

Research Progress on the Clinical Application of Systemic Immune-Inflammation Index in Traumatic Brain Injury

Weikang Yang, Maokun Li*

Department of Neurosurgery, The First Affiliated Hospital of Yangtze University, Jingzhou, China
Email: *1244662457@qq.com

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Abstract

In recent years, a number of studies have shown that inflammatory response and coagulation dysfunction play an important role in the development of patients with Traumatic Brain Injury (TBI). The systemic immune-inflammation index (SII) has important value in evaluating the severity and clinical prognosis of patients with TBI. This article reviews the clinical application of SII and TBI, and provides reference for clinical diagnosis, treatment and prognosis evaluation.

Keywords

Traumatic Brain Injury, Systemic Immune-Inflammation Index, Receiver Operating Characteristic Curve

1. Introduction

Traumatic Brain Injury (TBI) is a common acute and severe disease in neurosurgery, and the mortality rate of patients is high. Survivors will also be accompanied by varying degrees of neurological dysfunction, seriously affecting the daily life of patients [1]. Therefore, it is particularly important to evaluate the severity and prognosis of patients with TBI and to give targeted measures. In the past, most scholars believed that inflammatory indicators were secondary events of TBI, and often ignored the detection of inflammatory indicators [2]. Inflammatory reaction and neovascularization are the key to secondary injury in patients [3]. After severe TBI, a large number of nerve cells are necrotic, and inflammatory indexes related to blood cell count in neutrophils, lymphocytes and peripheral blood can also change in brain tissue [4]. In recent years, SII as a new comprehensive inflamma-

*Corresponding author.

tory marker, is a comprehensive inflammatory index based on peripheral blood neutrophil, lymphocyte and platelet count, which is calculated by a specific formula ($SII = \text{platelet count} \times \text{neutrophil count} / \text{lymphocyte count}$) [5]. Specifically, SII integrates the pro-inflammatory effect of neutrophils, the immunomodulatory effect of lymphocytes, and the pro-thrombotic and inflammatory participation of platelets. Compared with other inflammatory indicators, SII can better reflect the balance between host inflammation and immune status, thus providing a more comprehensive perspective of inflammation assessment [6]. At present, its research in the field of TBI is increasingly in-depth, showing great clinical potential. How to make full use of SII to better judge the clinical prognosis of TBI is one of the directions that need to be explored clinically.

2. Physiological Basis of SII

It has been known that neutrophils are the main effector cells of acute inflammatory response and the first line of defense against infection. It participates in the inflammatory response by engulfing pathogens and releasing a variety of inflammatory mediators (such as cytokines, chemokines). The increase in its number usually means that the body is responding to infection or tissue damage, representing the activation and pro-inflammatory state of innate immunity. In TBI, neutrophils rapidly infiltrate the site of injury, release a large number of inflammatory mediators, and aggravate brain tissue damage and brain edema. Therefore, elevated neutrophil counts are often associated with poor prognosis [7]. Lymphocytes are an important part of the body's immune system, including T cells, B cells and natural killer cells (NK cells) [8] [9]. In TBI, lymphocytes participate in the regulation of immune regulation and inflammatory response by secreting cytokines and regulating immune response. The decrease of lymphocyte count may reflect the inhibition of immune function. Platelets not only play a key role in hemostasis and thrombosis, but also participate in the inflammatory response by releasing a variety of inflammatory mediators. In TBI, platelets are activated and aggregated at the injured site, releasing inflammatory mediators and exacerbating brain tissue damage. At the same time, platelets also regulate the immune response by interacting with other immune cells [10] [11]. Therefore, SII has more advantages than a single blood cell index in assessing the body's inflammatory, immune, and coagulation network status.

3. The Pathological Mechanism of TBI

With the deepening of the research on secondary injury of TBI, it is shown that inflammatory response is the key factor to determine the degree of secondary injury and the prognosis of neurological function. Inflammatory response is a double-edged sword. In the early stage of brain injury, it is an essential defense and repair mechanism for the body to remove necrotic tissue and harmful substances. However, if it is not restricted, it will cause overreaction or even loss of control, which will further aggravate brain injury and lead to more serious neurological

deficits and poor prognosis. Inflammatory response significantly promotes the occurrence and development of secondary brain injury by destroying the blood-brain barrier (BBB), aggravating brain edema, inducing neuronal damage and triggering systemic inflammatory response [12] [13]. After TBI, the integrity of the blood-brain barrier is destroyed, and peripheral inflammatory cells and inflammatory mediators penetrate into the brain tissue to form a local inflammatory microenvironment [14]. This process not only directly damages neurons, but also aggravates oxidative stress by releasing reactive oxygen species (ROS), nitric oxide (NO) and other substances, further destroying the BBB and forming a vicious cycle. As the innate immune cells in the brain, microglia will release a large number of inflammatory factors after activation, and recruit peripheral immune cells to infiltrate and amplify the inflammatory response [15]. Under the stimulation of inflammatory response, platelets are rapidly released into the blood. After platelet activation, 5-HT is released, which leads to increased vascular permeability and aggravates brain edema. At the same time, activated platelets stimulate the microvascular system to produce substance P, which aggravates the neurogenic inflammatory response and forms a vicious circle. Platelets are also involved in thrombosis, platelet aggregation to form microthrombus, which in turn blocks the microvessels in the brain, resulting in local cerebral blood flow reduction. Under platelet activation, cerebral artery endothelial cells were damaged and inflammatory factors (IL-8, MCP-1) were released [16]. Platelets are not only involved in coagulation, but also can lead to further aggravation of the body's inflammatory response by interweaving with neutrophils and lymphocytes. Finally, inflammatory signals are transmitted to the whole body through the vagus nerve and humoral circulation, causing systemic inflammatory response syndrome (SIRS), leading to multiple organ dysfunction such as lung, liver and kidney, further deteriorating the prognosis of patients.

4. SII and TBI Grading

In clinical practice, we mainly reflect the severity of TBI by GCS score at admission, but in elderly patients, brain atrophy may affect the accuracy of GCS score [17]. At present, there are few literatures that directly study the relationship between SII and TBI disease classification, but existing studies have indirectly supported the association between SII and the severity of the disease by dynamically observing the changes of immune indicators in patients with different severity of TBI in the acute phase. For example, patients with severe TBI often have immunosuppressive manifestations such as decreased immunoglobulin levels and decreased lymphocyte subsets in the early stage after injury. These changes may be intrinsically linked to the increase of SII. Piotr *et al.* [18] divided the study population into two groups by GCS = 8 points. The results showed that the SII of patients with GCS \leq 8 was significantly higher than that of GCS $>$ 8, and the SII of patients with GCS \leq 8, including severe and critical head injury, was even 2 times higher, indicating that the higher the SII value, the more serious the patient's condition.

5. Predicting Prognosis

Prognostic prediction is the most important clinical application direction of SII. Many studies have pointed out that SII is closely related to the early poor prognosis and death risk of TBI patients. High SII values often indicate poor prognosis, such as increased mortality and poor neurological recovery. A study of 1266 sTBI patients by Li *et al.* [19] found that SII had better prognostic evaluation performance than PLR and NLR. The research team evaluated the Glasgow outcome score (GOS) of TBI patients 6 months after discharge, and concluded that the GOS score of patients with high SII value (≥ 2651.43) at admission was significantly lower than that of patients with low SII value at 6 months, and high SII value was an independent risk factor for poor prognosis. Moreover, the study also found that the combined application of SII and CO_2 had better prediction performance. SII and CO_2 can be used as new, accurate and objective clinical predictors, as well as coSII-CO_2 . Based on the combination of SII and CO_2 , it can be used to improve the accuracy of GOS prediction in TBI patients 6 months after discharge. Kadir Arslan *et al.* [20] also concluded that SII is an independent predictor of death in sTBI patients. Patients with a SII value of ≥ 2951 at admission had a significantly higher 28-day mortality. As a comprehensive indicator of the body's immune inflammatory state, the level of SII may reflect the severity of immune inflammatory response after TBI. In the field of pediatric craniocerebral trauma, children are a special group different from adults. SII may vary depending on the age or gender of the pediatric population. Muhammad *et al.* [21] compared the SII values in the 28-day group of children and found that the SII of the survivors group was higher than that of the mortality group. There are significant differences in SII among mild, moderate and severe TBI groups, and SII may be used as a neuroinflammatory biomarker to judge the clinical prognosis of TBI in children. However, there is currently no data indicating the correlation between SII and children's age. For sTBI patients, they need to stay in bed for a long time after operation, and the risk of coagulation is high. Chen *et al.* [22] found that SII has a significant correlation by studying the risk and prognosis of coagulation disease at 6 months after discharge. SII can predict coagulation disorders and poor prognosis, suggesting that SII may be a promising biomarker for predicting TBI-related coagulopathy and prognosis.

6. The Value of Dynamic Monitoring

We not only need to pay attention to the SII value of patients with TBI at admission, the disease is a changing process, and the dynamic changes of SII are also worth monitoring. Studies have shown that the persistent high or progressive increase of SII is closely related to the poor prognosis, and the early decline of SII may reflect the control of inflammation and indicate better rehabilitation potential. For example, Tang *et al.* [23] studied the trajectory of systemic immune-inflammation index (SII) in patients with moderate to severe traumatic brain injury after admission. Through GBTM (Group-Based Trajectory Modeling) analysis, it

was found that a continuous high level of SII trajectory can be used as a sign of disease deterioration. This finding highlights the necessity of implementing targeted interventions. Wang *et al.* [24] studied the SII of patients with traumatic brain injury at different time periods and found that the levels of SII and PLR (platelet-to-lymphocyte ratio) in patients with traumatic cerebral hemorrhage were significantly increased after operation. The predictive value of combined detection of SII and PLR on the third day after operation was higher than that on the first day after operation. It is concluded that the predictive efficacy can be further improved when SII and PLR are combined on the third day after operation. Therefore, the SII can be measured at the time of patient admission, before operation, 1 day after operation, 3 days after operation, and 7 days after operation, and the optimal monitoring time point can be identified by comparing the changes in SII. Early monitoring of dynamic changes in SII helps identify patients at relatively higher risk of death, optimize treatment strategies, and contribute to more targeted therapeutic approaches. Early monitoring of dynamic changes in SII helps identify patients at relatively higher risk of death, optimize treatment strategies, and contribute to more targeted therapeutic approaches.

7. Advantages and Limitations

The calculation of SII is simple and only requires the results of blood routine examination. It is easy to operate and has low cost, and is easy to be popularized and applied in clinical practice. Compared with traditional single cells and binary indicators such as neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), it can reflect the state of inflammation, immunity and coagulation system more comprehensively. It is helpful for early identification of high-risk patients. Through early monitoring and dynamic evaluation of its changing trend, combined with comprehensive analysis of other prognostic indicators, the condition of TBI patients can be evaluated more accurately and personalized treatment plans can be formulated.

The efficacy of SII may be affected by many factors such as patient age, injury mechanism, infection, drugs, stress, and underlying diseases. It is necessary to combine the patient's clinical manifestations and other examination results for comprehensive judgment. At present, there is no uniform standard for the optimal critical value of SII, and the results may be different among different study populations. At present, most of the evidence comes from retrospective studies, and the sample size of some studies is small, which may affect the stability and reliability of the results.

8. Future Prospects and Summary

In summary, inflammatory responses play an important role in secondary brain injury following traumatic brain injury, and SII may be related to the clinical prognosis of patients. In clinical practice, patient-specific circumstances should be analyzed in detail, and a comprehensive assessment should be made based on clinical

manifestations and other examination results, in order to more accurately evaluate patient prognosis and optimize treatment plans.

We can establish standardized SII cutoff values for different types of TBI and populations, and continue to combine with other biomarkers (IL-8, MCP-1) to build a more powerful prediction model. At present, the correlation between SII and the prognosis of TBI is relatively clear, but more accurate molecular mechanism still needs more basic research to prove. At the same time, as a potential therapeutic target, immunomodulatory therapies (including targeting neutrophils, protecting lymphocyte function, and using immunostimulators to reverse immunosuppression) are developed for the future. Prospective interventional studies were conducted to verify whether SII led individualized treatment can improve the clinical prognosis of patients. In a word, the research progress of SII in the field of TBI is rapid, and it has developed from a simple inflammatory index to a new comprehensive inflammatory immune index with great significance. It has shown potential and provided a new perspective in improving the precision medical treatment of patients with TBI.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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