DIAGNOSTIC UTILITY OF PRESEPSIN AND PROCALCITONIN IN CRITICALLY ILL PATIENTS WITH SUSPECTED SEPSIS: COMPARISON WITH RECENT CLINICAL CRITERIA OF SEPSIS-3

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Article Info: Received 18 May 2019; Accepted 20 June. 2019

DOI: <https://doi.org/10.32553/ijmbs.v3i6.309>

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Conflict of interest: No conflict of interest.

Abstract

Background: In this study, we aimed to investigate the diagnostic and prognostic utilities of presepsin and procalcitonin (PCT) in critically ill patients with suspected sepsis, for whom sepsis was diagnosed clinically based on the Survival Sepsis Campaign (SSC) criteria and to compare it with recent criteria of Sepsis-3.

Methods: Blood samples for biomarker measurements of presepsin and PCT were drawn on days 1, 3 and 7 of ICU admission in a total of 26 patients. All patients were followed-up until death or discharge. All studied biomarkers were analyzed according to the diagnosis and severity of sepsis and for prognosis (all-cause mortality) at days 1, 3 and 7. Agreement between the diagnosis of clinical sepsis and presepsin or PCT-based sepsis was assessed using Cohen's kappa

Results: Clinical sepsis (based on Sepsis-3) and presepsin or PCT-based sepsis showed poor agreement ($\text{Kappa} < 0.4$). Presepsin levels at day1 correlated significantly with mortality ($r = 0.45$, $P = 0.02$). The diagnostic value of both presepsin and PCT to diagnose sepsis was weak (Area under curve (AUC) < 0.75). The overall agreement in sepsis diagnosis was fair to good based on the both clinical criteria ($P < 0.05$, $\text{Kappa}: 0.5-0.75$). More than 80% of patients ($N = 21$) had sepsis based on presepsin upon admission. Both clinical criteria predicated that less than 20% of patients ($N = 5$) had sepsis upon admission.

Conclusion: Based on our findings, the overall agreement between the diagnosis of clinical sepsis and presepsin or PCT-based sepsis was poor. Also, our results show that the new Sepsis-3 definitions were accurate and equal to the previous definition of SSC guideline. Although, availability of diagnostic assays is variable in Iran, but, it seems that addition of developing decision tools that utilize biomarkers to help aid the rapid diagnosis of sepsis is necessary and may improve patient outcomes.

Keywords: Presepsin, Pro Calcitonin, Sepsis, Diagnosis

Introduction

Systemic Inflammatory Response Syndrome (SIRS) is a clinical response to a nonspecific insult of either infectious or noninfectious origin (e.g. pancreatitis, ischemia, trauma and severe tissue injury). Sepsis is defined as SIRS caused by infection [1, 2]. However, infections can be difficult to confirm. Currently blood cultures processed with standard microbiologic techniques are considered as gold standard for diagnosing infection, but, variety of factors, including

prior antibiotic therapy could affect the diagnostic value of blood culture [3]. Bacteremia is identified in only about 30% of patients [4].

On the other hand, delay in empiric treatment for sepsis and bacteremia increase mortality, length of stay and cost [5, 6]. Therefore, early recognition and timely initiation of appropriate therapy could lead to optimal outcome benefit [7]. At least 24-48 hours are necessary to results of blood culture become available, so rapid diagnosis and risk stratification of

sepsis is mandatory. The use of serum biomarkers has significantly improved the mentioned above issues [8].

Biomarkers are molecules which are activated and released through the host response to infection. White blood cell (WBC) count and C-reactive protein (CRP) level, used many years to diagnose sepsis, although their specificity is very low, recently, the 116-aminoacid polypeptide procalcitonin (PCT) had been used as diagnostic criteria for sepsis. The PCT has wide biological range, short time of induction after bacterial stimulus and long half-life [9]. In a meta-analysis by Wacker et al., [10] (2013) showed that PCT is a helpful biomarker for early diagnosis of sepsis in critically ill patients, but the results of tests must be interpreted carefully in the context of medical history, physical examination and microbiological assessment. In another meta-analysis by Liu et al., [11] (2015), 23 studies with 3994 patients were included. They concluded that the elevated PCT level was associated with a higher risk of death (RR: 2.6, 95% confidence interval (CI), 2.05-3.30). Also, initial PCT values were of limited prognostic value in patients with sepsis. PCT non-clearance was a prognostic factors of death in patients with sepsis (RR: 3.05, 95% CI, 2.35-3.95). Some PCT limitations are as follows: transient rise in nonspecific condition and SIRS (such as trauma, surgery, heat stroke) and undetectable in certain causes of sepsis [12, 13].

The ideal biomarker should retain high sensitivity and specificity and be cost-effective and promptly available. So far, no ideal biomarker has yet been identified with sufficient clinical sensitivity or specificity for the diagnosis of sepsis [14].

Cluster of differentiation 14 (CD14) is a multifunctional glycoprotein expressed on the membrane surface of monocytes and macrophages and serves as a receptor for complexes of lipopolysaccharides (LPSs) and LPS-binding proteins (LPBs). The LPS-LBP-CD14 complex is released into the circulation by shedding CD14 from the cell membrane, yielding soluble CD14 (SCD14), which is also directly secreted by hepatocytes. SCD14 has recently been identified and renamed as presepsin, which is increased in response to the severity of bacterial infection [15, 16]. Several studies suggest that the level of presepsin significantly differs in healthy individuals and in patients with local infection, SIRS, sepsis or severe sepsis [17-21].

Recent meta-analysis by Zhang et al., [22] (2015) suggest that presepsin exhibit very good diagnostic accuracy (area under the curve (AUC):0.89) for the diagnosis of sepsis. All the 8 included studies were performed in the emergency department involving a total of 1815 patients. The pooled sensitivity and specificity was 0.86 (95% CI: 0.79-0.91) and 0.78 (95% CI: 0.68-0.85) respectively. The authors recommended presepsin cannot be recommended as the single definitive test for sepsis diagnosis. Masson et al., [19] in a retrospective case-control study suggested that presepsin measurements may have useful prognostic information for patients with severe sepsis or septic shock. They selected 50 survivors and 50 non-survivors at the Intensive Care Unit (ICU) discharge. The presepsin was the only variable independently associated with ICU and 28-day mortality. It showed better prognostic accuracy than PCT in the range of Sequential Organ Failure Assessment (SOFA) score (AUC from 0.64 to 0.75 vs. AUC 0.53-0.63). Presepsin has also been shown to be helpful for assessing the severity of sepsis and for monitoring therapeutic responses. As most of the mentioned studies about the presepsin were conducted in the emergency department [18, 20, 23, 24], the clinical value of presepsin in critically ill patients is still unclear. Although widely used in some centers for diagnostic purposes, further multi-center studies are required before drawing firm conclusions.

The *Surviving Sepsis Campaign* (SSC) is a joint collaboration of the Society of Critical Care Medicine and the European Society of Intensive Care Medicine committed to reducing mortality and morbidity from sepsis and septic shock worldwide. This campaign provide evidence based and updated data to diagnosis of sepsis and also management of severe sepsis and septic shock. The SCC define sepsis as a systemic manifestation of infection (i.e. SIRS criteria) plus suspected infection [25]. In 2016, the definition of sepsis was updated by the Third International Consensus Group (Sepsis-3) to reflect greater understanding of the disease. This step was taken because the SIRS criteria were found to be too non-specific to be useful in defining sepsis: they defined sepsis as life-threatening organ dysfunction caused by a dysregulated host response to an infection. Rather than using the SIRS criteria to identify these patients (upon which the previous definition was based), the Sepsis-3 advised that sepsis should be defined using the SOFA criteria. The SOFA score is calculated based on the assessment of the lab values and vital signs,

with a score of ≥ 2 in a patient with a suspected infection being suggestive of sepsis. The 2016 Sepsis-3 definitions also recommend that the term 'severe sepsis', as previously defined, should be made redundant in light of revisions to the definition of sepsis [26].

According to the published reports, Iran is among countries with high antimicrobial resistance [27-29]. Incorrect and over-diagnosis of infectious diseases are the main reasons for excessive prescription of antibiotics. Alavi et al., [30] reported that more than half of the patients hospitalized due to primary diagnosis of sepsis, actually had no sepsis and diagnosis of sepsis in the Intensive Care Unit (ICU) is often inaccurate and based on the physician's decision. Availability of diagnostic assays is variable in Iran, making diagnosis of sepsis even more difficult. Therefore, uses of developing decision tools that utilize biomarkers to help aid the rapid diagnosis of sepsis is necessary. Numerous studies evaluating biomarkers in sepsis, though the majority of these studies have been in the United States and Europe.

In this study, we compare presepsin and PCT for early diagnosis of sepsis and staging the sepsis in critically ill patients with suspected sepsis (based on the SSC criteria) in the first week of ICU admission. Also, the diagnostic values of presepsin and PCT was compared with the recent clinical criteria of Sepsis-3. As well as, the association of presepsin level with mortality, Acute Physiology and Chronic Health Evaluation (APACHE II) score and SOFA scores, and length of ICU stay was evaluated as secondary outcomes.

Methods

This was a prospective observational study conducted in the ICUs (60 beds) of "Alzahra" teaching hospital affiliated to Isfahan University of Medical Sciences (IUMS) from March 2016 to November 2016.

In the present study, all consecutive patients who fulfilled the criteria for sepsis which is adopted from 2012 Surviving Sepsis Campaign (SSC) guideline [25] were enrolled. According to the guideline the inclusion criteria were as follows: (1) age above 18 years, (2) fulfillment of at least two or the SIRS criteria [temperature $> 38^{\circ}\text{C}$ or $< 36^{\circ}\text{C}$, heart rate > 90 beats/min, respiratory rate > 20 breaths/min or $\text{pCO}_2 < 32$ mm Hg, white blood cell (WBC) count $> 12,000/\text{mm}^3$ or $< 4000/\text{mm}^3$ or $> 10\%$ immature neutrophils] and (3) clinical suspicion of bacteremia and consecutive order of blood culture. The patients

stratified based on the guideline recommendations to severe sepsis and septic shock. Patients who did not fulfill the criteria considered as "no sepsis". We also categorized patients based on the criteria for sepsis which is adopted from the third international consensus for sepsis and septic shock (Sepsis-3) [26].

Patients who aged less than 18 years, received a massive transfusion (>10 units of packed cell in the previous 24 hours), patients with acute kidney injury (increase in serum creatinine (SrCr) more than 3 times of baseline or $\text{SrCr} > 4$ mg/dl or urine output $< 0.3\text{ml/kg/h}$ or anuria for 12 hours), patients with burns and acute pancreatitis were excluded. The study protocol was approved by the IUMS ethic committee (number of 394987). Written informed consent was obtained from all enrolled patients or next of kins.

All patients were treated according to the standard institutional protocol for management of sepsis and septic shock, based on recommendations from the surviving sepsis campaign. The duration of antimicrobial therapy was guided by culture data, site of infection and treating physician. The APACHE II and SOFA scores on day 1(admission), 3 and 7 of blood sampling were calculated. The APACHE II scoring system is designed to measure the severity of disease in patients admitted to the ICU. It is applied within 24 hours of admission of a patient to an ICU: an integer score from 0 to 71 is computed based on several measurements; higher scores correspond to more severe disease and a higher risk of death. The point score is calculated from a patient's age and 12 routine physiological measurements including: AaDO₂ or PaO₂ (depending on FiO₂), temperature (rectal), mean arterial pressure, pH arterial, heart rate, respiratory rate, Sodium (serum), Potassium (serum), Creatinine, Hematocrit, White blood cell count and Glasgow Coma Scale. These were measured during the first 24 hours after admission, and utilized in addition to information about previous health status (recent surgery, history of severe organ insufficiency, immunocompromised state) and baseline demographics such as age.

SOFA score, is used to track a person's status during the stay in an ICU to determine the extent of a person's organ function or rate of failure. The score is based on six different scores, one each for the respiratory, cardiovascular, hepatic, coagulation, renal and neurological systems and assigns a score based on the data obtained in each category. The

"worst" measurement was defined as the measure that correlated to the highest number of points. The SOFA score ranges from 0 to 24. The higher the SOFA score, the higher the likely mortality.

The following patient characteristics were recorded: age, sex, diagnosis on ICU admission, surgical cases, usage of mechanical ventilation, renal replacement therapy and vasopressor, culture results, length of ICU stay and in-hospital death. We recorded physiological and laboratory data on admission, during blood sampling and ICU discharge as follows: WBC count, serum CRP level, serum albumin level, hemoglobin level, platelet level, alanine transaminase (ALT), aspartate transaminase (AST) and total bilirubin level, International normalized ratio (INR), activated partial thromboplastin time (aPTT), prothrombin time (PT), Arterial Blood Gas (ABG) results (PH, PCO₂, PO₂, HCO₃) and procalcitonin levels. The recorded clinical data included: body temperature, heart rate, respiratory rate, blood pressure and Glasgow coma scale (GCS).

Measurement of biomarker

Presepsin was measured in serum samples that are collected on admission, day 3 and day 7 of enrollment. The venous blood sample (5ml) was drawn, and centrifuged at 3000 rpm for 10 minutes; and the supernatant was stored at -80°C until analysis. Serum levels were measured using enzyme linked immunosorbent assay (ELISA) according to the manufacturer's instruction (Abbexa, Cambridge, United Kingdom) (measurable range: 65-3000 pg/ml; limit of detection: 22pg/ml). Presepsin levels $\geq$ 530 pg/ml may indicate sepsis, levels $\geq$ 600 pg/ml indicate severe sepsis and levels $\geq$ 700 pg/ml indicate septic shock [17].

PCT levels 0.5 ng/mL to 2.0 ng/mL may indicate sepsis, levels above 2.0 ng/mL but less than 10 ng/mL indicate severe sepsis and levels $\geq$ 10 ng/ml indicate septic shock [11].

Statistical analysis

Continuous variables are expressed as mean $\pm$ standard deviation (SD) and categorical variables as frequencies and proportions. Chi-square test was used to compare the proportions. Pearson's rank correlation was used to test association of presepsin blood levels with medical parameters. For normally distributed data, the student t-test was applied. Otherwise, the Mann-Whitney u-test was used as a non-parametric test. Deviation from a Gaussian

distribution was tested by the Kolmogorov-smirnov test. Agreement between the diagnosis of clinical sepsis and presepsin or PCT-based sepsis was assessed using Cohen's kappa (agreement: <0.4 , poor; $0.4-0.75$, fair to good, >0.75 , excellent).

Receiver Operating Characteristic (ROC) curves were analyzed to compare presepsin and PCT in predicting in-hospital mortality and in diagnosing sepsis. The calculations were performed with SPSS software version 20. All analyses were exploratory and utilized a P-value of 0.05 (two-tailed) for significance.

Results

A total of 26 patients (20 male and 6 women) were included in the study. The mean age of the patients was 49.3 ± 21 years. The duration of ICU stay was 41.7 ± 29 days (range: 10-130 days). Baseline characteristics are given in Table 1. Number of patients with SIRS, sepsis, severe sepsis and septic shock and the levels of presepsin and PCT in measurement days is presented in Table 2. The most common primary site of infection was the lung (N=15) followed by urinary tract infection (N=5).

Table 3 shows the agreement rate when sepsis, severe sepsis and septic shock was diagnosed clinically or based on the presepsin and the PCT concentrations. As shown, in all three days of measurement the overall concordance rate between clinical sepsis and presepsin-based sepsis was poor. Also the agreement between presepsin and PCT-based sepsis was poor.

Presepsin levels were significantly correlated with clinical and laboratory parameters at day 1. Presepsin correlated with SOFA and APACHE II score ($r=0.64$, $P: 0.00$, and $r=0.51$, $P: 0.008$) respectively as well as with the bilirubin ($r=0.43$, $P: 0.03$). Significant correlation was observed between mortality and the presepsin level at day 1 ($r=-0.45$, $P: 0.02$). Presepsin levels were not correlated with patient's age ($P: 0.3$) and length of ICU stay ($P: 0.15$). Additionally, presepsin at day 1 correlated significantly with PCT ($r=0.65$, $P: 0.001$). Presepsin and PCT levels were not correlated with the CRP levels ($r=-0.13$, $P: 0.5$, and $r=0.35$, $P: 0.08$, respectively).

Figure 1 illustrates distribution of presepsin and PCT levels, according to the different group of sepsis severity at days 1, 3 and 7. We observed an inverse relationship between presepsin and PCT levels and sepsis severity at day 1. At days 3 and 7 the levels were increased, but not significantly ($P: 0.9$ and 0.6 ,

respectively). SIRS criteria were negative in 5 (45.5%) of septic patients at day3 and in 7 (58.3%) of these patients at day 7 of the study. The correlation was not significant (P:0.9). Also sepsis was not diagnosed in 15 SIRS positive patients at day 1.

Presepsin levels were higher in patients who died compared to those who survived, but not significantly (672 ± 307 vs. 623 ± 199 , P: 0.3). The prognostic AUCs of presepsin were not statistically significant at all-time points for all-cause mortality (AUC: 0.5, P: 0.9). We observed a similar trend for PCT (AUC: 0.68, P: 0.14). The APACHE II and SOFA scores also had not any prognostic value according to ROC curve analysis (AUC: 0.54 and AUC: 0.67, respectively).

According to our analysis, the diagnostic value of both presepsin and PCT to diagnose at least sepsis was weak. All of the AUC were less than 0.75 and

P>0.05. Also, the diagnostic value of presepsin levels to diagnose different stage of sepsis was weak (AUC<0.75 in all cases). More than 80% of patients had sepsis based on presepsin upon admission. Both clinical criteria predicated that less than 20% of patients had sepsis upon admission.

Table 3 shows the agreement rate when no sepsis, sepsis and septic shock which was diagnosed clinically based on the Sepsis-3 guideline recommendation or based on the presepsin and the PCT concentrations. The overall agreement based on Kappa was poor (<0.4). Also based on the Table 3, the overall agreement in sepsis diagnosis was fair to good based on the both clinical criteria (surviving sepsis campaign, 2012 and sepsis-3, 2016) (P<0.001, Kappa:0.5-0.75).

Table 1: Baseline characteristics of study patients.

Variables		Day 1	Day 3	Day7	P value
Age, years, mean $\pm$ SD	49.3 $\pm$ 21				
Gender, n (%)					
Male	20 (76.9)				
Female	6 (23.1)				
Site of infection, n (%)					
Lung	15 (57.7)				
Urinary tract	5 (19.2)				
Central nervous system	1 (3.8)				
Blood	1 (3.8)				
Other	4 (15.3)				
Culture results, n (%)					
<i>Acinetobacter baumannii</i>	10 (38.5)				
<i>Klebsiella pneumonia</i>	4 (15.4)				
<i>Pseudomonas aeruginosa</i>	3 (11.5)				
<i>Staphylococcus aureus.</i>	3 (11.5)				
<i>Proteus mirabilis</i>	2 (7.7)				

<i>Escherichia coli</i>	2 (7.7)				
<i>Candida albicans</i>	2 (7.7)				
Length of ICU stay, days	41.7 ± 29				
APACHE II, mean ± SD	15.8 ± 5.6				
All-cause mortality, n (%)					
Death	9 (34.6)				
Survivor	17 (65.4)				
Laboratory values, mean ± SEM					
White blood cells, 10 ⁹ /L		9.9 ± 6.7	10.5 ± 7.2	11.5 ± 1.1	0.1
Platelets, 10 ⁹ /L		242 ± 607	266 ± 252	292 ± 249	0.5
Bilirubin, mg/dl		1.3 ± 0.19	1.4 ± 0.25	1.3 ± 0.24	0.7
Creatinine, mg/dl		1 ± 0.12	0.9 ± 0.12	0.9 ± 0.14	0.9
Albumin, mg/dl		2.8 ± 0.08	2.8 ± 0.09	2.8 ± 0.12	0.9
pCO ₂ , mmHg		38 ± 2	37 ± 2	37 ± 2	0.8
CRP, mg/dl		58.2±9.8	58.2±8.7	60.6±8.8	0.6
SOFA score, mean ± SD		7.5 ± 1.8	6.8 ± 2.3	6.9 ± 2.2	0.1

APACHE II, acute physiology and chronic health evaluation, CRP:C reactive protein, ICU, intensive care unit, SOFA, sequential organ failure assessment

Table 2: Comparison of presepsin and procalcitonin concentrations and SOFA score according to different level of sepsis.

	Presepsin (mean ± SD)	Procalcitonin(mean ± SD)	SOFA score(mean ± SD)
Day 1			
No sepsis	784.2 ± 389.7	1.94 ± 3.3	7.4 ± 1.8
Sepsis	600.7 ± 121.7	1.95 ± 3.3	7.5 ± 2.1
Severe sepsis	559.9 ± 183.5	0.93 ± 0.9	8.3 ± 1.1
Septic shock	-	-	-
Day 3			
No sepsis	563.7 ± 384.5	1.5 ± 2.4	5.1 ± 2.8
Sepsis	604 ± 187	1.94 ± 1.3	6.3 ± 1.4

Severe sepsis	664.6 ± 369.5	0.7 ± 0.58	6.6 ± 1.1
Septic shock	-	-	-
Day 7			
No sepsis	574.2 ± 276.2	1.7 ± 2.8	6 ± 1.1
Sepsis	658.4 ± 413.7	0.98 ± 1.2	6.7 ± 2.4
Severe sepsis	676.3 ± 55.5	1.2 ± 0.8	7.2 ± 2.4
Septic shock	-	-	-

SOFA: Sequential Organ Failure Assessment

Table 3. Comparison between both clinical sepsis criteria and presepsin and procalcitonin-based sepsis.

Clinical sepsis (SSC), n (%)	Clinical sepsis (Sepsis-3), n (%)	Kappa*	p-value*	Presepsin-based sepsis, n(%)				Kappa1/ Kappa 2	Procalcitonin-based sepsis, n(%)				Kappa3
				No sepsis	Sepsis	Severe sepsis	Septic shock		No sepsis	Sepsis	Severe sepsis	Septic shock	
Day1	Day1												
No sepsis, 15 (57.7)	No sepsis, 15 (57.7)	0.75	<0.001	5 (19.2)				-0.1	10 (38.5)				0.050
Sepsis, 8 (30.8)	Sepsis, 8 (30.8)				3 (11.5)			/-0.009		11 (42.3)			
Severe sepsis, 3 (11.5)	Severe sepsis, 0					12 (46.2)					3 (11.5)		
Septic shock, 0	Septic shock, 3 (11.5)						6 (23.1)					2 (7.7)	
Day 3	Day 3												
No sepsis, 14(53.8)	No sepsis, 14(53.8)			7 (26.9)					9 (34.9)				
Sepsis, 5(19.2)	Sepsis, 9(34.6)		0.001		4 (15.4)			0.03/		10 (38.5)			-0.048
Severe sepsis, 7(26.9)	Severe sepsis, 0	0.5				11(42.3)		0.13			7 (26.9)		
Septic shock, 0	Septic shock, 7(26.9)						4 (15.4)					0	
Day 7	Day 7												
No sepsis, 13(50)	No sepsis, 12(46.2)			8 (30.8)					11 (42.3)				
Sepsis, 6(23.1)	Sepsis, 11(42.3)	0.5	0.002		1(3.8)			0.09/		10 (38.5)			0.054
Severe sepsis, 7(26.1)	Severe sepsis, 0					13 (50)		0.18			4 (15.4)		
Septic shock, 0	Septic shock, 3 (11.5)						4 (15.4)					1 (3.8)	

SSC: surviving sepsis campaign

* The Kappa and P-value related to comparison of the two clinical criteria

Kappa 1: Comparison between clinical sepsis (based on the sepsis-3 guideline criteria) and presepsin and procalcitonin-based sepsis (Pvalue>0.05)

Kappa 2: Comparison between clinical sepsis (based on the surviving sepsis campaign criteria) and presepsin and procalcitonin-based sepsis ((Pvalue>0.05)

Kappa3: Comparison between presepsin and procalcitonin-based sepsis (Pvalue>0.05)

Figure 1: Presepsin (top) and procalcitonin (bottom) levels in the first week of ICU admission.

*Left diagrams show results of biomarker measurements at day 1, middle diagrams show results at day 3 and right diagrams show results at day 7. Data are presented as medians with 25th and 75th percentiles (boxes) and 5th and 95th percentiles (whiskers). ICU: intensive care unit

Discussion

In this study we found poor agreement between the clinical diagnosis and presepsin and PCT-based diagnosis of sepsis. It seems that biomarker-guided strategies, over recognized sepsis in critically ill patients even compared with the recent clinical criteria of Sepsis-3 which is developed to faster diagnosis of sepsis clinically. Also, we observed an inverse association between presepsin and PCT with sepsis at day 1 of ICU admission.

Behnes et al.,[17] performed a study on 116 patients with suspected severe sepsis and septic shock during the first week of ICU treatment. Presepsin increased significantly from the lowest to the most severe sepsis group on day 1, 3 and 8 ($P < 0.03$). Also, presepsin levels showed a valuable diagnostic capacity to diagnose severe sepsis and septic shock at day 1, 3 and 8 (range of diagnostic AUC 0.72 to 0.84, $P: 0.0001$) compared to PCT, IL-6, CRP and WBC. Presepsin levels had significant prognostic value (range of diagnostic AUC 0.64 to 0.72, $P < 0.02$). The authors concluded that presepsin levels had valuable diagnostic and prognostic capacity compared to PCT,

IL-6 and CRP. The results of our study didn't confirm any of the above findings. Although our sample size was small, but, even by extrapolating the data, we reached the similar results. Hur et al.,[31] (2014) compared PCT-based diagnosis and clinically-based diagnosis of sepsis in 340 patients. The agreement between both methods was poor ($Kappa = 0.24$). However, the authors suggested that PCT-based sepsis diagnosis is more reliable and discriminating than clinical sepsis diagnosis. Based on our results, both clinical criteria predicated that less than 20% of patients had sepsis upon admission, compared to 80% with both studied biomarkers. Therefore, the sepsis will be under cognized in our setting if our physicians rely on clinical criteria for sepsis diagnosis or delay the diagnosis until the microbiological data be available. This matter will affect patients' outcome and delay starting of appropriate treatment in sepsis.

Recent trials mostly evaluated single measurement of presepsin in patients presenting to the emergency department for diagnosis of sepsis and also the prognostic role of this biomarker. Ulla et al.,[24] (2013) measured presepsin levels in 106 patients

presented to the emergency department (ED). Elevated concentrations of presepsin at presentation were observed in septic patients compared to control patients (AUC: 0.71). Mean presepsin values were significantly higher in non-survivor septic patients. Endo et al., [32] (2014) conducted a similar study in the ED and concluded that presepsin levels correlated with the severity of sepsis during follow-up in comparison with PCT, IL-6 and CRP.

Our results show that at day 1 of admission, the number of patients with sepsis was high based on both presepsin and PCT concentrations. In best setting, the culture's results of patients take at least 24 hours to be ready. The agreement between clinically-based sepsis diagnosis and presepsin-based was better at days 3 and 7, which we had the culture results. In spite of indefinite cutoff for presepsin based on our results, and considering the high level of both presepsin and PCT at ICU admission, we suggest biomarker-guided diagnosis of sepsis or at least risk stratification at day 1 of ICU admission. Despite the small sample size, but even with statistical method of extrapolation, we couldn't find any clinically relevant difference. Therefore, we think that even with larger sample size, these results will be repeated.

The definitions of sepsis and septic shock have been updated by the European Society of Intensive Care Medicine's and the Society of Critical Care Medicine's Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) in 2016 [26]. In the new criteria, the quick sepsis-related organ failure assessment score is used to assess just three symptoms in patients with suspected sepsis: altered mental status, fast respiratory rate, and low blood pressure. Blood tests are not required. The SSC offers clarification on the implications of the new definition statements and guidance for hospitals and practitioners. The SCC recommended that clinicians should continue to use signs and symptoms of infection to promote the early identification of patients with suspected or confirmed infection. Management should begin by obtaining blood and other cultures as indicated, administering tailored antibiotics as appropriate, and simultaneously obtaining laboratory results to evaluate the patient for infection-related organ dysfunction [33]. Fullerton et al., [34] evaluated the impact of adopting the proposed new diagnostic criteria for sepsis, based on SOFA criteria (sepsis-3), on the diagnosis and apparent mortality of sepsis in Australian

and New Zealand intensive care units. Of 926 patients diagnosed with sepsis on a study day using SIRS criteria, 796/923 (86.2% [95% CI, 84.0%-88.5%]) satisfied the SOFA criteria. The authors concluded that the adopting the SOFA criteria will increase the apparent incidence of sepsis in patients admitted to the ICU with infective conditions without affecting the mortality rate. They suggest prospective evaluation of the effect of adopting the new definition of sepsis is required. Based on our results the overall agreement between both clinical criteria in sepsis diagnosis was good; however as we mentioned the overall concordance with the new criteria and biomarkers-guided diagnosis was poor.

The early diagnosis and timely management of sepsis are known to be crucial in the reduction of sepsis-induced mortality. On the other hand, over diagnosis of sepsis result in unnecessary antibiotic usage and bacterial resistance which is very high in Iran. Biomarkers have been suggested as means of aiding early diagnosis and, therefore, early initiation of appropriate therapy in patients with sepsis in ICUs. They may also, in conjunction with other techniques, be useful for antibiotic stewardship and for predicting prognosis. Currently available sepsis markers can already assist in identifying and even more importantly ruling out sepsis, assessing disease severity, and indicating the need to re-evaluate ongoing therapy, when used in combination with repeated clinical evaluation. Despite extensive research, no single biomarker can yet serve as the lone diagnostic parameter. While there are publications that come out of Iran evaluating PCT [35] and other biomarkers in sepsis, the level of evidence is still not such to make definitive recommendations for use. Use of biomarkers in the future will help improve patient outcomes by improving diagnostic accuracy, reducing the time to effective treatment, and limiting unnecessary tests and treatments. On a more global level, the resultant improved antibiotic stewardship should help optimize antibiotic use, thus increasing patient safety, reducing costs and reducing the development of antibiotic resistance. All of these issues are very important in resource limited countries such as Iran.

Conclusion:

Although the overall agreement between the diagnosis of clinical sepsis and presepsin or PCT-based sepsis was poor in our study; but considering

all of the above points, we suggest addition of developing decision tools that utilize biomarkers to help aid the rapid diagnosis of sepsis. As well as, performing studies with better design and larger population and cost-effectiveness analyses suggested to determine potential rational implementation strategies in sepsis diagnosis and management. Also, according to our findings, the new Sepsis-3 definitions were accurate and equal to the previous definition of SSC guideline.

Funding Source

This study was granted by the research deputy of Isfahan University of Medical Sciences.

Author's contribution

"SM design of the work, analyzed the data, drafted the manuscript and approve the final article. BA interpretation of data for the work, revised the manuscript and approved the final manuscript. MN collected the data, revised and approved the final manuscript. All authors are in agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved."

References

1. Seymour CW, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A, et al. Assessment of clinical criteria for sepsis: for the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016;315(8):762-74. doi: 10.1001/jama.2016.0288. PubMed PMID:26903335, PubMed Central PMCID: [PMC5433435](#).
2. Sprung CL, Schein RM, Balk RA. The new sepsis consensus definitions: the good, the bad and the ugly. *Intensive Care Med*. 2016;42(12):2024-2026. doi: 10.1007/s00134-016-4604-0. PubMed PMID:27815588.
3. Singer M. The new sepsis consensus definitions (Sepsis-3): the good, the not-so-bad, and the actually-quite-pretty. *Intensive Care Med*. 2016;42(12):2027-2029. doi: 10.1007/s00134-016-4600-4. PubMed PMID: 27815587
4. Huttunen R, Aittoniemi J. New concepts in the pathogenesis, diagnosis and treatment of bacteremia and sepsis. *J Infect*. 2011;63(6):407-19. doi: 10.1016/j.jinf.2011.08.004. PubMed PMID: 21840338.
5. Shorr AF, Micek ST, Welch EC, Doherty JA, Reichley RM, Kollef MH. Inappropriate antibiotic therapy in Gram-negative sepsis increases hospital length of stay. *Crit Care Med*. 2011;39(1):46-51. doi: 10.1097/CCM.0b013e 3181fa41a7. PubMed PMID: 20890186.
6. Ferrer R, Martin-Loeches I, Phillips G, Osborn TM, Townsend S, Dellinger RP, et al. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program. *Crit Care Med*. 2014;42(8):1749-55. doi: 10.1097/CCM.0000000000000330. PubMed PMID: 24717459.
7. Sterling SA, Miller WR, Pryor J, Puskarich MA, Jones AE. The Impact of Timing of Antibiotics on Outcomes in Severe Sepsis and Septic Shock: A Systematic Review and Meta-Analysis. *Crit Care Med*. 2015;43(9):1907-15. doi: 10.1097/CCM.0000000000001142. PubMed PMID: 26121073, PubMed Central PMCID: [PMC4597314](#)
8. Bauer PR, Kashyap R, League SC, Park JG, Block DR, Baumann NA, et al. Diagnostic accuracy and clinical relevance of an inflammatory biomarker panel for sepsis in adult critically ill patients. *Diagn Microbiol Infect Dis*. 2016;84(2):175-80. doi: 10.1016/j.diagmicrobio.2015.10.003. Pub Med PMID: 26586579, PubMed Central PMCID: [PMC4716883](#)
9. Chu DC, Mehta AB, Walkey AJ. Practice Patterns and Outcomes Associated With Procalcitonin Use in Critically Ill Patients With Sepsis. *Clin Infect Dis*. 2017;64(11):1509-15. doi: 10.1093/cid/cix179. PubMed PMID: 28329238, PubMed Central PMCID: [PMC5434362](#).
10. Wacker C, Prkno A, Brunkhorst FM, Schlattmann P. Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis. *Lancet Infect Dis*. 2013;13(5):426-35. doi: 10.1016/S1473-3099(12)70323-7. Pub Med PMID: 23375419.
11. Liu D, Su L, Han G, Yan P, Xie L. Prognostic value of procalcitonin in adult patients with sepsis: a systematic review and meta-analysis. *PloS one*. 2015;10(6):e0129450. doi: 10.1371/journal.pone.0129450. PubMed PMID: 26076027, PubMed Central PMCID: [PMC4468164](#)
12. Becker KL, Snider R, Nylen ES. Procalcitonin assay in systemic inflammation, infection, and sepsis: clinical utility and limitations. *Crit Care Med*.

- 2008;36(3):941-52. doi: 10.1097/CCM.0B013E318165BABB. PubMed PMID: 18431284.
13. Vincent J-L, Teixeira L. Sepsis biomarkers. Value and limitations. *Am J Respir Crit Care Med*. 2014;190(10):1081-2. doi: 10.1164/rccm.201410-1895ED. PubMed PMID: 25398103
14. Jacobs L, Wong HR. Emerging infection and sepsis biomarkers: will they change current therapies? *Expert Rev Anti Infect Ther*. 2016;14(10):929-41. doi: 10.1080/14787210.2016.1222272. PubMed PMID: 27533847, PubMed Central PMCID: [PMC5087989](#)
15. Hudcova J, Poutsiaka D, Khan M, Waqas A, Homsy C, Nasraway S. Utility of presepsin in distinguishing sepsis from systemic inflammatory response syndrome. *Crit Care Med*. 2016;44(12):419.
16. Sato S, Ichihara K. Multivariate Analyses on Clinical Utility and Sources of Variation of Serum Presepsin as a Diagnostic Marker for Sepsis. *RinshoByori*. 2016;64(1):34-9. PubMed PMID: 27192794.
17. Behnes M, Bertsch T, Lepiorz D, Lang S, Trinkmann F, Brueckmann M, et al. Diagnostic and prognostic utility of soluble CD 14 subtype (presepsin) for severe sepsis and septic shock during the first week of intensive care treatment. *Crit Care*. 2014;18(18):507. doi: 10.1186/s13054-014-0507-z. PubMed PMID: 25190134, PubMed Central PMCID: [PMC4174283](#).
18. de Gadiana Romualdo LG, Torrella PE, González MV, Sánchez RJ, Holgado AH, Freire AO, et al. Diagnostic accuracy of presepsin (soluble CD14 subtype) for prediction of bacteremia in patients with systemic inflammatory response syndrome in the Emergency Department. *Clin Biochem*. 2014;47(7):505-8. doi: 10.1016/j.clinbiochem.2014.02.011. PubMed PMID: 24560955
19. Masson S, Caironi P, Spanuth E, Thomae R, Panigada M, Sangiorgi G, et al. Presepsin (soluble CD14 subtype) and procalcitonin levels for mortality prediction in sepsis: data from the Albumin Italian Outcome Sepsis trial. *Crit Care*. 2014;18(1):R6. doi: 10.1186/cc13183. PubMed PMID: 24393424, PubMed Central PMCID: [PMC4056046](#)
20. Carpio R, Zapata J, Spanuth E, Hess G. Utility of presepsin (sCD14-ST) as a diagnostic and prognostic marker of sepsis in the emergency department. *Clin ChimActa*. 2015;450:169-75. doi: 10.1016/j.cca.2015.08.013. PubMed PMID: 26296897
21. Di Serio F, Varraso L, Dalfino L, Cassano S, Renna R, Bruno F. Presepsin and procalcitonin for sepsis diagnosis and appropriateness of antibiotic therapy prediction in critically ill patients. *Clinical Chemistry and Laboratory Medicine*. 2015;53(11):eA179.
22. Zhang X, Liu D, Liu Y-N, Wang R, Xie L-X. The accuracy of presepsin (sCD14-ST) for the diagnosis of sepsis in adults: a meta-analysis. *Crit Care*. 2015;19(1):323. doi: 10.1186/s13054-015-1032-4. PubMed PMID: 26357898, PubMed Central PMCID: [PMC4566362](#).
23. Chenevier-Gobeaux C, Trabattoni E, Roelens M, Borderie D, Claessens Y-E. Presepsin (sCD14-ST) in emergency department: the need for adapted threshold values? *Clin ChimActa*. 2014;427:34-6. doi: 10.1016/j.cca.2013.09.019. PubMed PMID: 24076253.
24. Ulla M, Pizzolato E, Lucchiari M, Loiacono M, Soardo F, Forno D, et al. Diagnostic and prognostic value of presepsin in the management of sepsis in the emergency department: a multicenter prospective study. *Crit Care*. 2013;17(4):R168. doi: 10.1186/cc12847. PubMed PMID: 23899120, PubMed Central PMCID: [PMC4056762](#).
25. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med*. 2013;39 (2): 165-228. doi: 10.1007/s00134-012-2769-8. PubMed PMID: 23361625.
26. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus for sepsis and septic shock (Sepsis-3). *JAMA*. 2016;315(8):801-10. doi: 10.1001/jama.2016.0287. PubMed PMID: 26903338, PubMed Central PMCID: [PMC4968574](#)
27. Boroumand MA, Esfahanifard P, Saadat S, Sheikvatan M, Hekmatyazdi S, Saremi M, et al. A report of *Pseudomonas aeruginosa* antibiotic resistance from a multicenter study in Iran. *Indian J Med Microbiol*. 2007;25(4):435-6. PubMed PMID: 18087112.
28. Khorshidi A, Sharif A. Imipenem Resistance among Gram-Negative and Gram-Positive Bacteria in Hospitalized Patients. *Iran J Public*

- Health. 2010;39(2):110–3. PubMed PMID: 23113015, PubMed Central PMCID: [PMC3481750](#).
29. Shahcheraghi F, Nikbin Vs, shorej F. PCR detection of PER & amp; VEB & amp; SHV and TEM β -lactamases in multidrug resistant *P. aeruginosa* isolated from wound infections in two hospitals of Tehran. Iran J Med Microbiol. 2008;1(4):21–7.
30. Alavi SM, Sharifi M, Eghtesad M. Bacterial Sepsis: Challenges of Diagnosis and Treatment in a Teaching Hospital Southwest of Iran. Jundishapur Journal of Microbiology. 2014;7(3):e9082. doi:10.5812/jjm.9082. PubMed PMID: 25147683, PubMed Central PMCID: [PMC4138650](#).
31. Hur M, Kim H, Lee S, Cristofano F, Magrini L, Marino R, et al. Diagnostic and prognostic utilities of multimarkers approach using procalcitonin, B-type natriuretic peptide, and neutrophil gelatinase-associated lipocalin in critically ill patients with suspected sepsis. BMC Infect Dis. 2014;14(1):224. doi: 10.1186/1471-2334-14-224. PubMed PMID: 24761764, PubMed Central PMCID: [PMC4006080](#).
32. Endo S, Suzuki Y, Takahashi G, Shozushima T, Ishikura H, Murai A, et al. Presepsin as a powerful monitoring tool for the prognosis and treatment of sepsis: a multicenter prospective study. J Infect Chemother. 2014;20(1):30-4. doi: 10.1016/j.jiac.2013.07.005. PubMed PMID: 24462421.
33. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, Kumar A, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Intensive Care Med. 2017;43(3):304-377. doi: 10.1007/s00134-017-4683-6. PubMed PMID: 28101605
34. Fullerton JN, Thompson K, Shetty A, Iredell JR, Lander H, Myburgh JA, et al. New sepsis definition changes incidence of sepsis in the intensive care unit. Crit Care Resusc. 2017; 19(1):9-13. PubMed PMID: 28215126
35. Adib M, Bakhshiani Z, Navaei F, Saheb Fosoul F, Fouladi S, Kazemzadeh H. Procalcitonin: A Reliable Marker for the Diagnosis of Neonatal Sepsis. Iran J Basic Med Sci. 2012;15(2):777-782. PubMed PMID: 23493845, PubMed Central PMCID: [PMC3586883](#).