

Presepsin as a predictor of sepsis outcome in comparison with procalcitonin and C-reactive protein

Amr M. Mahmoud^a, Hossam M. Sherif^b, Hamdy M. Saber^a, Khaled M. Taama^b

^aCritical Care Medicine Department, Beni Suef University, Beni Suef, ^bCritical Care Medicine Department, Cairo University, Giza, Egypt

Correspondence to Khaled M. Taama, MD, 7985 Almadeena Almonawara Street, Mokattam, Cairo 11571, Egypt. Tel: +20 100 041 2603; e-mail: khaled.taama@kasralainy.edu.eg

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Introduction

Identification of predicted sepsis-related mortality is important for patient stratification. We evaluated the significance of presepsin in predicting sepsis-related mortality.

Patients and Methods

We enrolled 83 patients with sepsis according to the SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference in a prospective observational study.

Results

After excluding 28 patients owing to different exclusion criteria, 55 continued the study. Their age was 58 (47–65) years old and comprised 33 (60%) males. We measured serum presepsin, procalcitonin (PCT), and C-reactive protein (CRP) on admission and 24 and 72 h later. Acute Physiology and Chronic Health Evaluation II score and capillary leak index were estimated. The primary outcome was in-hospital mortality. The median (Q1–Q3) presepsin²⁴ and presepsin⁷² levels were 127.5 (835.75–2137.5) and 883 (429–1214.5) pg/ml, respectively, in survivors compared with 2321 (1264–3456) and 3421 (1900–5432) pg/ml, respectively, in nonsurvivors ($P=0.01$ and 0.000 , respectively). The serum CRP²⁴ and CRP⁷² were 123 (76–154) and 94 (42.5–127) mg/l, respectively, in survivors compared with 156 (101–201) and 187 (139–233) mg/l, respectively, in nonsurvivors ($P=0.02$ and 0.000 , respectively). PCT⁷² was 111.5 (66–186.25) pg/ml in survivors compared with 231 (187–324) pg/ml in nonsurvivors ($P=0.000$). Presepsin⁰, CRP⁰, PCT⁰, and PCT²⁴ were not significantly different between survivors and nonsurvivors ($P=0.4$, 0.7 , 0.5 , and 0.2 , respectively). The Acute Physiology and Chronic Health Evaluation II score was 18 (15–20.8) in survivors compared with 21 (19–24) in nonsurvivors, ($P=0.02$), whereas the capillary leak index was 42 (27.6–57.7) and 42.4 (33.3–62.3) in survivors and nonsurvivors, respectively ($P=0.8$). The area under the curve was the highest for presepsin⁷² (0.918). Presepsin⁷² of 1262 pg/ml was seen to be 92.3% sensitive and 81.3% specific for mortality prediction.

Conclusion

This study showed that the serum presepsin could be a valuable biomarker for predicting in-hospital mortality in sepsis.

Keywords:

C-reactive protein, presepsin, procalcitonin, sepsis prognosis

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Introduction

Sepsis is a well-known cause of death in critically ill. It was involved accordingly in many publications of the critical care medicine [1]. The patients' response to sepsis syndrome is extremely complex. It involves many inflammatory and anti-inflammatory reactions, endothelial and cellular dysfunction, and the release of innumerable humoral responses that could be used as biomarkers [2]. The evaluation of sepsis severity and outcome is complicated by the lack of gold standard for the diagnosis of sepsis and the variability in its presentation [3]. Many scores and biomarkers had been studied in this perspective, with Acute Physiology and Chronic Health Evaluation II (APACHE II) score being traditionally used for this context [4–7].

sCD14 subtypes (presepsin) is a biomarker that was evaluated for the diagnosis and prognosis of sepsis [8]. Compared with other biomarkers, presepsin seems to have a better sensitivity and specificity in the prognostic evaluation of sepsis. It was found that the plasma concentration of presepsin is significantly higher in nonsurvivors of sepsis [9].

This study was intended to assess the prognostic significance of presepsin in sepsis evaluation in

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comparison with procalcitonin (PCT) and C-reactive protein (CRP).

Patients and methods

Our study was done as a prospective observational cohort study including patients admitted to a single critical care center with sepsis during the period from January 2014 to December 2014. Sepsis was identified as the presence of SIRS according to the SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference [10] exhibiting two or more of the following signs: (a) temperature of more than 38°C or less than 36°C, (b) pulse rate of more than 90 beats/min, (c) respiratory rate of more than 20 breaths/min or hyperventilation with a partial pressure of arterial carbon dioxide of less than 32 mmHg, or (d) white blood cell count of more than 12 000/mm³ or less than 4000/mm³, or more than 10% immature cells in addition to the presence of infection identified by two independent experts according to the clinical and microbiological criteria of the CDC definitions [11].

Excluded from that study were patients less than 17 years old, patients who had received anti-inflammatory drugs or corticosteroids before admission, patients who received blood transfusion before enrollment, patients with terminal disease (e.g. metastatic malignancy), or those who died within 24 h of enrollment.

Full history taking and physical examination was done for all included patients, with Acute Physiology and Chronic Health Evaluation II score (APACHE II score) assessed on admission [6].

Routine laboratory investigations were done including complete blood count, alanine transaminase, aspartate transaminase, total and direct bilirubin, total protein, serum albumin, Prothrombin concentration (PC), Prothrombin time (PT), international normalization ratio, serum electrolytes, for example, Na⁺ and K⁺, and arterial blood gases.

At least two blood cultures from different sites were collected from each patient on admission. Cultures from any suspected site of infection such as sputum, wound, or urine were collected on admission.

Serum levels of presepsin were assessed on admission (presepsin⁰), 24 h (presepsin²⁴), and 72 h (presepsin⁷²) after admission. Presepsin was estimated using immunoassay analyzer (PATHFAST; Mitsubishi Chemical Medience Corporation, Tokyo, Japan)

[12]. Presepsin level was expressed as pg/ml; normal value is 60–360 pg/ml.

Serum levels of PCT were done using ELISA technique on admission (PCT⁰), 24 h (PCT²⁴), and 72 h (PCT⁷²) after admission. PCT level was expressed as pg/ml; normal value is less than 150 pg/ml.

Serum levels of CRP using ELISA technique were done on admission (CRP⁰), 24 h (CRP²⁴), and 72 h (CRP⁷²) after admission [13]. CRP level was expressed as mg/l; normal value is 1–3 mg/l.

We estimated the change of different biomarkers over time by the formulas $\Delta\text{presepsin} = \text{presepsin}^{72} - \text{presepsin}^0$, $\Delta\text{PCT} = \text{PCT}^{72} - \text{PCT}^0$, and $\Delta\text{CRP} = \text{CRP}^{72} - \text{CRP}^0$. Presepsin, PCT, and CRP were considered either increasing if 72-h measurements were more than day 0 measurements or decreasing if 72-h measurements were less than day 0 measurements.

The capillary leak index (CLI) was calculated as the admission CRP (mg/l) divided by the serum albumin (g/l) [7].

The primary outcome of the study was the in-hospital mortality, whereas the secondary outcome was the average ICU length of stay (ICU-LOS).

The study protocol was approved by the institutional review board at Cairo University.

Statistical analysis

Data were prospectively collected and coded before analysis using the statistical package of the social sciences (SPSS version 22, IBM, USA). Normal distribution of different dependent variables in relation to their independent variables was studied. A variable was considered normally distributed if the Shapiro–Wilk's test had a *P* value more than 0.05 [14,15] and with *z*-value of skewness and kurtosis between -1.96 and +1.96 [16]. Most of the variables were non-normally distributed. Accordingly, continuous variables were expressed as median, 25th, and 75th quartiles [median (Q1–Q3)]. Categorical variables were expressed as frequency and proportion. When two groups were studied, all variables were non-normally distributed. Accordingly, nonparametric test (Mann–Whitney *U*-test) was used for comparison between two groups regarding quantitative variables. χ^2 was used for comparison between two groups regarding qualitative data. Exact test was used instead when the expected frequency is less than 5. Spearman correlation coefficient test (*r*) was used to test a positive or

negative correlation between two variables (nonparametric). Receiver operator characteristic analysis was performed to define a cutoff value of a variable. The best cutoff values were calculated by using the Youden's index. Youden's index was estimated as (sensitivity+specificity) -1. The best cutoff values are those associated with highest index. Results were considered statistically significant if *P* value up to 0.05.

Results

A total of 83 patients were initially recruited for the study with the initial diagnosis of sepsis. After initial enrollment, 10 patients were excluded as they were maintained on corticosteroids and/or immunosuppressant therapy before admission, five were excluded owing to terminal disease, four received blood transfusion before enrollment, and nine died within 24 h of admission.

The remaining 55 patients represented the study population. They had a mean age of 58 (47–65) years old. There were 33 (60%) males and 22 (40%) females.

The baseline hemodynamics and the source of infection of the included population are seen in Table 1, and the baseline laboratory findings are seen in Table 2.

Table 1 Baseline hemodynamics and source of infection in our population

Parameters	Median (Q1–Q3)
SBP (mmHg)	80 (75–100)
DBP (mmHg)	60 (50–60)
MAP (mmHg)	66.7 (56.7–73.3)
HR (beats/min)	100 (95–111)
Temperature (deg.)	38.5 (38–39)
RR (breath/min)	21 (18–24)
CVP (cmH ₂ O)	11 (9–15)
GCS	10 (9–13)
Source	<i>N</i> (%)
Pneumonia	38 (69.1)
Soft tissue infection	
Diabetic foot	4 (7.3)
Necrotizing fasciitis	2 (3.6)
Bedsore infection	1 (1.8)
Abdominal sepsis	5 (9.1)
UTI	3 (5.5)
Empyema	2 (3.6)
Total	55 (100)

CVP, central venous pressure; DBP, diastolic blood pressure; GCS, Glasgow coma scale; HR, heart rate; MAP, mean arterial pressure; RR, respiratory rate; SBP, systolic blood pressure; UTI, urinary tract infection.

APACHE II score of our population was 20 (18–23). CLI was 42.4 (31.6–58.9) mg/g. Of our 55 patients, 47 (85.5%) needed mechanical ventilation, 44 (80%) needed vasoactive and/or inotropic support, and 12 (21.8%) needed renal replacement therapy. The ICU-LOS was 11 (9–13) days. Thirty-nine of our patients died, with an in-hospital mortality rate of 70.9%.

We measured presepsin, PCT, and CRP on admission and 24 and 72 h later. Presepsin⁰ had a median (Q1–Q3) of 1322 (890–2437) pg/ml. Presepsin²⁴ was 1879 (997–3421) pg/ml and presepsin⁷² was 2313 (1156–4331) pg/ml. PCT⁰ was 165 (79–231) pg/ml, PCT²⁴ was 189 (111–254) pg/ml, and PCT⁷² was 198 (121–319) pg/ml. CRP⁰ was 123 (89–177) mg/l, CRP²⁴ was 154 (98–189) mg/l, and CRP⁷² was 150 (111–211) mg/l.

The presepsin and PCT were decreased in 14 (25.5%) patients by 1242 (308–2537) and 55 (29.5–103.5) pg/ml, respectively and, were increased in 41 (74.5%) patients by 1412 (792.5–2758) and 78 (33.5–130) pg/ml, respectively. The CRP was decreased in 13 (23.6%) patients by 67 (50–87.5) mg/l, and it was increased in 42 (76.4%) patients by 60.5 (32–90.75) mg/l.

None of the studied biomarkers nor APACHE II score or CLI was significantly correlated with the ICU-LOS (Table 3).

Table 2 The baseline laboratory findings

Parameters	Median (Q1–Q3)
Hemoglobin (mg%)	9 (7.9–10.3)
Hematocrit (%)	25.7 (23–28)
TLC (×10 ³ /cm ³)	16 (12.6–21)
Platelet (×10 ³ /cm ³)	231 (137–311)
Na ⁺ (mEq/l)	137 (132–140)
K ⁺ (mEq/l)	3.9 (3.7–4.3)
Ca ⁺⁺ (mEq/l)	8 (7.7–8.6)
PO ₄ ⁺⁺ (mEq/l)	3.1 (3–4.5)
Presepsin ⁰ (pg/ml)	1322 (890–2437)
CRP ⁰ (mg/l)	123 (89–177)
PCT ⁰ (pg/ml)	165 (79–231)
Urea	55 (34–106)
Creatinine (mg%)	1.3 (0.9–2.5)
INR	1.3 (1.1–1.8)
SGOT	45 (30–112)
SGPT	43 (28–87)
Total bilirubin (mg%)	0.9 (0.8–1.5)
Direct bilirubin (mg%)	0.3 (0.2–0.8)
Serum albumin (mg%)	2.8 (2.5–3.6)

CRP⁰, C-reactive protein on admission; INR, international normalization ratio; PCT⁰, procalcitonin on admission; Presepsin⁰, admission presepsin; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; TLC, total leucocyte count.

Table 3 The correlation between different biomarkers and ICU length of stay

Variables	Correlation coefficient	P value
Presepsin ⁰	-0.08	0.6
Presepsin ²⁴	-0.05	0.7
Presepsin ⁷²	0.038	0.8
PCT ⁰	-0.13	0.4
PCT ²⁴	-0.17	0.22
PCT ⁷²	-0.03	0.9
CRP ⁰	0.038	0.8
CRP ²⁴	0.075	0.6
CRP ⁷²	0.071	0.6
CLI	0.053	0.7
APACHE II score	0.138	0.3

APACHE II, Acute Physiology and Chronic Health Evaluation II; CLI, capillary leak index; CRP, C-reactive protein; PCT, procalcitonin.

The presepsin²⁴, presepsin⁷², CRP²⁴, and CRP⁷² whereas not on admission were predictors for mortality. The presepsin²⁴ and presepsin⁷² were 1127.5 (835.75–2137.5) and 883 (429–1214.5) pg/ml, respectively, in survivors compared with 2321 (1264–3456) and 3421 (1900–5432) pg/ml, respectively, in nonsurvivors ($P=0.01$ for presepsin²⁴ and 0.000 for presepsin⁷²). The serum CRP²⁴ and CRP⁷² were 123 (76–154) and 94 (42.5–127) mg/l, respectively, in survivors compared with 156 (101–201) and 187 (139–233) mg/l, respectively, in nonsurvivors ($P=0.02$ for CRP²⁴ and 0.000 for CRP⁷²). The presepsin⁰ and CRP⁰ were, however, 1573 (945.5–3547.75) pg/ml and 133 (89.25–184.75) mg/l, respectively, in survivors compared with 1276 (890–2321) pg/ml and 123 (89–165) mg/l, respectively, in nonsurvivors ($P=0.4$ and 0.7 for presepsin⁰ and CRP⁰, respectively).

Only PCT⁷² was significantly lower in survivors and not PCT⁰ or PCT²⁴. The PCT⁰ and PCT²⁴ were 192 (115.5–233.25) and 162 (98–207.5) pg/ml, respectively, in survivors compared with 156 (78–231) and 198 (123–289) pg/ml, respectively, in nonsurvivors ($P=0.5$ and 0.2 for PCT⁰ and PCT²⁴, respectively). PCT⁷² was 111.5 (66–186.25) pg/ml in survivors compared with 231 (187–324) pg/ml in nonsurvivors ($P=0.000$; Fig. 1).

The APACHE II score but not the CLI was shown to be a significant mortality predictor. APACHE II score was 18 (15–20.8) in survivors compared with 21 (19–24) in nonsurvivors ($P=0.02$), whereas the CLI was 42 (27.6–57.7) and 42.4 (33.3–62.3) for survivors and nonsurvivors, respectively ($P=0.8$).

The cutoff values for mortality prediction were evaluated for the significant predictors using receiver

operator characteristic analysis (Fig. 2). The area under the curve was the highest for presepsin⁷² (0.918). It was seen that presepsin level of 1262 pg/ml at 72 h following admission is 92.3% sensitive and 81.3% specific for mortality prediction in patients with sepsis (Table 4).

The trend of the biomarkers was evaluated for mortality prediction. The increase of the three biomarkers was seen to be significantly associated with mortality (Table 5). The increase of presepsin over time was seen to be 100% sensitive and 87.5% specific for predicting mortality, with Positive predictive value (PPV) and Negative predictive value (NPV) of 95.1 and 100%, respectively (Table 6).

Discussion

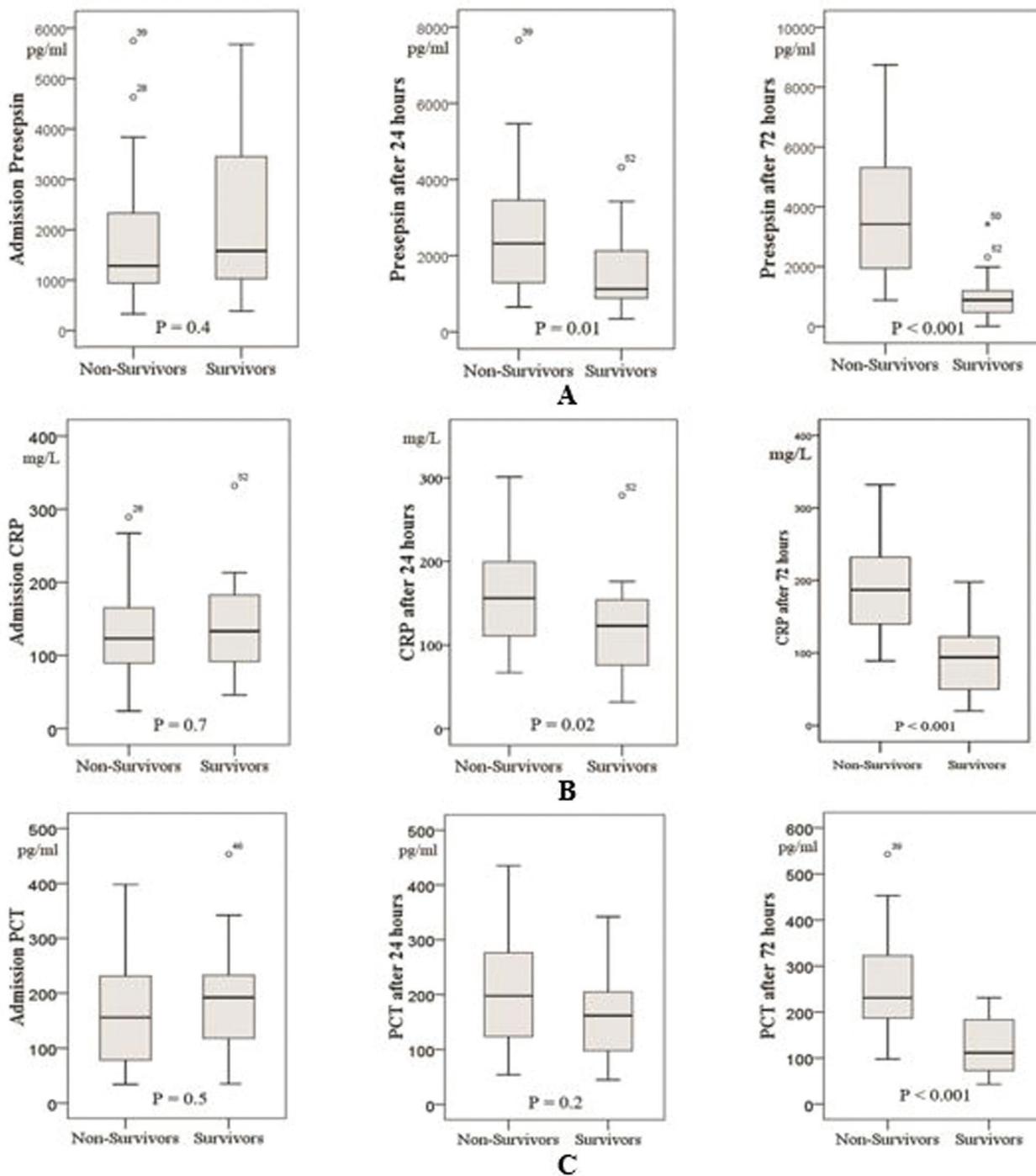
Identification of sepsis prognosis and predicted mortality is an important factor in patient stratification and management. High-risk patients may benefit from earlier interventions. The early prediction of mortality and ICU-LOS in critically ill patients is a cornerstone in patient/family counseling, an important socioeconomic factor, and improves satisfaction [17]. Traditionally, the APACHE II score was used in this context [6].

We intended in this study to evaluate the prognostic value of monitoring presepsin level in patients with sepsis and to compare it with PCT and CRP. We compared it also with the commonly used APACHE II score and with the CRP, PCT and CLI. We included a cohort of 55 patients with sepsis.

Till starting patient recruitment for this study, the gold standard for the diagnosis of sepsis was the 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference [10]. More recently following this study, a newer definition for sepsis was published considering 'confirmed' or 'suspected' infection as a prerequisite [18].

Our results demonstrated that none of the biomarkers studied nor APACHE II score and CLI were correlated with the ICU-LOS. These results are against the results of many others who revealed a positive correlation between average LOS and the APACHE II score, presepsin levels, and CRP levels [4,5,19,20]. They explained this association with the more lengthy ICU care by more disease severity. We included a cohort of patients with severe disease parameters indicated by the high median APACHE II score and a high in-hospital mortality of 70.9%.

Figure 1



The three measured biomarkers in survivors and nonsurvivors. (a) The three measured presepsin levels in survivors and nonsurvivors. (b) The three measured CRP levels in survivors and nonsurvivors. (c) The three measured procalcitonin levels in survivors and nonsurvivors.

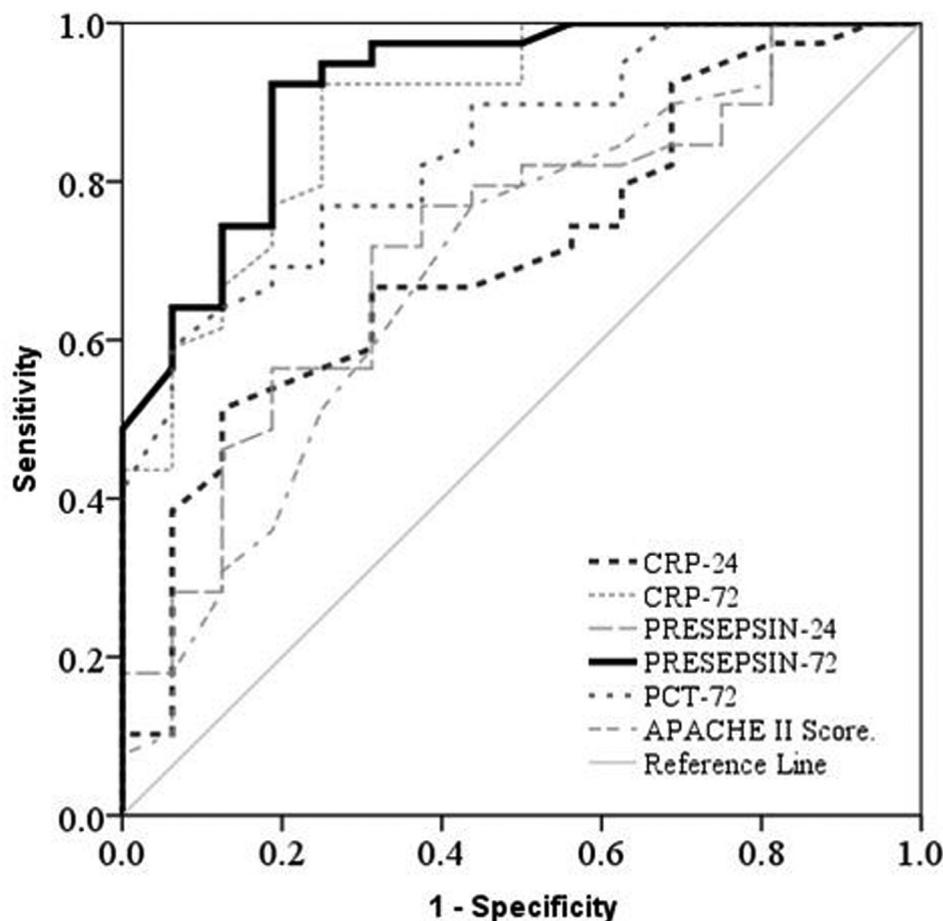
Early death of patients made it difficult to study the association with ICU-LOS in our study.

This study revealed that the presepsin and CRP levels after 24 and 72 h and not on admission can predict mortality. PCT after 72 h and admission APACHE II score were also significantly higher in nonsurvivors. The area under the curve (AUC) for the presepsin⁷² for survival prediction was the highest (0.918) compared

with PCT (0.84), CRP (0.888), and APACHE II score (0.695), with cutoff value of 1262 pg/ml to be 92.3% sensitive and 81.3% specific for predicting mortality in patients with sepsis.

El-Shafie *et al.* [9] showed that presepsin measures on admission and 2 and 4 days after admission are mortality predictors but none of the CRP measures. They revealed an AUC of 0.834 for presepsin at 4 days

Figure 2



Receiver operator characteristic curve for different variables.

Table 4 The area under the curve, the sensitivity, and the specificity of different variables for mortality prediction

Variables	AUC	Value	Sensitivity (%)	Specificity (%)
CRP ²⁴	0.706	155 mg/l	51.3	87.5
CRP ⁷²	0.888	114 mg/l	92.3	75
Presepsin ²⁴	0.723	1377 pg/ml	71.8	68.8
Presepsin ⁷²	0.918	1262 pg/ml	92.3	81.3
PCT ⁷²	0.841	211.5 pg/ml	59	93.8
APACHE II score	0.695	18.5	76.9	56

APACHE II, Acute Physiology and Chronic Health Evaluation II; AUC, area under the curve; CRP, C-reactive protein; PCT, procalcitonin.

after admission compared with 0.918 in our study. A lower cut of value of only 900 pg/ml was found to be 73% sensitive and 100% specific for predicting mortality. They, however, included all patients admitted by SIRS rather than sepsis only, as we did. Behnes *et al.* [19] found that the presepsin levels on days 1, 3, and 8 of admission as well as the APACHE

Table 5 The relation between the trend of the biomarkers and mortality

Biomarkers	Trend	Survivors	Nonsurvivors	P value
Presepsin	Increased	2	39	0.000
	Decreased	14	0	
CRP	Increased	3	39	0.000
	Decreased	13	0	
PCT	Increased	3	38	0.000
	Decreased	13	1	

CRP, C-reactive protein; PCT, procalcitonin.

Table 6 The sensitivity, specificity, PPV, and NPV for the trend of different biomarkers

Variables	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Increase in presepsin	100	87.5	95.1	100
Increase in CRP	100	81.3	92.9	100
Increase in PCT	97.4	81.3	92.7	92.9

CRP, C-reactive protein; PCT, procalcitonin.

II score but not the PCT nor the CRP levels had a significant 30-day and 6-month mortality prediction. The AUC for day 3 presepsin and APACHE II score

were 0.70 for 30-day mortality. On admission to the emergency department, Liu *et al.* [21] showed that the APACHE II score and PCT had higher AUC for 28-day mortality prediction (0.722 and 0.679, respectively) compared with presepsin (0.679). Compared with our study, they considered the T0 measures of ED admission, which was not significant mortality predictor in our study, but they used longer term mortality than we did (28-day mortality rather than in-hospital mortality). Liu *et al.* [21] had much lower cutoff value of presepsin than ours (556 pg/ml) to be 62% sensitive and 66% specific for mortality prediction. Ulla *et al.* [22] found that despite the ED admission presepsin level is significantly higher in nonsurvivors, the PCT was not. Silvestra *et al.* [23] showed similar results to ours regarding the lack of association between CRP and mortality which contradicts other results [24]. Presepsin, PCT, and CRP were also found to be elevated in nonsurvivors of patients with septic burn [25]. In a Korean population, Kweon *et al.* [26] found, however, that the presepsin does not correlate with 30-day mortality. In a systematic review and meta-analysis published in January 2018, Yang *et al.* [27] showed, however, that the first-day presepsin level had prognostic value to predict in-hospital or 30-day mortality in adult patients with sepsis.

In a prospective cohort study, Pettila *et al.* [28] showed, like us, that the PCT on day 3 is higher in nonsurvivors, whereas unlike our results, the CRP levels on days 1 and 3 were similar in survivors and nonsurvivors. They found an AUC for hospital mortality of 0.75 compared with 0.841 in our study.

Zhang *et al.* [29] studied the biomarkers for longer duration when the CRP and PCT were found to be significantly higher in nonsurvivors at days 10 and 14 after admission, with no significant difference between them in both groups up to 7 days of admission. They considered that PCT was more of a diagnostic tool rather than a prognostic tool. Others found that the baseline CRP did not differ between survivors and nonsurvivors whereas the PCT levels in nonsurvivors were almost four times higher than levels in survivors [30]. In a smaller study of 20 patients with sepsis and severe sepsis, both CRP and PCT were higher in nonsurvivors than survivors [31]. These findings might support the use of presepsin for predicting patients with more severe sepsis with worse outcome.

CLI was proposed by Malbrain *et al.* [7] to predict disease severity in patients with sepsis. They found that the CLI is correlated with LS, use of ICU resources, and organ failure. They also found that the CLI is an

independent predictor for mortality. It was assumed that an increased CRP [32] and decrease albumin [33] with the systemic inflammation of sepsis are the basis of this index. The lack of efficacy of the CLI was explained by the fact that it reaches its maximum on the third day of sepsis [34] and we estimated it using the admission measures only.

Rather than the absolute value of the biomarker, we studied its trend over time. We found that the decrease of the serum level of the three studied biomarkers was significantly associated with survival, with best sensitivity and specificity for presepsin (90 and 100%, respectively). In another Egyptian population but with patients with SIRS rather than those with only sepsis, El-Shafie *et al.* [9] found that decreasing trend of presepsin was 70% sensitive and 91% specific for predicting survival; however, they found no association between CRP trend and survival. Endo *et al.* [35] divided patients with sepsis to favorable and unfavorable groups and found that the patients with favorable group exhibited significant decrease of presepsin, PCT, and CRP on day 3, whereas in the unfavorable group, only presepsin did not decrease significantly.

Our study was limited by the small number of the study sample, which included only 55 patients. Owing to the small sample size, we could not analyze the relationship between the studied biomarkers and the infection site or the organism type. We considered only the in-hospital mortality rather than the long-term follow-up.

Conclusion

This study showed that the serum presepsin is a valuable biomarker in term of risk stratification and in in-hospital mortality prediction of patients with sepsis and might be more accurate than PCT and CRP in this context.

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Conflicts of interest

There are no conflicts of interest.

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