Combined suPAR and qSOFA as A Mortality Predictor in ICU Patients with Sepsis

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ABSTRACT
Introduction: Prediction of 28 days mortality in ICU patients with sepsis enables physicians to pay special attention to concerned patients and may affect their management. Scoring systems are widely used in clinical practice as mortality predictors. But all have their limitation. Different biomarkers also lack enough sensitivity and specificity. We studied the concentrations of suPAR, measured in serum on the first day of suspected sepsis, comparing combined suPAR and qSOFA with suPAR, qSOFA and SOFA (alone) as a predictor of 28 days mortality in ICU patients.
Method: This study was conducted in ICU at Zagazig University Hospitals. 131 sepsis patients were included and classified according to 28 days mortality into: survivors (113/86.3%) and non-survivors (18/13.7%). Serum sample for suPAR measurement, and parameters of SOFA were collected upon suspicion of sepsis. Then, SOFA and qSOFA were calculated.
Results: The best predictor of 28 days mortality was SOFA at cutoff 9 (AUC) followed by suPAR at cutoff 12.32 ng/ml (AUC 0.918 and 0.770) and (95% CI 0.849-0.988 and 0.634-0.906) respectively with no statistical difference between them. Combining suPAR and SOFA and combining suPAR and qSOFA increased AUC to 0.941 and 0.827 (95% CI 0.892-0.990 and 0.729-0.926) respectively. There was no statistical difference between AUC of combined suPAR and qSOFA and AUC of standard SOFA score.
Conclusion: In our model, suPAR had 28 days mortality prognostic ability comparable to SOFA and better than qSOFA. Combining suPAR and qSOFA increased the prognostic ability of qSOFA to be not inferior to that of SOFA.
Key words: suPAR, Sepsis, qSOFA, SOFA, ICU mortality

INTRODUCTION

The 3rd International Consensus (Sepsis-3) has described sepsis as a fatal/near fatal flawed organ function caused by an abnormal body reaction to infection. Detection of this flawed organ function should be by using the Sequential Organ Failure Assessment (SOFA) criteria or the 'quick' (q)SOFA criteria [1]. SOFA score uses 6 clinical and laboratory parameters to describe the degree of organ dysfunction and predict mortality in septic patients [2,3]. Delta SOFA score ≥2 points (from baseline) resultant to the infection would define sepsis [1,4]. Unless the patient is a known case of organ dysfunction, the initial SOFA score would be assumed as zero [5].

The qSOFA score was developed as a surrogate to SOFA score in sepsis screening. The positivity of 2 or more out of its 3 parameters will raise the suspension of high risk of mortality in patients with presumed infection. It has the advantage (over SOFA score) of not requiring laboratory tests and so can be assessed swiftly and frequently [5]. However, the latest International Guidelines for Management of Sepsis and Septic Shock 2021 recommended against using qSOFA- compared to other scoring systems- as a single screening tool for sepsis [6].

Other intensive care unit (ICU) scoring system are also on hand and widely applied in clinical practice as acute physiology and chronic health evaluation (APACHE II), simplified acute physiology score (SAPS), mortality prediction model (MPM). Each has its own uses and merits. However, all scoring systems have limitations. To be calculated, multiple laboratory and clinical parameters are required. So, in some instance, the calculation may be delayed. If health care is subject to financial restriction, their application will be limited. Moreover, none of these scores has perfect sensitivity or perfect specificity [7].

For long, positive blood culture was considered as the golden measure in sepsis diagnosis. But positivity occur in only 20-30% of sepsis patients and the result is obtained late [8]. And so, using biomarkers can improve the timeliness of sepsis diagnosis and as indicators of prognosis. C-reactive protein (CRP) and procalcitonin (PCT) are broadly used in these fields. However, both of them has low sensitivity and specificity as a prognostic marker in critical patients. In addition, results of infection's markers may be within normal in sepsis, especially in patients who are immunologically suppressed [9,10].

Soluble urokinase plasminogen activator receptor (suPAR) is another biomarker that shows a promising role as a prognostic marker in sepsis. suPAR is produced by proteolytic cleavage of the urokinase-plasminogen-activator-receptor from the cell surface and is believed to indicate activation of the immune system. It is involved in many steps in immune response including the plasminogen-activating pathway, and cell relocation [11].

As reviewed by various studies, suPAR has a potential prognostic value in the ICU [12,13].

The current study sought to test whether the concentrations of suPAR, measured in serum on the first

day of suspected sepsis, allows the prediction of 28 days mortality in ICU patients and finally to compare combined suPAR and qSOFA with qSOFA and SOFA (alone) to predict 28 days mortality.

PATIENTS AND METHODS

This prospective cohort observational study was performed in adult ICU at Zagazig University Hospitals/ Egypt.

A total of 563 patients were admitted to the ICU over an 11-month period and were screened for inclusion. Exclusion criteria included patients aged <18 years, patients expected to stay <24 hours in the ICU for postoperative follow up, refusal to participate, sepsis as a cause of admission and immunodeficient patients. Inclusion criteria in the study were: age over 18, systemic inflammatory response syndrome (SIRS) criteria ≥2 with evidence of infection. Samples for different cultures were collected according to the suspected primary site of infection (blood, urine, sputum, pus, and/or wound swab). 131 patients (53 male and 78 female) had at least one isolate and were included in the study, and 28 days mortality was recorded for each patient as a survivor or a non-survivor.

For these patients, venous blood samples were collected on 2 plain tubes for serum separation, one was used for immediate measurement of CRP (immunoturbidimetric assay), biochemical parameters (creatinine, urea, transaminases, bilirubin, albumin) (spectrophotometric assay), PCT (electrochemiluminescence assay). All were analyzed on Cobas 8000 (Roche Diagnostics, Germany). The separated serum from the 2nd tube was frozen at -80˚C until suPAR quantification using sandwich Eliza technique (Boster Biological Technology, California, USA). EDTA blood samples were analyzed for platelet count and WBCs count using Sysmex XN (Sysmex, Japan). Heparinized arterial blood samples were collected for blood gas analysis using Cobas211 blood gas analyzer (Roche Diagnostics, Germany).

SOFA score and qSOFA score were calculated using MedCalc software for standardization (Ostend, Belgium).

Ethical approval:

The Institutional Review Board of Zagazig University approved this study (IRB No. 4712). This work adheres to The Code of Ethics as per Declaration of Helsinki for studies on humans. Patients or their legal representatives approved the participation before inclusion.

Statistical analysis

Testing for normality of data was done by Kolmogorov-Smirnov test. All numerical data were non normally distributed (non-parametric). They were presented as median and interquartile range (IQR) and were compared by Mann Whitney U test. Qualitative data were expressed as number and percentage and were compared by chi-squared (χ^2) test.

The optimal cutoff value of suPAR and mortality scores were predicted by the Youden Index using ROC curve analysis in a univariate model. The outcome variable was 28 days ICU mortality. Binary logistic regression was used to calculate the predicted probability of combined predictors and ROC curves were plotted for them. All the previous statistical tests were carried out with SPSS® statistical software version 25.0 (SPSS Inc., Chicago, IL, USA). The comparison between area under the curve (AUC) for different ROC curves was tested as proposed by **DeLong and his colleagues** [14] using MedCalc v.14 (Ostend, Belgium). Statistical significance level was set at p-value < 0.05.

RESULTS

Total number of sepsis patients included was 131 (78 female and 53 male) with median age of 34. 28 days mortality rate was 13.7%, accordingly, patients were classified into: survivors and non-survivors. We found no statistical differences in gender, age or causes of admission between groups. Causes of ICU admission were grouped into medical causes (CNS, cardiovascular, renal tubular acidosis) and surgical causes (accidents, postoperative complications, intestinal obstruction). Medical causes were the commonest in both survivors and non-survivors.

Non-survivors had statistically higher AST, creatinine and suPAR levels. Meanwhile, they had statistically lower platelets count than survivors. Other biomarkers of infection (WBCs, CRP and PCT) showed no statistical difference between groups and so no further statistical analysis for them was done. Non-survivors were also sicker with statistically higher SOFA score and higher percentage of patients were classified as high mortality risk on qSOFA score (Table 1).

Table 1: Demographic and clinical data of the study population grouped into survivors and non-survivors

characteristics	Survivors (n/%) (113/86.3)	Non-survivors (n/%) (18/13.7)	*p*
Gender:			
Male (n/%)	47/41.6	6/33.3	0.507
Female (n/%)	66/58.4	12/66.7	
Age, years (median/IQ range)	34 (29-40)	33 (30-46)	0.723
Cause of admission:			
Medical causes (n/%)	81/71.7	13/72.2	0.962
Surgical causes (n/%)	32/28.3	5/27.8	
Laboratory and clinical findings: (median/IQ range)			
Temperature, ˚C	38 (37.5-38.5)	38.5 (37.15-39)	0.553
Heart rate, beat/min	94 (90-115.5)	106 (86-116)	0.644
Respiratory rate, breath/min	25 (23-29)	24 (22-25)	0.080
SBP, mmHg	134 (117-149)	135 (124-140)	0.489
Platelets count, x10^3/μL	269 (194-377)	159.5 (85.75-344)	0.01*
Total bilirubin, mg/dL	0.7 (0.4-0.96)	1.3 (0.4-2.44)	0.094
Albumin, g/dL	2.81 (2.37-3.31)	2.6 (2.27-3.15)	0.424
ALT, IU/L	31 (19-52)	34 (18.7-130)	0.616
AST, IU/L	35 (28.5-53.5)	62 (39.9-95)	0.006*
Creatinine, mg/dL	0.55 (0.37-0.84)	1.4 (0.61-3.25)	0.006*
BUN, mg/dL	15.1 (10-19)	14.85 (7-50.68)	0.669
Biomarkers of infection: (median/IQ range)			
WBCs count, x10^3/μL	12.5 (10.5-17)	12.6 (10.73-17.3)	0.968
CRP, mg/L	100 (61-155)	178 (69.98-188.75)	0.214
Procalcitonin, ng/dL	3.5 (1.6-14.3)	5.85 (2.12-33)	0.113
suPAR, ng/ml	4.65 (2.9-8.63)	13.99 (5.83-22.28)	<0.001*
ICU scoring:			
SOFA score (median/IQ range)	7 (5-8)	12 (9.75-14)	<0.001*
qSOFA (n/%) low mortality risk (score=1) high mortality risk (score ≥2)	54/47.8 59/52.2	2/11.1 16/88.9	0.003*

SBP (systolic blood pressure), ALT (Alanine transaminase), AST (Aspartate transaminase), BUN (Blood urea nitrogen), WBC (White blood cells), CRP (C reactive protein), suPAR (Soluble urokinase plasminogen activator receptor), ICU (intensive care unit), SOFA (Sequential Organ Failure Assessment), qSOFA (quick SOFA), IQ range (interquartile range)

Among the studied prognostic single variables, the best predictor of 28 days mortality was SOFA (AUC 0.918) followed by suPAR (AUC 0.770). Combining suPAR and SOFA and combining suPAR and qSOFA increased AUC to 0.941 and 0.827 respectively with no effect on statistical significance of single variables (Table 2).

Table 2: Receiver-operating characteristic curve (ROC) analysis for variables used in 28 days ICU mortality prediction

Parameter	Cutoff	Youden index J	sensitivity	specificity	AUC	95% CI	*p* value
suPAR (ng/ml)	12.32	0.6160	72.2	89.4	0.770	0.634-0.906	<0.001*
SOFA	9	0.7030	88.9	81.4	0.918	0.849-0.988	<0.001*
qSOFA	2	0.3668	88.9	47.8	0.683	0.567-0.799	0.013*
Combined suPAR and SOFA		0.7915	88.89	90.27	0.941	0.892-0.990	<0.001*
Combined suPAR and qSOFA		0.5669	61.11	95.58	0.827	0.729-0.926	<0.001*

suPAR (Soluble urokinase plasminogen activator receptor), SOFA (Sequential Organ Failure Assessment), qSOFA (quick SOFA), AUC (area under the curve), CI (confidence interval).

The pairwise comparison among predictors is shown in table (3) and figure (1).

Table 3: Pairwise comparison of ROC curves for the different variables studied

	Difference between areas	SE	95% CI	*p* value
qSOFA vs qSOFA+suPAR	0.144	0.0370	0.0715 - 0.217	<0.001*
qSOFA vs SOFA	0.235	0.0556	0.126 - 0.344	< 0.001*
qSOFA vs suPAR	0.0870	0.0901	-0.0896 - 0.264	0.3341
qSOFA+suPAR vs SOFA	0.0910	0.0660	-0.0385 - 0.220	0.1684
qSOFA+suPAR vs suPAR	0.0570	0.0611	-0.0628 - 0.177	0.3510
SOFA vs suPAR	0.148	0.0866	-0.0218 - 0.318	0.0875
SOFA vs SOFA+suPAR	0.0226	0.0107	0.00158 to 0.0436	0.0351*
suPAR vs suPAR+SOFA	0.171	0.0806	0.0126 to 0.329	0.0343*
qSOFA+suPAR vs SOFA+suPAR	0.114	0.0592	-0.00253 to 0.230	0.0552

AUCs and their 95 % confidence intervals (CIs) were estimated through regression models for different combinations of qSOFA, SOFA and suPAR in relation to 28 days ICU mortality.

suPAR (Soluble urokinase plasminogen activator receptor), SOFA (Sequential Organ Failure Assessment), qSOFA (quick SOFA), AUC (area under the curve), CI (confidence interval), SE (standard error)
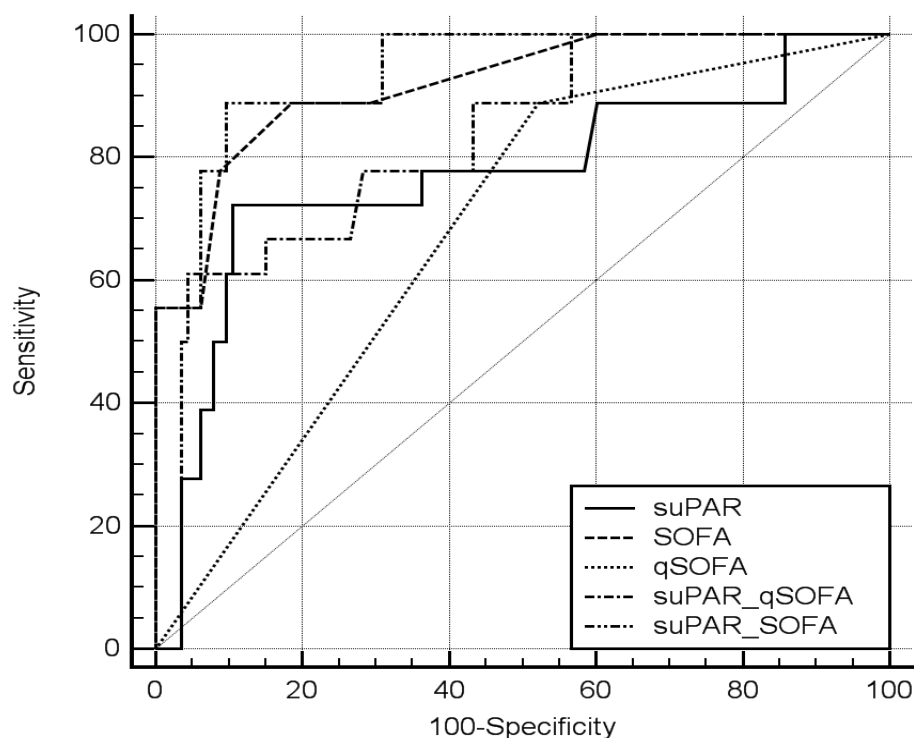

Figure (1): ROC curve for the studied mortality predictors.

DISCUSSION

Sepsis is a medical emergency defines patient's immunological response to an infectious process that may ultimately lead to end-stage organ failure and death. It represents one of the major causes of morbidity and mortality in ICU patients, despite substantial advancements in monitoring tools, and resuscitation procedures. Prediction of 28 days mortality in ICU patients with sepsis would enable physicians to pay special attention to concerned patients and may affect the management protocol of such patients.

Among the studied sepsis biomarkers, only suPAR had a significant difference between survivors and non-survivors. Using a cutoff 12.32 ng/ml, suPAR had 72.2% sensitivity and 89.4% specificity as a mortality predictor. Previous studies reported different cutoffs for suPAR as a prognostic marker in sepsis with different setting of the studies. An early study by **Kofoed and his colleagues** reported suPAR (> 6.61 ng/ml) as a good mortality predictor equal to admission SOFA score [15]. Later studies reported suPAR values range between 10.2 and 17.38 ng/ml as cutoff for mortality prediction in sepsis [16-19]. In the meta-analysis conducted by **Ni and his colleagues**, they concluded that serum suPAR ≥10 ng/mL, has an excellent specificity but a modest sensitivity in predicting mortality for patients with bacterial infection. No specific refer was done for sepsis nor for ICU patients [20]. Another meta-analysis by **Huang and his colleagues** showed that pooled sensitivity and specificity of suPAR in mortality prediction were 0.74 and 0.70 respectively with AUC of 0.78 [21].

Many ICU scoring systems were developed as a mortality predictor, e.g., SOFA and APACHE II score. SOFA score is simpler than other scoring systems such as APACHE II as it depends on 6 measured parameters only whereas APACHE II depends on 14 parameters. Quick SOFA (qSOFA) is even simpler and quicker way of evaluating patients than SOFA as its parameters are bedside-measured and no laboratory data are needed. Value of qSOFA in mortality prediction in some non-ICU setting is proved. However, its prognostic value in ICU sitting is of doubt [22].

Our results show that SOFA ≥9 is a better predictor (AUC=0.852, 95% CI, 0.757-0.946) of 28 days mortality with higher sensitivity than qSOFA ≥2 (AUC= 0.683, 95% CI, 0.567-0.799) in ICU patients with sepsis. In a recent study, SOFA ≥2 (AUC = 0.83, 95% CI, 0.76 - 0.90) and qSOFA ≥2 (AUC = 0.67, 95% CI, 0.54 - 0.80) showed the same relationship. However, the different setting of the mentioned study (patients with acute infectious disease with no special reference to ICU or sepsis) may explain the different cutoff values obtained for SOFA [23].

Comparing the performance of suPAR and SOFA as mortality predictor, we found no statistical difference between them. This doesn't necessarily mean that suPAR can replace SOFA as a tool for ICU patient evaluation. Each one evaluates a different aspect of patient clinical and immunological status. Which one to choose remains the physician decision on a patient-to-patient base. Combined suPAR and SOFA increased the sensitivity and specificity of mortality prediction to nearly 90%. And when comparing suPAR, SOFA as single markers with combined suPAR and SOFA as a panel, a statistical difference was found in favor of the panel. Taking into consideration the added cost and the marginal significant difference, we believe that using the combined panel have little value over single variables. Earlier study that evaluated combined SOFA and suPAR (among other variables) also concluded that the combined SOFA and suPAR resulted in only slight improvement in their prognostic characteristics [24].

However, combining suPAR measurement and qSOFA substantially improved qSOFA mortality prediction in our setting (with no effect on suPAR mortality prediction) to a degree comparable to that of standard SOFA score alone or combined with suPAR. The combined suPAR and qSOFA has the advantage of using only one laboratory parameter i.e., suPAR, compared to 3 parameters used in SOFA and so fewer blood samples were used, and lesser time was spent waiting for lab results. The availability of suPAR kit as point of care (e.g., suPARnostic by Virogates, Copenhagen, Denmark) adds an advantage of rapid, in-site result acquisition. Also, the combination evaluated patient's immune, in addition to, clinical status.

suPAR levels were previously combined with APACHE II score to stratify ICU patients for risks of morbidity and mortality. Researchers compared 4 different combinations of APACHE II (cutoff 17) and suPAR (cutoff 12 ng/mL) [17]. **Ho and Lan** used combined qSOFA and lactate in evaluating patients with suspected infection. They concluded an enhanced mortality prediction ability of critically ill patients comparable to SOFA score [25].

Finally, as sepsis is a very heterogeneous condition and due to the special nature of ICU patients, it is unlikely that a single mortality predictor can be accurately applied in all cases [6]. Panel of different markers and scoring system may play a better role based on each patient clinical condition. Whether introduction of suPAR in ICU setting is valuable or not is a matter of further evaluation. The use of combined suPAR and qSOFA as a substitute for SOFA is subjected to physician evaluation of the patient clinical condition.Evaluation of impact of implementing combined markers on patient management and so outcome is a point of further study. Non-septic ICU patients were not included in this study and so need further studies to evaluate suPAR levels in such patients.

CONCLUSION

In our model, suPAR had 28 days mortality prognostic ability comparable to SOFA and better than qSOFA. Combining suPAR and qSOFA increased the prognostic ability of qSOFA to be comparable to SOFA.

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