Prognostic value of Prognostic Nutritional Index (PNI) for 5-year recurrence-free survival in surgically resected gastrointestinal stromal tumors

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Mehmet Esat Duymus*, Mustafa Ugur*, Mehmet Burak Dal*, Ersin Rasim Aslan*, Yasemin Donmez*, Tumay Ozgur**, Ilke Evrim Secinti**, Yusuf Murat Bag***, Muhyittin Temiz*

**Department of General Surgery, Mustafa Kemal University, Hatay, Turkey*
***Department of Pathology, Mustafa Kemal University, Hatay, Turkey*
****Department of General Surgery, Division of Gastrointestinal Surgery, Van Training and Researcher Hospital, Van, Turkey*

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BACKGROUND: *Recent studies have investigated the role of neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic inflammation index (SII), and prognostic nutritional index (PNI) on prognosis for various malignancies. However, the value of these markers in determining the prognosis for gastrointestinal stromal tumors (GIST) remains controversial. We investigated the effect of NLR, PLR, SII, and PNI on 5-year recurrence-free survival (RFS) in patients with surgically resected GIST.*
MATERIALS AND METHODS: *We retrospectively analyzed patients (n=47) who had undergone surgical resection for primary, localized GIST at a single institution between 2010 and 2021. The patients were divided into two groups according to the recurrence status in the 5-year period as 5-year RFS(+) (patients with no recurrence (n=25) and 5-year RFS(-) (patients with recurrence (n=22) groups.*
RESULTS: *In univariate analyses, Eastern Cooperative Oncology Group Performance Status (ECOG-PS), tumor localization, tumor size, PNI, and risk category were significantly different between the RFS(+) and RFS(-) groups while NLR, PLR, SII were not. Multivariate analyses revealed that only the tumor size (HR =5.485, 95% CI: 0.210-143.266, p=0.016), and PNI (HR= 112.020, 95% CI: 8.755–1433.278, p<0.001) were independent prognostic factors for RFS. The patients with a high PNI (≥46.25) had a higher 5-year RFS rate than the patients with low PNI (<46.25) (95.2% to 19.2%, p<0.001).*
CONCLUSION: *A higher preoperative PNI is an independent positive predictor for 5-year RFS for patients with surgically resected GIST. However*, NLR, PLR, and SII have no significant effect.

KEY WORDS: GIST, Prognostic Nutritional Index, Prognostic Marker

Introduction

Gastrointestinal stromal tumor (GIST) is mesenchymal neoplasm of the digestive tract that origin from cajal cells. GIST is most frequent tumor among mesenchymal tumors accounts for 0.1% to 3% of all gastrointestinal malignancies. It most often occurs in the stomach followed by the small intestine, intraabdominal region, colon-rectum, soft tissue, esophagus, and pancreas [1].

Treatment methods are limited because GIST has no sensitivity to chemotherapy or radiotherapy, therefore curative surgical resection is the main therapy for localized disease. Despite the tyrosine kinase inhibitor (imatinib mesylate) which greatly improves survival rates, the

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Correspondence to: Mehmet Esat Duymus, MD, Department of General Surgery, Mustafa Kemal University, Alahan, 31060, Antakya, Hatay, Turkey (e-mail: esatduymus@hotmail.com)

recurrence of surgically resected GIST is common, especially in high-risk cases [2]. The 5-year recurrence rate is 50% - 90% in the postoperative period [3].
Currently, the Armed Forces Institute of Pathology (AFIP), National Institute of Health (NIH) and modified NIH criteria are being used to predict prognosis and recurrence. Pathological data are used to calculate these risk classification systems [4]. Recently, expression assessed by immunohistochemistry such as Ki-67 monoclonal antibody have also been suggested to predict prognosis and recurrence [5].
However, resected tumor specimens are required to evaluate these parameters. Therefore, there is a need for novel biomarkers that should be easily achieved, non-invasive, cost-effective, and can be used in the preoperative period to determine the prognosis and to decide on neoadjuvant therapy for GIST patients. Malnutrition is common in patients with undergone oncological surgery. It is also known that nutritional status is an important factor in cancer prognosis [6]. Prognostic nutritional index (PNI) obtained from blood laboratory tests (albumin value and lymphocyte count) has been found as an important prognostic marker in many cancers, such as gastric cancer [7], pancreatic cancer [8], and colorectal cancer [9]. Similarly, the systemic inflammatory index (SII) obtained from platelet, lymphocyte, and neutrophil counts such as lung [10], liver[11], and esophagus [12].
Although there are studies showing the prognostic value of PNI and SII in solid tumors, there is no consensus regarding the results in mesenchymal tumors. In this study, we investigated the effect of NLR, PLR, SII, and PNI on 5-year recurrence-free survival (RFS) in patients with surgically resected GIST.

Materials and Methods

Patients

The data of the patients with localized primary GIST who underwent curative resection (R0) between January 1, 2010, and December 31, 2020, were obtained from the hospital electronic database and pathology department.
The inclusion criteria were as follows: (1) patients older than 18 years; (2) patients with complete medical, laboratory, and survival records; (3) patients with no neoadjuvant therapy; (4) patients who treated with adjuvant imatinib after surgery.
The exclusion criteria were as follows: (1) patients under the 18 years; (2) incomplete follow-up data; (3) synchronous and/or metastatic disease; (4) patients with no curative resection after biopsy; (5) patients with R1 and R2 resection; (6) changes in diagnosis in the final immunohistochemistry; (7) patients with active connective tissue and/or infective diseases; (8) patients who treated with albumin and/or anticoagulants within 3 months before surgery. Computed tomography (CT) and/or magnetic resonance imaging (MRI) were used for preoperative staging.
In the postoperative follow-up, CT and/or MRI and/or positron emission tomography/CT (PET/CT) imaging were used for the diagnosis of recurrence. This study was approved by the Ethics Committee of Mustafa Kemal University (Date: 17/02/2022; IRB: 35).

Data Collection

The Clinicopathological data included age, sex, Eastern Cooperative Oncology Group Performance Status (ECOG-PS), tumor localization, tumor size, risk classification, mitotic index (number of mitoses/50 high-power fields), necrosis, Ki- 67, preoperative absolute neutrophil, platelet, lymphocyte counts and albumin levels. Blood samples were collected as close as possible to the date of the planned operation day (mean: 7.81 ± 4.65 days). There was no sign of infection at the time of blood sample collecting from patients.
The neutrophil-to-lymphocyte ratio (NLR) was calculated as absolute neutrophil count (10^9/L) divided by absolute lymphocyte count (10^9/L). The platelet-to-lymphocyte ratio (PLR) was calculated as absolute platelet count (10^9/L) divided by absolute lymphocyte count. PNI was calculated as 10 × serum albumin (g/dL) + 5 × absolute lymphocyte count (10^9/L). SII was calculated as absolute neutrophil count x absolute platelet count / absolute lymphocyte count.
Tumor histology was evaluated by a pathologist with expertise in GIST. Immunohistochemical staining was performed on formalin-fixed, paraffin-embedded tumors using standard protocols as previously described [13]. GIST histopathologic diagnostic criteria were the examination of the cell morphology, immunohistochemical staining for CD117 and KIT protein expression. AFIP criteria were used for risk classification [4].

Follow-Up

After surgery, the patients were followed up to evaluate tumor recurrence or distant metastasis every 3 months in the first year, every 6 months in the next two years, and annually thereafter. The follow-up deadline was December 21, 2021. CT or MRI were used in the follow-up. Endoscopy and PET/CT scanning were added if necessary.
RFS was calculated as the time from the date of surgery to the date of tumor recurrence or metastasis. The patients were divided into two groups according to the recurrence status in the 5-year period as 5-year RFS(+) (patients with no recurrence) and 5-year RFS(-) (patients with recurrence) groups.

Statistical Analysis

The IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA) was used for statistical analyses. The Kolmogorov-Smirnov test was performed for assessing the normality of the distribution of numerical variables. The normally distributed numerical variables were expressed as mean ± standard deviation (SD) and were analyzed by using the Student's t-test, while the non-normally distributed numerical variables were expressed as median (minimum-maximum) and were analyzed by using the Mann-Whitney U test. The categorical variables were expressed as frequency (percentages) and were analyzed by using the Chi-Square test or the Fisher's exact test where appropriate. Receiver operating characteristics (ROC) curves were used to analyze the optimal cut-off value of numerical variables, which were found to be significantly different after groups comparisons and the area under the curve (AUC), 95% confidence interval (CI), specificity, sensitivity were also calculated. Univariate and multivariate Cox regression analyses, including variables with p <0.1 in two groups comparisons or variables that may be clinically relevant, were performed to determine the independent prognostic factors for RFS. The results were given as Hazard ratios (HR), 95% CI, and p values. The Kaplan-Meier analysis and the log-rank test were used to analyze and compare the RFS. A two-sided p-value <0.05 was considered significant.

Results

Clinicopathological Characteristics

Of the 182 patients identified from the data, 135 were excluded not meeting the inclusion criteria and/or duplicated records. The flowchart of patients' selection process is shown in (Fig. 1).

The mean age of 47 patients was 58.64 ± 15.2 years. Among them, there were 21 (44.7%) male and 26 (55.3%) female. The most common localization was stomach 20 (42.6 %), followed by small bowel 13 (27.6%), soft tissue and mesentery 11 (23.4%), and colon-rectum 3 (6.3%).

(Table I) shows the clinicopathological features of the entire study group and subgroups classified by 5-year RFS. The ECOG-PS score was significantly lower in the 5-year RFS(+) group than 5-year RFS(-) group (p=0.029). Tumors with gastric localization were significantly more in the 5-year RFS(+) group than 5-year RFS(-) group (p=0.010).

There was a significant difference between the groups in terms of tumor diameter and risk category (p=0.018 and p=0.004; respectively). PNI was significantly higher in the 5-year RFS(+) group than the 5-year RFS(-) group (p<0.001). There was no significant difference between the two groups in terms of NLR, PLR, and SII (p=0.564, p=0.172, p=0.337, respectively).

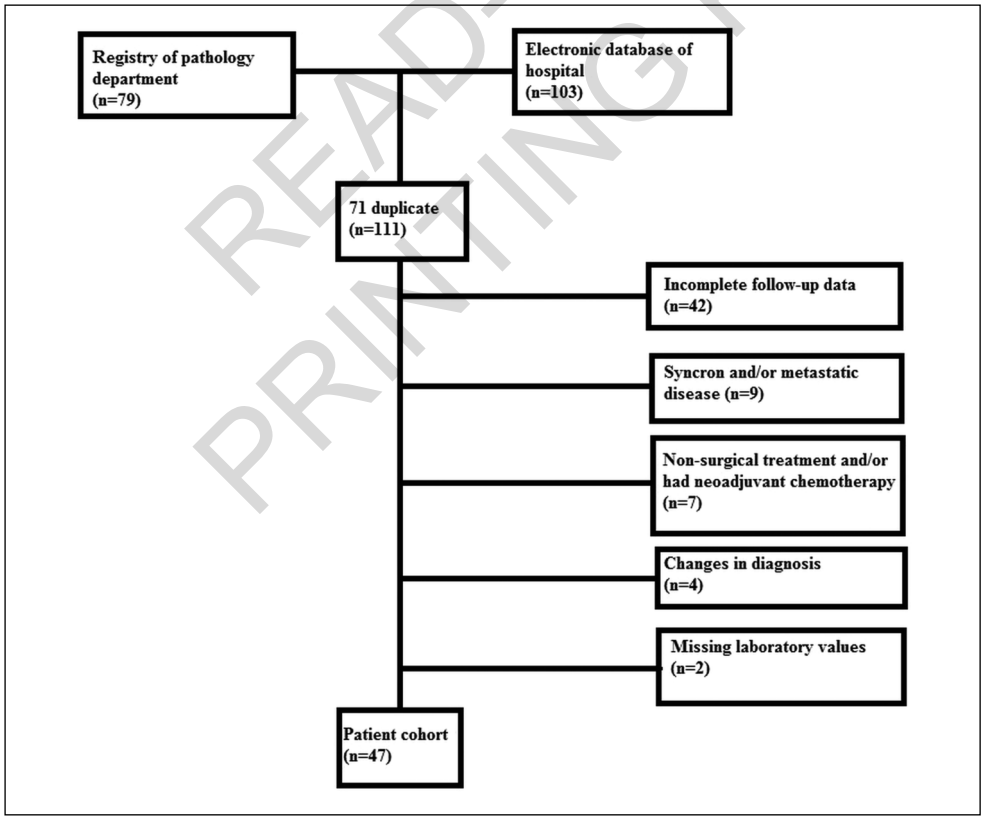

Fig. 1: The flowchart of patients' selection process.

Table I - *Results and comparisons of clinicopathological features of the entire study group, 5-year RFS(+) and 5-year RFS(-) subgroups .*

	Study group (n=47)	5-year RFS (+) group (n=25)	5-year RFS (-) group (n=22)	P value
Age (years)	58.64 ± 15.2	54.76 ± 14.03	63.05 ± 15.58	0.061
Gender (female)	26 (55.3%)	14 (56%)	12 (54.5%)	0.920
ECOG-PS				0.029
0	27 (57.4%)	18 (72%)	9 (40.9%)	
1	16 (34%)	7 (28%)	9 (40.9%)	
2	4 (8.5%)	-	4 (18.2%)	
Location				0.010
Gastric	20 (42.6%)	15 (60%)	5 (22.7%)	
Non-gastric	27 (57.4%)	10 (40%)	17 (77.3%)	
Tumor size (cm)				0.018
≤5	12 (25.5%)	10 (40%)	2 (9.1%)	
6-10	16 (34%)	9 (36%)	7 (31.8%)	
≥10	19 (40.4%)	6 (24%)	13 (59.1%)	
Mitotic index				0.066
≤5	21 (44.7%)	15 (60%)	6 (27.3%)	
6-10	11 (23.4%)	5 (20%)	6 (27.3%)	
≥10	15 (31.9%)	5 (20%)	10 (45.5%)	
Necrosis (yes)	15 (31.9%)	7 (28%)	8 (36.4%)	0.539
Ki-67 (%)				0.828
≤5	16 (34%)	9 (36%)	7 (31.8%)	
6-10	15 (31.9%)	7 (28%)	8 (36.4%)	
≥10	16 (34%)	9 (36%)	7 (31.8%)	
Risk category*				0.004
Low-moderate	19 (40.4%)	15 (60%)	4 (18.2%)	
High	28 (59.6%)	10 (40%)	18 (81.8%)	
PNI	44.07 ± 8.66	49.82 ± 5.97	37.54 ± 6.27	<0.001
NLR	2.8 (0.9-16.1)	2.8 (0.9-16.1)	2.75 (0.9-7.4)	0.564
PLR	162.7 (27.4-719.5)	153.5 (27.4-449.6)	194.5 (45.5-719.5)	0.172
SII	852.6 (101.8-2913.4)	821.7 (101.8-2913.4)	936.65 (131.9-2433.5)	0.337

* According to Armed Forces Institute of Pathology (AFIP) criteria; RFS recurrence free survival, ECOG PS eastern cooperative oncology group performance status, PNI prognostic nutritional index, NLR neutrophil-to-lymphocyte ratio, PLR platelet-to-lymphocyte ratio, SII systemic immune-inflammation index.

Roc Analysis

Roc curve analyses revealed a cut-off value of 46.25 (AUC:0.925; 95% CI:0.850-1.000; p<0.001) for PNI to predict 5-year RFS with 95.5% sensitivity and 80.0% specificity (Fig. 2). According to this cut-off value, the patients were evaluated in two groups as follows; high PNI (n= 21, 44.7%) and low PNI (n=26, 55.3%).

5-Year Rfs Analysis

Median follow-up time was 62.3 months (range 4-68 months), and there were 22 recurrences (46.8 %). In (Table II), the univariate analysis showed that age, ECOG-PS, tumor localization, tumor size, risk category, and PNI were crucial prognostic factors due to affecting RFS in GIST patients. In the multivariate analysis, tumor size (HR =5.485, 95% CI: 0.210-143.266, p=0.016), and PNI (HR =112.020, 95% CI: 8.755-1433.278, p<0.001) were independent prognostic factors for RFS, while the age, ECOG-PS, tumor localization, and risk category were not. The patients with a high PNI (≥46.25) had a higher RFS than the patients with low PNI (<46.25). The 5-year RFS rate for the patients with high PNI was 95.2% compared to 19.2% for the patients with low PNI (Fig. 3), (Log-rank Chi-Square=27.929, p<0.001).

Discussion

GIST is the most common sarcoma with high recurrence rates after curative surgery, therefore risk classification systems have been established for the prediction of the prognosis [14]. Recently, three different risk classification systems are used which are NIH, modified NIH and AFIP. All criteria include mitotic activity and tumor

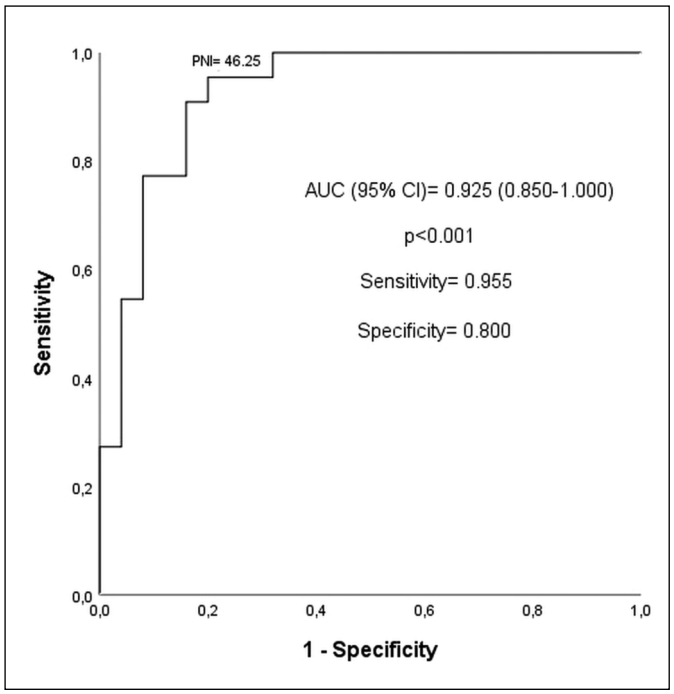

Fig. 2: Receiver operating characteristic curve (ROC) analysis of the prognostic nutritional index (PNI) for the prediction of 5-year recurrence-free survival (AUC= Area under the curve, CI= Confidence interval).

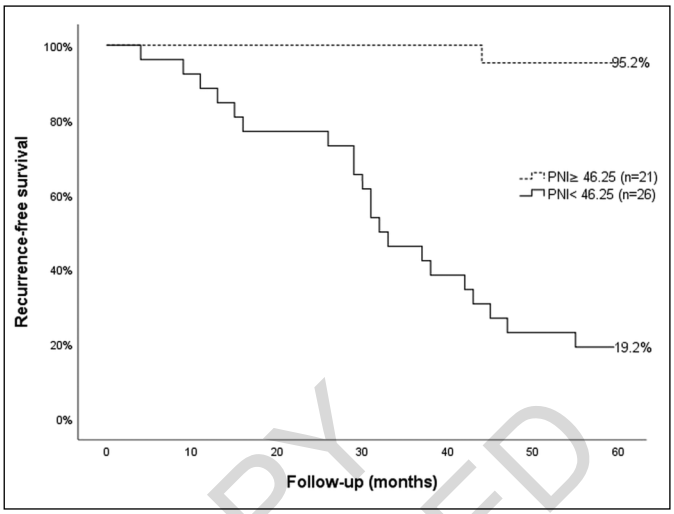

Fig. 3: Kaplan-Meier analysis of the 5-year recurrence-free survival curve of patients with primary localized gastrointestinal stromal tumor according to the cut-off value of the prognostic nutrition index (PNI) 46.25 (n=47, Log-rank Chi-Square=27.929, p<0.001).

size, also AFIP includes tumor localization [4]. In a study comparing three different risk classification systems, it was reported that all classifications can be used, but AFIP is more useful because it includes tumor localization. In the same study, it was shown that AFIP has the best independent prognostic value in 5-year RFS [15].
Recently, biomarkers such as NLR, PLR, SII, and PNI obtained from peripheral blood have been used to determine prognosis in the preoperative period because these are cost-effective and non-invasive [6-12]. In the multivariate survival analysis study, 5-year RFS was 57% in high PLR (≥245) and 84% in low PLR in resected GIST patients (p=0.039). High NLR (>2.04) was not associated with reduced RFS (p=0.214). A tumor size larger than 10 cm was associated with higher PLR (p=0.047), higher mitotic index (exceeding 10 mitoses/50 high-power fields) and higher NLR (p=0.016) [16]. In a similar study, high NLR (≥3.0) and high PLR (≥275) were associated with decreased RFS (p=0.012, p=0.01; respectively) [17]. In another study, 5-year RFS was significantly lower in high NLR (≥2.24) and high PLR (≥141.5) in univariate analysis (76.2% vs 83.6%, p=0.010; 65.7% vs 96.4%, p=0.004; respectively). But there was no significant difference in terms of NLR and PLR in multivariate analysis (p=0.534, p=0.655; respectively) [18]. In our study, NLR and PLR were not associated with 5-year RFS.
It is known that SII is a better indicator of the inflammatory response and immune system compared to NLR and PLR because it is calculated from three parameters [10-12]. However, in our study, we found that SII was not associated with 5-year RFS like NLR and PLR. In a study involving 45 resected GIST patients, cut-off values for NLR, SII, and PNI were determined. It was observed that RFS was higher in patients with low SII (<940) and high PNI (≥37.5). Median RFS was 132.9 months in patients with SII<940, it was 63.2 months in patients with SII≥940 (p=0.041). In addition, it was 133.2 months in patients with PNI≥37.5, it was 62.2 months in patients with PNI<37.5 (p=0.018). Only SII was found as an independent prognostic indicator in the Cox regression analysis [19]. In a similar, more comprehensive study, the effect of SII and Geriatric Nutrition Risk Index (GNRI) were investigated on RFS in resected GIST patients. In univariate analysis, SII, GNRI, Ki-67, mitotic index, tumor diameter, tumor localization were prognostic indicators for RFS, but in multivariate analysis, mitotic index, tumor diameter, tumor localization, and GNRI were associated with RFS (p=0.001, p=0.0039, p=0.045, and p=0.041; respectively). It was emphasized that SII also tended to be associated with RFS (p=0.062) [20]. In our study, in multivariate analysis, only tumor diameter was significantly different, while tumor localization, Ki-67, and mitotic index were not.
PNI was first defined by Onodera et al [21] on 200 patients with various gastrointestinal tumors in 1984. This study aimed to associate the risk of postoperative complications with the basic nutritional status. As a result of the study; it was reported that PNI is useful in determining the prognosis of terminal cancer patients. It was shown that patients with PNI<40 and total lymphocytes count remains below 1,000/mm^3 were more likely to die within the next two months. Senger et al.[22] investigat-

Table II - *Univariate and multivariate cox regression analyses of clinicopathological variables related to 5-year recurrence-free survival*

Variable	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI Lower-Upper	P value	Hazard ratio	95% CI Lower-Upper	P value
Age (years)			0.007			0.079
<67.5	1	-		1	-	
≥67.5	3.228	1.372-7.595		6.105	0.812-45.924	
Gender			0.639			0.670
Male	1	-		1	-	
Female	0.818	0.353-1.896		0.770	0.231-2.567	
ECOG-PS			0.009			0.677
0	1	-		1	-	
1	1.999	0.792-5.042		0.839	0.152-4.624	
2	8.767	2.519-30.518		2.343	0.137-40.171	
Location			0.013			0.401
Gastric	1	-		1	-	
Non-gastric	3.533	1.299-9.607		1.875	0.433-8.124	
Tumor size (cm)			0.014			0.016
≤5	1	-		1	-	
6-10	2.926	0.607-14.098		5.485	0.210-143.266	
≥10	6.140	1.380-27.329		496.160	2.453-100339.405	
Mitotic index			0.106			0.262
≤5	1	-		1	-	
6-10	2.094	0.673-6.515		6.478	0.635-66.053	
≥10	2.869	1.038-7.933		0.958	0.165-5.554	
Necrosis			0.441			0.417
No	1	-		1	-	
Yes	1.407	0.590-3.357		0.475	0.079-2.869	
Ki-67 (%)			0.892			0.124
≤5	1	-		1	-	
6-10	1.281	0.464-3.534		0.342	0.076-1.539	
≥10	1.137	0.399-3.244		3.130	0.447-21.938	
Risk category*			0.013			0.428
Low-moderate	1	-		1	-	
High	3.950	1.331-11.719		0.322	0.020-5.304	
PNI			0.001			<0.001
≥46.25	1	-		1	-	
<46.25	33.133	4.418-248.5		112.020	8.755-1433.278	

* According to Armed Forces Institute of Pathology (AFIP) criteria; CI confidence interval, ECOG PS eastern cooperative oncology group performance status, PNI prognostic nutritional index.

ed the effect of preoperative PNI on postoperative complications and prognosis in 314 patients who were operated for colorectal cancer. Postoperative complications were observed in 36 (37.1%) patients in the high PNI group and in 155 (71.4%) patients in the low PNI group, and this difference was significant (p<0.001). The mean survival expectancy was significantly higher in the high PNI group than the low PNI group (84.626±2.701 vs 68.112±2.646 months, p<0.001). In our study, we calculated the cut-off value for PNI as 46.25. We found the 5-year RFS rate was 95.2% in patients with PNI≥46.25, and it was 19.2% in patients with PNI<46.25 (p<0.001). In a study of 431 R0 resected GIST patients, the 5-year RFS rate was found significantly higher in patients with high PNI (≥47.25) than in patients with low PNI (89.8% vs 70.8%; p<0.001). It was emphasized that there was no difference in terms of NLR and PLR for 5-year RFS, therefore PNI was a better independent prognostic indicator [23]. In another similar study, NLR, PLR, and PNI were evaluated in 340 resected GIST patients. In multivariate analysis, NLR and PLR were not associated with RFS, while patients with PNI≥43.9 were found to have better RFS (HR: 0.509; 95%, CI 0.266-0.872; p=0.031). In subgroup analysis, for both gastric and non-gastric tumors, 5-year RFS rates were better in the high PNI group than in the low PNI group. (p<0.001, p=0.007, respectively). In the same study, the addition of PNI to the NIH criteria was also shown to improve prognostic classification (c-index, 0.725 vs. 0.686, p = 0.039) [24]. Contrary to the literature, another study could not show the effect of PNI on RFS. It was found 82 months in patients with PNI<43.5 and 100 months in patients with PNI>43.5 (p=0.411). But multivariate analysis was not

performed in this study. It was emphasized that necrosis, bleeding, ulceration, tumor size, mitosis and Ki-67 had an effect on recurrence (p<0.001, p=0.003, p=0.035, p<0.001, p=0.021, and p=0.031; respectively). The limitation of this study was the lack of multivariate analysis [25].

NPS (naples prognostic score) is another current nutritional index indicator calculated with more data (serum albumin, total cholesterol, absolute neutrophil count, absolute lymphocyte count, and absolute monocyte count) than PNI. NPS is scored normal values (0 point) and altered values (1 point) for each parameters. NPS is divided to 3 groups according to total points (NPS 0, NPS 1, and NPS 2) [26]. In a multivariate survival analysis study PNI, SII, NLR, and NPS were investigated in patients undergoing surgery for gastric cancer. As a result, in 5 year overall survival and 5-year RFS rates while there were no significant differences in terms of SII, PNI, and NLR; in patients with NPS 0 was significantly higher than in patients with NPS 1, and NPS 2. (p=0.024, and p=0.009; respectively). It has been reported that NPS is a stronger indicator than PNI [26]. In this study, we found that tumor size and PNI were independent prognostic indicators for 5-year RFS. However, we observed that NLR, PLR, and SII did not affect 5-year RFS.

There are several limitations of this study. First, it was a single-center retrospective study. Second, the sample size was relatively low. Third, the study was conducted on tumors with different localization.

Conclusion

Prognostic nutritional index (PNI) is a simple and useful independent prognostic biomarker for recurrence-free survival after surgical resection in GIST patients, while systemic inflammatory indexes (NLR, PLR, and SII) have no significant effect.

Riassunto

Studi recenti hanno confrontato il ruolo del rapporto neutrofili-linfociti (NLR), del rapporto piastrine-linfociti (PLR), dell'indice di infiammazione sistemica (SII) e dell'indice nutrizionale prognostico (PNI) sulla prognosi di vari tumori maligni. Tuttavia, rimane controverso il valore di questi marcatori nel definire la prognosi dei tumori stromali gastrointestinali (GIST). Abbiamo studiato l'effetto di NLR, PLR, SII e PNI sulla sopravvivenza libera da recidiva (RFS) a 5 anni in pazienti con GIST asportato chirurgicamente.

Lo studio si è svolto analizzando retrospettivamente 47 pazienti di una singola istituzione che erano stati sottoposti a resezione chirurgica di un GIST primitivo localizzato tra il 2010 e il 2021.

I pazienti sono stati divisi in due gruppi in base allo stato di recidiva nel periodo postoperatorio di 5 anni: e gruppo RFS(+) a 5 anni (pazienti senza recidiva, n=25) e RFS(-) a 5 anni (pazienti con recidiva, n=22).

RISULTATI: Nelle analisi univariate, l'Eastern Cooperative Oncology Group Performance Status (ECOG-PS), la localizzazione del tumore, la dimensione del tumore, il PNI e la categoria di rischio erano significativamente differenti tra i gruppi RFS(+) e RFS(-) mentre NLR, PLR, SII non erano difformi.

Le analisi multivariate hanno rivelato che solo la dimensione del tumore presentava un Hazard Ratio (HR) = 5,485, IC 95%: 0,210-143,266, p = 0,016) e PNI (HR = 112,020, IC 95%: 8,755–1433,278, p <0,001) risultavano fattori prognostici indipendenti per RFS. I pazienti con un PNI elevato (≥46,25) avevano un tasso di RFS a 5 anni più alto rispetto ai pazienti con PNI basso (<46,25) (95,2% a 19,2%, p<0,001).

CONCLUSIONE: Un PNI preoperatorio più elevato è un previsore positivo indipendente per RFS a 5 anni per pazienti con GIST asportato chirurgicamente. Al contrario NLR, PLR e SII non hanno dimostrato effetti significativi.

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