ORIGINAL RESEARCH

Combined suPAR and qSOFA for the prediction of 28-day mortality in sepsis patients

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Abstract

To determine the prognostic performance of soluble urokinase-type plasminogen activator receptor (suPAR) and quick Sequential Organ Failure Assessment (qSOFA) in predicting the 28-day mortality of sepsis patients admitted to the emergency department (ED). A prospective, single-center observational study was conducted between June 2018 and June 2019. In total, 175 patients with sepsis and septic shock admitted to the ED were enrolled based on the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). We assessed the qSOFA score on ED admission and measured serum suPAR levels by quantitative enzyme-linked immunosorbent assay. Univariate and multivariate analysis was performed to identify predictors of prognosis. Kaplan–Meier survival curves and areas under the receiver operating characteristic (ROC) curve for 28-day mortality were calculated. We estimated category-free net reclassification improvement (NRI) when suPAR was added to qSOFA. Increased suPAR levels were significantly associated with 28-day mortality [1.74 (1.24–2.51) ng/mL in survivors vs. 1.34 (0.96–2.00) ng/mL in non-survivors, $p = 0.011$] and with sepsis severity [1.34 (0.99–1.98) ng/mL in sepsis vs. 1.74 (1.22–2.65) ng/mL in septic shock, $p = 0.039$]. The area under the curve (AUC) for the prediction of 28-day mortality was 0.646 (95% confidence interval (CI): 0.553–0.740) for suPAR, 0.832 (95% CI: 0.692–0.923) for qSOFA and 0.864 (95% CI: 0.802–0.928) for combined suPAR and qSOFA. Serum suPAR did not significantly increase the AUC of the basic qSOFA, but a model containing suPAR and qSOFA had a continuous NRI of 11% (95% CI: 3.5–18.5%; $p = 0.004$). Serum suPAR was associated with sepsis severity and 28-day mortality. Adding suPAR to qSOFA increased the ROC curve area and improved its discrimination, suggesting that this might be a useful tool in sepsis mortality prediction models.

Keywords

Soluble urokinase-type plasminogen activator receptor; Quick Sequential Organ Failure Assessment; Combined model; Sepsis; 28-day mortality

1. Introduction

Sepsis [1] is a life-threatening organ dysfunction caused by an aberrant host response to infection and remains a major cause of morbidity and mortality worldwide. The global incidence of sepsis has been estimated at approximately 31.5 million cases and 5.3 million deaths annually [2]. Rapid detection of sepsis patients with poor prognosis and aggressive treatment initiatives have decreased the mortality of this disease [3]. The Third International Consensus Definition for Sepsis and Septic Shock (Sepsis-3) focused on organ function and highlighted incorporation of a Sequential Organ Failure Assessment (SOFA) score into the new definition of sepsis [4]. However, SOFA requires multiple laboratory tests which therefore increases the difficulty of detection in emergency department (ED) settings [5]. In contrast, quick SOFA (qSOFA) uses simple bedside criteria to identify adult patients who have suspected infection

and poor outcomes [1], especially in pre-ED settings. qSOFA does not depend on laboratory tests and can be evaluated rapidly and repeatedly. However, a recent editorial described qSOFA as an early detection system that should not replace clinical evaluation [6] and that has limited application for rapid prognostication in patients with a high mortality from sepsis. Used at the suggested cut-off of ≥ 2, qSOFA showed low sensitivity and high specificity [7]. The Hellenic Sepsis Study Group (HSSG) found that even patients with a qSOFA score of 1 had a significant risk of poor outcome at 28-days [8].

The existing biomarkers fall short of having the ideal accuracy for predicting sepsis mortality [9, 10]. Hence, there is an urgent need to identify a simple, accurate and effective biomarker to predict mortality from sepsis in the ED. Velissaris D *et al*. [11] recently described the prognostic value of suPAR, which is the soluble form of the cell membrane-bound urokinase plasminogen activator receptor (uPAR). suPAR may

prove to be a valuable biomarker for all patients that are admitted to ED.

uPAR is expressed at the surface of a variety of white blood cell types,endothelial cells and tumor cells. The suPAR expression level has been shown to correlate positively with activation of the immune system.

Following cleavage from the cell surface, suPAR is released into the blood and other body fluids. The expression of uPAR is up-regulated following activation of inflammatory cells by cytokines, thereby also increasing serum levels of suPAR [12].

Donadello *et al*. [13] have suggested that high levels of suPAR correlate with morbidity and patient survival, thus justifying the role of suPAR as a prognostic biomarker in patients with infection. Meta-analyses by Huang *et al*. [14] and by Pregernig A *et al*. [15] found that high suPAR levels were linked to poor outcomes in sepsis patients. Other authors have reported that serum suPAR levels in critically ill patients remained stable for several days or even weeks [16, 17].

Although high suPAR concentrations in the early stage of sepsis are linked to morbidity, the use of suPAR on its own to predict outcome in sepsis remains limited. Because suPAR is a non-specific biomarker, it can predict adverse outcome without knowledge of the underlying condition [11]. Therefore, Hall *et al*. [18] have suggested the performance of suPAR should be compared with other biomarkers and that it should also be evaluated together with existing severity of illness scores.

There have been few studies on the use of both suPAR and qSOFA to predict mortality in sepsis patients in an emergency setting. Hence, we aimed to determine the prognostic accuracy of suPAR when used in combination with qSOFA to predict mortality in sepsis patients admitted to ED in China.

2. Methods

2.1 Study population

This retrospective, observational study was performed from June 2018 to June 2019 in patients admitted to the ED of Renji Hospital (South Campus). This hospital is affiliated with the Shanghai Jiaotong University School of Medicine and is a university tertiary hospital with approximately 120,000 ED visitors per year. Consecutive, non-trauma cases (n = 190) that met Sepsis-3 criteria were enrolled. A total of 175 patients were included in the final analysis and these were classified as non-survivors or survivors according to 28-day mortality. All treatments and procedures were conducted according to the relevant guidelines for Sepsis 3.0. The study was approved by the Ethics Committee of the Renji Hospital (ethics NO.: 2016-109k). All surviving patients and legally authorized representatives of non-surviving patients gave written informed consent.

For the purposes of this study, sepsis was defined as: infection + SOFA score ≥ 2.

Septic shock was identified clinically as the need for a vasopressor to maintain the mean arterial pressure at 65 mmHg or greater and the serum lactate concentration at >2 mmol/L (>18 mg/dL) without hypovolemia.

The clinical criteria for quick SOFA (qSOFA) was a respiratory rate of ≥ 22/min, altered mentation, or systolic blood pressure of ≤ 100 mmHg.

Exclusion criteria were age <18 years, pregnancy, or presence of malignancy or end-stage disease. Patients were also excluded if they or their relatives declined participation in the study.

2.2 Sample size estimation

The type I error/significance level (two-sided) was set to $\alpha = 0.05$ and the type II error was set to $\beta = 0.10$ in order to provide 90% power. The test standard deviations were $Z\alpha = 1.96$ and $Z\beta = 1.282$. Assuming a 28-day mortality rate for sepsis of 10% and an AUC for qSOFA of 0.66 [1], the primary sample size calculated by PASS 11.0 (NCSS, USA) was estimated to be 180. A total of 190 patients were ultimately recruited to the study.

2.3 Data collection

Data collected for the study included patient age and sex, underlying diseases, infection site, clinical data, scores for severity of illness (qSOFA, SOFA and Acute Physiology and Chronic Health Evaluation [APACHE] II scores). Laboratory data including C-reactive protein (CRP), procalcitonin (PCT) and lactate levels for all enrolled patients within 24 h of their admittance to ED was also recorded.

2.4 Measurement of serum suPAR

Peripheral blood serum samples were obtained in the first 24 h of admission and prior to the use of intravenous antibiotics from clinical labin. These were collected into sterile, procoagulation tubes and stored at $-80\,°C$ prior to analysis.

An enzyme-linked immunosorbent assay (ELISA) kit (DUP00; R&D Systems, Minneapolis, MN, USA) was used to measure serum suPAR levels in duplicate according to the manufacturers' instructions. The sensitivity of the assay was 33 pg/mL and intra- and inter-assay coefficients of variation were each $<8\%$.

2.5 Measurement of serum CRP, PCT and lactate

The level of CRP was assessed with a latex-enhanced immunoturbidimetric method and the Beckman IMMAGE instrument [analytical range of 4–200 mg/L; reference range of <10 mg/L].

Quantitative measurements of PCT concentrations were performed using a fixed-time immunonephelometric assay and the Siemens BN II instrument (detection limit of 0.04 ng/mL).

Lactate levels were obtained from venous blood gas.

2.6 Statistical analysis

Continuous variables were expressed as the median and interquartile range, while categorical variables were expressed as a percentage. The chi-squared test or Fisher's exact test were used to compare categorical variables, while the *t*-test and Mann–Whitney U test for continuous variables or abnormally distributed variables, respectively, were used to compare two groups. Bivariate logistic regression analysis was used to

assess the impact of CRP, PCT, lactate and suPAR levels on 28-day mortality and thus identify independent predictors. Receiver operating characteristic (ROC) analysis was performed to compare survivors with non-survivors using Sigma Plot 14.0 (Systat Software, USA), with cut-off values determined using Youden's index. Areas under the ROC curve (AUCs), optimal threshold values, sensitivity and specificity were also determined, with the latter two used to determine positive and negative likelihood ratios, respectively. The Kaplan–Meier method was used to calculate 28-day survival curves, with patients divided into two groups as determined by the cut-off value using Youden's index. The log-rank test was used to compare survival curves, with a two-sided *p*-value of <0.05 considered to represent statistical significance. Confidence intervals (CIs) were set to 95%. In order to compare qSOFA models against suPAR and qSOFA models, the additional information on clinical variables was assessed using category-free net reclassification improvement (NRI) [19]. Statistical analysis was performed with GraphPad Prism version 8.0 (GraphPad Software, CA, USA) and R statistical software (Foundation for Statistical Computing, Vienna, Austria) version 3.4.0.

3. Results

3.1 Demographic and clinical characteristics of patients with sepsis

From June 2018 to June 2019, 190 patients were screened for eligibility and amongst these 15 were later excluded (5 patients declined to participate, 1 could not contact a legal representative, and blood samples for 9 patients were not available in a timely manner upon admission). The final 175 patients included in this study were classified as survivors (n = 134) and non-survivors (n = 41) (Table 1).

Non-survivors had a higher incidence of coronary heart disease (41.5% vs. 11.9%) and respiratory tract infection (95.1% vs. 49.3%), but lower incidence of urinary tract infection (4.9% vs. 25.4%) compared to survivors. Non-survivors were also more likely to be on mechanical ventilation (75.6% vs. 9.7%) and vasopressors (85.4% vs.13.4%) compared to survivors. Furthermore, non-survivors had higher qSOFA (3 vs. 1), SOFA (10 vs. 3) and APACHE II (29 vs. 12) scores, as well as higher lactate (2.80 vs. 2.20 mmol/L) and suPAR (1.74 [1.24–2.51] vs. 1.34 [0.96–2.00] ng/mL) levels compared to survivors. The 28-day mortality rate for the overall cohort was 23.4% (41/175).

3.2 Serum suPAR levels in patients with sepsis and septic shock, and in survivors and non-survivors

Fig. 1 shows the suPAR levels in patients with sepsis and septic shock, as well as in survivors and non-survivors. These were significantly higher in patients with septic shock compared to those with sepsis (1.74 [1.22–2.65] ng/mL vs. 1.34 [0.99–1.98] ng/mL, *p* = 0.039), and in non-survivors compared to survivors (1.74 [1.24–2.51] ng/mL vs. 1.34 [0.96–2.00] ng/mL, *p* = 0.011).
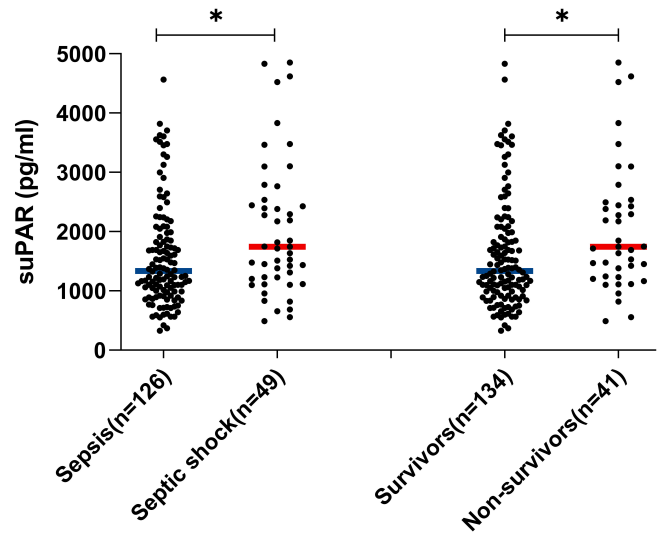

F I G U R E 1. Comparison of suPAR in patients with sepsis and septic shock, and in survivors and non-survivors. Sample collection: Peripheral venous waste blood serum samples were collected within 24 h of admission and prior to intravenous antibiotics; *p*: < 0.05; Test used by ELISA (R&D Systems).

3.3 Predictive value of suPAR for 28-day mortality in sepsis patients

Kaplan–Meier survival curves were used to evaluate suPAR as a predictor of 28-day mortality in sepsis patients (Fig. 2). The 28-day mortality rate in the high suPAR group (≥1.38 ng/mL) was significantly higher than in the low suPAR group (<1.38 ng/mL; log-rank, *p* = 0.0028). As shown in Table 2, univariate analysis (Table 2) revealed significant differences between survivors and non-survivors for both suPAR (*p* = 0.013) and qSOFA (*p* < 0.001). A multivariate logistic regression model adjusted for mechanical ventilation, vasopressor use, hemoglobin and creatinine levels found that both suPAR (*p* = 0.018) and qSOFA (*p* = 0.003) were independent predictors of survival (Table 2).
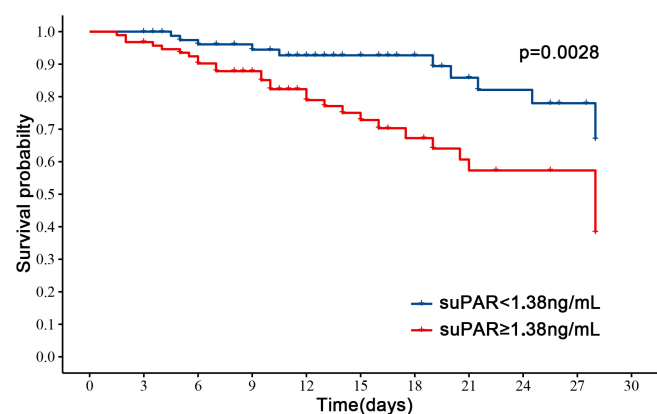

F I G U R E 2. Kaplan-Meier analysis for 28-day cumulative survival. Patients were separated into two groups based on the cut-off calculated by Youden's Index. Curves were compared using the log-rank test.

TABLE 1. Baseline characteristics of the overall septic patient cohort.

Characteristic	Total (n = 175)	Non–survivors (n = 41)	Survivors (n = 134)	p value
Age (years) median (IQR)	66 (53–77)	69 (53–81)	66 (53–75)	0.165
Sex (male) n (%)	110 (62.9)	26 (63.4)	84 (62.7)	1.00
Underlying diseases n (%)				
Hypertension	71 (40.6)	21 (51.2)	50 (37.3)	0.146
Diabetes mellitus	51 (29.1)	8 (19.5)	43 (32.1)	0.169
Coronary heart disease	33 (18.9)	17 (41.5)	16 (11.9)	<0.001
Cerebral infarction	35 (20)	10 (24.4)	25 (18.7)	0.503
Chronic pulmonary disease	15 (8.6)	6 (14.6)	9 (6.7)	0.121
Surgical history	36 (20.6)	9 (22)	27 (21.1)	0.827
Infection site n (%)				
Respiratory tract infection	105 (60)	39 (95.1)	66 (49.3)	<0.001
Urinary tract infection	36 (20.6)	2 (4.9)	34 (25.4)	0.004
Gastrointestinal infection	15 (8.6)	2 (4.9)	13 (9.7)	0.526
Hepatobiliary system infection	18 (10.3)	1 (2.4)	17 (12.7)	0.077
Skin infection	13 (7.4)	4 (9.8)	9 (6.7)	0.506
Intracranial infection	5 (2.9)	0 (0)	5 (3.7)	0.592
Bloodstream infection	41 (23.4)	5 (12.2)	36 (26.9)	0.142
Unknown origin	10 (5.7)	1 (2.4)	9 (6.7)	0.456
Severity related variable n (%) or median (IQR)				
Mechanical ventilation	44 (25.1)	31 (75.6)	13 (9.7)	<0.001
Vasopressor use	53 (30.3)	35 (85.4)	18 (13.4)	<0.001
CRRT	11 (6.3)	5 (12.2)	6 (4.5)	0.132
qSOFA	1 (0–2)	3 (1.5–3)	1 (0–1)	<0.001
SOFA	4 (2–8)	10 (7–14)	3 (2–6)	<0.001
APACHE II	14 (9–24)	29 (21–31.5)	12 (8–18)	<0.001
Septic shock	49 (28)	35 (85.4)	14 (10.4)	<0.001
Clinical variable median (IQR)				
WBC (×10^9/L)	10.12 (6.70–13.40)	12.05 (7.19–14.60)	9.56 (6.48–13.14)	0.134
Hb (g/L)	123 (107–137)	119 (95–133)	125 (108–137)	0.039
Plt (×10^9/L)	161 (99–217)	155 (64–215)	166 (107–217)	0.250
CRP (mg/L)	123 (39–200)	118 (43–190)	125 (33–200)	0.760
PCT (ng/mL)	1.94 (0.46–11.33)	1.75 (0.46–7.77)	2.07 (0.45–12.21)	0.428
Lactate (mmol/L)	2.39 (1.60–3.48)	2.80 (2.10–4.50)	2.20 (1.50–3.12)	0.003
Creatinine (umol/L)	91 (64–139)	109 (60–175)	86 (64–126)	0.048
suPAR (ng/mL)	1.45 (1.05–2.21)	1.74 (1.24–2.51)	1.34 (0.96–2.00)	0.010

Abbreviation: IQR, interquartile range; CRRT, continuous renal replacement therapy; SOFA, sequential organ failure assessment; qSOFA, quick SOFA; APACHE II, Acute Physiology and Chronic Health Evaluation II; WBC, white blood cell; Hb, hemoglobin; Plt, platelet; PCT, procalcitonin; CRP, C-reactive protein; suPAR, soluble urokinase-type plasminogen activator receptor.

3.4 Combination of suPAR and qSOFA for the prediction of 28-day mortality in sepsis patients

Table 3 and Fig. 3 show ROC analysis for the combination of suPAR and qSOFA, and for qSOFA alone, in predicting 28-day mortality in patients with sepsis. Table 3 also shows the AUCs for various factors in predicting 28-day mortality

in these patients based on Sepsis-3. The AUC obtained using the combination of suPAR and qSOFA (0.865, 95% CI: 0.802–0.0.928) was superior to that from qSOFA alone (0.833, 95% CI: 0.692–0.923), suPAR alone (0.647, 95% CI: 0.552–0.741) or lactate alone (0.664, 95% CI: 0.571–0.754). It was also superior to that from qSOFA combined with CRP (0.856, 95% CI: 0.790–0.919), PCT (0.861, 95% CI: 0.788–0.924)

TABLE 2. Binary logistic regression analysis of risk factors for 28-day mortality.

Variable	Univariate analysis			Multivariate analysis[#]		
	OR[*]	95% CI[*]	p value	OR	95% CI	p value
suPAR (ng/mL)	1.483	1.085–2.026	0.013	1.914	1.042–3.515	0.036
qSOFA	5.048	3.039–8.388	<0.001	3.098	1.473–6.514	0.003
CRP (mg/L)	0.999	0.995–1.004	0.759	0.854	0.992–1.007	0.999
PCT (ng/mL)	0.990	0.966–1.015	0.427	0.960	0.918–1.004	0.071
Lactate (mmol/L)	1.227	1.057–1.426	0.007	0.946	0.769–1.162	0.595

*: OR, odds ratio; CI, confidence interval; #: Adjusted for: Coronary heart disease, Respiratory tract infection, Urinary tract infection, Mechanical ventilation, Vasopressor use, Hemoglobin, Creatinine.

or lactate (0.850, 95% CI: 0.783–0.913). The combination of suPAR + qSOFA was statistically different compared to suPAR alone ($p < 0.001$, data not shown) but not when compared to qSOSA ($p = 0.082$, data not shown). A model containing suPAR in addition to qSOFA showed a continuous NRI of 11% (95% CI: 3.5–18.5%, $p = 0.004$) (data not shown). And there was no significant difference between AUC of combined or single model with CHD and without CHD ($p = 0.447$, data was not shown), on account of that suPAR is independently associated with the presence and severity of heart failure.
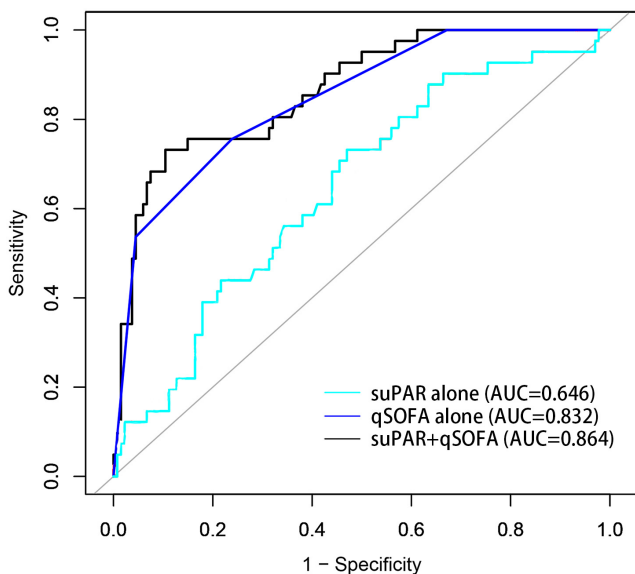

FIGURE 3. ROC analysis for predicting 28-day mortality in sepsis-3 patients.

4. Discussion

This is the first study of suPAR used in combination with the qSOFA score for sepsis patients as defined by Sepsis-3. We developed a simple model for the prediction of 28-day mortality in these patients by using the qSOFA score in combination with serum levels of the suPAR biomarker.

The present study,found that suPAR had better predictive value for 28-day hospital mortality of sepsis or septic shock patients than commonly used markers such as CRP, PCT and lactate. Moreover, the predictive power was slightly improved when suPAR was combined with qSOFA scores.

Sepsis is a complex physiopathological event that cannot be simply described by one measure only [20]. Consequently, no single clinical or biological parameter has proven to an ideal prognosticator. In critically sick patients, the Acute Physiology and Chronic Health Evaluation (APACHE) II score and the Sequential Organ Failure Assessment (SOFA) score are the accepted standards for evaluation of severity [21]. The use of scoring systems to help with decision making for sepsis patients is complicated, however, and are not readily available in pre-ED.

Some studies have suggested that qSOFA could be a helpful guide in ED settings outside of intensive care. In such situations, qSOFA could predict death of sepsis patients, but it could be overcome by rapid and accurate laboratory diagnostic tests [22]. The use of qSOFA score with a cut-off value of ≥2 showed low sensitivity but high specificity. However, when used on its own to screen for critical illness, positive qSOFA criteria could fail to identify many cases. The present study found the AUC of qSOFA alone was 0.832 for 28-day mortality. Moreover, we found qSOFA on its own had low post-test probability but this increased markedly when used in association with PCT [7]. In the study by Giamarellos-Bourboulis et al. [8], qSOFA showed insufficient sensitivity to be used for early risk assessment.

Commonly used markers have not proven superior to generic scores for predicting the survival of patients with sepsis [23]. Many workers have focussed on suPAR as a potential biomarker for survival outcome. Early increases in suPAR levels have been associated with 30- and 90-day hospital mortality rates in sepsis patients and also correlated with the severity of sepsis [24–26]. Here, we found that serum suPAR concentrations were significantly higher in the septic shock and non-survivor groups compared to the sepsis and survivor groups. These results are consistent with those of previous studies. Previous studies have shown that the AUC for suPAR to predict in-hospital mortality is in the range of 0.67 to 0.84 [20, 25, 27, 28]. Several studies have also shown the superiority of suPAR over conventional biomarkers such as CRP and PCT [17, 27, 29–31]. Consistent with previous reports, the AUC for suPAR to predict mortality in the present study was 0.646, which was also superior to both CRP (0.483) and PCT (0.470).

TABLE 3. Results of ROC analysis of variables for predicting 28-day mortality from sepsis.

Variable	AUC (95% CI)	p value	Cut-off (≥)	Youden's index	Sens. (95% CI)	Spec. (95% CI)	LR+ (95% CI)	LR– (95% CI)	PPV (95% CI)	NPV (95% CI)
suPAR (ng/mL)	0.646 (0.553–0.740)	0.005	1.382	0.261	0.732 (0.568–0.852)	0.53 (0.442–0.616)	1.556 (1.202–2.015)	0.506 (0.298–0.860)	0.323 (0.229–0.428)	0.866 (0.773–0.931)
qSOFA	0.832 (0.692–0.923)	<0.001	1.5	0.517	0.756 (0.594–0.871)	0.761 (0.678–0.829)	3.166 (2.234–4.487)	0.320 (0.185–0.554)	0.492 (0.364–0.621)	0.911 (0.842–0.956)
CRP (mg/L)	0.517 (0.417–0.618)	0.738	180.2	0.092	0.756 (0.594–0.871)	0.336 (0.258–0.432)	1.138 (0.921–1.407)	0.726 (0.403–1.309)	0.258 (0.183–0.346)	0.818 (0.691–0.909)
PCT (ng/mL)	0.530 (0.431–0.628)	0.563	9.24	0.111	0.805 (0.646–0.906)	0.306 (0.231–0.392)	1.160 (0.961–1.400)	0.638 (0.326–1.249)	0.262 (0.188–0.348)	0.837 (0.703–0.927)
Lac (mmol/L)	0.663 (0.571–0.754)	0.002	1.855	0.283	0.902 (0.754–0.968)	0.381 (0.299–0.469)	1.457 (1.233–1.721)	0.256 (0.098–0.667)	0.308 (0.227–0.399)	0.927 (0.824–0.980)
suPAR + qSOFA	0.864 (0.802–0.928)	<0.001	/	/	0.732 (0.568–0.852)	0.895 (0.828–0.940)	7.004 (4.126–11.889)	0.299 (0.180–0.498)	0.682 (0.524–0.814)	0.916 (0.855–0.957)
CRP + qSOFA	0.855 (0.790–0.919)	<0.001	/	/	0.781 (0.619–0.889)	0.754 (0.670–0.822)	3.169 (2.261–4.443)	0.291 (0.162–0.523)	0.492 (0.366–0.619)	0.918 (0.850–0.962)
PCT + qSOFA	0.860 (0.788–0.924)	<0.001	/	/	0.801 (0.644–0.904)	0.743 (0.660–0.812)	3.172 (2.287–4.400)	0.261 (0.139–0.491)	0.493 (0.368–0.618)	0.925 (0.859–0.968)
Lac + qSOFA	0.849 (0.783–0.913)	<0.001	/	/	0.683 (0.518–0.814)	0.858 (0.785–0.910)	4.816 (3.023–7.674)	0.370 (0.235–0.582)	0.596 (0.443–0.736)	0.898 (0.833–0.945)

*Abbreviation: AUC, areas under the receiver; CI, confidence interval; Sens., sensitivity; Spec., specificity; LR+, positive likelihood ratio; LR–, negative likelihood ratio; PPV, positive predictive value; NPV, negative predictive value; Lac, Lactate; *: vs. suPAR + qSOFA.*

Kaplan–Meier analysis revealed that suPAR ≥ 1.38 ng/mL was significantly associated with an increased 28-day mortality rate. Interestingly, this value is identical to the threshold value reported previously [20, 32].

Based on the above analysis, we propose that suPAR could be a clinically useful prognostic marker in patients with sepsis.

There have been several studies of suPAR in combination with other factors, or of qSOFA combined with other factors, for predicting the mortality of sepsis patients. Kofoed *et al*. [33] reported that suPAR showed superior prognostic value to PCT and CRP, and equal prognostic value to the SOFA score. These authors also reported that suPAR was almost equal in value to the Simplified Acute Physiology Score (SAPS) II score and that suPAR combined with age had superior predictive value compared to SAPS II alone. Julián-Jiménez *et al*. [34] reported that qSOFA scores showed better predictive value for 30-day mortality than systemic inflammatory response. In elderly patients admitted to ED because of infection, they also found that qSOFA plus mid-regional pro-adrenomedullin had better predictive value than qSOFA alone [34]. Serum lactate levels are commonly used as an indicator of the severity of illness severity. Baumann *et al*. [35] found that combining qSOFA ≥ 1 with lactate ≥ 2 considerably enhanced the sensitivity of detection for critical illness.

To our knowledge there have been no published studies on the value of combining suPAR with qSOFA. We propose improvement in the prognostication of 28-day mortality from sepsis by combining the qSOFA score with suPAR. This serum marker is readily tested on-site and a result can be obtained within an hour [36]. Our results show the AUC of the suPAR and qSOFA combination was better than that of qSOFA or suPAR alone, and better than other combinations tested (CRP + qSOFA, PCT + qSOFA, lactate + qSOFA).

Various authors have highlighted the limitations of AUC analysis, such as the challenges in interpreting minor changes and the relationship between the size of improvement and performance of the baseline model [37, 38]. These considerations have resulted in the notion of risk reclassification [39], which involves cross-tabulating the categories of predicted risk using two models. One model has the new marker being studied and the other does not, and then noting whether the patients are classified differently. NRI was used in this study to estimate the strength of associations. This evaluates the improvement in classification due to addition of the test variable, while achieving a balance between sensitivity and specificity. NRI is the sum of two percentages with different denominators and is therefore expressed as a proportion with a range of –2.0 to 2.0 [40]. In a previous study, only a small proportion of patients were considered as high risk for death because the high specificity of the current clinical model, qSOFA, likely resulted in limited reclassification of sepsis [41], Serum suPAR did not significantly increase the AUC of qSOFA in the present study. However, the qSOFA score in the suPAR model showed a marked improvement in patient reclassification, with an NRI of 11% compared to the qSOFA score. Therefore, addition of suPAR to the qSOFA model demonstrates the limited practical benefit of an existing marker in such a low-risk population. In summary, addition of suPAR to the clinical predictive model (qSOFA) could improve the predictive value for outcome of qSOFA alone.

5. Limitations

The present study has several limitations. First, serum suPAR levels were measured at the time of admission, and any subsequent changes in response to treatment were not evaluated. Second, several comorbidities such as diabetes mellitus [42] and CHD [43] could also influence suPAR values. However, our study reflected a real world setting and subgroup analysis according to the presence or absence of CHD was performed. Third, suPAR levels in healthy controls were not evaluated for comparison with patients due to funding limits and ethics. Finally, the NRI method as a basis for marker evaluation has its limitations [44]. Future studies should investigate the impact of changes in suPAR expression during the pathogenesis of sepsis in a larger sample size. Further research is also needed to assess the predictive values of suPAR and qSOFA when combined with other factors.

6. Conclusions

Serum suPAR levels were associated with the severity of sepsis and with 28-day mortality in sepsis patients. Addition of suPAR to the clinical model (qSOFA) may increase the ROC curve area and improve the predictive value of qSOFA for the outcome from sepsis in ED patients.

ABBREVIATIONS

suPAR, soluble urokinase-type plasminogen activator receptor; qSOFA, quick Sequential Organ Failure Assessment; SOFA, Sequential Organ Failure Assessment; ED, emergency department; AUROC, areas under the receiver operating characteristic; ELISA, enzyme-linked immunosorbent assay; NRI, net reclassification improvement; BNP, B-type natriuretic peptide; CRP, C-reactive protein; PCT, procalcitonin; WBC, Whole blood leukocyte count; OR, odds ratio; CI, confidence interval; IQR, Interquartile range; Sepsis-3, Third International Consensus Definitions for Sepsis and Septic Shock; APACHE, Acute Physiology and Chronic Health Evaluation; SAPS, Simplified Acute Physiology Score; MR-proADM, Mid regional pro-adrenomedullin; CHD, coronary heart disease; LR–, negative likelihood ratio; LR+, positive likelihood ratio.

AUTHOR CONTRIBUTIONS

LW and CT contributed equally to the writing of this manuscript. SH and YC participated in data interpretation and statistical analysis. CX revised the whole manuscript. All authors approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Procedures involving human participants were conducted in accordance with the ethical standards of the institutional and/or

national research committees and with the 1964 Helsinki Declaration and later amendments or comparable ethical standards. The study was approved by the Ethics Committee of Renji Hospital Affiliated to Shanghai Jiaotong University School of Medicine (ethics NO.: 2016-109k). All patients or legally authorized representatives of patients provided written informed consent.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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