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ORIGINAL ARTICLE

Impact of the perioperative neutrophil-to-lymphocyte ratio on the long-term survival following an elective resection of colorectal carcinoma

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Abstract
Purposes The present study was designed to evaluate the prognostic value of the perioperative neutrophil-to-lymphocyte ratio (NLR) for the long-term survival in patients with colorectal cancer.
Methods This was a retrospective study of 524 patients with histologically proven stage II or III colorectal cancer who underwent curative colorectal resection. We classified patients into a low NLR group or high NLR group base on their NLR values at three time points (before surgery (Pre), on the first postoperative day (POD1), and on the third or fourth postoperative day (POD3)) and evaluated the survival according to the group.
Results The cancer-specific survival was significantly longer in the groups with a low NLR on POD3. The disease-free survival was significantly longer in the group with a low NLR on Pre. We subsequently allocated a score of 1 to patients with a high NLR at each point and reclassified patients into those with a low perioperative NLR group (score of 0 or 1) and high perioperative NLR group (score of 2 or 3). Both the cancer-specific survival and disease-free survival rates were significantly different between the two perioperative NLR groups. Both univariate and multivariate analyses demonstrated that being in the high perioperative NLR group was an independent risk factor for both the cancer-specific survival and disease-free survival.
Conclusions Not only the preoperative but also the postoperative NTR is thus considered to be a predictor of the long-time survival in patients with colorectal cancer.

Keywords Colorectal cancer · Neutrophil-to-lymphocyte ratio · Perioperative inflammation · Survival

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Introduction

It has long been recognized that cancer progression is not only dependent on the local characteristics of the tumor but also on the systemic host response. In 1978, DerHagopian et al. reported "inflammatory oncotaxis," which was a phenomenon wherein the activation and growth of dormant neoplastic cells might occur secondary to inflammation at a site distant from the primary tumor [1]. Since then, there has been increasing evidence that the inflammatory status play an important role in the progression of a variety of tumors [2–4].

Surgery is known to cause significant alterations in metabolic, immune, and endocrine functions. There have been several reports that major surgery alters multiple immune parameters and accelerates tumor growth [5, 6]. In contrast, endoscopic surgery has been reported to cause a reduced immune response compared to open surgery [7, 8]. Several reports have pointed out the possibility of favorable survival in patients with cancer treated by laparoscopic surgery, compared to patients treated by open abdominal surgery [9–11].

As prognostic markers in patients with colorectal cancer, several inflammation-based scores, such as the Modified Glasgow Prognostic Score, Prognostic Index, or the platelet to lymphocyte ratio, have been proposed [12, 13]. The preoperative neutrophil-to-lymphocyte ratio (NLR) has been receiving attention because of its performance and ease of calculation [14–16]. However, the association between the

postoperative NLR and long-term survival in patients with colorectal cancer has not been fully investigated.

For these reasons, we focused on the postoperative NLR, which was considered as a simple index of the systemic inflammatory response in critically ill patients [17]. The aim of this study was to evaluate the prognostic value of the perioperative NLR for long-term survival in patients with colorectal cancer.

Patients and methods

This study was a retrospective study of 524 patients with histologically proven stage II or III colorectal cancer (TNM seventh classification [18]) who underwent a potentially curative resection via laparotomy between January 2001 and December 2006 at the National Defense Medical College Hospital (Tokorozawa, Saitama, Japan). Patients with an emergency operation, laparoscopic operation, multiple carcinoma, inflammatory bowel disease, preoperative clinical evidence of infection or other inflammatory conditions, and those undergoing resections with macro- or microscopically positive pathological margins (R1 and R2 resections) were excluded from this study. In addition, patients who had undergone re-operation within a week from the first operation, which was generally required due to postoperative complication, were also excluded. The characteristics of the patients in this study are presented in Table 1. The median age of the patients was 65 years (range 18–96 years). There were 292 men and 232 women, 381 colon cancers and 143 rectal cancers, and 250 stage II patients and 274 stage III patients.

Table 1 The patient characteristics (n=524)

Age at the time of the operation, years (median, IQR)	65 (59–72)
Sex	
Male	292
Female	232
Cancer site	
Right side	98
Transverse	51
Left side	19
Sigmoid colon	213
Rectum	143
Differentiation	
Well or moderate	473
Poor and others	51
T stage	
T1	8
T2	31
T3	375
T4	110
Lymph node metastasis	
Negative	250
Positive	274
Postoperative infectious complication(s)	
No	387
Yes	137

Patients were retrospectively evaluated for clinicopathological data (age, sex, cancer site, cancer stage, postoperative infectious complications, and perioperative laboratory measurement) on the basis of their medical and nursing charts. The postoperative infectious complications in this study included incisional surgical site infections (SSIs), organ/space SSIs, enterocolitis, urinary tract infections, pneumonia, and other infections, which require some kind of clinical treatment. We calculated the NLRs before surgery (Pre), on the first postoperative day (POD1), and on the third or fourth postoperative day (POD3).

Adjuvant chemotherapy using a 5-fluorouracil (5-FU)-based regimen, such as the Roswell Park Memorial Institute (RPMI) regimen [19], Mayo regimen [20], or an oral uracil/tegafur (UFT)/leucovorin (LV) regimen [21], was recommended for patients with stage III disease or those with a high potential of recurrence based on the pathological findings. As a result, adjuvant chemotherapy was performed in 156 patients (55.9 %) with stage III cancer and 38 patients (15.1 %) with stage II cancer.

The patients were regularly observed at our hospital or the outpatient clinic. They underwent a physical examination and complete blood cell count, blood chemical analysis, and serum tumor marker evaluations every 3 months for the first 3 years after surgery and every 6 months for the following 2 years. Contrast-enhanced computed tomography was performed every 6 months, while colonoscopy was performed 1 and 3 years after surgery. After 5 years, an annual follow-up was conducted through telephone conversations with the patients or their family. The median follow-up was 59 months (range 5.2–111.6).

The primary endpoint of this study was the cancer-specific survival. The cancer-specific survival time was measured from the date of resection to the date of death due to recurrence of the primary cancer. The secondary endpoint was disease-free survival. Disease-free survival time was measured from the date of resection to the date of radiological or histological identification of recurrence of the primary cancer.

The statistical analysis was performed using the JMP software program (SAS Institute Inc., Cary, NC). The statistical analyses were performed using either the Pearson's χ^2 test or the Wilcoxon rank sum test. The survival rates were calculated with the Kaplan-Meier method, and differences between the curves were tested using the log-rank test. The univariate and multivariate analyses were performed using the Cox

Table 2 The perioperative neutrophil-to-lymphocyte ratio (NLR)

	Pre	POD1	POD3
Median, IQR	2.29 (1.75–3.36)	7.90 (5.83–11.0)	5.10 (3.66–7.05)
Number of patients with a low NLR	255	249	237
Number of patients with a high NLR	259	259	238

POD postoperative day

proportional hazards regression model. A P value <0.05 was considered to be statistically significant.

Results

Within the observation period, 104 patients (19.8 %) developed recurrence and 74 patients (14.1 %) succumbed to recurrence of the primary tumor. Thirty patients (5.7 %) died due to other causes.

Table 2 shows the perioperative NLRs and the classification of these values. We classified the perioperative NLRs according to the median NLR. That is, the patients with higher than the median NLR were classified into the high group, and those with values lower than the median NLR were classified into the low group.

Figure 1 shows the Kaplan-Meier curves for the cancer-specific survival of patients with high and low perioperative NLR values. There was a statistically significant difference in the cancer-specific survival between the groups based on the NLR values on POD3, although there was no significant difference between the comparison of the NLR at the Pre and POD1 time points. With respect to the disease-free survival, there was a statistically significant difference between the comparisons of the NLR values on Pre, although there was no significant difference between the comparison of the NLR at the POD1 and POD3 time points (Fig. 2).

We also compared the survival time in subgroups with different stages of cancer. In the patients with stage II cancers, there was a statistically significant difference in the cancer-specific survival between the groups based on the NLR values on POD3 (Fig. 3). In patients with stage III cancers, there was a statistically significant difference in the disease-free survival between the groups based on the NLR values at the Pre and POD1 time points (Fig. 4).

In addition, we allocated a score of 1 to patients with a high NLR at each point (Pre, POD1, POD3). That is, patients with high NLR values at all points were allocated a score of 3, while patients with low NLR values at all points were allocated a score of 0. As a result, 96 patients were assigned a score of 0, 132 patients were assigned a score of 1, 124 patients were assigned a score of 2, and 110 patients were assigned a score

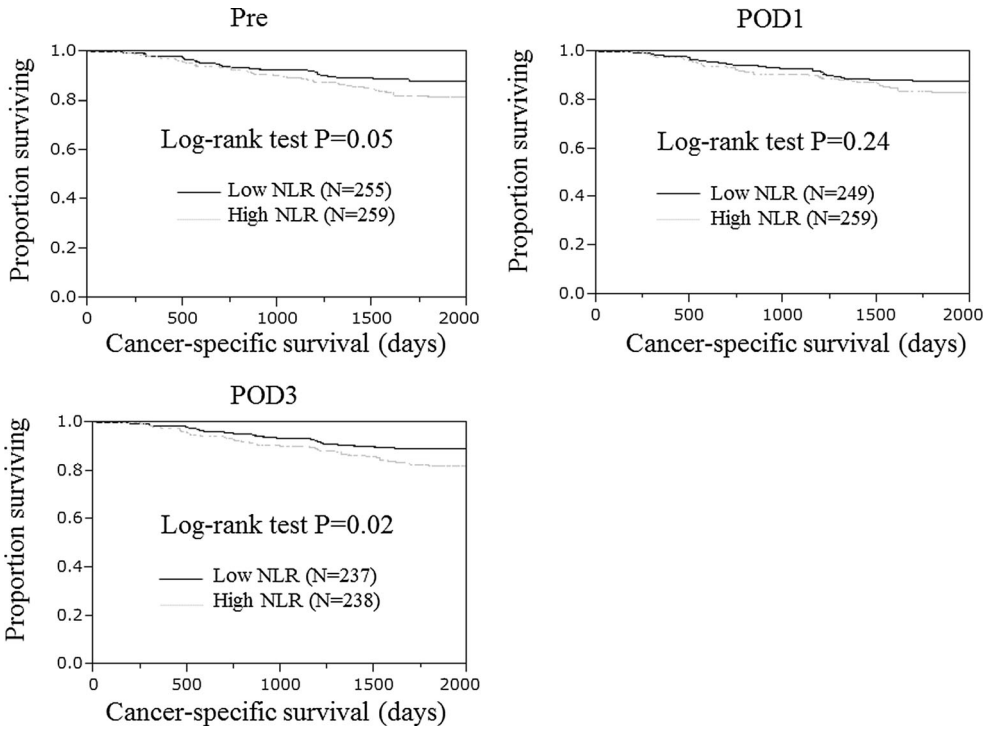

Fig. 1 The Kaplan-Meier curves for the cancer-specific survival after surgery with curative intent for stage II or stage III colorectal cancers based on the perioperative NLR

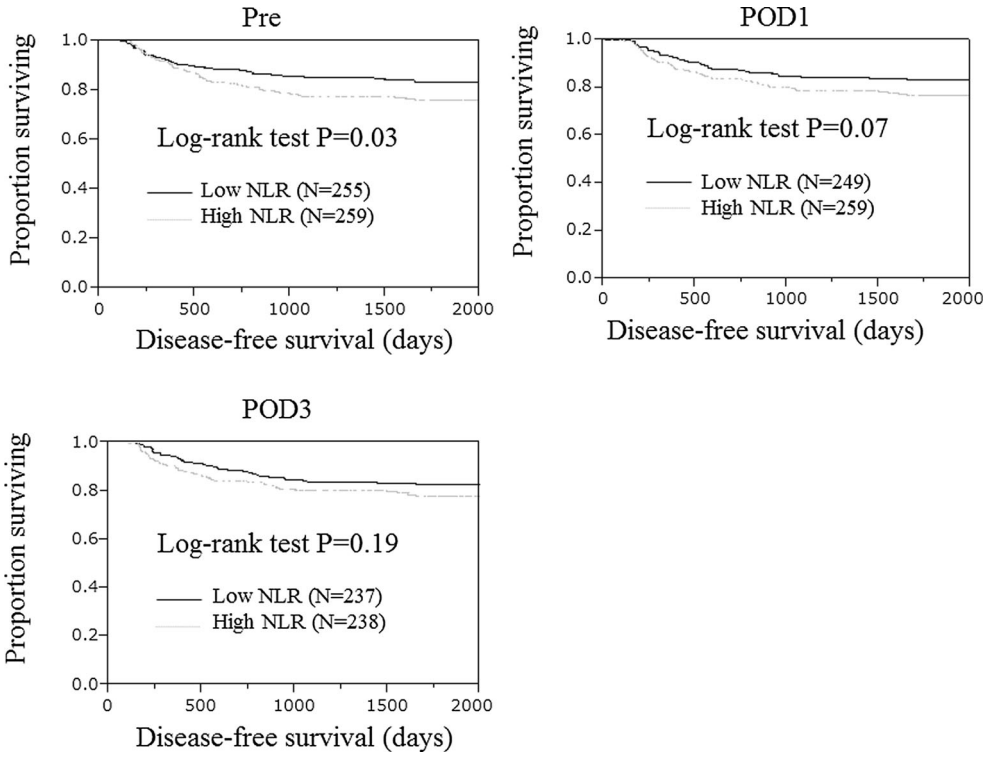

Fig. 2 The Kaplan-Meier curves for the disease-free survival after surgery with curative intent for stage II or stage III colorectal cancers based on the perioperative NLR

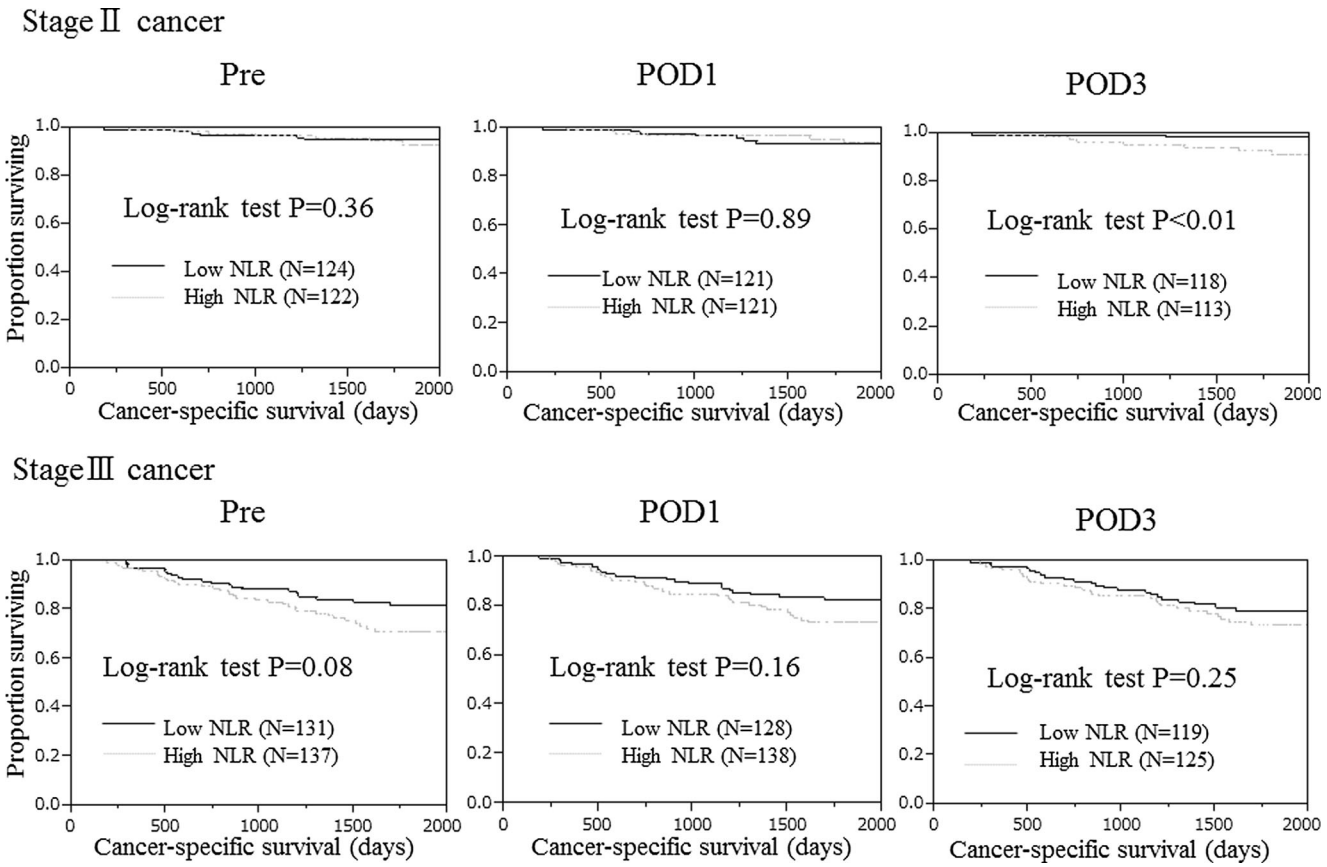

Fig. 3 The Kaplan-Meier curves for cancer-specific survival after surgery with curative intent in subgroups of colorectal cancer patients stratified by stage based on the perioperative NLR

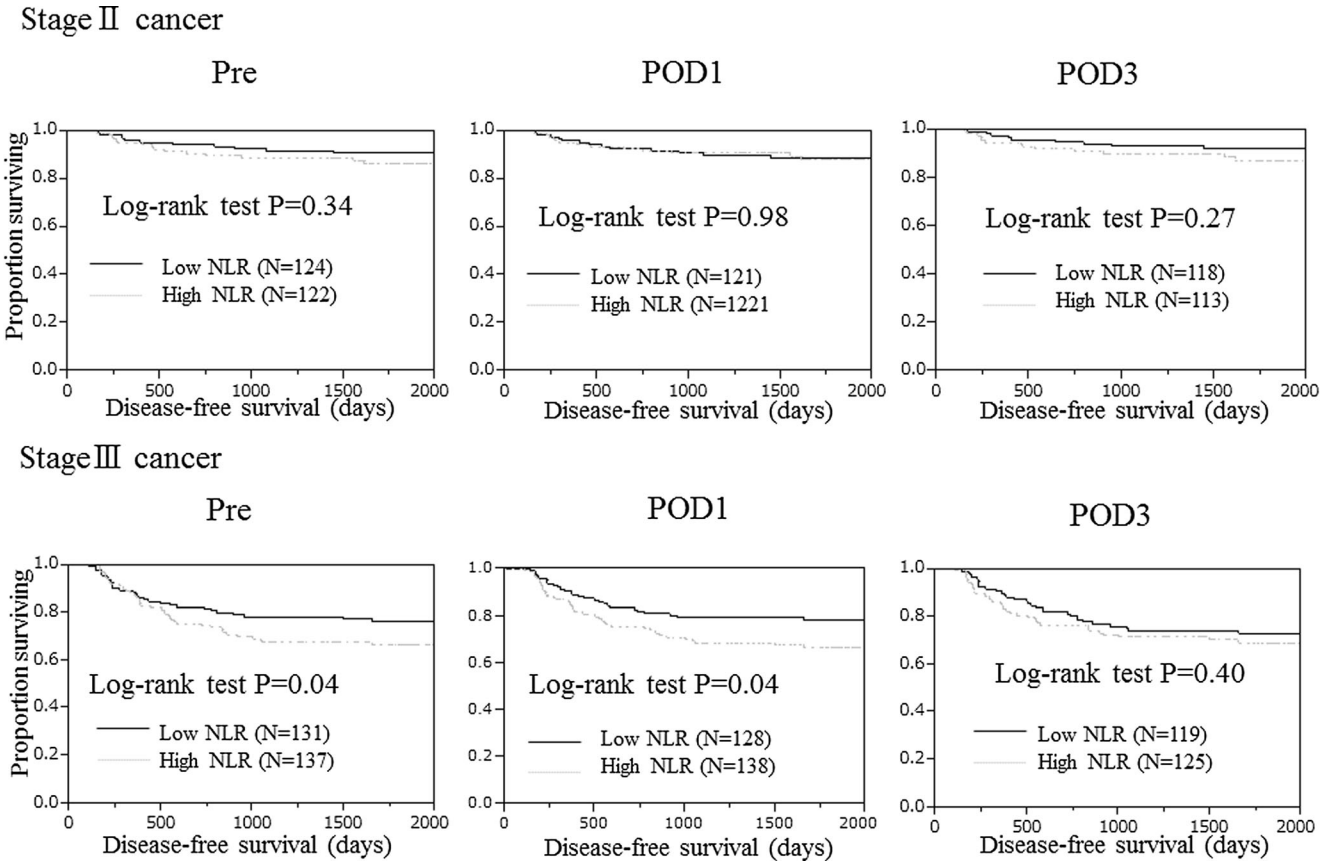

Fig. 4 The Kaplan-Meier curves for the disease-free survival after surgery with curative intent in subgroups of colorectal cancer patients stratified by stage based on the perioperative NLR

Table 3 The clinical and pathological features of patients with high and low perioperative NLR scores

	Low score (n=228)	High score (n=234)	P value
Age at the time of the operation, years (median, IQR)	64.0 (57–69)	65.5 (59–73)	0.08
Sex			0.78
Male	126	133	
Female	102	101	
Cancer site			<0.01
Colon	180	159	
Rectum	48	75	
Differentiation			0.01
Well or moderate	219	207	
Poor and others	13	30	
T stage			1.00
T1–3	192	197	
T4	36	37	
Lymph node metastasis			0.58
Negative	114	110	
Positive	114	124	
Postoperative infectious complication(s)			<0.01
No	183	158	
Yes	45	76	

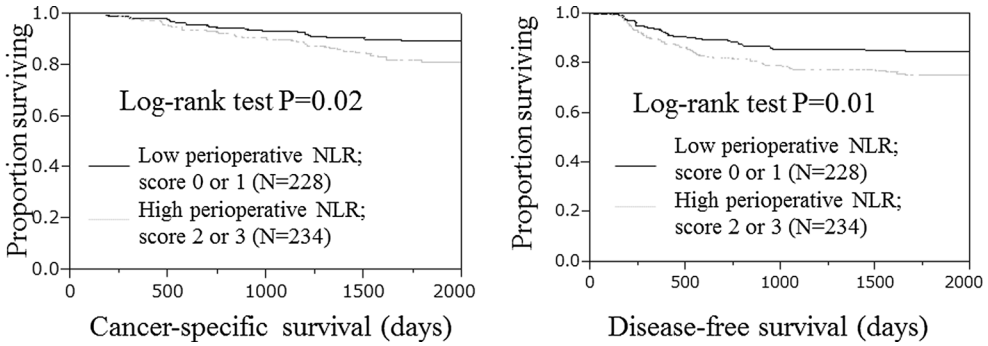

Fig. 5 The Kaplan-Meier curves for the cancer-specific and disease-free survival after surgery with curative intent for stage II or III colorectal cancer based on the perioperative NLR score; we allocated a score of 1 to patients with a high NLR at each point and reclassified patients into a low perioperative NLR group (score of 0 or 1) and a high perioperative NLR group (score of 2 or 3)

of 3. We also reclassified patients based on this scoring system: a low perioperative NLR group (score of 0 or 1) or high perioperative NLR group (score of 2 or 3).

Table 3 shows the associations between the clinicopathological factors and perioperative NLR scores. Although the cancer site, differentiation, and postoperative infectious complications were found to be associated with the perioperative NLR score, no other clinicopathological factors were related to the score.

Figure 5 shows the Kaplan-Meier survival curves for the patients with high and low perioperative NLR scores. There was a statistically significant difference in both the cancer-specific survival and disease-free survival between the groups based on a comparison of the perioperative NLR score. The 5-year cancer-specific survival rates in patients with a high perioperative NLR score and in those with a low perioperative NLR score were 81.0 and 89.4 %, respectively. The 5-year disease-free survival rates in patients with a high perioperative NLR score and in those with a low perioperative NLR score were 75.1 and 84.5 %, respectively.

The univariate and multivariate analyses of the clinicopathological factors and perioperative NLR score were performed.

Table 4 The results of the univariate and multivariate analyses of the relationship between the clinicopathological factors and perioperative NLR score with the cancer-specific survival in patients with colorectal cancer

	Univariate analyses HR (95 % CI)	*P* value	Multivariate analyses HR (95 % CI)	*P* value
Age at the operation (years)		0.08		
<75				
≥75				
Sex		0.43		
Male				
Female				
Cancer site		<0.01		0.01
Colon	1		1	
Rectum	1.98 (1.23–3.12)		2.02 (1.18–3.42)	
Differentiation		0.27		
Well or moderate				
Poor and others				
T stage		<0.01		<0.01
T1–3	1		1	
T4	2.35 (1.38–3.86)		2.77 (1.53–4.80)	
Lymph node metastasis		<0.01		<0.01
Negative	1		1	
Positive	4.01 (2.38–7.45)		4.54 (2.51–8.91)	
Perioperative NLR score		0.02		0.04
High	1.84 (1.12–3.09)		1.71 (1.03–2.88)	
Low	1		1	

HR hazard ratio, *CI* confidence interval

Table 5 The results of the univariate and multivariate analyses of the relationship between the clinicopathological factors and perioperative NLR score with the disease-free survival in patients with colorectal cancer

	Univariate analyses HR (95 % CI)	*P* value	Multivariate analyses HR (95 % CI)	*P* value
Age at the operation (years)		0.09		
<75				
≥75				
Sex		0.49		
Male				
Female				
Cancer site		<0.01		<0.01
Colon	1		1	
Rectum	2.01 (1.39–3.05)		2.05 (1.31–3.16)	
Differentiation		0.33		
Well or moderate				
Poor and others				
T stage		<0.01		<0.01
T1–3	1		1	
T4	2.03 (1.27–3.14)		2.45 (1.48–3.93)	
Lymph node metastasis		<0.01		<0.01
Negative	1		1	
Positive	3.05 (2.00–4.85)		3.24 (2.04–5.35)	
Perioperative NLR score		0.01		0.02
High	1.69 (1.11–2.60)		1.53 (1.01–2.37)	
Low	1		1	

HR hazard ratio, *CI* confidence interval

In the univariate analysis, the cancer site (colon vs rectum), T stage (T1–3 vs T4), lymph node metastases (negative vs positive), and perioperative NLR score (0, 1 vs 2, 3) were each found to be associated with the cancer-specific survival. The multivariate analysis also demonstrated that the cancer site, T stage, lymph node metastases, and perioperative NLR score were significantly associated with the cancer-specific survival (Table 4). Similarly, the multivariate analysis demonstrated that a high perioperative NLR score was an independent risk factor for the disease-free survival (Table 5).

Discussion

Conventional prognostic factors for colorectal cancer, represented by the TNM classification, were mainly based on the tumor characteristics. We herein investigated the usefulness of a host factor to support the conventional prognostic factors for risk stratification in colorectal cancer treatment. Specifically, we focused on the impact of the postoperative NLR and revealed that there were significant differences between the long-term survival after curative resection of colorectal cancer based on the postoperative NLR.

The NLR is known as an inflammation-based prognostic score and is presumed to be a combined indicator of inflammation and the immune status in patients with colorectal cancer [15, 22, 23]. Recently, numerous reports have supported the utility of the NLR as a prognostic factor in patients with colorectal cancer. However, to our knowledge, this study is the first to indicate the association between the postoperative NLR and long-term survival in patients with colorectal cancer.

Although the reason for the association between an elevated NLR and a poor prognosis remains to be elucidated, there have been several reports that have discussed potential mechanisms. First, patients with an elevated NLR are presumed to have a poorer lymphocyte-mediated immune response to malignancy and therefore an increased potential for tumor recurrence [24]. Several studies have reported that patients with weaker lymphocytic infiltration at tumor margins had a worse prognosis [25, 26]. Second, patients with an elevated NLR are presumed to have an increased number of circulating neutrophils secreting vascular endothelial growth factor (VEGF), which is a pro-angiogenic factor thought to be integral to tumor development [27]. Park et al. reported that strong VEGF-C expression on surgical specimens of intrahepatic cholangiocarcinoma was an independent and important prognostic factor [28]. On the other hand, Motomura et al. have

recently reported that an elevated NLR promoted hepatocellular carcinoma recurrence after living donor liver transplantation via the promotion of inflammatory microenvironment, which was provided by interleukin-17-producing cells and tumor-associated macrophages, not via lymphocytic infiltration or VGEF [24].

In addition to the utility of the preoperative NLR as prognostic factor, there have been several reports that postoperative infectious complications in patients undergoing gastrointestinal surgery lead to poor cancer-specific survival rates [29–31]. Although the precise mechanism is still unclear, we consider that an elevated postoperative NLR, caused by infection, may influence the long-term survival. For this reason, we hypothesized that a persistently elevated NLR might affect cancer progression. To verify this hypothesis, we allocated a score of 1 to patients with a high NLR at each point (preoperatively, on POD1 and on POD3) and classified the patients according to the perioperative NLR. As a result, the univariate and multivariate analyses demonstrated that a high perioperative NLR score, which means a persistently elevated NLR during the perioperative period, is an independent risk factor for both the cancer-specific survival and disease-free survival after curative resection of colorectal cancer.

There were several possible limitations associated with our study, including its retrospective nature. In addition, there was no completely fixed protocol for perioperative care. For example, POD3 in this study includes data collected on both the third and fourth postoperative days. The perioperative NLR values of patients in this study could not all be calculated, because routine laboratory measurements were sometimes missed.

In conclusion, our study provides evidence of an association of not only the preoperative but also the postoperative NLR with the long-term survival of patients with colorectal cancer. This needs to be confirmed in prospective and appropriately designed studies. The perioperative NLR score, which has no connection with the T stage or N stage, was an independent prognostic factor in patients with colorectal cancer. Further investigations are necessary to evaluate the mechanism underlying the association between the perioperative biological status and long-term survival in patients with cancer.

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