

Original Research

Blood Biomarkers for Prediction of Positive CT Findings in Mild Traumatic Brain Injury in Paediatric Population

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Abstract

Background: Paediatric Traumatic Brain Injury (TBI) has received less research attention compared to TBI in adults, despite its potential morbidity in all ages. Our aim was to determine whether neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR) and glucose levels at admission can reliably predict the need for imaging in children presenting with mild TBI. **Methods:** We retrospectively reviewed the clinical records of paediatric patients who presented in the emergency department with mild TBI within a 5 year period and had undergone computed tomography (CT) scan of the head. **Results:** Overall, 43 eligible patients were included in the study, with falls being the most commonly reported cause of injury. Twenty-three children had positive CT findings. Patients with abnormal CT findings were found to have higher NLR ratios compared with patients with normal CT, with the mean NLR on admission being 5.2 ± 3.8 . Children with abnormal CT findings had lower PLR levels and higher glucose levels at presentation compared to children with normal CT, however the differences were not statistically significant. Using the receiver operating characteristic (ROC) curve, we found that a NLR cut off value of 6.1 yielded a sensitivity of 54.2% and a specificity of 89.5% for the prediction of abnormal CT findings. **Conclusions:** The findings of this study suggest that NLR may have a role in CT decision-making in the emergency department for mild TBI in paediatric patients.

Keywords: biomarkers; emergency department; CT; Glasgow Coma Scale; head trauma; mild traumatic brain injury; neutrophil-to-lymphocytes ratio; radiation exposure; paediatrics; neurosurgery

1. Introduction

Traumatic Brain injury (TBI) remains one of the leading causes of death and morbidity, especially in the younger population and it affects approximately 10 million children worldwide each year [1]. On a global scale, the incidence of TBI in the paediatric population ranges from just over 10 cases to almost 500 cases per 100,000 inhabitants per year in Sweden and Australia respectively [2]. Almost 95% of head injuries in children attending the Emergency Departments (ED) are mild [3]. Despite a more favourable prognosis in children, the recovery period for children and adolescents is longer than adults, with persistent symptoms being reported at one month following the injury in almost one third of the patients [4].

When it comes to the diagnosis of TBI in children, computed tomography (CT) remains the diagnostic standard. However, head CT is associated with certain risks such as radiation exposure, increased cost, and even the need for sedation in uncooperative children. There is a positive association between the number of head CT a child has undergone and the risk of new intracranial tumours with a reported excess relative risk of 1.29 [5]. Interestingly,

there is a strong correlation between age and the risk of developing cancer even after a single CT of the brain, with infants being ten times more likely to develop cancer compared to adult patients [6]. The importance of a biomarker that would help decision making in traumatic brain injury in children is therefore paramount. Recent studies have explored the potential to identify blood biomarkers such as Glial Fibrillary Acidic Protein (GFAP), S100B and myelin basic protein (MBP) [7]. Many of these studies showed significantly elevated biomarker concentrations in affected compared to healthy children. However, these results have not been applied to clinical practice yet. This can be attributed to the limitations of biomarkers, with the most important being the elevated normative concentrations found in paediatric patients [8].

The scientific community has become increasingly interested in the role of inflammatory response in traumatic brain injury. Research has shown that neutrophils are one of the first immune cells to be activated after TBI and can be detected in brain tissue within 2 hours of the injury [9]. Additionally, peripheral lymphocytes have been found to be in an immunosuppressed state after TBI, with cell numbers recovering 7 days after the injury [10]. In view of these find-



ings, the Neutrophil-to-lymphocyte ratio (NLR) has been studied as a simple investigation that could reliably predict the need for imaging in adults with TBI [11]. Other biomarkers, such as blood glucose levels and the platelet-to-lymphocyte ratio (PLR), have also been proposed [12]. The purpose of this study is to investigate whether NLR, blood glucose levels, and PLR can be used to predict the need for CT scans in pediatric patients.

2. Materials and Methods

We performed a retrospective analysis of consecutive pediatric patients who presented in the emergency department with mild TBI over the past five years and were admitted under the Neurosurgical team. We obtained clinical data by reviewing admission charts from the emergency department and classified TBI as mild based on the initial Glasgow Coma Scale (GCS) score upon presentation. Inclusion criteria included patients under 18 years old with full blood count and glucose results available at presentation, non-contrast CT scans performed in the emergency department, and a diagnosis of mild TBI defined by a GCS score of 13–15, with a history of injury within the last 24 hours of arrival to the emergency department and admission to the Neurosurgical Department. Patients without available NLR, PLR, glucose levels, or CT scans at presentation, or who had moderate or severe TBI, were excluded. It is important to note that we only studied children who were hospitalized after being diagnosed with mild TBI, and did not include children who were sent home from the emergency department or patients with multiple extracranial injuries. Blood samples were taken and analyzed for complete blood count after presentation in the emergency department. We obtained information on the cause of injury, presenting symptoms, and CT head reports from patient records. CT scans were interpreted by radiologists according to hospital protocol, and positive findings were defined as skull fractures, epidural/subdural hematomas, post-traumatic subarachnoid hemorrhages, depressed skull fractures, skull base fractures, pneumocephalus and cerebral contusions. The institutional review board granted approval for the study (1/22-1-2020, 024) and adhered to the Declaration of Helsinki of the World Medical Association.

Statistical Analysis

Descriptive statistics (mean and standard deviation) were used to describe continuous data. Nonparametric Mann-Whitney U-test was used to detect differences of NLR, PLR and glucose levels between patients with normal and abnormal CT findings. The optimal cut-off for NLR values was identified using the Receiver operating characteristic (ROC) curve and the optimal corresponding sensitivities and specificities were calculated [13]. Values of p less than 0.05 were considered statistically significant [14]. All statistical analysis was carried out with MedCalc for Windows (Trial Version, MedCalc Software, Ostend, Belgium).

Table 1. Patient's characteristics.

Characteristics	Value	
Age	13.3 (+/- 2.4)	
Sex	Male	24 (55.8%)
	Female	19 (44.2%)
Mechanism of injury	Fall	17 (39.5%)
	Motor vehicle accident	1 (2.3%)
	Not reported	25 (58.2%)
Vomiting	Yes	14 (32.5%)
	No	29 (67.4%)
Loss of consciousness	Yes	1 (2.3%)
	No	42 (97.7%)
Post traumatic amnesia	Yes	5 (11.6%)
	No	38 (88.4%)

3. Results

A total of 54 children with a diagnosis of isolated mild TBI attended our emergency department and were hospitalized in the department of Neurosurgery. Of these patients, 11 were excluded for the reasons shown in Fig. 1.

There were slightly more males than females in the trauma population (55.8% versus 44.2%), in line with literature that suggests males are more likely to experience physical trauma [15]. The average age at presentation was 13.3 ± 2.4 years.

Falls (39.5%) were the most commonly reported mechanism of injury. Vomiting was reported in 32.5% of the cases. There was only 1 case of loss of consciousness after the injury and post traumatic amnesia was reported in 11.6% of cases. Notably, a post traumatic seizure was not reported in our cohort (Table 1).

The mean NLR ratio at presentation was 5.2 ± 3.8 . Patients with positive CT findings were found to have higher NLR ratios than patients with normal CT (median value 6.3 versus 3.6 respectively, $p = 0.04$). PLR levels were lower in children with abnormal CT findings (median value 128.9 versus 135.7 respectively, $p = 0.37$). Compared to children with normal CT scans, higher glucose levels at presentation were observed in those with abnormal CT findings, however this difference was not statistically significant (median value 100.5 versus 108.0 respectively, $p = 0.40$) (Table 2). Using the ROC curve analysis, the optimal threshold value for detection of patients with abnormal head CT 2 was identified as 6.1, with a sensitivity of 54.2% and a specificity of 89.5% (Area under the Curve, (AUC) 0.68 ± 0.083) (Supplementary Fig. 1).

In Table 3 we describe the most frequently encountered abnormal CT findings in our cohort of patients. There were 23 patients in total with positive CT findings. The most commonly reported abnormality was a skull fracture which was found in 18/23 (78.3%) followed by acute subdural hematoma which was diagnosed in 3/23 (13%) of cases.

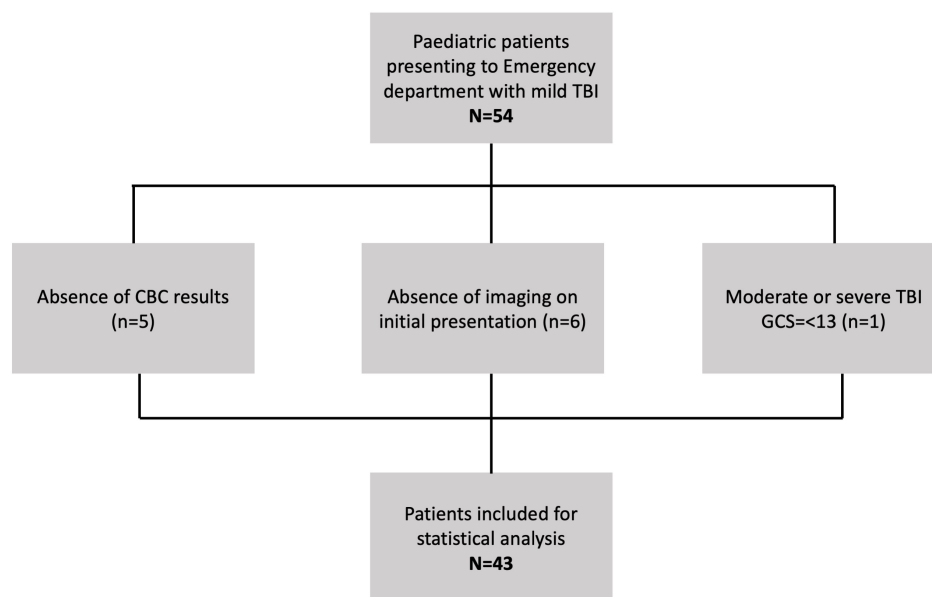


Fig. 1. Flow chart illustrating our exclusion criteria. CBC, complete blood count; TBI, Traumatic Brain Injury.

Table 2. Comparison of NLR, PLR and glucose levels between patients with normal and abnormal head CT.

	Normal CT	Abnormal CT	<i>p</i> -value
NLR (median value)	3.6	6.3	0.04
PLR (median value)	135.7	128.9	0.37
Glucose (median value)	100.5	108.0	0.40

NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; CT, computed tomography.

Table 3. Positive CT findings.

CT findings	n (%)
Skull fracture	18 (78.4%)
Acute subdural hematoma	3 (13%)
Traumatic subarachnoid hemorrhage	1 (4.3%)
Pneumocephalus	1 (4.3%)

CT, computed tomography.

4. Discussion

This study found that NLR levels are higher in children with mild head injury and abnormal CT scans upon arrival at the emergency department. A cut-off of 6.1 was identified as the optimal value to detect abnormal head CT with a sensitivity of 54.2% and specificity of 89.5%. PLR ratio and glucose levels at presentation did not reach statistical significant difference between patients with positive and normal CT findings. Although various studies have explored the predictive role of NLR and glucose levels in adults, there is limited evidence regarding their use in paediatric patients. Clinicians dealing with paediatric head injuries are faced with a difficult decision when it comes to whether or not a CT scan should be indicated. One of the

concerns, apart from radiation exposure, is the possibility of finding incidental abnormalities. According to a recent study, the incidence of incidental findings in paediatric head CT was 4%. These findings can cause distress to the parents and lead to unnecessary investigations [16]. Furthermore, during pandemic reduced waiting times in the emergency room, where there is a risk of viral transmission, would be made possible by a biomarker that might identify patients with mild traumatic brain injury who require a CT scan [17]. Therefore, an attempt should be made to reduce the number of unwarranted head CT scans.

The most commonly reported positive CT finding in our cohort of patients were skull fractures, found in 78.4% of patients with abnormal CT. The same figure was 45.1% in a recent study that included 1489 TBIs in a children's hospital in Australia [18]. The high incidence of skull fractures in our cohort of patients can be explained by the fact that we included patients that were admitted to the Neurosurgical department so the likelihood of abnormal head CT findings would be higher.

Clinical decision algorithms have been developed to aid clinicians to determine which subset of children with mild TBI would benefit from a head CT. One of the most popular ones is Canadian CT Head Rule. In a recent study, this diagnostic tool's sensitivity and specificity in detecting intracranial haemorrhage in patients with mild TBI were calculated 100% and 29% respectively [19]. Recently, the Pediatric Emergency Care Applied Research Network (PECARN) scoring system has been developed to help clinicians predict the need for imaging in children with mild TBI. Its sensitivity and specificity in detecting clinically important TBI (ciTBI) in the paediatric population was 100% and 57.8% respectively [20]. This tool has yet to be widely

accepted as shown by a study from Halaweish *et al.* [21] which measured the overuse rate for CT heads in minor TBI being 20.7% and 19.5% pre and postimplementation of the PECARN guidelines respectively. Thus, identifying a biomarker that could help clinicians determine the need for CT scans in paediatric TBI would be of great significance.

Changes to the immune system after a traumatic event have been shown to have a significant impact on the occurrence and progression of further brain damage [22]. As a result, there has been increasing interest in the use of NLR as a biomarker for inflammation in traumatic brain injury [23]. The NLR can be easily obtained and calculated from a routine laboratory study that analyzes the white blood cell differential count. It can also be integrated into daily clinical practice without additional cost. However, one disadvantage is that the average waiting time for NLR laboratory results in the emergency department is typically between 30 and 40 minutes and that might delay imaging and management. For example, even in mild TBI in case of suspicion of non-accidental injury, skull fracture, seizures or focal neurologic deficit a head CT should be obtained urgently within 1 hour [24].

There is limited data regarding the use of NLR in the diagnosis and management of TBI in children. Alimohammadi *et al.* [25] showed changes of NLR levels over time (referred to as Delta NLR) were associated with worse outcomes in a sample of 374 paediatric patients. In a sample of 219 paediatric cases with TBI, those with brain injuries detected on CT scans had a substantially higher absolute neutrophils count ($p = 0.007$) [26]. Kimball *et al.* [27] looked at a cohort of 188 pediatric patients and found significant differences in NLR between groups stratified according to the prognostic index Pediatric Glasgow Outcome Scale - Extended (GOS-E Peds) at 24 and 48 hours, suggesting that NLR could be a valuable and cost effective marker for predicting TBI outcomes in children. According to literature, there is an association between blood glucose levels and abnormal CT head findings after trauma in the adult population. In a study of 159 patients, blood glucose levels above 120 mg/dL were associated with positive CT findings, with a reported sensitivity and a specificity of 74.4% and 90.7% respectively [28]. Both NLR and glucose could also predict the risk of coagulopathy occurrence in adults [29,30]. Coagulopathy occurrence is directly associated with patients' outcome [31]. Although NLR has been described as predictor of adverse outcomes in TBI in paediatric population, this is the first study that demonstrated that NLR levels can help predict abnormal CT findings in paediatric patients with mild TBI [26].

Recent studies have attempted to identify biomarkers in order to evaluate functional outcomes after a TBI in the paediatric population. According to a systematic review, S100B, neuron-specific enolase (NSE), UCH-L1 have been extensively studied as potential predictive biomarkers for TBI in children, with S100B having received the most re-

search attention [32]. However, the results are conflicting with Babcock *et al.* [33] suggesting that S100B could not accurately predict the presence of positive CT scan findings in children with normal GCS upon presentation to the emergency department. Another biomarker is glial fibrillary acidic protein (GFAP) which can predict positive CT findings in children presenting with TBI with a sensitivity of 94% and a specificity of 47% [34].

This study has several limitations. Firstly, our data were collected retrospectively. Secondly, our sample was relatively small. Furthermore, we have excluded poly-trauma patients presenting with head injuries. It is also important to note that our control group with negative CT findings were children that were admitted to the ward for observation. Hence, we did not look at children with TBI discharged home from the emergency department.

5. Conclusions

Given the frequency of mild TBI in paediatric population and the potential impact of the ionizing radiation due to unnecessary CT scans in children, a cost effective biomarker that could help identify mild TBI is needed. In this study, in children presenting with mild TBI, there was a statistically significant correlation between increased NLR at admission and abnormal head CT findings. In order to determine the clinical application of the aforementioned findings, more prospective large scale studies are needed.

Abbreviations

AUC, Area under the Curve; CT, Computer Tomography; ED, Emergency Department; GCS, Glasgow coma scale; MBP, Myelin basic protein; NLR, Neutrophil to lymphocyte ratio; PLR, Platelet to lymphocyte ratio; PECARN, Pediatric Emergency Care Applied Research Network; ROC, Receiver operating characteristic analysis; TBI, Traumatic Brain Injury.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article.

Author Contributions

GAA and SV designed the research study. TS, PAG, GL, GK, DM, ESA, JZ performed the research. AS provided help and advice on data collection. TS, PAG, GAA, GK analyzed the data. TS, DM, ESA, JZ, AS wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of the University Hospital of Ioannina IRB (Approval number: 1/22-1-2020, 024).

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.31083/j.jin2204091>.

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