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Inflammatory markers in the prognosis of gastric cancer

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Abstract

We aimed to investigate whether these parameters can determine the prognosis of gastric cancer. In our study, patients who applied to Trakya University School of Medicine, Department of General Surgery for surgical treatment with a diagnosis of gastric cancer between January 2015 and March 2021 were evaluated, retrospectively. In this study, we have 219 consecutive gastric cancer patients who applied for surgical treatment between January 2015 and March 2021. There are 156 (71.2%) male patients and 63 (28.7%) female patients. The mean age is 65.6±11.2. 158 (72%) of our patients were over the age of 60. When each TNM stage was compared with each other, a statistically significant difference was found in the NLR, PLR, PNI, SIRI, and SII parameters. There was a statistically significant difference between the GPS when we compare the early stage and the advanced stage cancer. In our study, we showed that high SIRI, SII, NLR, PLR, and GPS as inflammatory and nutritional markers and low PNI value may be negative predictive factors for prognosis in gastric cancer patients.

Keywords: Gastric cancer, prognostic factor, inflammatory markers

Introduction

The second most common cause of cancer-related death is gastric cancer in all over the world [1]. The incidence of stomach cancer varies worldwide [2]. As of today, Japan and Korea are the two countries with the highest rates of gastric cancer [2]. In addition to environmental factors affecting gastric cancer, specific gene changes are thought to play a role, and H. pylori is still the most common known cause of gastric cancer [1,3].

Gastric cancers are usually either asymptomatic or show nonspecific symptoms in the early stages. In advanced stages of gastric cancer, symptoms such as dyspepsia, persistent stomach, loss of appetite, and weight loss may accompany [3].

It has been shown in many studies that systemic inflammatory markers have been defined as prognostic markers because they are easily applicable in many different types of cancer. There seems to be a lot of evidence showing that inflammation affects the emergence of malignant diseases, the progression of the disease, the rate of spread and the response to treatment [4]. Again, in some studies, it has been shown that with treatment methods that will reduce inflammation, benefits can be obtained both in the treatment of various types of cancer and in preventing the rate of progression. In fact, it is thought that smoking plays a role in cancer formation by affecting the formation of inflammation positively or negatively, thanks to various stimulating or suppressive mechanisms [5].

We retrospectively analyzed the preoperative SIRI, SII, PNI, GPS, NLR, PLR, and LMR values in stomach cancer patients who have had surgery. We aimed to interrogate the importance of these parameters in determining stomach cancer prognosis.

Material and Methods

Ethics

This study was approved by the Scientific Research Ethics Committee of Trakya University School of Medicine (Protocol Code: Protocol code: TÜTF-GOBAEK 2021/473).

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Patients

In this retrospective study, patients who appealed to Trakya University School of Medicine, Department of General Surgery, and had surgical treatment for gastric cancer between January 2015 and March 2021 were evaluated. Data were achieved from the hospital database. Including criterias of this study were being over the age of 18 and having had surgery for stomach cancer. Patients under the age of 18 and patients with hematological disorders that may affect blood parameters were excluded from the study.

Laboratory Tests

Routine laboratory measurements such as white blood cell (WBC) count, neutrophil count, lymphocyte count, monocyte count, platelet count, serum albumin, and C-Reactive Protein (CRP) were performed preoperatively. The neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and lymphocyte/monocyte ratio (LMR) were calculated. The PNI was calculated according to the following formula: 10x serum albumin (g/dl)+0.005 total lymphocyte count (per mm3). SII was calculated by applying the formula: platelet (P)×neutrophil (N)/lymphocyte (L). NLR was calculated by dividing the neutrophil count by the number of lymphocytes. GPS is estimated based on the measurement of CRP and albumin. In patients with CRP values >10(mg/L), and albumin <35(g/L) the GPS was accepted as 2, if albumin was ≥35 (g/L) and CRP ≤10(mg/L), then the GPS was considered as 1. In patients with CRP values >10, if albumin was ≥35(g/L) then the GPS values were accepted as 1, if albumin was ≥35(g/L) and CRP ≤10(mg/L) then the GPS values were accepted as 0, respectively. SIRI was defined: SIRI=(neutrophil×monocyte)/lymphocyte).

Statistical Analysis

The assumption of normal distribution was checked with the Shapiro-Wilk test. Percentages, mean, standard deviation, median and interquartile range were used as the descriptive statistics. Mann-Whitney U test was used for the variations which are contrary to the normal distribution range in the comparison of two groups. The relations between qualitative variations were studied by the Pearson Chi-Square test and Fisher's Exact test. Median and quarter values have been given for the quantitative variations and percentage and frequency rates were given for the qualitative variations as descriptive statistic evaluation. Significant value was determined as 0.05 for all statistical analyses. Cut-off values for the quantitative variations were also studied by the receiver operating characteristic (ROC) analysis. Statistical Package for the Social Sciences (SPSS), version 22.0 (IBM®, Chicago, USA) was used for statistical analysis.

Results

In this study, we have 219 consecutive stomach cancer patients who had surgical resection between January 2015 and March 2021.

There are 156(71.2%) male patients and 63 (28.7%) female patients. The mean age is 65.6±11.2. 158(72%) of our patients were over the age of 60. The descriptive statistics of the patients are presented in Table 1.

When each TNM stage was compared with each other, we found a statistically significant difference in the NLR, PLR, PNI, SIRI, and SII parameters for the most parts but if we consider TNM 1 and 2 as early stage and TNM 3 and 4 as advanced stage, we found that there was no statistically significant difference for the indexes within the early stage and within the advanced stage themselves. When we compare all the indexes without LMR, between the early and advanced stages, there was always a statistically significant difference [Table 2].

Table 1. Descriptive statisticse

	Number of patients	Median (IQR)
Age	219	65.68 ±11.2**
NLR	219	4.02 (4.09)
PLR	219	177 (129)
LMR	218*	2.67 (1.65)
PNI	219	340 (80.0)
SIRI	219	2.43 (2.50)
SII	219	1192 (1604)
CEA	95*	2.33 (3.23)
CA199	110*	29.8 (498)

*Missing data: LMR: 1, CEA: 124, CA199: 110
**Data were expressed as mean ± standard deviation.
IQR: interquartile range
NLR: neutrophil/lymphocyte ratio PLR: platelet/lymphocyte ratio LMR: lymphocyte/monocyte ratio PNI: SIRI: SII: CEA: CA199

Table 2. The Comparison of p values of NLR, PLR, PNI, SIRI, and SII between stages

TNM	NLR	PLR	PNI	SIRI	SII	LMR
1-2	0.018	0.714	<.001	0.004	0.002	0.972
1-3	<.001	0.003	<.001	<.001	<.001	0.975
1-4	<.001	<.001	<.001	<.001	<.001	1.000
2-3	<.001	0.016	<.001	<.001	<.001	1.000
2-4	<.001	<.001	<.001	<.001	<.001	0.880
3-4	0.013	0.542	<.001	0.007	<.001	0.905

If we consider TNM 1 and 2 as early-stage and TNM 3 and 4 as advanced stage, we found that advanced-stage disease is more common in men (72%) than women (54%). Also a statistically significant difference, was found between the GPS when we compare the early stage and the advanced stage. [Table 3].

Table 3. Comparison of GPS and gender between the TNM stages

TNM	GPS			Gender		Total
	0	1	2	Male	Female	
1	20 (64%)	10 (32%)	1 (3%)	18 (58%)	13 (42%)	31
2	27 (64%)	12 (28%)	3 (7%)	26 (62%)	16 (38%)	42
3	29 (25%)	66 (57%)	20(17%)	87 (75%)	28 (25%)	115
4	10 (32%)	20 (64%)	1 (3%)	25 (80%)	6 (20%)	31

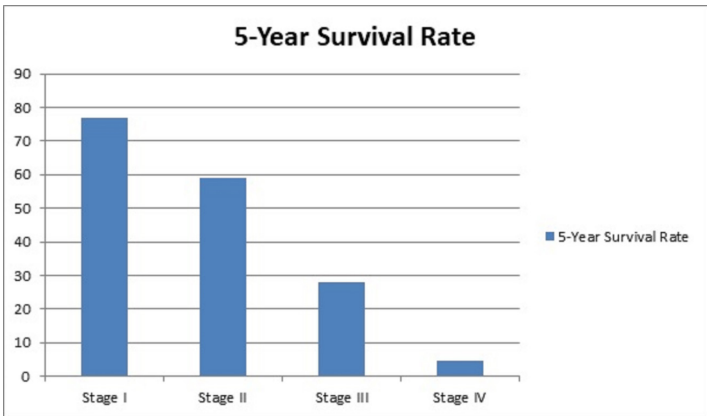

Figure 1. Comparison of 5-Year Survival Rate Between the Stages

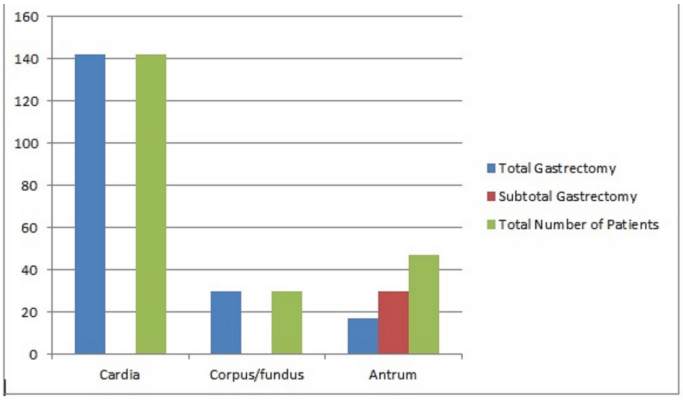

Figure 2. Preferred Resection Types According to Tumor Localization

Discussion

The incidence of gastric cancer is twice as high in men as in women in all regions (2,3). It is more common in the elderly and the average age is 60-70 years [6]. In our study, the gastric cancer rate was higher in male patients (71.2%) and patients over 60 years of age (72%).

We can divide the prognostic factors used in gastric cancer into three main groups preoperative, intraoperative, and postoperative. Preoperative factors are previous gastric resection, tumor location, and serum tumor markers. Intraoperative factors are surgical margins and the extent of lymphadenectomy. Postoperative factors are Tumor-Node-Metastasis (TNM) stage and histological type. The most important of these factors affecting the survival of gastric cancer patients is the pathological tumor stage [7,8].

Inflammatory response has an important role in gastric cancer prognosis and progression [9,10]. Accordingly it is known that systemic inflammatory cells may affect the formation of tumors and metastases. These cells include lymphocytes, monocytes, neutrophils and platelets which may have predictive value in the stomach cancer prognosis [11]. There are studies showing that neutrophil-lymphocyte ratio (NLR) and (platelet-lymphocyte ratio) PLR are important factors in gastric cancer prognosis [12,13,14].

Recently, Liu et al. concluded that the Systemic Inflammatory Response Index (SIRI) may be useful in evaluating the operable stomach cancer prognosis. Same study also accepted that changes in SIRI before and after surgery have a correlation with the prognosis [15].

Chen et al. found that SIRI had an important predictive value for the prognosis and treatment response in gastric cancer patients who need neoadjuvant chemotherapy as a first line treatment option. The study found that SIRI had a negative correlation with disease-free survival (DFS) and overall survival (OS) [16].

According to the findings of a retrospective study by Hirahara et al., there is a negative correlation between high Systemic Inflammation Index (SII) values and OS. The study stated that SII can be considered as an independent prognostic indicator, in particular in older patients [17].

A meta-analysis by Yang et al. determined that the Prognostic Nutrition Index (PNI) could be a predictive marker for the clinicopathological aspects, postoperative complications, and OS of patients [18].

In addition, Namikawa et al. concluded that a high Glasgow Prognostic Score (GPS) was an independent predictor of worse prognosis and OS in relapsed stomach cancer [19].

In the study of Çaycı et al., T4 (55%) and T3 (18%) were the most common T stages. Approximately 17-31 lymph nodes were removed [20]. In our study, we found the frequency of the patients' TNM stages as T4 (60.27%), T3 (24.2%). The mean value of the dissected lymph nodes was 28.

It has been shown in the literature that total gastrectomy is performed more frequently than subtotal gastrectomy [20]. In our study, 86.3% of the surgeries were total gastrectomy and 13.6% of them were subtotal gastrectomy.

The five-year survival rate was found below 20% in some studies [1,3]. However, this rate can reach 90% in Japan due to collective screening programs [2,3]. We found the 5-year survival rate to be 38.8%. This brings us to the importance of screening programs and diagnosis in the early stages.

Liu et al. found the optimal cut-off value for SIRI as 0.85 and divided the patients into two groups according to this value. They revealed that patients with a SIRI<0.85 had a longer overall survival and a better prognosis than those with a SIRI>0.85, and that high SIRI was associated with a high TNM stage [15].

Chen et al.The SIRI cut-off value was found to be 1.21. When the high and low SIRI groups were compared, a correlation was found between the low SIRI group and both of gender and primary tumor site. The low SIRI group was dominant in female patients. When comparing low and high SIRI patients, WBC, neutrophil count, monocyte count, NLR, MLR, and PLR were associated with the low SIRI group, while the low SIRI group was not corresponding with lymphocyte and hemoglobin count. Low SIRI correlated with long-term OS and DFS in both univariate and multivariate analyzes. The 5-year survival rate for low SIRI group was 14.5% for DFS and 19.4% for OS, respectively. The 5-year survival rate for high SIRI group was 2.2% for DFS and 2.2% for OS, respectively. The high SIRI has a negative correlation with 5-year DFS and OS. The OS and DFS are longer for the pathological Tis/T0+I+II stages than pathological III+IV stages. The low SIRI group has longer DFS and OS than the high SIRI group with Tis/T0+I+II stages and the high SIRI group with pathological stages III+IV [16]. Li et al. obtained that SIRI might be a predictive factor for gastric cancer patients independent of the TNM stage [21].

We found the SIRI cut-off value to be 2.41. High SIRI was found to be positively correlated with each of the T, N, M, and stage. Although SIRI was high, it was found to be negatively correlated with OS. And there is no relationship between DFS and the number of lymph nodes. The 5-year survival rate for low SIRI group was 38% for DFS and 45% for OS. The 5-year survival rate for high SIRI group was 8% for DFS and 33% for OS.

Hirahara et al. showed that high SII values in elderly patients have a negative correlation with OS. However, it was determined that SII was not an independent prognostic factor for OS and there was no correlation between these two parameters in young patients [17].

High SII was found to be associated with late TNM stage and poor outcome [22,23]. There was a correlation between SII and poor differentiation in both primary and validation cohorts. SII had strong correlations with NLR, PLR, and LMR. SII has a better predictive value than other parameters, also it can be considered as an independent prognostic factor [24].

We found the SII cut-off value of 1187.98. We found a negative correlation between SII and OS, a positive correlation between SII and each T, N, M, and stage, otherwise no correlation with DFS. We found a negative correlation between high SII and OS in older patients and no correlation in younger patients.

Yang et al., recommended that low PNI predicted shorter OS in gastric cancer patients at stages 1, 2, and 3, but found no significant association between OS and low PNI in stage 4 patients [18]. In another study, it was shown that low PNI was important in predicting short OS for stages 1 and 3 in gastric cancer patients, but not for stages 2 and 4 [18,25]. In another study, it was shown that low PNI showed a poor prognosis for stages 1 and 2 in gastric cancer patients, but not for stage 3 [18,26]. It has been observed that the incidence of low PNI increases with age and is significantly higher in TNM stages 3 and 4 and also in the pt3, pt4, and positive lymph node groups [18]. Since PNI reflects the immunological status with lymphocytes and the nutritional status with albumin, it was concluded that it may be a prognostic factor in cancer patients, and a correlation was found between low PNI and postoperative complications [18,27]. Results showed that a low PNI was related with more advanced tumor characteristics such as older age, higher TNM stages, and positive vascular and lymphatic invasion. Taken together, the data suggest that low PNI has a correlation with the extent of tumor progression, thereby it causes shorter survival of gastric cancer patients [18].

We found the PNI threshold value to be 340. We detected a negative correlation between PNI and each TNM stages. On the other hand, there was no correlation between PNI with DFS and OS. There were also significant differences between each TNM stage when PNI values were compared.

According to Namikawa et al., mean survival time was found to be significantly higher for GPS 0 than for GPS1 and GPS2. The study suggested that GPS1 or GPS2 were independent factors that predicted a poorer prognosis [19].

It has also been shown that the predictive value of combinations of CRP, serum albumin, or pre-albumin levels is better than traditional inflammatory indicators [28,29]. The results show that the GPS prognosis is comparable to the TNM stage [30].

We concluded that GPS1 and GPS2 can predict advanced stage (stage III and stage IV) in gastric cancer patients. Also, in late stage stomach cancer patients, those with GPS1 and GPS2 had lower OS than those with GPS0. As a result, these values can be evaluated as negative prognostic factors.

Inflammatory markers such as tumor necrosis factor-α and interleukin-3 (IL-3), and interleukin-6 (IL-6) are produced by tumor cells [31]. This relatively causes neutrophilia, thrombocytosis, and lymphocytopenia, thus high NLR-PLR rates [13,32]. Since tumor response cannot be determined before treatment, NLR-PLR ratios are factors that can predict prognosis before treatment. These values can be a guide as to which patients with advanced gastric cancer will need chemotherapy or radiotherapy [12].

Decreased circulating lymphocytes and their mediators increase NLR, which increases progression and decreases response to malignancy [32]. A reduced lymphocyte-mediated immune response weakens the lymphocyte-mediated immune response, which favors complications [33,34].

Studies have shown that high NLR-PLR is associated with the rapid progression of the disease [12]. In addition, when patients with high and low PLR were compared, it was observed that patients with low PLR were more prone to postoperative complications and large tumors [35]. They correlated increased PLR with a higher risk of advanced TNM stage in gastric cancer [36]. These results show that NLR and PLR scores can be used as predictive factors in clinical practice [12].

Low PLR is considered a disadvantage for the postoperative course since it can lead to complications such as malnutrition, immune disorders, inflammatory state, and susceptibility to microvascular thrombosis [33,34].

NLR and PLR may be determinative in evaluating the course of the disease and the treatment plan [12]. In their study, Wang et al. evaluated 120 patients with irresectable gastric cancer and showed that patients with high NLR and PLR values were much less responsive to chemotherapy [37].

When the NLR values were compared in our study, there were statistically significant differences between Groups 1-3, Groups 1-4, Groups 2-3, Groups 2-4 when we compared the PLR values. Considering that Groups 1 and 2 represent early stages, and Groups 3 and 4 represent advanced stages; We can say that high NLR and PLR values may be an indicator for advanced disease in gastric cancer patients. We have also concluded that higher NLR values may be a factor for shorter OS.

Deng et al. found that any decrease in lymphocyte count and functional abnormalities of lymphocyte are important factors in the inflammatory response to the tumor. The level of circulating monocytes also allows us to speculate about tumor-associated macrophages, and therefore a low lymphocyte-monocyte ratio (LMR) is seen in poor prognosis and clinical presentations [38].

They revealed that LMR was significantly associated with TNM stage . Low LMR values were detected in patients with T3-T4, N1-N3, metastatic and stage III-IV tumors, and it was shown that there was no correlation between LMR and tumor grade [38].

In our study, we compared all groups according to their LMR values and there found no statistically significant difference.

Therefore, we can say that there is no statistically significant relationship between LMR values and the stage of gastric cancer.

More clear results can be obtained with multicenter and prospective studies with longer follow-up period.

Conclusion

In our study, we showed that high SIRI, SII, NLR, PLR, and GPS as inflammatory and nutritional markers and low PNI value may be negative predictive factors for prognosis in gastric cancer patients. We need a prospective clinical study to understand the effects of markers on prognosis and to determine their importance in diagnosis and follow-up.

Conflict of interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical approval
This study was approved by the Scientific Research Ethics Committee of Trakya University School of Medicine (Protocol Code: Protocol code: TÜTF-GOBAEK 2021/473).

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