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Prognostic significance of systemic inflammatory response in stage II colorectal cancer

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ABSTRACT

Background: It is considered that stage II colorectal cancers have heterogeneous oncological outcomes. It remains to be determined whether inflammatory markers can predict survival after curative surgery in these patients. The aim of this study was to investigate the prognostic impact of preoperative inflammatory markers after curative surgery in stage II colorectal cancers.

Methods: Two hundred sixty-one patients with stage II colorectal cancers who underwent curative surgery between January 2006 and December 2011 were reviewed. Oncologic outcomes were analyzed with neutrophil count, lymphocyte count, monocyte count, neutrophil to lymphocyte ratio (NLR), and lymphocyte to monocyte ratio.

Results: Univariate analysis showed that high NLR (hazard ratio (HR), 3.506; 95% confidence interval [CI], 1.415-8.688; $P = 0.007$) and low LMR (HR, 2.436; 95% CI, 1.010-5.880; $P = 0.048$) were associated with worse disease-free survival (DFS), and high NLR (HR, 2.834; 95% CI, 1.419-5.662; $P = 0.003$) and low LMR (HR, 2.374; 95% CI, 1.188-4.742; $P = 0.014$) were associated with worse overall survival (OS) in stage II colorectal cancer. Cox multivariate analysis demonstrated that high NLR was independently associated with worse DFS (HR, 3.163; 95% CI, 1.058-9.455; $P = 0.004$) and OS (HR, 3.018; 95% CI, 1.467-6.207; $P = 0.003$) in stage II colorectal cancer.

Conclusion: Among the systemic inflammatory markers, NLR is a strong predictor of worse DFS and OS in stage II colorectal cancer.

Introduction

Administration of adjuvant chemotherapy is not routinely recommended for all patients with stage II colon cancer who have gone complete surgical resection because of indefinite benefit, costs, and drug side effects.[1] Currently, it is recommended for patients with high-risk factors, including T4 tumor, bowel obstruction or perforation, lymphovascular invasion, poorly differentiated tumor, and inadequate lymph node sampling.[2] However, there is little evidence that patients with any of high-risk factors gain benefit from adjuvant chemotherapy compared with patients without these high-risk factors.

It is expected that selective chemotherapy for stage II colon cancer patients with high-risk factors would improve their long-term survival rate to approach that of patients without high-risk factors. However, stage II colon cancer still represents an inhomogeneous group in terms of prognosis even after selective chemotherapy for stage II colon cancer patients with high-risk factors.

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Table 1 – Patient characteristics.

Variable	*n* (%)
Gender	
Male	143 (54.8)
Female	118 (45.2)
Median age (range, y)	65.0 (31-86)
Location	
Colon	211 (80.8)
Rectum	50 (19.2)
Tumor differentiation	
Well	49 (18.8)
Moderate	191 (73.2)
Poor	21 (8.0)
Tumor size	
≤5	91 (34.9)
>5	170 (65.1)
Depth of invasion	
T3	238 (91.2)
T4	23 (8.8)
Lymphatic invasion	
Positive	167 (64.0)
Negative	87 (33.3)
Not available	7 (2.7)
Venous invasion	
Positive	237 (90.8)
Negative	17 (6.5)
Not available	7 (2.7)
Perineural invasion	
Positive	231 (88.8)
Negative	22 (8.5)
Not available	7 (2.7)
Number of retrieved LN	
<12	40 (15.3)
≥12	221 (84.7)
Preoperative CEA	
<5	157 (60.2)
≥5	65 (24.9)
Not available	39 (14.9)
Adjuvant chemotherapy	
No	202 (77.4)
Yes	59 (22.6)
Albumin (g/dL)	
<3.5	18 (6.9)
≥3.5	243 (93.1)
WBC count ($\times 10^9$)	
<10	233 (89.3)
10-15	28 (10.7)
Neutrophil count ($\times 10^9$)	
<4.6	142 (54.4)
≥4.6	119 (45.6)
Lymphocyte count ($\times 10^9$)	
<1.83	107 (41.0)
≥1.83	154 (59.0)
Monocyte count ($\times 10^9$)	
<0.52	149 (57.1)
≥0.52	112 (42.9)
NLR	
<2.6	161 (61.7)
≥2.6	100 (38.3)
LMR	
<3.7	109 (41.8)
≥3.7	152 (58.2)

WBC = white blood cell; LN = lymph nodes.

Biomolecular markers, such as p53 mutations, microsatellite instability, and fascin-1, have been found to more precisely predict prognosis in colorectal cancer. However, these markers are not used in clinical settings because the cost of the tests is high.

Recently, the roles of the immune system and systemic inflammation in disease progression have been reported.[3] Systemic inflammation is reported to play an important role in invasion or metastases of cancer, and systemic inflammation-based markers such as a C-reactive protein, Glasgow Prognostic Score, and neutrophil to lymphocyte ratio (NLR) have been suggested to be significantly associated with poor prognosis in various cancers,[4-8] including colorectal cancers.[9]

The aim of this study was to investigate the prognostic impact of systemic inflammatory response markers after curative surgery in stage II colorectal cancers.

Patients and methods

Two hundred sixty-one patients with stage II colorectal cancers who underwent curative surgery between January 2006 and December 2011 were reviewed. Oncologic outcomes were analyzed based on neutrophil count, lymphocyte count, monocyte count, NLR, and lymphocyte to monocyte ratio (LMR). Exclusion criteria were as follows: patients with middle and lower rectal cancer ($n = 72$) and those with inflammatory conditions or with a history of other primary cancer ($n = 50$). Staging of colorectal cancers was performed according to the sixth edition of the American Joint Committee on Cancer (AJCC) tumor-node-metastasis staging system. This study was approved by the Institutional Review Board of Ajou University Hospital.

Preoperative blood samples were taken within 2 wk before surgery. Routine laboratory profiles, including white blood cell count, neutrophil count, lymphocyte count, and monocyte count, were included in this study. NLR was defined as the

Table 2 – Univariate analysis of disease-free and overall survival.

Variables	Disease-free survival		Overall survival	
	HR (95% CI)	P value	HR (95% CI)	P value
Gender				
Male	1.153 (0.486-2.737)	0.746	1.801 (0.878-3.696)	0.108
Female	1		1	
Age				
<65	1.206 (0.512-2.840)	0.668	1	
≥65	1		3.663 (1.595-8.412)	0.002
Location				
Colon	1.439 (0.424-4.885)	0.560	1	
Rectum	1		1.100 (0.479-2.526)	0.823
Tumor differentiation				
G1	1		1	
G2	0.912 (0.300-2.771)	0.871	0.799 (0.341-1.870)	0.604
G3	1.928 (0.431-8.619)	0.390	1.784 (0.566-5.622)	0.323
Tumor size				
≤5	1		1	
>5	1.018 (0.411-2.524)	0.969	1.736 (0.885-3.404)	0.109
Depth of invasion				
T1	1		1	
T2	2.448 (0.824-7.278)	0.107	1.017 (0.311-3.325)	0.978
Lymphatic invasion				
Negative	1		1	
Positive	2.309 (0.980-5.439)	0.056	2.444 (1.232-4.851)	0.011
Venous invasion				
Negative	1		1	
Positive	1.500 (0.349-6.440)	0.586	2.010 (0.707-5.719)	0.191
Perineural invasion				
Negative	1		1	
Positive	2.096 (0.613-7.161)	0.238	2.073 (0.798-5.386)	0.134
Number of retrieved LN				
<12	1		1	
≥12	1.737 (0.405-7.458)	0.458	1.327 (0.468-3.768)	0.595
Preoperative CEA				
<5	1		1	
≥5	2.413 (0.931-6.258)	0.070	3.297 (1.543-7.047)	0.002
Adjuvant chemotherapy				
No	1		1	
Yes	2.713 (1.143-6.439)	0.024	1.246 (0.581-2.669)	0.572
Neutrophil count ($\times 10^9$)				
<4.6	1		1	
≥4.6	2.025 (0.839-4.886)	0.116	1.795 (0.906-3.553)	0.093
Lymphocyte count ($\times 10^9$)				
<1.83	2.413 (1.000-5.822)	0.050	1.890 (0.960-3.719)	0.065
≥1.83	1		1	
Monocyte count ($\times 10^9$)				
<0.52	1		1	
≥0.52	2.275 (0.943-5.489)	0.067	1.545 (0.788-3.031)	0.205
NLR				
<2.6	1		1	

(continued)

Table 2 – (*continued*)

Variables	Disease-free survival		Overall survival	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
≥2.6	3.506 (1.415-8.688)	0.007	2.834 (1.419-5.662)	0.003
LMR				
<3.7	2.436 (1.010-5.880)	0.048	2.374 (1.188-4.742)	0.014
≥3.7	1		1	

LN = lymph nodes.

absolute neutrophil count divided by the absolute lymphocyte count. LMR was defined as the absolute lymphocyte count divided by the absolute monocyte count.

As presented in previous article,[10] the patients were followed up every 3-6 mo for the first 2 y after surgery, every 6 mo for the next 3 y, and every year thereafter. Each follow-up investigation included physical examinations and a serum carcinoembryonic antigen (CEA) assay. Chest X-ray, abdominopelvic computed tomography scan, and colonoscopy were performed yearly for 5 y. Positron emission tomography was performed on suspicion of recurrence.

Recurrence was detected by reviewing radiologic imaging in combination with the serum CEA level, and it was confirmed by pathologic examinations.

The patients were followed up until death or the cutoff date (December 31, 2015). Median follow-up time was 78.0 mo (range, 3-119 mo). Disease-free survival (DFS) and overall survival (OS) were calculated for all patients from the date of surgery until recurrence and death.

Statistics

The cutoff value for hematologic profiles was determined by analyzing the receiver-operating characteristic curve. The differences in the clinicopathologic features were assessed by using Pearson's chi-square test or Fisher's exact test. Kaplan-Meier survival analysis was used to estimate the DFS and OS for colorectal cancer. Differences between survival curves for hematologic profiles were compared by using the log-rank test. The prognostic significance of variables was assessed independently using Cox proportional hazards model. Variables with a *P* value < 0.20 were included in the multivariate analysis. Multivariate analysis was performed using the Cox proportional hazards model with a stepwise forward method. Statistical analysis was performed with SPSS software (SPSS Inc, Chicago, IL), using two-sided testing with a significance level of 0.05.

Results

Clinicopathologic characteristics

Table 1 shows the characteristics of patients who underwent curative resection for stage II colorectal cancer from 2006 to 2011. The 261 patients included 143 men and 118 women with a median age of 65.0 y (range, 31-86 y). Two hundred eleven patients had colon cancer and 50 patients had upper rectal

Table 3 – Multivariate analysis of disease-free and overall survival.

Variables	Disease-free survival		Overall survival	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Gender				
Male			2.163 (1.018-4.596)	0.045
Female			1	
Age				
<65			1	
≥65			3.990 (1.678-9.490)	0.002
Perineural invasion				
Negative			1	
Positive			3.928 (1.432-10.772)	0.008
Preoperative CEA				
<5			1	
≥5			2.965 (1.357-6.475)	0.006
NLR				
<2.6	1		1	
≥2.6	3.163 (1.058-9.455)	0.004	3.018 (1.467-6.207)	0.003

cancer. Of these tumors, 49 were well differentiated, 191 were moderately differentiated, and 21 were poorly differentiated. In clinical staging, 238 patients presented with T3 disease and 23 patients presented with T4 disease. Forty patients had a decreased number of harvested lymph nodes. Fifty-nine patients underwent adjuvant chemotherapy. One hundred of the 261 patients (38.3%) had a high NLR. One hundred nine of the 261 patients (41.8%) had a low LMR.

Univariate and multivariate analyses

The mean follow-up time was 77.7 mo (range, 3-119; median, 78.0). Univariate analysis showed that high NLR (HR, 3.506; 95% confidence interval [CI], 1.415-8.688; $P = 0.007$), low LMR (HR, 2.436; 95% CI, 1.010-5.880; $P = 0.048$), and adjuvant chemotherapy (HR, 2.713; 95% CI, 1.143-6.439; $P = 0.024$) were associated with decreased DFS in stage II colorectal cancer (Table 2). Cox multivariate analysis demonstrated that only high NLR (HR, 3.163; 95% CI, 1.058-9.455; $P = 0.004$) was independently associated with decreased DFS in stage II colorectal cancer (Table 3).

Univariate analysis showed that high NLR (HR, 2.834; 95% CI, 1.419-5.662; $P = 0.003$), low LMR (HR, 2.374; 95% CI, 1.188-4.742; $P = 0.014$), age (HR, 3.663; 95% CI, 1.595-8.412; $P = 0.002$), lymphatic invasion (HR, 2.444; 95% CI, 1.232-4.851; $P = 0.011$), and preoperative CEA (HR, 3.297; 95% CI, 1.543-7.047; $P = 0.002$) were associated with decreased OS in stage II colorectal cancer (Table 2). Cox multivariate analysis demonstrated that high NLR (HR, 3.018; 95% CI, 1.467-6.207; $P = 0.003$), gender (HR, 2.163; 95% CI, 1.018-4.596; $P = 0.045$), age (HR, 3.990; 95% CI, 1.678-9.490; $P = 0.002$), perineural invasion (HR, 3.928; 95% CI, 1.432-10.772; $P = 0.008$), and preoperative CEA (HR, 2.965; 95% CI, 1.357-6.475; $P = 0.006$) were independently associated with decreased OS in stage II colorectal cancer (Table 3).

Comparisons of recurrence and survival according to NLR

Table 4 shows correlation between clinicopathologic characteristics and NLR. Among the 261 patients, there were a total of 21 recurrences with a median time to recurrence of 16 mo (range, 3-53 mo). Among the 161 patients with a low NLR, seven patients had a recurrence, and among the 100 patients with a high NLR, 14 patients had a recurrence. There was marginal difference in recurrence pattern between high NLR group and low NLR group (Table 5). The 5-y DFS rates were lower in patients with a high NLR compared with those with a low NLR in stage II colorectal cancer (84.6% *versus* 95.1%, $P = 0.004$) (Figure, A). The 5-y OS rates were lower in patients with a high NLR compared with those with a low NLR in stage II colorectal cancer (79.9% *versus* 91.9%, $P = 0.002$) (Figure, B).

Table 4 – Correlation between clinicopathologic characteristics and NLR.

Variable	NLR < 2.6 ($n = 161$)	NLR ≥ 2.6 ($n = 100$)	P value
Gender			0.957
Male	88 (54.7)	55 (55.0)	
Female	73 (45.3)	45 (45.0)	
Age			0.850
< 65	76 (47.2)	46 (46.0)	
≥65	85 (52.8)	54 (54.0)	
Location			0.214
Colon	134 (83.2)	77 (77.0)	
Rectum	27 (16.8)	23 (23.0)	
Tumor differentiation			0.323
Well	27 (16.8)	22 (22.0)	
Moderate	123 (76.4)	68 (68.0)	
Poor	11 (6.8)	10 (10.0)	
Tumor size			0.004
≤5	67 (41.6)	24 (24.0)	
>5	94 (58.4)	76 (76.0)	
Depth of invasion			0.594
T3	148 (91.9)	90 (90.0)	
T4	13 (8.1)	10 (10.0)	
Lymphatic invasion			0.471
Positive	107 (66.5)	60 (60.0)	
Negative	49 (30.4)	38 (38.0)	
Not available	5 (3.1)	2 (2.0)	
Venous invasion			0.647
Positive	144 (89.4)	93 (93.0)	
Negative	12 (7.5)	5 (5.0)	
Not available	5 (3.1)	2 (2.0)	
Perineural invasion			0.676
Positive	140 (87.5)	91 (91.0)	
Negative	15 (9.4)	7 (7.0)	
Not available	5 (3.1)	2 (2.0)	
Number of retrieved LN			0.025
<12	31 (19.3)	9 (9.0)	
≥12	130 (80.7)	91 (91.0)	
Preoperative CEA			0.443
<5	99 (61.5)	58 (58.0)	
≥5	36 (22.4)	29 (29.0)	
Not available	26 (16.1)	13 (13.0)	
Adjuvant chemotherapy			0.011
No	133 (82.6)	69 (69.0)	
Yes	28 (17.4)	31 (31.0)	

LN = lymph nodes.

Discussion

We investigated the prognostic impact of hematologic factors in stage II colorectal cancer. The present study demonstrated that among these factors, NLR was found to be a powerful factor predicting DFS and OS in stage II colorectal cancer. NLR has already been reported to be a prognostic factor in colorectal cancer in previous studies.[11-16] However, the inclusion criteria differ among studies. Two studies focused on only patients who did not receive chemotherapy for stage II colon cancer.[11,12] Four additional studies included patients with more than one stage.[13-16] Furthermore, the number of patients with stage II disease who were included in those studies was small. Currently, the most powerful prognostic

Table 5 – Patterns of recurrence.

Parameter	NLR < 2.6	NLR ≥ 2.6	P value
Local and distant recurrence	7	14	0.088
Local	3 (42.9)	1 (7.1)	
Distant	4 (57.1)	13 (92.9)	

factor in colorectal cancer is tumor-node-metastasis staging. Therefore, any study dealing with prognostic factors in colorectal cancer should be performed separately according to the stage. We have already published a study that assessed the prognostic impact of NLR in stage I colorectal cancer.[9]

In case of stage II colon cancer, administration of adjuvant chemotherapy is recommended for patients with high-risk factors.[17] However, there is little evidence that patients with any of high-risk factors gain benefit from adjuvant chemotherapy compared with patients without high-risk factors. Hence, we included all the patients with stage II disease, including those who underwent adjuvant chemotherapy. They accounted for 22.3% of the patients with stage II disease.

In contrast to previous studies dealing with a single factor, we analyzed several hematologic factors including NLR to investigate the prognostic factors in stage II colorectal cancer. The presence of systemic inflammation can be measured by inflammatory markers such as neutrophil count, lymphocyte count, monocyte count, C-reactive protein level, and platelet count. Neutrophils may have a protumorigenic effect, and they appear to be responsible for the release of proangiogenic cytokines and other factors. Conversely, lymphocytes are involved in cytotoxic cell death and inhibition of tumor cell proliferation and metastasis by inducing an immune response against the tumor via cytokines.[18] Therefore, the host immune system plays an important role in proliferation and metastases of colorectal cancer. Monocytes play a major role in innate immunity, and they constitute about 5% of the circulating white blood cell pool and represent a microenvironment surrogate marker of tumor burden.

Several such parameters have been converted to ratios such as the NLR or the LMR. NLR can be used as a marker that represents the balance between proangiogenic systemic inflammation and antitumor immune responses. Actually, high NLR values have been suggested to be associated with advanced stages and worse prognosis in various malignancies,[4,19,20] including colorectal cancers.[21]

However, the role of NLR in stage II colorectal cancer remains to be clarified, although previous studies have suggested its association with poor prognosis. In this study, we confirmed that preoperative NLR was a powerful independent prognostic factor in stage II colorectal cancer, irrespective of adjuvant chemotherapy. In addition, we found that recurrence pattern was different between high NLR group and low NLR group. High NLR group had a tendency to recur as a distant metastasis, whereas low NLR group had a tendency to recur locally.

Therefore, addition of NLR, as a prognostic factor, to the current staging system should be considered. In addition, the role of current adjuvant chemotherapy in stage II colorectal cancer should be reappraised. The innate and adaptive immune responses are commonly impaired in cancer patients, and they are also impaired after exposure to surgical stress. This phenomenon may explain how disseminated tumor cells can evade immune surveillance and develop distant metastases. Immunosuppression and failure of immune surveillance are thought to be associated with the risk of recurrence. In addition, the presence of a systemic inflammatory response has been reported to be associated with chemoresistance. Park *et al.*[22] have suggested the potential role of antiinflammatory agents in reducing recurrence and improving survival in colorectal cancer patients who have undergone curative surgery. Therefore, an effort should be made to control cancer-related inflammation instead of current chemotherapy.

Although the optimal cutoff value for NLR remains to be established, high NLR values may be used as an indicator of the imbalance between the host and tumor environment. Although there is no immunotherapy available to maintain proper immune status, the administration of antiinflammatory agents has been reported to restore

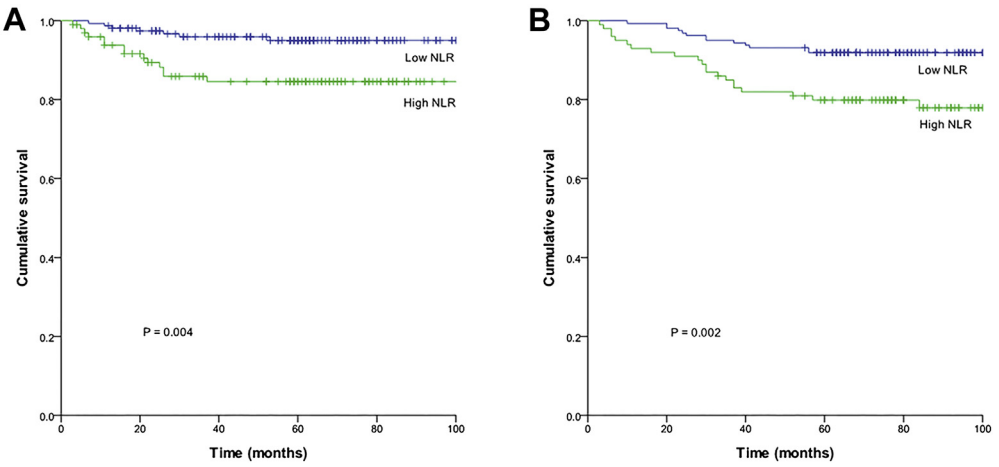

Figure – Comparisons of disease-free survival (DFS) (A) and overall survival (B) in patients with stage II colorectal cancer after curative surgery according to NLR. (Color version of figure is available online.)

immune cell activity in patients undergoing major surgery and in patients with cancer.[22] Therefore, stimulation of the immune system may be an ideal and efficient treatment for cancer, and NLR can be a useful indicator for monitoring the host immune status.

In our series, the NLR cutoff value was lower than that in previous reports. A lower NLR threshold was also selected by Galizia *et al.*[16] They suggested that this lower NLR value allowed the selection of a greater number of patients at risk of poor prognosis.

Other inflammatory markers including LMR were also marginally related to prognosis in stage II colorectal cancer, but they were not independent prognostic factors in this study. LMR is thought to be less related to early colorectal cancer, whereas it is closely related to advanced colorectal cancer, as shown in previous reports.[23,24]

Our study has a few limitations. First, a single-institution retrospective analysis has inherent selection bias. Second, the cutoff value should be further assessed in the future research.

Conclusion

Among the systemic inflammatory markers, NLR can be a strong predictor of worse DFS and OS in stage II colorectal cancer after curative surgery. This inflammatory marker might help to classify patients with stage II colon cancer according to their immune status, and it may represent a target for new adjuvant therapy in the future.

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Disclosure

The authors reported no proprietary or commercial interest in any product mentioned or concept discussed in the article.

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