

Research Article

Evaluation of PIV Score as a Predictor Biomarker for Pathologically Proven Intermediate-High Risk Gastric Gastrointestinal Stromal Tumors

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Abstract

Objectives: Pan-immune-inflammation value (PIV) score has been started to be used as a prognostic tool in cancer patients trendly in recent years. In this study, we aimed to evaluate the PIV score in patients with pathologically- proven intermediate-high risk gastric GIST to guide adjuvant therapy and to get better prognosis.

Methods: Patients followed up by Medical Oncology clinic with a diagnosis of gastric GIST were evaluated retrospectively.

Results: A total of 41 patients with a diagnosis of gastric GIST were examined. When the tumors were analyzed according to the AFIP prognostic model, 23 patients were identified as intermediate-high-risk tumors. According to the modified NIH model, intermediate-high risk tumors were noted in 26 patients. According to AFIP prognostic model, PIV scores were not different between risk groups ($p=0.27$). When the patients were classified according to modified NIH model, the platelet counts in patients with intermediate-high risk tumor were significantly higher than the other patients group ($p=0.01$). In addition, PIV scores were significantly higher in patients with intermediate-high risk tumor than other patients ($p=0.03$).

Conclusion: This study displayed that PIV score can be useful as a risk predictor in patients with gastric GIST. Future prospective analysis are needed to support our results.

Keywords: Gastric GIST, PIV score, modified NIH

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Gastrointestinal stromal tumors (GIST) constitutes 1–3% of all gastrointestinal cancers that seems as subepithelial neoplasms.^[1] Gastric GIST are most common subtypes of these neoplasms and they represents 50-60% of GIST.^[2,3] According to NCCN (National Comprehensive Cancer Network) guidelines, diagnosis of gastric GIST, found as incidentally or after using imaging methods in symptomatic cases, are clarified by evaluation of histopathologic and immunohistochemistry results and sometimes by some molecular alterations if can be analysed.^[4] Endoscopy with bi-

opsy, computed tomography (CT), abdominal ultrasound, magnetic resonance imaging (MRI) and endoscopic ultrasound (EUS) with fine needle biopsy are among the imaging methods that helpful in diagnosis of GIST.^[5] After diagnosis, surgical resection is the main treatment of choice in primary localized gastric GIST but tumors with size of less than 2 cm may be followed up or resected endoscopically.^[6] Gastric GIST are known to be associated with better survival outcomes than other GIST.^[7] Based on the characteristics of the primary tumor, the disease may differ in prognosis. Pa-

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tients with a diagnosis of GIST after surgery, are evaluated for prognosis. There are some models related to prognosis in patients with GIST. Armed Forces Institute of Pathology (AFIP) on GIST and National Institutes of Health (NIH) consensus, modified NIH are one of these prognostic models.^[7-9] In these models, tumor size and mitotic rate are distinctive prognostic factors to predict aggressiveness of the tumor. Furthermore, tumor rupture is stated as a prognostic factor in a modified version of the NIH consensus. Based on these models, patients are usually categorized as no risk, low risk, intermediate risk, or high risk for recurrence. National Comprehensive Cancer Network guidelines recommends adjuvant imatinib for patients with intermediate or high risk for recurrence in case imatinib-sensitive mutation is detected during analysis.^[4]

Pan-immune-inflammation value (PIV), newly discovered inflammation biomarker, is calculated using neutrophil, platelet, monocyte and lymphocyte counts.^[10] Firstly, Fuca et al. highlighted that PIV may be an important predictor of survival outcomes in patients with metastatic colorectal cancer.^[11] Then many studies on different types of malignancies have been conducted and the association between PIV score and cancer prognosis have been examined.^[12-16] Şahin et al. showed pre-treatment PIV levels may be as a predictor for pathological complete response and survival in breast cancer patients that received neoadjuvant chemotherapy.^[12] Furthermore, Karadağ et al emphasized that PIV score can be valuable prognostic biomarkers in patients with a diagnosis of hepatocellular carcinoma.^[17] Breast, lung, liver, colon, rectum, skin are among the most common origin of malignancies that are examined about association with PIV score.^[10-17]

This report is aimed to evaluate the PIV score in patients with pathologically- proven intermediate-high risk gastric GIST.

Methods

Patient Population

The patients being followed up by our Medical Oncology clinic with a diagnosis of gastric GIST were evaluated retrospectively. Fifty-eight patients with a diagnosis of pathologically proven gastric GIST were further analyzed. Patients met the inclusion criteria were examined in the analysis. Exclusion criterias were presence of secondary malignancies, diagnosis of comorbidities or medications that might be associated with inflammation as infections, steroid usage, romatological disease, chronic obstructive pulmonary disease. Also patients with inadequate data were not analyzed in the study. As a result total of 41 patients were enrolled in the study.

Data Collection

Demographic and clinical characteristics of the patients such as age, gender, stage of the disease, history of operation and also preoperative total blood count parameters including neutrophil, platelet, monocyte and also lymphocyte counts were recorded from hospital data retrospectively.

The Pan-immune-inflammation value was calculated as following equation: $[\text{neutrophil count (10}^3/\text{mL)} \times \text{platelet count (10}^3/\text{mL)} \times \text{monocyte count (10}^3/\text{mL)}] / \text{lymphocyte count (10}^3/\text{mL)}$.

Statistical Analysis

Statistical examination was conducted with the Statistical Package for the Social Sciences software version 23 (SPSS). Quantitative variables such as age, parameters of total blood count and PIV score were stated with median values (min-max), qualitative variables such as gender, histopathological characteristics of the tumor were expressed as proportions. To determine the overall survival (OS) and progression free survival (PFS) of the patients, Kaplan-Meier method was used. The Mann-Whitney U test was used to compare parameters of total blood count and PIV score. The cut off for PIV scores in predicting presence of intermediate-high risk were determined via ROC (Receiver Operating Characteristics) curve analysis. The p value <0.05 is accepted as a statistically significant during examination.

Results

A total of 41 patients with median aged of 67 years (28-87) were examined in the study. Baseline characteristics of the patient population are demonstrated in Table 1. Most of the patients were female (56.1%). Antrum was the most common found localization of the tumors (31.7%). Other tumor localizations were as follows; corpus (29.5%), cardia (26.8%), fundus (22%). In the histopathological examination, the spindle cell histology was the most common seen cell type (80.5%). When the tumor size was examined, the common pathologically measured tumor sizes were 2.1-5 cm and 5.1-10 cm. As well as the tumors with mitotic index ≤ 5 per high-power field were more common, tumor rupture was seen in only 2 patients (4.9%).

The tumors were examined according to AFIP and modified NIH prognostic models during pathological examination. Based on AFIP model, 17 tumors (41.5%) were determined as high risk and 6 tumors (14.6%) as intermediate risk. While 12 tumors (29.3%) were noted as low risk, 6 tumors (14.6%) were stated as very low risk. According to modified NIH, high risk tumors were the most common seen risk groups. (20 patients-48.8%). Intermediate risk tumors were noted

Table 1. Baseline characteristics of the patients and the pathological features of tumors

Parameters	Results
Age at diagnosis (years)	59 (22-79)
Female gender (n-%)	23 (56.1)
Gastric localization (n-%)	
Cardia	11 (26.8)
Fundus	9 (22)
Corpus	8 (19.5)
Antrum	13 (31.7)
Histology/cytology type (n-%)	
Spindle cell	33 (80.5)
Epithelioid	2 (4.9)
Mixed spindled-epithelioid	6 (14.6)
Tumor size (cm)	
≤2	3 (7.3)
2.1-5	14 (34.1)
5.1-10	14 (34.1)
>10	10 (24.4)
Mitotic index (per 50 HPFs)	
≤5	25 (61)
>5	16 (39)
Tumor rupture (n-%)	
No	39 (95.1)
Yes	2 (4.9)
Ki-67 index (%)(n-%)	
<5	27 (65.9)
≥5	14 (34.1)
Prognostic models	
AFIP (n-%)	
Very low risk	6 (14.6)
Low risk	12 (29.3)
Intermediate risk	6 (14.6)
High risk	17 (41.5)
Modified NIH (n-%)	
Very low risk	5 (12.2)
Low risk	10 (24.4)
Intermediate risk	6 (14.6)
High risk	20 (48.8)

AFIP: Armed Forces Institute of Pathology; NIH: National Institutes of Health.

in 6 patients (14.6%), low risk tumors in 10 patients (24.4%) and very low risk tumors in 5 patients (12.2%).

Comparison total blood count parameters of the patients according to risk status that determined using AFIP and modified NIH prognostic models are shown in Table 2. When the patients were classified as risk groups according to AFIP model, platelet counts and PIV scores were not different between the groups. But, the patients were classified according to modified NIH model, the platelet counts in patients with intermediate-high risk tumor were significantly higher than the other patient groups ($p=0.01$). In addition, PIV scores were significantly higher in patients with intermediate-high risk tumor than other patients ($p=0.03$). The cut off value for PIV score in predicting intermediate-high risk disease was stated as 669.3 after ROC analysis ($p=0.03$). The median follow-up period of the patients was 8 years (0.3-15.6). Eleven patients (26.8%) were died during follow up period. OS and PFS values of the patients were still immature.

Discussion

This report demonstrated that PIV score that calculated preoperatively might predict the intermediate-high risk of gastric GIST. Definition of risk category is important because it is known that use of imatinib as a adjuvant therapy has been shown to improve overall survival significantly.^[18] This was the first report that evaluate the association PIV score as risk estimator in gastric GIST patients.

Gastrointestinal stromal tumors are rare tumors that originates from gastrointestinal tract.^[3] These tumors are equally seen in both genders with a median age at diagnosis between 65 and 69 years.^[19, 20] In our study, median aged at diagnosis was 59 years and there was slightly higher tendency for females (56.1%). Concordance of these findings with literature supports that our report may reflect the real-world experience.

Table 2. Comparison total blood count parameters and PIV score according to prognostic models

	According to AFIP model			According to Modified NIH model		
	Patients with very low-low risk tumor (n=18)	Patients with intermediate-high risk tumor (n=23)	p	Patients with very low-low risk tumor (n=14)	Patients with intermediate-high risk tumor (n=27)	p
Neutrophil count ($10^3/ml$)	6.62 (3.2-14.8)	6.76 (2.91-12.2)	0.83	6.08 (3.2-14.8)	6.89 (2.91-12.2)	0.67
Platelet count ($10^3/ml$)	221 (123-385)	312 (162-463)	0.05	214 (123-372)	312 (162-463)	0.01
Monocyte count ($10^3/ml$)	0.64 (0.36-1)	0.63 (0.39-1.2)	0.84	0.6 (0.36-1)	0.7 (0.39-1.2)	0.48
Lymphocyte count ($10^3/ml$)	1.45 (0.4-3)	1.11 (0.26-3.38)	0.49	1.78 (0.4-3)	0.96 (0.26-3.38)	0.09
PIV score ($10^3/ml$)	449.4 (108.8-7987.3)	1152.8 (188.9-4910)	0.27	410.9 (108.8-2598.1)	1597.8 (188.9-7987.3)	0.03

AFIP: Armed Forces Institute of Pathology; NIH: National Institutes of Health; PIV: Pan-immune-inflammation value.

All GIST have a potential to develop metastasis. After surgical resection of tumors, use of tyrosine kinase inhibitors like imatinib is emphasized for better prognosis by authorities.^[4, 21] So, prediction of recurrence and metastasis is important and it is determined using prognostic models.^[7, 22] Among prognostic models, The AFIP and modified (NIH) are the most common used models^[7,8] that take into account primary tumor size, mitotic rate, tumor site, and also tumor rupture. In our study we used both models to predict risk. Where as according to AFIP model, 17 tumors (41.5%) were determined as high risk and 6 tumors (14.6%) as intermediate risk, according to modified NIH, 20 tumors (48.8%) were noted as high risk tumors and 6 tumors (14.6%) as intermediate risk. The difference in percentages of risk classification can be attribute to some different criterias such as tumor rupture.

Using easily accessible and economical biomarkers for predicting recurrence and metastasis risk is crucial. PIV score is one of them that is derived from hypothesis of relationship between inflammation and cancer. As known, inflammation is related to cancer promotion and progression.^[23] Platelets, monocytes, neutrophils and lymphocytes have important role in tumor pathogenesis. While activated platelets secrete many growth factors that facilitate tumor invasion, macrophages derived from monocytes have effect on angiogenesis, invasion, and also on immunosuppression.^[24-26] In addition, neutrophils are associated with tumor growth by secretion of chemokines and reactive oxygen species.^[27, 28] The lymphocytes also play an important role in anti cancer immunity as a driver.^[29] So, determining of uncontrolled inflammation can be crucial biomarker to predict cancer prognosis and to plan effective therapy.

In the literature, it is seen that many ratios were examined for accuracy and efficacy in cancer prognosis and treatment such as neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio.^[30, 31] In our study, we examined the PIV score that calculated as neutrophil count ($10^3/\text{mL}$) \times platelet count ($10^3/\text{mL}$) \times monocyte count ($10^3/\text{mL}$) / lymphocyte count ($10^3/\text{mL}$). When the patients were classified as risk groups according to modified NIH model, the platelet counts in patients with intermediate-high risk tumor were significantly higher than the other patient group. As stated in the literature, platelets play a crucial role in tumor invasion using growth factors; so this finding supports that this patients group should be follow up for recurrence and metastasis closely.^[24]

Pan-immune-inflammation value is examined in many studies with heterogenous patient population.^[10-17] These studies emphasized that PIV score can be used prognostic marker in many cancer types. Differently, Corti et al showed that PIV score should be monitored dynamically during treatment with immune checkpoint inhibitors to evaluate

response and survival outcomes in patients with colorectal cancer.^[14] PIV scores were significantly higher in patients with intermediate-high risk tumor than other patients in our study. This finding can be interpreted that PIV score can be used in this patient population for predicting the risk of recurrence/metastasis.

In the studies, different cut off values were stated for PIV score in heterogenous population.^[32] In our analysis, the cut off value for PIV score in predicting intermediate-high risk disease was stated as 669.3 after ROC analysis.

Since the modified NIH prognostic model includes tumor rupture, it may reveal the risk of recurrence more effectively in this patient group. In our study, the PIV score was significantly higher in the intermediate-high risk group according to modified NIH. No risk was found among the risk groups according to AFIP model. Although the number of patients is small, the modified NIH risk model may be a better prognostic indicator. Adding the PIV score to the modified NIH model may contribute to determining risk classifications.

There are some limitations of the study. It has a retrospective nature. Also, the study has compromised single center experience. Due to these factors, the study population could not have revealed the real-life results. Furthermore, missing data is another problem of the studies with retrospective design. In addition, the median OS and PFS values could not be reached in the patients yet. Therefore, we could not evaluate the relationship between PIV score, PFS and OS. As a result, studies with larger population and prospective design may provide more realistic results.

Conclusion

This study showed that PIV score might give information for estimating intermediate-high risk of gastric GIST patients. The PIV score may contribute to classification in the modified-NIH model. It can be preferred due to easy accessibility and cost issues. This report was the first evaluating the risk estimation of PIV score for patients with gastric GIST. Further prospective analysis are needed to support our findings.

Disclosures

Ethics Committee Approval: The study protocol was approved by the ethics committee of Gazi University Faculty of Medicine (2023-1018).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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