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Predictive value of inflammatory markers in gastric cancer

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ABSTRACT

Aim: Many recent studies are increasingly shedding light on the nature of the relationship between cancer and inflammation. Neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) platelet/neutrophil ratio (PNR), and Mean Platelet Volume (MPV) are proinflammatory markers, and their prognostic importance has been investigated in many solid cancers. In this study, we discussed the association of these derivative inflammatory markers, obtained from a cheap and simple peripheral blood test, with clinicopathologic variables in patients undergoing gastrectomy for gastric cancer.

Material and Method: The retrospective database of a total of 148 patients who were operated for gastric cancer in the Diyarbakır Gazi Yaşargil Training and Research Hospital Department of Surgery was analyzed. All blood results and pathology reports of the patients were reviewed retrospectively. Demographic characteristics of the patients and pathological features of the tumor were extracted from the database. NLR, PLR, PNR and MPV values were calculated from peripheral blood cell counts. Data were analyzed using SPSS version 24.0.

Results: PNR and MPV values were statistically significant according to N and T stage of the tumor, respectively (p=0.035, p=0.011). In MPV, this difference was statistically observed between T1 and T2 tumors (p=0.029). PLR and NLR values did not show a significant difference according to the size of the tumor (p>.05).

Conclusion: MPV values are significantly associated with tumor T stage. PNR values are significantly associated with tumor N stage. However, the clinical implications and the added value to clinical practice require further research.

Keywords: Inflammatory marker, gastric cancer, NLR, PLR, T stage

INTRODUCTION

The term biomarker originated in the 1950s and was defined by the National Institute of Health as a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathological processes, or pharmacological responses to a therapeutic intervention (1). Inflammatory biomarkers have widespread clinical use postoperatively after gastrointestinal procedures due to their success in predicting postoperative complications and mortality (2-4).

Cancer-related inflammation is defined as the 7th hallmark of cancer (5), and the systemic inflammatory response has cellular and humoral (Procalcitonin, C-reactive protein, albumin) components. The cellular-mediated inflammatory response (lymphocytes, neutrophils and monocytes) is increasingly recognized as having an important role in tumorigenesis and carcinogenesis. Therefore, diagnostic biomarkers such as free circulating tumor cells, DNA, miRNA, and exosomes in serum have been used to screen and detect cancer at an early stage; however, their clinical use is still limited due to their instability and high cost (6).

Derivative biomarkers (neutrophil-to-lymphocyte ratio (NLR) (7) , platelet-to-lymphocyte ratio (PLR), platelet-to-neutrophil ratio (PNR) (8) , and modified Glasgow prognostic score (mGPS) (9)) have also been described and reported to be associated with poor survival in patients undergoing potentially curative surgery. It is now recognized that cancer-related inflammation is closely related to the cancer development process (10, 11). High NLR is associated with larger tumor size (12), and both PLR and NLR have been shown to be closely associated with poor prognosis, recurrence and shorter survival (13,14).

Globally, gastric cancer is the fourth (7.7 %) leading cause of cancer-related death (15). Surgery remains

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the only potentially curative treatment. However, approximately 40% of patients develop recurrence and there is no definitive standard of care for medical treatment in these patients. Therefore, it is highly valuable for clinicians to identify biomarkers that can improve prognostic modeling, independent of contemporary staging, which may encourage new therapeutic targets.

Since these parameters obtained from peripheral blood tests are cheap, simple and easily accessible, their predictive value is very valuable for clinicians. Such studies in patients with gastric cancer will help clinicians in terms of diagnosis, treatment and survival prediction. In this study, we aimed to evaluate the clinical implications of NLR, PNR, PLR and MPV values obtained from peripheral venous blood test results at the time of diagnosis in patients undergoing curative gastrectomy by revealing their relationship with tumor characteristics.

MATERIAL AND METHOD

Data of 167 patients were analyzed and 19 patients were excluded from the study due to insufficient data. This study includes retrospective data of a total of 148 patients who met the inclusion criteria at the surgery clinic of Diyarbakır Gazi Yaşargil Training and Research Hospital following local ethics committee approval (Date: 30.12.2022, Decision No: 286). The study includes newly diagnosed cases of primary and metastatic gastric cancer who did not receive any treatment likely to affect hematologic parameters. Exclusion criteria for this study were as follows: residual gastric cancer, neoadjuvant chemotherapy, concurrent and metachronous malignancies, emergency surgery, recent blood transfusion, liver cirrhosis, evidence of any inflammatory condition, presence of concomitant hematologic malignancies or disorders, autoimmune disorders, recent steroid therapy, and incomplete/incorrect medical records.

Data on demographic characteristics and laboratory values of the patients were retrospectively reviewed through the hospital's medical database records. Clinicopathologic characteristics including age, gender, clinical TNM stage, histopathology report were collected. Patients were staged according to the TNM staging system of the American Joint Committee on Cancer (AJCC 7th edition, 2010). Medical blood records including neutrophil, platelet, lymphocyte counts and mean platelet volume (MPV) were obtained from recent preoperative peripheral whole blood analysis. Neutrophil to lymphocyte ratio (NLR) was calculated by dividing the absolute number of neutrophils by the absolute number of lymphocytes, Platelet to neutrophil ratio (PNR) was calculated by dividing the absolute number of platelets by the absolute number of neutrophils. Similarly, platelet/lymphocyte ratio (PLR) was defined as the absolute number of platelets divided by the absolute number of lymphocytes. Albumin values were also recorded from biochemical tests.

Patients' pathology reports were reviewed and type of operation, tumor localization and size, histopathological diagnosis, grade, lymph node status (total, metastatic), lymphovascular invasion (LVI) , perineural invasion were obtained.

Statistical Analysis

All data were presented as mean±standard deviation (SD) and minimum-maximum values. Parametric test assumptions were examined before the difference analysis was performed. Normality was checked by Shapiro-Wilk test. Homogeneity of variances was tested with Levene. If the assumptions were met, difference analysis was performed with one-way analysis of variance (ANOVA) and if not, with Kruskal-Wallis test. Pairwise comparisons were made with Mann-Whitney U test. Statistical analyses were performed at 95 percent confidence intervals. A P value less than 0.05 was considered statistically significant.

RESULTS

Of the remaining 148 patients, 38 (25.7%) were female and 110 (74.3%) were male. The mean age was 63.2±12.7 years. Preoperative diagnostic tests revealed primary carcinoma of the stomach in 148 patients. The tumor was located proximally in 47 patients (31.8%) and distally in 101 patients (68.2%). The clinicopathologic characteristics of the patients included the study are shown in **Table 1**. The PLR, and NLR values of the patients did not differ statistically significantly with the T and N stages of the tumor (p>.05). However, the PNR value was found to be statistically significant with the N stage (p=0.035). Similarly, the preoperative albumin values of the patients were not statistically significant according to the T and N stages (p>.05).

Preoperative MPV value showed a statistically significant difference according to the T stage of the tumor (p=0.011). However, this differentiation was not observed in N stage (p>.05) . This difference was statistically observed between T1 and T2 tumors (p=0.029). As a result, it was observed that the MPV value increased statistically significantly as the diameter of the tumor increased. The continuous data of the patients and the differentiation of the tumor according to T and N stage are shown in **Table 2**.

Table 1. Variables of gastric cancer	
Variables	**Total**
	148
Surgery Type	
Subtotal Gastrectomy	57 (38.5%)
Total Gastrectomy	91 (61.5%)
Cancer Type	
Adenocarcinoma	139 (93.9%)
GİST	4 (2.7%)
Neuroendocrine Tumor	5 (3.4%)
Histopathologic Feature	
Vascular Invasion	72 (48.6%)
Neural Invasion	79 (53.4%)
Staging (TNM Classification)	
I	25 (16.9%)
II	46 (31.1%)
III	77 (52%)
T Category	
I	17 (11.5%)
II	14 (9.5%)
III	87 (58.8%)
IV	30 (20.3%)
N Category	
0	35 (23.6%)
I	42 (28.4%)
II	31 (20.9%)
III	40 (27%)

Table 2. Correlation of inflammation markers and T/N category			
İnflammation Markers	**Mean (SD)**	**P-value**	
		T category	**N category**
Preoperative Albumin	7.39±10.47	.26	.231
Preoperative MPV	8.70±1.42	.011*	.159
NLR	4.46±3.69	.333	.893
PNR	54.67±28.71	.161	.035*
PLR	185.67±86.09	.31	.808
*ANOVA, MPV: Mean Platelet Volume			

DISCUSSION

The inflammatory reaction triggered by tumor-related tissue damage is a critical factor in the tumor cell microenvironment (16). As components of the systemic inflammatory response; lymphocytes, neutrophils and platelets, are increasingly recognized to have an important role in carcinogenesis and tumor progression (10,15).

It is known that neutrophils, by secreting circulating growth factors and proteases, predispose circulating tumor cells to metastasize to distant organs (14,16,17). Cytokines and chemokines produced by both tumor and inflammatory cells have been shown to contribute to the development of distant metastasis and recurrence (18). Neutrophilic response has been associated with poor prognosis as it suppresses the cytotoxic activity of T cells (19). On the contrary, the presence of lymphocytes in the environment has been associated with better response to cytotoxic therapy and prognosis in oncologic patients (20). Lymphocytes generally represent the immune response in the fight against cancer by increasing tumor cell apostosis with the cytokines they provide (21). Inflammation results in thrombocytosis, lymphocytopenia, neutrophilia, and leukocytosis (10, 22). Platelets can participate in the inflammatory reaction by increasing angiogenesis or releasing growth factors (21-23).

We examined several factors reflecting the systemic inflammatory response. Among these factors, preoperative albumin, NLR and PLR values were not significantly associated with the TNM stage of the tumor. However, MPV values were associated with T stage in gastric cancer patients. This relationship was significant between T1 and T2 stages. In our study, the PNR value was found to be associated with the N stage. Based on these findings, we found that the association of MPV in early stage gastric cancers (T1-2) and PNR in locally advanced gastric cancers (N1-3) is more significant. The complete blood count test is a simple, low-cost and repeatable parameter of inflammatory response, as it is routinely performed in all cancer patients without any additional effort. The concept of inflammation-based scores such as NLR and PLR has been introduced in many other cancer types. NLR has been reported to be a negative prognostic factor in hepatocellular carcinoma, colorectal cancer and breast cancer (21, 24). Although both PLR and NLR can reflect prognosis, NLR is superior to PLR in predicting overall survival (29). The Glasgow prognostic score, like the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), is an inflammation-based prognostic score derived from peripheral blood-based inflammatory components. The Modified Glasgow Prognostic Score (mGPS) has been reported to be the only SIR-related prognostic biomarker independently associated with both DFS and OS in gastric cancer (7).

Several studies have also shown that inflammation-based scores are associated with prognosis in gastric cancer (25,26). PNR is an easily measurable, reproducible and inexpensive marker of subclinical inflammation. This suggests that the cytokine microenvironment provided by neutrophils contributes to tumor growth. Inflammation-based scoring systems are derived from peripheral blood-based inflammation components and have been proposed by various authors, but their clinical applications have not yet been used in routine practice and there is no consensus on optimal cut-off levels (27,28). In summary, these results suggest that components of inflammation are important triggers of tumor growth. According to Proctor, this is consistent with the 'seed and soil' nature of cancer growth (8).

The major limitation of our study is that it is observational and single-center, and the comparison of clinicopathological features of the tumor requires larger patient series. Before the clinical implications of proinflammatory markers as cancer markers, more prospective studies are required and there is a need to determine precise cut-off values and optimal limits. In particular, the NLR value has been reported to be a sensitive prognostic marker.

CONCLUSION

The ability to predict a patient's exact prognosis is critical for choosing the optimal treatment plan and follow-up strategies. Although tumor, node, metastasis (TNM) stage is the only reliable prognostic factor, heterogeneous clinical presentations are often observed even within the same tumor stage. Therefore, further studies should be performed to provide a more credible prognostic factor. As proinflammatory markers can be easily determined from a complete blood count, a potentially simple and inexpensive test can provide cancer prognosis.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Diyarbakır Gazi Yaşargil Training and Research Hospital Ethics Committee (Date: 30.12.2022, Decision No: 286).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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