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ORIGINAL ARTICLE

A novel predictor in patients with gastrointestinal stromal tumors: Systemic immune-inflammation index (SII)

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Summary

Purpose: *Systemic inflammation and immune response are associated with tumors'prognosis. However, there is little information about inflammatory indexes in patients with gastrointestinal stromal tumor (GIST). In this study, we aimed to determine the prognostic significance of inflammation indexes such as neutrophil to lymphocyte ratio (NLR), systemic immune-inflammation index (SII), prognostic nutritional index (PNI) and Glasgow prognostic score (GPS) in GIST patients.*

Methods: *Forty-five patients diagnosed with GIST between 2003 and 2018 were included in the study. The effects of NLR, SII, PNI and GPS on progression-free survival (PFS) and overall survival (OS) estimated based on clinicopathological and laboratory data were evaluated by Kaplan-Meier and Cox regression analysis.*

Results: *The optimal cut-off values for NLR, SII and PNI were 2.54, 940, and 37.5, respectively. Low SII and higher PNI values were associated with longer PFS (p=0.041, p=0.018, respectively). In terms of OS, patients with high NLR, high SII and low PNI had a shorter lifespan. In multivariate analysis, only SII was found to be independent prognostic factor.*

Conclusion: *In cases with GIST, SII may predict recurrence and survival.*

Key words: *gastrointestinal stromal tumor (GİST), systemic immune inflammation index (SII), prognostic nutritional index (PNI), neutrophil-lympocyte ratio (NLR).*

Introduction

GISTs are mesenchymal malignancies which constitute the majority of soft tissue sarcomas. They originate from Cajal interstitial cells in the gastrointestinal system, and occurs due to mutations in the protooncogenes KIT and PDGFR [1,2]. GISTs are frequently seen in the stomach (60%), small intestine (30%), duodenum (4-5%) and rectum (4%) [2]. They are rarely seen in the esophagus, colon, appendix and other regions (peritoneum, retroperitoneum) [2]. The disease usually appears at a mean age of 60-65 years and patients often present with symptoms of pain, bleeding and/or anemia. The standard treatment for local primary GIST is surgical excision [3]. However, about half of the patients treated with surgery are at risk of recurrence [4]. Estimation of the risk of tumor recurrence is of great importance in the management of GIST because selecting appropriate patients for adjuvant imatinib treatment is based on accurate determination of the risk of tumor recurrence [5]. The primary tumor site, tumor diameter, Armed Forces Institute of Pathology (AFIP) risk criteria and mitotic index are commonly used prognostic factors in the determination of risk [6].

Inflammation plays a major role in the pathogenesis of cancer. Systemic inflammation stimulates tumor proliferation, invasion and angiogenesis by inhibiting apoptosis [7]. Neutro-

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phil, lymphocyte, monocyte and platelet counts and their relations with each other are used as indicators of systemic inflammation. It has been shown that various immuno-inflammatory-based prognostic indices, such as lymphocyte-monocyte ratio (LMR), neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), Glasgow prognostic score (GPS), prognostic nutritional index (PNI) predict recurrence and survival in patients with many solid tumors [8,9]. SII that reflects the balance between the patient's inflammatory and immune status, is based on platelet, neutrophil and lymphocyte counts. SII is a promising index for hepatocellular carcinoma, pancreatic cancer, small-cell lung cancer, gastric cancer, esophageal cancer and prostate cancer [10-12]. However, the prognostic value of SII in patients with GIST has not been reported. The aim of this study was to determine the prognostic significance of other inflammatory indexes (NLR, GPS, PNI) mainly SII, in patients with GIST.

Table 1. Sociodemographic and clinical characteristics of the patients

Characteristics	*n (%)*
Gender	
Male	26 (57.8)
Female	19 (42.2)
ECOG PS	
0-1	34 (75.5)
≥2	11 (24.5)
Smoking	
Yes	13 (28.9)
No	32 (71.1)
Location of the tumor	
Stomach	24 (53.3)
Small bowel	17 (37.8)
Retroperitoneum	4 (8.9)
Progression	
Yes	12 (26.7)
No	33 (73.3)
Metastatic region	
None	34 (75.6)
Liver	9 (20)
Retroperitoneum	2 (4.4)
Final outcome	
Survived	35 (77.8)
Dead	10 (22.2)
Stage	
I-II	36 (57.7)
III-IV	19 (42.2)

ECOG PS: Eastern Cooperative Oncology Group performance status

Methods

Forty-five patients diagnosed with GIST at the Ataturk University Research and Application Hospital (AURAH), and followed up for at least 6 months were included in the study. The files of the patients were retrospectively reviewed. Patients with a history of hematological diseases, autoimmune diseases, or other history of malignancy were excluded. Clinical variables such as gender, age, smoking status, Eastern Cooperative Oncology Group (ECOG) score, progression and/or recurrence site, tumor location, and laboratory findings such as neutrophil, lymphocyte, platelet counts, albumin, C-reactive protein (CRP) were obtained from AURAH electronic recording system.

Table 2. Pathological characteristics of the patients

Characteristics	*Total n (%)*
Ki67 proliferation index	
0-5	19 (42.2)
6-10	16 (35.6)
≥11	10 (22.2)
Necrosis	
Present	12 (26.7)
Absent	33 (73.3)
Ulcer	
Present	12 (26.7)
Absent	33 (73.3)
Bleeding	
Present	24 (53.3)
Absent	21 (46.7)
Mitosis (HPF)	
0-5	30 (66.7)
≥5	15 (33.3)
Cell type	
Spindle	27 (60)
Epitheloid	10 (22.2)
Mix	8 (17.8)
Lymphovascular invasion	
Present	3 (6.7)
Absent	42 (93.3)
Perineural invasion	
Present	9 (20)
Absent	36 (80)
AFIP risk criteria	
Low Risk	15 (33.3)
Moderate risk	13 (28.9)
High risk	17 (37.8)
T stage	
T1	9 (20)
T2	7 (15.6)
T3	19 (42.2)
T4	10 (22.2)

HPF: High power field (x50), AFIP: Armed Forces Institute of Pathology

Pathological findings such as necrosis, ulcer, bleeding, cell type, Ki-67 index, mitosis, lymphovascular invasion, perineural invasion, tumor diameter and AFIP risk criteria were obtained from the electronic registry of AURAH Pathology Department.

The AFIP criteria were developed by the pathologists Miettinen and Lasota based on thousands of GIST samples found in the AFIP files. Numerical risk classification is made according to tumor location and mitotic index and tumors are divided into low, medium and high risk groups [13]. Risk classification according to AFIP criteria was obtained from pathology reports.

SII was calculated by the formula: platelet (P)×neutrophil (N)/lymphocyte (L). NLR was calculated by dividing the neutrophil count by the number of lymphocytes. PNI was determined using the formula: 10x albumin (g/dL)+0.005 x total number of lymphocytes The most sensitive and specific cut-off values of laboratory parameters such as pretreatment NLR (2.54), SII (940) and PNI (37,5) were estimated for OS using ROC analysis. According to ROC analysis AUC values for NLR (0.66), SII (0.61), and PNI (0.63) were found as indicated.

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, and if albumin was ≥35 (g/L), then the GPS was considered as 1. In patients with CRP ≤ 10 (mg/L), if albumin was <35 (g/L) or ≥35 (g/L) then the GPS values were accepted as 1, and 0, respectively [14].

Statistics

OS was measured from the date of diagnosis to the date of death and censored at the date of last follow-up visit for survivors. PFS was measured from the date of diagnosis to the date of death or recurrence, and censored at the date of last follow-up visit for survivors without disease recurrence. The association among clinical characteristics, OS and PFS was analysed by the Kaplan–Meier method and log-rank test. Univariate and multivariate Cox regression analyses were used to evaluate the prognostic value of NLR, SII, PNI and GPS adjusted by lymphovascular and perineural invasion, AFIP risk criteria, ECOG score and stage status. Hazard ratios and 95% confidence intervals (CIs) were estimated using Cox regression analysis. Statistical analyses were performed with SPSS software version 21 (SPSS IBM Corp., Armonk, NY, USA), and differences were considered statistically significant at $p < 0.05$.

Results

Our study population consisted of 19 (42.2%) male and 26 (57.8%) female patients. The median patient age was 58 years (32-80). The sociodemographic and clinical features of the patients are shown in Table 1. According to ECOG performance score, 34 (75.5%) of the patients were in ECOG 0-1 and 11 (24.5%) in ECOG ≥2 group. The pathological features of the patients are shown in Table 2. The distribution of patients according to Ki-67 index was as follows: Ki-67 0-5 (n=19:42.2%), Ki-67 6-10 (n=16:35.6%), and Ki-67 ≥11 (n=10:22.2%). The patients had or had not necrosis (n=12:26.7% *vs* n=33: 73.3%), ulcers (n=12: 26.7% *vs* n=33: 73.3%), and tumor-related bleeding (n=24: 53.3% *vs* n=21: 46.7). The number of mitoses per HPF were 0-5 and ≥5 in

Table 3. The relationship between sociodemographic, clinical characteristics and PFS

Characteristics	*n (%)*	*PFS*		*OS*	
		Median	*p*	*Median*	*p*
Gender					
Male	26 (57.8)	68.294	0.067	88.07	0.735
Female	19 (42.2)	135.036		126.632	
ECOG PS					
0-1	34 (75.5)	143.777	0.013*	140.596	0.01*
≥2	11 (24.5)	51.640		57.250	
Smoking					
Yes	13 (28.9)	70.917	0.371	79.386	0.476
No	32 (71.1)	133.051		126.235	
Location of the tumor					
Stomach	24 (53.3)	90.729	0.072	96.509	0.015*
Small bowel	17 (37.8)	114.815		148.429	
Retroperitoneum	4 (8.9)	41.250		46.333	
Stage					
I-II	26 (57.7)	113.180	0.004*	110.393	0.031*
III-IV	19 (42.3)	74.678		105.647	

ECOG: Eastern Cooperative Oncology Group. Asterisks denote statistical significance

30 (66.7%), and 15 (33.3%) patients, respectively. There were 3 (6.7%) patients with lymphovascular invasion, 9 (20%) with perineural invasion, while lymphovascular and perineural invasion were not found in 42 (93.3%) and 36 (80%) patients, respectively. According to AFIP criteria, the patients were in the low (n=15: 33.3%), moderate (n=13: 28.9%), and high (n=17: 37.8%) risk groups. Twenty patients (44.4%) were in stage I, 6 (13.3%) in stage II, 12 (26.7%) in stage III and 7 (15.6%) in stage IV.

Regarding the study period, the patients were followed up for a median period of 48 months (6-184). During the study period the disease of 12 (26.7%) cases progressed and 10 (22.2%) patients died. The median PFS (118.6; 88.6-148.6 months), and OS (126.5; 97.1-155.8 months) of the study population were also calculated. The correlation between sociodemographic and clinical features and PFS and OS are shown in Table 3. Although median PFS/OS in female patients (135.036/126.632 months) were longer relative to male patients

Table 4. The relationship between pathological findings and PFS/OS

	n (%)	*PFS*		*OS*	
		Median	*p*	*Median*	*p*
Ki67					
0-5	19 (42.2)	138.344	0.049*	170.1	0.005*
6-10	16 (35.6)	92.063		80.75	
≥11	10 (22.2)	52.022		56.037	
Necrosis					
Present	12 (26.7)	70.644	0.138	84.143	0.397
Absent	33 (73.3)	122.965		131.396	
Ulcer					
Present	12 (26.7)	45.074	0.004*	52.778	0.003*
Absent	33 (73.3)	137.924		145.446	
Bleeding					
Present	24 (53.3)	114.670	0.351	98.369	0.022*
Absent	21 (46.7)	91.463		119.421	
Mitoses (per HPF)					
0-5	30 (66.7)	146.306	0.014*	153.232	0.025*
≥5	15 (33.3)	55.396		64.733	
Cell type					
Spindle	27 (60)	117.532	0.492	128.988	0.920
Epithelioid	10 (22.2)	110.571		94.6	
Mixed	8 (17.8)	76.375		88.313	
Lymphovascular invasion					
Present	3 (6.7)	26	0.088	27	0.009*
Absent	42 (93.3)	121.472		129.557	
Perineural invasion					
Present	9 (20)	53.114	0.239	53.667	0.049*
Absent	36 (80)	125.358		135.716	
AFIP risk criteria					
Low Risk	15 (33.3)	155.604	0.053	141.833	0.214
Moderate Risk	13 (28.9)	115.7		115.6	
High Risk	17 (37.8)	59.388		72.363	
T stage					
T1	9 (20)	32.267	0.123	42.75	0.504
T2	7 (15.6)	88.75		98.5	
T3	19 (42.2)	145.779		153.577	
T4	10 (22.2)	76.648		75.088	

AFIP: Armed Forces Institute of Pathology, HPF: High power field (x 50). Asterisks denote statistical significance

(68.294/88.07 months), the difference between genders was insignificant (p=0.067, p=0.735). Median PFS/OS were 70.917/79.386 months in smokers and 133.051/126.235 months in nonsmokers without statistically significant intergroup difference (p=0.371, p=0.476).

PFS/OS were 143.77/140.586 months in the group with ECOG scores 0-1 and 51.640/57.250 months in those with ECOG scores of ≥2 and PFS/OS were significantly longer in patients with ECOG score 0-1 (p=0.013, p=0.01). PFS/OS were 114.815/148.429 months if the tumor was localized in the small bowel, 90.729/96.509 months in the stomach and 41.25/46.33 months in the retroperitoneum. Although there was no difference in PFS between the locations of the tumors, the patients with tumors localized in the small intestine had statistically significantly longer survival (p=0.072, p=0.015). Median PFS/OS were 113.180/110.393 months in stage I-II and 74.678/105.647 months in stage III-IV and both PFS and OS were significantly longer in stage I-II group (p=0.004, p=0.031). The relationship between PFS and OS according to pathological findings of patients is shown in Table 4. The median PFS of the patients in the 0-5/6-10/≥11 groups according to the Ki-67 index estimated based on pathological findings was 138.344/92.063/52.022 months respectively with a statistically significant difference between groups (p=0.049). Similarly, the median OS of the corresponding Ki-67 groups were 170.1/80.75/56.037 months with a significant difference between the OS of these groups (p=0.005). The median PFS/OS in the groups with and without necrosis were 70.644/84.143 and 122.965/131.396 months, respectively. Although the median PFS/OS in the

Table 5. The relationship between inflammation-based scores and PFS/OS

	n (%)	*PFS*		*OS*	
		Median	*p*	*Median*	*p*
NLR					
<2.54	27 (60)	129.422	0.233	159.182	0.047*
≥2.54	18 (40)	70.009		72.142	
SII					
< 940	33 (73.3)	132.905	0.041*	157.450	0.016*
≥940	12 (26.7)	63.279		66.360	
PNI					
<37.5	14 (31.1)	62.277	0.018*	67.979	0.033*
≥37.5	31 (68.9)	133.231		153.110	
GPS					
0	20 (44.4)	89.264	0.472	111.286	0.226
1	16 (35.6)	110.981		98.031	
2	9 (20)	67.889		79.857	

NLR:neutrophil lymphocyte ratio, SII:systemic immune inflammation index, PNI:prognostic nutritional index, GPS:Glasgow prognostic score. Asterisks denote statistical significance

Table 6. Results of Cox regression analysis

	B	*SE*	*df*	*p*	*OR*	*95,0% CI for OR*	
						min	*max*
SII	2.869	1.279	1	0.025*	17.626	1.436	216.368
Lymphovascular invasion	3.347	1.838	1	0.069	28.418	0.775	1041.760
AFIP risk criteria	-0.829	0.700	1	0.236	0.437	0.111	1.720
ECOG PS	2.546	1.394	1	0.068	12.750	0.830	195.760
Perineural invasion	-1.676	1.590	1	0.292	0.187	0.008	4.226
Stage	2.258	1.304	1	0.083	9.567	0.742	123.357

SII: systemic immune inflammation index, AFIP: Armed Forces Institute of Pathology, ECOG PS: Eastern Cooperative Oncology Group perfomance status. Asterisk denotes statistical significance

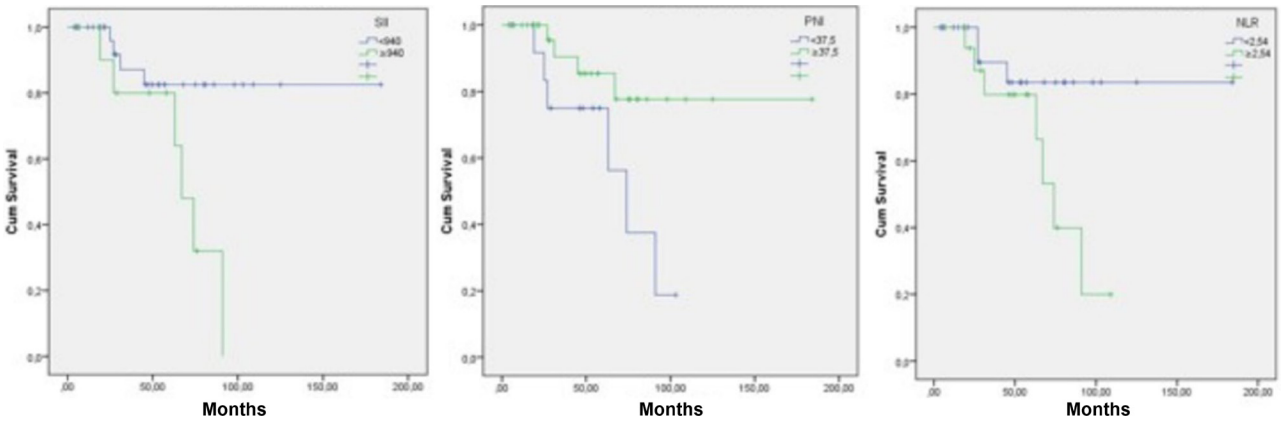

Figure 1. Kaplan-Meier OS curves of SII, PNI and NLR

group without necrosis was longer than the necrosis group, the difference between them was statistically insignificant (p=0.138, p=0.397). Median PFS/OS of the patients with and without ulcer were 45.074/52.778, and 137.924/145.446 months, respectively, and those without ulcers in their tumors had significantly longer PFS/OS (p=0.004, p=0.003).

The PFS of the patients with and without bleeding in the tumor was 114.670 and 91.463 months, respectively, without significant difference between them (p=0.351). The OS of the patients with and without bleeding in the tumor was 98.369 and 119.421 months, respectively, with a significant OS advantage in favor of those without bleeding in the tumor (p=0.022). Median PFS/OS in groups with 0-5, and >5 mitoses per HPF were 146.306/153.232 and 55.396/64.733 months, respectively. PFS/OS were longer in the group with smaller number of mitosis per HPF (p=0.014, p=0.025). PFS/OS were 117.532/128.988 months in patients with spindle cell tumors, 110.571/94.6 months in epithelioid cases and 76.375/88.313 months in patients with mixed type. There was no significant intergroup difference for PFS/OS (p=0.492, p=0.920). Patients with lymphovascular and perineural invasion had shorter OS when compared with those without (27 *vs* 129.5 months, p=0.009 and 135.716 *vs* 53, 667 months p=0.049), but there was no difference in terms of PFS (p=0.088, p=0.239). When classified according to AFIP risk criteria as low, moderate and high risk groups, and tumor size (T), no difference was found between groups for PFS and OS (PFS; p=0.053, p=0.123; OS; p=0.214, 0.504).

The relationship between inflammation-based scores and PFS and OS is shown in Table 5. Patients with NLR<2.54 had significantly longer OS (159.182 *vs* 72.142 months, p=0.042) than those with NLR>2.54, but no difference was found between groups for PFS (129.422 *vs* 70.009 months, p=0.233). Patients with low SII had a longer lifespan in terms of both PFS (132.905 *vs* 63.279 months, p=0.041) and OS (157.450 *vs* 66, 3660 months, p=0.016). Patients with a PNI score above 37.5 had significantly longer PFS/OS relative to those with lower PNI scores (PFS:133.231 *vs* 62.277 months, p=0.018; OS: 153.110 *vs* 67.979 months, p=0.033). The OS curves of SII, PNI and NLR are shown in Figure 1. There was no difference between the GPS groups in terms of both PFS and OS (p=0.472, p=0.226).

Cox regression analysis showed that SII was an independent risk factor related to OS (Table 6). The odds ratio (OR) for SII was 17.626 (95%CI:1.436-216.368, p=0.025). But multivariate analysis showed that lymphovascular invasion (p=0.069; OR:28.418, 95% CI 0.775-1041.760), AFIP criteria (p=0.236;OR:0.437, 95% CI 0.111-1.729), ECOG PS status (p=0.068; OR:12.750, 95% CI 0.830-195.760), perineural invasion (p=0.292; OR:0.187, 95% CI 0.008-4.226), and stage (p=0.083; OR:9.567, 95% CI 0.742-123.357) were not associated with prognosis.

Discussion

It is known that inflammation increases the risk of tumor development, triggers the onset of genetic mutations and it is an important mechanism in tumor progression and metastasis [15]. Therefore, in recent years it has been thought that inflammatory parameters may become good candidates as prognostic markers of cancer. In our study we have also found that NLR was prognostic only in terms of OS, while SII and PNI were prognostic for both PFS and OS. Besides, we have shown that SII is also an independent risk factor for OS. This is the first study to demonstrate the prognostic significance of SII in patients with GIST.

Tumor cells affect systemic inflammation by acting on proinflammatory mediators. This condition results in proliferation of tumor cells, forma-

tion of angiogenesis and inhibition of apoptosis. Neutrophils in peripheral blood are indicative of acute and chronic inflammation [16]. Neutrophils suppress the activity of both natural killer (NK) cells and lymphocytes, and also inactivate activated T cells. In this way, neutrophils have been reported to be capable of suppressing the immune system [17]. Furthermore, neutrophils may stimulate tumor growth over vascular endothelial growth factor (VEGF) and matrix metalloproteinase-9 (MMP-9) [18]. Lymphocytes, on the other hand, play an important role in body defense by stimulating cytotoxic cell death and inhibiting proliferation of tumor cells. Platelets can mediate the growth, survival and proliferation processes of tumor cells [19].

Platelets conceivably exert these functions by protecting circulating tumor cells from disintegration stress effective during circulation and by providing epithelial-mesenchymal transition (EMT) [20]. The SII is an easily performed, reproducible and cost-effective index based on platelet count and neutrophil /lymphocyte ratio. In addition, compared with scorings such as NLR and PLR which are based on only two types of inflammatory cells, SII that is estimated based on three types of inflammatory cells containing three types of inflammatory cells may be a better indicator of the balance between the inflammatory and immune systems of the host. In a hepatocellular carcinoma (HCC) study performed with 123 cases, Hu et al determined that patients with SII >330 had a higher recurrence and shorter survival rates. Hong et al investigated 919 cases with small cell lung cancer (SCLC) and presented SII as an independent factor in OS (cut off: 1600) [11]. In another study, Jiang et al. investigated 327 patients with nasopharyngeal carcinoma and detected that SII was prognostic for OS, but also more important than NLR, PLR and LMR [21]. In another study in which 140 advanced-stage non-small cell lung cancer (NSCLC) patients were examined, Guo et al (cut off:521) found that SII was an independent prognostic factor for both PFS (p=0.001) and OS (p=0.001) [22]. In addition, in a meta-analysis, Yang et al investigated 7196 patients from 22 studies, and demonstrated that SII has prognostic significance both for PFS and OS in many types of cancer including esophageal carcinoma, gastric, prostate, renal and biliary tract cancers [23]. In our study, similar to other studies demonstrating prognostic significance of SII, we found that patients with GIST having SII>940 had shorter PFS and OS. However, the prognostic significance of SII in GIST patients is still unclear. Because of our small number of patients, it is useful to confirm the cut-off value determined by the ROC curve with higher number of patients.

The prognostic value of NLR, which is another indicator of systemic inflammation in patients with GIST, has been determined by various investigators. In a study on 274 patients with GIST having NLR values above 2.24, Feng et al found that these patients had shorter PFS, and the only independent prognostic factor was tumor size [24]. In a recently published meta-analysis from 8 studies with 1676 patients with GIST, NLR was found to be prognostic in terms of PFS, but not significant regarding OS [25]. However, in the study of Rutkowski et al, patients with NLR values above 2.7 were found to have relatively shorter OS and PFS [26]. In our study, similar to the study performed by Rutkowski et al the group with NLR>2.54 had shorter PFS and OS, but NLR had prognostic significance only for OS.

In another inflammation-based study [27], PNI was dependent on the albumin levels and total lymphocyte counts. In a previous study with 341 cases, albumin and PNI have been found to be prognostic in NSCLC patients [27]. Wang et al showed that in a meta-analysis of 3165 HCC patients, PNI was predictive of both PFS and OS [28]. In another meta-analysis of 3203 patients from 9 studies it was shown that low PNI score was associated with poorer OS in patients with gastric cancer [29]. In our study, similarly, we found that patients with GIST having higher PNI scores had significantly longer PFS and OS relative to those with low PNI scores (p=0.018, p=0.033). However, since inadequate number of studies have been performed concerning PNI scores in patients with GIST, further investigations on this issue are needed.

In this study, the prognostic value of another inflammation-based score, namely GPS, has been also investigated. As systemic meta-analysis on GPS encompassing 1104 patients with lung cancer from 5 studies was published by Dolan et al and the authors demonstrated prognostic value of GPS. In the same meta-analysis similar results were found in 735 pancreatic and 11283 gastric cancer patients [30]. In another study by Tomita et al in patients with lung cancer the prognostic value of GPS was also proven [27]. It should be emphasized that there is no known study investigating the prognostic value of GPS in patients with GIST. In our study, no significant difference was found between GPS groups in terms of PFS and OS (p=0.472, p=0.472). Due to the small number of patients in our study, the prognostic significance of this scoring system might not be clear and consequently we think that there is a need for studies involving greater number of patients.

Our study has some important limitations. Firstly, it was retrospective and single-centered. The other limitation is the relatively low number of the patients. To confirm the predictive values of the parameters investigated in the study, prospective studies with greater number of patients are needed.

Conclusion

Systemic inflammation is important in tumorigenesis in GIST cases as in all types of cancer. This study was the first to show the prognostic significance of the inflammation-based SII and PNI indexes based on peripheral blood cell counts in patients with GIST. SII is an independent prognostic factor and may predict recurrence and survival in cases with GIST.

Compliance with ethical standards

All procedures performed in this study, involving humans participants, were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Conflict of interests

The authors declare no conflict of interests.

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