A High Preoperative Neutrophil–to–lymphocyte Ratio Is Associated with Poor Survival in Patients with Colorectal Cancer

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Abstract. *Background: Previous studies have reported that an elevated preoperative neutrophil-to-lymphocyte ratio (NLR) is associated with a poor prognosis in patients with various types of cancers. The aim of this study was to determine the prognostic significance of preoperative NLR in patients with colorectal cancer and to determine an appropriate cut-off value of the NLR. Patients and Methods: We enrolled 674 patients who underwent surgery for stage I–IV colorectal cancer. The mean NLR was 2.74±2.20. To determine the appropriate cut-off value of the NLR, we used a receiver operating characteristic curve. A total of 262 patients with an NLR of 2.5 or more were classified as high-NLR individuals in this study. The prognostic significance of a high NLR was evaluated using a multivariate analysis. Results: The cancer-specific survival was significantly (p<0.001) worse in the patients with a high NLR. The multivariate analysis indicated that the tumor diameter, the presence of lymph node or distant metastasis, and a high NLR were independent risk factors for poor survival. Conclusion: Preoperative NLR measurement is a convenient biomarker and predictor of a poor prognosis after surgery for colorectal cancer.*

Although staging according to the Union for International Cancer Control (UICC) TNM classification (1) is very important and useful for predicting the prognosis and determining the appropriate treatment in patients with colorectal cancer, it is not sufficient. Therefore, various serum markers, including carcinoembryonic antigen (CEA), carbohydrate antigen (CA19–9) and p53, have been examined and reported to be associated with recurrence and a poor prognosis in patients with colorectal cancer (2, 3). In recent years, the host inflammatory response to cancer cells has been reported to be associated with tumor progression (4, 5), and attention has been paid to its usefulness as a biomarker. A high preoperative C-reactive protein level has also been reported to be associated with a poor prognosis (6). The preoperative neutrophil-to-lymphocyte ratio (NLR) also reflects a patient's inflammatory status, clinical stage and survival among those with pancreatic, lung or gastric cancer (7-9). However, only limited information regarding the clinical and prognostic significance of NLR in patients with colorectal cancer has been reported (10-12). In addition, the cut-off value of NLR used in the present study is different from the ones reported previous studies (11, 13, 14). In this study, we measured the preoperative NLR in 674 patients with colorectal cancer to determine its clinicopathological and prognostic significance and to determine an appropriate cut-off value.

Patients and Methods

A total of 674 cases of colorectal cancer were reviewed. All patients underwent surgery for colorectal cancer at the Department of Surgical Oncology of Osaka City University between 2002 and 2009. Patients who received preoperative therapy, underwent emergency surgery for perforation or had inflammatory bowel disease were excluded from the analysis.

A total of 388 males and 286 females were included in this study. The median age of the patients at the initial surgery was 67.5 years (range= 26 to 91 years). The resected specimens were pathologically classified according to the seventh edition of the UICC TNM classification of malignant tumors (1). The distribution of cancer stages was as follows: stage I, 175; stage II, 201; stage III, 186; stage IV, 112 patients. All patients were followed up regularly with physical and blood examinations and mandatory screening using colonoscopy and computed tomography until December 2012 or death. The median duration of follow-up was 55 months (range, 1 to 119 months).

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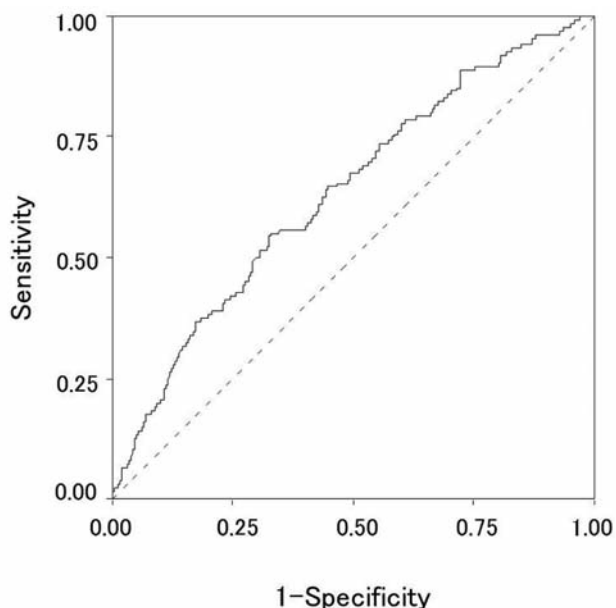
Figure 1. *Receiver operating characteristic curve analysis of the neutrophil-to-lymphocyte ratio in patients with colorectal cancer. Area under the curve=0.635, 95% Confidence interval=0.583-0.687, p<0.001.*

Blood sample analysis. Peripheral blood was obtained at the time of diagnosis before surgery. The NLR was calculated from the preoperative blood sample by dividing the absolute neutrophil count by the absolute lymphocyte count.

Statistical analysis. Firstly, we used a receiver operating characteristic (ROC) curve to determine an appropriate cut-off value. All patients were then classified into two groups according to the NLR. The significance of the correlation between the NLR and the clinicopathological characteristics was analyzed using the χ^2 test. A univariate survival analysis was carried out according to the Kaplan–Meier method. Differences in the survival curves were assessed with the log-rank test. A multivariate analysis was performed according to the Cox regression model. All statistical analyses were performed using the SPSS software package for Windows (SPSS Japan, Tokyo, Japan). Statistical significance was set at $p<0.05$.

Results

The mean preoperative NLR in the 674 patients was 2.74±2.20, with a median of 2.21 (range=0.52 to 23.50). We used the continuous variable NLR as the test variable and 5-year cancer-specific survival as the state variable. When we investigated the cut-off value of the NLR using the ROC curve, we found that the appropriate cut-off value of the NLR was 2.56 (the sensitivity was 55.1% and the specificity was 67.1%) (Figure 1). Therefore, we set 2.5 as the cut-off value and classified the patients into high-NLR (≥2.5) and low-NLR (<2.5) groups to predict prognosis.

Table I. *Associations between the neutrophil-to-lymphocyte ratio (NLR) and clinicopathological parameters in patients with colorectal carcinoma.*

		NLR		
	n	Low	High	*p*-Value
Gender				
Male	388	233	155	
Female	286	179	107	0.523
Age, years				
<70	421	271	150	
≥70	253	141	112	0.028
Tumor depth				
T1-2	204	154	50	
T3-4	469	258	211	<0.001
Tumor diameter, cm				
<5	342	246	96	
≥5	328	164	164	<0.001
Histology+				
Well, mod	609	384	225	
Poor, muc	62	28	34	0.009
Lymphatic involvement				
Negative	228	157	71	
Positive	427	247	180	0.007
Venous involvement				
Negative	518	332	186	
Positive	137	72	65	0.017
Lymph node metastasis				
Negative	394	265	129	
Positive	279	147	132	<0.001
Distant metastasis				
Negative	560	368	192	
Positive	113	43	70	<0.001
CEA (ng/ml)				
<5	350	239	111	
≥5	314	170	144	<0.001

+According to Japanese classification of colorectal carcinoma (19).

Based on the cut-off value of 2.5, 262 (38.9%) patients were classified into the high-NLR group. A high NLR exhibited significant relationships with age, the preoperative serum CEA level, tumor depth, tumor diameter, histological type and the presence of lymphatic involvement, venous involvement, lymph node metastasis and distant metastasis (Table I).

The NLR gradually increased in association with increasing tumor stage, from a mean±standard deviation (SD) of 2.22±1.41 in stage I to 3.99±3.62 in stage IV (Figure 2).

A total of 177 patients had died by the end of 2012; 136 out of these 177 patients died due to colorectal cancer. To investigate whether a high NLR reflected a poor prognosis, a Kaplan–Meier analysis and the log-rank test were performed. An assessment of the prognoses showed that patients with a high NLR had a significantly worse cancer-specific survival (5-year cancer-specific survival=65.6%) than patients with a low NLR (5-year cancer-specific survival=86.0%) (Figure 3).
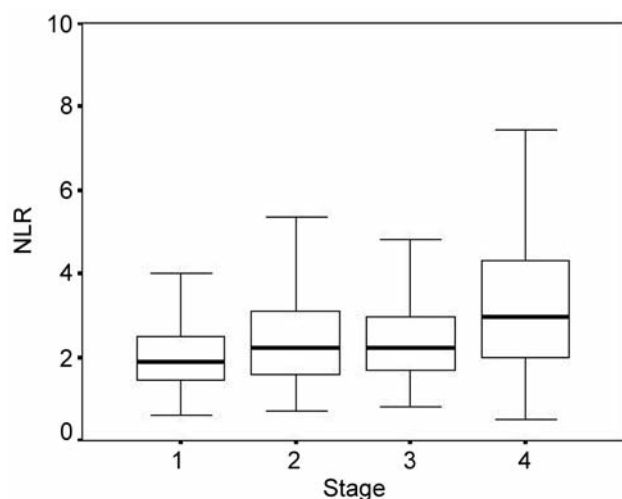
Figure 2. *Neutrophil-to-lymphocyte ratio (NLR) according to the pathological stage of colorectal cancer. Data are mean±standard deviation.*
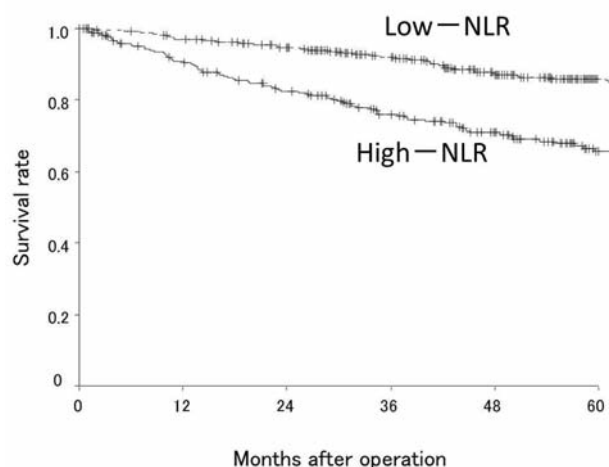

Figure 3. *Kaplan–Meier postoperative survival curves. The cancer-specific survival was significantly worse in the patients with a high neutrophil-to-lymphocyte ratio (NLR) (p<0.001).*

Table II. *Correlations between cancer-specific survival and various clinicopathological factors.*

	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	*p*-Value	Hazard ratio	95% CI	*p*-Value
Tumor depth	8.555	4.187-17.479	<0.001	2.036	0.907-4.569	0.085
Tumor diameter	2.297	1.605-3.288	<0.001	0.634	0.419-0.959	0.031
Histological type	1.752	1.079-2.846	0.023	1.344	0.807-2.236	0.256
Lymphatic involvement	4.299	2.548-7.253	<0.001	1.422	0.809-2.502	0.221
Venous involvement	3.721	2.640-5.244	<0.001	1.394	0.958-2.028	0.082
Lymph node metastasis	7.422	4.865-11.323	<0.001	3.089	1.928-4.948	<0.001
Distant metastasis	12.669	8.951-17.930	<0.001	6.232	4.118-9.431	<0.001
CEA	4.055	2.736-6.009	<0.001	1.374	0.874-2.160	0.169
NLR	2.436	1.736-3.419	<0.001	1.609	1.117-2.319	0.011

CI: Confidence interval; CEA: carcinoembryonic antigen; NLR: neutrophil-to-lymphocyte ratio.

The correlations between cancer-specific survival and various clinicopathological factors are shown in Table II. According to a univariate analysis, cancer-specific survival had significant relationships with the tumor depth, tumor diameter, histological type, the presence of lymphatic involvement, venous involvement, lymph node metastasis and distant metastasis, the preoperative serum CEA level and the NLR. However, a multivariate analysis indicated that only lymph node metastasis, distant metastasis and the NLR were independent risk factors for poor survival.

Discussion

An association between a high preoperative NLR and a poor prognosis has been reported for several types of carcinomas (7-9). Similar results were also obtained in our study. A high

preoperative NLR in patients with colorectal cancer was found to be associated with tumor progression and a poor prognosis. The difference in survival may be partly explained by differences in tumor volume between the low- and high-NLR groups, because the NLR was significantly associated with tumor progression. However, after controlling for these pathological parameters in a multivariate analysis, the NLR remained an independent prognostic factor, regardless of the TNM factors. As a difference in survival was observed in comparison of the patients with the same tumor stage (10), the NLR is thought to be an independent prognostic factor.

The cut-off value for the NLR used in the present study is different from that reported in previous studies. In previous reports, values of 3.0, 4.0 or 5.0 have been used as the cut-off value (11, 13, 14); however, in our study, the best cut-off value was 2.5 based on the ROC analysis. When we analyzed the

cancer–specific survival curves according to each NLR cut-off (2.5, 3.0 and 4.0), the survival rate was significantly worse in the patients with a high NLR for every cut-off value. However, only when setting 2.5 as the cut-off value did the multivariate analysis indicate that a high preoperative NLR was an independent risk factor for poor survival.

The increasing level of circulating neutrophils that ensues following a nonspecific systemic inflammatory response generated by a tumor results in relative lymphocytopenia and an elevated NLR (11). Although the mechanisms underlying the association between an elevated NLR and a poor prognosis in patients with colorectal cancer remain partially unknown, many issues regarding the connection between inflammation and tumorigenesis have gradually been clarified by the latest research (15, 16). Neutrophils play a key role in tumor proliferation, producing a number of ligands that induce tumor cell proliferation and invasion, and promoting tumor vascularization by releasing proangiogenic chemokines and other factors. Therefore, an increased number of neutrophils can promote tumor growth and metastasis. On the other hand, lymphocytes also play a key role in tumor suppression. They are responsible for the antitumor immune response of the host to the tumor (16, 17). Stated concretely, the function of lymphocytes is to induce cytotoxic cell death and cytokine production that inhibits the proliferation and metastatic activity of cancer cells. Therefore, a decreased number of lymphocytes impairs the host antitumor immune response and confers a poor prognosis. In brief, the NLR can be considered to reflect the balance between the pro-tumor inflammatory status and the antitumor immune status (18).

Because a peripheral blood cell count is a quick and easy assay to perform, measuring the NLR is a useful clinical biological marker for identifying patients with a high risk of a poor prognosis and allows planning of more frequent surveillance and intensive therapy.

Acknowledgements

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