

Systemic Inflammatory Response Following Preoperative Chemoradiotherapy Can Affect Oncologic Outcomes in MSI-H/dMMR Rectal Cancer

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Systemic inflammatory response (SIR) is a crucial determinant of disease progression and survival in patients with colorectal cancer. This study investigated the prognostic relevance of changes in the platelet count on survival and the predictive value of changes in the platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR) on the pathological tumor response to preoperative chemoradiotherapy (CRT) in patients with microsatellite instability-high (MSI-H) rectal cancer. From 2011 to 2022, data of 46 consecutive patients with MSI-H rectal cancer who were treated with preoperative CRT followed by curative surgery at Kyungpook National University Chilgok Hospital (Daegu, South Korea) were retrospectively analyzed. A 235 cut-off value was used to define whether PLR was high or low. Any change in the PLR or NLR was calculated on the basis of subtracting the pre-CRT PLR or NLR from the post-CRT values. Both pre-CRT and post-CRT values of the NLR and PLR were not significantly associated with clinical outcomes. Simple logistic regression analysis showed that a change in the PLR following CRT was not significantly associated with survival outcomes; however, patients who maintained a high change in the PLR following CRT showed significantly better pathologic T-stage. No statistically significant association was noted between changes in the platelet count and clinical outcomes of patients. The results suggested that changes in the PLR following CRT are associated with pathologic T-stage of the group. However, the SIR markers showed no prognostic values on the survival outcomes of the patients with MSI-H/mismatch repair-deficient (dMMR) locally advanced rectal cancer (LARC).

Key Words: Rectal Neoplasms; Microsatellite Instability; Chemoradiotherapy; Prognosis

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INTRODUCTION

Preoperative chemoradiotherapy (CRT) followed by total mesorectal excision (TME) is the standard treatment for locally advanced rectal cancer (LARC).¹ However, a major limitation of this strategy is the poor impact on distant control, with metastasis rates remaining between 25% and 35%.² In this situation, single-agent programmed death 1

blockade was remarkably effective in microsatellite instability-high (MSI-H)/mismatch repair-deficient (dMMR) in LARC, providing a clinical complete response in all 12 patients.³

MSI is a molecular marker of a defective function of the DNA MMR system that results in the accumulation of insertion or deletion mutations within microsatellite DNA regions.⁴ dMMR or MSI-H tumors are well known to exhibit a high tumor mutation burden, neoantigen load and im-

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mune infiltration, thereby making them well to immune checkpoint inhibitors (ICIs) in colorectal cancer (CRC).^{5,6} Among all patients diagnosed with rectal cancer, dMMR or MSI-H tumors account for approximately 3% of the population. Therefore, the identification of immune response related biomarkers is essential for facilitating patient selection and increasing the clinical benefit from a novel treatment including ICIs in rectal cancer.^{7,8}

Laboratory parameters reflecting systemic inflammation are relatively economical to evaluate, easily measurable, repeatable, and ready to use in daily clinical practice.⁹ There is increasing evidence that the neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) can be effective prognostic indicators for various malignant tumors.^{10,11} Particularly, a high NLR has been reported as an indicator of poor clinical outcomes in patients with LARC.¹² Additionally, the PLR has been correlated with the progression of CRC, and changes in the platelet count following chemotherapy were recently reported as a potential biomarker evaluating response.¹³ However, the prognostic impact of the NLR and PLR in patients with dMMR or MSI-H rectal cancer has not yet been investigated.

Accordingly, this study aimed at investigating the association between the NLR and PLR and changes in the platelet count following CRT with clinical outcomes in patients with dMMR or MSI-H LARC.

MATERIALS AND METHODS

1. Patient eligibility

This retrospective study included 46 patients with pathologically confirmed, locally advanced dMMR or MSI-H rectal adenocarcinoma. The participants completed preoperative CRT and underwent radical resection between January 2011 and January 2023 at Kyungpook National University Chilgok Hospital (KNUCH) (Daegu, Korea).

Total colonoscopy, computed tomography (CT), pelvic magnetic resonance imaging, and whole-body positron emission tomography/CT according to the tumor, node, and metastasis (TNM) staging system, eighth edition, 2018 (AJCC, 2018) were performed to assess clinical staging.¹⁴ Measurements of neutrophil, lymphocyte, and platelet counts and serum carcinoembryonic antigen and carbohydrate antigen 19-9 concentrations were performed before and after CRT. The CRT consisted of 45 Gy delivered in 25 daily fractions over 5 weeks either with concurrent 5-fluorouracil (400 mg/m²) and leucovorin (20 mg/m²) on days 1-4 and 29-32, or with concurrent oral administration of capecitabine (825 mg/m² twice daily) for 25 days. The TME was performed 6-8 weeks following CRT completion. This study was approved by the Institutional Review Board of KNUCH.

2. MSI analysis

Tumor tissue samples were obtained from each patient during surgery. Laboratory analysis was subsequently

performed at KNUCH, wherein the DNA extracted from each sample was amplified by polymerase chain reaction, and MSI testing was performed on the basis of five mononucleotide locus markers proposed by the National Cancer Institute.¹⁵ Using capillary electrophoresis, the samples showing instability at the two most sensitive markers (BAT25 and BAT26) among the five-marker panel were classified as exhibiting MSI-H. Additionally, a tumor sample was classified as MSI-L if one locus showed instability and MSI-S if all the loci were stable. Moreover, mismatch repair status was determined locally by immunohistochemistry analysis of the mismatch repair proteins MLH1, MSH2, MSH6, and PMS2; mismatch repair deficiency was defined as an absent expression of one or more of these proteins.

3. Definition of laboratory parameters

Peripheral blood samples were obtained from the patients during their first visit to the clinic (pre-CRT) and 2-4 weeks before surgery (post-CRT). For the platelet count, a cut-off value of $370 \times 10^3/\mu\text{L}$ was selected according to a previous study;¹⁶ any changes in platelet counts were calculated by subtracting pre-CRT values from the post-CRT values. According to our previous study, the NLR was classified into the following two categories: low < 5 or high ≥ 5 . When calculating the PLR, $\text{PLR} \geq 235$ was defined as high.¹⁷ Any changes in the NLR or PLR were determined as follows: pre-CRT NLR or PLR minus post-CRT NLR or PLR.

4. Statistical analysis

Statistical analyses were performed using R statistical software 4.3.1 (the R Foundation for Statistical Computing, Vienna, Austria, available at <http://www.r-project.org>). Disease-free survival (DFS) was calculated as the time from diagnosis to disease recurrence. Overall survival (OS) was defined as the date from diagnosis until death from any cause. Student's t-test and a chi-square test were both applied to qualitative variables. The survival analysis used the Kaplan-Meier method with a log rank test. Two-sided p-values of < 0.05 were considered statistically significant.

RESULTS

1. Patient characteristics

The baseline clinical characteristics and laboratory findings are summarized in Table 1. The median age of the patients was 60 (range, 24-84); the percentages of male and female patients were 87% and 13%, respectively. The following were the clinical stages before CRT: stage II (n=10, 21.7%) and stage III (n=36, 78.3%). Forty-two (91.3%) and thirty-seven (80.4%) patients had high initial NLR and PLR, respectively. Among the 46 patients, 10 (21.7%) experienced recurrence following CRT followed by surgical resection.

TABLE 1. Patient characteristics (n=46)

Factor	Subgroup	n (%)
Age	< 65 years	30 (65.2)
	≥ 65 years	16 (34.8)
Sex	Male	40 (87.0)
	Female	6 (13.0)
Clinical T-stage	T2	1 (2.2)
	T3	36 (78.3)
	T4	9 (19.5)
Clinical TNM	II	10 (21.7)
	III	36 (78.3)
CEA	< 5 ng/mL	34 (73.9)
	≥ 5 ng/mL	12 (26.1)
CA19-9	< 37 U/mL	37 (80.4)
	≥ 37 U/mL	9 (19.6)
Initial NLR	< 5	42 (91.3)
	≥ 5	4 (8.7)
Initial PLR	< 235	37 (80.4)
	≥ 235	9 (19.6)
Post-CRT NLR	< 5	36 (78.3)
	≥ 5	10 (21.7)
Post-CRT PLR	< 235	28 (60.9)
	≥ 235	18 (39.1)
TRG (JCO)	1	6 (13.0)
	2	8 (17.4)
	3	32 (69.6)
Pathological T	T1	2 (4.3)
	T2	6 (13.0)
	T3	38 (82.6)
Pathological TNM	I	8 (17.4)
	II	23 (50.0)
	III	15 (32.6)
Pathological response	Good	8 (17.4)
	Poor	38 (82.6)
Recurrence		10 (21.7)
Death		12 (26.1)

CEA: carcinoembryonic antigen, CA19-9: carbohydrate antigen 19-9, NLR: neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, CRT: chemoradiotherapy, TNM: the tumor, node, and metastasis, Good: pT1 and pT2, Poor: pT3 or node-positive, TRG: tumor regression grade, JCO: Journal of Clinical Oncology.

2. Pre-CRT NLR/PLR and clinical outcomes

A comparison between the clinicopathological characteristics of each group is presented in Table 2. High initial NLR and PLR were not significantly associated with clinical outcomes. Patients in the high NLR and PLR groups did not show differences in pathologic stage, tumor regression grade (TRG), and the rates of recurrence or death. However, the patients with high initial NLR had a tendency to experience better TRG status following CRT followed by surgery ($p=0.05$). Moreover, the group with high initial PLR had comparably lower TRG scores ($p=0.096$). However, the post-CRT NLR and PLR values were not associated with any clinical outcomes.

3. PLR changes and tumor response following CRT

The patients were categorized into two groups using a cut-off value of 115 (pre-CRT PLR subtracted by post-CRT PLR, low < 115 and high ≥ 115) (Table 3). The patients with high PLR change showed a statistically significant association with pathologic T-stage ($p=0.015$) but not with TRG status ($p=0.645$) and recurrence rate ($p=1.000$). No significant correlation was observed between PLR change and pathologic TNM ($p=0.099$). Univariate analysis indicated that patients' DFS and OS (DFS, $p=0.8$; OS, $p=0.8$) were not significantly different between the two groups (Fig. 1).

4. Association of changes in the platelet count with clinical outcomes

The patients were categorized into three groups on the basis of their pre- and post-CRT platelet counts with a cut-off of value $370 \times 10^3/\mu\text{L}$: low pre-CRT count, regardless of the post-CRT count (group A); high pre-CRT count and low post-CRT count (group B); and high pre-CRT and post-CRT count (group C) (Table 4). No statistically significant association was noted between changes in the platelet count and clinical outcomes of patients in the three groups. In the univariate analysis, the changes in the platelet count were not significantly related with patients' DFS and OS (DFS, $p=0.32$; OS, $p=0.45$, Fig. 2).

DISCUSSION

This study investigated the prognostic values of blood-based systemic inflammatory response (SIR) markers including the NLR, PLR, and changes in the platelet count in patients with d-MMR/MSI-H LARC, and identified that the PLR changes following CRT were significantly associated with pathologic T-stage. However, the SIR markers were not associated with survival in these patient groups.

Recognized as inflammation and homeostasis regulators, high neutrophil and platelet counts play a key role in inducing angiogenesis, facilitating tumor cell extravasation, and motivating metastatic spreading.^{18,19} In contrast, lymphocytes act as suppressors of the proliferation and spread of cancer cells through their cytotoxic activity and anti-tumor cytokine production. Based on this background, previous studies have investigated the possibility of SIR markers as effective prognostic markers and predictive indicators.^{20,21} In various types of malignancies, a high NLR and PLR resulted in worse OS and DFS.^{22,23} Furthermore, our previous study has reported that a high PLR change was a significant independent predictive marker of good responses to CRT in LARC.¹⁸ However, results have been inconsistent across several studies, and a retrospective study conducted by An et al.²⁴ observed that neither PLR nor NLR was associated with 5-year DFS in patients with LARC who received neoadjuvant CRT followed by curative resection. Furthermore, there remains insufficient evaluation of SIR in patients with MSI-H/dMMR.

TABLE 2. Association between clinicopathological features and the NLR and PLR

Factor	NLR		PLR		Post CRT NLR		Post CRT PLR	
	Low	High	Low	High	Low	High	Low	High
Sex								
Male	36 (85.7)	4 (100.0)	32 (86.5)	8 (88.9)	32 (88.9)	8 (80.0)	26 (92.9)	14 (77.8)
Female	6 (14.3)	0 (0.0)	5 (13.5)	1 (11.1)	4 (11.1)	2 (20.0)	2 (7.1)	4 (22.2)
p-value	0.973		1.000		0.835		0.301	
CEA								
< 5 ng/mL	31 (73.8)	2 (50.0)	26 (70.3)	7 (77.8)	24 (66.7)	9 (90.0)	19 (67.9)	14 (77.8)
≥ 5 ng/mL	11 (26.2)	2 (50.0)	11 (29.7)	2 (22.2)	12 (33.3)	1 (10.0)	9 (32.1)	4 (22.2)
p-value	0.668		0.971		0.292		0.694	
CA19-9								
< 37 U/mL	35 (83.3)	2 (50.0)	31 (83.8)	6 (66.7)	28 (77.8)	9 (90.0)	23 (82.1)	14 (77.8)
≥ 37 U/mL	7 (16.7)	2 (50.0)	6 (16.2)	3 (33.3)	8 (22.2)	1 (10.0)	5 (17.9)	4 (22.2)
p-value	0.344		0.489		0.681		1.000	
Clinical TNM								
II	9 (21.4)	1 (25.0)	9 (24.3)	1 (11.1)	10 (27.8)	0 (0.0)	7 (25.0)	3 (16.7)
III	33 (78.6)	3 (75.0)	28 (75.7)	8 (88.9)	26 (72.2)	10 (100.0)	21 (75.0)	15 (83.3)
p-value	1.000		0.681		0.147		0.762	
TRG (JCO)								
1	4 (9.5)	2 (50.0)	3 (8.1)	3 (33.3)	4 (11.1)	2 (20.0)	3 (10.7)	3 (16.7)
2	7 (16.7)	1 (25.0)	6 (16.2)	2 (22.2)	7 (19.4)	1 (10.0)	6 (21.4)	2 (11.1)
3	31 (73.8)	1 (25.0)	28 (75.7)	4 (44.4)	25 (69.4)	7 (70.0)	19 (67.9)	13 (72.2)
p-value	0.05		0.096		0.645		0.607	
Pathologic T-stage								
T1	2 (4.8)	0 (0.0)	2 (5.4)	0 (0.0)	1 (2.8)	1 (10.0)	0 (0.0)	2 (11.1)
T2	5 (11.9)	1 (25.0)	5 (13.5)	1 (11.1)	5 (13.9)	1 (10.0)	3 (10.7)	3 (16.7)
T3	35 (83.3)	3 (75.0)	30 (81.1)	8 (88.9)	30 (83.3)	8 (80.0)	25 (89.3)	13 (72.2)
p-value	0.704		0.751		0.594		0.150	
Pathologic TNM								
I	7 (16.7)	1 (25.0)	7 (18.9)	1 (11.1)	6 (16.7)	2 (20.0)	3 (10.7)	5 (27.8)
II	21 (50.0)	2 (50.0)	19 (51.4)	4 (44.4)	18 (50.0)	5 (50.0)	13 (46.4)	10 (55.6)
III	14 (33.3)	1 (25.0)	11 (29.7)	4 (44.4)	12 (33.3)	3 (30.0)	12 (42.9)	3 (16.7)
p-value	0.894		1.000		0.962		1.000	
Recurrence								
No	34 (81.0)	2 (50.0)	31 (83.8)	5 (55.6)	29 (80.6)	7 (70.0)	21 (75.0)	15 (83.3)
Yes	8 (19.0)	2 (50.0)	6 (16.2)	4 (44.4)	7 (19.4)	3 (30.0)	7 (25.0)	3 (16.7)
p-value	0.424		0.164		0.777		0.762	
Death								
No	31 (73.8)	3 (75.0)	28 (75.7)	6 (66.7)	26 (72.2)	8 (80.0)	18 (64.3)	16 (88.9)
Yes	11 (26.2)	1 (25.0)	9 (24.3)	3 (33.3)	10 (27.8)	2 (20.0)	10 (35.7)	2 (11.1)
p-value	1.000		0.898		0.929		0.131	

CRT: chemoradiotherapy, CEA: carcinoembryonic antigen, CA19-9: carbohydrate antigen 19-9, NLR: neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, TNM: the tumor, node, and metastasis, TRG: tumor regression grade, JCO: Journal of Clinical Oncology.

Recent findings provided by Corti et al.²⁵ reported that an immune-inflammatory blood-based biomarker had an independent role in patients with MSI-H/dMMR metastatic CRC receiving ICIs. Considering the very small number of patients with MSI-H/dMMR, the current findings may provide meaningful information for this subgroup, that is, SIR exhibits a host cellular immune response against tumors.²⁶

The current study showed that changes in the PLR following CRT were predictive or prognostic indicators of the pathological tumor response to preoperative CRT. Platelet

is significant hematologic component maintaining homeostasis and the tissue repair system; previous studies have demonstrated that initial thrombocytosis is considered a factor predicting poor pathological tumor regression and shorter recurrence-free survival in CRC.^{17,27} In the present study, the pathologic T-stage was significantly related with a change in the PLR following preoperative CRT. For example, the patient group that maintained a low PLR change had advanced pathologic T-stage (T3: 88.9% vs. 60.0%) compared with the group with a high PLR change

TABLE 3. Association of changes in the platelet count with clinical outcomes in patients categorized using a cut-off value of $370 \times 10^3/\mu\text{L}$: low pre-CRT count, regardless of the post-CRT count (group A); high pre-CRT count and low post-CRT count (group B) and high pre-CRT and post-CRT count (group C)

Factor	Group A (n=36)	Group B (n=8)	Group C (n=2)	p-value
Clinical TNM				
II	10 (27.8)	0 (0.0)	0 (0.0)	0.170
III	26 (72.2)	8 (100.0)	2 (100.0)	
TRG (JCO)				
1	5 (13.9)	0 (0.0)	1 (50.0)	0.180
2	6 (16.7)	1 (12.5)	1 (50.0)	
3	25 (69.4)	7 (87.5)	0 (0.0)	
Pathologic T-stage				
T1	2 (5.6)	0 (0.0)	0 (0.0)	0.749
T2	4 (11.1)	2 (25.0)	0 (0.0)	
T3	30 (83.3)	6 (75.0)	0 (0.0)	
Pathologic TNM				
I	6 (16.7)	2 (25.0)	0 (0.0)	0.625
II	17 (47.2)	4 (50.0)	2 (100.0)	
III	13 (36.1)	2 (25.0)	0 (0.0)	
Recurrence				
No	28 (77.8)	7 (87.5)	1 (50.0)	0.510
Yes	8 (22.2)	1 (12.5)	1 (50.0)	
Death				
No	25 (69.4)	7 (87.5)	2 (100.0)	0.398
Yes	11 (30.6)	1 (12.5)	0 (0.0)	
CEA				
< 5 ng/mL	23 (63.9)	8 (100.0)	2 (100.0)	0.081
≥ 5 ng/mL	13 (36.1)	0 (0.0)	0 (0.0)	
CA19-9				
< 37 U/mL	29 (80.6)	6 (75.0)	2 (100.0)	0.727
≥ 37 U/mL	7 (19.4)	2 (25.0)	0 (0.0)	

CRT: chemoradiotherapy, CEA: carcinoembryonic antigen, CA19-9: carbohydrate antigen 19-9, TNM: the tumor, node, and metastasis, TRG: tumor regression grade, JCO: Journal of Clinical Oncology.

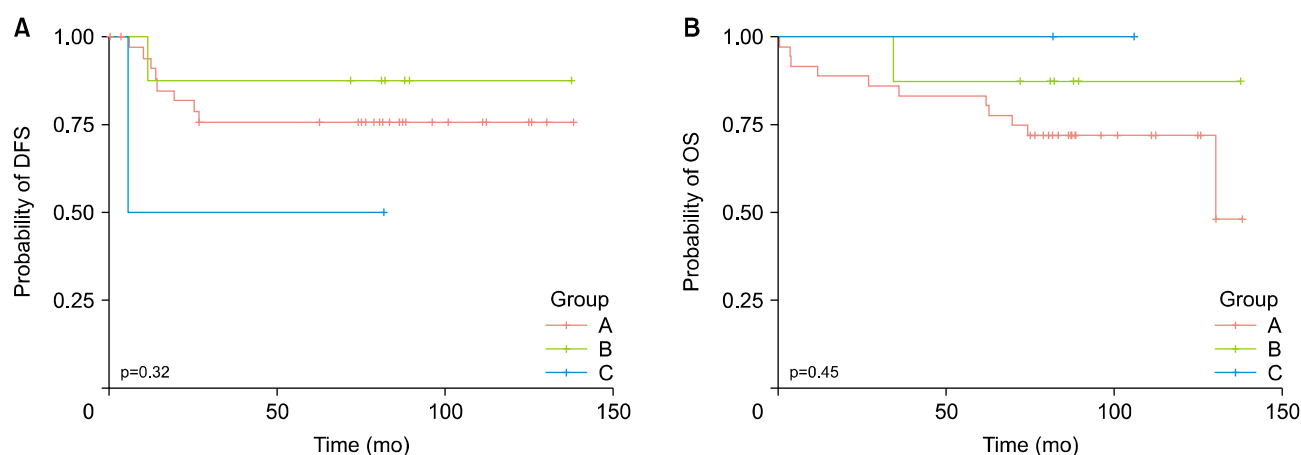


FIG. 1. Kaplan-Meier cumulative disease-free (DFS) (A) and overall (OS) (B) survival curves according to changes in the platelet count. Patients are divided using a platelet count cut-off value of $370 \times 10^3/\mu\text{L}$: low pre-chemoradiotherapy (CRT) count, regardless of the post-CRT count (group A); high pre-CRT count and low post-CRT count (group B); and high pre-CRT and post-CRT count (group C). (A) The 5-year DFS for group A is 66.7% versus 87.5% in group B versus 50.0% in group C ($p=0.423$). (B) The 5-year OS group A is 83.3% versus 87.5% in group B versus 100.0% in group C ($p=0.793$).

TABLE 4. Relationship between clinicopathological characteristics and PLR changes following CRT

Factor	Subgroup	PLR changes, n (%)		p-value
		Low (<115)	High (≥115)	
Age	< 65 years	21 (58.3)	9 (90.0)	0.138
	65 years	15 (41.7)	1 (10.0)	
Sex	Male	31 (86.1)	9 (90.0)	1.000
	Female	5 (13.9)	1 (10.0)	
Clinical TNM	II	8 (22.2)	2 (20.0)	1.000
	III	28 (77.8)	8 (80.0)	
TRG (JCO)	1	4 (11.1)	2 (20.0)	0.645
	2	7 (19.4)	1 (10.0)	
	3	25 (69.4)	7 (70.0)	
Pathologic T-stage	T1	2 (5.6)	0 (0.0)	0.015
	T2	2 (5.6)	4 (40.0)	
	T3	32 (88.9)	6 (60.0)	
Pathologic TNM	I	4 (11.1)	4 (40.0)	0.099
	II	19 (52.8)	4 (40.0)	
	III	13 (36.1)	2 (20.0)	
Recurrence	No	28 (77.8)	8 (80.0)	1.000
	Yes	8 (22.2)	2 (20.0)	
Death	No	26 (72.2)	8 (80.0)	0.929
	Yes	10 (27.8)	2 (80.0)	
CEA	< 5 ng/mL	25 (69.4)	8 (80.0)	0.796
	≥ 5 ng/mL	11 (30.6)	2 (80.0)	
CA19-9	< 37 U/mL	28 (77.8)	9 (90.0)	0.681
	≥ 37 U/mL	8 (22.2)	1 (10.0)	
NLR	< 5	32 (88.9)	10 (100.0)	0.639
	≥ 5	4 (11.1)	0 (0.0)	

CRT: chemoradiotherapy, CEA: carcinoembryonic antigen, CA19-9: carbohydrate antigen 19-9, PLR: Platelet-to-lymphocyte ratio, NLR: neutrophil-to-lymphocyte ratio, TNM: the tumor, node, and metastasis, TRG: tumor regression grade, JCO: Journal of Clinical Oncology.

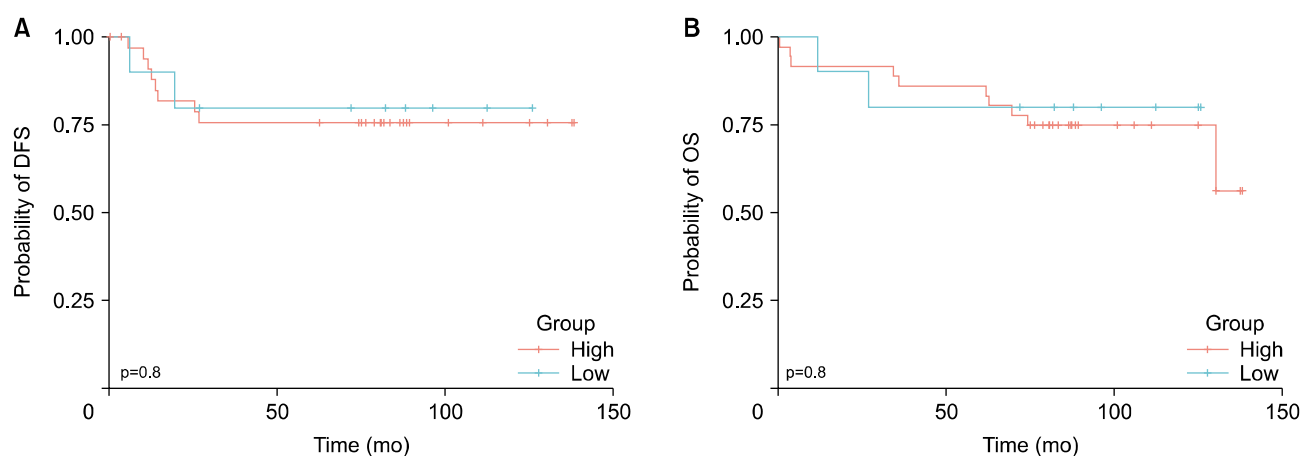


FIG. 2. Kaplan-Meier cumulative disease-free (DFS) (A) and overall (OS) (B) survival curves according to changes in the platelet-to-lymphocyte ratio (PLR). Patients are categorized using a cut-off value of 115 into low (<115) and high (≥115) changes following chemoradiotherapy (CRT). (A) The 5-year DFS for those with low PLR change is 69.4% versus 70.0% for those with high PLR change (p=1.000). (B) The 5-year OS for those with low PLR change is 86.1% versus 80.0% for those with high PLR change (p=1.000).

following CRT. This is consistent with a previous study, wherein the PLR was identified as an independent factor of the T-stage of the patients with CRC.²⁸ It is well known that down-staging provided better oncologic outcomes in

terms of disease-free survival and local recurrence in locally advanced rectal cancer patients.²⁹ Thus, a more suitable treatment with TNT or ICIs is needed to improve oncological outcomes in these low PLR change group. Mean-

while, a retrospective study of individuals in a Chinese population by Liu et al.³⁰ reported that MSI-H showed comparably low platelet volume and reduced platelet glycoprotein. These findings point to the possibility of platelet or the PLR as a biomarker in MSI-H/dMMR tumors, suggesting that platelet could be involved in immune response by incorporating into multiple significant cellular pathways.

This study had some limitations. First, although the current study had a homogeneous ethnicity and equivalent treatment application, the sample size of 46 patients was too small to retrospectively analyze. Second, a standard cut-off value for the SIR markers had not yet been clearly established. Lastly, as the level of laboratory markers was measured in the blood at a single timepoint, reflecting dynamic changes was highly difficult.

In conclusion, the current study suggests that the changes in the PLR following CRT are associated with the pathologic T-stage of the group. However, the SIR markers particularly the NLR, PLR, and platelet count showed no prognostic value for the survival outcomes of patients with MSI-H/dMMR LARC.

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CONFLICT OF INTEREST STATEMENT

None declared.

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