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Systemic inflammatory indices predict tumor response to neoadjuvant chemoradiotherapy for locally advanced rectal cancer

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Abstract. Systemic inflammatory responses are associated with the prognosis of patients with colorectal cancer. However, the value in predicting tumor responses to neoadjuvant chemoradiotherapy (nCRT) remains to be elucidated. The current study aimed to investigate the association between systemic inflammatory indices and pathological complete response (pCR). The training and validation cohorts included 225 and 96 patients with locally advanced rectal cancer. The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio were recorded prior to nCRT and radical surgery. Univariate and multivariate analysis were used to investigate the association between systemic inflammatory indices and pCR. Systemic inflammatory indices prior to or following treatment had no significant association with pCR; however, the percentage change in NLR from pre-nCRT to post-nCRT was associated with a poor response, and a percentage change of >21.5% NLR (P=0.006; OR=0.413; 95% CI=0.22-0.773) was a predictor of poor pCR. Therefore, in rectal cancer, the percentage change in NLR from pre- to post-nCRT was found to be a predictor of poor pCR.

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Abbreviations: nCRT, neoadjuvant chemoradiotherapy; LARC, locally advanced rectal cancer; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; pCR, pathological complete response; TRG, tumor regression grade; CEA, carcino-embryonic antigen

Key words: local advanced rectal cancer, neoadjuvant chemoradiotherapy, systemic inflammatory indices, colorectal cancer, pathological complete response

Introduction

Colorectal cancer has become one of the most common tumors and is the third most common malignancy. Globally, ~1.2 million patients are diagnosed with colorectal cancer and >600,000 die from the disease in 2008 (1). Neoadjuvant chemoradiotherapy (nCRT) prior to radical surgery and post-operative adjuvant chemotherapy is the standard treatment for locally advanced rectal cancer (LARC) (2,3). Certain complications can arise from radical surgery that decrease quality of life, including anastomotic leakage, anastomotic stenosis, urinary and/or sexual dysfunction, low anterior resection syndrome and increased probability of enterostomy (4-6).

Response to neoadjuvant therapy is heterogeneous and ~10-30% of patients with colorectal cancer achieve pathological complete response (pCR) (7). The 'watch and wait' strategy and local resection for patients with pCR following nCRT has become a focus of study (8,9). Generally, pCR is predicted through digital rectum examination, imaging examination, endoscopy and tumor-related markers (9-12). However, the predictions made using these techniques are not always in line with the pathology results (8,13). Currently, there are no affordable and reliable markers that can predict tumor response.

Systemic inflammatory responses have been reported to be predictors of prognosis for numerous types of solid tumors, including gastrointestinal (14,15), pancreatic (16), renal (17) and breast cancer (18). Systemic inflammatory responses can be reflected by hematologic parameters, including lymphocyte count and platelet count, or the ratio of different cell

types, including the platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR) (19,20). The tumor microenvironment is closely associated with the occurrence and development of cancer (21). In the peripheral circulation, neutrophils and lymphocytes act as immunocytes, reflecting the tumor microenvironment, and the number of immunocytes changes according to patient age and immunoreactivity (22). Changes in the NLR may be associated with changes in tumor size during regression due to the nCRT for rectal cancers (23). However, it remains unclear whether systematic inflammatory responses could be used as a marker for identifying patients with tumors achieving pCR following nCRT.

Therefore, the current study investigated pre- and post-nCRT systemic inflammatory indices and changes in these indices from pre-nCRT to post-nCRT to determine the association between these parameters and responsiveness to nCRT in patients with LARC.

Materials and methods

Patients. Data from patients with rectal cancer who received nCRT and radical surgery at the Sixth Affiliated Hospital between January 2013 and October 2018, were retrospectively analyzed. A total of 321 patients were included in this study. The mean age of patients was 58.5 years. A total of 218 patients were male (67.9%) and 103 patients were female (32.1%). The inclusion criteria were as follows: i) 18-75 years old; ii) diagnosis of rectal adenocarcinoma confirmed by biopsy pathology; iii) stage II (T3/T4; N0M0) or stage III (T1-4; N^+M0) evaluated by thoracic and abdominal pelvic CT, pelvic MRI or transluminal ultrasound prior to nCRT; iv) the distance from the anal verge evaluated by digital rectum examination or enteroscopy was <12 cm; v) an Eastern Cooperative Oncology Group score of 0-2; vi) (24) no radiotherapy, chemotherapy or surgical contraindications; and vii) no past medical history of malignant tumors. The exclusion criteria included the following: i) Absence of clinical data; ii) infections prior to new adjuvant therapy or surgery; iii) use of leukocyte enhancing drugs; and iv) incomplete new adjuvant therapy or radical surgery. Prior to the study, all patients provided written informed consent. The current study was approved by the Institutional Review Board of the Sixth Affiliated Hospital following rigorous review.

Treatment. All patients were assessed by a multiple disciplinary team at The Sixth Affiliated Hospital of Sun Yat-sen University and underwent nCRT and radical surgery. The total dose of radiotherapy given was 46-50.4, or 1.8-2.0 Gy for 23-28 fractions. Patients received one of the following two chemotherapy regimens: mFOLFOX6 [85 mg/m^2 oxaliplatin, 400 mg/m^2 leucovorin and 400 mg/m^2 fluorouracil (5-FU) administered through intravenous drip on day 1, followed by 2,400 mg/m^2 fluorouracil continuously administered through intravenous infusion for 48 h] or DeGramont (400 mg/m^2 leucovorin, 400 mg/m^2 F-5U administered through intravenous drip on day 1, followed by 2,400 mg/m^2 fluorouracil continuously administered through intravenous infusion for 48 h). The interval between radiotherapy and surgery was 4-12 weeks and the interval between chemotherapy and surgery was 2-4 weeks.

Peripheral blood examinations. Peripheral blood (2 ml) was collected from all patients within 1 week prior to the first nCRT (pre-nCRT) and 1 week prior to surgery (post-nCRT). Neutrophil, lymphocyte and platelet counts were obtained from the hospital information system. The PLR was calculated as the absolute count of platelets/lymphocytes and NLR was calculated as the absolute count of neutrophils/lymphocytes. The percentage change in NLR from pre-nCRT to post-nCRT was defined as [(post-NLR-pre-NLR)/pre-NLR x100%]. A result of ≥0 indicated that NLR following new adjuvant treatment was increased, whereas a result of <0 indicated that NLR after new adjuvant treatment was decreased. The percentage change in PLR from pre-nCRT to post-nCRT was defined as [(post-PLR-pre-PLR)/pre-PLR x100%].

Pathological assessment. Two experienced pathologists evaluated the tumor regression grades (TRG) of patients based on the American Joint Committee on Cancer (AJCC; 8th edition) (25) as follows: 0, no viable cancer cells (complete response); 1, single cells or rare small groups of cancer cells (near-complete response); 2, residual cancer with evident tumor regression and with single cells or rare small groups of cancer cells (partial response); and 3, extensive residual cancer with no evident tumor regression (poor or no response), pCR was defined as no signs of viable cancer cells in resected specimens and in the lymph nodes.

Statistical analysis. SPSS software (version 24.0; IBM Corp.) was used to analyze data. P<0.05 was considered to indicate a statistically significant difference. The χ^2 test was used to compare the differences between the qualitative variables of the cohorts. The Shapiro-Wilk test confirmed that the quantitative data did not conform to a normal distribution. Therefore, quantitative data between cohorts were compared by the Mann-Whitney U test. Tumor patients were strictly divided into a pCR group (TRG 0) and a non-pCR group (TRG 1-3) according to TRG stages. The 'cut-off' value of the indices was determined by the receiver operating characteristic curve (ROC). Parameters were compared using the χ^2 and t-tests between pCR and non-pCR groups. The association between systemic inflammatory indices and pCR were analyzed by univariate and multivariate logistic regression analysis. The multivariate analysis included the variables of P<0.1 in the univariate analysis.

Results

Patient characteristics. Baseline characteristics of patients in the two cohorts are presented in Table 1. In the training cohort, a total of 152 patients were male (67.6%) and 73 patients were female (32.4%). A total of 162 (72%) patients received a chemotherapy regimen with oxaliplatin (mFOLFOX6). Furthermore, 69 patients (30.6%) achieved pCR. In the validation cohort, 66 patients (68.7%) were male and 30 patients (31.3%) were female. A total of 67 patients (69.8%) received chemotherapy regimens with oxaliplatin. There were 26 patients (27.1%) who achieved pCR. No statistical differences were observed in clinical characteristics, treatment factors and systemic inflammatory indices between the two cohorts (P>0.05).

Table I. Baseline characteristics of the patients in the training and validation cohorts.

Variable	Training cohort	Validation cohort	P-value
Age, years			0.670
≤65	183	80	
>65	42	16	
Sex			0.834
Male	152	66	
Female	73	30	
CEA prior to treatment, μg/l			0.621
≤5	134	60	
>5	91	36	
Clinical T stage			0.977
T2	8	3	
T3	167	72	
T4	50	21	
Clinical N stage			0.574
N0	32	16	
N1-2	193	80	
Tumor size, cm			0.126
≤5	173	66	
>5	52	30	
Tumor circumference, %			0.838
≤50	91	40	
>50	134	56	
Mesorectal fascia			0.659
Positive	76	30	
Negative	149	66	
Distance from anal verge, cm			0.280
≤5	126	60	
>5	99	36	
Tumor differentiation			0.929
High	71	8	
Medium	133	56	
Low	21	32	
Operation interval of radiotherapy, weeks			0.178
≤7	93	32	
>7	132	64	
Chemotherapy regimens			0.689
With oxaliplatin	162	67	
Without oxaliplatin	63	29	
Chemotherapy courses			0.055
≤4	30	21	
>4	195	75	
Tumor response			0.520
pCR	69	26	
Non-pCR	156	70	
Mean value of pre-NLR (interval)	2.39 (0.59-17.04)	2.52 (0.79-27.46)	0.626
Mean value of pre-PLR (interval)	148.57 (40.31-536.00)	144.21 (47.92-448.84)	0.596
Mean value of post-NLR (interval)	3.66 (0.81-16.79)	3.09 (0.77-12.99)	0.078
Mean value of post-PLR (interval)	237.63 (77.25-1007.07)	220.87 (84.11-595.30)	0.556
Mean value of percentage change in NLR, % (interval)	80 (-81-1066)	57 (-91-412)	0.179
Mean value of percentage change in PLR, % (interval)	74 (-73-605)	69 (-60-343)	0.614

CEA, carcino-embryonic antigen; T, tumor; N, lymph node; pCR, pathological complete response; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

Table II. Association between systemic inflammatory indices and pCR in the training cohort.

Variable (mean)	pCR Group (n=69)	Non-pCR Group (n=156)	P-value
Pre-NLR	2.55	2.32	0.234
Pre-PLR	157.30	144.71	0.302
Post-NLR	3.34	3.80	0.071
Post-PLR	232.40	239.94	0.761
% change in NLR	63	87	0.036
% change in PLR	61	80	0.170

pCR, pathological complete response; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

Analysis for pCR in the training cohort. Associations between systemic inflammation indices and pCR for the training cohort are presented in Table II. The mean value of the percentage change in NLR was 63% in the pCR group and 87% in the non-pCR group. Additionally, the percentage change in NLR was significantly increased in the pCR group compared with the non-pCR group (P=0.036; Fig. 1). However, there were no significant differences in the other pre- and post-treatment systemic inflammation indices between the pCR and non-pCR group.

The area under the curve of the ROC analysis was 0.588 (P=0.036; Fig. 2). Therefore, we divided the percentage change in NLR into two categories for subsequent analyses: A percentage change of ≤21.5% NLR and a percentage change of >21.5% NLR.

Univariate analysis demonstrated that carcino-embryonic antigen (CEA) prior to treatment, tumor differentiation, chemotherapy regimens and the percentage change in NLR were associated with pCR (Table III). A total of 45% of patients with a percentage change of ≤21.5% NLR achieved pCR compared with 23% of patients with a percentage change of >21.5% NLR (P=0.001; Fig. 3). Multivariate analysis included all variables in the univariate analysis, including sex, CEA prior to treatment, tumor scope, tumor differentiation, chemotherapy regimens and the percentage change in NLR (P<0.1). However, only the percentage change in NLR (P=0.006; OR=0.413; 95% CI=0.22-0.773) and chemotherapy regimens (P=0.042; OR=2.257; 95% CI=1.031-4.942) were significant following multivariate analysis. Sex (P=0.345), CEA prior to treatment (P=0.052), tumor differentiation (P=0.173) and tumor circumference (P=0.294) were not significant. Thus, the percentage change in NLR and chemotherapy regimens were significant predictors of pCR.

Analysis for pCR in the validation cohort. Percentage change of 21.5% NLR was considered to be optimal to predict pCR events in the training cohort (Fig. 2). To verify the association between the percentage change in NLR and pCR, univariate and multivariate analysis for pCR were performed for the validation cohort (Table IV). Univariate analysis demonstrated that tumor differentiation, chemotherapy regimens and the percentage change in NLR were associated with pCR. However, only the percentage change in NLR (P=0.03; OR=0.337; 95% CI=0.126-0.9) was significant following multivariate analysis.

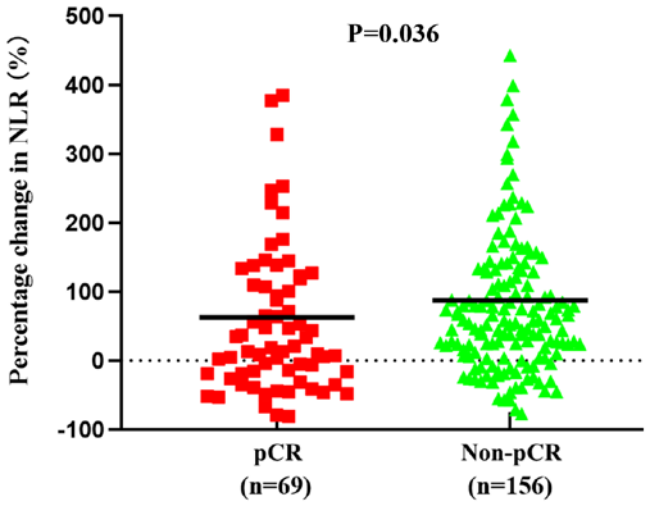

Figure 1. Mean percentage change in NLR values between the pCR and non-pCR groups in the training cohort (bold bar). NLR, neutrophil-to-Slymphocyte ratio; pCR, pathological complete response.

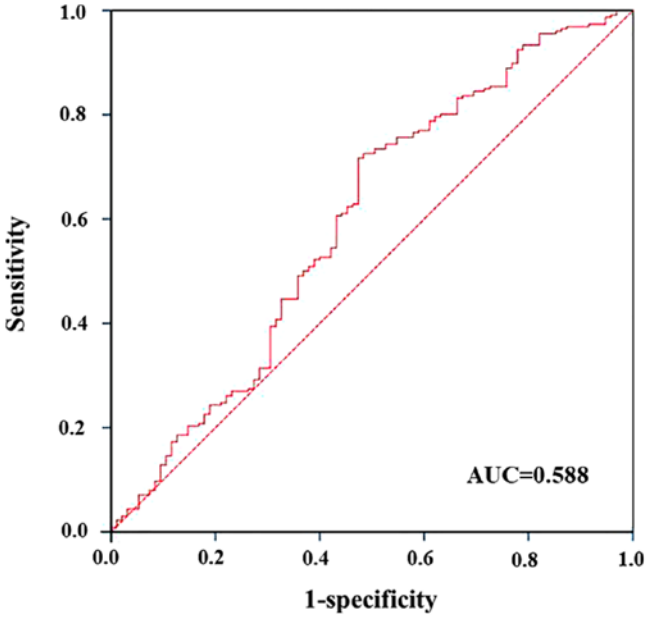

Figure 2. Receiver operator characteristic analysis of the percentage change in neutrophil-to-lymphocyte ratio for prediction of pathological complete response. AUC, area under the curve.

In summary, the results verified that the percentage change in NLR was a significant predictor of pCR.

Discussion

Systemic inflammatory responses have become a focus of interest for physicians, and cancer-related inflammatory responses have been recognized as a 'hallmark' of cancer development and progression (26). PLR and NLR are important indicators of systemic inflammatory responses (27,28) and the increase in these indicators has been confirmed as adverse factors for the prognosis of multiple malignant tumors, including colon cancer and rectal cancer (29,30). However, the association between systemic inflammatory responses

Table III. Univariate and multivariate analysis in the training cohort.

Variable	Univariate		Multivariate	
	OR value (95% CI)	P-value	OR value (95% CI)	P-value
Age (≤65 vs. >65 years)	1.14 (0.62-2.11)	0.668		
Sex (male vs. female)	0.47 (0.21-1.08)	0.070	1.38 (0.71-2.68)	0.345
CEA prior to treatment (≤5 vs. >5 μg/l)	0.44 (0.24-0.82)	0.009	0.53 (0.27-1.01)	0.052
Clinical T stage (T2 vs. >T3-4)	1.08 (0.55-2.13)	0.817		
Clinical N stage (N0 vs. N1-2)	0.97 (0.43-2.17)	0.955		
Tumor size (≤5 vs. >5 cm)	1.42 (0.74-2.72)	0.628		
Tumor circumference (≤50 vs. >50%)	0.59 (0.33-1.05)	0.073	0.72 (0.39-1.33)	0.294
Mesorectal fascia (negative vs. positive)	1.07 (0.59-1.94)	0.832		
Distance from anal verge (≤5 vs. >5 cm)	0.69 (0.39-1.23)	0.204		
Tumor differentiation (low vs. medium, high)	0.36 (0.17-0.90)	0.023	0.51 (0.19-1.34)	0.173
Operation interval of radiotherapy (≤7 vs. >7 weeks)	1.36 (0.76-2.44)	0.301		
Chemotherapy regimens (with oxaliplatin vs. without oxaliplatin)	3.04 (1.44-6.41)	0.003	2.26 (1.03-4.94)	0.042
Chemotherapy courses (≤4 vs. >4)	1.91 (0.74-4.91)	0.174		
% change in NLR (≤21.5 vs. >21.5)	0.36 (0.20-0.67)	0.001	0.41 (0.22-0.77)	0.006

CEA, carcino-embryonic antigen; T, tumor; N, lymph node; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio; CI, confidence interval.

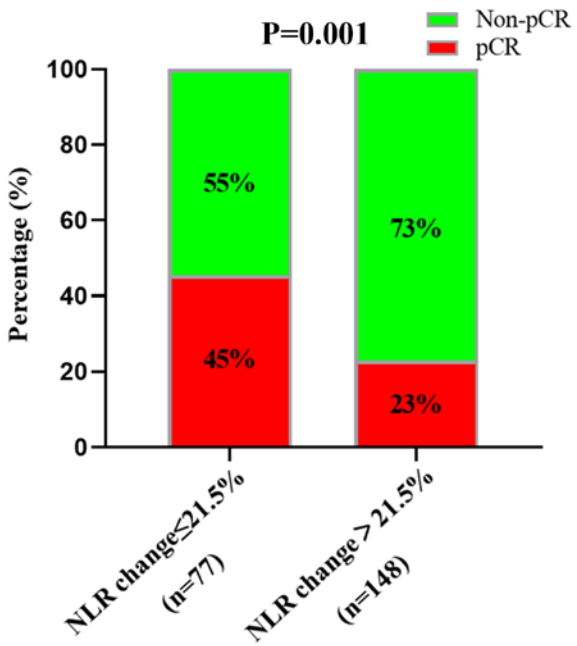

Figure 3. Responsiveness in patients with a percentage change of ≤21.5 and >21.5% NLR. NLR, neutrophil-to-lymphocyte ratio; pCR, pathological complete response.

and tumor regression following nCRT in patients with LARC remains unclear. In the current study, pre- and post-nCRT NLR and PLR, and changes in these indices from pre-nCRT to post-nCRT were investigated. Through logistic regression analysis, the results demonstrated that the percentage change in NLR was associated with pCR. These findings were validated by the validation cohort. To the best of our knowledge, the current study is the first to assess the predictive impact of NLR change on tumor treatment outcomes of nCRT in patients with LARC. The results demonstrated that the percentage change in NLR from pre-nCRT to post-nCRT could be used to identify patients achieving pCR following nCRT.

Previous studies have focused on the predictive value of baseline systemic inflammatory responses. Dudani *et al* (31) reviewed 1,527 patients with rectal cancer receiving nCRT and surgery, and revealed that NLR and PLR were not predictors for disease-free survival or overall survival, and could not predict pCR. Additionally, Shen *et al* (29) reported that there was no significant association between tumor response and NLR to nCRT. It has previously been reported that baseline systemic inflammatory responses could not predict tumor responses in colorectal cancer (32,33). In the present study, there was no significant association between pCR and NLR or PLR during nCRT.

Furthermore, the results also revealed that adding oxaliplatin to the chemotherapy regimens improved the rate of pCR. Currently, it is controversial whether combining Oxaliplatin with nCRT could improve prognosis and the rate of pCR. The results from the FOWARC study demonstrated that the application of oxaliplatin to nCRT for the treatment of middle and lower rectal cancer exhibited higher rates of pCR (34). Allegra *et al* (35) compared the rates of pCR in patients receiving neoadjuvant chemoradiotherapy with or without oxaliplatin, and the results did not indicate any significant differences (17.8 vs. 19.5%; P=0.42), which were inconsistent with the results obtained in the current study. This may be due to the higher dose used in the current study and the FOWARC study compared with that used in other studies (85 vs. 50-60 mg/m^2) (34,35).

In numerous studies involving rectal cancer, CEA levels were investigated as potential predictors of rectal cancer. Moureau-Zabotto *et al* (36) demonstrated that a pre-nCRT

Table IV. Univariate and multivariate analysis in the validation cohort.

	Univariate		Multivariate	
Variable	OR value (95% CI)	P-value	OR value (95% CI)	P-value
Age (≤65 vs. >65 years)	1.80 (0.58-5.58)	0.304		
Sex (male vs. female)	1.03 (0.39-2.73)	0.951		
CEA prior to treatment (≤5 vs. >5 μg/l)	1.64 (0.66-4.10)	0.286		
Clinical T stage (T2 vs. >T3-4)	1.10 (0.36-3.23)	0.862		
Clinical N stage (N0 vs. N1-2)	1.75 (0.46-6.72)	0.411		
Tumor size (≤5 vs. >5 cm)	0.80 (0.31-2.10)	0.650		
Tumor circumference (≤50 vs. >50%)	0.51 (0.20-1.26)	0.140		
Mesorectal fascia (negative vs. positive)	1.24 (0.48-3.21)	0.665		
Distance from anal verge (≤5 vs. >5 cm)	0.84 (0.33-2.16)	0.722		
Tumor differentiation (low vs. medium, high)	0.33 (0.08-1.45)	0.023	0.32 (0.07-1.55)	0.157
Operation interval of radiotherapy (≤7 vs. >7 weeks)	1.97 (0.70-5.54)	0.194		
Chemotherapy regimens (with oxaliplatin vs. without oxaliplatin)	3.06 (0.95-9.87)	0.054	2.18 (0.64-7.47)	0.213
Chemotherapy course (≤4 vs. >4 courses)	1.76 (0.53-5.84)	0.348		
Percentage change in NLR (≤21.5 vs. >21.5%)	0.34 (0.13-0.85)	0.019	0.34 (0.13-0.90)	0.030

CEA, carcino-embryonic antigen; T, tumor; N, lymph node; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio; CI, confidence interval.

serum CEA level of <5 ng/ml was significantly associated with pCR and tumor downstaging (36). However, other studies did not support this conclusion (37). In the current study, a pre-nCRT serum CEA level of ≤5 ng/ml was significantly associated with pCR according to univariate analysis; however, the results of multivariate analysis (P=0.052) were not significant. This result may be due to the small simple size used in the current study.

The present study had several limitations. Since data was obtained from a single center, the results could not be validated with those from another institute. Furthermore, the retrospective observational design of the current study may cause bias. Further prospective studies are required to validate the results of the present study. The results demonstrated an association between the percentage change in NLR and responsiveness to nCRT among patients with rectal cancer. However, the results failed to determine the cause of this association. Furthermore, a reduction in circulating immunocytes may be due to cytotoxic neoadjuvant chemotherapy. However, neoadjuvant radiation and chemotherapy have been reported to release neoantigens by killing tumor cells, and the immune reaction may cause an increase in circulating immunocytes (38). However, the ratios of different immunocytes as an independent prognostic factor, or parameters associated to therapeutic activity were not examined. Therefore, additional prognostic data is required.

In conclusion, the results of the current study investigated the pre- and post-nCRT systemic inflammatory indices and changes in these indices from pre-nCRT to post-nCRT. The association between the percentage change in NLR and responsiveness to nCRT among patients with rectal cancer was determined, and the results demonstrated that this association could identify patients who achieved pCR following neoadjuvant chemoradiotherapy. These results may provide a novel strategy for colorectal cancer treatment.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

SCL, LW, JD and LK designed the study. SLL and LH were responsible for data collection. ZL and SCL analyzed data. SLL, LH, JD, LW and LK drafted the manuscript. SCL, JD and LW revised the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study protocol was reviewed and approved by the Institutional Review Board of the Sixth Affiliated Hospital, Sun Yat-sen University, China. The present study was carried out in accordance with the recommendations of the Declaration

of Helsinki for biomedical research involving human patients. Written informed consent was obtained from patients prior to enrollment.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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