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Presepsin (sCD14-ST) as a biomarker of sepsis in clinical practice and in emergency department: a mini review

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Abstract: Presepsin is a 13-kDa protein that is a fragment of CD14 with truncated N-terminal, the receptor for lipopolysaccharide (LPS)/LPS-binding protein complexes. It is a novel marker being sought in many diseases such as sepsis, kidney failure, disseminated intravascular coagulation, etc. In this review, we aimed to clarify its utility in critical diseases and availability in critical care settings such as emergency departments and intensive care units.

Keywords: diagnostic value; presepsin; sepsis.

Introduction

Sepsis is a whole-body inflammation (systemic inflammatory response syndrome [SIRS]) caused by severe infection that may potentially result in death. Clinical manifestations of sepsis vary with a rapid progression. As a costly disease, sepsis not only lowers patients' quality of living, but also significantly increases mortality [1]. In recent years, studies focus on novel markers that may predict severity, prognosis, and treatment response of sepsis. Presepsin emerges as a novel promising marker in early detection of sepsis.

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Structure and mechanism of presepsin

Recently, the usefulness of presepsin – a soluble CD14 subtype – in diagnosis of sepsis has been increasingly recognized. Monocytes have been found to be the main source of presepsin in humans. Secretion of these markers from monocytes is thought to be triggered by bacterial phagocytosis or sterile phagocytic stimulus, such as monosodium urate crystals, rather than soluble inflammatory stimuli. Elastase, a serine protease in human monocytes, mediates CD14 cleavage to produce presepsin [2]. 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 triggers 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 [3]. The circulating soluble form of the CD14 subtype (sCD14-ST), presepsin, is mainly used in critical care settings, such as emergency departments (EDs) and intensive care units (ICUs), to distinguish between sepsis and SIRS and for early detection of a possible bacterial cause [4].

Presepsin and sepsis

Sepsis, severe sepsis, and septic shock represent a continuum of clinical syndromes that are common complications observed in patients with infection, trauma, and major surgeries. These syndromes start with infection-induced SIRS and evolve to sepsis-induced acute organ dysfunction and cardiovascular collapse [5]. Thus, studies on biomarkers that may be helpful in the diagnosis, assessment, determination of antibiotic treatment, and/or prognosis of sepsis attracts extensive attention from researchers. It

is well established that presepsin is a useful marker in the diagnosis of sepsis [1, 6–9]. Studies on comparison of presepsin with conventional biomarkers (C-reactive protein [CRP], procalcitonin [PCT], etc.) have also shown that presepsin may be used as a superior biomarker for early diagnosis and accurate treatment of sepsis [10–15]. It was also shown that presepsin not only helps physicians in making accurate diagnosis and predicting prognosis, but also helps in predicting accuracy of antibiotherapy [7, 11].

In a study with 144 consecutive patients presenting at the ED, the percentile of presepsin values in the ED population was found to be 750 ng/L. Presepsin was significantly increased in patients aged ≥70 years vs. younger patients (470 [380–601] ng/L vs. 300 [201–457] ng/L, $p<0.001$) [16].

Giavarina and Carta [4] proposed a reference limit of 55–184 pg/mL (90% confidence intervals [CIs], 45–58 and 161–214, respectively) for presepsin. They also reported that there were no significant differences between men and women, and the presepsin concentrations were not even particularly influenced by age.

In another study, the best diagnostic cutoff for presepsin was reported to be 600 pg/mL, with sensitivity of 78.95% (95% CI, 69.4–86.6) and specificity of 61.90% (95% CI, 50.7–72.3) [17]. Endo et al. [15] found that the cutoff value of presepsin for discrimination of bacterial and nonbacterial infectious diseases was determined to be 600 pg/mL, of which the clinical sensitivity and specificity were 87.8% and 81.4%, respectively.

Presepsin and sepsis in neonates

Elevated presepsin levels in maternal blood may be a risk factor for preterm delivery [18]. Topcuoglu et al. [19] also proposed presepsin as an indicator of late-onset sepsis (LOS) and treatment response in preterm infants. However, they could not determine the efficacy of presepsin in predicting severity and outcome of LOS. Accordingly, another study suggested presepsin as an accurate biomarker for the diagnosis of possible LOS. In this study, authors also stated that it might provide useful information for monitoring response to therapeutic interventions [20]. Mussap et al. [21] investigated presepsin levels of neonates with severe disease, and they could not determine any correlation between gestational age and presepsin levels. In another study with suspected bacterial meningitis or ventriculitis, presepsin was found to be present at a significantly higher level in cerebrospinal fluid (CSF) of children with clinically proven ventriculitis than in those without meningitis or ventriculitis. Diagnostic accuracies of presepsin were superior to those of leukocytes or proteins in CSF [22].

Presepsin in disseminated intravascular coagulation

The role of presepsin in DIC was compared with PCT by Takahashi et al. [23], and they reported that prognosis and severity of infection might be assessed accurately by measuring the presepsin levels until day 7. In another study, Ishikura et al. [24] proposed the use of presepsin together with protein C as a predictor of the severity of sepsis-induced DIC in suspected ED patients.

Presepsin and kidney functions in septic patients

Presepsin, owing to its molecular weight (13 kDa), is presumed to be filtered by glomeruli, reabsorbed, and catabolized within the proximal tubular cells. In theory, presepsin levels has been proposed to increase as kidney function decreases [16]. Presepsin levels in patients receiving hemodialysis were reported to be significantly higher than that of non-receivers [25]. Kotera et al. [26] reported that presepsin might be high patients with kidney dysfunction even though infection does not exist. This is a challenge for patients with impaired renal functions to diagnose sepsis.

In another study, presepsin concentrations were significantly high in patients with kidney dysfunction. Aging was an independent predictor of an elevated presepsin value. This study revealed that presepsin concentrations increase with age and kidney dysfunction [16].

Accordingly, Nakamura et al. [27] reported that presepsin level could be a reliable indicator of sepsis not only among patients without kidney injury but also in patients with less severe forms of acute kidney injury. However, it is not a reliable indicator of sepsis in patients with a more advanced form of kidney injury. They could not determine any significant difference in the level of presepsin between non-sepsis and sepsis groups among patients with kidney failure. In a study, presepsin was found to be more useful than other sepsis markers in predicting sepsis in patients with nephrolithiasis [28].

Presepsin and intensive care

Severe sepsis and septic shock represent major challenges in modern intensive care medicine [29]. Godnic et al. [30] investigated expression of CD64 on neutrophils

Table 1: Summary of studies on comparison of presepsin with CRP and/or PCT.

Study setting	CRP	PCT	Presepsin	References
42 premature infants with LOS			Superior in LOS and treatment response in preterm infants	[19]
388 patients in ICU	Has the highest AUC	Enables the difference between Gram-positive and Gram-negative bacteria	Superior when combined with CRP and MR-proADM	[6]
47 patients with SIRS, septic shock and sepsis	Determines possible infection	Predicts SIRS severity and distinguishes between sepsis and severe sepsis or septic shock	Determines possible infection	[30]
39 patients of nephrolithiasis who were diagnosed as SIRS			Higher diagnostic value	[28]
Reports of 4 cases with renal dysfunction			High, even infection does not exist	[26]
19 newborns with LOS			Useful for the diagnosis of LOS and monitoring the response to treatment	[20]
191 patients with SIRS			Superior in diagnosis of DIC	[23]
Review			Better sensitivity and specificity in the diagnosis of sepsis	[1]
116 patients with sepsis or septic shock			Better diagnostic and prognostic value	[29]
Comparison of infection and non-infection groups			Better in diagnosis and treatment of bacterial sepsis	[10]
Review			Superior in diagnosing sepsis, assessing the severity of the disease and providing a prognostic evaluation of patient outcome	[16]
21 patients in ICU with sepsis		Returns to normal levels during the transient remission phase	Remains high during the transient remission phase. Better in monitoring	[11]
226 patients with SIRS			Similar to PCT and superior to CRP in differentiating patients with bacteremia	[33]
Review	CRP is highly sensitive but lacks specificity in infection	Has prognostic value	Contributes to diagnosis and prognosis	[32]
103 patients with sepsis			Better correlation with severity of sepsis	[12]
82 patients with SIRS			Higher predictive value for DIC development	[24]
Comparison of presepsin with PCT in 100 patients in ICU			Better prognostic value	[13]
Comparison of presepsin with PCT in 859 patients with SIRS			Superior to PCT for diagnosing sepsis and predicting severe sepsis, septic shock and 28-day mortality in septic patients in the ED	[34]
106 patients with sepsis or septic shock		Higher diagnostic accuracy	Better prognostic value	[31]
30 patients with SIRS and 30 patients with sepsis			Better performance in discriminating the SIRS from the sepsis	[14]
207 patients with suspected sepsis (comparison of presepsin, PCT, and IL-6)			Superior diagnostic tool	[15]

AUC, Area under the curve; MR-proADM, mid-regional pro-adrenomedullin.

presented as CD64 index, sCD14-ST, CRP, and PCT in whole-blood or plasma samples in patients in the ICU. They included 47 hospitalized patients after procedures, who were divided into three groups: SIRS, sepsis, and septic shock. They reported that the CD64 index, CRP, and sCD14-ST served as good parameters to determine possible infection in patients that needed intensive care after major procedures. Behnes et al. [29] also reported in their study that measurements of presepsin levels had independent diagnostic and prognostic value in patients with severe sepsis and septic shock during the first week of intensive care treatment. They also found that presepsin levels had valuable diagnostic value for the diagnosis of sepsis, severe sepsis, and septic shock at days 1, 3, and 8 of ICU treatment compared to PCT, interleukin-6 (IL-6), CRP, and WBC.

Usefulness of presepsin in the emergency department

Sepsis, severe sepsis, and septic shock are common conditions with high mortality. Their early diagnosis in the ED is essential to decrease morbidity and mortality. There is a need for an ideal biomarker that has high sensitivity and specificity and is cost-effective and promptly available [31].

The emergency unit is one of the main places for acute medical care and therefore has a pivotal role in determining a diagnosis of bacterial infection and initiating antibiotic therapy [32].

Plasma CRP and PCT levels, when associated with documented or suspected infection, are now part of the definitions of sepsis. CRP is a biomarker of inflammation, not of infection. CRP is highly sensitive but lacks specificity. Moreover, there are few interventional studies evaluating its true added diagnostic value in the emergency unit, thus preventing the use of CRP as a biomarker of infection. Serum PCT dosage is more specific for diagnosis of bacterial infection. PCT levels do not increase or increase only slightly in non-bacterial inflammatory syndromes. PCT also provides prognostic information and risk stratification assessment in the emergency unit [16, 32].

Presepsin may be contributive for the diagnosis and prognosis of sepsis in EDs [32]. Romualdo et al. [33] reported that presepsin might contribute to rule out the diagnosis of bacteremia in SIRS patients admitted to the ED. In their study with 226 patients admitted to the ED with SIRS, presepsin, PCT, and CRP levels, besides blood cultures, were measured. Presepsin values were significantly higher in bacteremic SIRS group when compared with non-bacteremic SIRS group. Liu et al. [34] compared presepsin with PCT in ED setting. They reported that presepsin was a more valuable biomarker than PCT in the early diagnosis of sepsis, and presepsin, in combination with Mortality in Emergency Department Sepsis score or Acute Physiology and Chronic Health Evaluation II score, significantly increased the prognostic accuracy in septic patients. Ulla et al. [31] conducted a study with 106 patients admitted to two EDs due to suspected sepsis or septic shock and reported that presepsin was useful in the early diagnosis of infection in a complex population of patients with SIRS, sepsis, severe sepsis, and septic shock. Presepsin showed a significant prognostic value, and initial values were significantly correlated with in-hospital mortality of patients affected by sepsis, severe sepsis, or septic shock.

However, as presepsin level increases in elderly and patients with renal diseases, a threshold value must be adopted for these patients to prevent misdiagnoses in ED [16].

Presepsin was also studied in patients with community-acquired pneumonia, and that its combination with the Confusion/Urea/Blood Urea Nitrogen/Respiratory rate/Blood pressure/Older than 65 years (CURB65) scoring system was reported to be useful in predicting severity and outcome of the disease in ED [35]. Comparison of usefulness of presepsin with conventional biomarkers for sepsis is summarized in Table 1.

Conclusions

Early determination of sepsis in critical settings such as EDs and ICUs is a challenging issue. Biomarkers play a vital role in predicting sepsis and thus decrease morbidity and mortality. An ideal marker must both be available and easy to use in ED settings. Usefulness of PCT and CRP are well established in clinical practice. Presepsin has emerged as a novel marker in recent years. Studies reveal that it may be used in detection of sepsis. It is helpful not only in diagnosis but also in predicting prognosis and determining response to treatment. However, because presepsin levels are affected by advanced age and kidney failure, in such patients, more careful evaluation is needed.

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