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Original Article

Usefulness of presepsin as diagnostic and prognostic marker of sepsis in daily clinical practice

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Abstract

Introduction: Sepsis represents a major cause of morbidity and mortality in critically ill patients. Early diagnosis and appropriate treatment have a crucial influence on survival. The aim of this study was to evaluate the diagnostic and prognostic role of presepsin (sCD14) in patients with sepsis.

Methodology: Fifty-four consecutive adult patients with sepsis and 26 patients with aseptic meningitis as a control group were included in this prospective observational study. In all patients included in the study, levels of C-reactive protein (CRP), presepsin, lactate, and a count of leukocytes and neutrophils were determined on admission. In those with suspected bacterial infection, two separate blood cultures were obtained and procalcitonin (PCT) concentration was detected. Plasma presepsin and PCT concentrations in septic group patients were followed on days 2, 3 and 7 after enrollment.

Results: The median presepsin serum concentration in patients with sepsis was 1614 pg/mL and in the control group it was 203 pg/mL ($p < 0.001$). Presepsin levels in patients with septic shock were higher than in sepsis patients ($p < 0.014$). The mean presepsin concentrations were higher in deceased than in surviving patients ($p = 0.009$). The trend of changes in presepsin concentrations in deceased patients was significantly different than in the surviving patients ($p = 0.018$). There were no statistically significant differences in the concentration of presepsin or other biomarkers in patients with Gram negative or Gram positive bacteria.

Conclusions: Presepsin may be used as a diagnostic marker of systemic bacterial infection and can predict the severity and outcome of sepsis.

Key words: sepsis; inflammation markers; presepsin; diagnosis; prognosis.

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Introduction

Sepsis is a major public health problem. Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. Despite advances in diagnosis and treatment, overall sepsis morbidity and mortality remain unacceptably high [2]. Sepsis is also represented by high costs of treatment and long-term physical, psychological and cognitive impairment, which may affect the survivors [3].

Incidence of sepsis has increased over the years, probably due to aging of the population, the existence of more comorbidities, aggressive surgical and diagnostic interventions, immunosuppressive treatment and the emergence of resistant bacteria due to non-critical use of antibiotics. Mortality in patients with sepsis varies between 20% and 50% [4,5] and in patients with septic shock is frequently over 50% [6].

A number of studies have confirmed that rapid diagnosis and the onset of treatment with the appropriate antibiotic are the cornerstones to reducing mortality [7]. The initial treatment of sepsis is empiric and should be broad-spectrum to cover potential microorganisms responsible for the infection, and it depends on local epidemiological data, the anatomic site of infection, chronic comorbid diseases, age, immune status, recent and/or prolonged hospitalization, antimicrobial use, prior colonization or infection with a resistant organism, etc. The etiology of sepsis is confirmed by blood culture. However, final results are expected within 48 to 72 hours, or the culture remains negative due to previous antibiotic treatment [8]. Bacteraemia is detected in only 50% to 60% of patients who are clinically suspected of having sepsis [9,10]. On the other hand, false-positive results from bacterial contaminants usually lead to unnecessary antimicrobial

treatment, longer hospital stays, and selection of resistant microorganisms.

Early diagnosis and appropriate treatment of patients with sepsis remains a challenge for clinicians. Antimicrobial treatment is usually started according to clinical criteria and regarding elevated laboratorial inflammation markers like leukocytes in peripheral venous blood, C-reactive protein (CRP) and procalcitonin (PCT). Unfortunately, neither clinical signs nor inflammation markers are sensitive enough or specific for sepsis. CRP is sensitive but not very specific, being elevated in many non-infectious diseases [11]. PCT is more specific for sepsis than CRP, although it is also elevated in trauma patients and after major surgery, some cancers or vasculitis [12].

Presepsin or a soluble cluster of differentiation (sCD) 14 subtype (sCD14-ST), a new promising laboratory inflammatory biomarker for sepsis diagnosis, is formed during the inflammation in plasma from sCD14, a glycoprotein present on monocytes and macrophages membranes which acts as a receptor for lipopolysaccharide (LPS), binding the protein complex of bacteria [13]. Soluble CD14 is excreted from the liver cells and monocytes and mediates the immune signalling cascade. In small concentrations, it is present in healthy subjects, but greatly increases in bacterial infections. According to recent studies, its elevated values are associated with the severity of sepsis and its outcome [14,15].

The present research focused on the possibilities of using presepsin in everyday clinical use for discriminating between sepsis and viral infection, assessing the severity of sepsis, prognosis, finding differences in the presepsin level according to the aetiology of sepsis, and for monitoring the effectiveness of treatment.

Methodology

The study protocol was approved by the Ethics Committee of the Ministry of Health of the Republic of Slovenia (consent number 0120-402/2016-2), and was conducted in accordance with the Helsinki Declaration. Informed consent was obtained from all individual participants included in the study. Fifty-four consecutive adult patients with sepsis and twenty-six patients with aseptic meningitis as a control group admitted to the Department of Infectious Diseases, University Medical Centre Ljubljana between the years 2014 and 2016 were included in this prospective study. Detailed characteristics of the patients were recorded and acute physiology and chronic health evaluation (APACHE) II scores were calculated on admission. In all hospitalised patients with suspected bacterial infection, at least two separate blood cultures (Bactec, Sparks, BD, USA) were obtained within 24 hours of admission. The matrix-associated laser desorption ionization-time of flight (MALDI-TOF) MS for rapid identification of bacteria from positive blood culture bottles was performed. The result was considered positive if the same microorganism was identified in two different sets of cultures. An antimicrobial treatment in the previous 48 hours was an exclusion criterion. The experimental group was divided into two subgroups, namely sepsis (9/54) and septic shock (45/54), based on the third international consensus definitions published by SCCM and ESCIM [1,16]. The subgroup in the control group represented patients with tick-borne meningoencephalitis (TBE) (11/26); for all other patients the aetiology of the meningitis was not determined. However, biochemical CSF parameters and favourable clinical outcome without antibiotic treatment were consistent with viral infection. Neuroborreliosis was excluded by negative specific antibodies for *Borrelia burgdorferi sensu lato* (LIAISON® Borrelia burgdorferi, Diasorin, Saluggia, Italy) in serum and cerebrospinal fluid.

From all patients included in the study, blood samples were obtained on admission. The following reference ranges were used: CRP (Siemens, Möhnesee, Germany) < 5 mg/L, PCT (BRAHMS Diagnostica, Hennigsdorf, Germany) < 0.5 mcg/L, leukocyte concentration 4.0-10.0×10^9/L and lactate concentration 0.6-2.4 mmol/L. Presepsine (PATHFAST, Mitsubishi Chemical Europe, Düsseldorf, Germany) plasma concentrations were detected on admission and days 2, 3 and 7 in the experimental group, but only on admission in the control group. The serum concentrations of PCT were determined on admission only in patients with suspected bacterial infection and followed on days 2, 3 and 7.

A statistical significance was conducted with SPSS Statistics 17 (International Business Machines Corporation, Armonk, New York, USA) and p value < 0.05 was considered significant. The diagnostic properties of the test were calculated by receiver operating characteristic curves ROC analysis. The area under curve (AUC) was interpreted according to the following guidelines: low for 0.5-0.7, moderate for 0.7-0.9, and high for > 0.9.

Results

There were no statistically significant differences between the septic and control groups in terms of gender (male to female 33/21 vs. 15/11, p-value 0.811),

Table 1. Inflammatory parameters (presepsin, C-reactive protein, leukocyte concentration) and APACHE II score comparison between the sepsis and control group.

	PRES		APACHE II		LEUKO		CRP	
	Median	range	Median	range	Median	range	Median	range
Sepsis (n = 54)	1614	286-20000	24	6-43	13,0	0-350	240	37-457
Viral infection (n = 26)	203	53-987	2	0-8	9,8	4-16	17	5-154
p-value	< 0,001		< 0,001		0,025		< 0,001	

PRES: presepsin concentration (pg/mL); LEUKO: leukocyte concentration (×10^9/L); CRP: C-reactive protein concentration (mg/L).

while the septic group was statistically significantly older than the control group (Septic group = 62.54 ± 15.01 vs. Control group = 38.73 ± 13.45, p-value < 0.001). There were statistically significant differences between the septic and control groups when considering the outcome of the disease. All of the patients in the control group survived, while 21 out of 54 patients in the septic group died (p-value < 0.0001). Within the control group, there were no statistically significant differences in demographic characteristics, inflammatory parameters or outcome according to the aetiology.

Table 1 demonstrates the differences in the inflammatory markers and APACHE II score on admission between the experimental and control groups. All of the parameters were statistically significantly higher in the septic group compared to the control group. When comparing the sensitivity and specificity of individual inflammatory markers between the two groups to predict sepsis, the ROC curve (Figure 1) demonstrates that presepsin is the best predictor for discriminating between sepsis and viral infection (AUC = 0.832). Based on our results, for predicting sepsis, presepsin demonstrates 100% sensitivity at plasma concentrations of 283.50 pg/mL or less and 100% specificity at plasma concentrations of 1041.50 pg/mL or more. The highest specificity and sensitivity was found at a plasma concentration of 751.50 pg/mL (83.3% sensitivity, 96.2% specificity), the result is slightly lower at a plasma concentration of 379.50 pg/mL (94.4% sensitivity, 84.6% specificity).

The differences in inflammatory markers and the APACHE II score according to the severity, outcome and aetiology of sepsis are presented in Table 2. ROC analysis for prediction of severity of sepsis is shown in Figure 2. Presepsin is a good marker for differentiating between sepsis and septic shock (AUC = 0.839), whereas procalcitonin is only a fair indicator (AUC = 0.738) and lactate concentration is a poor indicator of

Figure 1. ROC curve comparing the different inflammatory parameters in predicting sepsis. Presepsin is the best predictor for discriminating between sepsis and viral infection.

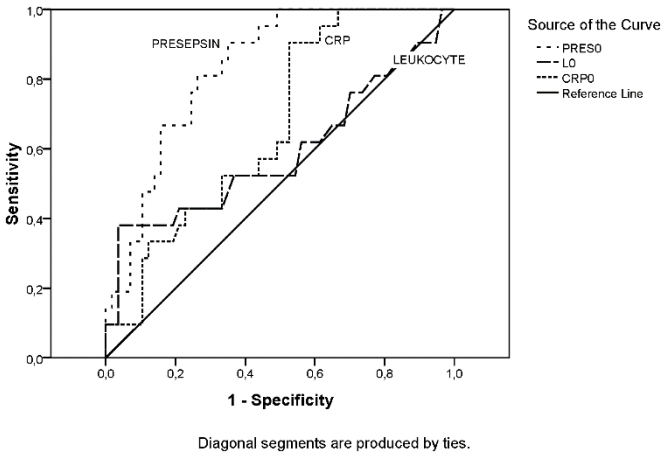


Table 2. Inflammatory parameters (presepsin, procalcitonin, C-reactive protein) and APACHE II score according to the severity, outcome and aetiology of sepsis.

		PRES		APACHE II		PCT		CRP	
		Median	range	Median	range	Median	range	Median	range
Diagnosis	Sepsis (n = 9)	771	286-5565	14	6-26	1,0	0-31	180	72-432
	Shock (n = 45)	1914	342-20000	26	13-43	19,0	0-499	246	37-457
	p-value	0,014		< 0,001		0,002		0,628	
Outcome	Died (n = 21)	3154	625-20000	29	15-43	19	2-499	233	37-457
	Survived (n = 33)	1208	286-12096	21	6-39	15	0-238	246	50-453
	p-value	0,009		0,002		0,136		0,382	
Aetiology	None (n = 19)	1941	342-20000	26	13-43	13,6	0-157	178	37-457
	G-pos. (n = 25)	1314	297-13332	23	12-37	19	0-499	292	75-457
	G-neg. (n = 10)	2906	286-11359	31	6-40	17,5	0-238	215	102-453
	p-value	0,381		0,224		0,969		0,863	

PRES: presepsin concentration (pg/mL); PCT: procalcitonin concentration (mcg/mL); CRP: C-reactive protein concentration (mg/L); G-pos.: Gram-positive sepsis/septic shock; G-neg.: Gram-negative sepsis/septic shock.

septic shock (AUC = 0.679). The other inflammatory markers fail to differentiate between the two groups based on severity (AUC is 0.594, 0.502, 0.429 for leukocyte concentration, CRP and segmented neutrophils fraction, respectively).

Based on our results, lactate concentration on admission is the only good predictor for patient outcome (Figure 3, AUC = 0.891), while presepsin is a poor predictor of patient outcome (AUC = 0.698), as is leukocyte concentration (AUC = 0.625). Furthermore, we looked at how presepsin and procalcitonin serum concentration in septic patients changes in time based on the outcome. Based on our results, we observed a positive downward trend for presepsin concentration in most patients who survived, compared to a negative upward trend in the patients who did not survive. The observed differences between the groups were statistically significant (p = 0.018). When comparing the procalcitonin concentration trend between the aforementioned groups, no statistically significant differences were observed (p = 0.051).

Discussion

This is the first study that compares presepsin levels in patients with sepsis to levels of presepsin in patients with viral infection. The diagnosis of sepsis has been based on clinical signs, laboratorial inflammation markers and positive blood cultures. Unfortunately, blood culture results are not available early in the course of the diagnostic procedure or may even remain negative, and no single clinical or blood inflammation marker is absolutely discriminatory between sepsis and viral infection. Compared with other markers, presepsin seems to have a higher sensitivity and specificity in the diagnosis of sepsis, which was also confirmed in the present study. Our results corroborate previous findings demonstrating the association of elevated presepsin with sepsis. A statistically significant higher presepsin concentration was found in patients with sepsis and septic shock, compared to patients with aseptic meningitis. In the septic group, a higher concentration of CRP and white blood cell count (WBC) was found than in the control group, as well. However, further analysis has proven presepsin to have the best useful predictive value for diagnosing sepsis compared to inflammation markers used daily. The area under the curve (AUC) was the greatest for presepsin (0.832), followed by CRP (0.666) and WBC (0.590). Similar results were found by Shozushima *et al*. [17], who reported that the diagnostic accuracy of presepsin predicting sepsis was higher than that of CRP. The high diagnostic value of presepsin to diagnose septic shock

Figure 2. ROC curve comparing the different parameters in predicting the severity of sepsis. Presepsin is a better marker for differentiating between sepsis and septic shock than procalcitonin or lactate. The other inflammatory markers fail to differentiate between the two groups based on severity.

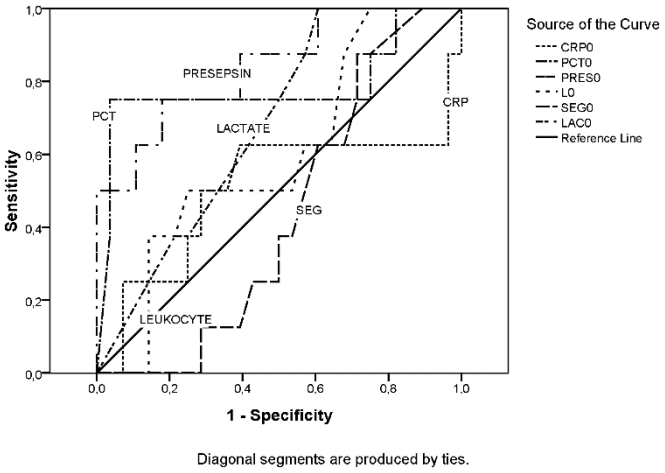
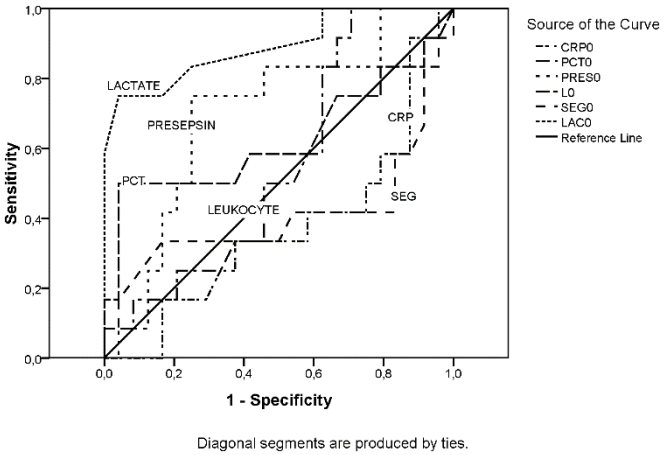


Figure 3. ROC curve comparing different parameters in predicting the outcome of patients with sepsis. Lactate concentration on admission may better predict the outcome of sepsis than presepsin or others.



at day 1 of ICU treatment was also confirmed by Behnes *et al*. [18], whereas CRP and WBC did not have valuable discriminative diagnostic capacity.

On the other hand, in the study published by Godnic *et al*. [19], CRP had higher diagnostic accuracy for bloodstream infection than presepsin. They have reported that the median presepsin value in septic patients was 868 pg/mL, while it was 1614 pg/mL in the present study. However, it is not clear what the presepsin concentration was according to the severity of sepsis. Similar diagnostic accuracy of the presepsin test for sepsis to what we found was also published by Wu *et al*. [20]. Nine studies were included in their meta-

analysis; the pooled sensitivity of presepsin for sepsis was 0.78 (0.76-0.80) and the pooled specificity was 0.83 (0.80-0.85). The AUC of the summary receiver operating characteristics curve was 0.89 (95% CI: 0.84 to 0.94). In another recently published meta-analysis, which included 19 observational studies involving 3012 patients, Kondo *et al*. [21]. reported similar diagnostic accuracy of presepsin for sepsis. ROC analyses revealed AUC 0.87 for presepsin and 0.84 for PCT. The pooled sensitivities and specificities for presepsin were 0.84 and 0.73, respectively. This meta-analysis focused only on studies evaluating participants with critical illnesses, but not healthy volunteers. On the other hand the importance of presepsin in distinguishing sepsis from viral infection was emphasized in our report, which is important in daily clinical practice.

However, it is clear that the results between the studies are not absolutely comparable because of the heterogeneity of the patients involved, the heterogeneity of the control groups, the different cut-off values of presepsin, and, last but not least, because of the different aetiology of sepsis. Presepsin plasma concentration is related to the level of endotoxin and plays an important role in regulating the inflammatory process on the endothelial surface of the microcirculation. In most studies, the sepsis aetiology is not clearly indicated. On the other hand, in the present study, gram negative sepsis was demonstrated in 19 percent of the patients, gram positive sepsis in 46 percent, and in 35 percent aetiology was not defined.

In our viral infection group the median presepsin concentration was 203 pg/mL, above the level usually found in healthy individuals. Giavarina *et al*. [22] reported reference values of presepsin concentration of 55 and 184 pg/mL in healthy subjects who participated in their study. There are few data of the presepsin plasma levels in patients with a documented viral infection. Demirpence *et al*. [23] focused on presepsin levels as a biomarker for Crimean-Congo hemorrhagic fever (CCHF), and the reported mean presepsin concentration was 1499 pg/mL. The much higher than normal presepsin level in CCHF patients was believed to be a consequence of reactive hemophagocytosis, which can occur in the pathogenesis of the disease. In our study the range of presepsin concentrations in the aseptic meningitis group was between 53 and 987 pg/mL, and ten out of twenty-six patients had a presepsin level above 200 pg/mL. The reasons for higher presepsin values in some patients with viral infection are not clear. Chenevier-Gobeaux *et al*. [24] reported that higher presepsin concentrations were found in patients aged 70 years or older compared to younger ones. However, a higher presepsin level in aseptic meningitis group patients who participated in our study was not related to age, because their age was no higher than the age of individuals with a concentration of presepsin below 200 pg/mL. And it is unlikely that an unrecognized concomitant bacterial infection was the reason, because the condition in all patients improved without antimicrobial treatment.

The optimal cut-off values of presepsin for distinguishing sepsis and viral infectious diseases is not known. In the present study the highest values, 83% specificity and 96% sensitivity of presepsin, for diagnosing sepsis calculated from the ROC curve were found at a plasma concentration of 751.50 pg/mL. Shozushima *et al*. [17] reported that the cut-off value of presepsin set at 415 pg/mL has 80% sensitivity and 81% specificity for diagnosing sepsis. At a similar cut-off value of 413 pg/mL, Godnic *et al*. [19] found that the sensitivity of presepsin for sepsis was 85% and specificity 63%. A lower optimal cut off value of 317 pg/mL was proposed by Liu *et al*. [14], and a higher value of 600 pg/mL was used by Endo *et al*. [25].

The AUC of presepsin in our study was significantly higher than the APACHE II score, PCT and lactate in predicting the severity of sepsis. WBC, CRP and segmented neutrophils had not achieved sufficient reliability to be recommended to assess the severity of the disease. To our knowledge, data on the comparison of presepsin and lactate in an assessment role for the severity of disease studied with the ROC curve are not available in peer-reviewed literature to date. Regarding the assessment of the severity of the disease, a statistically significant association of the APACHE II score and presepsin concentration was found, while an association of the APACHE II score and PCT, CRP or WBC was not confirmed. Our results corroborate published data demonstrating the association of plasma presepsin and PCT level with the severity of sepsis [14,26]. In the present study, lactate concentration on admission is the best predictor for survival (AUC = 0.891), followed by presepsin (AUC = 0.698) and leukocyte concentration (AUC = 0.625). All other parameters fail to differentiate between the two groups based on outcome (AUC for PCT = 0.552, AUC for CRP = 0.366). Our findings were compatible with Wen *et al*. who demonstrated that lactate (AUC = 0.711) indicated better prognostic accuracy than presepsin (AUC = 0.703) in the prediction of sepsis-related in-hospital mortality [27]. However, the difference was not so convincing as in our report. The accuracy of biomarkers for predicting mortality is different in published articles. Liu *et al*. [14] reported

that the AUCs for presepsin and PCT for predicting 28-day mortality were 0.658 and 0.679, respectively. On the other hand, a higher AUC at day 0 for presepsin than that of PCT was found by Takahashi *et al*. [26]. A study reported by Masson *et al*. [28] also found that the AUCs for presepsin for 28-day mortality were 0.69, 0.70, and 0.74 on days 1, 2, and 7, respectively. AUCs values for PCT were 0.56, 0.55, and 0.64, respectively. In a similar study Hassan and colleagues found [15] significantly higher presepsin levels at day 0 and 3 in non-survivors vs. survivors and it decreased over the three days in survivors. These results are consistent with our conclusions, where a higher probability of survival was associated with a decrease in presepsin concentration.

It is generally accepted that PCT may be used for monitoring the efficacy of the antimicrobial treatment of sepsis [29]. It is not clear whether presepsin may play the same role. We may speculate, as seen in our study, that a decline of the presepsin level in septic patients indicates a good clinical response and suggests a better prognosis. In light of the overuse of antibiotics, it might be particularly interesting to reduce the length of antibiotic treatment in bloodstream infections by presepsin level monitoring, which is already the practice with PCT.

The highest presepsin level was found in patients with Gram-negative sepsis, followed by patients with unconfirmed aetiology, and the lowest presepsin concentration was determined in patients with Gram-positive sepsis. The differences between the groups were not statistically significant, probably due to the insufficient number of patients involved in each group. We could not prove that Gram-negative infections were responsible for the higher presepsin concentrations, although CD 14 has a higher binding ability to lipopolysaccharides, which are found in abundance in Gram-negative bacteria membranes [30]. These results are in accordance with report of Hassan *et al*. who failed to demonstrate statistically significant differences in the presepsin plasma concentration between different microorganisms [15].

This study is important due to its clinical orientation. It is not uncommon for patients with viral infection to have clinical signs similar to those with sepsis, including leukocytosis and a higher CRP concentration, which usually leads to unnecessary antibiotic therapy. This is a strategy and clinical practice that has a very negative effect on the spread of bacterial resistance to antibiotics, exposes patients to the potential toxic effects of antimicrobials, and increases the cost of treatment. On the other hand, a delay in antimicrobial treatment could be fatal in the case of uncharacteristic and unrecognized sepsis. In daily clinical practice, we need a bedside marker of sepsis with higher sensitivity and specificity than standard laboratory inflammation parameters, such as leukocytes, neutrophils, CRP, and even PCT. Our study has some limitations. The number of patients included in each group that was statistically compared was relatively small, and bacterial or viral etiology was not confirmed in all patients. However, the clinical course of the disease was characteristic for sepsis on one hand and viral meningitis on the other. A favourable clinical outcome without antibiotics was consistent with viral infection in the aseptic meningitis group as well.

Conclusions

Our study confirmed that presepsin is a usable marker of sepsis and can predict the severity and outcome of sepsis. The different presepsin levels in plasma are probably not related only to the severity of bacterial infection but to the aetiology as well. However, for wide acceptance of presepsin as a laboratorial diagnostic test in sepsis, further prospective, larger studies with a defined bacterial cause of sepsis are necessary.

References

1. Seymour CW, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A, Rubenfeld G, Kahn JM, Shankar-Hari M, Singer M, Deutschman CS, Escobar GJ, Angus DC (2016) Assessment of clinical criteria for sepsis: For the third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA 315: 762–774.
2. Fleischmann C, Scherag A, Adhikari NK, Hartog CS, Tsaganos T, Schlattmann P, Angus DC, Reinhart K (2016) Assessment of global incidence and mortality of hospital-treated sepsis. current estimates and limitations. Am J Respir Crit Care Med 193: 259-272.
3. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR (2001) Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med 29: 1303–1310.
4. Brun-Buisson C, Meshaka P, Pinton P, Vallet B; EPISEPSIS Study Group (2004) EPISEPSIS: a reappraisal of the epidemiology and outcome of severe sepsis in French intensive care units. Intensive Care Med 30: 580-588.
5. Vincent JL, Sakr Y, Sprung CL, Ranieri VM, Reinhart K, Gerlach H, Moreno R, Carlet J, Le Gall JR, Payen D; Sepsis Occurrence in Acutely Ill Patients Investigators (2006) Sepsis in European intensive care units: results of the SOAP study. Crit Care Med 34: 344-353.
6. Annane D, Aegerter P, Jars-Guincestre MC, Guidet B (2003) Current epidemiology of septic shock: the CUB-Rea Network. Am J Respir Crit Care Med 168: 165-172.
7. Kumar A, Ellis P, Arabi Y, Roberts D, Light B, Parrillo JE, Dodek P, Wood G, Kumar A, Simon D, Peters C, Ahsan M, Chateau D (2009) Initiation of inappropriate antimicrobial therapy results in a five-fold reduction of survival in human septic shock. Chest 136: 1237–1248.

8. Grace CJ, Lieberman J, Pierce K, Littenberg B (2001) Usefulness of blood culture for hospitalized patients who are receiving antibiotic therapy. Clin Infect Dis 32: 1651–1655.
9. Martin GS, Mannino DM, Eaton S, Moss M (2003) The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med 348: 1546-1554.
10. Phua J, Ngerng WJ, See KC, Tay CK, Kiong T, Lim HF, Chew MY, Yip HS, Tan A, Khalizah HJ, Capistrano R, Lee KH, Mukhopadhyay A (2013) Characteristics and outcomes of culture-negative versus culture-positive severe sepsis. Crit Care 17: R202.
11. Sproston NR, Ashworth JJ (2018) Role of C-reactive protein at sites of inflammation and infection. Front Immunol 9: 754.
12. Ugarte H, Silva E, Mercan D, De Mendonca A, Vincent JL (1999) Procalcitonin used as a marker of infection in the intensive care unit. Crit Care Med 27: 498–504.
13. Wu J, Hu L, Zhang G, Wu F, He T (2015) Accuracy of presepsin in sepsis diagnosis: a systematic review and meta-analysis. Plos One 10: e0133057.
14. Liu B, Chen YX, Yin Q, Zhao YZ, Li CS (2013) Diagnostic value and prognostic evaluation of Presepsin for sepsis in an emergency department. Crit Care 17: R244.
15. Hassan EA, Abdel Rehim AS, Ahmed AO, Abdullahtif H, Attia A (2019) Clinical Value of Presepsin in Comparison to hsCRP as a Monitoring and Early Prognostic Marker for Sepsis in Critically Ill Patients. Medicina (Kaunas) 55: 2.
16. Shankar-Hari M, Phillips GS, Levy ML, Seymour CW, Liu VX, Deutschman CS, Angus DC, Rubenfeld GD, Singer M (2016) Developing a new definition and assessing new clinical criteria for septic shock: For the third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA 315: 775–787.
17. Shozushima T, Takahashi G, Matsumoto N, Kojika M, Okamura Y, Endo S (2011) Usefulness of presepsin (sCD14-ST) measurements as a marker for the diagnosis and severity of sepsis that satisfied diagnostic criteria of systemic inflammatory response syndrome. J Infect Chemother 17: 764–769.
18. Behnes M, Bertsch T, Lepiorz D, Lang S, Trinkmann F, Brueckmann M, Borggrefe M, Hoffmann U (2014) Diagnostic and prognostic utility of soluble CD 14 subtype (presepsin) for severe sepsis and septic shock during the first week of intensive care treatment. Crit Care 18: R507.
19. Godnic M, Stubljar D, Skvarc M, Jukic T (2015) Diagnostic and prognostic value of sCD14-ST-presepsin for patients admitted to hospital intensive care unit (ICU). Wien Klin Wochenschr 127: 521–527.
20. Wu J, Hu L, Zhang G, Wu F, He T (2015) Accuracy of presepsin in sepsis diagnosis: A systematic review and meta-analysis. PLoS One 10: e0133057.
21. Kondo Y, Umemura Y, Hayashida K, Hara Y, Aihara M, Yamakawa K (2019) Diagnostic value of procalcitonin and presepsin for sepsis in critically ill adult parients: a systematic review and meta-analysis. J Intensive Care 7: 22.
22. Giavarina D, Carta M (2015) Determination of reference interval for presepsin, an early marker for sepsis. Biochem Med 25: 64-68.
23. Demirpençe Ö, Doğan HO, Erşan S, Şahin M, Şahin H, Bakır M (2016) Presepsin levels of patients with Crimean-Congo hemorrhagic fever. Jpn J Infect Dis 69: 505-509.
24. Chenevier-Gobeaux C, Trabattoni E, Roelens M, Borderie D, Claessens YE (2014) Presepsin (sCD14-ST) in emergency department: the need for adapted threshold values? Clin Chim Acta 427: 34–36.
25. Endo S, Suzuki Y, Takahashi G, Shozushima T, Ishikura H, Murai A, Nishida T, Irie Y, Miura M, Iguchi H, Fukui Y, Tanaka K, Nojima T, Okamura Y (2012) Usefulness of presepsin in the diagnosis of sepsis in a multicenter prospective study. J Infect Chemother 18: 891–897.
26. Takahashi G, Shibata S, Ishikura H, Miura M, Fukui Y, Inoue Y, Endo S (2015) Presepsin in the prognosis of infectious diseases and diagnosis of infectious disseminated intravascular coagulation: a prospective, multicentre, observational study. Eur J Anaesthesiol 32: 199–206.
27. Wen MY, Huang LQ, Yang F, Ye JK, Cai GX, Li XS, Ding HG, Zeng HK (2019) Presepsin level in predicting patients' in-hospital mortality from sepsis under sepsis-3 criteria. Ther Clin Risk Manag 15: 733-739.
28. Masson S, Caironi P, Spanuth E, Thomae R, Panigada M, Sangiorgi G, Fumagalli R, Mauri T, Isgrò S, Fanizza C, Romero M, Tognoni G, Latini R, Gattinoni L (2014) Presepsin (soluble CD14 subtype) and procalcitonin levels for mortality prediction in sepsis: data from the Albumin Italian Outcome Sepsis trial. Crit Care 18: R6.
29. Pantelidou IM, Giamarellos-Bourboulis EJ (2015) Can procalcitonin monitoring reduce the length of antibiotic treatment in bloodstream infections? Int J Antimicrob Agents 46 Suppl 1: 10-12.
30. Le Roy D, Di Padova F, Adachi Y, Glauser MP, Calandra T, Heumann D (2001) Critical role of lipopolysaccharide-binding protein and CD14 in immune responses against Gram-negative bacteria. J Immunol 167: 2759-2765.

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