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# Prognostic Value of the Preoperative Neutrophil to Lymphocyte Ratio in Resectable Gastric Cancer

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**Abstract:** This study aimed to investigate the prognostic value of the preoperative neutrophil to lymphocyte ratio (NLR) in resectable gastric cancer (GC).

This was a retrospective review of 1030 patients with resectable GC managed between 2005 and 2011. Patients were stratified into 2 groups, those with a preoperative NLR  $>3.44$  and those with a preoperative NLR  $\leq 3.44$ . Clinicopathological data affecting patient prognosis were collected prospectively and analyzed.

The high NLR ( $>3.44$ ) group had a higher proportion of a platelet to lymphocyte ratio  $>132$ , tumor size  $>4.8$  cm, T4 lesions, metastatic tumors, a ratio of metastatic to examined lymph nodes  $>0.18$ , positive resection margins, and presence of vascular or lymphatic invasion than the low NLR ( $\leq 3.44$ ) group. Patients with a high preoperative NLR had significantly lower 3- and 5-year overall survival rates than those with a low preoperative NLR (55.1% vs 71.0% and 47.2% vs 64.1%, respectively;  $P < 0.001$ ). Preoperative NLR was a prognostic factor for resectable GC in multivariate analysis.

More aggressive tumor behavior was observed in patients with resectable GC with a high preoperative NLR than in those with a low preoperative NLR. High preoperative NLR was an independent unfavorable prognostic factor. Measurement of this ratio may serve as a clinically accessible and useful biomarker for patient outcomes.

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**Abbreviations:** GC = gastric cancer, HER2 = human epidermal growth factor receptor 2, NLR = neutrophil to lymphocyte ratio, PLR = platelet to lymphocyte ratio, PSK = polysaccharide-K, ROC = receiver operating characteristic, TNM = tumor-node-metastasis.

## INTRODUCTION

According to the GLOBOCAN database, gastric adenocarcinoma (GC) is the third-leading cause of cancer-related

death worldwide, after lung and liver malignancies, resulting in around 723,000 deaths in 2012.<sup>1</sup> Although there have been advances in diagnosis and management, most GC patients present with locally advanced or metastatic disease with a 5-year survival rate of  $<10\%$ .<sup>2,3</sup> The tumor-node-metastasis (TNM) staging mainly focuses on the tumor itself, that is, its biological behavior, and is the most important prognostic factor for GC.<sup>4</sup> However, the current staging system is not precise for predicting patient outcomes because the prognosis varies in patients with the same disease stage. Additional parameters need to be defined to better identify prognostic factors for patients, to allow tailored therapies. The neutrophil to lymphocyte ratio (NLR), which is suggested as the balance between pro-tumor inflammatory status and anti-tumor immune status, has been shown to be associated with outcomes in patients with various types of malignancies.<sup>5–8</sup> However, the prognostic role of the NLR in GC remains controversial.<sup>9,10</sup> Moreover, different studies enrolled GC patients with different disease stages to evaluate the prognostic role of the NLR, and variable cutoff values for the NLR were used in each study.<sup>9–12</sup> Therefore, the aim of the present study was to clarify the prognostic value of the preoperative NLR in resectable GC and to delineate the association between high NLR and clinicopathological factors.

## MATERIALS AND METHODS

### Ethics Statement

This study was reviewed and approved by the Institutional Review Board of Chang Gung Memorial Hospital. Written informed consent was obtained from all patients. All data were stored in the hospital database and used for research.

### Patients and Treatment

Between January 2005 and December 2011, 1030 GC patients undergoing gastrectomy at Chang Gung Memorial Hospital were enrolled. Patients underwent subtotal or total gastrectomy according to tumor size, tumor location, and the frozen section results of resection margins as determined intraoperatively. The standard procedure for a spleen- and pancreas-sparing D2 gastrectomy has been defined in a previous report.<sup>13</sup> Gastrectomy including the adjacent involved organ(s) was performed to accomplish clear resection margins.<sup>14</sup> In principle, resection was not performed in the metastatic GC patients who did not have tumor-associated symptoms or in those with peritoneal metastasis for which macroscopic curative resection was not expected. The patients with tumor-related symptoms or solitary distant visceral organ metastasis such as the ovary or liver for which complete resection of the metastatic tumor was feasible underwent gastrectomy (D1 or D2 lymphadenectomy) or gastrectomy (D2 lymphadenectomy) plus metastasectomy. No patient underwent preoperative chemotherapy or stent placement for obstruction symptoms. The 7th edition of

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**TABLE 1.** Clinicopathological Data of Patients With Resectable Gastric Cancer Stratified According to the Neutrophil to Lymphocyte Ratio

	Neutrophil to Lymphocyte Ratio		P Value
	≤3.44 (%)	>3.44 (%)	
No. of patients	773	257	
Age, yr			0.677
≤48	101 (13.1)	31 (12.1)	
>48	672 (86.9)	226 (87.9)	
Gender			0.120
Male	488 (63.1)	176 (68.5)	
Female	285 (36.9)	81 (31.5)	
Platelet to lymphocyte ratio			<0.001
≤132	444 (57.4)	33 (12.8)	
>132	339 (42.6)	214 (87.2)	
Gastrectomy			0.07
Total	224 (29.0)	90 (35.0)	
Subtotal	549 (71.0)	167 (65.0)	
Location			0.28
Upper	147 (19.0)	47 (18.3)	
Middle	159 (20.6)	42 (16.3)	
Lower	444 (57.4)	156 (60.7)	
Diffuse	23 (3.0)	12 (4.7)	
Tumor size, cm*			<0.001
≤4.8	516 (67.2)	120 (47.6)	
>4.8	252 (32.8)	132 (52.4)	
T status			<0.001
T1	222 (28.7)	46 (17.9)	
T2	104 (13.5)	24 (9.3)	
T3	129 (16.7)	34 (13.2)	
T4	318 (41.1)	153 (59.6)	
N status			0.08
N0	301 (38.9)	84 (32.7)	
N1	125 (16.2)	34 (13.2)	
N2	110 (14.2)	42 (16.3)	
N3	237 (30.7)	97 (37.8)	
M status			0.001
M0	718 (92.9)	222 (86.4)	
M1	55 (7.1)	35 (13.6)	
LN ratio†			0.007
≤0.18	528 (68.3)	152 (59.1)	
>0.18	245 (31.7)	105 (40.9)	
Resection margins			0.02
Negative	727 (94.0)	231 (89.9)	
Positive	46 (6.0)	26 (10.1)	
Differentiated			0.80
Yes	300 (38.8)	102 (39.7)	
No	473 (61.2)	155 (60.3)	
Vascular invasion*			0.001
Negative	670 (87.9)	200 (79.4)	
Positive	92 (12.1)	52 (20.6)	
Lymphatic invasion*			.03
Negative	370 (48.6)	103 (40.6)	
Positive	392 (51.4)	151 (59.4)	
Perineural invasion*			0.59
Negative	421 (55.3)	135 (53.4)	
Positive	340 (44.7)	118 (46.6)	

**TABLE 1.** Continued

	Neutrophil to Lymphocyte Ratio		P Value
	≤3.44 (%)	>3.44 (%)	
In-hospital mortality	18 (2.3)	23 (9.9)	<0.001
30-d mortality	8 (1.0)	11 (4.3)	0.002
Chemotherapy‡	382 (70.2)	117 (56.0)	<0.001

\* Not all data were available.  
 † Ratio of metastatic to examined lymph nodes.  
 ‡ Excluding T1/T2N0 cases.

the American Joint Committee on Cancer TNM classification was used for the tumor stage.<sup>4</sup> Patients with stages II to IV tumor received adjuvant or palliative chemotherapy with fluoropyrimidine-based or platinum-based regimens. Patients with stage IB disease did not routinely receive chemotherapy, except those with tumors showing dedifferentiation or existence of lymphovascular or perineural invasion.

**Blood Sample Tests**

Blood samples were obtained before surgery for the measurement of the complete blood counts and differential counts.

**Clinical Data Collection**

Data on demographics, clinicopathological parameters, perioperative results, and long-term survival were obtained from the prospectively collected hospital database. The median follow-up time was 30 months. The patients who died after surgery during the same hospitalization (in-hospital mortality) were not included in the survival analysis. Survival duration was calculated from the time of surgery to death or the last follow-up date (December 31, 2012), irrespective of the cause of death.

**Statistical Analysis**

Student *t* test or Pearson’s chi-squared test was used to compare clinical data, as appropriate. Kaplan–Meier methods were used to assess patient survival and the differences between subgroups were analyzed by the log-rank test. The optimal cutoff values were chosen for parameters including NLR, age, platelet to lymphocyte ratio (PLR), tumor size, and ratio of metastatic to examined lymph nodes according to the survival tree using R software, Version 3.1.3 (March 9, 2015; R Core Team, <http://www.r-project.org>). Potentially relevant factors obtained from univariate analysis (*P* < 0.05) were recruited in multivariate models; both analyses were conducted using Cox’s regression, and a *P* value of <0.05 was viewed statistically significant. The Statistical Package for the Social Sciences (SPSS, Inc., Chicago, IL) for Windows Version 13 was used for statistical analyses.

**RESULTS**

As shown in Table 1, no significant differences were found between the high NLR (>3.44) and low NLR (≤3.44) groups in terms of age, gender, type of gastrectomy, tumor location, nodal status, differentiation, or presence of perineural invasion. The

**TABLE 2.** Univariate Analysis of Prognostic Factors of Resectable Gastric Cancer

Factors	Mean, mo	95% CI of Mean	Survival Rate, %		P Value
			3-yr	5-yr	
Gender					0.93
Male (n = 635)	65.26	61.94–68.58	67.5	60.4	
Female (n = 354)	64.76	60.41–69.11	67.0	59.9	
Age, yr					0.002
≤48 (n = 129)	54.53	47.3–61.7	57.3	45.6	
>48 (n = 860)	66.74	63.9–69.6	68.9	62.5	
Neutrophil to lymphocyte ratio					<0.001
≤3.44 (n = 755)	68.25	65.12–70.95	71.0	64.1	
>3.44 (n = 234)	52.80	47.30–58.45	55.1	47.2	
Platelet to lymphocyte ratio					<0.001
≤132 (n = 466)	71.37	67.76–74.99	75.5	68.1	
>132 (n = 523)	59.33	55.59–63.07	59.9	53.0	
Gastrectomy					<0.001
Total (n = 302)	51.24	46.24–56.25	51.7	41.9	
Subtotal (n = 687)	70.90	67.90–75.89	74.0	67.9	
Location					<0.001
Upper (n = 188)	56.10	50.16–62.03	61.6	49.2	
Middle (n = 197)	68.45	62.69–74.22	70.9	63.1	
Lower (n = 574)	68.15	64.78–71.51	70.2	65.2	
Diffuse (n = 30)	19.38	14.26–24.50	17.5	0.0	
Tumor size, cm*					<0.001
≤4.8 (n = 620)	75.94	73.00–78.87	80.5	73.5	
>4.8 (n = 360)	44.52	40.15–48.89	42.6	35.4	
Differentiation					<0.001
Yes (n = 391)	76.85	73.19–80.51	79.5	74.5	
No (n = 598)	57.51	54.02–60.99	59.5	51.0	
T status					<0.001
T1 (n = 264)	93.70	91.97–95.42	98.2	97.6	
T2 (n = 124)	78.36	72.00–84.71	84.4	73.1	
T3 (n = 156)	63.28	56.67–69.89	66.2	63.9	
T4 (n = 445)	45.15	41.38–48.91	44.6	35.5	
N status					<0.001
N0 (n = 381)	88.79	86.31–91.26	94.1	91.5	
N1 (n = 151)	67.61	61.21–74.01	74.3	65.7	
N2 (n = 144)	59.90	52.76–67.03	57.7	51.5	
N3 (n = 313)	33.27	29.28–37.26	33.7	20.1	
LN ratio†					<0.001
≤0.18 (n = 663)	81.05	79.90–85.05	85.4	80.7	
>0.18 (n = 326)	30.73	31.68–39.35	29.2	15.8	
M status					<0.001
M0 (n = 909)	69.90	67.26–72.54	73.0	65.6	
M1 (n = 80)	11.10	9.13–13.07	3.7	0.0	
Resection margins					<0.001
Negative (n = 924)	68.29	65.64–70.95	70.7	64.2	
Positive (n = 65)	17.40	13.00–21.81	17.7	3.0	
Vascular invasion*					<0.001
Negative (n = 841)	68.37	65.61–71.13	71.8	63.8	
Positive (n = 134)	36.46	29.61–43.31	30.4	30.4	
Lymphatic invasion*					<0.001
Negative (n = 463)	83.65	80.84–86.46	88.4	84.0	
Positive (n = 512)	45.75	42.12–49.37	46.7	36.4	
Perineural invasion*					<0.001
Negative (n = 541)	79.43	76.51–82.35	82.8	78.5	
Positive (n = 432)	45.24	41.35–49.14	46.8	35.7	

TABLE 2. Continued

Factors	Mean, mo	95% CI of Mean	Survival Rate, %		P Value
			3-yr	5-yr	
Chemotherapy <sup>‡</sup>					0.54
Yes (n = 217)	56.20	50.10–62.30	57.3	50.3	
No (n = 497)	52.26	48.56–55.97	53.5	43.2	

CI = confidence interval.  
<sup>\*</sup> Not all data were available.  
<sup>†</sup> Ratio of metastatic to examined lymph nodes.  
<sup>‡</sup> Excluding T1/T2N0 cases.

high NLR group had a higher proportion of a PLR >132, tumor size >4.8 cm, T4 lesions, metastatic tumors, a ratio of metastatic to examined lymph nodes >0.18, positive resection margins, and presence of vascular or lymphatic invasion than the low NLR group. There were significant differences in in-hospital mortality or mortality within 30 days after surgery between the high and low NLR groups. Compared with the low NLR group, lower percentages of patients with a high NLR received chemotherapy.

The univariate analysis of various clinicopathological parameters related to surgical outcomes in patients with resectable GC was listed in Table 2. Age, NLR, PLR, type of gastrectomy, tumor location, tumor size, differentiation, T status, nodal involvement, M status, ratio of metastatic to examined lymph nodes, resection margin, and presence of vascular, lymphatic, and perineural invasion significantly influence patient prognosis. There was no evident difference in

overall survival period according to gender or the administration of postoperative chemotherapy. As shown in Table 3, NLR, resection margin, differentiation, T status, N status, M status, and ratio of metastatic to examined lymph nodes were independent prognostic predictors in multivariate analysis. Patients with a high NLR had significantly lower 3- and 5-year overall survival rates than those with a low NLR (55.1% vs 71.0% and 47.2% vs 64.1%, respectively;  $P < 0.001$ ; Figure 1).

## DISCUSSION

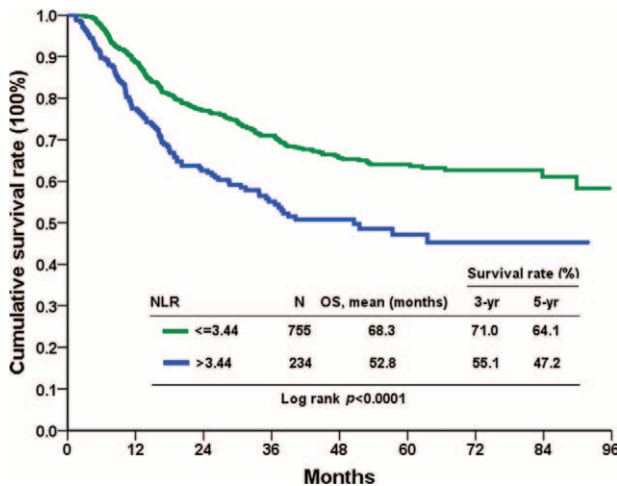
In the present study, we analyzed a cohort of 1030 consecutive patients with resectable GC at a single institute. A high preoperative NLR was associated with more aggressive tumor behavior than a low preoperative NLR. In multivariate analysis, independent prognostic factors were NLR, resection margin, tumor differentiation, T status, N status, ratio of metastatic to examined lymph nodes, and distant metastasis.

TABLE 3. Multivariate Analysis of Prognostic Factors of Resectable Gastric Cancer

Factors		Hazard Ratio (95% CI)	P Value
Neutrophil to lymphocyte ratio	>3.44/≤3.44	1.565 (1.198–2.044)	0.001
Platelet to lymphocyte ratio	>132/≤132	0.898 (0.696–1.159)	0.41
Type of gastrectomy	Total/subtotal	1.275 (0.944–1.722)	0.11
Resection margins	Positive/negative	1.768 (1.274–2.453)	0.001
Location	Upper/middle	1.077 (0.745–1.556)	0.69
	Lower/middle	0.928 (0.665–1.294)	0.66
	Diffuse/middle	0.962 (0.563–1.643)	0.89
Differentiation	No/yes	1.473 (1.119–1.939)	0.006
Tumor size, cm	>4.8/≤4.8	1.166 (0.905–1.501)	0.23
T status	T2/T1	4.568 (1.815–11.494)	0.001
	T3/T1	5.308 (2.153–13.083)	<0.001
	T4/T1	8.664 (3.650–20.568)	<0.001
N status	N1/N0	1.908 (1.120–3.249)	0.02
	N2/N0	2.058 (1.183–3.579)	0.01
	N3/N0	1.992 (1.056–3.758)	0.03
LN ratio <sup>*</sup>	>0.18/≤0.18	2.569 (1.727–3.821)	<0.001
M1 status	Yes/no	3.474 (2.579–4.680)	<0.001
Vascular invasion	Positive/negative	1.169 (0.884–1.546)	0.27
Lymphatic invasion	Positive/negative	1.026 (0.701–1.503)	0.89
Perineural invasion	Positive/negative	1.198 (0.920–1.562)	0.18

CI = confidence interval.

<sup>\*</sup> Ratio of metastatic to examined lymph nodes.



**FIGURE 1.** Overall survival (OS) rates of patients with resectable gastric cancer according to high and low neutrophil to lymphocyte ratios (>3.44 vs ≤3.44).

The prognostic role of the NLR in GC is still controversial. Studies have indicated that stages I to IV GC patients with a high NLR had unfavorable outcomes.<sup>15,16</sup> Wang et al<sup>17</sup> found that the NLR was not an independent poor prognostic factor in stage III GC. In contrast, Jung et al<sup>18</sup> suggested that an elevated preoperative NLR predicted poor disease-free and overall survival in stage III/IV resectable GC. Other researchers noted that patients with stage IV unresectable GC undergoing palliative chemotherapy had worse overall survival and progression-free survival in the high NLR group.<sup>19,20</sup> In the present study, patients with resectable stages I to IV GC with a high NLR (>3.44) had a significantly shorter overall survival time than those with a low NLR. Patients with a high preoperative NLR also presented with more aggressive tumor behavior than those with a low preoperative NLR, which might in part explain why patients with a high NLR had unfavorable outcomes.

Several mechanisms could explain the association between an elevated NLR and GC prognosis. Studies have shown that the ability of tumors to act aggressively and metastasize is dependent on the intrinsic characteristics of the tumor cells and the tumor microenvironment, which is an indispensable participant in the neoplastic process.<sup>21</sup> Experiments have revealed that an array of cytokines or other molecules produced by neutrophils contribute to a growth-stimulating microenvironment for cancer cells.<sup>22</sup> An elevation of NLR mirrors an increase of neutrophil-related inflammatory reaction and a reduction of lymphocyte-mediated antitumor response, which may reduce the lymphocyte-dependent antitumor cellular immune effect and result in tumor progression, metastasis, and unfavorable patient outcomes. Neutrophils in the circulation produce pro-angiogenic factors including vascular endothelial growth factor, inflammatory mediators, and matrix metalloproteinases, and promote tumor growth and progression.<sup>23,24</sup> In addition, elevated neutrophils surrounding the tumor may inhibit the antitumor effects of activated T cells, cytolytic activity of lymphocytes, and natural killer cells.<sup>25</sup> A recent study also addressed the possibility of exploiting neutrophils for monoclonal antibody-based immunotherapy for cancer.<sup>26</sup> Taken together, it is likely that a high NLR may reflect the combined effects of neutrophilia and lymphocytopenia, and may be a more meaningful prognostic factor for survival than either alone.

A randomized controlled study of adjuvant chemotherapy with or without protein-bound polysaccharide-K (PSK), a biological immunomodifier, supports this possibility in resectable GC, revealing that PSK significantly improved 5-year survival rates in patients with a high preoperative NLR.<sup>27</sup> However, in that study, no survival benefits were observed in patients with a low NLR through the addition of PSK to chemotherapy. The increased survival after treatment with PSK in patients with a high NLR may have resulted from the restoration of patient immunoreactivity. In contrast, patients with a low NLR and normal baseline immunocompetence treated with PSK would not have gained an additional survival benefit. Recently, Namikawa et al<sup>28</sup> observed that overall survival was significantly longer in GC patients treated with an oral fluoropyrimidine (S-1) and PSK than in those treated with S-1 alone. The mean NLR value 1 month after the administration of chemotherapy in the preoperative NLR ≥2.5 subgroup was significantly lower in patients treated with S-1 plus PSK compared to those treated with S-1 alone. Hence, the NLR may be a useful biomarker for predicting GC patient prognosis.

Numerous biomarkers have been identified and applied for predicting GC outcomes. Human epidermal growth factor receptor 2 is currently widely used in routine pathological assessment for locally advanced or unresectable GC. Studies have also reported that Ki-67, caspase-3, and p53 are associated with GC prognosis.<sup>29</sup> Recently, Wang et al<sup>30</sup> suggested that unique microRNAs could be further evaluated as biomarkers for early diagnosis of GC and prediction of prognosis or treatment response. Nonetheless, the above-mentioned predictors should be tested in cancer tissues, which limits their utility in monitoring disease status throughout the disease course clinically. In contrast, the NLR can be measured easily in serum or plasma and may be widely used in the clinic.

Although a number of studies have demonstrated the role of the NLR in predicting GC patient overall survival and disease-free survival, the cutoff value for defining a high NLR has not been standardized, and patients with different disease stages and undergoing resection or nonsurgical treatments have been enrolled, leading to between-study heterogeneity.<sup>10-12</sup> In the present study, the optimal cutoff value of the NLR was chosen according to the survival tree using R software rather than being defined by analyzing the receiver operating characteristic curve or simply arbitrarily, as in other studies, and this provides reliable predictive value. Furthermore, only patients with resectable GC were recruited into our study, which largely reduces the impact of tumor burden-related immune and inflammatory responses on the survival.

**CONCLUSIONS**

More aggressive tumor behavior was observed in patients with resectable GC with a high preoperative NLR than those with a low preoperative NLR. A high NLR was an independent unfavorable prognostic factor. Measurement of the NLR may serve as a clinically accessible and useful biomarker for patient outcomes in daily practice.

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