# Prognostic Value of Presepsin (Soluble CD14 Subtype) In Critically Ill Patients with Severe Sepsis and Septic Shock

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**Abstract**: **Introduction:** Biomarkers, which were introduced in diagnosis and risk assessment of sepsis, could contribute in predicting outcome in those patients affected by sepsis, severe sepsis, and septic shock who could benefit from a quick and appropriate therapy. Among different molecules that have been suggested as sepsis biomarkers in the last years is presepsin which appears quite promising due to its reported correlation with the septic process. The aim of this study was to evaluate and compare the prognostic value of presepsin with that of APACHE II score and C-reactive protein (CRP) in critically ill patients with severe sepsis and septic shock. ***Methods:*** The study was carried out on 40 adult patients of both sex suffering from severe sepsis and septic shock, all of them received the same treatment as recommended by the surviving sepsis campaign, 19 of them have survived (Group I), and the other 21 didn't (Group II). The study group patients are those who were admitted to the units of Critical Care Medicine Department in Alexandria Main University Hospital and who fulfilled the diagnostic criteria for severe sepsis or septic shock on arrival to ICU according to the SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Venous blood samples were obtained from Group I and Group II on admission and after 72 hours to determine presepsin level on admission and after 72 hours, CRP level on admission and after 72 hours, and APACHE II score on admission. Plasma presepsin concentrations (pg/ml) were determined using immunoassay analyzer (PATHFAST; Mitsubishi Chemical Medience Corporation, Japan). Patients were managed according to the surviving sepsis campaign guidelines. ***Results:*** This study showed that the mean values of presepsin on admission and APACHE II score were significantly higher in Group II than in Group I ($p$<0.001and $p$ =0.002, respectively). While the was no significant difference between both groups regarding mean CRP levels ($p$ =0.642). The best prognostic cutoff for presepsin on admission was 1640 pg/ml: at that level sensitivity and specificity were 90.48 percent and 78.95 percent, respectively. The best prognostic cutoff for APACHE II score was 24; at that level sensitivity and specificity were 71.43 percent and 73.68 percent, respectively. There was a significant correlation between presepsin levels on admission and APACHE II score (r=0.563, $p$ <0.001). Presepsin values in Group I were significantly higher on admission (median=1411.0 pg/ml) than on day three (median=1104.0 pg/ml) ($p$ =0.018), while presepsin values in Group II were significantly lower on admission (median=2199.0 pg/ml) than on day three (median=3580.0 pg/ml) ($p$ =0.030).***Conclusions:*** Presepsin is a new promising biomarker in predicting mortality in patients with severe sepsis and septic shock. The specificity and sensitivity of presepsin in predicting mortality were higher than those for APACHE II score. Prediction of mortality in patients with severe sepsis and septic shock can be improved by combination of both presepsin and APACHE II score on admission. Presepsin can be used as a marker for disease monitoring.

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**Key words:** Presepsin, CRP, APACHE II score, severe sepsis, septic shock.

## 1. Introduction

Sepsis is a potentially deadly medical condition characterized by a whole body inflammatory status that is triggered by an infection.(1) Severe sepsis and septic shock are major healthcare problems, affecting millions of individuals around the world each year, killing one in four and often more, and increasing in incidence.(2) In the United States alone, approximately 750,000 cases of sepsis occur each year, at least 225,000 of which are fatal.(3)

Septic patients are generally hospitalized for extended periods, rarely leaving the ICU before 2 to 3 weeks. Despite the use of antimicrobial agents and advanced life support tool, the case fatality rate for patients with sepsis has remained between 20% and 30% over the last two decades.(3,4)The speed and appropriateness of therapy administered in the initial hours after diagnosis of severe sepsis develops are likely to influence outcome.(4, 5)

Systemic inflammatory response syndrome (SIRS) is the clinical syndrome that results from a dysregulated inflammatory response to infectious and also noninfectious insult. It requires that two or more of the following abnormalities be present which are

Temperature >38.5ºC or <35ºC, Heart rate >90 beats/min, Respiratory rate >20 breaths/min or $PaCO_2$ <32 mmHg, and WBC >12,000 cells/$mm^3$, <4000 cells/$mm^3$, or >10 percent immature (band) forms.[6]

Sepsis is defined as SIRS in the presence of infection.[1] Sever sepsis is defined as sepsis associated with multiple organ dysfunction (MOD).Septic shock is defined as persistent hypotension in patients with sepsis inspite of adequate fluid resuscitation and in the absence of other causes for hypotension.[7]

There are different scoring systems are intended to serve as predictors of outcome. Among the most commonly used scoring systems are the multiple organ dysfunction score (MODS), sequential organ failure assessment (SOFA), acute physiology and chronic health evaluation (APACHE).[8-10]

Also many biomarkers such as lactate, C-reactive protein (CRP), and procalcitonin (PCT) are proved to be useful in the diagnosis, prediction and monitoring response to antibiotics in patients with sepsis, sever sepsis, and septic shock.[11, 12]

C - reactive protein is an acute phase protein and its plasma level is increased in most forms of acute and chronic inflammatory diseases.[13,14] A useful biomarker of infection, or rather the host response to infection, should provide additional information to the clinical picture in the fields of diagnosis, disease severity stratification and prognosis, and therapeutic guidance, CRP has been investigated in all these 3 areas.[15,16] CRP is perhaps the most widely used biomarker of infection in critically ill patients.[17,18]

CD14 is a glycoprotein expressed on the membrane surface of monocytes/ macrophages and serves as a receptor for complexes of lipopolysaccharides (LPS) and LPS binding protein (LPBP) activating the toll‐like receptor 4 (TLR4) specific pro‐inflammatory signaling cascade against infectious agents.[19]

Simultaneously, CD14 is shedded from the cell membrane forming soluble CD14 (sCD14) which can be found in serum with two different molecular weights[19]. Clinical studies have revealed elevated sCD14 levels in septic patients and an association with mortality.[20, 21] Recently another molecule fragment of sCD14 was discovered and named soluble sCD14 subtype (sCD14‐ST) or Presepsin.[22] Plasma presepsin levels are associated with systemic inflammation triggered by bacterial infections. First results of clinical studies suggested that presepsin may be a promising diagnostic and prognostic biomarker of systemic infections or sepsis.[18, 23, 24]

**Aim of the work**

The aim of the present study was to evaluate and compare the prognostic value of presepsin with that of APACHE II score and C-reactive protein (CRP) in critically ill patients with severe sepsis and septic shock.

**2. Patients and Methods**

The study was carried on 40 adult patients of both sex suffering from severe sepsis and septic shock, all of them received the same treatment as recommended by the surviving sepsis campaign, 19 of them have survived (Group I), and the other 21 didn't (Group II). The study group patients are those who were admitted to the units of Critical Care Medicine Department in Alexandria Main University Hospital and who fulfilled the diagnostic criteria for severe sepsis or septic shock on arrival to ICU according to the SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Exclusion criteria were: (1) patients aged less than 18 years; (2) Patients who were admitted after 24 hours from the recognition of severe sepsis or septic shock; (3) Pregnant females; and (4) patients with negative culture results from primary site of infection.

Subjects' data including name, age, sex, pre-existing medical conditions, and data obtained from clinical examination were recorded at enrollment. Laboratory investigations including complete blood count, blood chemistry, bleeding profile, blood gas analysis, blood cultures, and cultures from any site of infection were obtained. Also presepsin level and CRP levels were obtained from the 40 patients understudy on admission and after 72 hours. APACHE II score was calculated for all patients on admission. Plasma presepsin concentrations (pg/ml) were determined using immunoassay analyzer (PATHFAST; Mitsubishi Chemical Medience Corporation, Japan). CRP (mg/dl) levels were determined using commercial available kits following the instructions of the manufacturers. Patients were managed according to the surviving sepsis campaign guidelines.

**Statistical analysis[25]:**

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0.[26] Qualitative data (age, gender, and preexisting conditions) were described using number and percent. Quantitative data (Presepsin, APACHI II, and CRP) were described using median, minimum and maximum as well as mean and standard deviation. For qualitative variables (Age, gender, and preexisting conditions), Chi-square test was used. When more than 20% of the cells had expected count less than 5, correction for Chi-square was conducted using Fisher's Exact test or Monte Carlo correction. The distribution of quantitative variables was tested for normality using Kolmogrov-Smirnov test and Shapiro-Wilk test. D'Agstino test was used if there was a conflict between the two previous tests.

APACHI II and CRP revealed normal data distribution so parametric tests were applied.

Presepsin revealed abnormally distributed data so non-parametric tests were used. For APACHI II and CRP, independent t-test was used to analyze two independent populations. For presepsin, Mann-Whitney test (for data distribution that were significantly deviated from normal) was used to analyze two independent populations. To compare between presepsin on admission and on day3 Wilcoxon signed ranks test was applied. All statistical tests were two-tailed, and p <0.05 was considered statistically significant.

Agreement of presepsin and APACHI II was expressed in sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy using the following equations:

- Sensitivity = true positive/ true positive + false negative.
- Specificity = true negative/ true negative + false positive.
- PPV = true positive/ total positive.
- NPV = true negative/ total negative.
- Accuracy = true positive + true negative/ all the patients having the test.

Receiver operating characteristic curves (ROC) were drawn; the areas under the ROC curves denote the prognostic accuracy of presepsin and APACHI II.

## 3. Results

Group I and Group II were homogeneous in terms of size, demographic characteristics, and preexisting conditions with no statistically significant difference between them (Tables 1 and 2).

**Table (1):Comparison between Group I and Group II according to demographic characteristics**

| | Group I (n=19) | | Group II (n=21) | | *p* |
|---|---|---|---|---|---|
| **Gender** | **No.** | **%** | **No.** | **%** | |
| Male | 14 | 73.7 | 13 | 61.9 | 0.427 |
| Female | 5 | 26.3 | 8 | 38.1 | |
| **Age** | | | | | |
| Min. – Max. | 45.0 – 74.0 | | 49.0 – 75.0 | | 0.390 |
| Mean ± SD. | 62.89 ± 8.44 | | 60.67 ± 7.77 | | |
| Median | 65.0 | | 60.0 | | |

***p***, *p* value for comparing between the two groups; **SD**, standard deviation.

**Table (2): Comparison between Group I and Group II according to preexisting conditions**

| Preexisting Conditions | Group I(n=19) | | Group II(n=21) | | *P* |
|---|---|---|---|---|---|
| | **No.** | **%*** | **No.** | **%*** | |
| **DM** | 8 | 42.1 | 10 | 47.6 | 0.726 |
| **HTN** | 6 | 31.6 | 7 | 33.3 | 1.000 |
| **M.I** | 4 | 21.1 | 2 | 9.5 | FEp=0.398 |
| **HF** | 2 | 10.5 | 2 | 9.5 | FEp=1.000 |
| **Liver disease** | 3 | 15.8 | 3 | 14.3 | FEp=1.000 |
| **COPD** | 2 | 10.5 | 3 | 14.3 | FEp=1.000 |

***p***, *p* value for comparing between the two groups; $\chi^2$, Chi square test; **FE**, Fisher Exact test; D.M, Diabetes Mellitus; HTN, Hypertension; M.I, Myocardial Infarction; H.F, Heart Failure; **COPD**, chronic obstructive pulmonary disease.

APACHE II score was found significantly higher in Group II than Group I on admission. The mean levels of APACHE II score were 23.68 ± 5.61 in Group I and 30.67 ± 7.30 in Group II, with a statistically significant increase in Group II in comparison to Group I (*p* =0.002) (Table 3).

**Table (3):Comparison between the studied groups according to APACHE II score**

| APACHE II score | Group I (n=19) | Group II (n=21) | *p* |
|---|---|---|---|
| Min. – Max. | 16.0 – 39.0 | 21.0 – 42.0 | 0.002* |
| Mean ± SD. | 23.68 ± 5.61 | 30.67 ± 7.30 | |
| Median | 23.0 | 30.0 | |

t, Student t-test; *, Statistically significant at p ≤ 0.05

On studying presepsin, Presepsin levels on admission showed a statistically significant increase in Group II in comparison to Group I (Table 4).

**Table (4): Comparison between the studied groups according to presepsin levels on admission**

| Presepsin On admission | Group I (n=19) | Group II (n=21) | *p* |
|---|---|---|---|
| Min. – Max. | 950.0 – 3183.0 | 1587.0 – 6359.0 | |
| Mean ± SD. | 1570.11±550.11 | 2644.76±1283.1 | <0.001* |
| Median | 1411.0 | 2199.0 | |

Z, Z for Mann Whitney test; *, Statistically significant at *p* ≤ 0.05.

On studying CRP, there was no statistically significant difference between both groups regarding CRP levels on admission (table 5).

**Table (5): Comparison between the studied groups according to CRP levels on admission**

| CRP on admission | Group I (n=19) | Group II (n=21) | *P* |
|---|---|---|---|
| Min. – Max. | 110.0 – 200.0 | 101.0 - 237.0 | 0.642 |
| Mean ± SD. | 162.63 ± 22.04 | 166.10 ± 24.44 | |
| Median | 170.0 | 168.0 | |

t, Student t-test; ***p***, *p* value for comparing between the two groups.

The ROC (Receiver Operating Characteristic) curves of the studied biomarkers were designed and presented in figure 1. The AUCs (Areas Under the Curve) calculated from the ROC curves were 0.778 (*p*=0.003) for APACHE II score (red line), 0.865 (*p*<0.001) for presepsin levels on admission (blue line), and 0.867 (*p*<0.001) for presepsin on admission in combination with APACHE II score (green line).

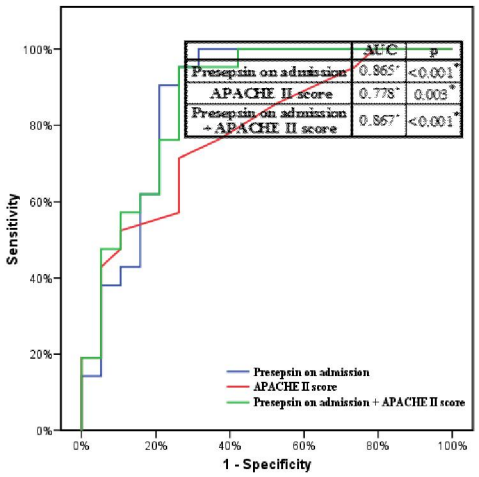


**Figure (1): ROC curve for presepsin on admission and APACHE II score.**

On comparison the previous AUCs the difference between them was not statistically significant (table 6).

**Table (6): Difference between areas under the curve calculated from ROC curve**

| | APACHE II score | Presepsin on admission + APACHE II score |
|---|---|---|
| **Presepsin on admission** | 0.314 | 0.939 |
| **APACHE II score** | ------ | 0.163 |

***p***, *p* value for comparing between the two groups.

The best prognostic cutoff for presepsin on admission was 1640 pg/ml: at that level the sensitivity and specificity were 90.48 percent and 78.95 percent, respectively. The best prognostic cutoff for APACHE II score was 24; at that level the sensitivity and specificity were 71.43 percent and 73.68 percent, respectively (Table 7).

**Table (7): Cutoff point, sensitivity, specificity, positive predictive value, negative predictive value, and accuracy for the different studied biomarkers**

| | Cutoff point | Sensitivity | Specificity | PPV | NPV | Accuracy |
|---|---|---|---|---|---|---|
| **Presepsin on admission** | **>1640** | 90.48 | 78.95 | 82.61 | 88.24 | 85.0 |
| **APACHE II score** | **>24** | 71.43 | 73.68 | 75.00 | 70.0 | 72.5 |

**PPV**, positive predictive value; **NPV**, negative predictive value.

This study showed a significant correlation between presepsin levels on admission and APACHE II score (r=0.563, *p*<0.001) (Figure 2).

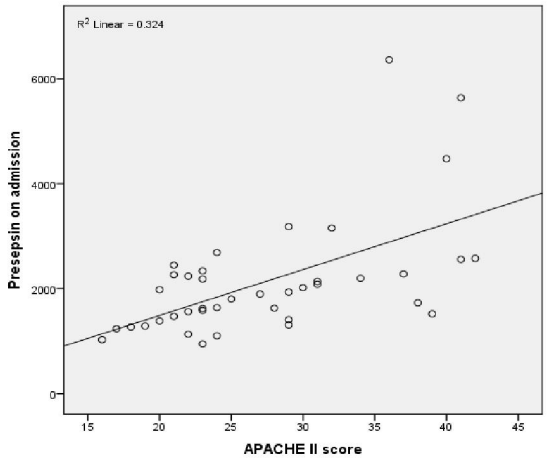


**Figure (2): Correlation between presepsin value on admission and Acute Physiology and Chronic Health Evaluation II (APACHE II) score.**

Presepsin values in Group I were significantly higher on admission than on day three while its values in Group II were significantly higher on day three than on admission (Table 8) (Figure 3).

**Table (8): Comparison between the two studied groups according to presepsin level on admission and on day three**

| Presepsin | On admission | On day three | *p* |
|---|---|---|---|
| **Group I** | | | |
| Min. – Max. | 950.0 – 3183.0 | 761.0 – 3140.0 | |
| Mean ± SD. | 1570.11±550.11 | 1296.05±579.24 | 0.018* |
| Median | 1411.0 | 1104.0 | |
| **Group II** | | | |
| Min. – Max. | 1587.0 – 6359.0 | 1205.0 – 7890.0 | |
| Mean ± SD. | 2644.76±1283.05 | 3626.62±1688.64 | 0.030* |
| Median | 2199.0 | 3580.0 | |

Z, Z for Wilcoxon signed ranks test for comparing between admission and on day three in each studied group; *, Statistically significant at $p \leq 0.05$.

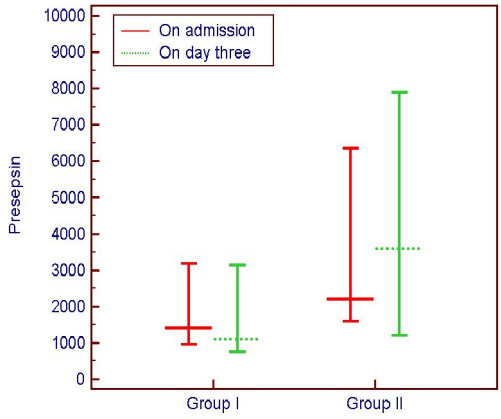


**Figure (3): Comparison between the two studied groups according to presepsin level on admission and on day three.**

## 4. Discussion

Sepsis still represents a major cause of morbidity and mortality in critically ill patients despite the use of

modern antibiotics and resuscitation therapies.[27] The case fatality rate for patients with severe sepsis has remained between 20 and 50% during the past two decade [28].

Biomarkers play an important role in early diagnosis, differential diagnosis, risk stratification, therapy monitoring and evaluation of prognosis of sepsis.[29] Among different molecules that have been suggested as sepsis biomarkers in last years, presepsin or soluble CD14 subtype (sCD14-ST) appears quite promising due to its reported correlation with the septic process.[29, 30] Recently a new, highly sensitive, and fully automated PATHFAST presepsin assay system have been developed based on the chemiluminescent enzyme immunoassay (CLEIA) principle, which can be used to analyze whole blood samples without the need for sample pretreatment, hence can be used for point-of-care.[31]

In the present study, Group I and Group II were homogeneous in terms of size and demographic characteristics with no statistically significant difference between them regarding age and gender ($p$=0.390, and $p$=0.427, respectively). Most of the patients enrolled in the present study were over 60 years old; the mean age was 62.89 for Group I and 60.67 for Group II.

Also, there was no statistically significant difference between Group I and Group II regarding preexisting conditions, diabetes mellitus and hypertension were the most common preexisting conditions found in both groups accounting for 8 patients (42.1%) and 6 patients (31.6%) in Group I, respectively, while they accounted for 10 patients (47.6%) and 7 patients (33.3%) in Group II, respectively.

Cultures from the primary site of infection showed that the incidence of gram-positive and gram-negative infections was nearly similar within the studied population. There was no significant difference between both groups regarding type of infecting organisms ($p$=0.657).

In the present study, APACHE II score was significantly higher in Group II (mean=30.67) than Group I (mean=23.68) ($p$ =0.002). This showed that APACHE II score has a good prognostic value for predicting mortality.

Although CRP levels were slightly higher in Group II (mean=166.10 mg/dl) than Group I (mean=162.63 mg/dl) but this difference was not statistically significant (p=0.642). This showed that the mean level of CRP concentrations in plasma on admission could not predict mortality.

In our study population, the median presepsin concentrations in plasma on admission showed a good prognostic value for predicting mortality as its levels were significantly higher in Group II (median=2199 pg/ml) than Group I (median=1411 pg/ml) ($p$ =<0.001).

In agreement with our study, Spanuth *et al.* [32] investigated the diagnostic and prognostic value of presepsin (soluble CD14 subtype) in emergency patients with early sepsis using the new assay PATHFAST presepsin. They found that presespin values on admission enabled reliable prognosis and early risk prediction of mortality ($p$ <0.001).

Similarly, Liu *et al.* [33] during their study on the diagnostic value and prognostic evaluation of presepsin for sepsis in an emergency department, they found that the median levels of presepsin were significantly higher in non-survivors than in survivors ($p$<0.001), which further confirmed that the higher the plasma presepsin level, the more adverse the outcome in septic patients.

Moreover and in conjunction, Ulla *et al.* [34] studied the diagnostic and prognostic value of presepsin in the management of sepsis in the emergency department through a multicenter prospective study. They found that the close correlation between presepsin initial values and in-hospital mortality suggested that this biomarker could be used in order to perform an early and reliable risk stratification and to identify high risk patients who could benefit of a more aggressive approach ($p$=0.04).

In addition, Masson *et al.* [35] investigated the presepsin (soluble CD14 subtype) and procalcitonin levels for mortality prediction in sepsis and they found that presepsin measurements may provide useful prognostic information in patients with severe sepsis and septic shock ($p$=0.0012).

In the present study, the ROC curves of APACHE II score and presepsin on admission were designed and the AUC calculated from the ROC curves were 0.778 ($p$ =0.003) for APACHE II score, and 0.865 ($p$<0.001) for presepsin on admission with no significant difference between both of them ($p$=0.314). The AUC of presepsin on admission in combination with APACHE II score (0.867; $p$<0.001) was slightly larger compared to presepsin alone or APACHE II score alone but this difference was also not statistically significant ($p$=0.939 and 0.163, respectively).

The best prognostic cutoff value for presepsin on admission, resulting from the ROC curve, was 1640 pg/ml: at that level sensitivity and specificity were 90.48% and 78.95% respectively, while for APACHE II score was 24: at that level sensitivity and specificity were 71.43% and 73.68%, respectively. At the previous cutoff values, the specificity and sensitivity of presepsin in predicting mortality were higher than those for APACHE II score.

In agreement with the present study, Spanuth *et al.* [32] during their study on the diagnostic and

prognostic value of presepsin (soluble CD14 subtype) in emergency patients with early sepsis using the new assay PATHFAST presepsin. The ROC curve was performed comparing the accuracy for the prediction of mortality of presepsin and APACHE II score. Presepsin and APACHE II score showed a good prognostic accuracy (0.878 and 0.815, respectively). The cutoff value for presepsin and APACHE II score were 1662 pg/ml, 23, respectively.

From another hand, Liu *et al.* [33] designed a ROC curve to study the prognostic value of presepsin in the management of sepsis in the emergency department. In their study[33], the AUC for presepsin on admission (0.658) was significantly smaller than for APACHE II score (0.722) ($p$ <0.05). The AUC of presepsin in combination with APACHE II score was 0.734, which was more statistically significant compared with presepsin alone (0.658; $p$<0.05), and there was no statistical difference for the combination of presepsin and APACHE II score compared with APACHE II score alone ($p$ >0.05). The cutoff value for presepsin on admission and APACHE II score were 556 pg/ml, and 16.5, respectively, which are lower than our study.

This can be explained by the large number of patients included in their study; 859 patients and the nature of their study group which include patients suffering from SIRS, sepsis, severe sepsis, and septic shock. While in the present study, the study group included only patients with the severest form of sepsis (severe sepsis and septic shock) and did not include patients with milder forms of sepsis.

In the present study, there was a significant correlation between presepsin levels on admission and APACHE II score (r=0.563, $p$<0.001), indicating that presepsin and APACHE II score may facilitate evaluation of the severity of sepsis and allow effective risk stratification.

In agreement with the present study, Liu *et al.* [33] found that the levels of plasma presepsin were positively correlated with APACHE II score in their study group.

In contrast to the present study, Nishida *et al.* (265) studied the usefulness of presepsin (soluble CD14 subtype) in septic patients and found that although the presepsin values were significantly higher in patients with the more severe septic condition (for example, sepsis, severe sepsis, septic shock), there was no significant correlation between APACHE II scores and presepsin values. This can be explained by the smaller number of patients in septic group (23 patients).

In the present study, Presepsin values in Group I were significantly higher on admission (median=1411.0 pg/ml) than on day three (median=1104.0 pg/ml) ($p$=0.018), while presepsin values in Group II were significantly lower on admission (median=2199.0 pg/ml) than on day three (median=3580.0 pg/ml) ($p$=0.030). This denotes that plasma presepsin levels were a good parameter for sepsis monitoring.

In agreement with the present study, Spanuth *et al.* [32] found that presepsin values in the course of the disease showed an increasing tendency in patients with unfavorable outcome while in patients with favorable outcome this tendency was decreasing.

In the present study, CRP values in Group I were higher on admission (mean=162.63 mg/dl) than on day three (mean=157.42 mg/dl) but with no statistically significant difference ($p$=0.497), also CRP values in Group II were lower on admission (mean=166.10 mg/dl) than on day three (mean=171.81 mg/dl) but with no statistically significant difference ($p$=0.568). This denotes that CRP is not a reliable biomarker in monitoring the course of severe sepsis and septic shock.

## Conclusion

Presepsin is a new promising biomarker in predicting mortality in patients with severe sepsis and septic shock. The specificity and sensitivity of presepsin in predicting mortality were higher than those for APACHE II score. Combination of both presepsin and APACHE II score was not superior to either of them separately. Presepsin can be used as a marker of sepsis monitoring in patients with severe sepsis and septic shock. CRP showed no role in prognosis or sepsis monitoring in patients with severe sepsis and septic shock.

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