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Is neutrophil-to-lymphocyte ratio a prognostic marker for traumatic brain injury in the pediatric population?

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Abstract. – OBJECTIVE: The neutrophil-to-lymphocyte ratio (NLR) is used for the prognosis of diseases characterized by inflammatory processes. This study aims to discuss the long-term outcomes and NLR in pediatric traumatic brain injury cases.

PATIENTS AND METHODS: This study investigated traumatic brain injury patients younger than 18 years. Patients were grouped into 5 groups according to their Glasgow outcome scores (GOS). Initial admission Glasgow coma scale (GCS) values, neurological examinations, pupil conditions, cardiopulmonary resuscitation (CPR) administration, and seizure occurrence were recorded. Neutrophil counts and lymphocyte counts, derived from complete blood count (CBC) values taken during the patient's first 8 hours of admission, were used to calculate the NLR value.

RESULTS: A total of 150 patients, 54 (36%) females and 96 (64%) males, were assessed in the study. The most frequent accident type was falling from a height [84 patients (56%)]. The GCS, CPR, pupillary reflex, anisocoria, surgical procedure, and neutrophil counts were significantly different between the GOS scores. There was no statistically significant difference between the GOS and the NLR (p=0.400). There was a significant difference in NLR value according to CPR, seizures, and brain injury type (p<0.05).

CONCLUSIONS: NLR values are not correlated with 1-year outcome scores in pediatric traumatic brain injury patients, unlike proven parameters such as initial GCS scores and neurological status.

Key Words:
Traumatic head injury, Pediatric trauma, Neutrophil-to-lymphocyte ratio, Glasgow coma scale, Glasgow outcome scale.

Introduction

Trauma is a notable cause of morbidity and mortality in all age groups, including the pediatric population, where it is particularly difficult to prevent. Traumatic injuries, specifically those affecting the brain, are the leading cause of death and a significant risk factor among children[1].

Traumatic brain injury (TBI) has been identified as the most common cause of mortality in cases of trauma involving individuals under the age of 18 in the United States. Lesions in the central nervous system are responsible for approximately 80% of trauma-related deaths[2]. Most children who survive their injury encounter adverse outcomes within a six-month period. In the context of nonfatal traumas, it is imperative to prevent disability and ensure the predictability of treatment outcomes[3].

TBI has a direct impact on normal cellular function in the brain, primarily through the application of rotational and shear forces. Secondary damage mechanisms arise due to both focal and diffuse damage mechanisms following an injury, accompanied by an inflammatory response that initiates within a time frame of 4 to 6 hours[4].

The neutrophil-to-lymphocyte ratio (NLR) is a quantitative measure obtained by dividing the neutrophil count by the lymphocyte count in the easily obtainable complete blood count (CBC). This method has been linked to assessing the prognosis of conditions characterized by inflammatory processes, including several types of cancer, cardiovascular diseases, and organ failure.

Although there is a rich literature investigating the importance of the NLR as a prognostic indicator in TBI among adults, a paucity of research has focused on the pediatric population[5,6]. Furthermore, they did not assess long-term outcomes and surgical interventions. This study investigates the utility and relevance of the NLR value for long-term prognosis assessment in pediatric TBI cases in a trauma center.

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Patients and Methods

Study Design

This study investigated patients who were admitted to the trauma center of our Prof. Dr. Suleyman Yalcin City Hospital during the period spanning from 2018 to 2023. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration. Ethics committee approval was granted from our Istanbul Medeniyet University with number 2023/0465.

The study included individuals who were younger than the age of 18 and investigated cases of trauma that were accompanied by TBI. The study excluded individuals who did not have any TBI. The study excluded individuals who had hematological, rheumatological, or oncological diseases, individuals who received immunosuppressive treatment, and individuals who were currently taking antibiotics for acute infection. The additional exclusion criteria included severe clinically diagnosed comorbidities, previous neurological disorders such as ischemic or hemorrhagic stroke, utilization of anticoagulant medication, steroids, or immunosuppressants, and pre-existing systemic conditions including uremia, liver cirrhosis, malignancy, chronic heart disease, diabetes, and hypertension. The patients were categorized into three groups based on the affected body region: isolated TBI, TBI-weighted multitrauma, and thoracic trauma-weighted multitrauma. Thus, patients were grouped into 5 groups according to their outcome scores, and the results were compared with each other. Initial admission Glasgow Coma Scale (GCS) values and neurological examinations were documented for trauma patients. On admission, pupil conditions, cardiopulmonary resuscitation (CPR) administration, and seizure occurrence were recorded. Neutrophil counts and lymphocyte counts, derived from CBC values taken during the patient's first 8 hours of admission, were used to calculate the NLR value.

Pediatric patients who applied for trauma and 197 patients who met the inclusion criteria were included in our study. The data and follow-up of the patients were planned prospectively and then analyzed retrospectively from the hospital's electronic reports. Randomization was not performed. After trauma, the patients were followed for 1 year. The outcome scores of the patients were decided by 1st-year hospital examinations. 47 patients with loss of communication at 1-year follow-up were excluded from the study. The records also included information regarding whether the patients underwent surgical procedures. The first year's outcomes were documented during the long-term follow-up period after the treatment. The classification of outcomes was determined by considering patient survival and the Glasgow Outcome Scale (GOS) score[7]. The calculation of individual NLRs involves dividing the absolute neutrophil count by the absolute lymphocyte count. No control group was used to investigate the difference of NLR on outcome.

Upon admission, the patients underwent radiological assessments using initial computed tomography (CT scan). In instances of focal hematoma, surgical intervention involving hematoma evacuation was performed. In cases of midline shift and edema, decompressive craniectomy was performed at the same time. If any of these factors were absent, the patients did not undergo surgical intervention.

Statistical Analysis

Data analysis was performed using the Statistics Package for Social Science (SPSS v. 23, IBM Corp., Armonk, NY, USA). A two-tailed Kolmogorov-Smirnov test was applied to examine whether the continuous quantitative variables followed a Gaussian distribution. Characteristics of patients, as n (percent) or median (minimum-maximum) for categorical and continuous variables, respectively, were reported. Nominal variables were compared using a two-tailed Chi-square or Fisher's exact test, when applicable. The "Mann-Whitney U" test was used in the comparison of the measurement values of two independent groups; the "Kruskal-Wallis H" test was used in the comparison of the measurement values of three or more independent groups. The statistical significance of differences between groups was determined by the Kruskal-Wallis test followed by post hoc Mann-Whitney U test with Bonferroni adjustment. The p-value was set at <0.05 for statistical significance.

Results

197 patients who met the inclusion criteria were included in our study. 47 patients with loss of communication at 1-year follow-up were excluded from the study. One hundred fifty patients in total, 54 (36%) female and 96 (64%) males, were assessed as part of the study. The patients' median age was 5, ranging from 0 to 17. The most

frequent trauma type, which accounted for 84 patients (56%), was falling from a height. Non-vehicle traffic accidents came in second, with 42 patients (28%). There were 59 patients (39.3%) with TBI from multiple traumas and 73 (48.7%) with isolated TBI. One hundred thirty of the patients (86.7%) underwent no surgical procedure. Twenty of all patients (13.3%) ended in death, and the majority (60.7%) had low impairment (good recovery) (Table I) (Figure 1).

There was a significant statistical difference in neutrophil-to-lymphocyte ratios among the accident types, with and without CPR and with and without seizures ($p<0.05$) (Table I).

The demographic and clinical characteristics of patients were analyzed according to their one-year GOS (Table II). Baseline data on GCS, CPR, pupillary reflex, anisocoria, surgical procedure, and absolute neutrophil count differed significantly between GOS groups ($p<0.05$). Notably, GCS scores were significantly different between death and low disability, severe disability and low disability, and moderate disability and low disability ($p<0.001$). There was a significant difference in absolute neutrophil count between patients who died and those with permanent disability ($p=0.018$). However, there was no statistically significant difference in NLR rate and 1-year GOS ($p=0.400$) (Figure 2) (Table II).

The demographic and clinical outcomes were categorized as dead or alive based on the GOS at the end of one year and are displayed in Table II. The deceased and living groups showed significant differences in GCS, CPR, pupillary reflex, surgical, and neutrophil values ($p<0.05$). Nonetheless, no statistically significant difference was observed in the NLR between the death and alive groups ($p=0.120$) (Table II).

Discussion

TBI is a widespread health problem characterized by increasing morbidity and mortality[8]. After the initial brain injury, it is beneficial to use evidence-based monitoring methods to reduce col-

Table I. Distribution of demographic and clinical findings by Neutrophil/Lymphocyte ratio.

Data	Characteristics (N=150)	n (%) or Median (Min-Max)	NLR Median (Min-Max)	*p*-value
Trauma Type	Blunt trauma[1]	5 (3.3)	3.6 (1.0-19.3)	**<0.001***
	Fall from height[2]	84 (56)	**4.7 (0.3-29.0)**	
	In-vehicle traffic accident[3]	11 (7.3)	9.5 (2.1-17.0)	
	Non-vehicle traffic accident[4]	42 (28)	**12.1 (0.7-49.2)**	
	TV drop[5]	8 (5.3)	5.6 (3.4-32.3)	
Body Part	Isolated head injury	73 (48.7)	8.4 (0.3-49.2)	0.402
	Multiple trauma-Head	59 (39.3)	6.0 (0.3-35.5)	
	Multiple trauma-Thorax	18 (12)	5.0 (1.2-37.1)	
CPR	No		**7.5 (0.3-49.2)**	**<0.001**
	Yes		**1.4 (0.3-6.8)**	
Pupillary reflex	Negative		3.5 (0.3-32.3)	0.282
	Positive		6.8 (0.3-49.2)	
Anisocoria	Negative		6.6 (0.3-49.2)	0.928
	Positive		5.5 (0.3-32.3)	
Seizure	No		**8.4 (0.3-49.2)**	**0.039**
	Yes		**3.7 (1.3-15.1)**	
GOS (1-year)	Death	20 (13.3)	2.6 (0.3-20.5)	0.400
	Persistent vegetative state	6 (4)	7.6 (2.6-14.9)	
	Severe disability	17 (11.3)	6.9 (2.3-23.1)	
	Moderate disability	16 (10.7)	11.1 (1.0-32.3)	
	Low disability	91 (60.7)	6.3 (0.3-49.2)	
Surgery	No		6.0 (0.3-49.2)	0.094
	Yes		9.6 (1.3-32.3)	

GCS: Glasgow Coma Scale, NLR: Neutrophil/ Lymphocyte ratio, CPR (Cardiopulmonary resuscitation), GOS: Glasgow Outcome Score. *The difference was between 2-4.

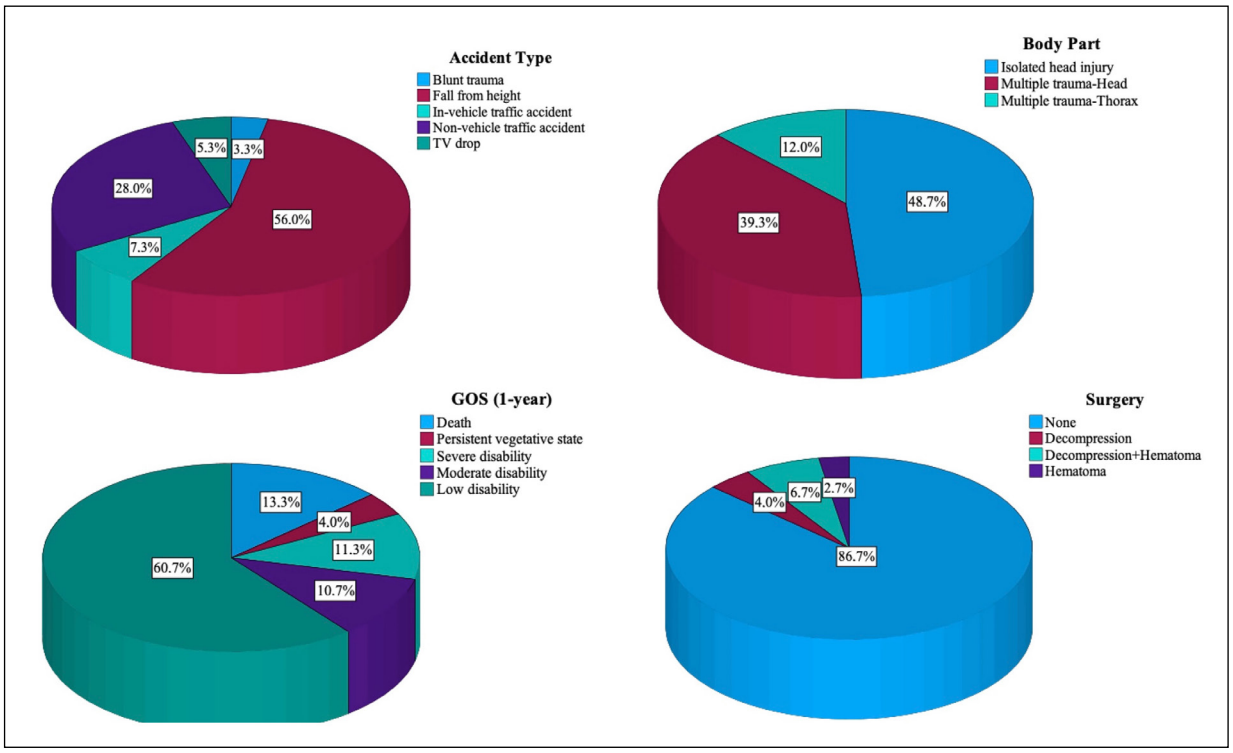

Figure 1. Distribution charts of patients with pediatric traumatic brain injury according to trauma type, body part, Glasgow outcome scale (GOS) and surgery.

lateral damage and consequently improve patient outcomes[9]. Among these secondary mechanisms, neuroinflammation is recognized as a major contributor to the progression of pathologies[10].

The occurrence of pathological inflammatory and anti-inflammatory responses within the initial hours after extensive trauma is a significant determinant of mortality in post-traumatic patients. These responses pose challenges in terms of control and differentiation from a normal immune reaction[11]. The recent focus has been on the examination of the interplay between these two opposing inflammatory responses in trauma patients and their potential as prognostic indicators for patient outcomes.

The NLR is a commonly accessible and easily measurable marker. It has been experimentally proven to possess substantial predictive capabilities for outcomes of various medical conditions, including COVID-19 infection[12], cardiovascular diseases[13], kidney disease[14], and oncology[15]. There are retrospective studies[16] in the adult population of trauma patients. However, there is not much data on pediatric patients in the literature. In our study, we aimed to investigate the effect of the inflammatory process that plays a role in TBI and to find out whether the NLR obtained from CBC blood taken in the first 8 hours can be used to predict the 1-year prognosis.

Studies[16-18] in adults to determine prognosis in TBI have worked with many patients and evaluated outcomes at 15 days[17] or 30 days[16], 6 months[18]. There was a significant correlation between these short-term prognoses and NLR. In fact, an NLR above 7.44 was considered an independent prognostic marker[17]. We believe that NLR alone cannot determine TBI prognosis due to its non-specific nature as a marker that increases after an inflammatory event in the body.

It is imperative to conduct separate examinations for pediatric cases due to the distinct characteristics of blood charts and inflammatory responses in pediatric patients compared to adults. Numerous parameters have been investigated to predict the prognostic outcome in pediatric patients with TBI. Neutrophils may harm the blood-brain barrier, cause neuronal cell death, and stimulate oxidase expression, resulting in a negative prognosis for patients with TBI[17]. Unlike adult patients, the pediatric population has a brain structure that is still developing. Neuronal regeneration is ongoing in the pediatric population[19]. Therefore,

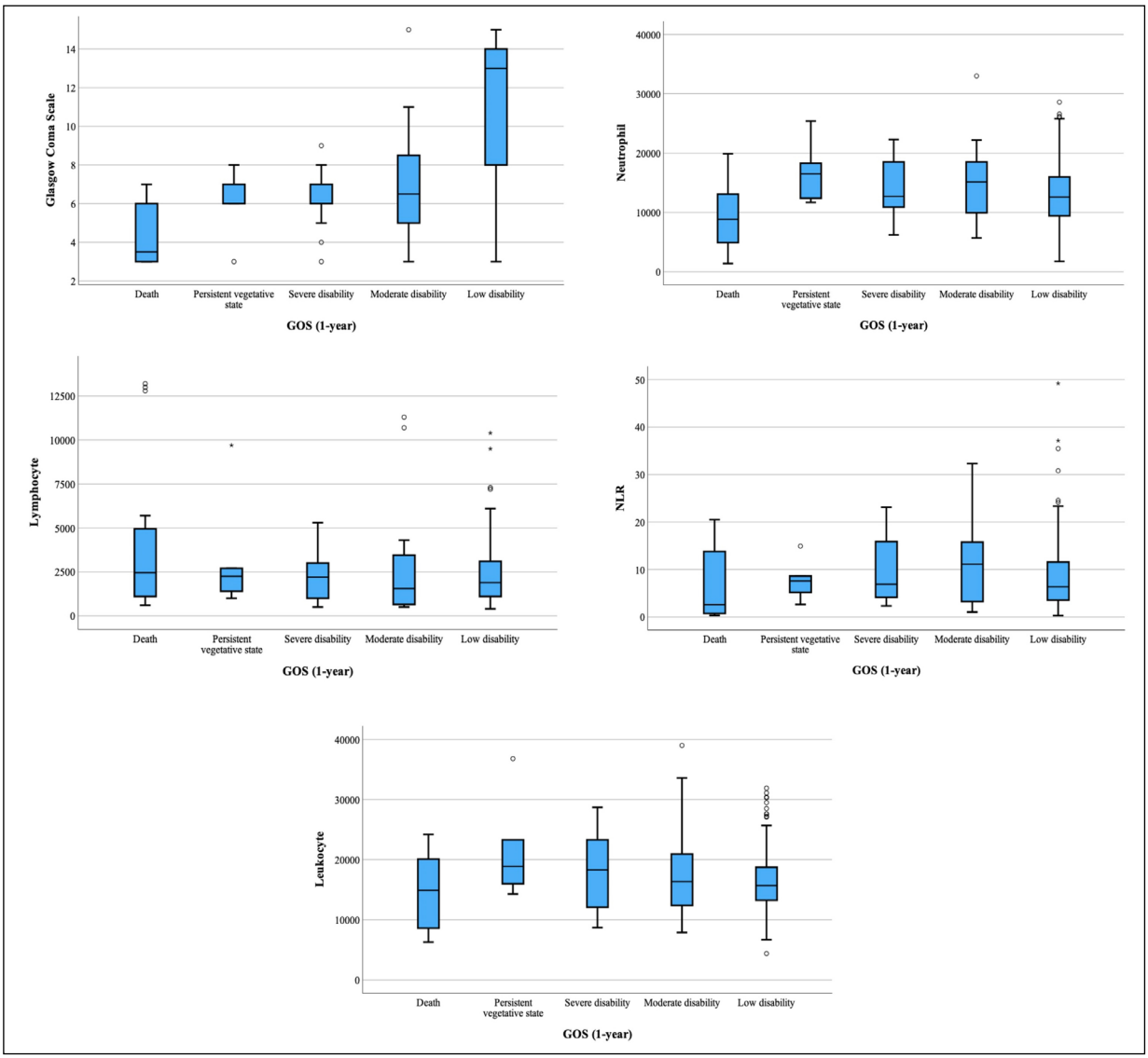

Figure 2. Box-plot charts showing the relationship between the 1st year Glasgow Outcome Scale (GOS) prognostic scale and Glasgow coma scale (GCS), leukocyte count, lymphocyte count, neutrophil count, and neutrophil/lymphocyte ratio (NLR) in pediatric traumatic brain injury (TBI) patients.

in our long-term results, neuronal recovery is also faster in pediatric patients, which makes the use of NLR in long-term prognosis meaningless. Another difference is that the blood-brain barrier is leakier in the pediatric population[19]. Because the blood-brain barrier is not very selective in the pediatric population, the normal structures can tolerate sudden inflammatory changes more easily. The use of NLR for prognosis in patients with a more favorable outcome, such as intraventricular hemorrhage (IVH), makes sense. A study[20] was conducted to examine the correlation between the mortality impact of IVH and the NLR in preterm infants. However, in TBI, which has a more morbid outcome, the long-term neuronal recovery process has already begun, and in our study, the NLR value in pediatric cases was found to be insignificant in terms of long-term outcome.

There are several parameters that have demonstrated effectiveness in treating TBIs. One study[1] evaluated the prognostic value of classifying TBI as mild, moderate, or severe based on GCS score in predicting mortality rates. It has been demonstrated that high intracranial pressure has a meaningful impact on the prognosis of pediatric patients[21]. Our study shows that GCS naturally impacts the outcome of pupillary reflexes, which are checked for CPR status and

Table II. Distribution of demographic and clinical findings by Glasgow outcome scale.

Characteristics (N=150)		GOS (1-year)								
		Death[1] (n=20)	PSV[2] (n=6)	SD[3] (n=17)	MD[4] (n=16)	LD[5] (n=91)	p	Death + PVS (n=26)	Alive[#] (n=124)	p
		n (%) or Median (Min-Max)						n (%) or Median (Min-Max)		
GCS	8 (3-15)	**3.5 (3-7)**	**6 (3-8)**	**6 (3-9)**	**6.5 (3-15)**	**13 (3-15)**	***<0.001****	**4.5 (3-8)**	**9.5 (3-15)**	**<0.001**
CPR		**7 (35)**	**1 (16.7)**	**0 (0)**	**0 (0)**	**1 (1.1)**	***<0.001***	**8 (30.8)**	**1 (0.8)**	**<0.001**
Pupillary reflex		**9 (45)**	**5 (83.3)**	**16 (94.1)**	**14 (87.5)**	**88 (96.7)**	***<0.001***	**14 (53.8)**	**118 (95.2)**	**<0.001**
Anisocoria		**4 (20)**	**1 (16.7)**	**2 (11.8)**	**4 (25)**	**3 (3.3)**	***0.019***	5 (19.2)	9 (7.3)	0.069
Seizure		2 (10)	1 (16.7)	3 (17.6)	1 (6.3)	14 (15.4)	0.839	3 (11.5)	18 (14.5)	1.000
No Surgery	130 (86.7)	**15 (75)**	**4 (66.7)**	**9 (52.9)**	**13 (81.3)**	**89 (97.8)**	***<0.001***	19 (73.1)	111 (89.5)	
Surgery		**5 (25)**	**2 (33.3)**	**8 (47.1)**	**3 (18.8)**	**2 (2.2)**		7 (26.9)	13 (10.5)	
Decompression	6 (4)	2 (40)	1 (50)	2 (25)	1 (33.3)	0 (0)		3 (42.9)	3 (23.1)	0.613
Decompression + Hematoma	10 (6.7)	3 (60)	1 (50)	4 (50)	0 (0)	2 (100)		4 (57.1)	6 (46.2)	1.000
Hematoma	4 (2.7)	0 (0)	0 (0)	2 (25)	2 (66.7)	0 (0)		0 (0)	4 (30.8)	0.249
Leukocyte 10^3 (µl)	16 (4.4-3.9)	14.9 (6.3-24.2)	18.9 (14.3-36.8)	18.3 (8.7-28.7)	16.350 (7.9-39)	15.7 (4.4-31.9)	*0.380*	16.2 (6.3-36.8)	15.95 (4.4-39)	0.833
Neutrophil 10^3 (µl)	12.35 (1.4-3.3)	8.84 (1.4-19.9)	16.5 (11.7-25.4)	12.7 (6.21-22.3)	15.15 (5.69-33)	12.6 (1.75-28.6)	*0.018***	11.3 (1.4-25.4)	12.6 (1.75-33)	0.120
Lymphocyte 10^3 (µl)	1.95 (0.4-13.2)	2.45 (0.6-13.2)	2.25 (1-9.7)	2.2 (0.5-5.3)	1.55 (0.5-11.3)	1.89 (0.4-10.4)	*0.741*	2.25 (0.6-13.2)	1.895 (0.4-11.3)	0.218
NLR	6.6 (0.3-49.2)	2.6 (0.3-20.5)	7.6 (2.6-14.9)	6.9 (2.3-23.1)	11.1 (1-32.3)	6.3 (0.3-49.2)	*0.400*	6.0 (0.3-20.5)	6.6 (0.3-49.2)	0.120

*: The difference was between 1-5, 3-5, 4-5; **: The difference was between 1-2; [#]Severe disability + Moderate disability + Low disability; GCS: Glasgow coma scale; NLR: Neutrophil/ Lymphocyte ratio; GOS: Glasgow outcome score; CPR: Cardiopulmonary resuscitation; PVS: Persistent vegetative state; SD: Severe disability; MD: Moderate disability; LD: Low disability.

brainstem herniation findings. Individuals with a GCS score of 13 or higher will likely experience a minimum level of disability after one year. Moreover, clinical data have demonstrated that individuals who have undergone CPR are highly prone to experiencing either mortality or a prolonged state of vegetative consciousness within one year. Furthermore, the prevalence of low disability is elevated among patients who do not necessitate surgical intervention, thereby encompassing individuals who do not require such procedures. The long-term prognosis is not influenced by the type of surgery performed. While the impacts of these parameters are documented, NLR alone is unsuitable for long-term outcomes in the pediatric population.

The Centers for Disease Control and Prevention (CDC) presently withholds their endorsement of serum markers as predictive tools, given their inconsistent results. Nonetheless, certain studies[5,6,22-25] on severe pediatric TBI have revealed prognostic significance for these markers (Table III). Specifically, research on pediatric TBI has concentrated on analyzing prognosis and NLR values within a 72-hour timeframe[5], as well as assessing hospital discharge outcomes[6].

Table III. Studies included NLR in pediatric traumatic brain injury patients.

Pediatric TBI Study	Number	Age group	Parameters	Outcome	Result
Siempis et al[23] (2023)	43	<18	GCS, NLR, PLR, CT findings	None	NLR is correlated with CT findings
Eser et al[24] (2022)	287	<18	NLR, RPR, LMR, CT findings	None	NLR, RPR, LMR is correlated with CT findings
Marchese et al[22] (2021)	219	2-18	GCS, NLR, neurological signs	None	NLR is correlated with CT findings and neurological signs
Alimohammadi et al[6] (2022)	374	<18	NLR, GOS, GCS	Hospital charge	Delta NLR is correlated with GOS
Mukherjee et al[25] (2020)	201	<18	WCC, Neutrophil count, NLR, PCPCS	6 months	WCC, NLR, neutropil count is correlated with hospital stay and PCPCS
Kimball et al[5] (2020)	188	<18	NLR, GOS, GCS	86 day	NLRs at 24 and 48 h has worse outcome

TBI: Traumatic brain injury; GCS: Glasgow coma scale; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet to lymphocyte ratio; CT: Computed tomography; RPR: Red cell distribution width-platelet ratio; LMR: lymphocyte-monocyte ratio; GOS: Glasgow outcome scale; WCC: White cell count; PCPCS; Pediatric cerebral performance category scale.

The term "pediatric population" pertains to individuals under 18 years old. Zhao et al[26] posited in their research of the 14 and older group that NLR holds prognostic significance in pediatric TBI. Marchese et al's[22] investigation focused on patients above 2 years old. Also, there is a correlation between NLR values and the occurrence of neurological symptoms[22]. Again, we believe that the results obtained from the age range are attributable to differences in brain development between different age groups[27].

Our study showed that NLR was significantly different in cases of low-energy trauma, such as falling from a height, and high-energy trauma, such as non-vehicle traffic accidents. The NLR may be useful for differentiating severe trauma from mild trauma.

None of the available literature has examined the relationship between the long-term outcome of TBI and NLR in the pediatric population. The relationship between short-term outcomes and the NLR has been extensively investigated, but a definitive consensus has not yet been reached, resulting in the subject being unknown. This study is the first to investigate long-term outcomes of pediatric TBI and its correlation with NLR at our trauma center.

In the analysis of the NLR value for prognostic prediction, there was no statistically significant disparity in the outcomes within the long-term pediatric cohort, in contrast to the adult population. Death can be potentially linked solely to a diminished count of neutrophils. Some literature established that the impact of trauma and the NLR on the outcome is typically associated with short-term prognosis. However, it is our belief that factors such as the GCS score upon admission and the neurological status of patients who have previously exhibited these factors do not surpass them in the long term. Despite the initial excitement surrounding the NLR value and its presentation as a simple prognostic tool for clinicians, its impact on long-term outcomes in the pediatric population was negligible. Additionally, while the underlying process of inflammation in TBI has been established, there is currently no feasible way to demonstrate a direct correlation between this process and the measurement of blood inflammatory parameters obtained from peripheral blood within the initial hours following the trauma.

Limitations

Since this study focuses on pediatric patients at a single center, the patient population could be expanded through multi-center studies. We recommend examining the effect of NLR on TBI, particularly with regard to differences in brain development stages among age groups. While the study was prospectively designed, the gathered data records were reviewed retrospectively.

Conclusions

The present single-center retrospective study did not observe any significant association between peripheral blood NLRs obtained following TBI and the prediction of long-term outcomes

within the first year in pediatric patients with TBI. Although some researchers have acknowledged the association between NLR and trauma outcomes in adults, it is worth noting that the pediatric population does not exhibit NLR values that exceed established parameters such as initial GCS scores and neurological status.

Ethics Approval
All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration. Ethics committee approval was granted from Ethics Committee of Clinical Research at Istanbul Medeniyet University dated 07.26.2023 and numbered 2023/0465.

Informed Consent
Informed consent was obtained from all parents or their legal guardian(s) of pediatric patients enrolled in the study.

Availability of Data and Materials
Not applicable.

Conflicts of Interest
The authors declare no conflicts of interest.

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Authors' Contributions
Conceptualization: H.S.C., E.U; Data curation: E.U., M.S.G.; Methodology: H.S.C.; Visualization: H.S.C., M.S.G; Writing – original draft: H.S.C., E.U.

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