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ORIGINAL SCIENTIFIC REPORT

The Prognostic Value of Preoperative Neutrophil-to-Lymphocyte Ratio in Colorectal Cancer

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ABSTRACT

Background The prognostic value of the neutrophil-to-lymphocyte ratio (NLR) has been reported in several cancers included colorectal cancer; however, it is not clear if there is an association between NLR and cancer-specific survival in colorectal cancer. And the optimal cut-off value is controversial. This study was designed to assess the prognostic value of preoperative NLR in colorectal cancer patients.

Methods Total 823 consecutive patients who underwent surgery for all stages of colorectal cancer in our hospital between January 2006 and December 2011 were included in the study. Preoperative NLR was calculated from their hospital records.

Results Using the receiver-operating characteristic curve, we found that the optimal preoperative NLR cut-off value that was strongly associated with cancer-specific survival was 2.1. Using this value, 505 patients were identified as having high NLR (≥2.1) and 397 patients were identified as having low NLR (<2.1). High NLR was associated with preoperative serum albumin values <4.0 g/dl ($p < 0.001$), positive preoperative serum C-reactive protein (CRP; $p < 0.001$), preoperative carcinoembryonic antigen (CEA) values ≥5.0 ng/dl ($p = 0.003$), and stage progression ($p = 0.002$). Cox proportional hazard analyses identified preoperative high NLR as an independent poor prognostic factor ($p = 0.020$, HR 1.66 (95 % CI: 1.08–2.63)). When comparing stage of disease, preoperative high-NLR patients with Stage III disease ($p = 0.024$) and Stage IV disease ($p = 0.036$) had significantly poorer prognoses.

Conclusions In this study, we have demonstrated that preoperative NLR ≥2.1 was a prognostic indicator for cancer-specific survival of colorectal cancer patients.

Introduction

Colorectal cancer is one of the most common causes of death in the world [1]. In Japan, the incidence rate has recently been increasing among almost all age groups for both sexes [2], so improvements in treatment outcomes for colorectal cancers are needed. The TNM staging system [3]—determined by tumor factors such as tumor depth, lymph node metastasis, and distant metastasis—is the most predictable prognostic factor for colorectal cancer. The Japanese classification of colorectal carcinoma also determines the tumor stage by the same tumor factors, and is strongly associated with prognosis [4]. Although the TNM

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staging system and the Japanese classification of colorectal carcinoma are widely used, there is a prognostic difference in the same stage groups. Within each stage group there are still different possible prognoses, suggesting that there are still factors that are different and important to identify to further aid prognostification. Recently, an association between prognosis and host-related factors has been reported. For example, the Glasgow prognostic score (GPS)—which is calculated by serum C-reactive protein (CRP) and serum albumin concentrations—is a prognostic factor [5], and serum albumin concentration is a predictor of operative mortality and morbidity [6]. Furthermore, anastomotic leakage has a negative association with survival [7, 8]. These host-related factors—such as nutritional status, systemic inflammation, and postoperative complications—are helpful for determining colorectal cancer treatment strategies.

The neutrophil-to-lymphocyte ratio (NLR) is attractive as an indicator of inflammation and immune function. Preoperative blood samples for neutrophil and lymphocyte counts are taken for almost all colorectal cancer patients, and the NLR can be simply calculated. It has been reported that NLR is a prognostic factor for various cancers, such as advanced cancer [9], pancreatic cancer [10], non-small cell lung cancer [11], cancer of esophagogastric junction [12], gastric cancer [13], lung cancer [14], and head and neck cancer [15]. Pre-treatment NLR has also been reported as a prognostic factor for colorectal cancer [16–24]. Li et al. reported that they concluded NLR gains a prognostic value for patients with colorectal cancer from a meta-analysis [25]. However, almost all previous reports analyzed overall survival or progression free survival rate [25]. It was reported that NLR was associated with a higher mortality in coronary artery disease patients [26]. Hence, the association between NLR and cancer-specific survival rate has not been fully elucidated. Furthermore, the optimal cut-off point to predict cancer-specific survival is controversial. The aim of this study is to confirm whether or not preoperative NLR is a prognostic factor for colorectal cancer patients using cancer-specific survival rate as an endpoint.

Materials and methods

Study population and treatments

This retrospective analysis included data from the hospital records of 852 consecutive patients who underwent surgery for colorectal cancer at the University Hospital of Kyoto Prefectural University of Medicine, Kyoto, Japan, between January 2006 and December 2011. We excluded three patients who were pathologically diagnosed with malignant lymphoma and gastrointestinal stromal tumor, 21 patients who underwent only colostomy, one case who underwent a laparotomy, and four cases who had no preoperative laboratory data. The remaining 823 patients were included in the study. The data examined were age, sex, preoperative serum albumin, preoperative serum CRP, preoperative carcinoembryonic antigen (CEA), postoperative severe complications (anastomotic leakage, intraperitoneal bleeding, and intraperitoneal abscess), histological type (G1, G2, G3, G4 based on TNM classification [3]), and pStage. NLR was calculated using preoperative laboratory data and following the formula: NLR = neutrophil rate (%)/lymphocyte rate (%).

The postoperative follow-up of these patients included physical examination, blood tests, checking the tumor biomarker (CEA and CA19-9), and image diagnoses, such as X-ray photograph, computed tomography, positron emission tomography, and gastrointestinal endoscopy, on a fixed interval. We decided that the endpoint of this study was cancer-specific survival.

Statistical analysis

Receiver-operating characteristic (ROC) curves and the area under the ROC curve (AUC) were used to assess the feasibility of using preoperative NLR as a predictive marker for cancer-specific survival. The Youden index was used to determine the cut-off value for preoperative NLR [27]. The Chi square test or Fisher's exact probability test was used for categorical variables.

For the analysis of survival rates, survival curves were estimated using the Kaplan–Meier method and statistical differences were examined using the log-rank test. Univariate and multivariate survival analyses were performed using the likelihood ratio test of the stratified Cox proportional hazards model. p values <0.05 were considered statistically significant. All statistical analyses were performed using the JMP 10.0 software program (SAS Institute, Cary, NC, USA).

Results

Patients, tumor characteristics, and treatment

The mean age of the 823 patients was 67.1 ± 10.4 years old. There were 457 male patients and 366 female patients. The pathological diagnoses were 69 patients with Stage 0 disease, 230 patients with Stage I disease, 215 with Stage II disease, 205 patients with Stage III disease, and 104 patients with Stage IV disease. Preoperative treatments included 26 patients that underwent preoperative endoscopic resection, 26 patients that underwent preoperative chemotherapy (either 5-fluorouracil (5-FU); 5-FU and

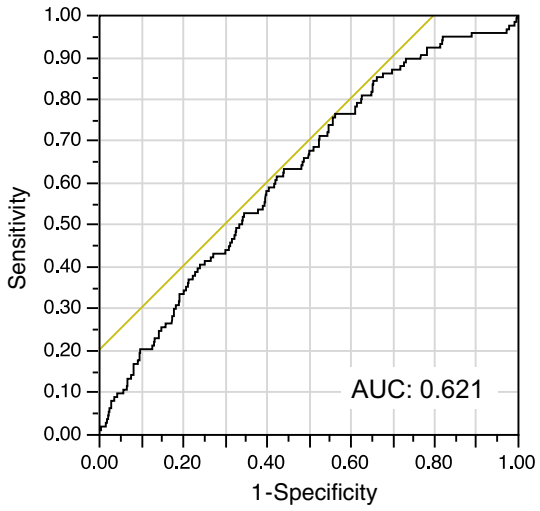

Fig. 1 ROC *curve* of the survival and preoperative neutrophil-to-lymphocyte ratio (NLR) in colorectal cancer. The area under the curve (AUC) was 0.621 with a sensitivity of 76.3 %, a specificity of 43.5 %, and an accuracy of 47.5 %

leucovorin; FOLFOX; or FOLFOX and bevacizumab), and 40 patients that underwent preoperative chemo-radiation therapy (IRIS (irinotecan and S-1) and radiation therapy (45 Gy)). The types of surgery included: open surgery in 274 patients, laparoscopic surgery in 518 patients, initially underwent laparoscopic surgery but were later converted to open surgery in 23 patients, and transanal surgery in eight patients. 747 patients received radical surgery and 76 patients palliative surgery. The surgical procedures comprised a tumorectomy in 11 patients, a local excision in five patients, a ileocecal resection in 68 patients, a segmental resection (transverse colon) in 35 patients, a right hemicolectomy in 146 patients, a left hemicolectomy in 34 patients, a sigmoidectomy in 207 patients, a subtotal colectomy in one patient, a total colectomy in four patients, a proctocolectomy in five patients, a high anterior resection in 61 patients, a lower anterior resection in 146 patients, a super lower anterior resection in seven patients, an intersphincteric resection in five patients, a Hartmann operation in 29 patients, an abdominoperineal resection in 52 patients, a total pelvic exenteration in four patients, and other operation in three patients with lymphadenectomy based on the Japanese colorectal cancer treatment guidelines [28]. 704 patients were Cur A, 32 patients were Cur B, and 87 patients were Cur C, respectively. The treatments after surgery were as follows: 561 patients were observation only, 165 patients underwent adjuvant chemotherapy (UFT, UFT/LV, 5-FU/LV, mFOLFOX6, Cape, S-1, IRIS), 74 patients underwent chemotherapy for unresectable regions (5-FU/LV, UFT/LV, mFOLFOX6 ± Bmab, CapeOX ± Bmab, FOLFIRI, S-1, Irinotecan), 13 patients underwent a hepatectomy for liver metastasis later, six patients underwent a pneumonectomy for lung metastases later, two patients underwent lymph node resection later, and two patients underwent radiation therapy. The median follow-up time was 1475 days.

Table 1 Comparison of clinicopathological characteristics and preoperative NLR

Factors	*n*	NLR ≥ 2.1	NLR < 2.1	
		n = 505	*n* = 318	*p* value
Sex				
Male	457	269	188	0.100
Female	366	236	130	
Age				
<65	358	204	154	0.024
≥65	465	301	164	
Preoperative Alb (g/dl)				
≥4.0	645	371	274	<0.001
<4.0	178	134	44	
Preoperative CRP (mg/dl)				
≥0.3	215	163	52	<0.001
<0.3	608	342	266	
Preoperative CEA (ng/dl)				
<5.0	539	311	228	0.003
≥5.0	284	194	90	
Postoperative complication				
negative	781	478	303	0.689
positive	42	27	15	
Stage				
0	69	38	31	0.002
I	230	118	112	
II	215	140	75	
III	205	138	67	
IV	104	71	33	
Histological type				
G1, G2	752	455	297	0.101
G3, G4	71	50	21	

NLR neutrophil-to-lymphocyte ratio, *Alb* albumin, *CRP* C-reactive protein; *CEA* carcinoembryonic antigen

Cut-off value of NLR associated with cancer-specific survival

To find a cut-off point of NLR that could predict cancer-specific survival, we used the AUC with the Youden index (Fig. 1). The value of the AUC was 0.621 and the optimal cut-off point of NLR was observed at 2.1, with a sensitivity of 76.3 %, a specificity of 43.5 %, and an accuracy of 47.5 %.

Table 2 Univariate and multivariate analysis of clinicopathological factors in colorectal cancer patients

Factors	*n*	Univariate	Multivariate analysis		
		p value	Risk ratio	95 %CI	*p* value
Sex					
Male	399	0.73	–	–	
Female	424		–	–	
Age					
<65	358	0.596	–	–	
≥65	465		–	–	
Preoperative Alb (g/dl)					
≥4.0	645	<0.001	1	–	<0.001
<4.0	178		2.192	1.440–3.306	
Preoperative CRP (mg/dl)					
≥0.3	215	0.001	1	–	0.420
<0.3	608		1.185	0.782–1.783	
Preoperative CEA (ng/dl)					
<5.0	539	<0.001	1	–	0.003
≥5.0	284		1.94	1.254–3.051	
Postoperative complication					
Negative	781	0.801	–	–	
Positive	42		–	–	
Stage					
0	69	0.001	1	–	<0.001
I	230		1.111	0.164–21.74	
II	215		2.289	0.451–41.72	
III	205		6.529	1.396–116.4	
IV	104		34.16	7.271–609.8	
Histological type					
G1, G2	752	<0.001	1	–	0.010
G3, G4	71		1.987	1.188–3.180	
NLR					
<2.1	318	<0.001	1	–	0.020
≥2.1	505		1.658	1.079–2.627	

CI confidence interval, *Alb* albumin, *CRP* C-reactive protein, *CEA* carcinoembryonic antigen, *NLR* neutrophil-to-lymphocyte ratio

Comparison of clinicopathological characteristics and preoperative NLR

We defined high NLR as patients whose preoperative NLR was 2.1 or higher and low NLR as patients whose preoperative NLR was lower than 2.1.We compared the clinicopathological characteristics between 505 high-NLR patients and the 318 low-NLR patients. Patients with the age ≥65 years old ($p = 0.024$), preoperative serum albumin ≤4.0 g/dl ($p < 0.001$), preoperative serum CRP ≥0.3 mg/dl ($p < 0.001$), preoperative CEA ≥5.0 ng/dl ($p = 0.003$), and stage progression ($p = 0.002$) included significantly more high-NLR patients. The high-NLR group tended to include more female and elderly patients. Postoperative complication was not associated with NLR (Table 1).

Prognostic value of preoperative NLR in colorectal cancer patients

In analyses of all the patients, using a cox proportional hazard model, univariate analyses showed that patients with preoperative serum albumin ≤4.0 g/dl ($p < 0.001$), preoperative serum CRP ≥0.3 mg/dl ($p < 0.001$), preoperative CEA ≥5.0 ng/dl ($p < 0.001$), stage progression ($p = 0.001$), histological type G3 or G4 ($p < 0.001$), or high NLR ($p < 0.001$) had a significantly poor prognosis. In multivariate analyses, preoperative serum albumin ≤4.0 g/dl ($p < 0.001$), preoperative CEA ≥5.0 ng/dl ($p = 0.003$), stage ($p < 0.001$), histological type G3 or G4 ($p = 0.010$), and high NLR ($p = 0.020$, HR = 1.658 (95 %CI: 1.079–2.627)) were independent poor prognostic factors (Table 2).

Comparison of survival curves in each pathological stage

We compared survival curves for each pathological stage between high NLR and low NLR by using the Kaplan–Meier method and log-rank test. In pStage 0, pStage I, and pStage II groups there was no significant difference in survival between each pathological stage (Fig. 2a (pStage 0 and pStage I not shown)). In pStage III, high-NLR patients had a significantly poorer prognosis than low-NLR patients ($p = 0.024$), and the 5-year survival rate with high NLR or low NLR was 75.7 or 91.8 %, respectively (Fig. 2b). In pStage IV, high-NLR patients also had a significantly poorer prognosis than low-NLR patients ($p = 0.036$), and the 5-year survival rate with high NLR or low NLR was 21.7 or 48.0 %, respectively (Fig. 2c). In all patients, high-NLR patients also had a significantly poorer prognosis than low-NLR patients ($p = 0.001$), and the 5-year survival rate with high NLR or low NLR was 79.8 or 91.3 %, respectively (Fig. 2d).

Discussion

In this study, we have demonstrated that preoperative high NLR in colorectal cancer patients predicts a significantly poorer prognosis of cancer-specific survival by multivariate analysis. Furthermore, high NLR is associated with preoperative serum albumin <4.0 g/dl, positive preoperative CRP, preoperative CEA ≥5.0 ng/dl, stage progression, and poor histological types G3 or G4.

In the comparisons of survival curves for each pathological stage, preoperative high-NLR patients demonstrated significantly poorer prognosis in both pStage III and

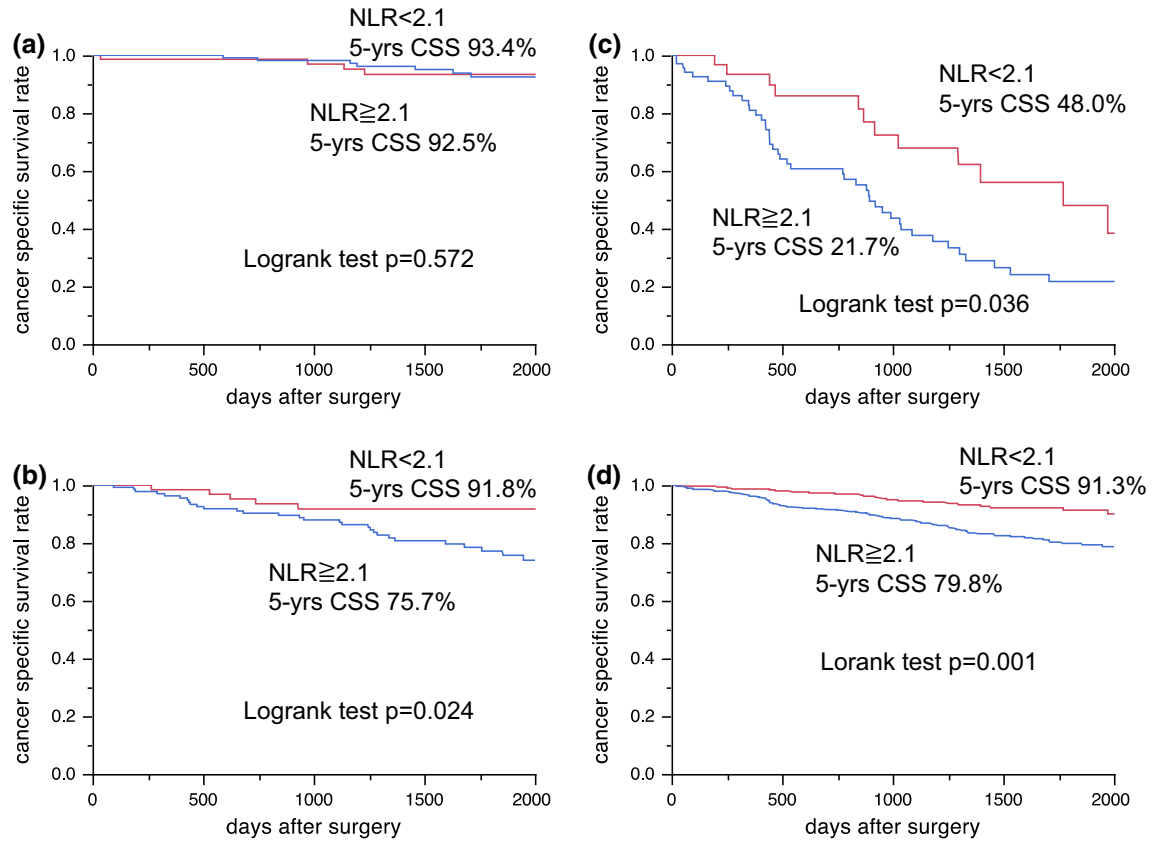

Fig. 2 Comparisons of Kaplan–Meier curves of five-year cancer-specific survival (5-year CSS) rates between two groups based on neutrophil-to-lymphocyte ratio (NLR) (High NLR ≥2.1; Low NLR <2.1) in each stage. The log-rank test was used for statistical analyses. **a** Stage II patients ($n = 215$; high NLR ($n = 140$) and low NLR ($n = 75$)). **b** Stage III patients ($n = 205$; high NLR ($n = 138$) and low NLR ($n = 67$)). **c** Stage IV patients ($n = 104$; high NLR ($n = 71$) and low NLR ($n = 33$)). **d** All patients ($n = 823$; high NLR ($n = 505$) and low NLR ($n = 318$))

IV patients. The NLR 2.1 cut-off point was not associated with prognosis in pStage II patients. Many previous reports used NLR 5.0 as a cut-off point [25]. Using NLR 5.0 in our cohort, there are 66 patients with NLR ≥5.0 (8 %), and prediction value of cancer-specific death are as follows: sensitivity, specificity, and accuracy were 11.4, 93.2, and 81.9 %, respectively. In our cohort, limited to pStage II patients with preoperative NLR ≥5.0 had a significantly poorer prognosis than patients with NLR <5.0. In contrast, there is statistically no significance between NLR ≥5.0 and NLR <5.0 in Stage IV patients (data not shown). However, a higher cut-off point like 5.0 is of high specificity and accuracy but the sensitivity is low, using a higher cut-off point may predict a prognosis in early stage cancer.

The reason why NLR levels are associated with prognosis is not clear, but there are some possible explanations. Firstly, the host's inflammatory response to the tumor. It is reported that transcription factors coordinate the production of inflammatory mediators, and a cancer-related inflammation is generated by these factors. This cancer-related inflammation has many tumor-promoting effects, such as infiltrate, angiogenesis, and survival of malignant cells in distant organs [29]. Another report showed that inflammation played an important role in the initiation and progression of a tumor in colorectal cancer [30]. It is reported that cytokines (interleukin 6, interleukin 8, interleukin 2Rα, etc.) which associate with tumor progression and poor survival correlated with high NLR [20]. Increasing the number of neutrophils, which elevates the NLR level, reflects the host's inflammation status and might affect prognosis. Secondly, the host's lymphocyte-mediated immune response to the tumor. It was reported that tumor-infiltrating lymphocytes along the invasive margin of rectal cancer were a prognostic factor [31]. Lymphocytic reactions were independent prognostic factors for a better survival and the number of T-lymphocytes was important in an immunohistochemical subset analyses in colorectal cancer [32]. Elevated NLR represents a relative lymphocytopenia and it might therefore affect the immune response to cancer tissues.

There are other systemic inflammation indicators such as serum CRP and the GPS calculated by serum CRP and albumin. It was reported that GPS was an independent

prognostic factor in colorectal cancer [5]. However, serum CRP levels are not always examined in all hospitals. Furthermore, in our cohort, serum CRP was a significant prognostic factor but was not independent in multivariate analysis. In contrast, NLR is simply obtained by routine preoperative examination and in colorectal cancer patients a high NLR was an independent prognostic factor. Therefore, NLR may predict prognosis more effectively than serum CRP.

The fact that preoperative high NLR ($\geq$2.1) indicates a poor prognosis is significant for colorectal cancer management because lymphocyte counts are also known to be an indicator of a patient's nutritional status [33]. Previously, it was reported that the prognostic nutritional index, which is calculated based on the serum albumin concentration and peripheral blood lymphocyte count, was a useful predictor of postoperative complications and survival in colorectal cancer patients [34]. There is a possibility that nutritional support improves the prognosis of colorectal cancer patients.

The limitations of this study are that it is a retrospective and a single-institutional study, so there is potential bias in the selection of patients and potential inaccuracy of the medical records. However, the results of the present study suggest that preoperative high NLR is a simple and useful tool for predicting cancer-specific survival in colorectal cancer patients. This index may help to determine the strategy for colorectal cancer patients' treatment additional to TNM staging.

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