How to Cite:
Abd-Elfattah, A. H., Khaled, M. M. Y., Ahmed, A. A., Yahia, M., & Kotrob, A. M. E.- bakry M. (2022). Comparison of Presepsin (CD14), Procalcitonin (PCT) and C- reactive protein (CRP) at different SOFA and APACHE II scores in sepsis patients. *International Journal of Health Sciences*, *6*(S3), 3840–3864. https://doi.org/10.53730/ijhs.v6nS3.6637

Comparison of Presepsin (CD14), Procalcitonin (PCT) and C- reactive protein (CRP) at different SOFA and APACHE II scores in sepsis patients

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***Abstract*---**Sepsis remains a major challenge in clinical practice with considerable morbidity and mortality despite modern treatments. Clinicians need good diagnostic and prognostic markers to identify infected patients who would rapidly benefit from prompt, empirical antibiotic therapy and other supportive treatment. to comparison of Presepsin (CD14), Procalcitonin (PCT) and C- reactive protein (CRP) at different SOFA and APACHE II scores in sepsis patients. A prospective cohort observational study was conducted in Critical Care Medicine Department, Faculty of medicine, Cairo University, Egypt recruiting admitted adult critically ill patients diagnosed. All subjects were recruited during the period from December 2013 to November 2015. All subjects were subjected to complete history taking, clinical examination, Complete blood count, Kidney and Liver function, Coagulation profiles, blood, urine, and sputum cultures ± wound or drain culture, presepsin, PCT and CRP plasma concentrations. Mean age of our study group was 49.8±16.05 years and mean APACHE II

score 14±4.4 with mean length of ICU stay was 13.6±7.06 days.There was significantly higher frequency of DM and HTN in Non- survivors group than Survivors.SOFA score was significantly higher at all assessments in Non- survivors as compared to survivors on admission and at day 1, 3,7 and 15. Procalcitonin and presepsin means were significantly higher from day 0 to 15 in non-survived group as compared to survived group on admission, day 1, 3,7 and 15. There was positive liner significant correlation between procalcitonin and values of APAHE score started from day 0. There was positive liner significant correlation between procalcitonin and values of SOFA score started from day 1with p value 0.005and started to show strong direct correlation till day 15. There was positive liner significant correlation between presepsin and values of SOFA score started from day 0 and started to show strong direct correlation till day 15. Our results concluded that to provide a more consistent and reproducible picture of sepsis incidence and outcomes, the task force sought to integrate the biology and clinical identification of sepsis with its epidemiology and coding.

***Keywords*---**sepsis, prognosis, outcome prediction, presepsin, CRP, procalcitonin, apache II scores.

Introduction

Sepsis is a complex multifactorial and rapidly progressing disease characterized by an excessive inflammatory response to infection that can lead to organ failure and eventual death. [1]. Sepsis remains a major challenge in clinical practice with considerable morbidity and mortality despite modern treatments. Clinicians need good diagnostic and prognostic markers to identify infected patients who would rapidly benefit from prompt, empirical antibiotic therapy and other supportive treatment [2].

Sepsis remains a leading cause of death in critically ill patients. 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 withother 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[9] found a presepsin 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 comparison of presepsin (CD14), procalcitonin (PCT) and C- reactive protein (CRP) plasma concentrations at different SOFA (Sepsis-relatedOrgan Failure Assessment) and the APACHE II scores during sepsis and MODS. As well as, evaluate the clinical usefulness of presepsin (CD14) as a diagnostic and prognostic marker for sepsis in comparison to C-reactive protein (CRP) and procalcitonin (PCT).

Patients and Methods

A prospective cohort observational study was conducted in Maady Armed Forces Compound Hospital, Cairo, Egypt recruiting admitted adult critically ill patients diagnosed to have SIRS according to the SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference [11]. All subjectswere recruited during the period from December 2013 to November 2015 exhibiting two or more of the following signs: temperature of >38 C or < 36C, pulse rate of >90 beats/min, respiratory rate of >20 breaths/min or hyperventilation with a partial pressure of arterial carbon dioxide (PaCO2) of <32 mmHg,or white blood cell (WBC) count of >12,000 lL-1 or<4000 lL-1, or >10% immature cells.

Ethical consideration

Approval of the study protocol by Ethical Scientific Committee of Cairo University was obtained and informed consent was taken from all subjects before their enrollment in the study.

Inclusion criteria

When systemic inflammatory response syndrome (SIRS) or sepsis criteria according to the ACCP/SCCM (American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference) definitions, were fulfilled for a period of no longer than 24 h.

Exclusion criteria

Patient with malignancy, Patient with autoimmune disease and Pregnant females.

All subjects included in the study were subjected to

- Complete blood counts with deferential count (The Sysmex Automated Haematology Analyzer KX-21N (Sysmex corporation, Kobe 651-0073, Japan).
- Renal function tests (AU 480 autoanalyzer, Beckman coulter, AU 480 chemical analyser, USA).
- Liver function testsUsing the Olympus AU640 autoanalyzer (AU 640 autoanalyzer, Diamond Diagnostic- USA).
- Coagulation profiles (PTT, PT, and INR), blood, urine, and sputum cultures ± wound or drain culture, arterial blood gases, chest x ray, urine analyses, presepsin, PCT and CRP plasma concentrations.

Presepsin, PCT and CRP plasma concentrations, the SOFA and the APACHE II scores were determined on observation day 1, 3, 7 and 15 after onset of symptoms of SIRS or sepsis. Pan-cultures will be taken at day 1and 7. Patients will be followed-up for 28 days and assigned to the group of survivors and non-survivors, respectively. Presepsin concentration was measured with a compact automatedimmune analyzer, PATHFAST (Mitsubishi Chemical Europe GmbH, Dusseldorf, Germany), based on a chemiluminescent enzyme immunoassay (CLEIA) combined with Maceration technology. Procalcitonin concentration will be measured by commercially available Enzyme linked immunosorbent assay (ELISA) (Roche Diagnostic, MAannheim, Germany).

C-reactive protein concentration was measured by the commercially available immunoturbidometric assay on the Roche Modular Psystem (Roch Diagnostic, Mannheim, Cermany). All patients were managed by conventional supportive measuresfor critically ill patients including fluids, oxygen therapy,and ventilatory support whenever required. However, whenevercriteria of infection appeared or suspected (according to CDC andguided by Surviving sepsis campaign guidelines), antibiotics wereimmediately instituted even in SIRS patients.The outcome parameters that were studied included ICU length of stay (ICU-LOS) and in-hospital mortality.

Statistical analysis

Analysis of data was done by DELL computer using Statistical Package for the Social Sciences (SPSS), Version 22 (SPSS Inc., Chicago, IL, USA) as follows: Description of quantitative variables as mean, standard (SD) or median and range as appropriate. Description of qualitative variables as number or frequency and percentage. Student's t-test, Mann-Whitney testwas used for comparison between two groups as regard quantitative variables,Spearman correlation coefficient test (r) was used to test a positive or negative correlation between two variables (non-parametric).Results were considered statistically significant if $P \leq 0.05$, and non-significant difference if $P > 0.05$. While, P-value < 0.001 was considered a highly significant.

Results

The current study revealed that Mean age of our study group was 49.8±16.05 years and mean APACHE II score 14±4.4 with mean length of ICU stay was 13.6±7.06 days.68.6 % of studied population were males and 31.4% were females. DM was the most common risk factor 60.8% followed by HTN 58.8%., as shown in Table (1). Also, there was progressive increment in CRP mean level till 7th day then it slightly declined at day 15, (Fig, 1). There was progressive increment in Procalcitonin mean level till 7th day then marked decline, (Fig,2). There was progressive increment in Presepsin mean level till 7th day then marked decline, (Fig, 3). Also, all population will be classified into 2 groups survived and un-survived group: UN-survived group showed a significantly higher age and APACHE score with p value 0.0001and insignificantly longer ICU stay with p value 0.538, as shown in Table (2).

Results in Table (3) showed that there was significantly higher frequency of DM in Non- survivors group than survivors with p value 0.007. There was significantly higher frequency of HTN in non- survivors group than survivors with p value 0.0001. Regarding, SOFA score was significantly higher at all assessments in non- survivors as compared to survivors with p value 0.007 on admission and 0.0001 at day 1, 3,7 and 15. While, CRP means were insignificant on admission and day 1 then start to be more significant only from day 3 to 15 in un survived group as compared to survived group,as shown in Table (4). The current study indicated that procalcitonin means were significantly higher from day 0 to 15 in non-survived group as compared to survived group with p value 0.0001 on admission, day 1, 3,7 and 15. Concerning, presepsin means were significantly and extremely higher from day 0 to 15 in un survived group as compared to survived group with p value 0.0001on admission, day 1, 3,7 and p value 0.006 atday15, as shown in Table (5).

In addition, there were weak positive liner correlation between CRP and values of APACHE score started from day 3 then become more correlated at day 7 with p value 0.004 then become more weak correlation at day 15 with p value 0.107, as shown intable (6)and figures (4). Furthermore, there were weak positive liner correlation between CRP and values of SOFA score started from day 3 then become more correlated at day 7 with p value 0.023 then become more weak correlation at day 15 with p value 0. 071, as shown in table (7) and figures (5). Results in Tables (8& 9) showed that there was positive liner significant correlation between procalcitonin and values of APAHE score STARTED FROM day 0 with p value 0.011 and started to show strong direct correlation till day 15 at which there was weak correlation, (Fig, 6). There was positive liner significant correlation between procalcitonin and values of SOFA score STARTED FROM day 1with p value 0.005and started to show strong direct correlation till day 15 with p value 0.0001, (Fig, 7).

Moreovere, Results in Tables (10 & 11) showed that there was significant correlation between presepsin and value of APAHE score at day 0 with p value 0.006 then insignificant correlation at day1 and started to show strong direct correlation at 3rd day with p value 0.0001 till day 15 at which there was weak correlation with p value 0.077, (Fig, 8). There was positive liner significant

correlation between presepsin and values of SOFA score STARTED FROM day 0 with p value 0.035 and started to show strong direct correlation till day 15 with p value 0.0001, (Fig, 9).

Table 1
Age, APACHE and length of ICU stay of the studied patients

	Mean ±SD	Range
Age	49.8±16.05	20 - 77
APACHE	14.6±4.44	8-28
Length of ICU stay	13.6±7.06	4 -35
	No	%
Gender: Male Female	35 16	68.6 31.4
Co morbid conditions and risk factors: Smokers	27	52.9%
DM	31	60.8%
HTN	30	58.8%
COPD	8	15.7%
Liver diseases	9	17.6%
Renal diseases	11	21.6%
CVS	8	15.7%
Previous ICU admission	8	15.7%

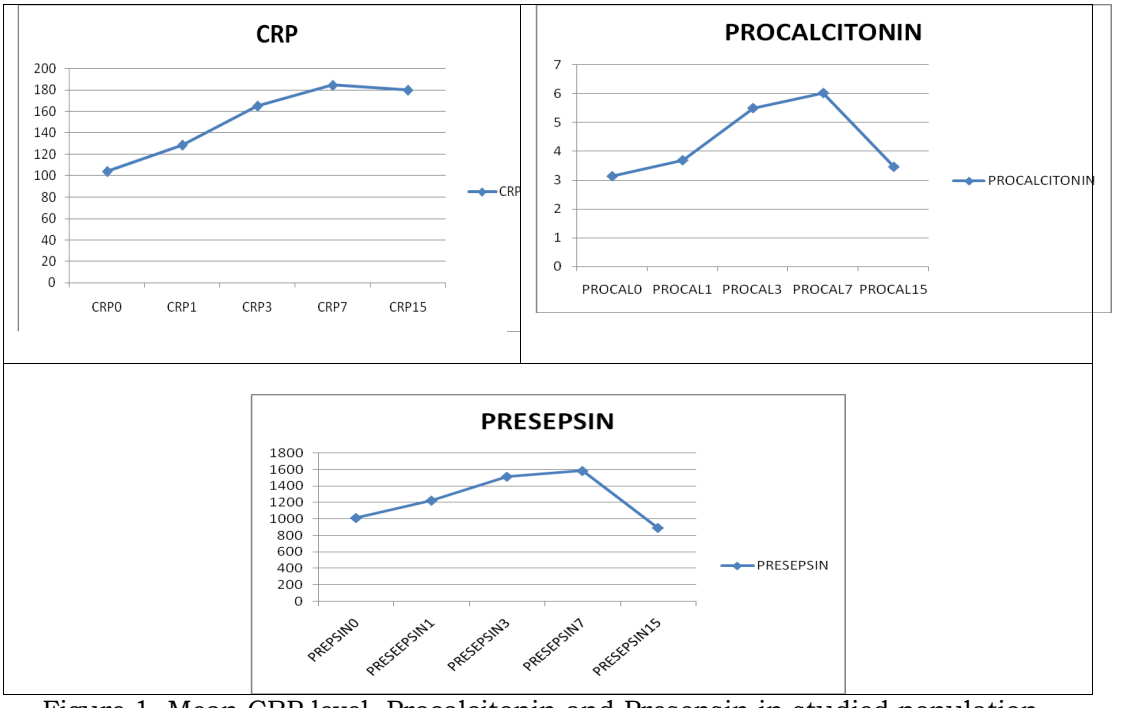


Figure 1. Mean CRP level, Procalcitonin and Presepsin in studied population

Table 2
Comparison between Non- survivors and Survivors regarding Age, APACHE score and LOS

Survival at day 28	Non- survivors (n=20) (Mean±SD)	Survivors (n=31) (Mean±SD)	P value
Age	59.9±11.8	43.3±15.2	0.0001
APACHE	17.7±4.8	12.7±2.8	0.0001
LOS	12.8±4.8	14.1±8.2	0.538

Table 3
Relation between DM and HTN with survival

	DM		p
	No DM	DM	
Non- survivors	3	17	0.007
Survivors	17	14	
	HTN		
	No HTN	HTN	
Non- survivors	2	18	0.003
Survivors	19	12	

Table 4
Relation between SOFA and CRP with survival

Survival at day 28	Non- survivors (n=20) (Mean±SD)	Survivors (n=31) (Mean±SD)	P value
SOFA0	9.0±5.5	6.3±3.5	0.007
SOFA1	11.2±5.3	6.5±2.4	0.0001
SOFA3	13.1±5.4	5.8±2.1	0.0001
SOFA7	14.1±5.2	4.9±1.4	0.0001
SOFA15	13.7±4.6	4.2±0.95	0.0001
CRP0	120.8±112.6	93.1±79.6	0.307
CRP1	153.6±109.9	112.6±81.2	0.132
CRP3	202.4±97.4	141.2±75.5	0.015
CRP7	220.6±85.9	162.5±95.5	0.035
CRP15	257.7±125.1	165.0±94.3	0.044

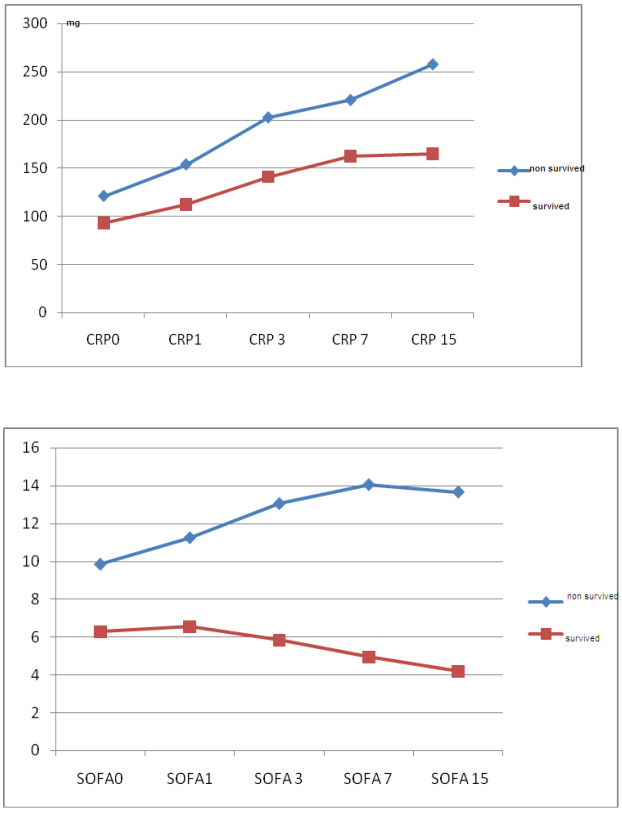


Figure 2. Relation between SOFA and CRP with survival.

Table 5
Comparison between Non- survivors and Survivors regarding Procalcitonin and Presepsin

Survival at day 28	Non- survivors (n=20) (Mean±SD)	Survivors (n=31) (Mean±SD)	P value
PROCAL0	6.1±4.2	1.2±0.9	0.0001
PROCAL1	7.7±5.4	1.1±0.9	0.0001
PROCAL3	11.8±8.6	1.4±1.3	0.0001
PROCAL7	13.5±8.4	1.4±1.3	0.0001
PROCAL15	13.4±6.9	0.9±0.8	0.0001
PRESEPSIN0	1602.3±885.2	627.9±467	0.0001
PRESEPSIN1	1829.9±438.5	850.5±936.6	0.0001
PRESEPSIN3	2580.7±1280.6	827.6±651.2	0.0001
PRESEPSIN7	2974.2±1231.4	732.4±539.0	0.0001
PRESEPSIN15	2860.0±1277.9	507.3±392.2	0.006

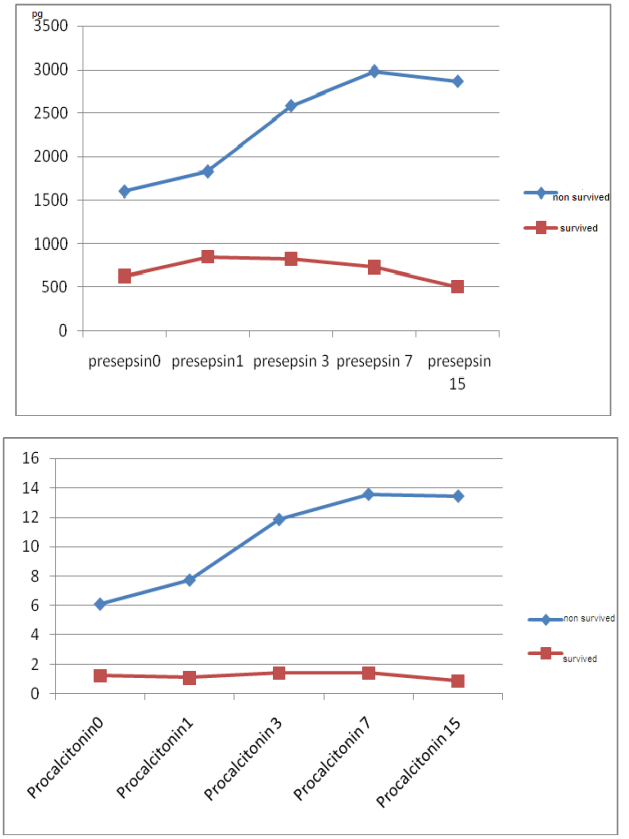


Figure 3. Comparison between Non- survivors and Survivors regarding Procalcitonin and Presepsin

Table 6
Correlation between CRP and APACHE

	CRP Day 0	Day 1	3	7	15
R	.021	.099	.273	.397**	.269
P-value	.882	.488	.05	.004	.107

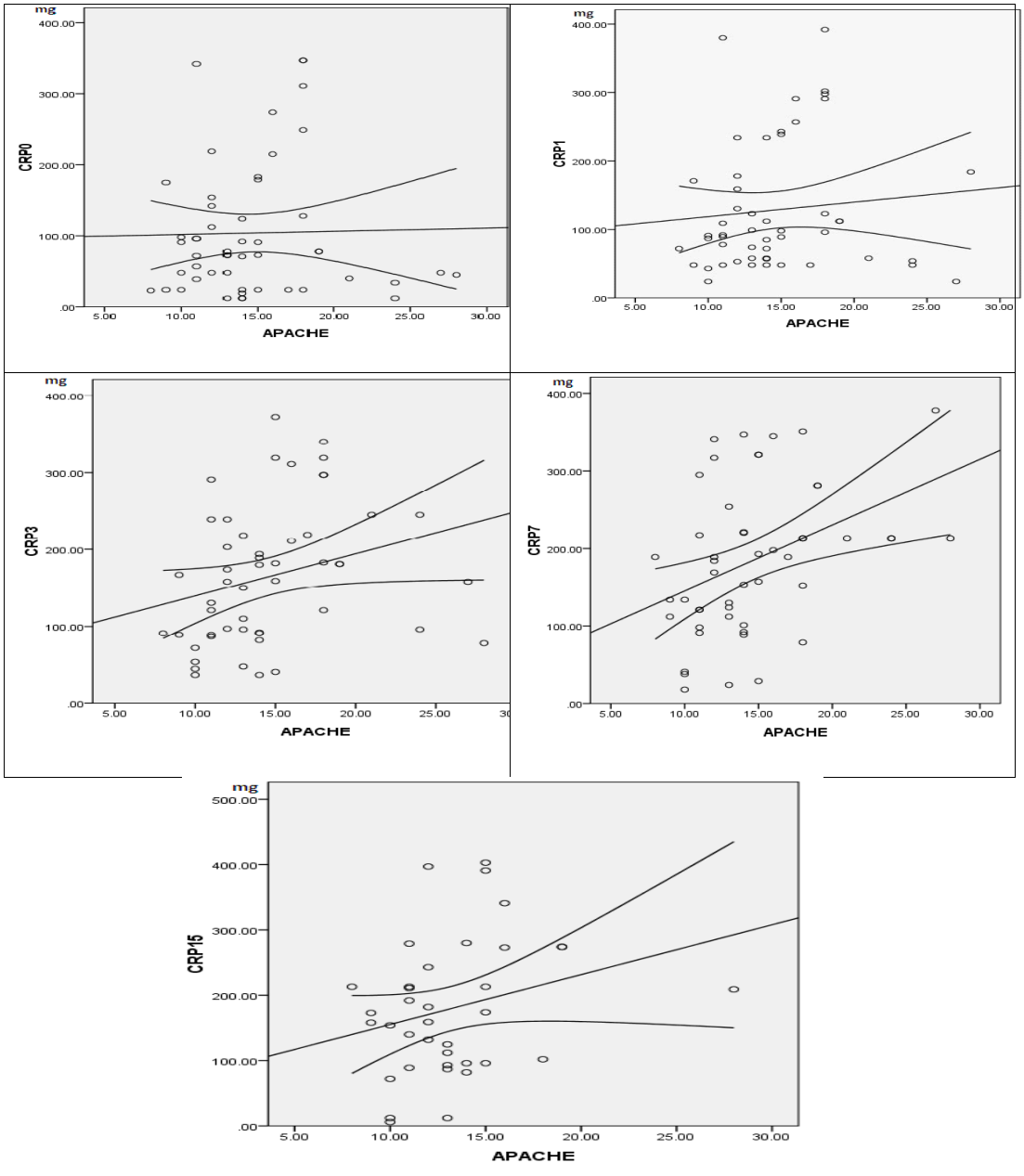
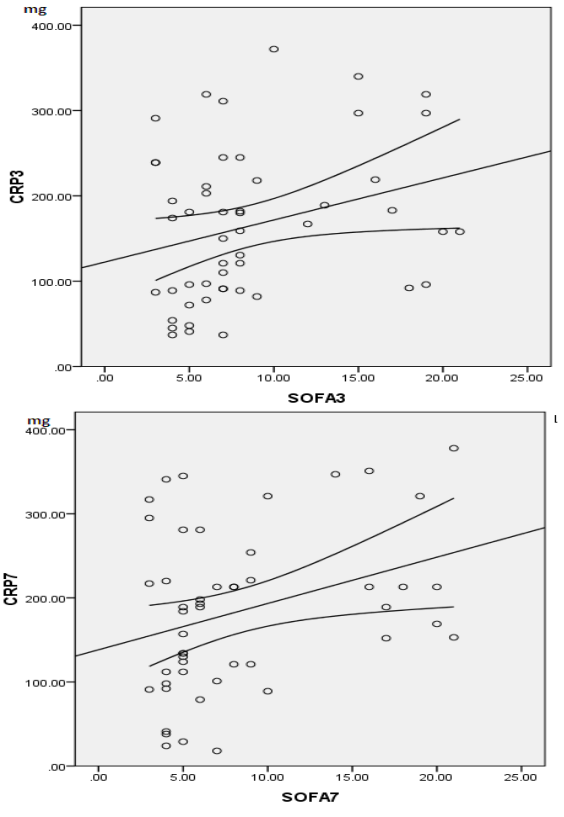


Figure 4. Correlation between CRP and APACHE

Table 7
Correlation between CRP and SOFA

	SOFA Day 0	Day 1	3	7	15
R	.108	.129	.284*	.322*	.300
P value	.450	.367	.044	.023	.071


mg
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200.00
100.00
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CRP3
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5.00
10.00
15.00
20.00
25.00
SOFA3
mg
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100.00
.00
CRP7
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5.00
10.00
15.00
20.00
25.00
SOFA7

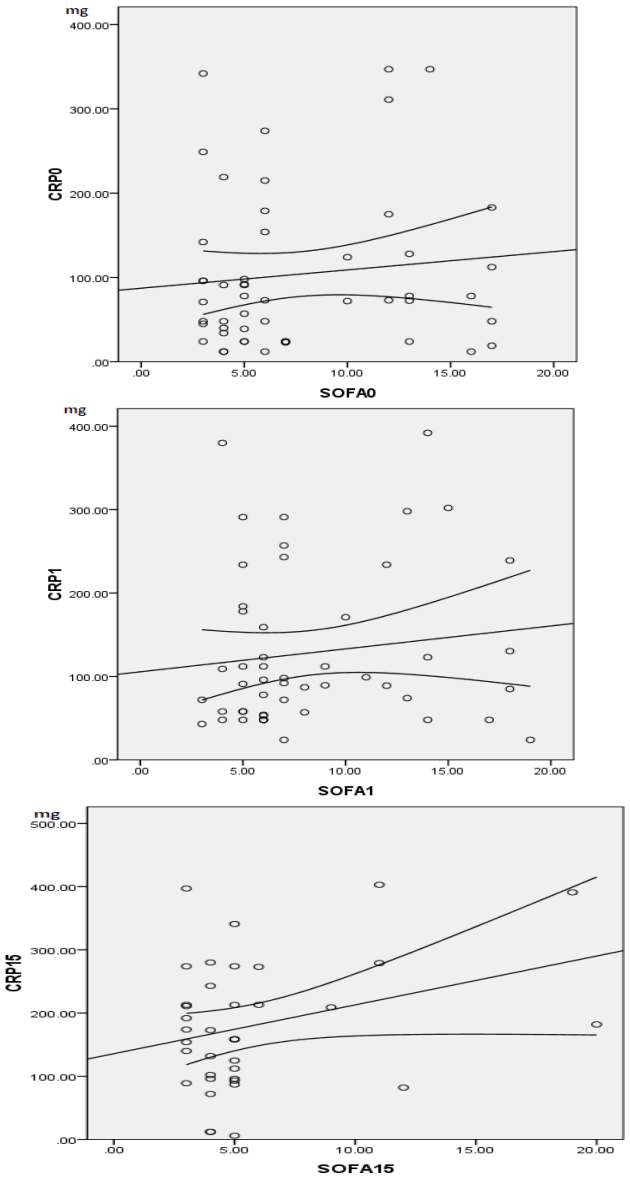
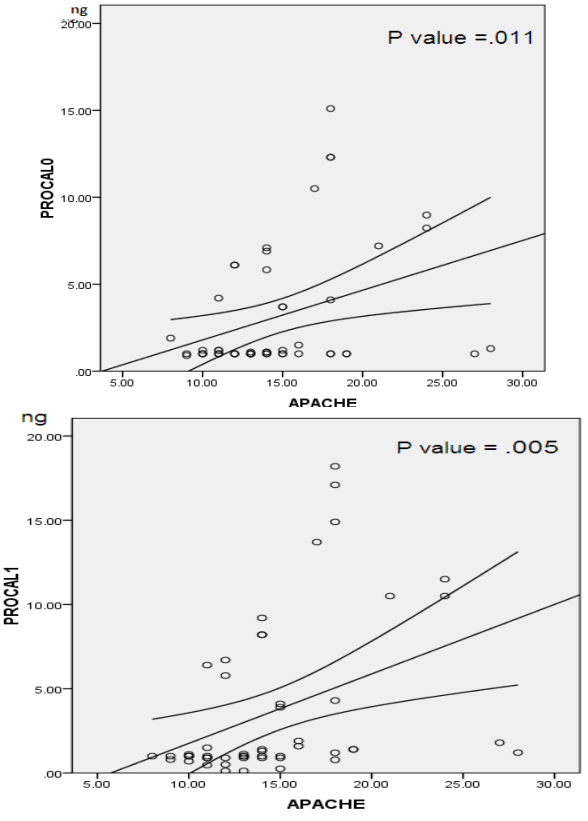


Figure 5. Correlation between CRP and SOFA

Table 8
Correlation between procalcitonin and APACHE

APACHE	Procalcitonin Day 0	Day 1	3	7	15
R	.353*	.387**	.468**	.490**	.185
P value	.011	.005	.001	.0001	.258

3852



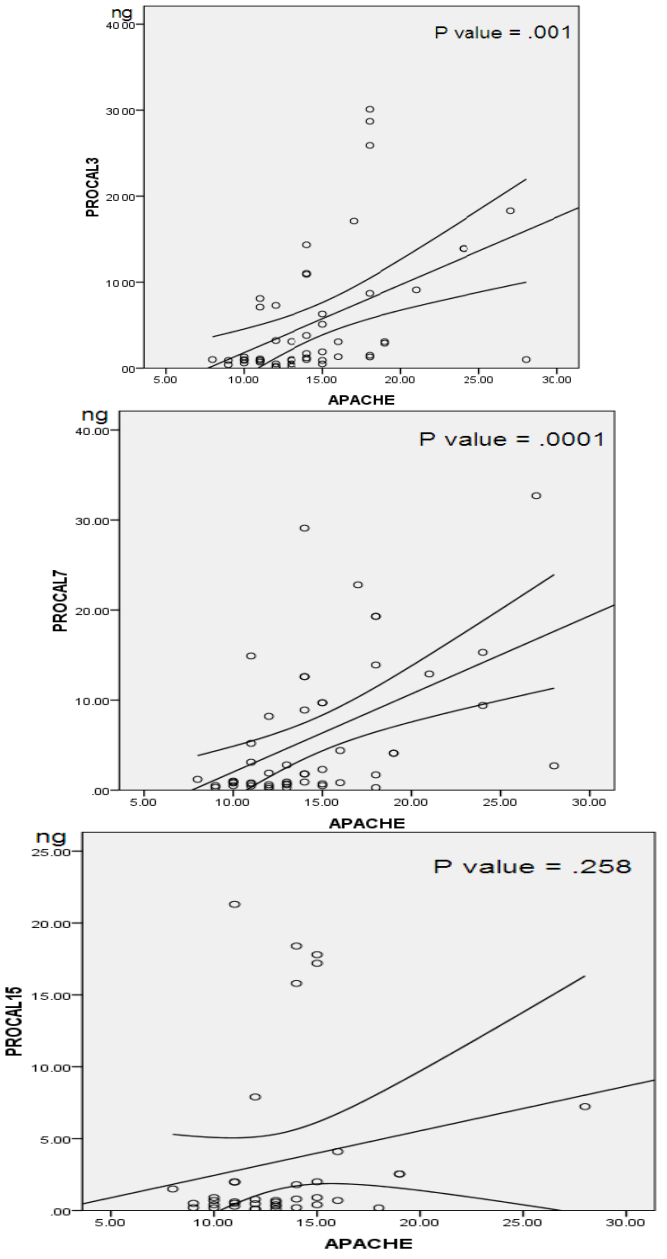
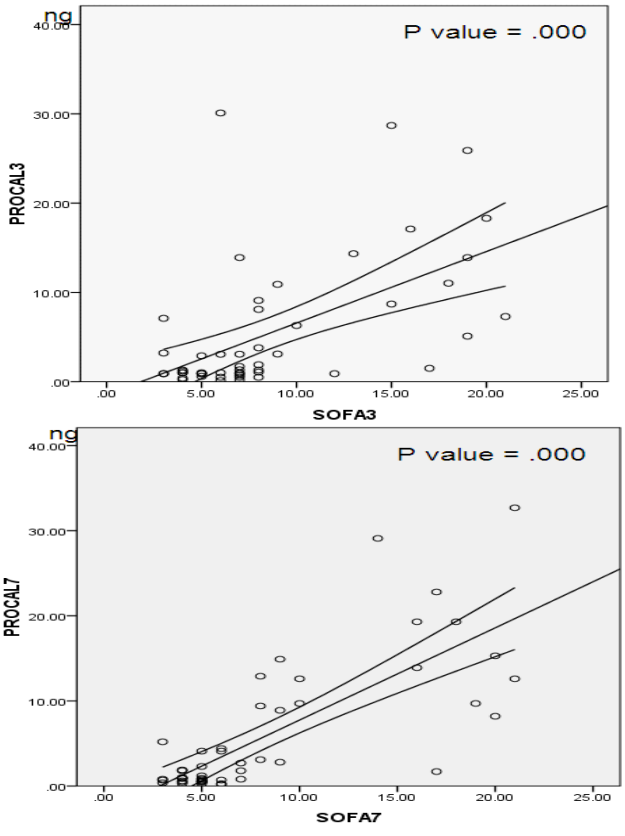


Figure 6. Correlation between procalcitonin and APACHE

Table 9
Correlation between procalcitonin and SOFA

APACHE	Procalcitonin Day 0	Day 1	3	7	15
R	.263	.390**	.549**	.766**	.723**
P value	.063	.005	.0001	.0001	.0001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SOFA3
ng
P value = .000
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SOFA7

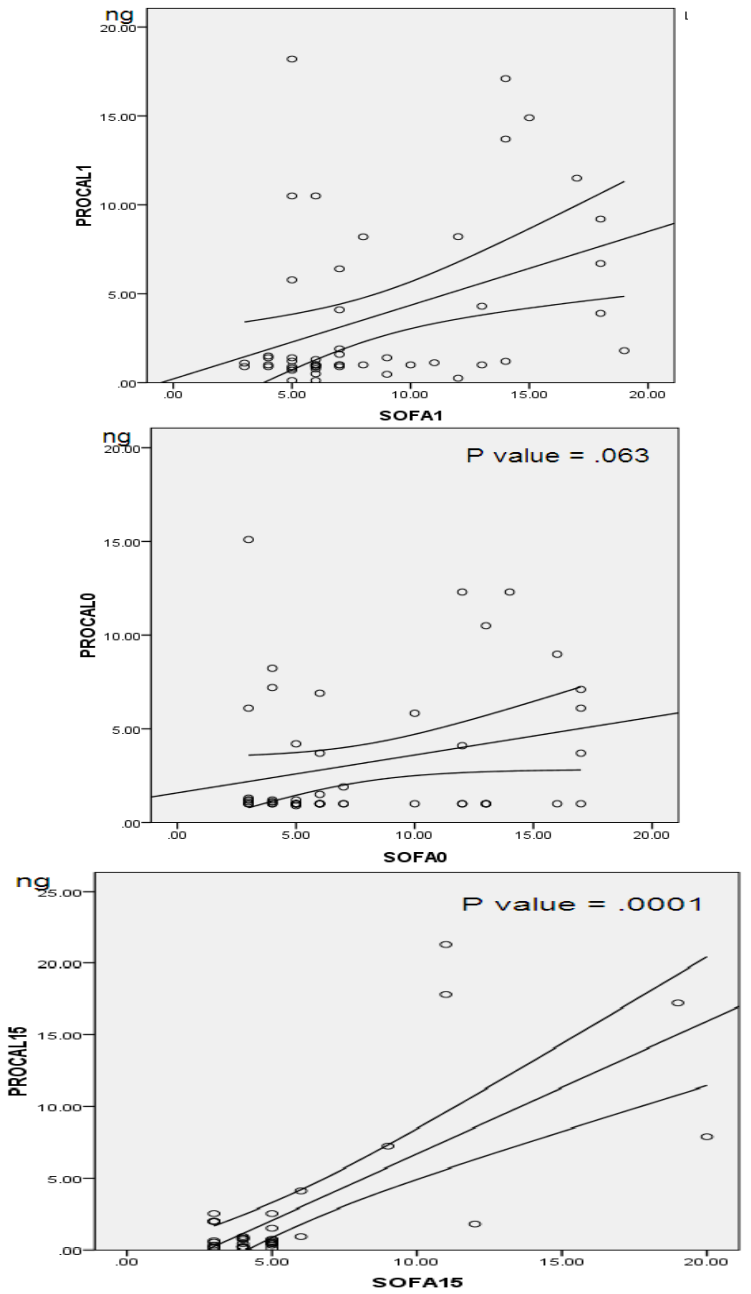
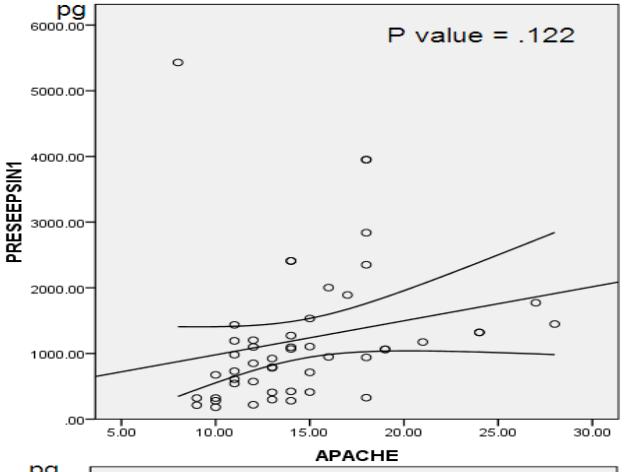


Figure 7. Correlation between procalcitonin and SOFA

Table 10
Correlation between PRESEPSEN andAPACHE

	PRESEPSEN Day 0	Day 1	3	7	15
R	.383**	.222	.528**	.672**	.295
P value	.006	.122	.0001	.0001	.077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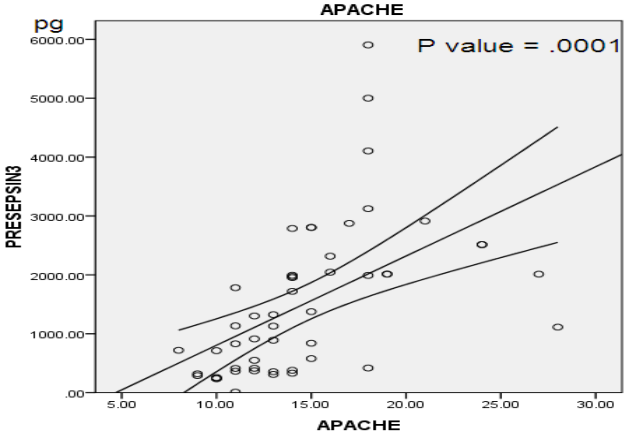
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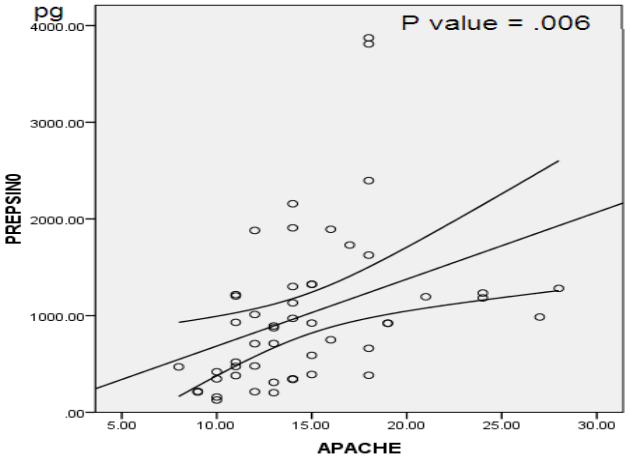
APACHE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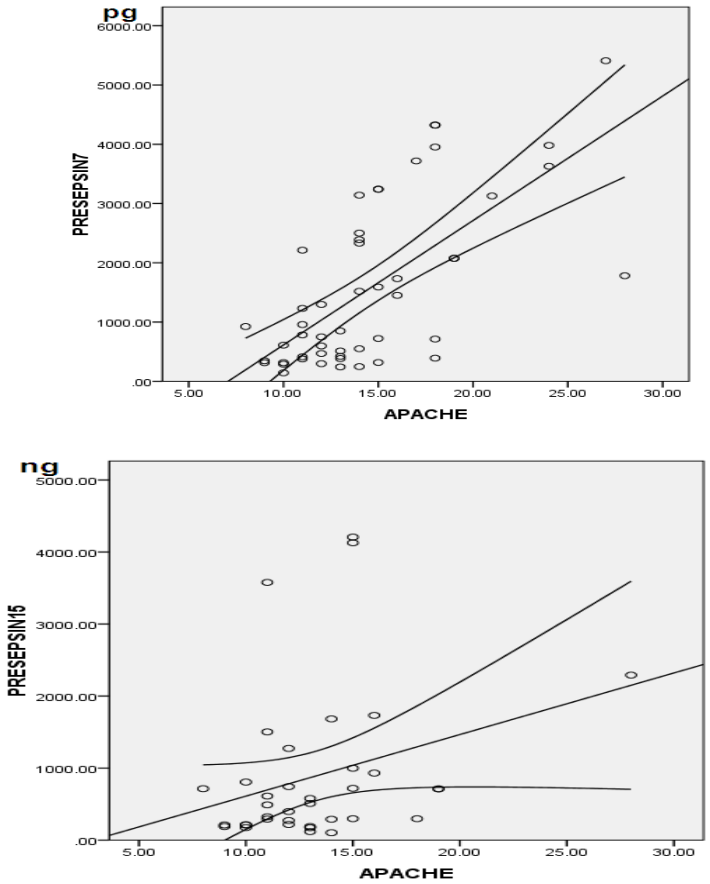
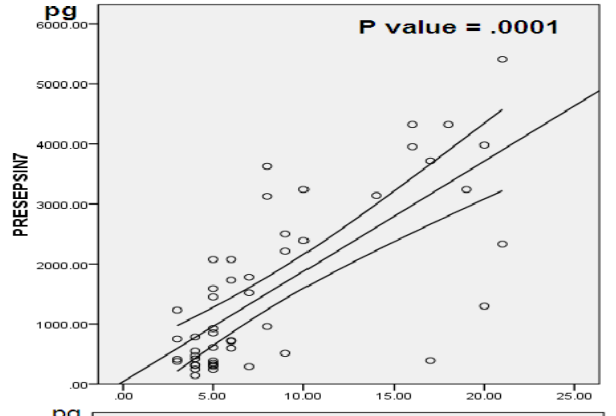


Figure 8. Correlation between PRESEPSEN and APACHE

Table 11
Correlation between PRESEPSEN and SOFA

	PRESEPSEN Day 0	Day 1	3	7	15
R	.296*	.340*	.493**	.735**	.703**
P value	.035	.016	.0001	.0001	.0001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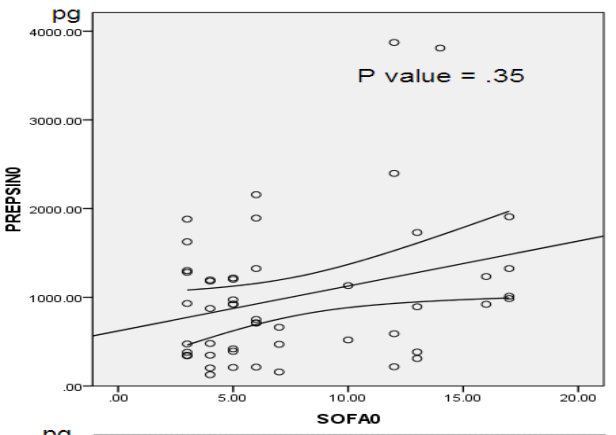
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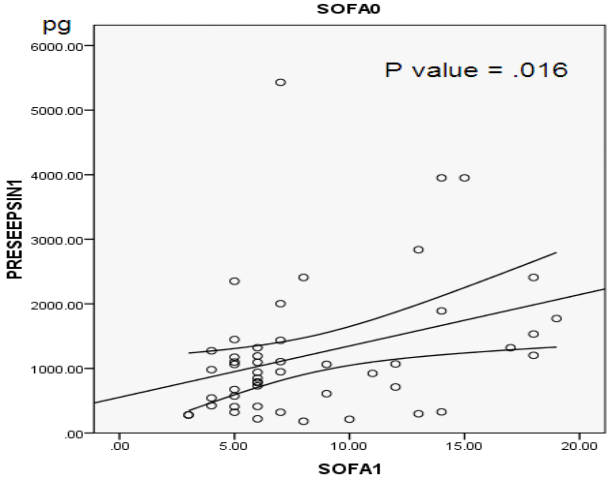
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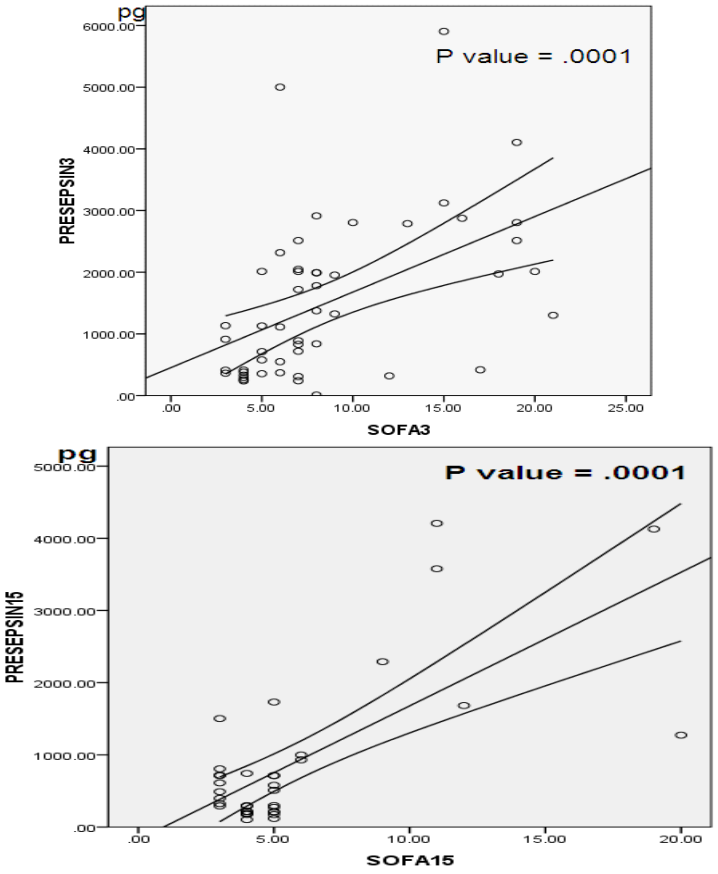

Figure 9. Correlation between PRESEPSEN and SOFA

Discussion

In our study the mean age of enrolled septic population was around fifties, in other studies there was a direct relationship between advanced age and the incidence of severe sepsis y septic shock, with a sharp increase in incidence in elderly people (12&13). The median age of patients with severe sepsis in most studies is between 60 to 65 years, and when the patients are stratified at the age of 65, the relative risk for sepsis was 13 times higher for patients aged 65 and above. Martin et al. (14) found that the incidence rates of sepsis increased 20.4% faster among older patients 65 years of age or older than among younger patients from 1979 to 2002 (mean increase per year, 11.5% versus 9.5%. by analysis of sepsis incidence that necessitated ICU admission there was increasingly rate in younger population in thirties as far as the increased co-morbid conditions.

Men are more likely than women to develop sepsis, with a mean annual relative risk of 1.28 (95% CI 1.24-1.32) (14). However, it is not clear whether this difference could be due to a higher prevalence of comorbidities in men, or whether women are protected against the inflammatory changes that occur in severe sepsis and septic shock (13 &14). Female gender has been found to substantially decrease the risk for developing severe sepsis, independent of other patient and

surgical risk factors, after elective surgery (6). That was in concordance to our study where we found that male population comprised 69% of the whole patients.

In our study the overall mortality was 39% and according to the Centers for Disease Control and Prevention has estimated that sepsis is the tenth leading cause of death overall in the United States (5). Severe sepsis is the most common cause of death in noncoronary critical care units. The deaths related to severe sepsis exceed the numbers of persons with other diseases that attract higher public awareness, such as breast cancer and AIDS (8). The mortality rates of severe sepsis and septic shock are 25 to 30% and 40 to 70%, respectively.

Moreover, in concordance to our study; the concentration of presepsin was positively correlated with APACHE II score and SOFA score. This was seen also in Ulla et al. [15] 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 [16]. 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. [17]. Kojika et al. [18] showed a significant correlation between presepsin values and both APACHE II and SOFA scores. These findings strengthened the hypothesis of presepsin use for prediction of more severe infection and reflecting patient condition.

In our study the septic group enrolled 35 patients and the mortality in this group was 15/35 had a significantly higher PCT, presepsin levels on day of admission that seemed that these two biomarkers had not only a diagnostic use but also could have a prognostic and severity assessment clinical use.Moreover, the level of presepsin was correlated with SOFA score, MOF score and hemodynamic stability. The 90-day mortality in patients with a high level of presepsin was significantly higher than the patients with a low level of presepsin (75% and 42%). In the former study the Presepsin was concluded to be superior to PCT in the assessment of prognosis in agreement to us. [15]

Presepsin was shown in their 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 as ours. It was seen by other authors that the concentration of presepsin was positively correlated with APACHE II and SOFA scores [33]. They and others [15,17,19] 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 andnot on admission to be significantly higher in sepsis compared to non-infectious SIRS groups. Yousef et al. [20] 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. (5)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].

Identification of prognosis and predicted mortality with sepsis is an important factor in patient stratification and management [21]. Many markers were studied and evaluated about their ability for mortality prediction on SIRS patients [2].Labelle et al. [22] 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.

Salih et al. [23] 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.Barie et al. [24] and Siddiqui et al. [25] strongly claimed in their studies that APACHE II score on admission is a reliable predictor of length of stay in ICU. Engel et al. [26] 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.Ferreira et al.[27] 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. [28] also demonstrated a strong correlation of initial and maximum SOFA scores with mortality outcome.

In the patient group who experienced adverse outcome, presepsin levels showed an increasing tendency. Masson et al. [16] 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 [16]. 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. [29] 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.

Conclusion

Our results concluded that to provide a more consistent and reproducible picture of sepsis incidence and outcomes, the task force sought to integrate the biology and clinical identification of sepsis with its epidemiology and coding.

Funding

This research was carried out without funding.

Conflicts of interest

No conflicts of interest declared.

Authors' contributions

All authors had equal role in design, work, statistical analysis and manuscript writing. All authors have approved the final article work.

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