GAVIN PUBLISHERS

Biomarkers & Applications

Research Article

Ponte STD, et al. Biomark Applic: BMAP-115.
DOI: 10.29011/BMAP-115. 100015

Diagnostic Value of Presepsin in Sepsis

Silvana Teixeira Dal Ponte[1*], Giordanna Andrioli [1], Luciano Passamani Diogo[1], Renato Seligman[2], Luciano Zubaran Goldani[2], Andre Pinheiro Weber[3], Gabriela Petitot Rezende[4], Pauline Simas Machado[4]

[1]Emergency Physician, Emergency department, Hospital de Clinicas de Porto Alegre- Rs, Brazil

[2]Professor of Medicine, Universidade Federal do Rio Grande do Sul, Brazil

[3]Resident Emergency Medicine, Hospital de Pronto Socorro de Porto Alegre-RS, Brazil

[4] Academic of Medicine, Universidade Federal do Rio Grande do Sul, Brazil

[*]**Corresponding author:** Silvana Teixeira Dal Ponte, Emergency physician, Emergency department, Hospital de Clinicas de Porto Alegre- Rs, Brazil. Tel: +555133598000; Email: sildalponte@gmail.com

Citation: Ponte STD, Andrioli G, Diogo LP, Seligman R, Goldani LZ, et al. (2017) Diagnostic Value of Presepsin in Sepsis. Biomark Applic: BMAP-115. DOI: 10.29011/BMAP-115. 100015

Received Date: 17 October, 2017; **Accepted Date:** 4 November, 2017; **Published Date:** 10 November, 2017

Abstract

Sepsis is a Systemic Inflammatory Response Syndrome (SIRS) caused by proven or presumed infection. Some studies show that early recognition, influence the outcome of patients decreasing mortality. Culture exams are the gold standard to diagnose sepsis, but have the time as inconvenience. The presepsin protein has been studied as a marker of sepsis diagnoses, and the results are available around 2 hours after collection of blood. This study aims to establish the diagnostic value of presepsin levels in sepsis. Prospective observational study Were included 109 patients with more than 18 years with criteria for sirs on arrival at the emergency services. The values of presepsin were measured in blood samples up to 06 hours of hospitalization and after 48 hours of hospitalization. Secondary data were obtained through medical records. Were excluded from the study patients less than 18 years of age Patients were separated into two groups, one of SIRS and the other with confirmed or probable sepsis(strong clinical suspicion).The mean values of presepsin in patients with confirmed / probable sepsis were 2,926(DP 1194) and 1749 (701) in the SIRS patients. The Student's T test was used for unpaired samples, and it was observed that, among the values of these 2 groups, there was difference with statistical significance ($p<0,01$).The accuracy of presepsin values for the detection of sepsis, through the ROC curve, presented Area Under The Curve (AUC) de 0,787(IC 95%- 0,686-0,889), $p < 0,01$. Presepsin proved to be a biomarker with good sensitivity and specificity in the diagnosis of sepsis.

Keywords: Biomarkers; Diagnosis; Emergency Department; Presepsin; Sepsis

Introduction

Sepsis, severe sepsis and septic shock are some of the most common conditions managed in the emergency room and Intensive Care Units (ICU), with the mortality remaining between 30 and 60 despite antibiotic therapy and cardiovascular and respiratory support. Sepsis is defined as the presence (likely or documented) of infection along with systemic manifestations of infection. Severe sepsis is defined as sepsis plus organ dysfunction or tissue hypoperfusion induced by sepsis. Septic shock is hypoperfusion induced by persistent sepsis despite adequate fluid resuscitation [1,2]. Definitions of sepsis and septic shock were last revised in 2001. Considerable advances have since been made into the pathobiology (changes in organ function, morphology, cell biology, biochemistry, immunology, and circulation), management, and epidemiology of sepsis, suggesting the need for reexamination. Then, a new score for sepsis was suggested in 2016. The baseline SOFA score can be assumed to be zero in patients not known to have preexisting organ dysfunction and a SOFA score ≥2 reflects an overall mortality risk of approximately 10% in a general hospital population with suspected infection. But this score is not used unanimously [3]. The sepsis process is complex, a dynamically controlled syndrome in which several immunological processes are activated and regulated. According to the latest guideline published in 2013 by the Surviving Sepsis Campaign (SSC), early recognition of sepsis and prompt and adequate therapy in the first few hours probably influences the outcome of septic patients. Recently, the concept of immunological dissonance in the sepsis process allows an approach

to the therapeutic aspect of immuno stimulation. The first critical step, however, is to identify which patients would truly benefit from this therapy [3-5].

Several biomarkers have been studied for the diagnosis of sepsis.CD14 is a glycoprotein found on the surface membranes of mononuclear cells and serves as a high affinity receptor specific for Lipopolysaccharide (LPS). Presepsin is a protein which is fused at the N-terminus of cd14. Recent studies have shown increased plasma presepsin in patients with bacterial infection, being the sevalues significantly elevated in septic patients and severe septic patients. Studies have shown that presepsin has greater specificity than other biomarkers for the diagnosis of sepsis, for its severity and for clinical monitoring of response to therapeutic interventions [6-10]. In a study that performed a model of sepsis with ligation and cecal puncture in rabbits, it was observed that presepsin increased 2hours after the onset of infection, reaching apeakin3 hours, and then began to decrease in 4to8 hours the plasma half-life of presepsin was observed for 4-5 hours. One of the mechanisms of production of this protein reported was the process of Phagocytosis and cleavage of the cd14 membrane by granulocyte lysosomal enzymes in an in vitro study using rabbit peritoneal leukocytes [8,11].

The test for the detection of presepsin in the blood is a Chemiluminescent Immunoassay (CLEIA) for the quantitative measurement of presepsin concentration. In this test, monoclonal antibodies and polyclonal antibodies recognizing presepsin are used. During incubation of the polyclonal alkaline phosphatase labeled anti-presepsin and anti- presepsin monoclonal antibody coated with magnetic particles, the presepsin of the sample binds to the anti-presepsin antibodies forming an antibody-labeled antibody immuno complex and the coated magnetic antibody particles. After removing the unbound substances, a chemiluminescent substrate is added. After a short incubation the intensity of the chemiluminescence generated by the enzyme reaction is measured. The intensity of the luminescence is related to the presepsin concentration of the sample which is calculated by means of a standard curve. Its rapidity and the high prognostic power still in the presentation of the patient, qualify this test of presepsin detection for use in emergency care and in ICU [12,13]. The main goal of this study was to determine the diagnostic value of Presepsin levels in patients with sepsis, i.e., establish the accuracy of Presepsin in patients with SIRS, sepsis documented and presumed sepsis. Additional goals included the development of cutoffs for SIRS and sepsis, and the study of correlations between presepsin expression and the length of hospitalization, the duration of antibiotic treatment, as well as in-hospital mortality.

Materials and methods

Study Design

This was a prospective observational cohort study. The project of this study was approved by the Committee of Ethics of Hospital of Clinics of Porto Alegre (HCPA), number 140100.

Samples

Inclusion criteria were: All patients with SIRS in the HCPA Emergency with 6 hours of admission. Of the patients who met the selection criteria, a free informed consent for all patients who agreed to participate was applied, or their families, if the patient was not able to sign. Blood for Presepsin measurements was collected from all patients with SIRS seen at the emergency department of the HCPA within 6 h of hospital admission. An additional sample was collected after 48 h of hospitalization.

According to the American College of Chest Physicians, SIRS is defined by the presence of at least two of the following: Body temperature > 38°C (fever) or < 36°(hypothermia); respiratory rate > 20 breaths/minute (tachypnea) or partial arterial CO2 pressure < 32 mmHg; heart rate > 90 bpm; significantly increased or decreased peripheral leukocyte counts (> 12,000 or < 4,000 cells/mm3) or presence of more than 10% (> 500) immature neutrophils (bands).Sepsis was diagnosed based on the presence of confirmed or suspected infection plus SIRS. Blood cultures are not routinely collected in the emergency department of the HCPA. Patients were divided into the following categories based on their clinical picture upon arrival and its evolution during the first 6 h of hospitalization: SIRS, or sepsis, which included patients with both severe sepsis and septic shock. The sepsis group was further divided into suspectedvs. Documented sepsis, with the latter combines all patients with positive cultures. Since the concept of sepsis encompasses both suspected and confirmed infection, we reviewed all medical records with a group of 3 specialists to discuss the cases of patients with no positive cultures. We believe that cultures were not collected in these cases because, as it often happens, fluid resuscitation and antibiotic treatment were initiated, and blood cultures were only obtained if the clinical picture worsened or if no response was seen after 48h, which hinders the study of sepsis in adults. The high sensitivity and low specificity of diagnostic criteria for SIRS have contributed to the increase in sepsis research, since the presence of two criteria alone in addition to infection are sufficient for a diagnosis of sepsis. Then, the suspected sepsis group included patients with no cultures performed or who produced contaminated samples, who met criteria for SIRS and were clinically suspected of infection due to fever and X-ray evidence of pneumonia, or leukocyte- and nitrite-positive urine, in the absence of vasculitis, pancreatitis, burns, trauma or surgery in the current hospitalization, all of which can trigger SIRS in the absence of infection.15 In this group we have not included patients with positive cultural. Patients who met criteria for SIRS but not for suspected or confirmed sepsis were placed in the SIRS group. Exclusion criteria were: under18years old; they declined to participate; discharge or death before 48 hours of admission.

Sample Size calculation

Sample size was calculated based on a previous biomarker study of presepsin, whose goals were similar to those of the present investigation. In the study performed by Ulla et al., the median presepsin values were 517 pg / ml in control participants (SIRS), 875 pg / ml in patients with sepsis and 1460 pg / ml in patients with severe sepsis/septic shock. At baseline, the study identified a significant difference in presepsin levels between control participants and the sepsis group ($p = 0.002$), and between controls and those with severe sepsis/septic shock ($p < 0.001$). No significant differences were identified between the sepsis and severe sepsis/septic shock groups ($p = 0.07$) [14]. To detect a 50% difference in Presepsin expression between all groups (SIRS no sepsis, sepsis, severe sepsis/septic shock) with a statistical power of 80% and a significance of < 0.05, a total sample of 109 patients would be required. Spearman/Pearson correlation coefficients were used to investigate associations between Presepsin levels and outcomes such as the length of hospitalization, the duration of antibiotic therapy and mortality rates.

Instruments and Data Collection Procedures

To evaluate the role of Presepsin in monitoring sepsis, serial measurements of this biomarker were required. The first of these (T0) was obtained within 6 hours of hospital admission, while the second (T1) was taken after 48 hours of hospitalization. Blood samples for Presepsin assessment were drawn into tubes containing EDTA anticoagulant by adequately trained research assistants. All samples were immediately sent to the HCPA laboratory. Secondary data were obtained from medical records. Patients were followed until hospital discharge or death, if occurring during hospitalization.

Statistical analysis

Continuous and normally distributed variables were described by mean and standard deviation. Variables which did not show a normal distribution were described using medians and inter quartile ranges. The comparison between mean values at baseline and after 48 hours was performed using Wilcox on paired-sample tests. Comparisons between all three patient groups were performed using the Kruskal-Wallis H-tests, followed by Bonferroni-corrected Mann-Whitney U tests. Results were considered significant when $p<0.05$. Dichotomous variables were compared using Chi-squared or Fischer's exact tests. Cut-offs to distinguish between SIRS and sepsis were determined using ROC curves.

Results

The number of patients who met criteria for the study was 109, of those 12 for SIRS, 45 Sepsis, 52 suspected Sepsis Baseline presepsin level differed significantly among groups. The mean rank (MR) in the SIRS group was 25,42, while the corresponding values in the confirmed and suspected sepsis groups were 53,18 and 56, respectively ($p < 0.0056$). Post-hoc analysis revealed a significant difference in presepsin level among the confirmed sepsis group (MR=30.23) and the SIRS group (MR=14.08), ($p = 0.001$). These values also differed between the suspected sepsis group (MR=34) and the SIRS group (MR17), ($p < 0.004$). However, no such differences were identified between patients with suspected (MR=43.96) and confirmed sepsis (MR=46.28), ($p=0.674$) (Figure 1).

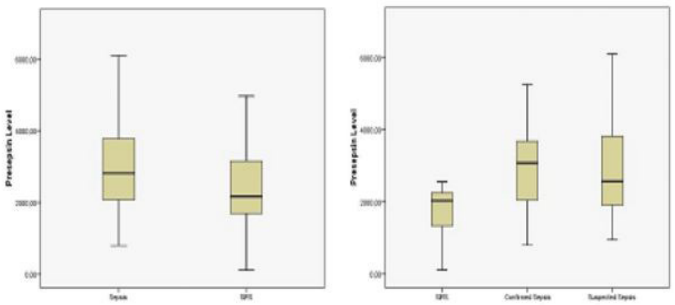

Figure 1: Concentration of presepsin in SIRS and Sepsis. N=109 (SIRS 12, Sepsis 45, Suspected sepsis 52).

The behavior of suspected and confirmed sepsis group's was quite similar, then, to practical proposes and based on results above, we create two new groups, the first one we maintain as a SIRS, the second was made by the merge of confirmed and suspected group, now called sepsis. The level of Presepsin amid this group was compared by Wilcox-Mann-Whitney test. The median level in sepsis group was 2810 (MR=25,42) and the SIRS group was 2032 (MR = 54,45), $p=0.001$. Using the area under the curve of ROC to test the accuracy of presepsin to diagnostic of sepsis we found a value of 0,787 (IC95%- 0,686-0,889) p=0,001. Because of nonparametric distribution of results, we are smoothing the ROC curve with the value of AUC 0, 7756 (95% CI: 0.5611-0.8566) (Figure 2).

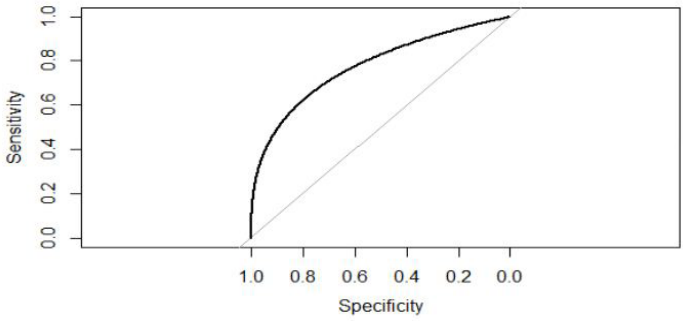

Figure 2: ROC curve AUC 0,77 (95% CI: 0,56-0.85).

Discussion

Presepsin was able to differentiate Sepsis from SIRS with accuracy early on admission to the emergency department. In another similar study of sepsis biomarkers, samples were collected

during the first assessment (T0), as well as 24 (T1) and 72 (T2) hours after admission. These authors found significantly higher values of biomarkers at T0 as compared to T1 and T2 [15].

Fourteen other patients in the suspected sepsis group had no positive cultures and were highly suspected of infection. In these cases, antibiotic treatment was initiated before cultures were collected. Twelve of these patients had blood cultures, eight had urine cultures, one had a negative CSF culture, and another had a negative sputum smear. The contaminated samples included 17 sputum smears, six urine samples and only one blood culture. All patients in the severe sepsis and septic shock group had positive cultures. According to Carvalho et al., despite all efforts to isolate microorganisms from blood cultures, these tend to be positive in 34% of patients, with estimates ranging from 9 to 64% [16].

It is possible to observe the importance of the Presepsin in the diagnosis of sepsis indifferent studies. Gerdes et al. described blood cultures as the gold-standard for the diagnosis of sepsis. However, its positivity rates vary widely, and range from 30 to 87%. Therefore, to facilitate and possibly accelerate the diagnosis of sepsis, clinicians must complement their examination with additional diagnostic tests. Elevated C-Reactive Protein (CRP) levels have also been used as a marker for sepsis, although the negative predictive value and specificity fall short of the criteria expected for a definitive diagnostic test [17- 19].

Conclusions

The present findings are in agreement with the existing literature, and suggest that presepsin a may be a useful biomarker for distinguishing between SIRS and sepsis, whether confirmed or suspected, with adequate sensitivity and specificity. Presepsina measurements are speed and may therefore contribute significantly to the early diagnosis and treatment of sepsis

Acknowledgments

We would like to thank the Universidade Federal do Rio Grande do Sul (UFRGS), the Emergency Department of the HCPA, FIPE HCPA, the Clinical Pathology Service of the HCPA and the Graduate Program in Medical Sciences, UFRGS.

Conflicts of Interest: The authors and institution declare no conflict of interest.

References

1. Ulla M, Pizzolato E, Lucchiari M, Loiacono M, Soardo F, et al. (2013) Diagnostic and Prognostic Value of Presepsin in the Management of sepsis in the Emergency Department: A Multicentre Prospective Study. Critical Care 17: R168.
2. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, et al. (2013) Surviving Sepsis Campaign International Guidelines for Management of Severe Sepsis and Septic Shock: 2012. Crit Care Med 41: 580-637.
3. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, et al. (2016) The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 315: 801-810.
4. Sáenz J Izura J, Manrique A, Sala F, Gaminde I (2001) Early Prognosis in Severe Sepsis Via Analyzing the Monocyte Immuno phenotype: 2001.Intensive Care Med 21: 970-977.
5. Monneret G, Venet F, Pachot A, Lepape A (2008) Monitoring Immune Dysfunctions in the Septic Patient: A New Skin for the Old Ceremony. Mol Med 14: 64-78.
6. Endo S, Suzuki Y, Takahashi G, Shozushima T, Ishikura H, et al. (2012) Useful ness of Presepsin in the Diagnosis of Sepsis in a Multicenter Prospective Study: 2012. J Infect Chemother 18: 891-889.
7.
8. Dupuy AM, Philippart F, Péan Y, Lasocki S, Charles PE, et al. (2013) Role of Biomarkers in the Management of Antibiotic Therapy: An Expert Panel Review: I - Currently Available Biomarkers for Clinical use in Acute Infections. Ann Intensive Care 3: 22.
9. Shirakawa K, Naitou K, Hirose J, Nakamura M, Takeuchi T, et al. (2010) The New Sepsis Marker, sCD14-ST, Induction Mechanism in the Rabbit Sepsis Models. Crit Care14: 19.
10. Yaegashi Y, Shirakawa K, Sato N, Suzuki Y, Kojika M, et al. (2005) Evaluation of a newly identified soluble CD14 subtype as a marker for sepsis. J Infect Chemother 11: 234-238.
11. Kojika M, Takahashi G (2010) Serum levels of soluble CD14sub type reflect the APACHEII and SOFAS cores. Med Post grad 48: 46-50.
12. Nakamura M, Takeuchi T, Naito K, Shirakawa K, Hosaka Y, et al. (2008) Early elevation of plasma soluble CD14 subtype, a novel biomarker for sepsis, in a rabbit cecal ligation and puncture model. Crit Care 12(suppl 2):194
13. Mitsubishi Chemical Medience Corporation: New Sepsis marker PATHFAST®Presepsin.
14. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis"1992. Crit Care Med 20: 864-874.
15. Annane D, Bellissant E, Cavaillon JM (2005) Septic shock. Lancet 365: 63-78.
16. Carvalho PR, Trotta Ede A (2003) Advances in the diagnosis and treatment of sepsis. J Pediatr (RioJ) 79: S195-204.
17. Gerdes JS (2004) Diagnosis and management of bacterial infections in the neonate. Pediatr Clin North Am 51: 939-959.
18. Gerdes JS (1991) Clinico pathologic approach to the diagnosis of neonatal sepsis. Clin Perinatol 18: 361-381.
19. Caldas JP, Marba, ST, Blotta MH, Calil R, Morais SS, et al. (2008) Accuracy of white blood cell count, C-reactive protein, interleukin-6 and tumor necrosis factor alpha for diagnosing late neonatal sepsis. J Pediatria 84: 536-542.