Abstract

Objective: The prognostic value of neutrophil-lymphocyte ratio, platelet-lymphocyte ratio and systemic immune-inflammatory index has been studied in many cancer types. Our aim is to show the prognostic value of neutrophil-lymphocyte ratio, platelet-lymphocyte ratio and systemic immune-inflammatory index in resected gastric cancer patients. In addition, to determine which parameter is a better predictor of survival.

Material and methods: The study included 95 patients resected gastric cancer between 2014-2018. Receiver operating curve analysis was used to determine neutrophil-lymphocyte ratio, platelet-lymphocyte ratio and systemic immune-inflammatory index cut-off values. Systemic immune-inflammatory index was evaluated as neutrophil×platelet/lymphocyte. Long rank and cox regression analysis were used.

Results: The median age was 62 (22-84) years. The median overall survival was 33 months. 49 (51.6%) patients were in stage 3 and 46 (48.4 %) patients were in stage 1-2. High neutrophil-lymphocyte ratio, platelet-lymphocyte ratio and systemic immune-inflammatory index values, tumor depth, stage of metastatic lymph node and tumor-node-metastasis stage were poor prognostic factors for overall survival and disease-free survival. When multivariant cox regression analysis was performed, only platelet-lymphocyte ratio was found to be independent prognostic factor (p = 0.037 for overall survival, p = 0.024 for overall survival).

Conclusion: High neutrophil-lymphocyte ratio, platelet-lymphocyte ratio and systemic immune-inflammatory index were found to be poor prognostic factors in predicting both overall survival and disease-free survival before treatment in patients who undergo curative resection for gastric cancer. As a result of multivariate analysis, only high platelet-lymphocyte ratio was determined as an independent poor prognostic factor for both overall survival and disease-free survival.

Keywords: gastric cancer, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, prognosis

Prognostic value of neutrophil-lymphocyte ratio, platelet-lymphocyte ratio and systemic immune-inflammatory index in resected gastric cancer

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Introduction
Gastric cancer (GC) is the third cause of cancer-related death and the fifth most common worldwide cancer diagnosis [1]. In 2018, 1.03 million new cases were diagnosed and 780,000 deaths occurred due to gastric cancer [2]. Despite advances in early diagnosis and treatment, one-third of gastric cancer patients who underwent curative surgery had recurrence [3-5]. The established prognostic factors were tumor depth (T), stage of metastatic lymph node (N), tumor-node-metastasis (TNM) stage and histological type of tumor [4,6]. However, the prognosis is different even in patients with the same stage [7]. Therefore, studies are conducted to investigate different factors affecting prognosis.

Systemic inflammatory response is a complex bio-system involving humoral and cellular components. These systemic inflammatory biomarkers have been reported to be associated with poor outcomes in patients with gastric cancer. Of these biomarkers, high neutrophil/lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) and systemic immune-inflammatory index (SII) have been reported to be associated with poor prognosis [3,5,8]. However, the clinical relevance of a blood score that combines NLR, PLR and SII has not been in patients with gastric cancer.

The aim of this study is to determine which one of these three systemic inflammatory markers is better for patients with gastric cancer.

Material and methods
The study included 95 patients with gastric cancer diagnosed and operated in the Medical Oncology Clinic of Ankara Dışkapı Yıldırım Beyazıt Training and Research Hospital between 2014-2018. Patients with metastasis, patients with active infection before treatment and patients with missing file records were excluded from the study. The tumors were staged according to the TNM staging system of the American Joint Committee on Cancer (AJCC 7th ed., 2010). Clinicopathological details, pretreatment laboratory data, survival data were collected by review of patients record, retrospectively. All patients underwent either a subtotal or total gastrectomy with standard D2 lymphadenectomy.
The NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count. Similarly, the PLR was defined as the absolute platelet count divided by the absolute lymphocyte count. Systemic immune-inflammatory index was calculated as platelet×neutrophil / lymphocyte.

The study was conducted according to the principles of the Declaration of Helsinki. The study was approved by the Ethics Committee of the Ankara Dışkapı Yılsırım Beyazıt Training and Research Hospital.

**Statistical analysis**

Statistical analyses were performed using SPSS 20.0 program. The optimal cutoff of NLR, PLR and SII were estimated by receiver operating characteristics (ROC) curve. The area under the curve (AUC), sensitivity, and specificity were calculated. The relationship between categorical variables was evaluated by chi-square test. The relationship between PLR, NLR, SII and disease-free survival (DFS), overall survival (OS) was evaluated by Kaplan-Meier method and log rank test. Multivariable analysis was conducted using the Cox regression analysis. P <0.05 was considered statistically significant.

**Results**

Clinicopathological features of the patients are summarized in Table 1. 69 (72.6%) patients were male. The median age was 62 years (range 22 to 84 years) at the time of diagnosis. During follow-up, 52 (54.7%) patients developed recurrence and 48 (50.5%) patients died. 68 (71.6%) patients received adjuvant therapy. 5-fluorouracil (5 FU) based chemotherapy was given as adjuvant chemotherapy in all patients.

For NLR, the best cut-off value estimated by ROC analysis was 2.66. The area under the curve (AUC) was 0.644, sensitivity 60.4%, specificity 68.1%. The number of patients with NLR less than 2.66 was 51 and the number of patients with high NLR was 44. Overall survival of patients with NLR above 2.66 was shorter than those with low NLR (p = 0.003). Overall survival was 21 months in the NLR high group, whereas DFS was not reached in the NLR low group (Figure 1a). Disease-free survival was significantly shorter in the NLR-high group than in the NLR-low group (p = 0.003). While DFS was 13 months in the NLR high group, disease-free survival was not reached in the NLR low group (Figure 1b).

| Table 1 | Clinicopathologic features of operated gastric cancer patients |
|---------|---------------------------------------------------------------|
| Age | 62 (22-84) |
| Gender (Female/Male n) | 26/69 |
| TNM Stage (n) | 45 |
| Stage 1/2 | 49 |
| Stage 3 | 47 |
| Lymph node stage (n) | 47 |
| N0/1 | 34 |
| N2/3 | 60 |
| Tumor depth (n) | Yes |
| T1/2 | 68 |
| T3/4 | No |
| Adjuvant treatment (n) | 27 |
| Yes | 35 |
| No | 39 |
| Grade (n) | 3 |

TNM: Tumor-node-metastasis

**Figure 1a** - Kaplan-Meier Curve for Overall survival of low and high neutrophil-lymphocyte ratio

**Figure 1b** - Kaplan-Meier curve for disease-free survival of low and high neutrophil-lymphocyte group
For PLR, the best predicted value was found to be 143 by ROC analysis. The sensitivity was 64.4%, the specificity was 66%, and AUC was 0.663. While the number of patients with PLR below 143 was 47, the number of patients with PLR above 143 was 48. In the PLR-high group, OS was significantly shorter than the PLR-low group (p = 0.001). In the PLR-high group, OS was 22 months. In the PLR-low group, OS could not be reached (Figure 2a). DFS was shorter in the PLR-high group than in the PLR-low group (p = 0.001). The disease-free survival of patients in the PLR-high group was 13 months, while the disease-free survival of patients in the PLR-low group was not reached (Figure 2b).

The best predicted value for SII was 644. There were 47 patients with SII levels above 644 and 48 patients below 644. In the ROC analysis, AUC was 0.663, sensitivity 64.4% and specificity 66%. Overall survival in the high SII group was significantly shorter than in the low SII group (p = 0.002). While OS was 21 months in the high SII group, the OS was not reached in the low SII group (p = 0.001). While DFS was 13 months in the high SII group, the DFS duration was not reached in the low SII group (Figure 3b).

When we looked at the relationship between NLR, PLR and SII values and clinicopathologic variables, only SII was associated with high TNM stage (p = 0.046). Age, gender, T stage, N stage, grade, need for adjuvant therapy were not associated with NLR, SII and PLR.

The median follow-up period was 26 months (range 3-61), and the median OS was 33 months. Prognostic factors for overall survival are summarized in Table 2. In univariant analysis, TNM stage, N stage, T stage, adjuvant therapy, NLR, PLR and SII values were statistically significant prognostic factors on overall survival, whereas age and gender were not significant prognostic factors. Overall survival was shorter in patients with high NLR, high PLR, high SII, TNM stage 3 disease, N stage 3/4 and T stage 3/4. Multivariate analysis showed that PLR was independent prognostic factor (Table 2). Median OS and DFS were poor in the high PLR group (p = 0.037 for GSK, p = 0.024 for HSK).

**Prognostic factors**

The median follow-up period was 26 months (range 3-61), and the median OS was 33 months. Prognostic factors for overall survival are summarized in Table 2. In univariate analysis, TNM stage, N stage, T stage, adjuvant therapy, NLR, PLR and SII values were statistically significant prognostic factors on overall survival, whereas age and gender were not significant prognostic factors. Overall survival was shorter in patients with high NLR, high PLR, high SII, TNM stage 3 disease, N stage 3/4 and T stage 3/4. Multivariate analysis showed that PLR was an independent prognostic factor (Table 2). Median OS and DFS were poor in the high PLR group (p = 0.037 for GSK, p = 0.024 for HSK).
Inflammation results in an increase in neutrophils and platelets [15]. Natural killer cells, dendritic cells, and cytokines released by the immune system (neutrophils, macrophages, lymphocytes, and T cells) may cause tumor growth and metastasis. Defense cells of the immune system prove to play an important role in the development and/or progression of several cancer types [13,14]. Defense cells of the immune system (neutrophils, macrophages, lymphocytes, natural killer cells, dendritic cells) and cytokines released from these cells may cause tumor growth and metastasis [15]. Inflammation results in an increase in neutrophils and platelets and a decrease in lymphocytes [16,17].

Lymphocytes play an important role in the immune response and are the most important cells in eliminating cancer cells and suppressing cancer development [18]. Studies in many cancer types have shown that lymphocytopenia is associated with poor prognosis [19].

The relationship between thrombocytosis and cancer has long been known. Platelets have an important role in tumor growth, formation and metastasis [20,21]. Platelets also inhibit the antitumor effects of NK cells, causing tumor cells to grow and spread [4]. High platelet count has been shown to cause short survival in many cancer types [16,22-26].

Neutrophil cells contribute to the formation, proliferation, and spread of cancer cells. The role of neutrophil in the development of metastasis is due to the release of reactive oxygen products, nitric oxide, vascular endothelial growth factor. Increased neutrophils also suppress the activity of lymphocytes, natural killer and activated T cells [27,28]. High neutrophil and platelet count and low lymphocyte count lead to high systemic immune-inflammatory index value. High SII is an indicator of strong inflammation and weak immune response in cancer patients. SII has been associated with poor survival in many solid tumors [29]. Studies have shown that increased NLR, PLR and SII levels are associated with poor outcomes in patients with gastric cancer [8]. In our study, high PLR, NLR and SII values were found to be associated with poor prognosis. However, the most important predictor of prognosis was PLR.

These parameters are required as routine blood tests from all patients before treatment. One of the aims of our study was to emphasize the importance of the inflammatory system in operated gastric cancer patients. Our other aim was to determine the best parameter that could help clinicians predict prognosis in patients with operated gastric cancer.

Because of our study was a single center data, it included a small number of patients. In addition, our study was performed retrospectively and all factors that could affect prognosis could not be evaluated. Therefore, prospective studies are needed.

### Conclusion

There is no study on which one of these reliable and inexpensive markers is better. In our study, high PLR, NLR and SII values before treatment were found to be poor prognostic markers. However, only PLR was found to be an independent prognostic factor. Our study shows that PLR is a better prognostic factor than the others in patients with operated gastric cancer.

### Disclosures:

There is no conflict of interest for all authors.

### Ethics approval:

The retrospective observational study was approved by the ethics committee of the Ankara Dışkapı Yıldırım Beyazıt Training and Researc Hospital.

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### Table 1

**Univarite and multivariate analyses for survival**

| Variables               | Univariate analysis | Multivariate analysis |
|-------------------------|---------------------|-----------------------|
|                         | P value (long rank) | Hazard ratio 95%CI   | p value |
| Age                     | 0.289               |                       |        |
| <65/≥65                 |                     |                       |        |
| Sex                     | 0.193               |                       |        |
| Female/male             |                     |                       |        |
| TNM stage               | 0.000               | 0.578                 | 0.130-2.568 | 0.472 |
| Stage 1-2/3             |                     |                       |        |
| Lymph node metastasis   | 0.000               | 0.748                 | 0.204-2.748 | 0.662 |
| N1-2/3-4                |                     |                       |        |
| Depth of tumor          | 0.000               | 0.735                 | 0.269-2.008 | 0.548 |
| T1-2/3                  |                     |                       |        |
| Adjuvant therapy        | 0.002               | 1.911                 | 0.749-4.872 | 0.175 |
| Yes/no                  |                     |                       |        |
| NLR                     | 0.003               | 0.824                 | 0.369-1.839 | 0.636 |
| <2/<2                   |                     |                       |        |
| PLR                     | 0.001               | 2.202                 | 1.049-4.622 | 0.037 |
| <143/<143               |                     |                       |        |
| SII                     | 0.002               | 0.908                 | 0.388-2.125 | 0.823 |
| <644/>644               |                     |                       |        |

TNM: Tumor-node-metastasis, NLR: neutrophil / lymphocyte ratio, PLR: platelet / lymphocyte ratio, SII: systemic immune-inflammatory index

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### Discussion

The aim of this study was to investigate the prognostic value of pre-treatment NLR, PLR and SII levels in patients with resected gastric cancer. In this study, high NLR, PLR and SII values were found to be associated with short disease-free survival and overall survival. Cox regression analysis showed that high PLR was an independent poor prognostic factor associated with OS and DSF.

Clinical and epidemiological studies have shown a strong association between acute / chronic infection and cancer [9-11]. Helicobacter pylori infection is characterized by inflammatory infiltration of T cells and neutrophils [12]. Chronic inflammation associated with infections and autoimmune diseases has been proven to play an important role in the development and/or progression of several cancer [13,14]. Defense cells of the immune system (neutrophils, macrophages, lymphocytes, natural killer cells, dendritic cells) and cytokines released from these cells may cause tumor growth and metastasis [15]. Inflammation results in an increase in neutrophils and platelets and a decrease in lymphocytes [16,17].

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