

Neutrophil-to-Lymphocyte Ratio as a Prognostic Indicator in Patients With Unresectable Gastric Cancer

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Abstract. *Background/Aim:* Although many prognostic indicators have been identified for resectable gastric cancer (GC), prognostic indicators for unresectable GC (urGC) have not been widely studied. The aim of the current study was to investigate prognostic indicators that could be determined through routine blood examinations in patients with urGC. *Patients and Methods:* We retrospectively analyzed clinicopathological factors in 92 patients with unresectable advanced and recurrent gastric adenocarcinoma. *Results:* Based on receiver operating curve analysis, neutrophil-to-lymphocyte ratio (NLR) had the highest area under curve for 1-year survival among patients with urGC. Among patients with urGC, NLR was significantly higher in those with advanced disease compared to those with recurrent disease ($p=0.0051$); and in those with peritoneal metastasis compared to those without peritoneal metastasis ($p=0.041$). Patients were divided into NLR^{High} ($NLR \geq 2.83$) and NLR^{Low} ($NLR < 2.83$). Their median survival times were NLR^{High} : 9.1 months and NLR^{Low} : 17.1 months ($p < 0.0001$). NLR was also inversely correlated with survival period ($r=0.496$, $p < 0.0001$); and NLR measured one month after starting chemotherapy was significantly associated with the prognosis of both NLR^{Low} and NLR^{High} patients with urGC. Multivariate analysis showed NLR to be an independent predictor of overall survival in these patients. *Conclusion:* NLR is useful for predicting the prognosis of patients with unresectable GC. An estimated 1,300,000 new cases of gastric cancer (GC)

and 819,000 deaths from GC occurred in 2015 worldwide, ranking GC the fifth most commonly diagnosed cancer and the third most common cause of death from cancer (1, 2).

Gastrectomy with regional lymph node dissection is the mainstay of curative GC treatment. However, many GC patients experience recurrence even after complete tumor removal (R0 resection) (3). Furthermore, some patients present with unresectable advanced gastric cancer at the time of diagnosis. The Japanese Gastric Cancer Treatment Guideline recommends chemotherapy (CT) for patients with unresectable GC (urGC) (4). Although advances in CT have improved prognosis of urGC patients, their median survival is still only 1 year (5, 6). In addition, CT is associated with various adverse events. Therefore, accurate prognostic indicators for urGC patients are necessary to determine optimal treatment strategies and to provide patients with important information concerning their outcome.

Markers that reflect inflammation and nutritional status, many of which can be determined through routine blood examinations, have been associated with the prognosis of cancer patients. For instance, peripheral neutrophil count and serum C reactive protein (CRP) level reflect inflammation, whereas serum albumin level and peripheral lymphocyte count (LC) reflect nutritional status. Some evaluation scores have been developed that combine inflammation-related and nutrition-related markers, such as the neutrophil-to-lymphocyte ratio (NLR) and prognostic nutritional index (PNI), both of which have been shown to predict prognosis in patients with GC (7, 8).

However, studies of prognostic indices in GC have been performed mainly for patients who have undergone surgery. Migita *et al.*, recently demonstrated that inflammation-based scores, including NLR and PNI, are also convenient prognostic predictors of survival times for patients with recurrent GC (9), however, prognostic indicators for urGC patients have not been widely studied thus far. The aim of the current study was to investigate prognostic indicators in patients with urGC.

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Key Words: Gastric cancer, NLR, prognosis, recurrence.

Patients and Methods

This study was a retrospective analysis of 92 patients with unresectable advanced and recurrent gastric adenocarcinoma, who were treated at our institution between January 2006 and September 2017. The clinicopathologic findings were determined according to the Japanese Classification of Gastric Carcinoma (10).

Following the diagnosis of recurrence and unresectable advanced GC, all patients underwent CT. Their CT regimens included: i) S-1 (n=13), ii) paclitaxel (n=3), iii) docetaxel (n=1), iv) CPT-11 (n=13), v) combined S-1 + cisplatin (n=25), vi) combined CPT-11 + cisplatin (n=3), vii) combined S-1 + docetaxel (n=12), viii) combined paclitaxel + ramucirumab (n=6), ix) combined S-1 + CPT-11 (n=1), x) combined S-1 + trastuzumab (n=1), xi) combined S-1 + oxaliplatin (n=3), xii) combined capecitabine + cisplatin (n=1), xiii) combined capecitabine + oxaliplatin (n=2), xiv) combined capecitabine + trastuzumab (n=2), xv) combined capecitabine + cisplatin + trastuzumab (n=1), xvi) combined capecitabine + oxaliplatin + trastuzumab (n=1), xvii) combined docetaxel + cisplatin + S-1 (n=2), xviii) combined S-1 + 5-FU + liver-infused mitomycin-C (n=1) and xix) combined S-1 + paclitaxel + intraperitoneally infused paclitaxel (n=1). Of the 92 patients who underwent CT for urGC, 33 (35.9%) received second-line CT, including paclitaxel (n=7), docetaxel (n=1), nab-paclitaxel (n=8), CPT-11 (n=9), combined S-1 + docetaxel (n=1), combined paclitaxel + ramucirumab (n=6), and combined capecitabine + cisplatin + trastuzumab (n=1). Ten patients received neoadjuvant chemotherapy before gastrectomy: i) combined S-1 + cisplatin (n=9) and ii) combined docetaxel + cisplatin + S-1 (n=1) and 46 patients received adjuvant chemotherapy after gastrectomy: i) S-1 (n=43), ii) combined S-1 + cisplatin (n=2) and iii) combined cisplatin + docetaxel (n=1).

Causes of death and patterns of recurrence were determined by reviewing medical records, including laboratory data, ultrasonography, computed tomography, scintigrams, peritoneal punctures and laparotomies, or by direct inquiry of family members.

Serum concentrations of CRP, albumin and carcinoembryonic antigen (CEA), and numbers of peripheral neutrophils, lymphocytes, and platelets at the time of diagnosis of urGC were obtained from patients' records. The NLR was obtained by dividing the peripheral neutrophil count (NC) by the peripheral LC. The PLR was obtained by dividing the peripheral thrombocyte count by the peripheral lymphocyte count. The platelet \times CRP multiplier value (P-CRP) was defined based on the product of the peripheral thrombocyte count \times the serum CRP level divided by 10^4 . PNI was calculated by $10 \times \text{Alb} + 0.005 \times \text{TLC}$. The CRP-to-albumin ratio was obtained by dividing the serum concentration of CRP by the serum albumin level. With regard to modified Glasgow Prognostic Score (mGPS), patients with elevated C-reactive protein levels (>0.5 mg/dL) and hypoalbuminemia (<3.5 g/dL) were assigned mGPS of 2, those with one abnormality in either parameter were assigned mGPS of 1, and those with neither abnormality were assigned mGPS of 0.

The Institutional Review Board of our institution approved of this study. The informed consent requirement was waived. All procedures performed in studies with human participants were in accordance with the ethical standards of the Institutional Research Committee and with the 1964 Helsinki Declaration and its later amendments or with comparable ethical standards. The authors have no conflicting financial interests.

Statistical analysis. Differences between the two groups were evaluated using the Mann–Whitney *U*-test. Correlation between

NLR and survival period was analyzed using the Spearman rank correlation coefficient. The Youden index was calculated using receiver operating characteristic (ROC) analysis to determine optimal cutoffs for the NLR in the survival analysis. Survival curves were calculated according to the Kaplan–Meier method. Differences between the curves were identified using the log-rank test. Multivariate analyses of factors considered as prognostic of overall survival (OS) were performed together with Cox's proportional hazards model and a stepwise procedure. $p < 0.05$ was considered significant. GraphPad Prism (GraphPad Software, Inc., La Jolla, CA, USA) and Stat View (Abacus Concepts, Inc., Berkeley, CA, USA) software packages were used for the statistical analyses.

Results

The median survival time (MST) of patients in this study was 13.5 months. Figure 1 shows the area under curve (AUC) of each examined prognostic indicator by ROC analysis for 1-year OS. Among those indicators, NLR had the highest AUC, *i.e.*, the highest predictive value. Table I shows correlations between clinicopathologic factors and NLR in patients with urGC. Among patients with urGC, NLR was significantly higher in those with advanced disease compared to those with recurrent disease ($p=0.0051$), and in those with peritoneal metastasis compared to those without peritoneal metastasis ($p=0.041$). ROC analysis showed the optimal cut-off value of NLR is 2.83 (AUC=0.782, $p < 0.0001$). Based on this cutoff value, patients were divided into NLR^{High} (NLR \geq 2.83, n=44) and NLR^{Low} (NLR $<$ 2.83, n=48). Their MSTs were NLR^{High}=9.1 months and NLR^{Low}=17.1 months ($p < 0.0001$, Figure 2). NLR and survival period were inversely correlated ($r=-0.496$, $p < 0.0001$, Figure 3). It is likely that the transition rate to second-line CT might be associated with survival. The rates of transition to second-line CT were 77.1% and 59.1 in NLR^{Low} and NLR^{High}, respectively, and the difference tended to be significant ($p=0.064$). Furthermore, patients who received second-line CT had a significantly longer median survival (14.5 months) compared to those who did not receive second-line CT (10.5 months, $p=0.011$).

Multivariate analysis (using Cox's proportional hazards model and a stepwise procedure) of sex, age, number of incurable factors, number of chemotherapy line, presence of peritoneal metastasis, hematogenous metastasis, and/or lymph-node metastasis, either non-resectable advanced GC or recurrent GC, neutrophil count, platelet count, serum albumin level, serum CRP ratio, PNI, CRP to albumin level, PNI, P-CRP, and NLR, indicated that only NLR was an independent prognostic indicator for OS (hazard ratio=1.116, 95% Confidence Interval=1.063-1.171, $p < 0.0001$).

We determined patients' NLRs 1 month after starting chemotherapy, and divided them into post-NLR^{High} (\geq 2.83) and post-NLR^{Low} ($<$ 2.83). Among the 48 patients initially in the NLR^{Low} group, *i.e.*, at diagnosis, 5 patients had shifted to post-NLR^{High}, and 43 patients were post-NLR^{Low}. Among

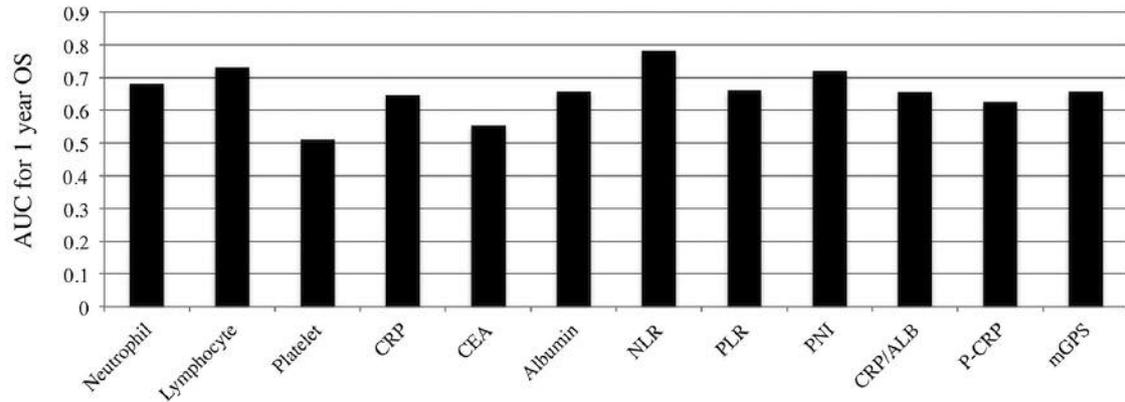


Figure 1. Area under curve for each examined factor for 1-year overall survival by receiver operating characteristic analysis in patients with unresectable gastric cancer. AUC: Area under curve; OS: overall survival.

the patients who were NLR^{Low} at diagnosis, prognosis of post-NLR^{High} patients was significantly worse compared to post-NLR^{Low} patients ($p=0.048$, Figure 4A). Among the 44 patients in the NLR^{High} group at diagnosis, 21 shifted to post-NLR^{Low} and 23 were post-NLR^{High}, and their post-NLR^{High} subgroup also had a significantly worse prognosis compared to their post-NLR^{Low} subgroup ($p=0.0095$, Figure 4B).

Discussion

Outcomes of patients with cancer are determined by both tumor-related and patient-related factors. In GC, depth of invasion and lymph node metastasis are the most important tumor-related prognostic factors (11, 12), whereas inflammation, malnutrition, and immune status are relevant patient-related factors. In this study, we determined the prognostic significance of serum parameters that could be obtained from blood tests, including NC, LC, PC, serum concentration of CRP, albumin, NLR, PLR, PNI, CRP/alb, P-CRP, and mGPS as patient-related factors, and CEA as a tumor-related factor, in urGC patients. Among these indicators, NLR had the most predictive value for urGC patients in the current study.

The reason behind poor prognosis in patients with high NLR remains unclear, although it is likely related to the respective functions of neutrophils and lymphocytes. High NLR reflects an elevated peripheral neutrophil count. Neutrophils are important components of the inflammatory response, which has dual roles in tumor development and metastasis. In response to cytokine stimulation, neutrophils can diverge towards antitumor (N1) or protumor (N2) phenotypes (13). In the acute inflammation state, neutrophils are activated to exert an antitumor effect (13). Conversely, neutrophils activated by chronic inflammation can promote tumor growth and metastasis. Inflammatory cytokines such

Table I. Relationship between NLR and clinicopathological variables in patients with unresectable advanced and recurrent gastric cancers.

Variable	NLR	p -Value
Unresectable cause		0.0051
Advanced cases (n=36)	4.39±4.77	
Recurrent cases (n=56)	2.81±2.12	
Gender		0.12
Male (n=73)	3.4±3.82	
Female (n=19)	3.53±1.72	
Age		0.44
<75 (n=69)	3.45±3.85	
≥75 (n=23)	3.36±2.13	
Peritoneal metastases		0.041
Present (n=44)	3.69±2.6	
Absent (n=48)	3.18±4.15	
Hematogenous metastases		0.55
Present (n=34)	3.99±4.87	
Absent (n=58)	3.09±2.31	
Lymph node metastases		0.59
Absent (n=36)	3.6±4.69	
Present (n=56)	3.32±2.47	
Number of metastases		0.068
One (n=72)	3.01±2.27	
Two and more (n=20)	4.93±6.0	
Number of chemotherapy line		0.068
One (n=29)	3.88±2.84	
Two and more (n=63)	3.21±3.75	

All results are expressed as mean±SD.

as G-CSF, IL-6, and TGF- β 1 can induce the N2 phenotype of neutrophils in bone marrow and tumor microenvironment (14). In addition, priming with IFN- γ and TNF- α can convert the phenotype from N2 to N1 (15). Neutrophils may, thus, exert either antitumoral or protumoral functions, depending on the mediating inflammatory cytokines. We have

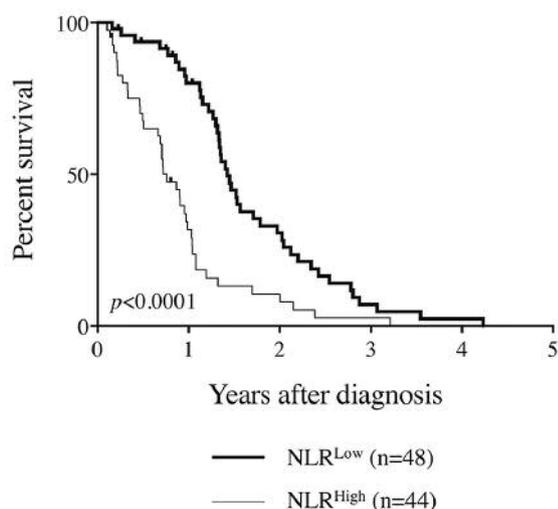


Figure 2. Overall survival curves by neutrophil-to-lymphocyte ratio in patients with unresectable gastric cancer.

previously reported that elevated serum IL-6 concentration can be observed in GC patients (16). Therefore, most of the increased numbers of neutrophils observed in patients with unresectable advanced and recurrent GC are probably of the N2 phenotype, which exert a protumoral effect. This could explain the close correlation between elevated NC and the poor prognosis of patients with unresectable advanced and recurrent GC in the current study.

High NLR also reflects a decreased LC. Several other studies have also shown that low preoperative LC is related to poor prognosis in various cancers, including pancreatic cancer (17), esophageal cancer (18), renal cancer (19), and sarcoma and lymphoma (20). Lymphocytes include CD4⁺ and CD8⁺ T cells, NK cells, NKT cells, gamma-delta T cells, and B cells, which are closely associated with tumor immunity. Therefore, the presence of low numbers of those cells is probably associated with impaired tumor immunity, which in turn results in tumor progression. In fact, several studies have shown that low numbers of tumor-infiltrating lymphocytes, such as CD4⁺ and CD8⁺ T cells, are associated with poor prognosis in some cancers (21-23). Furthermore, low numbers of immune cells, such as NK cells, B cells, and gamma-delta T cell have been associated with poor prognosis in both peripheral blood and cancer tissue for some cancer types (24-26). Therefore, peripheral LC might be a good indicator of cell-mediated immune status, including both acquired and adaptive immunity, and humoral immune status against GC.

A high transition rate to second-line CT might be associated with longer survival. In patients treated with palliative CT, second-line or subsequent CT had greater effects on survival time. In fact, we observed that patients who received second-line CT had a significantly longer

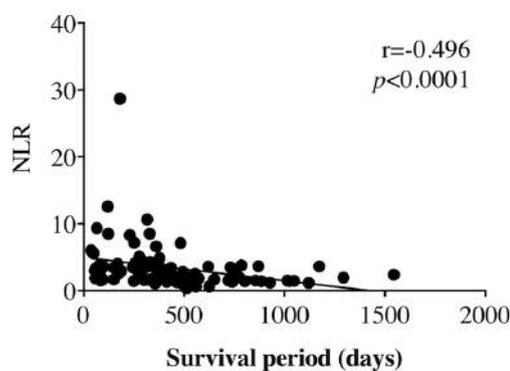


Figure 3. Correlation between survival period and neutrophil-to-lymphocyte ratio in patients with unresectable gastric cancer.

median survival compared to those who did not receive second-line CT. The rate of transition to second-line CT among low-NLR patients with unresectable recurrent GC cancer was reported to be significantly higher compared to high-NLR patients (9). This suggests that patients with low NLR could continue with second- or third-line treatments should they have adequate physical reserves. In the current study, the rate of transition to second-line CT in the low-NLR group also tended to be significantly higher compared to the high-NLR group. Therefore, high rate of transition to second-line CT would likely be associated with favorable prognosis in low-NLR patients with urGC.

Knowing if CT is efficacious as soon as possible after its introduction is extremely important. In the current study, therefore, we determined NLR one month after initiating CT and found that post-NLR was significantly associated with prognosis in both the NLR^{High} and NLR^{Low} groups, which implies that post-NLR can be used to assess CT efficacy.

Recently, nivolumab, the antibody to programmed cell death protein 1, was shown to be effective in the treatment of urGC (27). Svaton *et al.* has demonstrated that a laboratory panel reflecting chronic inflammation including NLR was a potential predictive marker of nivolumab treatment in patients with advanced non-small cell lung cancer (28). Therefore, NLR also might be a potential predictive marker of nivolumab treatment in patients with urGC. Further investigations are urgently required to determine the correlation between NLR and the efficacy of nivolumab treatment in patients with urGC.

Our study had a few limitations. First, since it was retrospective it was subjected to a bias. Second, we enrolled patients with both recurrent urGC and advanced urGC. However, NLR was significantly higher in patients with advanced disease compared to those with recurrent disease, which indicates that the prognostic significance of NLR might differ between these two disease aspects. Third, we

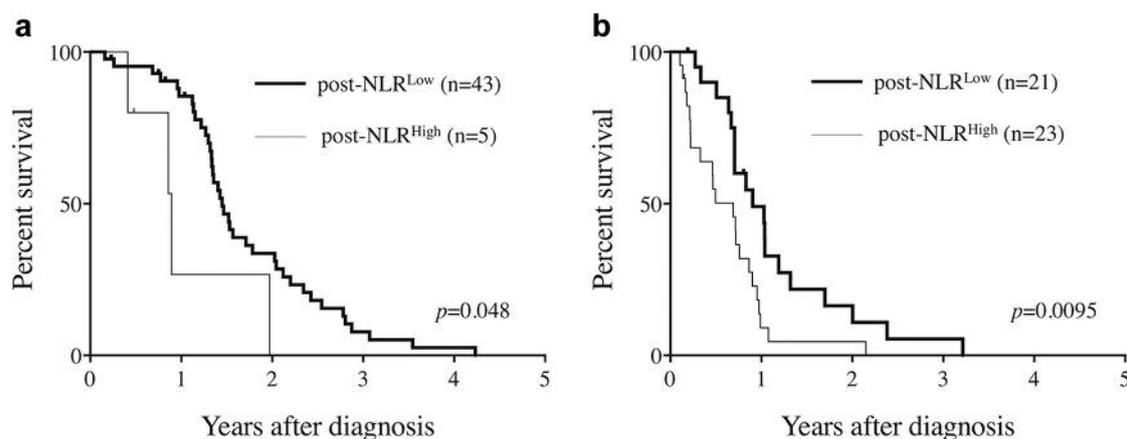


Figure 4. Correlations between survival period and neutrophil-to-lymphocyte ratio (NLR) measured 1 month after starting chemotherapy in patients with unresectable gastric cancer and previously found to have either: (A) NLR^{Low} (<2.83) or (B) NLR^{High} (≥ 2.83) at diagnosis.

determined the prognostic significance of NLR at the time of diagnosis of urGC in the current study, however, it is not clear whether this is the optimal timing to measure NLR. Fourth, the number of patients included in our study was small and the results must, therefore, be confirmed in a large-scale, prospective, randomized, controlled trial.

In conclusion, our study shows the potential utility of NLR at the time of diagnosis of urGC to predict the prognosis in patients with urGC. Because these serum markers are convenient and inexpensive to measure, NLR could be especially useful in routine clinical settings.

Conflicts of Interests

The Authors have no conflicts of interest.

Authors' Contributions

The study conception and design were performed by HS, the acquisition of data by YM, SS, YK, YS, KM, TM, and YF. The analysis and interpretation of data were performed by YM and HS, the drafting of the manuscript by YM and HS and the critical revision by YF. All authors approved the final version of the article.

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