training cohort

Establishing a nomogram model for predicting postoperative recurrence

Based on the results of the multivariate Cox regression model, we developed a nomogram to predict the RFS of patients with HCC. The nomogram incorporated age, tumor size, degree of differentiation, microvessel invasion, INR, and FIB as significant predictors ($P < 0.01$). For each patient with HCC, individual variables were scored on a scale from 0 to 100 using an integral system. This scoring allowed for the prediction of 1-, 3-, and 5-year RFS rates (Fig. 1).

Evaluation of predictive model performance

The calibration curve for the training and validation cohorts demonstrated strong agreement between the predictions of the prognostic nomogram and the actual 1-, 3-, and 5-year RFS outcomes (Fig. 2).

The clinical efficacy was compared using DCA. DCA calculates the clinical effectiveness of each model on the basis of the risk probability threshold (x-axis) and net benefit (y-axis). DCA revealed that, compared with the TNM, BCLC, CNLC, and CLIP staging systems, the prognostic nomogram had greater net benefits in both the training and validation cohorts (Fig. 3).

The C index values for the nomogram in the training, internal validation, and external validation cohorts were 0.71, 0.67, and 0.72, respectively. These values demonstrated superiority over those of the TNM, BCLC, CNLC, and CLIP staging systems (Fig. 4).

Additionally, the tdROC curves of the nomogram (1-, 3-, and 5-year) were plotted for the training and validation cohorts, and the AUCs indicated good performance of the predictive model (Fig. 5).

The total points of all patients were calculated and then stratified into three groups based on the optimal cut-off values calculated via X-tile. Kaplan–Meier analysis revealed significant differences in RFS among the three risk groups in both the training and validation cohorts ($P < 0.0001$) (Fig. 6).

Discussion

Hepatitis virus is the main pathogenic factor inducing HCC. There are several commonalities in the mechanism of HCC caused by hepatitis virus infection. For example, chronic infection with viral hepatitis leads to liver fibrosis and cirrhosis, which induce HCC. Moreover, different hepatitis viruses also have their own ability to induce HCC. For example, HBV and HCV molecules

Table 2 Univariate and multivariate analyses of RFS

Variables	Univariate analysis		Multivariable analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age	0.613 (0.470–0.799)	< 0.001	0.664 (0.506–0.872)	0.003
Sex	0.809 (0.596–1.099)	0.175		
hepatitis	1.144 (0.862–1.519)	0.351		
Tumor size	2.349 (1.889–2.920)	< 0.001	1.831 (1.440–2.328)	< 0.001
Differentiation degree	1.693 (1.384–2.069)	< 0.001	1.467 (1.192–1.805)	< 0.001
Microvascular invasion	2.241 (1.802–2.786)	< 0.001	1.767 (1.405–2.221)	< 0.001
Tumor number	2.210 (1.607–3.040)	< 0.001	1.472 (1.061–2.043)	0.021
cirrhosis	1.109 (0.890–1.382)	0.356		
PLT	1.406 (1.062–1.863)	0.017		
PCT	1.371 (1.050–1.789)	0.021		
PDW	0.927 (0.694–1.238)	0.609		
MPV	1.210 (0.976–1.500)	0.083		
P-LCR	0.902 (0.714–1.140)	0.387		
PT	1.301 (0.990–1.710)	0.059		
INR	1.383 (1.097–1.743)	0.006	1.454 (1.145–1.847)	0.002
APTT	1.420 (1.049–1.924)	0.023		
TT	0.922 (0.709–1.201)	0.548		
FIB	1.733 (1.359–2.209)	< 0.001	1.482 (1.121–1.959)	0.006
AFP	1.901 (1.528–2.365)	< 0.001	1.330 (1.057–1.673)	0.015
CEA	0.875 (0.627–1.223)	0.435		
CA199	1.226 (0.950–1.582)	0.117		

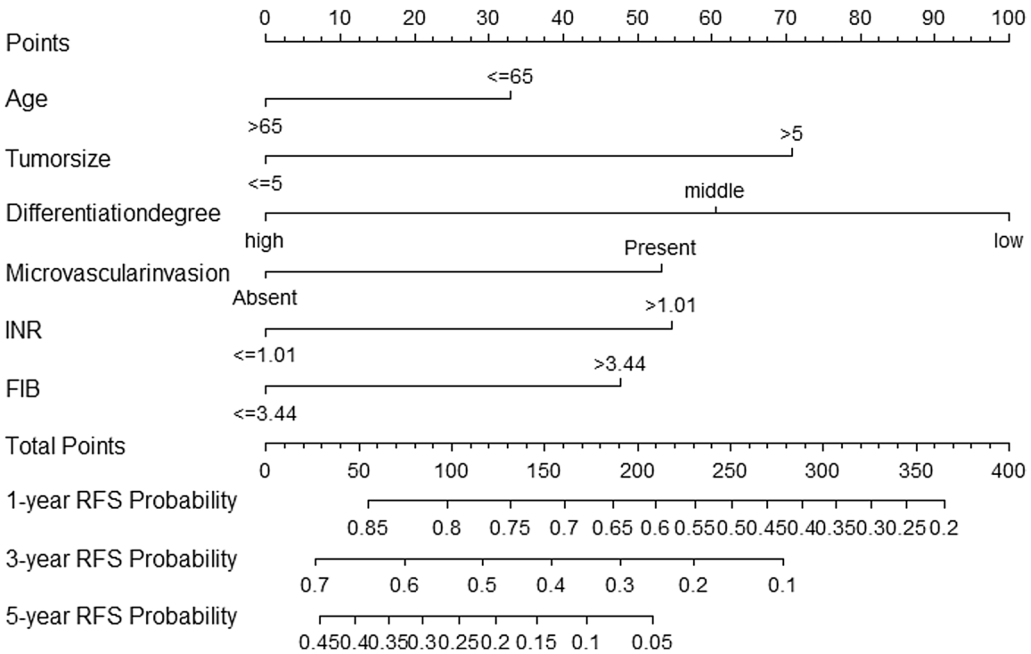

Fig. 1 Nomogram model for predicting the RFS of patients after radical resection of HCC at 1 year, 3 years and 5 years

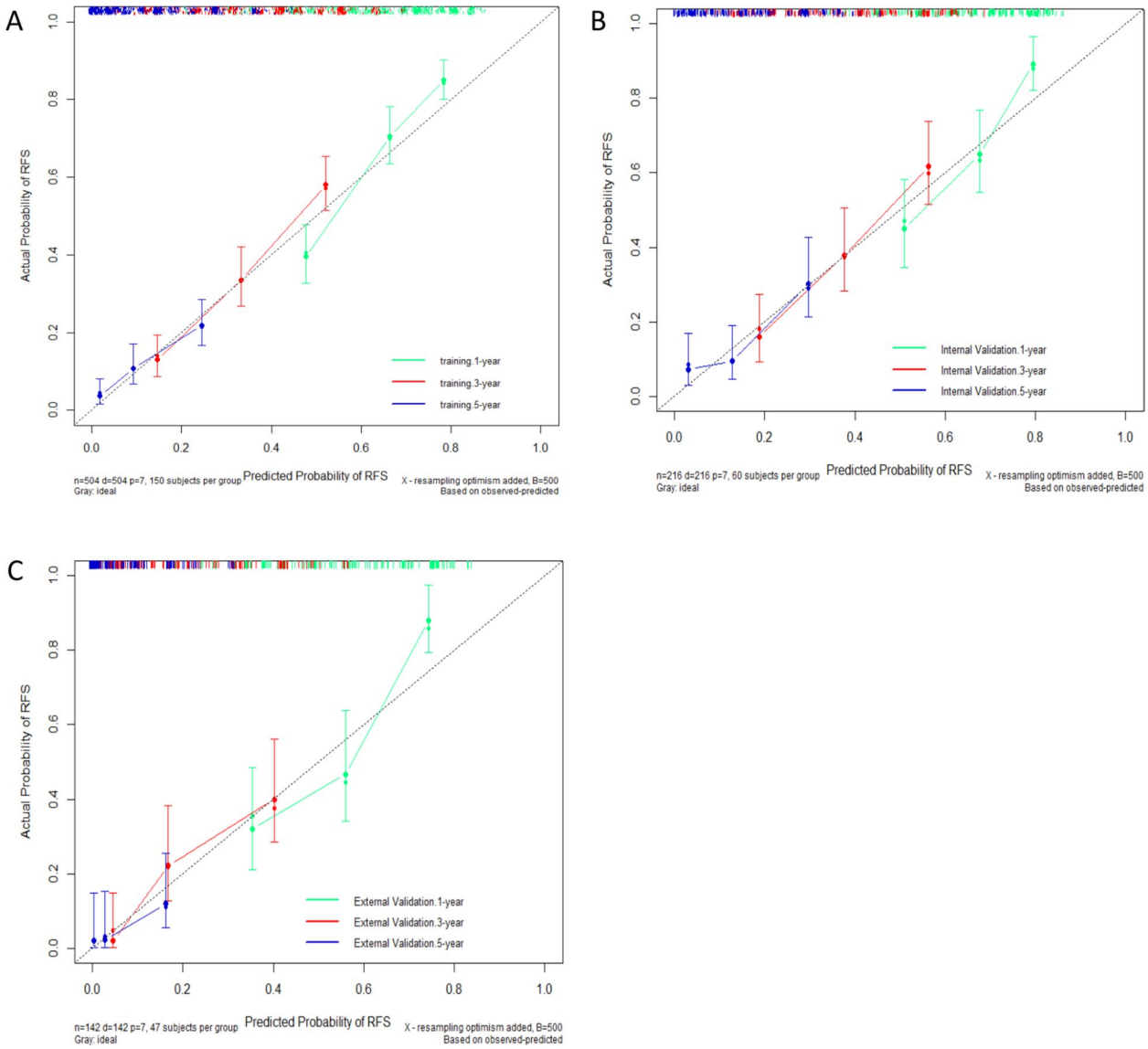

Fig. 2 Calibration curves for prognostic nomograms in predicting 1-, 3-, and 5-year RFS. **A** Training cohort for predicting RFS; **B** internal validation cohort for predicting RFS; **C** external validation cohort for predicting RFS

can induce HCC by affecting cellular apoptosis and proliferation through their respective viral proteins. Surgical resection is the recommended first-line treatment for HCC in patients with single or multiple lesions, without extrahepatic metastasis, and with satisfactory liver function and anatomical resectability [7]. However, postoperative recurrence of HCC remains a significant barrier to improving patient survival and prognosis. Clinically, several risk factors are associated with HCC recurrence, including tumor diameter, number of tumors, vascular invasion, and surgical margins [8]. Understanding the recurrence patterns and associated risk factors for HCC after surgery is essential. This knowledge enables the prediction of high-risk populations, the implementation of effective preventive measures, and the selection of optimal treatment strategies upon recurrence, ultimately enhancing the efficacy of radical resection surgery for HCC. In this study, we developed and validated a nomogram incorporating factors such as age, tumor size, degree of tumor differentiation, microvascular invasion, international normalized ratio (INR), and fibrinogen (FIB) to predict the prognosis of patients with hepatocellular carcinoma who have undergone radical resection. The C-index and DCA of our nomogram demonstrated superior prediction performance compared with the TNM, BCLC, CNLC, and CLIP staging systems.

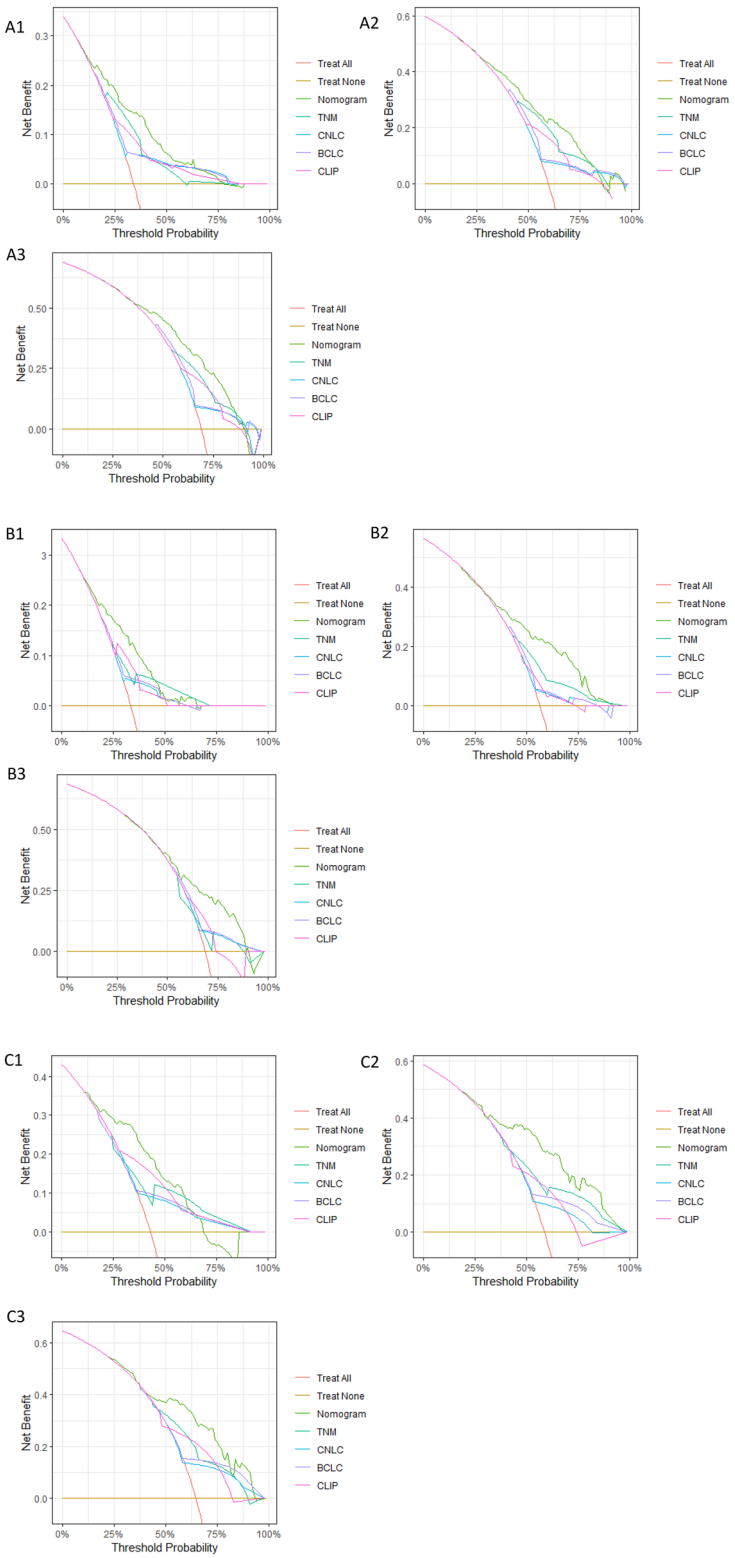

Fig. 3 Comparison of decision curve analysis between the prognostic nomogram and other staging systems. **A1**–**A3** Training cohort for the prediction of 1-, 3-, and 5-year RFS. **B1**–**B3** Internal validation cohort for the prediction of 1-, 3-, and 5-year RFS. **C1**–**C3** External training cohort for the prediction of 5-year RFS

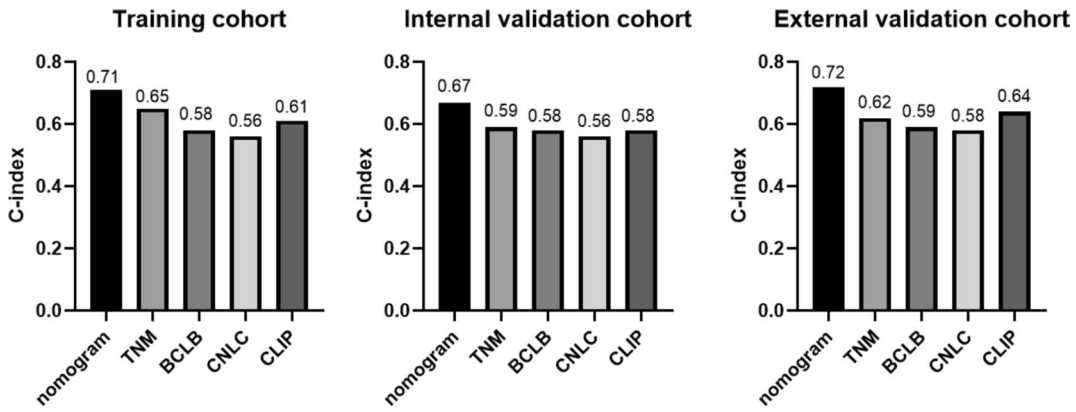

Fig. 4 Comparison of the C-index between the nomogram and the TNM, BCLC, CNLC, and CLIP staging systems in predicting RFS

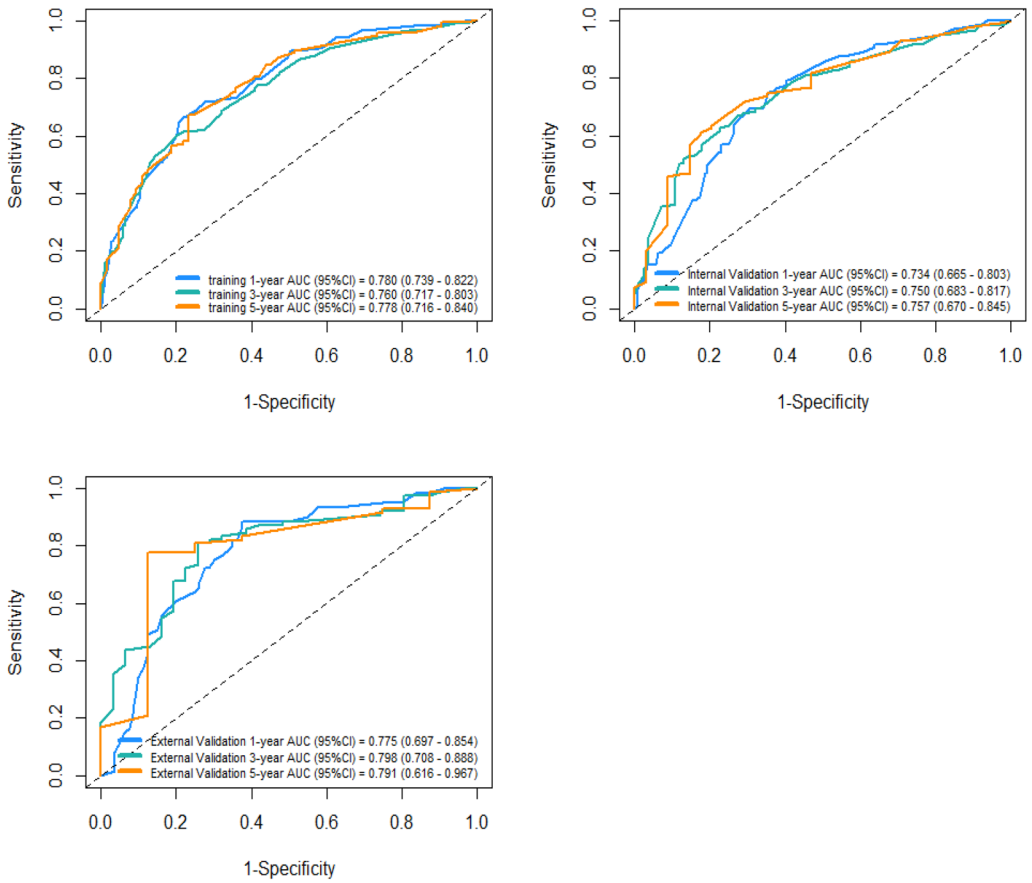

Fig. 5 | Time–dependent receiver operating characteristic (tdROC) curve of the prognostic nomogram in the training, internal validation, and external validation cohorts

Additionally, the calibration curve indicated a strong correlation between the predicted results and actual outcomes.

Coagulation is a multifaceted process that occurs after vascular injury, restoring vascular integrity through a sequence of events: platelet activation, adhesion, and aggregation (primary hemostasis), followed by the coagulation cascade reaction, thrombin generation, and fibrin clot deposition (secondary hemostasis). A significant interaction exists between malignant tumors and the coagulation system, with hypercoagulability being closely associated with cancer progression. Notably,

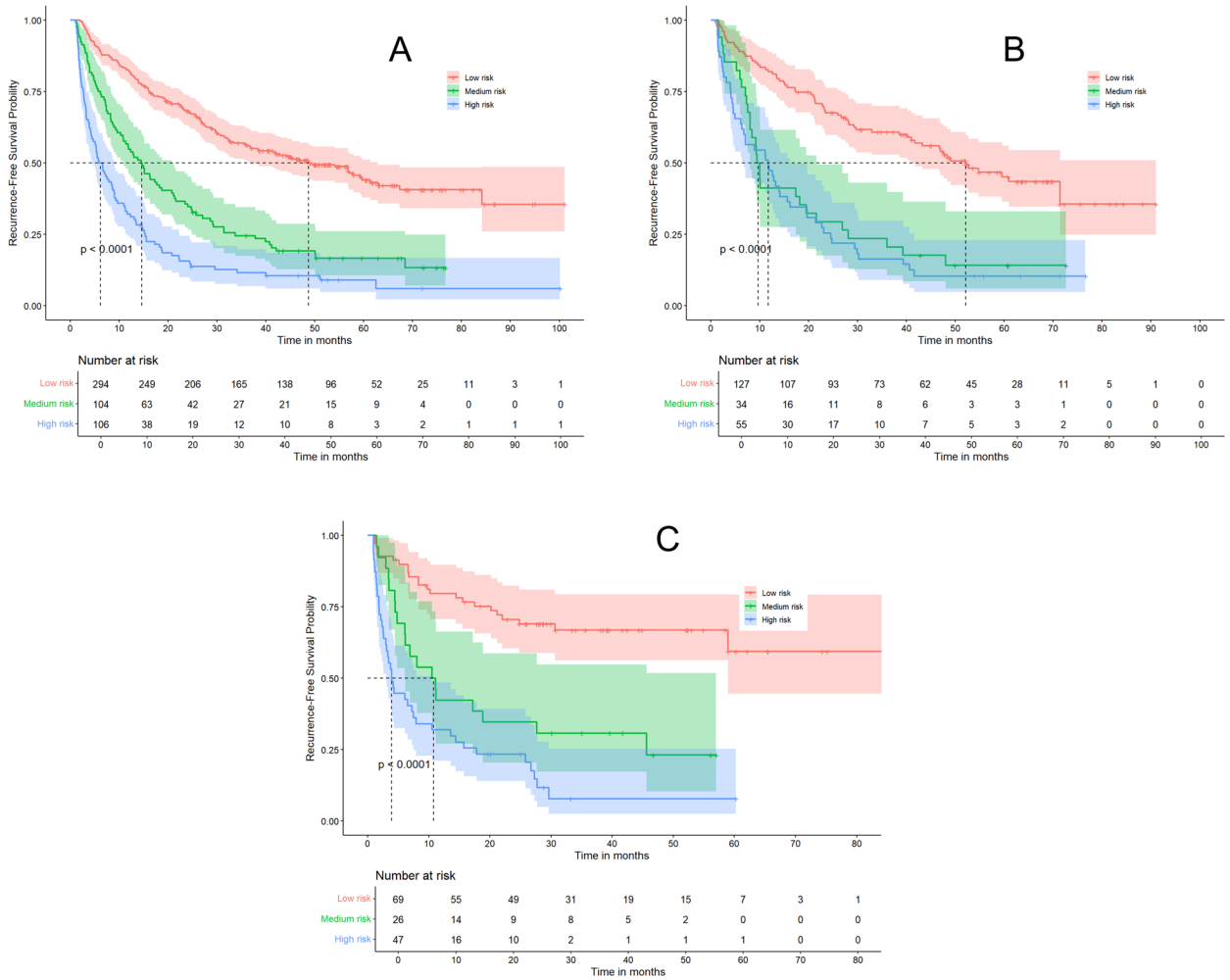

Fig. 6 Kaplan–Meier curves for RFS in the low-risk, medium-risk, and high-risk groups defined by the prognostic nomograms. **A** Training cohort for RFS; **B** internal validation cohort for RFS; **C** external validation cohort for RFS

cancer-related thrombosis ranks as the second leading cause of death among cancer patients, surpassed only by organ failure resulting from metastatic disease [9]. Platelets are associated with tumor progression and thrombosis, promoting tumor growth, survival, and metastasis in numerous ways. They are often referred to as "tumor promoters" because of their ability to increase the invasion capability of tumor cells and stimulate angiogenesis by increasing the expression of vascular endothelial growth factor (VEGF). A reduction in mean platelet volume hastens platelet movement, increases the likelihood of adhesion to vascular endothelial cells, augments neovascularization, ameliorates oxygenation and the blood supply to tumor cells, and fosters epithelial–mesenchymal transition (EMT) [10]. Platelet parameters, such as the platelet count (PLT), platelet volume distribution width (PDW), plateletcrit (PCT), mean platelet volume (MPV), and large platelet cell ratio (P-LCR), are significantly correlated with the prognosis of various malignant tumors [11–13]. Nevertheless, studies on the relationship between platelet parameters and the prognosis of hepatocellular carcinoma patients are scarce. Our research indicates that both the PLT and PCT serve as risk factors for postoperative recurrence in patients with hepatocellular carcinoma.

In this investigation, patients who underwent surgery for hepatocellular carcinoma and were under the age of 65 years presented a heightened risk of recurrence, and age was identified as an independent risk factor for postoperative recurrence. Research has indicated that the likelihood of early recurrence is increased in patients younger than 50 years, which is attributed to the propensity for younger individuals to present with more advanced tumors and increased aggressiveness [14]. Sohn et al. [15] further demonstrated that age at the time of hepatocellular carcinoma resection serves as

an independent risk factor for late recurrence following HBV-related HCC surgery.

Microvascular invasion (MVI) is characterized by the presence of cancer cell clusters within the vascular lumen, which are lined with endothelial cells, primarily in the portal vein branches adjacent to the cancer [16]. Zhang et al. [17] identified MVI as an independent risk factor for early recurrence of HCC after surgery; Park et al. [18] also suggested that MVI could independently predict the postoperative recurrence of HCC. In this study, patients with hepatocellular carcinoma and MVI were more likely to experience postoperative recurrence, indicating that MVI was an independent risk factor for the postoperative recurrence of HCC. Previous research has demonstrated two distinct forms of intrahepatic recurrence of HCC: intrahepatic metastasis (IM) and multicentric occurrence (MO). MVI may be associated with IM, which contributes to the postoperative recurrence of HCC [19].

Studies have demonstrated that the degree of tumor tissue differentiation influences the prognosis of patients with HCC following radical resection. Kim et al. [20] reported a significantly increased risk of early recurrence in patients with HCC with poor differentiation. Similarly, Li et al. [21] identified a correlation between the degree of tumor differentiation and HCC recurrence. This study further established that the degree of tumor differentiation serves as an independent risk factor for the postoperative recurrence of HCC. Specifically, patients with poorly differentiated HCC have a greater risk of postoperative recurrence than do those with moderately or highly differentiated HCC. The mechanism underlying this phenomenon may be attributed to the low degree of tumor differentiation, which results in reduced adhesion among tumor cells and a less compact arrangement. This condition leads to a lack of supportive structure and increased invasiveness of tumor cells, thereby facilitating their spread and metastasis.

This study confirmed that tumor diameter was an independent risk factor for postoperative recurrence of HCC. The survival analysis revealed a positive correlation between tumor size and the risk of postoperative recurrence. Previous studies have indicated that a tumor diameter exceeding 5 cm can independently predict the postoperative recurrence of HCC [22]. Wakayama et al. [23] demonstrated that a tumor diameter greater than 10 cm is associated with early recurrence of HCC postsurgery. This finding may be attributed to the increased invasiveness of large tumors, as giant HCC often presents with microvascular invasion (MVI).

The international normalized ratio (INR) is widely used in clinical settings. The formula for the INR is (prothrombin time of patients/average prothrombin time of normal people) ^{ISI}, where ISI is the international sensitivity index. The INR is highly valuable for evaluating the prognosis of patients with hepatocellular carcinoma. Kang et al. reported that the INR is an independent risk factor for the overall survival of patients with advanced hepatocellular carcinoma [24]. In a retrospective study of patients with resectable HCC, Lai et al. [25] demonstrated that those patients with an international normalized ratio (INR) < 1.1 had a better overall survival rate. Ans et al. [6] reported that an INR > 1.6 on the second postoperative day was an independent prognostic marker after hepatectomy (OR = 21.05, P < 0.001). Feng et al. [26], using multivariate Cox regression analysis, showed that the INR is a strong independent predictor of early recurrence after HCC resection (HR = 8.88, P < 0.001). Similar to previous research results, we concluded that the recurrence-free survival time of patients with higher INRs was significantly lower than that of patients with lower INRs (P < 0.001), and the difference was statistically significant. The INR can be used to evaluate the prognosis of patients with liver cancer after surgery.

Fibrinogen, a glycoprotein synthesized by the liver in response to serum cytokines, plays a pivotal role in blood coagulation. It also serves as an acute phase reaction protein, increasing rapidly during inflammatory states and exhibiting a close correlation with tumor onset and progression. Studies have shown that fibrinogen can facilitate tumor cell proliferation, angiogenesis, EMT, and hematogenous dissemination, and it can increase tumor invasion [27–29]. These capabilities may be attributed to the direct interaction of fibrinogen with vascular endothelial growth factor (VEGF), transforming growth factor-β (TGF-β), platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF) [30, 31]. Current research indicates that elevated fibrinogen levels in the plasma of tumor patients are independent risk factors for a poor prognosis across various malignancies [32–35]. Additionally, fibrinogen has been identified as an independent risk factor for patients with hepatocellular carcinoma [36, 37].

Survival analyses revealed significant differences in recurrence-free survival (RFS) across the high-, medium-, and low-risk groups, underscoring its clinical relevance. The validity of our model was further confirmed using an external dataset, which yielded satisfactory results. Consequently, for patients with a heightened risk of postoperative recurrence, it is advisable to reduce the follow-up interval and promptly administer postoperative adjuvant therapy. However, this study has several limitations: (1) there are no data from multiple medical centers for external validation of the model; (2) the limited sample size may introduce statistical bias and diminish the generalizability

of the findings; (3) the X-tile method was employed to determine the optimal critical value of the coagulation index, which requires further validation through large-scale, multicenter clinical trials and evidence-based medical research; (4) the study did not include some other factors influencing HCC prognosis, such as post-operative targeted therapy and chemotherapy, postoperative nutritional status. (5)the overall survival rate of patients was not followed.

Conclusion

The nomogram model developed in our study incorporates six objective variables that are readily accessible, thereby minimizing subjective bias. This model is user friendly and yields a calibration curve with a good fit. Additionally, the predicted probabilities align closely with the actual outcomes. When benchmarked against established staging systems, such as TNM, BCLC, CNLC, and CLIP, our model exhibited superior predictive efficacy.

Author contributions

Ming Lu and Hai-bo Yuan contributed equally to this manuscript; Ming Lu designed the article form, collected the data and wrote the manuscript; Hai-bo Yuan assisted in collecting the data and writing the manuscript; Meng-jie Wu and Heng Li were responsible for the statistical analysis; Cong-yin Tu and Kong-wang Hu designed the main study and critically revised the manuscript; all the authors read and approved the final manuscript.

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Data availability

The data are available from the corresponding author upon reasonable request. No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The present study was reviewed and approved by the Ethics Committee of the West Campus of the First Affiliated Hospital of China University of Science and Technology (Anhui Provincial Cancer Hospital) (Approval No. 2024-ZHW-01).

Informed consent

Patients were not required to provide informed consent for this study, as the analysis used anonymous clinical data that were obtained after each patient agreed to treatment via written consent.

Competing interests

All the authors declare that they have no conflicts of interest related to this article.

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