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Clinical Significance of Dynamic Neutrophil-lymphocyte Ratio Changes in Patients With Colorectal Cancer

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Abstract. *Background/Aim: Elevated neutrophil-lymphocyte ratio (NLR) has been reported to be a poor prognostic factor in patients with colorectal cancer (CRC). However, no studies have focused on the dynamic change of preoperative NLR (pre-NLR) in CRC patients. We investigated the prognostic value of the change in NLR (ΔNLR) in CRC patients before and after surgery. Patients and Methods: We retrospectively analyzed the data from 307 patients with stage II or III CRC. We compared the clinicopathological factors, OS, and DFS among the various NLR factors. Results: The 5-year OS rate of the high ΔNLR group was significantly lower than that of the low ΔNLR group (p<0.01). The 5-year DFS rates of the high ΔNLR groups were worse than those in the low ΔNLR groups. In the multivariate analysis, ΔNLR was an independent prognostic factor (p=0.011). Conclusion: Decreasing post-NLR was related to better OS and DFS even in high pre-NLR patients with CRC.*

Globally, colorectal cancer (CRC) is the third most common cancer in men and the second most common cancer in women. CRC is also the fourth most common cause of death from cancer (1). Cancer staging systems, *i.e.*, the UICC/AJCC Cancer Staging System, are used for treating patients with CRC according to the strategies determined by each staging. However, therapeutic effect is different even in the same stage. Currently, there is a need for other potential biomarkers that will help in identifying patients with poor prognosis.

It has been reported that local immune response and systemic inflammation play important roles in tumor progression and survival of patients with cancer (2). The neutrophil-to-lymphocyte ratio (NLR) is one of the non-specific markers of systemic inflammation. Elevated NLR has been reported to be a predictive marker associated with poor prognosis in various cancers, including gastric, esophageal, and colorectal cancers (3-5).

In a meta-analysis study that was performed to explore the value of NLR in predicting prognosis of patients with CRC, elevated preoperative NLR was significantly associated with poorer OS and DFS, and it was concluded that NLR has a prognostic value for patients with CRC (6). However, previous studies mainly focused on only preoperative NLR (pre-NLR) or postoperative NLR (post-NLR). The changes in NLR before and after surgery (ΔNLR) were not fully studied. Especially, no studies have reported the changes in an elevated preoperative NLR group. This study aimed to distinguish between good and poor prognosis groups from an elevated pre-NLR group by evaluating the dynamic changes in NLR before and after surgery.

Patients and Methods

Patients. We retrospectively analyzed a total of 307 patients who underwent scheduled curative operation for pathological stage II or III colorectal cancer at the University of Yamanashi Hospital from January 2005 to October 2014.

Ethics statement. This study was approved by the Yamanashi University Ethics Committee (approval number: 2043) and followed the Helsinki Declaration and its amendments. All the patients provided written informed consent for sample and data use.

Patient selection. The inclusion criteria were as follows: 1) patients who underwent curative operation at the University of Yamanashi Hospital for pathologically confirmed stage II or III CRC and 2) patients who underwent routine analysis of blood before and after surgery. The exclusion criteria were as follows: 1) patients with obvious inflammatory condition caused by diseases other than CRC or CRC complications, including obstructive enteritis and intestinal perforation before colorectal resection; 2) patients who had died because of postoperative complications; and 3) patients who had no or insufficient data before or after discharge. Patient selection

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according to these criteria is shown in Figure 1. The median follow-up period was 1835 days (range=1369-2217 days).

Patient data. The clinicopathological data of all the patients were collected from the hospital records. Staging was based on the International Union Against Cancer UICC/TMN classification of Malignant Tumors (8th edition) (7).

Peripheral blood parameters. Preoperative blood routine test was obtained within one week before the curative resection. There had been no standard to use as basis for measuring the appropriate timing of inflammation index after surgery. To exclude the effects of postoperative complications, postoperative blood routine test was obtained at the first outpatient after discharge (29 days after surgery (range=24-41 days). Neutrophil and lymphocyte data were collected from the blood routine test.

Definition and calculation of NLR. The NLR was calculated as the absolute neutrophil count divided by the absolute lymphocyte count. NLR >4 was defined as high NLR. NLR ≤4 was defined as low NLR. This cut-off value was based on previous papers (8, 9).

Definition and calculation of ΔNLR. ΔNLR was calculated as the post-NLR derived by the pre-NLR. ΔNLR <1 was defined as low ΔNLR. ΔNLR >1 was defined as high ΔNLR. There is no study about ΔNLR (post/pre). This value was selected because it was easy to understand if the NLR reduced before or after surgery, and it was easy to use in the clinical practice.

Statistical analysis. The data were analyzed using JMP statistical software (SAS Institute Inc.). Chi-square test or Fisher's exact test was used to assess differences among proportions, and Student's *t*-test was used to assess continuous variables. The Kaplan–Meier method was used to calculate survival curves, and differences in survival were evaluated by the log-rank test. Cox proportional hazard regression model was used to analyze the independent prognostic factors. A *p*-value of less than 0.05 was considered to indicate a statistically significant difference.

Results

A total of 601 patients underwent surgical resection for CRC at the University of Yamanashi Hospital from January 2005 to October 2014. Based on the exclusion criteria, 294 patients were excluded. Thus, a total of 307 patients were enrolled in this study. A value of 4 was used as the NLR cut-off value. This cut-off value was based on previous papers (8, 9). NLR >4 was defined as high NLR, and NLR ≤4 was defined as low NLR.

Clinicopathological characteristics of the 307 patients are shown in Table I. The low pre-NLR and the high pre-NLR groups included 234 patients (76.2%) and 73 patients (23.8%), respectively. Preoperative neutrophil counts were significantly higher in the high pre-NLR group than in the low pre-NLR group ($p<0.001$), whereas preoperative lymphocyte counts were significantly lower in the high pre-NLR group compared to the low pre-NLR group ($p<0.001$). Pre-NLR was 2.42±0.78 and 5.71±1.66 in the low pre-NLR group and high pre-NLR group, respectively. Preoperative CEA was significantly higher in the high pre-NLR group than in the low pre-NLR group ($p=0.003$). Maximum tumor size was significantly larger in the high pre-NLR group than in the low pre-NLR group ($p=0.001$). The percentages of patients who received the neoadjuvant chemotherapy and who had postoperative complications (Clavien–Dindo grade III or higher) were similar in the two groups. Other baseline characteristics were not significantly different.

On assessing the relationship between pre-NLR and prognosis we observed that the 5-year overall survival (OS) rate of the high pre-NLR group (65.0%) was significantly lower than that of the low pre-NLR group (84.8%) ($p<0.001$) (Figure 1). Moreover, the 5-year disease-free survival (DFS) rate of the high pre-NLR group (58.4%) was significantly lower than that of the low pre-NLR group (72.9%) too ($p=0.012$) (Figure 2).

We focused on the high pre-NLR group and assessed the relationship between ΔNLR (post/pre-NLR) and prognosis. The clinicopathological characteristics of the high pre-NLR group are shown in Table II. The low ΔNLR group, the group with lower post-NLR than the preoperative, had 63 patients (86.3%), and the high ΔNLR group had 10 patients (13.7%). Postoperative neutrophil counts were significantly higher in the high ΔNLR group than in the low ΔNLR group ($p=0.004$). Postoperative lymphocyte counts were significantly lower in the high ΔNLR group than in the low ΔNLR group ($p<0.001$). Post-NLR was 2.80±1.15 and 11.0±7.03 in the low ΔNLR group and high LNLR group, respectively. Furthermore, lymphatic invasion was significantly more in the low ΔNLR group than in the high ΔNLR group ($p=0.008$). Adjuvant chemotherapy was performed more frequently in the low ΔNLR (50%) than in the high ΔNLR group (10%) ($p=0.264$). Other baseline characteristics were not significantly different.

The 5-year OS rate of the high ΔNLR group (33.3%) was significantly lower than that of the low ΔNLR group (69.8%) ($p<0.01$) (Figure 3). The 5-year DFS rates of the low and high ΔNLR groups were 62.2% and 33.3%, respectively ($p=0.0776$).

The univariate analysis showed that the presence of deeper tumor invasion ($p=0.046$), and adjuvant chemotherapy ($p=0.020$) was correlated with a poorer 5-year OS (Table III). Furthermore, the multivariate analysis showed that the presence of deeper tumor invasion [hazard ratio (HR)=3.321, $p=0.013$], and ΔNLR value were independent prognostic factors (HR=0.2393, $p=0.011$) (Table IV).

Discussion

This study investigated whether the prognosis of the high pre-NLR group, which is usually poor, improves by lowering the postoperative NLR compared with the preoperative one. To our knowledge, this is the first report to describe the

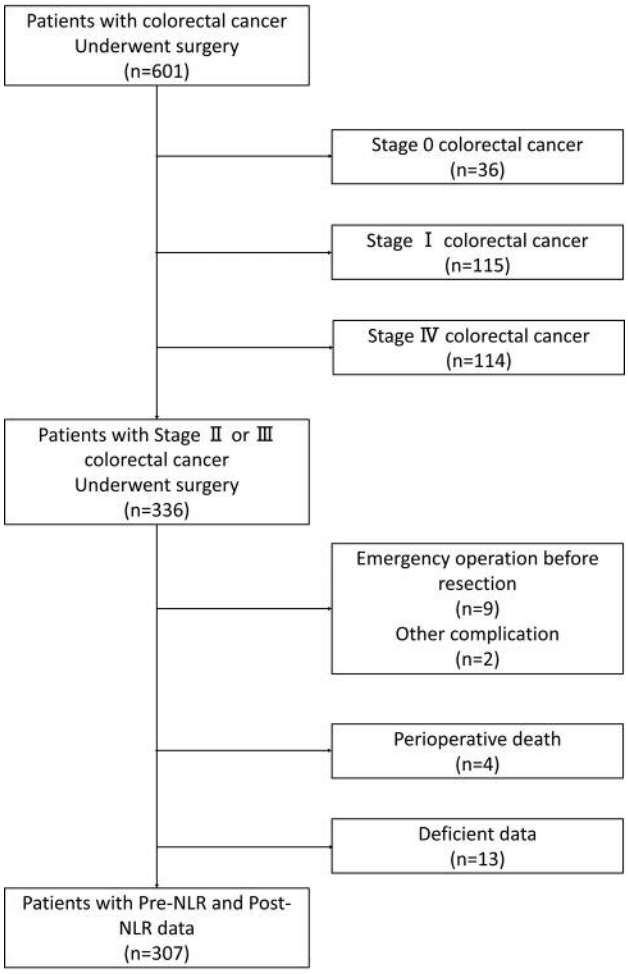

Figure 1. *Diagram showing the process of patient selection.*

Table I. *Correlation between clinicopathological features and pre-NLR.*

Variable	NLR ≤4 (n=234)	NLR 4< (n=73)	*p*-Value
Gender			
Male	139 (59.4)	44 (60.2)	1
Female	95 (40.6)	29 (39.8)	
Age, years	66.9±11.9	67.8±16.7	0.592
Location of the tumor			
Cecum	20 (8.6)	3 (4.1)	0.924
Ascending	39 (16.8)	15 (20.6)	
Transverse	23 (9.9)	7 (9.7)	
Descending	6 (2.7)	1(1.3)	
Sigmoid	52 (22.3)	16 (21.9)	
Rs	34 (14.7)	9 (12.3)	
Ra	26 (11.2)	13 (17.8)	
Rb	32 (13.8)	9 (12.3)	
Tumor size, mm	49.2±21.8	59.2±17.2	0.001
Histological type			
Differentiated	206 (75.5)	59 (80.8)	0.122
Undifferentiated	28 (24.5)	14 (19.2)	
Depth of tumor			
T1	7 (3.0)	1 (1.4)	0.064
T2	15 (6.4)	1 (1.4)	
T3	162 (69.2)	46 (63.0)	
T4	50 (21.4)	25 (34.2)	
Lymph node metastasis			
Negative	121 (51.7)	41 (56.2)	0.023
Positive	113 (48.3)	32 (43.8)	
Lymphatic invasion			
Negative	64 (27.4)	23 (31.5)	0.552
Positive	170 (72.6)	50 (68.5)	
Venous invasion			
Negative	74 (31.6)	21 (28.8)	0.772
Positive	160 (68.4)	52 (71.2)	
Adjuvant chemotherapy			
Negative	148 (68.2)	52 (71.2)	0.260
Positive	86 (36.8)	21 (28.8)	
Complications (CD3<)			
Negative	207 (88.5)	61 (83.6)	0.412
Positive	27 (11.5)	12 (16.4)	
Pre neutrophil count $\times 10^3/\mu l$	3.55±1.34	5.36±2.33	<0.001
Pre lymphocyte count $\times 10^3/\mu l$	1.52±0.51	0.96±0.38	<0.001

Values are n(%) or mean±SD unless otherwise indicated. CD: Clavien-Dindo classification.

relationship between ΔNLR in the high pre-NLR group and prognosis in stage II or III patients with CRC who underwent curative surgeries. The results showed that the group with lower postoperative NLR compared to preoperative in the high pre-NLR group had significantly improved prognosis.

Recent retrospective cohort studies demonstrated that high pre-NLR was associated with worse prognosis in colon cancer (10, 11). A previous systematic review also showed that NLR was associated with outcomes in patients with operable disease, in particular gastrointestinal cancer (12). Only a few studies have evaluated the prognostic significance of ΔNLR. Furthermore, an increased post-NLR was associated with poorer prognosis in small hepatocellular carcinoma (13, 14), renal cell carcinoma (15), gastric cancer (16), and colorectal cancer (17). In accordance with other studies, our study demonstrated that high pre-NLR was significantly associated with worse OS ($p<0.001$) and DFS ($p=0.012$). We focused on the high pre-NLR group who had poor OS and DFS. The low ΔNLR group had favorable prognosis in the high pre-NLR group. This may be biologically plausible. An increased NLR revealed relatively high neutrophil count and low lymphocyte count. Total lymphocyte counts were used as an indicator for assessing nutritional status and as a marker for identifying malnourished cases with abnormal serum albumin and total cholesterol levels (18). In addition, as tumor suppressors and having a role in tumor immunity, lymphocytes were also

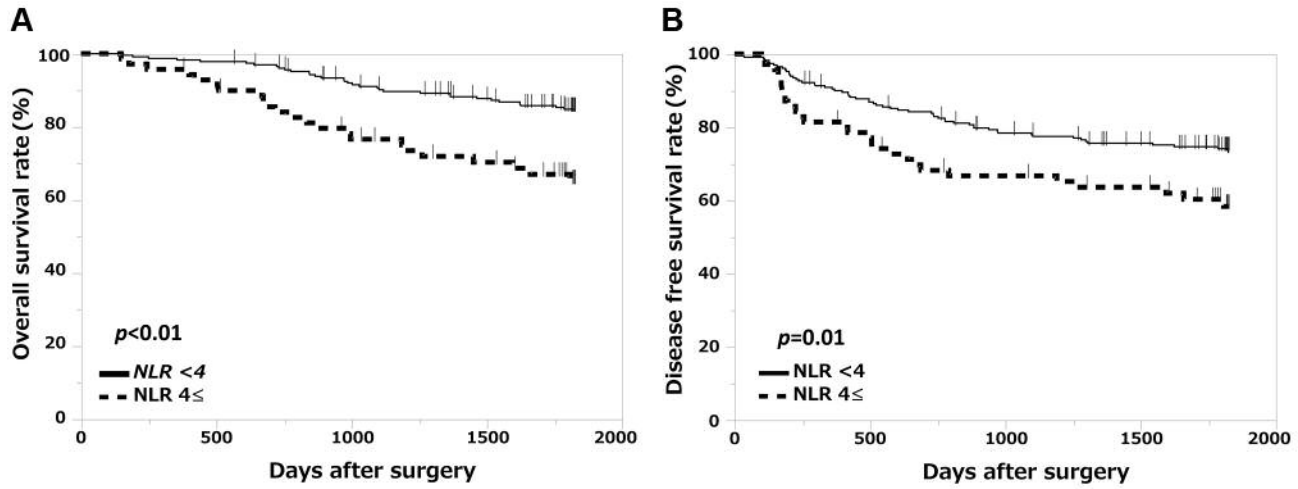

Figure 2. *OS (A) and DFS (B) rates in the low and high pre-NLR groups.*

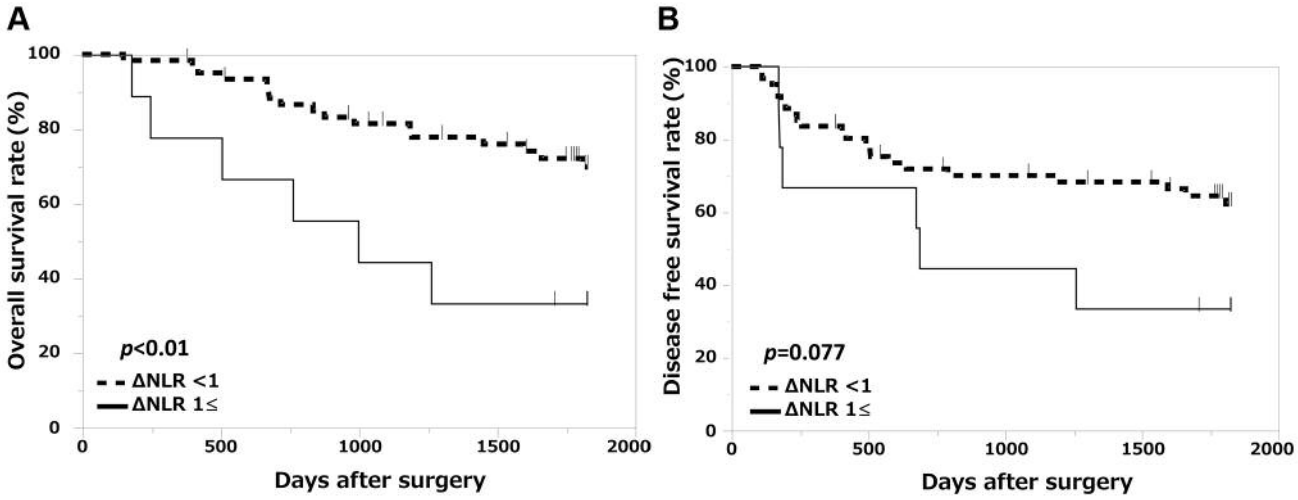

Figure 3. *OS (A) and DFS (B) rates in the low and high ΔNLR groups.*

used as indicators of immunity (19, 20). Lymphocytes can eliminate tumor cells by releasing lytic components and direct cell–cell interactions (21). However, neutrophils increase tumor cell production because of inflammation and production of large amount of arginase, VEGF, MMP-6, and several chemokines, including CCL2, CCL5, and CXCL4, which promote tumor growth, proliferation, angiogenesis, and metastasis in various tumor cells (22, 23). These neutrophils are known as tumor-associated neutrophils (TANs). Recent studies have suggested that the tumor microenvironment induces differentiation of TANs into anti-tumorigenic N1 and pro-tumorigenic N2 phenotypes. Inhibition of TGF-β and interferon-β induces N1 (17, 24). N1 phenotype has the potential to kill tumor cells and inhibit tumor cell growth by oxidative damage caused by reactive oxygen species secreted from neutrophils, thus mediating Fas-ligand-associated apoptosis and the production of tumor necrosis factor (TNF)-α and intercellular adhesion molecule (ICAM)-1 (24, 25).

It was assumed that CRC resection caused changes in the environment around the neutrophils resulting in N1 differentiation.

This study demonstrated that there were patients with relatively favorable and poor prognosis in the high pre-NLR group. These patients were either stage II or III, and these outcomes were not affected by other baseline factors.

Considering the study's background, preoperative CEA was significantly higher in the high pre-NLR group than the low pre-

Table II. *Correlation between clinicopathological features and ΔNLR.*

Variable	ΔNLR		*p*-Value
	<1 (n=63)	1≤(n=10)	
Gender			
Male	37 (58.7)	7 (7.0)	0.73
Female	26 (41.3)	3 (30.0)	
Age, years	67.6±15.6	69.5±23.1	0.746
Location of the tumor			
Cecum	3 (4.8)	0 (0)	0.321
Ascending	12 (19.0)	3 (30.0)	
Transverse	4 (6.3)	3 (30.0)	
Descending	2 (3.2)	0(0)	
Sigmoid	14 (22.2)	2 (20.0)	
Rs	9 (14.3)	0 (0)	
Ra	9 (14.3)	2 (20.0)	
Rb	10 (15.9)	0 (0)	
Tumor size, mm	61.5±28.1	44.5±16.5	0.066
Histological type			
Differentiated	52 (82.5)	7 (70.0)	0.392
Undifferentiated	11 (17.5)	3 (30.0)	
Depth of tumor			
T1	1 (1.6)	0 (0)	0.611
T2	1 (1.6)	0 (0)	
T3	38 (60.3))	8 (80.0)	
T4	23 (36.5)	2 (20.0)	
Lymph node metastasis			
Negative	33 (52.4)	8 (80.0)	0.170
Positive	30 (47.6)	2 (20.0)	
Lymphatic invasion			
Negative	16 (25.3)	7 (70.0)	0.008
Positive	47 (74.7)	3 (30.0)	
Venous invasion			
Negative	16 (25.4)	5 (50.0)	0.139
Positive	47 (74.6)	5 (50.0)	
Adjuvant chemotherapy			
Negative	42 (66.7)	9 (90.0)	0.264
Positive	21 (33.3)	1 (10.0)	
Complications (CD3<)			
Negative	54 (85.7)	7 (70.0)	0.352
Positive	9 (14.3)	3 (30.0)	
Post neutrophil count $\times 10^3/\mu l$	3.70±1.19	4.93±1.45	0.004
Post lymphocyte count $\times 10^3/\mu l$	1.47±0.63	0.54±0.28	<0.001
Post NLR	2.80±1.15	11.0±7.03	<0.001

Values are n(%) or mean±SD unless otherwise indicated. CD: Clavien-Dindo classification.

Table III. *Univariate analysis for prognostic factors associated with 5-year overall survival.*

Variable	Number n=119	5-year OS rate (%)	*p*-Value
Gender			
Male	44	61.8	0.555
Female	29	66.9	
Age, years			
<70	35	70	0.319
70≤	38	49.9	
Location			
Right side	22	68.4	0.918
Left side	37	67.3	
Tumor size, mm			
<50	21	69.3	0.475
50≤	38	66.3	
Histological type			
Differentiated	59	61.5	0.206
Undifferentiated	14	83.3	
Depth of tumor			
T2, T3	48	72.4	0.046
T4	25	50.3	
Lymph node metastasis			
Negative	41	69.1	0.391
Positive	32	58.9	
Lymphatic invasion			
Negative	23	67.3	0.700
Positive	50	64.2	
Venous invasion			
Negative	21	63.1	0.033
Positive	52	65.9	
Adjuvant chemotherapy			
Negative	52	55.8	0.020
Positive	21	85.2	
ΔNLR			
<1	63	69.8	0.007
1≤	10	33.3	

OS: Overall survival.

NLR group. This result is similar to a previous study, wherein high NLR was reported to correlate with high CEA (26).

Tumor size was also significantly larger in the high pre-NLR group than the low pre-NLR group. This is consistent with previous studies, which also showed that high NLR was correlated with larger tumor size (<5 cm) (27, 28). However, there was no discussion about why larger tumor size was associated with elevated NLR in these papers. We considered that this relationship between larger tumor size and elevated NLR might be due to the cancer cachexia syndrome, such as appetite loss, weight loss, and undernutrition. Systemic inflammation and tumor metabolism have been suggested to be important features of cancer cachexia. NLR has been reported to indicate tumor status, ongoing inflammation, and cachexia (29, 30).

It is assumed that a patient with a larger tumor size is more likely to have cachexia. In addition, this study revealed that tumor size was relatively larger in the low ΔNLR group than the high ΔNLR group. These may suggest that larger tumors are less susceptible to inflammation after resection.

Although the neutrophils were reduced in the low ΔNLR group after the resections, there was a considerable increase in the lymphocyte count. Therefore, it is suggested that improving nutritional status is very important in addition to

Table IV. *Multivariate analysis for prognostic factors associated with 5-year over-all survival.*

Variable	OR	95%CI	*p*-Value
Depth of tumor			
T2, T3 *versus* T4	3.321	1.292-8.534	0.013
Adjuvant chemotherapy			
Negative *versus* Positive	0.3429	0.097-1.204	0.095
ΔNLR			
<1 *versus* 1≤	0.2393	0.079-0.717	0.011

OR: Odds ratio; CI: confidence interval.

curative resection. However, the lymphocytes were low in the high ΔNLR group. Furthermore, there were patients who could not receive adjuvant chemotherapy because they were very old or had complications that caused malnutrition. Although the lymphocytes were significantly low in the high ΔNLR group, there was no difference in Hb and Alb values before and after surgery, surgery time, and anesthesia time (data are not shown). This implies that not only undernutrition but also potential residual cancer may be the reason why NLR did not decline. We suggest a liquid biopsy for cell-free DNA and circulating tumor cells to detect the minute cancer residue.

Several limitations were noted in this study. First, this is a retrospective study at a single institution. Second, it is a small population study. Therefore, a large prospective study is required.

In this study, we used 4 as the cut-off value to assess pre-NLR and 1 as the cut-off value to assess ΔNLR. However, various NLR cut-off values have been reported. From the viewpoint of universality of the evaluation and eliminating differences between facilities, a specific cut-off value is expected to be required in the future.

Conclusion

In conclusion, we demonstrated that ΔNLR is an independent prognostic factor for patients with stage II or III colorectal cancer, who underwent curative resection. Furthermore, decreasing postoperative NLR than preoperative NLR was associated with better OS and DFS, even in the high pre-NLR patients.

Conflicts of Interest

The Authors declare no conflicts of interest regarding this study.

Authors' Contributions

Naoki Ashizawa performed the majority of experiments and wrote the manuscript. Shinji Furuya designed the research and helped to draft the manuscript. All Authors reviewed the manuscript.

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