Pan-immune-inflammatory values predict survival in patients after radical surgery for non-metastatic colorectal cancer: A retrospective study

KEJIN LI[1], XIANGYUE ZENG[1], ZIYI ZHANG[1], KUAN WANG[1], YIPENG PAN[2], ZHIMIN WU[3], YI CHEN[4] and ZELIANG ZHAO[1]

[1]Department of Gastrointestinal Surgery, The Affiliated Cancer Hospital of Xinjiang Medical University, Urumqi, Xinjiang Uygur Autonomous Region 830000, P.R. China; [2]Department of Gastroenterology, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang 310020, P.R. China; [3]Guiyang Maternal and Child Health Care Hospital, Guiyang Children's Hospital, Guiyang, Guizhou 550003, P.R. China; [4]Department of Breast and Thyroid Surgery, The Affiliated Cancer Hospital of Xinjiang Medical University, Xinjiang Key Laboratory of Oncology, Urumqi, Xinjiang Uygur Autonomous Region 830000, P.R. China

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Abstract. The present study aimed to further investigate the predictive value of pan-immune-inflammatory values (PIVs) in patients with non-metastatic colorectal cancer after radical surgery. Additionally, the study sought to develop a predictive scoring model to predict the survival of patients with colorectal cancer after surgery. A total of 470 non-metastatic patients who attended The Affiliated Cancer Hospital of Xinjiang Medical University (Urumqi, China) for radical colorectal cancer surgery were retrospectively collected based on specific inclusion and exclusion criteria. Patients were categorized into the Low-PIV group and the High-PIV group according to the optimal cut-off value of PIV and a survival analysis was performed. Cox regression was performed for one-way multifactorial analysis. After independent risk factors were screened, a simple score prediction model was constructed and evaluated. The study indicated that PIV was significantly associated with the T stage, Tumor-Node-Metastasis stage, differentiated degree and nerve invasion (all P<0.05). Survival tanalysis showed that patients in the Low-PIV group had a significantly higher 5-year overall survival (OS) rate compared with those in the High-PIV group (88.7 vs. 46.3%; P<0.001). Through multifactorial Cox regression analysis, N stage [hazard ratio (HR), 2.00; 95% confidence interval (CI), 1.04-3.84; P=0.039], differentiated degree (HR, 1.98; 95% CI, 1.16-3.38; P=0.012), neutrophil/lymphocyte ratio (HR, 4.00; 95% CI, 2.19-7.29; P<0.001) and PIV (HR, 4.12; 95% CI, 2.04-8.32; P<0.001) were found to be independent predictors of OS. These variables were included in a column chart to create a scoring system. The concordance index was 0.789 (95% CI, 0.746-0.832). The 1-, 3- and 5-year calibration curves for this column-line diagram demonstrated high confidence. The area under the curve of the predictive model for 1-, 3- and 5-year OS were 0.823, 0.845 and 0.845, respectively. PIV was shown to be a reliable biomarker for the prognosis of patients with non-metastatic colorectal cancer. The current simple predictive scoring model can predict the effective survival of patients following radical surgery for non-metastatic colorectal cancer and could therefore play a substantial role in clinical decision-making.

Correspondence to: Dr Yi Chen, Department of Breast and Thyroid Surgery, The Affiliated Cancer Hospital of Xinjiang Medical University, Xinjiang Key Laboratory of Oncology, 789 Suzhou East Street, Xinshi, Urumqi, Xinjiang Uygur Autonomous Region 830000, P.R. China
E-mail: chenyicsu@outlook.com

Professor Zeliang Zhao, Department of Gastrointestinal Surgery, The Affiliated Cancer Hospital of Xinjiang Medical University, 789 Suzhou East Street, Xinshi, Urumqi, Xinjiang Uygur Autonomous Region 830000, P.R. China
E-mail: zlzhao71@163.com

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Introduction

Cancer is a significant public health concern globally, affecting millions of individuals and causing considerable mortality and social burden. Among the numerous types of cancer, colorectal cancer (CRC) is one of the most prevalent malignant tumors, with an estimated 5-year prevalence of >5.2 million individuals worldwide. Furthermore, CRC accounts for the second-highest cancer mortality rate (9.4%) worldwide (1). The high morbidity and mortality rates suggest that current diagnostic and therapeutic approaches have their limitations. Despite the considerable progress made in the diagnosis and treatment of CRC in recent years, particularly in early screening techniques, minimally invasive surgical approaches, chemotherapy and targeted therapies, the incidence of this disease

continues to rise (2) and the overall prognosis of patients remains unsatisfactory. A significant proportion of patients are diagnosed at an advanced stage of the disease, which limits the therapeutic benefits that can be offered and results in relatively low survival rates. This situation emphasizes the urgent need for more accurate and validated prognostic tools to guide treatment decisions and improve patient survival in clinical practice.

Chronic inflammation significantly contributes to tumor development, which may be triggered by several factors, including infections, abnormal immune responses or environmental factors (such as smoking, inhalation of pollutants or dietary factors) (3). Inflammation and immune response play an important role in the mechanisms underlying CRC (4,5). A previous study found that inflammatory processes substantially affect the postoperative recovery and prognosis of patients with CRC (6).

Immune-inflammatory biomarkers that can influence the prognosis of CRC have a more favorable predictive effect than traditional tumor-related biomarkers. It is expected that biomarkers based on inflammatory processes will prove to be significant predictors of surgical outcomes and long-term prognosis (7). Some peripheral blood parameters, including the neutrophil/lymphocyte ratio (NLR), monocyte/lymphocyte ratio (MLR) and platelet count-to-lymphocyte count ratio (PLR), have been identified as potential prognostic markers for a range of malignant tumors, such as lung, gastric and breast cancer (8,9).

In recent years, there has been a growing interest in using pan-immune-inflammatory values (PIVs) derived from peripheral blood parameters to thoroughly assess the immune-inflammatory response. The PIV is a new biomarker that integrates peripheral neutrophils, platelets, monocytes and lymphocytes (neutrophils x platelets x monocytes/lymphocytes) (10,11), and has demonstrated a good predictive role in the prognosis of numerous cancer types, including colorectal, liver cand esophageal cancer (12-14).

Nevertheless, additional evidence is needed to support the use of PIVs in predicting the prognosis of patients with CRC. In this regard, the present study aimed to examine the potential value of PIV in forecasting outcomes for CRC and to establish a new reference point for clinical decision-making.

Patients and methods

Patients. The present study retrospectively analyzed 470 patients with non-metastatic CRC who underwent radical surgery at the Cancer Hospital of Xinjiang Medical University (Urumqi, China) between January 2016 and December 2017. The mean age of the cohort was 58.3 years, with an age range of 20-87 years. The sample size was determined based on a priori power analysis to ensure sufficient statistical power to detect clinically meaningful differences. With a significance level set at α=0.05, the sample size provided >80% statistical power to identify significant differences between groups. This calculation was based on previous studies (15-18). Inclusion criteria were as follows: i) Age >18 years old; ii) postoperative pathological diagnosis of clear CRC; and iii) complete and reliable clinical and follow-up data. Exclusion criteria were as follows: i) Patients with other malignant tumors; ii) previous history of blood disease, autoimmune disease or chronic inflammation; iii) previous history of blood transfusion; iv) inability to undergo radical surgery; v) preoperative neoadjuvant chemotherapy; and vi) distant metastasis. The sample size was determined based on the number of eligible patients meeting the inclusion and exclusion criteria during the specified time frame. A post hoc sample size calculation, assuming a hazard ratio (HR) of 2.0, an event rate of 30% and a power of 80% at a significance level of 0.05, indicated that 354 patients were required. The actual sample size of 470 patients exceeded this requirement, ensuring sufficient statistical power for the analyses performed. The study set March 2023 as the follow-up cutoff to ensure that all patients had at least 5 years of follow-up data, which is critical for analyzing long-term survival outcomes in CRC. The Ethics Committee of Xinjiang Medical University Cancer Hospital approved the ethical review of this study after reviewing the study for compliance with ethical principles (approval no. K-2024056). Written informed consent was obtained from all participants.

Follow-up. The patients were strictly monitored during follow-up. The primary endpoint of the study was overall survival (OS). OS time was defined as the time from surgery to all-cause death or last follow-up. Follow-up continued until death or March 2023.

Data collection. All patient data were obtained from the electronic information system of Xinjiang Medical University Cancer Hospital. The following data variables were collected: Age, sex, body mass index (BMI), smoking history, alcohol consumption, carcinoembryonic antigen (CEA) level, preoperative blood counts (lymphocytes, monocytes, neutrophils and platelets), T stage, N stage, Tumor-Node-Metastasis (TNM) stage, differentiated degree, nerve invasion, intravascular tumor emboli and follow-up information (survival outcome and survival time). Tumor staging was performed according to the seventh edition of the Union for International Cancer Control-American Joint Committee on cancer classification for CRC (19). The calculation formulae were as follows: PIV=[neutrophil count (10^9/l)] x [monocyte count (10^9/l)] x [platelet count (10^9/l)]/[lymphocyte count (10^9/l)] (16); NLR=[neutrophil count (10^9/l)]/[lymphocyte count (10^9/l)] (20); MLR=[monocyte count (10^9/l)]/[lymphocyte count (10^9/l)] (21); and PLR=[platelet count (10^9/l)]/[lymphocyte count (10^9/l)] (22).

Statistical analysis. Continuous variables are expressed as the median and interquartile range. Categorical variables are expressed as frequencies and percentages. In the univariate analysis, categorical variables were analyzed using the χ^2 test or Fisher's exact test, while continuous variables were assessed using Student's t-test for unpaired data or the rank-sum test for non-normally distributed variables. The optimal cutoff values for continuous variables were determined using maximally selected rank statistics, which stratified patients into the Low-PIV and High-PIV groups based on baseline PIV. Survival curves were constructed using the Kaplan-Meier method and differences between groups were compared with the log-rank test. Univariate analysis was further performed using Cox proportional hazards regression. Variables that were

identified as significant (P<0.05) in the univariate analysis were included in the multivariate analysis to determine the independent risk factors associated with OS. Nomograms were constructed to predict OS rate at 1-, 3-, and 5-year postoperatively based on independent risk factors. The performance of the nomograms was assessed using the consistency index (C-index) and receiver operating characteristic curve (ROC). Calibration curves were used to assess the agreement between predicted and observed survival. P<0.05 was considered to indicate a statistically significant difference. All analyses were conducted using SPSS (version 26.0; IBM Corp.) and R software (version 4.2.3; https://cran.r-project.org).

Results

Association between preoperative PIV levels and clinical characteristics. Using maximally selected rank statistics, the optimal cut-off value for PIV in the entire cohort was 426.86 (Fig. 1). The same methodology was employed to ascertain the optimal cut-off values for NLR (3.08), MLR (0.38) and PLR (166.48) (Fig. S1). A total of 470 patients were included in the study. The cohort was divided according to the optimal cut-off value, resulting in 388 patients in the preoperative Low-PIV group and 82 patients in the preoperative High-PIV group. The association between clinical characteristics and PIV throughout the study is represented in Table I. There were no statistically significant differences between the two groups in terms of age distribution, sex and BMI (P=0.176, P=0.867 and P=0.375, respectively). Regarding lifestyle factors, history of smoking (P=0.965) and alcohol consumption (P=0.636) were also not statistically significantly different between the two groups. Among the pathological features, T stage, TNM stage, differentiated degree and nerve invasion were significantly different between the two groups (all P<0.05). However, N stage, intravascular tumor emboli and CEA level did not exhibit a significant difference between the two groups (all P>0.05). Preoperative platelet count, neutrophil count, monocyte count and lymphocyte count were $239x10^9$/l, $3.62x10^9$/l, $0.45x10^9$/l and $1.79x10^9$/l, respectively (Table I). Overall, these findings provide insights into the baseline characteristics of the study population, underscoring potential areas of discrepancy that may influence predictive outcomes.

Survival analysis. The cohort was divided into High-PIV and Low-PIV groups based on the optimal cut-off value. A 5-year OS analysis demonstrated that patients in the Low-PIV group exhibited a significantly higher OS rate than those in the High-PIV group (88.7 vs. 46.3%; P<0.001; Fig. 2A). In addition, patients were grouped according to the best cut-off values of other peripheral blood inflammation indicators. In terms of survival outcomes, patients in the Low-NLR group (NLR <3.08) had a significantly higher 5-year OS rate than patients in the High-NLR group (NLR ≥3.08) (87.6 vs. 45.1%; P<0.001; Fig. 2B), and patients in the Low-PLR group (PLR <166.48) had a significantly higher 5-year OS rate than patients in the High-PLR group (PLR ≥166.48) (87.1 vs. 65.9%; P<0.001; Fig. 2C). Similarly, in the MLR subgroup, patients in the Low-MLR group (MLR <0.38) had a significantly higher 5-year OS rate than patients in the High-MLR group (MLR ≥0.038) (85.9 vs. 56.8%; P<0.001; Fig. 2D). In addition, a subgroup survival analysis was performed to assess the prognostic value of PIV. Patients were categorized into elderly (age ≥60 years) and non-elderly (age <60 years) subgroups according to their age. Both in the non-elderly group (84.0 vs. 46.9%, P<0.001; Fig. 3A) and the elderly group (89.7 vs. 43.9%, P<0.001; Fig. 3B), the 5-year OS was significantly higher in the Low-PIV group than that in the High-PIV group.

Additionally, patients were divided into N0/1 and N2 subgroups according to their N stage. The 5-year OS was significantly higher in the Low-PIV group compared with the High-PIV group in both the N01 group (90.3 vs. 51.5%, P<0.001; Fig. 3C) and the N2 group (70 vs. 20%, P<0.001; Fig. 3D). Patients were categorized into stage I/II and stage III subgroups according to their Tumor stage. In the stage I/II group (51.2 vs. 88.8%, P<0.001; Fig. 3E) and the stage III group (34.9 vs. 81%, P<0.001; Fig. 3F), the 5-year OS was significantly worse in the High-PIV group compared with that in the Low-PIV group. Other subgroup analyses provided similar results. In multiple subgroups, including sex, age, BMI and various tumor characteristics (T stage, N stage and TNM stage), high PIV was consistently associated with poorer overall survival (Fig. 4).

Univariate and multivariate Cox regression analyses. Table II shows the results of the univariate and multivariate Cox regression analyses. In the univariate analysis of variance, T stage (HR, 3.65; 95% CI, 1.58-8.43; P<0.001), N stage (HR, 3.13; 95% CI, 1.92-5.11; P<0.001), TNM stage (HR, 1.96; 95% CI, 1.23-3.12; P=0.005), differentiated degree (HR, 3.24; 95% CI, 1.98-5.29; P<0.001), Nerve invasion (HR, 3.20; 95% CI, 1.98-5.18; P<0.001), Intravascular tumor emboli (HR, 1.92; 95% CI, 1.16-3.20; P=0.012), CEA level (HR, 1.66; 95% CI, 1.04-2.64; P=0.033), NLR (HR, 8.39; 95% CI, 5.24-13.43; P<0.001), PLR (HR, 3.19; 95% CI, 2.00-5.06; P<0.001), MLR (HR, 5.68; 95% CI, 3.55-9.08; P<0.001) and PIV (HR, 8.74; 95% CI, 5.47-13.97; P<0.001) exhibited significant differences between the High-PIV and Low-PIV groups. Poor differentiation was observed in 13.40% of the High-PIV group compared with 25.61% of the Low-PIV group (P=0.014), while nerve invasion was present in 16.24% of the High-PIV group compared with 25.61% of the Low-PIV group (P=0.005). These findings suggest that these variables may influence survival outcomes and interact with PIV in predicting prognosis. Subsequently, variables that demonstrated significant prognostic value in the univariate analysis were included in a multifactorial regression framework to identify independent risk factors. The results of the multifactorial analysis showed that N stage (HR, 2.00; 95% CI, 1.04-3.84; P=0.039), differentiated degree (HR, 1.98; 95% CI, 1.16-3.38; P=0.012), NLR (HR, 4.00; 95% CI, 2.19-7.29; P<0.001) and PIV (HR, 4.12; 95% CI, 2.04-8.32; P<0.001) were independent predictors of OS.

Construction and validation of nomogram model. Nomogram models were constructed to predict 1-, 3- and 5-year OS based on independent risk factors identified through multifactorial Cox proportional risk regression (Fig. 5A and B). The C-index of the conventional nomogram, which included the N stage and differentiated degree, was 0.642. The C-index of the nomogram based on inflammatory indicators, including N staging, differentiated degree, NLR and PIV, was 0.789

Table I. Association between clinical characteristics and PIV in patients with colorectal cancer.

Characteristics	Overall patients (n=470)	Low-PIV group (n=388)	High-PIV group (n=82)	P-value
Age, n (%)				0.176
≥60 years	209 (44.47)	167 (43.04)	42 (51.22)	
<60 years	261 (55.53)	221 (56.96)	40 (48.78)	
Sex, n (%)				0.867
Male	279 (59.36)	231 (59.54)	48 (58.54)	
Female	191 (40.64)	157 (40.46)	34 (41.46)	
BMI, n (%)				0.375
<18.5 kg/m^2	14 (2.98)	10 (2.58)	4 (4.88)	
18.5-24 kg/m^2	203 (43.19)	165 (42.53)	38 (46.34)	
24-28 kg/m^2	189 (40.21)	162 (41.75)	27 (32.93)	
≥28 kg/m^2	64 (13.62)	51 (13.14)	13 (15.85)	
Smoking, n (%)				0.965
Yes	150 (31.91)	124 (31.96)	26 (31.71)	
No	320 (68.09)	264 (68.04)	56 (68.29)	
Alcohol, n (%)				0.636
Yes	89 (18.94)	75 (19.33)	14 (17.07)	
No	381 (81.06)	313 (80.67)	68 (82.93)	
T stage, n (%)				0.001
T1	33 (7.02)	31 (7.99)	2 (2.44)	
T2	71 (15.11)	66 (17.01)	5 (6.10)	
T3	335 (71.28)	271 (69.85)	64 (78.05)	
T4	31 (6.60)	20 (5.15)	11 (13.41)	
N stage, n (%)				0.713
N0	282 (60.00)	236 (60.82)	46 (56.10)	
N1	112 (23.83)	90 (23.20)	22 (26.83)	
N2	76 (16.17)	62 (15.98)	14 (17.07)	
TNM stage, n (%)				0.014
I	94 (20.00)	87 (22.42)	7 (8.54)	
II	190 (40.43)	150 (38.66)	40 (48.78)	
III	186 (39.57)	151 (38.92)	35 (42.68)	
Differentiated degree, n (%)				0.005
Poorly	73 (15.53)	52 (13.40)	21 (25.61)	
Moderately	385 (81.91)	328 (84.54)	57 (69.51)	
Well	12 (2.55)	8 (2.06)	4 (4.88)	
Nerve invasion, n (%)				0.044
Positive	84 (17.87)	63 (16.24)	21 (25.61)	
Negative	386 (82.13)	325 (83.76)	61 (74.39)	
Intravascular tumor emboli, n (%)				0.377
Positive	87 (18.51)	69 (17.78)	18 (21.95)	
Negative	383 (81.49)	319 (82.22)	64 (78.05)	
CEA, n (%)				0.192
High	171 (36.38)	136 (35.05)	35 (42.68)	
Normal	299 (63.62)	252 (64.95)	47 (57.32)	
PLT (x10^9/l)[a]	239.00 (198.00, 290.00)	231.00 (191.00, 268.00)	316.50 (250.25, 374.50)	
NE (x10^9/l)[a]	3.62 (2.92, 4.52)	3.38 (2.84, 4.03)	5.60 (4.65, 6.62)	
MONO (x10^9/l)[a]	0.45 (0.35, 0.56)	0.42 (0.33, 0.51)	0.64 (0.56, 0.78)	
LY (x10^9/l)[a]	1.79 (1.45, 2.19)	1.84 (1.50, 2.20)	1.56 (1.30, 2.10)	

[a]Data are presented as the median (interquartile range). BMI, body mass index; PIV, pan-immune-inflammatory value; CEA, carcinoembryonic antigen; PLT, platelet count; NE, neutrophil count; MONO, monocyte count; LY, lymphocyte count.

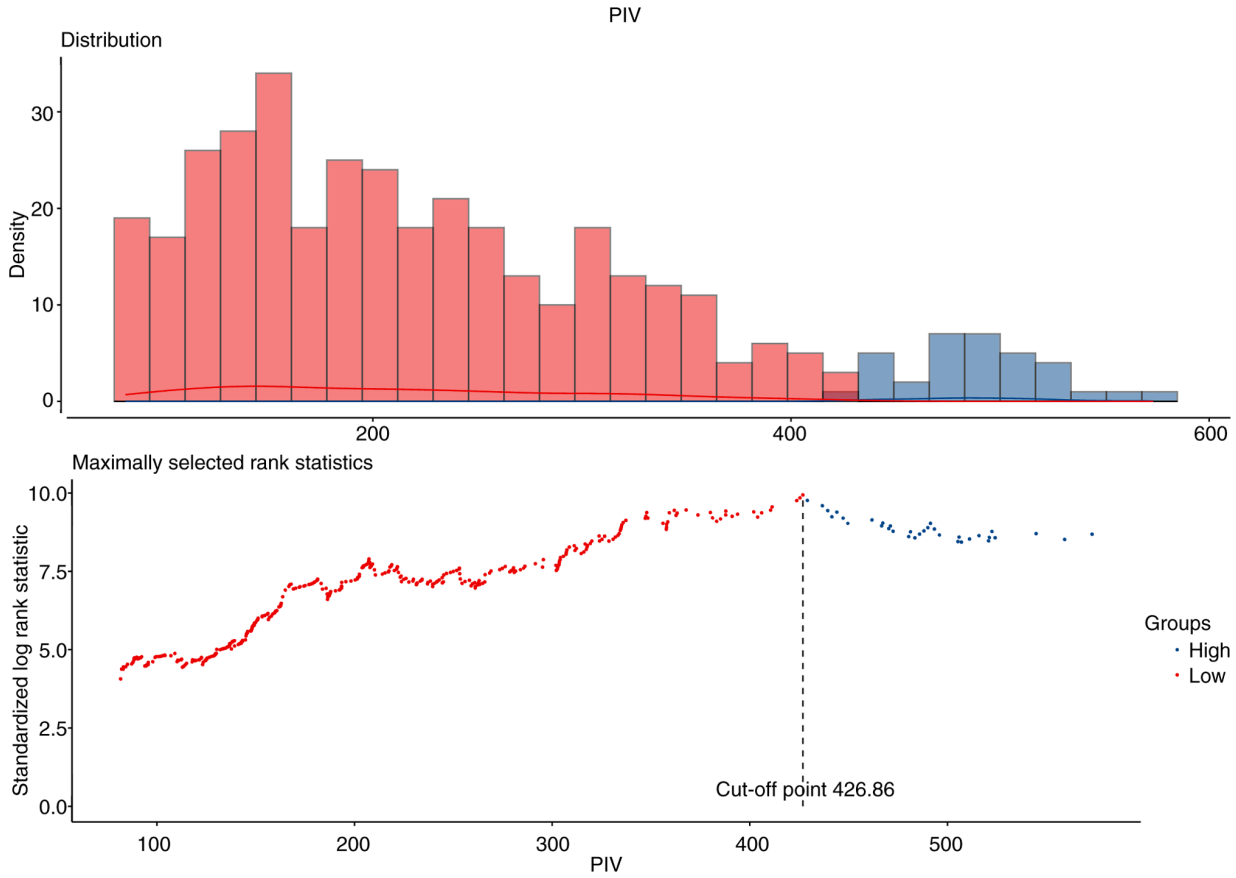

Figure 1. Optimal cutoff value of PIV. PIV, pan-immune-inflammatory value.

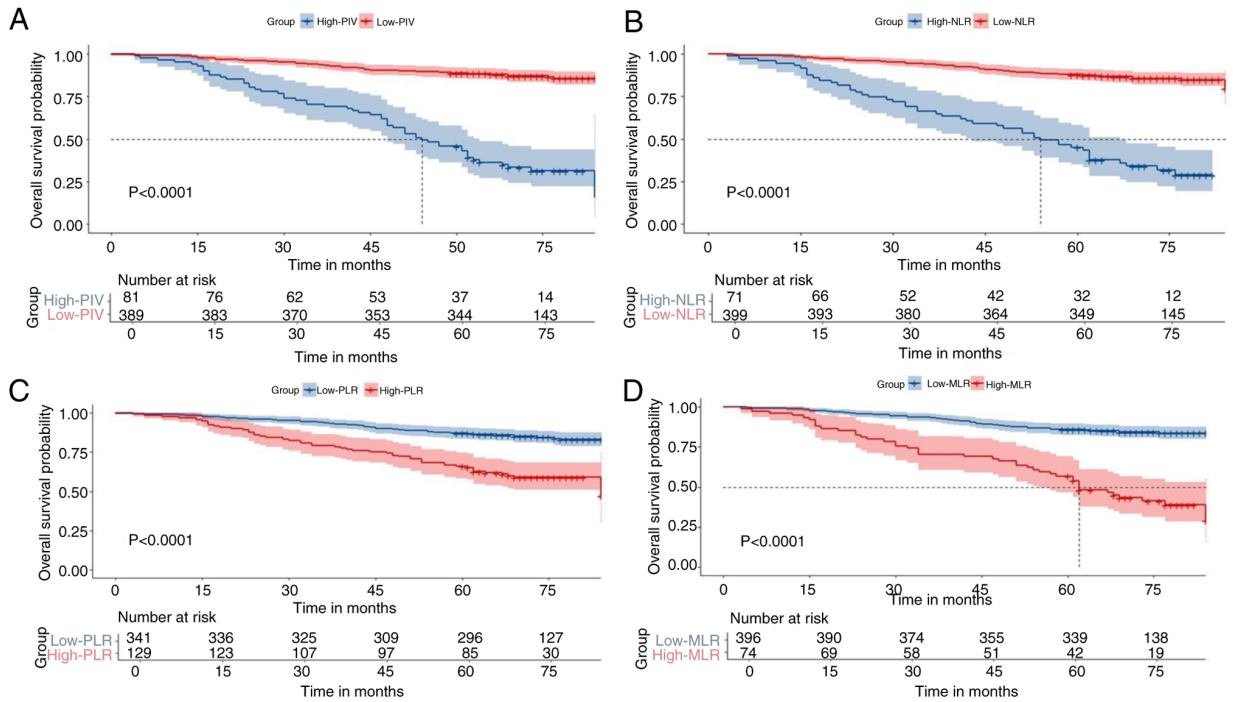

Figure 2. Survival analysis of different indicators of peripheral blood inflammation. Survival curves for (A) PIV, (B) NLR, (C) PLR and (D) MLR. PIV, pan-immune-inflammatory value; NLR, neutrophil/lymphocyte ratio; MLR, monocyte/lymphocyte ratio; PLR, platelet count-to-lymphocyte count ratio.

(95% CI, 0.746-0.832). Adding an inflammation index to the conventional model improved the prediction of 5-year OS. The calibration curves of the 1-, 3- and 5-year survival rates of the nomogram prediction model based on inflammation indicators

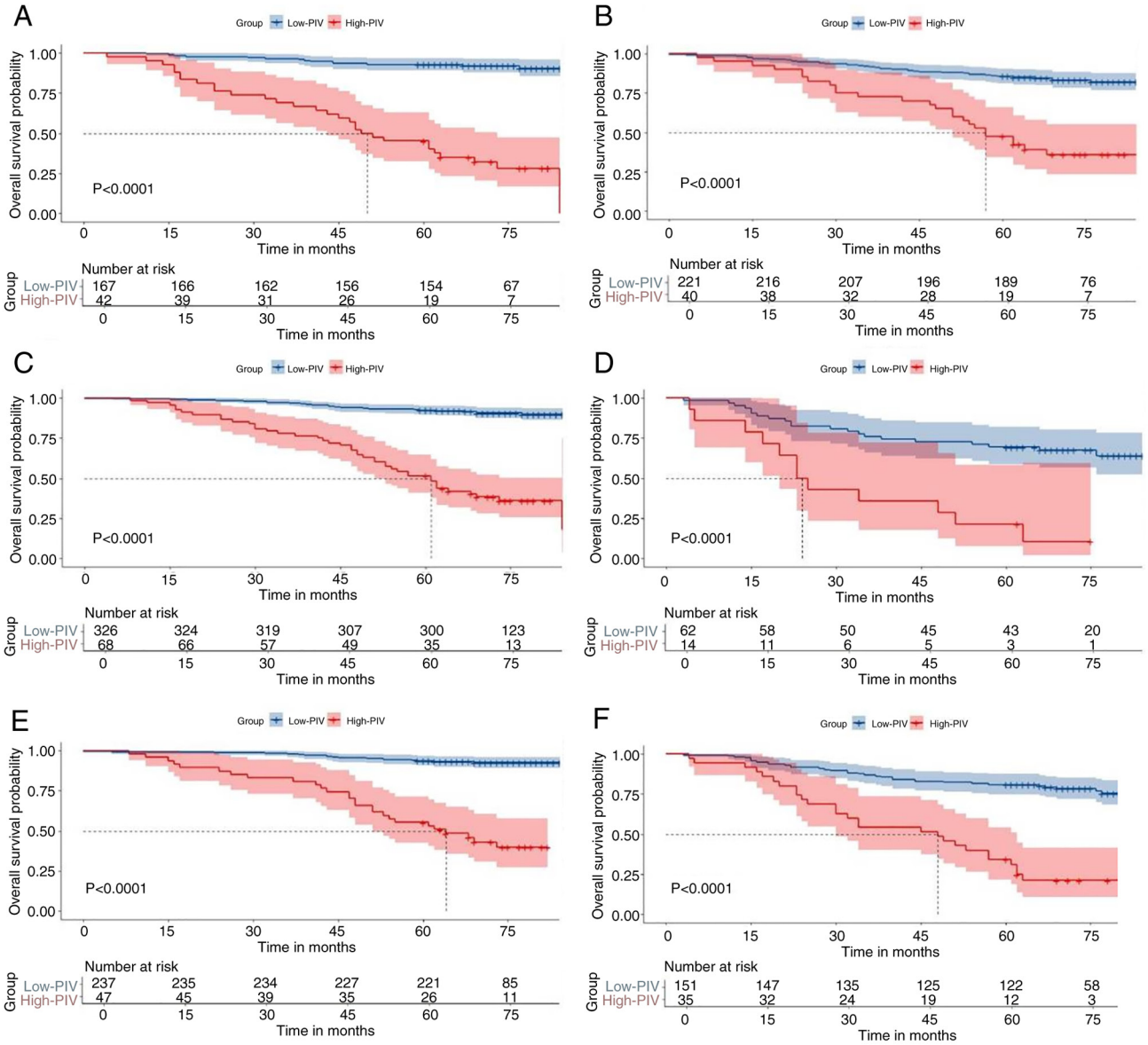

Figure 3. Kaplan-Meier method to plot survival endpoints in different PIV groups (low vs. high). Survival curve in the (A) non-senior and (B) senior groups, in the (C) N0/1 and (D) N2 groups, and in the (E) stage I/II and (F) stage III groups. PIV, pan-immune-inflammatory value.

were close to the ideal curve, suggesting that the predicted survival probability of the whole cohort had a good calibration relationship with the actual survival probability (Fig. 6). The ROC analysis showed that the area under the curve (AUC) values of the nomogram model for predicting the 1-, 3- and 5-year OS were 0.823, 0.845 and 0.845, respectively, demonstrating that the model had a much better predictive ability than TNM staging or PIV alone (Fig. S2; Table III).

Discussion

CRC is a gastrointestinal tumor that is becoming increasingly prevalent worldwide. Determining the prognosis of patients with CRC remains a significant challenge, and the identification of optimal prognostic markers requires further investigation and validation. To the best of our knowledge, the present study is the first to discuss the impact of PIV and survival status in patients with non-metastatic CRC. This retrospective study collected baseline blood parameters and clinical information from 470 patients and analyzed them to examine the association between PIV and clinical prognosis. In the present study, significant differences were found in key clinical characteristics, such as the degree of differentiation and nerve invasion, between the High-PIV and Low-PIV groups. These variables may themselves be independent determinants of disease prognosis, suggesting that the between-group differences may have had a confounding effect on the predictive ability of PIV as a prognostic indicator. To minimize this effect, adjustments for these potentially confounding variables were made in multivariate analyses, which showed that PIV still had significant independent predictive value. The results of the survival analysis indicated that patients in the High-PIV group were significantly associated with a poor prognosis. Furthermore, the nomogram model was constructed based on multivariate Cox regression analysis to predict the prognosis of patients with CRC. Subsequently, a comprehensive assessment was

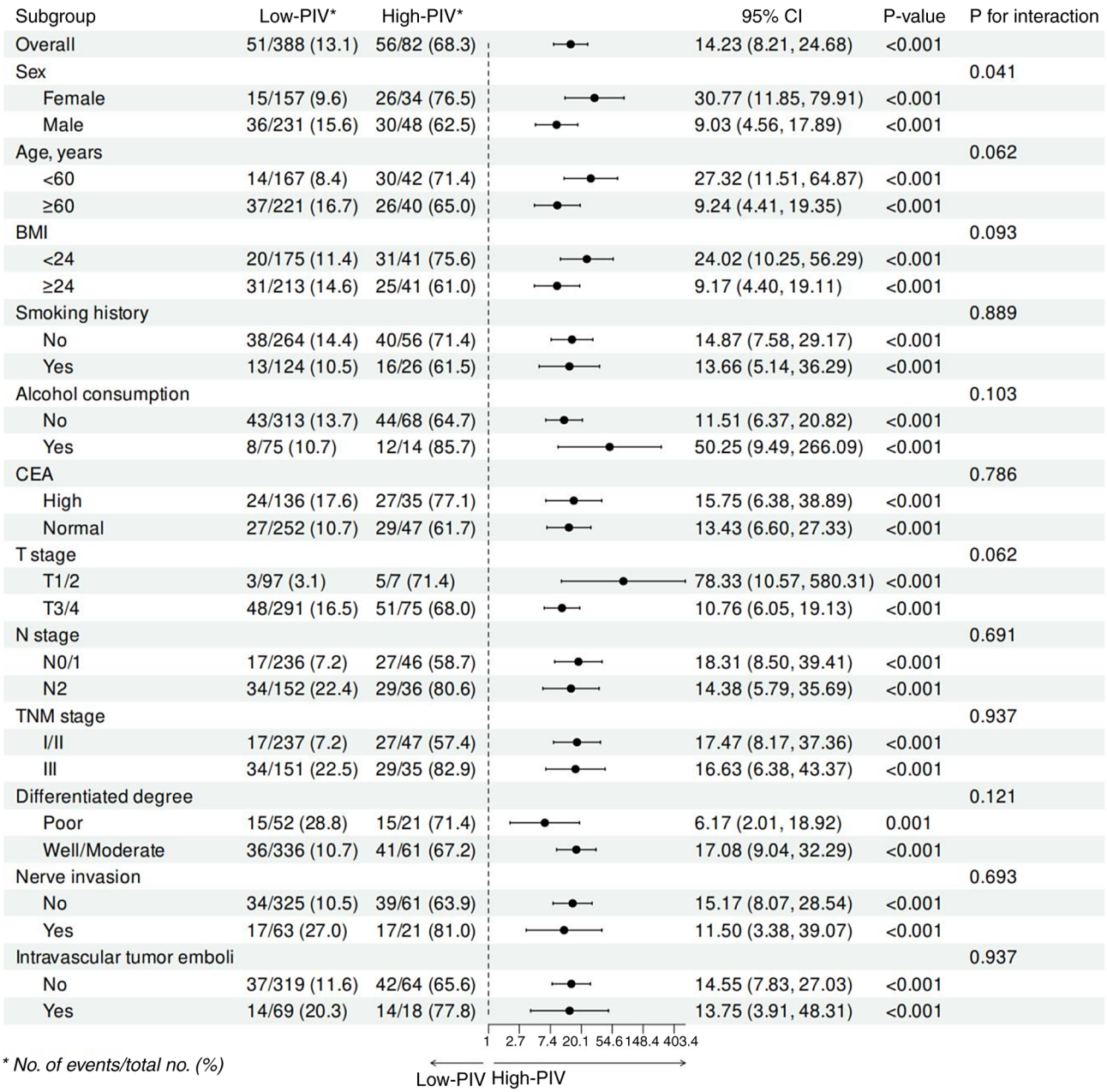

Figure 4. Subgroup analyses of the association between the PIV and overall survival risk. Subgroup analysis adjusted for age, sex, BMI, smoking history and alcohol consumption, CEA, T stage, N stage, TNM stage, differentiated degree, nerve invasion and intravascular tumor emboli. BMI, body mass index; CEA, carcinoembryonic antigen; TNM, Tumor-Node-Metastasis; PIV, pan-immune-inflammatory value.

conducted on the predictive performance of the nomogram model, which demonstrated robust discriminatory and predictive capabilities. This indicates that PIV may serve as a potential marker for identifying patients with potential adverse clinical outcomes.

The significant association observed between PIV and survival outcomes may stem from the intricate interplay between inflammation and cancer progression. Inflammation has an important role in the development and progression of CRC (23). As a comprehensive biomarker, PIV contains various components of the systemic inflammatory response, including neutrophils, monocytes, platelets and lymphocytes.

Neutrophils exhibit a dual role in tumor biology (24). The regulation of the tumor microenvironment and the production of cytokines, chemokines and growth factors by neutrophils can facilitate the removal of tumor cells under certain conditions (25). However, this same process can also directly promote tumor progression, metastasis and angiogenesis (26). Additionally, neutrophils are capable of producing interleukins (ILs) and other tumor-associated factors that are involved in tumor invasion and metastasis (27). For instance, IL-1β is involved in cell proliferation, differentiation and apoptosis, while also promoting the production of angiogenic factors by stromal cells within the tumor microenvironment (TME). These factors induce tumor angiogenesis, endothelial cell activation and the development of immunosuppressive cells. Secondly, some neutrophils also promote epithelial-mesenchymal transition through the TGF-β/Smad signaling pathway (28). This is also considered to be a key factor in tumor development and progression (29).

Table II. One-way multifactor regression analyses were performed using the Cox proportional risk model.

	Univariate analysis		Multivariate analysis	
Characteristics	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (≥48 vs. <48 years)	1.25 (0.78-2.00)	0.354	-	-
Sex (male vs. female)	0.74 (0.46-1.20)	0.221	-	-
BMI (<18.5 vs. ≥18.5 kg/m^2)	0.85 (0.53-1.34)	0.480	-	-
Smoking history (yes vs. no)	1.33 (0.78-2.27)	0.290	-	-
Alcohol consumption (yes vs. no)	0.93 (0.52-1.67)	0.811	-	-
T stage (T3/4 vs. T1/2)	3.65 (1.58-8.43)	<0.001	1.14 (0.46-2.86)	0.775
N stage (N2 vs. N0/1)	3.13 (1.92-5.11)	<0.001	2.00 (1.04-3.84)	0.039
TNM stage (I/II vs. III)	1.96 (1.23-3.12)	0.005	1.15 (0.63-2.10)	0.644
Differentiated degree (well/moderate vs. poor)	3.24 (1.98-5.29)	<0.001	1.98 (1.16-3.38)	0.012
Nerve invasion (yes vs. no)	3.20 (1.98-5.18)	<0.001	1.66 (0.95-2.90)	0.076
Intravascular tumor emboli (yes vs. no)	1.92 (1.16-3.20)	0.012	1.14 (0.63-2.05)	0.671
CEA (high vs. normal)	1.66 (1.04-2.64)	0.033	1.45 (0.85-2.49)	0.175
NLR group (≥ 3.08 vs. <3.08)	8.39 (5.24-13.43)	<0.001	4.00 (2.19-7.29)	<0.001
PLR group (≥166.48 vs. <166.48)	3.19 (2.00-5.06)	<0.001	1.10 (0.63-1.93)	0.745
MLR group (≥0.38 vs. <0.38)	5.68 (3.55-9.08)	<0.001	1.02 (0.48-2.17)	0.955
PIV group (≥426.86 vs. <426.86)	8.74 (5.47-13.97)	<0.001	4.12 (2.04-8.32)	<0.001

All variables were converted to categorical variables. HR, hazard ratio; CI, confidence interval; BMI, body mass index; CEA, carcinoembryonic antigen; TNM, Tumor-Node-Metastasis; PIV, pan-immune-inflammatory value; NLR, neutrophil/lymphocyte ratio; MLR, monocyte/lymphocyte ratio; PLR, platelet count-to-lymphocyte count ratio.

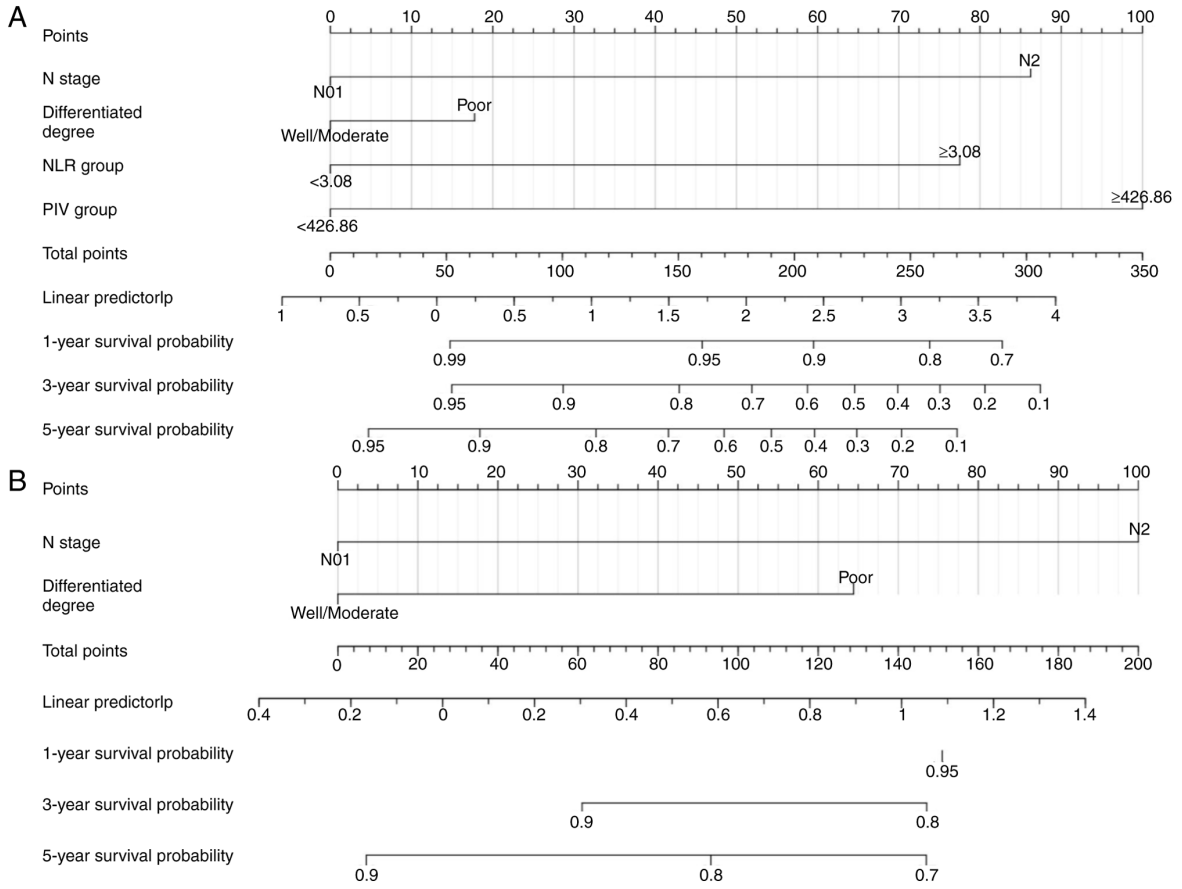

Figure 5. Nomogram to predict 1-, 3- and 5-year overall survival in patients with colorectal cancer. (A) Conventional nomogram based on inflammatory markers and important clinical factors. (B) Conventional nomogram with significant clinical factors. NLR, neutrophil/lymphocyte ratio; PIV, pan-immune-inflammatory value; predictorlp, linear predictor derived from the statistical model.

Table III. Evaluation of predictive models for OS.

AUC	Nomogram	TNM	PIV
1-year OS	0.823	0.582	0.772
3-year OS	0.845	0.753	0.761
5-year OS	0.845	0.580	0.751

AUC, area under the curve; OS, overall survival; TNM, Tumor-Node-Metastasis; PIV, pan-immune-inflammatory value.

Monocytes are the origin of tumor-associated macrophages, dendritic cells and myeloid-derived suppressor cells, which control the immune response and cancer cell biology in the TME (30). Monocytes contribute to both cancer development and progression, with various subpopulations exhibiting functions such as phagocytosis, secretion of tumor-killing mediators, promotion of angiogenesis, remodeling of the extracellular matrix, recruitment of lymphocytes, and differentiation into tumor-associated macrophages and dendritic cells (31,32). Monocytes can generate antitumor responses and activate antigen-presenting cells to exert antitumor effects (33).

Several mechanisms have been identified whereby platelets are involved in the development and progression of cancer (34). It seems that platelet activation is a crucial factor in the growth of tumors and the successful establishment of metastatic colonies. The activation of platelets releases a multitude of factors that regulate the tumor microenvironment, including vascular endothelial growth factor and fibroblast growth factor, lipids and extracellular vesicles rich in genetic material (35). These substances induce phenotypic alterations in target cells, including immune, stromal and tumor cells, thereby facilitating the formation of cancerous lesions and metastases (36). There is a significant degree of interaction between platelets and cancer cells during the progression of cancer. Activation of platelets results in the modulation of the migration of hematopoietic and immune cells towards the tumor site, thereby exacerbating cancer-associated inflammation (37). Furthermore, the activation of platelets enables cancer cells to utilize them as a physical barrier against blood shear forces and natural killer cells (38). Evidence suggests that inhibiting platelet function may impede tumor growth, thereby enhancing overall patient survival (39-41).

Lymphocytes associated with the inflammatory response are involved in the formation of the association between tumor cells and the surrounding microenvironment. Lymphocytes also serve a dual function in the progression of cancer (42). On the one hand, lymphocytes can induce apoptosis in tumor cells by triggering an antitumor response within the immune system (43). On the other hand, activated lymphocytes inhibit the proliferation of $CD4^+CD25^-$ and $CD8^+CD25^+$ T cells, leading to immunosuppression and thus inhibiting the immune attack on tumor cells (44,45).

As a peripheral blood cell-based biomarker, the PIV integrates different peripheral blood immune cell subsets. A meta-analysis of the prognostic value of PIV in patients with CRC, comprising 1,879 subjects across six studies, revealed that patients in the high baseline PIV group exhibited inferior OS rates and progression-free survival (PFS) rates compared with those in the low baseline PIV group (14). Furthermore, in a retrospective study by Zhao *et al* (46), PIV was found to be significantly different in patients with different pathological N and TNM stages ($P<0.05$), which may aid in assessing tumor staging based on preoperative PIV. The lack of significant prognostic value for T staging in the present dataset may be attributed to the relatively homogenous distribution of T staging among patients, with a predominance of T3 cases. This imbalance could reduce the ability to detect meaningful differences. Additionally, the sample size in early (T1-T2) and advanced (T4) subgroups may have been insufficient to achieve statistical power. Future studies with larger and more balanced cohorts are needed to confirm the prognostic role of T staging in non-metastatic CRC. Notably, PIV also has a potential role in monitoring disease progression in patients with metastatic CRC receiving first-line chemotherapy (47). One study found that PIV not only serves as an independent prognostic factor for OS, but that it can also predict the occurrence of postoperative complications in CRC (48). The current study aligns with previous findings that the High-PIV group exhibited a higher tumor stage and poorer survival outcomes compared with the Low-PIV group.

The present study has several strengths. First, it provides a novel predictive model based on the PIV, which integrates multiple inflammatory components into a single biomarker. Compared with traditional tumor markers, the PIV offers a more comprehensive assessment of tumor-host interactions. Second, the study included a relatively large cohort of patients with non-metastatic CRC, ensuring robust statistical power and reliable conclusions. Third, the nomogram model demonstrated excellent predictive performance, as indicated by its C-index and AUC values. Compared with prior research (49), which primarily focused on individual inflammatory markers such as NLR, PLR and MLR, the present study highlights the superior predictive value of PIV, a composite biomarker. The significant associations between the risk scores of the nomogram model and the clinicopathological factors, such as differentiation and nerve invasion, highlight its clinical value. By reflecting established prognostic variables, the model demonstrates its applicability in real-world clinical settings. Future studies should validate its use across diverse cohorts to ensure generalizability. The association of the PIV with prognosis has been reported in other cancer types, including lung (49), breast (50), and esophageal (15) cancer, further supporting its potential utility in oncology. Future research should validate the nomogram model using larger, multicenter cohorts to improve generalizability. Investigating the biological mechanisms underlying the prognostic value of the PIV, including its role in immune escape and metastasis, will provide deeper insights. Additionally, dynamic monitoring of the PIV during treatment may enhance its applicability in clinical practice.

The present study does, however, have a few limitations. Firstly, this is a single-center, retrospective study with a small sample size and there may be selective bias. While the present study included 470 patients, which exceeds the required sample size based on statistical power calculations, there are limitations to consider. As a single-center, retrospective study, the generalizability of the findings may be constrained by the homogeneity of the study population. The patient cohort represents a specific

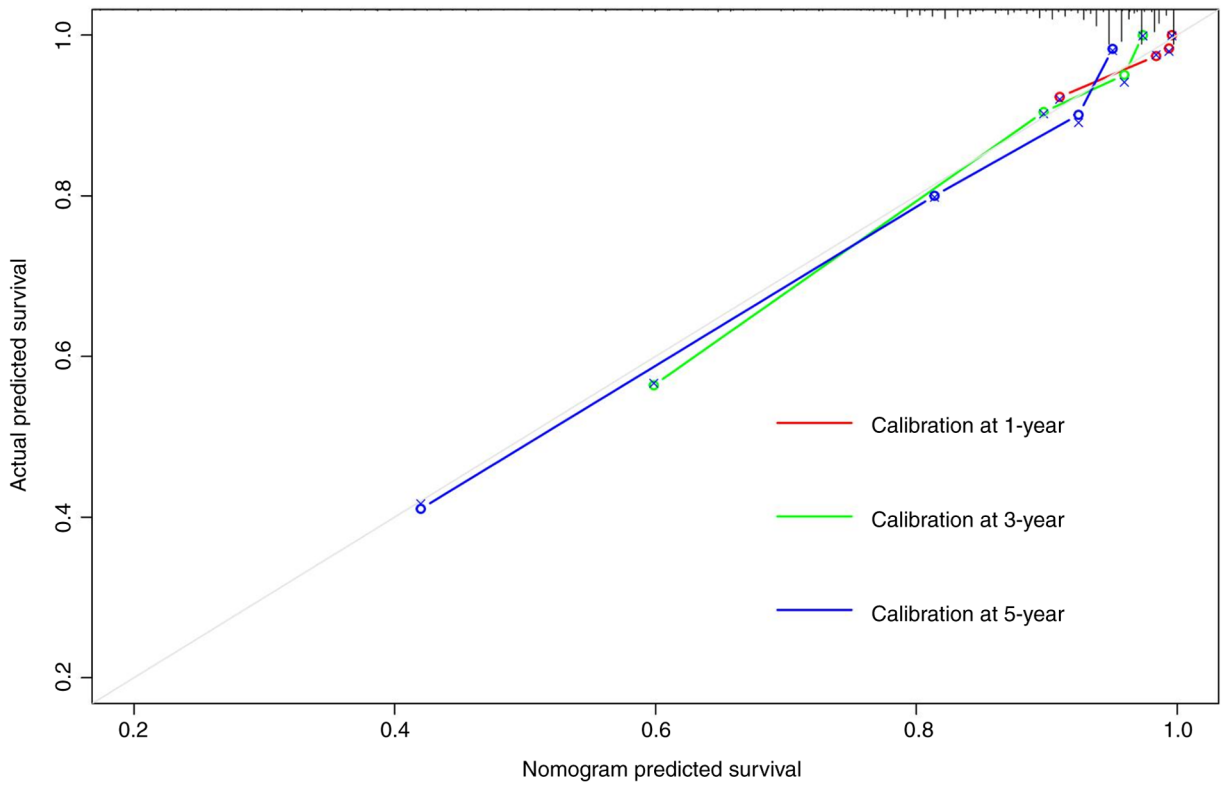

Figure 6. Calibration curve of nomogram for predicting 1-, 3- and 5-year overall survival.

geographic and institutional context, which might limit the applicability of these results to broader, more diverse populations. Moreover, although the sample size was sufficient to meet statistical requirements, a larger, multicenter cohort would provide greater external validation and strengthen the reliability of the findings. Future prospective studies involving multiple centers and larger sample sizes are warranted to confirm the prognostic value of PIV in non-metastatic CRC and further validate the constructed nomogram model. These efforts would not only enhance the robustness of the findings, but also facilitate the development of widely applicable, individualized prognostic tools to guide clinical decision-making. Prospective studies with larger sample sizes are needed to validate the current results. Second, the patients were only from one institution, and external validation was not possible. It would have been better if external validation could have been performed to verify the general applicability of the present findings. Thirdly, this study only analyzed patients with non-metastatic CRC and could not be replicated in a wider population. This limits the generalizability of the findings to metastatic CRC and other tumor types. Therefore, there is an urgent need for future studies to conduct multicenter, large-scale prospective studies supplemented by external validation to strongly improve the reliability and scientific validity of the findings. In future studies, the present authors plan to incorporate molecular biomarkers, expand the sample size, and validate the performance of the model at longer follow-up times and in a broader population. Fourthly, the present study combined the N0 and N1 groups into one category for the purpose of statistical analysis. We acknowledge that N stage is a critical factor influencing the prognosis of CRC, and that N0 and N1 stages usually have distinct prognostic implications. However, due to the limited sample size in the cohort, separating these two stages for analysis could have resulted in insufficient statistical power, particularly in subgroup analyses. This could have introduced additional variability and uncertainty into the results. Preliminary analyses indicated that the survival outcomes of the patients in the N0 and N1 groups were relatively similar within the cohort. This observation led to the merging of these groups to enhance the robustness of the statistical analyses and to maintain a meaningful comparison between groups. Additionally, this grouping strategy allowed better control for potential confounding factors in the models. Despite these considerations, we recognize that this grouping strategy could obscure finer differences between the N0 and N1 stages, which may affect the precision of the conclusions. The lack of a sufficient sample size to analyze these groups individually is a limitation of the current study. Future studies with larger sample sizes should explore the individual prognostic significance of N0 and N1 stages in greater detail to confirm whether the observed similarities in survival outcomes are generalizable. In addition, the integration of PIV into routine clinical practice still requires further clinical validation and standardization work to ensure its reliable application in different diseases and populations. Nevertheless, the present study further demonstrated that PIV can be an independent prognostic factor for the prognosis of patients with CRC. Since elevated preoperative PIV is a poor prognostic factor and is independently associated with an increased risk of a poor prognosis, identifying the inflammatory status of patients preoperatively can help predict their survival and provide timely prophylaxis to patients. In addition, it may help healthcare professionals make informed treatment choices and follow-up strategies.

In conclusion, in the present study, the PIV was found to be an independent predictor of prognosis in patients with non-metastatic

colorectal. In addition, a new nomogram model was developed, which showed good calibration and the ability to distinguish outcomes. Therefore, the model can be used as an effective tool to identify patients at high risk for adverse outcomes.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

KJL and ZLZ contributed to study concept and design. ZYZ collected clinical data. YC, YPP, ZMW, KW and XYZ contributed to analyze the data. KJL contributed to the preparation of the manuscript. ZLZ provided critical feedback on methods and supervised the study. ZLZ and YC confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The guidelines of the Declaration of Helsinki were followed during the investigation. The study was approved by the Ethics Committee of the Affiliated Cancer Hospital, Xinjiang Medical University (Urumqi, China; approval no. K-2024056). All methods were performed in accordance with relevant guidelines and regulations. Written informed consent was obtained from each patient or their guardian.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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