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Prognostıc and diagnostic importance of the systemic immune-inflammation index in pediatric head trauma

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Abstract

Head trauma is a leading cause of mortality and morbidity in pediatric patients. The trauma itself leads to the activation of a biomolecular cascade of damage. Purinergic receptors and ATP release play an important role in the activation of astroglia, microglia, monocyte-macrophages, neutrophils, and T cells in this process. The systemic immune inflammation index can be easily calculated, cheap, only requires hemogram parameters, and does not include any subjective findings. Therefore, we believe that it could be a prognostic predictor and a diagnostic marker for pediatric head trauma cases. Our study was designed as a retrospective and single-center study. The study was conducted with pediatric patients who presented to the emergency department with isolated head trauma between June 15, 2022, and December 15, 2022. Demographic data, medical history, white blood count, platelet count, neutrophil count, systemic immune inflammation index (SIII), Glasgow Coma Score, and the presence of pathology on brain computed tomography were recorded on the case report form. The study was conducted with 112 cases. In cases with bleeding, the median value of GCS was significantly lower ($p<0.001$), while WBC, Neutrophil, Platelet, NLR and SIII were significantly higher ($p=0.008$, $p=0.001$, $p<0.001$, $p=0.011$, and $p<0.001$, respectively). There was no significant difference between lymphocyte values and bleeding status. We believe that a higher SIII may be associated with persistent pericontusional inflammation in the brain and may be a good marker for predicting intracranial pathology and prognosis of the pathology caused by head trauma.

Keywords: Pediatric brain trauma, prognosis, systemic immune-inflammation index

Introduction

Traumatic brain injury (TBI) is one of the leading causes of mortality and morbidity in pediatric patients in developed countries. TBI is the most common type of injury encountered [1]. Approximately 10 million children worldwide suffer from traumatic brain injury, and these injuries lead to significant increases in mortality and morbidity [2,3].

Due to higher cerebral activity and lower energy substrate availability for use in pediatrics, delays in treatment, and more frequent occurrence of secondary lesions, mortality rates may be higher in children than in adults [4]. The trauma itself leads to the activation of a biomolecular cascade that causes damage. During this process, purinergic receptors and ATP release play an important role in the activation of astrocytes, microglia, monocytes-macrophages, neutrophils, and T cells. Neutrophils are the first responders to tissue damage in the nervous system. Like in other neurological pathologies, these cells play a pro-inflammatory role and contribute to blood-brain barrier damage, the release of cytokines and oxygen radicals, cell death, and

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the activation of glial cells in the central nervous system. This contributes to both neuronal repair and the amplification of the inflammatory process [5]. Platelets help by adhering to the damaged vessel wall and aiding in the release of platelet granules, which is also crucial for thrombus formation. Additionally, platelets play an important role in local inflammation. They can activate some white blood cells, including granulocytes, lymphocytes, and monocytes, and these cells can promote the release of inflammatory cytokines [6].

White blood cells, neutrophil, lymphocyte and platelet (PLT) values, which are among the complete blood count parameters, and the ratios of these values to each other (neutrophil lymphocyte ratio and platelet lymphocyte ratio) are used as inflammatory markers. These are an inflammatory marker that can be examined in routine hemogram examination recently [7].

The systemic immune inflammation index (SIII) is a new systemic inflammatory indicator that has been used as both a diagnostic and prognostic predictor in many internal and surgical diseases [8]. The SIII provides accurate information about the acute inflammatory process by evaluating changes in the number of neutrophils, lymphocytes, and platelets from inflammatory cells. The SIII can be easily calculated, cheap, only requires hemogram parameters, and does not include any subjective findings. Therefore, we believe that it could be a prognostic predictor and a diagnostic marker for pediatric TBI cases.

Material and Methods

The study was conducted as a retrospective, single-center study after obtaining approval from the Başakşehir Çam and Sakura City Hospital Clinical Research Ethics Committee (Ethics Committee No: 2022-210). The study was conducted on pediatric patients who presented to the emergency department with isolated head trauma between June 15, 2022, and December 15, 2022, and met the inclusion criteria for the study. The patients were identified through the hospital's automated medical record system (HBYS). The study included patients who were under 18 years of age, had isolated head trauma, underwent brain computed tomograpy (CT) imaging and complete blood count, and whose data could be accessed through the HBYS system. Patients who were over 18 years of age, had trauma other than head trauma, had missing data, were pregnant, had a known malignancy, hematological disease, or bone marrow pathology, or had suspected infection were excluded from the study.

The demographic data, medical histories, WBC, platelet count, neutrophil count, SIII, Glasgow Coma Scale, and the presence or absence of pathology on the brain CT were obtained from the hospital automation system and recorded on the case form. Patients were divided into two groups based on the presence or absence of pathology on the brain CT scan. A total of 132 patients who presented to the emergency department with isolated head trauma were included in the study. Thirteen patients were excluded from the study due to missing data, and seven patients were excluded due to having hematological malignancy or suspected infection. The remaining 112 patients were divided into two groups; 47 with pathology detected on brain CT and 65 with no pathology detected.

The study used the hemogram results obtained for each case to make calculations. P, N, and L refer to peripheral platelet, neutrophil, and lymphocyte counts, respectively. Based on these values, NLR (N/L Ratio) and SIII ((P x N)/L ratio) were calculated [8].

Statistical analysis

The statistical analysis of the study was conducted using the IBM SPSS Statistics 26.0 program for Windows® (IBM Inc. Chicago, IL, USA). Descriptive statistics including number, percentage, mean, standard deviation, median, minimum, and maximum were used to present the data. The normality of the data was evaluated using the Kolmogorov-Smirnov test. Pearson's chi-square test and Fisher's exact test were used for the comparison of categorical data. The Mann-Whitney U test was used to compare numerical data that did not follow a normal distribution. ROC curve analysis was performed to describe the success of NLR and SIII in detecting pathology and bleeding in brain CT scans. The level of significance was set at $p<0.05$, with a 95% confidence interval.

Results

The study was conducted with 112 cases. Of the cases, 62.5% (n=70) were women and the median age was 8 (2.25-13.75) years. The cases were evaluated and 58% (n=65) had no pathology, while 42% (n=47) had pathology. Demographic, clinical, and laboratory values of the cases were examined according to the presence of pathology, and presented in Table 1. There was no significant difference in age between cases with and without pathology. There was no significant relationship between gender and the presence of pathology. In cases with pathology, the median value of GCS was significantly lower ($p<0.001$), while WBC, Neutrophil, PLT, NLR, and SIII were significantly higher ($p=0.001$, $p<0.001$, $p=0.025$, $p=0.014$, and $p=0.002$, respectively). There was no relationship between median lymphocyte values and the presence of pathology.

Of the cases, 59.8% were discharged after evaluation and testing, 17.9% were hospitalized for follow-up and treatment, 21.4% were hospitalized in the ICU for follow-up and treatment, and only 1 case (0.9%) was considered deceased despite interventions in the emergency department. When all cases were evaluated, mortality was observed in 3.6% (n=4) of the cases (Table 1).

When the outcomes and mortalities of the cases were examined according to the presence of pathology, it was observed that hospitalizations in the ward and intensive care unit were significantly higher in cases with pathology. Mortality was only observed in cases with detected pathology (Table 1).

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Table 1. Analysis of demographic, clinical and laboratory data of the cases according to the presence of pathology

Parameter		All cases n (%)/Median (IQR)	Pathology (-) (n=65) n (%)/Median (IQR)	Pathology (+) (n=47) n (%)/Median (IQR)	p
Age (year)		8.0 (2.25-13.75)	8.0 (2.5-13.5)	8.0 (2.0-14.0)	0.885[m]
Gender	**Female**	42 (37.5)	25 (38.5)	17 (36.2)	0.805[p]
	Male	70 (62.5)	40 (61.5)	30 (63.8)	
GKS		15 (15-15)	15 (15-15)	14 (8-15)	**<0.001[m]**
WBC (x10³/mm³)		11.06 (8.23-15.57)	9.89 (7.87-12.23)	14.13 (9.5-17.9)	**0.001[m]**
Neu (x10³/mm³)		5.8 (3.76-9.68)	4.8 (2.92-7.10)	8.45 (5.20-12.93)	**<0.001[m]**
Lenf (x10³/mm³)		3.34 (2.31-5.13)	3.47 (2.04-5.01)	3.13 (2.44-5.54)	0.688[m]
Plt (x10³/mm³)		290.0 (239.3-345.8)	281.00 (227.0-326.5)	305.0 (254.0-391.0)	**0.025[m]**
NLR		1.76 (1.05-3.26)	1.53 (0.74-3.01)	2.18 (1.38-4.27)	**0.014[m]**
SIII (x10³/mm³)		566.42 (265.72-1022.41)	455.24 (217.82-788.10)	758.22 (409.40-1226.01)	**0.002[m]**
Outcome	**Discharge**	67 (59.8)	60 (92.3)	7 (14.9)	**<0.001[p]**
	Service admission	20 (17.9)	4 (6.2)	16 (34.0)	
	ICU admission	24 (21.4)	1 (1.5)	23 (48.9)	
	Emergency exitus	1 (0.9)	0 (0.0)	1 (2.1)	
Mortality	**Yes**	108 (96.4)	65 (100.0)	43 (91.5)	**0.029[f]**
	No	4 (3.6)	0 (0.0)	4 (8.5)	

IQR: inter quarter range, GCS: glasgow coma scale, WBC: white bloodcell, Neu: neutrophil, Lymph: lymphocyte, Plt: platelet, NLR: neutrophil lymphocyte ratio, SIII: systemic immune inflammatory index, mm: millimeters, p: pearson $\chi 2$ tests, m: Mann Whitney U-test, f: Fisher's exact test

The pathology types and lesion locations of cases with detected pathology are shown in Table 2. As a result of the evaluation, no pathology was found in 58% (n=65) of the cases. It was observed that only fractures were present in 17.9% of the cases, fractures with epidural bleeding were present in 5.4%, fractures with parenchymal bleeding were present in 7.1%, fractures with subarachnoid bleeding were present in 6.3%, only parenchymal bleeding was present in 3.6%, and subarachnoid bleeding was present in 1.8% of the cases. It was observed that 29.8% of these lesions were in the frontal region, 17% were in the temporal region, 17% were in the parietal region, 12.8% were in the occipital region, 8.5% were in the parenchyma, and 14.9% were in other regions.

An evaluation was made of the cases, where 75.9% (n=85) had no bleeding and 24.1% (n=27) had bleeding. The demographic, clinical, and laboratory values of the cases were examined according to the presence of bleeding, and presented in Table 3. There was no significant difference in age between cases with bleeding and those without bleeding. There was no significant relationship between gender and bleeding presence. In cases with bleeding, the median GCS value was significantly lower ($p<0.001$), while WBC, Neutrophil, Platelet, NLR, and SIII were significantly higher ($p=0.008$, $p=0.001$, $p<0.001$, $p=0.011$, and $p<0.001$, respectively). There was no significant difference in lymphocyte values according to the bleeding status.

Only one of the cases with bleeding was discharged, while all other cases were hospitalized. 70.4% (n=19) of these cases were followed in the ICU, and only one of them died in the emergency department. All cases with mortality had bleeding ($p=0.003$) (Table 2).

When the results of the ROC Curve analysis to determine the power of NLR and SIII in detecting the presence of pathology in cases were examined, it was seen that NLR had an AUC of 0.637 for the cutoff value of 1.16 to detect the presence of pathology in CT, and had a sensitivity of 87.2% and specificity of 38.5% at this cutoff value (95% CI=0.537-0.739). Similarly, it was seen that SIII had an AUC of 0.669 for the cutoff value of 276.27 (x103/mm3) to detect the presence of pathology in CT, and had a sensitivity of 89.4% and specificity of 38.5% at this cutoff value (95% CI=0.570-0.769). When these values were examined, it was seen that SIII was more significant than NLR in detecting the presence of pathology in CT in pediatric cases with head trauma. Likewise, when the power of NLR and SIII in detecting the presence of bleeding in CT was examined, it was seen that NLR had an AUC of 0.662 for the cutoff value of 2.67, and had a sensitivity of 55.6% and specificity of 72.9% at this cutoff value (95% CI=0.546-0.779). Similarly, it was seen that SIII had an AUC of 0.739 for the cutoff value of 633.64 (x103/mm3), and had a sensitivity of 77.8% and specificity of 64.7% at this cutoff value (95% CI=0.635-0.844). When these values were examined, it was seen that SIII was more significant than NLR in detecting the presence of bleeding in CT in pediatric cases with head trauma (Table 3 and Figure 1).

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Table 2. Analysis of demographic, clinical and laboratory data of the cases according to bleeding status

Parameter		Bleeding (+) (n=27) n (%)/Median (IQR)	Bleeding (-) (n=85) n (%)/Median (IQR)	p
Age (year)		6.0 (2.0-13.0)	8.0 (3.5-14.0)	0.628[m]
Gender	**Female**	12 (28.6)	30 (71.4)	0.392[p]
	Male	15 (21.4)	55 (78.6)	
GKS		10.0 (6.0-14.0)	15.0 (15.0-15.0)	**<0.001[m]**
WBC (x10³/mm³)		15.09 (9.47-19.03)	10.14 (8.14-13.31)	**0.008[m]**
Neu (x10³/mm³)		9.32(5.39-13.34)	5.13 (3.39-8.18)	**0.001[m]**
Lenf (x10³/mm³)		3.06 (2.30-5.65)	3.48 (2.32-5.13)	0.825[m]
Plt (x10³/mm³)		358.0 (290.0-412.0)	280.0 (225.0-324.5)	**<0.001[m]**
NLR		2.73 (1.53-5.93)	1.55 (0.92-3.09)	**0.011[m]**
SIII (x10³/mm³)		925.09 (640.97-1516.81)	437.010 (231.71-798.26)	**<0.001[m]**
Outcome	**Discharge**	1 (3.7)	66 (77.6)	**<0.001[p]**
	Service admission	6 (22.2)	14 (16.5)	
	ICU admission	19 (70.4)	5 (5.99)	
	Emergency exitus	1 (3.7)	0 (0.0)	
Mortality	**Yes**	23 (85.2)	85 (100.0)	**0.003[f]**
	No	4 (14.8)	0 (0.0)	

IQR: inter quarter range, GCS: glasgow coma scale, WBC: white bloodcell, Neu: neutrophil, Lymph: lymphocyte, Plt: platelet, NLR: neutrophil lymphocyte ratio, SIII: systemic immune inflammatory index, mm: millimeters, p: pearson $\chi 2$ tests, m: Mann Whitney U-test, f: Fisher's exact test

Table 3. ROC Curve analysis results of NLR and SIII for pathology detection and bleeding detection in CT

Parameter		Cut off	AUC	Sensitivity	Specificity	p	%95 CI
Pathology (+)	**NLR**	1.16	0.637	87.2	38.5	**0.014**	0.537-0.739
	SIII	276.27	0.669	89.4	38.5	**0.002**	0.570-0.769
Pathology (-)	**NLR**	2.67	0.662	55.6	72.9	**0.011**	0.546-0.779
	SIII	633.64	0.739	77.8	64.7	**<0.001**	0.635-0.844

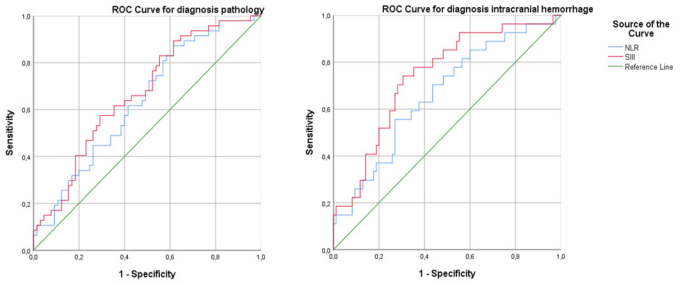

Figure 1. ROC Curve analysis of NLR and SIII for pathology detection in CT

Discussion

Numerous studies in the literature have shown that NLR is a good predictor of outcomes after traumatic brain injury [9-12]. However, this is the first study to compare the role of the SIII with NLR in predicting outcomes in pediatric patients with head trauma. This study showed that the SIII was a successful predictor of the presence of cranial pathology in pediatric patients presenting to the emergency department with head trauma. When comparing the neutrophil-to-lymphocyte ratio with the SIII in predicting the presence of pathology on CT in pediatric patients with head trauma, the SIII was found to have higher sensitivity and statistically more significant results than NLR.

In cases where pathology was detected on computed tomography, leukocyte and neutrophil counts were high while the mean GCS score was low, which was already expected in cases of brain hemorrhage. Experimental studies have shown that neutrophils migrate to the lesion area within the first hour, and since neutrophils make up 50-70% of circulating leukocytes, an increase in neutrophil and leukocyte counts is expected [13,14]. Eser et al. stated in their study on pediatric patients with head trauma that the neutrophil-to-lymphocyte ratio was higher in cases with pathological findings on brain CT. When comparing cases with fractures detected on brain CT with cases with intracranial hemorrhage, it was seen that NLR was higher in cases with bleeding. Our study had similar results. However,

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in the same study, it was noted that platelet counts were lower in cases requiring surgery. In our study, it was observed that platelet counts were higher in cases with pathological findings. We think that this difference is due to the comparison of cases requiring surgery and those who do not in the study by Eser et al. [15]. In another study by Kimball et al., it was stated that high NLR was associated with poor outcomes [16].

In a study by Luo et al on patients with subarachnoid hemorrhage, high SIII values were shown to be associated with unfavorable functional outcomes [17]. Chen et al. showed in their study on adult patients with severe traumatic brain injury that patients with high SIII had worse prognosis [18]. In another study conducted by Yun at al on 680 patients with subarachnoid hemorrhage, they similarly reported that high SIII values could be an independent predictor of poor prognosis [19]. In a study by Hou and colleagues on aneurysmal subarachnoid hemorrhage patients, they showed that high SIII values at admission were associated with worse clinical status and functional outcomes [20]. In our study, it was observed that SIII values were higher in pediatric patients with head trauma who had both bleeding and fracture.

Conclusion

Pediatric head trauma is a clinical condition that can lead to serious consequences. The inflammatory process that occurs as a result of head trauma can vary depending on the patient's clinical condition and diagnosis at the time of initial presentation. Based on our findings, a higher SIII may be associated with persistent pericontusional inflammation in the brain, and may serve as a good predictor of both intracranial pathology and prognosis of the pathology following head trauma. However, this hypothesis needs to be confirmed in further studies.

Limitation

The most important limitation of the presented study is that it is a retrospective study, it is single-centered, and the number of cases is low.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical Approval
The study was conducted as a retrospective, single-center study after obtaining approval from the Başakşehir Çam and Sakura City Hospital Clinical Research Ethics Committee (Ethics Committee No: 2022-210).

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