ORIGINAL ARTICLE

Evaluation of Presepsin as an Early Biomarker of Sepsis in Elderly Patients with Community-acquired Pneumonia

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Abstract

Pneumonia is the most prevalent cause of sepsis. Early detection of sepsis is essential. Presepsin is an emerging biomarker. To analyze the diagnostic efficacy of presepsin for identifying sepsis and evaluate its predictive accuracy, a study was conducted for 18 months involving 100 elderly (≥60 years) patients diagnosed with community-acquired pneumonia (CAP) and fulfilling the Systemic Inflammatory Response Syndrome (SIRS) criteria. Clinical details were recorded, and the quick Sequential Organ Failure Assessment (qSOFA) score was calculated. Presepsin values were determined and correlated with culture findings. All patients were divided into two groups: the diagnostic group (based on culture findings) and the prognostic group (based on clinical outcome). Subgroups of the diagnostic group were culture-proven and culture-sterile, and those of the prognostic group were survivors and nonsurvivors. Presepsin values were higher in culture-proven patients and nonsurvivors. Presepsin and qSOFA scores correlated positively. Presepsin can be used to predict mortality from sepsis in addition to being a superior biomarker for predicting bacteremia.

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Introduction

Pneumonia is defined as an acute infection of the respiratory system parenchyma. The types of pneumonia identified by the clinical settings in which the infection was contracted include community-acquired pneumonia (CAP), ventilator-associated pneumonia, healthcare-associated pneumonia, and hospital-acquired pneumonia.[1]

Community-acquired pneumonia is a pulmonary parenchymal infection in otherwise healthy individuals that is acquired from a normal environment.[2] The most frequent antecedent infection, pneumonia, is responsible for almost half of sepsis cases.[3] Globally, CAP incidence ranges from 5 to 11/1,000 population, with higher rates noted in the elderly.[4] The most common etiologic agents causing CAP are bacterial; however, viral and fungal agents have also been reported.[5]

Sepsis is a potentially fatal condition marked by organ dysfunction, most often affecting the cardiovascular, renal, respiratory, or hematological systems, as a consequence of an uncontrolled host response to infection. A significantly elevated risk of death might result from the underlying circulatory and metabolic abnormalities in septic shock, a subtype of sepsis.[6] Elderly patients are especially vulnerable to sepsis because their immunity is weakened due to certain underlying conditions, such as diabetes or any malignancy.[7]

To assist with the early detection and risk assessment of individuals suffering from sepsis and septic shock, a variety of criteria and scoring systems have been proposed. One very simple method for quickly assessing those who may be prone to sepsis is the quick Sequential Organ Failure Assessment (qSOFA) scoring system. It was designed for use in the emergency room as an immediate diagnostic tool at the bedside.[8,9]

The assessment of several sepsis-related biomarkers that could be employed in infection diagnosis and early detection has recently drawn interest. Procalcitonin, C-reactive protein, cytokines (IL-6), presepsin, among others, are examples of these biomarkers. With these, sepsis could be suspected even when there is not an obvious source of infection, particularly in older adults who frequently exhibit nonspecific symptoms.[8]

Presepsin is a soluble component of cluster of differentiation 14 (CD14) that stimulates toll-like receptor 4, initiating a proinflammatory signaling cascade that induces an inflammatory response against microbes. CD14 appears in two forms: membrane-bound (mCD14) and soluble form (sCD14). It is located in plasma and is cleaved by cathepsin D to produce a 13 kDa fragment, which is referred to as presepsin. Plasma levels of presepsin increase after bacterial infections and decrease following antibiotic treatment.[10]

Blood culture serves as the gold-standard diagnostic method to identify any bacterial bloodstream infection. Once the organism is identified, the antibiotic susceptibility profile can help in making therapeutic decisions.[11] Sputum culture aids in the microbiological diagnosis of CAP in cases where expectorated sputum is a readily available specimen.[12] However, the turnaround time is relatively longer compared to that of other methods, and many times the condition of the patient warrants immediate intervention.[11]

Biomarkers are one of the most important aspects of antibiotic stewardship programs. The assessment of presepsin's function as a biomarker in the early diagnosis of sepsis is underrepresented in the Indian scientific literature. Hence, this study aims to evaluate the role of presepsin as an early biomarker of sepsis and its correlation with blood and sputum culture in cases of CAP.

Methodology

Study Design and Population

At a tertiary care hospital in Chandigarh, 100 consecutive patients with a clinical diagnosis of CAP took part in an 18-month cross-sectional observational study. Every participant in this study provided written informed consent. The study was ethically approved by the Institutional Ethics Core Committee at GMCH, Chandigarh, per letter no. GMCH/IEC/2020/497R/160 dated 8th April 2021. It was carried out in compliance with the Declaration of Helsinki and the guidelines established by the Central Ethics

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Committee on Human Research (CECHR) of the Indian Council of Medical Research (ICMR), New Delhi.

The study included elderly patients (aged ≥60 years) diagnosed with CAP and fulfilling the criteria for Systemic Inflammatory Response Syndrome (SIRS),[13] that is, the presence of two or more of the following: respiratory rate (RR) >20/minute or $PaCO_2$ <32 mm Hg, heart rate >90/minute, total leukocyte count >12 × 10^9/L or <4 × 10^9/L, or the presence of >10% immature neutrophils, and temperature >38.0°C or <36.0°C. Patients with known malignancies, such as leukemia, who were undergoing radiation or chemotherapy were excluded from the study.

A comprehensive clinical examination was completed upon admission, which included recording vital parameters, namely respiratory rate, oxygen saturation, body temperature, blood pressure (BP), heart rate, etc. The three criteria that determined the qSOFA score were altered mental state (Glasgow Coma Scale <15), systolic BP ≤100 mmHg, and RR of >22 breaths per minute. One point was given for each of the three parameters, and a score of ≥ 2 was considered highly suggestive of sepsis.[8,9]

Two milliliters of blood was obtained for complete blood counts (CBC), peripheral blood film analysis, and erythrocyte sedimentation rate (ESR) estimation. Additionally, 2 mL of blood was obtained for measuring presepsin levels in serum; 10 mL of blood was obtained in two bottles (5 mL each) for culture; and a sterile container containing a sputum sample was obtained for microbiological analysis and culture before initiating any antibiotic treatment. CBC was performed using 2 mL of ethylenediaminetetraacetic acid (EDTA) blood sample and run on the Sysmex XN-1000 automated cell counter.[14] ESR was calculated using a 2 mL EDTA blood sample *via* an automated method on the VES-MATIC Cube 80.[15] The Human Presepsin Enzyme-Linked Immunosorbent Assay (ELISA) Kit (Cat. No. E3745Hu) from Bioassay Technology Laboratory, Shanghai, China, was used to determine presepsin levels in serum samples.[16]

Outcomes

Clinical outcomes and sputum/blood culture findings were used to further subdivide these patients. Patients were tracked from the time they were admitted until discharge or death. Identifying the diagnostic accuracy of presepsin blood levels in predicting sepsis was the primary outcome. Evaluation of presepsin's predictive accuracy for mortality was a secondary outcome.

Statistical Analysis

Mean and standard deviation were used to describe presepsin. Diagnostic accuracy was evaluated using the area under the receiver operating characteristic curve (AUROC), which comprised the test's sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Presepsin was compared between bacteremia and nonbacteremia causes of CAP. Patients were tested for significance of difference using Student's *t*-test. The association between presepsin and outcomes was tested using the Chi-square test of significance. Correlation between presepsin and qSOFA score was assessed using Spearman correlation. The most recent release of Statistical Package for the Social Sciences (SPSS) was used to analyze the data.

Results

Clinical Profile

The study participants' average age was 70.69 years. Sixty-five percent of patients were male, while 35% were female. Comorbidities and risk factors were present in 84% of the patients; diabetes mellitus accounted for 41% of these, followed by hypertension (36%), smoking (34%), and other conditions. The majority of patients had a chief complaint of fever (99%), followed by shortness of breath (97%), cough with or without expectoration (61%), and altered sensorium (23%). A qSOFA score of 3 was observed in 52% of patients, and a qSOFA score of 2 was observed in 48% of patients.

Blood and/or Sputum Culture Findings

Blood and/or sputum cultures were positive in 41% of patients and sterile in 59% of patients. The most frequently isolated pathogens included *Klebsiella pneumoniae* and *Escherichia coli*. As illustrated in Figure 1, other isolated organisms were *Staphylococcus aureus*, methicillin-resistant *Staphylococcus aureus* (MRSA), *Acinetobacter*, and *Pseudomonas aeruginosa*.

The whole study population was split into two groups: First, based on blood/sputum culture findings, that is, the diagnostic group; and second, based on clinical outcome, that is, the prognostic group. Under the diagnostic group, two subgroups were formed, namely, culture-proven and culture-sterile, which included 41 and 59% of patients, respectively. Under the prognostic group, two subgroups were formed, that is, survivors and nonsurvivors, which included 75 and 25% of patients, respectively. Regarding clinical profile and culture results, there were statistically insignificant differences between the subgroups of both the diagnostic and prognostic groups.

Presepsin

The normal range of the Human Presepsin ELISA Kit derived in our study was 17.58–93.94 ng/L [mean ± 2 standard deviations (SD)]. Among all 100 patients, the values (in ng/L) ranged from 112.82 to 595.51, with a mean (SD) of 207.71 (102.01).

The two subgroups of the diagnostic group ($p < 0.001$) and prognostic group ($p = 0.017$) differed significantly in terms of presepsin, with the culture-proven and nonsurvivor subgroups having the highest mean presepsin values, respectively (Table 1).

Prediction Analysis

With an area under the receiver operating characteristic curve (AUROC) of 0.995, presepsin (ng/L) had a very high ability to predict culture positivity [95% confidence interval (CI): 0.989–1]. At $p < 0.001$, it was statistically significant. It predicted positive culture with 100% sensitivity, 100% negative predictive value (NPV), 96% diagnostic accuracy, 93% specificity, and 91.1% positive predictive value (PPV) at a cutoff of presepsin ≥176.71 ng/L (Fig. 2).

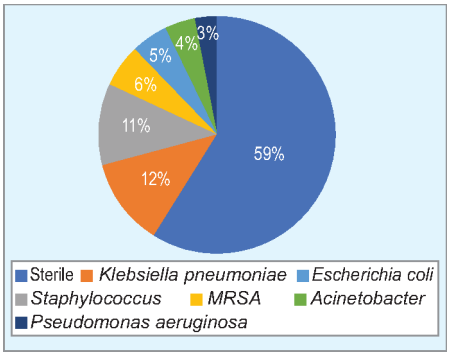

Fig. 1: Pie chart showing findings on blood and/or sputum culture of all patients

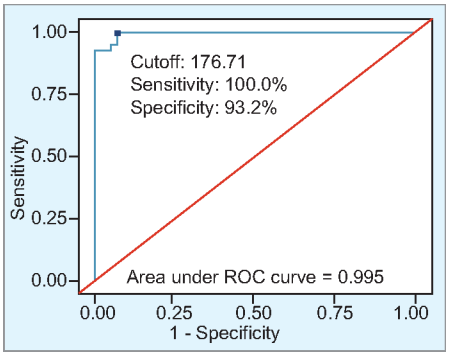

Fig. 2: ROC curve analysis showing diagnostic performance of Presepsin (ng/L) in predicting culture positivity

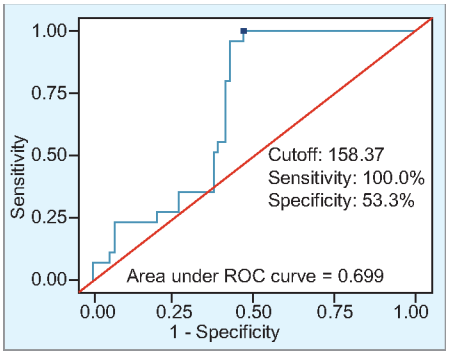

Fig. 3: ROC curve analysis showing diagnostic performance of Presepsin (ng/L) in predicting mortality

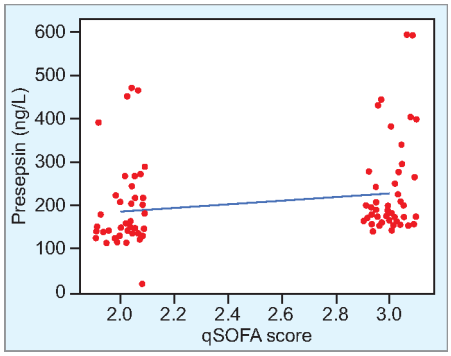

Fig. 4: Correlation between qSOFA Score and Presepsin (ng/L)

Table 1: Comparison of subgroups of Diagnostic and Prognostic groups in terms of Presepsin and their *p*-value

Group	*Subgroup*	*Mean (SD) of presepsin*	*p- value*
Diagnostic	Culture proven	291.67 (113.94)	<0.001
	Culture sterile	149.36 (19.03)	
Prognostic	Survivors	193.77 (85.57)	0.017
	Non-survivors	249.52 (133.85)	

The AUROC for presepsin (ng/L) predicting mortality was 0.699 (95% CI: 0.596–0.802), thus demonstrating poor diagnostic performance. It was statistically significant ($p = 0.017$). It predicted mortality with 100% sensitivity, 100% NPV, 65% diagnostic accuracy, 53% specificity, and 41.7% PPV at a cutoff of presepsin ≥ 158.37 ng/L (Fig. 3).

Correlation of Presepsin with Quick Sequential Organ Failure Assessment Score Using the Correlation Coefficient (*r*)

A moderate positive correlation between qSOFA score and presepsin (ng/L) was detected, which was statistically significant (rho = 0.37, $p < 0.001$), as shown in Figure 4.

Discussion

Sepsis is a potentially fatal condition that presents itself in a variety of clinical manifestations, making it difficult to detect and treat. The primary cause of sepsis is CAP, which results in significant mortality and morbidity.[7] Higher risk is noted in the elderly population because of the presence of comorbidities and atypical presentation.[17]

To optimize therapy and avoid subsequent consequences, early detection of sepsis is crucial. Scoring criteria, such as the qSOFA score, hematological measures, and different biomarkers, have been proposed as a result of the quest for early identification and treatment of sepsis, and these tools all contribute to more efficient management. Presepsin is an emerging biomarker of sepsis, and its importance in the early detection of sepsis cannot be underestimated.[18]

The recently identified sepsis biomarker presepsin is derived from the glycoprotein CD14, which exists on the surface of macrophages and monocytes.

In its primary role, it acts as a high-affinity receptor for lipopolysaccharides (LPS), which are essentially released from the outer wall of gram-negative bacteria. There are two types of CD14: soluble CD14 (sCD14) and membrane-bound CD14 (mCD14). In healthy individuals, sCD14 levels in the blood are usually rather low. It is the LPS-CD14 complex that is released into the bloodstream when mCD14 separates from the cell membrane to generate sCD14, which aids in immune regulation. Proteases cleave sCD14 under inflammatory circumstances to produce presepsin, or soluble CD14 subtype (sCD14-ST), a 64-amino-acid N-terminal fragment. Presepsin's physiological function mostly involves the phagocytosis of bacteria and the lysosomal cleavage of different microorganisms. Presepsin levels in the blood rise in response to a microbial infection. Within 2 hours of infection, levels begin to climb and peak within 3 hours.[18,19]

In our study, the mean presepsin level at admission among all CAP patients was found to be 207.71 ng/L. Presepsin levels were significantly higher in the culture-proven subgroup ($p < 0.001$) than in the culture-sterile subgroup. Our study suggested that, at admission, presepsin ≥176.71 ng/L significantly predicts culture positivity, that is, bacteremia. Higher presepsin levels were substantially related to bacteremia, which is in accordance with research by Romualdo et al. and Imai et al.[20,21] Those who did not survive also had higher presepsin levels ($p = 0.017$) than those who survived. Our study suggested that, at admission, presepsin ≥158.37 ng/L significantly predicts mortality. This is consistent with research conducted by Liu et al.; higher levels of presepsin significantly predicted mortality.[22]

The association between qSOFA score and presepsin was moderately positive and statistically significant (rho = 0.37, $p < 0.001$). This is consistent with research conducted by Ozkan et al.[23] This correlation signifies that higher levels of presepsin and a higher qSOFA score are indicators of mortality risk.

Conclusion

This research concludes that presepsin is an important tool for detecting sepsis in elderly CAP patients. Greater presepsin concentrations at admission can accurately predict bacteremia and mortality risk, thereby assisting in risk stratification and prompt care. The current study's limited sample size constituted a major limitation. Thus, further investigation is required to evaluate the function of presepsin.

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