ORIGINAL RESEARCH

Dynamic impact of inflammation-based indices in colorectal cancer patients receiving FOLFOX-based chemotherapy

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Background: Inflammatory cellular response is implicated in the pathogenesis of colorectal cancer (CRC). Nevertheless, the dynamic effects of inflammatory index coNLR (neutrophil-to-lymphocyte ratio)-PLR (platelet-to-lymphocyte ratio) during chemotherapy remain elusive.

Methods: The baseline clinical data and laboratory parameters of 480 CRC patients who received palliative resection of primary tumors and FOLFOX-based chemotherapy from January 2007 to January 2013 were retrospectively analyzed. Receiver operating characteristic curves were plotted to obtain the predictive NLR and PLR values, and to calculate the coNLR-PLR score. The Kaplan–Meier method was used to estimate the rates of recurrence-free survival (RFS) and overall survival (OS), and the Cox proportional hazards model was employed for analysis.

Results: The dynamic cut-off values of NLR during four periods of chemotherapy were 3.029, 2.466, 2.102 and 1.795, respectively, and those of PLR were 216.438, 187.572, 169.027 and 174.368, respectively. A higher coNLR-PLR was significantly associated with lower rates of RFS and OS ($P<0.05$). Both univariate and multivariate analyses showed that coNLR-PLR was a significant independent prognostic factor for RFS and OS ($P<0.05$).

Conclusions: CoNLR-PLR was a significant prognostic predictor for CRC patients who received FOLFOX-based chemotherapy. Evaluating this index can accurately predict the clinical treatment outcomes after chemotherapy.

Keywords: colorectal cancer, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, FOLFOX-based chemotherapy, coNLR-PLR

Introduction

Recently, colorectal cancer (CRC) has become the third most frequent malignant tumor worldwide and the fourth deadliest cancer due to recurrence and metastasis.[1] In China, patients diagnosed as advanced CRC account for approximately 6–8% of malignancies. Accumulating evidence has confirmed that the overall survival (OS) and recurrence-free survival (RFS) of patients with locally advanced CRC can be improved through perioperative chemotherapy besides surgical resection (R0).[2–4] Regardless of improvements of surgical methods and combined chemotherapeutic regimens, the prognostic outcomes remain unsatisfactory.[5] Conventionally, clinical and pathological characteristics, including high cancer stage, inadequate sampling from lymph nodes, poorly differentiated histology and lymph-vascular invasion, have been identified as significant risk factors for poor prognosis.[6] The guidelines

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of the National Comprehensive Cancer Network (NCCN) recommend using adjuvant chemotherapy to prevent postoperative tumor recurrence. However, these traditional markers may sometimes be incapable of accurate prediction of the prognosis. Therefore, it is of great significance to find easily available and reliable prognostic factors for distinguishing high-risk cases and providing the optimum chemotherapeutic strategy, aiming to further enhance the therapeutic effects.

Several retrospective studies have revealed that adjuvant chemotherapy caused severer systemic inflammatory reaction and weaker adaptive immune response, bringing about an imbalance between inflammation and malignant tumor to stimulate cancer progression and recurrence.[7,8] Predictive peripheral blood factors of inflammatory response include counts of neutrophils, white blood cells, monocytes, lymphocytes and platelets, together with expressions of acute-phase proteins. Moreover, platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR) are well-known biomarkers closely associated with the survival of patients with biliary tract cancer, gastric cancer, ovarian cancer and CRC.[9–12] Nevertheless, the roles of the two inflammatory indices remain controversial.[13,14]

To verify the predictive values of these biomarkers, we proposed a novel prognostic scoring system (coNLR-PLR) that combined NLR with PLR to evaluate the prognosis of CRC patients more accurately. We then employed this system to explore the potential role in augmenting the predictive capacity for the prognosis of chemotherapy.

Materials and methods

The study has been approved by the ethics committee of No. 3 Hangzhou People's Hospital, and was performed in compliance with the standards of the Declaration of Helsinki. Before the study started, written informed consent has been obtained from all patients.

Selection of patients

A total of 480 patients with primary CRC, who received postoperative FOLFOX-based chemotherapy in Department of Colorectal Surgery, No. 3 Hangzhou People's Hospital from January 2007 to January 2013, were enrolled and retrospectively analyzed. Inclusion criteria: (1) Patients who received surgical resection for CRC and were pathologically defined as TNM stage III/IV; (2) without hematological diseases, infections, renal dysfunction or hyperpyrexia; (3) without using drugs including NSAIDs; (4) without

inflammation-related diseases or vascular disorders; (4) without receiving radiotherapy, chemotherapy or any other targeted therapies.

Protocol for adjuvant chemotherapy according to NCCN guidelines

All patients received adjuvant chemotherapy with the FOLFOX regimen according to the NCCN guidelines. FOLFOX regimen: 85 mg/m^2 oxaliplatin, 200 mg/m^2 calcium levofolinate and 400 mg/m^2 bolus 5-fluorouracil (5-FU), all on day 1; infusion with 2,400 mg/m^2 5-FU on days 1–3. The regimen was performed once every 2 weeks, 12 cycles in total.

Clinical, pathological and laboratory data

To determine the predictive value, we collected the clinical, pathological and laboratory data of patients before receiving the 1st, 4th, 8th and 12th cycles of adjuvant chemotherapy. The clinical and pathological characteristics, such as gender, age, body mass index (BMI), as well as tumor site, differentiation, TNM stage and histological type, were collected from the medical records. Laboratory measurements were performed on the day before chemotherapy, which included counts of neutrophils, white blood cells, lymphocytes and platelets, as well as expressions of some biochemical factors such as serum carbohydrate antigen 199 (CA199), carcinoembryonic antigen (CEA) and C-reactive protein (CRP). Furthermore, the ratio of absolute count of neutrophils to that of lymphocytes was defined as NLR, and the ratio of absolute count of platelets to that of lymphocytes was defined as PLR.

NLR and PLR scoring method

Based on the optimum cut-off value obtained from the receiver operating characteristic (ROC) curve, the score of NLR was 1 or 0 when patient had a high or low NLR during each chemotherapy. Likewise, the score of PLR was 1 or 0 in the case of a high or low PLR. During the same period of chemotherapy, coNLR-PLR, ie, the combined score, was assigned a score of 1 when patient had a high NLR or PLR and a score of 0 when both values were low. Also, the score was 2 in the case of two high values. Therefore, the scores throughout the four periods of chemotherapy ranged from 0 to 8 scores. The coNLR-PLR scores during one period were defined as the sum of NLR and PLR scores.

Follow-up data of survival prognosis

Patients were regularly followed up through telephone calls and letters every 3–6 months until deadline or death. Colonoscopy and computed tomography were conducted at appointments during follow-up. Death was informed by outpatient medical records, social security death index of patient or notification from the family members. The time from the first day of palliative chemotherapy to recurrence or disease progression was defined as RFS, and the time from the first day of palliative chemotherapy to the last follow-up or death because of any reason was defined as OS. Follow-up was ended after January 1, 2018.

Statistical analysis

The best cut-off values for PLR and NLR as predictive markers for OS were determined by ROC analysis with the You-den Index. The association between PLR and NLR was analyzed by linear regression. The associations between coNLR-PLR score and pathological and clinical characteristics were assessed by the Fisher's exact probability test or Chi-square test. To study prognosis, the Kaplan–Meier method was employed to calculate PFS and OS, with the differences compared by the log-rank test. Univariate and multivariate analyses were carried out by using the Cox proportional hazards model with 95% confidence interval to evaluate the effect of the above-mentioned characteristics and some significant prognostic factors (eg, PLR and NLR). $P \leq 0.05$ was considered statistically significant. All analyses were conducted using SPSS 11.5 for Windows.

Results

Patient characteristics and outcomes

Table 1 summarizes the detailed clinical and pathological characteristics together with laboratory parameters of the 480 eligible patients. The average age was (62.7±18.19) years old, and the male/female ratio was 1.39. Of these patients, 297 and 183 were diagnosed as primary rectal cancer and colon cancer, respectively. Besides, 63.13% of the CRC patients were at stage III and 36.87% were at stage IV. The maximum size of primary lesion in 155 patients was 5 cm, and most tumors presented poorly differentiated histology (G3/G4) (59.79%). Most lesions of 281 patients (58.54%) reached an invasive depth of T3, and 203 patients (42.29%) were subjected to local nodal metastasis (≥2). The positive expression rates of serum

CEA and CA199 were 60.21% and 53.13%, respectively. According to nutritional indices, a majority of the patients had normal BMI (65%) and high level of albumin (67.08%). With regard to laboratory parameters, the abnormal percentages of neutrophils, white blood cells, platelets, lymphocytes and CRP were 37.91%, 56.04%, 37.29%, 48.75% and 61.04%, respectively.

Analysis of coNLR-PLR scoring system

Based on ROC curves, the optimum cut-off values of PLR and NLR for OS divided into four periods of chemotherapy were calculated (Figure 1). The optimum cut-off values of NLR were 3.029, 2.466, 2.102 and 1.795, respectively, and those of PLR were 216.438, 187.572, 169.027 and 174.368, respectively (Table 2). Clearly, these values gradually dropped, but the AUC values hardly changed. Then, linear regression analysis was performed to study whether there was significant correlation between NLR and PLR in each period ($P<0.001$) (Figure 2). Furthermore, NLR scores were more closely associated with coNLR-PLR scores during chemotherapy (Figure 3).

Relationships of clinical characteristics with coNLR-PLR scores

Table 1 lists the baseline clinical characteristics according to coNLR-PLR scores. The age, BMI, gender, lymph node metastasis, tumor site and size, CA199 level, albumin level, white blood cell count, lymphocyte count and platelet count of all groups were similar ($P>0.05$). In contrast, cancer stage, grade, invasion, serum CEA level, neutrophil count and CRP level were significantly associated with coNLR-PLR scores ($P<0.05$). In detail, the patients with high scores had high cancer stage, grade, invasive capacity, serum CEA level, neutrophil count and CRP level. Collectively, high coNLR-PLR scores were closely related with poor prognosis.

Survival prognosis for each coNLR-PLR score

According to the follow-up results, 184 (38.33%) patients underwent recurrence, of whom 54 and 130 were subjected to local recurrence and distant metastasis, respectively. Additionally, 201 (44.79%) patients were dead due to tumor recurrence (169 cases), chemotherapeutic toxicity (2 cases) and unknown reasons. Table 3 lists the relationships of clinical characteristics with prognosis of RFS and OS. High cancer stage (IV), severe invasion (T4), abnormal neutrophil count (high/low) and evaluated coNLR-PLR

**Table 1** Relationships between clinical characteristics and coNLR-PLR

Characteristics	Total n=480	Score 0 n=28	Score 1 n=39	Score 2 n=47	Score 3 n=56	Score 4 n=69	Score 5 n=74	Score 6 n=72	Score 7 n=50	Score 8 n=45	P
Age (years)											0.235
<60	221	18	15	19	31	31	33	37	21	16	
≥60	259	10	24	28	25	38	41	35	29	29	
BMI (kg/m^2)[1]											0.237
Normal	312	19	28	30	40	45	47	36	35	32	
High/low	168	9	11	17	16	24	27	36	15	13	
Gender											0.468
Male	279	17	23	28	34	33	50	37	31	26	
Female	201	11	16	19	22	36	24	35	19	19	
Location											0.393
Colon	183	11	12	20	18	35	23	27	19	18	
Rectal	297	17	27	27	38	34	51	45	31	27	
Tumor size(cm)											0.374
<5	325	15	29	33	38	41	56	46	35	32	
≥5	155	13	10	14	18	28	18	26	15	13	
Cancer stage											0.015
III	303	20	29	35	38	48	39	42	34	21	
IV	177	8	10	12	18	21	35	30	16	24	
Cancer grade											0.015
G1/G2	193	18	22	22	25	27	28	22	15	14	
G3/G4	287	10	17	25	31	42	46	50	35	31	
Tumor invasion											<0.001
T3	281	18	29	34	42	49	31	32	21	25	
T4	199	10	10	13	14	20	43	40	29	20	
Lymph node metastasis											0.457
<2	277	15	23	28	34	33	50	37	31	26	
≥2	203	13	16	19	22	36	24	35	19	19	
CEA (ng/ml)[2]											0.013
<5	289	17	26	34	38	48	44	30	29	23	
≥5	191	11	13	13	18	21	30	42	21	22	
CA199 (kU/L)[3]											0.140
<35	225	12	20	26	35	24	33	32	21	22	
≥35	255	16	19	21	21	45	41	40	29	23	
Albumin (g/dL)											0.193
<3.5	158	15	17	18	17	21	25	20	13	12	
≥3.5	322	13	22	29	39	48	49	52	37	33	
WBC count (×10^9/L)[4]											0.424
Normal	211	16	22	22	27	29	31	30	17	17	
High/low	269	12	17	25	29	40	43	42	33	28	

(Continued)

Table 1 (Continued).

Characteristics	Total n=480	Score 0 n=28	Score 1 n=39	Score 2 n=47	Score 3 n=56	Score 4 n=69	Score 5 n=74	Score 6 n=72	Score 7 n=50	Score 8 n=45	P
Neutrophil count ($\times10^9$/L)											0.038
Normal	298	17	24	30	41	48	52	41	24	21	
High/low	182	11	15	17	15	21	22	31	26	24	
Lymphocyte count ($\times10^9$/L)											0.309
Normal	246	18	14	20	31	31	42	35	23	16	
High/low	234	10	17	19	25	38	32	37	27	29	
Platelet count ($\times10^9$/L)											0.074
Normal	301	20	27	33	41	45	44	45	25	21	
High/low	179	8	12	14	15	24	30	27	25	24	
CRP (mg/L)[5]											0.025
Normal	187	18	20	22	24	22	21	24	19	17	
High	293	10	19	25	32	47	53	48	31	28	

Abbreviations: BMI, body mass index; CEA, carcinoembryonic antigen; CA199, carbohydrate antigen; WBC count, white blood cell count; CRP, C-reactive protein; coNLR-PLR, combined neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio.
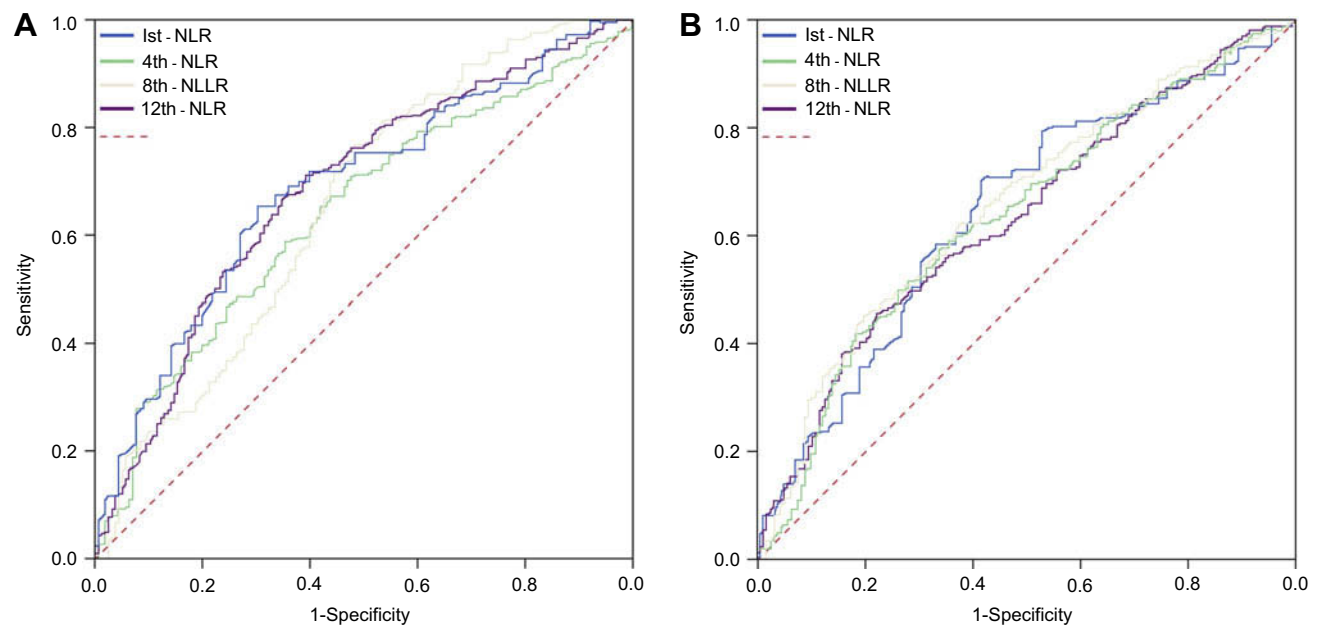
Figure 1 Receiver operating characteristic curve analysis for OS and RFS between NLR and PLR in four periods of chemotherapy. (**A**) For NLR, the optimal cut-off values were 3.029, 2.466, 2.102 and 1.795 in periods of chemotherapy. (**B**) For PLR, the optimal cut-off values, respectively, were 216.138, 187.572, 160.027 and 171.368 in periods of chemotherapy.
Abbreviations: NLR, neutrophil-to-lymphocyte; PLR, platelet-to-lymphocyte; ROC, receiver operating characteristic; AUC, area under the curve.

scores had significant associations with poor OS and RFS ($P<0.05$). As suggested by the log-rank test and Kaplan–Meier curve, the median OS was significantly shortened with increasing coNLR-PLR score ($P<0.001$) (Figure 4A).

Similarly, the median RFS also decreased as the coNLR-PLR score increased ($P<0.001$) (Figure 4B). Thus, patients can be effectively differentiated using the coNLR-NLR scoring system.

Table 2 Combined score of NLR-PLR by ROC curve analysis

	NLR						PRL					
	AUC	95%CI	P	Cut-off	High	Low	AUC	95%CI	P	Cut-off	High	Low
1st Chemotherapy	0.725	0.637–0.736	<0.001	3.029	251	209	0.646	0.594–0.699	<0.001	216.138	234	226
4th Chemotherapy	0.686	0.590–0.693	<0.001	2.466	237	223	0.637	0.585–0.690	<0.001	187.572	219	241
8th Chemotherapy	0.702	0.601–0.709	<0.001	2.102	221	239	0.656	0.605–0.708	<0.001	160.027	226	234
12th Chemotherapy	0.673	0.632–0.734	<0.001	1.795	203	257	0.583	0.583–0.686	<0.001	174.368	198	262

Abbreviations: OS, overall survival; RFS, recurrence-free survival; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.
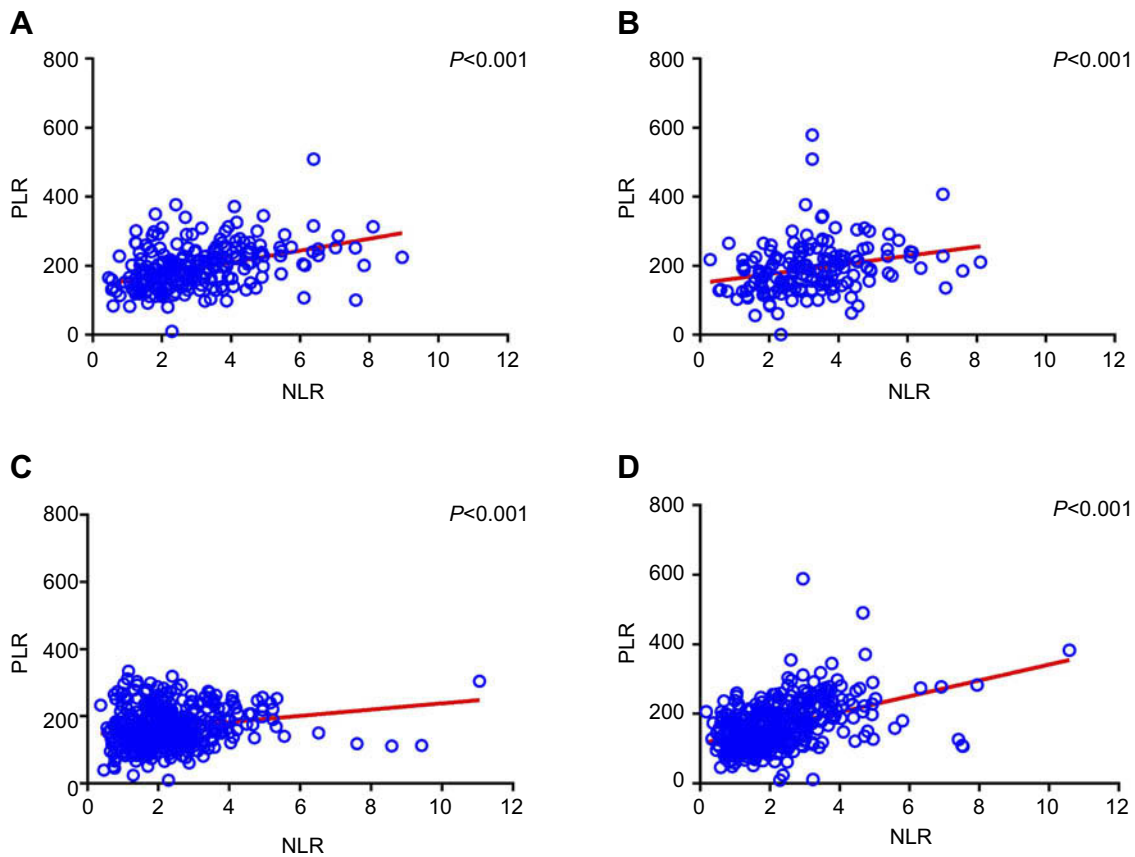

Figure 2 Linear regression of NLR and PLR during the four periods of adjuvant chemotherapy. (**A**) During the 1st period, the linear correlation coefficient of NLR and PLR was 0.672 and *P*-value was less than 0.001. (**B**) During the 4th period, the linear correlation coefficient of NLR and PLR was 0.622 and *P*-value was less than 0.001. (**C**) During the 12th period, the linear correlation coefficient of NLR and PLR was 0.781 and *P*-value was less than 0.001.
Abbreviations: RFS, recurrence-free survival; OS, overall survival; BMI, body mass index; CEA, carcinoembryonic antigen; CA199, carbohydrate antigen; WBC, white blood cells; CRP, C-reactive protein; coNLR-PLR, combined neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio.

Independent prognostic value of elevated coNLR-PLR score for poor survival

Univariate and multivariate analyses were carried out for various parameters to identify independent factors for survival prognosis (Tables 4 and 5). Univariate analysis revealed that high cancer stage, low differentiation grade, severe invasion, lymph node metastasis, serum CEA level, neutrophil count and raised coNLR-PLR score were all significantly associated with both OS and RFS (*P*<0.05). Platelet count and serum CA199 were significantly associated with RFS (*P*<0.05) but not OS. Nevertheless, lymphocyte count was significantly associated with OS (*P*=0.037) instead of RFS. Subsequently, the significant factors (*P*<0.05) in univariate analysis were included in the Cox proportional hazards model for multivariate analysis.
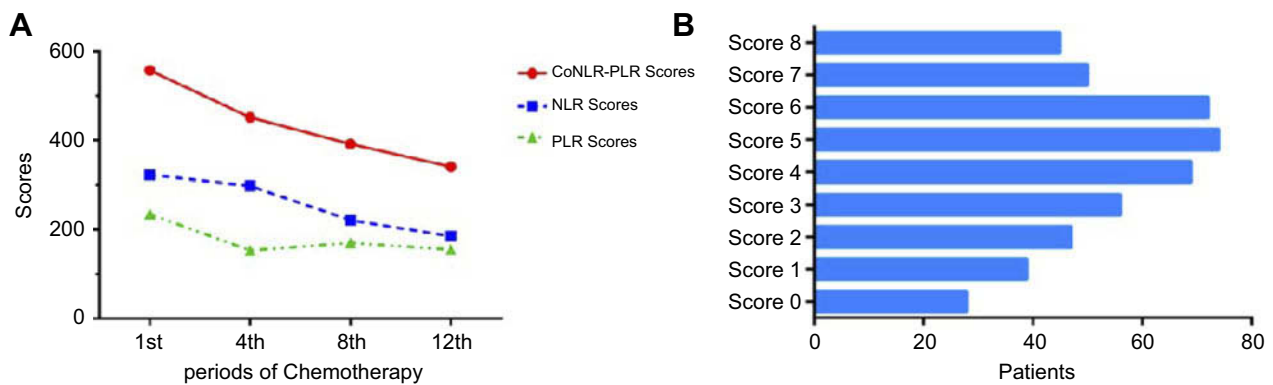
Figure 3 Distribution between score and chemotherapy period. (**A**) According to the four periods, NLR score curve was closer to coNLR-PLR than PLR. (**B**) According to the coNLR-PLR score, distribution of the number of patients was in each score.
Abbreviations: OS, overall survival; BMI, body mass index; CEA, carcinoembryonic antigen; CA199, carbohydrate antigen; WBC, white blood cells.

High cancer stage, severe invasion, lymph node metastasis and increased coNLR-PLR score had significant associations with poor prognosis of RFS and OS ($P<0.05$).

Discussion

Because of persistent response to chronic inflammation, some predictive biomarkers can dynamically indicate the survival prognosis of patients receiving adjuvant chemotherapy.[15] Cell factors in the peripheral blood, such as NLR and PLR, typically reflect the inflammatory status.[16,17] In this study, we proposed a novel index combining NLR with PLR, which could accurately predict the survival prognosis of CRC patients receiving FOLFOX-based chemotherapy.

Researchers have endeavored to unravel the mechanisms for the inflammatory responses of malignant tumors for decades.[18] The growth of tumor cells promotes the necrosis, hypoxia and injury of local tissues, thereby disturbing the homeostasis and activating immune responses. As a result, IL-1, IL-6, IL-8, vascular endothelial growth factor, tumor necrosis factor and some other pro-inflammatory cytokines are secreted by tumor cells and/or inflammatory cells related with tumors. These cytokines thereafter result in tumor growth, angiogenesis, metastasis and invasion, reverse adaptive immune responses, and boost the resistance to cytotoxic substances.[19,20] Notably, elevated PLR and NLR were accompanied by increase of platelet and neutrophil counts but decrease of lymphocyte count, indicating that inflammatory responses associated with platelets and neutrophils were enhanced and the antitumor immune responses mediated by lymphocytes were attenuated.

In the presence of inflammatory signals, neutrophils are activated quickly and migrate to inflammatory sites.[21] Because of chronic inflammation, the persistent stimulus to neutrophils aggravates oxidative stress that damages the epithelium and

induces pro-mutagenic DNA lesions.[22] Besides, neutrophils may suppress lymphocyte activity upon antitumor immune responses and promote remodeling of the extracellular matrix.[23,24] Herein, neutrophil count was significantly associated with prognosis only in univariate analysis.

Baseline platelet count has been recognized as an index of chemotherapy prognosis for advanced CRC.[25] Aggregation of platelets in the circulation is able to protect tumor cells from immune surveillance and shear stress by forming platelet cloaks.[26] Moreover, chemoresistance can be triggered by platelets throughout epithelial–mesenchymal transition, direct protection, anti-apoptotic pathways mediated by PAI-1 or immunosuppression regulated by NKG2-D down-regulation.[27] We herein assessed the predictive value of platelet count in CRC patients receiving chemotherapy, which was an independent factor for RFS only in univariate analysis.

Additionally, lymphocytes play an important role in antitumor immune responses.[28] By changing the tumor microenvironment, lympho-depletion probably contributes to the attenuation of intestinal tumorigenesis and anti-tumor immune responses.[29,30] Furthermore, lymphopenia has also been linked to elevated circulating IL-7 level that facilitates lymphangiogenesis, tumor proliferation, and metastasis.[31] Hence, the CRC chemotherapy-related lymphopenia in this study may be partly explained.

Given that these inflammatory indices are intrinsically correlated, NLR and PLR before treatment are significant factors for predicting the responses of a variety of cancers to chemotherapy.[32] Nevertheless, using only one index may bring about bias and risk in detection. Therefore, we employed a coNLR-PLR scoring system to analyze RFS and OS more accurately during four periods of FOLFOX-based chemotherapy. The coNLR-PLR score was calculated by adding up

Table 3 Association of clinical baseline characteristics with RFS and OS

Characteristics	Total n=480	RFS n(%) of recurrence	*P*-value	OS n(%) of deaths	*P*-value
Age (years)			0.746		0.231
<60	221	83 (45.11%)		99 (49.25%)	
≥60	259	101 (54.89%)		102 (50.75%)	
BMI (kg/m^2)			0.386		0.749
Normal	312	124 (67.39%)		129 (64.18%)	
High/low	168	60 (32.61%)		72 (35.82%)	
Gender			0.696		0.365
Male	279	109 (59.24%)		112 (55.72%)	
Female	201	75 (40.76%)		89 (44.28%)	
Location			0.185		0.160
Colon	183	77 (41.85%)		84 (41.79%)	
Rectal	297	107 (58.15%)		117 (58.21%)	
Tumor size (cm)			0.472		0.072
<5	325	121 (65.76%)		127 (63.18%)	
≥5	155	63 (34.24%)		74 (36.82%)	
Cancer stage			<0.001		<0.001
III	303	93 (50.54%)		86 (42.79%)	
IV	177	91 (49.46%)		115 (57.21%)	
Cancer grade			0.013		0.198
G1/G2	193	61 (33.15%)		74 (36.82%)	
G3/G4	287	123 (66.85%)		127 (63.18%)	
Tumor invasion			0.015		0.019
T3	281	95 (51.63%)		104 (51.74%)	
T4	199	89 (48.37%)		95 (47.26%)	
Lymph node metastasis			0.081		0.134
<2	277	97 (52.72%)		108 (53.73%)	
≥2	203	87 (47.28%)		93 (46.27%)	
CEA (ng/ml)			0.092		0.703
<5	289	102 (55.43%)		119 (59.20%)	
≥5	191	82 (44.57%)		82 (40.80%)	
CA199 (kU/L)			0.372		0.551
<35	225	91 (40.44%)		91 (40.44%)	
≥35	255	93 (50.54%)		110 (43.14%)	
Albumin (g/dL)			0.493		0.534
<3.5	158	64 (34.78%)		63 (31.34%)	
≥3.5	322	120 (65.22%)		138 (68.66%)	
WBC count (×10^9/L)			0.085		0.107
Normal	211	90 (48.91%)		97 (48.26%)	
High/low	269	94 (51.07%)		104 (51.74%)	
Neutrophil count (×10^9/L)			0.018		0.025
Normal	298	102 (55.43%)		113 (56.22%)	
High/low	182	82 (44.57%)		88 (43.78%)	

(Continued)

Table 3 (Continued).

Characteristics	Total n=480	RFS n(%) of recurrence	P-value	OS n(%) of deaths	P-value
Lymphocyte count (×10⁹/L)			0.002		0.197
Normal	246	111 (60.33%)		96 (47.76%)	
High/low	234	73 (39.67%)		105 (52.24%)	
Platelet count (×10⁹/L)			0.152		0.855
Normal	301	108 (58.70%)		127 (63.18%)	
High/low	179	76 (41.30%)		74 (36.82%)	
CRP (mg/L)			0.367		0.483
Normal	187	67 (36.41%)		82 (40.80%)	
High	293	117 (63.59%)		119 (59.20%)	
CoNLR-PLR			<0.001		<0.001
Score 0	28	6 (3.26%)		5 (2.48%)	
Score 1	39	8 (4.35%)		10(4.98%)	
Score 2	47	13 (7.07%)		15 (7.46%)	
Score 3	56	18 (9.78%)		16 (7.96%)	
Score 4	69	19 (10.33%)		22 (10.95%)	
Score 5	74	29 (15.76%)		33 (16.42%)	
Score 6	72	31 (16.85%)		34 (16.92%)	
Score 7	50	28 (15.22%)		31 (15.42%)	
Score 8	45	32 (17.38%)		35 (17.41%)	

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.
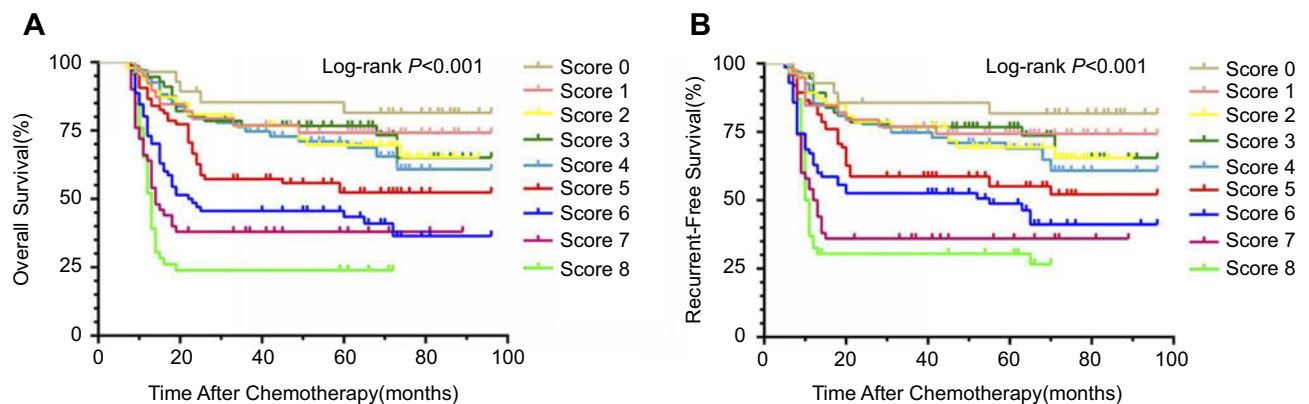
Figure 4 Comparison of survival prognosis in each coNLR-PLR score. (**A**) For overall survival, patients with higher had poorer prognosis (log-rank *p*<0.001). (**B**) For recurrent-free survival, patients with higher had poorer prognosis (log-rank *p*<0.001).
Abbreviations: RFS, recurrence-free survival; CEA, carcinoembryonic antigen; CA199, carbohydrate antigen; WBC, white blood cells; CRP, C-reactive protein.

continuous cycles of optimum cut-off values according to ROC curve analysis, unlike the Glasgow prognostic score with three stratifications (0, 1 and 2).[33] To the best of our knowledge, this is a rare study regarding the association between coNLR-PLR score and the prognosis of CRC patients receiving chemotherapy. This index was a significant independent prognostic factor, and a higher one suggested poorer prognosis for RFS and OS. Also, the coNLR-PLR scoring system was superior to NLR or PLR alone.

Similar to the results of literature before, factors related with cancer stage and invasion besides coNLR-PLR were also identified by univariate and multivariate analyses as significant prognostic indices.[34,35] However, only univariate analysis showed that serum CEA and CA199 levels had associations with poor prognosis, which was contrary to a previous study.[36] This inflammatory biomarker, which is facilely detectable, simple, objective, economical and reproducible, can be tested at the beginning of chemotherapy and

Table 4 Prognostic factors associated with OS in univariate and multivariate analysis

Characteristics	Univariate analysis			Multivariate analysis		
	HR	95% CI		P	HR	95% CI		P
Age (years)	1.024	0.713	1.47	0.721				
BMI (kg/m^2)	1.982	0.972	1.433	0.511				
Gender	0.935	0.648	1.348	0.412				
Location	0.933	0.644	1.352	0.214				
Tumor size (cm)	0.862	0.585	1.27	0.453				
Cancer stage	2.333	1.264	3.907	<0.001	2.383	1.454	3.907	0.001
Cancer grade	2.545	1.076	4.716	<0.001	2.993	0.78	3.423	0.082
Tumor invasion	1.649	2.962	4.423	<0.001	0.446	0.003	0.094	0.011
Lymph node metastasis	2.906	2.662	3.73	<0.001	2.051	1.223	4.141	0.024
CEA (ng/ml)	1.369	1.959	2.451	0.021	1.045	0.971	1.249	0.223
CA199 (kU/L)	1.379	0.819	1.841	0.342				
Albumin (g/dL)	1.527	0.911	2.159	0.534				
WBC count (×10^9/L)	1.281	0.699	1.847	0.493				
Neutrophil count (×10^9/L)	2.112	1.431	3.766	0.002	1.462	0.855	2.143	0.249
Lymphocyte count (×10^9/L)	1.961	1.574	3.497	0.037	1.041	0.744	1.953	0.201
Platelet count (×10^9/L)	1.174	0.944	1.731	0.322				
CRP (mg/L)	0.914	0.851	1.564	0.291				
CoNLR-PLR Scores								
Score 0	0.935	1.512	2.742	0.559				
Score 1	1.312	1.334	2.753	0.453				
Score 2	0.997	1.412	2.316	0.361				
Score 3	1.103	1.024	2.212	0.237				
Score 4	1.088	0.972	1.724	0.422				
Score 5	1.122	1.043	2.019	0.371				
Score 6	1.033	1.012	2.019	0.013	0.784	0.427	1.639	0.349
Score 7	2.319	2.017	4.324	<0.001	0.436	0.14	1.363	0.016
Score 8	2.029	1.331	4.123	<0.001	3.112	1.624	4.379	<0.001

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; coNLR-PLR, combined NLR ratio and PLR ratio.

dynamically monitored throughout the treatment process.[37] As a complicated model, coNLR-PLR may provide more reliable prognostic evidence for clinicians.

Regardless, this study still has limitations. First, it is a single-center retrospective study. In addition, prospective studies are in need to clarify whether the proposed index can be incorporated into the stratification systems for patients with cancers to individualize treatment regimens.

Conclusion

In summary, we proposed a coNLR-PLR scoring system, as a novel index correlated independently with survival prognosis, and verified that peripheral blood cells dominantly bridged the interaction between cancer and host during adjuvant chemotherapy. Nevertheless,

these findings ought to be validated by in-depth prospective studies.

Abbreviation list

CRC, colorectal cancer; BMI, body mass index; CEA, carcinoembryonic antigen; CA199, carbohydrate antigen; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; coNLR-PLR, combined neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio; NCCN, National Comprehensive Cancer Network; RFS, recurrence-free survival; OS, overall survival.

Author contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Table 5 Prognostic factors associated with RFS in univariate and multivariate analysis

Characteristics	Univariate analysis for RFS			Multivariate analysis for RFS		
	HR	95% CI		*P*	HR	95% CI		*P*
Age (years)	1.013	0.705	1.457	0.643				
BMI (kg/m$^{2)}$)	1.088	0.745	1.588	0.463				
Gender	0.971	0.673	1.401	0.475				
Location	0.97	0.669	1.407	0.373				
Tumor size (cm)	0.918	0.623	1.353	0.665				
Cancer stage	2.449	1.675	3.581	<0.001	2.511	1.305	4.131	0.009
Cancer grade	2.061	1.175	3.689	0.007	1.62	0.742	2.771	0.383
Tumor invasion	6.333	4.429	9.932	<0.001	1.049	0.914	1.991	0.043
Lymph node metastasis	3.52	2.406	5.152	<0.001	0.911	0.769	1.553	0.007
CEA (ng/ml)	2.901	1.651	3.741	0.001	1.611	1.102	2.731	0.219
CA199 (kU/L)	2.121	0.974	4.322	0.041	1.003	0.871	1.942	0.119
Albumin (g/dL)	1.704	0.748	1.544	0.199				
WBC count (×10^9/L)	1.004	0.679	1.445	0.283				
Neutrophil count (×10^9/L)	2.006	1.696	3.453	0.025	1.413	0.722	2.69	0.317
Lymphocyte count (×10^9/L)	1.717	1.336	2.532	0.391				
Platelet count (×10^9/L)	2.322	1.421	4.402	0.004	2.017	1.552	4.754	0.001
CRP (mg/L)	0.997	0.876	1.543	0.279				
CoNLR-PLR Scores								
Score 0	1.283	1.031	2.734	0.371				
Score 1	1.072	0.943	1.861	0.452				
Score 2	1.529	1.042	2.943	0.461				
Score 3	2.118	1.541	3.142	0.393				
Score 4	1.255	1.003	2.248	0.319				
Score 5	1.058	0.857	1.942	0.037	2.101	1.271	3.562	0.181
Score 6	1.021	1.007	2.645	0.013	1.46	1.003	3.519	0.049
Score 7	1.058	1.02	2.789	0.008	1.829	1.097	3.012	0.102
Score 8	1.721	0.973	3.061	<0.001	2.551	1.335	3.906	0.019

Abbreviation: coNLR-PLR, combined neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio.

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