



Can pretreatment platelet-to-lymphocyte and neutrophil-to-lymphocyte ratios predict long-term oncologic outcomes after preoperative chemoradiation followed by surgery for locally advanced rectal cancer?

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Purpose: Systemic inflammation is associated with various malignancies, including colorectal cancer, as possible prognostic predictors. We aimed to evaluate the correlation of pretreatment the platelet-to-lymphocyte (PLR) and the neutrophil-to-lymphocyte (NLR) ratio with long-term oncologic outcomes and pathologic complete response (pCR) in locally advanced rectal cancer patients who received neoadjuvant concurrent chemoradiotherapy (CRT) followed by curative resection.

Methods: Between October 1996 and December 2015, 168 rectal cancer patients treated with preoperative CRT followed by surgery were enrolled. The set cut-off/mean PLR and NLR were 170 and 2.8. We analyzed the relationship between PLR, NLR, and the 5-year overall survival (OS), disease-free survival (DFS), and pCR rate.

Results: The 5-year OS rates were 75.9% and 59.8% in the high and low-PLR groups. The 5-year DFS rates were 62.9% and 50.8% in the high- and low-PLR groups, with no significant difference. In addition, the 5-year OS rates were 75.7% and 58.4%, and the 5-year DFS rates were 62.5% and 50.0% in the high- and low-NLR groups, respectively, both without any significant difference. Multivariate analysis showed only pretreatment PLR as an independent prognostic factor for OS (hazard ratio, 1.850; 95% confidence interval, 1.041–3.287; $P=0.036$), and both serologic markers were not independent prognostic factors for 5-year DFS.

Conclusion: Neither PLR nor NLR was associated with 5-year DFS nor pCR to neoadjuvant CRT. Only pretreatment PLR can be used in predicting OS in locally advanced rectal cancer patients who received neoadjuvant CRT followed by curative resection.

Keywords: Rectal neoplasms; Neoadjuvant therapy; Inflammation; Biomarkers; Survival

INTRODUCTION

Colorectal cancer (CRC) is the third most common malignancy and one of the leading causes of cancer-related deaths worldwide [1]. Specifically, rectal cancer accounts for 30% to 40% of CRCs,

and its treatment strategy is different and more complicated than that of colon cancer. Neoadjuvant chemoradiotherapy (CRT) followed by total mesorectal excision and adjuvant chemotherapy is the standard treatment strategy for locally advanced rectal cancer, which has led to a better prognosis of rectal cancer patients [2]. However, the 5-year overall survival (OS) of rectal cancer patients remains at approximately 60% [3]. To obtain more favorable oncologic outcomes, reliable markers predicting poor prognosis could help identify high-risk patients, allowing more careful follow-up and determining appropriate adjuvant treatment. The most well-known prognostic factor in rectal cancer patients is the TNM staging system proposed by the American Joint Committee on Cancer (AJCC). In addition, tumor markers, genetic information, and additional pathologic features, such as venous, lymphatic, and perineural invasion are used to predict tumor recur-

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rence and long-term prognosis. However, patients with similar clinicopathologic characteristics and staging may have different prognoses.

The inflammatory response of the host has become an interesting concern in recent clinical research. Systemic inflammation is known to play an important role in carcinogenesis and cancer progression, and several hematological markers can reflect the host's inflammatory status. In this context, there have been a number of studies investigating several pretreatment inflammatory laboratory markers have helped in diagnosing cancer and predicting short-term and long-term prognosis in the recent decade [4, 5]. Such pretreatment laboratory markers can be easily assayed in routine blood tests, and their prognostic value for various types of cancer, including CRC, has been confirmed through previous studies [4, 6]. Among various laboratory markers, the most frequently studied are neutrophils, lymphocytes, platelets, and their combinations. Platelet-to-lymphocyte (PLR) and neutrophil-to-lymphocyte (NLR) ratios have been widely used as prognostic tools in various malignancies, based on the theory that platelets and neutrophils are pro-tumorigenic factors and lymphocytes are protective factors against tumors [7, 8]. Some studies have reported that elevated PLR and NLR can reflect poor oncologic outcomes as well as response to neoadjuvant CRT in rectal cancer patients [9, 10]. However, there are still debates about the prognostic effect of PLR and NLR for locally advanced rectal cancer cases because of existing contradictory results [9, 11].

Therefore, we aimed to evaluate the long-term prognostic role of pretreatment PLR and NLR, as well as other hematological markers, for locally advanced rectal cancer patients who received neoadjuvant CRT followed by curative surgical resection. We also analyzed whether these serologic markers were correlated with pathologic tumor response to CRT. We hypothesized that elevated pretreatment PLR may be associated with poor long-term oncologic outcomes.

METHODS

Patients

We retrospectively reviewed data from 168 patients with histologically proven rectal adenocarcinoma who received neoadjuvant CRT followed by curative resection, between October 1996 and December 2015, at the Yonsei University Wonju Severance Christian Hospital. All patients underwent clinical evaluation, including digital rectal examination, basic laboratory tests, tumor marker assays, and colonoscopy. Computed tomography and pelvic magnetic resonance imaging (MRI) were used for clinical staging. The final diagnosis was confirmed by pathological reports. The exclusion criteria were as follows: metastatic rectal cancer at diagnosis (stage IV), emergency cases, palliative surgery, incomplete neoadjuvant chemotherapy or radiotherapy, and concomitant hematologic or coagulation disorders.

Informed consent was obtained from all patients and the study

protocol was approved by the Institutional Review Board of Wonju Severance Christian Hospital (No. CR321067), in accordance with the Declaration of Helsinki.

Hematologic markers

Peripheral blood samples were obtained 1 week prior to neoadjuvant CRT and 1 week prior to the index surgery. White blood cell (WBC), neutrophil, lymphocyte, and platelet counts, along with albumin and C-reactive protein levels, were included. The PLR and NLR were determined by dividing the absolute platelet and neutrophil count, respectively, by the absolute lymphocyte count. The cut-off PLR and NLR were also set as the mean values.

Outcomes

The primary outcomes were 5-year OS and disease-free survival (DFS). The secondary outcome was the pathologic response to neoadjuvant CRT. OS was defined as the date of diagnosis to the date of all-cause death, and DFS was defined as the date of diagnosis to the date of recurrence or all-cause death. Pathologic complete response (pCR) was defined as the absence of residual invasive cancer cells in resected specimens and harvested lymph nodes.

Treatment protocol and follow-up

All included patients received a total radiation dose of 50.4 Gy over 5 weeks (45 Gy in 25 fractions to the whole pelvis and 5.4 Gy in 3 fractions to the primary tumor). Concurrent chemotherapy was administered via an intravenous bolus of 5-fluorouracil (425 mg/m²/day) and leucovorin (20 mg/m²/day) for 5 days during the 1st and 5th weeks of radiation therapy, or via oral capecitabine (1,650 mg/m²/day), twice daily, during the whole radiation therapy period. Post-CRT pelvic MRI was performed for restaging. Six to 8 weeks after the completion of neoadjuvant CRT (mean duration, 7.6 weeks), curative total mesorectal excision was performed by 2 experienced colorectal surgeons. The pathologic (yp) stage was recorded according to the eighth edition of the AJCC TNM classification. Postoperative adjuvant chemotherapy was administered using intravenous 5-fluorouracil (425 mg/m²) and leucovorin (20 mg/m²) for 4 to 8 weeks. Patients were followed up every 3 months for the first 2 years postoperatively, semiannually for the next 3 years, and annually thereafter. Physical examinations and laboratory tests for tumor markers were performed at each follow-up, and abdominopelvic computed tomography was performed semiannually. Colonoscopy was performed annually or when the patient had recurrent or other abnormal symptoms. Patients were followed up for 5 years and additional diagnostic tests, such as MRI, were performed for suspected recurrence or metastasis.

Statistical analysis

Categorical variables were described by frequencies and percentages and were analyzed using the chi-square test or Fisher exact

test. Continuous variables were described as means and standard deviations and were analyzed using the Student t-test or Mann-Whitney U-test. Kaplan-Meier curve analysis with log-rank test and the Cox proportional hazard model were used for survival analysis. Variables in multivariate analysis were selected by backward stepwise method. All statistical analyses were performed us-

ing IBM SPSS Statistics for Windows ver. 25.0 (IBM Corp., Armonk, NY, USA), and the P-values of <0.05 were considered statistically significant.

Table 1. Baseline characteristics of the patients

Characteristic	Data
Age (yr)	61.06 ± 10.76
< 65	97 (59.9)
≥ 65	65 (40.1)
Sex	
Male	121 (74.7)
Female	41 (25.3)
Tumor location from anal verge (cm)	6.34 ± 3.26
Carcinoembryonic antigen (ng/mL)	
Pre-CRT	8.41 ± 16.93
Post-CRT	4.05 ± 6.74
Operation	
LAR	127 (78.4)
Hartmann	8 (4.9)
APR	25 (15.4)
Local excision	1 (0.6)
Diverting stoma	
None	14 (8.6)
Ileostomy	116 (71.6)
Colostomy	32 (19.8)
Tumor size (cm)	3.112 ± 1.71
No. of harvested lymph nodes	16.61 ± 8.68
Stage	
0	17 (10.5)
I	39 (24.1)
II	58 (35.8)
III	48 (29.6)
Tumor differentiation	
WD	30 (18.5)
MD	120 (74.1)
PD, mucinous	8 (4.9)
Pathologic complete response	
Yes	17 (10.5)
No	144 (88.9)

Values are presented as mean ± standard deviation or number (%). CRT, chemoradiotherapy; LAR, low anterior resection; APR, abdominoperineal resection; WD, well differentiation; MD, moderate differentiation; PD, poorly differentiation.

RESULTS

Patient characteristics

Among 168 patients with locally advanced rectal cancer who underwent neoadjuvant CRT, 2 with hematologic disorders and 4 who underwent palliative surgery were excluded. Among the 162 included patients, the median follow-up period was 66 months (range, 0–234 months), the median age was 61 years (range, 38–85 years), and 121 (74.7%) were male. The pre- and post-CRT mean serum carcinoembryonic antigen (CEA) levels were 8.41 ng/mL and 4.05 ng/mL, respectively. Low anterior resection was the most commonly performed operation (78.9%), and approximately 71.6% of the patients underwent protective diversion to ensure a safe anastomosis site. The tumors were located at a mean of 6.34 cm above the anal verge, with a mean size of 3.11 cm. After preoperative CRT, 17 patients (10.5%) showed pCR. The stages after surgery were as follows: stage I, 9.9% (n = 17); stage II, 24.1% (n = 39); and stage III, 29.6% (n = 48) (Table 1).

Laboratory profiles

The mean WBC, neutrophil, lymphocyte, and platelet counts were $7.4 \times 10^9/L$, $4.7 \times 10^9/L$, $1.9 \times 10^9/L$, and $300 \times 10^9/L$, respectively. The mean serum albumin and C-reactive protein levels were 4.13 g/dL and 1.06 mg/dL, respectively. The mean/cut-off NLR and PLR used were 2.80 and 170, respectively (Table 2).

Relationships between clinicopathologic serologic factors and pathologic complete response to neoadjuvant chemoradiotherapy

On univariate analysis, pCR to neoadjuvant CRT was not associated with clinicopathologic features such as age, sex, tumor differentiation, or tumor location. Tumor size was significantly smaller in the group showing pCR (1.72 ± 0.78 cm vs. 3.22 ± 1.72 cm,

Table 2. Pretreatment laboratory markers

Laboratory profile	Mean ± 2SD	Median (IQR)
WBC	7,426.63 ± 2,086.62	7,510 (6,020–8,845)
Neutrophil	4,709.00 ± 1,720.24	4,500 (3,520–5,520)
Lymphocyte	1,986.63 ± 732.25	1,970 (1,510–2,360)
Platelet	300,088.05 ± 86,951.05	294,500 (239,750–350,500)
Albumin	4.13 ± 0.49	4.2 (3.9–4.5)
C-reactive protein	1.06 ± 2.41	0.29 (0.14–0.615)
NLR	2.80 ± 2.92	2.31 (1.69–3.21)
PLR	170.28 ± 98.65	152 (114–202)

SD, standard deviation; IQR, interquartile range; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

$P=0.005$). There was no association between pCR and serologic markers, including WBC, neutrophil, lymphocyte, and platelet counts, and serum albumin and C-reactive protein levels. In addition, pCR to neoadjuvant CRT did not show any association with pre-CRT PLR and NLR ($P=0.799$ and $P=0.422$, respectively), but was significantly associated with the pre-CRT and post-CRT CEA levels (4.16 ± 3.92 ng/mL vs. 8.90 ± 17.86 ng/mL, $P=0.008$; and 2.23 ± 0.35 ng/mL vs. 4.86 ± 7.97 ng/mL, $P=0.001$; respectively) (Table 3).

Survival analysis

During the 5-year follow-up period, there were 15 cases of local

recurrence (9.3%) and 37 cases of systemic recurrence (22.8%). In addition, the overall 5-year OS and DFS rates were 70.4% and 58.6%, respectively. According to the Kaplan-Meier survival analysis, the 5-year OS rates were significantly different between the high- and low-PLR groups (75.9% vs. 59.8%, $P=0.033$). However, the 5-year DFS rates were not significantly different between the 2 groups (62.9% vs. 50.8%, $P=0.125$). In terms of NLR, the 5-year OS rates were 75.7% in high NLR group and 58.4% in low NLR group ($P=0.035$); and 5-year DFS rates were 62.0% in high NLR group and 50.0% in low NLR group, respectively ($P=0.173$, respectively) (Fig. 1). In addition, we further analyzed the correlation between survival and inflammatory markers by dividing pa-

Table 3. The association between pathologic complete response (pCR) and serologic markers

Variable	pCR (n = 17)	Non-pCR (n = 145)	P-value
Age (yr)			
< 65	10 (58.8)	86 (59.7)	
≥ 65	7 (41.2)	58 (40.3)	> 0.999
Sex			
Male	10 (58.8)	110 (76.4)	
Female	7 (41.2)	34 (23.6)	0.142 ^a
Tumor differentiation			
WD	2 (11.8)	28 (19.9)	
MD	15 (88.2)	105 (74.5)	
PD, Mucinous	0 (0)	8 (5.7)	0.541 ^a
Tumor location from anal verge (cm)	5.94 ± 3.27	6.39 ± 3.27	0.604
Tumor size (cm)	1.72 ± 0.78	3.22 ± 1.72	0.005 ^b
White blood cell ($\times 10^9/L$)	$7,498.24 \pm 1,708.019$	$7,392.25 \pm 2,117.024$	0.843
Neutrophil ($\times 10^9/L$)	$4,713.53 \pm 1,666.437$	$4,684.30 \pm 1,714.003$	0.947
Lymphocyte ($\times 10^9/L$)	$1,982.35 \pm 362.793$	$1,985.99 \pm 767.797$	0.974
C-reactive protein (mg/dL)	0.48 ± 0.50	1.08 ± 2.52	0.430
Albumin (g/dL)	4.282 ± 0.354	4.118 ± 0.506	0.195
Platelet ($\times 10^9/L$)			
< 300	8 (47.1)	77 (54.6)	
≥ 300	9 (52.9)	64 (45.4)	0.613
PLR			
< 170	11 (64.7)	86 (60.6)	
≥ 170	6 (35.3)	56 (39.4)	0.799
NLR			
< 2.8	13 (76.5)	91 (64.1)	
≥ 2.8	4 (23.5)	51 (35.9)	0.422
Pre-CRT CEA (ng/mL)	4.157 ± 3.916	8.903 ± 17.860	0.008
Post-CRT CEA (ng/mL)	2.23 ± 0.349	4.86 ± 7.93	0.001

WD, well differentiation; MD, moderate differentiation; PD, poorly differentiation; PLR, plate-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; CRT, chemoradiotherapy; CEA, carcinoembryonic antigen.

Analyzed using ^aFisher exact test and ^bMann-Whitney test.

tients into 3 groups, as follows: group A, with lower PLR and NLR than the cut-off values; group B, with only one marker lower than the cut-off value, and group C: with higher PLR and NLR than the cut-off values. The 5-year OS rates were 77.2%, 69.0%, and 55.7% in groups A, B, and C, respectively, with statistically significant differences between groups A and C, but not group B ($P =$

0.019). The 5-year DFS rates were 66.3%, 59.0%, and 53.7% in groups A, B, and C, respectively, with no statistically significant intergroup differences ($P = 0.250$) (Fig. 2).

Univariate and multivariate analyses using the Cox proportional hazard model were performed to identify independent prognostic factors for OS and DFS. Univariate analysis showed that stage III

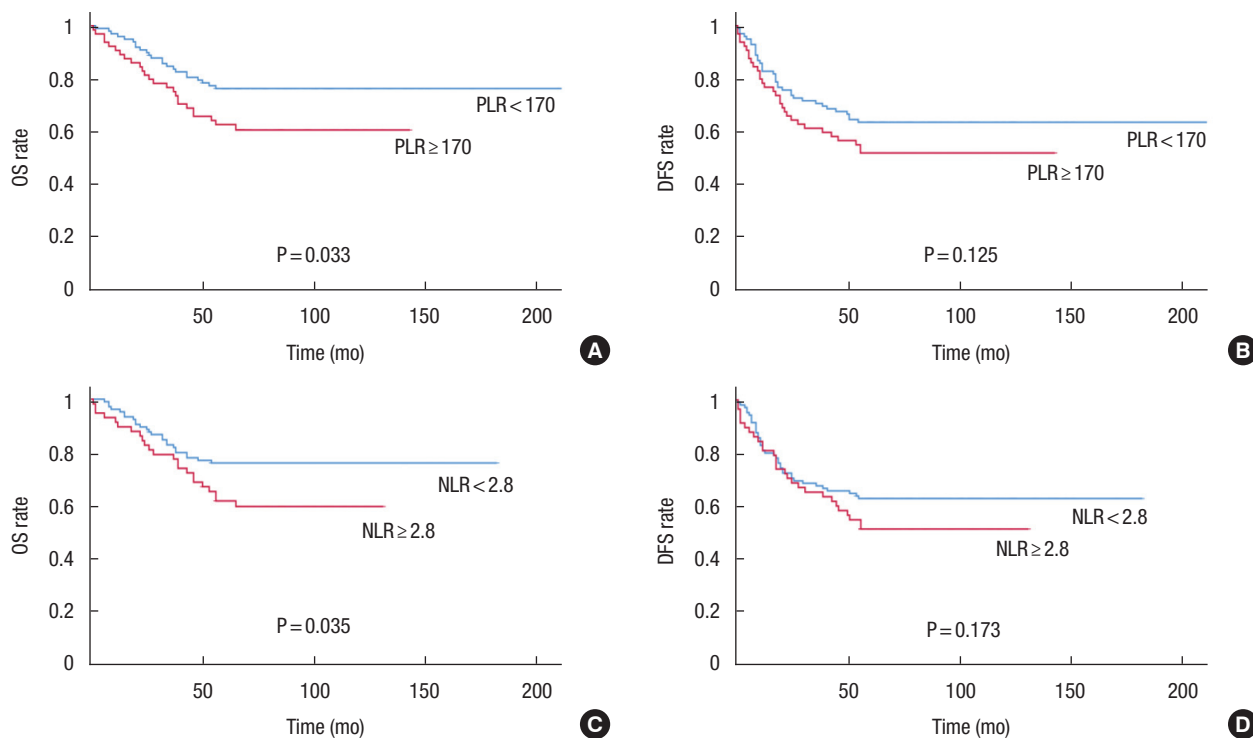


Fig. 1. Survival rates according to laboratory markers. (A) The 5-year overall survival (OS) rates were 75.9% and 59.8% in the high- and low-PLR groups, respectively ($P = 0.033$). (B) The 5-year disease-free survival (DFS) rates were 62.9% and 50.8% in the high- and low-PLR groups, respectively ($P = 0.125$). (C) The 5-year OS rates were 75.7% and 58.4% in the high- and low-NLR groups, respectively ($P = 0.035$). (D) The 5-year DFS rates were 62.5% and 50.0% in the high- and low-NLR groups, respectively ($P = 0.173$). PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio.

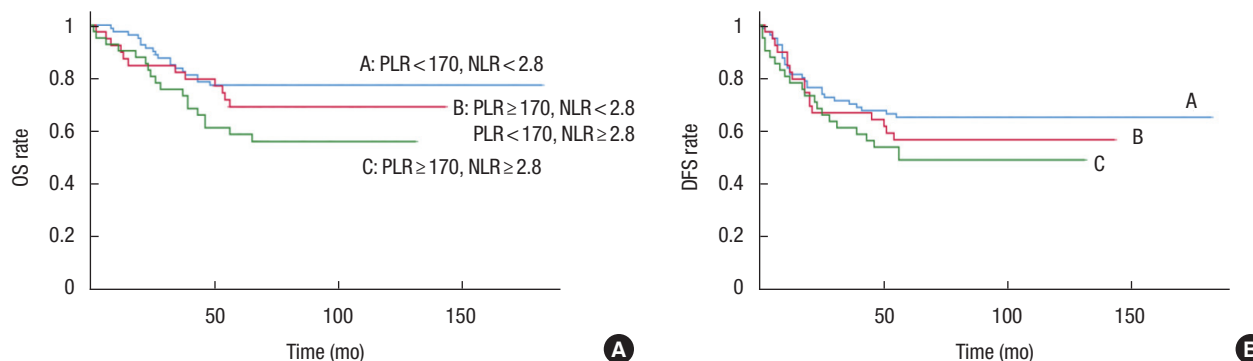


Fig. 2. Survival curves according to the number of elevated laboratory markers. (A) The 5-year overall survival (OS) rates were 77.2%, 69.0%, and 55.7% in groups A, B, and C, respectively, with statistically significant differences between groups A and C, but not group B ($P = 0.019$). (B) The 5-year disease-free survival (DFS) rates were 66.3%, 59%, and 53.7% in groups A, B, and C, respectively ($P = 0.250$). PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio.

Table 4. Cox regression analysis for 5-year overall survival

Variable	Category	Univariate analysis		Multivariate analysis	
		HR (95% CI)	P-value	HR (95% CI)	P-value
Age (yr)	<65 vs. ≥65	1.001 (0.561–1.786)	0.997		
Sex	Male vs. female	1.163 (0.615–2.198)	0.643		
Stage	0, I, II vs. III	2.535 (1.428–4.499)	0.001	2.445 (1.360–4.396)	0.003
pCR	Yes vs. No	1.099 (0.626–1.928)	0.743		
Albumin (g/dL)	<3.5 vs. ≥3.5	1.486 (0.631–3.501)	0.365		
Platelet ($\times 10^9/L$)	<300 vs. ≥300	1.071 (0.608–1.887)	0.812		
PLR	<170 vs. ≥170	1.833 (1.040–3.230)	0.036	1.786 (1.007–3.169)	0.047
NLR	<2.8 vs. ≥2.8	1.819 (1.032–3.205)	0.038		
Pre-CRT CEA (ng/mL)	<5 vs. ≥5	1.556 (0.881–2.746)	0.128		
Post-CRT CEA (ng/mL)	<5 vs. ≥5	3.492 (1.866–6.533)	<0.001	2.780 (1.440–5.365)	0.002

HR, hazard ratio; CI, confidence interval; pCR, pathologic complete response; PLR, plate-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; CRT, chemoradiotherapy; CEA, carcinoembryonic antigen.

Table 5. Cox regression analysis for 5-year disease-free survival

Variable	Category	Univariate		Multivariate	
		HR (95% CI)	P-value	HR (95% CI)	P-value
Age (yr)	<65 vs. ≥65	1.086 (0.669–1.765)	0.738		
Sex	Male vs. female	1.043 (0.601–1.808)	0.881		
Stage	0, I, II vs. III	2.225 (1.360–3.640)	0.001	2.177 (1.319–3.595)	0.002
pCR	Yes vs. No	1.114 (0.619–2.008)	0.718		
Albumin (g/dL)	<3.5 vs. ≥3.5	0.889 (0.284–2.057)	0.783		
Platelet ($\times 10^9/L$)	<300 vs. ≥300	1.320 (0.818–2.132)	0.256		
PLR	<170 vs. ≥170	1.451 (0.898–2.346)	0.129		
NLR	<2.8 vs. ≥2.8	1.396 (0.859–2.269)	0.178		
Pre-CRT CEA (ng/mL)	<5 vs. ≥5	1.749 (1.082–2.826)	0.022		
Post-CRT CEA (ng/mL)	<5 vs. ≥5	3.500 (2.006–6.109)	<0.001	3.291 (1.853–5.845)	<0.001

HR, hazard ratio; CI, confidence interval; pCR, pathologic complete response; PLR, plate-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; CRT, chemoradiotherapy; CEA, carcinoembryonic antigen.

(hazard ratio [HR], 2.535; 95% confidence interval [CI], 1.248–4.499; $P=0.001$), $PLR \geq 170$ (HR, 1.833; 95% CI, 1.040–3.230; $P=0.036$), $NLR \geq 2.8$ (HR, 1.819; 95% CI, 1.032–3.205; $P=0.038$), and post-CRT CEA level ≥ 5 ng/mL (HR, 3.492; 95% CI, 1.866–6.533; $P<0.001$) were statistically significant prognostic factors for worse OS. On multivariate analysis, stage III (HR, 2.445; 95% CI, 1.360–4.396, $P=0.003$), $PLR \geq 170$ (HR, 1.786; 95% CI, 1.007–3.169; $P=0.047$), and post-CRT CEA level ≥ 5 ng/mL (HR, 2.780; 95% CI 1.440–5.365; $P=0.002$) were independent poor prognostic factors for OS (Table 4). In addition, univariate analysis for DFS showed that stage III (HR, 2.225; 95% CI, 1.360–3.640; $P=0.001$), pre-CRT CEA level ≥ 5 ng/mL (HR, 1.749; 95% CI, 1.082–2.826; $P=0.022$), and post-CRT CEA level ≥ 5 ng/mL (HR, 3.500; 95% CI, 2.006–6.109; $P<0.001$) were significant poor prognostic factors. Multivariate analysis showed that stage III

(HR, 2.177; 95% CI, 1.319–3.595; $P=0.002$) and post-CRT CEA level ≥ 5 ng/mL (HR, 3.291; 95% CI, 1.853–5.845; $P<0.001$) were independent prognostic factors for poor DFS (Table 5).

DISCUSSION

We investigated the prognostic role of pretreatment PLR and NLR in patients with locally advanced rectal cancer who received neoadjuvant CRT followed by curative resection. In summary, a smaller tumor size and lower CEA level, but not pretreatment PLR and NLR, were associated with pCR to neoadjuvant CRT. In terms of oncologic outcomes, pretreatment high PLR and NLR were associated with poor 5-year OS on univariate analysis, but only pretreatment high PLR was an independent prognostic factor on multivariate analysis. However, neither serologic inflam-

matory marker was associated with 5-year DFS.

The mechanisms underlying the relationship between systemic inflammation and tumor biology are not yet fully understood; to our knowledge, chronic inflammation induces tissue damage, and repeated regeneration processes result in permanent genetic mutations, such as point mutations, deletions, or rearrangements. Activated inflammatory cells produce numerous chemokines and cytokines, which can influence tumor growth, migration, and differentiation by releasing growth factors. Platelets, which stop bleeding by adhering and aggregating at the injured tissue area, also play important roles in host inflammation and the immune system [12, 13]. Increased and activated platelets release growth factors that facilitate tumor growth and invasion, and contribute to tumor metastasis by helping in cancer cell adhesion and extravasation [14]. Thrombocytosis is associated with the long-term prognosis of CRC patients [15, 16]. Lymphocytes are a subtype of WBCs that are responsible for innate immunity. Lymphocytes are known to play a key role in fighting tumor progression, and a high density of lymphocytic infiltration of the tumor is a known prognostic factor for improved survival in numerous malignancies [17]. Neutrophils are the most abundant WBCs and play an important role in the acute inflammatory response. In addition, neutrophils are associated with various carcinogenic processes, such as tumor growth and proliferation, and tumor angiogenesis by releasing reactive oxygen and nitrogen species, or proteases. Neutrophils can also cause metastatic spread by suppressing natural killer functions and promoting extravasation of tumor cells [18].

In our analysis, 17 patients (10.5%) showed a pCR to neoadjuvant CRT, which is consistent with previously published data. pCR after neoadjuvant CRT is associated with favorable long-term outcomes [19, 20]. Patients with pCR showed a lower incidence of local recurrence and distant metastasis, and higher long-term survival. Sell et al. [19] analyzed the results of 10-year follow-up for stage II to III rectal cancer patients, and reported that patients who achieved pCR after neoadjuvant CRT showed excellent 10-year DFS and OS. In this context, there are many studies on organ-preserving approaches, such as wait-and-watch, or local excision suggesting that a pCR has been acquired after neoadjuvant CRT through imaging and endoscopic studies [21, 22]. According to previous literature, organ-preserving approaches have been determined as feasible and comparable in terms of long-term survival, even if salvage surgery was performed because of recurrence during the close follow-up period. However, in our analysis, the association between pCR and survival was not demonstrated, probably because the number of cases was small.

In addition to imaging tests, an organ-preserving treatment strategy may determine robust prognostic predictors that can help evaluate the response to neoadjuvant CRT. In our analysis, the correlation between the pretreatment serologic markers and pCR was not confirmed, and only tumor size and CEA level were confirmed to be related to pCR. There have been several studies on

whether inflammatory serologic markers are useful in predicting pCR, but there is still debate [10, 23]. Policicchio et al. [24] reported that a high platelet count ($> 350 \times 10^9/L$) and neutrophil count ($> 7,500 \times 10^9/L$) had predictive value with respect to pCR. Sun et al. [10] demonstrated that both elevated NLR (> 3.05) and PLR (145.98) were independent predictors of a good response to neoadjuvant CRT. Andras et al. [23] reported that NLR is a simple and cost-effective marker for predicting neoadjuvant treatment response in LARC, with a cut-off value of 4.5. In contrast, Dudani et al. [25] analyzed 1,237 rectal cancer patients who underwent neoadjuvant CRT, and showed that neither pretreatment PLR nor NLR predicted pCR. However, some studies have focused on changes in serologic markers before and after neoadjuvant CRT. Lee et al. [26] reported that changes in PLR after neoadjuvant CRT could be used as a predictive marker for pCR in rectal cancer patients. In their analysis, the degree of increase in PLR after CRT was the strongest predictor of pCR among various serologic markers. Lai et al. [27] demonstrated that pretreatment PLR and NLR did not correlate with pCR, but a 21.5% change in NLR after neoadjuvant CRT was a predictor of poor pCR.

In terms of survival rate, many studies have investigated whether pretreatment serologic markers, such as PLR and NLR, are associated with long-term oncologic survival as well as pCR in rectal cancer patients who underwent neoadjuvant CRT. A retrospective study by Ke et al. [9] revealed that a pre-CRT elevated PLR (> 188) was an independent prognostic factor for poor DFS, but not for OS, and that a pre-CRT elevated NLR (> 3.5) was an independent prognostic factor for both poor DFS and OS. Zhang et al. [28] reported that a high NLR (≥ 2.3) was associated with unfavorable OS and DFS, and they also reported that NLR was the most effective prognostic marker according to time-dependent ROC analysis. In a study where the cut-off value of NLR was the same as ours, elevated NLR was associated with poor OS, but not with DFS. In addition, NLR did not reflect the response to neoadjuvant CRT [29]. In contrast, there have been several studies showing that pretreatment serologic markers are not related to the survival rate of rectal cancer patients who underwent neoadjuvant CRT followed by curative resection. Dudani et al. [25] conducted a study by setting the cut-off values of PLR and NLR to 150 and 4, respectively, and reported that PLR and NLR were not independent prognostic factors of DFS or OS. Portale et al. [11] found neither PLR nor NLR to be associated with survival in rectal cancer patients. In our analysis, both PLR and NLR showed a correlation with OS, but not with DFS. Further analysis also showed that the cases with a high NLR and PLR showed a poor tendency for DFS compared to those with a low NLR and PLR, but this was not statistically significant. In addition, these serologic markers did not show any association with local recurrence or distant metastasis. In multivariate analysis, only PLR, among the 2 markers, was found to be an independent prognostic factor for OS. Because the cut-off values of these laboratory markers differ from study to study, caution should be taken when generalizing the findings of

individual studies. According to a recent meta-analysis by Hamid et al. [30] which included rectal cancer patients, elevated NLR was an independent factor for poor OS (HR, 2.07; 95% CI, 1.57–2.74; $P < 0.001$) and DFS (HR, 1.80; 95% CI, 1.42–2.28, $P < 0.001$), and the results were the same in the subgroup analysis of patients who received neoadjuvant CRT. In addition, the study demonstrated that the prognostic effect of NLR was superior to that of PLR when comparing the relative HR and other markers.

Our study has several limitations. First, the present study may have selection bias due to its retrospective design. Second, the total number of patients included in this study was relatively small. Third, because the data were obtained from a single center, it may not include the characteristics of various types of patients. Fourth, information on gene profiling and some important pathological reports, such as lymphovascular invasion and perineural invasion, were not assessed because old medical records did not include such additional pathologic features. Fifth, patient factors, such as comorbidities and nutritional status, were not analyzed. Therefore, additional well-designed large-scale studies are needed to confirm the prognostic effect of inflammatory markers with a high level of evidence.

In conclusion, pretreatment PLR may be considered as a potential biomarker for predicting OS in patients with locally advanced rectal cancer who received neoadjuvant CRT followed by curative resection. Although the TNM staging system is still the strongest prognostic factor for rectal cancer, pretreatment laboratory inflammatory markers and tumor markers may provide helpful additional prognostic information. If future related large-scale studies will prove the utility of these economically advantageous serologic biomarkers, it may help clinicians in treatment decision-making for locally advanced rectal cancer patients.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;68:394-424.
2. Benson AB, Venook AP, Al-Hawary MM, Arain MA, Chen YJ, Ciombor KK, et al. NCCN guidelines insights: rectal cancer, version 6.2020. *J Natl Compr Canc Netw* 2020;18:806-15.
3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin* 2020;70:7-30.
4. Dolan RD, McSorley ST, Park JH, Watt DG, Roxburgh CS, Horgan PG, et al. The prognostic value of systemic inflammation in patients undergoing surgery for colon cancer: comparison of composite ratios and cumulative scores. *Br J Cancer* 2018;119:40-51.
5. Watt DG, Ramanathan ML, McSorley ST, Walley K, Park JH, Horgan PG, et al. Clinicopathological determinants of an elevated systemic inflammatory response following elective potentially curative resection for colorectal cancer. *Ann Surg Oncol* 2017;24:2588-94.
6. Dolan RD, Laird BJ, Horgan PG, McMillan DC. The prognostic value of the systemic inflammatory response in randomised clinical trials in cancer: a systematic review. *Crit Rev Oncol Hematol* 2018;132:130-7.
7. Ozawa T, Ishihara S, Nishikawa T, Tanaka T, Tanaka J, Kiyomatsu T, et al. The preoperative platelet to lymphocyte ratio is a prognostic marker in patients with stage II colorectal cancer. *Int J Colorectal Dis* 2015;30:1165-71.
8. Huang XZ, Chen WJ, Zhang X, Wu CC, Zhang CY, Sun SS, et al. An elevated platelet-to-lymphocyte ratio predicts poor prognosis and clinicopathological characteristics in patients with colorectal cancer: a meta-analysis. *Dis Markers* 2017;2017:1053125.
9. Ke TM, Lin LC, Huang CC, Chien YW, Ting WC, Yang CC. High neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio predict poor survival in rectal cancer patients receiving neoadjuvant concurrent chemoradiotherapy. *Medicine (Baltimore)* 2020;99:e19877.
10. Sun Y, Huang Z, Chi P. An inflammation index-based prediction of treatment response to neoadjuvant chemoradiotherapy for rectal mucinous adenocarcinoma. *Int J Clin Oncol* 2020;25:1299-307.
11. Portale G, Cavallin F, Valdegamberi A, Frigo F, Fisco V. Platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio are not prognostic biomarkers in rectal cancer patients with curative resection. *J Gastrointest Surg* 2018;22:1611-8.
12. Ruggeri ZM, Mendolicchio GL. Adhesion mechanisms in platelet function. *Circ Res* 2007;100:1673-85.
13. Jenne CN, Kubes P. Platelets in inflammation and infection. *Platelets* 2015;26:286-92.
14. Haemmerle M, Stone RL, Menter DG, Afshar-Kharghan V, Sood AK. The platelet lifeline to cancer: challenges and opportunities. *Cancer Cell* 2018;33:965-83.
15. Gu D, Szallasi A. Thrombocytosis portends adverse prognosis in colorectal cancer: a meta-analysis of 5,619 patients in 16 individual studies. *Anticancer Res* 2017;37:4717-26.
16. Belluco C, Forlin M, Delrio P, Rega D, Degiuli M, Sofia S, et al. Elevated platelet count is a negative predictive and prognostic marker in locally advanced rectal cancer undergoing neoadjuvant chemoradiation: a retrospective multi-institutional study on 965 patients. *BMC Cancer* 2018;18:1094.
17. Ohtani H. Focus on TILs: prognostic significance of tumor infiltrating lymphocytes in human colorectal cancer. *Cancer Immun* 2007;7:4.

18. Ocana A, Nieto-Jiménez C, Pandiella A, Templeton AJ. Neutrophils in cancer: prognostic role and therapeutic strategies. *Mol Cancer* 2017;16:137.
19. Sell NM, Qwaider YZ, Goldstone RN, Cauley CE, Cusack JC, Ricciardi R, et al. Ten-year survival after pathologic complete response in rectal adenocarcinoma. *J Surg Oncol* 2021;123:293-8.
20. Habr-Gama A, Perez RO, Nadalin W, Sabbaga J, Ribeiro U Jr, Silva e Sousa AH Jr, et al. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. *Ann Surg* 2004;240:711-7.
21. Dossa F, Chesney TR, Acuna SA, Baxter NN. A watch-and-wait approach for locally advanced rectal cancer after a clinical complete response following neoadjuvant chemoradiation: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* 2017; 2:501-13.
22. Park IJ, Lee JL, Yoon YS, Kim CW, Lim SB, Yu CS, et al. Oncologic outcomes of organ preserving approaches in patients with rectal cancer treated with preoperative chemoradiotherapy. *Ann Coloproctol* 2019;35:65-71.
23. Andras D, Crisan D, Craciun R, Nemes A, Caziuc A, Drasovean R, et al. Neutrophil-to-lymphocyte ratio: a hidden gem in predicting neoadjuvant treatment response in locally advanced rectal cancer? *J BUON* 2020;25:1436-42.
24. Policicchio A, Mercier J, Digkila A, Voutsadakis IA. Platelet and neutrophil counts as predictive markers of neoadjuvant therapy efficacy in rectal cancer. *J Gastrointest Cancer* 2019;50:894-900.
25. Dudani S, Marginean H, Tang PA, Monzon JG, Raissouni S, Asmis TR, et al. Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios as predictive and prognostic markers in patients with locally advanced rectal cancer treated with neoadjuvant chemoradiation. *BMC Cancer* 2019;19:664.
26. Lee JH, Song C, Kang SB, Lee HS, Lee KW, Kim JS. Predicting pathological complete regression with haematological markers during neoadjuvant chemoradiotherapy for locally advanced rectal cancer. *Anticancer Res* 2018;38:6905-10.
27. Lai S, Huang L, Luo S, Liu Z, Dong J, Wang L, et al. Systemic inflammatory indices predict tumor response to neoadjuvant chemoradiotherapy for locally advanced rectal cancer. *Oncol Lett* 2020;20:2763-70.
28. Zhang Y, Liu X, Xu M, Chen K, Li S, Guan G. Prognostic value of pretreatment systemic inflammatory markers in patients with locally advanced rectal cancer following neoadjuvant chemoradiotherapy. *Sci Rep* 2020;10:8017.
29. Shen L, Zhang H, Liang L, Li G, Fan M, Wu Y, et al. Baseline neutrophil-lymphocyte ratio (≥ 2.8) as a prognostic factor for patients with locally advanced rectal cancer undergoing neoadjuvant chemoradiation. *Radiat Oncol* 2014;9:295.
30. Hamid H, Davis GN, Trejo-Avila M, Igwe PO, Garcia-Marín A. Prognostic and predictive value of neutrophil-to-lymphocyte ratio after curative rectal cancer resection: a systematic review and meta-analysis. *Surg Oncol* 2021;37:101556.