Serum plasminogen activator urokinase receptor predicts elevated risk of acute respiratory distress syndrome in patients with sepsis and is positively associated with disease severity, inflammation and mortality

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Abstract. The present study aimed to evaluate the predictive value of serum soluble urokinase plasminogen activator receptor (suPAR) regarding the risk of acute respiratory distress syndrome (ARDS) in sepsis patients, and investigate its correlation/association with disease severity, inflammation and mortality in sepsis patients with ARDS. A total of 57 sepsis patients with ARDS and 58 sepsis patients without ARDS were recruited for the present case-control study. Laboratory tests, acute physiology and chronic health evaluation (APACHE) II score and sequential organ failure assessment (SOFA) score were evaluated, and mortality during hospitalization was recorded. Blood samples were collected and serum suPAR was detected by ELISA. Furthermore, tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, IL-8, IL-10 and IL-17, as well as C-reactive protein (CRP) were detected. The results indicated that the serum levels of suPAR in sepsis patients with ARDS were higher than those in sepsis patients without ARDS. Receiver operating characteristics (ROC) curve analysis indicated that it was possible to distinguish sepsis patients with ARDS from sepsis patients without ARDS based on their serum suPAR levels, and multivariate logistic regression analysis suggested that serum suPAR levels were an independent predictor of the risk of ARDS in sepsis patients. In sepsis patients with ARDS, serum suPAR levels were positively correlated with the APACHE II score, SOFA score and the levels of CRP, TNF-α, IL-1β and IL-8. In addition, serum suPAR levels were lower in survivors compared with those in non-survivors, and ROC curve analysis suggested that serum suPAR was able to predict the probability of mortality. In conclusion, serum suPAR independently predicted an elevated risk of ARDS in patients with sepsis, and was correlated/associated with greater disease severity, higher inflammation and increased mortality in patients with sepsis and ARDS.

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Introduction

Sepsis is a life-threatening condition caused by unbalanced host responses to severe infection (1). Based on a global epidemiologic report, the incidence of sepsis ranges from 38 to 110 cases per 100,000 individuals, and the mortality rate is 22-55% (2). Due to systemic inflammation, it is estimated that one third of patients with sepsis develop acute respiratory distress syndrome (ARDS), a common lethal disease characterized by acute and diffuse lung injury causing severe hypoxemia (3). Despite recent improvements in critical care and the significant research effort in basic research and clinical trials on sepsis complicated with ARDS, the recovery rate remains poor and the associated mortality remains high (4). Several biomarkers, including interleukin (IL)-18, IL-15 and interferon (IFN)-γ, are known to be closely correlated with inflammation and the development of lung disease (5,6). Further research into additional biomarkers is essential to predict the risk of ARDS in patients with sepsis. Such markers may be also useful for monitoring disease development in cases of sepsis-induced ARDS, which may also improve clinical outcomes.

Soluble plasminogen activator urokinase receptor (suPAR) is a 55-60 kDa glycoprotein that occurs in three forms (I-III, II-III and I), and is the soluble form of uPAR, which is cleaved by proteases from the cell surface into its soluble form in response to inflammatory stimulation (7-9). suPAR may be detected in blood serum, urine, and bronchoalveolar lavage and cerebrospinal fluid, and its serum concentration remains stable under certain circadian changes and fasting, and due to its stability, it may be an excellent diagnostic and prognostic biomarker (10). Studies have demonstrated that suPAR may have a pro-inflammatory effect in several inflammatory diseases and, as a plasminogen activator, it has been demonstrated to facilitate coagulation as well as fibrinolytic cascades (11,12).

Overexpression of suPAR has also been reported to be associated with a high risk of 30-day mortality in sepsis patients (13). Furthermore, its upregulation was demonstrated to be positively correlated with higher disease severity in patients with ARDS (14). Considering the association of suPAR with the severity of ARDS and its potential value as a prognostic indicator, the present study hypothesized that suPAR may have a critical role in patients with sepsis complicated with ARDS. Therefore, the present study aimed to evaluate the predictive value of serum suPAR regarding the risk of ARDS in patients with sepsis, and to investigate the correlation of suPAR with disease severity, inflammation and mortality.

Materials and methods

Patients. Between January 2015 and December 2017, 57 patients with sepsis complicated by ARDS treated at The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology (Wuhan, China) were recruited for the present study. The inclusion criteria were as follows: i) Diagnosis with sepsis according to the 2001 International Sepsis Definitions Conference criteria (15); ii) complication of ARDS, which was diagnosed in accordance with the Berlin criteria (16); iii) age >18 years. Patients were excluded if the following applied: i) No inflammatory status; ii) other complications/malignancies; iii) human immunodeficiency virus infection; iv) pregnancy. None of the sepsis patients received any treatments for sepsis prior to enrolment in the present study. During the same period, patients diagnosed with sepsis without the complication of ARDS, who were admitted to the hospital's intensive care unit (ICU) and did not meet any of the exclusion criteria described for patients with ARDS, were recruited for the present study. Thereby, a total of 58 patients with sepsis and without ARDS, who were age- and gender-matched with the ARDS group, were selected as a control group. The present study was approved by the Ethics Committee of The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology (Wuhan, China), and all participants or their guardians provided written informed consent prior to enrollment.

Data collection. Clinical data for each patient, including age, gender, body mass index (BMI), history of smoking and chronic comorbidities [including chronic obstructive pulmonary disease (COPD), cardiomyopathy, chronic kidney failure and cirrhosis] of all patients were recorded in a case report form after enrollment. For the patients with ARDS, laboratory tests [including serum creatinine (Scr), albumin, white blood cells (WBC), C-reactive protein (CRP) and procalcitonin (PCT)] were performed within 24 h after the onset of ARDS, and the acute physiology and chronic health evaluation (APACHE) II score and sequential organ failure assessment (SOFA) score were evaluated at the same time. As for the patients without ARDS, the laboratory tests were performed within 24 h after ICU admission, and their APACHE II score and SOFA score were also assessed. The APACHE II score value was calculated based on the initial scoring of 12 components with a range of 0 to 71 points, and a higher score was associated with higher severity (17). In the SOFA scoring scheme, 1-4 points were assigned regarding the dysfunction levels of six organ systems (respiratory, circulatory, renal, hematological, hepatic and central nervous systems), resulting in a total score of 0-24 points, with higher scores being associated with higher severity (18). The patients were followed up until discharge from hospital and mortality during hospitalization was recorded.

Blood sample collection. Blood samples of the patients with ARDS were collected within 24 h after the occurrence of ARDS. As for the patients without ARDS, blood samples were extracted within 24 h after ICU admission. All samples were collected in serum separator tubes, allowed to clot for 30 min and then immediately centrifuged for 15 min at 2,000 x g at 4˚C to separate the serum. Subsequently, the serum was aliquoted and stored at -20˚C until use.

Measurement of suPAR and inflammatory cytokines. The serum suPAR levels of all patients were detected using a commercial ELISA kit (cat. no. ml060583; Shanghai Enzyme-linked Biotechnology Co., Ltd.), according to the manufacturer's protocol. The levels of inflammatory cytokines, including tumor necrosis factor (TNF)-α, IL-1β, IL-6 (cat. no. ml058097), IL-8 (cat. no. ml028580), IL-10 (cat. no. ml064299), IL-17 (cat. no. ml058051), IL-1β (cat. no. ml058059) and TNF-α (cat. no. ml077385) in the blood serum were also measured using human ELISA kits (Shanghai Enzyme-linked Biotechnology Co., Ltd.), according to the manufacturer's protocols.

Statistical analysis. SPSS 22.0 (IBM Corp.) and GraphPad Prism 7.0 (GraphPad Software, Inc.) were used for statistical data processing and generation of figures. Shapiro-Wilk test was used to determine the normality of continuous variables. Normally distributed continuous variables were expressed as the mean ± standard deviation, non-normally distributed continuous data were presented as the median (25th-75th quartiles) and categorical variables were expressed as n (%). Comparisons of normally distributed continuous variables between groups were performed using Student's t-test, differences in non-normally distributed continuous variables between groups were determined by Wilcoxon's signed-rank sum test and comparisons of categorical variables between groups were performed by Chi-squared tests. Correlation analyses were performed using Spearman's test. Receiver-operating characteristic (ROC) curves were drawn and the area under the ROC curve (AUC) was determined to assess the feasibility of serum suPAR as a potential biomarker to predict the risk of ARDS in patients with sepsis, as well as to assess its value in predicting the risk of mortality. Univariate and multivariate logistic regression model analyses were used to determine the value of suPAR in predicting the risk of ARDS in patients with sepsis. Sepsis severity was assessed by the correlation analysis of suPAR, which was performed using the Spearman test. $P<0.05$ was considered to indicate statistical significance.

Results

Baseline characteristics. The mean age of the patients with sepsis without ARDS (n=58) and with ARDS (n=57) was

Table I. Baseline characteristics of patients with sepsis with/without ARDS.

Characteristics	Sepsis without ARDS (n=58)	Sepsis with ARDS (n=57)	P-value
Age (years)	57.6±9.2	56.3±10.1	0.488
Gender (male/female)	40/18	40/17	0.888
BMI (kg/m^2)	23.0±4.4	23.0±4.7	0.978
History of smoking	14 (24.1)	29 (50.9)	0.003
Chronic comorbidities			
COPD	8 (13.8)	12 (21.1)	0.304
Cardiomyopathy	22 (37.9)	22 (38.6)	0.941
Cardiovascular disease	23 (39.7)	24 (42.1)	0.789
Type 2 diabetes	9 (15.5)	11 (19.3)	0.593
Chronic kidney failure	6 (10.3)	4 (7.0)	0.763
Cirrhosis	10 (17.2)	9 (15.8)	0.834
Scr (mg/dl)	1.4 (0.9-2.1)	1.4 (1.1-2.0)	0.535
Albumin (g/l)	26.9 (22.4-36.8)	28.7 (21.3-39.0)	0.873
WBC (10^9/l)	12.5 (3.1-28.6)	12.3 (3.9-26.3)	0.851
CRP (mg/l)	83.1 (53.4-132.4)	79.7 (53.3-162.8)	0.535
PCT (ng/ml)	14.1 (8.5-21.6)	19.9 (8.7-29.1)	0.170
APACHE II score	15.2±5.6	17.4±4.5	0.018
SOFA score	8.3±4.0	9.6±3.9	0.082
TNF-α (pg/ml)	148.7 (80.4-225.5)	159.0 (98.9-226.1)	0.437
IL-1β (pg/ml)	9.6 (4.4-18.9)	10.3 (4.2-23.0)	0.821
IL-6 (pg/ml)	115.2 (77.3-226.6)	164.5 (79.6-225.3)	0.595
IL-8 (pg/ml)	199.4 (113.0-380.2)	212.9 (132.6-337.0)	0.623
IL-10 (pg/ml)	14.2 (9.1-22.9)	15.4 (8.3-26.4)	0.871
IL-17 (pg/ml)	136.6 (67.4-214.8)	154.2 (105.3-228.0)	0.238

Values are expressed as the mean value ± standard deviation, n (%) or median (25th-75th quartiles). Comparisons of normally distributed continuous variables between groups were performed using Student's t-test, comparisons of non-normally distributed continuous data between groups were determined by Wilcoxon's signed-rank sum test and comparisons of categorical variables between groups (including gender, smoking and chronic comorbidities) were determined with the Chi-squared test. ARDS, acute respiratory distress syndrome; BMI, body mass index; COPD, chronic obstructive pulmonary disease; Scr, serum creatinine; WBC, white blood cells; CRP, C-reactive protein; PCT, procalcitonin; APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment; TNF, tumor necrosis factor; IL, interleukin.

57.6±9.2 and 56.3±10.1 years [Patients with sepsis without ARDS: Age range, 39.0-79.0 years (median age, 56.5 years); Patients with sepsis with ARDS: Age range, 31.0-82.0 years (median age, 56.0 years)], respectively (Table I). The number of patients with ARDS with a history of smoking was higher compared with that in the control group (P=0.003), and the APACHE II score was increased in patients with ARDS compared with that in patients without ARDS (P=0.018). In addition, the SOFA score was numerically higher in patients with ARDS compared with that in patients without ARDS, but this difference was not significant (P=0.082). No differences in any other demographic parameters, clinical features or laboratory test indexes were identified between the two groups (Table I).

Serum suPAR levels predict an elevated risk of ARDS in patients with sepsis. The median serum suPAR levels in patients with ARDS were higher compared with those in the control group [15.17 (12.77-18.01) vs. 13.14 (10.78-15.8) ng/ml; P=0.005; Fig. 1A]. The ROC curve revealed that the serum suPAR levels were able to distinguish patients with sepsis and ARDS from sepsis patients without ARDS (AUC, 0.651; 95% CI, 0.550-0.751; Fig. 1B). The sensitivity and specificity were 63.2 and 63.8%, respectively. In addition, the serum suPAR level was 14.01 ng/ml at the best cut-off point, where the sum of sensitivity and specificity reached its maximum value.

Factors affecting the occurrence of ARDS in patients with sepsis. In order to explore the factors affecting the occurrence of ARDS in patients with sepsis, a logistic regression analysis was performed (Table II). Univariate logistic regression analysis revealed that smoking (P=0.004), high serum suPAR expression (P=0.007) and high APACHE II scores (P=0.020) were associated with a higher incidence of ARDS in patients with sepsis. Further multivariate logistic regression analysis demonstrated that smoking (P=0.020) and high serum suPAR expression (P=0.045) are independent predictors of elevated risk of ARDS in patients with sepsis.

Correlation of serum suPAR levels with APACHE II score, SOFA score and levels of inflammatory factors in patients

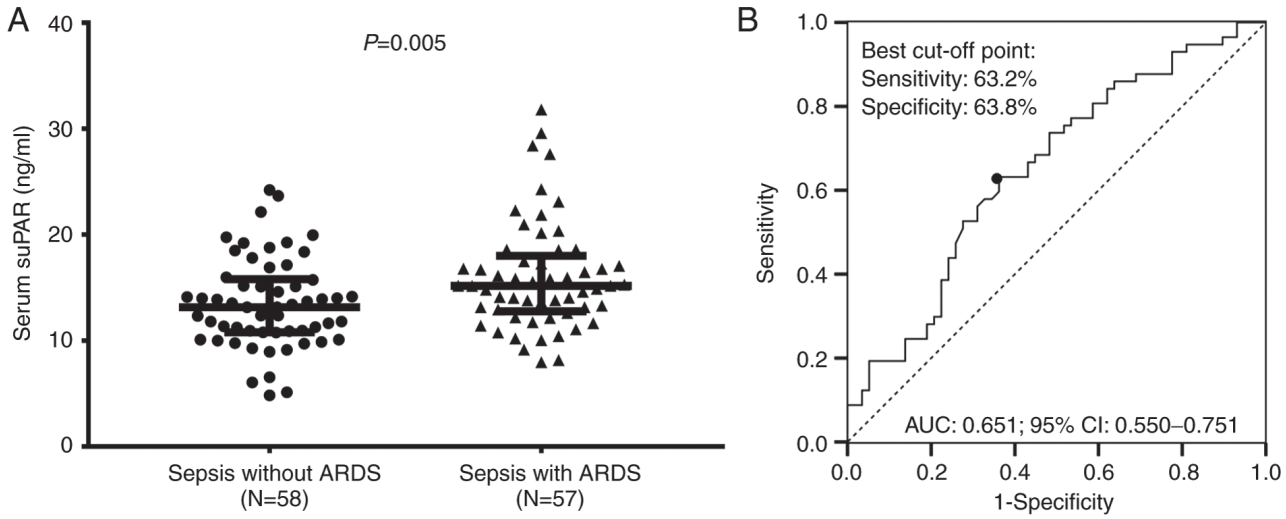

Figure 1. (A) Sepsis patients with ARDS had higher serum suPAR levels compared to sepsis patients with ARDS. (B) Serum suPAR levels were able to predict the risk of ARDS in sepsis patients, with the best cut-off set at 14.01 ng/ml. SuPAR, soluble urokinase plasminogen activator receptor; ARDS, acute respiratory distress syndrome; AUC, area under curve.

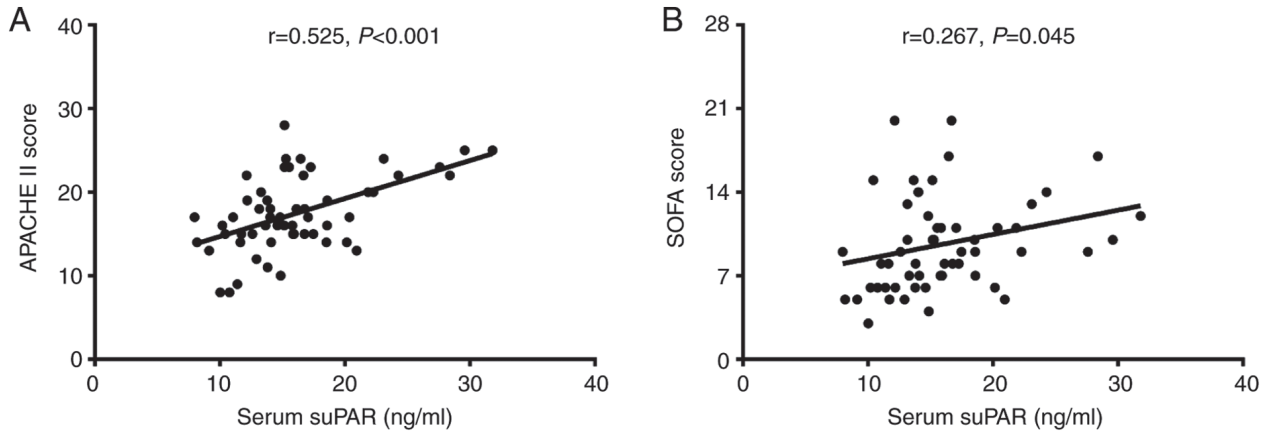

Figure 2. Correlation of serum suPAR levels with APACHE II score and SOFA score in sepsis patients with ARDS. (A) Serum suPAR levels were positively correlated with the APACHE II score in sepsis-ARDS patients. (B) Serum suPAR levels were positively correlated with the SOFA score in sepsis-ARDS patients. Correlation analysis was performed using the Spearman test. SuPAR, soluble urokinase plasminogen activator receptor; APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment.

with ARDS. In patients with ARDS, the serum suPAR levels were positively correlated with the APACHE II score (r=0.525, P<0.001; Fig. 2A) and the SOFA score (r=0.267, P=0.045; Fig. 2B). Regarding their association with the levels of inflammatory factors (Fig. 3), serum suPAR levels were positively correlated with the levels of CRP (r=0.454, P<0.001; Fig. 3A), TNF-α (r=0.418, P=0.001; Fig. 3C), IL-1β (r=0.334, P=0.011; Fig. 3D) and IL-8 (r=0.315, P=0.017; Fig. 3F), and negatively correlated with IL-10 levels (r=-0.309, P=0.019; Fig. 3G) in patients with sepsis and ARDS. However, there was no correlation of serum suPAR levels with PCT levels (r=0.242, P=0.070; Fig. 3B), IL-6 levels (r=0.161, P=0.232; Fig. 3E) or IL-17 levels (r=0.156, P=0.246; Fig. 3H) in patients with sepsis and ARDS.

Serum suPAR levels are a good predictor of survival in patients with sepsis complicated with ARDS. The cohort of patients with sepsis and ARDS comprised 23 non-survivors and 34 survivors. The median serum suPAR levels in non-survivors and survivors were 17.5 (13.8-22.3) and 14.7 (12.0-16.5) ng/ml, respectively (P=0.023; Fig. 4A). ROC curve analysis indicated that serum suPAR levels were capable of distinguishing survivors from non-survivors, with an AUC of 0.679 (95% confidence interval, 0.529-0.829) in patients with ARDS (Fig. 4B). The sensitivity and specificity were 91.2 and 52.2%, respectively. Furthermore, the serum suPAR level of 17.38 ng/ml was the best cut-off point.

Discussion

The results of the present study may be summarized as follows: i) Serum suPAR levels were higher in patients with sepsis with ARDS compared with those in patients with sepsis without ARDS, and were an independent predictor of an elevated risk of ARDS; ii) serum suPAR levels were positively correlated with the APACHE II score, the SOFA score and levels of certain pro-inflammatory factors in patients with ARDS; iii) serum

Table II. Factors associated with a risk of ARDS in sepsis determined by logistic regression analysis.

	Univariate logistic regression				Multivariate logistic regression			
			95% CI				95% CI	
Factors	P-value	OR	Lowest	Highest	P-value	OR	Lowest	Highest
Age	0.484	0.986	0.949	1.025	0.396	0.979	0.932	1.028
Gender (male vs. female)	0.888	1.059	0.478	2.344	0.524	1.376	0.515	3.676
BMI	0.978	1.001	0.923	1.086	0.888	1.008	0.904	1.124
Smoke (yes vs. no)	0.004	3.255	1.471	7.205	0.020	3.017	1.189	7.654
Chronic comorbidities								
COPD (yes vs. no)	0.307	1.667	0.625	4.446	0.366	1.733	0.526	5.717
Cardiomyopathy (yes vs. no)	0.941	1.029	0.485	2.182	0.452	1.463	0.543	3.942
Chronic kidney failure (yes vs. no)	0.529	0.654	0.174	2.453	0.614	0.633	0.107	3.749
Cirrhosis (yes vs. no)	0.834	0.900	0.336	2.411	0.450	0.621	0.180	2.140
Serum suPAR	0.007	1.129	1.034	1.233	0.045	1.131	1.002	1.277
Scr	0.756	0.955	0.714	1.277	0.306	0.791	0.506	1.238
Albumin	0.874	0.997	0.959	1.036	0.662	0.986	0.924	1.052
WBC	0.974	1.000	0.974	1.025	0.836	1.004	0.963	1.048
CRP	0.315	1.003	0.997	1.008	0.432	0.994	0.978	1.010
PCT	0.255	1.015	0.989	1.042	0.475	1.020	0.966	1.077
APACHE II score	0.020	1.094	1.014	1.179	0.203	1.090	0.955	1.244
SOFA score	0.085	1.087	0.989	1.195	0.940	1.006	0.864	1.170
TNF-α	0.448	1.001	0.998	1.004	0.486	1.002	0.996	1.009
IL-1β	0.641	1.008	0.976	1.041	0.962	1.001	0.945	1.061
IL-6	0.886	1.000	0.997	1.003	0.390	0.998	0.993	1.003
IL-8	0.636	1.000	0.999	1.002	0.902	1.000	0.996	1.003
IL-10	0.982	1.000	0.989	1.012	0.698	1.003	0.988	1.018
IL-17	0.131	1.002	0.999	1.005	0.082	1.003	1.000	1.007

Factors affecting ARDS in sepsis were determined by univariate and multivariate logistic regression analyses. ARDS, acute respiratory distress syndrome; OR, odds ratio; CI, confidence interval; BMI, body mass index; COPD, chronic obstructive pulmonary disease; suPAR, soluble urokinase plasminogen activator receptor; Scr, serum creatinine; WBC, white blood cell; CRP, C-reactive protein; PCT, procalcitonin; APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment; TNF, tumor necrosis factor; IL, interleukin.

suPAR levels (collected within 24 h after the occurrence of ARDS) were able to distinguish survivors from non-survivors (in-hospital mortality) in the sepsis+ARDS group of patients.

suPAR, a protein derived from the cleavage of the cell membrane-bound uPAR, is involved in various biological and pathological processes, including inflammatory response, immune activation, signal transduction and tissue remodeling (7,10,19-24). Due to its role in inflammation, suPAR has been reported to not only possess direct chemotactic properties to promote recruitment of inflammatory cells (including monocytes and neutrophils), but has also been reported to suppress neutrophil efferocytosis and obstruct the engulfment of apoptotic neutrophils, leading to the dysregulation of the host's immune response (25-28). In addition, suPAR has been reported to act as a plasminogen activator, facilitating coagulation and fibrinolytic cascades (11).

Recently, suPAR has been reported to be upregulated in several inflammatory diseases, including inflammatory bowel disease, arthritis and central nervous system infections (29-31). For instance, suPAR is highly expressed in patients with Crimean-Congo hemorrhagic fever (CCHF) compared to healthy controls, and it is able to distinguish CCHF patients from healthy controls with an AUC of 0.94 (32). Another study including 273 critically ill patients with sepsis revealed that the concentration of serum suPAR is higher in these patients compared with that in healthy controls, and the AUC for sepsis prediction was 0.62 (12). Of note, suPAR may also be an emerging biomarker for patients with lung diseases. Previous studies have revealed that it is also highly expressed in patients with COPD, asthma and inhalation trauma (33-35). Considering that suPAR may be involved in the development of inflammatory diseases and lung injury-associated pathologies, it was hypothesized that suPAR may have an important role in the development of ARDS in patients with sepsis.

The present study demonstrated that suPAR is highly expressed in the serum of patients with sepsis with ARDS complications compared with patients diagnosed with sepsis but without ARDS, and it is an independent predictor of an elevated risk of ARDS in sepsis patients. ARDS may develop due to suPAR-mediated inhibition of neutrophil efferocytosis

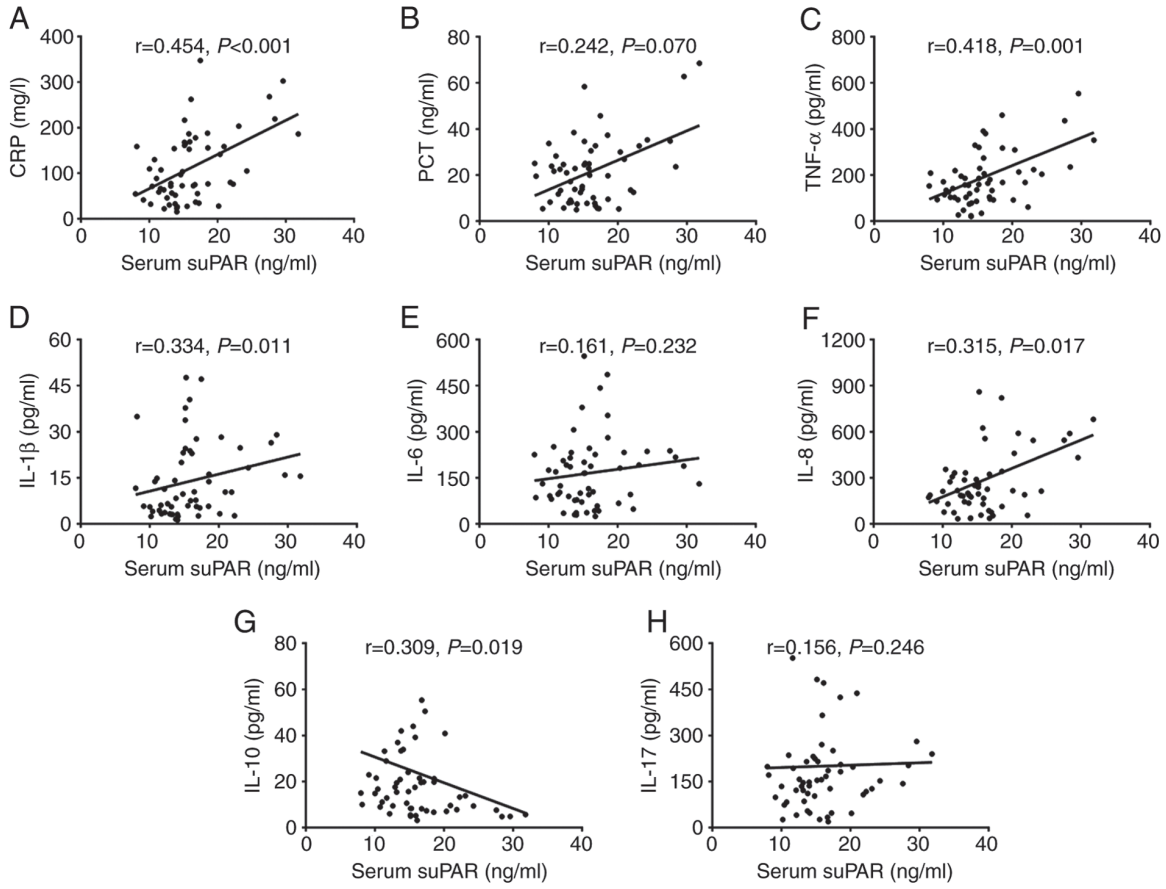

Figure 3. Correlation of the serum levels of suPAR with those of inflammatory factors (A) CRP, (B) PCT, (C) TNF-α, (D) IL-1β, (E) IL-6, (F) IL-8, (G) IL-10, (H) IL-17 in sepsis-ARDS patients. Correlation analysis was performed using the Spearman test. CRP, C-reactive protein; PCT, procalcitonin; TNF, tumor necrosis factor; IL, interleukin; suPAR, soluble urokinase plasminogen activator receptor.

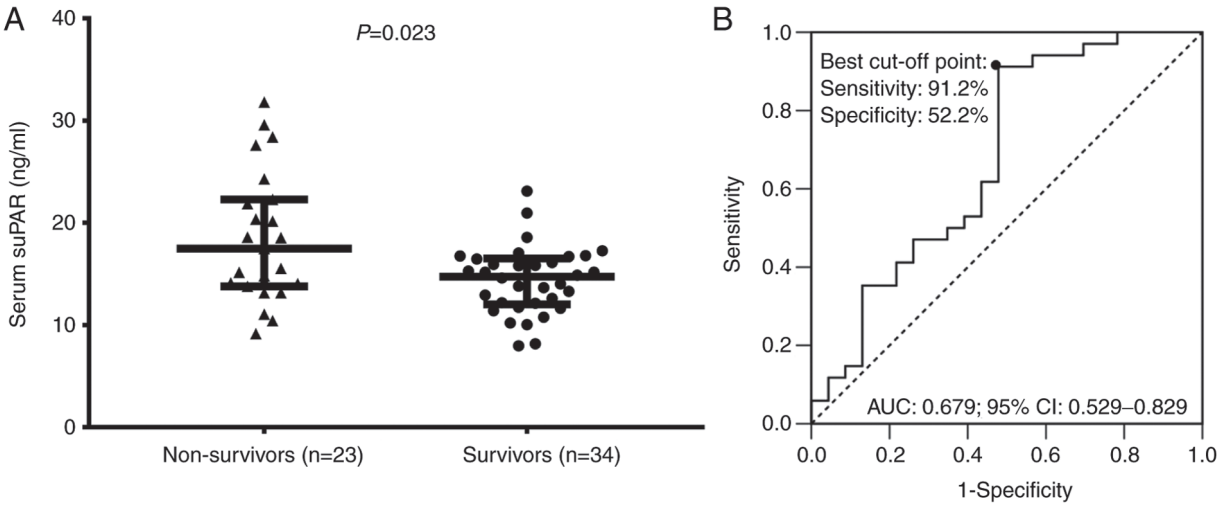

Figure 4. (A) Comparison of serum suPAR levels between non-survivors and survivors among patients with sepsis and ARDS. Non-survivors had higher serum suPAR levels than survivors. (B) Serum suPAR levels were a good prognostic predictor for survival in sepsis-ARDS patients, and the best cut-off was set at 17.38 ng/ml. SuPAR, soluble urokinase plasminogen activator receptor; ARDS, acute respiratory distress syndrome; AUC, area under curve.

and obstruction of apoptotic neutrophil engulfment, which may weaken the host defenses, thus leading to a higher risk of ARDS in patients with sepsis (25,26). In addition, suPAR may stimulate the recruitment of inflammatory cells (including monocytes and neutrophils), promoting inflammation, and accelerate coagulation via fibrinolytic cascades, achieved by activation of the plasminogen pathway. In turn, this process may induce acute lung injury and increase the risk of ARDS in patients with sepsis (27,28). However, the AUC value, as well as the sensitivity and specificity, were relatively low in the ROC analysis, and the predictive value of the clinical parameters was also low, and only three factors (age, smoking history and

COPD) were identified as good predictive factors for the risk of ARDS. Despite these low AUCs, as well as sensitivity and specificity values, the predictive value of suPAR for the risk of ARDS remained high. Therefore, studies with more patients and further subgroup analyses are required to explore which subgroup has relatively higher sensitivity and specificity values.

Several studies have investigated the correlation of suPAR with disease severity and inflammation in patients with inflammatory or lung diseases. In critically ill patients with sepsis, serum suPAR levels were observed to be positively correlated with acute physiology score (SAPS) II, APACHE II and SOFA scores (12). Another recent study also revealed that the levels of suPAR are associated with the SAPS II score, the APACHE II score and the concentration of pro-inflammatory factors (including TNF-α and CRP) in patients with sepsis (12). A study including 632 patients with ARDS revealed that higher suPAR levels are associated with more severe ARDS (14). The present study also indicated that serum suPAR levels were positively correlated with the APACHE II score, SOFA score and the levels of pro-inflammatory factors, including CRP, TNF-α, IL-1β and IL-8, in patients with sepsis and ARDS, which may be explained by the facilitation of the inflammatory response by suPAR. Therefore, due to suPAR-mediated inhibition of engulfment of apoptotic neutrophils and bacteria, multiple organ dysfunction (including lung, liver and kidney) may occur following an increase in suPAR levels, leading to severe inflammation and increased disease severity in patients with sepsis and ARDS. In addition, suPAR may regulate several genes or proteins (including β3 integrin and glycosyl-phosphatidylinositol protein), thus affecting the levels of inflammatory factors and contributing to increased inflammation and higher disease severity (36).

In clinical practice, biomarkers are used not only for diagnosing a pathological condition and distinguishing disease severity, but also for their ability to predict morbidity and clinical outcomes (37). In addition, overexpression of suPAR is associated with poorer prognosis in patients with systemic inflammation or infection (13,14,33,36,38). For instance, in sepsis patients, serum suPAR independently predicted a higher risk of 30-day mortality (13). As for ARDS patients, serum suPAR levels were increased in non-survivors compared to survivors, with serum suPAR exhibiting an AUC for predicting ARDS-associated mortality of 0.62 (14). These previous studies indicated that suPAR may have a potential role in predicting a poorer prognosis in patients with sepsis, with or without ARDS complications. In the present study, serum suPAR levels were also higher in non-survivors compared with those in survivors, and they were able to distinguish survivor from non-survivor patient groups. This further strengthened the possibility that suPAR is associated with higher disease severity, resulting in a poorer prognosis of patients with sepsis complicated with ARDS. Furthermore, higher suPAR levels may also be associated with higher treatment resistance, thereby contributing to the poorer prognosis. However, this possibility requires further study and validation. A previous study evaluated the last two uric acid measurements (taken prior to discharge or mortality) in patients with sepsis or ARDS, and revealed that uric acid, one of the major non-enzymatic anti-oxidants in the blood, serves as a useful biomarker predicting worse clinical outcomes of patients with sepsis or ARDS with an AUC of 0.714 (95%CI: 0.615-0.813) (37). In comparison, the prognostic value of suPAR in the present study was relatively lower with an AUC of 0.679 (95%CI: 0.529-0.829) in sepsis patients with ARDS, which may be due to different patients and the relatively small sample size of the present study. However, suPAR still had a certain prognostic value in sepsis patients with ARDS, and the results of the present study may provide a novel perspective and evidence regarding the role of suPAR in sepsis patients with ARDS.

The present study had certain limitations. First, the number of patients with sepsis complicated with ARDS was matched with that of patients diagnosed with sepsis but exhibiting no symptoms of ARDS. Thus, the incidence of ARDS was not properly evaluated. Furthermore, the sample size was relatively small, which may have decreased the statistical power of the results of the present study. Hence, additional studies with large sample sizes are required for further validation of the present results. In addition, all patients were from one single hospital, and studies including more patients from multiple centers may be beneficial to deepen the understanding of this pathology. The mechanistic roles of suPAR in sepsis complicated with ARDS remain to be fully elucidated, and further experiments are required. Finally, considering that suPAR is a soluble form of uPAR, the study of uPAR levels may also provide useful insight into the development of this pathology, and may also be a good biomarker for the prediction of clinical outcomes of patients with sepsis or ARDS.

In conclusion, the present study demonstrated that serum suPAR was an independent predictor of an elevated risk of ARDS in patients with sepsis, and it was positively correlated/associated with higher disease severity, higher inflammation and increased mortality in patients with sepsis complicated with ARDS.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

LY designed the study, DC, XW and JY performed the experiments, and XW and LY analyzed the data. DC, XW, JY and LY wrote the manuscript and revised it.

Ethics approval and consent to participate

The study was performed according to the established tenets in the Declaration of Helsinki and approved by the Ethics Committee of The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology (Wuhan, China). Written informed consent was obtained from all patients or their guardians.

Patient consent for publication

Not applicable.

Competing interest

The authors declare that they have no competing interests.

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