Research Progress on Peripheral Blood Lymphocyte Count and Cytokines for Sepsis

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Abstract: Sepsis is a life-threatening organ dysfunction caused by infection leading to host immune dysregulation, and many studies display that it occurs high mortality and occupies a large of medical resources. Early diagnosis and timely treatment can significantly improve the prognosis of patients, and early anti-infective treatment is one of the most important treatment measures for serious infections, as it prevents the transition from pre-sepsis to sepsis and prevents direct death from infection.However, the current criterion, Sepsis-3, does not fully meet the definition of sepsis, and is not suitable for outpatient patients, so it is urgent to explore other ways to assist in early screening of sepsis. Starting from the pathophysiological mechanism of sepsis, this article summarizes the research progress on lymphocyte and cytokines for sepsis, and found that lymphocyte, IL-10 and IL-6 may be used as a joint indicator to diagnose sepsis and the prognosis so as to improve the prognosis of sepsis.

Keywords*:* Sepsis; IL-6; IL-10; Lymphocytes; Early Diagnosis

Introduction

Sepsis is a life-threatening organ dysfunction caused by infection leading to host immune dysregulation and is the leading cause of death in critically ill patients, which greatly occupies medical resources. Early intervention can significantly improve the prognosis of patients. The diagnosis of sepsis has gone through 3 stages: Sepsis-3 proposed by SCCM/ESICM in 2016 are the latest one, and it still has obvious shortcomings. Well known, the hallmark of onset is any organ dysfunction far from the site of infection, while some of these patients who meet Sepsis-3 do not meet the definition. Therefore, there will inevitably be a high misdiagnosis rate in the application of Sepsis-3, and are prone to advanced antibiotic abuse. In addition, to comply with Sepsis-3, it is necessary to meet the SOFA of 2 or greater, which means the body has had organ dysfunction, so unavailable in early screening for sepsis. In order to better treat sepsis, it is necessary to identify sepsis as early as possible in outpatient and emergency departments, and the current sepsis screening method commonly used outside the ICU cannot fully meet this need. Early inflammatory factor storms and immunosuppression in sepsis are considered to be important pathophysiological features of sepsis. Starting from the pathophysiological mechanism, a more intuitive and simple method may be found.

1. Cytokine storm

When hit by a severe infection, the body will produce a stronger immune response. Nowadays, most current studies believe that the emergence of sepsis is accompanied by strong pro-inflammatory and anti-inflammatory immune responses, which jointly affect the development of the disease; In the early stages, it is mainly manifested by excessive inflammatory reaction; In the later stage, the anti-inflammatory response is the mainstay, and the immunosuppression is further enhanced, which is also the reason for the poor prognosis of sepsis in the late stage[1].

1.1 Pro-inflammatory factors

Based on previous studies, IL-6 is a key factor in inflammatory response. IL-6 is a polypeptide molecule with a molecular weight of 21 kD in the IL-6 family, which is genetically mapped to chromosome 7. It plays an important role in promoting the development of inflammation. The gene expression of IL-6 is related to NF-kB, NF-IL6 and hypoxia-inducible factor-1α, and plays a role through two pathways, classical signaling and trans-signaling pathways, leading to anti-inflammatory and pro-inflammatory responses, respectively. IL-6 is elevated under the guidance of infection, trauma, surgery and other factors, but the degree is different. When the body is stimulated by severe infection, it will produce lyaggrin metalloproteinase-17 to activate the trans signaling pathway to promote inflammation[2, 3]and IL-6 rises rapidly and significantly within 2 hours. Previous studies have confirmed the importance of IL-6 in the diagnosis and treatment of sepsis. A prospective study in recent years showed that IL-6 could distinguish between sepsis and healthy controls at an optimal cut-off value of 52.6 pg/mL, with high sensitivity and specificity (97% and 97.2%, respectively). At an optimal cut-off value of 348.92 pg/mL, septic shock can be identified, and its sensitivity is still high, while the specificity is poor (63.2%)[4],there have been some same conclusion . However, it was not possible to compare whether there was a clear difference in IL-6 between sepsis and mild infections. And because both infection and trauma can cause elevated IL-6, the reliability of a single indicator was poor. In addition, the study was carried out in the neonatal population, it is not easy to draw adult patterns[5]. In addition, IL-6 exhibits excellent kinetics in monitoring the effectiveness of antibiotic therapy and can be used to monitor therapeutic efficacy[6]. In summary, IL-6 is preferred as a representative biological index of pro-inflammatory factors as one of the joint indicators for early screening of sepsis.

1.2 Anti-inflammatory factors

IL-10 is considered to play a more critical role in the anti-inflammatory response[7].IL-10 was first discovered in 1989 as a class of inhibitory factors for cytokine synthesis secreted by T helper 2 cells; and it is located on human chromosome 1's gene encodes with a molecular weight of 35 kD. Subsequent studies have found that IL-10 can be produced by almost all leukocyte subsets, and the production pathways are closely related to extracellular signal-regulatory kinases (ERKs), transcriptional activator pathways (STATs), and Toll-like receptors (TLRs) [8]. When the body is stimulated by severe infection, serum IL-10 levels can rise markedly early (within six hours) [9]and persist for a long time. In addition, there have been many previous studies suggesting a close relationship between IL-10 and sepsis. Potjo et al. found that serum IL-10 was elevated more significantly in patients with sepsis than noninfectious SIRS[10], and it can effectively distinguish noninfectious SIRS and sepsis. This is also reflected in neonatal sepsis, but it is less effective in diagnosing sepsis alone[11]. A recent prospective study has reached the same conclusion and demonstrated the advantages of IL-10 as a combination screening for sepsis[12], however, this conclusion was not strictly based on Sepsis-3, and the study population of high-quality studies was limited to neonates. IL-10 also plays an important role in predicting the prognosis of sepsis, and Fabri et al. found that elevated serum IL-10 correlates with the severity of sepsis and can be used to predict organ dysfunction in sepsis[13]. Several studies on sepsis have suggested that IL-10 level were higher in the death group than in the survival group[14]. Moreover, compared with IL-6, elevated serum IL-10 levels are more reflective of sepsis than the strong inflammatory response and immune dysregulation in patients with mild infections.

2. Peripheral blood lymphocytes

Lymphocytes is one kind of white blood cells, which play a key role in adaptive immunity. Lymphocytes were previously considered associated with viral infection usually, but as follow-up studies progress, it has been found that infections such as Klebsiella and Pseudomonas aeruginosa can damage the host's lymphocyte DNA and thus affect lymphocyte count[15]. Decreased lymphocytes can occur in both viral and bacterial infections. Other than that Post-infectious immunosuppression is considered to be one of the core components of sepsis pathogenesis. When severe infection occurs, T

cells in vivo are gradually depleted through the expression of negative costimulatory molecule on the cell surface, regulatory T cells, neuroendocrine, and others, at the same time there is a decrease in lymphocyte count and function in peripheral blood, and it runs throughout the stages of sepsis. Previous studies on Lymphocyte and sepsis mostly focus on prognosis, such as sepsis-induced continuous lymphocyte count reduction is positively correlated with adverse sepsis outcomes, and long-term low levels increase the risk of nosocomial infection[16]. However, in recent years, there have also been concerns about the importance of lymphocyte in the diagnosis of sepsis, and a small sample size prospective study has found lymphocyte at the optimal cut-off value of 0.76×10^9/L in the case of non-viral infection has a certain value in the diagnosis of sepsis[17], and persistent reduction is indicative of higher mortality.

In hospital, infectious diseases account for a large part, and patients with clinically suspected or confirmed infection can often be seen in the emergency department, but not all patients can eventually transform into sepsis. The current diagnostic criteria include subjective and objective indicators, and patients with high requirements for perfect diagnosis and treatment procedures and unclear previous organ function damage further increase the difficulty. Commonly used screening methods in emergency have poor sensitivity and specificity, and should not be used alone. By summarizing previous studies, lymphocyte, IL-10 and IL-6 were found to have certain value in the diagnosis and treatment of sepsis.

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