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Impact of neutrophil-to-lymphocyte ratio and platelet -to-lymphocyte ratio on long-term survival for colorectal cancer patients with adjuvant chemotherapy

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Abstract: **Increasing evidences suggest that cancer-triggered inflammation was associated with survival prognosis from colorectal cancer (CRC). However, neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) predict prognosis in adjuvant chemotherapy are rarely investigated. A retrospective clinical data and baseline laboratory parameters of 215 CRC patients with adjuvant chemotherapy were collected between January 2007 to January 2012. The clinicopathological characteristics were compared. Statistical analysis was used to identify the predictive value of NLR and PLR associated with survival prognosis. The optimal prechemotherapy NLR and PLR cut-off value was 2.32 and 178 by the ROC analysis. Elevated NLR (≥2.32) and PLR (≥178) were obviously correlated with poor OS and RFS (all P<0.05). Moreover, statistical analysis concluded elevated NLR (≥2.32) as an prognostic factor for poor OS (P=0.005, RR 1.942, 95%CI 1.253-3.051), RFS (P=0.010, RR 1.492, 95%CI 0.458-3.281) while elevated PLR (≥178) was for poor OS (P=0.020, RR 1.585, 95%CI1.072-2.527). Thus, prechemotherapy increased NLR and PLR may server as useful clinical prognostic predictors in CRC patients with adjuvant chemotherapy, which were associated with poor prognosis.**

Keywords: Neutrophil-to-lymphocyte ratio; Platelet-to-lymphocyte ratio; Colorectal cancer; Adjuvant chemotherapy

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1. Introduction

Recently, colorectal cancer (CRC) is regarded as a type of cancer associated with chronic inflammation and adjuvant chemotherapy that was initially applied for the treatment of inoperable locally advanced tumors[1]. Several randomized trials have confirmed that adjuvant chemotherapy benefits the patients with CRC[2-3]. Despite no table improvements in the treatment of chemotherapy, the prognostic outcome is poor in 5-year survival[4]. Therefore, exploring the pivotal molecular machinery participating in tumor chemotherapy and determining the effective prognostic biomarkers for the evaluation of chemotherapeutic efficacy necessitates further exploration. These predictive factors originate from the clinicopathological characteristics of the tumor, such as stage, type, and grade, which have been widely utilized as biomarkers in the prognosis post-chemotherapy[5]. However, the tumor management posed several challenges while predicting the heterogeneous prognosis of similar clinicopathological tumors including CRC. Hence, identifying the potential biomarkers that can predict the associations between the survival prognosis and adjuvant chemotherapy is imperative.

The systemic inflammatory response is known to play a vital role as the leading cause of neoplastic process and is actively engaged in genesis and propagation of various cancers, including CRC[6,7]. Accumulating evidence suggests that systemic inflammation is indicated by parameters of peripheral blood including white blood cells, neutrophils, lymphocytes, as well as, platelets. During, the neutrophil-to-lymphocyteratio (NLR) and the platelet-to-lymphocyte ratio (PLR) have been confirmed as the systemic inflammatory response indicators in several malignancies such as pancreatic cancer[8], gastric cancer[9], and lung cancer[10]. To the best of our knowledge, NLR and/or PLR have also been previously linked to the survival or response to treatment in CRC[11]. Those results indicated that both NLR and PLR could participate in the inflammatory response to cancer etiology and play a guiding role for the current clinical treatment. Furthermore, the increased levels of both markers would indicate poor prognosis and an insensitive response to chemotherapy or radiotherapy[12,13]. Therefore, the fluctuating NLR and PLR are designated as potential predictors for the prognosis of chemotherapy in CRC patients, thereby reflecting the status of tumor-inflammation interaction.

Given the correlation of immune inflammation in chemotherapeutics, we hypothesized that both predictors are associated with the response to chemotherapy in CRC patients following the mFOLFOX6or XELOX regimen. Therefore, the present study aimed to explore the clinical significance of NLR and PLR as prognostic factors in CRC patients with adjuvant therapy and identify the independent factor with an effective role.

2. Methodsand Materials

2.1. Patient selection

We retrospectively reviewed the records of CRC patients treated with adjuvant chemotherapy at the Department of Colorectal Surgery at Zhejiang Chinese Medicine University Affiliated No.3 Hangzhou Hospital from January 2007 to January 2012. Patients were enrolled when they fulfilled the following inclusion criteria: (1) aged 35-74 years, whose expected survival prognosis was >5 years; (2) diagnosed with primary colorectal adenocarcinomas and clinical stage III or IV; (3) received 6 cycles or more than 6 cycles of adjuvant chemotherapy after diagnosis and under wentcurative-intent surgery postoperatively; (4) none of the patients suffered from infection, hematological diseases, hyperpyrexia, renal dysfunction, diabetes mellitus, and other acute or chronic diseases. A total of 215 CRC patients met the inclusion criteria. The demographic features, clinicopathological characteristics, and laboratory data of all patients were collected from the electronic medical records and follow-up. All the patients provided written informed consent prior to the present study, which was approved by the Hospital Ethics Committee.

2.2. Adjuvant chemotherapy protocol

All patients were treated with the adjuvant chemotherapy regimen of mFOLFOX6 or XELOX according to the National Comprehensive Cancer Network (NCNN) guidelines. mFOLFOX6 regimen once every 2 weeks, 6 cycles: oxaliplatin (OXA) 85mg/m^2, levofolinate calcium (l-LV) 200mg/m^2, bolus 5-fluorouracil(5-FU) 400mg/m^2, all on day 1; infusion 5-FU 2400mg/m^2 on days 1-3..XELOX regimen once every 3 weeks, 8 cycles: oxaliplatin (OXA) 130mg/m^2 on day 1; capecitabine1000mg/m^2 on days 1-14.

2.3. Peripheral NLR and PLR grouping

All blood samples were withdrawn from patients with empty stomach prior to the first cycle of chemotherapy. The hematological parameters were evaluated by Sysmex XT-1800i Automated Hematology System (Hangzhou, China). For the calculation of the NLR and PLR, the absolute neutrophilcount divided by the absolute lymphocyte count.

2.4. Data collection and follow-up

Medical records were assimilated with respect to thepatients'age, sex, adjuvant chemotherapy regimen, clinicopathological characteristics (such as location, size, histological type, TNM stage, invasion, lymph node), and laboratory data (such as NLR and PLR). All patients were followed up regularly by letters and telephone interviews every3-6 months until death or 5 years. The recurrence-free survival (RFS) was defined as the time from the first day of palliative chemotherapy to the disease progression or recurrence. The overall survival (OS) time was defined as the time from first day of palliative chemotherapy to death by any cause or to thelast follow-up. Follow-ups were ended after January 1, 2017.

2.5. Statistical analysis

Receiver operator characteristic (ROC) analysis with the Youden Index (YI) determined the best cut-off valuefor NLR and PLR as a predictivemarker for OS. Linear regression was performed to evaluate the association between NLR and PLR. The association between the clinicopathological characteristics and NLR as well as PLR were compared by the chi-square test or Fisher's exact probability test. The survival curves were generated using the Kaplan-Meier method, and the differences were compared using the log-rank test. The univariate analysis assessed the prognostic factors and multivariate analysis (Cox's proportional hazards regression model) evaluated the independent factors for survival prognosis. P-values<0.05 were considered statistically significant. The statistical analysis was performed using the SPSS version 17.0 (SPSSInc., Chicago, IL, USA).

3. Results

3.1. Patient characteristics

We identified 215 CRC patientswere eligible for analysis and the baseline characteristics ofthe study subjects are summarized in table 1. The mean age of the CRC patients was 69.21±23.4 years and male to female ratio was 124:91. Most of patients (73.49%) suffered from rectal cancer. And 60% of patients presented tumor size ≥5cm. The clinical TNM stage revealed the pathological diagnoses as follows: 159 patients of III stage and 56 patients with IV stage. Moreover, the histological grade revealed124 patients in G1/G2 and 91 patients in G3/G4. In terms of cancer invasion, high grade (T3/T4) constituted128 patients, and the other grade (T1/T2) was 87. A total of 121 patients presented lymph node with negative tumor (N0), while 94 patients were positive.

Table 1. Baseline characteristics of total 215 colorectal cancer patients and stratified by PLR and NLR

Characteristics	Total n(%) n=215	NLR			PLR		
		≥2.32	< 2.32	P	≥178	< 178	P
Age (years)				0.218			0.112
<60	72 (33.49%)	34	38		41	31	
≥60	143(66.51%)	92	51		78	65	
Sex				0.134			0.409
Female	91(42.33%)	23	68		32	59	
Male	124(57.67%)	103	21		87	37	
Location				0.107			0.558
Colon	57(26.51%)	29	28		26	31	
Rectal	158(73.49%)	97	61		93	65	
Tumor size(cm)				0.524			0.133
<5	129(60.00%)	105	24		72	57	
≥5	86(40.00%)	11	62		47	39	
Cancer stage				0.003			0.004
III	159(73.95%)	88	71		78	81	
IV	56(26.05%)	38	18		41	15	
Cancer grade				0.005			0.029
G1/G2	124(57.67%)	65	59		55	69	
G3/G4	91(42.33%)	61	30		64	27	
Tumor invasion				0.170			0.542
T1/T2	87(40.47%)	28	58		12	74	
T3/T4	128(59.53%)	98	31		112	22	
Lymph node				0.004			0.014
N0	121(56.28%)	61	60		46	75	
N1/N2/N3	94(43.72%)	65	29		73	21	

3.2. Optimal cut-off value for NLR and PLR

ROC curve could calculate the sensitivity and specificity levels of NLR and PLR as a predictor of OS. We identified the optimal cut-off point of both indices by the areas under the curve (AUC) with YI index. As shown in Figure 1, the AUC analysis indicated that NLR and PLR were calculated as 0.775 and 0.564, respectively. The AUC value closer to 1 indicated that the diagnostic test was reliable. We defined the AUC>0.50 as a predictive biomarker for subsequent analysis. Therefore, the optimal value of NLR was calculated as 2.32, with a specificity of 61.34%, the sensitivity of 79.62%, and an accuracy of 65.63%. Moreover, the optimal value of PLR was at 178, with a specificity of 60.26%, the sensitivity of 66.94%, and an accuracy of 53.78%. In addition, there was a positive association between NLR and PLR (P<0.001) in Figure 2.

3.3. Association between clinicopathological characteristics and NLR and PLR

We compared the clinicopathological characteristics grouped by the optimal value of NLR and PLR in table 1. With regard to the optimal cut-off value, high NLR was defined as ≥2.32, and low NLR was <2.32. Similarly, highPLR was considered as ≥178, and low PLR was <178. Patients with higher cancer stage, poorer differentation, more lymph node metastasis included significantly elevated NLR and PLR (all P<0.05). On the contrary, no difference was observed in the baseline characteristics such as age, gender, tumor location, size, and invasion.

3.4. Comparison of CRC survival curves and NLR, PLR

According to the follow-up information, 72(33.49%) patients had recurrence that 21 patients presentedlocal recurrence and 51 patients developed distant metastasis. 89 (41.40%) patients were dead, 61 patients from tumor recurrence, 1 from chemotherapeutic toxicity and the other patients due to unknown reasons. For prognosis of patients according to the Kaplan-Meier curve and log-rank test, median OS was significantly shorter in patients with elevated NLR and PLR in figure 3 (all Log-rank P<0.05). In addition, results of median RFS coincided was also shorter in patients with elevated NLR and PLR (all Log-rank P<0.001). Thus, both two indicators can effectively predict the prognosic survival of CRC patients in this present study.

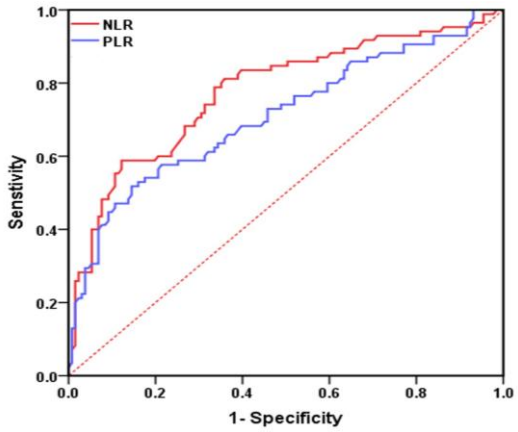

Figure 1. Receiver operating characteristic curve analysis. For NLR, it is indicated by the red line (AUC:0.775; YI index: 0.564). For PLR, it is indicated by the blue line (AUC:0.692; YI index: 0.612).

3.5. Prognostic variables for RFS, OS, and CSS

With respect to all prognostic factors, table 2 and 3 showed the results of univariate and multivariate analysis of various parameters in terms of RFS and OS. The univariate analysis indicated that patients with high cancer stage (IV) as well as elevated NLR (≥2.32) and PLR (≥178) were obviously associated with worse RFS and OS (all P<0.05). Although severer invasion were signifcantly associated with poor OS (P<0.05), it was not related to RFS. On the other hand, poorer differentiation grade and lymph node metastasis was associated with RFS (all P<0.05), but not the same to OS. Factors with P<0.05 in univariate analysis, were conducted in the COX model for further multivariate analysis. By statistical analysis above, patients with higher cancer stage and increased value of NLR, PLR had significant assocation with poor prognosis of OS, RFS (all P<0.05).

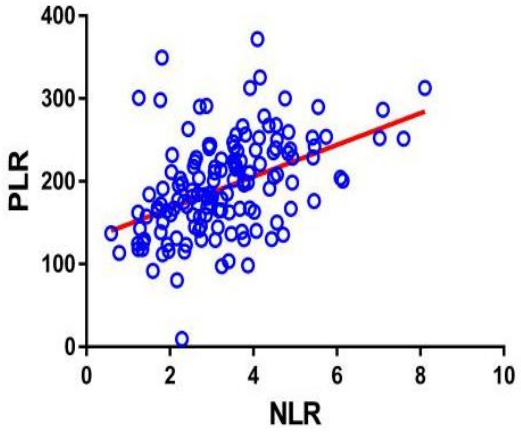

Figure 2. Liner regression of NLP and PLR. NLP and PLR were positively associated with each other (R^2=0.414; P<0.001).

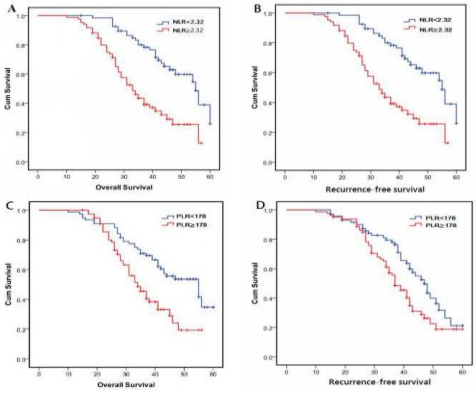

Figure 3. Patients with elevated NLR and PLR had worse prognosis (all log-rank P<0.05). A, B for NLR; C, D for PLR.

4. Discussion

Although the adjuvant chemotherapy of colorectal cancer has greatly improved over several decades, the survival outcomes yet demonstrate a poor prognosis, rendering it as the most common cause of cancer-related deaths[14]. For an enhanced survival, it is vital to find some accurate and sensitive indicators for predicting prognosis.

The current study proved our hypothesis and confirmed the influence of pre-chemotherapeutic NLR and PLR on survival prognosis. Furthermore, the principal findings of our analysis stated that patients with both elevated NLR (≥2.32) and PLR (≥178) demonstrated significantly worse prognosis such as decreased RFS and OS. In other words, pretreatment NLR and PLR to prognostic no mograms provide strong evidence on the predictive value of RFS and OS respectively. Moreover, we demonstrated that the biomarker of NLR served as an independent factor of worse survival prognosis as assessed by multivariate analysis. To date, only a few

studies have determined whether pretreatment NLR is an independent predictor of prognosis in patients with adjuvant chemotherapy. Similar to the previous reports, the current conclusions also clarified the associations between elevated NLR and worse prognosis in many malignancies with chemotherapy, such as breast cancer[15] and gastriccancer[16], especially colorectal cancer[17]. In addition, the parameters of PLR also exhibited worse survival. Although the correlation of both elevated NLR (≥2.24) and PLR (≥186) with poor prognosis remains unclear, the link between systemic inflammatory response and cancer has long been suspected [18].

Table 2. Univariate and multivariate analysis of OS by the Cox proportional hazard model

Variables	Univariate analysis			Multivariate analysis		
	Risk ratio	95% CI	P	Risk ratio	95% CI	P
Age (≥60 vs <60)	0.842	0.467-1.577	0.642			
Gender (male vs female)	1.142	0.411-2.046	0.686			
Location (rectal vs colon)	0.622	0.278-1.175	0.192			
Tumor size(≥5 vs <5)	0.419	0.174-0.868	0.112			
Cancer stage (IV vs III)	3.412	1.391-8.351	<0.001	1.942	1.138-3.180	0.010
Cancer grade (G3/G4 vs G1/G2)	1.316	0.792-2.142	0.291			
Tumor invasion (T3/T4 vs T1/T2)	2.294	1.622-5.079	0.013	1.242	0.841-2.002	0.415
Lymph node (N1/N2/N3 vs N0)	1.439	0.759-2.476	0.173			
NRL (≥2.32 vs <2.32)	2.193	1.382-3.069	<0.001	1.942	1.253-3.051	0.005
PLR (≥178 vs <178)	1.372	0.532-1.988	0.004	1.585	1.072-2.527	0.020

Table 3. Univariate and multivariate analysis of RFSby the Cox proportional hazard model

Variables	Univariate analysis			Multivariate analysis		
	Risk ratio	95% CI	P	Risk ratio	95% CI	P
Age (≥60 vs <60)	1.002	0.462-1.995	0.691			
Gender (male vs female)	1.214	0.677-2.535	0.797			
Location (rectal vs colon)	0.566	0.221-1.171	0.237			
Tumor size(≥5 vs <5)	1.185	0.783-1.842	0.483			
Cancer stage (IV vs III)	2.275	1.418-4.752	<0.001	2.076	1.555-5.016	0.001
Cancer grade (G3/G4 vs G1/G2)	1.776	1.005-3.100	0.007	1.374	0.762-2.623	0.272
Tumor invasion (T3/T4 vs T1/T2)	1.722	0.767-3.209	0.231			
Lymph node (N1/N2/N3 vs N0)	2.027	1.462-4.052	0.012	1.467	0.571-4.24	0.005
NRL (≥2.32 vs <2.32)	1.372	0.637-2.922	0.007	1.492	0.458-3.281	0.010
PLR (≥178 vs <178)	1.412	0.263-2.902	0.012	1.671	1.172-3.642	0.021

To our knowledge, the tumor and systemic inflammation are closely associated with each other, which confirmed that the inflammatory response plays an essential role in the progression of tumor microenvironment; thus, altered inflammatorycells might serve as a predictor of prognosis. Various studies have indicated that changes in immune cellular components in peripheral venous blood could reflect the inflammation status of the tumor that is valuable in predicting survival prognosis [19]. It has been increasingly speculated that the inflammation and tumor are correlated, resulting in the establishment of novel biomarkers of cancer for the evaluation of the prognostic significance. Reportedly, the neutrophils reflect the status of the systematic inflammation and accelerate the remodeling of the extracellular matrix. This, in turn, stimulates the tumor-cell proliferation, migration, and metastasis via the enzymatic actions, such as the release of reactive oxygen species (ROS), nitric oxide (NO), and anginas[20]. Moreover, neutrophilia activates the inflammatory response to promote the tumor growth by pro-angiogenic and growth factors[21].Another study showed the lymphocyte infiltration response to the tumor. The increased lymphocytic reactions have been connected to a better prognosis in chemotherapy[22-23]. Therefore, elevated NLR represents the tumor-inflammatory response, which indicates the degree of tumor progression and contributes towards the prediction of survival prognosis.

Furthermore, PLR is another systemic inflammation biomarker. The platelet and lymphocyte counts were known to be associated with the prognosis in CRC chemotherapy as circulating biomarkers for inflammation, immune response, and coagulation status[24]. Another study confirmed that CRC patients who received oxaliplatin-based combination chemotherapy had worse disease control in those with a high PLR[25].The mechanisms underlying the role of PLR in tumor chemotherapy have not yet been elucidated; however, recent experimental and clinical data may provide several potential explanations. A growing body of evidence reported that high PLR could activate the invasiveness of tumor cells by enhancing the formation of tumor stroma and supporting the stable adhesion of tumor cells to the endothelium[26]. In addition, platelets could secrete the cellular growth factors such as platelet-derived growth factor, vascular endothelial growth factor, transforming growth factor beta, and platelet factor 4, followed by the stimulation of tumor angiogenesis and growth[27]. Thus, clinical values of high PLR could predict a poor prognosis for chemotherapy.

Additionally, the applicable thresholds for both two factors were calculated by the ROC curve. The optimal value of 2.32 for NLR and 178 for PLR exhibited a superior prognostic value regarding high risk, which had the highest sensitivity and specificity and the largest AUC for overall survival. Several previous reports have used an NLR of 5.0 as the cut-off value[28]. In a recent study, high value of NLR resulted in the selection of a higher cut-off value that allowed the enrollment of a small number of patients in clinical practice[29]. Moreover, a higher cut-off value represents higher specificity and accuracy but lower sensitivity. On the other hand, increased PLR also lead to a lower sensitivity.

Nevertheless, our study has some limitations that should be mentioned. First, it is a retrospective investigation; thus, a potential bias in the selection of patients is inevitable. Second, we did not evaluate the chemotherapy-induced adverse reactions, which might affect the patients' quality of life and survival. Finally, the current study lacked any evaluation of tumor-associated neutrophils and lymphocytes, which could cause different immune responses.

5. Conclusion

In summary, the current study suggested that pre-chemotherapy NLR and PLR might be good predictors for prognosis in CRC patients with adjuvant chemotherapy. Thus, these are recommended as practical tools to assess the prognosis of RFS and OS. Therefore, these findings provided an in-depth understanding of the patients, which would guide the customized therapeutic strategy.

Author Contributions

Guangen Yang came up with the hypothesis, designed the whole set of the program. Yang Tao collected the clinical data of selected patients and writing the article. Jianming Qiu analyzed the data for ROC as well as Kaplan-Meier method. Dong Wang, Hongtao Wang and Chao Fuanalyzed the data for the univariate and multivariate analysis

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Conflicts of Interest

All authors have no conflict of interest to declare.

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