

# Pediatric traumatic brain injury: a new relation between outcome and neutrophil-to-lymphocyte ratio

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**Abstract.** Leading causes of death in industrialized countries are traumatic injuries and acquired disability, and entry to the emergency department in childhood. TBI (traumatic brain injury) may involve the onset of both primary lesions and a complex immune response (sterile immune reaction to brain injury), which, in addition to neuro-protective effects, can mediate secondary neurological injury. The neutrophil-to-lymphocyte ratio (NLR), as a circulating inflammatory marker, has been related to outcomes in adult patients with non-neurologic diseases (such as gut tumours) or neurologic diseases (such as stroke or brain tumours), and to the prognosis of traumatic brain injury in adolescents and adults. However, the potential role of NLR in predicting outcomes in paediatric head trauma is not clearly defined. The aim of this retrospective observational study is to evaluate the association between clinical features predictive of intracranial and extracranial lesions in TBI and NLR and to establish whether an elevation of NLR is indirectly associated with adverse outcomes in pediatric patients with TBI. We analysed a sample of 219 pediatric patients, between 2-18 years old, after a TBI, and evaluated if differences in NLR were associated with neurological signs or positive CT in pediatric patients. We then compared the NLR values between healthy subjects and patients with TBI. ([www.actabiomedica.it](http://www.actabiomedica.it))

**Keywords:** Emergency Department, Neutrophil-To-Lymphocyte Ratio, Traumatic Brain Injury.

## Introduction

In industrialized countries, injuries are the leading cause of death and acquired disability and the most common cause of admission to pediatric emergency departments. This is particularly true for traumatic brain injuries (1-3). About 10 million children per year in the world experience TBI, with a significant impact on general morbidity and mortality in pediatric age, which also configures the disease as an important global public health problem (4, 5).

The incidence of TBI in the pediatric population, on a global scale, is in a wide spectrum ranging from

just over 10 (Sweden) to almost 500 (Australia) per 100,000 inhabitants per year (6). Data of the Emergency Department considered in SINIACA-IDB estimated that in Italy, about 2 million people yearly access the ED due to traumatic accident (or violence), of which about 20% between 0 and 14 years of age.

Epilepsy, intellectual disability, alcohol and male gender (after 2 years old) increased the risk of traumatic injuries (7). The significant incidence in the paediatric population stems from adult dependence and the inability to protect themselves in addition to anatomical features. The latter make them more susceptible to traumatic injury: head volume, in children, is

proportionally wider if compared with the total body surface; moreover, head stability is ensured by ligament rather than bone structures. The infant skull, therefore, has greater flexibility and this means that in small patients' internal injury to the cranial theca may occur even without a bone table's fracture (8, 9). Simultaneously, head trauma's prognosis is more favourable in children than in adults with the same head trauma characteristics, even though full recovery time is longer in children (from months to years) than in adults (on average 6 months) (10-13).

TBI, occasionally can generate secondary injuries, which follow from a series of pathophysiological processes of inflammatory nature that begin immediately after the primary injury and persist over time.

The more intense cerebral metabolism, typical of children, and the lack of usable metabolic substrates can cause greater morbidity than in adults, especially if considered the nuanced clinic and consequent delay in therapeutic intervention, with a higher frequency of secondary lesions. The initial *noxa* produces a cascade of inflammatory biomolecular signals and the alteration of tissue metabolism, which causes alterations in the microcirculation, neuronal damage, and neuronal apoptosis, also extended to cells that initially remained unscathed. Trauma itself, induces the activation of the biomolecular pattern associated with damage (damage associated molecular pattern - Damps), in which the purinergic receptors and the release of ATP play a key role in the activation of astrocytes, microglia, monocytes-macrophages, neutrophils and T cells (14-16). Neutrophils are the first cell to respond to tissue damage in the nervous system. As reported for other neurological pathologies, these cells have a pro-inflammatory role, causing lesion of the blood-brain barrier, cell death through the release of numerous factors (such as cytokines and oxygen radicals), and activation of glial cells in the CNS, which contribute both to neuronal repair and to amplify the inflammatory process (17-21).

Lastly, some studies seem to indicate that inflammation induced by neutrophils may induce neurodegeneration even years after the trauma, and that traumatized patients may have greater predisposition to the development of neurodegenerative symptoms or pathologies (22). However, not enough studies have

evaluated the relationship between neutrophils and TBI yet. The aim of the present study is to establish the role of neutrophils and NLR in pediatric head trauma, more specifically the relationship with the outcome of TBI.

## Materials and Methods

### *Setting*

The Study was carried out on patients belonging to the Pediatric Emergency Department of the University Hospital of Pisa (AOUP), Italy. Located in the context of a third-level university hospital, this Unit has about 700 cases per year of head trauma in age between 29 days and 18 years.

### *Study design*

For each patient, retrospectively collected data about the degree of TBI was evaluated according to the inclusion and exclusion criteria.

NLR was calculated on the blood count at entry into hospital. The NLR<sub>n</sub> was calculated for each patient by dividing the absolute number of neutrophils by the absolute number of lymphocytes; the percentage (NLR%) was obtained by dividing the percentage number of neutrophils by the percentage number of lymphocytes.

Epidemiological parameters collected from each patient were: age at presentation and gender (M / F).

Clinical parameters collected were the loss of consciousness (LOC) > 5 minutes; the evidence of peritraumatic amnesia; the severity of head injury or pediatric GCS expressed in the range of: pGCS 3-8: severe TBI; pGCS: 9-13: moderate TBI; pGCS 14-15: mild TBI.

Other parameter considered was minor / major head injury, intended as LOC > 5 minutes, or GCS less than or equal to 13 or rapid drop by 2 or more points, or fracture at the base of the skull, or complicated fracture of the cranial vault, or focal neurological deficits, or post-traumatic seizure. Finally, was considered the evidence of not severe / severe dynamics, described as a fall from a height of more than 90 cm for

children under 2 years of age, or more than 1,5 m for children over 2 years of age, or as a high-speed blunt force trauma, or as a car accident with expulsion of the passenger, or with overturning of the vehicle, or with death of another passenger, or in case of accident between cyclist without helmet and vehicle.

Blood chemistry parameters and instrumental tests evaluated in the present study were neutrophil-lymphocyte ratio at entry, value expressed both in absolute number and as a percentage (NLR% at T0); cranial-brain CT results meant as negative or positive for skull fractures with or without lesions of the structures contained in the cranial theca, or positive for lesions of the structures contained in the cranial theca in the absence of fractures.

As a normal protocol from our hospital, CT scan was required when pGCS was less than or equal to 14 or when there was altered mental state or signs of basilar skull fracture accordingly with PECARN guidelines (23, 24).

As control groups, healthy patients were retrospectively collected among those patients who come to the hospital for blood analysis checking in complete wellness: these patients underwent routine blood tests for monitoring, at the request of the paediatrician, in complete well-being or, for functional disorders.

### *Statistical analysis*

Statistical analysis was conducted on the NCSS 2020 Statistical Software, vers. 2020 (NCSS, LCC. Kaysville, Utah, USA). Normality tests were conducted on Shapiro. Chi-square tests, student's T-test were used, where appropriate, to test for differences between groups. The differences between mean values were calculated with ANOVA test when appropriate. Values of  $p < 0.05$  were considered significant.

## **Results**

From January 2015 to December 2019, data from 3460 patients were retrospectively collected. Among the whole population, 3215 patients were excluded since they did not meet the inclusion criteria or since data or blood cells count was partial. Moreover, due to

the low numericity of patients under 2 years of age and for their intrinsic differences on blood cells count than older patients, these patients were excluded. Inclusion criteria was the diagnosis of isolated TBI and availability of at least one blood count upon admission to the emergency room.

Exclusion criteria were: significant trauma in one or more other areas of the body associated with head trauma, such as polytrauma, wounds that required surgical suture, comorbidity such as fever or infectious symptoms present at the time of trauma, neurological or neuropsychiatric underlying diseases in childhood (PCI, autism), metabolic or haematological (sickle cell anaemia, thalassemia).

Final analysis was conducted on 219 patients (median age 12.05 years, IQR 5.37-15.32 years); of these patients, 31.7% had a female gender. From the whole population, the majority of patients had an age between 9 and 18 years old ( $n = 160$ ; 73,1%) while 59 patients were between 3 and 8 years old (26.9%).

In order to compare the patient data analyzed with a group of healthy patients, a number of 100 age-matched healthy patients ( $p 0.26$ ) was collected among those who performed blood counts as a normal routine evaluation without any specific illness.

Glasgow Coma Scale (GCS) was calculated for each patient and was 15/15 in 206 patients (94,06 %), 14/15 in 10 cases (4.6 %) and only a single patient had a GCS of 12/15 (0.46%). High energy mechanism of trauma (HEMT) was anamnesticly reported in 57 cases (26.1%) and neurological signs were evident in 137 patients (62.6%).

In 42 patients (19,18%) a witness (usually the parents) declared a loss of consciousness, and in only 58 patients (26,5%) there was a peri-traumatic amnesia. As a result, in only 24 cases (10.96%) major traumatic brain injury (TBI) was evinced.

As a normal protocol for our emergency department, 128 patients needed a brain CT and 35 cases (27,34%) reported a brain lesion while 24 cases (18,8%) reported head bone fracture: for these reasons, 59 patients (26.9%) required a neurosurgery evaluation.

These data and blood cell count results are summarized in Table 1.

*Correlation with neurological clinical manifestations.* Neutrophils, both in percentage terms and in absolute

**Table 1.** Descriptive data of included patients in final analysis

	TBI patients		Healthy patients		p
	Mean	SD	Mean	SD	
Age (years)	11.54	4.79	10.9	4.8	0.26
	No (n)	Yes (n)			
major traumatic brain injury (mTBI)	195	24			
HEMT	162	57			
Neurological signs	82	137			
Cephalaea	178	41			
Loss of Consciousness (LOC)	177	42			
Peritraumatic Amnesia	161	58			
CT positive for internal lesions (128 total CT)	93	35			
CT positive for Head bone lesions (128 total CT)	104	24			

values, were higher in patients with demonstrated neurological signs (p 0.019 and p 0.028, respectively) and, inversely, lymphocytes, both in percentage terms and in absolute values, were lower in the same group of patients (p 0.043 and p 0.036, respectively); NLR (n) was significantly higher in patients with neurological signs (p 0.0051) and the same results was obtained with NLR (%) (p 0.015) (Table 2).

*Correlation with Peritraumatic amnesia.* Neutrophils, in percentage terms, were higher in patients with peri-traumatic amnesia (p 0.022) and, inversely, lymphocytes, both in percentage terms and in absolute values, were lower in the same group of patients (p 0.036 and p 0.0013, respectively). NLR (n) and (%)

**Table 2.** Mean and standard deviation of blood cells count in patients with and without neurological signs

	No neurological signs		With neurological signs		p
	Mean	SD	Mean	SD	
Neutrophils (n)	6112,59	2708,67	7255,55	3908,22	0,019*
Neutrophils (%)	59,93	14,52	65,34	14,07	0,028*
Lymphocytes (n)	2896,57	1359,58	2521,23	1220,85	0,036*
Lymphocytes (%)	29,53	13,41	25,65	11,61	0,043*
NLR (n)	2,61	1,83	3,94	4,02	0,005*
NLR (%)	2,75	2,00	3,90	3,88	0,015*

**Table 3.** Mean and standard deviation of blood cells count in patients with and without peritraumatic amnesia

	No peritraumatic amnesia		With peritraumatic amnesia		p
	Mean	SD	Mean	SD	
Neutrophils (n)	6937,02	3607,61	6591,64	3422,25	0,49
Neutrophils (%)	62,13	14,90	66,03	13,05	0,022*
Lymphocytes (n)	2825,24	1342,51	2289,85	1059,58	0,0013*
Lymphocytes (%)	28,10	12,91	24,83	11,00	0,036*
NLR (n)	3,25	3,14	3,88	3,99	0,046*
NLR (%)	3,26	3,09	3,96	3,86	0,028*

was significantly higher in patients with peri-traumatic amnesia (p 0.046 and 0.028, respectively) (Table 3).

*Correlation with CT demonstration of brain injury.* Patients with demonstrated Brain injury by brain CT, reported a significantly higher absolute value of neutrophils (p 0.007). NLR (n) and (%) was significantly lower in patients without documented brain injury (p 0.0128 and p 0.0219, respectively) (Table 4).

*Comparison with healthy subjects.* Healthy patients, used as a control group, reported significantly lower val-

**Table 4.** Mean and standard deviation of blood cells count in patients with and without CT positivity for internal injuries.

	No CT positivity for internal injuries		With CT positivity for internal injuries		p
	Mean	SD	Mean	SD	
Neutrophils (n)	6384,19	3296,63	8344,86	4319,13	0.007*
Neutrophils (%)	62,78	13,79	65,45	18,14	0.37
Lymphocytes (n)	2578,49	1147,25	2748,26	1627,92	0.51
Lymphocytes (%)	27,55	11,87	24,82	13,58	0.27
NLR (n)	3,10	2,60	4,97	5,78	0.0128*
NLR (%)	3,15	2,50	4,83	5,71	0.0219*

ues of Neutrophils, both in absolute values and percentage terms ( $p < 0.0001$  for each one), lymphocytes in percentage terms ( $p < 0.0001$ ) and for NLR both in absolute values and percentage terms ( $p < 0.0001$  for each one): in other words, only Lymphocytes in absolute value reported similar values with healthy patients ( $p 0.5$ ). As clearly described in Table 5, healthy patients demonstrated significantly lower values for each sub-group.

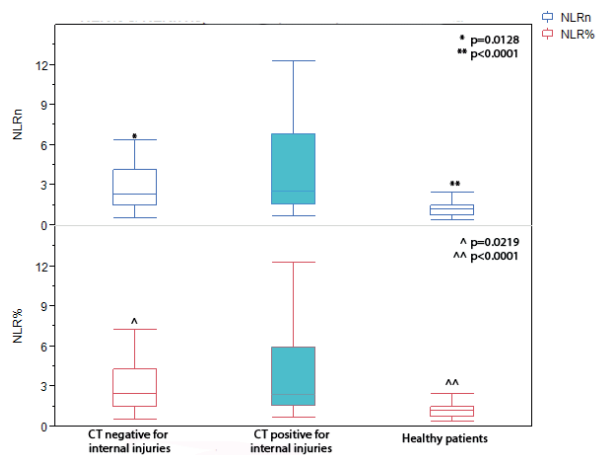
**Discussion**

Our data provide the prognostic value of neutrophils and NLR in TBI from a cohort of children over 2 years of age. Although several studies have been conducted on the role of neutrophils in neurological and non-neurological pathologies in adult patients, there is still little evidence in the paediatric field. There is even less scientific evidence on the prognostic role of the NLR in head trauma in children.

One of the most significant studies is that conducted by Zhao et. al, of the University of Shanghai, which assessed the prognostic value of NLR in comparison to the outcome at 6 months, in a cohort of over 1200 patients over 14 with head trauma. Here NLR proved to be an independent prognostic indicator of outcome in TBI, with a significance of poor prognosis (25). The limitation of this study is that it does not include patients under 14.

More recently, in June 2020, Kimball et al., of Atlantic University of Florida, published a retrospective observational study that evaluated the role of NLR in

predicting TBI outcomes in a cohort of 188 patients aged 0 to 18 years from 2007 to 2017. The analysis revealed statistically significant differences in NLR at 24 and 48 hours between groups of patients stratified according to the prognostic index GOS- E Peds. Furthermore, the NLR at admission was significantly higher in patients who presented loss of consciousness than in patients who did not. For this reason, the study suggests that NLR may result in a useful and relatively inexpensive tool for predicting TBI outcomes. On the other hand, there were no statistically significant differences in terms of NLR, in any of the measurement timelines (entry, 24.48 and 72 hours from trauma), between patients stratified by GCS score and the presence or absence of peritraumatic amnesia (26).



**Figure 1.** Median and Interquartile range of NLRn and NLR% in patient with and without confirmed internal injuries by CT and comparison between the former and healthy subjects

**Table 5.** Mean and Standard deviation of blood cells count in healthy patients and comparison with patients after TBI divided by groups

	Healthy patients		Healthy Vs no neurological signs		Healthy Vs neurological signs		Healthy Vs noperitraumatic amnesia		Healthy Vs peritraumatic amnesia		Healthy Vs noCT positivity		Healthy Vs CT positivity	
	Mean	SD	p	p	p	p	p	p	p	p	p	p	p	
Neutrophils (n)	3002,60	966,62	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	
Neutrophils (%)	45,44	10,34	<0.0001*	<0.0001*	<0.0001*	0.003*	0.03*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	
Lymphocytes (n)	2788,40	985,46	0.5	0.74	0.19	<0.0001*	<0.0001*	<0.0001*	<0.0001*	0.32	0.88			
Lymphocytes (%)	42,27	10,46	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	
NLR (n)	1,21	0,63	<0.0001*	<0.0001*	0.01	<0.0001*	<0.0001*	<0.0001*	<0.0001*	0.0009*	<0.0001*	<0.0001*	<0.0001*	
NLR (%)	1,21	0,63	<0.0001*	<0.0001*	0.005	<0.0001*	<0.0001*	<0.0001*	<0.0001*	0.0005*	<0.0001*	<0.0001*	<0.0001*	

With our study we confirmed what the literature had previously demonstrated about: the peak incidence in adolescence (5, 7, 27), the prevalence of mild head trauma and of not severe dynamics in TBI (28), and the difference in NLR and neutrophils between healthy subjects and patients with TBI (26).

From our study it emerged that, on the whole sample, there are statistically significant differences in NLR, both in absolute number and in percentage value, between the group that presented neurological signs and the group without neurological signs.

Secondly, from our analysis it is observed that, on the whole sample, there are no statistically significant differences in NLR, both in absolute number and in percentage value, between the group with severe dynamics of trauma and the group without severe dynamics of trauma.

Thirdly, we highlighted that, between the ages of 2 and 18, the neutrophils were, in percentage terms, higher in patients with peri-traumatic amnesia and, inversely, lymphocytes, both in percentage terms and in absolute values, were lower in the same group of patients. NLR (n) and (%) was significantly higher in patients with peri-traumatic amnesia.

Finally, we have shown that, patients with demonstrated brain injury by brain CT, reported a significantly higher value of neutrophils and NLR (n) and, in addition, the patients without documented brain injury had a significantly lower value of NLR (%).

Our study therefore seems to suggest that NLR was higher in patients with positive CT, peritraumatic amnesia and neurological signs.

Limitations of the study are that it was conducted on a limited number of cases. Furthermore, the observation was carried out retrospectively; therefore, the data collection was influenced by the availability of data in the systems used. In addition to the above, not all patients with TBI in our ED had carried out blood tests, so we cannot affirm that the sample realistically reflects the entire panorama of pediatric cranial traumas presented to the emergency room of our institute (29).

A further limitation, due to the retrospective method of data collection, was given by the impossibility of obtaining NLR measurements for all patients at the time of the post-trauma times and it was not possible

to evaluate the association between NLR and severity of trauma.

Finally, the study missed of a follow up after discharge, and it was therefore not possible to investigate the possible direct relationship of NLR with distant outcome, with complications or neurological disability secondary to trauma.

## Conclusion

This study explored the strict correlation between neutrophil-to-lymphocyte ratio and traumatic brain injury. We have demonstrated that NLR values were significantly higher in TBI in paediatric population compared to controls. Moreover, NLR values are related both with the presence of neurological signs such as peritraumatic amnesia and with the presence of CT positivity for internal lesions after TBI.

Considering the limits previously mentioned, further studies are still required to study the potential prognostic value of NLR and in particular, prospective clinical studies and data on the medium to long-term prognosis of traumatised pediatric patients.

**Conflict of Interest:** Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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