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Original Article

The predictive value of preoperative neutrophil-lymphocyte and platelet-lymphocyte ratio on overall survival in patients with operable gastric cancer

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Abstract

Aim: Elevated preoperative neutrophil–lymphocyte ratio (NLR) and platelet–lymphocyte ratio (PLR) predict overall survival rates among patients with several types of cancer. The current study was conducted to clarify whether NLR and PLR are clinically useful in predicting overall survival among patients undergoing curative resections for gastric cancer.

Material and Methods: 202 gastric cancer patients were reviewed retrospectively who had been appealed to our clinic between 2006 and 2013. 192 patients who had local disease, and underwent curative surgery for gastric cancer were included to the study. Data regarding potential prognostic factors including age, sex, preoperative neutrophil, lymphocyte, and platelet counts, postoperative tumor characteristic such as tumor location, tumor size, lymph node metastasis, tumor–nodes–metastasis staging, Lauren's classification of subtypes and survival times were obtained from medical records.

Results: No significant correlations were noted between NLR, PLR and tumor location, size, Lauren's classification of subtypes, histology, stage, and type of gastrectomy. Univariate analysis revealed that metastasis at the follow up, sex, T, N stage, and lymph node ratio (LNR) were predictors of worse overall survival. In multivariate analysis, metastasis at follow up (p=0.014; HR:1.81; CI:1,126-2,911) and LNR (p=0.001; HR:3,564; CI:2,175-5,842) were found to be independent variables with worse overall survival.

Conclusion: Preoperative NLR and PLR cannot be used as independent variables for prediction of overall survival in patients with operable gastric cancer.

Keywords: Gastric cancer; inflammation; neutrophil-lymphocyte ratio, platelet-lymphocyte ratio

INTRODUCTION

Gastric cancer is the fifth most common neoplasm and third most common cause of cancer related death in the world. Average 5-year survival is about 31% in United States and 26% in Europe (1). Prognosis and treatment is there after guided by pathologic analysis of the tumor such as stage, resection margins, and lymph node involvement (2). However, it is only possible to determine these factors after surgery, based on the postoperative histological specimen.

Currently tumor, node, metastasis (TNM) staging is gold standard for tumor staging but its accuracy is limited due to individual differences in gastric cancer patients and studies have shown that heterogeneous clinical courses are frequently observed even within the same tumor stage (3,4). For these reasons we believe it is important that further may provide a more reliable prognostic factor.

In addition to benign diseases such as infections and autoimmune disorders, malignant diseases also induce a chronic inflammatory response (5,6). It is important to note that not only factors associated with tumor but also patient related factors, especially those involving the systemic inflammatory response (SIR) play a critical role in the prognosis (7,8). The exact cause of the SIR which occurs in cancer patients is still a cause for debate but hypoxia secondary to tumor necrosis, alterations in production of acute phase proteins, synthesis of interleukin, and neuroendocrine metabolism have been held responsible (9).

Increase in platelet/lymphocyte ratio (PLR) and neutrophil/lymphocyte ratio (NLR) were suggested as important prognostic factors in certain cancers such as esophageal, renal, gynecologic, pulmonary and colorectal cancers (2,5,6,10-13). Research has showed that NLR and PLR are cost-effective, reproducible, and widely available

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(14,15). These studies are imperative as the capability to predict the accurate prognosis of a patient is crucial for determining appropriate treatment method and follow-up plans. The prognostic role of PLR and NLR in evaluating the systemic response has been also been reported in gastric cancers (4-6,16) but these studies have also included patients with metastatic and unresectable tumors.

The aim of retrospective cohort study was to evaluate prognostic significance of PLR and NLR levels in patients who underwent curative gastric resection.

MATERIAL and METHODS

Two hundred and two gastric cancer patients were reviewed retrospectively who had been appealed to our clinic between 2006 and 2013. Gastric cancer diagnosed was histopathological evaluation of gastroscopic biopsies. 20 patients were excluded from the study due to palliative surgery, have distant metastasis or peritoneal dissemination, and have previously chemotherapy or hematological disease history, having inflammatory conditions or clinical evidence of infection. 192 patients who had local disease, and underwent curative surgery for gastric cancer were included to the study. In this study; curative surgery for gastric cancer was regarded as subtotal or total gastrectomy, to achieve adequate gastric resection through 5-cm negative margins, and D2 lymphadenectomy with or without splenectomy.

Patients' demographic features, laboratory analysis, operative findings and final pathology reports were obtained from hospital medical records.

Age, sex, preoperative platelet, lymphocyte, and neutrophil counts, size, location and subtypes of the tumor, involvement of lymph nodes, TNM staging (17), and survey of the patients' were accepted as potential prognostic factors. The NLR and PLR values were determined from patients' full blood count day before surgery. NLR was calculated with dividing the neutrophil to lymphocyte count, and PLR was calculated with dividing the platelet to lymphocyte count. Follow up periods for all patients were, 3 months for first two years, 6 months for second three years, and 1 year to the death after surgery.

Statistical analysis

When PLR and NLR were accepted as prognostic factors, the optimal cutoff values were calculated with Receiver Operating Characteristic (ROC) analysis. Best cutoff value was determined by selecting the nearest value to the point maximum specificity and sensitivity combination. Correlations between clinical features and PLR/NLR levels were determined by Chi Square test. Survival outputs were calculated by the Kaplan-Meier method and compared by the log-rank test.

Overall survival was accepted as primary endpoint of the study, and determined by the time of surgery to the date of the last follow-up or the date of death from any cause. The univariate and multivariate Cox proportional hazards model was used to analyze the prognostic values of clinical features and PLR/NLR. Multivariate analysis was calculated with variables which were determined as significant in univariate analysis. A P-value < 0.05 was accepted as statistically significant. All statistical analyses were performed using SPSS 21 software.

RESULTS

Patient characteristics

Among patients, 124 (64.5%) were male and 68 (35.5%) were female. Median age was 58 years (min: 26 max: 88 years). The median follow-up duration was 28 months (1-132 months). The 5-year OS rate was 31.4%.

Table 1. Indication groups for hospitalization and ICU admission

	Neutrophil–lymphocyte ratio (NLR)		
Characteristics	**NLR low (n=66)**	**NLR high (n=87)**	**p Value**
Median Age (years)	56	63	**0.010**
Gender(%)			0.311
Female	28 (39.6)	29 (49.1)	
Male	38 (60.4)	58(50.09)	
Tumor location			0.639
Upper one-third	14 (21.2)	20 (22.9)	
Middle one-third	19 (28.8)	28 (32.1)	
Lower one-third	33 (50)	39 (45.0)	
Tumor size(%)			0.07
<5 cm	35(52.2)	32 (36.8)	
≥5 cm	31 (47.8)	54 (63.2)	
Lauren type(%)			0.203
Intestinal	29 (36.8)	35 (40.2)	
Diffuse	22 (33.3)	36(41.4)	
Mixt	2(3.03)		
Unspecified	13(26.87)	16(39.4)	
Lymph node metastasis(%)			0.084
pN0	14 (21.2)	25 (28.7)	
pN1	15 (22.7)	22 (25.3)	
pN2	14 (21.2)	19 (21.8)	
pN3a	12 (18.2)	18 (20.7)	
pN3b	11(16.7)	3(3.4)	
TNM stage (%)			0.206
I	9 (13.6)	7 (8.04)	
II	9 (13.6)	21 (24.1)	
III	48 (72.8)	59 (67.86)	
Metastases at follow-up(%)	26(39.3)	22(25.2)	0.06

ROC curve analysis to determine NLR and PLR cutoff values

The patients were divided into two groups according to the optimal cutoff values of PLR (low, <155; high, ≥155) and NLR (low, <2.55; high, ≥2.55), which were calculated with ROC analysis.

Prognostic variables according to NLR and PLR

There were no significant correlations between NLR, PLR and tumor location, size, subtypes, histology, stage, or type of gastrectomy. In contrast to NLR, there were a significant correlation between PLR and lymph node metastasis. There was significant correlation also between age and both PLR/NLR (Table 1,2).

Table 2. Platelet–lymphocyte ratio correlations

	Platelet–lymphocyte ratio (PLR)		
Characteristics	**PLR low (n=69)**	**PLR high (n=87)**	**p Value**
Median Age (years)	56	62	0.038
Gender(%)			0.242
Female	22 (31.9)	35 (41.7)	
Male	45 (68.1)	49(58.3)	
Tumor location			0.684
Upper one-third	13 (18.8)	21 (25)	
Middle one-third	20 (29)	27 (32.1)	
Lower one-third	36 (52.2)	36(42.9)	
Tumor size(%)			0.255
<5 cm	34(49.3)	33 (39.8)	
≥5 cm	35 (50.7)	50(60.2)	
Lauren type(%)			0.09
Intestinal	21 (30.4)	39 (46.4)	
Diffuse	30 (33.3)	32(38.1)	
Mixt	2(2.9)		
Unspecified	16(23.2)	13(15.5)	
Lymph node metastasis(%)			**0.012**
pN0	16 (23.2)	23 (27.4)	
pN1	15 (21.7)	22 (26.2)	
pN2	15 (21.7)	18 (21.4)	
pN3a	12 (17.4)	18 (21.4)	
pN3b	11(15.9)	3(3.6)	
TNM stage (%)			0.66
I	7 (10.6)	9(10.7)	
II	12 (14.3)	18 (21.4)	
III	50 (74.1)	60 (67.9)	
Metastases at follow-up(%)	20(28.9)	28(32.1)	

Univariate analysis of clinicopathological characteristics indicated that metastases at the follow up (p=0,003; HR:2,06; CI:1,276-3,183) , male sex (p=0,014; HR:1,708; CI:1,115-2,618), presence lymphovascular invasion (p=0,008; HR:1,919; CI:1,187-3,104), T stage (p=0,001; HR:1,638; CI:1,298-2,067), N stage(p=0,001; HR:1,378; CI:1,196-1,598) lymph node ratio(LNR) (p=0,001; HR:3,564; CI:2,175-5,842) and PLR (p=0,021; HR:1,924; CI:1,103-3,357) were predictors of worse overall survival.

Multivariate analysis revealed that metastases at the follow up (p=0,014; HR:1,81; CI:1,126-2,911) and LNR (p=0,001; HR:7,602; CI:3,415-16,921) were predictors of worse overall survival. Other parameters were not found to be in correlation with overall survival (Figure 1).

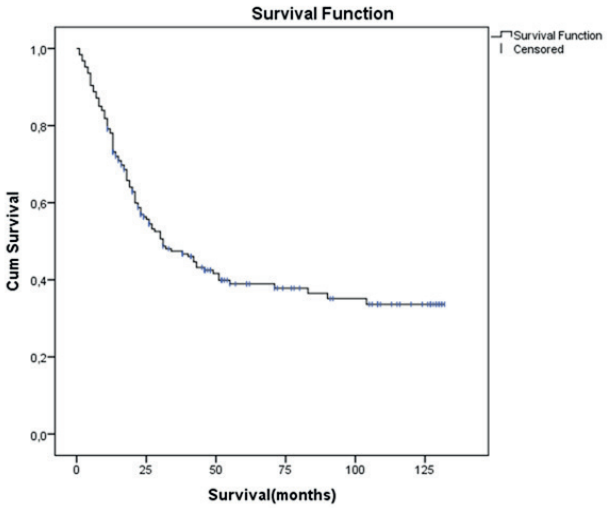

Figure 1. Overall surviaval of patients (Kaplan Meier analysis)

Comparison of NLR and PLR

When AUC values of PLR and NLR compared by ROC analysis for further evaluation of prognostic values, the PLR had a higher value (0.558; CI 95%:0,406-0,709; P = 0.078) than NLR (Figure 2).

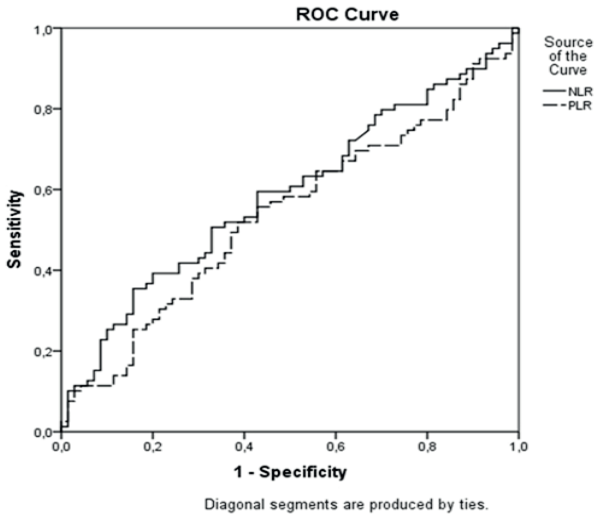

Figure 2. Prognostic value comparison of NLR and PLR (ROC curve analysis)

DISCUSSION

Gastric cancer has poor prognosis, which is affected by many different conditions. The systemic inflammatory response is one of the most important factors. An important marker of this response includes the NLR, and PLR. Although the exact etiology is undetermined, recent studies have indicated that high values of platelet and neutrophil counts prior to treatment have been correlated with poor survival in several malignancies (18). It has been argued that inflammatory reaction which is caused by tissue damage has a critical role in the tumor cell microenvironment. These inflammatory cells are responsible for cell, angiogenesis, proliferation, migration, invasion, and metastasis. Additionally, cancers can originate from sites of inflammation, possibly due to the migration of inflammatory cells, and their products such as chemokines, cytokines (19, 20).

Clinical tumor staging may help to determine the appropriate treatment strategy in gastric cancer patients but can't predict patients' prognosis at postoperative period (4).

Both epidemiological and clinical studies have indicated a relation between chronic inflammation and gastric cancer (14). For this reason we want to reveal whether peripheral neutrophil, platelet, and lymphocyte counts could predict the overall survival in patients who had radical surgery for gastric cancer (2). The main difference of our study from the literature was that we did not find a relationship between NLR and PLR when overall survival was taken into account(21-23). We believe the reason for this was that our patient population was early stage or locally advanced. The only factor to show correlation with overall survival was metastasis detected during postoperative follow up, which was shown with multivariate analysis. A similar result was also observed in 2 other studies one which evaluated stage 3 tumors (8) and the other which evaluated operable or neoadjuvant chemotherapy receiving patients (24). An evaluation of the literature has been given in Table 3.

Table 3. Literature reviews about the relationship between gastric cancer and the preoperative NLR and PLR

	Cancer stage	Study	Study population	Overall survival correlation
Correlation (+)	Operable (early/ local advanced)	Mohri Y et al., 2010	early gastric cancer	NLR positive correlation
		Kim EY. et al., 2015	early gastric cancer	NLR and PLR positive correlation
		Jiang N et al., 2014	only stage 2 and 3	NLR positive correlation
		Graziosi L et al., 2015	early stages (stage I to II or N0 patients)	NLR positive correlation
		Aliustaoğlu M. et al., 2010	locally advanced gastric cancer	NLR and PLR positive correlation
		Pan QX et al., 2015	early and local advanced gastric cancer	NLR positive correlation
	Advanced /metastatic	Jung MR et al., 2011	late stage gastric cancer	NLR positive correlation
		Yamanaka T et al., 2007	stage IV gastric cancer	NLR positive correlation
		Aldemir MN et al., 2015	advanced gastric cancer patients	NLR and PLR positive correlation
		Lee S et al., 2013	advanced gastric cancer receiving chemotherapy	NLR and PLR positive correlation
		Wang F et al., 2015	advanced gastric cancer receiving chemotherapy	NLR and PLR positive correlation
		Hirahara T et al., 2019	advanced gastric cancer receiving chemotherapy	NLR and PLR combination positive correlation
	Both	Shimada H et al., 2010	early and late primary gastric cancer	NLR positive correlation
		Gunaldi M et al., 2015	with every stage of gastric cancer	NLR positive correlation
Correlation (-)	Operable (early/ local advanced)	Wang D et al., 2012	only stage 3	No correlation of overall survival with PLR and NLR
		Dutta S et al., 2012	operable stage 1 to 3 and some neoadjuvant chemotheraphy	No correlation of overall survival with NLR

In the literature, there is inconsistency in the cutoff values for PLR and NLR, due to using different methods for determining these values in different tumors. Some studies have used the cut off value of previous studies or their best cutoff values according to the median value for gastric cancer (25). However, several studies have used the ROC curve to calculate the ideal cutoff value. Kim et al found that both PLR and NLR can predict the overall survival of gastric cancer with cutoff level for 126 and 2 respectively (3). On the contrary, Lee et al. (26) put forward a PLR of 160 and an NLR of 3 as the optimal cutoff levels by selecting values with the most marked difference in the univariate analysis of overall survival curves was used. Shimada et al. (27) suggested the ideal cutoff value for NLR was 4.0 by using a similar method. In this study, optimal cutoff values were calculated as 2.55 for NLR and 155 for PLR by using ROC curve analysis.

The Glasgow Prognostic (GPS) score has been shown as a prognostic factor in malignant solid tumors such as renal, ovarian, colorectal, non-small cell lung, and liver cancers (28). GPS can be defined as inflammation-based score which was calculated by serum C-reactive protein (CRP) and albumin levels. However, studies concerning GPS in the prognosis of gastric cancer are scarce, because CRP is not routinely measured during treatment (29). NLR, PLR, and GPS are gaining interest as SIR markers in various clinical circumstances. Inflammation play an essential role in cancer development (30).

Many inflammation-based scores like NLR/PLR have been performed in several types of cancer. The NLR was determined as an independent predictor for survival in liver cancer (31). In metastatic colorectal cancer patients, He et al. indicated that NLR was superior to PLR as an adverse prognostic factor (32). In contrast, Portale et al (33) reported that neither NLR nor PLR were correlated with survival after rectal cancer surgery. On the other hand in breast cancer patients, Azab et al. (34) showed that the PLR and NLR were predictors of long-term mortality. Hirahara et al (16) indicated that combination of NLR and PLR score can predict chemotherapy response and prognosis in patients with advanced gastric cancer. A combination of NLR/PLR also has been shown as a predictive of pathological complete response after neoadjuvant chemotherapy in breast cancer patients with negative correlation (35). The NLR and PLR are basic, easy-to-use laboratory variables. Even though that they are continuous variables, NLR and PLR are also able to show acute changes in the inflammatory condition of a patient, which may lead to a more precise and dynamic result (4).

In our study we were able to show a significant relationship between PLR, NLR and age. This is compatible with the literature as other studies have similar results (27). It has been argued that the reason for this elevation could be due to an age-related dysfunction of immuno-surveillance for cancers (25). In a meta-analysis evaluating the prognostic role of PLR a strong association was observed between poor survival and elevated PLR. This association was seen in several different types of solid malignancies including both metastatic and non-metastatic tumors. This analysis showed that the strongest correlation was observed between survival and PLR in metastatic disease when compared with local disease (36). The cases included in our study were those with operable gastric cancer and no correlation was found between preoperative NLR/PLR and overall survival. Studies have shown the increase in cancer-related SIR cause increase in PLR and NLR values especially in advanced stage cancer (14). So, the negative result may be because of the exclusion of patients with advanced stage cancer from the study.

Low number of patients and retrospective nature are the limitations of this study. Further prospective studies with large number of patients are required. Indeed, the cut-off value NLR of 2.55 and PLR of 155 are requires further investigation.

CONCLUSION

Preoperative platelet-lymphocyte and neutrophil-lymphocyte ratios cannot be used as predictors for overall survival in patients with operable gastric cancer. Larger-scale, multicenter, and prospective studies are needed for more accurate results.

Competing interests: The authors declare that they have no competing interest.

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