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Diagnostic Value Of Systemic Immune–Inflammation Index (SIII) in Acute Ischemic Stroke

Akut İskemik İnmede Sistemik İmmün-İnflamasyon Endeksinin (SIII) Tanısal Değerliliği

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Abstract

Aim: Calculated based on platelet, neutrophil and lymphocyte counts, the systemic immune-inflammation index is thought to be associated with many malignancies in the literature. Despite the existing investigations on its diagnostic value, there have been no clear results reported regarding its diagnostic value in stroke patients. The current study is therefore intended to demonstrate the diagnostic value of the systemic immune-inflammation index and its prognostic value in cases of acute ischemic stroke.

Material and Method: A total of 150 cases of acute stroke and a control group of 150 individuals were retrospectively examined. The data recorded for each case included age, gender, history, vital findings, NIHSS, SIII, and outcome.

Results: In the current study, the group of stroke patients had significantly higher SIII than the control group. According to the diagnostic examinations, in stroke, the diagnostic value of SIII was greater than that of neutrophil-to-lymphocyte ratio at a statistically significant level. The present study also found that, compared to the SIII, the (Lymphocyte x Platelet)/Neutrophil ratio (called the reverse SIII) had a higher statistical significance in diagnosing the stroke and predicting early hospital mortality.

Conclusion: The SIII can be a good marker for both diagnostic evaluation and for predicting early hospital mortality in stroke cases. Additionally, it is approved to be a useful index since it can be calculated inexpensively and easily.

Keywords: Ischemic stroke, systemic immune-inflammation index, emergency department, prognosis

Öz

Amaç: Trombosit, nötrofil ve lenfosit sayılarına göre hesaplanan sistemik immün-enflamasyon indeksinin literatürde birçok malignite ile ilişkili olduğu düşünülmektedir. Tanısal değeri ile ilgili mevcut araştırmalara rağmen inme hastalarında tanısal değeri ile ilgili net sonuçlar bildirilmemiştir. Bu nedenle mevcut çalışma, akut iskemik inme vakalarında sistemik immün-enflamasyon indeksinin tanısal değerini ve bunun prognostik değerini göstermeyi amaçlamaktadır.

Gereç ve Yöntem: Toplam 150 akut inme olgusu ve 150 kişilik kontrol grubu retrospektif olarak incelendi. Her vaka için kaydedilen veriler yaş, cinsiyet, öykü, hayati bulgular, NIHSS, SIII ve sonucu içeriyordu.

Bulgular: Mevcut çalışmada, inmeli hasta grubunda kontrol grubuna göre anlamlı olarak daha yüksek SIII vardı. Tanısal incelemelere göre inmede SIII'ün tanısal değeri nötrofil/lenfosit oranından istatistiksel olarak anlamlı düzeyde daha yüksekti. Bu çalışma ayrıca, SIII ile karşılaştırıldığında, (Lenfosit x Trombosit)/Nötrofil oranının (yeni SIII olarak adlandırılır) inme tanısında ve erken hastane mortalitesini tahmin etmede daha yüksek bir istatistiksel öneme sahip olduğunu bulmuştur.

Sonuç: SIII, inme vakalarında hem tanısal değerlendirme hem de erken hastane mortalitesini öngörmek için iyi bir belirteç olabilir. Ayrıca ucuz ve kolay hesaplanabilmesi nedeniyle faydalı bir parametre olduğunu düşünmekteyiz.

Anahtar Kelimeler: İskemik inme, sistemik immün-inflamasyon indeksi, acil servis, prognoz

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INTRODUCTION

The World Health Organization (WHO) defines stroke as "rapidly developed clinical signs of focal or global deficit, lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin".[1] Acute ischemic stroke (AIS) remains one of the leading causes of mortality and morbidity worldwide.[2]

In the diagnosis of AIS, must suspect in the clinical evaluation, must conduct the physical examinations, and support the diagnosis with imaging tests or make a differential diagnosis. In cases of stroke, the computed tomography of the brain is performed to differentiate between hemorrhagic stroke and ischemic stroke, while the diffusion-weighted magnetic resonance imaging (MRI) is used to confirm AIS.[3,4] Besides the radiation exposure of patients in CT, the infeasibility of diffusion-weighted MRI in patients with metal implants can also render the diagnosis of AIS difficult.[5] Considering these difficulties, it is understood that there is a need for new diagnostic markers or indices to support the diagnosis in the diagnosis of AIS.

Modulation of the inflammatory cell function plays a role in repairing brain damage after ischemia. There is data in the literature reporting that systemic inflammatory response may be involved in the prognosis of AIS.[6,7]

Recently developed based on platelet, neutrophil and lymphocyte counts to examine patients simultaneously for immune status and inflammatory response, the systemic immune-inflammation index (SIII) was reported to be associated with poor prognosis in patients with malignancy in the literature.[8-10]

The current study investigates the SIII as a marker that facilitates easier diagnosis of AIS and analyzes it to establish whether it was a useful marker for clinicians for help to diagnosis AIS.

MATERIAL AND METHOD

Study Setting

The present study was retrospectively conducted between September 1, 2021 and December 1, 2021. The study included a study group of 150 patients with confirmed diagnosis of AIS and a control group of 150 individuals with non-AIS diagnoses.

Study Population

Among of study patients, those patients under the age of 18, pregnant patients and patients with missing data were excluded from the study. Patients who could not have a diffusion-weighted MRI since they had metal prosthesis implanted in their body, as well as those patients whose outcomes could not be followed up and whose medical histories were unknown were excluded from the study. And also included patients with any diagnosis of malignancies in their medical history, patients with history of hematologic disease, as well as septic patients with elevated laboratory values presenting with obvious infectious symptoms were excluded from the study.

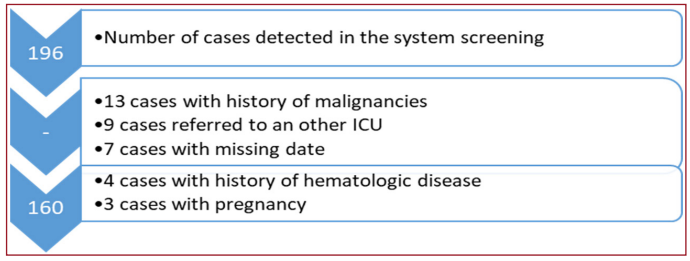
Patients aged 18 years and older, who came with a pre-diagnosis of AIS, whose medical history was known, and who did not have a history of any hematologic disease were included in the study. Patients who were in shock and whose vitals were unstable were not included in the study.

Data collection

To conduct the study, the file and automation system (Hospital Information Management System (HIMS)) was screened for patients to be included. The ICD10 diagnostic codes "I63.0-9, I64.0-9, I65.0-9, I66.0-9, I67.0-9 and I68.0-9" were used to screen for patients with AIS on the system. 196 patients were detected in the system screening. Of the 196 cases identified, 13 patients were excluded since they had history of malignancies, 9 were excluded as they were referred to another healthcare center due to lack of space in the intensive care unit (ICU), 7 were excluded because of missing data, 4 were excluded since they had history of hematological disease, and 3 were excluded due to pregnancy. Of the remaining 160 cases, 150 were randomized according to the date and time of hospital admission.

The control group was randomized in accordance with the inclusion and exclusion criteria of the study and in line with mean age of the patients. The control group included 150 patients who presented with "headache" but were not diagnosed with acute ischemic or hemorrhagic stroke. These patients were volunteers with known medical history.

Study Group



Data Calculation

In the present study, the laboratory results obtained in each case were used to calculate SIII ((NeutrophilxPlatelet)/ Lymphocyte), NLR (Neutrophil-to-Lymphocyte Ratio), PLR (Platelet-to-Lymphocyte Ratio), PNR (Platelet-to--Neutrophil Ratio), LNR (Lymphocyte-to-Neutrophil Ratio), and NSIII (is calculated Lymphocyte x Platelet) / Neutrophil). For those who were regularly smoking, it was allowed to smoke 1/2 package/ day. Mortality was based on the mortality of the patients during hospital stay. Due to the retrospective nature of the study, the patients were not followed up for their mortality status and causes after discharge.

Statistical Analyses

The SPSS 23.0 for Windows® statistics program (IBM Inc. Chicago, IL, USA) was used for the statistical analyses. The descriptive data were presented as number, percentage, mean, standard deviation, median, minimum, and maximum values. The distribution normality of the data was analyzed using the Kolmogorov-Smirnov Test. Pearson's chi-squared test and Fisher's Exact test were used to compare the categorical data. T Test was used to compare two independent groups of

numerical data and Kruskal Walles Test was used to compare three groups of numerical data. The obtained results were considered to be statistically significant at p<0.05, with a 95% confidence interval.

Ethical Considerations

Ethics committee approval was obtained from the ethics committee of our tertiary hospital (Ethics Committee no: 2021.04.34).

RESULTS

In our study, the data included demographic data of both the study and control groups, as well as their vascular risk factors, vitals at the time of admission, laboratory findings and SIII, NLR, PLR, PNR, LNR and reverse SIII values. According to these results, the rates of HT, CAD and smokers were found to be higher in the group of patients diagnosed with AIS. Similarly, the mean values of systolic and diastolic blood pressure were significantly higher in the study group. The group of patients with AIS had significantly higher neutrophil counts than the control group, while there was no difference between the two groups in terms of mean values of lymphocyte count and platelet count. The NLR and SIII calculated in the study group were significantly higher than in the control group and the PNR, LNR and NSIII were significantly lower in the study group than in the control group, while there was no difference between the two groups in terms of PLR (**Table 1**).

Table 1. Comparison of the demographic and clinical data of the study and control groups

Parameters	Study Groups (n=150) Mean±sd	Control Groups (n=150) Mean±sd	p
Demographic Data			
Male n (%)	90 (60.0)	85 (56.7)	0.558
Age (year)	65.49±12.89	65.21±12.29	0.848
Vascular Risk Factor			
Hypertension n (%)	87 (58.0)	62 (41.3)	0.004
Diabetes Mellitus n (%)	41 (27.3)	39 (26.0)	0.794
Coronary Artery Disease n (%)	56 (37.3)	36 (24.0)	0.012
Smoking n (%)	75 (50.0)	55 (36.7)	0.020
Vital Parameters			
Systolic BP (mmHg)	147.31±26.15	132.28±19.74	0.036
Diastolic BP (mmHg)	88.73±16.66	82.46±13.28	0.042
Pulse (beats/min.)	91.11±23.01	88.11±20.76	0.184
Laboratory Tests			
Neutrophil (x109/L)	5.50±5.43	4.11±4.84	0.020
Lymphocyte (x109/L)	1.87±0.95	2.03±0.94	0.129
Platelet (x109/L)	248.96±77.45	254.28±66.46	0.524
Ratings			
NLR	5.50±5.43	4.11±4.84	0.020
PLR	176.48±127.98	157.09±12.84	0.165
PNR	40.62±17.55	51.63±24.11	<0.001
LNR	0.31±0.20	0.42±0.25	<0.001
SIII	1367.96±1475.73	981.43±1031.34	0.009
NSIII	79.89±57.49	109.61±72.68	<0.001

sd: standard deviation; Smoking was considered positive for >1/2 pack/day use. BP: blood pressure; NLR: Neutrophil-lymphocyte ratio; PLR: Platelet lymphocyte ratio; PNR: Platelet neutrophil ratio; LNR: Lymphocyte neutrophil ratio; SIII: Systemic immune-inflammatory index; NSIII: The Novel systemic immune-inflammatory index

In the data analysis based on mortality status in the study group, mortality was found to be significantly higher in male cases. In addition, mortality was found to be higher in patients with history of HT and CAD. The mean value of neutrophil count of the cases with mortality was higher than that of the discharged group. The NIHSS score calculated based on the examination of the study group was significantly higher in the subgroup of patients with mortality (12.57±4.49 & 7.22±4.55; p<0.001). The rate of infarcts occurring in the MCA (Middle Cerebral Artery) and PCA (Posterior Cerebral Artery) watershed was significantly greater in the mortality subgroup compared to the subgroup of discharged patients, while the rate of infarcts in the ACA (Anterior Cerebral Artery) watershed was significantly lower in the mortality subgroup. The treatments administered were not associated with any significant difference in mortality. To compare the two subgroups of mortality and discharged patients, the NLR, PLR and SIII were statistically significantly higher and the PNR, LNR and NSIII were significantly lower in the mortality subgroup than in the subgroup of discharged patients. As expected, the rate of mortality was high in patients admitted to the intensive care unit. Again, the durations of hospital stay were found to be significantly higher in the subgroup of mortality (**Table 2**).

The cases were also studied for the time from the onset of the complaints until their admission by the emergency department, which was set and grouped as up to 4.5 hours and longer than 4.5 hours. Lymphocyte counts were significantly higher in patients admitted within the first 4.5 hours than in those admitted after 4.5 hours, while platelet counts were found to be significantly higher in patients admitted within the first 4.5 hours. We also found that PLR was significantly lower in the group of patients diagnosed with AIS (**Table 3**).

Table 3. Analysis of the demographic and clinical data by time until hospital admission

Parameters	Patient group admitted in the first 4.5 hours (n=69) Mean±sd	Patient group admitted after 4.5 hours (n=81) Mean±sd	p
Age (year)	64.23±13.60	66.57±12.24	0.270
Systolic BP (mmHg)	149.43±28.51	145.49±23.98	0.359
Diastolic BP (mmHg)	91.29±16.05	86.56±16.96	0.083
Pulse (beats/min.)	92.78±22.80	89.69±23.21	0.414
Neutrophil (x109/L)	7.26±3.82	6.93±2.80	0.545
Lymphocyte (x109/L)	2.06±1.01	1.70±0.88	0.021
Platelet (x109/L)	234.44±72.53	261.32±79.78	0.034
NLR	4.86±4.44	6.04±6.12	0.187
PLR	143.41±89.57	204.66±148.12	0.003
PNR	38.45±17.03	42.47±17.87	0.163
LNR	0.34±0.21	0.29±0.19	0.112
SIII	1093.91±1036.11	1601.40±1738.87	0.035
NSIII	83.57±59.19	76.76±56.19	0.472

Sd standard deviation; BP: blood pressure; NLR: Neutrophil-lymphocyte ratio; PLR: Platelet lymphocyte ratio; PNR: Platelet neutrophil ratio; LNR: Lymphocyte neutrophil ratio; SIII: Systemic immune-inflammatory index; NSIII: The Novel systemic immune-inflammatory index

Table 2. Comparison of demographic and disease data of discharged and exitus cases

Parameters	Exitus (n=19) Mean±sd	Discharge (n=131) Mean±sd	p
Demographic data			
Male n (%)	82 (64.6)	8 (34.8)	0.007
Age (year)	68.78±16.10	64.90±12.20	0.185
Vascular risk factor			
Hypertension n (%)	68 (53.5)	19 (82.6)	0.009
Diabetes Mellitus n (%)	36 (28.3)	5 (21.7)	0.513
Coronary artery disease n (%)	43 (33.9)	13 (56.5)	0.039
Smoking n (%)	62 (48.8)	13 (56.5)	0.497
Vital parameters			
Systolic BP (mmHg)	146.78±28.44	147.40±25.83	0.917
Diastolic BP (mmHg)	90.22±15.44	88.46±16.92	0.644
Pulse (beats/min.)	100.87±26.71	89.35±21.91	0.027
Laboratory tests			
Neutrophil (x10^9/L)	9.15±4.96	6.70±2.77	0.001
Lymphocyte (x10^9/L)	1.75±1.27	1.89±0.89	0.527
Platelet (x10^9/L)	239.78±82.26	250.62±76.77	0.539
Complaints start-hospital application time (hour)	4.83±3.39	11.10±17.40	0.088
NIHSS	12.57±4.49	7.22±4.55	<0.001
Ischemia area			
ACA	10 (7.9)	7 (30.4)	0.020
MCA	85 (66.9)	12 (52.2)	
PCA	32 (25.2)	4 (17.4)	
Treatment performed			
Medical	85 (66.9)	14 (60.9)	0.266
Thrombolytic reperfusion therapy	15 (11.8)	1 (4.3)	
Thrombectomy reperfusion treatment	27 (21.3)	8 (22.9)	
Rating			
NLR	8.24±6.80	5.00±5.01	0.008
PLR	226.19±198.41	167.48±109.37	0.043
PNR	31.59±14.53	42.25±17.60	0.007
LNR	0.22±0.19	0.33±0.20	0.014
SIII	1944.37±1955.37	1263.57±1355.02	0.041
NSIII	55.98±51.27	84.22±57.68	0.030
Place of hospitalization			
Service	3 (13.0)	78 (61.4)	<0.001
ICU	20 (87.0)	49 (38.6)	
Hospitalization period			
Service admission (day)	3.96±6.51	8.94±5.42	<0.001
ICU Hospitalization (day)	12.04±13.37	2.43±4.97	<0.001
Total Hospitalization (days)	16.00±13.82	11.37±7.17	0.017

sd: standard deviation; Smoking was considered positive for >1/2 pack/day use. BP: blood pressure; NLR: Neutrophil-lymphocyte ratio; PLR: Platelet lymphocyte ratio; PNR: Platelet neutrophil ratio; LNR: Lymphocyte neutrophil ratio; SIII: Systemic immune-inflammatory index; NSIII: The Novel systemic immune-inflammatory index

In study group, the factors that affected the diagnosis were analyzed and the logistic regression analysis was given in **Table 4**. HT, CAD, SIII, NLR, PNR and NSIII were found to be associated with increased suspicion for AIS diagnosis at a significant level.

Table 4. Evaluation of the results obtained in the multi-variate regression analysis in AIS diagnosis

Parameters	B	OR	%95 CI	p
Gender	-0.121	0.241	0.697-1.827	0.664
Smoking	0.421	2.69	0.397-1.085	0.101
Hypertension	-0.139	0.242	0.660-1.999	0.623
Diabetes Mellitus	0.649	6.73	0.320-0.753	0.009
Coronary Artery Disease	0.555	4.154	0.337-0.779	0.042
SII	0.410	1.326	1.026-1.874	0.008
NSII	0.294	1.246	1.140-1.728	0.034
NLR	0.368	1.392	0.896-1.644	0.038
PLR	0.260	3.35	0.998-1.055	0.165
PNR	0.304	1.425	1.096-1.848	0.028
LNR	0.221	1.164	1.002-1.774	0.053

Smoking was considered positive for >1/2 pack/day use; NLR: Neutrophil-lymphocyte ratio; PLR: Platelet lymphocyte ratio; PNR: Platelet neutrophil ratio; LNR: Lymphocyte neutrophil ratio; SIII: Systemic immune-inflammatory index; NSIII: The Novel systemic immune-inflammatory index

DISCUSSION

In a study, the human immune system is divided into two parts, innate and acquired immune system. The natural immune system constitutes the first line of defense against pathogens. The acquired immune system constitutes the secondary line of defense against inflammatory processes that are not caused by pathogens. It is one of the inflammatory processes that activates the immune system in AIS.[11]

In ischemic strokes, neutrophil migration occurs in the intra-parenchymal perivascular area within 6 to 24 hours following the ischemia, and neutrophils damage the blood-brain barrier with the cytokines they release into this area.[11] Lymphocytes migrate to the area 3 to 6 days after the stroke, and unlike neutrophils, undertake a regulatory function rather than acting with destructive impact. In this way, lymphocytes induce neuroprotection.[12,13] Apart from this regulatory effect of lymphocytes, the acquired immunity also leads to immunosuppression, which paves the way for opportunistic infections.[14]

In a study, platelets participate in immune response in addition to participating in hemostasis and thrombosis.[15] After stroke, activations begin in microglial cells, macrophages and mast cells, and proinflammatory cytokines are released as a result of these activations. With these released proinflammatory cytokines, activations begin in the hypothalamic–pituitary–adrenal axis and the release of catecholamines is induced by the activation of the sympathetic system.[16] As a result of all these activations, the stroke-induced inflammatory process begins. In the literature, Agus et al. reported that NLR, PNR and SIII calculated based on the blood cell counts were suitable for giving an insight about the balance between the innate and acquired immune systems.[17]

Our study investigates the diagnostic and prognostic values of NLR, LNR, PNR, PLR and NSIII, as well as of SIII, in patients admitted to the emergency department during the 4-month study period with suspected AIS and examined and then diagnosed with AIS by an experienced neurologist.

In our study, the mean NLR was found to be significantly higher in study group than in the control group. NLR was also found to be significantly higher in patients with mortality, compared to those surviving. Several underlying mechanisms are considered responsible for the poor progression in AIS that is attributed to NLR. In one of these mechanisms, after ischemic stroke, the NLR rate increases since the damaged brain tissue will produce a strong inflammatory response.[18] In some studies; in another mechanism, it is reported that circulating lymphocytes decrease due to the immunosuppression caused by catecholamines released from the sympathetic nervous system after the onset of stroke, and this mechanism is even reported to elevate the risk of infection after stroke.[19,20] This mechanism allows the use of neutrophils or lymphocytes alone to expose the imbalance between overactive inflammation and protective regulations.[21] In a study by Wang et al., the researchers reported that NLR was a successful index in predicting the risk of bleeding and predicting 3-month mortality in cases of AIS.[22]

In the studies available in the literature; the SIII, which combines platelet counts, neutrophil and lymphocyte clusters, represents the systemic immune response and has been found to be associated with poor outcome.[23] One of the major reasons here is the joint migration of leukocytes and platelets to the ischemia region and their interaction there. In an animal study, this interaction has been shown to control Cyclophilin D, a mediator of necrosis, and increase brain damage in the ischemic brain via this mediator.[24] In a study where Weng et al. included stroke cases that were performed intravenous thrombolytic, it is stated that the SIII is a good biomarker for predicting stroke severity and 3-month poor outcome.[25] Also, in a study where Zhou et al. included stroke patients, SIII is reported to be an independent predictor of negative outcomes of 3 months in patients. Additionally, the same study states that nomogram scoring with the SIII that is calculated in the next few hours after hospital admission can offer information for clinicians by predicting the likelihood of short-term negative outcomes in stroke cases.[26] In a study where Hu et al. focus on stroke, compared to other inflammatory markers, high SIII values are reported to be of a significantly higher value in determining post-stroke depression.[27] In a study of patients with aneurysmal subarachnoid hemorrhages, Yun et al. stated that SIII can be a useful indicator for poor prognosis.[28] In a study where Yi et al. included patients with AIS who underwent thrombectomy, high SIII is reported to be associated with poor results and may be a prognostic marker in AIS cases with large artery occlusion.[29] In our study, the mean SIII was found to be significantly higher in the cases of AIS than in the control group.

The SIII in the group of stroke patients admitted after 4.5 hours was found to be significantly higher than that of those admitted within the first 4.5 hours following the onset of symptoms. Similar to NLR, the mean SIII was significantly higher in the subgroup of mortality than in the subgroup of surviving cases. In addition, compared to NLR in terms of diagnostic value, the success of SIII in predicting AIS was significantly greater. In our study, we found that the SIII may be a utile biomarker for determining both diagnostic and early in-hospital mortality. Our data support the studies available in the literature.

In our study, we noticed that we had a noteworthy finding based on the data we obtained with the SIII. The (lymphocyte x platelet) / neutrophil ratio (i.e. the inversed version of neutrophil-to-lymphocyte ratio), which we called NSIII, had a higher statistical significance in AIS cases compared to the SIII that we calculated in our study ($p=0.009$ and $p<0.001$). In addition, this correlation continued in cases with mortality ($p=0.041$ and $p=0.030$). In addition, compared to the control group, LNR and PNR were statistically more significant than NLR and PLR in the group of AIS cases. However, this data needs to be verified with further studies to be done in the literature.

To conclude, in our study, the SIII was found to be significantly higher in the group of AIS cases than in the control group. The SIII was higher at a statistically significant level in the patients with early in-hospital mortality. We believe that this finding will serve as a warning to clinicians so they pay greater attention to the risk of mortality in cases with high SIII. Again, the group of stroke patients admitted after 4.5 hours had significantly higher SIII than those admitted within the first 4.5 hours. This result supports our opinion that SIII may be a guiding index in cases that requires a decision to be made to administer thrombolytic treatment, which may be further investigated by future studies.

Limitations of Study

There are several limitations in our study. The first of these limitations is the small number of participants included in both of the study and control group although the numbers foreseen by the power analysis data were used. The second limitation is that the study is limited to the data that was available to the clinicians although our study is retrospective and despite the proper recording of the data used here. Another limitation is that the time until hospital admission in each case was recorded as per the history reported by each individual patient. We do not think that the errors that will occur due to this data would be substantial to an extent where they could affect the results of the study.

CONCLUSION

According to many studies, compared to other ratios and indexes, the SIII is promising in demonstrating a systemic immune-inflammation response. Our study suggests that SIII is a good marker in diagnosing AIS, evaluating the response based on the time until hospital admission, and predicting early in-hospital mortality. We also found that the index called NSIII, which we created using the formula (lymphocyte x platelet)/ neutrophil, had a significantly higher diagnostic and predictive value in predicting early in-hospital mortality than the SIII had. However, this data needs to be supported by further studies to be conducted in the literature.

ETHICAL DECLARATIONS

Ethics Committee Approval: The Ethics committee approval was obtained for this study from Ministry of Healthy Başaksehir Çam and Sakura State Hospital Ethics Committee (Decision No: 2021.04.34)

Informed Consent: All participants 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.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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