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Hematological markers for prediction computed tomography findings in mild traumatic brain injury

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ABSTRACT

Aims: This study aims to examine the levels of the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR) in mild head injury (mTBI) patients to determine their predictive value for the necessity of head computed tomography (CT).

Methods: mTBI patients admitted to the emergency department demographic details, levels of NLR and PLR, and outcomes from brain CT scans were evaluated. Based on the CT scan outcomes, patients were classified into two groups: one with no detectable abnormalities (group 1) and another with detected abnormalities as acute epidural hematoma, acute subdural hematoma, or subarachnoid hemorrhage (group 2). The levels of NLR and PLR were then compared across these groups.

Results: In the study, out of 221 patients, 131 (59.3%) were male, and the overall mean age was 51.47±13.91 years. The most common cause of admission was traffic accidents, accounting for 70 patients (31.7%). The mean Glasgow Coma Scale score of the patients was 13.99±0.94. Group 2 consisted of 66 patients (29.9%), with 44 (66.7%) having an acute subdural hematoma, 16 (24.2%) with subarachnoid hemorrhage, and 6 (9.1%) with acute epidural hemorrhage. The mean NLR and PLR were 1.85±0.77 and 133.99±51.70, respectively. NLR values in group 2 were significantly higher than those in group 1 ($p<0.000$), whereas no significant difference was found in PLR values between the groups ($p>0.05$). The optimal cutoff value for NLR was determined to be >1.64.

Conclusion: NLR levels, readily derived from standard hematological assessments, function as an objective and inflammatory biomarker. Initial NLR measurements hold the potential for forecasting abnormal findings in head CT scans associated with mTBI patients.

Keywords: Traumatic brain injury, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, computed tomography, mild head injury

INTRODUCTION

The emergency department (ED) is often the first point of care for patients with traumatic brain injury (TBI). TBI is defined as damage to the brain caused by an external mechanical force, common causes include falls, strikes by objects, car crashes, assaults, and self-harm.[1,2] TBI stands as the principal reason for morbidity and mortality in individuals younger than 40 years in both developed and developing countries, imposing a substantial economic burden.[3]

Mild TBI (mTBI) involves a Glasgow Coma Scale (GCS) score ranging from 13 to 15 at 30 minutes after the injury, with short-term or localized neurological disturbances that do not involve loss of consciousness for more than 30 minutes or post-traumatic amnesia for less than a day.[4]

A head computed tomography (CT) scan is an effective diagnostic tool for detecting traumatic intracranial conditions following mTBI.[5] About 10% of mTBI patients develop intracranial complications, 1% of these cases require neurosurgical treatment, and the fatality rate is 0.1%.[6] The decision to perform a CT scan on a patient with mild head trauma is ultimately up to the discretion of a medical specialist.[7] Systematic screening of all mTBI patients in the ED would be costly, and the associated ionizing radiation presents certain health risks.[8]

Identifying a biomarker that facilitates decision-making for conducting head CT scans in patients with mTBI is crucial. Although blood biomarkers such as C-terminal hydrolase-L1, glial fibrillary acidic protein, and S100B

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have been explored for predicting traumatic cerebral injuries on CT scans, they remain expensive and not broadly accessible.[9]

TBI is a complex multi-system condition characterized by interactions between the brain, peripheral, and immune systems.[10,11] Two pathological processes are pivotal in TBI.[12] The initial neurological damage, known as primary injury, occurs directly at the moment of impact and mechanically harms brain tissue. This damage can trigger a secondary pathological process where injured brain cells release various inflammatory factors and neurotransmitters, initiating and perpetuating an inflammatory cascade. This results in neuroinflammation, further exacerbating brain damage, referred to as secondary brain injury.[13]

Recently, the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR) have gained attention for their roles in indicating inflammation.[14] These ratios, which are easily calculated from the complete blood count available in routine laboratory tests, are part of our daily medical assessments.

This study aims to examine the levels of the NLR and the PLR in mTBI patients to determine their predictive value for the necessity of head CT.

METHODS

This retrospective analysis was conducted from February 1, 2023, to September 1, 2023, in the ED of our hospital. Ethical approval was granted by the Ankara Etlik City Hospital Clinical Researches Ethics Committee (Date: 27.09.2023, Decision No: 2023-588). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients aged 18 and older who were admitted to the ED with isolated head trauma and mTBI characterized by a GCS score of 13-15 were included in the study. Exclusion criteria for patients included ED admission over three hours post-injury, pregnant patients suffering from drug overdoses, those with a history of neoplastic, cardiac, hepatic, renal diseases, bone marrow dysfunction, ischemic or hemorrhagic stroke, penetrating brain injuries, or those with incomplete medical records. During the patient file review, the study incorporated comprehensive neurological assessments, etiologies of trauma, and symptomatic reports from patients, including headaches, nausea, vomiting, episodes of loss of consciousness, and seizure durations, as documented in their medical histories.

Venous blood samples were systematically drawn from the patients upon arrival and promptly analyzed for a complete blood count in the hospital's laboratory.

Computed Tomography Scan

Noncontrast head CT scans were performed utilizing multislice CT technology within 30 to 60 minutes of ED admission. Data collected included demographic profiles, NLR, PLR, and brain CT scan results. Based on the outcomes of the head CT scans, patients were stratified into two cohorts: group 1, consisting of patients without detectable CT abnormalities, and group 2, comprising patients with identified abnormalities such as acute epidural hematoma, acute subdural hematoma, or subarachnoid hemorrhage. Subsequently, a comparative analysis of NLR and PLR levels was conducted between the groups.

Statistical Analysis

Descriptive statistics for continuous variables encompassed the calculation of mean values, standard deviations, medians, and ranges (minimum and maximum values). For categorical variables, frequencies and percentages were reported. The Shapiro-Wilk test was applied to evaluate the adherence of continuous data to a normal distribution. For comparisons of nominal variables across different groups, the Chi-Square test was utilized. The Mann-Whitney U test facilitated the analysis of differences between two groups in continuous variables. The diagnostic efficacy of NLR and PLR was quantified using Receiver Operating Characteristic (ROC) curve analysis, specifically the area under the curve (AUC). The optimal cutoff point was determined using Youden's Index. Furthermore, the diagnostic accuracy parameters for NLR, including sensitivity, specificity, positive predictive value, and negative predictive value, were calculated. Data analyses were conducted using IBM SPSS for Windows version 20.0 (SPSS Inc., Chicago, IL), and statistical significance was set at a p-value of less than 0.05.

RESULTS

In this study, the cohort comprised 221 patients, of whom 131 (59.3%) were male. The average age across all patients was 51.47±13.91 years. The predominant cause of admission among the patients was traffic accidents, accounting for 70 patients (31.7%) (**Figure 1**). The mean GCS score was 13.99 ± 0.94. Within group 2, there were 66 patients (29.9%), with 44 (66.7%) diagnosed with acute subdural hematoma, 16 (24.2%) with subarachnoid hemorrhage, and 6 (9.1%) with acute epidural hemorrhage. The average NLR among the patients was 1.85±0.77, and the PLR was 133.99±51.70.

In group 2, the GCS scores were significantly lower than those observed in group 1 ($p<0.000$). NLR levels were notably higher in group 2 compared to group 1 ($p<0.000$). However, no significant differences were observed in PLR levels between the two groups ($p>0.05$), as shown in **Table 1**.

Table 1. Comparison of patients in group 1 and group 2					
Parameter	**Group 1 (n=155)**		**Group 2 (n=66)**		**p-value**
Gender	n		%		n
Female	67	43.2	23	34.8	0.246 c
Male	88	56.8	43	65.2	
	Mean±SD	Median (min-max)	Mean±SD	Median (min-max)	
Age	49.57±14.34	55 (18-69)	55.94±11.79	58.5 (25-72)	0.001 b
GCS	14.04±1.01	14 (6-15)	13.86±0.78	14 (13-15)	0.066 b
NLR	1.59±0.52	1.45 (1.00-4.06)	2.48±0.88	2.10 (1.12-4.42)	<0.000* b
PLR	150.27±72.91	130.11 (67.34-398.0)	127.06±37.59	112.5 (60.63-206.19)	0.155 b

b: Mann-Whitney U test, c: Chi-Square test, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet to-lymphocyte ratio, Min: Minimum, Max: Maximum, SD: Standart deviation

The predictive accuracy of NLR for indicating positive CT findings was statistically significant, with the AUC demonstrating significance ($p<0.001$). The optimal cutoff value for NLR was determined to be >1.64 (Table 2, Figure 2).

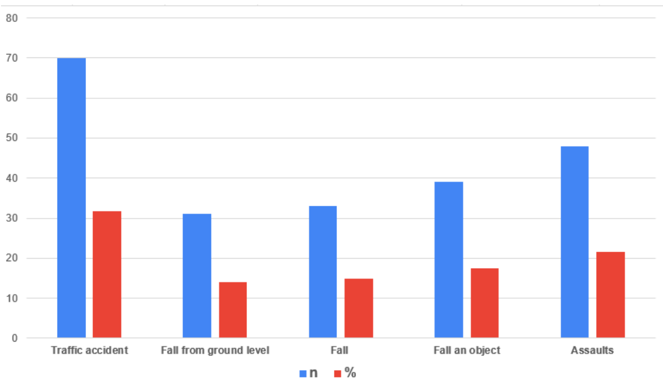

Figure 1. Patient admission cause to among the participants was traffic accidents

Table 2. Diagnostic performance of neutrophil-to-lymphocyte ratio levels in distinguishing positive findings on head computed tomography					
Parameter	**AUC (95% CI)**	**p-value**	**Cut-off**	**Sensitivity**	**Specificity**
NLR	0.805 (0.743-0.867)	<0.000	1.64	84.8% 74.3–91.6	63.2% 55.4–70.4

NLR: Neutrophil-to-lymphocyte ratio

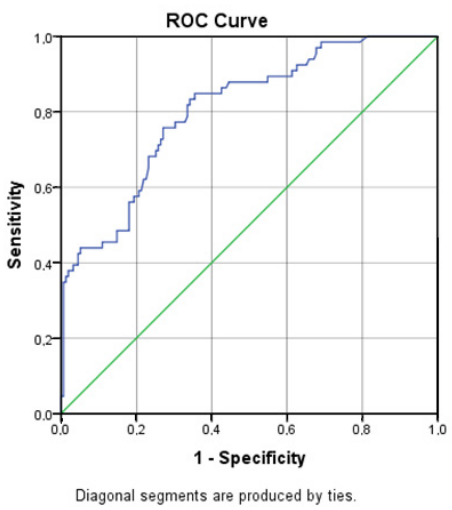

Figure 2. The predictive accuracy of NLR with ROC curve
ROC: Receiver Operating Charasteristics, NLR: Neutrophil- to-lympocyte ratio

DISCUSSION

mTBI constitutes a substantial public health challenge globally, exerting significant impacts on individuals. Noncontrast CT serves as the definitive standard for evaluating mTBI. The decision to perform a CT scan predominantly resides with the emergency physician. Medical professionals tasked with managing mTBI patients encounter complex decisions regarding the advisability of CT examinations. It is imperative to restrict unnecessary head CT scans to mitigate radiation exposure, particularly in patients with mTBI.[15] Moreover, the economic implications of redundant CT scans are not trivial, encompassing costs related to false-positive results and potential patient transfers to alternative medical facilities when CT capabilities are unavailable.[16]

In this study, it was determined that patients with mTBI presenting at the ED exhibited elevated NLR levels when head CT scans showed abnormalities. A threshold value of >1.64 was identified as the optimal cutoff for detecting abnormal head CT findings, achieving a sensitivity of 84.8% and a specificity of 63.2%. Conversely, the PLR levels at admission did not show statistically significant differences between patients with abnormal and normal CT scan results.

In cases of TBI, neurological impairments are initially induced by direct mechanical forces at the moment of impact, constituting the primary injury. These impairments subsequently evolve into a secondary injury phase, during which inflammation plays a critical role in exacerbating brain damage.[16] TBI leads to the disruption of the blood-brain barrier, triggering the mobilization of macrophages, neutrophils, and lymphocytes to the injury site.[17]

Under normal conditions, neutrophils are absent from the brain parenchyma due to the protective function of the blood-brain barrier; however, they are found in limited numbers within the cerebrospinal fluid, pia, and meninges.[18] Neutrophils contribute to increased oxidative stress, further damage to the blood-brain barrier, and the promotion of neuronal cell death.[19] Conversely, lymphocytes play a crucial role in the repair of damaged brain tissue, not only by secreting growth factors but also by regulating microglial activity.[3]

The NLR is determined by dividing the absolute neutrophil count by the absolute lymphocyte count, both of which are derived from a complete blood count test.[13] NLR serves as a biomarker that integrates two aspects of the immune system: the innate immune response, predominantly mediated by neutrophils, and the adaptive immune response, facilitated by lymphocytes.[20] An increased NLR indicates a predominance of neutrophils relative to lymphocytes, suggesting the presence of an active inflammatory response.

Corbett et al.[21] identified that elevated NLR levels hold prognostic value in severe TBI patients undergoing decompressive craniectomy. In their study involving 144 adult patients, the median GCS score at admission was five. An NLR exceeding 15.63 upon admission was predictive of 28-day mortality. Furthermore, elevated NLR values during the first week of treatment were associated with severe disability in TBI patients.[22] In a longitudinal study, unfavorable outcomes at the 1-year follow-up were observed in 73.8% of head trauma patients. In this cohort, a high admission NLR for severe TBI correlated with poorer clinical outcomes. The sensitivity and specificity of an elevated NLR in predicting adverse outcomes were determined to be 60.2% and 71.1%, respectively.[23]

A comprehensive study on TBI involving 1.291 patients identified several factors as independent predictors of negative outcomes six months post-injury. These factors included age, admission GCS scores, the presence of subdural hematoma, intraparenchymal hemorrhage, traumatic subarachnoid hemorrhage, coagulopathy, and an elevated NLR.[24] Xie et al.[25] conducted a retrospective study with 93 patients suffering from diffuse axonal injury and found that a higher NLR at admission was independently associated with unfavorable outcomes at six months. Furthermore, the combinations of NLR-GCS and NLR-coma duration demonstrated superior predictive performance compared to using NLR, GCS, or coma duration alone. However, it is important to note that the sample size of this study was relatively small, and it primarily included patients with severe TBI. Research has demonstrated that in patients with TBI, those suffering from diffuse axonal injury exhibit significantly elevated NLR compared to patients with other TBI-related conditions such as cerebral edema, intracranial hematoma, subdural and/or epidural hematoma, and subarachnoid hemorrhage.[22]

In a study by Acar et al.[26] involving 200 patients with minor head trauma, significant differences in NLR were observed between those with brain pathologies and those with normal CT scans. A cutoff value of 4.29 was determined to effectively differentiate patients with traumatic brain injuries that involved brain pathology from those without, yielding a specificity of 90%.

In a study by Alexiou et al.[17] involving 130 patients with mTBI, 74 exhibited positive CT findings. The mean NLR at presentation was 5.6±4.8, and significantly higher NLR levels were noted in patients with positive CT findings. ROC analysis established an NLR threshold of 2.5 for detecting positive CT results, with a sensitivity of 78.1% and a specificity of 63%. Furthermore, patients with a GCS score of 14 or lower demonstrated a sensitivity of 26% and a specificity of 98.1% for detecting positive CT findings. Notably, the mean age in this study was 61.6±19.9 years, which is older than the population in our study. It is recognized that age can influence the inflammatory response and outcomes in TBI.[16]

The initial injury mechanism of TBI typically results in the rupture of capillaries and vessels, disrupting the blood-brain barrier. This breach prompts interactions between platelets and either endothelial cells or the subendothelial matrix, culminating in platelet adhesion, activation, and the formation of platelet emboli at the site of injury to promote hemostasis27. A reduced PLR might signal an early imbalance in coagulation and an increase in neuroinflammatory responses.[27]

Moreover, a study encompassing 247 participants found that elevated PLR values were correlated with poor clinical outcomes in individuals with subarachnoid and intracranial hemorrhages.[28] In a study involving 54 children diagnosed with isolated mTBI, it was observed that NLR levels were elevated in children presenting with mild head injuries and abnormal CT scans at the ED. An optimal cutoff value of 2.5 was determined for detecting abnormal head CT scans, with a sensitivity of 54.2% and a specificity of 89.5%. The mean NLR levels at presentation were recorded at 5.6±4.8. Additionally, children with abnormal CT findings exhibited lower PLR levels at presentation compared to those with normal CT scans, although the differences were not statistically significant.[29] Similarly, our study found that patients with abnormal CT findings also had lower PLR levels at presentation compared to those with normal CT scans, with no statistically significant differences. We hypothesize that this may be due to the PLR levels being measured early in the course of mTBI. We believe that conducting further studies with multiple measurements of PLR levels at different time points could provide more definitive guidance on this issue.

Limitations

The limitations of our study include its single-center, retrospective design, and relatively small sample size.

Such a structure might not fully capture the diversity and complexity of mTBI cases seen in a broader, real-world setting where patients often present with varied types of injuries. Understanding the interactions between different injury types is essential for more comprehensive clinical decision-making and for evaluating the efficacy of predictive biomarkers. Additionally, while patients with TBI were admitted to the ED within three hours of their head injury, the precise timing of the head injury itself could not always be accurately determined. There's variability in how much time passed since the injury. The exact timing of trauma could influence NLR and PLR levels, as inflammatory responses evolve over time. More detailed information on injury-to-sample time might refine the interpretation of results. Further research, including prospective studies and multi-center trials, is needed to validate the utility of these biomarkers in broader clinical practice.

CONCLUSION

Limiting unnecessary head CT scans is crucial in the management of mTBI. Inflammation plays a critical role in the pathology of TBI, and the NLR is a rapidly accessible, low-cost, objective, and reproducible inflammatory biomarker, easily calculated from routine hematological tests. The measurement of NLR at admission shows promise for predicting abnormal head CT findings in mTBI cases, potentially averting complications associated with delayed diagnosis and treatment. Furthermore, NLR can be seamlessly integrated into daily clinical practice without incurring additional costs.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Ankara Etlik City Hospital Clinical Researches Ethics Committee (Date: 27.09.2023, Decision No: 2023-588).

Informed Consent

Because the study was designed retrospectively, no written informed consent form were obtained from patients.

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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