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Original Article

Prognostic value of systemic inflammatory and nutritional markers in patients with resectable colon cancer: a retrospective observational study

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Abstract: Background: Colorectal cancer remains a leading cause of global cancer morbidity. While pathological staging is a cornerstone of prognosis, host-related factors, including systemic inflammatory response and nutritional status, are increasingly recognized as critical determinants of outcomes. Methods: This single-center retrospective study investigated the prognostic value of preoperative hematologic markers - neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index, C-reactive protein-to-albumin ratio, prognostic nutritional index (PNI), and the Controlling Nutritional Status score - in 113 patients who underwent radical colectomy between December 2020 and June 2022. The primary and secondary endpoints were 3-year disease-free survival (DFS) and overall survival (OS), respectively. Results: The cohort demonstrated 3-year DFS and OS rates of 74.1% and 77.0%, respectively, and an overall recurrence rate of 23.9% within the follow-up period. Multivariate Cox analysis identified a high PNI (≥ 43.62) as an independent protective factor for 3-year DFS (hazard ratio [HR] = 0.057, 95% confidence interval [CI]: 0.016-0.125, $P < 0.01$), and a high PLR (≥ 169.27) as an independent risk factor (HR = 7.910, 95% CI: 2.048-30.558, $P < 0.01$). Conclusion: Preoperative PNI and PLR are readily accessible, independent prognostic biomarkers for patients with resectable colon cancer. They augment traditional Tumor, Node, Metastasis staging by reflecting the critical balance between pro-tumor inflammation and host immunonutritional status within the tumor microenvironment.

Keywords: Colon cancer, inflammatory markers, nutritional markers, prognosis, retrospective study, disease-free survival

Introduction

Colorectal cancer is one of the most prevalent gastrointestinal malignancies worldwide, with persistently high incidence and mortality rates posing a major challenge to global health systems [1, 2]. While advancements in surgical techniques, perioperative management, and comprehensive treatment strategies have significantly improved overall outcomes for colon cancer, recurrence and metastasis following surgery remain the leading causes of treatment failure and patient mortality [3]. Clinical experience demonstrates that even among patients with similar clinicopathological features - including tumor stage and differentiation grade- long-term survival rates can vary substantially [4, 5]. This observation suggests the presence of additional, significant biological factors that influence disease progression and patient outcomes, factors not fully captured by current standard oncological assessment systems.

The Tumor, Node, Metastasis (TNM) classification system, established by the American Joint Committee on Cancer, remains the cornerstone for treatment planning and prognostic assessment in colon cancer [6]. This system

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stages tumors based on the depth of local invasion, regional lymph node involvement, and the presence of distant metastasis, offering considerable objectivity and clinical utility [7]. However, TNM staging primarily provides an anatomical level description and fails to adequately capture the complex biology of tumor-host interactions, particularly the host's systemic inflammatory and immune status [8]. Consequently, there is a need to identify readily accessible biological prognostic factors that can effectively complement the TNM system, thereby improving risk stratification and enabling more personalized treatment strategies.

Over the past few years, an increasing amount of evidence has demonstrated that the onset and subsequent development of malignancy is not a solitary phenomenon, but is instead strongly interconnected with the systemic milieu of the host [9]. Among these factors, systemic inflammatory response and nutritional status have been widely discussed as two fundamental host-related determinants [10]. On the one hand, persistent systemic inflammation is regarded as the seventh hallmark of cancer, which may facilitate tumor cell growth, angiogenesis, and suppression of anti-tumor immune responses, thereby providing a conducive microenvironment for tumor progression and metastasis [11, 12]. Tumor-associated macrophages, neutrophils, and lymphocytes are key immune and inflammatory cells implicated in the progression and unfavorable survival outcomes of colorectal cancer [13, 14]. Based on this understanding, routine blood count parameters have been transformed into easily calculable biomarkers, such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and the systemic immune-inflammation index (SII, which integrates neutrophil, platelet, and lymphocyte counts). These biomarkers have been proposed as prognostic tools in a variety of studies [15, 16].

Conversely, the nutritional status of cancer patients cannot be overlooked. Malignancy itself is a highly catabolic condition, which in most cases leads to malnutrition and even cachexia in patients, characterized by the loss of skeletal muscle mass (sarcopenia) and overall weight loss [17]. Worsening nutritional status is not only associated with a deterioration in the patient's physical condition and tolerance to treatment, but may also have a direct negative impact on immune function, which consequently influences the efficacy of antitumor treatment and overall survival (OS) [18]. Metrics such as the prognostic nutritional index (PNI) and the controlling nutritional status (CONUT) score, which incorporate albumin and lymphocyte measurements, provide a multidimensional assessment of nutritional and immune status. These integrated parameters have demonstrated significant predictive value for outcomes in a number of solid tumors [19, 20].

The above inflammatory and nutritional indicators have shown promising clinical relevance; however, several aspects warrant further investigation. First, the majority of the studies have tended to analyze these indicators in a single-dimensional manner (focusing on either inflammation or nutrition), rather than integrating both closely related host factors into a unified framework for systematic comparison and comprehensive evaluation. Therefore, it is difficult to determine which indicators possess the most central predictive value [21]. Second, when selecting indicators - including emerging and theoretically more comprehensive ones (like SII) and traditional ones (like NLR) - their comparative advantages and disadvantages must be confirmed within a homogenous patient cohort [22]. Moreover, it is essential to determine whether these indicators can be regarded as independent prognostic predictors, not influenced by conventional factors like TNM staging, to facilitate their clinical translation.

The study was thus a retrospective observational study aiming to examine the prognostic value of known preoperative markers, including systemic inflammation markers (NLR, PLR, SII) and nutritional status indicators (PNI, CONUT), in patients who underwent radical colectomy for colon cancer. The objective was to evaluate the association of these indicators with 3-year disease-free survival (DFS) and OS, and to identify any independent prognostic predictors among them.

The exploration of this study involved assessing both inflammatory and nutritional status on the same analytical platform to evaluate them

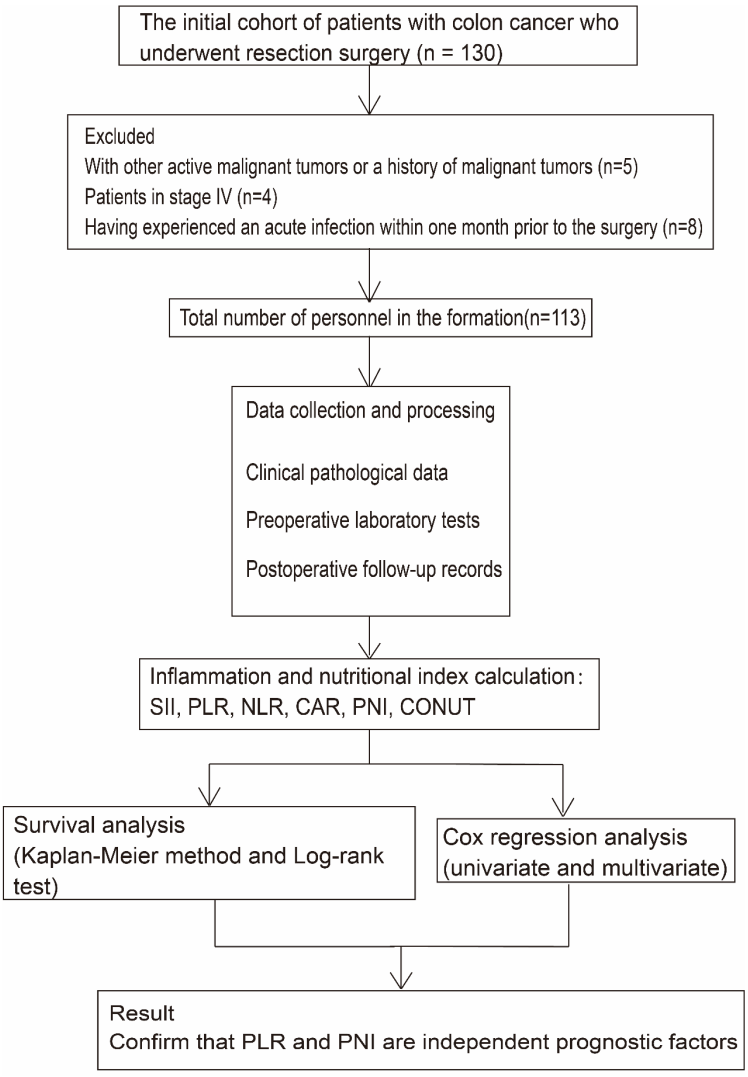


Figure 1. Study flowchart. Note: NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; CAR, C-reactive protein-to-albumin ratio; PNI, prognostic nutritional index; CONUT, controlling nutritional status.

jointly rather than separately. A combined analysis and systematic comparison of these two categories was conducted in a carefully selective, relatively homogeneous group of patients undergoing radical surgery, in order to examine their relative prognostic value and potential correlation. We hypothesized that the SII, which combines multidimensional information from neutrophils, platelets, and lymphocytes, along with the PNI reflecting nutritional reserves and immune function, may provide richer prognostic information compared to traditional single indicators. Through this comprehensive assessment, we aimed to investigate a more feasible methodology for risk stratification after colon cancer surgery based on conventional low-cost tests, which could offer a potential reference for identifying high-risk patients, optimizing adjuvant treatment decisions, and personalizing follow-up strategies.

Research subjects and methods

Research subjects

This single-center retrospective study initially identified potential subjects from our hospital's database as consecutive patients who underwent radical colon cancer surgery between December 2020 and June 2022. The final study cohort was determined by applying specific inclusion and exclusion criteria to this initial list, as detailed in **Figure 1**.

Inclusion and exclusion criteria

Inclusion Criteria [23]: (1) Postoperative pathological examination confirmed primary colon adenocarcinoma; (2) Underwent radical resection (R0) for colon cancer; (3) Age between 18 and 80 years; (4) Had complete preoperative clinical information and postoperative follow-up data.

Exclusion criteria [24]: (1) Presence of other active malignancies-defined as malignancies at any other site receiving active treatment (surgery, chemotherapy, radiotherapy, targeted or immunotherapy) or under follow-up surveillance without meeting clinical criteria for cure (except basal-cell carcinoma of the skin or carcinoma in situ of the cervix) - or a history of any other malignancy within 5 years prior to the diagnosis of the current colon cancer; (2) Preoperative identification of distant metasta-

ses (stage IV disease); (3) Complications directly leading to death within 90 days after surgery, including but not limited to: anastomotic leakage with septic shock, postoperative hemorrhage requiring secondary surgical intervention, severe cardiopulmonary complications (e.g., myocardial infarction, acute respiratory distress syndrome), refractory sepsis, or other perioperative deaths due to severe complications, which would preclude entry into the effective follow-up period; (4) Acute infection within 1 month before surgery (defined within 30 days preoperatively as any condition requiring systemic antibiotic, antiviral, or antifungal therapy, accompanied by clinical signs such as fever > 38°C, laboratory evidence including significantly elevated white blood cell count, procalcitonin or C-reactive protein (CRP), or imaging confirmation of active infection), major trauma, surgery, or known chronic inflammatory/autoimmune diseases that significantly affect inflammatory marker levels (e.g., rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, active tuberculosis, chronic active hepatitis). Disease activity was determined based on specialist diagnosis, ongoing use of immunosuppressants or biologics, or significant abnormalities in laboratory indicators (erythrocyte sedimentation rate, CRP, specific antibodies); (5) Incomplete clinical data or loss to follow-up.

Detection indicators

This study methodically evaluated six systemic inflammation and nutritional indices based on preoperative routine laboratory tests: (1) NLR [25]: Calculated as the absolute neutrophil count divided by the absolute lymphocyte count, reflecting the balance of systemic immune status. (2) PLR [26]: Calculated as the platelet count divided by the lymphocyte count; an elevated PLR suggests a pro-tumor inflammatory microenvironment. (3) SII [27]: Considered a more comprehensive measure of inflammation, calculated as (platelet count × neutrophil count)/lymphocyte count. (4) PNI [28]: Calculated as serum albumin level (g/L) + 5 × total lymphocyte count (× 10^9/L), reflecting nutritional status and immune competence. (5) CONUT [29]: A holistic screening tool for nutritional status. (6) C-reactive protein-to-albumin ratio (CAR) [30]: An inflammatory parameter calculated as serum CRP level divided by albumin level, reflecting both inflammatory activity and nutritional reserve depletion.

All indices were derived from raw laboratory data obtained from venous blood tests conducted within one week prior to surgery to ensure they accurately reflected the preoperative physiological state of the patients.

Observation indicators

(1) The main endpoint in this study was 3-year DFS, which was calculated from the date of surgery until the first reported incidence of tumor recurrence, metastatic progression, or mortality (radiologically or histologically verified). Event-free subjects on the cutoff date of analysis were censored at their final follow-up. The 3-year DFS rate was calculated as the percentage of patients who had not experienced the above events at 36 months postoperatively.

(2) Secondary endpoints were 3-year OS and early recurrence rate. 1) OS was measured over a 3-year period, defined as the time interval between surgery and death. The alive and lost to follow-up subjects were censored at their last known survival date. The 3-year OS rate was obtained as the percentage of patients who survived at 36 months of the postoperative period. 2) Early recurrence rate is categorical, namely, the percentage of patients in the entire study population who experienced an objectively documented local recurrence or distant metastasis within 24 months (2 years) following radical surgery. The index was applied to evaluate the effect of inflammation and nutritional status on short-term disease control.

These outcome measures were calculated retrospectively through imaging reports, pathology records, and the follow-up registration system from regular outpatient visits. All events were calculated on the basis of the time of original medical records.

Sample size calculation

The sample size for this study was estimated during the project design phase based on the generally accepted rule of thumb of “10 events per variable” for retrospective studies. This rule aims to ensure that subsequent multivariate Cox proportional hazards regression models

yield stable and reliable parameter estimates. The final multivariate model was planned to include approximately six major independent variables, analyzed simultaneously, encompassing markers of inflammation (SII, PLR), nutritional markers (PNI), and significant clinicopathological characteristics (TNM stage). According to this calculation, at least 6 × 10 = 60 events (i.e., recurrences or deaths) were required to stabilize the model. With reference to prior literature by Miri et al. [31], the probability of DFS events (recurrence or death) within 3 years following surgery is about 61% in patients undergoing radical colectomy for colon cancer. Based on this calculation, the theoretical minimum sample size of the present research was 60/0.61 ≈ 98 cases. The 113 patients who were ultimately incorporated in this study had met the theoretical sample size criteria, which guaranteed the validity and genuineness of the data.

Statistical methods

The following statistical procedures were performed. All statistical analyses were done using IBM SPSS Statistics (version 28.0; IBM Corporation, USA). Using the X-tile software (version 3.6.1), with the 3-year DFS period as the endpoint, the software's built-in algorithm was used to traverse all possible splitting points. The value that produced the smallest Log-rank test *p*-value was selected as the optimal critical value. Normality of continuous variables was assessed by the Shapiro-Wilk test. Normally distributed variables (e.g., age) are presented as mean ± standard deviation (SD) and were compared between groups using Student's *t* test. Non-normally distributed variables, including NLR, PLR, SII, CAR, PNI, and CONUT score, are presented as median, and comparisons between groups were performed using the Mann-Whitney U test. Categorical variables are described as frequencies and percentages, and intergroup comparisons were made using either the chi-square test or the Fisher's exact test, as appropriate based on the expected number of cells. The most important survival outcomes, which were OS and DFS, have been examined with the help of the Kaplan-Meier approach, and the survival curves of both groups were compared with the Log-rank test. A two-step regression method was used to assess the independent prognostic value of different indices. First, univariate Cox proportional hazards models was fitted. Subsequently, a multivariate analysis was conducted to include all the significant variables in the univariate analysis ($P < 0.05$). The last model gave modified hazard ratios and 95% confidence intervals. A significance level of $P < 0.05$ was used for all statistical tests.

Ethical statement

This study adhered to the ethical provisions of the Declaration of Helsinki. Ethical approval was provided by the Institutional Review Board of The Second Clinical Medical College of Yangtze University/Jingzhou Hospital Affiliated to Yangtze University. The board determined that, as a retrospective study utilizing fully de-identified data derived from routine clinical practice, the research posed minimal risk to participants and waived the requirement for individual informed consent. All collected data were kept strictly confidential and were not disclosed to any third party.

Results

Baseline information

The cohort of the study included 113 patients with colon cancer that had undergone radical resection. As summarized in **Table 1**, the population consisted of 66 (58.41%) men and 47 (41.59%) women, which is approximately 1.4:1. The average age was 65.15 ± 9.85 years with a range of 30 to 88.

According to the American Joint Committee on Cancer 8th edition classification, pathological staging identified 49 patients (43.36%) at stage II and 64 patients (56.64%) at stage III. In 70 cases (61.95%), the major location of the tumor was the left colon, and in 43 cases (38.05%), it was the right colon. Tumors were well-to-moderately differentiated in 90 patients (79.65%) and poorly differentiated in 23 patients (20.35%). The patients with neurovascular invasion were 32 (28.32%).

On the treatment side, 82 (72.57%) patients were treated through adjuvant chemotherapy guided by the guidelines following radical surgery, and the rest 31 (27.43%) patients underwent surgery alone.

Table 1. Patient baseline information

Characteristic		Total Cohort (n = 113)	Statistical Test
Age (years)		65.15 ± 9.85	Student's *t* test
Gender (n, %)	Male	66 (58.41)	Chi-square test
	Female	47 (41.59)	
Tumor site (n, %)	Left colon	70 (61.95)	Chi-square test
	Right colon	43 (38.05)	
TNM staging (n, %)	Phase II	49 (43.36)	Chi-square test
	Phase III	64 (56.64)	
BMI (kg/m^2)		23.44 ± 3.12	Student's *t* test
Tumor differentiation (n, %)	Well/moderately differentiated	90 (79.65)	Chi-square test
	Poorly differentiated	23 (20.35)	
Neurovascular invasion (n, %)	No	81 (71.68)	Chi-square test
	Yes	32 (28.32)	
Adjuvant chemotherapy (n, %)	No	31 (27.43)	Chi-square test
	Yes	82 (72.57)	

Note: BMI, body mass index; TNM, Tumor-Node-Metastasis.

Table 2. 3-year DFS rate outcomes

Outcome	Entire Cohort (n = 113)
Event-free (Censored)	84 (74.34)
DFS event	29 (25.66)

Note: DFS, disease-free survival.

Table 3. Secondary survival outcomes

Outcome	Entire Cohort (n = 113)
3-year overall survival	87 (76.99)
2-year recurrence-free rate	86 (76.11)

Primary and secondary outcomes

The total 3-year DFS rate was 74.34% (**Table 2**), and 29 patients recurred or died within the period of observation. The total survival rate of 3 years was 76.99% (**Table 3**), which means that 26 patients died. Interestingly, a closer examination of the early postoperative recurrence trends showed that 25.66% of the entire cohort had 2-year postoperative recurrence rates. This implies that over three-quarters (76.11%) of patients did not have disease recurrence, yet 27 patients had disease recurrence at this early phase, which represents a large proportion of total recurrent events.

Inflammatory and nutritional indices

Four systemic inflammatory indicators, as demonstrated in **Table 4**, had a heterogeneous distribution in the cohort, indicating that different patients had different levels of systemic inflammatory response. The average SII was 501.51 (interquartile range [IQR]: 335.00-735.80). The best cutoff value (548.41) based on prognosis, as identified by the X-tile software, was used to classify a total of 47 (41.59%) patients as the high SII group (≥ 548.41) and the other 66 (58.41%) as the low SII group. The median NLR was 2.58 (IQR: 1.21-7.10). With a cutoff of 2.65, 53 (46.90%) patients were classified into the high NLR group (≥ 2.65) and 60 (53.10%) patients into the low NLR group (< 2.65). The distributions of the PLR and CAR followed a comparable trend. The proportions of patients in the high PLR group (≥ 169.27) and the high CAR group (≥ 0.157) were 55.75% (N = 63) and 23.89% (N = 27), respectively.

Assessment of nutritional indicators (**Table 5**) showed that a considerable percentage of patients in this cohort are exposed to nutritional immune imbalance. When the optimal cutoff value of 43.62 was used to group them, the median PNI was 47.80 (IQR: 36.20-59.00), and 100 patients (88.50%) were in a low PNI state (< 43.62), indicating that their nutritional reserve and immune functioning were impaired. The median CONUT was 3 (range: 1-4). A score of ≥ 3 was considered to be moderate to severe malnutrition based on its inherent clinical grading criteria. Based on the optimal cutoff value of 2, among the patients with CONUT ≥ 2, 50 (44.25%) patients represented

Table 4. Distribution of systemic inflammatory indices

Parameter	Median (IQR)	Optimal Cutoff	Group [Number (%)]
NLR	2.58 (1.21-7.10)	2.65	Low NLR group: 60 (53.10)
			High NLR group: 53 (46.90)
PLR	158.68 (121.00-210.05)	169.27	Low PLR group: 50 (44.25)
			High PLR group: 63 (55.75)
SII	501.51 (335.00-735.80)	548.41	Low SII group: 66 (58.41)
			High SII group: 47 (41.59)
CAR	0.096 (0.040-0.182)	0.157	Low CAR group: 86 (76.11)
			High CAR group: 27 (23.89)

Note: NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; CAR, C-reactive protein/albumin ratio; IQR, interquartile range.

Table 5. Distribution of nutritional indices

Parameter	Median (IQR)	Optimal Cutoff	Group [Number (%)]
PNI	47.80 (36.20-59.00)	43.62	Low PNI group: 100 (88.50)
			High PNI group: 13 (11.50)
CONUT score	3.00 (1.00-4.00)	2	Low CONUT score group: 50 (44.25)
			High CONUT score group: 63 (55.75)

Note: PNI, prognostic nutritional index; CONUT, controlling nutritional status; IQR, interquartile range.

Table 6. Kaplan-Meier survival analysis and Log-rank test results for 3-year DFS

Parameter (Group)		Mean DFS (days) ± SE	df	*p*	95% CI		χ^2
					Lower	Upper	
SII	Low SII	1550.83 ± 41.10	1	< 0.001	1470.28	1631.38	15.595
	High SII	1105.32 ± 68.23	1		971.59	1239.05	
PNI	Low PIN	1562.52 ± 29.96	1	< 0.001	1503.80	1621.24	93.718
	High PIN	588.00 ± 74.736	1		441.52	734.48	
PLR	Low PLR	1526.30 ± 49.20	1	0.029	1429.87	1622.73	4.779
	High PLR	1252.70 ± 61.43	1		1132.30	1373.10	
NLR	Low NLR	1596.20 ± 34.68	1	< 0.001	1528.22	1664.18	21.361
	High NLR	1110.28 ± 65.66	1		981.58	1238.98	
CAR	Low CAR	1389.733 ± 53.92	1	0.844	1284.06	1495.41	0.039
	High CAR	1183.85 ± 36.13	1		1113.05	1254.66	
CONUT	Low CONUT	1345.50 ± 114.07	1	0.440	1121.92	1569.08	0.597
	High CONUT	1346.72 ± 43.78	1		1260.92	1432.52	

Note: CI, confidence interval; df, degrees of freedom; SE, standard error; DFS, disease-free survival; CONUT, controlling nutritional status; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; CAR, C-reactive protein-to-albumin ratio; PNI, prognostic nutritional index.

a clear nutritional risk. The rest 63 patients (55.75%) were either normal in their nutritional status or mildly malnourished (0-2 points).

Kaplan-Meier survival analysis and Log-rank test

Kaplan-Meier analysis (**Table 6**) showed significant differences in 3-year DFS between patients stratified by the optimal cutoff values of several indices. The DFS of the high SII group (≥ 548.41) was significantly lower than that of the low SII group (< 548.41) (χ^2 = 15.595, P < 0.001). The survival curve for the high SII group showed a steady decline compared to the more favorable curve of the low SII group. In the case of NLR stratification, the high (≥ 2.65) and the low (< 2.65) curves started to diverge signifi-

cantly after 12 months, and the difference continued to increase with time. This statistically significant difference in 3-year DFS was found (χ^2 = 21.361, P < 0.001). The low PNI group (< 43.62) exhibited significantly poorer DFS from the early postoperative phase, and this difference continued to widen during the follow-up (χ^2 = 93.718, P < 0.001). Conversely, the separation of the curves between high (≥ 2) and low (< 2) scores was observed in the CONUT groups, but it was not statistically significant (χ^2 = 0.597, P = 0.440). The corresponding survival curves are presented in **Figure 2**.

Cox regression analysis

Prior to constructing the multivariate Cox model, multicollinearity among all planned independent variables was assessed by calculating variance inflation factors (VIF). A VIF ≥ 5 is generally considered to indicate the presence of moderate or above collinearity, and VIF ≥ 10 indicates the presence of severe collinearity. VIFs for all included variables in this study are < 5, indicating that collinearity issues do not affect model stability. In order to further estimate the independent prognostic value of preoperative inflammatory and nutritional parameters for 3-year DFS, we used Cox proportional hazards regression modeling. The analytical process was carried out in two phases: an initial univariate screening step to identify possible prognostic variables, and a multivariate analysis to identify predictors that were independent of other clinicopathological variables. The results of the univariate analysis (**Table 7**) proved that 3-year DFS was significantly correlated with a number of inflammatory markers, nutritional indices, and conventional clinicopathological features. Patients who had high SII (≥ 548.41) had a higher risk of recurrence or death (hazard ratio [HR] = 4.481, 95% confidence interval [CI]: 1.983-10.128, P < 0.001). On the same note, a high NLR (≥ 2.65) had significant prognostic value (HR = 7.073, 95% CI: 2.693-18.576, P < 0.001). Increased PLR also had a strong correlation with decreased 3-year DFS (HR = 2.412, 95% CI: 1.068-5.448, P < 0.05). On the other hand, PNI became a powerful protective factor, and the low PNI (< 43.62) group showed a 15.335-fold risk of recurrence as compared to the high PNI (HR = 15.335, 95% CI: 6.983-33.674, P < 0.001). Among the traditional prognostic factors, the disease at stage III was significantly associated with increased risk of recurrence (HR = 2.727, 95% CI: 1.164-6.388, P = 0.021), and the neurovascular invasion also had a significant impact on the adverse outcomes (HR = 2.264, 95% CI: 1.088-4.712, P = 0.029).

Only two factors had independent prognostic value in the following multivariate Cox model that controlled all the significant univariate variables (P < 0.05), such as TNM stage, neurovascular invasion, SII, and NLR (**Table 8**). PNI retained a high predictive ability, and the low PNI group had a considerably high recurrence risk (adjusted HR = 13.585, 95% CI: 3.815-48.368, P < 0.001). Also, the PLR was found to be an independent prognostic factor, where the high PLR group had an adjusted HR of 2.412, with a 95% CI of 1.068-5.448 and a P-value of less than 0.001.

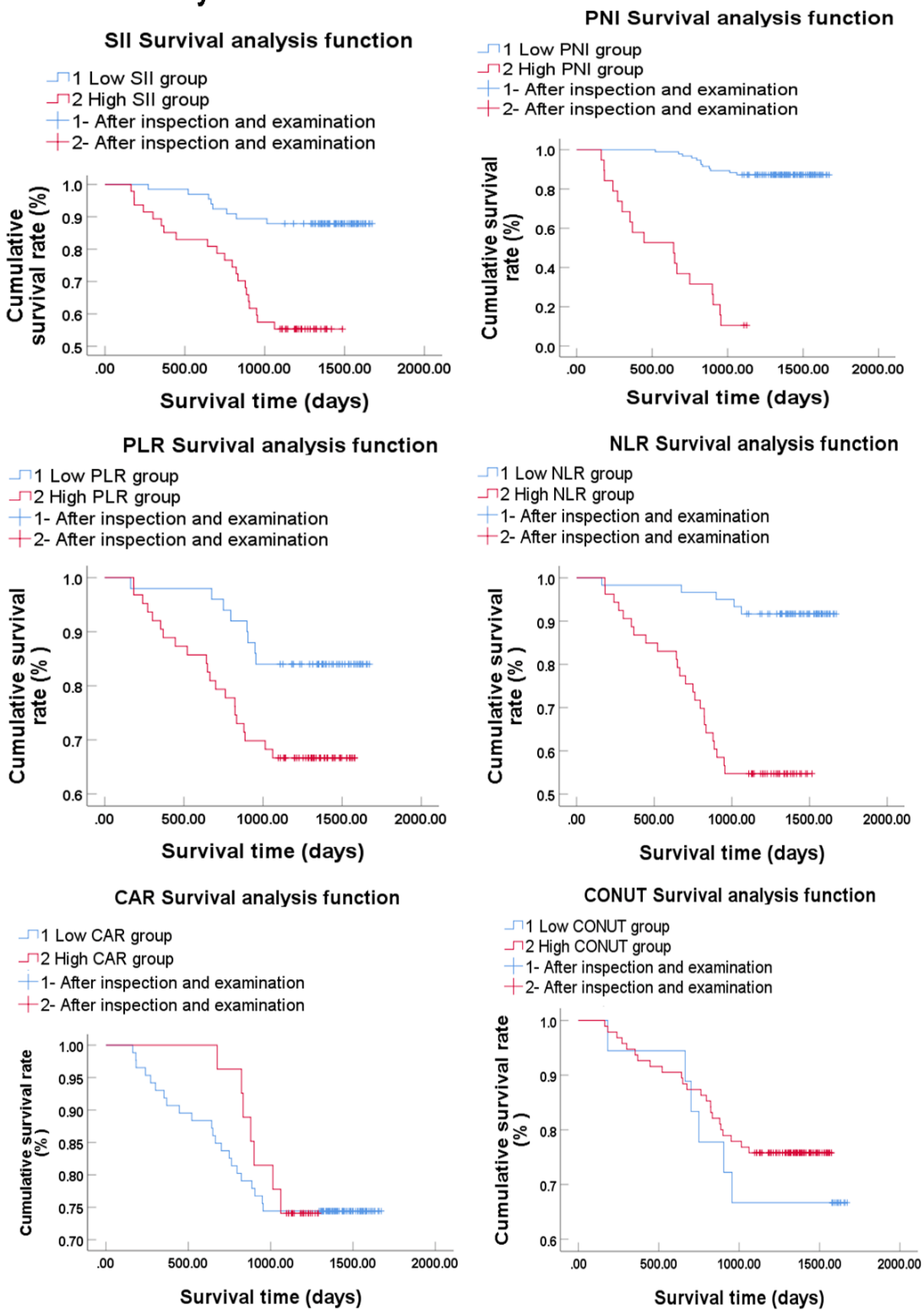
Joint risk stratification based on TNM staging, PLR, and PNI

After joint risk stratification of PLR and PNI combined with traditional TNM staging based on the cohort data of this study, the results of our study are as follows: The significant differences in 3-year DFS among subgroups of patients provide direct evidence of the added prognostic value of the aforementioned measures (**Table 9**). In a total of 64 stage III patients, the overall 3-year DFS rate was 68.75%. Further stratification by PLR and PNI revealed a clear prognostic gradient: The low-risk subgroup (n = 27), defined by low PLR (< 169.27) and high PNI (≥ 43.62), achieved a 3-year DFS rate of 92.59%. In contrast, the high-risk stage III subgroup (N = 5) with the characteristics of "high PLR (≥ 169.27) and low PNI (< 43.62)" had a significantly reduced survival rate to 60.00%. The difference in survival between the two groups was 32.59 percentage points. Similarly, in 49 patients with Stage II disease, the OS rate was 77.55%, but the low-risk subgroup (low PLR and high PNI, N = 25) among them had a survival rate of 92.00%, which was similar to that of the low-risk subgroup. In the high-risk subgroup (high PLR and low PNI, N = 3), survival was 66.67%, a difference of 25.33 percentage points.

Discussion

Colon cancer is a common gastrointestinal malignancy in the world, and despite the fact

A Survival analysis curve



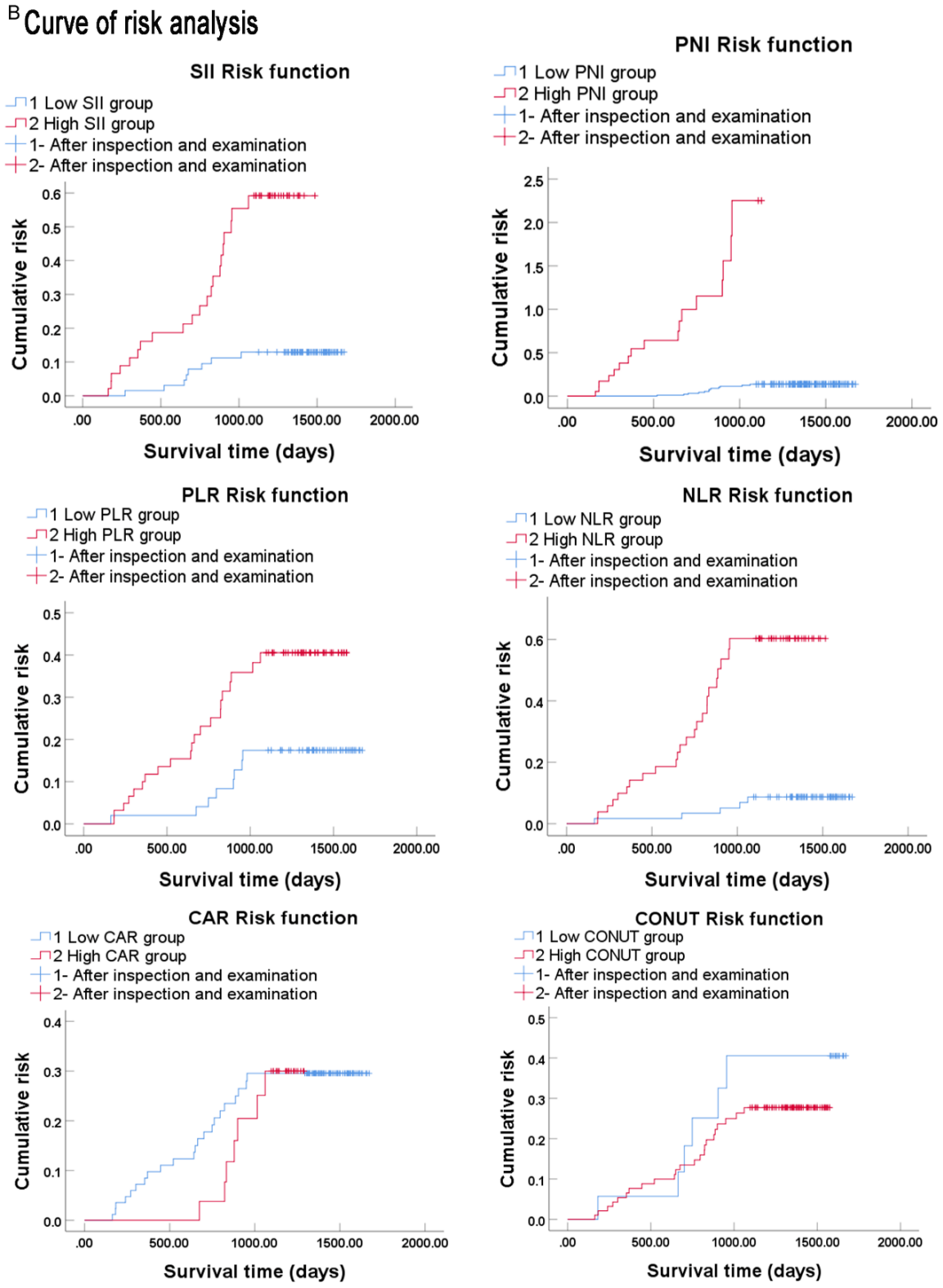


Figure 2. Kaplan-Meier survival curves and hazard function curves for the six prognostic indices. The figure shows the results of survival analysis and risk analysis of six biomarkers (SII, PNI, PLR, NLR, CAR, CONUT) in prognostic assessment, with a total of 12 sub-plots. A. Survival analysis curves: The horizontal axis is "Survival time (days)" and the vertical axis is "Cumulative survival rate (%)". Each subplot compares the cumulative survival probability over time between the low-value and the high-value groups (defined by the optimal cut-offs in **Table 6**). The curves

show that the cumulative survival rate of the low SII, low PNI, low PLR, low NLR, low CAR, and low CONUT groups was significantly higher than that of the corresponding high value groups, suggesting that low levels of these indicators are associated with better survival prognosis of patients. B. Risk analysis curves: The horizontal axis is also "Survival time (days)" and the vertical axis is "Cumulative risk". The subplots show the risk change trend of the different groups during the follow-up period. The high SII, low PNI, high PLR, high NLR, high CAR, and high CONUT groups show higher risk function values, corroborating the findings from the survival curves. Overall, this set of charts systematically compared the value of SII, PNI, PLR, NLR, CAR, and CONUT in predicting patient survival outcomes through Kaplan-Meier curves and hazard function curves, providing a visual basis for clinical prognosis evaluation.

Table 7. Univariate Cox regression analysis of factors associated with 3-year DFS (N = 113)

Parameter	B	Wald χ^2	df	*p*	HR [Exp (B)]	95% CI
Age	-0.035	3.291	1	0.070	0.965	0.929-1.003
BMI	0.058	1.014	1	0.314	1.060	0.947-1.186
Tumor site	-0.193	0.243	1	0.622	0.825	0.383-1.774
TNM staging	1.003	5.332	1	0.021	2.727	1.164-6.388
Tumor differentiation degree	0.019	0.002	1	0.967	1.019	0.415-2.503
Neurovascular invasion	0.817	4.778	1	0.029	2.264	1.088-4.712
Adjuvant chemotherapy	0.209	0.232	1	0.630	1.232	0.526-2.885
SII group (high vs. low)	1.500	12.995	1	0.000	4.481	1.983-10.128
PNI group (high vs. low)	2.730	46.276	1	0.000	15.335	6.983-33.674
PLR group (high vs. low)	0.880	4.483	1	0.034	2.412	1.068-5.448
NLR group (high vs. low)	1.956	15.765	1	0.000	7.073	2.693-18.576
CAR group (low vs. high)	-0.085	0.039	1	0.844	0.918	0.392-2.150
CONUT group (low vs. high)	-0.353	0.591	1	0.442	0.703	0.286-1.727

Note: HR, hazard ratio; CI, confidence interval; df, degrees of freedom; DFS, disease-free survival; BMI, body mass index; TNM, Tumor-Node-Metastasis; PNI, prognostic nutritional index; CONUT, controlling nutritional status; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; CAR, C-reactive protein-to-albumin ratio.

Table 8. Multivariate Cox regression analysis of independent prognostic factors for 3-year DFS (N = 113)

Parameter	B	Wald χ^2	df	*p*	Adjusted HR	95% CI
TNM staging	0.133	1.313	1	0.781	1.142	0.449-2.906
Neurovascular invasion	0.506	1.313	1	0.252	1.659	0.698-3.944
SII group	0.675	2.241	1	0.886	1.922	0.804-4.603
PNI group	2.609	16.214	1	0.000	13.585	3.815-48.368
PLR group	1.841	0.697	1	0.009	6.115	1.559-23.987
NLR group	0.462	0.670	1	0.413	1.588	0.525-4.804

Note: HR, hazard ratio; CI, confidence interval; df, degrees of freedom; DFS, disease-free survival; TNM, Tumor-Node-Metastasis classification; PNI, prognostic nutritional index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index.

Table 9. Risk stratification and 3-year DFS based on TNM staging combined with PLR/PNI

Risk stratification	Number of patients (N)	DFS events	3-year DFS rate (%)
All stage III patients	64	44	68.75
Stage III + low risk (low PLR and high PNI)	27	25	92.59
Stage III + high risk (high PLR and low PNI)	5	3	60.00
All stage II patients	49	38	77.55
Stage II + low risk (low PLR and high PNI)	25	23	92.00
Stage II + high risk (high PLR and low PNI)	3	2	66.67

Note: DFS, disease-free survival; TNM, Tumor-Node-Metastasis classification; PNI, prognostic nutritional index; PLR, platelet-to-lymphocyte ratio.

that the treatment of colon cancer has been enhanced over the years, postoperative recurrence and metastasis remain the leading causes of treatment failure [32]. Conventional prognostic evaluation is predominantly based on pathological staging; nevertheless, in clinical practice, there are often significant variations in clinical outcomes of patients with the same stage, indicating that, as well as the nature of the tumor itself, the systemic condition of the host is also a major determinant of disease progression [33]. Systemic inflammatory response, which is becoming an established feature of malignancy, has been demonstrated to support the development and progression of cancer by modulating tumor growth, invasion, angiogenesis, and immune evasion through a variety of pathways [34]. The microenvironment that is favorable to tumor growth and inhibits effective anti-tumor immune responses can be formed by inflammatory cells and their mediators [35]. Simultaneously, being a very consuming disease, the tumor itself tends to cause malnutrition, which, in addition to weakening the tolerance of the patient to the treatment process, undermines the immune system, creating a vicious circle where inflammation and malnutrition feed off each other [36].

Many studies have also started to concentrate on haematological biomarkers, which can be used to indicate systemic inflammation and nutritional condition in this biological context [37]. Due to their easy access, low cost, and high reproducibility, such indicators have generated a hot topic in the research of cancer prognosis [38]. Composite markers such as NLR, PLR, and SII are among the inflammatory indices that have been widely studied. On the same note, the nutritional assessment instruments like the PNI and the CONUT score that combine nutritional and immune variables have proven to be a valuable prognostic tool [39]. These biomarkers are highly correlated with prognosis in different solid tumors, including colorectal cancer [40]. An extensive literature review of the articles on inflammatory markers in colorectal cancer has shown that serum-based indices such as NLR, PLR, SII, Glasgow Prognostic Score, and PNI have a significant relationship with patient prognosis [41]. These markers are a valuable insight into the role of host factors in tumor prognosis.

The Cox regression multivariate analysis in our study revealed that the PNI and the PLR were both independent prognostic factors of 3-year DFS in colon cancer patients. This result is in accordance with the findings of some previous studies [42, 43]. Nevertheless, there are also differences that are worth studying in detail. Notably, SII and NLR, which were significant in univariate analysis, did not maintain independent prognostic value in the multivariate model. There may be several reasons for this. First, the emergence of PLR as an independent predictor may partially encompass the prognostic information carried by SII and NLR. Both SII (platelet × neutrophil lymphocyte) and NLR are highly dependent on neutrophil counts, and are highly dependent on neutrophil counts. PLR uniquely emphasizes the interaction between platelets and lymphocytes. The results of the present study suggest an imbalance between platelet-mediated pro-tumor processes (such as promotion of metastasis and angiogenesis) and lymphocyte-represented anti-tumor immunity in the context of colon cancer; it may have more specific prognostic significance than the usual inflammatory response that is neutrophilic. Second, SII and NLR may be more colinear with TNM stage, i.e., advanced tumors themselves trigger a more intense systemic inflammatory response, so their additional independent predictive power is attenuated after adjusting for stage.

This paper confirms the importance of PNI as a nutritional marker by showing that lower PNI values are associated with worse prognosis in colon cancer patients, as is the case in other forms of cancer. Evidence can be supported by Hirahara et al.'s gastric cancer study, which also found postoperative PNI to be an independent predictor of survival. Their outstanding similarity in optimal cutoff (44.3) and ours (44.80) is another indicator of the prognostic relevance of PNI in the case of digestive tract tumors, which shows its wide applicability [44]. PNI is a combination of serum albumin concentrations and lymphocytes, which can not only indicate the nutritional reserves of proteins in the body but also indicate the status of the immune functions. This could be the key determinant of its good predictability. Other studies have also established that albumin, being a vital constituent of PNI, is also correlated with prognosis. A retrospective study by Chen et al.

revealed that low albumin concentrations, preoperative and postoperative, were significantly correlated with poorer OS in patients with colorectal cancer, which was a significant finding in support of the prognostic value of the PNI [45].

In terms of inflammatory markers, in our multivariable analysis, only PLR was considered as an independent predictor compared to other indices, e.g., SII or NLR. Although the finding is in contrast to some past reports, it shows the complicated nature of interactions between inflammatory biomarkers in prognostic stratification. An example of this is a study of bladder cancer patients, which found SII, PNI, and PLR as a combined set of independent prognostic factors after radical cystectomy, which is somewhat similar, but not identical, to our findings [46]. This difference can be explained by the biological peculiarities of various types of tumors, or it might be explained by the variation in the study population and statistical models.

One of the most interesting results of this paper is that the PLR was found to have a stronger prognostic value than other inflammatory markers in the multivariate analysis. This could be explained by the fact that it is the only one that captures the interaction between the platelets and lymphocytes. Platelets promote tumor growth by secreting a number of growth factors that promote angiogenesis and metastasis, whereas lymphocytes play the most important role in the anti-tumor immune response of the host. PLR is a concurrent indicator of the condition of these two important processes. Another study by Liang et al. on patients with liver cancer examined the correlation between other inflammatory combined scores, such as PLR and PNI, and survival following transarterial chemoembolization, and identified and established that the overall inflammatory-nutritional indicators are capable of enhancing the prognostic discrimination capacity compared to a single indicator. This is in line with the findings of this study that PLR and PNI are independent prognostic variables, which implies that the combined evaluation of inflammatory and nutritional variables can give more detailed prognostic data [47].

When it comes to the possible mechanisms through which PLR and PNI influence prognosis, the existing studies have presented some possible explanations. Being a marker of systemic inflammatory reaction, an increase in PLR can be an indicator of the lack of balance between the pro-tumor and anti-tumor immune reactions. When activated, platelets secrete a variety of mediators that promote tumor progression, and lymphocytes play a critical role in coordinating the immune response to cancer [48]. Thus, a high PLR can be a sign of an immune condition of the tumor microenvironment and a favorable disease progression. Being a complex indicator of both nutritional and immune conditions, low PNI level is evidence of resource loss and weakening of the immune system. In particular, low albumin concentrations and lymphocytopenia can all impair antitumor responses. The existing relationship between hypoalbuminemia and unfavorable prognosis in patients with colorectal cancer provides a biological background to the prognostic value of PNI. It is noteworthy that complicated interactions between inflammation and nutritional conditions can exist. The chronic inflammatory conditions can cause malnutrition, malnutrition can also aggravate the inflammatory condition, creating a vicious circle [49] between them. This effect could be partly the reason behind the simultaneous independent prognostic value of PLR and PNI in this study, which could be the measure of different components of this multifaceted interaction. The primary conclusion of this research is that it was found that with the help of statistical analysis, it was noticed that PLR and PNI were independent of the prognosis of patients in the identical colon cancer radical surgery cohort. This result offers initial data in support of the joint evaluation of host inflammatory conditions and nutritional conditions. This study tries to study the prognostic value of the two types of indicators simultaneously, as compared to traditional studies, which primarily concentrated on one type of indicator, which offers a more holistic picture of the role of host factors in the prognosis of colon cancer. Our analysis findings justify the use of the PLR as a useful biomarker in the prognosis of colon cancer patients. Despite the fact that PLR as the indicator of inflammation has been mentioned in earlier research, its role in the prognostic evaluation of colon cancer remains not entirely unclear. This research study concluded that PLR was an independent predictive variable in multivariate analysis and this

factor can be of clinical importance and should be considered further.

This study found that PLR and PNI can provide additional prognostic information beyond TNM stage, achieving fine-grained risk stratification of patients with the same stage. In patients with Stage III disease (overall 3-year DFS was 68.75%), combining PLR with PNI stratified patients into subcohorts with significantly different prognoses: the subgroup of patients with 'low PLR and high PNI' characteristics (N = 27) had a 3-year DFS rate of 92.59%. The subgroup of patients with 'high PLR and low PNI' (N = 5) dropped to 60.00%. The survival difference between the two subgroups was highly significant by the Log-rank test ($P < 0.001$). Similarly, a similar stratification effect was observed within stage II patients. This proves that PLR and PNI can effectively identify patients with a hidden high risk of recurrence or a potentially favorable prognosis that cannot be identified by the traditional TNM staging system, thus providing an important supplement to individualized clinical decision-making.

Clinically, this research proposes that the host factor indicators (PLR and PNI), in addition to conventional TNM staging, can be used to aid in a more holistic evaluation of the prognosis of colon cancer patients. TNM staging is primarily based on the anatomical area of tumor invasion, whereas these blood-based biomarkers give data about the general state of the host. This multi-angle evaluation tool can offer additional reference points for the treatment choices of clinicians, including its usefulness in the identifying patient groups that might need more rigorous follow-up. Regarding further research directions, we think that there are a number of aspects that should be explored further. The first one is that the value of PLR and PNI in the prognosis evaluation of colon cancer in prospective studies needs to be checked, particularly whether the dynamic changes of these indicators can predict the disease better than a one-time measurement. Secondly, future research should investigate whether interventions (e.g., anti-inflammatory or nutritional support) in patients identified as high-risk by PLR and PNI can improve prognosis. Such findings would more effectively demonstrate the clinical utility of these indicators. Also, the analysis of the relationship between these indicators and tumor molecular features (including specific gene mutations) could be used to gain insights into their predictive power in various molecular subtypes of patients. Furthermore, given that "The UPS is extensively involved in the regulation of various cancer-related signaling pathways, transcription factors, and metabolic enzymes" [50], future investigations could explore whether the prognostic power of PLR and PNI correlates with the expression or activity of key components of the ubiquitin-proteasome system (UPS) in tumor tissues, potentially uncovering a more unified molecular basis for these host-derived biomarkers.

Limitations

Being a retrospective observational study, the findings of the study are necessarily at risk of selection bias, and the identified correlations cannot be directly interpreted as causal relationships. Although we adjusted for known confounders by multivariate analysis, we did not find significant differences between groups; however, unmeasured or unaccounted-for confounders (such as socioeconomic status, treatment adherence, microbiome differences, etc.) may still influence the results. This is a single-center study and has a rather small sample size, which can be a limitation in terms of statistical power, particularly in the process of identifying smaller effect sizes. Also, the best critical values of inflammation and nutritional indicators identified in the present study should be externally confirmed in larger and multi-centered prospective cohorts to guarantee their generalizability. The clinical application of these indicators still faces major questions. These include how to dynamically adjust treatment strategies based on their changes, and whether anti-inflammatory or nutritional interventions for high-risk patients can ultimately improve survival. Future research is needed to address these issues. One of the most interesting results of Mulkut et al. was that tumor budding has a positive relationship with CRP levels in patients with middle-lower rectal cancer. This finding emerged from their comparative study of middle-lower rectal cancer and upper rectal cancer in the non-metastatic setting [51]. This implies that the inflammatory

process might be connected with the invasive biological action of the tumor, yet it also stresses that the difference between various populations might exist and should be explored in more depth in the future.

Conclusion

The paper validates the claim that PLR and PNI are independent prognostic factors of patients with resectable colon cancer and supports the importance of using systemic inflammation and nutritional measurements as part of the routine prognostic assessment. The results contribute to the understanding of host-related issues in cancer development and pave the way for new adjunct therapeutic strategies based on the control of inflammation and nutritional state. In that way, this work helps to make colon cancer management more accurate and individualized. Future research must focus on prospective confirmation of the clinical usefulness of these biomarkers and whether they can be used to develop targeted interventions that improve long-term survival. This translation from prognostic measurement to clinical practice is a crucial next step.

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Disclosure of conflict of interest

None.

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