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Research Article
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Correlation of Neutrophil/Lymphocyte Levels with Cognitive Dysfunction Impairment in Mild and Medium-Sized Traumatic Brain Injury

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Abstract

Background: To explore the correlation between Neutrophil/Lymphocyte (NLR) levels and mild and medium-sized traumatic brain injury and cognitive impairment, to provide early diagnosis and intervention of possible traumatic brain injury and cognitive impairment in high levels of NLR.

Methods: Selected from September 2022 to September 2023 in Chaohu Hospital affiliated to Anhui Medical University neurosurgery of traumatic brain injury light and medium cognitive dysfunction each 100 cases, and the same period to the health center of 100 cases, all the enrolled object are complete general data collection, biochemical and NLR detection, MoCA scale score, head CT examination. TBI is diagnosed according to a clinician outside the professional god.

Results: NLR, WBC and TBIL were significant. Moreover, the combination of leukocytes and NLR can significantly improve the predictivity of TBI in cognitive dysfunction.

Conclusion: We conclude that the serum inflammatory markers of TBI NLR, WBC and the antioxidant straight bilirubin are predictive of cognitive dysfunction in TBI.

Keywords: Neutrophils/Lymphocytes; Inflammation; Antioxidants; Traumatic brain injury; Cognitive dysfunction

Introduction

Traumatic Brain Injury (TBI) is a common multi-morbidity with high mortality and high disability rates worldwide. The Glasgow Coma Scale (GCS) TBI is clinically mild, moderate and severe, with associated permanent disability rates of 10%, 60% and 100%, and the total mortality rate of 20% to 30%. By 2030, the incidence of TBI-related disability will be 2 to 3 times higher than Alzheimer's Disease (AD) and cerebrovascular disease [1,2]. Clinical outcomes after TBI may include overall disability, neurobehavioral impairment, and psychological comorbid [3].

It has been suggested that multiple concussions appear to be risk factors for cognitive impairment and mental health problems in some people [4]. The early assessment and prognosis of cognitive impairment after TBI is one of the current research hotspots in the field of neurocognitive rehabilitation, among which more studies are inflammatory reaction, nitric oxide and endothelial dysfunction and oxidative stress, and studies have shown that cognitive impairment is expected to become a major public and community health problem in the future [5]. These changes lay the foundation for the study of the prognosis and the principle and mechanism of cognitive impairment after TBI. And, it has been shown that cognitive impairment is expected to become a major public and community health problem for in the future [6,7]. The early assessment and prognosis of cognitive impairment after TBI is one of the current research hotspots in the field of neurocognitive rehabilitation, in which more studies are inflammatory reaction, nitric oxide and endothelial dysfunction, and increased oxidative stress. TBI itself causes lifetime cognitive deficits. It has been suggested that multiple concussions appear to be risk factors for cognitive impairment and mental health problems in some people [4].

A widely accepted phenomenon is that neutrophils are one of the first responders to injured tissue in the peripheral and central nervous system [8,9]. Bilirubin, the end product of heme metabolism, has long been considered to require expulsion because it is simply viewed as a cytotoxic waste, however, recent studies found that bilirubin has anti-inflammatory properties under physiological conditions [10]. Several studies have implicated bilirubin in cognition and reduced serum bilirubin

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concentrations in patients with Mild Cognitive Impairment (MCI) [11]. Based on the above studies, because oxidative stress is associated with the cognitive function of TBI and bilirubin has antioxidant effects, we believe that serum total bilirubin concentration may affect cognitive function in patients with TBI. The purpose of this study was to investigate the correlation between Neutrophil/Lymphocyte (NLR) levels in TBI and mild and medium-sized traumatic brain injury and cognitive impairment in TBI, and to provide research ideas for early diagnosis, intervention and prevention.

Research Objects and Methods

Study subjects

Collected from TBI patients hospitalized in the neurosurgery department of Chaohu Hospital affiliated to Anhui Medical University from September 2022 to September 2023. According to the GCS score, 3–8 were severe, 9–12 moderate, and 13–15 mild. The MoCA score can divide TBI patients into cognitive dysfunction (<26 points) and normal cognitive work and cognitive function (26 points). Here, 200 cases of mild and medium-sized TBI were collected, and 100 healthy controls matched to the TBI group were recruited simultaneously. This prospective study has been approved by the Ethics Committee of Chaohu Hospital affiliated to Anhui Medical University, with both patient consent and signed informed consent.

Inclusion criteria: 1) TBI was clearly diagnosed by clinical and imaging; admission within 12 h after 2) injury; 3) age 18 to 85 years.

Exclusion criteria: 1) Previous brain injury, cerebral infarction, multiple sclerosis and other neurological diseases that may affect uric acid levels; 2) previous history of gout, and/or taking allopurinol; 3) with one or more serious underlying diseases, such as coronary heart disease, renal insufficiency, cirrhosis; 4) with other injuries, such as multiple rib fractures, femoral fractures, etc.

Statistical method

Statistical analyses were performed with SPSS27.0 software and Prism. Measurement data are expressed as the mean ± standard deviation (x ± s), and classification data are expressed as a percentage. Normality tests for baseline data were performed by the Kolmogorov-Smirnov method. Age, MoCA score, serum DBIL, IBIL, TBIL, UA, CR, BUN, WBC, and NLR values were compared by the Kruskar-Walli's test or Analysis of Variance (ANOVA). The significance values were adjusted by Bonferroni correction and compared using the Chi-square test. Diagnostic value test was performed by ROC analysis. Correlation analysis The Spearman correlation analysis was used. The Logistic regression analysis was used to evaluate the influencing factors.

Table 1: Comparison of the results of direct bilirubin, indirect bilirubin, total bilirubin, uric acid, creatinine, urea, white blood cells, and neutrophils/lymphocytes.

	Mild	Moderate	Control	P value
Age (years)	60.48 ± 2.02	60.91 ± 1.1	58 ± 1.29	0.358
Male, n (%)	111 (64.2%)	28 (16.2%)	34 (19.7%)	0.442
DBIL	7.02 ± 4.26	6.08 ± 2.89	4.92 ± 2.42	<0.01
IBIL	10.1 ± 5.7	9.91 ± 5.1	10.46 ± 4.88	0.658
TBIL	276.24 ± 108.15	280.33 ± 110.01	307.22 ± 75.75	0.834
UA	61.12 ± 22.4	74.26 ± 69.98	64.72 ± 15	0.054
CR	5.75 ± 1.88	5.86 ± 1.99	5.46 ± 1.71	0.081
BUN	9.98 ± 4.36	10.98 ± 9.69	5.59 ± 1.54	0.486
WBC	8.57 ± 7.84	8.39 ± 4.9	2.75 ± 1.23	<0.01
NLR	8.39 ± 7.62	8.52 ± 7.16	3.05 ± 0.08	<0.01
MoCA	15.19 ± 0.39	11.96 ± 0.66	26.02 ± 0.26	<0.001

A total of 300 clinical data were collected in this study, including 200 patients with TBI, including 166 in mild TBI cognitive dysfunction group, mean age (60.48 ± 2.02), 111 were male, 34 in moderate TBI cognitive dysfunction group, and mean age (60.91 ± 1.1), of which 28 were males. In the normal group, 100 individuals, of whom 34 were males.

Results

Impact factors affecting mild and medium-sized cognitive dysfunction of TBI

The results showed that there were no differences in age, sex, direct bilirubin, total bilirubin, uric acid, creatinine, leukBC, light neutrophil/lymphocyte ratio, moderate TBI, DBC, WBC, NLR, MoCA score (P<0.05) (Table 1), while age, sex, UA, IBIL, TBIL, CR value (p>0.05).

Comparison of serum antioxidant levels by severity in patients with TBI and healthy population

A) Compared with the control group, mild and moderate) in the two TBI groups, mild and healthy WBC. B) The mean NLR for mild TBI and moderate TBI varied significantly from that of the healthy group. C) The mean DBIL for mild TBI was significantly different from the healthy group (p<0.010), * p <0.05; **** p<0.01 (Figure 1).

Spearman correlation analysis

Spearman analysis showed significant negative correlation between MoCA scores and NLR and WBC values between the three groups (r= -0.420, r= -0.475, all p<0.001) (Figure 2).

ROC curves were used to assess whether serum NLR and WBC values could be used as diagnostic markers for cognitive impairment in mild and medium-sized TBI. The results showed that the area under the ROC curve (AUC>0.7) was relatively high in distinguishing both light TBI and medium TBI groups (Figure 3).

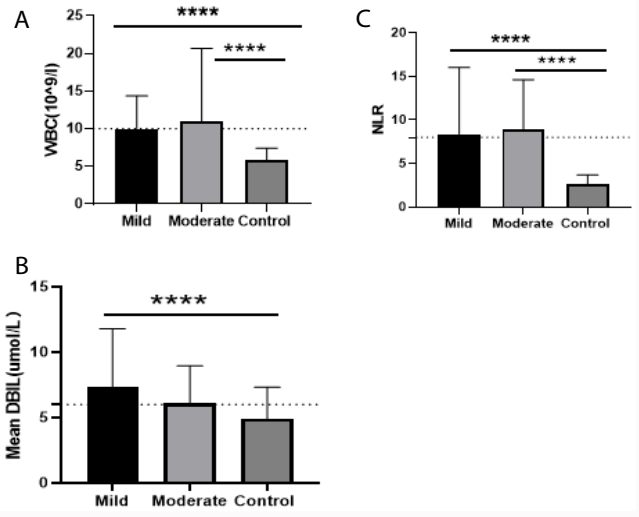

Figure 1: Comparison of serum antioxidant levels by severity in patients with TBI and healthy population.

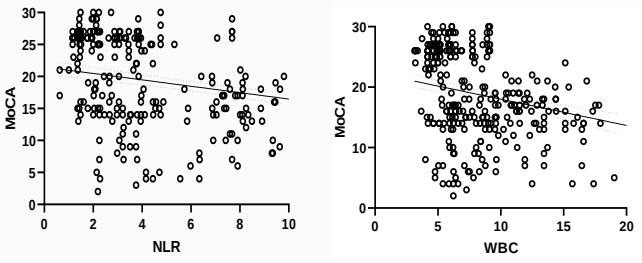

Figure 2: Spearman correlation analysis showed significant negative correlation between MoCA scores and NLR and WBC values.

Discussion

Traditionally, TBI was identified as mild, moderate or severe by a measure called the Glasgow Coma Scale (GCS). Although most of the literature on outcomes and long-term effects of TBI focuses on moderate to severe cases, Emergency Department (ED) visits with mild TBI (mTBI) have the highest rate of [12]. There are current studies providing new knowledge about the recovery patterns of key cognitive communication abilities, the importance of rehabilitation concerns for each ability [13]. Four years after the injury, social reasoning (explaining verbal and non-verbal social cues) decreased significantly in the TBI group, even after controlling for cognitive function, suggesting that even mTBI may affect overall function. In another study using patients with mild to moderate injuries, younger (23-63 years) reported more psychological symptoms, *e.g.* anxiety, while older (65-91 years) reported more physical symptoms, such as fatigue, balance, and coordination problems. Other studies have found that mTBI across the age span is associated with persistent headache, vestibular dysfunction, depression and cognitive problems. The adults with motor-related concussion show significant cognitive deficits in verbal memory, recall and attention compared with adults without a history of concussion and 10 years after retirement [14]. Despite these limitations, this is the first study to examine the relationship between early chronic inflammation and cognitive outcomes after TBI, and through this work has identified novel inflammatory markers associated with cognition, which may help to identify modifiable therapeutic targets to reduce the systemic inflammation burden after TBI [15]. Neutrophils are the first-line cells of the innate immune system. These effector leukocytes are equipped with interesting antimicrobial mechanisms and thus show high cytotoxic potential. Accurate neutrophil recruitment is essential for combating microbes and restoring homeostasis, regulation and resolution of inflammation, wound healing, and tissue repair. However, after completing the appropriate effector function, inhibition of neutrophil activation and infiltration is essential to prevent host damage. The expression level of chemoattractant receptors depends on the level of neutrophil maturation and activation status, which plays a key regulatory role in the (inflammatory) environment. Here, we provide an overview of the chemoattractant receptors expressed by neutrophils in health and disease. Depending on the (pathological) physiological context, specific chemoattractant receptors may be up- or downregulated in different neutrophil subsets, thereby setting beneficial or harmful consequences, thus opening a new window for the identification of disease biomarkers and potential drug targets [16]. Over the past decade, a large body of emerging evidence has highlighted the importance of inflammation in the secondary injury response to neurodegenerative and neurologic deficits following TBI. It causes disruption of the Blood-Brain Barrier (BBB) and the release of macrophages, neutrophils and lymphocytes at the site of injury [17]. Systemic inflammation alters brain inflammatory responses, but improved monitoring of neuroinflammatory responses and better management of systemic infection may improve the outcome of acute brain injury [18]. Cognitive dysfunction after TBI has gradually become a hotspot of recent studies, with large previous data remaining significant but not in participants with low inflammatory state. Showed a fairly high incidence of cognitive impairment after TBI. The mTBI can be found with or without consciousness disturbance or post-traumatic amnesia. Long-term cognitive impairment has a greater impact on the injured. In general, cognitive deficits in moderate to severe TBI were more severe and persistent; 65% of moderate to severe injuries had chronic cognitive deficits (longer than 6 months), and 43% were disabled due to cognitive impairment, half of whom could not return to work. 80% to 85% of mTBI patients without lesions and no other complications have complete cognitive deficit within 6 months; but one third of the patients had cognitive impairment over 3 months, half of which may have long-term cognitive deficit [19]. In this cross-sectional study with the general population aged 18 to 85 years, patients with TBI showed a significant association with cognitive impairment. The association between TBI

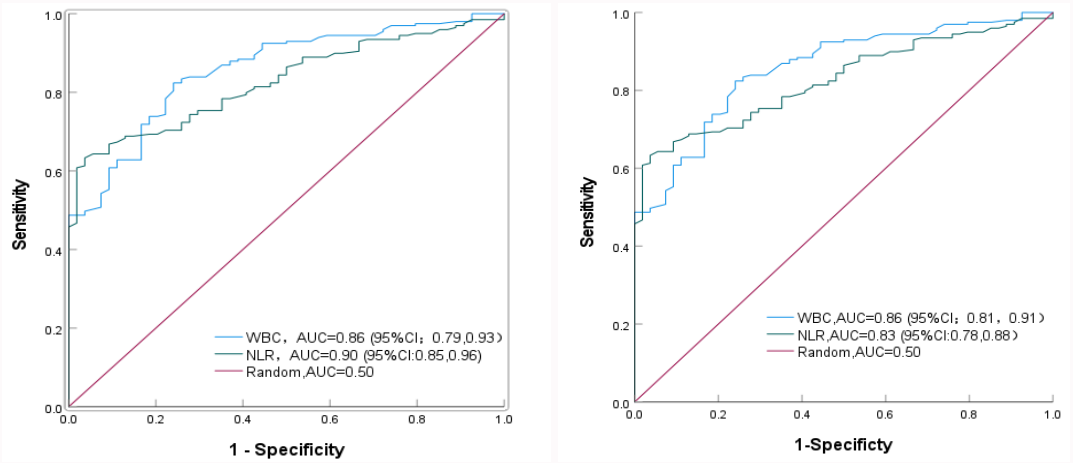

Figure 3: ROC curves were used to assess whether serum NLR and WBC values could be used as diagnostic markers for cognitive impairment in mild and medium-sized TBI.

and cognitive impairment was only in participants in a hyperinflammatory state. In order to clarify the significance of NLR changes and explore the causes of high NLR and the relationship with the prognosis of cognitive impairment in TBI, this study showed that NLR, WBC, and DBIL are more likely to have cognitive impairment in TBI. In this study, a total of 200 patients with mild and moderate craniocerebral trauma found that the average total score of the scale was lower than that of the control group, and the difference was statistically significant, indicating that patients with mild and middle craniocerebral injury had cognitive dysfunction. This is consistent with the results of previous studies. Shenton et al. have suggested that about 15% to 30% of patients with mTBI have cognitive, physiological and clinical symptoms disorders [20]. The Neutrophil/Lymphocyte Ratio (NLR) is a new, inexpensive, and easily detectable marker in the blood. The normal range of NLR is between 1 and 2, and adult values above 3.0 and below 0.7 are pathological. The NLR in the gray zone between 2.3 and 3.0 can serve as an early warning of pathological states or processes, such as cancer, atherosclerosis, infection, inflammation, mental illness, and stress [21]. Neutrophils are abundant populations of circulating leukocytes and are often the first responders to peripheral and CNS tissue damage. Trauma immunology and animal studies suggest a potential role of neutrophils in adverse sequelae after TBI. It combines two aspects of the immune system: The innate immune response (mainly caused by neutrophils) and adaptive immunity (supported by lymphocytes) [22]. The Neutrophil/Lymphocyte Ratio (NLR) is a new, inexpensive, and easily detectable marker in the blood. The normal range of NLR is between 1 and 2, and adult values above 3.0 and below 0.7 are pathological. The NLR in the gray zone between 2.3 and 3.0 can serve as an early warning of pathological states or processes, such as cancer, atherosclerosis, infection, inflammation, mental illness, and stress [23]. Neutrophils are abundant populations of circulating leukocytes and are often the first responders to peripheral and CNS tissue damage. Trauma immunology and animal studies suggest a potential role of neutrophils in adverse sequelae after TBI. It combines two aspects of the immune system: The innate immune response (mainly caused by neutrophils) and adaptive immunity (supported by lymphocytes) [24]. The role of lymphocytes can be reflected in the adaptive immune response. The reduction of its value serves as a marker of stress. When the body is subjected to non-congenital infection or virus vaccination, this acute stress can react specifically with the antigen, thus enhancing the body's immunity [25]. Having a better understanding of disease pathophysiology and proposing more ready and cost-effective screening tools, cognitive dysfunction to provide acceptable estimates of disease risk/diagnosis early in the disease before dementia develops, as in these early lifestyle changes can more effectively prevent and delay significant cognitive impairment recently, with a more detailed but incomplete understanding of the inflammatory component of AD pathophysiology. Inflammatory response in AD, hyperactivation of neutrophils, marked changes in their subpopulations and migration of lymphocytes to the Central Nervous System (CNS) increase the impaired Blood-Brain Barrier (BBB). These changes in the different AD allow the pursuit of a new cost-effective and more widely accessible method diagnostic tool, Neutrophil to Lymphocyte Ratio (NLR) [26]. In conclusion, the high level of NLR represents two distinct immune pathways, and this study aimed to critically evaluate the available evidence and identify for the first time the gap in knowledge of NLR in predicting cognitive functional outcomes in TBI. This result supports the above conclusion. Another case-control study reported a negative association between NLR and cognitive function [27]. Even in mild TBI, NLR is associated with poor prognosis [28]. Studies showed that NLR factors have significant differences in TBI prognosis regarding cognitive function. The results of correlation analysis indicated an inverse relationship between NLR and MMSE, at present, domestic and foreign studies are uncertain about the relationship between WBC and cognitive function. Studies have shown that peripheral inflammatory cytokines activated by TBI can activate microglia and increase the permeability of the Blood-Brain Barrier (BBB), leading to the delivery of immune cells and neurotoxic factors. These lead to chronic neuroinflammation and the formation of β-amyloid plaques, leading to cognitive impairment through neuronal cell damage or death. Our study showed that the dysfunction of TBI with cognitive function only remains significant in the hyperinflammatory state. Neurodegeneration is sometimes accompanied by leukocytosis or increased peripheral White Blood Cells (WBC) [29]. New interventions have the potential to simultaneously target both psychiatric symptoms and adapt to cognitive difficulties. However, because adaptive cognitive behavioral therapy interventions need to be delivered by mental health professionals, additional cognitive rehabilitation options that may be provided by non-mental health specialists and/or non-doctoral-level clinicians may further improve accessibility to certain settings (*e.g.*, occupational therapy clinics).

In this study, serum NLR and WBC levels were highly valuable when diagnose the severity of cognitive impairment in TBI. First, high-value serological diagnostic indicators can serve as a powerful reference for the current widely used MoCA score, helping clinicians to control patients' condition more accurately. Second, the higher diagnostic value indicates that they can increase with the severity, a trend that facilitates a more detailed understanding of the degree of the condition. Finally, the trend of serum NLR and WBC levels changing with the degree of TBI disease has laid the foundation for its better prediction of patient prognosis.

The theoretical basis needs to be verified by large-scale clinical trials. This sample size may be due to the general old age, which may cause indicators of NLR and other indicators, and may have its own decline. Symptoms of traumatic brain injury in this disease generally include dizziness, nausea and vomiting. In the self-measurement table, patients may cause mood fluctuations due to the disease, causing irritability, which may bring deviation to the data.

In conclusion, the serum NLR and WBC levels were significantly increased in TBI patients and could provide a reference for early clinical assessment of injury degree. Moreover, rising serum NLR and WBC levels are associated with poor cognitive impairment prognosis of patients, and are good biological indicators to predict prognosis.

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