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Original Article

The role of lymphocyte-monocyte ratio and platelet to lymphocyte ratio in predicting risk groups in gastrointestinal stromal tumors

Oguz Catal[1] · Bahri Ozer[1] · Mustafa Sit[1] · Songul Peltek Ozer[2]

[1]*Department of General Surgery, Bolu Abant Izzet Baysal University, Medical School, Bolu, Turkey*

[2]*Department of Pathology, Bolu AIBU Training and Research Hospital, Bolu, Turkey*

ABSTRACT

Aim: Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumors of the gastrointestinal tract. Armed Forces Institute of Pathology (AFIP) criteria which is the basis of our study, is also known as Miettinen's criterion is used in classification of GIST. Lymphocyte-monocyte ratio (LMR), and platelet lymphocyte ratio (PLR) have been shown as novel markers in chronic systemic inflammatory response, therefore, we aimed to study LMR levels of the subjects with moderate to high risk GIST and to compare to those in the subjects with low or very low risk GIST.

Methods: Thirty GIST patients who underwent surgery were retrospectively evaluated. Patients were divided into two groups according to the AFIP risk scoring system: the first group (group 1) included very low and low risk patients and the second group (group 2) included moderate and high risk patients. Inflammatory indicators; LMR and PLR of the groups were compared.

Results: LMR value was higher in Group 1 (5.25 ± 2.55) than the LMR of group 2 (2.92 ± 1.76). PLR value was significantly lower in group 1 (139.68) compared to the PLR of group 2 (185.04).

Conclusion: We think that LMR is effective in identifying low and very low risk patients compared to AFIP. From this point of view, we suggest that LMR can identify high and medium risk patients by excluding low and very low risk patients and may be an independent risk factor in GIST scoring systems.

Keywords: Gastrointestinal stromal tumors, lymphocyte monocyte ratio, AFIP risk score.

✉ *Dr. Oguz Catal*
Department of General Surgery, Bolu Abant Izzet Baysal University, Medical School, Bolu, Turkey
E-mail: otuzogur@gmail.com
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Introduction

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumors of the gastrointestinal tract. The incidence of GIST is 14-20 per ml [1]. GIST are myenteric plexus small settled a kit positive cell population Cajall originate from cell neoplasms [2]. The main cause of GIST is presence of abnormal tyrosine protein kinase, which is known as CD117 that causes uncontrolled growth of gastrointestinal cells. GIST can occur anywhere in the gastrointestinal tract, such as, gastric (50-60%) and small bowel (30-35%), and less frequently in the colon and the rectum (5%). It is very rare (1%) in esophagus [3] .

Although it may occur at any age, advanced age is a risk factor for GIST. The average age reported in previous studies is 60 years.

Different risk classification systems are used in GIST. Armed Forces Institute of Pathology (AFIP) criteria, which is the basis of our study, is also known as Miettinen's criterion is useful in risk stratification in GIST [1].

Virchow stated that there is a connection between cancer and inflammation and that lymphocytic infiltrate in the areas of chronic inflammation may constitute the origin of cancer [4]. Indeed, chronic inflammation has been documented in different types of cancer [5]. Since the systematic inflammatory response (SIR) indirectly reflects the host immune status, it probably reflects the prognosis of various malignancies, including gastrointestinal cancers. Alternatively, the lymphocyte-monocyte ratio (LMR), which is the ratio of monocyte count in peripheral blood to lymphocyte count, has been shown as a novel marker of chronic SIR. This is because monocytes, monocytes-derived macrophages and lymphocytes play primary role in chronic inflammation rather than acute inflammation [6]. Some studies have reported that LMR was a prognostic factor for disease-free survival and overall survival in colorectal cancer [7] and pancreatic cancer [8].

In this study, we investigated the effect of hemogram parameters obtained from preoperative blood count tests of subjects with GIST in predicting low and very low risk GIST patients according to AFIP scoring.

Materials and Methods

Thirty patients with gastrointestinal stromal tumors who underwent surgery in the general surgery clinic of Bolu Abant Izzet Baysal University (BAIBU) Medical Faculty between 2012 and 2018 were retrospectively evaluated. The study was approved by BAIBU, Clinical Research Ethics Committee, decision number 2016/369, dated 01/06/2016. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration, as revised in 2000.

When the files were retrospectively examined, hemogram values were included in the study seven days before the operation date. Preoperative hemogram parameters white blood cells (WBC), neutrophil, lymphocyte, monocyte, and platelet values were recorded. The ratio of neutrophil to lymphocyte ratio (NLR) by the ratio of neutrophil count to lymphocyte count, and lymphocyte monocyte ratio (LMR) by ratio of lymphocyte count to monocyte count; the ratio of platelet count to lymphocyte count provided the platelet lymphocyte ratio (PLR); monocyte leucocyte ratio (MWR) was obtained by ratio of monocyte value to leukocyte value.

Postoperative pathology specimens of the patients were examined. The patients were categorized according to the AFIP [9, 10] risk classification in the pathology specimens. This criterion also considers the anatomical region of the tumor. According to these criteria, in gastric GIST ≤10 cm and 5 mitoses per 50 HPF have a low risk for metastasis, however 50 HPF >5 mitosis and> 5 cm diameter have a high risk for metastasis in gastric GIST. On the other hand, regardless of mitotic rate, all intestinal GIST greater than 5 cm are at least moderately at risk for metastases, and the risk of metastasis is known to be high in all> 5 mitoses per 50 HPF. Intestinal GIST ≤5 mitosis per 50 HPF and ≤5 cm metastasis risk is low. Immunohistochemical features in the pathology report were removed and their microscopic and macroscopic features were examined. Thirty patients were divided into two groups

according to the AFIP risk scoring system: the group 1 included very low and low risk patients and the group 2 included moderate and high risk patients. Inflammatory indicators LMR, PLR and MWR were compared between the groups. Since the number of cases is limited, all patients were included in the study. There were no excluded cases.

Statistical analyses

Kolmogorov-Smirnov test was used to check whether the variables were normally distributed or not. While t-test was applied for variables showing normal distribution; Mann-Whitney U tests were used for the analysis of variables not showing normal distribution. The receiver-operating characteristic (ROC) curve was used to identify the optimal cut-off values of statistically significant variables that identified the low-risk patient group. All the analyses were performed with the Statistical Package for Social Sciences 25.0 for Windows (SPSS Inc., Chicago, Illinois, USA) and the results with a level of $p < 0.05$ were considered to be significant.

Results

The demographic information and clinicopathological characteristics of 30 patients with GIST are shown in Table 1. The age of the study population was 65.63 (29-86) years. The age of the group 1 was 65.21 (41-85) years and the age of the group 2 was 66 (29-86) years *($p = 0.75$)*. According to gender, 13 of 30 patients were female and 17 were male. It was seen that 8 of the patients in the group 1 were male and 5 of them were female and 12 of the patients in the group 2 were male and 5 of them were female. There was no significant difference between groups according to the gender of the subjects *($p = 0.078$)*.

Table 1. The demographic information and clinicopathological characteristics of 30 patients with GIST.

Variable	**n (%)**
Median age (range, yr)	66 (29-86)
Gender	
Female	13 (43)
Male	17 (57)
According to AFIP classification	
Very Low Risk	5 (17)
Low Risk	8 (27)
Moderate	7 (23)
High Risk	9 (30)
Insufficient information	1 (3)
Tumor size (cm)	
≤2	3 (10)
>2 and ≤5	7 (23)
>5 and ≤10	11 (37)
>10	9 (30)
Tumor location	
Stomach	18 (60)
Jejunum/ileum	12 (40)
colon and rectum	
Mitosis	
≤5/50HPFs	22 (73)
>5/50HPFs	8 (27)
Cellular Type	
Fusiform Cell	18 (60)
Mixed	10 (33)
Epithelioid	2 (7)
Necrosis	
Yes	12 (40)
No	18 (60)
Ulcer	
Yes	12 (40)
No	18 (60)
Bleeding	
Yes	11 (37)
No	19 (63)

When the localization of GIST was examined, it was found that 18 cases were located in the stomach, 12 cases were located in the jejunum / ileum, colon and rectum. One of the patients in Group 1 had GIST located in the small intestine, 12 of them were in the stomach, 11 of the patients in group 2 were located outside the stomach, and 6 of them were located in the stomach.

LMR value was significantly higher in group 1 patients (5.25 ± 2.55) than group 2 patients (2.92 ± 1.76) in the preoperative hemogram parameters *(p = 0.006)*. PLR of Group 1 (139.68) (77.15-370) *(p=0.016)* was significantly lower than the PLR of Group 2 (185.04) (104.3-430.6) (Table 3). In addition, MWR of group 1 (0.05) (0.03-0.16) was significantly lower than the MWR of group 2 (0.08) (0.04-0.17) *(p = 0.014)*.

Table 2. Comparisons of preoperative blood test parameters in the groups.

Variables	Group 1 (n=13)	Group 2 (n=17)	*p*
Neutrophil	4.34(2.29-9.08)	4.85(2.49 -0.74)	*0.676*
LMR	5.25(±2.55)	2.92 (±1.76)	***0.006***
MWR	(0.05) (0.03-0.16)	(0.08) (0.04-0.17)	***0.014***
NLR	4.23 (1.25 - 28.3)	3.84 (1.30 – 8.84)	*0.098*
PLR	139.6 (77 - 370)	185.04 (104 - 430	***0.016***

LMR: lymphocyte monocyte ratio. MWR: monocyte leucocyte ratio. NLR: neutrophil to lymphocyte ratio. PLR: platelet lymphocyte ratio.

ROC analysis was performed to determine the cut-off values of significant LMR values. In patients with GIST, the LMR value above 1.609 level (Figure 1) can be predicting with 84% sensitive and 77% specifically the low or very low risk patients. Area value under the curve was found to be AUC: 0.765.

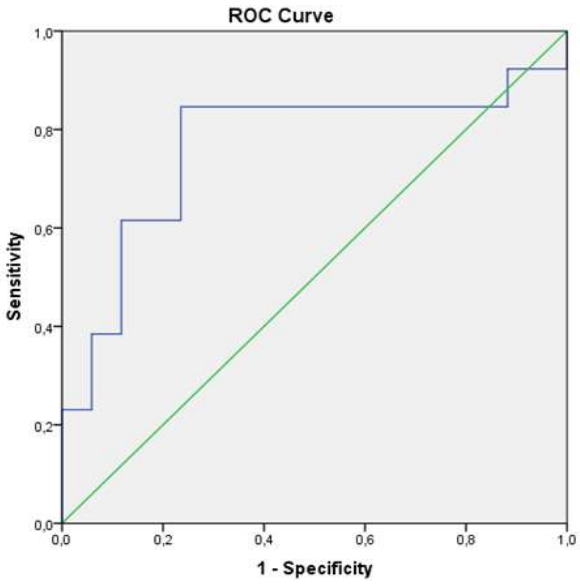

Figure 1. ROC analysis of lymphocyte monocyte ratio (LMR) value.

Discussion

In this study, LMR was found to be significantly higher in group 1(low and very low-risk GIST) patients compared to group 2 (moderate and high-risk GIST) patients. In addition, LMR value above 1.609 had 84% sensitivity and 77% specificity for low and very low-risk GIST patients. Studies in GIST have focused on determining recurrence or prognosis. Discussions have suggested scoring systems or nomograms to better predict the risk and prognosis of recurrence. These scoring systems or nomograms include mitotic activity, tumor size, and tumor site [10-12] , which are independent prognostic factors. We also used the AFIP scoring system in our study.

Gastric GIST have a lower risk of relapse than non-gastric GIST cases [3, 11]. In our study, tumor site was significantly different between groups 1 and 2. The rate of extra-gastric GIST was higher in the patients with moderate and high risk group *(p = 0.002)*.

The use of these criteria aims to identify patients who may benefit from adjuvant

systemic therapy to reduce recurrence. In our study, the AFIP scoring which we evaluated also provides guidance in predicting recurrence after surgery in patients. Patients with low-risk scoring systems usually have positive outcomes and do not require adjuvant therapy [3].

Recent studies aim to predict the prognosis of GIST with inflammatory indicators in blood parameters. Kargin and colleagues [13] evaluated the relationship between elevated blood neutrophil-lymphocyte ratio and prognosis in GIST patients. The authors found that this rate increased significantly in high-risk patients and was associated with short survival [13]. In our study, we found that high LMR values predict low-risk GIST patients.

Studies have shown that systemic inflammatory response and platelets, especially NLR ratio, dNLR (derived Neutrophil Lymphocyte) ratio, LMR ratio and PLR ratio, can predict important clinical outcomes in a wide range of cancers. PLR is also predictive of poor diabetic control in patients with type 1 diabetes mellitus, characterized by low inflammatory burden [14]. Chronic inflammation occurs locally in solid cancers and contributes to tumor growth and progression [15]. LMR, esophageal squamous cell carcinoma [16] and stomach [17], colorectal [18] cancers such as cancers in patients with advanced T stage prognostic importance has been made in studies. In addition, LMR was found to correlate primarily with local cancer progression rather than metastasis and was associated with T stage, similar to other inflammatory markers, but not always with N stage [6]. In the study of LMR in soft tissue sarcomas undergoing curative surgery, it was shown to be an independent prognostic factor in patients [6, 19]. In our study, we found that high LMR values indicate low and very low risk patients in the AFIP scoring system.

In the light of the above statements, the use of adjuvant therapy in low-risk and very low-risk GIST patients was found to be unnecessary, but adjuvant therapy had a place in moderate and high-risk GIST patients. These risk groups can be determined by scoring systems. In our study, we found that the inflammatory indicators LMR, PLR and MWR obtained from preoperative blood values were compatible with AFIP. LMR, PLR and MWR values were statistically significant in predicting low and high risk patients according to AFIP interrogation system. When we evaluate ROC analysis, LMR, PLR and MWR can predict the low and very low risk patients in AFIP scoring system and we just found that the curve of LMR is significant.

The limitation of our study was the limited number of patients. Another limiting factor was the retrospective study. The study should be supported with larger patient series. However, we think that the number of our studies for a rare disease such as GIST will not be underestimated.

Conclusions

As a result of our study, we think that LMR is effective in identifying low and very low risk patients compared to AFIP. From this point of view, we suggest that LMR can identify high and medium risk patients by excluding low and very low risk patients and may be an independent risk factor in GIST scoring systems. We think that low and very low risk patients who do not require adjuvant therapy according to AFIP scoring can be predicted by determining LMR values in the preoperative period.

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ORCID iD of the author(s)

Oguz Catal / 0000-0002-4067-251X
Bahri Ozer / 0000-0002-4326-2102
Mustafa Sit / 0000-0002-7475-7298
Songul Peltek / 0000-0001-7334-219X

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