

Research progress of biomarkers for prognosis of patients with acute post-traumatic sepsis

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Abstract: Acute post-traumatic sepsis refers to systemic inflammatory response syndrome caused by secondary infection of pathogens after trauma. Acute circulatory failure occurs based on serious infection, which is life-threatening. The early diagnosis and prognosis evaluation of post-traumatic sepsis are very important. However, due to the lack of specific clinical manifestations and early diagnostic indicators of sepsis, the patient's condition is dangerous and changeable, and its diagnosis and treatment are one of the puzzles faced by clinicians at present. Studies have shown that for every 1-hour delay in antibiotic treatment of sepsis, survival rates decrease by 8%. The short-term mortality rate of sepsis patients is decreasing, but the long-term mortality rate remains high. Therefore, there is an urgent need for early, timely, and rapid identification of sepsis indicators. Currently, serum biomarkers have penetrated people's field of vision and can provide corresponding guidance for diagnosis. Currently, there are more than 200 biomarkers for diagnosis and prognosis of sepsis, and new biomarkers appear every year. In this paper, the biomarkers related to sepsis and their prognosis were reviewed.

Keywords: Sepsis, Biomarkers, Acute trauma, Prognosis

1. Introduction

Studies have shown that the current incidence of emergency trauma is about 250,000 people/year, the in-hospital mortality of emergency trauma patients is as high as 22% [1], and the main cause of death of patients is sepsis. Acute post-traumatic sepsis refers to systemic inflammatory response syndrome caused by pathogens secondary to trauma. Acute circulatory failure occurs based on a serious infection, which is life-threatening. Early diagnosis and prognosis assessment of post-traumatic sepsis are crucial [2]. Sepsis is a disease caused by the host's dysfunctional response to infection and is defined as a life-threatening organ dysfunction disease. With the aggravation of the disease, tissue hypoperfusion and organ dysfunction will be induced, which is an important factor causing the death of infected patients [3]. Sepsis is one of the major causes of death in critically ill patients around the world [4]. According to statistics, the number of sepsis cases has increased to 48.9 million in 2020, including 11 million deaths, accounting for 19.7% of the total global deaths. However, sepsis caused by acute trauma accounts for 10%-20% of sepsis cases, with high morbidity and mortality. Sepsis is an important cause of death in critically ill patients. Sepsis has greater harm to the body and a worse prognosis [5]. Early correct judgment of the occurrence and condition of sepsis in critically ill patients, to timely and effective treatment, can reduce the occurrence of multiple organ failure in patients and is also the key to reducing mortality. Sepsis is a life-threatening organ dysfunction, which is a major global health problem due to host dysregulation in response to infection [6]. For decades, sepsis was recognized as a systemic spread of infection, resulting in systemic clinical manifestations involving damage to multiple organs and systems, and high morbidity and mortality. Systemic manifestations of infection can occur through inflammatory mediators without the need for microbial transmission, thus giving rise to the modern concept of sepsis. Proinflammatory mediators induced by severe trauma or infection are produced in large numbers, thus triggering a series of acute systemic inflammatory reactions such as the imbalance of the body's inflammatory response and the decline of immune defense function. If not controlled early, it can easily progress to multiple organ dysfunction syndrome [7]. The gold standard for the diagnosis of sepsis is to confirm the patient's pathogenic infection through culture, but blood culture takes a long time and cannot provide information to distinguish the two at an early stage. Therefore, it is more important to identify the disease by serum markers in the early stage [8].

2. Prognostic biomarkers for sepsis

2.1. C-reactive protein (CRP)

CRP is a marker reflecting inflammation in the body. The content of CRP in normal people is low, only 0.057 ~ 8.200 g/L. CRP is a non-specific acute-phase protein. It is a non-specific marker of systemic inflammatory response in the acute phase synthesized by the liver. It plays an important role in innate immunity by binding with immunoglobulin receptors through opsonism and complement activation. CRP may be abnormally elevated in a short period if various infections, tissue damage, and immune reactions occur in body tissues [9]. In normal people, when the body is infected by pathogenic microorganisms and causes inflammation, CRP begins to rise at 4-6 hours, can be doubled every 8 hours, and reaches a peak at 36-50 hours, and the peak can even reach more than 1000 times the normal value. Its half-life is very short, about 4-7 hours, when the inflammation subsides, it will rapidly decline. It can be reduced to the baseline level in 7-10 days. Studies have shown that CRP has a protective effect on the body 24 hours before infection, but no protective effect after 24 hours. It is highly sensitive in the diagnosis of inflammation and is widely used in the diagnosis of sepsis due to its characteristics [10]. Studies have shown that serum CRP should be dynamically monitored in patients with sepsis to improve the diagnostic and prognostic value of sepsis [11].

2.2. White blood cell count (WBC)

WBC is an important immune cell in the human body. For pathogenic microorganisms, WBC is the first line of defense of the human body. The total number of WBCs and the percentage of various WBCs may change due to inflammation or other diseases. Clinically, WBC is regarded as an important index for the clinical evaluation of infection and stress state of bacteria, viruses, and other pathogens [12].

2.3. Lactic acid (LAC)

LAC is the final product of the anaerobic metabolism of glucose, which can reflect the conditions of tissue oxygenation metabolism [13]. Lactic acid has become an important biomarker for the risk stratification of infection and has also been applied to measure the adequacy of fluid resuscitation. In healthy individuals, lactic acid production and clearance is a dynamic cyclic process, but in critically ill shock patients, lactic acid will be elevated due to microcirculatory hypoperfusion, cellular hypoxia, and other factors. For patients with sepsis, the body's effective circulating blood volume is often insufficient, leading to severe hypoxia in cells and tissues, accelerating the speed of glycolysis, and thus promoting the body to produce a large amount of LAC. Once the metabolic load of the liver is exceeded, LAC will accumulate in the liver [14]. Therefore, LAC can be used as an important indicator to monitor the severity of infection. The measurement of lactate can be arterial blood or venous blood. It was originally suggested to measure arterial lactate, but the extraction of arterial blood is more painful, complications are relatively many, and other shortcomings, so some studies have shown that venous lactate may replace arterial lactate to reduce the pain of patients, and there is no significant difference between the two values. However, some studies have shown that the consistency between venous lactate and arterial lactate is poor. It is not recommended to replace arterial lactate with venous lactate. However, when venous lactate is greater than 4.5mmol/L, it may be valuable for the diagnosis of sepsis and the prediction of arterial lactate. With the increase of lactic acid value, the mortality of patients will also increase, but this is not absolute, because the metabolism time of lactic acid is relatively long, for patients without shock, can not rely solely on lactic acid to exclude life-threatening sepsis, even if the lactic acid level ≤ 2 mmol/L is also associated with high mortality. The accuracy of predicting 28-day mortality in patients with sepsis with initial lactate > 4 mmol/L was 85.7%." With active treatment of patients, we can use the lactic clearance rate to judge the prognosis of patients. When the clearance rate exceeds 20%, the survival rate of patients can be greatly improved [15].

2.4. Procalcitonin (PCT)

PCT is a glycoprotein without hormone activity, is almost produced by parafollicular cells (C cells) of the thyroid gland. When the body is infected, PCT can be synthesized by macrophages and monocytes of the liver, increasing rapidly within 2-3 hours and reaching a peak within 6-8 hours. After proper treatment, PCT will decrease rapidly on days 2-3 of infection control. PCT plays an important role in the diagnosis, prognosis, and antibiotic application of sepsis. Elevated PCT in hospitalized

patients may indicate poor prognosis, but its prediction accuracy is insufficient, and PCT detection should not be routinely performed on sepsis patients in the emergency department to predict prognosis. Discharged patients with high PCT levels are compared with those with high PCT levels. The ICU re-admission rate was significantly higher and the prognosis was worse, but no significant difference was found in the total mortality between the two groups. Individualized antibiotic therapy for patients is widely accepted. Studies have shown that PCT has some value in diagnosing fungal sepsis [16]. PCT can be regarded as an independent risk factor for short-term death in patients with septic shock. Even though PCT can identify and predict the prognosis at an early stage, it still has certain limitations and cannot be used as a single biomarker to accurately guide the prognosis of sepsis patients [17].

3. The application value of biomarkers in prognostic judgment

Inflammation and infection are common pathophysiological processes after trauma, and the resulting sepsis is an important cause of death in patients. However, due to the lack of specific clinical manifestations and early diagnostic indicators of sepsis, the patient's condition is dangerous and changeable, and its diagnosis and treatment are one of the puzzles faced by clinicians at present [18]. Studies have shown that for every 1-hour delay in antibiotic treatment of sepsis, the survival rate will decrease by 8%. The short-term mortality rate of sepsis patients is decreasing, but the long-term mortality rate remains high. A retrospective study in the United States showed that the short-term fatality rate of sepsis patients decreased from 28.5% to 15.8% from 1996 to 2008, while the 3-year fatality rate decreased from 73.5% to 71.3%, showing no significant improvement. The long-term case fatality rate of sepsis is high and has not been significantly improved with the progress of treatment. Although the morbidity and mortality of sepsis have been significantly reduced in the past 20 years, management still needs to be improved [19]. The decline in mortality associated with sepsis can be attributed in part to early awareness and interventions, as well as advances in understanding the disease process. Early diagnosis of post-traumatic sepsis and assessment of prognosis are critical. The gold standard for the diagnosis of sepsis is to confirm the patient's pathogenic infection by culture method, but blood culture takes a long time and can not provide information to distinguish the two at an early stage. Therefore, it is more important to identify the disease by serum markers in the early stage.

3.1. Prognosis assessment of patients with sepsis by CRP

Studies have shown that the contribution of CRP use to mortality prediction ranges from 5.7% to 18.1% by assessing the prognostic role of CRP in patients with sepsis [20]. Although this study suggests that CRP use in patients diagnosed with infection provides prognostic benefits, other studies have suggested that a single serum CRP level lacks specificity, that acute rejection and surgery may also cause abnormal increases in serum CRP, and that serum CRP levels decline slowly after the cessation of inflammatory stimulation. Thus, the prognosis of the disease cannot be accurately assessed [20].

3.2. Prognosis assessment of patients with sepsis by WBC

Studies have pointed out that WBC level has significant predictive value in the early diagnosis of sepsis and can be used as an important indicator for the early diagnosis of sepsis. Foreign scholars have preliminarily observed these indicators, indicating their practicability in the diagnosis of sepsis. The value of WBC in early identification of sepsis has been emphasized, thus potentially improving the prognosis of patients [21].

3.3. Prognosis assessment of patients with sepsis by LAC

LAC accumulation in sepsis has been proven to be highly specific in predicting acute and in-hospital mortality. Monitoring LAC levels is closely related to patient mortality. Dynamic monitoring of blood LAC changes can be used as a good indicator of prognosis in patients with sepsis, and those with a short-term return to normal blood LAC level have a better prognosis [22]. LAC, as one of the metabolic products of the body, can effectively reflect the oxygenation metabolism of the body tissue and help clinicians to effectively judge the disease. Studies have confirmed that monitoring LAC level has good prognostic value, and the higher the LAC level of patients, the higher the mortality [23]. However, LAC concentration reflects the overall changes in systemic metabolism, so its sensitivity is not strong. Recently, some scholars have discussed the relationship between the changes in blood LAC levels in children with severe sepsis, indicating that children with severe sepsis have increased blood

viscosity, less tissue perfusion, and increased LAC synthesis and secretion, which induces the occurrence of hyperlacticemia and leads to the occurrence of local acidosis. Children with severe sepsis can involve multiple organs, resulting in cardiopulmonary insufficiency, reducing the oxygen supply of the body, aggravating the hypoxia state of the body, and resulting in increased LAC metabolism. The results showed that LAC level in children with severe sepsis was higher than that in non-severe children at all time points, suggesting that LAC level was closely related to the condition of children with sepsis. Some scholars also pointed out through research that the higher the level of LAC, the worse the prognosis of sepsis patients, LAC has a high predictive value for the prognosis of sepsis patients, suggesting that clinical monitoring of the changes of the above indicators can guide the implementation of specific diagnosis and treatment plans to improve the poor prognosis of sepsis patients.

3.4. WBC, CRP and PCT were used to evaluate the prognosis of patients with sepsis

Blood routine WBC and CRP combined with PCT were selected as observational indicators to explore the application value of WBC and serum CRP combined with PCT detection in the early diagnosis of sepsis, and the differences in WBC, serum CRP, and PCT levels between non-sepsis infected patients and sepsis patients were analyzed. The results confirmed that serum WBC, CRP, PCT detection, and combined detection have significant predictive value in the early diagnosis of sepsis, and combined detection has the highest predictive value, which can be used as an important indicator for the early diagnosis of sepsis. However, the results of this study did not observe the therapeutic effect and prognosis of sepsis patients after treatment [24].

3.5. Short-term prognostic value of CRP and PCT in patients with septic shock

Some scholars have studied the short-term prognostic value of CRP and PCT in patients with septic shock, and found that CRP and PCT have certain value in predicting death within 28 days in patients with septic shock, but the specificity is poor, and the sensitivity and specificity of the combined prediction are higher than that of the single prediction. It suggests that PCT and PCT have certain predictive values for the short-term prognosis of septic shock, but the combined predictive value is higher [25]. CRP and PCT are the most widely used and studied biomarkers to date. Both increase briefly during sepsis, and the combination of these two biomarkers may improve their ability to rule out sepsis. In recent years, the abnormal increase of these indicators by relevant experts and scholars has been helpful for the diagnosis of sepsis, but the predictive value of the relationship with the prognosis of sepsis is still insufficient [26].

4. Discussion

The incidence and mortality of sepsis have declined significantly in the last two decades, but improved management is still needed. The decline in mortality associated with sepsis can be attributed in part to early awareness and interventions, as well as advances in understanding the disease process. Early diagnosis of post-traumatic sepsis and assessment of prognosis are critical. Therefore, it is more important to identify the disease by serum markers in the early stage. However, in terms of practical value, current studies have found that a single biomarker is not enough to accurately make early diagnosis, guide antibiotic use, or judge prognosis, so we should still combine the potential value of multiple serological factors to improve the ability of early diagnosis and prognosis judgment. Therefore, it is necessary to conduct more in-depth research on sepsis-related biomarkers. Rational use of biomarkers can intervene in patients with sepsis at an early stage, effectively control the development of the patient's disease, improve the patient's prognosis, bring clinical benefits, and improve the quality of medical treatment.

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