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Original Article

Correlation of plasma suPAR expression with disease risk and severity as well as prognosis of sepsis-induced acute respiratory distress syndrome

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Abstract: The aim of this study was to investigate the association of plasma suPAR expression with disease risk and severity as well as prognosis of sepsis-induced acute respiratory distress syndrome (ARDS). 162 ARDS patients were consecutively enrolled in this study and categorized into sepsis-induced ARDS group (N=104) or non-sepsis-induced ARDS group (N=58) according to the cause of ARDS. Disease severity was evaluated as mild, moderate and severe disease based on lowest PaO_2/FiO_2 ratio. Acute Physiology and Chronic Health Evaluation (APACHE) II as well as Sequential Organ Failure Assessment (SOFA) scores were calculated. Serum procalcitonin (PCT) was detected by electro chemiluminescence immunoassay, and plasma suPAR was determined by enzyme-linked immunosorbent assay. Sepsis-induced ARDS presented with elevated plasma suPAR level (P<0.001), serum PCT level (P<0.001), APACHE II score (P<0.001) and SOFA score (P<0.001) compared with patients with non-sepsis-induced ARDS. Plasma suPAR level was positively correlated with disease severity (P<0.001), PCT level (P<0.001), APACHE II score (P<0.001) and SOFA score (P<0.001). Among 104 sepsis-induced ARDS patients, 73 cases survived (survival group) while other 31 cased dies (non-survival group). Plasma suPAR level was greatly increased in non-survival group compared to survival group (P<0.001). Furthermore, ROC curve analysis illustrated that suPAR level presented good diagnostic value in predicting mortality with AUC 0.81 (95% CI: 0.73-0.89). Plasma suPAR is increased in sepsis-induced ARDS patients, and it correlates with higher disease severity and unfavorable prognosis.

Keywords: Sepsis, acute respiratory distress syndrome (ARDS), suPAR, disease severity, prognosis

Introduction

Despite of much improvements in the diagnosis and treatment of acute respiratory distress syndrome (ARDS), there remains a high morbidity and mortality in ARDS patients [1]. ARDS may occur in patients with direct or indirect lung injuries, such as bacterial or viral pneumonia, toxic inhalation, sepsis, major trauma, blood transfusion, among which sepsis is the most common cause [2, 3]. And sepsis-induced ARDS presents with increased disease severity, unfavorable recovery and elevated mortality compared to non-sepsis-induced ARDS [4, 5]. Thus investigation of biomarkers for diagnosis and prognosis of sepsis-induced ARDS is greatly needed.

Soluble urokinase plasminogen activator receptor (suPAR), as a soluble form of the urokinase-type plasminogen activator receptor (uPAR), is initially proposed as a marker associated with cancer [6]. Previous studies indicate that plasma level of suPAR illuminates a strong association with higher disease severity and increased mortality in critically ill patients [7, 8]. Another case-control study discloses that plasma suPAR is elevated in patients with sepsis compared to patients with systemic inflammatory response syndrome (SIRS) and controls, and it reveals a good value in distinguishing sepsis from SIRS and controls [9].

However, the correlation of suPAR expression in the development and progress of sepsis-induced ARDS remains unknown. Thus, the aim of this study was to investigate the association of plasma suPAR expression with disease risk and severity as well as prognosis of sepsis-induced ARDS.

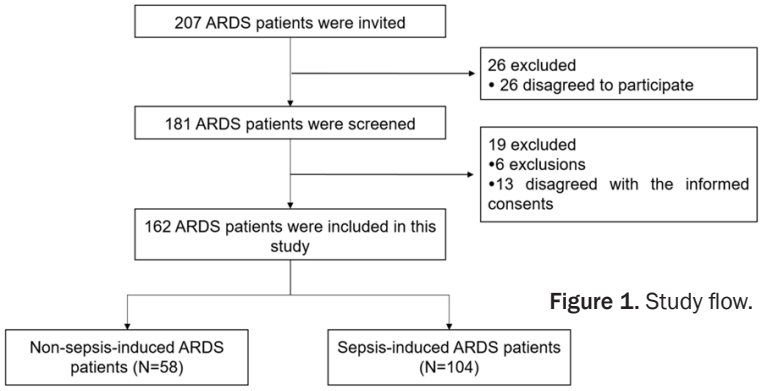

Figure 1. Study flow.

Materials and methods

Participants

162 ARDS patients between January 2013 and January 2016, in Wuhan Central Hospital, Tongji Medical College, Huazhong University of Science and Technology, were consecutively enrolled in this study. The inclusion criteria were: (1) Diagnosed as ARDS according to the criteria stated by Berlin definition [10]. (2) Age above 18 years. Patients who were confirmed to have malignant tumor, pulmonary tuberculosis, HIV, coagulation disorders (such as deep venous thrombosis or pulmonary embolism), previous immunosuppressive drugs application were excluded.

Ethics

This prospective cohort study was approved by the Research Ethical Committee of Wuhan Central Hospital, Tongji Medical College, Huazhong University of Science and Technology. This study was conducted in accordance with the Declaration of Helsinki. All participants or their guardians provided written informed consents before included.

Groups and measurements

Patients were categorized into two groups according to the cause of ARDS: sepsis-induced ARDS group (N=104) or non-sepsis-induced ARDS group (N=58). Blood samples were collected from all patients on the first day when they were admitted to ICU, and Acute Physiology and Chronic Health Evaluation (APACHE) II as well as Sequential Organ Failure Assessment (SOFA) scores were calculated at the same time. Disease severity were also evaluated as mild, moderate and severe disease in 104 sepsis-induced ARDS patients according to the assessment of lowest PaO_2/FiO_2 on admitted to the intensive care unit (ICU) within 24 h.

Laboratory procedures

Venous blood (2 mL) was collected into EDTA-containing tubes. Plasma was isolated and stored at -80°C until plasma suPAR concentrations were measured by the suPAR enzyme-linked immunosorbent assay (ELISA) Kit (ViroGates A/S, Birkerød, Denmark) following the manufacturer's instructions. An additional 2 mL of venous blood was taken into coagulant-containing tubes and then the serum was separated to test procalcitonin (PCT) using electro chemiluminescence immunoassay (ECLIA) (Cobas e411, Roche, Germany).

Statistical analysis

SAS 9.1 (SAS Institute Inc., USA) was used for statistical analysis. R Software 3.2.5 was used to draw figures. Data were mainly presented as mean ± standard deviation or median (1/4-3/4 quartile) for continuous variables, or number (percentage) for discrete data. T test, Wilcoxon rank sum test or Chi-square test was used for comparison between two groups. Kruskal-Wallis H rank sum test was used for comparison among three groups. Receiver operating characteristics (ROC) curves were constructed and the area under the curve (AUC) was calculated to assess the discriminative power of suPAR formortality in sepsis-induced ARDS patients. Spearman rank correlation test was used to examine the association between two variables. *P* value <0.05 was considered to be statistically significant.

Results

Study flow

As presented in **Figure 1**, 207 ARDS patients were invited initially, while 26 cases were excluded due to disagreement to participate, the remaining 181 ARDS patients were screened for eligibility, among which 19 were excluded

Table 1. Patients' characteristics

Parameters	Non-sepsis-induced ARDS (n=58)	Sepsis-induced ARDS (n=104)	*P* Value
Age (years)	56.60±1.75	57.24±3.64	0.134
Male/Female	41/17	69/35	0.570
Plasma suPAR (ng/ml)	9.80±0.96	14.05±4.52	<0.001
Serum PCT (ng/mL)	5.47±3.05	21.03±6.42	<0.001
APACHE II score	10.60±3.68	20.61±6.71	<0.001
SOFA score	6.58±1.20	11.18±4.10	<0.001

Data werepresented mean ± standard deviation or count. Comparison was determined by t test or Chi-square test. P<0.05 was considered significant. ARDS, acute respiratory distress syndrome; suPAR, soluble urokinase plasminogen activator receptor; PCT, procalcitonin; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment.

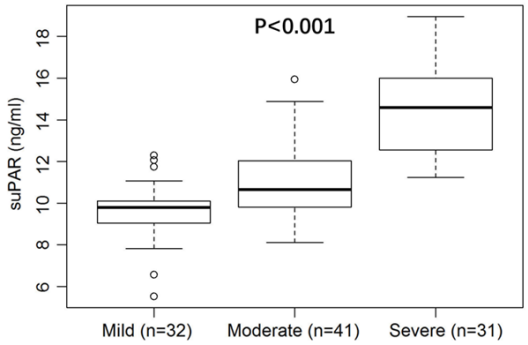

Figure 2. Correlation of plasma suPAR level with disease severity. Plasma suPAR level was increased in sepsis-induced ARDS patients with higher disease severity (P<0.001).

(6 cases for exclusions and 13 cases for disagreement with the informed consents), thus 162 ARDS patients were finally included in this study, and were classified into sepsis-induced ARDS group (N=104) or non-sepsis-induced ARDS group (N=58) according to the cause of ARDS.

Patient's characteristics

69 male and 35 female patients with age 57.24±3.64 years were included in sepsis-induced ARDS group, while 41 male and 17 female patients with age 56.60±1.75 years were included in non-sepsis-induced ARDS group, no difference of age (P=0.134) and gender (P=0.570) was discovered between two groups (**Table 1**). However, patients with sepsis-induced ARDS disclosed elevated serum PCT level (P<0.001), APACHE II score (P<0.001) and SOFA score (P<0.001) compared with patients with non-sepsis-induced ARDS, indicating that sepsis-induced ARDS presented with severer disease condition. As to suPAR expression, it was observed to be increased in sepsis-induced ARDS group than in non-sepsis-induced ARDS group (P<0.001).

Correlation of suPAR with disease severity in sepsis-induced ARDS patients

As presented in **Figure 2**, plasma suPAR level was positively correlated with disease severity in sepsis-induced ARDS patients (P<0.001). In addition, spearman rank correlation test was performed to explore the association of suPAR level with serum PCT level, APACH II score and SOFA score in sepsis-induced ARDS patients, which revealed that plasma suPAR was positively correlated with serum PCT level (R=0.769, P<0.001, **Figure 3A**), APACH II score (R=0.769, P<0.001, **Figure 3B**) and SOFA score (R=0.769, P<0.001, **Figure 3C**). These indicated the positive correlation of suPAR with disease severity indexes.

Correlation of suPAR with disease prognosis in sepsis-induced ARDS patients

Among 104 sepsis-induced ARDS patients, 73 cases survived and categorized into survival group while other 31 cased dies and categorized into non-survival group. Plasma suPAR level was discovered to be greatly increased in non-survival group compared to survival group (P<0.001, **Figure 4A**). Furthermore, ROC curves were performed, which illustrated that suPAR level presented good diagnostic value in predicting mortality with AUC 0.81 (95% CI: 0.73-0.89) (**Figure 4B**), and the sensitivity and specificity were 96.4% and 60.8% respectively at best cut-off value (suPAR level 14.30 ng/ml). The best cut-off value was defined as the point achieving maximum of sensitivity plus specificity.

Discussion

In this present study, we observed that: (1) Sepsis-induced ARDS patients presented with elevated plasma suPAR level compared to non-sepsis-induced ARDS patients. (2) Plasma suPAR level was positively correlated with dis-

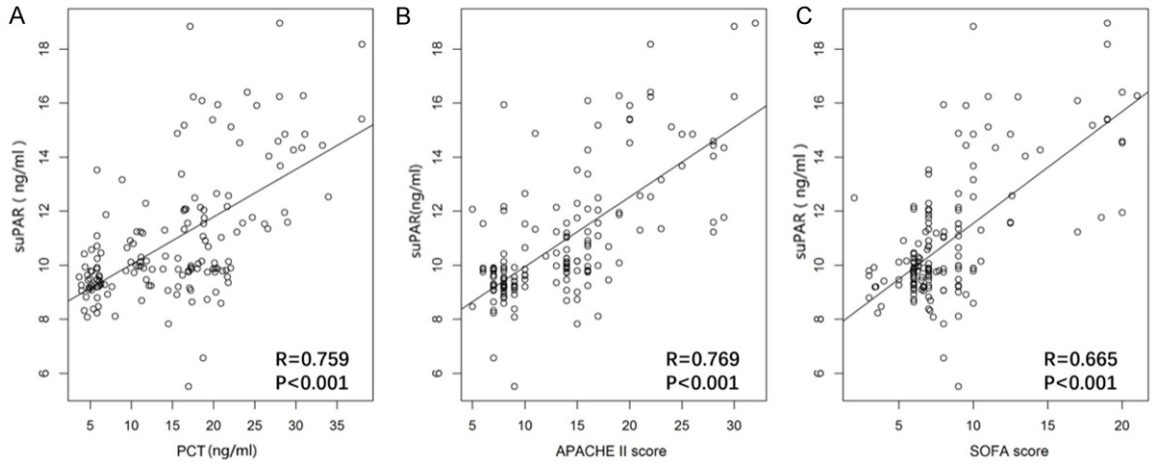

Figure 3. Correlation of plasma suPAR level with PCT, APACHE II score and SOFA score. Plasma suPAR level was positively correlated with PCT level (A), APACHE II score (B) and SOFA score (C) in sepsis-induced ARDS patients.

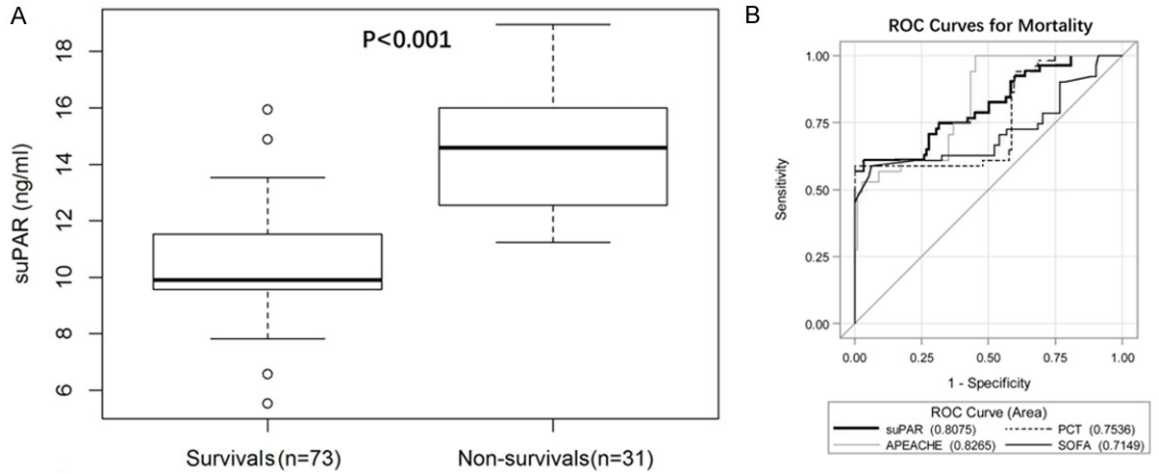

Figure 4. SuPAR correlated with higher mortality. In sepsis-induced ARDS patients, plasma suPAR level was increased in non-survivals compared with survivals (A), and ROC curve illuminated that suPAR level presented with good predictive value for mortality (B).

ease severity indexes in sepsis-induced ARDS patients. (3) Higher plasma suPAR was correlated with worse prognosis (increased death) in sepsis-induced ARDS patients.

Accumulating evidences illuminate that suPAR could be served as biomarker for disease monitoring and prognosis in sepsis [11, 12]. However, the investigation of suPAR function in ARDS is seldom reported. Only a prospective cohort study discloses that no significant difference in serum suPAR level between the ARDS and sepsis patientson admission was discovered, while patients with ARDS complicated with sepsis or induced by sepsis patients were not included [13]. In this present study, we observed that plasma suPAR level was increased in sepsis-induced ARDS patients compared to non-sepsis-induced ARDS patients. Although the pathophysiological differences between sepsis-induced ARDS and non-sepsis-induced ARDS remain largely unknown, the possible explanations for elevated suPAR level in sepsis-induced ARDS patients might be as follows: Previous studies observe that procalcitonin, soluble intercellular adhesion molecule-1, neopterin, soluble E-selection and Willebrand factor antigen levels were all increased in patients with sepsis-induced ARDS than patient withnon-sepsis-induced ARDS [14, 15]. In the meanwhile, pro-inflammatory cytokines such as interleukin-6, -8 levels are disclosed to be higher in patients with ARDS caused by sepsis and pneumonia [16]. Therefore, sepsis-induced

ARDS presents with a higher degree of acute inflammation, endothelial cells activity, and coagulation activation than non-sepsis-induced ARDS. In the meanwhile, suPAR, as a receptor released from cell-membrane-bound uPAR, has been illuminatedto be not only involved in cells adhesion, cells migration, and cells proliferation, but also in coagulation, fibrinolysis, inflammation and immune response [17]. Thus, an elevated suPAR level was found in sepsis-induced ARDS patients than non-sepsis-induced ARDS patients in this present study.

As to correlation of suPAR with disease severity in ARDS patients, a previous cohort study conducted in Netherland exhibits that plasma suPAR level on day 1 positively correlates with disease severity of ARDS [18]. Another cohort study completed in China illustrates that plasma suPAR level on admission is independently correlated with higher disease severity of ARDS [19]. In line with previous studies, we found plasma suPAR was positively associated with disease severity, serum PCT level, APACH II score and SOFA score, these might result from that suPAR expression reflects coagulation, fibrinolysis, inflammation and immune response in sepsis-induce ARDS which affects the disease severity a lot.

A previous cohort study in Netherland discloses that plasma suPAR expression is increased in non-survivors compared with survivors of ARDS patients, which also presents a good value in distinguishing non-survivors from survivors by ROC curve [18]. Another study in Italy shows that baseline suPAR level correlates with increased 7-day and 30-day mortality in patients with sepsis [20]. And a Chinese prospective cohort study reveals that plasma suPAR higher expression was independently correlated with unfavorable outcomes in patients with sepsis [12]. These indicate suPAR could predict disease prognosis in ARDS patients or sepsis patients, while no previous study investigates the prognostic role of suPAR in sepsis-induced ARDS. In this present study, we discovered that plasma suPAR was elevated in non-survivors compared with survivors of sepsis-induced ARDS, and it illuminated good value in predicting mortality in sepsis-induced ARDS by ROC curve analysis. These might be on account of that higher suPAR correlates with increased coagulation, fibrinolysis, inflammation and immune response as well as elevated disease severity indexes in sepsis-induce ARDS patients, leading to worse prognosis.

There were some limitations in this study. Firstly, the sample size was small, which might result in a significant bias due to patient selection and data collection as well as lack of statistical power. Secondly, only plasma suPAR was measured in this study, while suPAR is mainly produced locally in the lungs of ARDS patients, comparing the prognostic value and bioavailability of suPAR between plasma and bronchoalveolar lavage fluid would be of importance.

In conclusion, plasma suPAR is increased in sepsis-induced ARDS patients, and it correlates with higher disease severity and unfavorable prognosis.

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Disclosure of conflict of interest

None.

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