Exhaled breath analysis for the diagnosis of pneumonia

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SOLUBLE UROKINASE PLASMINOGEN ACTIVATOR RECEPTOR (SUPAR) FOR THE PREDICTION OF VENTILATOR-ASSOCIATED PNEUMONIA (VAP)

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**ABSTRACT**

Diagnosing ventilator-associated pneumonia (VAP) remains challenging. Soluble urokinase plasminogen activator receptor (suPAR) has prognostic value in critically ill patients with systemic infection. We hypothesized that plasma suPAR levels accurately predict development of VAP.

This observational, multicentre, prospective cohort study compared patients at risk for VAP with a control group. Plasma and tracheal aspirate samples were collected. Plasma suPAR levels were measured on the day of diagnosis and three days before.

The study included 24 VAP patients and 19 controls. The suPAR concentration measured three days before the diagnosis was significantly increased in VAP patients vs. matched samples of non-VAP patients \( (p=0.04, \text{AUROCC 0.68; 95%-CI: 0.52-1}) \). Similar results were found on the day of diagnosis \( (p=0.01, \text{AUROCC 0.77; 95%-CI 0.6-0.93}) \). Plasma suPAR was significantly higher in deceased patients \( (p<0.001, \text{AUROCC 0.79; 95%-CI 0.57-1}) \). Combining suPAR with CPIS, CRP and/or PCT led to a significantly increased discriminative accuracy for predicting VAP and an increased specificity.

SuPAR can be used to diagnose VAP with a fair diagnostic accuracy and has a moderate prognostic accuracy to be used in critically ill ICU patients. Its performance improves when added to other clinically available biomarkers (CRP, PCT) or scoring systems (CPIS, SOFA).
INTRODUCTION

Ventilator-associated pneumonia (VAP) is accountable for approximately one third of nosocomial pneumonia cases, associated with a longer Intensive Care Unit (ICU) and hospital length of stay (LOS) and increased healthcare costs. VAP is associated with significant mortality, excess morbidity and an increased duration of mechanical ventilation.

Due to the absence of a clinically available gold standard, the diagnosis of VAP remains challenging. The clinician has to rely on clinical parameters and radiological, laboratory and microbiological results, which may take hours to days to become available. A prompter predictive test is urgently needed, enabling a more accurate prediction of pneumonia and thus limiting antimicrobial misuse.

Multiple biomarkers – measured in serum and in bronchoalveolar lavage fluid (BALF) – have been investigated for their diagnostic value in infections, e.g. sTREM-1, IL-1β and IL-8, C-reactive protein (CRP) and procalcitonin (PCT). As of yet, none of these biomarkers have been proven to have sufficient diagnostic or prognostic quality to be used in patients receiving antibiotic treatment for VAP. Soluble urokinase plasminogen activator receptor (suPAR) has become of interest as an inflammatory biomarker that seems to positively correlate with activity of the immune system and has been shown to have prognostic value in critically ill patients with systemic infection regarding mortality prediction. In patients with acute respiratory distress syndrome (ARDS) significantly higher suPAR plasma levels were found with increasing disease severity. In critically ill patients, higher plasma suPAR levels were associated with longer duration of mechanical ventilation and increased ICU LOS, a higher incidence rate of readmission and an increased mortality rate. In VAP and sepsis patients, suPAR has been shown to be an independent predictor of an unfavourable outcome.

We hypothesized that suPAR measured in plasma of critically ill patients can predict VAP three days before clinical symptoms occur and we postulate that we will confirm the prognostic value of suPAR for mortality and ICU LOS. For this purpose, we performed a post-hoc analysis of carefully defined VAP cases and matched controls recruited in the ‘BioVAP’ study.
METHODS

Study design and ethical approval
This was a post-hoc study of the investigator-initiated observational, multicentre, prospective ‘Biomarkers in the diagnosis and management of Ventilator-Associated Pneumonia’ (BioVAP) study\(^1\), a study that ran in the ICUs of four university teaching hospitals. The study was registered at www.clinicaltrials.gov (identifier: NCT02078999), and the study protocol was approved by the institutional review board and the local ethics committee of the four participating hospitals. Written informed consent was acquired from all patients or their legally authorized proxies.

Study population
Consecutive patients admitted to a participating ICU were screened for eligibility for recruitment over a three year period. Only the first ICU admission and the first VAP episode were included in the study. Patients were included when (1) they were on mechanical ventilation for >72 hours; (2) there were no signs of pneumonia on the chest radiograph at admission; (3) they had not been receiving antibiotic treatment within five days prior to admission to the ICU; (4) expected duration of mechanical ventilation was >72 hours and (5) on admission no antibiotics were prescribed by the responsible clinician (except for prophylactic purposes).

Exclusion criteria involved current or past participation in an intervention trial conflicting with the BioVAP study (e.g. studies into MV, antibiotic therapy or VAP prophylaxis), previous endotracheal intubation of more than 12 hours within 30 days prior to recruitment, BMI >40, age below 18 years, pregnancy, patients with known bronchiectasis, cystic fibrosis and/or witnessed pulmonary aspiration prior to or at intubation, and patients of whom informed consent was not obtained.

The control group consisted of ICU patients that were mechanically ventilated for more than seven days, but did not develop VAP. This cut-off was selected because it corresponds to the median day of VAP development for the cases.
Primary and secondary endpoints
The primary endpoint was the diagnostic accuracy of suPAR for the diagnosis of VAP. The secondary endpoints were the predictive accuracy of suPAR regarding mortality and ICU LOS.

Definition of VAP
VAP was defined as described elsewhere: a respiratory infection developing at least 48 hours after the start of invasive mechanical ventilation in patients that had no signs of pneumonia at time of tracheal intubation and without signs of pneumonia on their chest radiograph at admission to the ICU. The definition of VAP was either based on 1) clinical criteria (new or progressive pulmonary infiltrates on chest radiographs, together with at least two of the following: temperature >38°C or <36°C, white cell count >10,000/mm³ or <4000/mm³ or purulent sputum), or 2) a simplified clinical pulmonary infection score (CPIS) ≥6 (after 48 hours of mechanical ventilation). Pneumonia was microbiologically confirmed by the presence of at least one potentially pathogenic microorganism (PPM) in respiratory samples above certain predefined thresholds: for BALF samples above 10⁴ colony forming units (CFU)/mL, for sputum or tracheobronchial aspirate samples above 10⁵ CFU/mL.

Follow-up
Follow-up of patients was established up until the 21st day after ICU admission, the day of successful weaning and extubation, the day of an ICU-acquired infection different than VAP, or the day of clinical diagnosis of VAP. Death, ICU discharge and hospital discharge was assessed as well. On the 90th day after ICU admission a telephone interview was performed in order to assess outcome.

Sample collection and measurements
Blood samples were obtained from an arterial line once daily from the moment of ICU admission onwards and throughout the period of mechanical ventilation. SuPAR was measured in the samples taken on the day of diagnosis, as well as in the samples taken three days before diagnosis. For the non-VAP patients (i.e. the control group) samples were obtained in parallel: samples matched when they were collected after the same amount of days after exposure to the risk factor (i.e. start of mechanical ventilation).
The blood samples were collected using sterile Vacutainer tubes containing citrate and were centrifuged afterwards for 10 minutes at 4°C at 1800g. SuPAR detection was performed by enzyme-linked immunosorbent assay (ELISA) using the suPARnostic kit provided by ViroGates (Birkerød, Denmark), which can determine suPAR concentrations as ng/mL plasma.

A quantitative tracheal aspirate was obtained for all patients: the first sample was collected on ICU admission and subsequently twice a week (Mondays and Thursdays or Tuesdays and Fridays). These samples were used for microbiological confirmation of VAP.

**Statistical analysis**

Data are shown as medians with their interquartile ranges (IQRs). Plasma suPAR levels were compared between groups (patients who developed VAP versus those that did not develop VAP) using the nonparametric Mann-Whitney U test. This was done for plasma suPAR measured at the moment of diagnosis, as well as three days before the diagnosis. For the non-VAP patients matched samples were used, which were collected after the same amount of days after start of mechanical ventilation. The area under the receiver operating characteristic curve (AUROCC) was used to assess the discriminative ability, the sensitivity and the specificity of suPAR levels: an AUROCC of 0.6-0.7 was considered as poor; 0.7-0.8 as fair; 0.8-0.9 as good and 0.9-1.0 as excellent. The default “delong method” in the roc.test function in R statistics was used to compare AUROCCs. A p-value <0.05 was considered statistically significant. Linear regression was performed to assess the relation between hospital LOS and ICU LOS. Statistical analyses were performed in R statistics via the R-studio interface.

**RESULTS**

Data and samples were collected from 43 patients (Table 1); a flowchart reflecting patient inclusion is shown in Figure 1. VAP was microbiologically confirmed in 24 patients, which were considered cases; 19 non-infected patients served as controls. Simplified Acute Physiology Score II (SAPS II) and Sepsis-Related Organ Failure Assessment (SOFA) scores were significantly higher between cases and controls. Also ICU LOS differed significantly in cases vs. controls (p<0.001), as well as the mortality rate (p=0.001).
Figure 1.

Flowchart reflecting patient inclusion.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Units</th>
<th>Control N = 19</th>
<th>VAP N = 24</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Mean - SD</td>
<td>49.89</td>
<td>53.96</td>
<td>0.53</td>
</tr>
<tr>
<td>Male</td>
<td>N - %</td>
<td>10</td>
<td>18</td>
<td>0.21</td>
</tr>
<tr>
<td>COPD</td>
<td>N - %</td>
<td>0</td>
<td>4</td>
<td>0.12</td>
</tr>
<tr>
<td>Diabetes</td>
<td>N - %</td>
<td>2</td>
<td>2</td>
<td>1.0</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>N - %</td>
<td>0</td>
<td>1</td>
<td>1.0</td>
</tr>
<tr>
<td>Heart failure</td>
<td>N - %</td>
<td>2</td>
<td>1</td>
<td>0.58</td>
</tr>
<tr>
<td>Liver failure</td>
<td>N - %</td>
<td>0</td>
<td>1</td>
<td>1.0</td>
</tr>
<tr>
<td>Renal failure</td>
<td>N - %</td>
<td>1</td>
<td>2</td>
<td>1.0</td>
</tr>
<tr>
<td>APACHE II</td>
<td>Median – [Q1-Q3]</td>
<td>22 [17.5-24.5]</td>
<td>25.5 [20.75-33]</td>
<td>0.11</td>
</tr>
<tr>
<td>SAPS II</td>
<td>Median – [Q1-Q3]</td>
<td>44 [23.5-50.5]</td>
<td>57 [46.75-71]</td>
<td>0.004</td>
</tr>
<tr>
<td>CPIS</td>
<td>Median – [Q1-Q3]</td>
<td>3 [1-4]</td>
<td>3 [1-3.5]</td>
<td>0.59</td>
</tr>
<tr>
<td>ICU LOS</td>
<td>Median – [Q1-Q3]</td>
<td>8 [6-10]</td>
<td>19.5 [14-23.75]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospital LOS</td>
<td>Median – [Q1-Q3]</td>
<td>21 [15.5-24]</td>
<td>30 [20-43.25]</td>
<td>0.08</td>
</tr>
<tr>
<td>ICU mortality</td>
<td>N - %</td>
<td>0</td>
<td>10</td>
<td>0.001</td>
</tr>
</tbody>
</table>

**Table 1.** COPD = Chronic Obstructive Pulmonary Disease; APACHE II = Acute Physiology and Chronic Health Evaluation II; SAPS II = Simplified Acute Physiology Score; WBC = white blood cell count; CPIS = Clinical Pulmonary Infection Score; ICU = Intensive Care Unit; LOS = length of stay; Q1 = first quartile / 25th percentile; Q3 = third quartile / 75th percentile
**Microbiology of VAP**

For the 24 VAP patients a total of 27 isolates were distinguished in the respiratory samples: methicillin-susceptible Staphylococcus aureus (MSSA) in 6 patients; Haemophilus influenzae (4 patients); Escherichia coli (3 patients); Klebsiella pneumoniae (3 patients); methicillin-resistant Staphylococcus aureus (MRSA) (2 patients); Pseudomonas aeruginosa (2 patients); Citrobacter spp. (2 patients); Streptococcus spp. (1 patient); Acinetobacter baumanii (1 patient); Moraxella catarrhalis (1 patient); Proteus spp. (1 patient); Enterobacteriaceae spp. (1 patient). The respiratory sample contained more than one pathogen in three cases.

**Accuracy of suPAR levels for prediction of VAP, three days before diagnosis.**

SuPAR levels were significantly higher in the plasma of confirmed VAP patients (median 6.2 ng/mL, interquartile range (IQR) 4.2–12.2) compared to controls (median 4.5, IQR 3.5–5.9) when measured three days before VAP diagnosis ($p=0.04$, AUROCC 0.68; 95%–CI: 0.52-1) (Figure 2).

![Figure 2.](image)

Difference in suPAR levels between diagnosed VAP patients and controls, measured three days before VAP diagnosis.
When measured three days before pneumonia diagnosis, the AUROCC for CPIS alone was 0.63 [95%-CI 0.46-0.8], \( p = 0.16 \). The combination of CPIS and suPAR led to an AUROCC of 0.68 [95%-CI 0.52-0.84]. The difference between the two ROCs was not significant (\( p = 0.54 \)). The net reclassification improvement was 0.06 (or 6%, \( p = 0.005 \)), resulting in a higher specificity. CRP measured three days before diagnosis showed an AUROCC of 0.68 [95%-CI 0.5-0.86], \( p = 0.04 \). The combination of CRP and suPAR had an AUROCC of 0.74 [95%-CI 0.56-0.92]. The difference between these two AUROCCs was not significant: \( p = 0.36 \). The NRI was 0.07 (7%, \( p = 0.17 \)), leading to an increased specificity. A weak positive correlation was found between suPAR and CRP, with a correlation coefficient of 0.21.

PCT had an AUROCC of 0.73 [95%-CI 0.55-0.91, \( p = 0.06 \)] when measured three days before pneumonia diagnosis. PCT combined with suPAR resulted in an AUROCC of 0.81 [95%-CI 0.64-0.97]. Again, the difference between the two AUROCCs was not significant (\( p = 0.29 \)). The NRI was 0.11 (11%, \( p < 0.001 \)), which led to a higher specificity. The combination of CRP, PCT and suPAR showed an AUROCC of 0.91 [95%-CI 0.77-1.0]. All AUROCCs are visualized in Figure 3.

A correlation coefficient of 0.1 was found between suPAR and the SAPS II score at admission. SAPS II showed an AUROCC of 0.57 for diagnosing pneumonia (\( p = 0.42 \)). The combination of suPAR and SAPS II resulted in an AUROCC of 0.71 [95%-CI 0.56-0.87]. The difference between these two AUROCCs was not significant (\( p = 0.18 \)). The NRI was 0.09 (9%, \( p = 0.002 \)), accompanied by an increased specificity.

**Accuracy of suPAR levels for diagnosis of VAP.**

Also on the day of diagnosis plasma suPAR levels were elevated in the VAP cases (\( p = 0.01 \), AUROCC 0.77; 95%-CI 0.6-0.93) (Figure 4), with a median of 6.6 ng/mL (IQR 5.7–7.7) for the VAP patients vs. 4.7 (IQR 3.6–6.3) for the controls. In deceased patients suPAR levels were significantly higher three days before VAP diagnosis (\( p < 0.001 \), AUROCC 0.79; 95%-CI 0.57-1).

On the day of VAP diagnosis, the ROC for the CPIS alone had an AUROCC of 0.85 [95% CI 0.74-0.96], \( p = 0.001 \). The AUROCC of the combination of CPIS plus plasma suPAR was 0.88 [95% CI 0.77-0.99]. The difference between both AUROCCs was not significant.
suPAR for the prediction of VAP

(p=0.66). When testing this difference using the net reclassification index (NRI), the net reclassification improvement was 0.07 (or 7%, p=0.005) when adding the suPAR values to the CPIS, increasing the sensitivity for predicting VAP.

Figure 3.

The ROC curves for (combinations of) CPIS, suPAR, CRP and PCT: measurements three days before VAP diagnosis. X-axis: false positive fraction; y-axis: true positive fraction.

CRP had an AUROCC of 0.64 [95%-CI 0.47-0.8, p=0.09], when measured on day of pneumonia diagnosis. CRP combined with suPAR resulted in an AUROCC of 0.82 [95%-CI 0.69-0.96]. No significant difference (p=0.09) was seen between these two AUROCCs. The NRI was 0.14 (14%, p=0.003), leading to an increased sensitivity. A similarly weak positive correlation was found between suPAR and CRP when measured on the day of VAP diagnosis, with a correlation coefficient of 0.23.
PCT showed an AUROCC of 0.71 [95%-CI 0.55-0.87, \(p=0.15\)]. The combination of PCT and suPAR had an AUROCC of 0.85 [95%-CI 0.73-0.97]. The difference between the two AUROCCs was not significant (\(p=0.19\)). An increased sensitivity was seen, with an NRI of 0.12 (12%, \(p=0.01\)). The combination of CRP, PCT and suPAR resulted in an AUROCC of 0.88 [95%-CI 0.78-0.99] (Figure 5).

The SOFA score and suPAR level – both determined at the day of VAP diagnosis – had a correlation coefficient of 0.15. The SOFA score could discriminate pneumonia cases from controls with an AUROCC of 0.83 [95%-CI 0.71-0.95, \(p=0.003\)]. SuPAR combined with the SOFA score led to an AUROCC of 0.88 [95%-CI 0.78-0.98]. The NRI was 0.07 (7%, \(p=0.02\)), resulting in a higher sensitivity.

**Figure 4.**

Difference in suPAR levels between diagnosed VAP patients and controls, measured on day of VAP diagnosis.
Figure 5. The ROC curves for (combinations of) CPIS, suPAR, CRP and PCT: measurements on the day of VAP diagnosis. X-axis: false positive fraction; y-axis: true positive fraction.

Predictive accuracy

Plasma suPAR levels appeared to be significantly different between alive and deceased patients, both when measured three days before diagnosis ($p=0.005$) and on day of pneumonia diagnosis ($p=0.04$) (Figure 6).

Figure 7 represents the association between measured plasma suPAR levels and ICU LOS, showing an odds ratio (OR) of 1.43 ($p=0.02$). The association between plasma suPAR and hospital LOS appeared not to be significant: OR 1.0 ($p=0.99$).
Chapter 7

**Figure 6.**

Difference in suPAR levels between alive and deceased patients, measured three days before VAP diagnosis.

**Figure 7.**

Association between plasma suPAR levels and ICU LOS.
DISCUSSION

Based on the results from this study we conclude that plasma suPAR levels are elevated three days before the diagnosis of VAP and have a moderate predictive accuracy. Classification improves when combined with CPIS, CRP and PCT. The diagnostic accuracy was also moderate and does not seem to be sufficient to justify further evaluation. We confirmed moderate prognostic accuracy of suPAR in critically ill ICU patients.

Our data suggest that a plasma biomarker may have limited value when used by itself, but when added to a clinical scoring system its performance can increase substantially. In general, biomarkers can be used for diagnostic purposes, response prediction, or therapeutic monitoring\(^26\). The relevance of plasma suPAR may lay in its additive predictive value on top of clinical judgement and/or in addition to a scoring system like CPIS or when used in conjunction with other biomarkers\(^27\). Procalcitonin (PCT) has been investigated extensively regarding its value to be used as a biomarker to guide antibiotic stewardship\(^28\)-\(^32\). As of yet PCT seems to have a poor predictive performance\(^12\) for VAP. Furthermore, the utility of CRP as a marker for VAP has not yet been demonstrated either\(^13\). Nevertheless, CRP has been used for indication of emerging VAP infection\(^34\) and was used to monitor response to antibiotic treatment in VAP patients\(^12\).

Irrespective of initiation of the appropriate treatment, suPAR remains stable in the systemic circulation of survivors as well as non-survivors within the first 10 days of disease course\(^19\). The elevated plasma suPAR concentration remains robust for days to weeks, with a half-life of >7–10 days\(^35\). Our results are in accordance with that: hardly any change was seen between the suPAR concentration three days before and on the day of VAP diagnosis, neither for the VAP patients, nor for the control group. As a result, plasma suPAR seems ineligible to evaluate therapy response\(^36\) or guide antibiotic stewardship in VAP. Nevertheless it could serve as a good early predictor for this disease and thus should be regarded as an extra indicator to distinguish patients at risk of developing VAP.

Serum suPAR has been shown to be associated with disease severity (ICU admission and/or mortality) in patients with community-acquired pneumonia (CAP)\(^37,38\) and VAP\(^20\). Also in systemic inflammatory response syndrome (SIRS), suPAR levels seemed to be important as a possible predictor of mortality\(^39\). In our cohort, plasma suPAR levels – when measured three days before VAP diagnosis – appeared to have a fair predictive value for
mortality in critically ill patients. Whilst there was no association between suPAR and hospital LOS, suPAR levels showed a good correlation with ICU LOS. Since the plasma concentration of suPAR reflects immune activation, a recent meta-analysis assessed the usefulness of suPAR for the prognosis of bacterial infections\textsuperscript{40}. After pooling the data, a fair performance was found for suPAR regarding mortality prediction, with an AUROCC of 0.77. Regarding potential of suPAR for diagnosing infection, the same meta-analysis\textsuperscript{40} found a pooled sensitivity and specificity of 0.73 and 0.79 respectively, accompanied by an AUROCC of 0.82. An earlier study\textsuperscript{27} investigating the diagnostic potential of suPAR for diagnosing VAP reported AUROCCs of 0.45 for suPAR levels on the first day of mechanical ventilation and 0.25 for suPAR level within 24 hours after VAP diagnosis. The discrepancy between those and the AUROCCs found in our study, might be partly explained by the different composition of the control group. The control group in the study by Sunnetcioglu et al. consisted of non-VAP patients which were matched based on age and gender. In our study the control group consisted of non-VAP patients who were on matched based on days of mechanical ventilation.

Within the pathophysiology of pneumonia, Gram negative or Gram positive bacteria induce an upregulated uPAR – from which suPAR derives – expression on monocytes and neutrophils, contributing to the host defense against pulmonary infection, especially demonstrated for respiratory infections caused by Pseudomonas aeruginosa\textsuperscript{41}. A reduced neutrophil migration and impaired phagocytosis in the lungs has been shown to occur in uPAR-knockout mice: thus patients with an impaired suPAR system may show decreased effect of the neutrophil-mediated bactericide reaction\textsuperscript{42}. Due to this potential affinity of suPAR to pulmonary processes in particular, it might be specifically interesting – according to our study results – to be added to currently available clinical biomarkers like CRP and PCT, or clinical scoring systems like CPIS and SOFA.

Our study investigated the use of suPAR concentrations measured in blood plasma. Alternatively, suPAR can be determined in various other body fluids, e.g. in urine, cerebrospinal fluid or cystic fluid. When measured locally in pleural effusion fluid, suPAR has shown to be potentially useful for exclusion of infection in ICU patients\textsuperscript{43}. Detected suPAR concentrations in saliva appeared not to be correlated to suPAR levels in simultaneously obtained plasma samples\textsuperscript{44}, indicating that care should be taken when directly comparing suPAR values acquired by analysis of fluid samples of different origin.
The strength of this study lays in the multicentre and prospective nature of its design, collecting data for six days from all non-infected patients that were mechanically ventilated for >72 hours. Limitations involve the small sample size of only 43 patients and the absence of a validation cohort. Another limitation is the absence of available suPAR values in patients who were (in part) clinically suspicious for VAP but who had VAP negative or sub-threshold microbiology results, since suPAR was only measured in patients who had positive ETA results. On the other hand, we could argue that the CPIS captures this clinical suspicion of VAP in a composite of clinical variables and we have been able to show the additive value of suPAR to this clinical score. Also the absence of a clinically available gold standard for VAP diagnosis is an important limitation of the study: microbiological examination of bronchoalveolar lavage fluid is currently the best available reference standard and is, as such, widely accepted by the research community. Future studies into the function of plasma suPAR as a diagnostic biomarker for VAP should use an independent cohort to validate our aforementioned findings.

To conclude, suPAR can be used to diagnose VAP with a fair diagnostic accuracy and has a moderate prognostic accuracy to be used in critically ill ICU patients. Its performance improves when added to other clinically available biomarkers (CRP, PCT) or scoring systems (CPIS, SOFA).
REFERENCES


