Research Progress of Platelets, Lymphocytes and Neutrophils in Sepsis

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Abstract: Sepsis is a life-threatening organ dysfunction syndrome caused by the body's disregulated response to infection [1]. Platelets, lymphocytes and neutrophils are important cells in the immune response process of sepsis and play an important role in the progression of sepsis. Recently, research has found that platelet can inhibit bacteria, mediate inflammatory reaction process and secrete pro-inflammatory factors in addition to coagulation function. Lymphocytes act as adaptive immune cells, and low lymphocyte count can be a manifestation of immunosuppression. Neutrophils are important innate immune cells and represent the first barrier of immunity. Moreover, neutrophils, platelets and lymphocytes are common clinical indicators, which can be obtained in blood routine examination. As a new inflammatory index, Platelet-lymphocyte ratio and Neutral-lymphocyte ratio have gradually become the focus of the inflammatory index in the immune response process. In this paper, the value of platelet, lymphocytes and neutrophils in sepsis is reviewed.

Keywords: Sepsis; Platelet; Lymphocyte; Neutrophil; Immune Response

1. Introduction

Sepsis is a life-threatening organ dysfunction syndrome caused by a dysregulated body response to infection[1]. Innate immune cells, such as neutrophils, macrophages, and dendritic cells, are the first responders to infection and play a critical role in initiating the inflammatory response. Adaptive immune cells, such as T and B lymphocytes, are important for providing long-term protection against infection. The purpose of this review is to find out the important immune cells involved in the immune response process in sepsis, to better understand the development process of sepsis.

2. Immune cells in sepsis

2.1 Platelets are involved in the immune response process of sepsis

The role of platelets on coagulation function has been recognized. In recent years, studies have found that platelets have various functions besides hemostasis[2]: platelets have been shown to inhibit bacterial growth and spread; platelets can affect the recruitment and function of leukocytes, inhibit cytokines and affect the activated of vascular endothelial coagulation reaction; Platelets help to maintain vascular integrity, especially in a strongly proinflammatory environment. Platelets play an important role in the process of immune regulation and inflammation by inducing the release of inflammatory cytokines, and with different types of bacteria and immune cells (including neutrophils, T lymphocytes, natural killer cells (NK) cells and macrophages) interaction, which lead to the start of the inflammatory process or intensified[3]. In the progress of sepsis, a low platelet count may be associated with an adverse outcome. In a large study including 931 patients with sepsis, Claus Hughes et al reported that patients with lower platelet counts at the ICU admission had higher disease severity and an increased risk

of mortality[4]. In addition, low thrombocytopenia is the most common cause of coagulopathy in septic patients, associated with platelet consumption and also with higher mortality.

Platelets originate from megakaryocytes. When pathogens invade the body, platelets can rapidly activate and release substances that promote the death of pathogens, and activate the innate and adaptive immune system, such as reactive oxygen species, antimicrobial proteins, kallikrein and other antibacterial molecules, to directly kill the pathogen[5]. Among them, the platelet antimicrobial protein, stored in platelet granules and platelet cells, is a small cationic polypeptide that kills the pathogen. CD40L, generated on the surface of activated platelets, can directly stimulate B cell proliferation and release antibodies, and enhance the cell killing ability of cytotoxic T cells. Meanwhile, CD40L interacts with CD40 of immune cells and can serve as a regulatory mechanism of inflammation, participating in helper T cell-driven activation, proliferation, and differentiation[6]. The trigger receptor-1 (triggering receptors expressed on myeloid cells-1, TREM-1) expressed by myeloid cells is an important molecule used to amplify the inflammatory response. It is selectively expressed on various cell surfaces, such as neutrophils, CD14 + monocytes / macrophages. Activated platelets were found to produce ligands for TREM-1, which combined with TREM-1 to enable its activation. Activated TREM-1 upregulates pro-inflammatory factors and suppresses the expression of anti-inflammatory factors. Ligand levels of TREM-1 were correlated with sepsis severity. Neutrophil extracellular traps (neutrophil extracellular traps, NETs), as another mechanism to control the pathogen, also involve platelets. NETs have a control disease.

2.2 Lymphocytes participate in the sepsis immune response process

Acquired immunity of the body is mainly mediated by lymphocytes, and the lymphocytes expand rapidly when stimulated by cytokines and specific antigens to produce a specific immune response. Normally, lymphocyte apoptosis removes itself or maintains immune cell activation; while lymphocyte apoptosis during sepsis significantly increases low lymphocyte count, which partly represents the degree of immunosuppression and inflammatory response [7, 8]. There are also reports in the literature associated with inflammatory diseases, such as cardiovascular disease and type 2 diabetes[7, 8].

Based on these findings, the Platelet-lymphocyte ratio (PLR) is suggested as a new indicator of systemic inflammation, and has gradually become a research hotspot. Yanfei Shen et al found that high PLR (> 200) was associated with poor outcome in sepsis outcomes, while low PLR was not associated with poor outcome[11].

2.3 Neutrophils are the first line of defense in the immune response process

As an indicator of inflammation, NLR has also attracted much attention in recent years. Neutrophils, as the first line of defense to provide rapid warning and elimination of pathogens, play a crucial role in innate immunity. Of the lymphocyte response-specific immune processes. NLR is a rapid and simple parameter reflecting systemic inflammation and stress, which can indicate the severity of disease in critically ill patients and is clinically an important clinically accessible inflammatory marker. Neutrophilic lymphocyte ratio reflects indicators of systemic inflammation and stress status, and is associated with the degree of critical illness, often appearing in symbiosis with PLR. The NLR reflects the balance between innate and adaptive immunity. Moreover, NLR is also a readily accessible biomarker that can be analyzed based on the whole blood count and has been reported to be associated with various diseases, including inflammation, cerebral infarction, cancer and traumatic[12].

2.4 Progress on the value of Platelet-lymphocyte ratio (PLR) and Neutrophil-lymphocyte ratio (NLR) in sepsis

PLR and NLR in sepsis . NiJ, Wang H et al found that NLR could act as an independent predictor of death in patients

with sepsis[12]. Can E， Emrah MD et al in a cross-sectional study including 122 neonates found a statistically significant positive association between NLR and neonates with early-onset sepsis[13]. The physiological immune response of leukocytes to many stress events in the circulatory system is characterized by an increased neutrophil count and a decreased lymphocyte count. The inflammatory response leads to an increase in the total number of leukocytes and neutrophils caused by microbial infection. Therefore, these counts may be used as diagnostic markers for microbial infection. The NLR is becoming a more valuable marker for inflammation than neutrophil or lymphocyte counts alone for predicting bacterial infection [14, 15]. NLR and PLR have become inflammatory markers of sepsis due to changes in neutrophil, platelet, and lymphocyte counts due by inflammation.

The neuroinflammatory hypothesis suggests that the inflammatory response of central nervous cells is the underlying pathogenesis leading to confusion and cognitive dysfunction. Is a more popular hypothesis. Theory suggests that acute peripheral inflammatory stimuli, glial activation, and overexpression of proinflammatory cytokines can lead to apoptotic neuronal cell apoptosis and synaptic dysfunction. Promote the occurrence and development of brain dysfunction. It is well known that delusion is a common manifestation of the organ dysfunction induced in sepsis. Martin et al found that psychosis was the most common cause of psychosis in the ICU, and sepsis and psychosis were closely related[16]. Moreover, systemic inflammation may be an important trigger. Increasing evidence suggests that prostst, IL-8, IL-6, and S100 β play an important role in the development of confusion. Furthermore, C-reactive protein levels were found to predict the severity and duration of the postoperative delusion. Overall, inflammation is the underlying mechanism of encephalopathy. Xuandong Jiang[17]. A retrospective study found that high ICU admission PLR (> 100) was associated with a higher incidence of delusion and that high PLR (> 100) was an independent risk factor for delusion. Therefore, the study concluded that PLR could be a useful predictor of developing disturbance of consciousness in critically ill patients. It is also confirmed that the inflammatory response may be an important cause of brain dysfunction in septic patients. There are no studies on neutrophil lymphocyte ratio and platelet lymphocyte ratio in predicting sepsis-related encephalopathy.

3. Conclusion

Sepsis is a life-threatening organ dysfunction syndrome caused by the imbalance of the immune response to infection, and its core process is the imbalance of the immune response. Platelets, lymphocytes and neutrophils all have important roles in the process of immune inflammatory response. Platelets mediate proinflammatory responses in sepsis immune regulation and participate in the injury process of multiple organ dysfunction in sepsis. In sepsis, common lymphocytes decrease, representing the trend of immunosuppression in the process of immune regulation. Neutrophils are the first line of defense of immunity and are a commonly used indicator of the inflammatory response and stress status of the body. In recent years, NLR and PLR have often entered the research hotspot field as a new inflammatory indicator, and their ratio reflects the balance between innate immunity and adaptive immunity, and between proinflammatory response and antiinflammatory response. This index has been clinically verified for the diagnosis and prognosis evaluation of sepsis and the evaluation of organ function damage, but whether there is an association with sepsis-related encephalopathy still needs further verification.

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