

# Presepsin: A Novel and Potential Diagnostic Biomarker for Sepsis

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**Abstract** Sepsis is a potential clinical condition which is a consequence of infectious disease or a severe inflammatory reaction secondary to infection or injury. Sepsis in Greek means putrefaction or decay, correlating well with the multiple organ failure and severe shock resulting in death of the patient suffering from severe sepsis. Clinical management of sepsis requires prompt laboratory diagnosis and formulation of effective patient management strategies that may include antimicrobial chemotherapy in case of sepsis induced by infectious microbe. Although many laboratory biomarkers are available for the diagnosis of sepsis, only few markers have proven to be beneficial in differentiating infectious disease sepsis and sepsis of non-infectious origin. Of the available markers only few have prognostic value. We in this review discuss the utility of a novel and emerging sepsis marker, the presepsin which has a better diagnostic and prognostic value, and has been effective in predicting the survival of the sepsis patients.

**Keywords:** presepsin, sepsis marker, management of sepsis

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## 1. Introduction

Sepsis and septic shock are among the most important medical emergencies throughout the world. Advancement in the life support technologies have proven to be insufficient in reducing the mortality and morbidity arising from severe sepsis. In the era of multi-drug resistance, it becomes imperative that such cases should be diagnosed at the earliest and appropriate treatment and management measures should be initiated for better patient outcome/care [1]. Sepsis is defined as the two fold increase in inflammatory indicators. Some of the biomarkers currently available include C-reactive protein (CRP), procalcitonin (PCT), Interleukin-6 (IL-6), Plasma transforming growth factor-b1, Pro-vasopressin, pro-adrenomedullin (proADM), pro-atrial natriuretic peptide and myeloid cells expressing triggering receptor-1 (TREM-1), soluble urokinase-like plasminogen receptor (suPAR) [2-8]. Among the available biomarkers of sepsis, the CRP is still routinely used as a sepsis indicator in neonates [9]. Millions of deaths are reported due to sepsis throughout the world including both developed and developing nations [10]. Sepsis has been attributed to

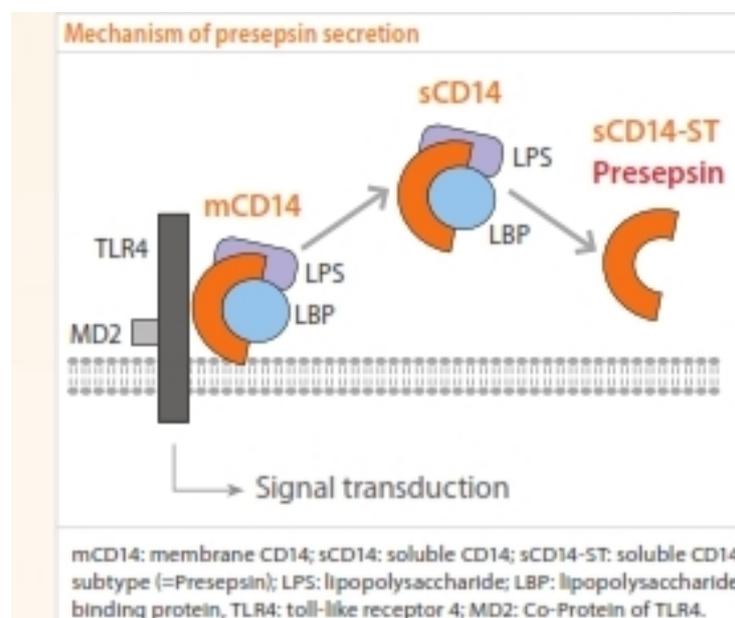
occur in 1-2% of hospitalized patients including those who are undergoing treatment in intensive care units (ICU) [11]. Among the many biomarkers which have been evaluated for their prognostic significance only PCT was found useful until recently [12]. Although the available biomarkers of sepsis have proven to be useful, the drawbacks include their elevated activities during non septic conditions like trauma, surgery, myocardial infarction and other conditions like systemic inflammatory response syndrome (SIRS), and immune response during septic conditions. Considering the fact that sepsis due to infection is microbiologically confirmed only in 30% of the cases, it is inevitable that there is need for other indicators of sepsis [13].

## 2. Presepsin: Soluble Subtype of CD14 (SCD14-ST)

Some of the biomarkers currently available have proven to be having less prognostic value and cannot be useful for predicting mortality [14]. Research in this direction has paved the way for identification of CD14, a glycopeptides expressed on macrophages and monocytes, which serves as a receptor for lipopolysaccharide-lipopolysaccharide

binding protein (LPS-LPB) of microorganisms as a potential biomarker. CD14 is a 55-kDa glycosyl phosphatidyl inositol-anchored protein lacking a cytoplasmic domain. CD14 is expressed on most innate immune response cells and exists either in an anchored membrane form (mCD14) or in a circulating soluble form

(sCD14). The latter is a 43-53 kD glycoprotein that derives from either protease-mediated membrane CD14 shedding or liver synthesis as a type II acute-phase reactant. During inflammation, plasma protease activity generates CD14 fragments (Figure 1).



**Figure 1.** Mechanism of presepsin synthesis (acquired from medesa.testujeme.cz/Data/.../Presepsin/PF\_Folder\_SEPSIS\_0605\_IL.pdf)

The SCD14-ST, a soluble CD14 subtype, a 13 kDa truncated N terminal fragment of 64 aminoacid residues is called as presepsin. This has been found to activate proinflammatory cascade on encountering microorganisms. It has been noted that plasma protein activity results in the production of SCD14 fragments. Among the fragments the SCD14 –ST fragment is recognised as a sepsis marker [15,16].

### 3. Current Research on Utility of Presepsin

Previous studies have evaluated the activities of SCD14-ST among healthy, mild sepsis, severe sepsis and systemic inflammatory response syndrome (SIRS) patients. Studies on the activities of presepsin in adults, neonates and post-mortem cases have highlighted the utility of presepsin as an efficient biomarker in the prognosis of sepsis when compared to others [17,18,19,20]. These studies have found that although PCT has a better diagnostic value, presepsin was instrumental in knowing the survival chances of the patient as observed from higher mean presepsin activities in non-survivors as compared to survivors. A study published recently has compared the utility of both presepsin and pro-calcitonin in sepsis patients. This study had included 21 patients undergoing treatment at the critical care unit in a hospital in Italy. Results of this study has revealed that activities of both presepsin and PCT were lower among healthy individuals as compared to sepsis and severe sepsis patients ( $p < 0.001$ ). Results of the study have also confirmed the ability of both markers to differentiate between severe sepsis and systemic inflammatory response syndrome (SIRS). The study has also confirmed that when evaluating the treatment response, the presepsin

was considerably superior over PCT in assessing the real condition of the patient [21]. The activities of presepsin in the diagnosis of bacteraemia among patients with systemic inflammatory response syndrome (SIRS) and non-SIRS was studied recently and found that presepsin levels were higher among patients with SIRS and bacteraemia when compared to non-SIRS patients with bacteraemia. This study has also noted that increased activities of presepsin ( $>720$  pg/mL) correlated well with mortality [22]. A study recently has compared the activities of PCT, presepsin and interleukin-6 (IL-6) for diagnosing bacterial and non-bacterial infectious disease related sepsis. The results of the study showed that at a cut-off of 600 pg/mL of presepsin, has been found useful in predicting bacterial and non-bacterial induced sepsis. This study has also revealed that presepsin (91.9%) was more sensitive than blood culture (35.4%) in diagnosing sepsis [23]. In a recent prospective observational study performed by Filippo Mearelli et al. among SIRS patients attending emergency care department evaluated the activities of presepsin, PCT, pro-adrenomedullin (proADM), fibrin degradation products and lactate. Results of this study have revealed higher levels of PCT, proADM and presepsin among infectious disease sepsis patients as compared to no-infectious sepsis patients [24]. Tatjan Vodnik et al. in their recent study evaluated the performance of presepsin pre-operative diagnosis of abdominal sepsis and found that presepsin was significantly higher in severe sepsis ( $1508.3 \pm 866.6$  pg/mL) group when compared to healthy individuals ( $258.7 \pm 92.53$ ) and SIRS patients ( $430.0 \pm 141.33$  pg/m) [25]. Diagnosis of sepsis is difficult in patients with burns since these patients suffer from altered post burn metabolic profile. Özlem Çakır Madenci et al. in a recent study have compared the activities of PCT, CRP, white blood cell

count (WBC) and presepsin in burns patients. This study has measured the activities of biomarkers tested every six hours starting from admission. The diagnostic accuracy of the measured sepsis markers including presepsin (83.4%), PCT (84.7%), CRP (81.9%) and WBC (50.8%) was found to be variable [26]. A recent study from Korea that evaluated the activities of presepsin, PCT, interleukin 6 (IL-6), and high-sensitivity C-reactive protein (hs-CRP) for their utility in the diagnosis of sepsis has revealed that among the biomarkers tested presepsin activities significantly differed in infectious (1403.47 pg/mL) and non infectious (239.00 pg/mL) group highlighting the importance of presepsin in the diagnosis and prognosis of sepsis [27]. A multicenter prospective study conducted recently by Shigeatsu Endo et al. has shown that presepsin activities correlated well with the severity of sepsis at presentation and during follow-up [28]. Presepsin activities were also measured among the major organ transplant patients for possible sepsis diagnosis and the study results revealed that activities of presepsin were significantly higher ( $3034.43 \pm 2880.791$ ) among transplant patients which correlated well with blood cultures [29].

#### 4. Conclusion and Future Perspectives

Severe Immunological response to microbial infection (commonly by bacteria and occasionally by fungi, viruses and parasites) presenting as a systemic illness which may lead to multiple organ dysfunctions is termed as sepsis. Sepsis may also be observed in cases of trauma, burns patients, transplant patients and chronic organ failures (kidney, lungs and liver). Sepsis is a result of heightened inflammatory response during an infection/injury. Emergency laboratory and clinical management of patients suffering from sepsis is required to reduce the resultant morbidity and mortality. Neonates, pregnant women, patients undergoing transplantations, burns patients and geriatric age group are more susceptible to severe sepsis. Many laboratory biomarkers either singly or in combination have been routinely used for the laboratory diagnosis of sepsis. Presepsin is a novel sepsis biomarker that has been available recently. Although only few studies have attempted to evaluate the usefulness of presepsin, the literature available thus far clearly impresses up on the fact that presepsin has a potential role not only as a diagnostic marker but is also efficient in knowing the prognosis and survival chances of the sepsis patients. Further research on large scale multi-centric and comparative studies (with other available and newer biomarkers) in different geographical areas and patient groups is required to confirm the utility of presepsin as a potential sepsis biomarker.

#### References

- [1] Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Intensive Care Med* 2008; 34: 17-60. global death.
- [2] Dupuy, F. Philippart, Y. Pean et al., "Role of biomarkers in the management of antibiotic therapy: an expert panel review. I: currently available biomarkers for clinical use in acute infections," *Annals of Intensive Care*, vol. 3, no. 22, article 1, 2013.
- [3] Wu HP, Chen CK, Chung K, Jiang BY, Yu TJ, Chuang DY. Plasma transforming growth factor- $\beta$ 1 level in patients with severe community-acquired pneumonia and association with disease severity. *J Formos Med Assoc* 2009; 108: 20-27.
- [4] Guignant C, Voirin N, Venet F, Poitevin F, Malcus C, Bohé J, et al. Assessment of pro-vasopressin and pro-adrenomedullin as predictors of 28-day mortality in septic shock patients. *Intensive Care Med* 2009; 35: 1859-1867.
- [5] J. P. Hinson, S. Kapas, and D. M. Smith, "Adrenomedullin, a multifunctional regulatory peptide," *Endocrine Reviews*, vol. 21, no. 2, pp. 138-167, 2000.
- [6] Seligman R, Papassotiriou J, Morgenthaler NG, Meisner M, Teixeira PJ. Prognostic value of midregional pro-atrial natriuretic peptide in ventilator-associated pneumonia. *Intensive Care Med* 2008; 34: 2084-2091.
- [7] Y. Wu, F. Wang, X. Fan et al., "Accuracy of plasma sTREM-1 for sepsis diagnosis in systemic inflammatory patients: a systematic review and meta-analysis," *Critical Care*, vol. 16, no. 6, article R229, 2012.
- [8] Y. Backes, K. van der Sluijs, D. Mackie et al., "Usefulness of suPAR as a biological marker in patients with systemic inflammation or infection: a systematic review *Intensive Care Medicine*, vol. 38, no. 9, pp. 1418-1428, 2012.
- [9] N. Hofer, E. Zacharias, W. Müller, and B. Resch, "An update on the use of C-reactive protein in early-onset neonatal sepsis: current insights and new tasks," *Neonatology*, vol. 102, no. 1, pp. 25-36, 2012.
- [10] Longo Dan. *Harrison's principles of internal medicine*. New York: McGraw-Hill, 2011: 271 millions death.
- [11] Qi Zou, Wei Wen, Xin-chao Zhang. Presepsin as a novel sepsis biomarker. *World J Emerg Med* 2014; 5 (1): 16-19.
- [12] Cesar Henriquez-Camacho and Juan Losa, "Biomarkers for Sepsis," *BioMed Research International*, vol. 2014, Article ID 547818, 6 pages, 2014.
- [13] D. W. Bates, K. Sands, E. Miller et al., "Predicting bacteremia in patients with sepsis syndrome. Academic Medical Center Consortium Sepsis Project Working Group," *Journal of Infectious Diseases*, vol. 176, no. 6, pp. 1538-1551, 1997.
- [14] P. Hausfater. Biomarkers and infection in the emergency unit. *Médecine et Maladies Infectieuses* Volume 44, Issue 4, April 2014, Pages 139-145.
- [15] Elisa Pizzolato, Marco Ulla, Claudia Galluzzo, Manuela Lucchiarri, Tilde Manetta, Enrico Lupia et al. Role of presepsin for the evaluation of sepsis in the emergency department. *Clinical Chemistry and Laboratory Medicine (CCLM)*. Volume 0, Issue 0, ISSN (Online) 1437-4331.
- [16] Ulla et al.: Diagnostic and prognostic value of presepsin in the management of sepsis in the emergency department: a multicenter prospective study. *Critical Care* 2013 17: R168.
- [17] Mussap M, Noto A, Fravega M, Fanos V: Soluble CD14 subtype presepsin (sCD14-ST) and lipopolysaccharide binding protein (LBP) in neonatal sepsis: new clinical and analytical perspectives for two old biomarkers. *J Matern Fetal Neonatal Med* 2011, 24(Suppl 2): 12-14.
- [18] Mussap M, Puxeddu E, Burrai P, Noto A, Cibecchini F, Testa M, Puddu M, Ottonello G, Dessì A, Irmesi R, Gassa ED, Fanni C, Fanos V: Soluble CD14 subtype (sCD14-ST) presepsin in critically ill preterm newborns: preliminary reference ranges. *J Matern Fetal Neonatal Med* 2012, 25(Suppl 5):51-53.
- [19] Palmiere C, Mussap M, Bardy D, Cibecchini F, Mangin P: Diagnostic value of soluble CD14 subtype (sCD14-ST) presepsin for the postmortem diagnosis of sepsis-related fatalities. *Int J Legal Med* 2013, 127:799-808.
- [20] Masson et al.: Presepsin (soluble CD14 subtype) and procalcitonin levels for mortality prediction in sepsis: data from the Albumin Italian outcome sepsis trial. *Critical Care* 2014; 18: R6.
- [21] Valeria Sargentini, Giancarlo Ceccarelli, Mariadomenica D'Alessandro, Daniela Collepardo, Andrea Morelli, Annalia D'Egidio et al. Presepsin as a potential marker for bacterial infection relapse in critical care patients. A preliminary study. *Clinical Chemistry and Laboratory Medicine (CCLM)*. Volume 0, Issue 0, ISSN (Online) 1437-4331.
- [22] Luis García de Guadiana Romualdo, Patricia Esteban Torrella, Monserrat Viqueira González, Roberto Jiménez Sánchez, Ana Hernando Holgado, Alejandro Ortín Freire et al. Diagnostic accuracy of presepsin (soluble CD14 subtype) for prediction of bacteremia in patients with systemic inflammatory response

- syndrome in the Emergency Department. *Clinical Biochemistry* Volume 47, Issues 7-8, May 2014, Pages 505-508.
- [23] Endo S, Suzuki Y, Takahashi G, Shozushima T, Ishikura H, Murai A et al. Usefulness of presepsin in the diagnosis of sepsis in a multicenter prospective study. *J Infect Chemother*. 2012 Dec; 18(6): 891-7.
- [24] Filippo Mearelli et al. Procalcitonin, presepsin, pro-adrenomedullin, fibrin degradation products, and lactate in early diagnosis and prognosis of septic patients newly admitted to the intermediate care unit from the emergency department. *Critical Care* 2013, 17(Suppl 4):P17.
- [25] Tatjana Vodnik, Goran Kaljevic, Tanja Tadic, Nada Majkic-Singh. Presepsin (sCD14-ST) in preoperative diagnosis of abdominal sepsis. *Clinical Chemistry and Laboratory Medicine*. Volume 51, Issue 10, Pages 2053-2062.
- [26] Özlem Çakır Madenci, Sezer Yakupoğlu, Nur Benzonana, Nihal Yücel, Derya Akbaba, Asuman Orçun Kaptanağası. Evaluation of soluble CD14 subtype (presepsin) in burn sepsis. *Burns* Volume 40, Issue 4, June 2014, Pages 664-669.
- [27] Oh Joo Kweon, Jee-Hye Choi, Sang Kil Park, Ae Ja Park. Usefulness of presepsin (sCD14 subtype) measurements as a new marker for the diagnosis and prediction of disease severity of sepsis in the Korean population. *Journal of Critical Care* Available online 21 June 2014.
- [28] Shigeatsu Endo, Yasushi Suzuki, Gaku Takahashi, Tatsuyori Shozushima, Hiroyasu Ishikura, Akira Murai. Presepsin as a powerful monitoring tool for the prognosis and treatment of sepsis: A multicenter prospective study. *Journal of Infection and Chemotherapy* Volume 20, Issue 1, January 2014, Pages 30-34.
- [29] Novelli, G, Morabito, V, Ferretti, G., Pugliese, F, Ruberto, F, Rossi, M et al. PATHFAST Presepsin assay for early diagnosis of bacterial infections in surgical patients. Preliminary study.: 423 Transplantation: 27 November 2012 - Volume 94 - Issue 10S - p 532.