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ORIGINAL ARTICLE

Presepsin as a Diagnostic Marker in Central Line Associated Blood Stream Infection in Intensive Care Unit Patients

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ABSTRACT

Background: *Central line associated bloodstream infection (CLABSI) is considered one of commonest complications that are associated with increased cost of care, extended hospital stay and increased mortality. An early and accurate diagnosis is critical for improving the prognosis in patients with CLABSI. Presepsin is a biological biomarker which has a good value in early detection of different infections.* ***Objective:*** *to investigate the value of serum presepsin in diagnosis of CLABSI in adult patients admitted to intensive care units (ICUs).* ***Methodology:*** *The study was conducted on 56 clinically suspected CLABSI cases, admitted to ICUs of Ain Shams University hospitals and 30 healthy individuals of matched age and sex as control group. Blood samples were collected from patients for conventional blood culture and for detection of 16S & 18S rDNA by nested multiplex PCR for culture negative samples. Quantitative measurement of serum presepsin by Human Presepsin ELISA kit was applied for both, patients with confirmed CLABSI (n=30) and healthy controls (n=30).* ***Results:*** *CLABSI diagnosis was confirmed in 30 patients, with most common isolated organisms were Klebsiella pneumoniae and Enterococcus spp. (6/31, 19.4% for each). The mean value of serum presepsin among confirmed CLABSI cases was higher than healthy controls and the difference was statistically highly significant (819.33ng/L versus 161.33 ng/L). Serum presepsin could be used to discriminate cases from controls at a cutoff level of ≥ 455 ng/L.* ***Conclusions****: Serum presepsin is a promising biomarker that aids in early diagnosis of CLABSI, thus offering early antimicrobial treatment which leads to improving patients' mortalities. Further studies on large scales are recommended to assess the prognostic value of serum presepsin in such critically ill patients and to monitor patients' response to therapeutic actions.*

INTRODUCTION

Central venous catheters (CVCs) allow administration of intravenous medications, intravenous fluids in resuscitation, and are essential in monitoring hemodynamic stability as in patients with septic shock, decompensated heart failure or pulmonary hypertension[1].Central line associated bloodstream infection (CLABSI) is a bloodstream infection that develops at least 2 full days following insertion of the CVC and confirmed by laboratory investigations[2]. It is a common complication that is associated with increased cost of care, extended hospital stay and increased mortality[3].

The national Egyptian surveillance program conducted by Talaat et al.[4] reported that high percentage of Healthcare acquired infections (HAIs) in ICU were caused by organisms showing multi-resistance pattern in antibiogram reports. In this surveillance study CLABSI represented 63.4% of overall HAIs reported in the 91ICUs in the hospitals participated in phase 2 of the surveillance program

Microbial cultures can identify serious bacterial infections, but these often produce false negative results, especially after the empiric use of antibiotics and are also affected by contamination of blood culture giving false positive growth reports. In addition, microbial cultures have a time delay (2–3 days), the inevitably to start antimicrobial therapy especially for critical cases leads to the emergence of multiple drug-resistant bacteria as a serious threat in many healthcare settings[5].

Cluster of differentiation 14 (CD14) is one of the expressed antigens on macrophages, monocytes, and granulocytes. It binds to the lipopolysaccharide (LPS)-LPS binding protein complexes initiating series of signal transduction. Such signals potentiate the immune response against the invading microorganisms[6,7]. CD14 has two forms: membrane-bound CD14 (mCD14) and soluble CD14 (sCD14). The N-terminal fragments of sCD14 which is called sCD14 subtype (sCD14-ST) or

presepsin is released by the effect of cathepsin or other proteases on sCD14. A high plasma level of presepsin is an indicator of active innate immune response against the attacking pathogens[8].

Presepsin is stable in blood circulation and automated measurements are available, the results being available in less than 20 minutes[9]. The potential value of presepsin in diagnosis of sepsis as well as other types of infections has been investigated in many studies and reviewed in many literatures but with no definite conclusion regarding the degree of validity of measuring serum presepsin as diagnostic marker on commercial level[10].The aim of the present study was to determine the diagnostic value of serum presepsin in CLABSI in adult patients admitted to intensive care units (ICUs).

METHODOLOGY

Study population:

This is a case control study conducted at the Surgery and Internal Medicine ICUs of Ain Shams University Hospitals, in the period from September 2018, to March 2019. The study included 86 individuals; 56 adult patients suspected clinically as CLABSI and 30 apparently healthy persons with matched age and sex. Clinical suspicion of CLABSI was based on the appearance of following criteria; fever> 38°C, chills, and/or hypotension, 48 hours after CVC insertion and after exclusion of other apparent source of infection[2]. The exclusion criteria included pretreatment with antibiotics before blood sample collection and cases with other HAI as catheter associated urinary tract infection or ventilator associated pneumonia.

The approval on the study protocol was signed by the Ethics Committee of Ain Shams University Hospitals, blood samples were collected only after approval upon the informed consent by the patients or their relatives as well as control subjects participating in the study.

Samples collection and processing:

Peripheral venous blood samples have been collected under complete aseptic conditions from patients twice with at least half an hour between both samples as per guidelines for diagnosis of CLABSIs[2]. Eight ml of collected blood sample was inoculated into blood culture bottle (EDM, Egypt), the isolated pathogens were identified according to **Wilson et al**.[11].

Two ml of the collected blood samples were inoculated into EDTA-treated tubes stored at - 80^{o}C & were reserved until analysis by nested multiplex PCR assay for samples yielded negative blood culture results. Another 2 ml of patient's blood samples as well as all controls were collected in sterile tubes and allowed to clot then sera collected and stored at -80°C till used for quantitative measurement of serum presepsin levels.

Microbial DNA detection by nested multiplex PCR assay:

Microbial DNA was isolated & purified using QIAamp DNA blood Mini Kit (Qiagen, Germany) according to the manufacturer's protocols. Microbial DNA ampilification and detection was done by a nested multiplex PCR assay. The assay is based on *16S rDNA* and *18S rDNA* sequence-specific external and internal primers; allowing the identification of most species of bacteria and fungi. Step One™ Real-Time PCR System (Applied Biosystems, USA) was used; the primer's sequence and the reactions' conditions were completed according to Gosiewski el. al [12].

Serum presepsin level measurement:

Serum samples from patients diagnosed as confirmed CLABSI; either by blood culture or nested multiplex PCR, and controls were tested for presepsin levels by Human Presepsin ELISA kit (BT-Laboratory, China).This kit employs a double-antibody sandwich ELISA using 96- wells plate which has been pre-coated with human soluble cluster of differentiation14 (sCD14) monoclonal antibody. It was done according to the manufacturer's instructions. Standards as well as samples were added to the wells. The wells were washed then soluble cluster of differentiation 14(sCD14) antibodies labeled with biotin were added, and combined with Streptavidin-HRP to form immune complex. The excess uncombined enzyme was washed before adding chromogen solutions. The optical density (OD) was measured at 450 nm wavelength by spectrophotometer. The corresponding sample's concentration was calculated according to standards' concentration and the corresponding OD values. Duplicates were analyzed for patients' samples to calculate the median value of each.

Statistical analysis:

Kolmogorov–Smirnov's test was used to evaluate the normal distribution of data. All results were presented as mean and standard deviation (SD) values. Presepsin was compared using Mann–Whitney U-test between cases and controls. Correlation analysis between presepsin and other laboratory data was done using Pearson's method. Receiver–operating characteristics(ROC) curve was used in order to determine the cutoff value of presepsin for diagnosis of cases .All statistical procedures were carried out using SPSS version15 for Windows (SPSS Inc, Chicago, IL, USA).

RESULTS

Fifty six cases of clinically suspected CLABSI were included in this study. Twenty five (44.6%) had positive blood culture results. Thirty one had negative blood culture results (55.4%) and were tested for microbial DNA by nested multiplex PCR assay; 5 (16.13%) had positive results (3 positive samples for bacterial

pathogens and 2 for fungal pathogens). A total of 30 patients were diagnosed as confirmed CLABSI (group I) (10 males and 20 females).The mean age among group I was 44.8 ±15.2 years. Laboratory data of the patient group is illustrated in table (1). Group II comprised the 30 healthy participants (16 males and 14 females) as controls. The mean age among group II was 37.07 ±7.70 years.

Table 1: Clinical and laboratory data of patients:

	Mean±SD	Minimum	Maximum
Age	44.83±15.27	20.00	75.00
Temperature	38.79±0.52	38.00	39.80
TLC nx10³/µL	13.44±7.67	1.90	30.90
ESR mm/h	99.47±27.29	55.00	154.00
CRP mg/dl	179.30±116.16	45.00	480.00

CRP: C-reactive protein, ESR: Erythrocyte Sedimentation Rate, TLC: Total Leukocytic Count

Out of the 25 culture positive patients; 19 had single pathogen, and 6 had two pathogens with total 31 isolates from blood cultures. The most common isolated organism were *Klebsiella pneumoniae* and *Enterococcus spp.* (6/31, 19.4% each), followed by *Staph aureus* (5/31, 16.1%), coagulase negative Staphylococci (4/31, 12.9%), *Candida tropicalis* (3/31, 9.7%), *E.coli and Pseudomonas aeruginosa* (2/31, 6.5%), and least were *Proteus mirabilis, Enterobacter spp., and Acinetobacter spp.* (1/31, 3.2% each).

On comparing the levels of serum presepsin between the studied groups, group I had higher levels of serum presepsin than group II and the difference was statistically highly significant (table 2).

Table2: Serum presepsin level in patients and control:

	Group										P	Sig
	Group I					Group II						
	Mean	±SD	Median	IQR		Mean	±SD	Median	IQR			
Serum presepsin (ng/L)	819.33	199.22	810.0	680.0	950.0	161.33	88.81	100.0	100.0	200.0	0.001	HS*

HS*: highly significant

ROC curve analysis was performed, serum presepsin had excellent diagnostic accuracy in distinguishing cases from controls, with an area under the curve (AUC) of 1 ,and at a cut-off point of ≥ 455 ng/L, the sensitivity and specificity were 100% (table 3 , figure 1). No statistically significant correlations were found between serum presepsin levels and other laboratory results among patients (table 4).

Table 3: The discriminative ability of serum presepsin level in predicting microbiologically confirmed CLABSI patients.

Cutoff level of presepsin (ng/L)	AUC (CI)	Sensitivity	Specificity	PPV	NPV	P	Sig
≥455	1.0(1-1)	100%	100%	100%	100%	.0001	HS*

HS*: highly significant, AUC: the area under the receiver operating characteristic curve, CI: confidence interval.

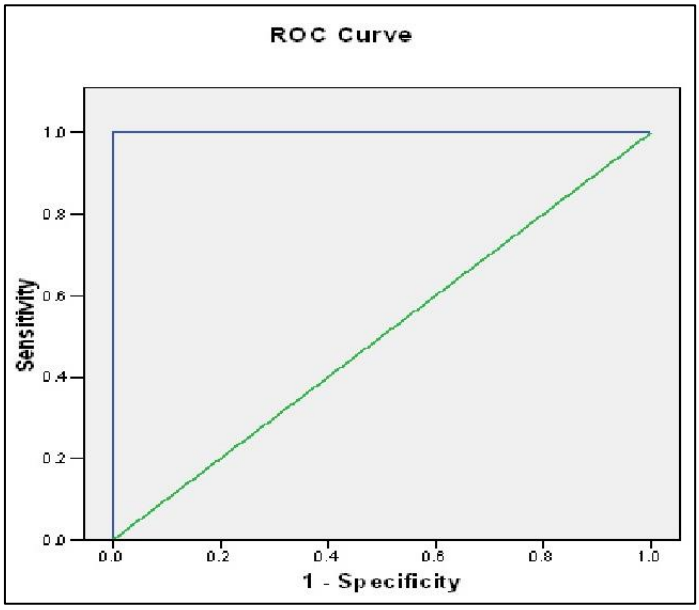

Fig. 1: ROC curve for serum presepsin level.

Table 4: Correlation analysis between presepsin and other laboratory data:

		TLC	ESR	CRP
Serum presepsin	Correlation coefficient*	-0.062	0.136	0.09
	P	0.744	0.473	0.636
	Sig	NS	NS	NS

CRP: C-reactive protein, ESR: Erythrocyte Sedimentation Rate, TLC: Total Leukocytic Count, * Pearson Correlation

DISCUSSION

Presepsin has been reported as a regulatory biomolecule and its plasma levels is an indicator of activated innate immune effector cells in response to invasive pathogens[8]. The aim of this study was to investigate the value of serum presepsin level measurement in diagnosis of cases of CLABSI by comparing presepsin levels in CLABSI cases with healthy controls as there is not enough amounts of studies interpreting worth of presepsin as a diagnostic and screening test in CLABSI infections in adults.

Our study reported that the most common isolated organism from patients were *Klebsiella pneumoniae* and *Enterococcus spp.* (6/31, 19.4% each), followed by *Staph aureus* (5/31, 16.1%). One study in Egypt done by Hassan et al.[13] found that the most frequent bacteria causing CLABSI were *Staphylococcus aureus and Enterococcus spp* (27.3% for each). Ahmed et al.[14] found *E.coli* was the most common isolated (36%), followed by *Klebsiella pneumoniae* (34.4%) from positive blood cultures at Benha University Hospital. Another study in India done by Jaggi et al.[15] reported that the predominant microorganism in CLABSI was *Klebsiella spp.* (32%). The difference can be explained by the different spectrum of organisms causing CLABSI from time to time, from region to region, and even from hospital to hospital according to the state of development of countries and according to infection control practice[16].

In this study the presepsin values (mean ± standard deviation) were 819.33 ± 199.22 ng/L and 161.33 ±88.81ng/L; for confirmed CLABSI cases and healthy controls, respectively and the difference was statistically highly significant, such results highlighted the value of presepsin in rapid diagnosis of CLABSI that is associated with higher mortality and morbidity rates especially for ICU patients. In accordance to the present study, Shozushima et al. [17] in their study conducted on patients admitted to emergency department suffering from sepsis and local infections, reported that the presepsin levels were 294.2 ± 121.4 ng/L for normal controls, 817.9 ± 572.7 ng/L for sepsis cases, and 1,992.9 ± 1509.2 ng/L for severe sepsis, and the patients with local infection or sepsis had significantly higher presepsin levels than normal controls. In another study done by Kweon et al. [18], the presepsin values have been reported for the healthy as 258.7 ± 92.53 ng/L , SIRS (systemic inflammatory response syndrome) as 430.0 ± 141.33 ng/L, and sepsis group as 1508.3 ± 866.6 ng/L. In a study by Basaranoglu et al. [19], they compared serum presepsin levels between confirmed cases and suspected

cases (SIRS) of CLABSI in children admitted to ICU, and healthy controls, presepsin level was statistically higher in patient groups in comparison to controls but no statistically significant difference was detected between SIRS and confirmed cases of CLABSI. Different presepsin values reported by different study groups could be explained by the difference in clinical settings of the different studies (if the study was done for patients in hot areas as emergency department and ICU or not), the selection criteria of patients included in the studies, the difference of specimen processed as serum or whole blood and the technique used for presepsin measurement also affects greatly its detected levels[20].

Ismail et al.[21] conducted a study on another promising biomarker in preterm neonates; thiobarbituric acid reactive substance which was significantly higher in sepsis than non-sepsis.

The ROC curve for our study results demonstrated that serum presepsin had excellent diagnostic accuracy in distinguishing confirmed CLABSI cases from healthy controls, with an AUC of 1 and at a cut-off point of ≥ 455 ng/L; hadsensitivity and specificity of100%. Other studies found similar results. Kweon et al. [18] reported the optimal cut off value of presepsin was 430 ng/L, sensitivity, and specificity were 88 %, 82 %, respectively, and the AUC value was 0.937, that is significantly higher than that of other biomarkers (e.g. C-reactive protein, procalcitonin). For the prediction of infection in the ICU sepsis, the sensitivity of presepsin was reported by Koh et al.[22] as 84.6% while the specificity was 62.5% for patients with hematological malignancy and the cutoff value was 466.5 ng/L. Other studies reported higher cut off values for presepsin in discrimination of sepsis. In a multicenter study by Endo et al.[23] to compare between bacterial and nonbacterial infections, in patients admitted to emergency department, they reported 600 ng/L as a cutoff value, sensitivity and specificity were 87.8 %, 81.4 %, respectively, and the AUC was 0.908. Another study conducted by Cakir Madenci et al.[24], found optimum cut off for presepsin in diagnosing sepsis complicating extensive burn infections was 542 ng/L, with a sensitivity of 77.3% and specificity 76.4%, the AUC was 0.83. The reported cut-off value was 990 ng/L by Basaranoglu et al. [19], they explained this by high presepsin levels that were unexpectedly elevated in some healthy children included in that study. On the other hand, Shozushima et al. [17] found lower cut off values for presepsin 415ng/ L, sensitivity and specificity were 80.1 %, 81 %, respectively, the AUC was 0.879. Another study by Godnic et al.[25] reported cut off value for presepsin of 413ng/L with a sensitivity of 84.6% and specificity of 62.5%, and the AUC was 0.705. Amer et al.[26] reported the best discriminative cut off value of presepsin between patients and controls was320 ng/ L with sensitivity 100% and specificity 68%. However, to discriminate between septic patients and SIRS patients the best cut off point was 395 ng/ L with sensitivity 100%, specificity 100% and the AUC was 1. The different cut-off values of presepsin reported by different studies could be due to the different patient groups included as some studies exclude severe infections (burn patients or severe trauma patients) from their study plan to overcome falsely elevated values of presepsin that are observed in these conditions and not related to presence of infection[27].

We found no significant correlations between serum presepsin levels and other laboratory results among patients. This agrees with Amer et al.[26].The relative small sample size of the studied group may have led to these statistically non-significant results. Presepsin was reported to have earlier and faster increase in sepsis than procalcitonin, and to perform a good monitoring of the severity of sepsis[28,29,30]. In addition, presepsin can be measured by a bedside easy procedure that takes less than 17 min [31]. Change in presepsin levels may be an appropriate indicator for monitoring antibiotic therapy that improve the prognosis and increase the survival rate in severe sepsis or septic shock cases[32].

CONCLUSION

Serum presepsin is a promising biomarker; it aids in early diagnosis of CLABSI and offers early antimicrobial treatment which leads to improving patients' mortalities. Further large scale studies will be helpful to assess the prognostic value of serum presepsin in such critically ill patients, and its value in monitoring the response to different therapeutic decisions.

Conflicts of interest:

- The authors declare that they have no financial or non financial conflicts of interest related to the work done in the manuscript.
- Each author listed in the manuscript had seen and approved the submission of this version of the manuscript and takes full responsibility for it.
- This article had not been published anywhere and is not currently under consideration by another journal or a publisher.

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