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ORIGINAL ARTICLE

Soluble Urokinase-type Plasminogen Activator Receptor as a Diagnostic Biomarker for Sepsis in Intensive Care Unit Patients.

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ABSTRACT

Background: Sepsis is one of the main causes of morbidity and mortality in the intensive care units (ICUs).It is difficult to differentiate it accurately and timely from other confusing conditions. So, it is of utmost importance to evaluate new biomarkers with a differentiation ability between sepsis and non-sepsis conditions. Soluble urokinase-type plasminogen activator receptor (suPAR) is a stable biomarker of inflammation. The aim of the study is to evaluate the value of suPAR in the diagnosis of septic ICU patients and to compare it (if present) with that of C-reactive protein (CRP) and procalcitonin (PCT).

Methods: A case-control study was conducted at Zagazig University Hospitals from December 2017 to October 2019. A total of 90 subjects were enrolled in the study. Based on Systemic Inflammatory Response Syndrome (SIRS) criteria, they were divided into 2 groups: (i)Group A: 60 septic ICU admitted patients;(ii)Group B: 30 non-septic ICU admitted patients as control group.Single determination of level of serum suPAR was measured by enzyme-linked immunosorbent assay (ELISA) for all the participants.

Results: Septic ICU patients had statistically significant higher serum suPAR, CRP and PCT levels than non-septic patients. suPAR had a sensitivity of 72%, specificity of 70% and AUC of 0.7 in sepsis diagnosis.

Conclusion: Serum suPAR is a fair diagnostic test for septic ICU patients at cut-off 3.983 ng/ml but does not surpass that of PCT or CRP.

Keywords: Sepsis, Soluble urokinase-type plasminogen activator receptor, Intensive care units, C-reactive protein, Procalcitonin

INTRODUCTION

Sepsis is a state caused by microbial invasion from a local infectious source into the bloodstream leading to signs of systemic illness in remote organs[1]. Whereas Systemic Inflammatory Response Syndrome (SIRS) refers to any inflammatory response that occurred systemically due to exposure to a variety of severe clinical insults (infectious or otherwise). SIRS criteria constitute the following: (i)Patient's temperature of >38ºC or <36ºC;(ii)Patient's heart rate of >90 beats/min;(iii)Patient's respiratory rate of >20 breaths/min. or partial CO_2 pressure (pCO_2) of <32 mmHg;(iv)Patient's white blood cell (WBC) count of >12000/µl or <4000/µl or >10% immature forms (i.e. bands). In presence of ≥ 2 SIRS criteria and clinical suspicion of infection, the patient can be classified as septic even in absence of positive microbiological

culture[2]. However, these criteria lack the needed sensitivity and specificity to diagnose sepsis on its own. Although blood culture is considered as a golden standard for diagnosis of sepsis, its main disadvantage is the long turn-around time and the possibility of obtaining negative culture due to antibiotic administration or the presence of slow growing or fastidious organisms[3].

It is very crucial to differentiate sepsis accurately and timely from other confusing conditions as it is one of the main causes of morbidity and mortality in the intensive care units (ICUs). Now, it is of utmost importance to evaluate new biomarkers with a differentiation ability between sepsis and non-sepsis conditions[3].These inflammatory biomarkers may help improve sepsis outcome by restriction of injudicious antimicrobial use[4].

Urokinase-type plasminogen activator receptor (uPAR)- CD87 is expressed on various cell types and participates in numerous immunologic functions including migration, adhesion, angiogenesis, fibrinolysis, and cell proliferation. During inflammatory stimulation, uPAR is cleaved from the cell surface by proteases, producing the soluble form of the receptor, suPAR, which can be detected in blood, urine, and cerebrospinal fluid[5].

Serum concentrations of suPAR increases during inflammatory and infectious diseases, such as arthritis, liver fibrosis, human immunodeficiency virus (HIV) infection, bacterial infection, and malaria, reflecting the activation of the immune system, and the severity of systemic inflammation[6,7].

suPAR can be easily and rapidly measured in the emergency department[8].Some studies have showed that the diagnostic value of high suPAR level in acutely ill patients is not superior to other biomarkers such as CRP, PCT[1].However, others concluded that the diagnostic efficacy of suPAR is good in septic patients, exceeding that of C-reactive protein (CRP) and procalcitonin (PCT)[9] and that soluble urokinase-type plasminogen activator receptor has the potential to diagnose infectious diseases[10].

In the current study, we aimed to evaluate the value of suPAR in the diagnosis of septic ICU patients in Zagazig University hospitals and to compare it with that of CRP and PCT.

SUBJECTS AND METHODS

This is a case-control study carried out at Zagazig University Hospitals from December 2017 to October 2019. The study was approved by Zagazig Medical Institutional Review Board (IRB#:4712/13-6-2018) and was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Informed consent was obtained from patients or 1st degree relative before being included in the study.

The sample size was calculated using OPEN-EPI program. A total of 90 patients were enrolled in the study. Based on Systemic Inflammatory Response Syndrome (SIRS) criteria, they were divided into 2 groups: (i)Group A: 60 septic ICU admitted patients;(ii)Group B: 30 age and sex matched non-septic ICU admitted patients as control group. Exclusion criteria included:(i)Cardiovascular diseases;(ii)Malignanttumors;(iii)Immunodeficiencydiseases;(iv)Focal segmental glomerulosclerosis;(v)Type II diabetes.

Thorough history taking, full clinical examination and Sequential Organ Failure Assessment (SOFA) scoring were considered for all subjects. Suitable volumes of blood were collected in suitable vacutainer tubes for measurement of: complete blood count (CBC) on Sysmex XN-2000 autoanalyzer (Siemens diagnostic ,Germany),CRP on Cobas c702/8000 autoanalyzer (Roche diagnostics, Germany), PCT on Cobas e411 autoanalyzer (Roche diagnostics, Germany).Measurement of serum suPAR was done using commercially available human suPAR enzyme-linked immune sorbent assay (ELISA) kit (Boster Biological Technology, California, USA) according to the manufacturer's instructions.

This kit depends on sandwich ELISA technique with analytical sensitivity <0.004 ng/ml, and detection range: 0.0625-4 ng/ml.

Based on manufacturer claim, no significant cross-reactivity or interference between suPAR and other relevant proteins were observed, CV% for intra assay precision was 4.8%, and CV% for inter-assay precision was 6.3%.

STATISTICAL ANALYSIS

The collected data was tabulated and statistically analyzed using Statistical Package of Social Services, version 25 (SPSS) (IBM Corp., USA).Kolmogorov-Smirnov test was used to determine the distribution characteristics of variables and variance homogeneity. Quantitative data were expressed as mean ± SD and qualitative data as number and percentage. Student's T test and Mann-Whitney U test were used to compare between two groups for parametric and non-parametric variables, respectively. Spearman's correlation coefficient was considered. ROC curve was plotted to determine the best cut-off value of suPAR, CRP and PCT for sepsis diagnosis. P values < 0.05 were considered significant.

RESULTS

The mean±SD age (in years)for group A and B was 35.1 ± 6.6 and 34.2 ± 8.1 respectively (p=0.6). Male/female ratio was 24/36 and 15/15 for group A and B respectively (p=0.4). The most encountered cause of admission was multi-trauma followed by neurosurgical causes (28 (46.7%) vs 14 (46.7%) and 13(21.7%) vs 11 (36.7%) for group A and B respectively. Other causes included respiratory diseases, obstetric and intestinal resection complications with no statistical difference between the groups (p=0.3).Sequential Organ Failure Assessment (SOFA) score ranged between 4-12 for group A and ranged between 0-6 for group B. Table (1) summarize the clinical and laboratory data of the studied groups. All SIRS criteria parameters (temperature, respiratory rate and heart rate) and biomarkers of sepsis (CRP, PCT and suPAR) were higher in group A compared to group B with statistically significant difference (p<0.001). In septic patients' group (group A), suPAR was significantly correlated with respiratory rate, WBCs count, and PCT (r=0.3, p=0.004; r=0.32, p= 0.002; and r=0.24, p= 0.02) respectively (table 2).

Table (3) and figure (1) summarize and compare the diagnostic performance of suPAR, CRP and PCT in sepsis. Areas under the curve for the three biomarkers were: 0.7, 0.71 and 0.99 respectively and they were statistically significant (p= 0.003, 0.001 and<0.001 respectively)

Table (1): Clinical and laboratory variables

Variables	Group A (n=60)	Group B (n=30)	Test of sig.	P
Temperature (ºC): Mean ± SD	37.7±0.8	37.0±0.6	t=4.2	**<0.001**
Heart rate (beat/minute): Mean ± SD	107.9±21.2	89.5 ± 3.4	t=4.7	**<0.001**
Respiratory rate (breath/minute): Mean ± SD	24.8±5.6	20.0±2.9	t=4.4	**<0.001**
WBCs (x10^3/µl): Median IQ range	11.6 8.6 – 17.2	8.0 7.2 – 10.4	MW=5.9	**<0.001**
CRP (mg/l): Median IQ range	75.5 55.0 – 120.0	39.0 30.8 – 68.0	MW=3.3	**<0.001**
PCT (ng/ml): Median IQ range	21.3 8.3 – 40.0	0.13 0.1 – 0.3	MW=7.7	**<0.001**
suPAR (ng/ml): Median IQ range	6.607 3.354 – 12.320	3.883 2.869 – 6.4313	MW=3.0	**<0.001**

WBCs: white blood cells, CRP: C-reactive protein, PCT: procalcitonin, suPAR: soluble Urokinase-type plasminogen activator receptor.

t: Student's t-test MW: Mann-Whitney U test.

Bold values are significant at p< 0.05

Table (2): Correlation between suPAR and other variables in septic patients (group A)

Variables	r	p
Age	-0.04	0.6
Temperature	-0.16	0.1
Heart rate	0.1	0.4
Respiratory rate	0.3	**0.004**
WBCs	0.32	**0.002**
CRP	0.1	0.4
PCT	0.24	**0.02**

WBCs: white blood cells, CRP: C-reactive protein, PCT: procalcitonin
Bold values are significant at p < 0.05

Table (3): Diagnostic performance of biomarkers of sepsis:

	suPAR	CRP	PCT
Cut off point	3.983 ng/ml	54.5mg/l	1.15 ng/ml
AUC (95% CI)	0.70 (0.59 – 0.80)	0.71 (0.60-0.82)	0.99 (0.98-1.00)
Sensitivity (%)	72.0	80.0	95.0
Specificity (%)	70.0	70.0	93.3
Accuracy (%)	71.1	76.7	94.4
p value	**0.003**	**0.001**	**<0.001**

AUC: area under the curve, CI: confidence interval
Bold values are significant at p< 0.05

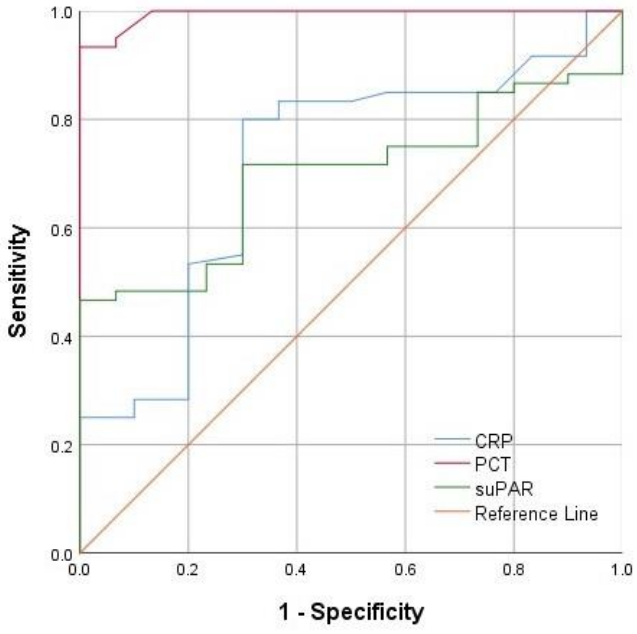

Figure (1): Receiver Operating Characteristics Curve of suPAR, CRP and PCT in diagnosis of sepsis

DISCUSSION

The problem of managing sepsis in ICU patients represents a burden on the health system. Rapid and accurate diagnosis followed by proper treatment and monitoring measures are a must to decrease the mortality and morbidity rates of sepsis. The complicated nature of sepsis pathophysiology hinders the dependance on clinical assessment for its diagnosis, even the microbiological evidence including positive blood culture is not available in >50% of cases clinically suspected to be sepsis. All these factors make the need

for specific and sensitive biomarkers more compiling [11].

In the current study, we used SIRS criteria as an initial diagnostic tool for sepsis. The septic patients had significantly higher temperature, heart rate, respiratory rate and WBCs than non-septic ones. However, there is no agreement among scientists about the value of SIRS criteria in sepsis diagnosis. Some emphasis on its high value as a diagnostic tool developed specifically to identify sepsis[12,13]. Others criticized the suboptimal diagnostic sensitivity of SIRS for septic cases [3,14].

As an acute phase reactant, CRP has long been used as a marker of inflammation and a non-specific biomarker of infection. PCT is another widely used biomarker of infection and sepsis with a good discriminative power between infectious and non-infectious causes of systemic inflammation in addition to its role in antibiotic stewardship (i.e., directing the use of antibiotic in cases of infection) [15]. The soluble form of urokinase plasminogen activator receptor (suPAR) is considered as a good and stable biomarker of inflammation that is positively correlated to other well-established markers of inflammation including CRP, tumor necrosis factor α and total leucocytic count[9]. As reviewed by Henriquez-Camacho and Losa[1], the data concerning the value of these biomarkers as a diagnostic biomarker in sepsis is controversial. In our study, the three biomarkers of sepsis (i.e., CRP, PCT and suPAR) were significantly higher in septic vs non-septic patient. Using correlation study, suPAR was positively correlated with PCT but not with CRP, also it was positively correlated with respiratory rate and WBCs count.

Using ROC analysis, we were able to define their operating characteristics as diagnostic biomarkers of infection. In our setting, PCT had the greatest AUC, then CRP and then suPAR. At a cut-off 1.15 ng/ml for PCT, it had a 95% sensitivity and 93% specificity for diagnosis of sepsis. For CRP, at 54.5 mg/l as cut-off, it had 80% sensitivity and 70% specificity. For suPAR, at 3.983ng/ml as cut-off, it had 72% sensitivity and 70% specificity. These findings denote that suPAR has a fair diagnostic ability for sepsis in ICU patients but does not mount above that of PCT or CRP. The findings of Henriquez-Camacho and colleagues[1] agree with our findings. In a review conducted by Ni and colleagues [7], the overall AUC for suPAR was 0.82 with pooled sensitivity and specificity of 73% and 79% respectively, this indicates a moderate diagnostic accuracy. The study conducted by Georgescu and colleagues in 2018[9] concluded that suPAR at a cut-off 10.600 ng/ml surpasses that of PCT and CRP in critically ill septic patients. Moreover, they concluded that CRP was not significantly higher in sepsis vs non sepsis patients.

Further studies are needed to confirm the value of suPAR in diagnosis of sepsis using larger number of patients and to study if the source of infection causing sepsis or the causative microorganism will result in different findings.

CONCLUSION:

Septic ICU patients have significantly higher suPAR levels than non-septic patients and suPAR levels are positively correlated with PCT but not with CRP levels. suPAR is a fair diagnostic test for sepsis in ICU-admitted patients at cut-off 3.983 ng/mlbut does not surpass that of PCT or CRP.

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