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Contents

Weekly Volume 30 Number 33 September 7, 2024

EDITORIAL

ORIGINAL ARTICLE

Retrospective Cohort Study

Observational Study

LETTER TO THE EDITOR

ABOUT COVER

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ORIGINAL ARTICLE

Retrospective Cohort Study

Pan-immune-inflammation value as a prognostic biomarker for colon cancer and its variation by primary tumor location

Qian-Yu Wang, Wen-Tao Zhong, Yi Xiao, Guo-Le Lin, Jun-Yang Lu, Lai Xu, Guan-Nan Zhang, Jun-Feng Du, Bin Wu

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Abstract

BACKGROUND

A growing body of research indicates significant differences between left-sided colon cancers (LCC) and right-sided colon cancers (RCC). Pan-immune-inflammation value (PIV) is a systemic immune response marker that can predict the prognosis of patients with colon cancer. However, the specific distinction between PIV of LCC and RCC remains unclear.

AIM

To investigate the prognostic and clinical significance of PIV in LCC and RCC patients.

METHODS

This multicenter retrospective cohort study included 1510 patients with colon cancer, comprising 801 with LCC and 709 with RCC. We used generalized lifting regression analysis to evaluate the relative impact of PIV on disease-free survival (DFS) in these patients. Kaplan-Meier analysis, as well as univariate and multivariate analyses, were used to examine the risk factors for DFS. The correlation between PIV and the clinical characteristics was statistically analyzed in these patients.

RESULTS

A total of 1510 patients {872 female patients (58%); median age 63 years [inter-

quartile ranges (IQR): 54-71]; patients with LCC 801 (53%); median follow-up 44.17 months (IQR 29.67-62.32)} were identified. PIV was significantly higher in patients with RCC [median (IQR): 214.34 (121.78-386.72) *vs* 175.87 (111.92-286.84), $P < 0.001$]. After propensity score matching, no difference in PIV was observed between patients with LCC and RCC [median (IQR): 182.42 (111.88-297.65) *vs* 189.45 (109.44-316.02); $P = 0.987$]. PIV thresholds for DFS were 227.84 in LCC and 145.99 in RCC. High PIV (> 227.84) was associated with worse DFS in LCC [PIV-high: Adjusted hazard ratio (aHR) = 2.39; 95% confidence interval: 1.70-3.38; $P < 0.001$] but not in RCC (PIV-high: aHR = 0.72; 95% confidence interval: 0.48-1.08; $P = 0.114$).

CONCLUSION

These findings suggest that PIV may predict recurrence in patients with LCC but not RCC, underscoring the importance of tumor location when using PIV as a colon cancer biomarker.

Key Words: Colon cancer; Left-sided colon cancer; Right-sided colon cancer; Pan-immune-inflammation value; Systemic inflammatory biomarkers; Prognosis

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Core Tip: This study underscores the critical role of tumor location in shaping the prognostic significance of the pan-immune-inflammation value in colon cancer patients. The findings reveal that a high pan-immune-inflammation value is strongly correlated with poorer disease-free survival in patients with left-sided colon cancer, while no such association was observed in right-sided colon cancer. These results suggest that integrating tumor location into prognostic evaluations could improve the identification of high-risk patients and facilitate more precise, personalized treatment strategies in clinical practice.

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INTRODUCTION

Inflammation plays a crucial role in tumor initiation, progression, and metastasis, in malignancies including colorectal cancer (CRC)[1,2]. As an emerging biomarker of the systemic inflammatory response (SIR), the pan-immune-inflammation value (PIV) has been demonstrated to predict prognosis[3,4] and sensitivity to anticancer treatment[5-7] in patients with various solid tumors in multiple meta-analyses and retrospective studies. In patients with CRC, an elevated PIV is independently associated with poor prognosis[8-10].

However, despite a growing body of research indicating significant distinctions between left-sided colon cancers (LCC) and right-sided colon cancers (RCC)[11-14], the existing research has concentrated on analyzing the role of PIV in CRC[8-10]. The utility and significance of PIV, as well as other SIR markers, may differ based on tumor location within the colon. Moreover, the majority of participants in these studies were recruited outside of China[8-10]. Only one study conducted in China reported a correlation between PIV and the clinical staging of CRC without exploring its relationship with prognosis[15]. These factors may lead to significant differences in PIV thresholds[8-10] and limit their clinical application. Given the geographic heterogeneity in the genomic landscape of CRC[16] and the variability in CRC location[11-14], such as LCC and RCC, PIV values may exhibit variations owing to these factors. Therefore, whether the findings of these studies apply to Chinese patients, particularly considering the differences between RCC and LCC, remains unknown.

To address these issues and assist clinicians in identifying potentially high-risk patients with colon cancer, we conducted a multicenter, retrospective cohort study in China. This study focused on patients with LCC and RCC who underwent radical surgery. The primary aim of this study was to assess the correlation between PIV and recurrence in these two groups.

MATERIALS AND METHODS

Patients and materials

This study included patients with colon cancer treated at two institutes: The Peking Union Medical College Hospital from 2014 to 2021, and the 7th Medical Center of PLA General Hospital from 2015 to 2019. This study excluded patients with distant metastasis, non-adenocarcinoma, or those receiving neoadjuvant therapy, such as chemotherapy or chemoradiotherapy. A total of 1510 participants were included (Figure 1). A total of 180 participants were excluded from the analyses because of incomplete data such as clinicopathological characteristics and follow-up data.

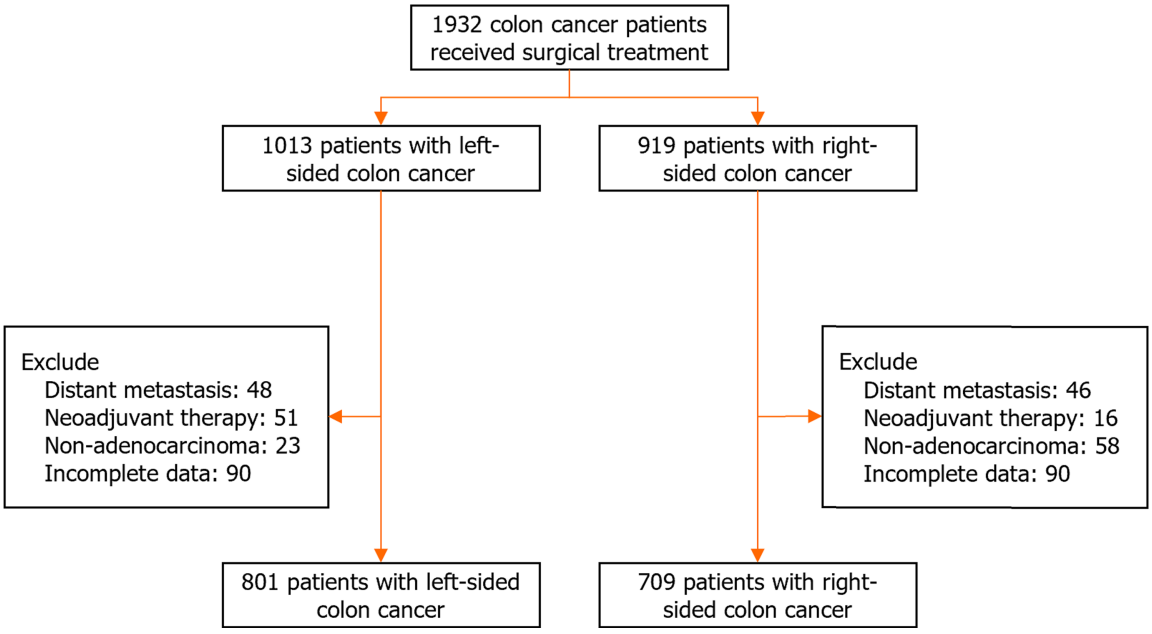

Figure 1 Flowchart for cohort selection with inclusion and exclusion criteria.

Clinicopathological characteristics

The clinicopathological characteristics included sex, age, American Joint Committee on Cancer (AJCC) stage, tumor size, tumor grade [grades well and moderately differentiated (G1-2); grade poorly differentiated (G3)], tumor location, vascular invasion, perineural invasion, and DNA mismatch repair (MMR) [MMR-proficient (pMMR) and MMR-deficient (dMMR)]. Tumors located in the sigmoid, descending, and transverse colon near the spleen were defined as LCC. Tumors located in the transverse colon near the liver, ascending colon, and cecum were defined as RCC.

This study also included pre-operative tumor markers such as carbohydrate antigen 19-9 (CA19-9), and carcinoembryonic antigen (CEA). The neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), and PIV were calculated based on pre-operative peripheral blood data. The NLR was calculated as the neutrophil count divided by the lymphocyte count. The PLR was calculated as the platelet count divided by the lymphocyte count. The SII was calculated as NLR multiplied by the platelet count. PIV was calculated as the SII multiplied by the monocyte count. The time between radical surgery and recurrence during follow-up was defined as disease-free survival (DFS). Various thresholds were used to evaluate DFS[17]. Subsequently, the patients were categorized into two cohorts based on whether their NLR, PLR, SII, PIV, CEA, and CA19-9 levels were above or below the identified optimal cutoff values.

Statistical analysis

R version 4.2.1 was used for this study. The χ^2 test and Fisher's exact test were used to analyze categorical variables. The χ^2 test and Fisher's exact test were used to analyze categorical variables. The Shapiro-Wilk test was used to assess the normal distribution of continuous variables. For normally distributed variables, the *t*-test was applied, whereas the Mann-Whitney *U* test was used for non-normally distributed variables. We used Kaplan-Meier analysis, as well as univariate and multivariate Cox regression analyses to examine the risk factors for DFS. A nomogram integrating five independent prognostic factors was created to estimate the DFS probability. Calibration curves were drawn to compare the predictive and actual survival probabilities at the 3-year and 5-year time points to assess the predictive performance of the nomogram. Generalized lifting regression analysis was used to evaluate the relative impact of SIR markers on DFS. Logistic multivariate analysis was used to identify variables associated with PIV. All statistical methods used a two-sided analysis, and $P < 0.05$ was considered statistically significant. We performed a propensity score-matched analysis. Patients with RCC were matched 1:1 to those with LCC using nearest-neighbor matching with a caliper value of 0.01.

RESULTS

Patients' clinicopathological characteristics and PIV

Complete data from 1510 patients with colon cancer were analyzed in the present analysis (Supplementary Table 1). Of these patients, 872 (58%) were women, and the median age was 63 years [interquartile range (IQR): 54-71]. Median follow-up was 44.17 months (IQR: 29.67-62.32). We also compared the baseline characteristics of the included and excluded participants (Supplementary Table 2). No significant differences were observed between the two groups in terms of clinicopathological characteristics such as age, sex, AJCC stage, tumor grade, MMR, and tumor size.

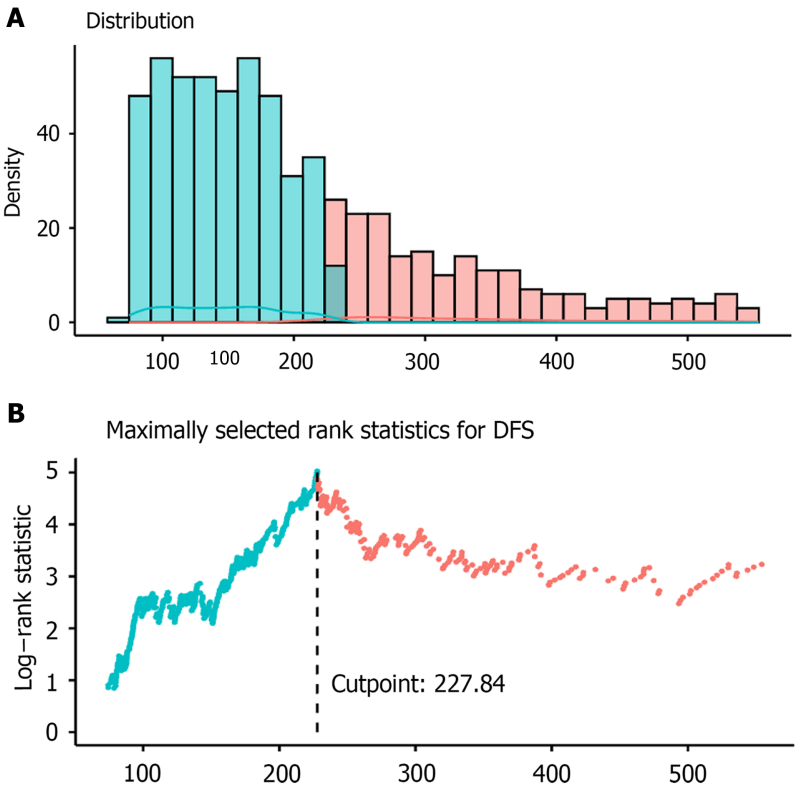

Figure 2 Distribution of pan-immune-inflammation value and threshold evaluation. A: Distribution of pan-immune-inflammation value; B: Threshold evaluation using maximum log-rank test statistic. DFS: Disease-free survival.

Compared with patients with LCC, PIV was significantly higher in those with RCC [median (IQR): 214.34 (121.78-386.72) *vs* 175.87 (111.92-286.84); $P < 0.001$, Supplementary Table 1]. Similar results were observed for other SIR markers, such as NLR, PLR, and SII (Supplementary Table 1). To mitigate the potential influence of the clinical and pathological features of LCC and RCC on PIV, we employed propensity score matching by incorporating all relevant clinical and pathological indicators. In this propensity score-matched cohort, no statistically significant difference was observed at baseline between the 475 patients with LCC and 475 patients with RCC (Supplementary Table 3). There was no difference in PIV between patients with LCC and RCC [median (IQR): 182.42 (111.88-297.65) *vs* 189.45 (109.44-316.02); $P = 0.987$]. No differences were observed in NLR, and SII (Supplementary Table 3) as well. The patients with LCC had lower PLR [median (IQR): 144.85 (113.71-189.84) *vs* 165 (121.12-218.89); $P < 0.001$].

Prognostic value of PIV in LCC and RCC patients

First, we evaluated the role of PIV in predicting the DFS in patients with LCC. For patients with LCC, the optimal cutoff value of PIV for DFS was determined to be 227.84 (Figure 2). We also evaluated the optimal cutoff values of other indicators for DFS and categorized them into two groups: High and low (Supplementary Table 4). A total of 282 patients (35%) had high PIV (Table 1). Kaplan-Meier analysis showed that the PIV-high group exhibited worse DFS than the PIV-low group [PIV-high: Adjusted hazard ratio (aHR) = 2.39, 95% confidence interval (CI): 1.70-3.38; $P < 0.001$; Figure 3A]. In univariate Cox regression analysis, high NLR, SII, and PLR were significantly associated with worse DFS (Table 2). Moreover, multivariate Cox regression analysis showed that among all SIR markers, only high PIV was independently associated with worse DFS (PIV-high: aHR = 2.12, 95%CI: 1.30-3.47; $P = 0.003$, Figure 4A). Additionally, the AJCC stage, vascular invasion, perineural invasion, and CEA levels were independently associated with DFS in patients with LCC (Table 2, Figure 4A). The generalized boosted regression model showed that PIV exhibited a higher relative influence on DFS than other SIR markers, such as NLR, PLR, and SII (Figure 3B).

For patients with RCC, the optimal cutoff value of PIV for DFS was determined to be 145.99 (Supplementary Table 4). A total of 482 patients (68%) had a high PIV (Supplementary Table 5). Kaplan-Meier analysis did not reveal a significant association with DFS (PIV-high: aHR = 0.72, 95%CI: 0.48-1.08; $P = 0.114$; Figure 3C). Univariate Cox regression analysis also indicated that the NLR, PLR, and SII were not significantly associated with DFS (Table 2). Multivariate Cox regression analysis showed that the AJCC stage, CEA levels, CA19-9 levels, MMR, and vascular invasion were associated with DFS in patients with RCC (Table 2, Figure 4B).

A PIV nomogram predicts the prognosis of patients with LCC and RCC

To accurately predict the prognosis of patients with LCC, we developed a nomogram to predict the probability of 3- and 5-year DFS using DFS-based multivariate Cox regression analysis in the LCC patient cohort. The nomogram included five independent prognostic factors: Vascular invasion, perineural invasion, stage, PIV, and CEA levels (Figure 5A). The

Table 1 Baseline characteristics in left-sided colon cancer

Variables	Patients			*P* value
	All (*n* = 801)	PIV-high (*n* = 282)	PIV-low (*n* = 519)	
Sex, *n* (%)				0.044
Female	495 (62)	188 (67)	307 (59)	
Male	306 (38)	94 (33)	212 (41)	
Age, median (IQR), years	63 (54, 70)	62.5 (54, 70.75)	63 (54, 69)	0.743
Tumor grade, *n* (%)				0.010
G1-2	743 (93)	252 (89)	491 (95)	
G3	58 (7)	30 (11)	28 (5)	
Vascular, *n* (%)				0.961
Invasion	184 (23)	64 (23)	120 (23)	
No-invasion	617 (77)	218 (77)	399 (77)	
Perineural, *n* (%)				0.727
Invasion	116 (14)	43 (15)	73 (14)	
No-invasion	685 (86)	239 (85)	446 (86)	
MMR, *n* (%)				< 0.001
dMMR	85 (11)	48 (17)	37 (7)	
pMMR	716 (89)	234 (83)	482 (93)	
T stage, *n* (%)				0.001
T1-2	143 (18)	33 (12)	110 (21)	
T3-4	658 (82)	249 (88)	409 (79)	
N stage, *n* (%)				0.192
N0	446 (56)	152 (54)	294 (57)	
N1	261 (33)	89 (32)	172 (33)	
N2	94 (12)	41 (15)	53 (10)	
NLR, median (IQR)	2.13 (1.62, 2.92)	3.06 (2.39, 4.15)	1.8 (1.44, 2.23)	< 0.001
PLR, median (IQR)	141.67 (111.31, 183.98)	182.76 (143.89, 238.09)	127.47 (100, 155.05)	< 0.001
SII, median (IQR)	502.24 (357.54, 742.37)	856.81 (650, 1299.84)	402.6 (307.71, 508.28)	< 0.001
PIV, median (IQR)	175.87 (111.92, 286.84)	361.93 (271.07, 644.13)	133.11 (91.46, 172.42)	< 0.001
CEA, median (IQR), ng/mL	3.5 (2, 7.58)	4.4 (2.3, 10.52)	3.2 (1.88, 6.73)	< 0.001
CA19-9, median (IQR), U/mL	11.6 (7, 20.1)	11.95 (6.73, 21.8)	11.5 (7.2, 19.6)	0.772
Tumor size, median (IQR), cm	4 (3, 5)	5 (3.78, 6)	4 (3, 5)	< 0.001

PIV: Pan-immune-inflammation value; G1-2: Grades well and moderately differentiated; G3: Grade poorly differentiated; MMR: Mismatch repair; dMMR: Mismatch repair-deficient; pMMR: Mismatch repair-proficient; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; SII: Systemic immune-inflammation index; CEA: Carcinoembryonic antigen; CA19-9: Carbohydrate antigen 19-9; IQR: Interquartile range.

Table 2 Cox proportional hazards regression models for disease-free survival in left-sided colon cancer and right-sided colon cancer

Variables	LCC (*n* = 801)				RCC (*n* = 709)			
	aHR (95%CI)[1]	*P* value[1]	aHR (95%CI)[2]	*P* value[2]	aHR (95%CI)[1]	*P* value[1]	aHR (95%CI)[2]	*P* value[2]
Sex								
Female	1 (Reference)	NA			1 (Reference)	NA		

Male	1.17 (0.82-1.65)	0.387			1.13 (0.76-1.68)	0.541		
Age, years								
< 65	1 (Reference)	NA			1 (Reference)	NA		
≥ 65	1.31 (0.93-1.85)	0.124			1.44 (0.96-2.15)	0.074		
Tumor grade								
G1-2	1 (Reference)	NA			1 (Reference)	NA		
G3	1.63 (0.92-2.90)	0.094			0.88 (0.49-1.58)	0.676		
AJCC stage								
I	1 (Reference)	NA	1 (Reference)	NA	1 (Reference)	NA	1 (Reference)	NA
II	2.12 (0.89-5.06)	0.089	1.55 (0.65-3.75)	0.325	1.58 (0.56-4.50)	0.390	1.31 (0.46-3.74)	0.619
III	5.76 (2.52-13.15)	< 0.001	3.70 (1.59-8.62)	0.002	5.10 (1.86-14.00)	0.002	3.15 (1.13-8.83)	0.029
Tumor size								
< 5 cm	1 (Reference)	NA	1 (Reference)	NA	1 (Reference)	NA		
≥ 5 cm	1.61 (1.14-2.27)	0.007	1.24 (0.86-1.80)	0.253	0.88 (0.59-1.31)	0.521		
Vascular								
No-invasion	1 (Reference)	NA	1 (Reference)	NA	1 (Reference)	NA	1 (Reference)	NA
Invasion	2.17 (1.52-3.10)	< 0.001	1.48 (1.00-2.19)	0.049	3.01 (2.02-4.47)	< 0.001	2.02 (1.32-3.11)	0.001
Perineural								
No-invasion	1 (Reference)	NA	1 (Reference)	NA	1 (Reference)	NA	1 (Reference)	NA
Invasion	2.22 (1.49-3.32)	< 0.001	1.58 (1.02-2.45)	0.040	2.24 (1.39-3.60)	< 0.001	1.06 (0.63-1.77)	0.831
MMR								
pMMR	1 (Reference)	NA			1 (Reference)	NA	1 (Reference)	NA
dMMR	0.74 (0.40-1.37)	0.339			0.45 (0.25-0.78)	0.005	0.56 (0.32-1.00)	0.049
CEA								
Low	1 (Reference)	NA	1 (Reference)	NA	1 (Reference)	NA	1 (Reference)	NA
High	2.80 (1.93-4.06)	< 0.001	1.81 (1.22-2.70)	0.003	2.51 (1.69-3.73)	< 0.001	1.83 (1.20-2.79)	0.005
CA19-9								
Low	1 (Reference)	NA	1 (Reference)	NA	1 (Reference)	NA	1 (Reference)	NA
High	2.02 (1.31-3.13)	0.002	1.34 (0.85-2.11)	0.201	2.65 (1.69-4.15)	< 0.001	1.75 (1.09-2.81)	0.020
PIV								
Low	1 (Reference)	NA	1 (Reference)	NA	1 (Reference)	NA		
High	2.39 (1.70-3.38)	< 0.001	2.12 (1.30-3.47)	0.003	0.72 (0.48-1.08)	0.114		
SII								
Low	1 (Reference)	NA	1 (Reference)	NA	1 (Reference)	NA		
High	1.89 (1.31-2.72)	< 0.001	0.92 (0.53-1.62)	0.782	0.68 (0.44-1.04)	0.076		
NLR								
Low	1 (Reference)	NA	1 (Reference)	NA	1 (Reference)	NA		
High	1.72 (1.20-2.47)	0.003	1.18 (0.74-1.90)	0.487	1.37 (0.77-2.46)	0.288		
PLR								
Low	1 (Reference)	NA	1 (Reference)	NA	1 (Reference)	NA		
High	1.73 (1.14-2.61)	0.009	0.87 (0.54-1.38)	0.545	1.58 (0.94-2.66)	0.088		

[1]Univariable.

[2]Multivariable.

LCC: Left-sided colon cancer; RCC: Right-sided colon cancer; aHR: Adjusted hazard ratio; CI: Confidence interval; PIV: Pan-immune-inflammation value; G1-2: Grades well and moderately differentiated; G3: Grade poorly differentiated; MMR: Mismatch repair; dMMR: Mismatch repair-deficient; pMMR: Mismatch repair-proficient; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; SII: Systemic immune-inflammation index; CEA: Carcinoembryonic antigen; CA19-9: Carbohydrate antigen 19-9; AJCC: American Joint Committee on Cancer; NA: Not available.

predictive models exhibited substantial accuracy with a concordance index of 0.739 for DFS. The calibration curve sets showed good consistency between the actual and predicted probability of 3-year and 5-year DFS rates in the LCC patient cohort (Figure 5B). The 1-, 3-, and 5-year area under the receiver operating characteristic curve values of the nomogram for DFS were 0.761, 0.769, and 0.743, respectively (Figure 5C).

To accurately predict the prognosis of patients with RCC, we developed a nomogram to predict the probability of 3- and 5-year DFS using DFS-based multivariate Cox regression analysis in the RCC patient cohort. The nomogram included five independent prognostic factors: Vascular invasion, stage, MMR, CEA levels, and CA19-9 levels (Figure 6A). The predictive models exhibited substantial accuracy with a concordance index of 0.742 for DFS. The calibration curve sets showed good consistency between the actual and predicted probability of 3-year and 5-year DFS rates in the RCC patient cohort (Figure 6B). The 1-, 3-, and 5-year area under the receiver operating characteristic curve values of the nomogram for DFS were 0.734, 0.739, and 0.742, respectively (Figure 6C).

Relationship between PIV and clinicopathological characteristics

The clinicopathological characteristics of patients with LCC in the PIV-high and PIV-low groups were compared (Tables 1 and 3). Compared to PIV-low patients, a higher proportion of PIV-high patients were female (67% *vs* 59%; $P = 0.044$), had G3 tumors (11% *vs* 5%; $P = 0.010$), higher dMMR (17% *vs* 7%; $P < 0.001$), higher CEA levels [median (IQR): 4.4 (2.3-10.52) *vs* 3.2 (1.88-6.73); $P < 0.001$], larger tumor size [median (IQR): 5 (3.78-6) *vs* 4 (3-5); $P < 0.001$], and higher T stage (T3-4: 88% *vs* 79%; $P = 0.001$). Logistic multivariable analysis showed that LCC patients were more likely to have high PIV if they had larger tumor size [≥ 5 cm: Adjusted odds ratio (aOR) = 2.55; 95%CI: 1.85-3.51; $P < 0.001$], higher CEA levels (high: aOR = 1.94; 95%CI: 1.28-2.95; $P = 0.002$), and dMMR (dMMR: aOR = 2.53; 95%CI: 1.53-4.18; $P < 0.001$).

Next, we compared baseline characteristics between the PIV-high and PIV-low groups of patients with RCC (Supplementary Table 5, Table 3). Compared to the PIV-low group, the PIV-high group was significantly associated with G3 tumors (G3: 18% *vs* 8%, $P < 0.001$), higher T stage (T3-4: 91% *vs* 80%, $P < 0.001$), dMMR (dMMR: 30% *vs* 18%, $P < 0.001$), higher CEA levels [median (IQR): 3.6 (2-9.46) *vs* 3.04 (1.64-7.16), $P = 0.013$], and larger tumor size [median (IQR): 5.1 (4-7) *vs* 4 (3-5.35), $P < 0.001$]. Logistic multivariable analysis showed that patients with RCC were more likely to have high PIV if they had larger tumor size (≥ 5 cm: aOR = 2.19; 95%CI: 1.55-3.10; $P < 0.001$), higher pT stage (T3-4: aOR = 2.07; 95%CI: 1.26-3.39; $P = 0.004$), dMMR (dMMR: aOR = 1.80; 95%CI: 1.18-2.76; $P = 0.006$), G3 tumors (G3: aOR = 2.05; 95%CI: 1.17-3.60; $P = 0.013$), older age (≥ 65 years: aOR = 1.47; 95%CI: 1.04-2.07; $P = 0.028$), and were female (female: aOR = 1.49; 95%CI: 1.06-2.10; $P = 0.022$) (Table 3).

DISCUSSION

To our knowledge, this is the largest multicenter retrospective study on Chinese patients with colon cancer who underwent curative surgery to evaluate the association between PIV and DFS. We analyzed the data from 1510 patients with colon cancer, focusing on the differences in PIV between patients with LCC and RCC. Our study found that an elevated PIV was an independent adverse factor for DFS in patients with LCC, but not in patients with RCC.

In our study, an elevated PIV was associated with worse DFS in LCC, which is consistent with the findings of other CRC studies[8-10]. Neutrophils have been associated with cancer development and metastasis by generating reactive oxygen species, suppressing the antitumor immune response, and influencing various paracrine signaling pathways[18,19]. Conversely, lymphocytes play a pivotal role as primary drivers of the antitumor immune response within the tumor microenvironment (TME)[20,21]. A growing body of research suggests that platelets play a role in promoting tumor initiation, progression, and metastasis through an intricate crosstalk with cancer cells[22,23]. Specifically, platelets can release numerous factors, including those that support survival, angiogenesis, and immunomodulation, without direct contact, contributing to the formation and maintenance of both primary and metastatic TME[23]. Similarly, monocytes can affect the TME through various mechanisms that induce immune tolerance, and angiogenesis, and increase tumor cell dissemination[24,25]. These findings underscore the multifaceted role of these immune and hematologic components in shaping the TME and modulating tumor biology.

However, PIV was not significantly associated with DFS in patients with RCC. Similar outcomes were noted when examining other SIR markers such as NLR, PLR, and SII. Another study highlighted the prognostic significance of NLR exclusively in LCC and its lack of predictive prognostic value in RCC[26]. These findings underscore the heterogeneity of the SIR across different colon cancer subtypes. Further investigations into the underlying mechanisms driving the observed differences in PIV and other SIR markers between LCC and RCC are required.

We found that patients with larger tumors, higher CEA levels, and dMMR were more likely to have elevated PIV, similar to observations in other studies on CRC[9,15]. Elevated PIV was independently associated with DFS even after adjusting for these and other factors. Additionally, PIV exhibited superior performance compared to other SIR markers (NLR, PLR, and SII) in predicting DFS in patients with LCC. In a study by Fucà *et al*[27] involving patients with metastatic

Table 3 Logistic multivariable analysis for high pan-immune-inflammation value ratio in left-sided colon cancer and right-sided colon cancer

Variables	LCC		RCC	
	aOR (95%CI)	*P* value	aOR (95%CI)	*P* value
Sex				
Male	1 (Reference)	NA	1 (Reference)	NA
Female	1.36 (0.98-1.88)	0.062	1.49 (1.06-2.10)	0.022
Age				
< 65	1 (Reference)	NA	1 (Reference)	NA
≥ 65	1.00 (0.73-1.38)	0.979	1.47 (1.04-2.07)	0.028
Tumor grade				
G1-2	1 (Reference)	NA	1 (Reference)	NA
G3	1.45 (0.80-2.62)	0.217	2.05 (1.17-3.60)	0.013
T stage				
T1-2	1 (Reference)	NA	1 (Reference)	NA
T3-4	1.52 (0.96-2.41)	0.076	2.07 (1.26-3.39)	0.004
N stage				
N0	1 (Reference)	NA	1 (Reference)	NA
N1	0.97 (0.68-1.39)	0.874	1.29 (0.85-1.95)	0.237
N2	1.58 (0.93-2.67)	0.089	1.11 (0.63-1.945)	0.715
Tumor size				
< 5 cm	1 (Reference)	NA	1 (Reference)	NA
≥ 5 cm	2.55 (1.85-3.51)	< 0.001	2.19 (1.55-3.10)	< 0.001
Vascular				
No-invasion	1 (Reference)	NA	1 (Reference)	NA
Invasion	0.83 (0.56-1.25)	0.379	0.86 (0.56-1.30)	0.470
Perineural				
No-invasion	1 (Reference)	NA	1 (Reference)	NA
Invasion	1.09 (0.69-1.72)	0.726	0.61 (0.36-1.02)	0.059
MMR				
pMMR	1 (Reference)	NA	1 (Reference)	NA
dMMR	2.53 (1.53-4.18)	< 0.001	1.80 (1.18-2.76)	0.006
CEA				
Low	1 (Reference)	NA	1 (Reference)	NA
High	1.94 (1.28-2.95)	0.002	1.20 (0.80-1.80)	0.376
CA19-9				
Low	1 (Reference)	NA	1 (Reference)	NA
High	1.01 (0.62-1.62)	0.982	1.55 (0.87-2.74)	0.134

LCC: Left-sided colon cancer; RCC: Right-sided colon cancer; aOR: Adjusted odds ratio; CI: Confidence interval; PIV: Pan-immune-inflammation value; G1-2: Grades well and moderately differentiated; G3: Grade poorly differentiated; MMR: Mismatch repair; dMMR: Mismatch repair-deficient; pMMR: Mismatch repair-proficient; CEA: Carcinoembryonic antigen; CA19-9: Carbohydrate antigen 19-9; NA: Not available.

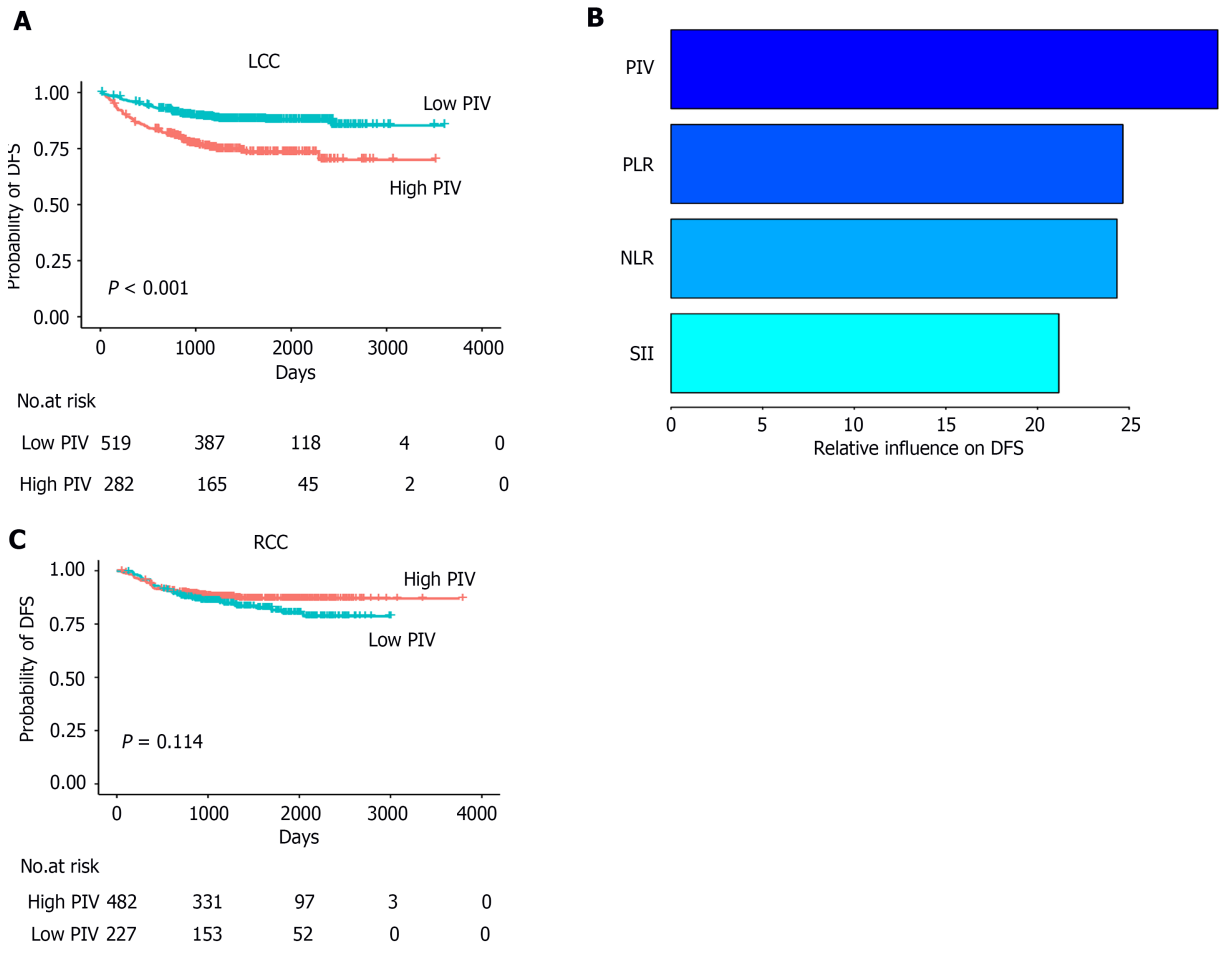

Figure 3 The relationship between pan-immune-inflammation value and disease-free survival in patients with left-sided colon cancer and right-sided colon cancer. A: In the left-sided colon cancer group, pan-immune-inflammation value (PIV)-high patients had a worse disease-free survival (DFS) than that of PIV-low patients; B: The generalized boosted regression model evaluated the relative impact of systemic inflammatory response markers on DFS, with PIV showing the highest relative influence among systemic inflammatory response markers in left-sided colon cancer patients; C: In the right-sided colon cancer group, there was no significant difference in DFS between PIV-high and -low. LCC: Left-sided colon cancer; RCC: Right-sided colon cancer; PIV: Pan-immune-inflammation value; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; SII: Systemic immune-inflammation index; DFS: Disease-free survival.

CRC, the PIV score outperformed other SIR markers (NLR, PLR, and SII) in logistic regression. Similarly, among the various SIR markers (PLR, SII, PIV, and NLR), only PIV was an independent predictor of the prognosis of patients with HER2 (+) advanced breast cancer[28]. These findings suggest that PIV may be more promising than other SIR markers for predicting patient prognosis. This advantage may be attributed to the comprehensive nature of PIV, which encompasses all pro-inflammatory cells in the blood. This broader scope may contribute to more effective risk stratification than the NLR, PLR, or SII markers.

Consistent with prior studies[15,29], we found that patients with RCC were more likely to have elevated SIR markers (NLR, PLR, SII, and PIV) than patients with LCC. This observation may be attributed to the increased frequency of RCC with higher levels of pro-inflammatory factors, such as higher T and N stages, higher tumor grade, dMMR, higher CEA levels, and larger tumor size. However, no statistically significant difference in PIV between patients with LCC and those with RCC was observed after propensity score matching to eliminate baseline differences. This evidence suggests that baseline clinical and pathological features may influence the PIV variation between the two groups.

This study has certain limitations. First, retrospective studies may suffer from selection bias. Secondly, owing to the variance in treatment methods, patients with rectal cancer were excluded from this study. Therefore, further research is essential to evaluate the role of PIV in predicting the prognosis and sensitivity to neoadjuvant therapy in rectal cancer. Finally, we did not collect information on the patients' adjuvant therapy, which may have introduced additional bias in the recurrence analyses.

CONCLUSION

In this multicenter retrospective study of patients with colon cancer who underwent surgery, we analyzed the role of PIV in predicting DFS in subgroups of patients with LCC and RCC. Our study suggests that elevated PIV may be an independent adverse factor for DFS in patients with LCC but not in those with RCC, highlighting the importance of

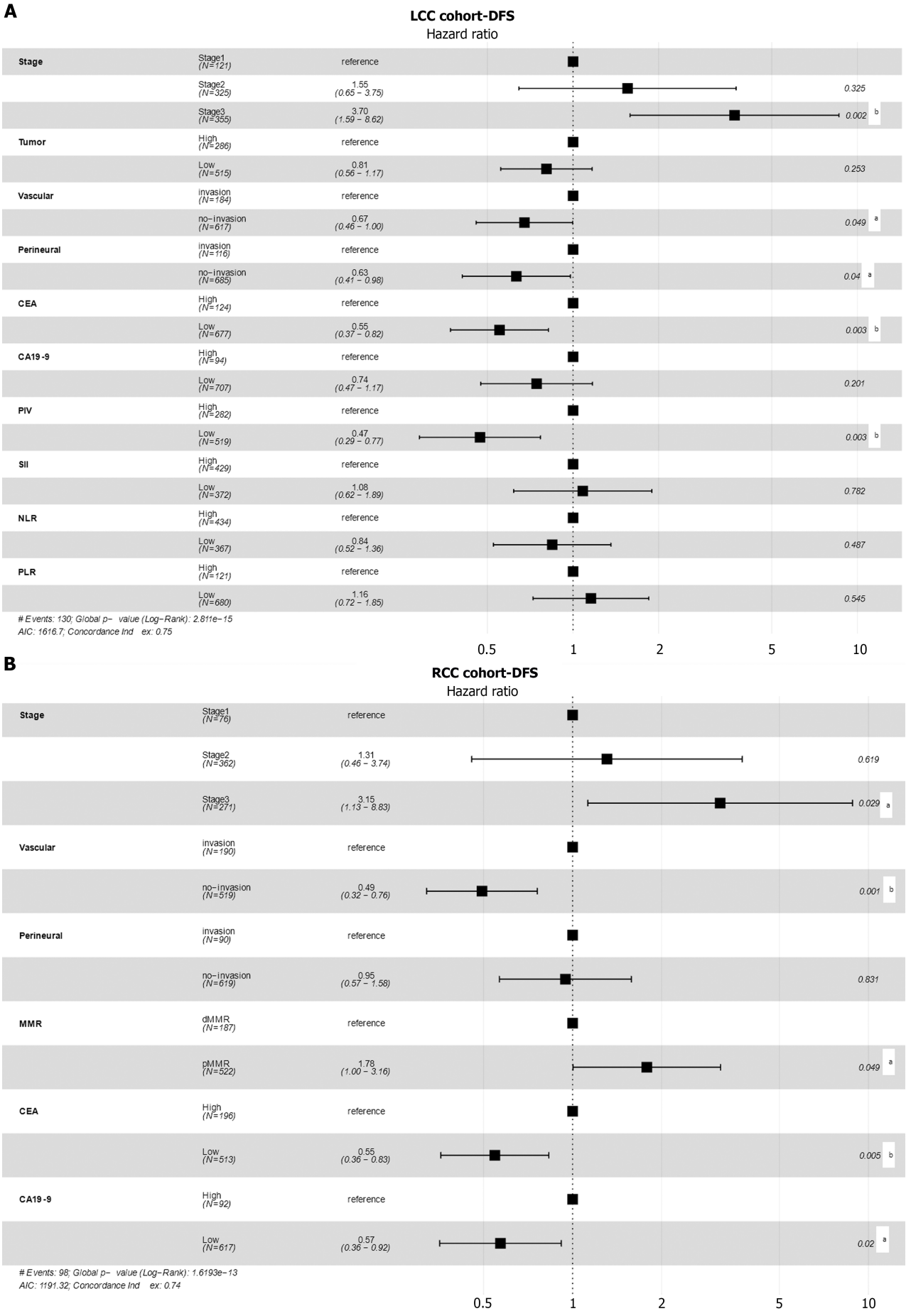

Figure 4 The forest plots for clinicopathological factors in disease-free survival-based multivariate Cox models. A: The hazard ratios, as well

as the 95% confidence intervals and statistical significances, in disease-free survival-based multivariate Cox models for the left-sided colon cancer cohort; B: The hazard ratios, as well as the 95% confidence intervals and statistical significances, in disease-free survival-based multivariate Cox models for the right-sided colon cancer cohort. [a]*P* < 0.05; [b]*P* < 0.01. LCC: Left-sided colon cancer; RCC: Right-sided colon cancer; DFS: Disease-free survival; PIV: Pan-immune-inflammation value; CA19-9: Carbohydrate antigen 19-9; CEA: Carcinoembryonic antigen; MMR: Mismatch repair; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; SII: Systemic immune-inflammation index.

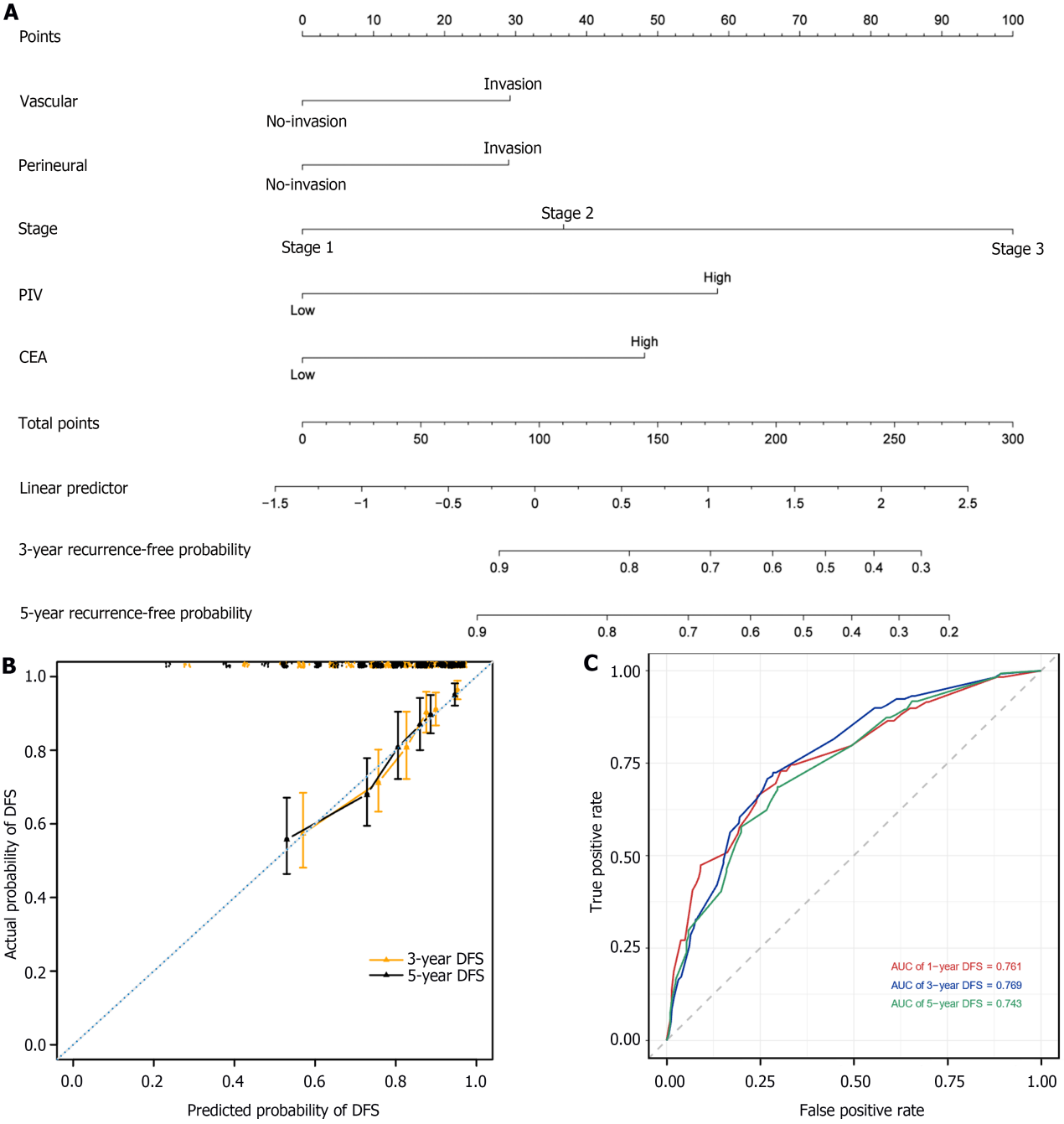

Figure 5 Construction and validation of a nomogram based on multivariate Cox regression analysis. A: The nomogram integrating vascular invasion, perineural invasion, stage, pan-immune-inflammation value, and carcinoembryonic antigen for the disease-free survival (DFS) prediction of patients with left-sided colon cancer; B: Calibration curves for predicting DFS at 3-year and 5-year time points in left-sided colon cancer patients. The x-axis indicates the predictive survival probabilities by the nomogram, while the y-axis indicates the actual survival probabilities; the 45° dotted line indicates ideal prediction; C: 1-, 3-, and 5-year area under the curves DFS. DFS: Disease-free survival; PIV: Pan-immune-inflammation value; CEA: Carcinoembryonic antigen; AUC: Area under the receiver operating characteristic curve.

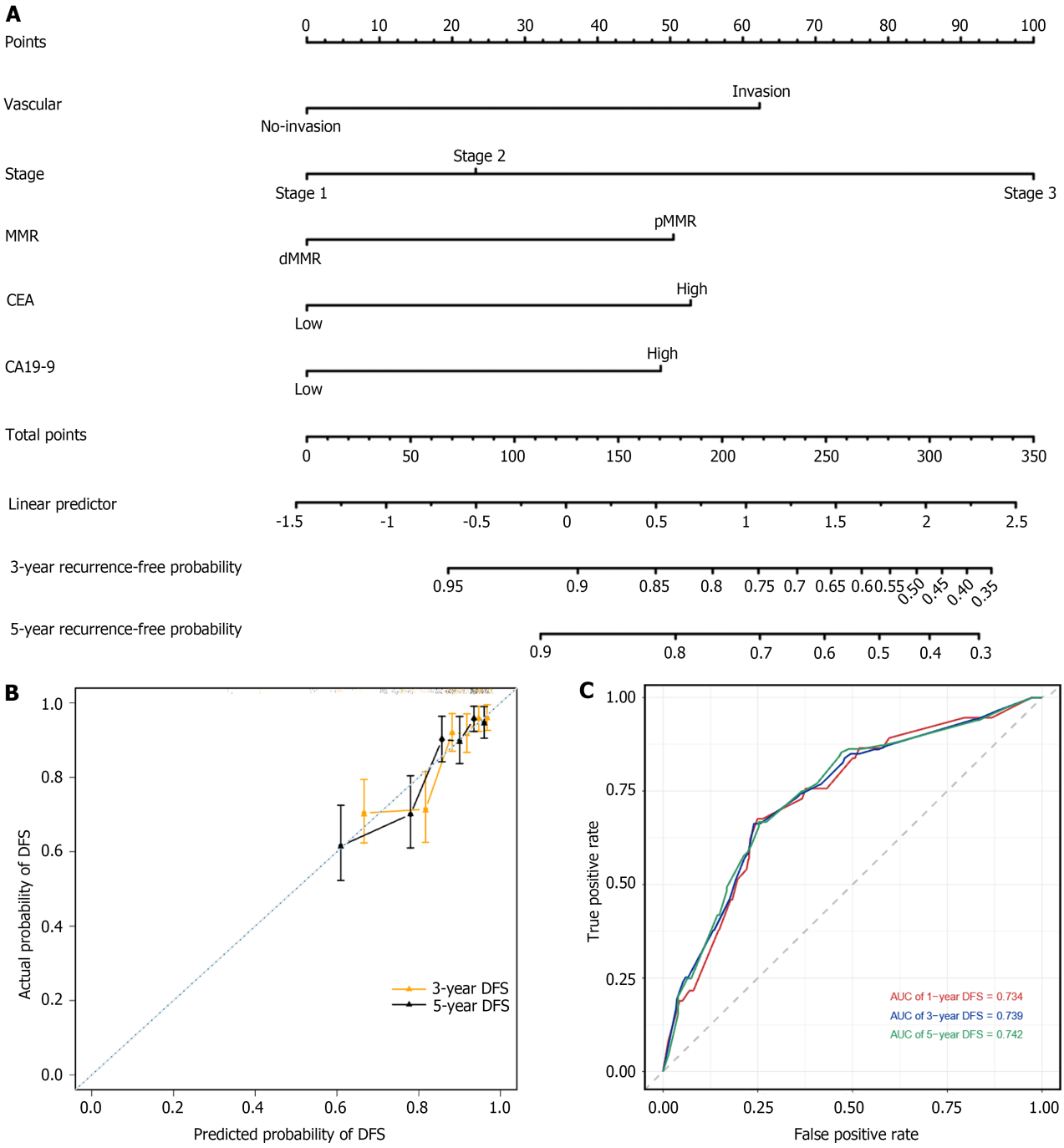

Figure 6 Construction and validation of a nomogram based on multivariate Cox regression analysis. A: The nomogram integrating vascular invasion, perineural invasion, stage, pan-immune-inflammation value, and carcinoembryonic antigen for the disease-free survival (DFS) prediction of patients with right-sided colon cancer; B: Calibration curves for predicting DFS at 3-year and 5-year time points in right-sided colon cancer patients. The x-axis indicates the predictive survival probabilities by the nomogram, while the y-axis indicates the actual survival probabilities; the 45° dotted line indicates ideal prediction; C: 1-, 3-, and 5-year area under the curves DFS. DFS: Disease-free survival; CA19-9: Carbohydrate antigen 19-9; CEA: Carcinoembryonic antigen; dMMR: Mismatch repair-deficient; pMMR: Mismatch repair-proficient.

considering tumor location when using PIV as a prognostic biomarker in colon cancer.

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FOOTNOTES

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