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ORIGINAL RESEARCH

Pan-Immune-Inflammation Value as a Prognostic Biomarker for Hepatocellular Carcinoma Patients Undergoing Hepatectomy

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Purpose: Hepatocellular carcinoma (HCC) poses a substantial threat to global health, characterized by its high incidence and mortality rates. This research aims to assess the prognostic value of a systematic serum inflammation index, the pan-immune-inflammation value (PIV), in patients with HCC who have undergone hepatectomy.

Patients and Methods: A total of 1764 HCC patients who underwent surgery were included in the study. These patients were divided into two groups based on the median PIV value. The Cox regression model was utilized to ascertain the independent risk factors that influence the prognosis of patients. A PIV-based nomogram was constructed and its performance was evaluated by the C-index, calibration curve, ROC curve, and DCA curve. Finally, a comparison was made between the nomogram and existing staging models.

Results: Patients with elevated PIV exhibited diminished OS and RFS compared to those with lower PIV. Univariate and multivariate Cox analyses revealed that PIV is an independent predictor of prognosis. The PIV-based nomogram demonstrated excellent discrimination, calibration, and clinical net benefit. The proposed nomogram outperformed the other existing staging systems, as evidenced by a higher AUC value.

Conclusion: PIV exhibits potential as a prognostic factor for both OS and RFS in patients with HCC who have undergone hepatectomy. The PIV-based nomogram can serve as an additional tool in conjunction with the existing liver cancer staging system, thereby facilitating more personalized treatment decisions for clinicians.

Keywords: hepatocellular carcinoma, pan-immune- inflammation value, hepatectomy, prognosis

Introduction

Hepatocellular carcinoma (HCC) is the sixth most prevalent cancer globally, with the third highest cancer-related mortality.[1] Due to difficulties in early diagnosis and lack of effective treatment, the five-year survival rate of HCC is less than 15% in China.[2] For early-stage HCC, hepatectomy represents the primary radical treatment option.[3] Additionally, it has been reported that hepatectomy is more efficacious than non-surgical treatment for certain carefully selected intermediate and advanced HCC cases.[4] However, even patients who have undergone radical resection are at high risk of recurrence.[5] What's more, HCC patients with similar traditional clinical characteristics can have very different outcomes even if they receive identical therapeutic interventions.[6] Given the significant heterogeneity of HCC, identifying patients at high risk of recurrence or mortality is important to improve HCC prognosis.[7] It is therefore imperative to develop novel biomarkers to better predict patient prognosis and personalize HCC treatment.[8]

A mounting body of evidence has recently confirmed that chronic inflammation plays a key role in the onset, development and metastasis of tumors.[9] To illustrate, the process of inflammation can result in the development of immune tolerance, which enables tumor cells to evade immune surveillance.[10] For instance, in the progression of chronic hepatitis to HCC, $CD4^+CD25^+$ regulatory T cells have been observed to promote the production of inhibitory

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cytokines, such as IL-10. These cells have been shown to exert an immunosuppressive function, thereby promoting the occurrence and development of HCC.[11] The inflammatory interactions between tumors and hosts provide a foundation for the development of a prognostic index based on inflammation. Several immune-inflammatory biomarkers(IIBs), including neutrophil-to-lymphocyte ratio(NLR), platelet-to-lymphocyte ratio(PLR), and systemic immune-inflammation index (SII), have shown excellent prognostic predictive efficacy in various cancers.[12–14] Similarly, the pan-immune-inflammation value (PIV), as a pioneering IIB, has exhibited remarkable prognostic and predictive capabilities across a diverse range of cancer types.[15–18] Nevertheless, there is currently a paucity of literature examining the prognostic utility of PIV in the context of HCC. Thus far, neither of the two extant reports has addressed the application of PIV in HCC patients undergoing surgical treatments.[19,20] It remains unclear whether PIV has any predictive value with regard to the postoperative prognosis of HCC. It is therefore essential to conduct further research into the potential of PIV in forecasting the recurrence and mortality of HCC in the postoperative period.

The aim of this study is to clarify the prognostic value of PIV in hepatocellular carcinoma patients undergoing hepatectomy. Moreover, an effort was made to develop a PIV-based risk model with the aim of enhancing prognostic stratification and predicting treatment outcomes.

Material and Methods

Patients

The study population comprised 1764 patients with HCC who underwent hepatectomy at Guangxi Medical University Cancer Hospital from January 2012 to December 2019. The inclusion criteria were as follows: (1) a pathological diagnosis of hepatocellular carcinoma was made following hepatectomy; (2) R0 resection, characterized by complete removal of the tumor, with negative margins observed under the microscope; (3) age over 18 years old; (4) receipt of a blood routine examination within one week before surgery. The exclusion criteria were applied to patients who (1) had incomplete clinical data; (2) died within 30 days after surgery; (3) had a history of other malignancies; (4) had a concurrent presence of acute infection, autoimmune diseases, or hematological diseases; (5) had received anti-tumor treatments such as radiotherapy and chemotherapy before surgery.

This study was conducted in accordance with the ethical standards set forth in the Declaration of Helsinki and received approval from the Ethics Committee of Guangxi Medical University Cancer Hospital (Approval No. KY2024860). Informed consent for treatment was required; however, written informed consent for enrolment into this study was not required, as this was a retrospective study. The medical data of patients was handled with the utmost confidentiality, without any intervention.

Data Collection and Definition

The list of patients who underwent hepatectomy at our hospital was obtained from the follow-up department. Subsequently, preoperative laboratory data and clinical data, including age, gender, absolute neutrophil count, lymphocyte count, monocyte count, platelet count, infection status of Clonorchis sinensis, HBV DNA load, hepatitis B surface antigen (HBsAg), alpha-fetoprotein (AFP), BCLC (Barcelona Clinic Liver Cancer) staging, Child Pugh grading and cirrhosis, were extracted from the patients' medical records. The postoperative pathological reports were consulted to obtain further characteristics, including the number of tumors, the diameter of the largest tumor, the integrity of the tumor capsule, microvascular invasion (MVI), and the degree of tumor differentiation, as well as the presence of cytokeratin 19 (CK19).

The IIBs were calculated in accordance with the following formulas: NLR = neutrophil count (10^9/L)/lymphocyte count(10^9/L); PLR = platelet count (10^9/L)/lymphocyte count (10^9/L); SII = platelet count (10^9/L) × neutrophil count (10^9/L)/lymphocyte count(10^9/L); and PIV = neutrophil count (10^9/L) × platelet count (10^9/L) × monocyte count (10^9/L)/lymphocyte count (10^9/L).

Follow-up

The initial follow-up assessment was conducted one month following the surgical procedure. Subsequently, follow-up examinations were conducted at two- to three-month intervals during the first two years. After two years, the interval between each follow-up was set at six months. The following procedures were deemed essential for each follow-up: a physical examination, liver function tests, a test for serum AFP, and an imaging examination (either an abdominal enhanced computed tomography scan or magnetic resonance imaging). The primary outcome of this study was overall survival(OS), which referred to the period from hepatectomy to death from any cause or the last follow-up. The recurrence-free survival (RFS) was defined as the interval between hepatectomy and either tumor recurrence, the last follow-up, or death.

Statistical Analysis

The median value was employed as the cutoff value for PIV. The threshold values for other continuous variables, such as age, HBV DNA quantity, AFP concentration, and the maximum tumor diameter, were ascertained based on prior research or clinical practice.

The categorical data were subjected to chi-square analysis. In order to ascertain the potential independent prognostic factors, univariate and multivariate Cox regression analysis were conducted. Receiver operating characteristic (ROC) curves and area under curve (AUC) were used to compare the discrimination power of different IIBs. A nomogram was formulated utilizing the Cox regression model as a foundation. The model was assessed using a number of statistical techniques, including the ROC curve, calibration curve, Harrell's C-index and decision curve analysis (DCA) curve. Moreover, the total scores obtained from the nomogram were used to stratify each patient into one of three risk groups: high, medium, or low. The Log rank test and Kaplan-Meier estimator were employed for analyzing the disparities in OS and RFS between distinct patient groups. The evaluation of the aforementioned analyses was conducted using the R software (version 4.4.0), with a p-value of less than 0.05 deemed statistically significant.

Results

Baseline Characteristics

A total of 1764 patients diagnosed with HCC met the inclusion and exclusion criteria of the study. As illustrated in Table 1, the patient demographics included a median age of 52 years, with 1524 males (86.39%) and 240 females (13.61%). The majority of patients were diagnosed with chronic hepatitis B infection, with 84.18% of cases exhibiting a positive result for HBsAg. The cohort predominantly comprised BCLC stage A (58.73%), followed by stage C (20.8%) and stage B (20.46%). The median PIV was employed to categorize all patients into two distinct groups: a low PIV group and a high PIV group, with 882 patients in each group. The patients in the low PIV group demonstrated a higher mean age; however, the proportion of patients over 65 years of age did not increase. Compared to patients with high PIV, those with low PIV demonstrated earlier BCLC staging, with higher rates of HBsAg positivity(87.76% vs 80.61%) and cirrhosis(57.26% vs 45.80%). In contrast, low-PIV patients had lower proportions of male gender (84.13% vs 88.66%), AFP >400 ng/mL (35.71% vs 47.17%), tumor size >5 cm (42.06% vs 73.02%), and microvascular invasion (26.87% vs 27.44%) in comparison to those with high PIV. The patients were randomly assigned to either a training set or a testing set, with a ratio of 70% to 30%. This resulted in a training set comprising 1236 patients and a testing set comprising 528 patients. The chi-squared test was employed to ascertain whether there were any significant differences between the baseline characteristics of the two groups. No significant differences were found (Supplementary Table 1).

Identification of the Best IIBs for OS and RFS

In order to identify the most effective IIBs for predicting the postoperative prognosis of HCC, we plotted ROC curves for OS and RFS and calculated AUC for each IIB individually. As illustrated in Figure 1A, PIV demonstrated the most robust capacity to forecast OS, exhibiting the highest AUC value (0.604). The AUC values for NLR, PLR, and SII were 0.599, 0.572, and 0.597, respectively. Similarly, PIV also demonstrated the best ability to predict RFS (Figure 1B), with the highest AUC value (0.563). The AUC values predicted by NLR, PLR, and SII for RFS were 0.559, 0.543, and 0.557, respectively.

Table 1 Characteristics of HCC Patients

Variables	Overall (n=1764)	PIV_Low (n=882)	PIV_High (n=882)	p Value
Gender				0.0068
Female	240 (13.61)	140 (15.87)	100 (11.34)	
Male	1524 (86.39)	742 (84.13)	782 (88.66)	
Age, years				0.6806
>65	247 (14.00)	120 (13.61)	127 (14.40)	
≤65	1517 (86.00)	762 (86.39)	755 (85.60)	
Clonorchis				0.1593
No	1471 (83.39)	747 (84.69)	724 (82.09)	
Yes	293 (16.61)	135 (15.31)	158 (17.91)	
Child_Pugh				0.6452
A	1685 (95.52)	845 (95.80)	840 (95.24)	
B	79 (4.48)	37 (4.20)	42 (4.76)	
BCLC				<0.0001
0-A	1036 (58.73)	578 (65.53)	458 (51.93)	
B	361 (20.46)	179 (20.29)	182 (20.63)	
C	367 (20.80)	125 (14.17)	242 (27.44)	
HBV_DNA,IU/mL				0.6299
<500	747 (42.35)	368 (41.72)	379 (42.97)	
≥500	1017 (57.65)	514 (58.28)	503 (57.03)	
HBsAg				0.0001
Negative	279 (15.82)	108 (12.24)	171 (19.39)	
Positive	1485 (84.18)	774 (87.76)	711 (80.61)	
AFP,ng/mL				<0.0001
≤400	1033 (58.56)	567 (64.29)	466 (52.83)	
>400	731 (41.44)	315 (35.71)	416 (47.17)	
Cirrhosis				<0.0001
No	855 (48.47)	377 (42.74)	478 (54.20)	
Yes	909 (51.53)	505 (57.26)	404 (45.80)	
Tumor number				0.6773
Solitary	1237 (70.12)	623 (70.63)	614 (69.61)	
Multiple	527 (29.88)	259 (29.37)	268 (30.39)	
Diameter, cm				<0.0001
≤5	749 (42.46)	511 (57.94)	238 (26.98)	
>5	1015 (57.54)	371 (42.06)	644 (73.02)	
Capsule				0.9583
Complete	1246 (70.63)	624 (70.75)	622 (70.52)	
Incomplete	518 (29.37)	258 (29.25)	260 (29.48)	
Differentiation				0.7384
G1-G2	830 (47.05)	419 (47.51)	411 (46.60)	
G3-G4	934 (52.95)	463 (52.49)	471 (53.40)	
MVI				0.0007
Negative	952 (53.97)	512 (58.05)	440 (49.89)	
Positive	812 (46.03)	370 (41.95)	442 (50.11)	
CK19				0.8304
Negative	1285 (72.85)	645 (73.13)	640 (72.56)	
Positive	479 (27.15)	237 (26.87)	242 (27.44)	

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; HBV, Hepatitis B virus; AFP, alpha-fetoprotein; MVI, microvascular invasion; CK19, cytokeratin 19; PIV, Pan-immune-inflammation value.

PIV Predicting Prognosis

PIV demonstrated excellent predictive capacity for postoperative prognosis of HCC. Both OS (Figure 1C) and RFS (Figure 1D) exhibited a notable decline in patients with elevated PIV in comparison to those with low PIV. The median

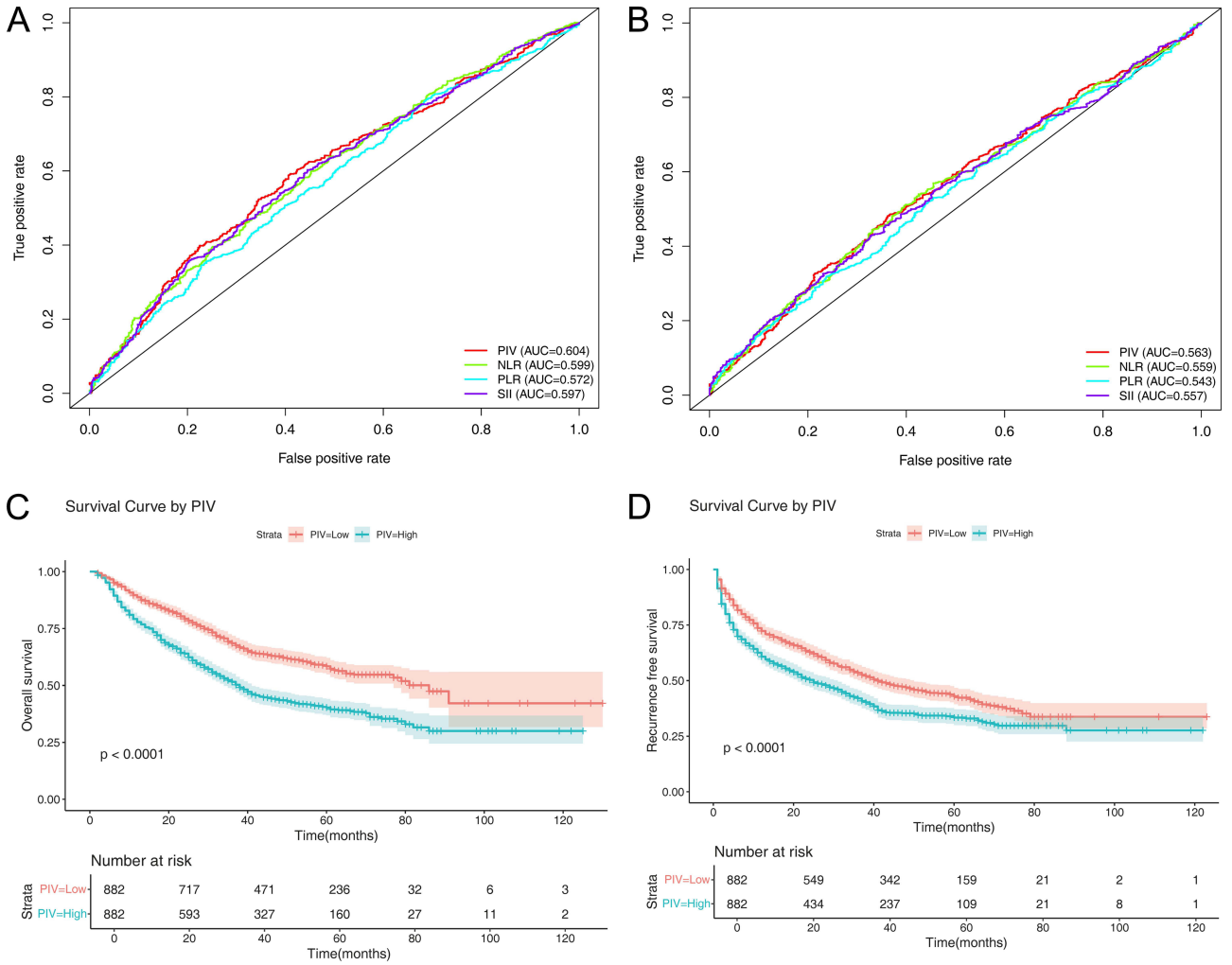

Figure 1 PIV as the best IIB to predict prognosis. (**A**) ROC curves of different IIBs to predict OS. (**B**) ROC curves of different IIBs to predict RFS. (**C**) OS survival curve based on PIV classification. (**D**) RFS survival curve based on PIV classification.

OS and median RFS for the low PIV group were 81 months and 41 months, respectively, which were considerably higher than the 37 months and 24 months observed in the high PIV group. The OS rates for the low PIV group at one, three, and five years were 88.71%, 68.49%, and 58.37%, respectively. In comparison, the OS rates for the high PIV group were 77.82%, 51.54%, and 40.31%, respectively (Figure 1C). With regard to the one-year, three-year, and five-year RFS rates, the low PIV group exhibited rates of 72.31%, 53.44%, and 42.92%, respectively, which were markedly higher than the high PIV group's rates of 60.73%, 42.00%, and 33.37% (Figure 1D).

Identification of Independent Prognostic Factors

Univariate and multivariate Cox regression analyses were conducted using the training dataset, and the results demonstrated that Child-Pugh B grade, BCLC B or C stage, HBV DNA ≥ 500 IU/mL, diameter > 5 cm, poor differentiation (G3 or G4), MVI positivity, CK19 positivity, and elevated PIV were all independent risk factors affecting OS. With regard to RFS, the following factors were identified as independent prognostic indicators: gender, age, BCLC, HBV-DNA, AFP, diameter, differentiation, MVI, and PIV. The aforementioned results are presented in Tables 2 and 3, respectively, with the corresponding forest plots displayed in Supplementary Figures 1–4.

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Table 2 Univariate and Multivariate Analysis for OS

Variables	Univariate Analysis			Multivariate Analysis		
	***P* Value**	**HR**	**95% CI**	***P* Value**	**HR**	**95% CI**
Gender	0.009	1.42	(1.09–1.84)	0.096	1.25	(0.96–1.63)
Age	0.038	1.29	(1.01–1.64)	0.649	1.06	(0.83–1.36)
Clonorchis	0.637	1.06	(0.84–1.32)			
Child_Pugh	0.012	1.55	(1.1–2.18)	0.042	1.44	(1.01–2.03)
BCLC						
A						
B	<0.001	2.08	(1.69–2.55)	<0.001	1.58	(1.25–2.02)
C	<0.001	4.13	(3.42–5.01)	<0.001	2.49	(2.00–3.09)
HBV_DNA	<0.001	1.52	(1.28–1.8)	<0.001	1.42	(1.19–1.68)
HBsAg	0.243	1.15	(0.91–1.45)			
AFP	<0.001	1.62	(1.38–1.9)	0.172	1.13	(0.95–1.34)
Cirrhosis	0.842	1.02	(0.86–1.2)			
Tumor_number	<0.001	1.51	(1.28–1.79)	0.279	1.11	(0.92–1.35)
Diameter	<0.001	2.15	(1.81–2.57)	0.001	1.37	(1.13–1.66)
Capsule	0.002	1.32	(1.11–1.57)	0.183	1.13	(0.95–1.34)
Differentiation	<0.001	1.40	(1.19–1.65)	0.002	1.30	(1.10–1.53)
MVI	<0.001	2.19	(1.86–2.58)	<0.001	1.62	(1.36–1.92)
CK19	<0.001	1.58	(1.33–1.88)	0.001	1.36	(1.14–1.64)
PIV	<0.001	1.80	(1.52–2.12)	<0.001	1.44	(1.21–1.71)

Table 3 Univariate and Multivariate Analysis for RFS

Variables	Univariate Analysis			Multivariate Analysis		
	***P* Value**	**HR**	**95% CI**	***P* Value**	**HR**	**95% CI**
Gender	<0.001	1.60	(1.25–2.05)	0.004	1.45	(1.13–1.86)
Age	<0.001	1.56	(1.24–1.97)	0.02	1.33	(1.05–1.69)
Clonorchis	0.579	1.06	(0.86–1.3)			
Child_Pugh	0.549	0.88	(0.59–1.32)			
BCLC						
A						
B	<0.001	2.05	(1.7–2.46)	<0.001	1.64	(1.31–2.04)
C	<0.001	3.19	(2.66–3.82)	<0.001	2.27	(1.85–2.79)
HBV_DNA	<0.001	1.58	(1.35–1.85)	<0.001	1.36	(1.14–1.62)
HBsAg	0.01	1.34	(1.07–1.68)	0.626	1.06	(0.83–1.37)
AFP	<0.001	1.63	(1.4–1.89)	0.003	1.28	(1.09–1.50)
Cirrhosis	0.513	1.05	(0.91–1.22)			
Tumor_number	<0.001	1.55	(1.32–1.81)	0.291	1.10	(0.92–1.32)
Diameter	<0.001	1.72	(1.47–2.01)	0.02	1.23	(1.03–1.45)
Capsule	0.248	1.10	(0.94–1.3)			
Differentiation	<0.001	1.35	(1.16–1.57)	0.006	1.24	(1.06–1.44)
MVI	<0.001	1.63	(1.41–1.9)	0.015	1.22	(1.04–1.43)
CK19	<0.001	1.36	(1.16–1.61)	0.143	1.14	(0.96–1.35)
PIV	<0.001	1.43	(1.23–1.66)	0.012	1.22	1.05–1.43)

Development and Validation of the Nomograms

Nomograms were constructed to forecast 1-, 3-, and 5-year OS (Figure 2A) and RFS (Figure 2B) based on the identified independent prognostic factors. In order to facilitate the convenient calculation of the individual risk of OS and RFS, the nomogram-based scores for all variables are presented in the Supplementary Table 2 for OS and Supplementary Table 3

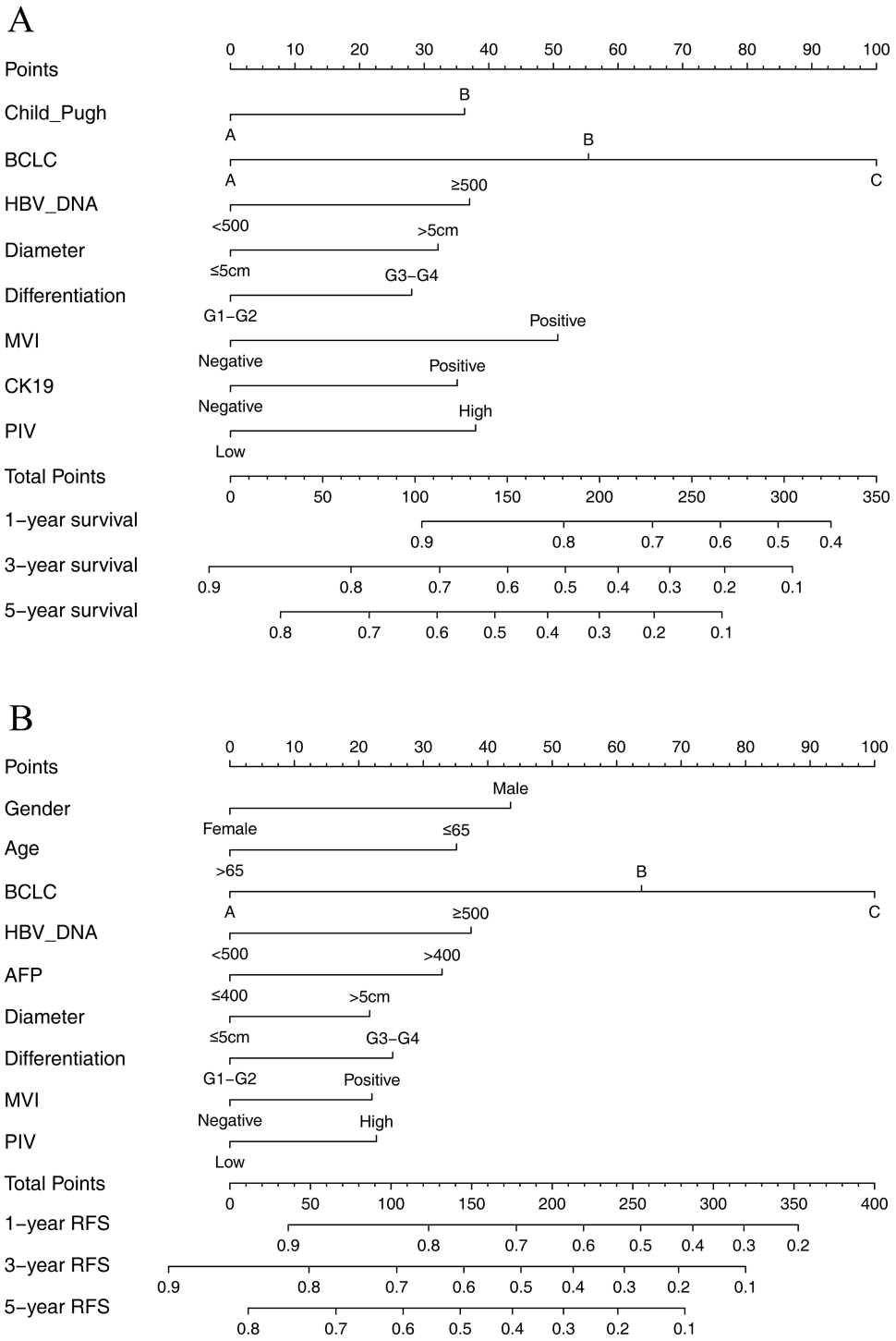

Figure 2 Construction of prognostic nomograms. (**A**) The PIV-based nomogram to predict OS. (**B**) The PIV-based nomogram to predict RFS.

for RFS. The corresponding interactive nomograms are accessible via the following websites: https://gxmuhcc.shinyapps.io/DynNom_OS/ and https://gxmuhcc.shinyapps.io/DynNom_RFS/.

The C-index was calculated through 1000 bootstrapped resamples in order to evaluate the model's accuracy. The C-index values for the nomogram predicting OS in the training set and validation set were 0.723 (95% CI, 0.684, 0.762) and 0.715 (95% CI, 0.652, 0.778), respectively. The nomogram predicting RFS rates exhibited a C-index of 0.694 (95% CI, 0.655, 0.733) for the training set and 0.667 (95% CI, 0.608, 0.726) for the validation set.

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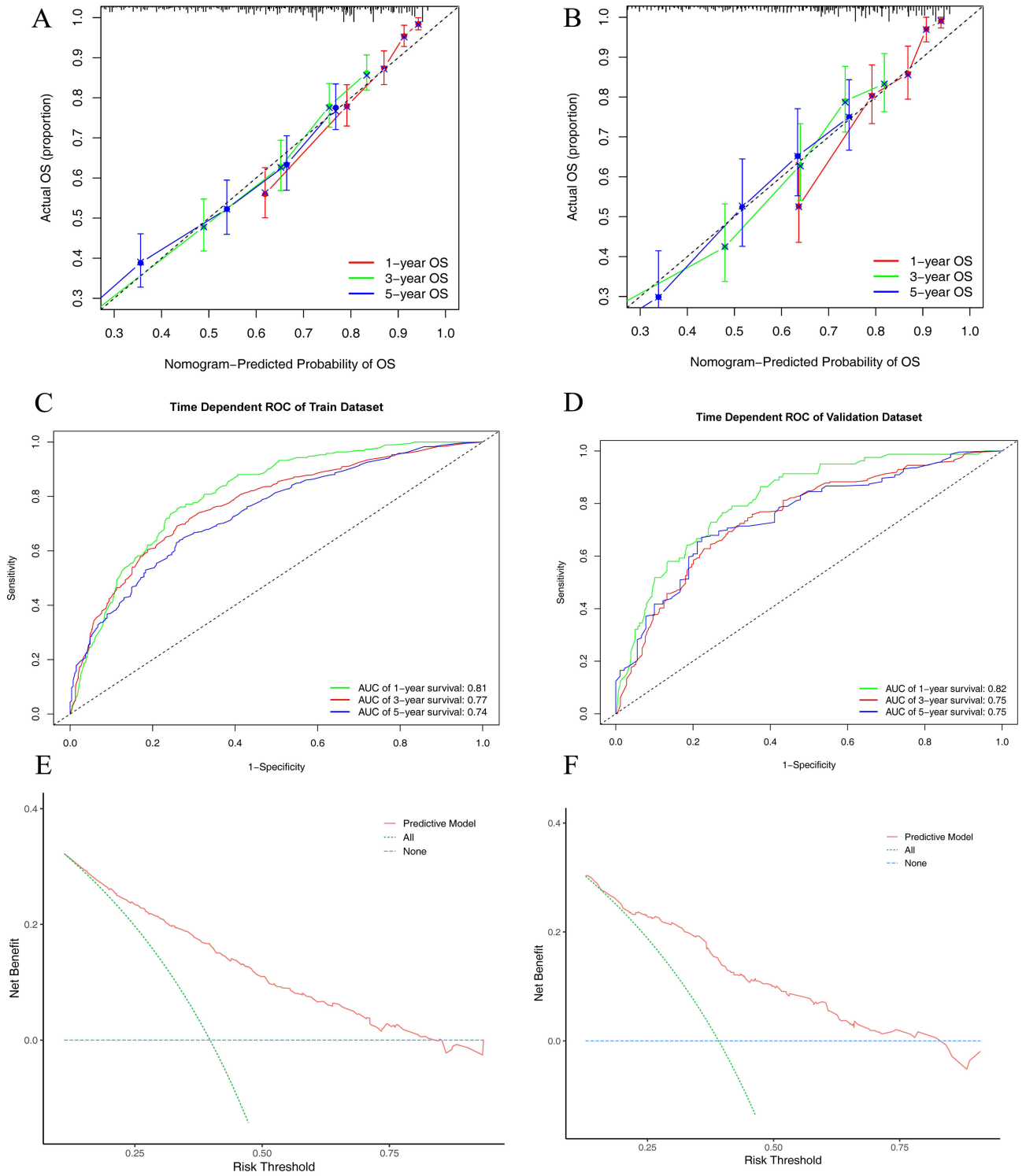

Figure 3 Assessment of the nomogram predicting OS. (**A**) Calibration curves in the training cohort. (**B**) Calibration curves in the validation cohort. (**C**) Time-dependent ROC curves in the training cohort. (**D**) Time-dependent ROC curves in the validation cohort. (**E**) DCA curve in the training cohort. (**F**) DCA curve in the validation cohort.

The calibration curves demonstrated that the observed survival rates were in close alignment with the nomogram predictions, irrespective of whether the training or validation cohort was considered (see Figure 3A and B for OS and Figure 4A and B for RFS).

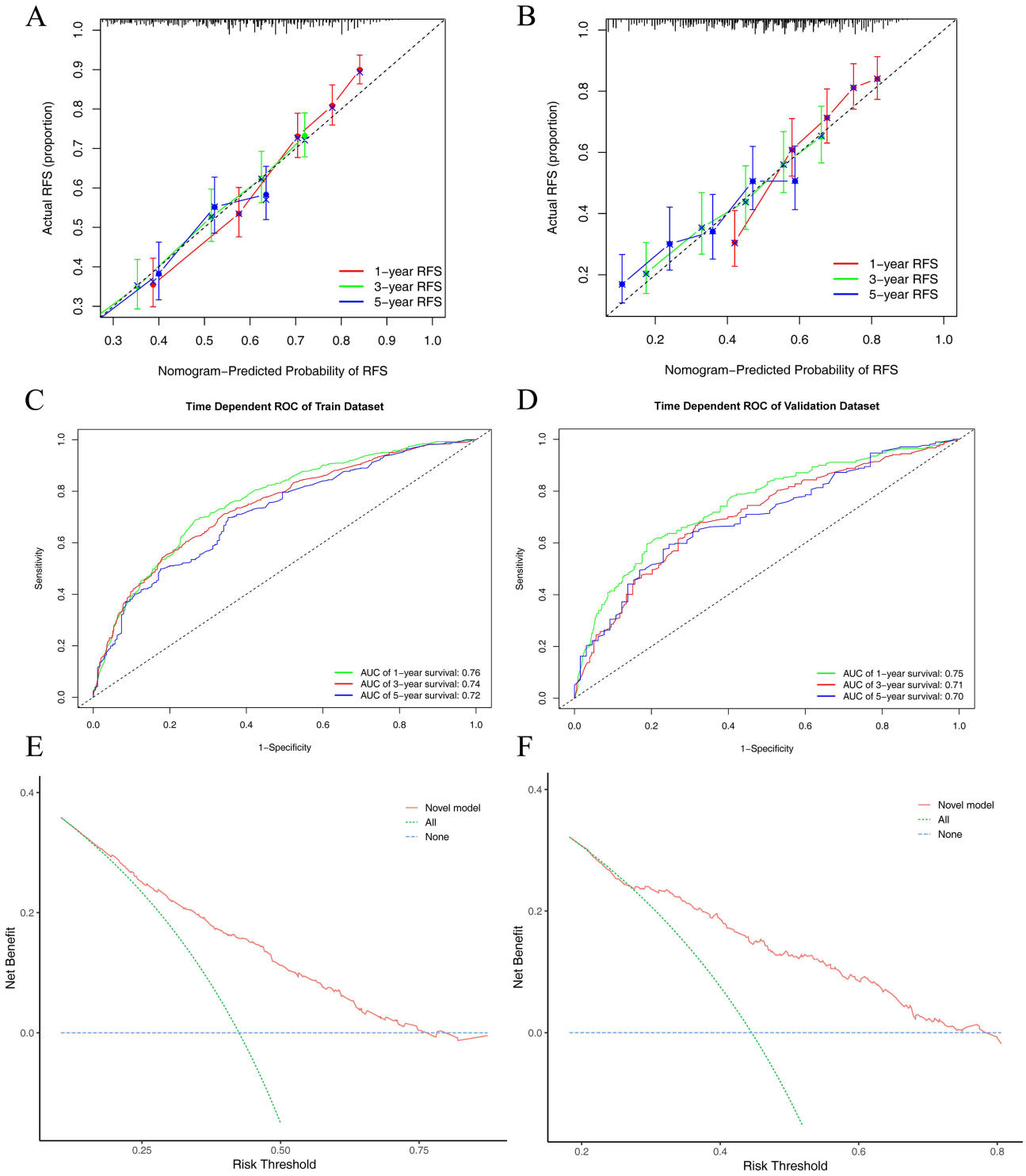

Figure 4 Assessment of the nomogram predicting RFS. (**A**) Calibration curves in the training cohort. (**B**) Calibration curves in the validation cohort. (**C**) Time-dependent ROC curves in the training cohort. (**D**) Time-dependent ROC curves in the validation cohort. (**E**) DCA curve in the training cohort. (**F**) DCA curve in the validation cohort.

Furthermore, time-dependent ROC curves were generated to evaluate the model's predictive capacity. ROC analyses for predicting 1-, 3-, and 5-year OS manifested AUC values of 0.81, 0.77, and 0.74 in the training cohort (Figure 3C), and 0.82, 0.75, and 0.75 in the validation set for the same time points (Figure 3D). With regard to the 1-, 3-, and 5-year

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RFS prediction, the AUC values for the training and validation cohorts were 0.76, 0.74, 0.72, 0.75, 0.71, and 0.70, respectively (see Figure 4C for the training set and Figure 4D for the validation set).

Subsequently, we plotted DCA curves to further assess the nomograms. The DCA curve allows for the identification of two distinct status levels. The horizontal dotted line represents a scenario in which no individual has received any intervention, and the net benefit rate is 0. Conversely, the slanted dotted line represents a scenario in which all individuals have received intervention, and the net benefit rate is a negative-sloping line. As illustrated in Figure 3E/F (DCA curve for OS in training and validation cohort respectively) and Figure 4E/4F (DCA curve for RFS in training and validation cohort respectively), the nomogram curves were mostly above the baselines, irrespective of the training or validation datasets. This observation indicated that the nomogram models demonstrated robust predictive consistency, thereby enhancing the accuracy of prognosis forecasting for HCC patients undergoing hepatectomy.

Ultimately, the patients were classified into three risk categories based on the nomogram scores: high-, medium-, and low-risk. The Kaplan-Meier curves demonstrated a statistically significant discriminatory capacity in both the training and validation cohorts for predicting OS and RFS (Figure 5).

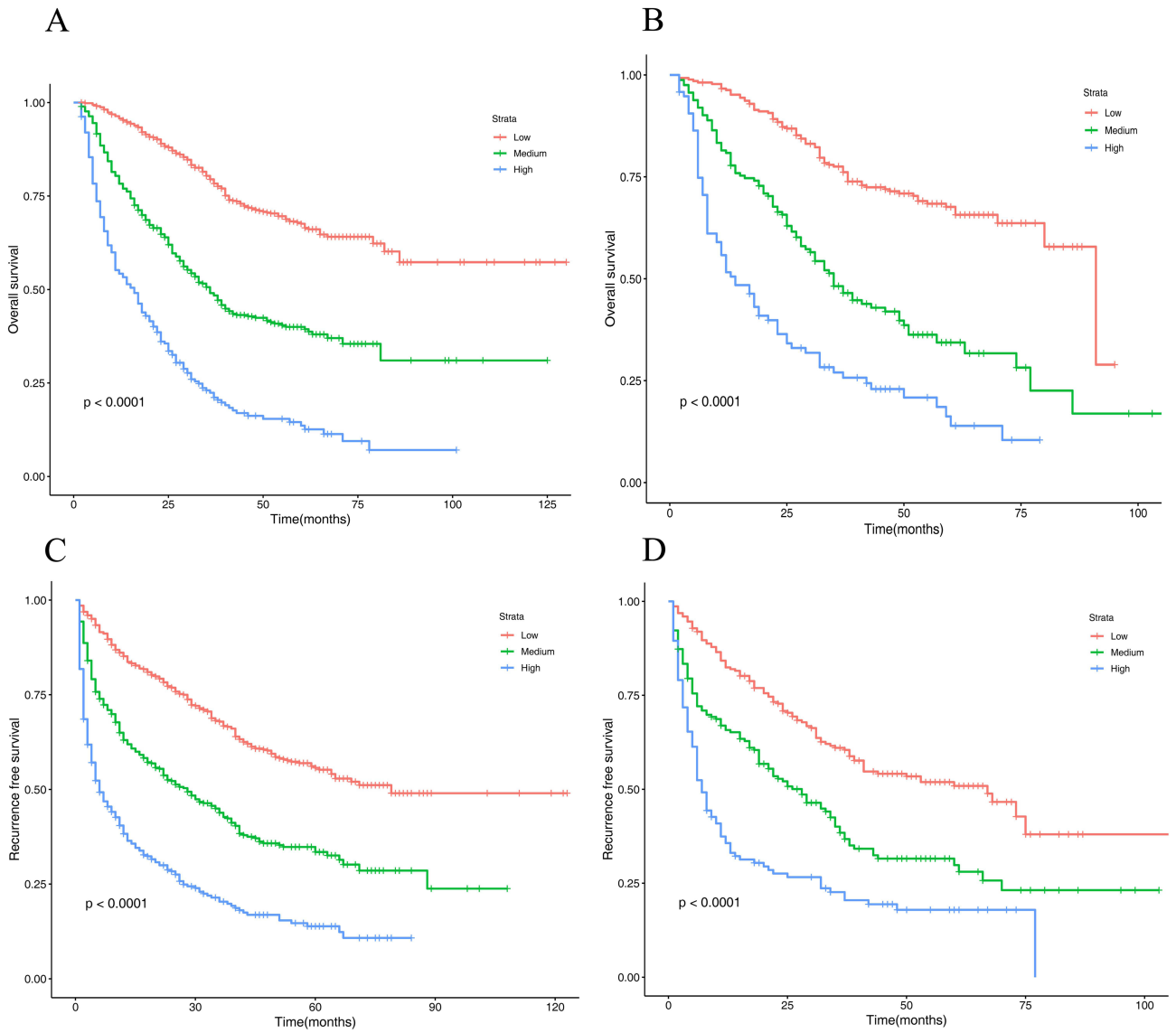

Figure 5 Risk stratification based on the nomograms. (**A**) K-M survival curves of OS stratification in the training cohort. (**B**) K-M survival curves of OS stratification in the validation cohort. (**C**) K-M survival curves of RFS stratification in the training cohort. (**D**) K-M survival curves of RFS stratification in the validation cohort.

Comparative Analysis of Various Models

A comparative analysis was conducted between the nomograms and several traditional staging models for liver cancer, namely the BCLC, the eighth edition of the American Joint Committee on Cancer Tumor-Node-Metastasis (TNM), and the China Liver Cancer (CNLC) staging systems. The outcomes demonstrated that the AUC values for both the OS and RFS nomogram were superior to those of the aforementioned traditional staging systems (Figure 6).

Discussion

The findings of the present study indicate that PIV is an independent prognostic biomarker for both OS (HR=1.44, 1.21–1.71) and RFS (HR=1.22, 1.05–1.43) in patients with HCC following curative hepatectomy. The novel prognostic indicator demonstrated superior predictive performance in comparison to other IIBs (NLR/PLR/SII), exhibiting the largest AUC values (0.604 for OS and 0.563 for RFS). The PIV-based nomograms exhibited an exceptional ability to categorise patients into distinct risk groups, namely high-, medium-, and low-risk.

Tumor development is characterized by a complex interplay of biological processes, one of which is chronic inflammation. This phenomenon plays a pivotal role in the genesis, progression and management of tumors.[21] To illustrate, PTX3, an exogenous tumor suppressor, participates in the regulation of the tumor microenvironment by modulating complement-dependent inflammatory responses.[21] CXCL3, which is an important chemokine in

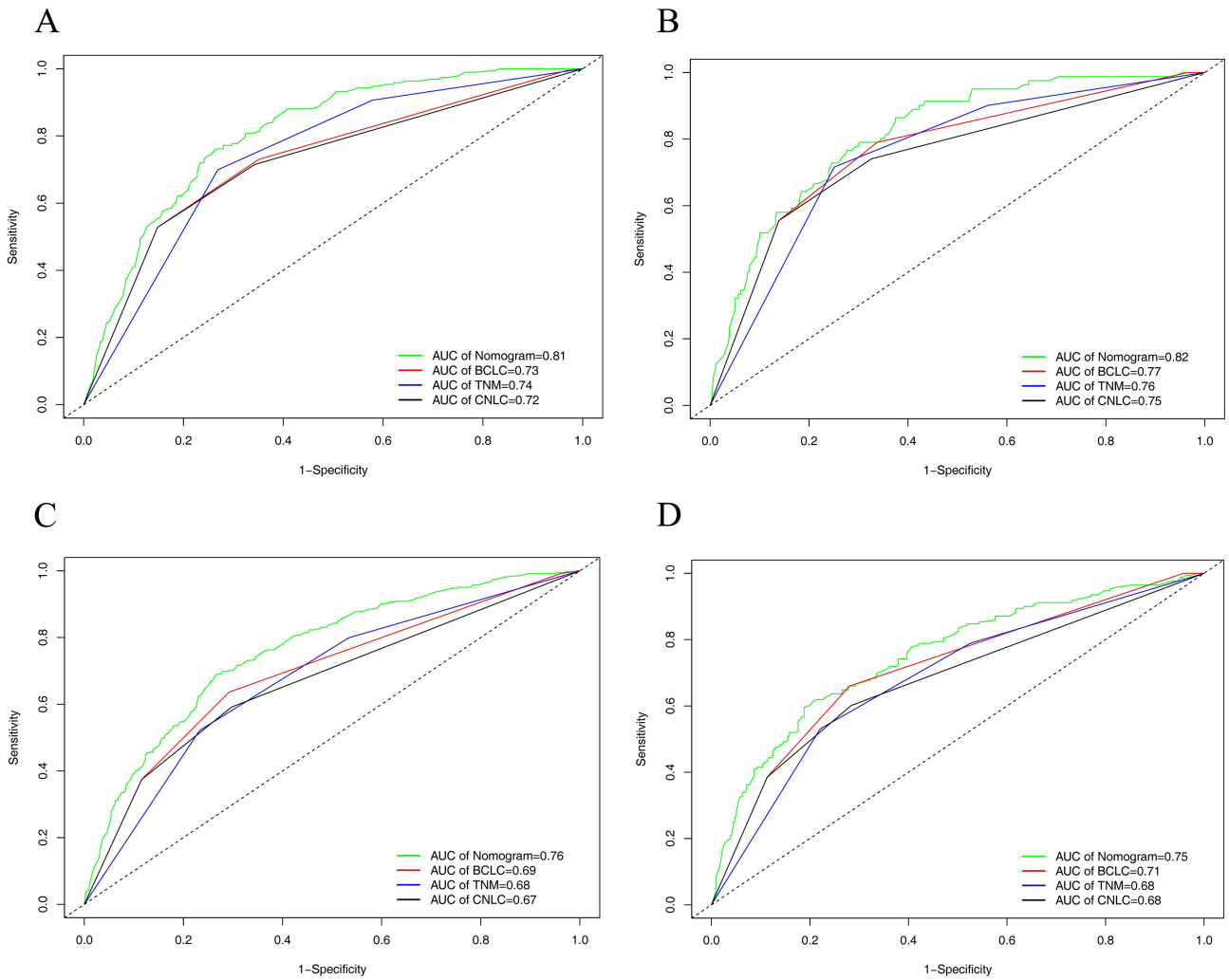

Figure 6 Comparison of predicted outcomes between the nomograms and traditional staging models using the ROC curves. (**A**) 1-year OS prediction in the training cohort. (**B**) 1-year OS prediction in the validation cohort. (**C**) 1-year RFS prediction in the training cohort. (**D**) 1-year RFS prediction in the validation cohort.

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inflammatory response, attracts neutrophils to tumor lesions and significantly influences the tumor microenvironment, thereby fostering the migration and proliferation of cancer cells.[22] The function of white blood cell is a multifaceted phenomenon. Neutrophils, monocytes, and platelets predominantly function to promote an inflammatory and pro-tumorigenic environment, whereas lymphocytes primarily exert anti-inflammatory and anti-tumor effects. It has been demonstrated that neutrophils facilitate tumor development and progression by discharging an array of pro-inflammatory mediators, including reactive oxygen species, cytokines, chemokines, granule proteins, and lipid mediators.[23] In particular, neutrophil extracellular traps have been demonstrated to promote tumor growth by stimulating lymphangiogenesis and impeding the activity of cytotoxic lymphocytes in various cancers.[24,25] Monocytes have the capacity to transform into M2 macrophages, which have been demonstrated to facilitate tumor growth through the promotion of angiogenesis, extracellular matrix remodeling, and many other biological processes.[26] The potential mechanisms by which platelets promote tumor growth include immune escape, angiogenesis, tumor cell homing and exudation.[27] Lymphocytes can directly kill tumor cells and enhance the body's defense against tumors by regulating immune responses.[28] Given their pivotal function in tumor-related inflammatory and immune responses, the quantity and functionality of these cells can serve as indicators of the local immune microenvironment of the tumor, the overall state of the body, and the interaction between the tumor and the host.

Nevertheless, the information obtained by simply counting a certain type of blood cell is limited, and measuring cell function is a relatively complex process, which limits the clinical application of individual blood cell indicators. In light of the above issues, numerous studies have adopted comprehensive indicators, or IIBs, which integrate multiple blood cells, effectively circumventing the aforementioned challenges. In previous studies, the most commonly used IIBs were NLR, PLR, SII, and so forth.[12–14] Although the above-mentioned IIBs have been demonstrated to be effective biomarkers, PIV, as an integrated marker calculated from a greater number of indicators of blood cells than other IIBs, may provide a more comprehensive reflection of the local immune microenvironment of tumors, as well as the overall inflammatory and immune status of the host.[29] It is hypothesized that a high PIV level may indicate more obvious chronic inflammatory damage, weaker anti-tumor immune response, and ultimately leads to poor prognosis.[16]

Given the above considerations, an increasing number of research initiatives are directing their attention toward the investigation of PIV as a prospective novel biomarker. The inaugural study on PIV was published in 2020, which proposed an innovative hypothesis that PIV can serve as a prognostic marker for metastatic colorectal cancer following first-line chemotherapy.[18] Subsequently, the diagnostic and prognostic value of PIV in other diseases has also been gradually corroborated. For instance, in addition to its function as a prognostic biomarker, PIV also has the potential to serve as a biomarker for predicting pathological complete response,[30] postoperative complications,[31] and lymph node metastases.[32] Moreover, several studies have reported that PIV has superior efficacy in diagnosis and prognosis prediction than other traditional IIBs.[16,30,33,34] In the field of HCC, only two publicly reported literature sources are currently available for review that relate to PIV. The initial study to demonstrate the potential of PIV as a prognostic biomarker in patients with HCC was published in 2022.[19] However, as a retrospective study, the sample size was limited to 110 patients, and there was considerable heterogeneity among patients, with 19.2%, 13.3%, and 33.3% of patients undergoing surgical resection, radiofrequency ablation, and sorafenib targeted therapy, respectively. The other study included 398 patients with early-stage HCC who underwent radiofrequency ablation.[20]

To our knowledge, our study is the first investigation into the prognostic value of PIV in HCC patients undergoing liver resection. What's more, our study encompassed 1760 patients, a considerably larger sample size than that of previous studies. This markedly augmented the statistical power, ensuring robust stability and consistency. One noteworthy phenomenon is the considerable discrepancy in the PIV thresholds established across disparate studies. In the two preceding studies, the cut-off values for PIV were established at 286.15 and 120, respectively. In contrast, our study utilized a median cut-off value of PIV of 176. It is hypothesized that this may be associated with the staging of HCC, where a higher PIV value is observed in cases with more advanced staging. So further research is required to identify the optimal cut-off values for different populations of HCC patients.

The findings of our research indicated that Child-Pugh grading was an independent risk factor for OS. The prognostic significance of Child–Pugh liver function grading in HCC patients following surgery remains a topic of contention. Accordingly, various clinical guidelines have offered divergent recommendations regarding the suitability of surgical

intervention for patients with Child-Pugh B classification.[35–37] In a study conducted by Yukihiro Watanabe, it was found that the Child-Pugh grading did not serve as an independent risk factor for OS in patients with HCC who underwent liver resection.[38] The baseline data and surgical methods employed in this study differ significantly from those used in ours, which may be the primary reason for the disparate conclusions. In Yukihiro Watanabe's study, a notable proportion of patients received preoperative anti-tumor treatment, and all patients underwent laparoscopic liver resection. It should be noted, however, that the present study included only patients with HCC who had not previously undergone anti-tumor treatment, and the predominant surgical approach was open abdominal surgery. Since the impact of Child Pugh grading on the prognosis of liver resection is still controversial, further research is essential in the future.

CK19, also designated as cytokeratin 19, is a biomarker of tumor stem cells, and its positive expression is correlated with a poor prognosis in a range of neoplasms.[39,40] A number of studies have demonstrated that patients with HCC who test positive for CK19 often exhibit a poorer degree of tumor differentiation, a higher prevalence of MVI positivity, and a greater propensity for distant metastasis.[41] These findings are consistent with those of our study.

The proposed nomogram incorporates a greater number of variables than the BCLC, TNM, and CNLC staging systems, which are commonly employed in clinical practice. These variables encompass not only preoperative indicators but also postoperative pathological results. They reflect the characteristics of the tumor itself and indicate the host's overall state. Accordingly, this model is capable of more accurately predicting the prognosis of patients than the aforementioned staging systems, as evidenced by more favorable indicators such as the AUC value. In conclusion, our model can serve as an additional tool in conjunction with the existing liver cancer staging system, thereby facilitating more personalized treatment decisions for clinicians.

It is important to acknowledge the limitations of our research, which must be considered when interpreting the findings. Firstly, it should be noted that the study population was primarily comprised of hepatitis B-related HCC, whereas the aetiology of HCC in Japan and many Western countries is predominantly attributed to hepatitis C virus infection, non-alcoholic fatty liver disease, and alcohol abuse. Secondly, as a retrospective study, the findings are susceptible to the influence of potential biases. Thirdly, the study lacks an external validation cohort, which would have enabled a more robust assessment of the results. Finally, this study only focuses on the prediction of postoperative efficacy of HCC by PIV. As HCC enters the immunotherapy era, PIV - a composite biomarker reflecting multiple immune cell types - shows promise for stratifying responses to immunotherapy. It is further acknowledged that future exploratory endeavours should be undertaken in this regard.

Conclusion

To conclude, we first evaluated the value of PIV in HCC patients undergoing liver resection and constructed a PIV-based nomogram for predicting prognosis. The results of this study may facilitate the precise estimation of survival probability, which can be used to answer patients' queries, make individualized treatment decisions, and design prospective clinical trials. However, further validation of these findings is required.

Data Sharing Statement

In consideration of the fact that the data utilized in this study pertains to patient privacy, it will not be made publicly available. Should the original data be required, the corresponding author may be contacted for its provision.

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Disclosure

The authors state that they have no conflicts of interest to disclose in connection with this research.

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