Scientific Research Publishing

Open Journal of Medical Microbiology, 2021, 11, 267-281
https://www.scirp.org/journal/ojmm
ISSN Online: 2165-3380
ISSN Print: 2165-3372

Presepsin and Procalcitonin as Potential Biomarkers for Early Diagnosis and Prognosis of Sepsis in Critically Ill Patients

Reham Sabry[1], Hend Maghraby Maghraby[2*], Amany Mohamed Abd Allah[2]

[1]Clinical Pathology Department, Faculty of Medicine for Girls, Al-Azhar University, Cairo, Egypt
[2]Internal Medicine Department, Faculty of Medicine for Girls, Al-Azhar University, Cairo, Egypt
Email: *drhendms@gmail.com

How to cite this paper: Sabry, R., Maghraby, H.M. and Allah, A.M.A. (2021) Presepsin and Procalcitonin as Potential Biomarkers for Early Diagnosis and Prognosis of Sepsis in Critically Ill Patients. *Open Journal of Medical Microbiology*, **11**, 267-281.
https://doi.org/10.4236/ojmm.2021.113017

Received: August 12, 2021
Accepted: September 23, 2021
Published: September 26, 2021

Abstract

Background: Sepsis has a poor prognosis for critically ill patients, even with intensive management. Early diagnosis of sepsis and detection of patients with worsening prognosis are important for immediate intervention to improve the clinical outcome. **Objective:** To investigate serum presepsin (PS) and procalcitonin (PCT) as early diagnostic and prognostic biomarkers for sepsis in critically ill patients. **Methods:** 60 critically ill patients with sepsis were subdivided into three groups of sepsis, severe sepsis and septic shock according to Acute Physiology and Chronic Health Evaluation II (APACHEII) and quick Sequential Organ Failure Assessment (qSOFA) scores. Patients were compared with 20 age and sex matched controls. Serum PS and PCT were measured by enzyme linked immunosorbent assay (ELISA). **Results:** Serum PS and PCT levels were significantly increased in septic patients than controls, and their increase was positively correlated with progression of sepsis severity till reached the highest levels in septic shock. Receiver operating characteristic (ROC) curve for predicting sepsis revealed that PS has the highest area under curve (AUC) (0.967) with 97.5% sensitivity, 85% specificity and cut-off of >635.5 pg/mL, followed by PCT that has AUC (0.946), 97.5% sensitivity, 95% specificity and cut-off of >319.7 pg/mL. C-reactive protein (CRP) showed the lowest AUC (0.902) with 75% sensitivity, 100% specificity and cut-off of >7 mg/L. ROC curve for predicting septic shock showed that PS has the highest AUC (0.969) with 90% sensitivity, 97.5% specificity and cut-off of >5500.6 pg/mL, followed by CRP that has AUC (0.945), 90% sensitivity, 87.5% specificity and cut-off of >63 mg/L. PCT showed the lowest AUC (0.889) with 90% sensitivity, 97.5% specificity and cut-off of >822.1 pg/mL. **Conclusions:** Serum PS and PCT were promising biomarkers for early diagnosis and prognosis of sepsis in critically ill patients, but PS was superior to PCT.

Keywords

Sepsis, Septic Shock, Diagnosis, Presepsin, Procalcitonin

1. Introduction

Sepsis is a life-threatening systemic reaction to infection characterized by hyper-inflammatory response followed by immunosuppression during which multiple organ dysfunctions are present [1]. Sepsis is the most common cause of death in critically ill patients. It develops in about 25% of intensive care unit (ICU) patients [2]. The mortality rates range from 20% to 50% in patients with sepsis and are >50% in patients with septic shock [3]. Early diagnosis and timely intervention of those patients is important to decrease mortality and improve sepsis-related survival [4].

Clinical scores have been introduced to predict hospital outcomes for critically ill patients e.g., Acute Physiology and Chronic Health Evaluation II (APACHEII), Sequential Organ Failure Assessment (SOFA) and quick (q) SOFA scores. However, the complicated methods for using these clinical scoring systems, proposing blood biomarkers as promising alternatives [5].

Blood culture is considered the gold standard for the diagnosis of blood infections, but it is time-consuming, even in the most advanced systems, and has poor sensitivity [6]. In addition, C-reactive protein (CRP) is considered as an early marker of infection or inflammation and could help with the monitoring of the progress of inflammation, but it is non-specific and cannot differentiate infectious from non-infectious inflammation as its level can be increased in autoimmune diseases, tumors, myocardial infarction, severe trauma, invasive surgical procedure and burns [7].Therefore, hundreds of the circulating biomarkers have been investigated for early diagnosis, risk stratification and prognosis of sepsis [8].

The soluble cluster of differentiation 14 subtype (sCD14-ST) or presepsin (PS) is a high-affinity receptor in monocytes, macrophages and granulocyte cells and their cell membranes that bind to lipopolysaccharide (LPS)/LPS-binding protein complexes [9]. Following infection, PS is produced and released into circulation either by secretion following phagocytosis of the CD14-pathogen complex or through shedding of CD14 from the cell membrane yielding soluble CD14 [10]. Many studies found that PS levels were elevated in patients with cardiac surgery and renal or liver disorders such as severe chronic kidney disease or liver cirrhosis without infection [2].

Procalcitonin (PCT) is the precursor of calcitonin that is normally synthesized in the C cells of the thyroid gland from pre-procalcitonin [11]. However, during infection, PCT is ectopically secreted into the circulation by liver, kidneys, spleen, lungs, pancreas, small intestine and leukocytes due to inflammatory stimuli mediated by interleukin 6 (IL-6) and tumor necrosis factor-alpha (TNF-α) [12]. PCT

levels can be increased in conditions other than infection such as severe trauma, invasive surgical operations, major burns, cancers, autoimmune diseases and tissue necrosis after ischemic heart diseases [13].

An increasing number of studies have shown the ability of PS and PCT to differentiate between sepsis and systemic inflammatory response syndrome (SIRS) of non-infectious origin [14].

We aimed to investigate the role of the serum PS and PCT as early diagnostic and prognostic biomarkers for sepsis in critically ill patients.

2. Subjects and Methods

2.1. Subjects

This case-control study was conducted on adult critically ill patients who were admitted to ICU of Internal Medicine Department, Al-Zahraa University hospital, Cairo, Egypt, during the period from January 2020 to November 2020. The patients who were diagnosed with sepsis were enrolled in the study. The severity of sepsis was assessed according to APACHE II and qSOFA scoring systems at the time of admission and we selected 20 patients with sepsis, 20 patients with severe sepsis and 20 patients with septic shock to be included in the study. In addition, 20 age and sex matched apparently healthy individuals were included as a control group.

Informed consent was taken from all participants before enrollment in the study. The study was done after approval from Research Ethics Committee of Faculty of Medicine for Girls Al-Azhar University, and was conducted in accordance with the previsions of the Declaration of Helsinki (ethical approval number 20202151).

2.1.1. Inclusion Criteria

Adult critically ill patients (>18 years) diagnosed with sepsis as they fulfilled at least 2 criteria for SIRS which were: 1) temperature > 38˚C or <36˚C, 2) heart rate > 90 beats/minute, 3) respiratory rate > 20 breaths/minute or $PaCO_2$ < 32 mmHg when on mechanical ventilation, 4) white blood cell count > 12,000/μL or <4000/μL, or an increase in the number of immature band forms (>10%) [15].

2.1.2. Exclusion Criteria

Pregnancy, immunosuppressive drugs, invasive surgical operations, cancers, acquired immunodeficiency syndrome, autoimmune diseases, ischemic heart diseases and end-stage liver and renal diseases.

2.1.3. Assessment of Subjects

1) Medical history taking and thorough clinical examination for all patients at the time of ICU admission, with special attention for the patient's vital signs and sepsis parameters. The patients were observed for 28 days, and the mortality rate was recorded.

2) Radiological investigations: based on the patients' signs and symptoms, to

determine the source of infection.

- Abdominal and urogenital imaging: x-ray, ultrasound and/or tomography.
- Thoracic imaging: x-ray and/or tomography.
- Electrocardiogram.

3) Laboratory investigations:

- Urine analysis.
- Urine, stool, sputum and wound swap cultures: (according to the patients' signs and symptoms).
- Complete blood count (CBC).
- Liver and kidney functions tests.
- CRP.
- Serum PS level.
- Serum PCT level.

2.2. Samples Collection and Preparation

About 7 ml of venous blood were drawn from each participant (within 1 hour after the diagnosis of sepsis) and divided into four aliquots: the first aliquot was 2 ml blood transferred to an EDTA tube for CBC using automated hematology cell counter (Cell dyne Ruby, Germany), the second aliquot was 2 ml blood transferred to plain tube for liver and kidney functions tests using fully automated chemistry analyzer (Cobas c 311, Roche Diagnostics kits, Germany) and the third aliquot was 3 ml blood transferred to plain tube, centrifuged at 3000 rpm for 20 minutes, then serum was separated and stored at −20˚C for measurement of PS, PCT and CRP by enzyme-linked immunosorbent assay (ELISA) in one assay to avoid repeated freeze-thaw cycles.

2.3. Measurement of PS and PCT Serum Levels

The concentrations of PS and PCT in serum were analyzed according to the manufacturer's instructions by quantitative sandwich ELISA technique, with a complete set of ELISA reader (das 1851), using human Presepsin ELISA kit (Catalog number: 11141), supplied by Glory Science, China, and human Procalcitonin ELISA kit (Catalog number: E0977Hu), supplied by Bioassay Technology Laboratory, China.

2.4. Statistical Analysis

Data were coded and entered to the Statistical Package for Social Science (SPSS) version 23. Data were summarized using numbers and percentages for qualitative data; mean ± standard deviations (SD) for quantitative parametric data and median with inter-quartile range (IQR) for quantitative non parametric data. The comparison between qualitative data was done using Chi-square test, while the comparison between quantitative data was done using independent t-test for parametric and Mann-Whitney test for non-parametric data. The comparison between more than two groups was done by using One Way ANOVA followed

by post hoc analysis by least significant difference (LSD) for quantitative parametric data. The correlations between quantitative data were done using Spearman correlation coefficients. Receiver operating characteristic (ROC) curve was performed with area under curve (AUC) analysis to detect the best cut off value, sensitivity and specificity of sUPAR, IL-34 and FIB-4 score for differentiation between patients and controls, and also between patients with severe and mild to moderate hepatic fibrosis. P-values less than 0.05 were considered statistically significant.

3. Results

Our study included 60 critically ill patients with sepsis and 20 controls. The patients were divided into three groups according to the severity of sepsis: group 1 included patients with sepsis (n = 20), group 2 patients with severe sepsis (n = 20) and group 3 patients with septic shock (n = 20). Comparison between patients and controls demonstrated a significant increase in PS, PCT, CRP, APACHE II and qSOFA scores ($P < 0.001$) in patients than controls. No significant difference was found in age ($P = 0.247$) and sex ($P = 0.796$) between patients and controls. The source of infection and number of survivors and non-survivors in the patient group are presented in (Table 1).

The median PS and PCT levels in each patient group and controls are shown in (Table 2) that demonstrated a significant increase in serum PS and PCT levels in each patient group than controls ($P < 0.001$), in severe sepsis than sepsis ($P < 0.001$ and 0.004 respectively), in septic shock than severe sepsis ($P < 0.001$) and in septic shock than sepsis group ($P < 0.001$).

It was found that PS and PCT levels were significantly higher in non-survival patients than survivors ($P = 0.007$ and 0.019 respectively) (Table 3).

The correlation of PS with other parameters revealed a significant positive correlations with APACHE II score ($r = 0.792$, $P < 0.001$), qSOFA score ($r = 0.796$, $P < 0.001$) and CRP level ($r = 0.814$, $P < 0.001$). In addition, PCT showed a significant positive correlations with APACHE II score ($r = 0.728$, $P < 0.001$), qSOFA score ($r = 0.761$, $P < 0.001$) and CRP level ($r = 0.781$, $P < 0.001$). There was a significant positive correlation between PS and PCT levels ($r = 0.855$, $P < 0.001$) (Table 4).

Furthermore, by using the ROC curve, the ability of PS for predicting sepsis in critically ill patients revealed the highest AUC (0.967) with 97.5% sensitivity, 85% specificity, 92.9% PPV, 94.4% NPV and cut-off of >635.5 pg/mL, followed by PCT that has AUC (0.946) with 97.5% sensitivity, 95% specificity, 97.5% PPV, 95% NPV and cut-off of >319.7 pg/mL. CRP showed the lowest AUC (0.902) with 75% sensitivity, 100% specificity, 100% PPV, 66.7% NPV and cut-off of >7 mg/L (Figure 1, Table 5).

The AUC of a combination of PS and PCT (0.989) or PS & CRP (0.989) or PCT & CRP (0.986) in predicting sepsis was significantly higher than that of PS or PCT or CRP alone (Figure 2, Table 5).

Table 1. Demographic and clinical characteristics of critically ill patients with sepsis and the controls.

Variables		Patients	Controls	Test value	P-value
		n = 60	n = 20		
Age (years)	Mean ± SD	52.40 ± 14.58	47.95 ± 15.32	1.167•	0.247
	Range	20 - 70	23 - 70		
Sex (n, %)	Female	32 (53.3%)	10 (50.0%)	0.067*	0.796
	Male	28 (46.7%)	10 (50.0%)		
Source of infection • GE • Pneumonia • UTI • Diabetic foot • Infective endocarditis	n & %	 6 (10.0%) 29 (48.3%) 14 (23.3%) 7 (11.7%) 4 (6.7%)	---	---	---
Presepsin (pg/ml)	Median	4233.4	211.4	−6.378≠	< 0.001
	IQR	2229.3 - 5774.9	151.75 - 482.3		
Procalcitonin (pg/ml)	Median	721.55	239.9	−5.411•	<0.001
	IQR	569.3 - 968.9	203.9 - 303.3		
CRP (mg/L)	Median	46.5	5	6.124•	<0.001
	IQR	32.5 - 90	3.5 - 5.5		
APACHE II score	Median	24.5	2	−6.679≠	<0.001
	IQR	21 - 30	0.5 - 2		
qSOFA score	Median	2	0	−6.707	<0.001
	IQR	2 - 3	0 - 0		
28-day mortality	n &%	16 (26.7%)	---	---	---

•Independent t-test; *Chi-square test; ≠Mann Whitney test. P-value <0.05: Significant. SD, standard deviation; IQR, inter-quartile range; GE, gastro enteritis; UTI, urinary tract infection; CRP, C-reactive protein; APACHE, Acute Physiology and Chronic Health Evaluation; qSOFA, quick Sequential Organ Failure Assessment.

Table 2. Comparison between sepsis, severe sepsis and septic shock groups as regards PS and PCT levels.

Variables		Controls	Sepsis	Severe sepsis	Septic shock	P-value
		n = 20	n = 20	n = 20	n = 20	
Presepsin (pg/ml)	Median	211.4	1791.75	4269.65	6228.55	<0.001
	IQR	151.75 - 482.3	1170.15 - 2229.3	3945.3 - 4979.2	5599.95 - 6347.7	
Procalcitonin (pg/ml)	Median	239.9	506.5	767.25	1338.65	<0.001
	IQR	203.9 - 303.3	469.15 - 577.7	701.65 - 815.3	957.3 - 2006.4	

•One Way ANOVA test; P-value < 0.05: Significant; IQR, inter-quartile range.

Post Hoc analysis by LSD test						
Variables	**P1**	**P2**	**P3**	**P4**	**P5**	**P6**
Presepsin (pg/ml)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Procalcitonin (pg/ml)	<0.001	<0.001	<0.001	0.004	<0.001	<0.001

LSD, least significant difference; P-value < 0.05: Significant. P1: sepsis vs controls; P2: severe sepsis vs controls; P3: septic shock vs controls; P4: severe sepsis Vs sepsis; P5: septic shock Vs severe sepsis, P6: septic shock Vs sepsis.

Table 3. Comparison between survivors and non survivors as regards PS and PCT levels.

Variables		Survivors	Non survivors	Test value	P-value
		n = 44	n = 16		
Presepsin (pg/ml)	Median	3945.3	5474.4	2.675≠	0.007
	IQR	2016.85 - 5520.45	3561 - 6347.7		
Procalcitonin (pg/ml)	Mean±SD	684.85	822.75	2.34≠	0.019
	IQR	500 - 866.7	680 - 1576.65		

≠ Mann Whitney test; P-value < 0.05: Significant; IQR, inter-quartile range.

Table 4. Correlation of PS and PCT levels with other parameters.

Parameters	Presepsin (pg/ml)		Procalcitonin (pg/ml)	
	r	p-value	r	p-value
APACHE II score	0.792	<0.001	0.728	<0.001
qSOFA score	0.796	<0.001	0.761	<0.001
CRP (mg/L)	0.814	<0.001	0.781	<0.001
Presepsin (pg/ml)	---	---	0.855	<0.001
Procalcitonin (pg/ml)	0.855	<0.001	---	---

P-value < 0.05: Significant; APACHE, Acute Physiology and Chronic Health Evaluation; qSOFA, quick Sequential Organ Failure Assessment; CRP, C-reactive protein.

Table 5. Diagnostic accuracy of various parameters to predict sepsis.

Parameters	AUC	Cut-off	Sensitivity %	Specificity %	PPV %	NPV %
Presepsin (pg/ml)	0.967	>635.5	97.5	85	92.9	94.4
Procalcitonin(pg/ml)	0.946	>319.7	97.5	95	97.5	95
CRP (mg/L)	0.902	>7	75	100	100	66.7
Presepsin & Procalcitonin	0.977	-	100	90	95.2	100
Presepsin & CRP	0.989	-	97.5	95	97.5	95
Procalcitonin & CRP	0.986	-	100	95	97.6	100

AUC, area under curve; PPV, positive predictive value; NPV, negative predictive value; CRP, C-reactive protein.

Finally, the ROC curve of PS and PCT for predicting septic shock in septic patients showed that PS has the highest AUC (0.969), with 90% sensitivity, 97.5% specificity, 94.7% PPV, 95.1% NPV and cut-off of >5500.6 pg/mL, followed by CRP that has AUC (0.945) with 90% sensitivity, 87.5% specificity, 78.3% PPV, 94.6% NPV and cut-off of >63 mg/L. PCT showed the lowest AUC (0.889) with 90% sensitivity, 97.5% specificity, 94.7% PPV, 95.1% NPV and cut-off of >822.1 pg/mL (**Figure 3**, **Table 6**).

The AUC of a combination of PS and PCT (0.971) or PS & CRP (0.980) or PCT & CRP (0.983) in predicting septic shock was significantly higher than that of PS or PCT or CRP alone (**Figure 4**, **Table 6**).

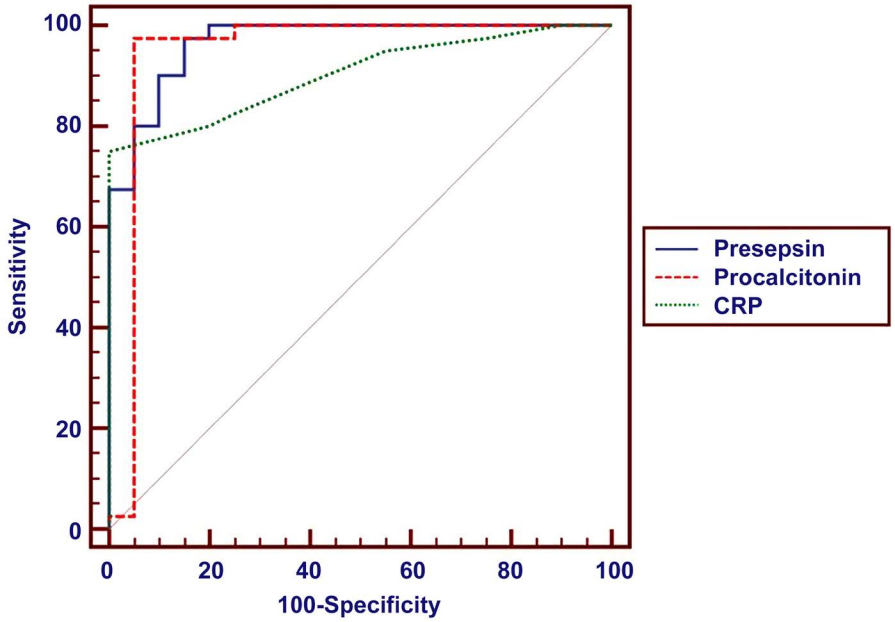

Figure 1. Roc curve of various parameters to predict sepsis.

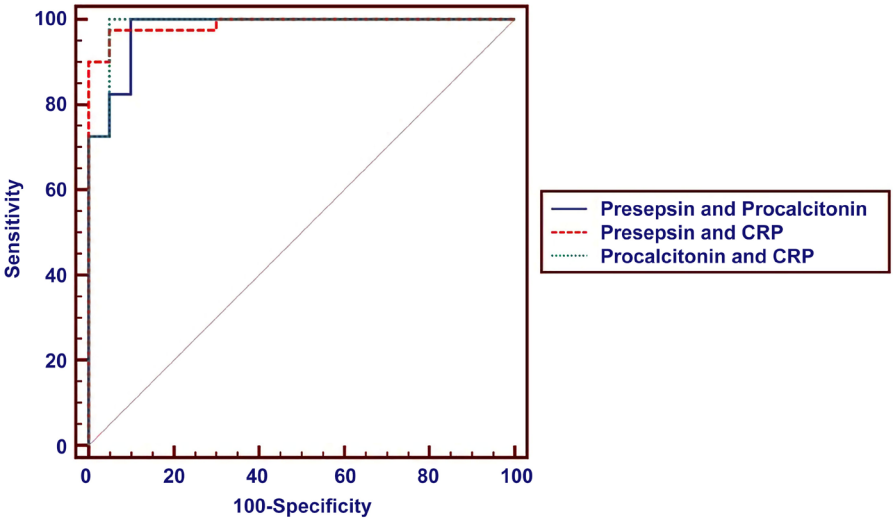

Figure 2. Roc curve of combination of parameters to predict sepsis.

Table 6. Diagnostic accuracy of various parameters to predict septic shock.

Parameters	Cut-off	AUC	Sensitivity %	Specificity %	PPV %	NPV %
Presepsin (pg/ml)	>5500.6	0.969	90	97.5	94.7	95.1
Procalcitonin (pg/ml)	>822.1	0.889	90	97.5	94.7	95.1
CRP (mg/L)	>63	0.945	90	87.5	78.3	94.6
Presepsin & Procalcitonin	-	0.971	95	97.5	95	97.5
Presepsin & CRP	-	0.980	95	90	82.6	97.3
Procalcitonin & CRP	-	0.983	95	95	90.5	97.4

AUC, area under curve; PPV, positive predictive value; NPV, negative predictive value; CRP, C-reactive protein.

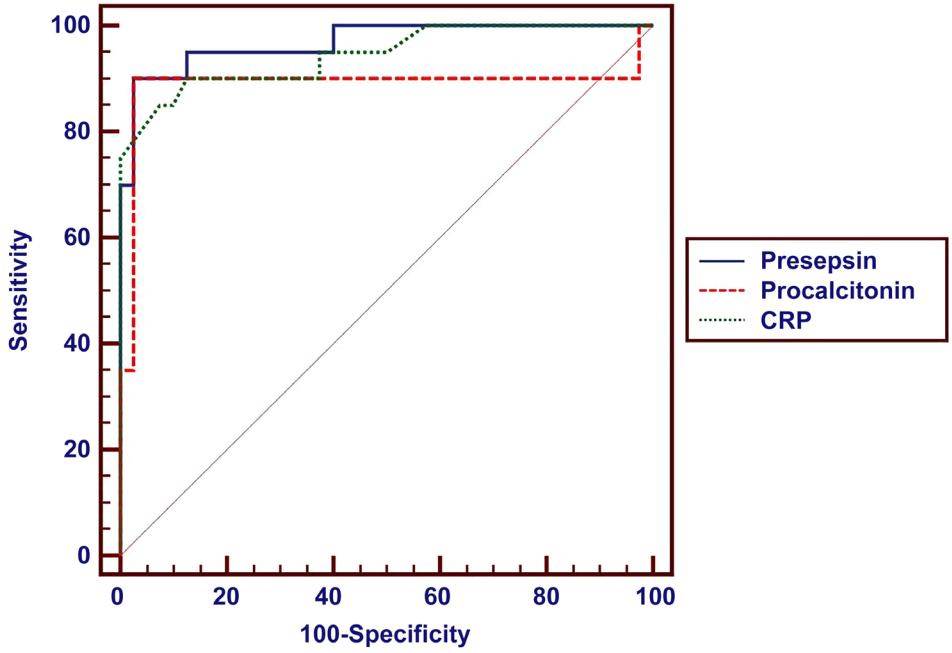

Figure 3. Roc curve of various parameters to predict septic shock.

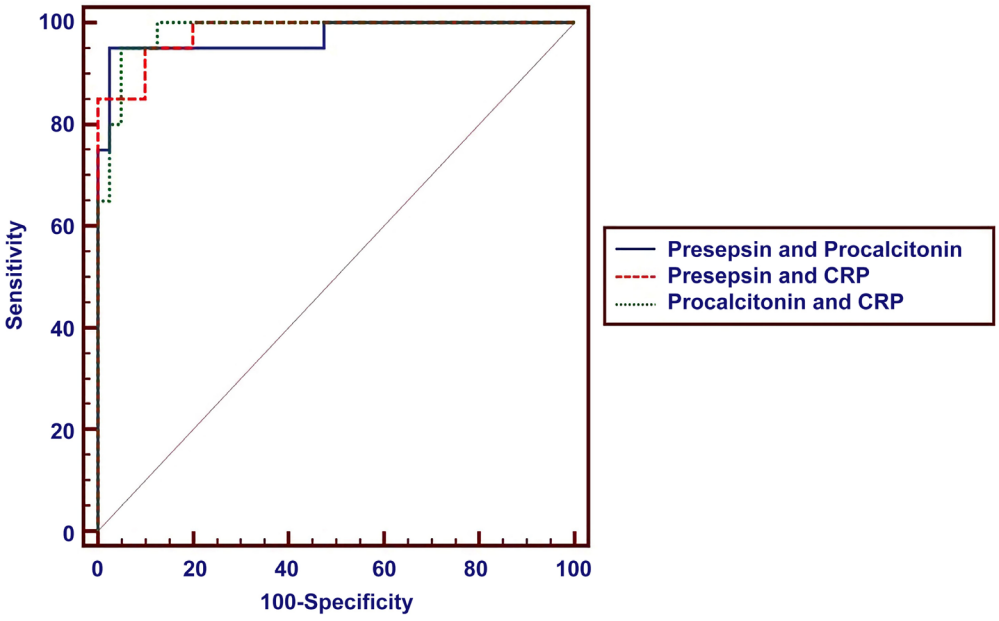

Figure 4. Roc curve of combination of parameters to predict septic shock.

4. Discussion

Despite new advances in critical care management, the incidence of sepsis is still increasing among hospitalized patients and early diagnosis still constitutes a challenge [16]. Since the use of the currently available tests were found to be limited, this justifies our aim to investigate the utility of serum PS and PCT as early diagnostic biomarkers of sepsis in critically ill patients and predictors of patients prognosis.

The current study showed a significant increase in PS level in patients with early sepsis than in healthy controls. This was in accordance with Kahveci *et al.*, who found that the plasma PS level in the sepsis group was higher than that in the healthy control group [3].

Liu *et al.*, reported that PS was a valuable biomarker for early diagnosis of sepsis and it is highly specific for diagnosing bacterial infections because it is produced in association with bacterial phagocytosis [17].

In addition, we found that with progression of sepsis severity, the serum PS level increased accordingly, and reached the highest level in septic shock. Similarly to our results, a great number of studies reported significantly higher levels of PS in septic shock patients compared to septic patients without shock [18] [19].

Masson *et al.*, stated that PS was a robust circulating biomarker for sepsis, early stratification of its severity, as well as for patient prognosis. They explained their results by PS that appears to be released in the plasma as a consequence of cellular phagocytosis after bacterial infection and are therefore an indirect marker of sepsis. In addition, PS was a good marker of the host response, and its higher levels, independently of the type of infection, may indicate a state of immune paralysis, leading to a spreading of the related inflammatory reaction, which may lead to multiple organ failure and death [20].

In contrast, Kahveci *et al.*, did not detect a significant difference in plasma PS levels between patients with septic shock and those with severe sepsis [3]. This could be explained by that their study included a less number of patients with acute kidney injury that increased the plasma PS levels. Therefore, a significant difference may not have appeared between the sepsis and septic shock groups. Nakamura *et al.*, reported that not only sepsis but also accompanying kidney injuries contributed to an increase in PS levels [21].

Similarly, our study showed a significant increase in PCT level in patients with early sepsis compared with controls. This was in line with Kibe *et al.*, who concluded that PCT was a biomarker currently used for diagnosis of sepsis [22].

We also found that PCT level increased with increase of sepsis severity till reached the highest level in septic shock patients. This was in agreement with De Oliveiria-Netto *et al.*, who detected a significant increase in PCT in septic shock patients compared with those with sepsis and explained that by the hemodynamic changes presented in septic shock [23].

In contrast, Aliu-Bejtaa *et al.*, did not find association of PCT levels with severity of sepsis [24]. Similarly, Kweon *et al.*, did not report a difference in PCT levels among sepsis, severe sepsis and septic shock groups [25].

We found that the first-day PS and PCT levels were significantly higher in non-survivor septic patients than survivors. Our results confirmed the prognostic value of PS and PCT in adult patients with sepsis by being able to differentiate between patients with sepsis and those with septic shock, as well as between survivors and non-survivors.

In consistence to our results, Zhu *et al.*, found that there is no statistically significant difference between both PS and PCT in predicting mortality of septic patients implying that both were promising prognostic biomarkers of sepsis [2].

In addition, Brodska *et al.*, reported significantly higher PS levels in deceased patients [26]. In another study, Kim *et al.*, reported higher mortality rates in patients with high PS levels [27]. Hassan *et al.*, reported that increasing PS levels within the first week of hospitalization predicted ICU and 90-day mortality [15]. Jedynak *et al.*, revealed that a high PCT level was associated with 28-day mortality in patients with sepsis [28].

While in opposite to our results, Kahveci *et al.*, did not observe a significant difference in PS and PCT levels between survivor and non-survivor patients [3]. Yu *et al.*, found that PCT levels had no statistical difference between survival and non-survival groups and within 12 days, PCT levels in both groups decreased synchronously. Comparatively, they found that PS levels in the survival group decreased persistently, while they rose gradually in the non-survival group [29].

The correlation studies revealed that the PS and PCT levels were positively correlated with APACHE II score, qSOFA score and CRP level, supporting the view that PS and PCT are potential markers for diagnosing sepsis and differentiating sepsis severity that significantly correlates with the activation of the systemic inflammatory state induced by sepsis. We also found that PS and PCT were positively correlated with each other.

Similar to our results, Behnes *et al.*, found significant correlations between PS and PCT, as well as SOFA and APACHE scores, and subsequently severity of the disease [30]. In accordance with these findings, Drăgoescu *et al.*, identified significant correlations between PS and the SOFA score and CRP [31]. Aliu-Bejtaa *et al.*, revealed a strong correlation of PS with SOFA score, thus letting them believe that PS might be a specific sepsis biomarker [24]. However, Brodska *et al.*, reported that initial PS concentrations do not correlate with SOFA score [26]. The fact that the results of the reported studies are incompatible necessitates further research.

We evaluated the diagnostic accuracy of PS and PCT to predict sepsis in comparison to CRP, by using ROC curve analysis. Our results revealed that PS has the highest AUC value for discrimination between control group and patients with early sepsis followed by PCT, while CRP has the lowest AUC value for its discrimination ability in comparison to PS and PCT. We also found that the combinations of PS and PCT, PS and CRP or PCT and CRP improved the accuracy of early diagnosis of sepsis.

Our results could be explained by the rapid pharmacokinetics of PS molecule that makes its level rises within 2 hours of any infection, with a maximum concentration after 3 hours, which is earlier than that reported for PCT and CRP that have significantly longer kinetics in bacterial or fungal infections. This specific feature of PS makes it a superior biomarker to PCT and CRP for early diagnosis of sepsis, while, both PCT and CRP might be still not reliable enough as early indicators for sepsis [32].

This was in agreement with Yamamoto *et al.*, who found that PS had the highest diagnostic accuracy for discriminating non-sepsis from sepsis compared to PCT and CRP [33]. Tan *et al.*, evaluated the diagnostic performance of PCT for the diagnosis of sepsis and found that PCT has a significantly higher diagnostic accuracy than CRP [34].

Different to our findings, Wu *et al.*, suggested that there was no obvious better performance of PS than PCT in the diagnosis of sepsis. In addition, they observed that there was non-significant difference between CRP and PS as biomarkers for the early stage of sepsis [35].

Moreover, Enguix-Armada *et al.*, showed that PCT had the highest AUC in the first 24 h after ICU admission. Also PCT and CRP showed similar diagnostic values [36]. While, Venkataraman *et al.*, found that the diagnostic performance of PCT as a biomarker of sepsis was low and concluded that PCT therefore could not reliably differentiate sepsis from other conditions in critically ill adult patients [37].

Finally, we tested whether PS and PCT could predict septic shock in comparison to CRP, through ROC curve analysis. PS was found to yield higher AUC value than PCT and CRP, while PCT showed the lowest value. The combinations of any two biomarkers increased the accuracy of diagnosis of septic shock.

Liu *et al.*, showed that PS had a higher predictive value than PCT for septic shock in patients with sepsis and the combination with other severity scores proved to be better, which was in line with our results [17]. However, different to our results, Behnes *et al.*, observed that the AUC of PS to diagnose septic shock at day 1 of ICU treatment, was comparable to that of PCT [30].

There were some limitations for our study. First, the relatively low number of patients because it was a single-center study performed with no external funding. Second, a control patient group (non-sepsis ICU patient) was not included in the study. Third, the lack of repeated measurements for the study parameters over time as this was a single time-point measurement study only.

5. Conclusion

Our study demonstrated that the serum PS and PCT levels were found to be promising biomarkers for the early diagnosis of sepsis in critically ill patients, but PS has more diagnostic accuracy than PCT and CRP. Moreover, PS served as a prognostic index towards the progression of sepsis and severe sepsis to septic shock with higher diagnostic accuracy than PCT and CRP. While CRP level was more successful in predicting septic shock compared to the PCT level. The combinations of biomarkers improved the accuracy of early diagnosis of sepsis and septic shock. More comprehensive studies are necessary for further confirmation of our results.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Shimoyama, Y., Umegaki, O., Kadono, N. and Minami, T. (2020) Urinary Neutrophil Gelatinase-Associated Lipocalin Values alone and Combined with Prognostic Index Predict Septic AKI, DIC, and Shock: A Pilot Study. *BMC Research Notes*, **13**, Article No. 387. https://doi.org/10.1186/s13104-020-05232-w

[2] Zhu, Y., Li, X., Guo, P., Chen, Y., Li, J. and Tao, T. (2019) The Accuracy Assessment of Presepsin (sCD14-ST) for Mortality Prediction in Adult Patients with Sepsis and a Head-to-Head Comparison to PCT: A Meta-Analysis. *Therapeutics and Clinical Risk Management*, **15**, 741-753. https://doi.org/10.2147/TCRM.S198735

[3] Kahveci, U., Ozkan, S., Melekoglu, A., Usul, E., Ozturk, G. and Cetin, E. (2021) The role of Plasma Presepsin Levels in Determining the Incidence of Septic Shock and Mortality in Patients with Sepsis. *Journal of Infection in Developing Countries*, **15**, 123-130. https://doi.org/10.3855/jidc.12963

[4] Elkareem, R.M.A., Ahmed, H.M., Meabed, M.H., Elias, S.S. and Elmaraghy, M.A. (2020) Diagnostic Value of CD64 in Early Detection of Neonatal Sepsis. *Comparative Clinical Pathology*, **29**, 639-643. https://doi.org/10.1007/s00580-020-03100-4

[5] Lee, J., Kim, S., Kim, K.H., Jeong, N.R., Kim, S.C. and Oh, E. (2021) The Association between Dynamic Changes in Serum Presepsin Levels and Mortality in Immunocompromised Patients with Sepsis: A Prospective Cohort Study. *Diagnostics*, **11**, Article No. 60. https://doi.org/10.3390/diagnostics11010060

[6] Sakyi, S.A., Enimil, A., Adu, D.K., Ephraim, R.D., Danquah, K.O., Fondjo, L., *et al.* (2020) Individual and Combined Bioscore Model of Presepsin, Procalcitonin, and High Sensitive C-Reactive Protein as Biomarkers for Early Diagnosis of Paediatric Sepsis. *Heliyon*, **6**, e04841. https://doi.org/10.1016/j.heliyon.2020.e04841

[7] Wang, X., Sun, Y. and Shao, X. (2019) Predictive Value of Procalcitonin for Infection of Patients with Type 2 Diabetes Mellitus. *Experimental and Therapeutic Medicine*, **18**, 722-728. https://doi.org/10.3892/etm.2019.7611

[8] Yang, H.S., Hur, M., Yi, A., Kim, H., Lee, S. and Kim, S. (2018) Prognostic Value of Presepsin in Adult Patients with Sepsis: Systematic Review and Meta-Analysis. *PLoS ONE*, **13**, e0191486. https://doi.org/10.1371/journal.pone.0191486

[9] Kaplan, M., Duzenli, T., Tanoglu, A., Guney, B.C., Tastan, Y.O. and Bicer, H.S. (2020) Presepsin: Albumin Ratio and C-Reactive Protein: Albumin Ratio as Novel Sepsis-Based Prognostic Scores. *Wiener klinische Wochenschrift*, **132**, 182-187. https://doi.org/10.1007/s00508-020-01618-9

[10] Hashem, H.E., Abdel Halim, R.M., El Masry, S.A., Mokhtar, A.M. and Abdelaal, N.M. (2020) The Utility of Neutrophil CD64 and Presepsin as Diagnostic, Prognostic, and Monitoring Biomarkers in Neonatal Sepsis. *International Journal of Microbiology*, **2020**, Article ID: 8814892. https://doi.org/10.1155/2020/8814892

[11] Omar, J., Isa, S., Ismail, T.S.T., Yaacob, N.M. and Soh, N.A.C. (2019) Procalcitonin as an Early Laboratory Marker of Sepsis in Neonates: Variation in Diagnostic Performance and Discrimination Value. *Malaysian Journal of Medical Sciences*, **26**, 61-69. https://doi.org/10.21315/mjms2019.26.4.7

[12] Yunus, I., Fasih, A. and Wang, Y. (2018) The Use of Procalcitonin in the Determination of Severity of Sepsis, Patient Outcomes and Infection Characteristics. *PLoS ONE*, **13**, e0206527. https://doi.org/10.1371/journal.pone.0206527

[13] Wacker, C., Prkno, A., Brunkhorst, F.M., Shankar-Hari, M., Annane, D., Bauer, M., *et al.* (2013) Procalcitonin as a Diagnostic Marker for Sepsis: A Systematic Review and Meta-Analysis. *Lancet Infectious Diseases*, **13**, 426-435. https://doi.org/10.1016/S1473-3099(12)70323-7

[14] Hayashida, K., Kondo, Y., Hara, Y., Aihara, M. and Yamakawa, K. (2017) Head-to-Head Comparison of Procalcitonin and Presepsin for the Diagnosis of Sepsis in Critically Ill Adult Patients: A Protocol for a Systematic Review and Meta-Analysis. *BMJ Open*, **7**, Article ID: e014305. https://doi.org/10.1136/bmjopen-2016-014305

[15] Hassan, E.A., Abdel Rehim, A.S., Ahmed, A.O., Abdullahtif, H. and Attia, A. (2019) Clinical Value of Presepsin in Comparison to hsCRP as a Monitoring and Early Prognostic Marker for Sepsis in Critically Ill Patients. *Medicina*, **55**, Article No. 36. https://doi.org/10.3390/medicina55020036

[16] Venugopalan, D.P., Pillai, G. and Krishnan, S. (2019) Diagnostic Value and Prognostic Use of Presepsin versus Procalcitonin in Sepsis. *Cureus*, **11**, Article No. e5151. https://doi.org/10.7759/cureus.5151

[17] Liu, B., Chen, Y., Yin, Q., Zhao, Y. and Li, C. (2013) Diagnostic Value and Prognostic Evaluation of Presepsin for Sepsis in an Emergency Department. *Critical Care*, **17**, Article No. R244. https://doi.org/10.1186/cc13070

[18] Masson, S., Caironi, P., Fanizza, C., Thomae, R., Bernasconi, R., Noto, A., *et al.* (2015) Circulating Presepsin (Soluble CD14 Subtype) as a Marker of Host Response in Patients with Severe Sepsis or Septic Shock: Data from the Multicenter, Randomized ALBIOS Trial. *Intensive Care Medicine*, **41**, 12-20. https://doi.org/10.1007/s00134-014-3514-2

[19] Klouche, K., Cristol, J.P., Devin, J., Gilles, V., Kuster, N., Larcher, R., *et al.* (2016) Diagnostic and Prognostic Value of Soluble CD14 Subtype (Presepsin) for Sepsis and Community-Acquired Pneumonia in ICU Patients. *Ann Intensive Care*, **6**, Article No. 59. https://doi.org/10.1186/s13613-016-0160-6

[20] Masson, S., Caironi, P., Spanuth, E., Thomae, R., Panigada, M., Sangiorgi, G., *et al.* (2014) Presepsin (Soluble CD14 Subtype) and Procalcitonin Levels for Mortality Prediction in Sepsis: Data from the Albumin Italian Outcome Sepsis Trial. *Critical Care*, **18**, Article No. R6. https://doi.org/10.1186/cc13183

[21] Nakamura, Y., Hoshino, K., Kiyomi, F., Kawano, Y., Mizunuma, M., Tanaka, J., *et al.* (2019) Comparison of the Accuracy of Presepsin and Procalcitonin Concentrations in Diagnosing Sepsis in Patients with and without Acute Kidney Injury. *Clinica Chimica Acta*, **490**, 200-206. https://doi.org/10.1016/j.cca.2018.09.013

[22] Kibe, S., Adams, K. and Barlow, G. (2011) Diagnostic and Prognostic Biomarkers of Sepsis in Critical Care. *Journal of Antimicrobial Chemotherapy*, **66**, ii33-ii40. https://doi.org/10.1093/jac/dkq523

[23] De Oliveira-Netto, A.S., Morello, L.G., Dalla-Costa, L.M., Petterle, R.R., Fontana, R.M., Conte, D., *et al.* (2019) Procalcitonin, C-Reactive Protein, Albumin, and Blood Cultures as Early Markers of Sepsis Diagnosis or Predictors of Outcome: A Prospective Analysis. *Clinical Pathology*, **12**, 1-7. https://doi.org/10.1177/2632010X19847673

[24] Aliu-Bejtaa, A., Ateljb, A., Kurshumliuc, M., Dreshaja, S. and Baršić, B. (2020) Presepsin Values as Markers of Severity of Sepsis. *International Journal of Infectious Diseases*, **95**, 1-7. https://doi.org/10.1016/j.ijid.2020.03.057

[25] Kweon, O.J., Choi, J.H., Park, S.K. and Park, A.J. (2014) Usefulness of Presepsin (sCD14 Subtype) Measurements as a New Marker for the Diagnosis and Prediction of Disease Severity of Sepsis in the Korean Population. *Journal of Critical Care*, **29**, 965-970. https://doi.org/10.1016/j.jcrc.2014.06.014

[26] Brodska, H., Valenta, J., Pelinkova, K., Stach, Z., Sachl, R., Balik, M., *et al.* (2018) Diagnostic and Prognostic Value of Presepsin vs. Established Biomarkers in Critically Ill Patients with Sepsis or Systemic Inflammatory Response Syndrome. *Clinical*

Chemistry and Laboratory Medicine, **56**, 658-668.
https://doi.org/10.1515/cclm-2017-0839

[27] Kim, H., Hur, M., Moon, H.W., Yun, Y.M. and Di Somma, S. (2017) Multi-Marker Approach Using Procalcitonin, Presepsin, Galectin-3, and Soluble Suppression of Tumorigenicity 2 for the Prediction of Mortality in Sepsis. *Annals of Intensive Care*, **7**, Article No. 27. https://doi.org/10.1186/s13613-017-0252-y

[28] Jedynak, M., Siemiatkowski, A., Mroczko, B., Groblewska, M., Milewski, R. and Szmitkowski, M. (2018) Soluble TREM-1 Serum Level can Early Predict Mortality of Patients with Sepsis, Severe Sepsis, and Septic Shock. *Archivum Immunologiae et Therapiae Experimentalis*, **66**, 299-306. https://doi.org/10.1007/s00005-017-0499-x

[29] Yu, H., Qi, Z., Hang, C., Fang, Y., Shao, R. and Li, C. (2017) Evaluating the Value of Dynamic Procalcitonin and Presepsin Measurements for Patients with Severe Sepsis. *The American Journal of Emergency Medicine*, **35**, 835-841.
https://doi.org/10.1016/j.ajem.2017.01.037

[30] Behnes, M., Bertsch, T., Lepiorz, D., Lang, S., Trinkmann, F., Brueckmann, M., *et al.* (2014) Diagnostic and Prognostic Utility of Soluble CD 14 Subtype (Presepsin) for Severe Sepsis and Septic Shock during the First Week of Intensive Care Treatment. *Critical Care*, **18**, Article No. 507. https://doi.org/10.1186/s13054-014-0507-z

[31] Drăgoescu, A., Pădureanu, V., Stănculescu, A.D., Chiut, L.C., Florescu, D.N., Gheonea, I.A., *et al.* (2021) Presepsin as a Potential Prognostic Marker for Sepsis According to Actual Practice Guidelines. *Journal of Personalized Medicine*, **11**, Article No. 2. https://doi.org/10.3390/jpm11010002

[32] Chenevier-Gobeaux, C., Bardet, V., Poupet, H., Poyart, C., Borderie, D. and Claessens, Y.E. (2016) Presepsin (sCD14-ST) Secretion and Kinetics by Peripheral Blood Mononuclear Cells and Monocytic THP-1 Cell Line. *Annales de Biologie Clinique*, **74**, 93-97. https://doi.org/10.1684/abc.2015.1112

[33] Yamamoto, T., Nishimura, T., Kaga, S., Uchida, K., Tachibana, Y., Esaki, M., *et al.* (2019) Diagnostic Accuracy of Presepsin for Sepsis by the New Sepsis-3 Definitions. *American Journal of Emergency Medicine*, **37**, 1936-1941.
https://doi.org/10.1016/j.ajem.2019.01.025

[34] Tan, M., Lu, Y., Jiang, H. and Zhang, L. (2019) The Diagnostic Accuracy of Procalcitonin and C-Reactive Protein for Sepsis: A Systematic Review and Meta-Analysis. *Journal of Cellular Biochemistry*, **120**, 5852-5859. https://doi.org/10.1002/jcb.27870

[35] Wu, C., Lan, H., Han, S., Chaou, C., Yeh, C., Liu, S., *et al.* (2017) Comparison of Diagnostic Accuracy in Sepsis between Presepsin, Procalcitonin, and C-Reactive Protein: A Systematic Review and Meta-Analysis. *Ann Intensive Care*, **7**, Article No. 91. https://doi.org/10.1186/s13613-017-0316-z

[36] Enguix-Armada, A., Escobar-Conesa, R., La Torre, A.G. and La Torre-Prados, M.V. (2016) Usefulness of Several Biomarkers in the Management of Septic Patients: C-Reactive Protein, Procalcitonin, Presepsin and Mid-Regional Pro-Adrenomedullin. *Clinical Chemistry and Laboratory Medicine*, **54**, 163-168.
https://doi.org/10.1515/cclm-2015-0243

[37] Venkataraman, R. and Kellum, J.A. (2013) Sepsis: Update in the Management. *Advances in Chronic Kidney Disease*, **20**, 6-13.
https://doi.org/10.1053/j.ackd.2012.10.013