Levels of Soluble Urokinase Plasminogen Activator Receptor in Pediatric Lower Respiratory Tract Infections

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Background: Lower respiratory tract infections (LTRIs) are the most common cause of pediatric emergency department visits and are associated with significant morbidity and mortality. The aim of this study was to evaluate the soluble urokinase plasminogen activator receptor (suPAR) levels in pediatric patients with LTRIs and to investigate the correlation of suPAR with disease severity.

Methods: This is a prospective case–control study of children with LTRIs. Demographic data, diagnoses, vital signs, disease severity scores, length of hospital stay, laboratory findings, and viral polymerase chain reaction results for nasopharyngeal aspirates were recorded. Blood samples for suPAR were collected and assessed by enzyme-linked immunosorbent assay.

Results: There were 94 patients with LTRIs and 32 children in the control group. Patients were further subdivided into 2 groups based on diagnosis of acute bronchiolitis (n : 31, 33%) or pneumonia (n : 63, 67%). The median levels of suPAR were significantly higher in patients with LTRIs than in healthy controls (4.3 and 3.5 ng/mL, respectively; $P=0.003$). There was an association between suPAR levels and disease severity in pneumonia patients. suPAR values were higher in patients with severe pneumonia than mild pneumonia (5.5 and 3.6 ng/mL, respectively; $P<0.001$).

Conclusion: We have shown that suPAR levels increased in patients with LTRIs and suPAR values were higher in patients with severe pneumonia than mild pneumonia. Further studies with large case series are needed to clarify the role of suPAR levels in children with LTRIs.

Keywords: children, pneumonia, bronchiolitis, suPAR

Introduction

LOWER RESPIRATORY TRACT infections (LTRIs) are the most common cause of pediatric emergency department visits.¹ According to the World Health Organization, there are 156 million cases of pneumonia each year in children younger than 5 years and half of these cases require hospitalization.² Approximately 100,000 bronchiolitis admissions occur annually in the United States.³ Between 5% and 16% of LTRI patients are admitted to the intensive care unit and require mechanical ventilation.⁴ In young children, and especially those under 5 years of age, LTRIs cause 1.4 million deaths annually worldwide.⁵ LTRIs are an important cause of illness and a source of morbidity and mortality in childhood. It is very difficult to detect the causative pathogen in pediatric patients with LTRIs. Although direct culture from lung tissue is the gold standard for diagnosis, obtaining such samples requires invasive methods. For this reason, indirect methods are used. The incidence of bacterial coin-

fections in LTRIs has been reported as 29%–38%.^{6,7} This leads physicians to initiate empiric antibiotics, which causes antibiotic resistance and unnecessary patient costs. Therefore, there is a need for research to determine the disease severity and to distinguish viral and bacterial agents in pediatric patients with LTRIs.

Early recognition of severe LTRIs is essential in making management decisions and determining the prognosis. It is easier to achieve these aims in adults than in children. Using clinical symptoms and demographic characteristics, disease severity can be predicted in children,⁸ but it is quite difficult and not objective in daily practice. Using biochemical markers is more practical, objective, and sensitive in children with LTRIs.

Biochemical studies to determine the severity of LTRIs are increasing, and new prognostic and diagnostic biomarkers are being sought in the literature. One of these biomarkers is the soluble urokinase plasminogen activator receptor (suPAR). suPAR is the soluble form of the urokinase-type

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plasminogen activator receptor (uPAR/CD 87), which is connected to the surface of cells of the immune system, such as neutrophils, monocytes, and macrophages.^{9,10} suPAR plays an important role in cellular adhesion and migration, cell–stroma interaction, induction of chemotaxis, and proteolysis.¹¹ suPAR is released from uPAR after proteolysis and can be present in plasma, cerebrospinal fluid, urine, and saliva or pleural, peritoneal, and pericardial fluids.^{11,12} High suPAR levels are thought to be associated with immune system activation and inflammatory processes.^{13,14} There are many studies reporting high suPAR levels, such as in cases of viral, bacterial, and parasitic infections or in neoplastic diseases, and suPAR has been shown to have a prognostic value in some of these cases.^{11,15,16} In a study of critically ill patients in an intensive care unit, it was shown that suPAR levels were higher in patients with bacterial sepsis due to pneumonia than in those without sepsis, and these levels were related to the severity of the disease.¹⁷

In this study, we aimed to assess suPAR levels in children with LTRIs to investigate the correlation of suPAR with disease severity and the role of viral/bacterial agent differentiation in ill children.

Materials and Methods

Patients

This was a prospective case–control study of children with LTRIs in the Dokuz Eylül University pediatric emergency department between January 2016 and January 2017. The study protocol was approved by the local ethics committee. Patients who were diagnosed with LTRIs between the ages of 1 month and 18 years and whose parents signed an informed consent form were included in the study. The control group was selected from among children evaluated in the outpatient clinic of our hospital for routine well-child visits and none of them had any signs of infection or a history of chronic disease. Newborns were excluded, as were children with chronic lung disease, diabetes mellitus, organ insufficiency (cardiac, renal, adrenal, hypophyseal, or thyroidal), metabolic disorders, congenital or acquired immune deficiencies, and medical interventions (biologics or immunomodulators). We tested the suPAR level in children with LTRIs to investigate its correlation with disease severity and the role of viral/bacterial agent differentiation in ill children.

Study design

Patients were subdivided into 2 groups according to clinical and radiological findings as having acute bronchiolitis or pneumonia. Patients who had tachypnea, retractions, and expiratory wheezing or/and rales on physical examination were considered as having acute bronchiolitis¹⁸ and those with tachypnea, crackles on auscultation, and infiltration on chest X-ray were considered as having pneumonia.¹⁹ The Wang Respiratory Score was used to indicate disease severity in patients with acute bronchiolitis,²⁰ while patients were classified as having mild or severe pneumonia according to the British Thoracic Society guidelines.¹⁹ For differential diagnosis, the white blood cell (WBC) count, C-reactive protein (CRP) level, procalcitonin (PCT) level, blood gas measurements, and viral polymerase

chain reaction (PCR) results for nasopharyngeal aspirates were obtained from all patients. Patients who had lobar infiltration on chest X-ray and had negative viral PCR results were considered as having bacterial pneumonia. The demographic, clinical, and laboratory data of patients were recorded by a pediatric emergency fellow at admission to the emergency department. Vital findings were monitored by a nurse, and patients were evaluated by a pediatric assistant and a pediatric emergency fellow. The clinical data recorded were age, sex, prematurity, symptoms, vital signs, physical examination findings, disease severity score, treatment, and length of hospital stay. The recorded laboratory findings included pH, pCO₂, HCO₃, initial lactate of venous blood gas, WBC count, CRP level, PCT level, suPAR level, and viral PCR results of nasopharyngeal aspirates.

Enzyme-linked immunosorbent assay for suPAR

Venous blood samples for suPAR measurements were collected in plain tubes upon admission to the emergency department. The tubes were centrifuged at 2,000g for 10 min and serum samples with clots removed were added to Eppendorf tubes using plastic Pasteur pipettes. They were stored at –80°C until analysis. The total time from sample collection to analysis of results was 6 months. Serum suPAR levels (Cat. No. A001; ViroGates A/S, Birkerød, Denmark) were measured with an enzyme-linked immunosorbent assay kit based on the principle of sandwich enzyme immunoassay. The assays had a sensitivity of <0.1 ng/mL, detection range of 0.1–25 ng/mL, intra-assay coefficient of variation (CV) of <5%, and interassay CV of <10%.

Statistical analyses

We performed power calculations with the G*Power program, version 3.1.9.2 for Windows. All statistical analyses were performed using SPSS 22.0 (IBM Corp., Armonk, NY). Data are presented as medians with interquartile ranges (IQRs) and 25th–75th percentiles. Histograms were used to assess the normality of sample distributions. For comparison of groups, categorical variables were analyzed with the chi-square test (χ^2) or Fisher's exact test (when chi-square test assumptions did not hold due to low expected cell counts). Skewed variables were compared with the Mann–Whitney U test. Correlations between suPAR levels and clinical and laboratory markers were assessed with Spearman's rank correlation coefficient. Cutoff values were determined for pneumonia severity by using a receiver operating characteristic (ROC) curve. Values of $P < 0.05$ were considered significant.

Results

Patient characteristics

There were 94 patients with LTRIs and 32 children in the control group. The median ages were 9.5 months (IQR: 6.0–24.0) and 14 months (IQR: 8.5–24.0) for patients and controls, respectively. Fifty-four (57.4%) of the patients were male and 40 patients (42.6%) were female. The 2 groups did not display any notable difference in terms of age ($P = 0.108$) or sex distribution ($P = 0.075$). Twenty-four (25%) patients had a history of prematurity. Patients were

divided into 2 subgroups based on diagnosis: those with acute bronchiolitis (n : 31, 33%) and those with pneumonia (n : 63, 67%). According to the disease severity score, in the pneumonia group, 58.7% (n : 37) of the cases were mild and 41.3% (n : 26) were severe. In the other disease subgroup, 16 patients had moderate bronchiolitis and 15 patients had severe bronchiolitis. Among the patients, 79.7% were found to have infiltration on chest X-ray, and of those cases, 6.4% were lobar, 51% were consolidated, and 22.3% were interstitial. All patients with LTRIs had viral PCR testing of nasopharyngeal aspirates; 74 of these cases (78.7%) were found to be positive, while 20 (21.3%) were negative. Viral PCR results were positive for 93.5% and 71.4% of patients in the acute bronchiolitis and pneumonia groups, respectively. The most common positively identified microorganisms were respiratory syncytial virus (23.4%), rhinovirus (22.3%), metapneumovirus (12.8%), and adenovirus (6.4%). All blood cultures taken from patients with pneumonia before starting antibiotics were negative. Thirty-nine patients (41.5%) were treated with high-flow nasal cannula (HFNC)

and 6 (6.4%) of them were intubated and admitted to the intensive care unit. Fifty-seven (60%) of the patients were admitted to the hospital. Characteristics of patients are shown in Table 1.

Levels of suPAR and disease severity

The median suPAR value in patients with LTRIs was 4.3 ng/mL (IQR: 3.3–5.3), while in healthy controls it was 3.5 ng/mL (IQR: 2.8–4.0); this difference was statistically significant ($P=0.003$) (Fig. 1). The median suPAR level was 4.3 ng/mL (IQR: 3.5–5.1) in acute bronchiolitis patients and 4.3 ng/mL (IQR: 3.2–5.8) in pneumonia patients, respectively, and the difference was not statistically significant ($P>0.05$). Comparing the severity of disease in bronchiolitis patients, the suPAR level was not significantly different between moderate and severe cases ($P>0.05$). However, the median level of suPAR was 3.6 ng/mL (IQR: 3.0–4.7) and 5.5 ng/mL (IQR: 3.9–7.5) in patients with mild and severe pneumonia, respectively, and this was a statistically significant difference ($P<0.001$) (Fig. 2). Among patients with a history of prematurity, 58.3% had severe disease, and we found that suPAR levels were higher in this subset of patients.

The suPAR level was 4.3 ng/mL (IQR: 3.3–5.1) in patients with positive nasal PCR results and 4.3 ng/mL (IQR: 3.1–7.4) in those with negative results. There was no statistically significant difference ($P>0.05$). When comparing the severity of disease in viral PCR-positive patients, we found that rhinovirus-positive patients were more likely to have severe illness (57%) than the others, but the suPAR values were not statistically significantly different. When comparing the value of suPAR in hospitalized versus non-hospitalized patients, there was again no statistically significant difference between groups ($P>0.05$).

ROC analysis was performed and the value of the area under the curve (AUC) for suPAR levels in pneumonia cases was found to be 0.770 (95% confidence interval: 0.648–0.892, $P<0.001$). At a cutoff level of 3.9 ng/mL, the sensitivity and specificity of suPAR for severe pneumonia were 77% and 61%, respectively (Fig. 3). The AUC value for suPAR levels was greater than those for CRP and PCT levels, as shown in Fig. 4.

There was a positive correlation between suPAR levels and laboratory and clinical markers such as CRP, PCO₂, heart rate per minute, days of onset symptoms, duration of HFNC usage, and length of hospital stay, but there was a negative correlation between suPAR and capillary blood saturation, which may be related to disease severity. When multivariate logistic regression analysis was performed, the results were not statistically significant. There was no association between suPAR and WBC count, neutrophil count, PCT level, or blood gas parameters (Table 2).

Discussion

This study yielded 2 main findings. First, suPAR levels at admission were significantly elevated in children with LTRIs compared with healthy controls. Second, the values of suPAR were higher in patients with severe pneumonia than in those with mild pneumonia, suggesting that suPAR can discriminate severe pneumonia from mild pneumonia. This is important as it suggests that suPAR measurements

TABLE 1. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF PATIENTS

Characteristics	Overall ($n=94$)
Age, median (IQR), months	9.5 (6.0–24.0)
Gender, n (%)	
Male	54 (57.4)
Female	40 (42.6)
Prematurity, n (%)	24 (25)
Initial diagnosis, n (%)	
Acute bronchiolitis	31 (33)
Pneumonia	63 (67)
Disease severity, n (%)	
Acute bronchiolitis	
Moderate	16 (51.6)
Severe	15 (48.4)
Pneumonia	
Mild	37 (58.7)
Severe	26 (41.3)
Findings of chest X-ray, n (%)	
No infiltration	10 (10.6)
Hyperinflation	9 (9.6)
Interstitial	21 (22.3)
Consolidated	48 (51.1)
Lobar	6 (6.4)
Nasopharyngeal PCR results, n (%)	
None	20 (21.3)
RSV	22 (23.4)
Rhinovirus	21 (22.3)
Metapneumovirus	12 (12.8)
Adenovirus	6 (6.4)
Bocavirus	4 (4.3)
Influenza B	3 (3.2)
Coinfections	6 (6.4)
High-flow nasal cannula support, n (%)	39 (41.5)
Intubated, n (%)	6 (6.4)
Hospitalization, n (%)	57 (60)
Length of hospitalization, median (IQR), days	5.5 (4–7)

IQR, interquartile range; PCR, polymerase chain reaction; RVS, respiratory syncytial virus.

FIG. 1. suPAR levels in children with LTRIs and the control group. LTRIs, lower respiratory tract infections; suPAR, soluble urokinase plasminogen activator receptor.

can lead to identification of disease severity in pneumonia cases.

Levels of suPAR have been studied in many infections and diseases, including sepsis, systemic inflammatory response syndrome, tuberculosis, and HIV, and they were found to be high.^{21–23} However, studies in the literature demonstrating the role of suPAR in pediatric patients are limited. Wrotek et al. reported that suPAR levels were higher in children with community-acquired pneumonia than in healthy controls and they found a correlation between higher suPAR levels and CRP and PCT levels.²⁴ However, suPAR has not yet been studied in all types of LRTIs, and this is one of the few studies evaluating the role of suPAR in pediatric patients with LTRIs. In this study, we found that suPAR levels were increased in patients with LTRIs. We think that this finding suggests that suPAR levels are related to the inflammatory process.

A study of adult patients with bacteremia showed that median suPAR levels were markedly higher compared with values in healthy individuals.²⁵ However, Kofoed et al. showed that serum suPAR values do not help in differentiating bacterial from nonbacterial causes of inflammation and that the utility of suPAR as a single marker is poor.²⁶ In our study, suPAR values were not different between bronchiolitis and pneumonia cases or between nasal PCR-negative and PCR-positive patients. This is thought to be due to detection of a positivity rate of 80% for viral agents in our patients. suPAR has a specific affinity to pulmonary conditions. Its levels are independent of etiology and related to immunological system activation in the lung tissue. In this study, suPAR values did not help in distinguishing between moderate and severe disease in patients with acute bronchiolitis.

Early identification of patients with severe disease is important and a major goal for improving patient treatment

FIG. 2. suPAR levels in patients with mild versus severe pneumonia.

FIG. 3. Receiver operating characteristic curve analyses of suPAR levels.

in cases of pneumonia. It is difficult to identify patients at an increased risk of severe disease development. The prognostic value of suPAR has attracted attention in many studies. A study of critically ill children found that the admission suPAR level seemed to be a promising marker for diagnosis of sepsis and for prediction of mortality.¹⁷ In a study of patients with ventilator-associated pneumonia,

Savva et al. reported that higher suPAR values were observed in patients with severe sepsis and septic shock.²⁷ Loonen et al. found that suPAR and PCT levels were associated with severe disease development in adult pneumonia patients.²⁸ Wrotek et al. showed that there was a correlation between suPAR levels and fever, time for defervescence, and length of hospital stay.²⁹ In the present study, we found that suPAR levels were significantly higher among patients with severe pneumonia than those with mild pneumonia. Moreover, ROC analysis was applied to discriminate patients with severe pneumonia, and the AUC value for suPAR levels was found to be greater than those for CRP and PCT levels. This suggests that compared with traditional markers, suPAR can be a more useful biomarker in distinguishing disease severity in patients with pneumonia. There was also a positive correlation between suPAR and laboratory and clinical markers, which may be related to disease severity. The outcomes of our study suggest that suPAR may be an important biomarker in severe pneumonia cases, and elevated serum levels of suPAR may lead clinicians to administer immediate treatment and close follow-up in the pediatric emergency department.

There were some limitations to our study. First, this was a single-center study with few patients. Second, we had a positivity rate of 80% for viral agents, and viral/bacterial agents could not be distinguished in our patients. Third, our patients with acute bronchiolitis did not have mild disease and because of that the suPAR values may not have been able to determine the clinical severity in patients with acute bronchiolitis.

In conclusion, we have shown that suPAR levels are increased in patients with LTRIs. The suPAR values were higher in patients with severe pneumonia than mild pneumonia, and suPAR may be an important marker in determining the clinical severity of pneumonia in pediatric

FIG. 4. Receiver operating characteristic curve analyses of suPAR, CRP, and PCT levels. CRP, C-reactive protein; PCT, procalcitonin.

TABLE 2. SPEARMAN'S CORRELATION RANK COEFFICIENT (*r*) BETWEEN SOLUBLE UROKINASE PLASMINOGEN ACTIVATOR RECEPTOR AND SELECTED PARAMETERS

Characteristics	r	P
Fever (°C)	NS	NS
Heart rate (per minute)	0.27	0.008
Respiratory rate (per minute)	NS	NS
Capillary blood saturation (%)	−0.31	0.002
CRP (mg/dL)	0.20	0.04
PCT (ng/mL)	NS	NS
WBC ($\times 10^3/\mu\text{L}$)	NS	NS
pH	NS	NS
pCO ₂ (mmHg)	0.28	0.006
Lactate (mM)	NS	NS
Onset symptoms (days)	0.22	0.03
Duration of HFNC (days)	0.39	0.01
Length of hospitalization (days)	0.34	0.001

CRP, C-reactive protein; HFNC, high-flow nasal cannula; NS, nonsignificant; PCT, procalcitonin; WBC, white blood cell.

patients. Further studies with large case series are needed to clarify the role of suPAR levels in identifying viral and bacterial agents and disease severity in children with LTRIs.

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Author Disclosure Statement

All authors have no conflicts of interest or financial ties to disclose.

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