ORIGINAL ARTICLE

Comparison of Diagnostic Accuracy of Presepsin and Procalcitonin for Sepsis in Critically Ill Patients: A Prospective Observational Study

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Abstract

Objective: Early diagnosis of sepsis is crucial to institute appropriate therapy and then to avert a possible negative outcome. We planned this study to evaluate the diagnostic value of presepsin, its sensitivity and specificity for diagnosing sepsis in critically ill patients, and its ability to prognosticate the outcome of sepsis.

Methods: In this prospective observational study, adult patients admitted to the intensive care unit (ICU) at our institute were screened, and those with features suggestive of sepsis were recruited into the study. Procalcitonin (PCT) and presepsin were assessed on the day of admission and day 7 of the ICU stay, apart from routine investigations. Patients were followed for outcome in terms of mortality till 28 days.

Results: The study comprised 82 patients who satisfied the inclusion criteria. Presepsin sensitivity for sepsis diagnosis was determined to be 78%, while that of PCT was determined to be 69%. This gave a combined sensitivity of presepsin and PCT of 93% when used in parallel for the diagnosis of sepsis.

Conclusion: A combination of PCT and presepsin provides higher sensitivity and can be used to screen for sepsis in the ICU.

Keywords: Presepsin, Procalcitonin, Sepsis.

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Highlights

- Early detection of sepsis is vital for initiating treatment.
- In this study, procalcitonin (PCT) and presepsin levels were measured on admission and on the seventh day of intensive care unit (ICU) stay.
- Combination of PCT and presepsin provides higher sensitivity and can be used to screen for sepsis in the intensive care unit.

Introduction

Sepsis is a potentially fatal organ dysfunction produced by a dysregulated host response to infection.[1] It is common in hospitals and ICU, resulting in millions of fatalities globally.

The key to preserving lives in sepsis is early detection and treatment with antimicrobials as soon as possible. A variety of proteins generated by the body during the acute phase of sepsis can help with early sepsis diagnosis. C-reactive protein, interleukin-1, interleukin-6, and cytokines like tumor necrosis factor-α (TNF-α) have all been examined in the past, but while these markers are raised in sepsis, none of them is sensitive or specific enough to be used as biomarkers for the diagnosis of sepsis. Of course, blood and tissue cultures are the gold standards.[2] It is, however, a time-consuming process that will prolong the diagnosis of sepsis and, in its quest to provide an accurate diagnosis, will consume the patient's all-too-limited valuable time, negating the benefit of an early diagnosis of sepsis. As a result, a precise and timely biomarker for identifying sepsis is required, one that can be measured easily, quickly, and accurately.

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Procalcitonin is one such biomarker that is being used for the diagnosis of sepsis.[3] Despite its unquestioned utility in the early detection of sepsis, PCT can be elevated in various non-infectious diseases, including major surgery, severe trauma without infections, and significant burns. Furthermore, due to its short half-life, PCT rises quickly in response to systemic inflammation. As a result, its utility in predicting the prognosis of sepsis is limited. In a systematic review by Hoeboer et al., the sensitivity of PCT for diagnosing sepsis is 76% with a specificity of 69%.[4] It demonstrates much room for novel sepsis markers to be discovered.

Presepsin is a glycoprotein truncated version of CD-14's N-terminal fragment. The soluble region of CD-14 is split from the membrane-bound portion during inflammation, which is detected as presepsin. It not only rises earlier after the commencement of infection, but it is also unaffected by severe trauma, burns, or major surgery, all of which cause systemic inflammation but not sepsis.[5–7]

In several studies conducted worldwide, presepsin has been demonstrated to be a useful inflammatory indicator for sepsis. It was found to have high sensitivity and diagnostic accuracy in diagnosing sepsis.[8] In the only study conducted on adult patients in the Indian population, Venugopalan et al. reported that presepsin was superior to PCT in detecting sepsis, with the sensitivity and specificity of presepsin being 46.2 and 100, respectively. In contrast, PCT had a sensitivity of 46.2 and a specificity of 31.8.[9] However, samples were taken only at the time of suspicion of sepsis, and no further sampling was done to determine the prognostic value in the Indian population.

Presepsin could be a better alternative to established biomarkers for identifying sepsis, guiding antibiotic therapy, and predicting the patient's prognosis. As a result, we performed this study to compare the diagnostic accuracy of presepsin with that of PCT, a well-established biomarker utilized in our institution, and to correlate it with the patient's prognosis.

Methods

Study Design and Setting

This prospective observational study was conducted in the ICU of a tertiary care center. Approval was taken from the institutional ethics committee (IEC Reg No. AIIMS/IEC/2019-20/996 dated 1 January 2020). Enrolment of patients started in February 2020 and ended in July 2021.

Study Participants

Patients aged 18 years or older with clinical characteristics indicative of sepsis according to the sepsis-3 definition at the time of ICU admission and whose family members provided informed consent were included in the research. Patients with a terminal disease (cancer, acquired immunodeficiency syndrome, and end-stage liver or renal disease), HIV, HbsAg, HCV infections, autoimmune disorders, metabolic diseases or on long-term steroids, immunosuppressants, or chemotherapy were excluded from the research.

Blood samples were collected as part of standard sampling on ICU admission for routine investigations, and 5 mL whole blood was taken from the same sample for serum PCT and presepsin estimation, with no additional needle pricks or sampling done for the study (day 1). As a sepsis biomarker, serum PCT is routinely measured on admission to our ICU. These tests were repeated seven days after the first sample was taken (day 7).

The whole blood sample was collected in plain vacutainers from the recruited subjects. One hour was given for the sample to clot. At room temperature, serum was separated by centrifugation at 3000 rpm for 10 minutes. The serum was collected and kept in the biochemistry laboratory at −80°C. As our institution does not routinely test for presepsin, enzyme-linked immunosorbent assay (ELISA) kits were acquired. According to the manufacturer's instructions, the serum samples were used for presepsin estimation with an ELISA kit.

Routine cultures were sent from blood, urine, trachea, and any drain site at the time of ICU admission to screen for the presence of any suspected bacteremia. All sent cultures were followed up on, and a definitive sepsis diagnosis was made based on the organisms that grew in the cultures.

Patient outcome was noted regarding death or discharge at 28 days from admission. The primary outcome was to evaluate the sensitivity and specificity of presepsin and PCT to detect sepsis. The secondary outcome was to evaluate presepsin as a predictor of the outcome of sepsis in terms of 28 days' mortality.

Sample Size

Yoon et al. reported that presepsin had 94% sensitivity and PCT 76% for diagnosing Sepsis in ICU.[10] Considering the lower proportion of 76% for calculations, we estimated a sample size of 82 subjects at a 95% confidence level, 10% absolute precision, and 15% contingency for dropouts.

$n = (Z^2 \times p \times q)/d^2$

$n = (1.96^2 \times 76 \times 24)/10^2$

$n = 71$

$n = 82$ after adding 15% contingency for dropouts.

Statistical Analysis

The data were entered into a Microsoft Excel spreadsheet, and the final analysis was performed with version 28.0 of IBM's Statistical Package for the Social Sciences (SPSS) software. The significance level was determined at $p < 0.05$. The mean and standard error (SE) were reported for the normally distributed quantitative data. The areas under the receiver operating characteristic curve (ROC) curve (AUROCs) were utilized to depict the discriminatory powers of the biomarkers under consideration. The Youden index determined the optimal cutoff value for each ROC curve. The paired *t*-test was used to determine whether there was a significant change between the biomarker levels on days 1 and 7.

Results

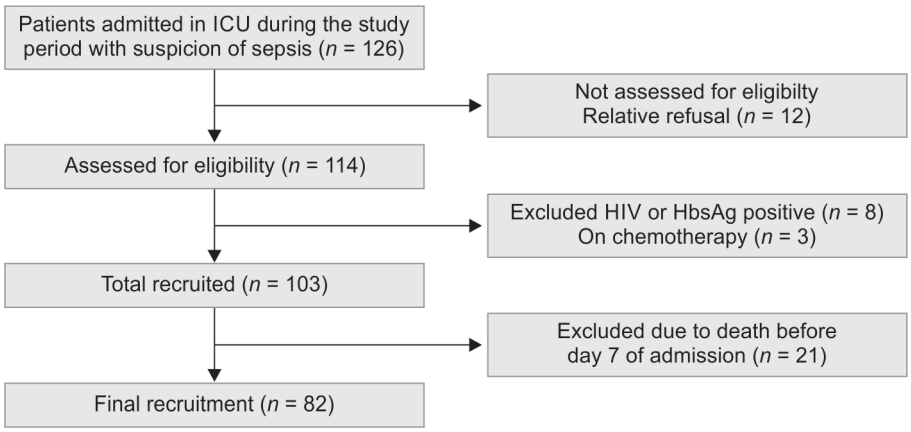
In this study, a total of 114 patients admitted with the suspicion of sepsis during the study period were assessed for eligibility. Thirty-two patients were excluded since they did not match the criterion for inclusion. Finally, 82 patients were recruited for the study (Flowchart 1).

The age of the patients recruited in the study was 53.43 ± 1.76 (mean ± SE) years. Of the 82 patients, 51 (62.20%) were males, and 31 (37.80%) were females. Fifty-two (63.41%) patients were found positive for a culture test. In this study, 47 patients died within 28 days of the onset of symptoms representing a 28-day mortality of 57.32%, while 35 were discharged.

The mean value of PCT in patients who were culture negative was 5.04 ± 2.15 ng/mL on D1 and on D7 was 5.95 ± 2.97 ng/mL. The mean value of PCT in patients who were culture positive was 10.34 ± 2.94 ng/mL on D1 and 20.66 ± 3.84 ng/mL on D7. The mean value of PCT in patients who died after 7 days during their ICU stay or during 28 days of follow-up was 4.77 ± 1.16 ng/mL on D1, and D7 was 25.44 ± 4.20 ng/mL. The mean value of PCT in patients discharged from ICU and alive during 28 days of follow-up was 13.13 ± 4.35 ng/mL on D1 and 1.21 ± 0.22 ng/mL on D7.

The mean value of presepsin in patients who were culture negative was 62.70 ± 8.76 ng/L on D1, and D7 was 58.08 ± 7.67 ng/L. The mean value of presepsin in patients who were culture positive was 66.21 ± 5.30 ng/L on D1 and 83.89 ± 7.56 ng/L on D7. The mean value of presepsin in patients who died after 7 days during their

Flowchart 1: Flow diagram



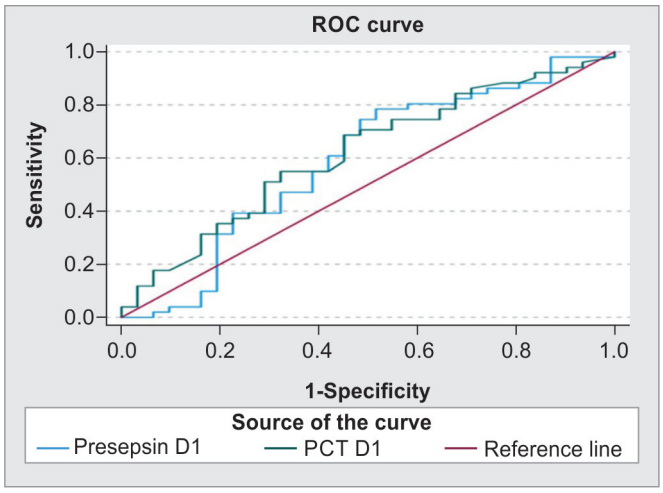


Fig. 1: The ROC curve of presepsin and PCT values on D1 against culture positivity for diagnosis of sepsis

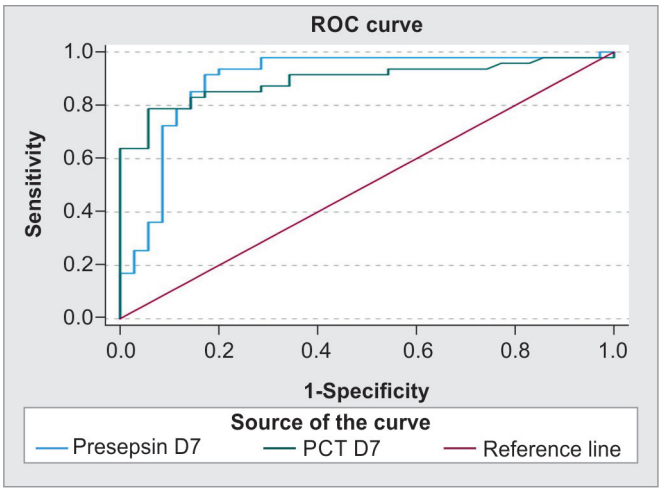


Fig. 3: The ROC curve of presepsin and PCT values on D7 against outcome to prognosticate 28-day mortality

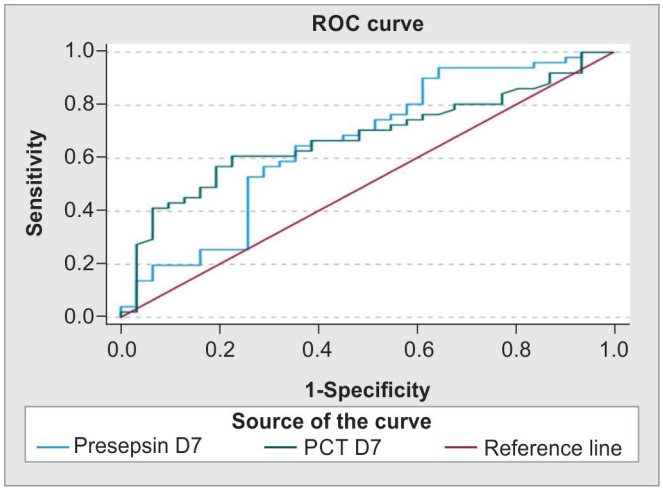


Fig. 2: The ROC curve of presepsin and PCT values on D7 against culture positivity for diagnosis of sepsis

ICU stay or during 28 days of follow-up was 64.85 ± 5.59 ng/L on D1, and D7 was 99.48 ± 7.38 ng/L. The mean value of presepsin in patients discharged from ICU and alive during 28 days of follow-up was 64.93 ± 7.97 ng/L on D1 and 40.10 ± 4.57 ng/L on D7.

As indicated by the coordinates of the ROC (Fig. 1), the presepsin value on day 1 with the best sensitivity and specificity in diagnosing sepsis was 36.9 ng/L, while the cutoff value of PCT to diagnose sepsis was 1.68 ng/mL. The sensitivity at this value was 78% for presepsin compared to PCT, which was 69%. The specificity of presepsin was 53%, while PCT was 56% in diagnosing sepsis. The AUROC for presepsin day 1 was 0.616 ($p = 0.06$) and that for PCT was 0.590 ($p = 0.19$). This suggests that day 1 values of presepsin were better able to discriminate between sepsis and non-sepsis patients than PCT day 1 reading. The combined sensitivity when the two biomarkers were used in parallel was 93%.

The sensitivity in diagnosing sepsis on day 7 was 80% for presepsin compared to PCT which was 66% (Fig. 2). At this time, specificity was 39% for presepsin and 59% for PCT. At this time, the area under the curve (AUROC) was 0.677 ($p < 0.05$) for presepsin and 0.657 ($p < 0.05$) for PCT and was a satisfactory indicator.

The presepsin value on day 7, enabling the best mortality prediction, was 50.35 ng/L, while the PCT value on day 7, allowing the best prognostication of 28-day mortality, was 3.2 ng/mL (Fig. 3). The AUROC was 0.896 ($p < 0.05$) for presepsin and 0.894 ($p < 0.05$)

Table 1: Paired *t*-test depicting trend of PCT and presepsin from D1 to D7 in culture-negative and positive groups

					95% Confidence interval		
Cultures			*Mean*	*Standard error*	*Lower*	*Upper*	*p-value*
Negative	Pair 1	PCT D1–PCT D7	0.902	3.607	8.270	6.465	0.804
	Pair 2	Presepsin D1–Presepsin D7	4.629	7.008	9.684	18.943	0.514
Positive	Pair 1	PCT D1–PCT D7	10.315	4.832	20.022	0.608	0.038
	Pair 2	Presepsin D1–Presepsin D7	17.685	7.746	33.244	2.127	0.027

PCT, procalcitonin

Table 2: Paired *t*-test depicting trend of PCT and presepsin from D1 to D7 in death and discharge groups

					95% Confidence interval		
Outcome			*Mean*	*Standard error*	*Lower*	*Upper*	*p-value*
Death	Pair 1	PCT D1–PCT D7	20.666	3.655	28.025	−13.308	<0.001
	Pair 2	Presepsin D1–Presepsin D7	34.628	6.657	48.029	−21.228	<0.001
Discharge	Pair 1	PCT D1–PCT D7	11.922	4.412	2.955	20.888	0.011
	Pair 2	Presepsin D1–Presepsin D7	24.830	5.908	12.822	36.838	<0.001

PCT, procalcitonin

for PCT, which denoted excellent discrimination between patients likely to die from those likely to survive. Thus, the sensitivity of presepsin for prognostication of 28-day mortality was 91%, and specificity was 82% at this cutoff. The sensitivity of PCT at this cutoff for prognostication of 28-day mortality was 78%, and the specificity was 94%.

The paired sample *t*-test results showed that in the culture-negative group, there is no significant change in PCT and presepsin levels from D1 to D7. In the culture-positive group, there is a significant change in PCT levels from D1 to D7 ($p = 0.038$). There is also a significant change in presepsin levels from D1 to D7 ($p = 0.027$) (Table 1).

Similar to this, when PCT trends were seen from D1 to D7 in the mortality group, there was a significant change in levels of PCT ($p < 0.001$). Even with presepsin, a significant change in level was seen from D1 to D7 ($p < 0.001$). In the survivor group, significant changes in PCT levels were seen from D1 to D7 ($p = 0.01$), while values of presepsin also showed a significant change from D1 to D7 ($p < 0.001$) (Table 2).

Discussion

Sepsis has long been considered a terrible disease with possibly fatal implications.[1] As a result, it is critical to diagnose sepsis as soon as possible, so that effective treatment may be started. This study compared the diagnostic and short-term prognostic utility of presepsin against PCT in sepsis patients in the first week of intensive care therapy on days 1 and 7.

Due to the relative novelty of presepsin as an inflammatory marker and the paucity of research in the Indian population, we initially sought to establish a diagnostic cutoff value for presepsin in the Indian population. It was established that 36.9 ng/L of presepsin provides the highest sensitivity and specificity for the diagnosis of sepsis. At this cutoff threshold, the sensitivity of presepsin for the diagnosis of sepsis was 78%. A similar analysis for PCT was done, which defined a cutoff value of 1.68 ng/mL as optimum. The sensitivity of PCT at this value was marginally less than presepsin at 69%. The specificities of both presepsin and PCT were moderate, at 53% for presepsin and 56% for PCT.

Yamamoto et al.[11] performed a prospective investigation of presepsin to diagnose sepsis in which 91 patients participated. They found that presepsin has 87% sensitivity and 86% specificity for diagnosing sepsis with a threshold of 508 pg/mL. Procalcitonin sensitivity was determined to be 68% and specificity to be 86% using a 1.5 ng/mL threshold. Our study similarly showed a higher sensitivity for presepsin as compared to PCT.

The varying cutoff values reported by different research studies are evident. This could be attributed to the difference in study design (retrospective versus prospective), sepsis severity, comorbidities, ELISA kit specifications, population demographics (Indian population vs Western population), and clinic settings (emergency department vs ICU). Presepsin is a sensitive biomarker for sepsis diagnosis, and it can be used to screen for sepsis in the emergency room or ICU. In our study, when PCT is administered as a supplement to presepsin, the combined sensitivity is high (93%).

Our study showed an optimal cutoff value of presepsin for prognostication of 28-day mortality to be 50.35 ng/L. At this cutoff, presepsin had a high sensitivity of 91% and a high specificity of 82%. The PCT value allowing the best prognostication was 3.2 ng/L. The sensitivity of PCT at this cutoff for prognostication of 28-day mortality is 78%, and the specificity is 94%.

Park et al.[12] recommended a cutoff value of 755 pg/mL for presepsin for predicting 28-day mortality. This threshold's sensitivity was 77.5%, and its specificity was 62%. According to Ulla et al.,[13] patients with elevated presepsin levels of 1000 pg/mL had a higher probability of dying within 60 days. In a retrospective analysis of patients with sepsis, Masson et al.[14] demonstrated persistently elevated presepsin levels in deceased patients and demonstrated its significant prognostic value for both 28-day and 90-day all-cause mortality, whereas PCT did not show prognostic information. Therefore, compared to PCT, presepsin has consistently performed well predicting 28-day mortality, as evidenced by multiple studies.

This is comparable to our study, where we also established a cutoff value for the Indian population for a 28-day mortality prognosis.

Most studies have concentrated on single presepsin measurement in patients arriving at the emergency department or ICU to establish presepsin as an early single-shot biomarker for emergency medical care. Our study measured presepsin and PCT at two time points—days 1 and 7. We found a significant rise from days 1–7 in the value of presepsin in the decedents ($p < 0.001$). On the other hand, in the survivors, presepsin showed a significant decline from day 1 to day 7 ($p < 0.001$). This demonstrates that trends in presepsin levels may be used to evaluate the success of therapy, whether causative, therapeutic, or both.

Even though cultures are the gold standard for diagnosing an infection, they are not always reliable. Antibiotics, occult infections, and the etiology of sepsis may negatively impact culture findings. They are also time consuming. In this situation, having quick and reliable assays in our arsenal to diagnose sepsis is critical. Our study establishes presepsin as a robust predictive biomarker in patients with sepsis, especially when coupled with PCT. Presepsin is also an excellent marker for predicting 28-day mortality compared to PCT, especially at an early stage. Using presepsin in combination with PCT, it will be possible to diagnose sepsis early and to forecast the risk of 28-day mortality. This way, it may be possible to improve mortality rates or halt the progression to organ failure by identifying patients with a risk of potentially adverse outcomes and enabling early and aggressive treatment. This is one of the first studies of presepsin in an adult Indian population in India. We have attempted to define a presepsin cutoff value in the Indian population with this study.

This study has certain limitations. First, a relatively small number of patients were included. More research in larger populations is needed to identify better cutoff values for the diagnosis of sepsis and prediction of 28-day mortality in the Indian population. Second, this was a single-center study. A multicenter study to evaluate the perfect cutoff point of such biomarkers in the Indian population is recommended. PCT was measured by point-of-care testing, while presepsin was measured by ELISA, which may contribute to some errors in the result. Though the serial rise in presepsin was measured by taking samples on day 1 and day 7, further multiple measurements at shorter intervals may yield more information, especially regarding 28-day mortality.

Conclusion

Presepsin can reliably predict sepsis in adult Indian patients presenting to the ICU owing to its predictive sensitivity at the thresholds. However, we propose that the combination of presepsin and PCT has a high combined sensitivity and may be used to screen for patients with sepsis. Presepsin is an independent risk factor for 28-day mortality in patients with sepsis. Initiating aggressive therapy early in those who are at high mortality risk, as indicated by presepsin, can improve outcomes.

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