


Prognostic Value of Platelet-to-Lymphocyte Ratio, Neutrophil-to-Lymphocyte Ratio, and Lymphocyte-to-White Blood Cell Ratio in Colorectal Cancer Patients Who Received Neoadjuvant Chemotherapy

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Abstract

Background: The objective of this study was to assess the prognostic value of pretreatment platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), and lymphocyte-to-white blood cell ratio (LWR) of CRC patients who received neoadjuvant chemotherapy. **Methods:** We analyzed the peripheral blood routine parameters and other clinical data of 145 patients with colorectal cancer who had undergone neoadjuvant chemotherapy between January 2011 and February 2014. Pretreatment blood parameters of 145 patients were collected, and PLR, NLR, and LWR were calculated. The utility of PLR, NLR, and LWR in predicting treatment efficacy and patient survival was statistically evaluated using the chi-square test, log-rank test, Kaplan-Meier curves and logistic regression models, and Cox regression models. **Results:** Receiver operating characteristic curve showed that the best cutoff values of PLR, NLR, and LWR were 154.31, 3.01, and 0.22, respectively. In univariate analysis, tumor location ($P = 0.044$), differentiation degree ($P = 0.001$), lymph node metastasis ($P = 0.020$), and high PLR ($P = 0.042$) were significantly correlated with a lower overall response rate (ORR). In addition, clinical stage, lymph node metastasis, and high PLR were correlated with short OS ($P < 0.01$) and DFS ($P < 0.01$). Moreover, WBC count was correlated with a short OS. Multivariate analysis showed that tumor location ($P = 0.013$), differentiation degree ($P = 0.001$), and lymph node metastasis ($P = 0.033$) were independent predictors of ORR. In addition, lymph node metastasis independently predicted a shorter OS ($P = 0.011$). Lymph node metastasis ($P = 0.013$) and high PLR ($P = 0.022$) were independent prognostic factors for short DFS. **Conclusions:** For CRC patients who received NAC, clinical pathological stage and lymph node metastasis were correlated with lower ORR and survival, while a high PLR that may be of prognostic relevance in CRC patients receiving NAC.

Keywords

colorectal cancer, neoadjuvant chemotherapy, PLR, NLR, LWR

Abbreviations

NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LWR, lymphocyte-to -white blood cell ratio; CRC, colorectal cancer; NAC, neoadjuvant chemotherapy; OS, overall survival; DFS, disease-free survival.

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Background

Colorectal cancer (CRC) is one of the most common malignant tumors of the gastrointestinal tract, and it is the third most common malignancy worldwide.^{1,2} In China, the incidence of CRC has been increasing due to recent changes in living standards, lifestyle and eating habits.^{3,4} At present, the treatment

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pattern of early and progressive CRC is a comprehensive treatment consisting of surgery, radiotherapy, chemotherapy, interventional therapy, biotherapy, and photothermal therapy. Those comprehensive treatments led to an enormous increase in 5-year survival time of 71% in the early stage and 41% in the progressive stage.⁵ However, the 5 year survival rate of patients with advanced CRC, namely metastatic CRC (mCRC), even after surgery, radiotherapy, chemotherapy, and other treatments is only 14%.⁵ Therefore, exploring effective new treatment strategies is considerable for the treatment of mCRC. Most CRC patients do not experience symptoms during the early disease stage and are thus diagnosed at the late stage. Therefore, prognostic indicators for timely detection and to improve prognosis are needed. The interaction between systemic inflammation and local immune response was considered to be the seventh sign of cancer, and it had been demonstrated to play a role in the initiation, development and progression of several malignant tumors.⁶ The levels of white blood cells, neutrophils, lymphocytes, platelets and C-reactive protein are closely related to the degree of cancer-related inflammation.⁷ In recent years, research on the relationship between inflammation and tumors has significantly increased. The combinations of these systemic inflammation parameters, such as PLR, NLR, and LWR are markers of active tumor inflammation, which had an important role in promoting tumor progression. Although cancer and inflammation are closely related, the mechanism by which NLR, PLR, and LWR are elevated in patients with poor prognosis needs further study.⁸ The relation between preoperative NLR, PLR, and LWR and prognosis in CRC patients has been widely discussed.⁹⁻¹¹ Studies have confirmed that NLR and PLR are correlated with tumor invasion, recurrence and metastasis, and prognosis.^{12,13} Thus, they have been widely used as indicators to predict the inflammatory response and prognosis of cancer patients.^{14,15} However, few researchs have assessed the value of these parameters in predicting the efficacy of NAC or the prognosis of patients who under neoadjuvant chemotherapy (NAC). Therefore, the objective of this research was to investigate the significance of PLR, NLR, and LWR as prognostic predictors for survival of CRC patients who received NAC.

Methods

Patients and Study Design

This was a retrospective research of 145 patients with CRC received oxaliplatin + capecitabine or a FOLFOX6 regimen as NAC between January 2011 and February 2014. The selection criteria were 1) pathological tissue biopsy was diagnosed as CRC, 2) NAC before surgery, and 3) available data on routine blood test results, chemotherapy regimen, efficacy evaluation, surgery, and postoperative adjuvant therapy. The exclusion criteria were 1) infections or other inflammatory diseases before preoperative NAC, 2) presence of other tumors, 3) radiotherapy and endocrine therapy before NAC, 4) serious complications or death during the perioperative period, and 5) other systemic diseases (e.g., hematological or autoimmune disorders).

Calculation of Blood Parameters

Clinicodemographic data including age, sex, tumor location, pathological type, degree of differentiation, clinical stage, chemotherapy regimen, and follow-up before preoperative NAC were collected. Peripheral routine blood test results in 145 patients before preoperative NAC, including WBC count, neutrophil, platelet, and lymphocyte count, were tested by hematology analyzer (Sysmex XN-2000 hematology analyzer manufactured by Sysmex Medical Electronics Shanghai Company) and were collected, and NLR, PLR, and LWR were calculated. We selected the qualified routine blood samples without clots, hemolysis and blood collection that meet the requirements at room temperature and complete the test within 4 hours. NLR was expressed as the ratio of the neutrophil to lymphocyte count; PLR, the ratio of the platelet to lymphocyte count; and LWR, the ratio of the lymphocyte to WBC count. The ROC curve was established, and the best cut-off value of PLR, NLR and LWR were determined by the highest value of Yoden index. The patients were then divided according to the cutoff value into the high group and the low group.

Neoadjuvant Chemotherapy Regimen and Follow-Up

The indication for NAC for colorectal cancer: 1) Preoperative pathological stage is resectable T3N0M0 or N1-2M0. 2) Pathological stage of CRC is T4M0. 3) Pathological stage of local unresectable CRC is M0. 4) Resectable or potentially convertible resectable metastases are limited to CRC of the liver or lungs. 5) Diffuse metastatic CRC. The preoperative NAC regimen included oxaliplatin + capecitabine or FOLFOX6 for a 21-day cycle. Efficacy and surgical treatment were evaluated after 2 to 7 cycles of treatment. The remaining chemotherapy course was completed after surgical treatment. The overall survival (OS) time refers to the time from the date of diagnosis and treatment of CRC to the date of death or final follow-up. From the date of diagnosis and treatment of CRC to the date of recurrence or final follow-up was considered as the disease-free survival (DFS).

Evaluation of Treatment Response

The efficacy of preoperative NAC was assessed using the Response Evaluation Criteria in Solid Tumors (RECIST)¹⁶ as complete response (CR, i.e. disappearance of the target lesion), partial response (PR, i.e. at least 30% reduction of the target lesion), progressive disease (PD, i.e. an increase of >20% of the target lesion or development of new lesions), and stable disease (SD, i.e. the shrinkage of the target lesion does not reach PR or the increase does not qualify for PD). The change in tumor diameter was evaluated by taking 2 consecutive measurements of the tumor diameter. Tumor diameter was measured by CT and MRI. Because CT and MRI were 2 kinds of auxiliary imaging examinations that can observe the size of the tumor more accurately. The density resolution of CT is relatively high, and it can display the density of various tissues of the

Table 1. Relationship Between PLR, NLR, and LWR With Patient Characteristics (n = 145).

Clinical characteristics	Number of cases	PLR		c ² and P value	NLR		c ² and P value	LWR		c ² and P value
		<154.31	≥154.31		<3.01	≥3.01		<0.22	≥0.22	
Sex										
Male	89	26	30	1.025	61	28	1.153	12	77	11.278
Female	56			0.311	43	13	0.283	21	35	0.001
Age (Years)										
≥58	74	39	35	0.058	51	23	0.586	19	55	0.732
<58	71	36	35	0.81	53	18	0.444	14	57	0.392
Tumor location										
Colon cancer	45	15	30	8.838	21	24	20.201	19	26	14.061
Rectal cancer	100	60	40	0.003	83	17	<0.001	14	86	<0.001
Clinical stage										
II	59	30	29	0.031	35	24	7.545	18	41	3.399
III	86	45	41	0.861	69	17	0.006	15	71	0.065
Differentiation degree										
Medium and high	112	53	59	3.82	82	30	0.539	24	88	0.495
low	33	22	11	0.051	22	11	0.463	9	24	0.482
Whether lymph node metastasis										
Yes	87	45	42	0	70	17	8.814	15	72	3.766
No	58	30	28	1	34	24	0.004	18	40	0.052

human body. In particular, the display of calcification is significantly better than that of magnetic resonance. The resolution of magnetic resonance for soft tissues is relatively high, and the lesions of soft tissues are significantly better than CT. Therefore, both methods were used for all patients. Objective response rate (ORR) was calculated as: number of cases of CR+PR/total number of cases × 100%.

Statistical Analysis

Normally distributed data were represented as the mean ± standard error ($\bar{x} \pm s$). Count data were represented as the frequency or rate (%). Continuous and categorical variables were analyzed by independent-sample t-test and the chi-square test, respectively. Survival curves on the basis of cumulative incidences were constructed by Kaplan-Meier curves and compared by the log-rank test. Univariate and multivariate analyses through logistic regression models were conducted to identify predictors of objective response. Predictors of OS and DFS were identified via univariate and multivariate analyses by Cox regression models. *P* value less than 0.05 means that the comparison is statistically different. The 95% confidence level was used to represent all confidence intervals (CI). All statistical analyses were conducted by the SPSS 22.0 software (SPSS, Inc, Chicago, IL, USA).

Results

Patient Characteristics

Of the 145 patients, 89 (61.38%) were men and 56 (38.62%) were women. The median age was 58 years (range, 26 to 78 years), and the average age was 55.92 ± 11.19 years. The tumor was located in the colon and rectum in 45 (31.04%) and

100 (68.96%) patients, respectively. With respect to clinical stage, 59 (40.69%) patients had stage II disease, while 86 (59.31%) had stage III. Overall, 87 (60%) had lymph node metastasis. Regarding the degree of differentiation, 112 (77.24%) patients had high-middle differentiation, and 33 (22.76%) patients had poor differentiation (Table 1). There were 98 (67.59%) patients who received the oxaliplatin and capecitabine regimen, and 47 (32.41%) patients received the FOLFOX6 chemotherapy regimen.

Optimal Cutoff Values of PLR, NLR, and LWR

The results of ROC analysis show that the AUCs related to PLR, NLR, and LWR were 0.644 (*P* = 0.032), 0.714 (*P* = 0.009) and 0.661 (*P* = 0.029), respectively. The cut-off value is also called the judgment standard, which is used to determine the boundary value of the test to be positive or negative. The optimal cut-off-values of PLR, NLR, and LWR were 154.31, 3.01, and 0.22, respectively. Accordingly, the patients were divided into high PLR group (PLR ≥ 154.31) and low PLR group (PLR < 154.31); high NLR group (NLR ≥ 3.01) and low NLR group (NLR < 3.01); and high LWR group (LWR ≥ 0.22) and low LWR group (LWR < 0.22) (Figure 1).

Relationship of PLR, NLR, and LWR With Clinical Features

Table 1 shows the patient characteristics according to the PLR, NLR, and LWR. Patients with higher clinical stages and lymph node metastasis had a significantly lower NLR (*P* < 0.05). Sex was correlated with LWR (*P* < 0.001), while tumor location was correlated with PLR, NLR, and LWR (all *P* < 0.05). Other

characteristics were no correlated with PLR, NLR, and LWR (all $P > 0.05$) (Table 1).

Relationship of PLR, NLR, and LWR With Chemotherapy Efficacy

In total, 93 (64.13%) patients achieved CR and PR, 41 (28.27%) patients achieved SD, and 10 (6.90%) patients had local recurrence or distant metastasis. The ORR was 72% (54/75) in the low PLR group and 61.44% (43/70) in the high PLR; 67.30% (70/104) in the low NLR group and 53.67% (22/41) in the high NLR group; and 67.86% (76/112) in the high LWR group and 54.55% (18/33) in the low LWR group. However, a higher PLR ($c^2 = 1.827$, $P = 0.176$), higher NLR ($c^2 = 1.827$, $P = 0.176$), and lower LWR ($c^2 = 1.827$, $P = 0.176$) were not significantly correlated with a lower ORR (Table 2).

Survival Analysis

The median OS was 61 months (range, 29 to 79 months), and the average was 59.28 ± 9.65 months. The median DFS was 48 months (range, 20 to 64 months), and the average was

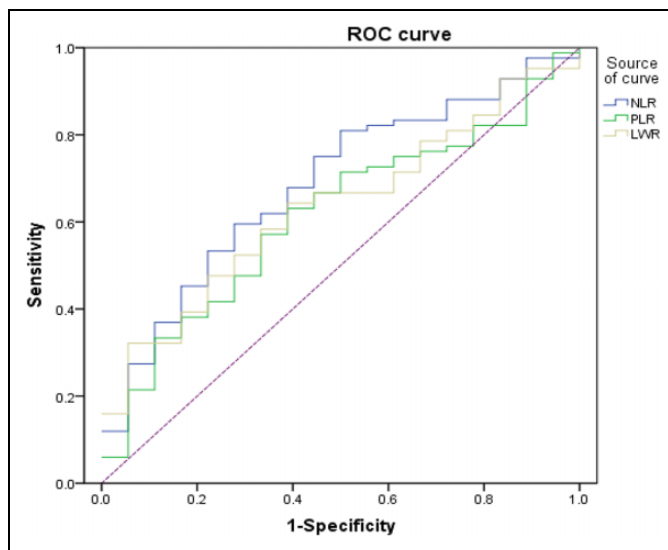


Figure 1. ROC curve of PLR, NLR, and LWR. Note: PLR: AUC = 0.644; sensitivity: 65.8%; specificity: 67.7%; NLR: AUC = 0.714; sensitivity: 67.5%; specificity: 70.6%; LWR: AUC = 0.661; sensitivity: 64.3%; specificity: 65.1%.

47.14 ± 9.61 months (Table 3). Survival assessed as mean \pm standard error ($\bar{x} \pm s$) showed that the high PLR (≥ 154.31) and the high NLR (≥ 3.01) groups had a shorter OS and DFS. However, the high LWR (≥ 0.22) showed longer OS and DFS (Table 3). Kaplan-Meier curves demonstrated that a high PLR (≥ 154.31) was significantly related to a shorter OS ($c^2 = 7.858$, $P = 0.005$) and DFS ($c^2 = 9.127$, $P = 0.003$). Further, NLR (≥ 3.01) was significantly correlated with a shorter OS ($c^2 = 8.889$, $P = 0.003$) and DFS ($c^2 = 6.497$, $P = 0.011$). Meanwhile, a high LWR (≥ 0.22) was associated with a longer OS ($c^2 = 10.081$, $P = 0.001$) and DFS ($c^2 = 8.337$, $P = 0.004$) (Figures 2, 3, and 4).

Univariate and Multivariate Analysis of Clinical Factors Related to Chemotherapy Efficacy

In univariate analysis, the independent predictors of objective response were tumor location (OR = 0.490, 95% CI = 0.237-1.011, $P = 0.044$), degree of differentiation (OR = 0.249, 95% CI = 0.110-0.560, $P = 0.001$), lymph node metastasis (OR = 0.566, 95% CI = 0.276-1.160, $P = 0.020$), and high PLR (OR = 0.727, 95% CI = 0.366-1.444, $P = 0.042$) (Table 4). In multivariate analysis, tumor location (OR = 0.350, 95% CI = 0.152-0.803, $P = 0.013$), degree of differentiation (OR = 0.241, 95% CI = 0.103-0.565, $P = 0.001$), and lymph node metastasis (OR = 0.418, 95% CI = 0.188-0.930, $P = 0.033$) were independent predictors of objective response for patients with CRC who had undergone NAC (Table 5). We used univariate logistic regression analysis to select multivariate analysis variables ($P < 0.10$) (Table 4).

Univariate and Multivariate Analysis of Clinical Factors Affecting OS and DFS of CRC

In univariate Cox regression analysis, clinical stage (OR = 0.490, 95% CI = 0.237-1.011, $P = 0.054$), lymph node metastasis (OR = 0.566, 95% CI = 0.276-1.160, $P = 0.020$), and WBC count (OR = 0.249, 95% CI = 0.110-0.560, $P = 0.001$) were independent risk factor affecting short OS. In addition, clinical stage (OR = 1.482, 95% CI = 1.025-2.144, $P = 0.037$) and lymph node metastasis (OR = 2.552, 95% CI = 1.569-4.150, $P < 0.001$) were independent risk factor affecting short DFS. Meanwhile, a high PLR independently predicted a shorter OS (OR = 0.626, 95% CI = 0.398-0.983,

Table 2. Correlation of PLR, NLR, and LWR With the Efficacy of Neoadjuvant Chemotherapy.

Group	CR	PR	SD	PD	c^2 value	P value
PLR < 154.31 (n = 70)	5 (6.67%)	49 (65.33%)	20 (26.67%)	1 (1.33%)	1.827	0.176
PLR \geq 154.31 (n = 75)	4 (5.72%)	39 (55.72%)	22 (31.42%)	5 (7.14%)		
LWR < 0.22 (n = 33)	1 (3.03%)	17 (51.52%)	13 (39.39%)	2 (6.06%)	1.981	0.159
LWR \geq 0.22 (n = 112)	9 (8.04%)	67 (59.82%)	29 (25.89%)	7 (6.25%)		
NLR < 3.01 (n = 104)	9 (8.65%)	61 (58.65%)	26 (25%)	8 (7.70%)	2.362	0.124
NLR \geq 3.01 (n = 41)	1 (2.44%)	21 (51.23%)	16 (39.02%)	3 (7.31%)		

Table 3. Comparison of OS and DFS Between High Group and Low Group (Month, $1 \times \pm s$).

Group	OS	<i>P</i> value	DFS	<i>P</i> value
PLR < 154.31 (n = 70)	61.17 ± 9.38	0.026	48.89 ± 9.94	0.023
PLR ≥ 154.31 (n = 75)	57.24 ± 9.60		45.27 ± 8.94	
LWR < 0.22 (n = 33)	54.39 ± 10.22	0.034	43.03 ± 9.51	0.035
LWR ≥ 0.22 (n = 112)	60.71 ± 9.04		48.35 ± 9.34	
NLR < 3.01 (n = 104)	60.84 ± 8.96	0.041	48.38 ± 9.30	0.043
NLR ≥ 3.01 (n = 41)	55.29 ± 10.30		44.00 ± 9.79	

$P = 0.042$) and DFS (OR = 0.482, 95% CI = 0.296-0.783, $P = 0.003$), and there was statistically difference ($P < 0.10$) (Table 4). Multivariate analysis indicated that lymph node metastasis independently predicted a shorter OS (OR = 2.782, 95% CI = 1.267-6.106, $P = 0.011$). Lymph node metastasis (OR = 2.851, 95% CI = 1.153-6.488, $P = 0.013$) and high PLR (OR = 0.559, 95% CI = 0.340-0.918, $P = 0.022$) were independent risk factors affecting short DFS, and the difference was statistically significant ($P < 0.05$) (Table 5). We used univariate analysis to select multivariate analysis variables ($P < 0.10$) (Table 4).

Discussion

The occurrence and progression of CRC is closely correlated with the body's inflammatory response and immune status.¹⁷ Many research results have demonstrated that inflammation is related to the occurrence, progression, and metastasis of many cancers, such as colorectal, liver, esophageal, kidney, and lung cancers.¹⁸⁻²⁰ Inflammation may accelerate cancer progression through several mechanisms such as gene mutation, cancer cell proliferation, and angiogenesis.²¹⁻²³ NAC is widely used to treat patients with locally advanced CRC, and patients with surgical CRC to decrease the tumor size, increase eligibility for surgery and lessen surgical invasion, reduce the risk of recurrence, and extend the life cycle.²⁴ However, there are currently no reliable biomarkers to predict the efficacy of NAC.

Inflammatory biomarkers, including NLR, PLR, and LWR, are closely associated with the clinical outcome of patients.²⁵ However, the optimal cutoff values of PLR, NLR, and LWR have varied between previous studies.²⁶⁻²⁸ Thus, it is important to set a standard optimal cutoff value for PLR, NLR, and LWR that can be used to predict prognosis and treatment response. In this study, we studied the prognostic value of PLR, NLR, and LWR in CRC patients who received NAC. The best cutoff values of PLR, NLR, and LWR were 154.31 (sensitivity, 64.3%; specificity, 67.7%), 3.01 (sensitivity, 67.5%; specificity, 70.6%), and 0.22 (sensitivity, 64.3%; specificity,

65.1%), respectively. Our findings suggest that NLR, PLR, and LWR can affect treatment response and prognosis of CRC patients who had undergone NAC. Specifically, low NLR was also related to high clinical stages and lymph node metastasis. Sex was related to LWR, whereas tumor location was associated with PLR, NLR, and LWR. Elevated PLR was closely correlated with ORR, and higher PLR was an independent factor that can predict OS and DFS. In addition, our results revealed that NLR and LWR were not independent predictors of OS and DFS. Apart from inflammatory indices, we also analyzed the relationship of clinicodemographic factors with the efficacy of chemotherapy and survival. We found that tumor location, degree of differentiation, and lymph node metastasis were independent factors influencing ORR. Further, lymph node metastasis was an independent factor that can predict OS and DFS.

Our results are consistent with those of previous studies that have shown that these hematological indicators of systemic inflammatory states, including platelet count, NLR, PLR, and WBC count, were independent risk factors that affect the prognosis of several types of cancer.²⁹⁻³¹ In addition, the ORR of the high PLR (61.44%), high NLR (53.67%) and low LWR (54.55%) group are significantly lower than the low PLR (72%), low NLR (67.30%) and high LWR (67.86%) group. Tang *et al* found that the PLR and NLR before chemotherapy can predict the chemotherapy efficacy and prognosis of CRC patients to a certain extent.^{32,33} Kwon *et al*³⁴ and Szkandera *et al*³⁵ also verified the effect of PLR in assessing the prognosis of CRC patients. In addition, He *et al* showed that NLR and PLR are influencing factors of worse prognosis in patients with CRC and confirmed that NLR has better predictive capability than PLR.³⁶ Jia *et al* reported that both NLR and PLR may be reference indicators for early diagnosis and treatment strategies for CRC.³⁷ Lower LWR was related to worse OS and DFS in CRC.^{38,39}

Some mechanisms may lead to adverse reactions and prognosis in CRC patients with low LWR and elevated PLR and NLR. Neutrophils secrete various cytokines that can stimulate capillary proliferation and promote tumor growth and metastasis.^{29,40,41} Neutrophils may enhance the biological tumor behavior to promote its grow and metastasize. Higher neutrophil count can upregulate the expression of growth factors, such as chemokines, increasing tumor development and progression.⁴²⁻⁴⁴ White blood cells, including neutrophils, monocytes, and eosinophils, are believed to play the most important role in the immune system. WBCs can generate reactive oxygen species and nitric oxide species, which can damage cellular proteins, lipids, and DNA. This can, in turn, lead to genetic instability that can affect single-nucleotide polymorphisms or upregulate the PI3K-Akt pathway to cause cancer.^{45,46} Lymphocyte response can also induce cytotoxic cell death and inhibit tumor cell proliferation or migration, thereby controlling the progression of cancer. When the lymphocyte count is low, the antitumor immune function of the body is weakened and can result in the growth of a large number of tumor cells and disease progression. This can induce cell proliferation, promote

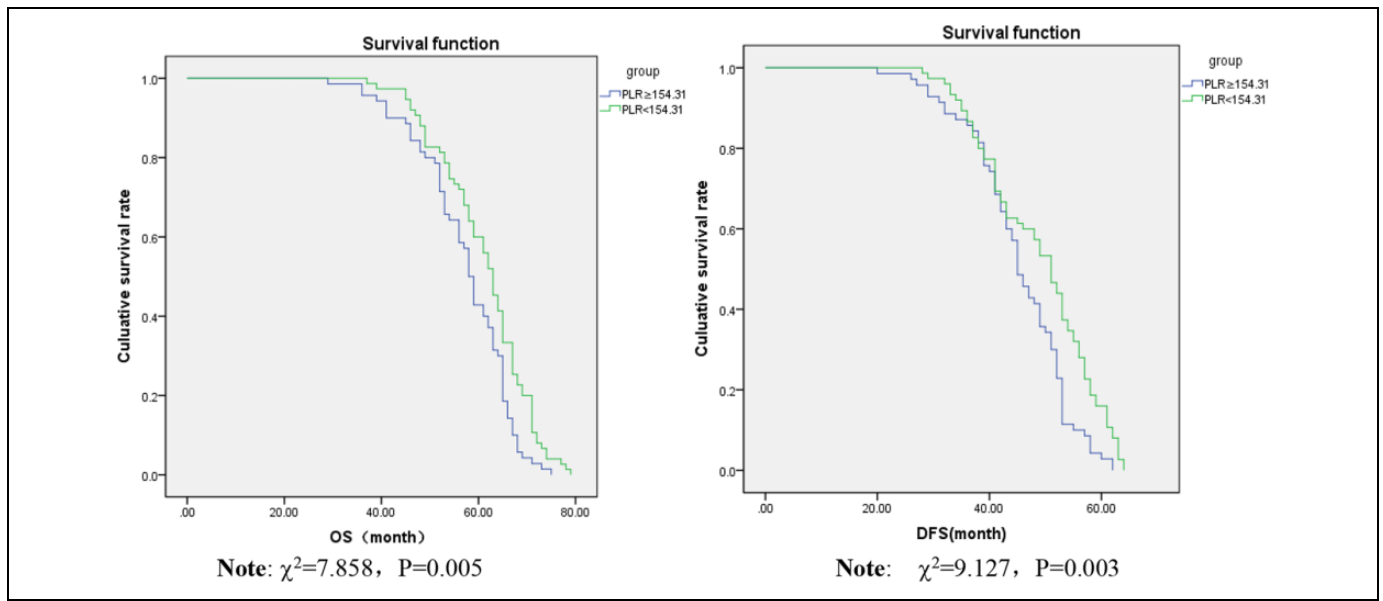


Figure 2. Kaplan-Meier curve of OS and DFS of high PLR and low PLR group.

tumor development, and increase tissue infiltration by promoting angiogenesis, which results in tumor spread.⁴⁷ Platelets can secrete platelet chemotactic growth factor, blood platelet factor 4, β -transforming growth factor, and vascular endothelial growth factor to increase angiogenesis, microvascular permeability and tumor cell extravasation, thereby promoting tumor growth.^{48,49} Tumor cells can also induce platelet aggregation and manipulate platelet activity to promote tumor progression.^{50,51}

Therefore, elevated platelet, neutrophil, and WBC counts or a decreased lymphocyte count lead to worse prognosis. Accordingly, high PLR, NLR, and low LWR can lead to a

poorer prognosis for patients. However, in this study, only patients with high PLR had shorter OS and DFS. Increased platelet count can promote tumor development, while decreased lymphocyte count can lead to weakened immunity that can lead to tumor progression.^{32,33} However, the efficacy of PLR, NLR, and LWR as prognostic factors in CRC is still conflicting. While some previous studies reported them to be reliable.³⁴⁻³⁹ other studies suggested that PLR, NLR, and LWR are not prognostic factors.⁵²⁻⁵⁸ In the univariate analysis, PLR was related to DFS and OS, but NLR and LWR were not. The results of multivariate analysis showed that PLR is an independent risk factor affecting DFS.

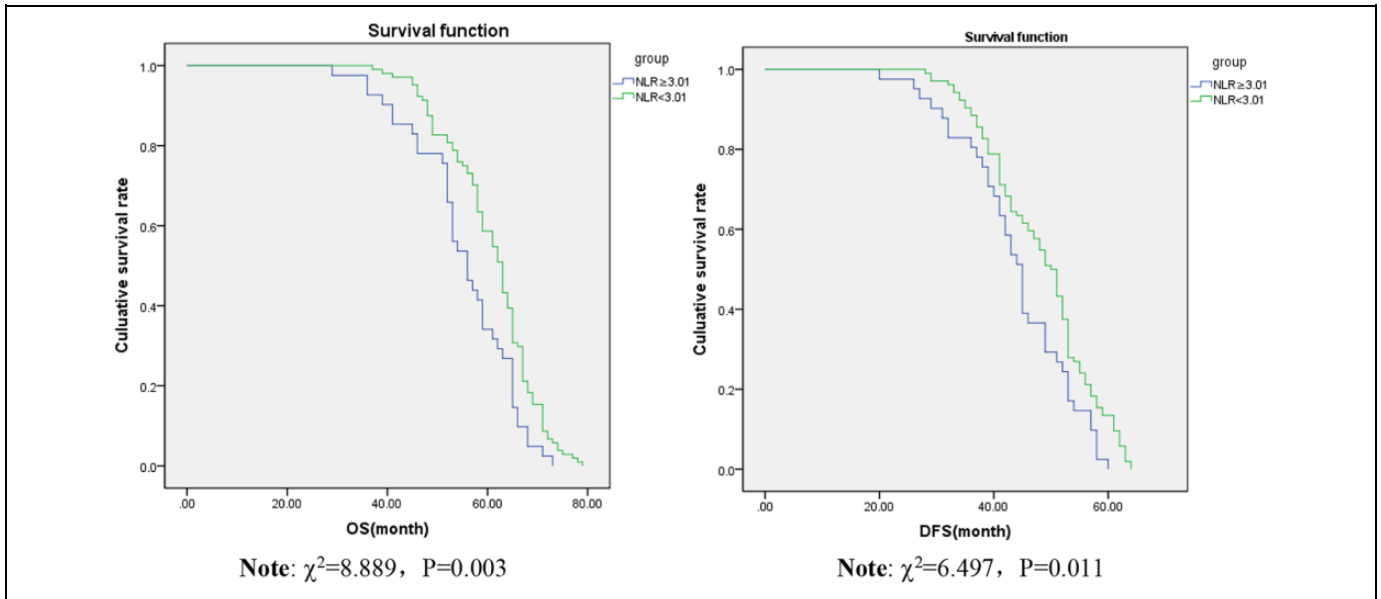


Figure 4. Kaplan-Meier curve of OS and DFS of high NLR and low NLR group.

Table 4. Univariate Analysis of Objective Response, Overall Survival, and Disease-Free survival.^a

Variable	Objective response		OS		DFS	
	OR (95%CI)	P-value	HR (95%CI)	P-value	HR (95%CI)	P-value
Gender (Male/female)	0.747 (0.373 ~ 1.498)	0.411	0.941 (0.606 ~ 1.461)	0.787	0.956 (0.598 ~ 1.527)	0.850
Age (≥58/<58 years)	1.444 (0.728 ~ 2.864)	0.293	0.798 (0.516 ~ 1.234)	0.310	0.705 (0.445 ~ 1.117)	0.136
Tumor location (colon/rectum)	0.490 (0.237 ~ 1.011)	0.044	1.324 (0.798 ~ 2.199)	0.277	1.460 (0.834 ~ 2.553)	0.185
Clinical stage (II/III)	0.610 (0.305 ~ 1.222)	0.163	1.410 (0.987 ~ 2.013)	0.059	1.482 (1.025 ~ 2.144)	0.037
Differentiation degree (Low/medium-high)	0.249 (0.110 ~ 0.560)	0.001	1.547 (0.862 ~ 2.775)	0.144	1.185 (0.617 ~ 2.274)	0.610
Whether lymph node metastasis (yes/no)	0.566 (0.276 ~ 1.160)	0.020	2.317 (1.431 ~ 3.753)	0.001	2.552 (1.569 ~ 4.150)	<0.001
White blood cell count (≥10 ⁹ / <lt;10<sup>9)</lt;10<sup>	0.777 (0.192 ~ 3.143)	0.723	0.455 (0.193 ~ 1.071)	0.071	0.573 (0.204 ~ 1.609)	0.291
Platelet count (≥300 ⁹ / <lt;300<sup>9)</lt;300<sup>	1.223 (0.594 ~ 2.517)	0.585	0.930 (0.575 ~ 1.503)	0.767	0.754 (0.452 ~ 1.256)	0.278
Lymphocyte count (≥1 ⁹ / <lt;1<sup>9)</lt;1<sup>	0.450 (0.049 ~ 4.137)	0.481	0.340 (0.095 ~ 1.627)	0.198	1.028 (0.142 ~ 7.460)	0.978
Neutrophil count (≥6.02 ⁹ / <lt;6.02<sup>9)</lt;6.02<sup>	0.909 (0.342 ~ 2.420)	0.849	0.799 (0.410 ~ 1.557)	0.509	0.798 (0.378 ~ 1.686)	0.554
NLR (≥3.01/<3.01)	1.262 (0.597 ~ 2.665)	0.542	0.701 (0.407 ~ 1.205)	0.199	0.840 (0.453 ~ 1.556)	0.579
PLR (≥154.31/<154.31)	0.727 (0.366 ~ 1.444)	0.042	0.626 (0.398 ~ 0.983)	0.042	0.482 (0.296 ~ 0.783)	0.003
LWR (≥0.22/<0.22)	0.670 (0.302 ~ 1.482)	0.322	1.363 (0.733 ~ 2.534)	0.328	1.229 (0.604 ~ 2.501)	0.569

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LWR, lymphocyte-to-white blood cell ratio.
^aP < 0.05 indicates that there is a statistical difference between the two.

Therefore, the predictive value of PLR, NLR, and LWR remain controversial and their mechanism needs further research.

The current study has some limitations. First, the data were collected from a single institution, and thus the possibility of selection bias cannot be eliminated. Second, the sample size

Table 5. Multivariate Analysis of Clinical Factors Related to Objective Response, OS, and DFS.^a

Variable	Objective response		OS		DFS	
	OR(95%CI)	P-value	HR(95%CI)	P-value	HR(95%CI)	P-value
Tumor location (Colon/rectum)	0.350 (0.152 ~ 0.803)	0.013				
Clinical stage (II/III)			0.776 (0.393 ~ 1.531)	0.464	0.790 (0.378 ~ 1.651)	0.530
Differentiation degree (Low/medium-high)	0.241 (0.103 ~ 0.565)	0.001				
Whether lymph node metastasis (yes/no)	0.418 (0.188 ~ 0.930)	0.033	2.782 (1.267 ~ 6.106)	0.011	2.851 (1.253 ~ 6.488)	0.013
White blood cell count ($\geq 10^9 < 10^9$)			0.483 (0.202 ~ 1.154)	0.101		
PLR ($\geq 154.31 < 154.31$)	0.657 (0.303 ~ 1.426)	0.288	0.778 (0.485 ~ 1.248)	0.298	0.559 (0.340 ~ 0.918)	0.022

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyteratio; LWR, lymphocyte-to-white blood cell ratio.

^a $P < 0.05$ indicates that there is a statistical difference between the two.

was small, thus limiting the generalizability of our results. In addition, the cutoff values in the current is different from those in previous studies. Further studies with a prospective and multi-center design are needed to verify our research results and establish a standard optimal cut-off value that can predict the prognosis of CRC.

Conclusion

For CRC patients who had undergone NAC, clinical stage and lymph node metastasis were correlated with lower ORR and survival, while a high PLR that may be of prognostic relevance in CRC patients receiving NAC.

Authors' Note

JW and YL conducted data acquisition, analysis and interpretation. And drafted the work or substantively revised it. JW and NH used new software in this work to analyze the research results. JW, XB and ZP participated in the conception and design of this research. All authors have carefully read and approved the manuscript. This research was approved by the Research Ethics Committee of the Affiliated Cancer Hospital of Zhengzhou University (Ethics Approval No. 2017177). The all participant's written informed consent was dropped because the study was a retrospective. Verbal informed consent was obtained from all participants and the ethics committee approved this procedure. All study protocols were performed in accordance with relevant guidelines and regulations. Availability of data and material: Data and material are available.


Declaration of Conflicting Interests

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