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Original Article

High Postoperative Neutrophil-Lymphocyte Ratio is Associated with Poor Outcomes After Curative Resection for Locally Advanced Gastric Cancer

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ABSTRACT

Background: Neutrophil-lymphocyte ratio (NLR) is associated with the inflammatory status of patients with some cancers. We tested the hypothesis that postoperative NLR (post-NLR) was associated with outcomes in patients with stage II/III gastric cancer.

Methods: We retrospectively analyzed data from 193 patients with stage II/III gastric cancer who underwent curative gastrectomy at St. Luke's International Hospital between 2000 and 2012. All patients underwent baseline staging, including blood testing, computed tomography, and endoscopic biopsy. The association of post-NLR with clinical outcomes was analyzed by univariate and multivariate analyses.

Results: Average age was 67.7 (95% confidence interval, 43.5 − 91.9) years, and most patients were male. After surgery, 92 (47.7%) patients underwent adjuvant chemotherapy. Median follow-up time was 78.4 (95% confidence interval, 70.3 − 86.6) months. In univariate analyses, age, stage, preoperative NLR, baseline carbohydrate antigen (CA)19-9 level, postoperative white blood cell count, postoperative hemoglobin level, post-NLR, and adjuvant chemotherapy were associated with overall survival (OS). In multivariate analyses, age ($p < 0.01$), stage ($p < 0.01$), and post-NLR ($p < 0.01$) were associated with OS. When the post-NLR cutoff value was set at 3, outcomes were worse for patients with high post-NLR than for those with low post-NLR ($p < 0.001$).

Conclusions: High post-NLR was associated with poor OS and recurrence-free survival in patients with locally advanced gastric cancer, which indicates that post-NLR might be a useful marker for individualized therapy.

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KEYWORDS: neutrophil-lymphocyte ratio, postoperative inflammation, gastric cancer, prognostic indicator, adjuvant chemotherapy

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Gastric cancer is the third leading cause of cancer death worldwide[1] and the second leading cause of cancer-related mortality in Japan.[2] Despite dramatic improvements in diagnosis and treatment, the prognosis for patients with gastric cancer remains poor.[3–5] The frequently observed heterogeneity in outcomes for similarly staged patients receiving comparable therapies could be related to distinct molecular mechanisms or the microenvironment of cancer cells.[6] Accumulating evidence suggests that cancer-associated inflammation is a key determinant of outcomes in patients with cancer. The inflammatory response to cancer cells was reported to be associated with tumor progression.[7, 8] Additionally, postoperative inflammation caused by surgical complications was associated with poor outcomes.[9] These findings indicate that the inflammatory environment of cancer cells might accelerate cancer cell proliferation.[10]

Neutrophil-lymphocyte ratio (NLR) is an important biomarker of systemic inflammation status. Preoperative NLR (pre-NLR) was found to be associated with outcomes for various malignancies, including gastric cancer.[11, 12] However, few studies have evaluated postoperative NLR (post-NLR) as a prognostic marker in patients who undergo curative tumor resection. In this study, we tested the hypothesis that post-NLR was associated with outcomes in patients with gastric cancer and evaluated the prognostic importance of post-NLR in patients with locally advanced gastric cancer who underwent curative gastrectomy and lymphadenectomy.

Methods

Patients

We searched a prospectively maintained database for patients with gastric cancer treated at St. Luke's International Hospital and identified 193 consecutive patients with stage II/III gastric cancer who underwent curative surgery between 2000 and 2012. Patients with histologic documentation of adenocarcinoma, data on blood testing results, and findings from thoracic and abdominal computed tomography were included in this study. All eligible patients were aged 18 years or older. Staging was determined by using the criteria specified in the seventh edition of the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) TNM staging system.[13] No other selection criteria were used. Stored information on the number of resected lymph nodes, surgical curability, and adjuvant chemotherapy were collected and analyzed. The institutional review board of St. Luke's International Hospital approved this study (approved number: 16-R108).

Surgery

The gastrectomy types performed for this cohort were distal, total, proximal, and laparoscopic gastrectomy. Appropriate lymph node dissection (D1, D1+, or D2) was based on clinical staging and/or the preoperative condition of patients. Billroth I, Billroth II, Roux-en-Y, or double-tract reconstruction were performed after gastrectomy. All patients received prophylactic antibiotics; most received cephazolin (1 g, three doses) during the first 24 hours postoperatively.

Blood analyses

Peripheral blood samples were obtained at the time of diagnosis (baseline), at 4 − 12 weeks after surgery, and immediately before deciding on initiation of adjuvant therapy. White blood cell (WBC) count was determined with a hemocytometer. Absolute counts of specific cell populations were calculated by multiplying the percentage of cells by the total number of WBCs.

Follow-up and survival

Patients were periodically followed-up for at least 5 years or until death. Additional follow-up data were obtained from a review of hospital records. Duration of follow-up was calculated from the date of surgery to the date of death or last contact.

Statistical analysis

The patient database was prospectively maintained using standardized fields. All statistical analyses were performed with the IBM SPSS Statisticus version 21.0 Software Package (International Business Machines [IBM] Corp., Armonk, NY, USA). Differences between groups were analyzed with the Student *t*-test, for continuous variables, or the Fisher exact or χ^2 test, for categorical variables. Univariate Cox regression analysis was performed with disease recurrence or death as outcomes and significance defined as $p \leq 0.05$. Covariates that were significant at $p \leq 0.25$ were included in the multivariate Cox regression analysis. Backward stepwise Wald elimination at $p = 0.10$ was used to develop a final model that contained only significant variables. Analyses of overall survival (OS) and recurrence-free survival (RFS) were performed by using the Kaplan-Meier method, and differences were assessed with the log-rank test.

Results

Patient characteristics

Selected patient characteristics are shown in Table 1. In total, 193 consecutive patients with stage II/III gastric cancer who had undergone curative surgery were included in the final analysis. Average age was 67.7 (95% confidence interval [CI], 43.5－91.9) years, and 64.2% of the patients were male. Ninety-two patients (47.7%) underwent adjuvant chemotherapy, and the most frequent regimen was oral pyrimidine. Average pre-NLR and post-NLR were 3.23±7.66 and 3.04±10.32, respectively, and median pre-NLR and post-NLR were 2.54 and 1.87, respectively.

Table 1 Patient characteristics

Covariate	Number (%) or average±SD
Sex	
Male	124 (64.2)
Female	69 (35.8)
Age	
Average (years)	67.7±24.2
Stage	
Ⅱ	98 (50.8)
Ⅲ	95 (49.2)
Tumor histology	
Intestinal	58 (30.1)
Diffuse	127 (65.8)
Other	8 (4.1)
Adjuvant therapy	
Yes	92 (47.7)
No	101 (52.3)
Surgery	
Distal gastrectomy	124 (64.2)
Total gastrectomy	63 (35.8)
Other	6 (3.1)
Preoperative NLR	
Average	3.23±7.66
Postoperative NLR	
Average	3.04±10.32

SD: standard deviation, NLR: neutrophil-lymphocyte ratio

Survival and recurrence

Median duration of follow-up was 78.4 (95% CI, 70.3－86.6) months. Estimated overall 5-year OS and RFS rates were 65.4% (95% CI, 58.0－72.8) and 57.9% (95% CI, 50.5－65.3), respectively. As of September 2016, there have been 71 (36.8%) deaths.

Univariate and multivariate analyses

The results of univariate analyses of factors associated with OS and RFS are shown in Table 2. OS and RFS were significantly associated with age, clinical stage, baseline carbohydrate antigen (CA)19-9, pre-NLR, post-NLR, postoperative WBC count, postoperative carcinoembryonic antigen (CEA), and adjuvant chemotherapy. In multivariate analysis, older age (p=0.007), higher baseline clinical stage (p＜0.001), and higher post-NLR (p=0.001) were independently associated with poor OS (Table 3). Additionally, higher baseline clinical stage (p=0.001) and post-NLR (p=0.002) were associated with worse RFS.

Relationship of post-NLR with clinical outcomes

The overall average post-NLR was 3.04 (range, 0.13－47.0). In accordance with a previous meta-analysis,[12] we

Table 2 Univariate Cox proportional hazards analysis of associations of clinical variables with overall survival (OS) and recurrence-free survival (RFS)

Variables		OS		RFS	
		HR (95% CI)	p value	HR (95% CI)	p value
Age	Continuous	1.05 (1.03-1.07)	＜0.001	1.03 (1.00-1.04)	0.009
Sex	Female vs. male	1.00 (0.62-1.63)	0.99	0.97 (0.63-1.49)	0.88
Preoperative NLR	Continuous	1.06 (1.01-1.10)	0.008	1.07 (1.03-1.11)	＜0.001
Baseline CEA	Continuous	1.01 (0.99-1.04)	0.40	1.02 (1.01-1.04)	0.01
Baseline CA19-9	Continuous	1.00 (1.00-1.00)	0.01	1.00 (1.00-1.00)	0.06
Stage	Ⅱ vs. Ⅲ	0.28 (0.17-0.48)	＜0.001	0.27 (0.17-0.43)	＜0.001
Postoperative WBC	Continuous	1.00 (1.00-1.00)	＜0.001	1.00 (1.00-1.00)	＜0.001
Postoperative NLR	Continuous	1.10 (1.06-1.15)	＜0.001	1.09 (1.05-1.13)	＜0.001
Postoperative CEA	Continuous	1.03 (1.01-1.05)	＜0.001	1.07 (1.04-1.10)	＜0.001
Postoperative CA19-9	Continuous	1.00 (0.99-1.00)	0.74	0.99 (0.99-1.00)	0.63
Adjuvant chemotherapy	No vs. yes	1.63 (1.01-2.63)	0.04	1.16 (0.77-1.76)	0.48

HR: hazard ratio, CI: confidence interval, NLR: neutrophil-lymphocyte ratio, CEA: carcinoembryonic antigen, CA19-9: carbohydrate antigen 19-9, WBC: white blood cell

Table 3 Multivariate Cox proportional hazards analysis of associations of clinical variables with overall survival (OS) and recurrence-free survival (RFS)

Variables		OS		RFS	
		HR (95% CI)	p value	HR (95% CI)	p value
Age	Continuous	1.05 (1.01-1.08)	0.007	1.02 (0.98-1.01)	0.20
Sex	Female vs. male	1.02 (0.53-1.97)	0.95	0.97 (0.97-1.10)	0.92
Initial NLR	Continuous	1.04 (0.99-1.09)	0.09	1.04 (1.14-1.25)	0.10
Stage	Ⅱ vs. Ⅲ	0.24 (0.11-0.50)	<0.001	0.30 (0.53-1.06)	0.001
NLR after surgery	Continuous	1.08 (1.03-1.13)	0.001	1.07 (1.39-2.75)	0.002
Adjuvant chemotherapy	No vs. yes	1.63 (0.75-3.53)	0.22	1.36 (0.29-0.61)	0.38

HR: hazard ratio, CI: confidence interval, NLR: neutrophil-lymphocyte ratio

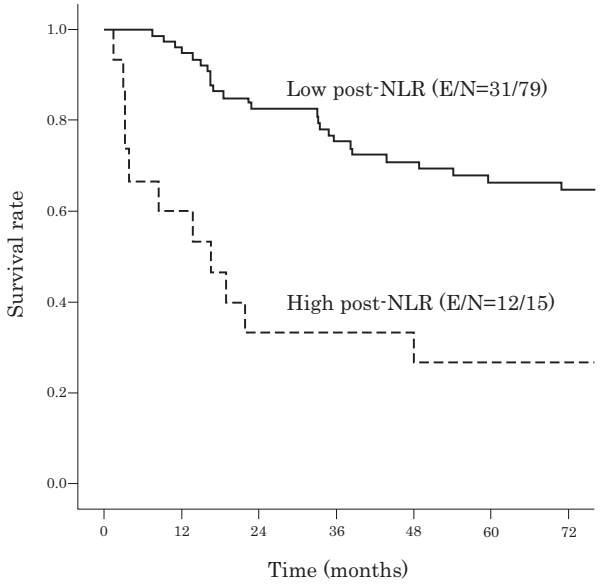

Fig. 1 Kaplan-Meier curves of estimated overall survival, with a postoperative neutrophil-lymphocyte (post-NLR) value of 3 as the cutoff. Overall survival was significantly better in patients with a low post-NLR ($p<0.001$, log-rank test).
E: event, N: number

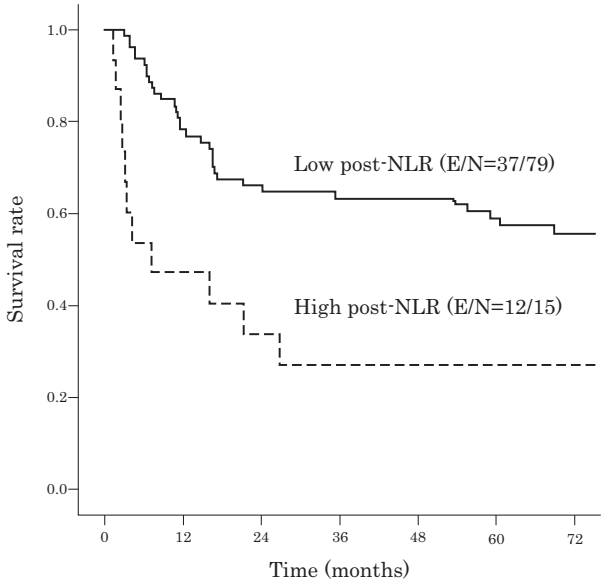

Fig. 2 Kaplan-Meier curves of estimated recurrence-free survival probability, with a postoperative neutropil-lymphocyte (post-NLR) value of 3 as the cutoff. Recurrence-free survival was significantly better in patients with a low post-NLR ($p=0.001$, log-rank test).
E: event, N: number

used a post-NLR cutoff value of 3 to categorize patients in the analysis of the association of post-NLR with clinical outcomes. Patients with a high post-NLR (>3) had poor clinical outcomes, namely, a mean 5-year survival rate of 26.7% (95% CI, 0.0 − 49.5). In contrast, the mean 5-year survival rate was 66.3% (95% CI, 55.1 − 77.5) for patients with a low post-NLR (≤3). The difference between these groups was statistically significant ($p<0.001$; Fig. 1), as was the difference in 5-year RFS between the high and low post-NLR patients (p=0.001; Fig. 2).

Association of post-NLR with interval to assessment

The interval to post-NLR assessment did not differ between patients with high and low post-NLR values (p=0.76; Table 4). In addition, post-NLR values did not significantly differ in relation to the interval to post-NLR assessment (≤8 vs. >8 weeks; p=0.79; Table 5).

Discussion

Surgical resection of the primary tumor and regional lymph nodes is imperative for locally advanced gastric cancer.[3, 14, 15] Definitive chemoradiation is another option

Table 4 Interval from surgery to postoperative neutrophil-lymphocyte (post-NLR) assessment in patients with high and low post-NLR values

	High post-NLR	Low post-NLR	p value
Duration (average, days)	65.1 ± 33.3	68.1 ± 26.8	0.76

Table 5 Postoperative neutrophil-lymphocyte (post-NLR) values in relation to the interval to post-NLR assessment (≤8 vs. >8 weeks)

	Short interval (≤8 weeks)	Long interval (>8 weeks)	p value
Post-NLR (average)	2.86 ± 8.12	3.17 ± 11.70	0.79

for patients with severe comorbidities; however, clinical outcomes are less than satisfactory.[16] Surgical stress adversely affects the immune system and is deleterious for cancer treatment.[17] Postoperative inflammation is an important cause of recurrence of malignant tumors and is associated with poor prognosis.[10] Thus, it might partly explain the present association of post-NLR with poor outcomes. Additionally, elevated neutrophil counts and/or a decrease in the number of lymphocytes might suppress lymphokine-activated killer cells, thereby increasing the risk of local recurrence or distant metastasis.[18]

Several guidelines recommend that patients with locally advanced (stage II/III) gastric cancer undergo adjuvant therapy. In Western countries, guidelines recommend perioperative chemotherapy or postoperative chemoradiotherapy for patients with locally advanced gastric cancer.[19, 20] Japanese guidelines recommend starting adjuvant chemotherapy during the 6 weeks after curative surgery.[21] In practice, patients start adjuvant therapy at 4－12 weeks after surgery. In the present study, data on clinical variables for patients with locally advanced gastric cancer, including the results of blood testing, were collected at the time of diagnosis and at 4－12 weeks after resection, *i.e.*, immediately before the start of adjuvant therapy. Moreover, we confirmed that post-NLR was not associated with the timing of post-NLR assessment (Table 4) and that the timing of such assessment was not affected by post-NLR values (Table 5). The period 4－12 weeks after resection might therefore be ideal for assessing postoperative inflammation status, as the result is less likely to be affected by the stress of surgery and adjuvant therapies.

Most patients with high post-NLR values had stage III disease (80.0%), and only 13.3% of patients underwent adjuvant therapy. As of October 2016, the mortality rate was 84.6% among the present patients with high post-NLR values who did not undergo adjuvant chemotherapy, which suggests that adjuvant therapy should be recommended to patients with locally advanced gastric cancer and a high post-NLR.

Helicobacter pylori (HP) contributes to gastric cancer development. Recently, Farah et al reported that NLR values were higher among HP-infected atrophic gastritis patients than among patients without HP.[22] We have no data on HP infection or chronic atrophic gastritis in our patients. HP infection status might affect pre-NLR; however, because the area of chronic atrophic gastritis is resected, it is unclear if HP infection influences post-NLR. A few patients received HP eradication therapy after distal gastrectomy, to minimize the risk of gastric cancer recurrence.[23] However, no patient underwent eradication therapy during the 3 months after gastrectomy, as most patients do not have a satisfactory nutritional status immediately after surgery.

This study has limitations that warrant mention. First, it was retrospective. Second, our results may not be generalizable, as this was a single-center study. Third, the univariate and multivariate analyses did not include all clinical variables, which was inevitable because of the retrospective design of this study. Nevertheless, the present study did investigate a large cohort of patients. Furthermore, this is the first report showing that postoperative NLR was associated with outcomes in patients with gastric cancer. Finally, this study provides strong evidence that post-NLR is a potential biomarker in this patient subgroup.

In conclusion, our data suggest that post-NLR has prognostic value in patients with gastric cancer who undergo curative resection. In addition, postoperative adjuvant therapy should be considered for patients with locally ad-

vanced gastric cancer, particularly for those with a high post-NLR.

Disclosure statement: The authors have no conflicts of interest to declare.

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