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Original Article

Neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio correlate with the occurrence and prognosis of progressive hemorrhagic injury in patients with traumatic brain injury

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Abstract: Objective: To identify risk factors associated with progressive hemorrhagic injury (PHI) in patients with isolated traumatic brain injury (TBI) and to develop prognostic models for predicting patient outcomes. Methods: A total of 137 patients with isolated TBI who underwent additional CT scans were included in the retrospective study. Single-factor analysis and multivariate logistic regression analysis were performed to identify significant risk factors associated with PHI development. Receiver operating characteristic (ROC) curve analysis was conducted to evaluate the diagnostic value of specific markers for predicting PHI. Results: Single-factor analysis revealed significant differences between the PHI group (62 patients) and the non-PHI group (75 patients) in various factors, including gender, etiology, pupillary size and reflex, midline shift, associated brain contusion, D-dimer (D-D) levels, neutrophil-to-lymphocyte ratio (NLR), platelet count, blood glucose levels, and Glasgow Coma Scale (GCS) score. Multivariate logistic regression analysis identified NLR, blood glucose level, and GCS score as significant risk factors for PHI in isolated TBI patients, and also identified GCS score, NLR, platelet-to-lymphocyte ratio (PLR), and age as significant factors for predicting prognosis. ROC curve analysis showed that NLR had significant auxiliary diagnostic value for predicting PHI. Conclusion: NLR, blood glucose level, and GCS score are significant risk factors for PHI development in isolated TBI patients. The constructed prognostic model incorporating age, GCS score, NLR, and PLR offers valuable predictive capabilities for PHI patient outcome in isolated TBI cases.

Keywords: Progressive hemorrhagic injury (PHI), isolated traumatic brain injury, risk factors, prognostic models, neutrophil-to-lymphocyte ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR)

Introduction

Traumatic brain injury (TBI) refers to the pathologic and physiologic changes in the brain caused by external violence, such as impact or blunt force, resulting in altered brain function and impairment [1]. TBI is the second most common injury, after limb injuries, but it carries a high risk of disability and fatality. According to the World Health Organization (WHO), 1/3 to 1/2 of trauma-related deaths are attributed to traumatic brain injury [2]. Severe traumatic brain injury (sTBI) leads to a disability rate of approximately 30%-40% and is a major cause of disability in individuals under the age of 40 [3]. It is estimated that over 50 million people worldwide receive treatment for TBI every year (939/100,000), and this number is increasing annually [4]. TBI may even surpass cardiovascular diseases and cancer as the leading cause of global fatalities [5]. Additionally, the annual healthcare costs associated with TBI exceed $400 billion, imposing a significant burden on society, families, and individuals [6].

Progressive brain injuries refer to those that worsen over time following the initial insult, such as post-traumatic intracranial bleeding or expanding hematomas leading to increasing symptoms and complications like elevated intracranial pressure and brain herniation. In contrast, non-progressive brain injuries are ol-

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der injuries, such as those from past inflammation or trauma, where the damage has stabilized and is no longer advancing [7, 8].

The inflammatory response is a key mechanism underlying coagulation dysfunction following brain injury, with one of its primary manifestations being progressive hemorrhagic injury (PHI). Sanuss et al. [9] defined PHI as a new intracranial bleed identified on follow-up CT findings or an increase of more than 25% compared to the initial CT findings. Due to its multifactorial nature and rapid progression, there is a lack of specific tests in clinical practice to predict the occurrence of PHI. Reported rates of PHI occurrence vary from 20% to 60% [10]. Recent studies have reported the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR) as valuable indicators for predicting the progression and prognosis of PHI [11].

Our study aims to investigate the predictive role of NLR and PLR for predicting PHI following isolated brain injury. The findings of this study provide evidence to support clinical strategies for preventing and treating PHI in these patients. The innovation of our research lies in the comprehensive evaluation of NLR and PLR in combination with traditional clinical factors, such as age and GCS score, to develop a predictive model for PHI. This model may enhance clinical decision-making by providing a reliable tool to identify patients who may benefit from more intensive monitoring or intervention.

Materials and methods

General information

From August 2021 to April 2023, a total of 137 patients with isolated brain injuries were admitted to the Neurosurgery Department of The First Medical Center of Chinese PLA General Hospital. All patients underwent head CT scans, which showed significant brain injuries such as hemorrhage and contusion. This retrospective study was approved by the Medical Ethics Committee of the General Hospital of the Chinese People's Liberation Army (approval number: 2024-0420).

Inclusion criteria: (1) Isolated brain injury without the need for emergency surgery; (2) Emergency cranial CT scan performed within 8 hours after traumatic brain injury, with a repeat scan in 24 hours; (3) Age between 18 and 80 years old; (4) Initial blood routine and coagulation function tests performed within 3 hours after brain injury. Exclusion criteria: (1) Severe multiple injuries; (2) Recent use of anticoagulants or antiplatelet drugs; (3) Blood system diseases, immune system diseases, or serious cardiovascular, liver, lung, kidney diseases; (4) Age under 18 or over 80 years old; (5) No obvious abnormalities found in the first head CT scan, or immediate craniotomy performed after the first head CT scan, or patients who did not undergo a second head CT scan due to death or other reasons.

Head CT scans were repeated within 24 hours after injury. PHI was defined as the presence of new bleeding or an increase in hemorrhagic contusion greater than 25% compared to the initial CT scan. The hematoma volume was calculated using the Modified Tada Formula: $V = \pi/6 \times k \times a \times b \times c$, where a is the longest diameter of the hematoma, b is the maximum width diameter, c is the number of layers, and k is the thickness per layer. Hemorrhage involving 2/3 or more of the brain injury lesion was classified as an intracranial hematoma; otherwise, it was considered a cerebral contusion. According to whether the patient's repeat CT scan met the diagnostic criteria for PHI, patients were divided into a PHI group and a non-PHI group.

Observation indicators

Upon admission, patients were evaluated using the Glasgow Coma Scale (GCS) to assess consciousness, along with an examination of pupil appearance (Vision One by Suzhou Dinner Automation Technology Company) and a head CT scan (CT scanners by United Imaging Healthcare). Blood routine values, including white blood cells (WBC), neutrophils (NEU), lymphocytes (LYM), monocytes (MONO), hemoglobin (Hb), red blood cells (RBC), red cell distribution width (RDW), and platelets (PLT), were measured using the ADVIA® 2120i automated blood analyzer (Siemens Healthcare Diagnostics Inc.). Blood glucose levels were assessed using equipment from Ascensia Diabetes Care (Roche Diagnostics). Coagulation function indicators, such as prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (aPTT), and fibrinogen degradation products (FDP), were analyzed using the CX-9000 fully automatic coagulation ana-

Table 1. Comparison of baseline information between PHI group and non-PHI group

Variable	Non-PHI group (n=75)	PHI group (n=62)	t/x^2	P
Gender			x^2=6.252	0.015
Male	45	52		
Female	30	10		
Age (years)	44.30±17.158	45.67±17.202	t=1.942	0.053
Underlying disease			x^2=0.353	0.602
Hypertension	15	18		
Diabetes	8	10		
Cardiovascular disease	5	7		
Average hospital stay (days)	7.5±3.1	9.2±4.5		0.012
ICU stay (days)	2.1±1.9	3.4±2.6		0.023
Mortality	2 (2.7%)	8 (12.9%)		0.001
Cause of injury			x^2=10.408	0.015
Motor vehicle accidents	34	30		
Falls from heights	18	15		
Blunt impact	13	9		
Bruise	10	8		

Note: PHI: Progressive hemorrhagic injury.

lyzer (Mindray Medical). The NLR and PLR were calculated based on the complete blood count results obtained from the Sysmex XN-9000 blood analyzer (Sysmex Co., Ltd., Japan).

During the 6-month follow-up period after head trauma, patients were assessed using the Glasgow Outcome Scale (GOS) scoring system [12] during outpatient visits or telephone interviews. Based on their scores, patients were classified into a good prognosis group (GOS score of 4-5) and a poor prognosis group (GOS score of 1-3). Scoring criteria: 1 point for death, 2 points for a persistent vegetative state, 3 points for severe disability, 4 points for moderate disability with the ability to live independently, and 5 points for good recovery. Factors associated with patient prognosis were analyzed.

Statistical analysis

SPSS 22.0 software was used for statistical analysis. Normally distributed data were expressed as mean ± standard deviation (x ± s), and independent sample t-tests were used to compare the means between two groups. Non-normally distributed data were analyzed using the Mann-Whitney U test. Counted data (n, %) were compared using the chi-square test. Logistic regression analysis was performed to identify risk factors associated with PHI development after TBI. Receiver operating characteristic (ROC) curve analysis was performed to assess further the diagnostic performance of key variables. A *P* value of less than 0.05 was considered significant.

Results

Univariate analysis

This study included 107 males and 30 females, with a male-to-female ratio of 3.57. The age range was 18 to 80 years old, with an average age of (47.46±16.72) years old. The causes of injury included motor vehicle accidents (64 cases), falls from heights (33 cases), blunt impact (22 cases), and bruising (18 cases). Among the 137 patients with isolated brain injuries who underwent subsequent CT scans, 62 patients (45.3%) exhibited progressive hemorrhagic injury (PHI group), while the remaining 75 patients (54.7%) did not show progressive hemorrhagic injury (non-PHI group) (**Table 1**).

The results of univariate analysis revealed significant differences between the two groups in terms of pupil size and light reflex, cisternal changes, midline shift, associated cerebral contusion, D-dimer level, NLR, PLR, platelet count, blood sugar, and GCS score (all P<0.05). The NLR and PLR in the PHI group (21.492± 11.805, 252.280±133.775) were significantly

higher than those of the non-PHI group (10.753±7.427, 182.109±84.037), as shown in **Table 2**.

Risk factors for progressive hemorrhagic injury (PHI) in isolated brain injury

Multivariate logistic regression analysis was performed to identify the risk factors associated with the occurrence of PHI after isolated brain injury, using significant factors such as NLR, PLR, and other indicators from univariate analysis. The results showed that NLR, blood glucose level, and GCS score were significantly correlated with the occurrence of PHI after isolated brain injury (**Table 3**).

Diagnostic value of NLR for PHI

To evaluate the diagnostic utility of the NLR for predicting PHI, an ROC curve was constructed to determine its optimal cutoff point and analyze its performance (**Figure 1**). The area under the ROC curve (AUC) for NLR was 0.801 (95% CI: 0.743-0.859, P=0.022), with a sensitivity of 72.6% and specificity of 77.5%. The optimal NLR cutoff point was identified as 14.59, providing the best balance between sensitivity and specificity.

Multivariable logistic analysis for factors affecting patient prognosis

Among the 137 patients, 94 had a good prognosis and 43 had a poor prognosis. To assess the factors associated with patient prognosis, a multivariable logistic regression analysis was conducted, with the patient prognosis as the dependent variable and the statistically significant factors mentioned above as independent variables. The analysis was performed using a stepwise regression method. The results showed that a lower admission GCS score, higher NLR, higher PLR, and older age were independent risk factors for poor prognosis in TBI patients (**Table 4**).

Construction of prognostic models based on risk factors

Prognostic models were constructed based on the results of the multivariable regression analysis. Four models were created: Model 1 incorporating age and GCS score; Model 2 incorporating age, GCS score, and NLR; Model 3 incorporating age, GCS score, and PLR; and Model 4 incorporating age, GCS score, NLR, and PLR. The AUCs for Models 1, 2, 3, and 4 were 0.685, 0.822, 0.671, and 0.864 respectively, indicating that Model 4 had the highest predictive efficiency for prognosis (**Figure 2**).

Discussion

Abnormal coagulation function after brain injury can lead to cerebral thrombosis, cerebral hemorrhage, and cerebral edema. Progressive hemorrhagic injury (PHI) is a primary manifestation of coagulation dysfunction. Due to the small volume of the cranial cavity, the mechanism of coagulation dysfunction caused by brain trauma is more complex compared to other injuries, and is not yet fully understood [13]. The pathogenic mechanisms mainly include hypoperfusion, brain tissue hypoxia, release of tissue factors, platelet activation, protein C activation, inflammatory response, endothelial cell dysfunction, and hyperfibrinolysis. Among these, immune abnormalities (inflammatory reactions) are considered significant contributors to coagulation dysfunction after brain injury, including central immune cells such as microglia and peripheral immune cells (neutrophils, monocytes, lymphocytes) that promote inflammation [14].

Studies have shown that during the acute phase of brain injury, the inflammatory response plays a crucial role in maintaining the blood-brain barrier, clearing necrotic tissue, producing trophic neuroproteins, and facilitating tissue repair [15]. However, in the context of coagulation dysfunction after traumatic brain injury, the inflammatory response can promote thrombus formation, leading to hypercoagulability, and then consumes a large amount of clotting substrates, resulting in hypocoagulability, ultimately leading to PHI [16]. This includes endothelial cell activation and damage, platelet activation, and alterations in platelet function and quantity as well as complement system and coagulation system. The complex and intense inflammatory response adversely promotes the progression of brain injury. In addition, serine proteases in the coagulation system, such as thrombin, also participate in intercellular reactions, especially the inflammatory response. Thrombin can also mediate inflammatory responses through protease-activated receptors (PAR1, 2, 3, 4) via G proteins. Another serine protease, FXa, can mediate inflammatory responses through PAR2 or 3 [17].

Table 2. Comparison of laboratory, imaging data and other relevant information between the PHI group and the non-PHI group

Variable	Non-PHI group (n=75)	PHI group (n=62)	t or x^2	*P*
D-dimer			x^2=24.111	0.000
≥6500 μg/L	10	7		
<6500 μg/L	65	55		
Systolic blood pressure			x^2=0.496	0.481
≥140 mmHg	36	31		
<140 mmHg	39	31		
Pupil size			x^2=26.731	0.000
Normal	72	50		
Mydriasis	1	11		
Miosis	2	1		
Pupillary light reflex			x^2=26.006	0.000
Normal	72	51		
Abnormal	3	11		
Ring pool changes			x^2=14.345	0.000
Normal	75	52		
Abnormal	0 (0%)	10		
Midline shift			x^2=26.092	0.000
≥5 mm	0	8		
<5 mm	75	54		
With or without fracture			x^2=4.403	0.064
No fracture	32	10		
Fracture	43	52		
Associated cerebral contusion			x^2=5.766	0.016
Yes	37	34		
No	38	28		
Merge Subarachnoid hemorrhage			x^2=3.571	0.059
Yes	39	38		
No	36	24		
High blood pressure			x^2=0.016	0.744
Yes	5	4		
No	70	58		
Diabetes			x^2=0227	0.634
Yes	2	1		
No	73	61		
Lymphocytes ($\times10^9$/L)	1.250±0.660	1.17±0.615	*t*=1.396	0.164
NLR	10.753±7.427	21.492±11.805	*t*=7.904	0.000
PLR	182.109±84.037	252.280±133.775	*t*=4.680	0.000
PLT ($\times10^9$/L)	193.17±59.626	174.31±43.155	*t*=2.639	0.009
Blood sugar (mmol/L)	6.31±1.623	7.79±2.575	*t*=4.982	0.000
PT (s)	11.829±0.964	11.585±0.1.385	*t*=1.515	0.131
INR	1.068±0.087	1.959±9.104	*t*=0.988	0.326
aPTT (s)	31.98±4.967	30.88±3.855	*t*=1.833	0.680
FDP (g/L)	2.96±1.320	2.61±1.423	*t*=1.886	0.061
GCS score	13.97±1.919	11.63±3.505	*t*=5.985	0.000

Note: NLR: Neutrophil-to-Lymphocyte Ratio, PLR: Platelet-to-Lymphocyte Ratio, PLT: Platelets, PT: Prothrombin Time, INR: International Normalized Ratio, aPTT: Activated Partial Thromboplastin Time, FDP: Fibrinogen Degradation Products, GCS score: Glasgow Coma Scale score; PHI: Progressive hemorrhagic injury.

Table 3. PHI associated factors identified by Multivariate Logistic regression analysis

Risk factor	B	S.E	Wals	Df	Sig	Exp (B)	95% CI	
							Lower limit	Upper limit
NLR	0.107	0.022	23.306	1	0.000	1.116	1.094	1.290
Blood sugar (mmol/L)	0195	0.092	4.474	1	0.034	1.205	0.715	0.923
GCS score	0.167	0.069	5.960	1	0.015	0.846	0.739	0.968

Note: PHI: Progressive hemorrhagic injury, B: Coefficient or estimated effect size, S.E: Standard Error, Wals: Wald statistic, Df: Degrees of Freedom, Sig: Significance (*p*-value), Exp (B): Exponential of the coefficient (Odds Ratio), 95% CI: 95% Confidence Interval, NLR: Neutrophil-to-Lymphocyte Ratio, GCS score: Glasgow Coma Scale score.

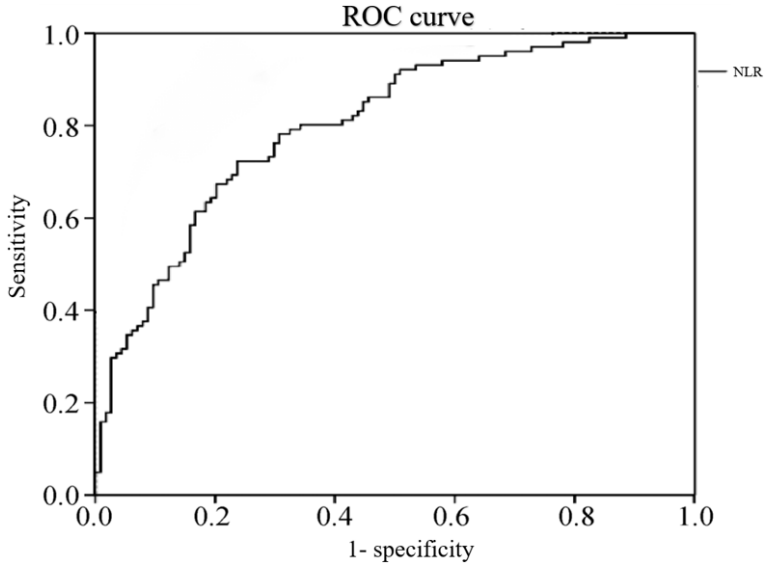

Figure 1. ROC curve of NLR for predicting PHI. NLR: Neutrophil-to-Lymphocyte Ratio, PHI: Progressive hemorrhagic injury.

Table 4. Patient prognosis-associated factors identified by multivariate logistic regression analysis

Variable	Regression coefficient	Standard error	Wald x^2	OR	95% CI
GCS score	-0.885	0.271	10.686	0.421	0.243-0.701
NLR	0.293	0.11	7.095	1.335	1.081-1.664
PLR	0.023	0.009	7.21	1.021	1.006-1.041
age	0.089	0.043	4.37	1.087	1.006-1.189

Note: NLR: Neutrophil-to-Lymphocyte Ratio, PLR: Platelet-to-Lymphocyte Ratio, GCS score: Glasgow Coma Scale score, PHI: Progressive hemorrhagic injury.

Coagulation dysfunction and inflammatory responses are intricately linked, forming a delicately balanced network. These systems have extensive overlap and interconnections, where any imbalance in one component can disrupt the overall balance, leading to different degrees of inflammation and thrombus formation-related diseases [18]. The degree of inflammatory response often reflects abnormalities in coagulation function. Various inflammatory markers, such as leukocytes, C-reactive protein (CRP), and erythrocyte sedimentation rate, have been widely studied in cardiovascular diseases, tumors, and autoimmune diseases. NLR, a relatively novel indicator, has been gaining attention due to its association with the prognosis of cerebral hemorrhage, cerebral infarction, cardiovascular diseases, and tumors [19]. Elevated NLR is suggested as an acute inflammatory marker and a predictor of thrombus formation. NLR serves as an indicator of subclinical inflammation, offering several unique advantages. First, it is derived from routine complete blood counts, which are cost-effective, easily obtainable, and repeatable. Second, NLR is less influenced by factors such as dehydration, physical activity, or fluid replacement. Third, NLR represents the ratio of two different but complementary immune pathways-neutrophil activation for nonspecific inflammation and the regulatory role of lymphocytes in inflammation [20]. Therefore, NLR has greater predictive value than total WBC count or neutrophil count alone in vascular diseases, reflecting a disrupted inflammatory balance in the body. RDW is thought to reflect inflammation-induced changes in red blood cell characteristics, and there may be multiple inflammatory factor receptors on red blood cells that contribute to the inflammatory process. As in-

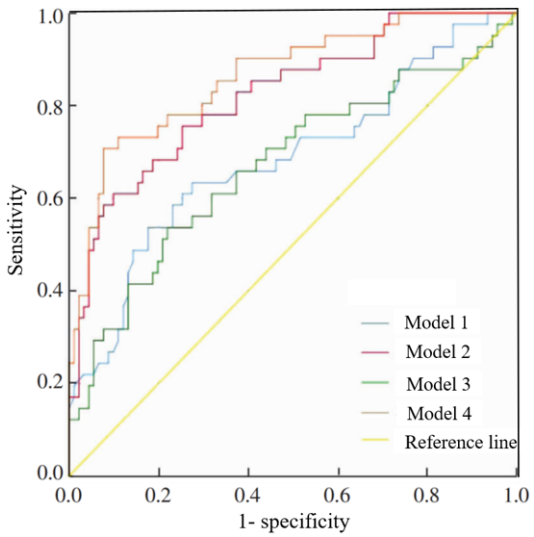

Figure 2. ROC analysis of constructed prognostic models.

flammation increases, so does RDW, further reinforcing its use as an inflammation-related biomarker [21].

This study found that significant changes in routine blood tests and coagulation function tests may occur within 3 hours after brain trauma. A study has shown that inflammatory reactions can occur as early as 15 minutes after brain trauma, leading to changes in platelet quantity and function [22]. The WBC count and neutrophil count gradually increase and become significantly elevated in patients with brain trauma. This study found that lymphocyte counts were significantly lower in patients with PHI than in those without PHI after brain trauma. Although NLR and PLR do not fully reflect the complexity of immune responses and inflammation status after brain trauma, they can indicate the occurrence of inflammation and its effect on coagulation function. Specifically, NLR can serve as a predictive factor for PHI after brain trauma. In general, both infectious and non-infectious inflammation can cause an increase in neutrophil count and a decrease in lymphocyte count. The results of this study suggest that the inflammatory status in patients with PHI may be more severe than in those without PHI. Patients with high NLR values after brain trauma should be monitored closely to prevent the occurrence of PHI.

The results of this study indicate that age is an independent risk factor for poor prognosis in TBI patients. In elderly patients, increased brain atrophy and expansion of the subdural space can enhance the brain's buffering capacity against elevated intracranial pressure. This can mask the manifestation of enlarged intracranial hemorrhage, leading to delayed clinical symptoms and signs. Some elderly individuals with degenerative cognitive impairments may be unable to accurately express disease manifestations, further delaying diagnosis [23]. However, as the intracranial hemorrhage progresses and exceeds the brain's buffering capacity, patients often experience rapid deterioration of neurological function. Caterino et al. [23] found that elderly TBI patients have worse prognoses and significantly higher mortality rates compared to young individuals with the same GCS score. Among elderly TBI patients, the mortality rate was 1.4 times (95% CI: 1.07-1.83) higher when the GCS score decreased from 15 to 14, and 2.3 times (95% CI: 1.57-3.52) higher when the GCS score decreased from 14 to 13. A meta-analysis indicated that the incidence of TBI gradually increases with age, with individuals aged 75 and above having the highest rates of TBI-related hospitalization and mortality. The mortality rate for elderly individuals with severe TBI within six months of injury is 74% [24]. The prognosis of elderly patients after TBI is relatively poor, consistent with the findings of other researchers [25].

Through ROC curve analysis, this study found that the optimal cutoff point for NLR in predicting PHI after traumatic brain injury was 14.59. Inflammatory responses play a dual effect in the early stage of TBI. While they are essential for tissue repair and recovery after brain damage, they can also disrupt coagulation function [26]. Therefore, anti-inflammatory drugs should be cautiously used in the early stage of traumatic brain injury [27].

In conclusion, this study found that both NLR and PLR are significantly elevated after TBI, with NLR being especially high in PHI patients. These easily obtainable inflammatory markers hold clinical value as predictive factors for PHI. However, this study was a retrospective analysis with cases from a single treatment center, and the blood testing occurred approximately 20 minutes after patient admission, which may have affected the accuracy of the results. Therefore, future prospective and randomized

clinical studies are necessary to assess further the predictive value of NLR for PHI after brain injury.

Disclosure of conflict of interest

None.

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