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Original article

Role of presepsin compared to C-reactive protein in sepsis diagnosis and prognostication

Mohamed El-Saied El-Shafie [a], Khaled M. Taema [a,*], Moataz M. El-Hallag [a], Abdallah Mohamed Abdallah Kandeel [b]

[a] Critical Care Medicine, Cairo University, Egypt
[b] Critical Care Medicine, El-Sahel Teaching Hospital, Egypt

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ABSTRACT

Early identification of sepsis and its differentiation from non-infective SIRS are important for sepsis outcome. We intended to evaluate the use of presepsin in differentiating sepsis from noninfectious SIRS and its prognostic value compared to CRP. We included 31 patients (median age 60 year old, 16 males) admitted with SIRS to El-Sahel Teaching Hospital, Egypt after excluding 21 patients with preadmission corticosteroids therapy, blood transfusion, immunosuppressive illness, and ICU length of stay (ICU-LOS) less than 24-hours. Patients were classified into non-infective SIRS group (13 patients) and sepsis group (18 patients). Presepsin, CRP and SOFA score were measured on admission and on days 2 and 4 of admission. The outcome parameters studied were ICU-LOS and in-hospital survival. Apart from temperature and AST which were significantly higher in sepsis group, the two groups were comparable. All the presepsin levels and CRP on days 2 and 4 were significantly higher in sepsis than in SIRS groups. The ICU-LOS was positively correlated with all the presepsin levels and with the CRP levels on days 2 and 4. All presepsin values were significantly higher in survivors while none of the CRP levels were significantly different in survivors and non-survivors. The decrease of presepsin over time was significantly associated with better survival. It was found to be 70% sensitive and 91% specific for predicting survival in SIRS patients. This relation was not found in CRP levels. We concluded that the presepsin can be used for early differentiation between sepsis and non-infectious SIRS and predict higher mortality.

1. Introduction

Despite the advances in its diagnosis and management, sepsis remains a leading cause of death in critically ill patients [1,2]. It is well established now that early identification and timely therapeutic interventions are the cornerstone in outcome affection [3].

Early recognition of sepsis is not always straightforward and clinical signs at presentation can be misleading and very heterogeneous due to frequent comorbidities or variable demographic characteristics. In the emergency setting therefore an urgent need for a reliable diagnostic procedure, allowing early discrimination between SIRS and sepsis, is mandatory. Biomarkers, such as C-reactive protein (CRP) and procalcitonin (PCT), introduced among the diagnostic criteria of sepsis [4], could contribute to promptly identify patients affected by sepsis, severe sepsis and septic shock who could benefit from quick and appropriate therapy. C-reactive protein is one of the commonest biomarkers that are used during the management of sepsis. It was seen by some researchers to be significantly higher in sepsis patients compared to non-infectious SIRS [5].

CD14 was identified to be a glycoprotein expressed on the surface membrane of monocytes/macrophages (mCD14) and serves as a receptor for complexes of lipopolysaccharides (LPS) and LPS binding protein (LPBP) and it co-localizes with toll-like receptor 4 (TLR4) [6].

Presepsin [soluble CD14 subtype (sCD14-ST)] is a proposed biomarker with high sensitivity and good specificity for sepsis diagnosis. It was seen to be significantly correlated with mortality of patients with severe sepsis and septic shock [7]. Being a glycoprotein expressed on the surface membrane of monocytes/macrophages and serves as a receptor for lipopolysaccharides (LPS) and LPS binding protein (LPBP) complex [6] and react with

* Corresponding author.
E-mail address: khaled.toaima@kasralainy.edu.eg (K.M. Taema).
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other conserved surface bacterial ligands including gram-positive peptidoglycans [8], it was supposed that the presepsin is to be increased with bacterial infection whether gram positive or negative. Giavarina and Carta found a presepsis serum level of 55–184 pg/mL in normal subjects with no gender or age difference [9]. Preliminary findings provide a solid basis for its use however; more data are needed concerning the pathophysiological conditions associated with presepsin release. The added value of this biomarker for clinical decision-making in terms of diagnosis, risk stratification and therapy monitoring should also be clarified [10].

We intended in this study to evaluate the value of monitoring serum presepsin in critically ill patients for early diagnosis and differentiation between sepsis and non-infectious SIRS and to evaluate its prognostic value in comparison with CRP.

2. Patients & methods

The study was conducted in El Sahel Teaching Hospital, Cairo, Egypt recruiting amitted adult critically ill patients diagnosed to have SIRS according to the SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference [11] in our prospective cohort observational study during the period from December 2012 to August 2013 exhibiting two or more of the following signs: (1) temperature of >38 °C or < 36 °C, (2) pulse rate of >90 beats/min, (3) respiratory rate of >20 breaths/min or hyperventilation with a partial pressure of arterial carbon dioxide (PaCO2) of <32 mmHg, or (4) white blood cell (WBC) count of >12,000 μL^{-1} or <4000 μL^{-1}, or >10% immature cells.

We excluded from the study patients who received *anti*-inflammatory drugs or corticosteroids before admission, patients who had immunosuppressive illness, patients who had received massive blood transfusion and those who had ICU length of stay less than 24 h.

The presence of infection was defined according to the clinical and microbiological criteria of the CDC definitions [12] and was held as a gold standard and determined by two independent experts who were blinded to the serum Presepsin and CRP results and examined the patients daily for the 1st 48 h of admission. According to presence or absence of infection, our patients were divided into two groups; group A included patients with non-infectious SIRS (SIRS group) and group B included patients with infection (sepsis group). Additional ten clinically free individuals were included as a control.

The study protocol was approved by the institutional review board at Cairo University together with representatives of study conduction site.

2.1. For all cases the following was performed

Full History taking and physical examination, with acute physiology and chronic health evaluation II score (APACHE II score) assessed on admission [13] and sequential organ failure assessment (SOFA) score to be assessed on admission, and on days 2 and 4 [14].

The following laboratory investigations were done to all included patients:

• Complete blood count (CBC)	• Total bilirubin
• Serum urea	• Aspartate aminotransferase (AST)
• Serum creatinine	• Alanine aminotransferase (ALT)
• Serum sodium	• INR
• Serum potassium	• Serum albumin

At least two blood cultures from different sites were collected from each patient on admission using 10 ml of blood withdrawn aseptically after disinfection of the venipuncture site on the patient's skin with iodine for at least 5 min and allowing drying or with alcohol 70% for at least 30 s and allowing drying. Cultures from any suspected site of infection as sputum, wound or urine were collected on admission.

Presepsin values (pg/ml) using immunoassay analyzer (PATHFAST; Mitsubishi Chemical Medience Corporation, Japan) [15] and CRP (mg/dl) using commercial available kits following the instructions of the manufacturers [16] were done on days 0, 2 and 4.

All patients were managed by conventional supportive measures for critically ill patients including fluids, oxygen therapy, and ventilatory support whenever required. However, whenever criteria of infection appeared or suspected (according to CDC and guided by Surviving sepsis campaign guidelines), antibiotics were immediately instituted even in SIRS patients.

The outcome parameters that were studied included ICU length of stay (ICU-LOS) and in-hospital mortality.

3. Statistical analysis

Data were prospectively collected and coded prior to analysis using the statistical package of social science (SPSS version 16). 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 $p > 0.05$ [17,18] and with z-value of skewness and kurtosis between −1.96 and +1.96 [19]. Being non-normally distributed, 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, nonparametric test (Mann-Whitney *U* test) was used for comparison between two groups as regard quantitative variables. Chi-Square Test (x^2) was used for comparison between two groups as regards qualitative data. Exact test was used instead when the expected frequency is less than 5. Receiver operator characteristic (ROC) analysis was performed to define a cutoff value of a variable. Spearman correlation coefficient test (r) was used to test a positive or negative correlation between two variables *(non-parametric)*. Sensitivity was estimated as $\frac{True\ positive}{(True\ positive+False\ negative)}$ and specificity was estimated as $\frac{True\ negative}{(True\ negative+False\ positive)}$. Positive predictive value (PPV) was estimated as $\frac{True\ positive}{(True\ positive+False\ positive)}$, and negative predictive value (NPV) was estimated as $\frac{True\ negative}{(True\ negative+False\ negative)}$. Results were considered statistically significant if $P \leqslant 0.05$.

4. Results

In addition to the ten clinically free control individuals, Fifty-two patients were initially recruited for the study with the initial diagnosis of SIRS. Out of those patients, 21 patients were excluded (4 patients died and 5 transferred to other hospital during their 1st 24 h of admission, 5 were maintained on corticosteroids therapy, 6 had a recent history of blood transfusion before their ICU admission and 1 immunocompromised patient with renal transplantation). The remaining 31 patients represented the study population. They had a median age of 60 and (Q1–Q3) of (52–69) years old, including 16 males (51.6%) and 15 females (48.38%). The cause of admission was medical in 26 patients (83.3%) and surgical in 5 patients (16.1%). The control patients had a median age of 64 years old with IQR (61.5–70.25), including 5 males (50%) and 5 females (50%). The mean presepsin level in the healthy control group was 116.5 (108.25–126.75) pg/ml.

The associated co-morbid medical conditions, baseline hemodynamics, and baseline laboratory findings are seen in Table 1.

Admission APACHE II score was 20 (13–26) and SOFA score was 7 (4–8). Eleven of our patients died during study period with mortality rate of 35.5%.

According to presence or absence of infection, our patients' population was classified into two groups; group A of patients with non-infective SIRS that included 13 patients (41.9%) and group B of patients with sepsis that included 18 patients (58.1%).

The two groups were comparable with no significant differences regarding demographic data and co-morbid conditions (Table 2).

Apart from temperature and aspartate aminotransferase (AST) which were significantly higher in sepsis group, the baseline clinical and laboratory data were comparable between the two groups (Table 3).

4.1. Severity scoring systems

Despite non-significant difference in most of the baseline clinical and laboratory data, there were significantly higher admission SOFA and APACHE II scores in sepsis group. The SOFA score was 7.5 (6.75–8.25) in the sepsis group compared to 4 (3–8) in SIRS group, (P value = 0.03) (Fig. 1). The APACHE II score was 24.5 (20.75–30.25) vs. 13 (9.5–15) in sepsis and SIRS subgroups respectively, (P < 0.001) (Fig. 2).

4.2. Presepsin and CRP on days 0, 2, and 4

Two serum biomarkers (serum presepsin and serum CRP) were compared in both groups in days 0, 2, and 4. The serum presepsin level on days 0, 2, and 4 revealed significant higher levels in sepsis group than in SIRS group [1228.5 (694–1819.5) pg/mlVs200 (122–210) pg/ml, P < 0.001], [905 (767–1925) pg/ml Vs 210 (153–310) pg/ml, p < 0.001] and [700 (500–2036) pg/ml Vs 190 (165–275) pg/ml, p < 0.001] respectively as shown in (Fig. 3).

Serum CRP levels on admission were 64 (50–73.25) mg/dL in sepsis group compared to 55 (45–65) mg/dl in SIRS group (P = 0.2) which is statistically not significant. Days 2 and 4 serum levels of CRP were significantly higher in sepsis group than in SIRS group [72 (55–80) mg/dL and 107.5 (69–187.5) mg/dL Vs 55 (50–67.5) mg/dl and 65 (55–110) mg/dL, P value = 0.01 and 0.02 respectively] (Fig. 4).

We analyzed the area under the receiver operator curve of the studied markers for the diagnosis of sepsis. The highest AUC were that of the admission, day 2, and day 4 presepsin levels (Table 4).

The cut-off levels of these markers were then studied. We found a serum presepsin of 422 pg/mL on admission, of 427.5 pg/mL on day 2, and of 410.5 pg/mL on day 4 to have a sensitivity and specificity of 100% for prediction of sepsis (Fig. 5).

4.3. Biomarkers and disease severity

There were significant positive correlations between the SOFA and APACHE II scores and the three presepsin levels; on admission and on days 2 and 4 (Fig. 6).

On admission, the CRP was correlated with SOFA score but not with APACHE II score. There was significant positive correlation between serum CRP on day 2 and the admission SOFA and APACHE II scores. The CRP on day 4 was however not significantly correlated with the admission SOFA or APACHE II scores (Fig. 7).

4.4. ICU length of stay

The median ICU-LOS of our population was 9 with IQR (7–11) days for both groups. The average stay was significantly higher in sepsis group [10 (8–11.75) days] as compared to [8 (6–9.5) days] in SIRS group (p = 0.04).

Within the whole population, there was a significant positive correlation between ICU-LOS and admission SOFA and APACHE II scores, presepsin levels on admission and on days 2 and 4, and the CRP levels on days 2 and 4 (Table 5).

4.5. Mortality analysis

There was no significant mortality difference between the two studied groups. Eight patients (44.4%) of the sepsis group patients died compared to three patients (23.1%) of the SIRS group patients (P = 0.27).

We studied the different serum markers as a predictor for mortality. Presepsin values on days 0, 2, and 4 were significantly different in survivors and non-survivors. Serum presepsin level on admission was 422.5 (143.75–897) pgm/l in survivors compared to 1768 (210–1899) pgm/ml in non-survivors (P = 0.02). Survivors had presepsin level of 427.5 (202.5–791.7) pgm/ml and 410.5 (190–533.75) pgm/ml compared to 1900 (320–2223) pgm/ml and 2000 (380–2222) pgm/ml on days 2 and 4 respectively in non-survivors (p = 0.004 and 0.002) (Fig. 8).

Serum CRP level in survivors was 56 (45–65) mg/dL, 57.5 (55–72.5) mg/dL, and 69 (61.25–185.25) mg/dL on admission, day 2, and day 4 respectively compared to 65 (50–96) mg/dL, 71 (50–80) mg/dL, and 105 (70–170) mg/dL in non-survivors (P = 0.5,

Table 1
Associated co-morbid medical conditions, baseline hemodynamics, and baseline laboratory findings of the whole study population.

		No (%)		Median (Q1–Q3)
Co-morbid conditions	HTN	21 (67.7%)	HR (bpm)	120 (105–130)
	DM	20 (64.5%)	MAP (mmHg)	73.3 (63.3–83.3)
	CHD	2 (6.5%)	RR (breath per minute)	29 (27–32)
	CKD	1 (3.2%)	CVP (cm H_2o)	3 (0–8)
	CLD	4 (12.9%)	Temperature (°C)	38.9 (38.5–39.5)
		Median (Q1–Q3)		Median (Q1–Q3)
Hemoglobin (gm%)		10.5 (9.3–13.2)	Urea (mg/dL)	58 (38–107)
TLC (×103/ mm3)		14.9 (14–22.7)	Creatinine (mg/dL)	1.7 (1.28–2.62)
Platelets ($\times 10^3$/ mm^3)		182 (150–250)	Na^+ (meq/dL)	134 (132–138)
ALT (μ/l)		35 (20–70)	K^+ (meq/dL)	3.7 (3.4–4)
AST (μ/l)		51 (24–99)	Albumin (g/L)	3.1 (2.8–3.5)
INR		1.49 (1.28–1.67)		
Total bilirubin (mg/dl)		1.9 (1.2–2.6)		

HTN: Hypertension, DM: Diabetes mellitus, CHD: Coronary heart disease, CKD: Chronic kidney disease, CLD: Chronic Liver disease, HR: Heart rate, MAP: Mean arterial pressure, RR: Respiratory rate, CVP: Central venous pressure, TLC: Total leucocytic count, ALT: Alanine transaminase, AST: Aspartate aminotransferase, INR: International normalization ratio, Na^+: Sodium, K^+: Potassium.

Table 2
Baseline demographic data and co-morbid conditions.

		SIRS (N:13)	Sepsis (N:18)	P value
Age (year old, median (IQR)		55 (30–65)	62.5 (58.75–69.25)	0.1
Gender [N (%)]	Male	6 (46.2%)	9 (50%)	1
	Female	7 (53.8%)	9 (50%)	
HTN [N (%)]		7 (53.8%)	14(77.8%)	0.24
DM [N (%)]		9 (69.2%)	11 (61.1%)	0.7
CHD [N (%)]		0 (0%)	2 (11.1%)	0.49
CKD [N (%)]		0 (0%)	1 (5.5%)	0.163
CLD [N (%)]		1 (7.6%)	3 (16.7%)	0.6
Cause of admission	Medical	10	16	0.68
	Surgical	3	2	
Co-morbidity	1 Co-morbidity	2	6	0.26
	2 Co-morbidities	6	8	
	More than two co-morbidities	1	3	

HTN: Hypertension, DM: Diabetes mellitus, CHD: Coronary heart disease, CKD: Chronic kidney disease, CLD: Chronic Liver disease.

Table 3
The baseline clinical and laboratory data in both groups.

	SIRS (N:13) Median (Q1–Q3)	SEPSIS (N:18) Median (Q1–Q3)	P value
HR (bpm)	110 (105–121)	120 (110–139)	0.1
SBP (mmHg)	110 (92–125)	95 (88–110)	0.1
DBP (mmHg)	70 (60–75)	60 (50–70)	0.1
MBP (mmHg)	83 (71–92)	72 (63–85)	0.1
RR (breath/minute)	28 (25–30)	30 (29–33)	0.08
Temperature (°C)	38.5 (38.2–38.7)	39.5 (39–39.6)	**0.001**
CVP (Cm H_2O)	6 (2–8)	2 (-2–6)	0.08
Serum Urea (mg/dl)	50 (28–71)	75.5 (44.3–125.3)	0.3
Creatinine (mg/dl)	1.7 (0.9–2.4)	1.7 (1.5–3)	0.6
Na^+ (meq/dl)	136 (133–138)	134 (130–138.3)	0.8
K^+ (meq/dl)	3.7 (3.3–4)	3.6 (3.4–4.2)	0.7
AST (μ/l)	41 (19–68.5)	80 (32.3–117)	**0.03**
ALT (μ/l)	35 (19–41.5)	47 (23–72.8)	0.11
Albumin (g/l)	3.2 (2.9–3.5)	3 (2.3–3.5)	0.4
INR	1.5 (1.3–1.8)	1.4 (1.3–1.6)	0.3
Hemoglobin (gm%)	11.9 (10.1–11.9)	10 (8.8–12.8)	0.19
Platelet ($\times 10^3/mm^3$)	155 (150–281)	182.5 (144–241.5)	0.9
TLC ($\times 10^3/mm^3$)	14.5 (13.9–18.4)	18.6 (14.2–24.3)	0.1

HR: Heart rate, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial pressure, RR: Respiratory rate, CVP: Central venous pressure, Na^+: Sodium, K^+: Potassium, AST: Aspartate aminotransferase, ALT: Alanine transaminase, INR: International normalization ratio, TLC: Total leucocytic count.
Bold indicates the statistically significant items.

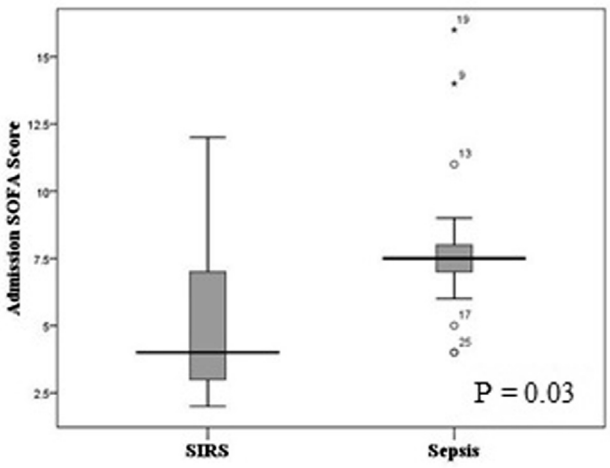

Fig. 1. Admission SOFA score in both groups.

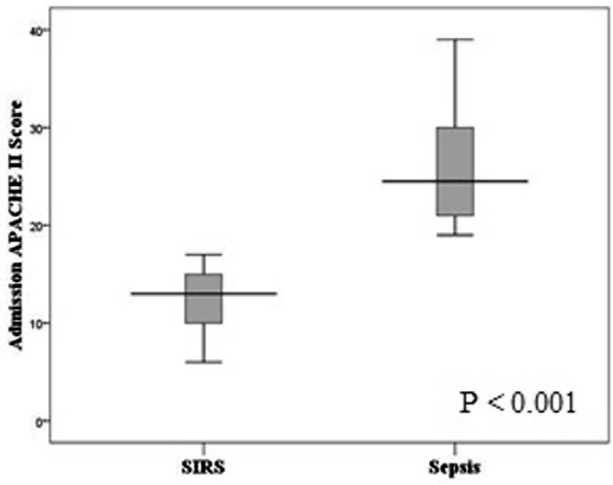

Fig. 2. Admission APACHII score in both groups.

0.22, and 0.4 respectively). These changes are statistically insignificant (Fig. 9).

The admission SOFA and APACHE II scores were also significantly lower in the survivors compared to the non-survivors. The Admission SOFA score was 5.5 (3.25–7) in survivors compared to 8 (7–12) in non-survivors (p = 0.003). The APACHE II score was 18 (11–22.5) and 27 (17–32) in survivors and non-survivors respectively (p = 0.008) (Fig. 10).

We analyzed the area under the receiver operator characteristic curve of the different studied markers and severity scores for mortality prediction. The largest AUC for ROC curves were for day 4 presepsin and admission SOFA score (Table 6).

We identified a presepsin level of 900 pgm/ml on day 4 of admission to have a sensitivity of 73% and specificity of 100% and an admission SOFA score of 7.5 were 73% sensitive and 80% specific for predicting mortality in patients with SIRS (Fig. 11).

We evaluated the relation of the trend of different biomarkers over time with mortality prediction. If the biomarker level on day 4 of admission was higher than admission value, it was considered as increasing biomarker and if it is lower, it was considered as decreasing. The presepsin was decreased in 15 patients (48.4%) and was increased 16 patients (51.6%). Of the 15 patients with decreased presepsin, 14 were survivors and only one was non-survivor and of the 16 patients with increased presepsin, 10 were non-survivors and 6 were survivors. This relation between presepsin decrease and survival was statistically significant (P = 0.001) (Table 7). The decrease of presepsin on day 4 from

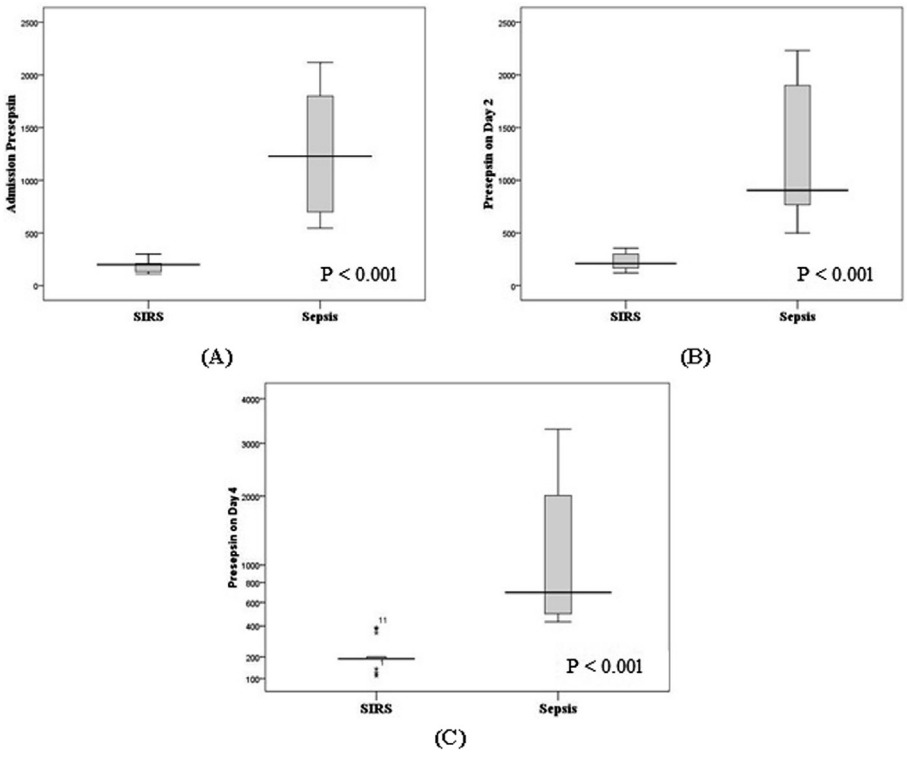

Fig. 3. Presepsin level on admission (A), in day 2 (B) and in day 4 (C).

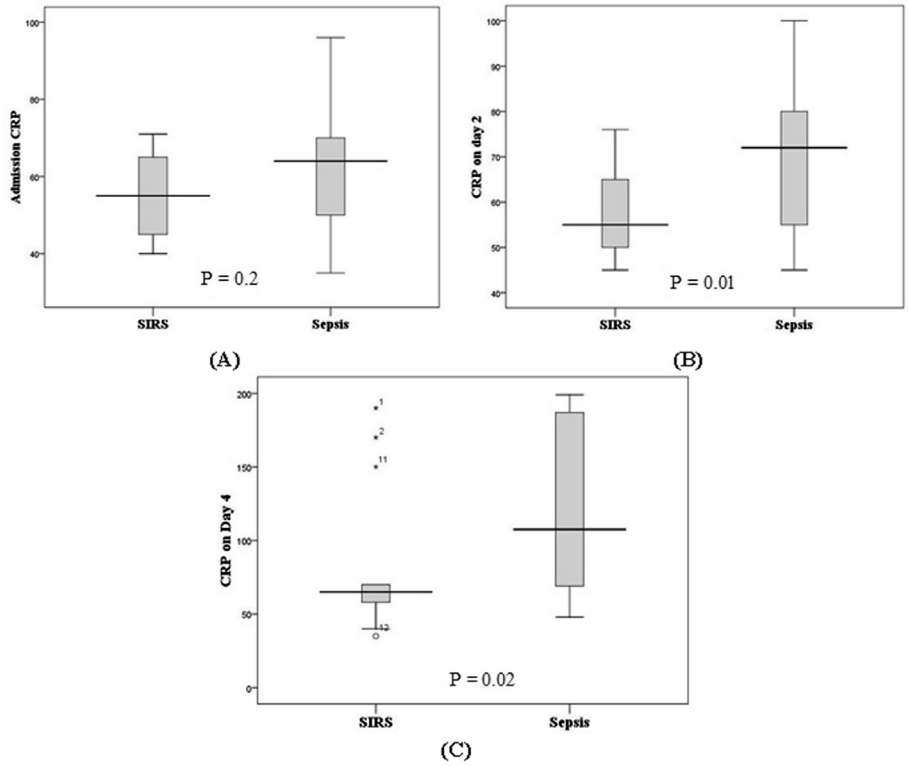

Fig. 4. Serum CRP level on admission (A), in day 2 (B), and in day 4 (C).

admission value was found to be 70% sensitive and 91% specific for predicting survival in patients with SIRS with PPV of 93% and NPV of 63%.

The CRP level was decreased in 5 patients (16.1%) and increased in 26 patients (83.9%). Of the 5 patients with decreased CRP, 3 were survivors and 2 were non-survivor and of the 26 patients with

Table 4
ROC analysis for different markers in sepsis prediction.

	Area	P value	95% Confidence interval	
			Upper bound	Lower bound
Admission presepsin	1	<0.001	1.00	1.00
Presepsin on day 2	1	<0.001	1.00	1.00
Presepsin on day 4	1	<0.001	1.00	1.00
CRP on day 2	0.763	0.014	0.595	0.931
CRP on day 4	0.744	0.022	0.563	0.925

ROC: Receiver operator characteristic, CRP: C-reactive protein.

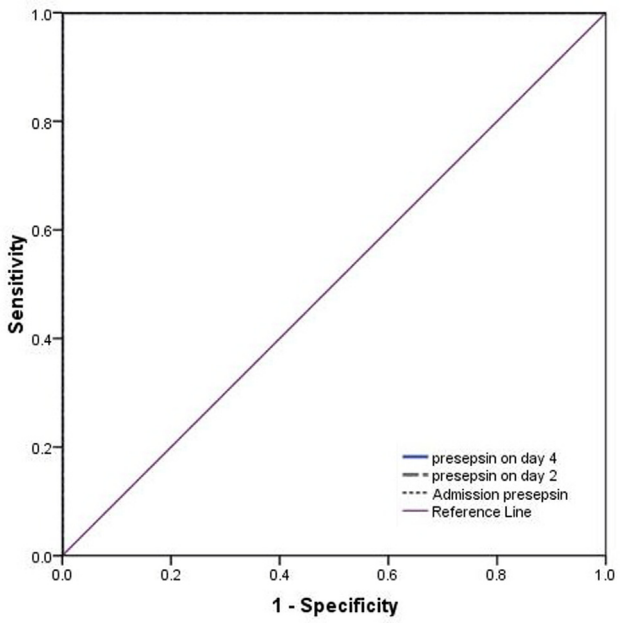

Fig. 5. ROC curve for cut-off values of presepsin on admission and on days 2 and 4.

increased CRP, 9 were non-survivors and 17 were survivors. This relation was statistically insignificant (P = 0.6) (Table 7).

5. Discussion

The early diagnosis and timely management of sepsis are known to be crucial in the reduction of sepsis-induced mortality. This indicates that the early differentiation between sepsis and non-infectious SIRS has a significant impact on outcome [20].

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 [11] and depending on culture results which usually delay the diagnosis, has a high false negative results, [21] and may be influenced by several factors including previous use of antibiotics [22]. More recently in february 2016, a new definition for sepsis was published considering confirmed or "suspected" infection as a prerequisite [23]. Considering that these diagnosis conflicts might jeopardise sepsis management, there were intense need for the search of a rapid, sensitive, and specific gold standard for the diagnosis of sepsis, differentiating sepsis from non-infectious SIRS, and predicting its severity and outcome. The idea of a "Biomarker" for sepsis was enthusiastic for these issues with a resulting hundreds or even thousands of publications that studied numerous molecules that were supposed to be related to sepsis. Presepsin or soluble CD14 subtype is one of these biomarkers that have been suggested to be promising in sepsis diagnostic and prognostic implications [24,25].

We intended in this study to evaluate the value of monitoring presepsin level in critically ill patients for early diagnosis and differentiation between sepsis and non-infectious SIRS and to evaluate the prognostic value of monitoring presepsin level and its impact on mortality in comparison to the widely used CRP marker.

This prospective study was carried out on a cohort of thirty-one Egyptian critically ill patients admitted to surgical/medical ICU with SIRS. Our patients had age of 60 (52–69) years old, including 16 males (51.6%) and 15 females (48.38%). After enrollment, our study group patients were classified into two groups according to the diagnosis that included non-infectious SIRS (SIRS group) and patients with infection (sepsis group).

Both groups were comparable with no significant differences as regard their demographic, clinical data and co-morbidities, except baseline temperature which was significantly higher in sepsis group and this was in agreement with study by Giuliano et al. [26] who found that the presence of an elevated temperature was associated with the highest risk of sepsis. Shapiro et al. [27] however showed that the higher temperature may also be observed in a wide variety of non-infectious inflammatory conditions and it may be absent in patients with serious infections, especially in elderly individuals, and thus it is not pathognomonic to sepsis.

We reported a higher degree of disease severity and organ failure in sepsis group as indicated by significantly higher SOFA and APACHE II scores in septic patients. Liu et al. [7] showed no difference in APACHE II score between SIRS and sepsis however it was significantly higher in severe sepsis and septic shock than in sepsis. Yousef and Suliman [28] showed higher SOFA score in sepsis patients.

We found that the presepsin levels on the 1st 4 days of admission can differentiate between sepsis and non-infectious SIRS. The presepsin level on days 0, 2, and 4 were significantly higher in sepsis group than in SIRS group. Yaegashi et al. [29] found that presepsin levels in sepsis patients were significantly higher than those in patients with SIRS or the healthy control subjects. These data demonstrated that the concentration of presepsin is specifically increased during sepsis. Shozushima et al. [30] also found that the concentration of presepsin was 333.5 ± 130.6 pg/mL in the SIRS group, 817.9 ± 572.7 pg/mL in the sepsis group, and 1992.9 ± 1509.2 pg/mL in the severe sepsis group and it was 294.2 ± 121.4 pg/mL in normal subjects. Ulla et al. [31] in a prospective single center study found that presepsin levels increased in early sepsis, and the levels were significantly higher than in SIRS patients which is in agreement with the present study also. The release of presepsin as a response to bacterial infection and phagocytosis against bacteria [30,32] could explain its association with sepsis rather than SIRS.

Presepsin was shown in our study to be also correlated with sepsis severity as shown by the significant positive correlation between admission presepsin and both the SOFA and APACHE II scores. It was seen by other authors that the concentration of

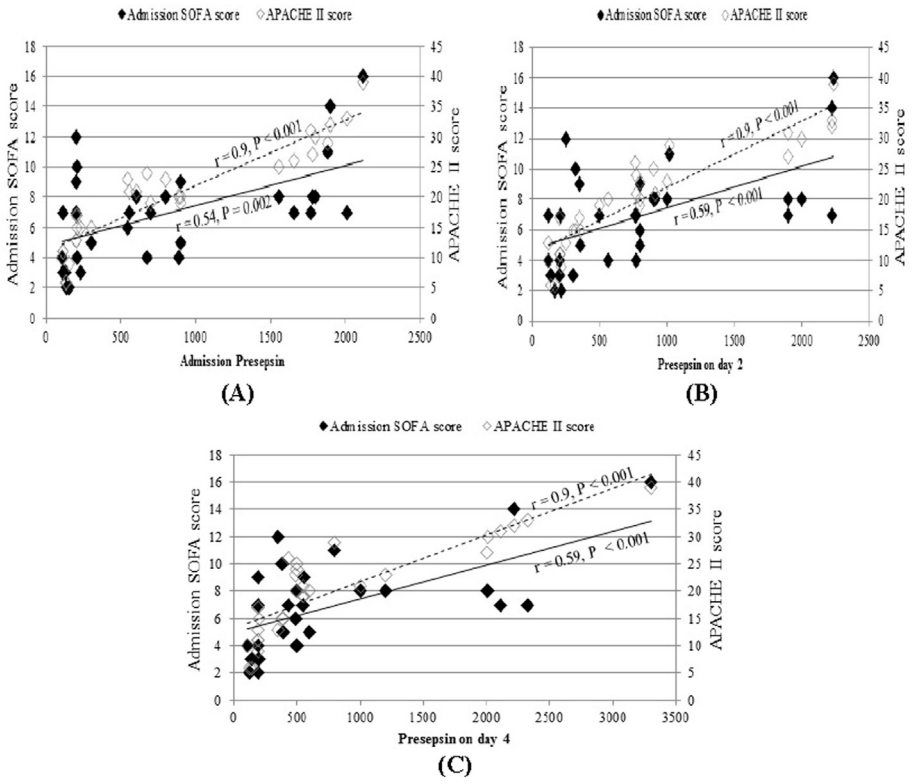

Fig. 6. Correlation between admission SOFA and APACHE II scores and admission presepsin (A), on day 2 (B) and on day 4 (C).

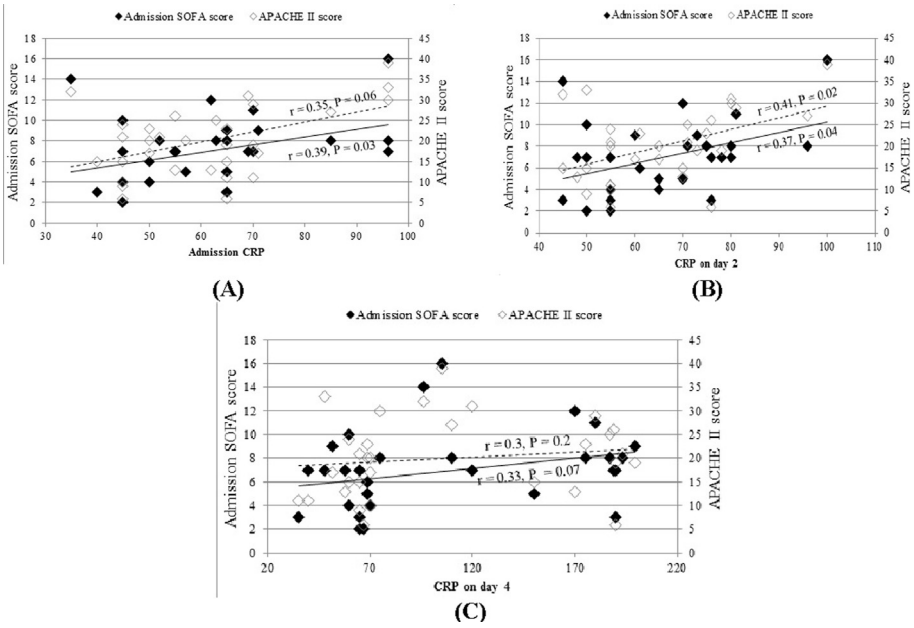

Fig. 7. Correlation between admission SOFA and APACHE II scores and CRP on admission (A), on day 2 (B) and on day 4 (C).

presepsin was positively correlated with APACHE II and SOFA scores [33]. They and others [30,31,33] showed that the presepsin level in emergency department was significantly higher in severe sepsis patients than in sepsis patients. These results support the enthusiasm resulting from the initial optimistic results of using the presepsin as a biomarker for sepsis diagnosis.

The serum CRP was widely used as a biomarker for sepsis evaluation. In our study, we found a serum CRP level on 2nd and 4th day following admission and not on admission to be significantly higher in sepsis compared to non-infectious SIRS groups. Yousef et al. [34] showed also that the CRP on admission cannot differentiate between the two groups but only the CRP level on the 4th day is significantly higher in sepsis compared to non-infectious SIRS group. Contrary to this, Farag et al. found an elevated CRP on admission and on days 2 and 4 to be significantly higher in septic patients than in non-infectious SIRS [5].

Table 5
Correlation between some variables and ICU length of stay.

ICU Stay	ALOS	
	Correlation coefficient (r)	P value
Admission SOFA score	0.383	0.03
APACHE II score	0.45	0.011
Admission presepsin	0.44	0.013
Presepsin on day 2	0.51	0.003
Presepsin on day 4	0.45	0.005
Admission CRP	0.236	0.2
CRP on day 2	0.522	0.003
CRP on day 4	0.472	0.007

For the evaluation of the accuracy of both biomarkers in differentiation between sepsis and non-infectious SIRS, we studied the area under the receiver operator characteristics curve. The AUC was 1 for all presepsin measurements and it was ranging from 0.7 to 0.744 for CRP. We found a serum presepsin level of 422 pg/mL on admission, of 427.5 pg/mL on day 2, and of 410.5 pg/mL on day 4 to have a sensitivity and specificity of 100% for diagnosis of sepsis.

When Shozushima et al. [30] compared presepsin with CRP, and procalcitonin, their results showed that the AUC value for presepsin was the highest among the measured markers followed by CRP and procalcitonin (0.845 vs 0.815 and 0.652 for presepsin, CRP, and procalcitonin respectively). Endo and his colleagues [35] also found a higher sensitivity of presepsin for the diagnosis of sepsis which was 91.9% compared to 89.9% for procalcitonin and 35.4% for blood culture. These findings were in agreement with the present study demonstrating that presepsin may be advantageous in the diagnosis of sepsis compared to the other biomarkers. Shozushima and his colleagues [30] in the study just discussed found a cutoff value of presepsin of 399 pg/ml to have a sensitivity of 80.3% and a specificity of 78.5% for the diagnosis of sepsis compared to no sepsis including normal subjects. When used for discriminating non-infectious SIRS and sepsis, they [30] found however a lower cutoff value of presepsin of 415 pg/ml which was close to ours to have a sensitivity and specificity of 80.1% and 81% respectively. Endo et al., [35] found a cutoff value of presepsin for discrimination of bacterial and nonbacterial infectious diseases to be 600 pg/ml, of which the clinical sensitivity and specificity were 87.8% and 81.4%, respectively. The AUC of 1 with 100% sensitivity and specificity are however too high to be true. This could be explained by the small sample size of the study despite we used nonparametric Mann-Whitney *U* test for statistical analysis. This small sample size may accordingly affect the accuracy of the ROC analysis in determining the cutoff values in our study.

Identification of prognosis and predicted mortality with sepsis is an important factor in patient stratification and management [36]. Many markers were studied and evaluated about their ability for mortality prediction on SIRS patients [2]. Labelle et al. [37] showed that in patients with septic shock who received adequate antimicrobial therapy, the acquisition of infection in the intensive care unit and severity of illness to be the most important determinants of clinical outcome. Presepsin as a biomarker was supposed to be not only suitable for the early diagnosis of sepsis, but also for the assessment of its severity and prognosis.

In present study we had a limited number of populations that hindered against subgrouping into more segments that enroll severe sepsis and septic shock. We applied accordingly correlation between presepsin levels and both SOFA and APACH II scores as indirect parameters for sepsis severity. In the present study, we found a significant positive correlation between admission SOFA score and the three presepsin levels on days 0, 2 & 4.

This was seen also in Ulla et al. [31] study who found a significant correlation between presepsin levels and SOFA score on admission, as a severity index of organ failure. Moreover, the level of presepsin was seen in data from ALBIOS study to be correlated with SOFA score, and hemodynamic stability [38]. There was a strong significant positive correlation between presepsin levels and APACHE II score in our study that was also shown by Shozushima et al. [30]. Kojika et al. [39] showed a significant correlation between presepsin values and both APACHE II and SOFA scores. These findings strengthened the hypothesis of presepsin use for

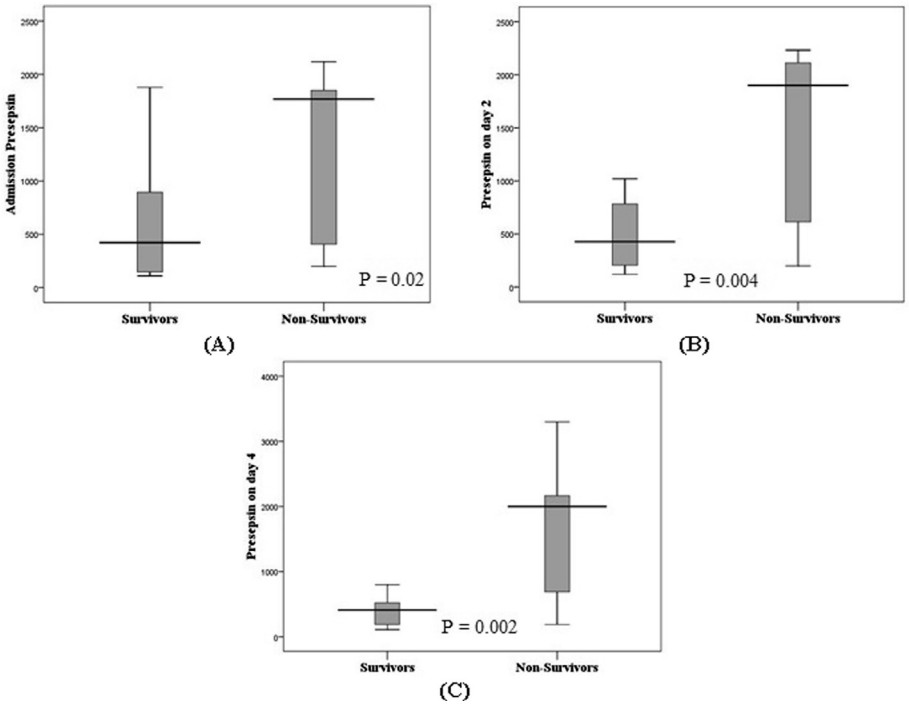

Fig. 8. Presepsin on admission (A), on day 2 (B) and on day 4 (C) in survivors and non-survivors.

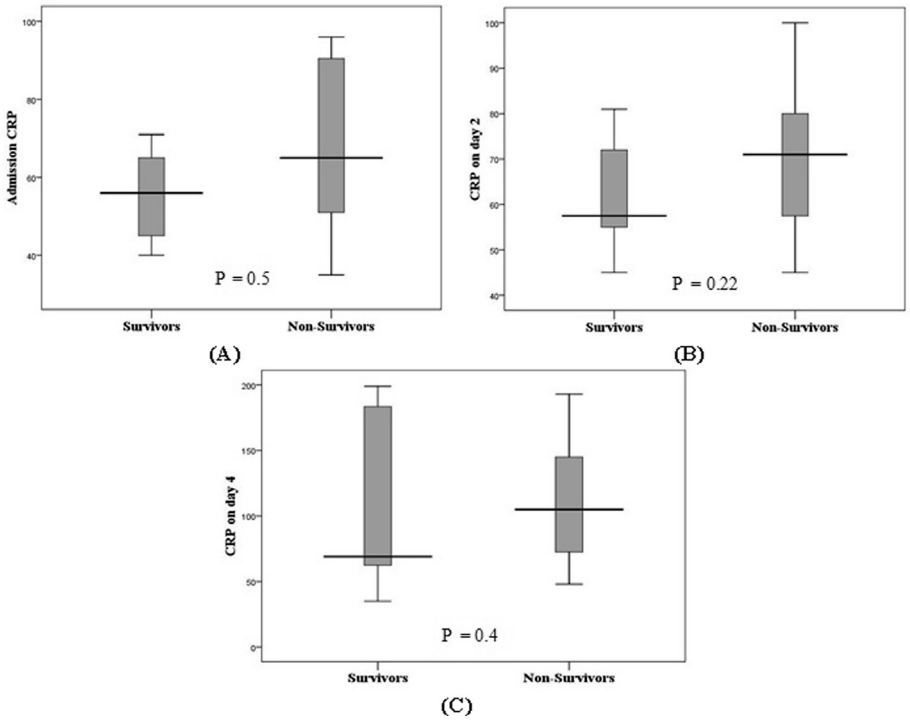

Fig. 9. CRP on admission (A), on day 2 (B) and on day 4 (C) in survivors and non-survivors.

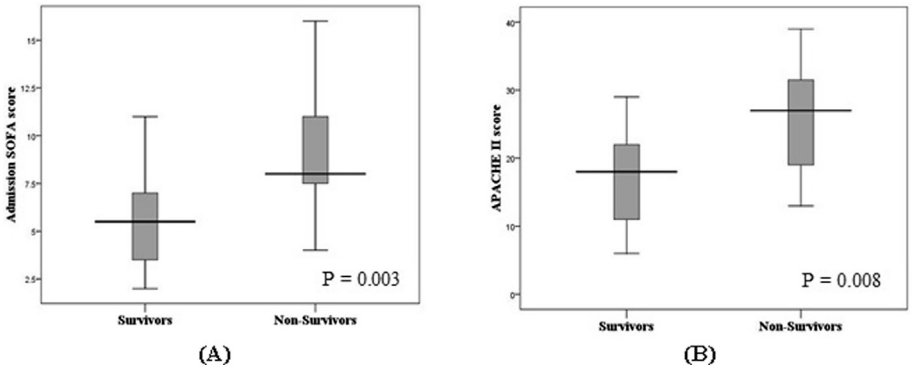

Fig. 10. Admission SOFA score (A) and APACHE II score (B) in survivors and non-survivors.

Table 6
ROC analysis for different markers in mortality prediction.

	Area	P value	95% Confidence interval	
			Upper bound	Lower bound
Admission presepsin	0.755	**0.021**	0.938	0.571
Presepsin on day 2	0.807	**0.005**	0.994	0.619
Presepsin on day 4	0.834	**0.002**	1	0.661
Admission SOFA score	0.811	**0.005**	0.967	0.655
APACHE II score	0.786	**0.009**	0.961	0.612

Bold indicates the statistically significant items.

prediction of more severe infection and reflecting patient condition.

On the other hand, the admission CRP was positively correlated with SOFA score and not with APACHE II score. This relation was lost on the CRP on the 4th day of admission. Similar results were seen by Taema and El-Kholy [40] and Lobo et al. [41] who found that the admission CRP level is positively correlated with the SOFA score but not the APACHE II score.

Besides being an outcome measure, prediction of the average length of ICU stay (ICU-LOS) is a cornerstone in family counseling and is an important socioeconomic factor [42]. Our study and that of Yousef et al. [34] found that the average stay was significantly higher in sepsis than in SIRS group however Ferreira et al. [14] showed no significant difference in the length of stay among the groups. The three presepsin levels in our study were positively correlated with ICU-LOS. Behnes et al. [43] also showed that the

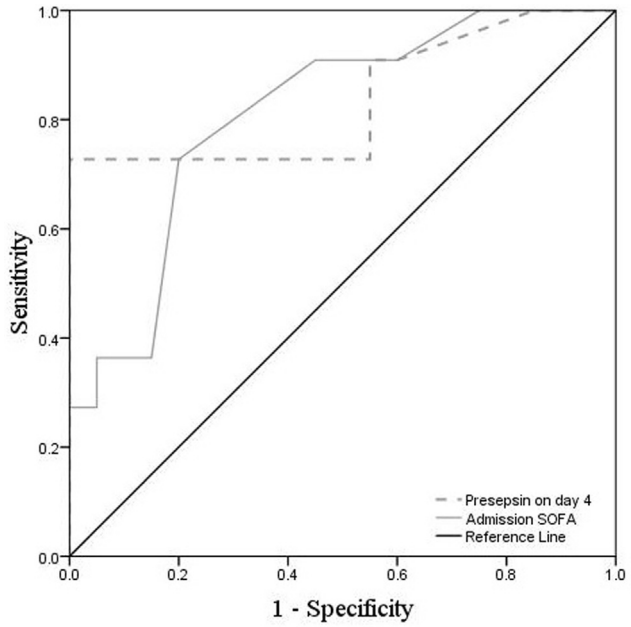

Fig. 11. The ROC curve for admission SOFA score and presepsin in day4 for mortality prediction.

presepsin had significant correlation with length of stay in ICU. The association between the presepsin level and the disease severity can explain its association with more lengthy ICU care. These results supported the use of presepsin as a predictor of ICU length of stay.

When we studied the use of CRP as a predictor of the ICU-LOS, we showed that the days 2 and 4 and not the admission levels were positively correlated with the ICU-LOS. Other studies showed that the admission CRP correlated positively with length of stay [40,44] while Salih et al. [45] reported that CRP levels did not show any significant relation with length of stay and that it had no value as an indicator for prognosis and this disagreed with our study.

The admission SOFA and APACH II scores were positively correlated with ICU-LOS in our study. Barie et al. [46] and Siddiqui et al. [47] strongly claimed in their studies that APACHE II score on admission is a reliable predictor of length of stay in ICU. Engel et al. [48] reported a positive correlation between admission SOFA and ICU-LOS like our results but in their study they concluded that the maximum SOFA and the change of SOFA over time are better than admission SOFA score in prediction of the ICU-LOS.

We found in our study that the presepsin levels on admission and on days 2 and 4 are predictors for survival. They were significantly higher in non-survivors than in survivors. Similar results were concluded by Ulla et al. [31] and Liu et al. [7] who found that the presepsin concentrations at the first evaluation in ED are higher in non-survivor septic patients than in survivors. They concluded that presepsin was better than CRP in assessing the risk of death within 30 days after onset of sepsis. In the ALBIOS trial by Masson et al., [38] the admission presepsin concentration was found to be significantly higher in nonsurvivors than in survivors.

In our study, the CRP levels did not show any significant difference between survivors and non survivors on days 0, 2, or 4. Silvestre et al. [49] in 2009 studied the prognostic value of initial APACHE II, SOFA and CRP and they concluded that CRP was not an adequate marker for the prognosis of sepsis patients. Ho et al. [50] showed however that a high CRP level was an independent risk factor of mortality. Hogarth et al. [51] reported also that non-survivors had a significantly higher median CRP concentration on admission than that measured in survivors.

In the present study, the admission SOFA score and APACH II score were significantly lower in the survivors compared to non-survivors. These results were in agreement with Qiao et al. [52] who found that the APACHE II and SOFA scores were significantly lower in survivors. Additionally, Komatsu et al. [53] reported that the APACHE II score of $\geqslant$19 or SOFA score of $\geqslant$8 to be associated with higher mortality in patients with colorectal perforation. Ferreira et al.[14] reported also a mortality rate of 50% in patients with increase in SOFA score during the first 48 h in the ICU. Decreasing SOFA score was however associated with only 27% mortality. Moreno et al. [54] also demonstrated a strong correlation of initial and maximum SOFA scores with mortality outcome.

When the ROC curves of different studied markers and severity scores were evaluated, the results showed that the AUC value for presepsin on day 4 (0.834) was the highest among the measured markers followed by admission SOFA (0.811) and APACHE II scores (0.786) indicating that day 4 presepsin might have a better ability to predict the risk of death. Masson and colleagues [10] found AUCs for presepsin of 0.96, 0.70, and 0.74 on days 1, 2, and 7 respectively for predicting death during the hospital stay. When Liu et al. [7] extended the mortality prediction beyond hospital stay to include 28 days mortality in septic patients, they found an AUC of presepsin to be (0.658) that was slightly lower than that of APACHE II score (0.722) and procalcitonin (0.679). The higher AUC of presepsin on day 4 rather than in day 0 in our study in nonsurvivors may indicate a poor response to treatment compared to presepsin in earlier time points.

We found a cut off value of day 4 presepsin of 900 pg/mL to have a sensitivity of 73% and specificity of 100% in mortality prediction in SIRS patients. A lower cut off value (556 pg/ml) were found by Liu et al. [7] for predicting longer term mortality (28 days) in septic patients than in our study was found to be 62.2% sensitive and 66.8% specific. Admission SOFA score of 7.5 was 73% sensitive and 80% specific for predicting mortality in patients with SIRS. Qiao et al. [52] found that initial SOFA score of 3.5 was 58.8% sensitive and 66.7% specific for predicting mortality in elderly critically ill patients.

We evaluated the relation between the trends of change in the serum levels of both markers over time. The decrease of presepsin on day 4 compared to admission was significantly associated with survival. The decrease of presepsin on day 4 from admission value was found to be 70% sensitive and 91% specific for predicting survival in patients with SIRS with PPV of 93% and NPV of 63%. Spanuth et al. [33] showed a decreased presepsin from baseline to 72 h in patients with favorable outcome. In the patient group

Table 7
The trend of biomarkers over time and survival.

		Survivors	Non-survivors	P value
Presepsin level	Decreased	14	1	0.001
	Increased	6	10	
CRP level	Decreased	3	2	0.6
	Increased	17	9	

who experienced adverse outcome, presepsin levels showed an increasing tendency. Masson et al. [10] also reported that increasing concentrations of presepsin from day 1 to day 7 predicted higher ICU and 90-day mortality. On the 7th day, the presepsin level of the surviving patients declined significantly compared to the dead patients. This opens a newer hypothesis of using the presepsin level to monitor the efficacy of the therapy. The decline in presepsin levels in survivors may represents successful treatment and the increased level may represents a poor response to therapy with exaggerated inflammatory response [10].

This relation couldn't be elucidated with the serum CRP as the relation between CRP decrease and survival was statistically insignificant in our study. Contrary to our results, Lobo et al. [41] showed that patients with a decrease in CRP level 48 h after admission to ICU was associated with a mortality rate of 15.4%, while an increased CRP level was associated with a mortality rate of 60.9%. This study was conducted on a heterogenous ICU patients rather than SIRS or sepsis patients.

Our study was limited by the small sample size that included only 31 patients. We measured the biomarkers only in three samples; on admission and on days 2 and 4. Other measurements in more time periods might add benefits in understanding the time course of the biomarker. The limited number of the sample size and limited samples for assay were due to financial constraints. Similar to other studies involving sepsis, there is no gold standard for sepsis diagnosis. Some of the patients that were early classified in one group were later reclassified to the other. The diagnosis conflicts in the study included also patients with milder form of sepsis that might be classified as SIRS or patients with sterile SIRS that might be classified as sepsis. The researchers couldn't evaluate the relation between the serum presepsin and neither the type of the organism nor the infection site due to the small sample size. Further studies with larger sample size for the evaluation of the presepsin are warranted.

We concluded that the presepsin can be a promising and readily available biomarker for early differentiation between sepsis and non-infectious SIRS. It can also predict poor outcome, more organ failure, and subsequently, mortality. In this context, the presepsin was seen to be more accurate than CRP.

Conflict of interest

None.

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