Review Article

Presepsin as a novel sepsis biomarker

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BACKGROUND: In 2004, a new biomarker sCD14-subtypes (presepsin) was found and its value was shown in the diagnosis and evaluation of sepsis. This article is a brief overview of the new biomarker.

DATA SOURCES: A literature search using multiple databases was performed for articles, especially meta-analyses, systematic reviews, and randomized controlled trials.

RESULTS: Compared with other markers, presepsin seems to have a better sensitivity and specificity in the diagnosis of sepsis. Presepsin as a biom1arker is not only suitable for the early diagnosis of sepsis, but also for the assessment of its severity and prognosis.

CONCLUSIONS: Presepsin has a higher sensitivity and specificity in the diagnosis of sepsis as a new biomarker, and is a predictor for the prognosis of sepsis. More importantly, preseptin seems to play a crucial role as a supplemental method in the early diagnosis of sepsis. Since there is no multicenter study on the relationship between presepsin and sepsis, further studies on the clinical values of presepsin are needed.

KEY WORDS: Presepsin; Sepsis; Diagnosis

INTRODUCTION

Sepsis is a potentially fatal whole-body inflammation (a systemic inflammatory response syndrome or SIRS) caused by severe infection.[1] Its clinical manifestations vary with a rapid progression. As a costly disease, sepsis not only lowers patient's living quality, but also increases the mortality significantly.

Sepsis causes millions of deaths globally each year.[2] In the United States, sepsis affects approximately 3 per 1 000 people,[3] and severe sepsis contributes to more than 200 000 deaths each year.[4] Sepsis occurs in 1%–2% of all hospitalized patients and accounts for as much as 25% of ICU cases. Consensus on the treatment of sepsis indicates that early anti-infection treatment should be given before comprehensive treatment. However, due to the existence of non-infectious SIRS in many critical patients, how to differentiate sepsis from SIRS at the early stage has become a hot topic for many years. There are many reported biological markers such as procalcitonin (PCT), interleukins, pro-vasopressin, C-reactive protein (CRP) and myeloid cells expressing triggering receptor-1

(TREM-1).[5–8] The studies of these biomarkers on sepsis concerning the diagnosis, assessment, antibiotic treatment, and prognosis have attracted extensive attention from researchers. Except PCT, however, the clinical values of the other biomarkers are still uncertain or controversial. In 2004, a new biomarker sCD14-subtypes (presepsin) was found[9] and its value was shown in the diagnosis and evaluation of sepsis. This article will give a brief overview of this new biomarker.

BIOLOGICAL CHARACTERISTICS OF PRESEPSIN

CD14 is the receptor of lipopolysaccharide-lipopoly-saccharide binding protein (LPS-LBP) complexes. With the help of thinositol lipid structure, the carboxyl terminus of the molecule anchors in cell membrane and transducts the endotoxin signal through the Toll-like receptor-4.[10] A series of downstream tyrosine protein kinases and mitogen-activated protein kinase are gradually activated including the nuclear transcription factor NF-κB, thus

leading to the release of cytokines such as tumor necrosis factor-α, IFN-γ, IL-1β, IL-8 and IL-6.[11] Subsequently, the activation of the secondary inflammatory cascade and acquired immunity stimulate mononuclear macrophages, neutrophils and endothelial cells to release more cytokines and cell adhesion molecules. This could trigger intense and excessive systemic inflammatory response and activate the coagulation and fibrinolytic systems, resulting in SIRS, sepsis shock, disseminated intravascular coagulation (DIC), and multiple organ dysfunction syndrome (MODS).[12] CD14 has two forms: membrane-bound CD14 (mCD14) and soluble CD14 (sCD14). The former has a high affinity to LPS, and is mainly expressed on the cell surface of monocytes/macrophages or distributed a little bit on the cell surface of neutrophils. The latter is seen in plasma, and is produced by mCD14 fall-off or cell secretion.[13,14] Two kinds of sCD14 could be detected in the plasma of healthy people at microgram level: 49KD and 55KD. sCD14 plays an important role in mediating the immune responses to LPS of CD14-negative cells such as endothelial cells and epithelial cells. sCD14 is cleaved by cathepsin D and other proteases in plasma[15] and the N-terminal fragments of 13kDa constitutes sCD14 subtype (sCD14-ST) which has been named as presepsin recently.[16]

ROLE OF PRESEPSIN IN SEPSIS

As a receptor of the LPS-LBP complex, CD14 could activate a series of signal transduction pathways and inflammatory cascades, and lead to systemic inflammatory response.[17] Some clinical studies[18,19] on the relationship between sCD14 and sepsis showed that the level of sCD14 increased significantly in patients with sepsis and septic shock compared with healthy people, and the change was significantly related to the severity and prognosis of the disease. The specificity of sCD14 was poor, and the level of sCD14 significantly increased in patients with coronary heart disease, heart failure, liver cirrhosis, high blood glucose and so on. Presepsin is generated as the body response to bacterial infection, and phagocytosis against bacteria may play a major role other than simply give an inflammatory response,[15,20] although it is not clear about how presepsin is produced in the body. Researchers believe that presepsin is likely to be a sepsis diagnostic biomarker with a high sensitivity and specificity. Further studies have shown encouraging results.

DIAGNOSIS

Because of the better sensitivity and specificity,[21,22] PCT, CRP and IL-6 are commonly used as biomarkers in the diagnosis of sepsis, while assessing the severity of infection and guiding the use of antibiotics. But meta-analysis found that the sensitivity and specificity of PCT[23,24] and CRP[25] varied in the diagnosis of sepsis. The sensitivity of IL-6 was not high and declined gradually as the time of infection extended.[26] These findings questioned their ability to distinguish sepsis from SIRS.

Compared with the other markers, presepsin seems to have a better sensitivity and specificity in the diagnosis of sepsis. Studies[27,28] found that the plasma concentration of presepsin was significantly higher in infected patients than in non-infected patients. Shozushima et al[20] found that the concentration of presepsin was 333.5±130.6 pg/mL in the SIRS group, 721.0±611.3 pg/mL in the local infection group, 817.9±572.7 pg/mL in the sepsis group, and 1 992.9±1 509.2 pg/mL in the severe sepsis group. The blood concentration of presepsin among the groups increased sequentially. Spanuth et al[21] studied the concentration of presepsin in emergency patients on admission, and they found that it was significantly higher in sepsis patients than in healthy people, and also significantly higher in severe sepsis patients than in sepsis patients. Moreover the concentration of presepsin was positively correlated with APACHE II score and SOFA score. When ROC curve was used to evaluate the value of the four markers in the diagnosis of sepsis, the AUC of presepsin was 0.845. Presepsin was preferred to PCT (0.652), IL-6 (0.672), and CRP (0.815). With 399 pg/mL of presepsin as a cut-off value, the sensitivity of the diagnosis of sepsis was 80.3%, and the specificity was 78.5%. Whereas 600 pg/mL was taken as a cut-off value, the sensitivity for the diagnosis of sepsis was 87.8%, the specificity 81.4%, the positive predictive value 88.6%, and the negative predictive value 80.3%.[20] The sensitivity of presepsin for the diagnosis of sepsis was 91.9%, PCT 89.9%, IL-6 88.9%, and blood culture 35.4%.[27] The results suggest that presepsin may be advantageous in the diagnosis of sepsis.

Blood culture was performed for 48–72 hours to diagnose sepsis, but the positive rate was low. PCT increased in 4 hours after infection, reached a plateau slowly at 8–24 hours, and peaked one day after infection. Compared with PCT, presepsin increased earlier and faster in patients with sepsis,[17] at 2 hours after infection in the CLP sepsis model, peaked at 3 hours, and declined at 4–8 hours.[29,30] It could be detected in the early stage of infection by using the ELISA method.

The rescue principles indicate that sepsis should be diagnosed early (the infection foci should be detected within 6 hours) and treated early (antibiotics treatment given within 1 hour after the diagnosis of

sepsis[29]). Clinically, sepsis biomarkers with a high sensitivity and specificity are required in addition to rapid detection methods. According to the principles of chemiluminescent enzyme immunoassay, 21 minutes are taken for PATHFAST analysis to detect presepsin. The accuracy of this method is similar to that of ELISA; moreover in this detection, plasma, serum heparin, heparin whole blood, and EDTA anti-coagulated serum can be used as the detection samples.[30]

ASSESSMENT OF SEVERITY AND PROGNOSIS

Presepsin as a biomarker is not only suitable for the early diagnosis of sepsis, but also for the assessment of its severity and prognosis. In the ALBIOS trial, 100 patients with severe sepsis and septic shock were subjected to the assessment of the concentrations of presepsin and PCT. The median (Q1–Q3) concentration of presepsin was 2 268 (1 145–4 305) pg/mL in dead patients the first day on admission, which was significantly higher than 1 184 (855–2 158) pg/mL in surviving patients (*P*=0.001). On the 7th day, the presepsin level of the surviving patients declined significantly to 974 (674–1 927) pg/mL, and that of the dead patients was 2 551 (1 438–5 624) pg/mL (*P*=0.02). Moreover, the level of presepsin was correlated with SOFA score, MOF score and hemodynamic stability. The 90-day mortality in patients with a high level of presepsin was significantly higher than the patients with a low level of presepsin (75% and 42%). Presepsin was superior to PCT in the assessment of prognosis (AUC 0.69 and 0.56, *P*=0.07).[31] Another study showed that the level of presepsin was significantly different between the survival group and the death group, even between the sepsis group, severe sepsis group and septic shock group. Presepsin was better than IL-6, CRP and PCT in assessing the risk of death within 30 days after onset of sepsis.[32] When the cut-off value of presepsin was 1 622 pg/mL and the cut-off value of PCT 13.43 ng/mL in PCT group, 23% of the surviving patients could be allocated to the death group, 40% of the dead patients were assigned to the surviving patients. Combined with MEDS and presepsin could reclassify them into the correct groups, indicating that presepsin might have a better ability to predict the risk of death.[21]

DEFICIENCY

Preliminary studies have shown that presepsin is highly accurate and specific in the diagnosis of sepsis.

It is fast and convenient to detect sepsis and to assess the severity and prognosis of sepsis; but as a receptor, LPS is a component of the gram-negative bacterial cell wall. It is easy to imagine whether presepsin is a predicator for sepsis caused by gram-positive cocci infection. Studies[27–30] have shown that the sensitivities of presepsin, PCT, and IL-6 were 95.5%, 95.5% and 100% in patients with gram-positive bacterial infection, and 77.8%, 86.1% and 88.9% in gram-negative bacterial infection. The sensitivity of presepsin was not different significantly between patients with gram-positive and gram-negative bacterial infections. Additionally, the level of presepsin could be increased in patients with fungal infection, but not in patients with virus infection. There were no immediate reports on presepsin levels of patients with atypical pathogen infection but without mycobacterium tuberculosis infection. A recent study[33] has found that in patients with renal failure, the median levels of presepsin in patients with no sepsis (*n*=14) and those with sepsis (*n*=27) were 1 607 pg/mL (range 454 to 8 516) and 1 523 pg/mL (range 293 to 16 764), respectively. There were no differences between the two groups. However, the median levels of presepsin were significantly different in patients without sepsis and those with sepsis in non-AKI patients, risk patients, and injured patients. It was clear that the diagnosis of presepsin level was affected by the kidney function.

In summary, studies showed that presepsin has a higher sensitivity and specificity in the diagnosis of sepsis as a new biomarker, and is a predictor for the prognosis of sepsis. More importantly, preseptin seems to play a crucial role as a supplemental method in the early diagnosis of sepsis. Since there is no multicenter study on the relationship between presepsin and sepsis, further studies on the clinical values of presepsin are needed.

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