Original Article

Comparison between presepsin, procalcitonin, and CRP as biomarkers to diagnose sepsis in critically ill patients

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Abstract

Background and Aims: Mortality associated with sepsis continues to remain high. Early diagnosis and aggressive management may improve outcomes. Biomarkers may help in early diagnosis, but the search for an ideal biomarker continues. Presepsin has been introduced as a new biomarker, however, it still needs validation before its use becomes routine. In this study, we aimed to compare the efficacy of various biomarkers in patients with suspected sepsis.

Material and Methods: A retrospective analysis of 100 patients with suspected infection, admitted in the medical intensive care unit (ICU) was conducted. Diagnosis of sepsis was made on the basis of the current surviving sepsis guidelines criteria.

Results: Out of 100 patients, 70 were diagnosed to have sepsis, and overall ICU mortality was 22%. Overall, C-reactive protein (CRP) was positive in 98, procalcitonin in 75, and presepsin in 64 patients. For diagnosis of sepsis the sensitivity, specificity, and AUC, respectively, for CRP was 98.6%, 3.3%, and 0.725. For procalcitonin (>0.5 ng/ml) it was 87.1%, 53.3%, and 0.776, and for procalcitonin (>1 ng/ml) 70%, 70%, and 0.816, respectively. For presepsin sensitivity, specificity, and AUC, respectively, for diagnosis of sepsis was 77.1%, 66.7%, and 0.734. For ICU mortality, sensitivity and specificity for CRP was 95.5% and 1.3%, for procalcitonin (>0.5) 72.7% and 24.4.%, for procalcitonin (>1) 59.1% and 42.3%, and for presepsin 61.5% and 27.3%, respectively.

Conclusion: Inflammatory markers may be raised in a large proportion of ICU patients, even in those without sepsis. Procalcitnonin and presepsin had similar efficacy in diagnosing sepsis. However, none of the three biomarkers studied were accurate in predicting ICU mortality.

Keywords: Biomarkers, CRP, presepsin, procalcitonin, sepsis

Introduction

Sepsis remains a major global health problem, especially in intensive care units (ICUs). Up to 30% of patients are admitted with sepsis or develop sepsis during their ICU stay.[1] Mortality associated with sepsis also continues to remain high, up to 35%, despite better understanding, awareness, and medical advancements.[1] Early diagnosis and aggressive management can improve outcomes in these patients. Hence, a number of biomarkers, such as procalcitonin, C-reactive protein (CRP), lipopolysaccharide-binding protein (LBP), interleukins, pro-vasopressin, and myeloid cells expressing triggering receptor-1 (TREM-1), have been developed, but they have limited utility in the early diagnosis of sepsis.[2-6] All the biomarkers have their own advantages and disadvantages, and hence, the search for an "ideal biomarker" continues, and more comparative studies are required before we label one biomarker as superior to others. CRP and procalcitonin are currently the most widely used and studied biomarkers, but each of these have their own shortcomings restricting their widespread use.[7,8]

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A glycoprotein called CD14 is expressed on monocytes and macrophages. It acts as a receptor for binding lipopolysaccharides (LPS) of bacteria and helps in activating the inflammatory cascade. It exists in two forms, membrane-bound (mCD14) and a soluble form (sCD14). Presepsin is a subtype of soluble CD14 (sCD14-ST), which increases significantly after an infective insult and can be measured readily with chemiluminescent enzyme immunoassay. Early studies have shown that presepsin levels are significantly higher in septic patients and it can be used as a marker to differentiate between bacterial infections and non-infectious SIRS.[9,10]

However, there is limited data regarding the efficacy of presepsin in critically ill patients and its comparison to other more commonly used biomarkers like CRP and procalcitonin. Hence, we conducted this retrospective analysis in patients with suspected sepsis and aimed to assess the efficacy of presepsin in diagnosing sepsis and compare it with that of CRP and procalcitonin.

Material and Methods

The study was approved by the Institutional Ethics Committee of Max Super Speciality Hospital, Saket, New Delhi (Approval No: TS/MSSH/SKT-2/CC/IEC/18-44). This study was a retrospective cohort study in which data were collected from 100 patients with suspected infection, admitted in medical ICUs of a tertiary care hospital from February 2018 to October 2018. All patients with suspected infection, whose serum biomarkers CRP, procalcitonin and presepsin, were sent within the first 24 hours of presentation, were included for the analysis. Patients younger than 18 years and those with incomplete data were excluded from the analysis.

Data were collected regarding the age, gender, reason for ICU admission, presence of sepsis, initial blood cultures, levels of CRP, procalcitonin, presepsin, and need for organ support in the form of invasive mechanical ventilation (IMV), vasopressors/inotropes, or renal replacement therapy (RRT). Basic laboratory variables, at the time of ICU admission, required to calculate the severity of illness scores, Acute Physiology and Chronic health Evaluation score II (APACHE II) and Sequential Organ Failure Assessment (SOFA) score were also collected in the prescribed proforma.

Diagnosis and management of sepsis and septic shock was performed as per the international guidelines and the patients were divided into two groups, sepsis and non-sepsis.[11,12] Primary objective of the study was to compare the efficacy of the various biomarkers in respect to the diagnosis of sepsis. The secondary objectives were to evaluate the ICU mortality and compare the efficacy of these biomarkers in predicting mortality.

Statistical methods

SPSS version 16.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for data management and statistical analysis. Data were presented as discrete variables. Area under receiver-operating characteristic (AUROC) curve analysis was used to evaluate the efficacy of CRP, procalcitonin and presepsin to diagnose sepsis. Analyses were performed by the Chi-square test, Fisher's exact test, or independent sample *t*-test, as appropriate. All tests were two-tailed, with P value less than 0.05 defined as being significant.

Results

Data from 100 patients were collected as per the inclusion criteria. Seventy patients were diagnosed to have sepsis, out of these 31 patients were diagnosed to have septic shock as per the surviving sepsis criteria.[11,12] Overall ICU mortality was 22%, 17 out of 70 patients with sepsis died (24.3%). Patients with septic shock had a higher mortality rate of 25.8% (8/31). Among the non-septic patients, the mortality rate was 16.7% (5/30). Comparison of baseline patient characteristics, their biomarkers and ICU course is presented in Table 1.

Initial CRP levels were high (>5 mg/l) in almost all the critically ill patients (98%), whereas procalcitonin was more than 0.5 ng/ml in 75% and more than 1 ng/ml in 58% of the patients. Presepsin levels were more than 729 pg/ml in 64% of the patients [Table 2]. The sensitivity and specificity for the various biomarkers in diagnosing sepsis and predicting ICU mortality is presented in Table 3. All the scores tested fared poorly in predicting ICU mortality.

The AUROC was calculated for all the biomarkers to assess their efficacy in diagnosing sepsis [Figure 1]. For serum lactate AUROC was 0.71, 95% confidence interval (CI) 0.607-0.817, for CRP it was 0.725 (95% CI: 0.614-0.835), for procalcitonin it was 0.776 (95% CI: 0.677-0.875) and for presepsin it was 0.734 (95% CI: 0.624-0.844). Even though the AUROC was best for procalcitonin, followed by presepsin and then CRP, the difference was not statistically significant ($P = 0.141$).

Discussion

In this retrospective analysis, data were analyzed from 100 patients with suspected sepsis. Overall mortality was 22%, but in patients with sepsis it was 24.3%. Presepsin, the newer biomarker, did not perform better than the other

Table 1: Comparison between of patient parameters between survivors and non-survivors

Parameter	Total cases (*n*=100)	Survivors (*n*=78)	Non-survivors (*n*=22)	*P*
Age	62.8±15	62.9±15.2	62.5±15	0.731
Sex (males)	63 (63%)	50 (64.1%)	13 (59.1%)	0.706
Diabetics	41 (41%)	33 (42.3%)	8 (36.4%)	0.807
Hypertensives	49 (49%)	38 (48.7%)	11 (50%)	1.000
CRP (>5 mg/l)	98 (98%)	77 (98.7%)	21 (95.5%)	0.393
Procalcitonin (>0.5 ng/ml)	75 (75%)	59 (75.6%)	16 (72.7%)	0.785
Procalcitonin (>1 ng/ml)	58 (58%)	45 (57.7%)	13 (59.1%)	1.000
Presepsin (>729 pg/mL)	64 (64%)	48 (61.5%)	16 (72.7%)	0.452
Positive blood cultures	9 (9%)	7 (9%)	2 (9.1%)	1.000
Sepsis	70 (70%)	53 (71.8%)	17 (77.3%)	0.445
Septic shock	31 (31%)	23 (29.5%)	8 (36.4%)	0.605
APACHE II score	16.8±7.3	16.7±7.4	17.2±7.1	0.799
APACHE II PDR	25.6±18.4	25.2±18.6	26.9±18.3	0.699
SOFA score	6.5±3.5	6.2±3.3	6.7±3.7	0.281
Need for IMV	41 (41%)	31 (39.7%)	10 (45.5%)	0.633
Need for RRT	29 (29%)	24 (30.8%)	5 (22.7%)	0.598
Need for ionotropic support	41 (41%)	33 (42.3%)	8 (36.4%)	0.807

CRP – C-reactive protein, APACHE – acute physiology and chronic health evaluation, PDR – predicted death rate, SOFA – sequential organ failure assessment, IMV – invasive mechanical ventilation, RRT – renal replacement therapy

Table 2: Comparison between different biomarkers for diagnosis of sepsis

Biomarker	Total positivity (*n*=100)	Sepsis (*n*=70)	Non septic patients (*n*=30)	*P*
CRP (>5 mg/l)	98 (98%)	69 (98.6%)	29 (96.7%)	0.512
Procalcitonin (>0.5 ng/ml)	75 (75%)	61 (87.1%)	14 (46.7%)	0.000*
Procalcitonin (>1 ng/ml)	58 (58%)	49 (70%)	9 (30%)	0.000*
Presepsin (>729 pg/mL)	64 (64%)	54 (77.1%)	10 (33.3%)	<0.001*

**Statistically significant. CRP – C-reactive protein*

Table 3: Sensitivity and specificity of different biomarkers in diagnosing sepsis and predicting ICU mortality

Outcome	CRP (>5 mg/l)		Procalcitonin (>0.5 ng/ml)		Procalcitonin (>1 ng/ml)		Presepsin (>729 pg/ml)	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
Sepsis	98.6%	3.3%	87.1%	53.3%	70%	70%	77.1%	66.7%
ICU mortality	95.5%	1.3%	72.7%	24.4%	59.1%	42.3%	61.5%	27.3%

CRP – C-reactive protein, ICU – intensive care unit

more common and widely available biomarkers like CRP and procalcitonin. For the diagnosis of sepsis the sensitivity, specificity, and AUC, respectively, for CRP was 98.6%, 3.3%, and 0.725. For procalcitonin (>0.5 ng/ml) it was 87.1%, 53.3%, and 0.776 and for procalcitonin (>1 ng/ml) 70%, 70%, and 0.816. For presepsin, sensitivity, specificity, and AUC, respectively, for diagnosis of sepsis was 77.1%, 66.7%, and 0.734. None of these three biomarkers had good efficacy in predicting ICU mortality.

Sepsis and septic shock are associated with high mortality. Early aggressive care may improve outcomes and hence early diagnosis is of utmost importance. Many biomarkers have been developed for this purpose, hence the biomarkers which increase early after the infective insult may be better suited for making an early diagnosis. CRP level increases in four to six hours after infective insult and peaks in 48–72 hours.[13] However, procalcitonin increases in 8 to 24 hours and peaks after 24 hours.[14] Hence, these biomarkers may lose advantage to presepsin which starts to increase within two hours and peaks in three hours.[14]

Biomarkers are commonly used for diagnosing, monitoring, and risk stratification in patients with sepsis and septic shock. CRP and procalcitonin have been studied extensively for their role in diagnosing sepsis, assessing response to therapy and predicting mortality. In head-to-head comparison, procalcitonin seems to fare better than CRP;[15] however, none of these biomarkers are "ideal" and have shown conflicting results in different studies. The sensitivity and specificity of CRP have ranged from 35-100%, and 18-84%, respectively, in the recently published reviews. Similarly, sensitivity and specificity of procalcitonin has ranged from 42-100%, and 48-100%, respectively. Even though CRP had good sensitivity of 98.6%, but because it was positive in almost all our patients, it reduced its specificity.

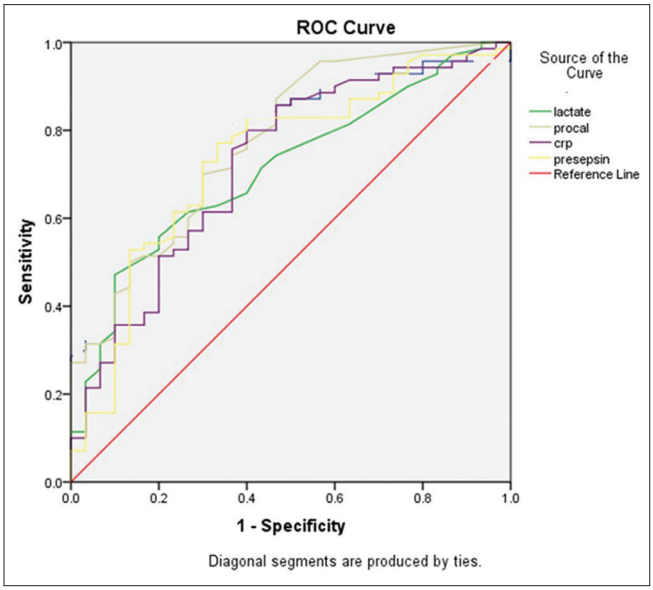

Figure 1: Area under the curve comparing various biomarkers for diagnosing sepsis

The sensitivity and specificity of procalcitonin depends on the chosen cut-off. Hence, in our study, by increasing the cut-off to 1 ng/ml, we could get a sensitivity and specificity of 70%, which falls in between the reported range.

Presepsin is a comparatively newer biomarker and is not as extensively studied. It has been used to diagnose sepsis and prognosticate outcomes of patients with sepsis. A recently published review including all the publications on presepsin from the last decade also reported that presepsin may be useful, if used along with other biomarkers for the diagnosis of sepsis. However, they also noted that most of the studies were limited by their small sample size, mostly less than 100 patients, and hence further studies are required before we start using it routinely for sepsis diagnosis.[16]

Earlier studies showed that presepsin has high sensitivity and good specificity for diagnosing sepsis and it may be a better marker than CRP and procalcitonin.[17] Sensitivity of 95% has been reported with a cut-off value of 729 pg/ml in a previous study performed in patients presenting to emergency department.[18] However, in our cohort of critically ill patients, with the same cut-off values, its sensitivity was 77.1%. Several studies have shown conflicting evidence and a large meta-analysis of 11 studies showed that presepsin may only be clinically useful if used as an adjunct with other biomarkers and when used alone it may not be able to reliably rule-in or rule-out sepsis.[19] The specificity of presepsin to diagnose sepsis was only 66.7% in our patient cohort, which is similar to that reported in other studies.[18]

In the present study, all the biomarkers were high in a majority of patients. This affected their specificity. Apart from sepsis, these biomarkers may be raised in a variety of other non-infective clinical conditions too. Apart from infectious causes, CRP levels have been shown to increase in many inflammatory diseases like rheumatoid arthritis and systemic lupus erythematosus, malignancy and even after severe drug reactions.[20] Mild elevations in CRP have also been reported in females, elderly or obese patients, diabetics, smokers, and in patients with insomnia or depression.[21] Similarly, serum procalcitonin levels have been shown to be raised after major surgery, major trauma, severe burns, and cardiogenic shock.[22] Presepsin levels are elevated in patients with acute heart failure, acute coronary syndrome, acute ST-elevation myocardial infarction, and post-chemotherapy neutropenia.[23-25] As it is primarily excreted through the kidneys, it may be falsely elevated in patients with acute or chronic renal disease too.[26] Many of these factors are commonly present in critically ill patients. Furthermore, some critically ill patients may have many of these factors making interpretation of the biomarker levels difficult. The specificity of these biomarkers may be increased by using a panel of biomarkers rather than relying on a single test.

There is a dearth of studies assessing the role of presepsin in critically ill patients. In another similar comparative study in critically ill patients, similar results were obtained for diagnosis of bacterial infections with AUROC being 0.764 (CRP), 0.824 (procalcitonin), and 0.681 (presepsin).[27] A recent meta-analysis in critically ill patients also reported similar efficacy of procalcitonin and presepsin. The pooled sensitivity and specificity of procalcitonin was 0.80 and 0.75, respectively, and that for presepsin was 0.84 and 0.73, respectively. The AUROC was also 0.84 and 0.87 for procalcitonin and presepsin, respectively. However, only nine studies had performed head-to-head comparison between procalcitonin and presepsin in critically ill patients.[28] Hence, availability, cost-effectiveness and a much larger experience of use may favor procalcitonin over presepsin.

In the present study, all the three biomarkers had poor efficacy in predicting ICU mortality. Similar results have been reported by other authors too, comparing biomarkers in critically ill patients.[28] Takahashi *et al.* reported that for predicting 28-day mortality, the AUROC values for day-1 biomarker levels was 0.502 (CRP), 0.557 (procalcitonin), and 0.642 (presepsin). These results are very similar to our results and they emphasize the fact that day-1 values of these biomarkers may not be reliable in predicting mortality of critically ill patients as many factors play a role in determining outcome in these patients.

Strengths and limitations

There are only a few studies with limited sample sizes which have compared presepsin with other biomarkers in critical care settings. This study adds to the emerging literature

which suggests that newer biomarkers may not always be more accurate. However, this was a single-center retrospective study and hence was prone to information bias. Because of a small cohort size, it was not possible to determine the factors associated with poor outcome.

Conclusions

Inflammatory markers may be raised in a large proportion of ICU patients, even in those without sepsis. Newer markers have been developed in order to enable early diagnosis of sepsis with increased efficacy. These biomarkers need to be validated in different patient populations before they are widely accepted and applied. In our patient cohort, procalcitonin and presepsin had similar efficacy in diagnosing sepsis. However, none of the three biomarkers studied were accurate in predicting ICU mortality.

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Conflicts of interest
There are no conflicts of interest.

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