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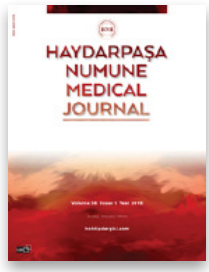

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ORIGINAL ARTICLE

Evaluation of Traumatic Brain Injury with Hematological Parameters: Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio

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Abstract

Introduction: Traumatic brain injury (TBI) is one of the leading causes of death and disability, affecting millions of people worldwide[1]. Theoretically, neutrophil-to-lymphocyte ratio (NLR) and thrombocyte-to-lymphocyte ratio (TLR) have the potential to be used as a marker of the severity of the secondary brain injury process in TBI. The aim of this study was to investigate the changes in routine blood tests in patients with severe TBI and analyze the relationship between NLR, TLR, and TBI outcomes.

Methods: In this study, we collected the data using the routinely analyzed hematological parameters of the patients admitted to our hospital for TBI and who underwent surgery in the past 10 years. GCS score and pupillary reaction of the patient at admission, demographical data, computed tomography (CT) scans, analysis of the blood sample is routinely performed at admission. White blood cell count, hemoglobin, mean corpuscular volume, red blood cell distribution width (RDW), platelet, and neutrophil count data were recorded from blood sample analysis.

Results: There was a significant difference between the good outcome and bad outcome groups in terms of the mean age, pupillary activity, and GCS. While the groups were significantly different in terms of their hematological parameters, such as RDW, mean platelet volume (MPV), and neutrophil count (p=0.005, 0.017, and 0.043, respectively), no difference could be detected in terms of TLR and Glasgow Outcome Scale (p=0.14). However, NLR was observed to be higher in the patient group with bad outcome (p=0.0078).

Discussion and Conclusion: Secondary brain injury in patients with head trauma is associated with the inflammatory process, and although the results in our study were not significant in terms of TLR, blood count tests such as NLR and TLR, which affect prognosis, are indicators of inflammation. Therefore, the increase in NLR and TLR may be a guide for CT scan and surgical treatment. Moreover, we believe that neutrophil, RDW, and MPV values in routine blood count tests may also be prognostic indicators. Nevertheless, more advanced, comprehensive, and prospective studies are required to support the current results.

Keywords: Neutrophil-to-lymphocyte ratio, Platelet-to-lymphocyte ratio, Traumatic brain injury

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Traumatic brain injury (TBI) is one of the leading causes of death and disability, affecting millions of people worldwide[1]. It can lead to deterioration in cognitive and physical functions that patients can experience throughout their lives. At the same time, due to the need for long-term treatment and rehabilitation, these problems are costly and cause the deterioration of the quality of life[2]. Therefore, a biomarker that can predict the severity of secondary brain injury (SBI) in TBI patients is required. Thereby, the effectiveness of TBI treatment can be increased and the progression of SBI can be prevented in cases with TBI. Primary brain injury is caused by brain tissue exposure to mechanical force and results in axonal, vascular, and glial cell damage[3-5]. SBI results from the emergence of inflammatory cascades by the release of various inflammatory factors and neurotransmitters from damaged neuronal and glial cells in the brain[5]. With treatment, SBI is preventable. SBI can determine whether the development and recovery after TBI will be good or bad[5]. The increase in systemic inflammatory response can be inferred from an increase in the count of inflammatory cells such as neutrophils or an increase in the level of inflammatory biomarkers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)[6,7]. CRP and ESR are widely used in the clinic to monitor the progression of inflammatory diseases, but these laboratory analyses are not routinely performed in patients with trauma. On the other hand, neutrophil, thrombocyte, and lymphocyte counts can be obtained using complete blood count (CBC), which is performed more routinely compared to CRP and ESR tests in patients with trauma. Complete blood count is primarily used to monitor trauma-related hemorrhage by measuring hemoglobin and hematocrit levels. CBC test is available in almost every hospital. Furthermore, the CBC test is a cheaper and more convenient laboratory analysis[8]. Some studies have shown that the neutrophil-to-lymphocyte ratio (NLR) is a very easy method and can act as an indicator of clinical outcomes caused by cancer, cardiovascular diseases, and stroke[9-11]. In addition, there are studies showing that in addition to NLR, the platelet-to-lymphocyte ratio (PLR) may also function as a marker in determining the severity of an inflammatory reaction[7]. Moreover, a study by Pan et al.[7] has shown that NLR and PLR were positively correlated with high-sensitivity CRP and ESR in patients with autoimmune inflammatory disease such as Takayasu's arteritis.

However, the predictive value of NLR and thrombocyte-to-lymphocyte ratio (TLR) in TBI cases is still unclear and has not been extensively studied. Theoretically, NLR and TLR have the potential to be used as a marker of the severity of the SBI process in TBI. NLR and TLR results in TBI patients are still not put into full use in daily medical practice. The aim of this study was to investigate the changes in routine blood tests such as white blood cell count (WBC), hemoglobin, mean corpuscular volume (MCV), red blood cell distribution width (RDW), platelet, and neutrophil count in patients with severe TBI and analyze the relationship between NLR, TLR, and TBI outcomes. If this relationship can be demonstrated, it will be possible to predict the prognosis and severity of the condition in patients with TBI by monitoring the hematological parameters, which is a routine practice.

Materials and Methods

In this study, the plan was to use the data collected using the routinely analyzed hematological parameters of the patients admitted to our hospital for TBI and who underwent surgery in the past 10 years (between January 2010 and January 2020). Inclusion criteria were being over 18 years of age, being admitted to the hospital due to isolated head trauma and TBI, and being operated. Exclusion criteria were being younger than 18 years of age, using steroids or immunosuppressants, having liver cirrhosis, and having missing data.

The study was conducted by reviewing clinical data and records after Ethics Committee approval (2021/29–23) was obtained in accordance with the Declaration of Helsinki. The severity of TBI was assessed on the basis of the first post-resuscitation GCS score at admission. All computed tomography (CT) scans were performed according to the neuroradiology department protocol. Researchers reading the scans were blind to clinical information. CT classification was done by a radiologist and classified as traumatic subarachnoid hemorrhage, epidural hematoma, subdural hematoma, or diffuse axonal injury. Analysis of the blood sample is routinely performed at admission. WBC, hemoglobin, MCV, RDW, platelet, mean platelet volume (MPV), neutrophil, lymphocyte, NLR, and TLR data were recorded from blood sample analysis. NLR was calculated by dividing the neutrophil count by the lymphocyte count, and TLR by dividing the platelet count by the lymphocyte count. The researchers who collected and handled the data were blind to all patient details. The Glasgow Outcome Scale (GOS) is a scale for patients with brain injury (Table 1)[12-14]. The GOS applies to patients with brain injuries and allows for an objective assessment of their recovery in five categories. It predicts the long-term course of rehabilitation to return to

Table 1. Glasgow Outcome Scale[13,14]

1	**Dead**	**Bad outcome**
2	Permanent vegetative state	
3	Severe disability	
4	Moderate disability	Good outcome
5	Good recovery	

work and everyday life[12]. Functional outcome was based on the GOS score. GOS scores were determined as negative, bad (GOS 1–3) and positive, good (GOS 4–5). Standard treatment and routine physical therapy protocols in accordance with TBI guidelines were applied to all patients.

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 20 (SPSS Inc.; Chicago, IL, USA). Kolmogorov–Smirnov test was performed to determine whether the data fit the normal distribution. Continuous variables were presented as mean±standard deviation and compared with Student's t-test. Categorical variables were expressed as numbers (n) and percentage (%) and compared using the Chi-square test. Receiver operating characteristic analysis was used to evaluate the diagnostic performance of hematological parameters. The significance level of all statistical evaluations was set to $p<0.05$.

Results

During the study, 149 patients were admitted to our hospital with the diagnosis of isolated head trauma. Thirteen of these patients were excluded for the reasons such as younger than 18 years of age, using steroids or immunosuppressants, having liver cirrhosis, and having missing

Table 2. General characteristics of the patients (demographic and clinical characteristics and comparison of CT scan results and GOS results)

Prognostic factors	Good outcome	Bad outcome	p
Age (years), (Mean±SD)	52.09±20.57	44.66±28.55	0.01*
Gender (n)			
Female	27	6	0.029¥
Male	97	6	
Pupillary activity (n)			
Bilateral activity	114	5	0.001¥
Unilateral activity	8	5	
Reactive	2	2	
Computed tomography results (n)			
Traumatic subarachnoid hemorrhage	63	6	>0.05
Epidural hematoma	33	2	
Subdural hematoma	13	3	
Diffuse axonal injury	1	0	
No intracranial hemorrhage	14	1	
GCS (n)			
GCS (3–8)	5	13	0.001¥
GCS (9–15)	112	6	
Surgical intervention (n)	15	4	>0.05¥
No surgical intervention (n)	102	15	

*Student t-test; ¥Chi-square test. CT: Computed tomography; GOS: Glasgow Outcome Scale.

Table 3. Hematological parameters of the patients

	Good outcome	Bad outcome	p
WBC (10^3/μL)	13.67± 6.01	18.20±10.09284	0.29
Hemoglobin (g/dL)	12.87±2.06	12.85±1.87350	0.54
MCV (fL)	87.80±7.49	84.08±5.00	0.29
RDW (fL)	13.88±1.75	15.9±3.68	0.005
Platelet (10^3/μL)	233.66±92.29	244.16±80.9	0.08
MPV (fL)	8.33±0.96	8.20±0.99	0.017
Neutrophil (10^3/μL)	9.85±5.93	14.61±9.23	0.043
Lymphocyte (10^3/μL)	2.78±2.97	2.26±1.95	0.31
NLR	7.00±6.53	8.52±5.12	0.0078
TLR	138.24±88.61	161.03±80.96	0.14

WBC: White blood cell count; MCV: Mean corpuscular volume; RDW: Red blood cell distribution width; NLR: Neutrophil-to-lymphocyte ratio; MPV: Mean platelet volume.

data. A total of 136 people were included in the analysis. Demographic and clinical characteristics of the patients were compared with CT scan results and laboratory examination and GOS results (Tables 2 and 3). Analysis of laboratory results showed that TLR was not associated with GOS outcome scores. However, NLR was statistically higher in the bad outcome group.

Discussion

There was a significant difference between the good outcome and bad outcome groups in terms of the mean age (52.09±20.57 years and 44.66±28.55 years, respectively), pupillary activity, and GCS. GOS was not found to be better in the group of patients who underwent surgery (p>0.05). While the groups were significantly different in terms of their hematological parameters, such as RDW, MPV, and neutrophil count (p=0.005, 0.017, 0.043, respectively), no difference could be detected in terms of TLR and GOS (p=0.14). However, NLR was observed to be higher in the patient group with bad outcome (p=0.0078).

Aydın et al.,[15] in their study of patients with normal sedimentation and CRP values, evaluated the results of approximately 72,000 measurements and found the mean NLR in individuals aged 20–29 years to be 1.19 in men and 1.01 in women. They also stated that the gender difference was not significant for this age group. Similarly, in our study, no significant difference was found between genders in terms of NLR and TLR, regardless of age groups. On the other hand, Akgül Kalkan et al.[16] found that the mean NLR values in men were higher and there was a statistically significant difference between the genders in terms of mean NLR values. However, the authors stated that this result may be due to the fact that the majority of the patient population was male (85%). Similarly, in our study, 90% of the patient population was male. Aydoğdu et al.[17] reported that NLR reference values differed according to age and gender, but other studies reported that no relationship was found between NLR mean or cutoff values and gender.

In our study, only 14% of the patients were identified as the group requiring surgical intervention, and when the GOS results were analyzed, it was found that there was no significant difference between the groups in terms of the GOS values of the patients who underwent surgery. The Glasgow Coma Scale has been found to be prognostically valuable in many of the previous studies[18]. Similarly, in our study, the GCS score at admission was lower in the patient group with bad outcome (p=0.0001).

Haselberger et al.[19] report that the mortality rate rises from 47% to 80% when the time between hospitalization and surgery is longer than 2 h, whereas in another study, Stone et al.[20] reported that there was no significant difference between the outcome of the operations performed within the first 4 h after the trauma and the outcomes of the operations performed after this time. In our study, it was not possible to determine how long after the trauma the patients requiring surgery were operated. This may be one of the limitations of this study.

In the recently published study of Wang et al.,[21] when acute renal failure (ARF) was evaluated using RDW in patients with TBI, it was concluded that it is an independent risk factor for ARF and mortality in patients with TBI. Similarly, in our study, RDW was found to be statistically significantly higher in the patient group with negative outcome and low GOS values. Although the underlying relationship between RDW and mortality has not been fully elucidated, there are various explanations. TBI can trigger a massive release of inflammatory mediators such as tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β) and interleukin 6 (IL-6), and CRP, which can accelerate neuroinflammation and systemic organ damage. It was confirmed that elevation of inflammatory cytokines, including TNF-α, IL-1β, and IL-6, can inhibit erythropoietin-induced erythrocyte (RBC) maturation[22]. In addition, RDW causes an increase in the amount of juvenile erythrocytes. Second, oxidative stress inhibits erythropoiesis and may contribute to anisocytosis by impairing the deformability of the red blood cell membrane. This shortens the circulatory half-life of the red blood cell and causes an increase in the RDW value[23,24].

It has been demonstrated in previous studies that neuroinflammatory cascade is triggered by endothelial cell damage caused by infiltration of neutrophils into the tissue, secretion of cellular adhesive molecules, production of inflammatory mediators, and disruption of superficial anticoagulant mechanisms in TBI[25-27]. Similarly, in our study, neutrophil count was found to be higher in the group with bad outcome. This corroborates the view that high neutrophil count may be a predisposing factor for secondary brain injury in patients.

Previous studies have shown that high NLR in patients with minor head trauma can be used as a parameter indicating brain pathologies,[28] and while NLR is higher in patients with acute and acute subdural hemorrhage, it was reported that it is higher in patients with chronic subdural hemorrhage compared to the control group[15]. In addition, it has been shown that high NLR values are associated with mortality in patients with trauma and patients

with massive hemorrhagic trauma[9]. In a study by Tuzcu et al.,[29] it was shown that the mean NLR value was 6.24. It has been reported that this value is obtained in acute subdural hemorrhages, whereas NLR in chronic subdural hemorrhage is 2.79. The patients included in our study were patients with TBI and chronic patients were not included in the evaluation. Acar et al.[30] evaluated the hematological markers of patients with isolated minor head trauma versus the control group, and determined that the NLR was significantly higher in patients with head trauma with identified pathology. The researchers concluded that elevated marker levels in minor head trauma may be the cause of inflammation[30]. In our study, NLR was found to be significantly higher in patients with bad outcome, which was concordant with the literature (p=0.0078). We believe that the results of our study can be explained by inflammation, which is in line with the literature.

In conclusion, secondary brain injury in patients with head trauma is associated with the inflammatory process, and although the results in our study were not significant in terms of TLR, blood count tests such as NLR and TLR, which affect prognosis, are indicators of inflammation. Therefore, the increase in NLR and TLR may be a guide for CT scan and surgical treatment. Moreover, we believe that neutrophil, RDW, and MPV values in routine blood count tests may also be prognostic indicators. Nevertheless, more advanced, comprehensive, and prospective studies are required to support the current results.

Ethics Committee Approval: The study was conducted by reviewing clinical data and records after Ethics Committee approval (2021/29–23) was obtained in accordance with the Declaration of Helsinki.

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