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ARTICLE

Elevated soluble urokinase plasminogen activator receptor (suPAR) predicts mortality in *Staphylococcus aureus* bacteremia

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Abstract The soluble form of urokinase-type plasminogen activator receptor (suPAR) is a new inflammatory marker. High suPAR levels have been shown to associate with mortality in cancer and in chronic infections like HIV and tuberculosis, but reports on the role of suPAR in acute bacteremic infections are scarce. To elucidate the role of suPAR in a common bacteremic infection, the serum suPAR levels in 59 patients with *Staphylococcus aureus* bacteremia (SAB) were measured using the suPARnostic™ ELISA assay and associations to 1-month mortality and with deep infection focus were analyzed. On day three, after the first positive blood culture for *S. aureus*, suPAR levels were higher in 19 fatalities (median 12.3; range 5.7–64.6 ng/mL) than in 40 survivors (median 8.4; range 3.7–17.6 ng/mL, $p=0.002$). This difference persisted for 10 days. The presence of deep infection focus was not associated with elevated suPAR levels as compared to patients with no deep infection focus. suPAR was found to be prognostic for mortality in receiver operator characteristic (ROC) curve analysis, which was not observed for serum C-reactive protein (CRP); the area under the curve (AUC) for suPAR was 0.754 (95% confidence interval [CI], 0.615–0.894, $p=0.003$) and for CRP, it was 0.596 (95% CI, 0.442–0.750, $p=0.253$). The optimal suPAR cut-off value in predicting 1-month mortality was 9.25 ng/mL. In conclusion, our study demonstrates that the new promising biomarker, serum suPAR concentration, was able to predict mortality in SAB.

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Introduction

Staphylococcus aureus is the second most common pathogen in bacteremic infections, and it still carries high mortality [1, 2]. The clinical course of *S. aureus* bacteremia (SAB) is determined by its complications, particularly by the development of deep infections and thromboembolic events [3–6]. Prognostic markers that would assist in the detection of complications or risk of mortality would be useful in order to allocate the use of limited healthcare resources to those who would benefit the most.

At least 170 different biomarkers have been evaluated for clinical use in bacteremic infections, but only a few are used in daily clinical practice [7]. Low protein C levels were shown to correlate to increased mortality in sepsis [8]. The use of protein C in diagnostics is helpful in the most severely ill patients [8]. Procalcitonin (PCT) has been shown to be useful in assessing the severity of sepsis. PCT has been found to be useful in discerning bacterial infections from other causes of inflammatory response [9]. C-reactive protein (CRP) is a part of an acute phase response [10] and it is used in the detection of sepsis or organ dysfunction [11]. In everyday practice, CRP changes have been used to observe the treatment response, while the decline of CRP level has been shown to be one of the earliest markers of improved condition [12]. Though CRP seems to be a good marker of systemic inflammation and an important clinical tool in severe infections [13], it has not been found to be helpful as a prognostic factor [14]. A biomarker that would be easy and rapid to analyze and

would predict complications and risk for mortality in severe bacteremic infections is still needed.

Soluble urokinase plasminogen activator receptor (suPAR) is a new promising biomarker. suPAR is the soluble form of the urokinase-type plasminogen activator receptor (uPAR/CD87), which is expressed on several different cell types, including monocytes, macrophages, and neutrophils [15, 16]. suPAR is derived from proteolytical cleavage and release from the cell membrane-bound uPAR [17]. suPAR is present in various sites, such as serum or plasma, urine, and cerebrospinal fluid [18–20]. Elevated suPAR levels have been shown to reflect the level of inflammation and immune activation [21, 22], and have been associated with poor prognosis in a number of chronic infectious diseases, such as HIV [23], tuberculosis [24], and in certain types of cancer [24–26].

Plasma suPAR levels might be useful also in acute infections, although the exact biochemical and molecular mechanisms of its function have not yet been described in detail [27]. uPAR/CD87 has been released in patients with urosepsis [28]. Elevated plasma suPAR levels ≥10.1 ng/mL on admission have been detected to be markers of poor prognosis in pneumococcal bacteremia [29]. In *Plasmodium falciparum* malaria, the serum levels of suPAR were associated with the degree of parasitemia in children [30]. However, in systemic inflammatory response syndrome (SIRS), suPAR had only a limited value as a single marker in detecting bacterial causes from non-bacterial causes of inflammation [31].

The aim of the present study was to evaluate whether serum suPAR levels could be useful in the detection of complications like deep infection foci or risk for mortality in SAB by using a new commercially available assay to analyze plasma suPAR levels.

Patients and methods

Patient population

Patients with SAB and belonging to one of the three groups, (1) patients with fatal outcome, (2) patients with a deep infection focus, and (3) patients without deep infection focus, were included from a larger prospective study. The aim was to include at least 15 patients in each group where serum samples from the first 10 days after the positive blood culture for SAB were available (with the exception of deceased patients). In total, 59 numerically ordered patients were included for this study from only one study site, Helsinki University Central Hospital.

The original prospective study consisted of 430 patients with blood culture positive for *S. aureus* recruited consecutively from five university hospitals and seven tertiary care hospitals in Finland between January and May 1999 and between January 2000 and August 2002 [6]. The trial aimed primarily to examine the potential of two fluoroquinolones (trovafloxacin or levofloxacin) to reduce the high mortality and complication rates in SAB, when added to the standard treatment. The exclusion criteria have been published earlier in the original article [6]. Each patient was recruited into the study only once in order to avoid double inclusion in repeated bacteremia. The protocol was approved by the ethics committees of all study sites. Written informed consent was obtained from all patients or their representatives.

Definitions

Intravenous drug users (IDUs) were defined as patients who had injected drugs within the past 6 months before randomization based on a history taken on admission. SAB was hospital-acquired if the first positive blood culture was obtained ≥48 h after admission or the patient was a resident in a long-term care facility or had attended hemodialysis within the preceding two months. Prognosis or severity of underlying diseases were characterized as healthy, nonfatal, or ultimately or rapidly fatal disease according to the criteria of McCabe and Jackson [32]. Infection focus was documented by clinical, bacteriological, radiological, or pathological investigations. Intravenous catheter-associated bacteremia was defined using the guidelines of the Infectious Disease Society of America (IDSA) [33]. Deep infection focus was classified as endocarditis, pneumonia, deep-seated abscess, osteomyelitis, septic arthritis, meningitis, septic thrombophlebitis, mediastinitis, urinary tract infection, infection of a prosthetic device, or recurrent SAB, as described in our previously published article [34]. Altered mental status was classified as unconsciousness or severe confusion.

Analytical methods

The serum samples were drawn on average on the third, fourth, or tenth day, and one month after the first positive blood culture and stored frozen at −70°C until analyzed. The mean time interval from the blood culture to the first suPAR sample collection was three days (standard deviation [SD] 1.1; range 2–5 days). The suPAR level was measured using the suPARnostic™ kit (ViroGates, Copenhagen, Denmark) (V-suPAR), as described in detail elsewhere [31]. The kit comes with catching monoclonal antibody pre-coated plates and a horseradish peroxidase (HRP)-labeled detection monoclonal antibody, which is added to the sample dilution buffer. Then, 25 μl of sample is mixed with 225 μl of dilution buffer and 100 μl in

Table 1 Characteristics and underlying diseases of 59 patients with *Staphylococcus aureus* bacteremia (SAB) grouped according to outcome as fatal and as patients with and without a deep infection focus

Characteristics	Total, n=59	Fatalities, n=19	Deep infection focus, n=25	No deep infection focus, n=15	p-value[d]
Age >65 years	48%	74%***	28%	47%	0.012
Male sex	59%	68%	60%	47%	0.444
Predisposing factors					
Hospital-acquired	68%	74%	56%	80%	0.238
Prosthetic or intravascular device	41%	53%	40%	27%	0.315
Central intravenous catheter	33%	21%	12%	40%	0.121
Previous surgery[a]	19%	11%	12%	40%	0.051
Corticosteroid use ≥1 month	14%	26%	8%	7%	0.169
Alcohol abuse	14%	26%	8%	7%	0.147
Intravenous drug abuse[b]	12%	0	24%*	7%	0.042
Immunosuppressive therapy	10%	16%	4%	13%	0.400
Underlying diseases					
Coronary artery disease	36%	53%	24%	33%	0.147
Chronic renal failure	26%	26%	16%	40%	0.245
Diabetes	24%	16%	24%	33%	0.386
Chronic lung disease[c]	22%	21%	16%	33%	0.657
Malignancy	19%	21%	12%	27%	0.494
Autoimmune disease	14%	16%	12%	13%	0.937
Hepatic cirrhosis	3%	11%	0	0	0.622
HIV	3%	0	4%	7%	0.558
McCabe's classification					
Ultimately or rapidly fatal	56%	74%***[†]	28%	33%	0.007

[a] During the 3 months preceding the positive blood culture

[b] During the 6 months preceding the positive blood culture

[c] Chronic obstructive pulmonary disease, bronchial asthma, or other pulmonary disease

[d] Kruskal–Wallis test

***p<0.01 versus deep infection focus, Mann–Whitney U-test

*p<0.05 versus deep infection focus, Mann–Whitney U-test

[†] p<0.05 versus no deep infection focus, Mann–Whitney U-test

duplicates are added to the pre-coated plate and incubated for 1 h. Following washing, 100 µl of substrate is added for 20 min and the reaction stopped with 100 µl 0.5 M H_2SO_4. The plates are measured at 450 nM with a reference distance of 630 nM. The within-assay coefficient of variation (CV) was 3.4% and the inter-assay CV was 4.11%. The CVs were comparable to those reported in the manufacturer's kit insert of 2.7% and 3.0%, respectively.

Serum concentrations of CRP were measured in the study site laboratory by standard laboratory methods. The serum or plasma (use of plasma instead of serum commenced 18.3.2002) was subjected to automatic immunoturbidimetric analysis using the analyzers 917 or Modular PP Analyzer (Hitachi Ltd., Tokyo, Japan) and Tina-quant CRP reagents (Roche Diagnostics). The normal value of CRP concentration was <10 mg/L for both methods.

Statistics

Statistical analyses were performed using SPSS® version 17.0 (SPSS Inc., Chicago, IL, USA). The associations between categorical variables were analyzed by the χ^2-test or Fisher's exact test, as appropriate. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated in order to estimate the significance of differences in the groups. Non-parametric comparisons between groups were done using the Kruskal–Wallis H- and the Mann–Whitney U-tests. In the multivariate logistic regression analysis, covariates were added in a stepwise method in the order of strength of their association with the outcome variable. When a new explanatory variable was shown to contribute to the variance, its influence on the variables already in the model and possible collinearity with them was assessed. All

Table 2 Median serum soluble urokinase plasminogen activator receptor (suPAR) levels (range) ng/mL in three groups of patients with SAB

Day	Fatalities	N	Deep infection focus	N	No deep infection focus	N	p^1
			p=0.001				
3	12.3 (5.7-64.6)	19	7.9 (5.0-16.3)	25	9.2 (3.7-17.6)	15	0.005
			p=0.017				
			p=0.001				
4	11.5 (4.7-20.6)	18	6.6 (2.5-15.2)	25	7.3 (3.4-14.9)	15	0.003
			p=0.002				
			p=0.001				
10	11.8 (6.1-17.8)	16	6.1 (3.0-17.3)	20	7.5 (2.3-14.9)	14	0.001
30	12.4 (11.8-12.9)	2	6.1 (1.8-18.7)	23	8.2 (7.6)	13	0.174

Day is the mean time from the first positive blood culture for *S. aureus* (min.–max 2–7 days, SD 1.1)
[1] p-value of the Kruskal–Wallis test. In the pairwise comparison, p-value of the Mann–Whitney U-test

tests were two-tailed and $p<0.05$ was considered as significant.

Results

Patients were divided into three groups, i.e., those with a fatal outcome (n=19) and those with a verified deep infection (n=25) and without deep infection focus (n=15) (Table 1). All deceased patients also had a deep infection focus: they differed from the other groups by being significantly older and more often having a fatal underlying disease, and none of them were IDUs (Table 1).

The serum suPAR levels were significantly higher in patients who died compared to the two groups of surviving patients on the third, fourth, and tenth days after the first positive blood culture for *S. aureus* (Table 2, Fig. 1a). No difference was observed in the serum suPAR concentrations between surviving patients with a deep infection focus or without it. In addition, no differences in suPAR levels between any patient groups were found one month after the bacteremic event. However, at this time point, there were only two patients left in the patient group with fatal outcome.

To investigate the value of suPAR as a prognostic marker for fatal outcome, the patient material was dichotomized based on the one-month survival. The suPAR levels on days three, four, ten, and 30 were compared according to survival. On day three, the median suPAR level of the fatalities was significantly higher (12.3 ng/mL; n=19, range 5.7–64.6 ng/mL) than the median suPAR level of the survivors (8.4 ng/mL; n=40, range 3.7–17.6 ng/mL) (p=0.002) (Fig. 1b). The difference in suPAR levels remained significant for the entire first week: on day four, the median suPAR level of the fatalities was 11.50 ng/mL (n=18, range 4.70–20.60 ng/mL) and of the survivors, it was 7.1 ng/mL (n=40, range 2.50–15.20 ng/mL) (p=0.001). On day seven, the median suPAR concentration of the fatalities was 11.75 ng/mL (n=16, range 6.10–17.80 ng/mL) and of the survivors, it was 6.5 ng/mL (n=40, range 2.3–17.30 ng/mL) ($p<0.0001$).

To analyze possible confounding factors or selection bias in the patient material, we also analyzed associations of the patient characteristics and underlying diseases with the one-month mortality. Out of the patients with fatal outcome, 14 (74%) were >65 years old as compared to 14 (35%) survivors (p=0.011). Ultimately or rapidly fatal underlying diseases were found in 14 (74%) fatalities as compared to only 12 (30%) survivors (p=0.002). Differences in the

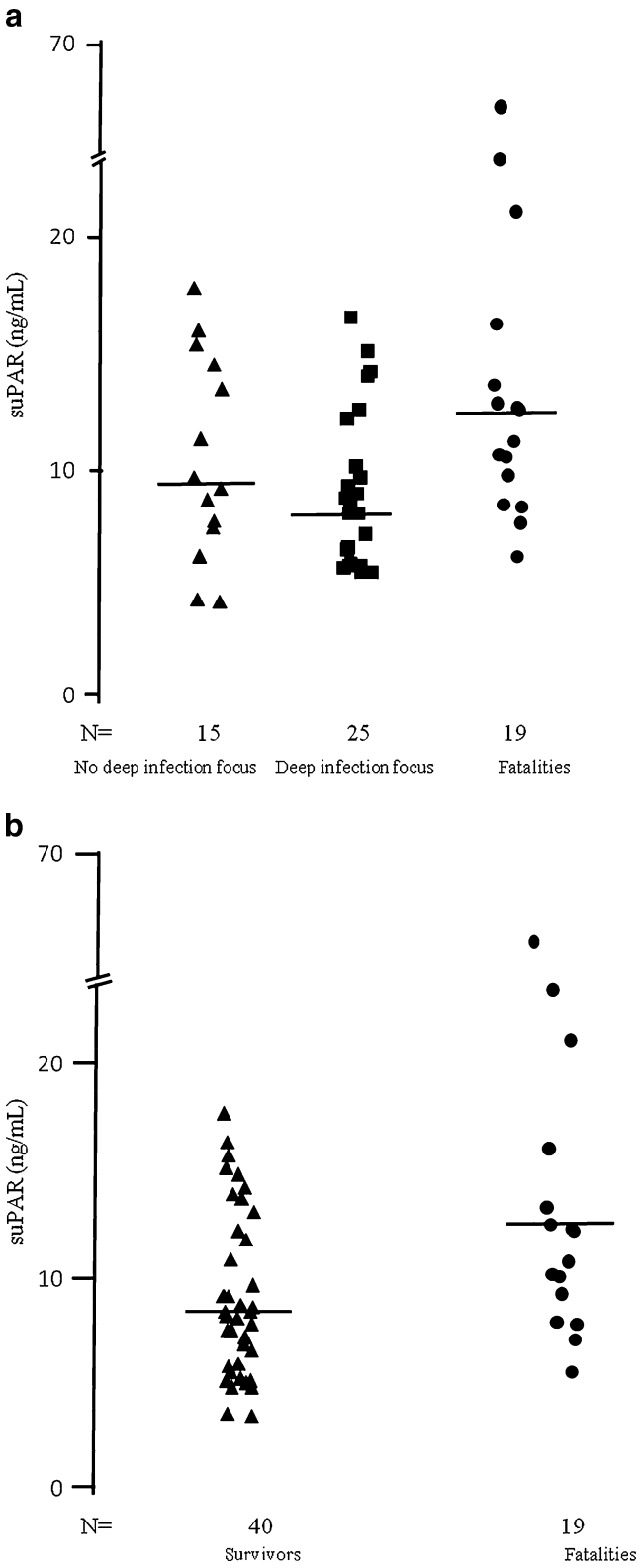

Fig. 1 Serum soluble urokinase plasminogen activator receptor (suPAR) concentrations in 59 patients on the third day after the first positive blood culture for *Staphylococcus aureus*. In **a**, the patients have been divided into three groups according to outcome: those with a fatal outcome during 30 days and those with and without a deep infection focus. In **b**, the patients are divided according to the 30-day mortality. The number of patients in each group is shown below at the bottom of the figure and the horizontal lines denote the median suPAR concentration

distribution of age >65 years (OR, 5.2; 95% CI, 1.6–17.4; p=0.011), underlying diseases (OR, 6.5; 95% CI, 1.9–22.2; p=0.002), and suPAR levels >9.25 ng/mL (OR, 7.8; 95% CI, 2.2–28.2; p=0.002) were all significantly associated with the mortality. Moreover, differences in the clinical parameters at the beginning of SAB (during the first three days after the first positive blood culture) were assessed based on the survival. Altered mental status during the first three days was associated with the mortality (OR, 4.1, 95% CI, 1.1–15.3; p=0.042). In addition, during the first three days, three patients among the fatalities were given treatment for hypotension, while none of the survivors needed it (p=0.030), but no OR was calculated due to the insufficient number of patients.

Receiver operator curve (ROC) characteristics were calculated for day three suPAR levels and compared with CRP in order to analyze the sensitivity of these markers as predictors of fatal outcome (Fig. 2). The area under the curve (AUC) of the ROC curve was significant only for suPAR (p=0.003). The optimal cut-off value for suPAR on day three was 9.25 ng/mL [sensitivity 0.79 (95% CI, 0.69–0.88), specificity 0.68 (95% CI, 0.61–0.75), and positive likelihood ratio 2.5].

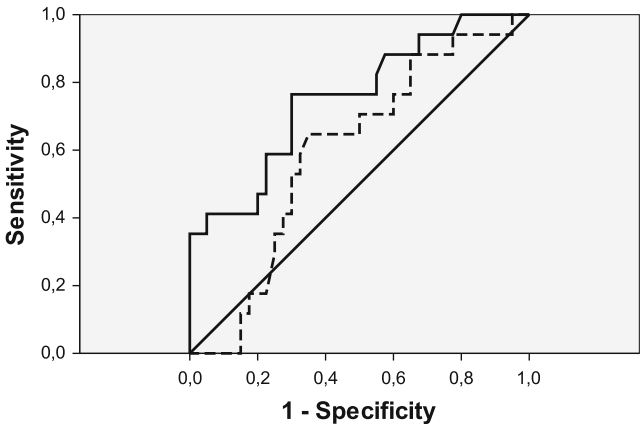

Fig. 2 Receiver operator characteristic (ROC) curves of serum suPAR and C-reactive protein (CRP) with respect to the one-month mortality in *Staphylococcus aureus* bacteremia. The ROC curve for suPAR is shown by the *continuous line* and for CRP by the *dashed line*. The area under the curve (AUC) (95% CI) for day three suPAR was 0.754 (0.615–0.894) (p=0.003) and for day three CRP, it was 0.596 (95% CI, 0.442–0.750) (p=0.253)

Table 3 Characteristics and underlying diseases of 59 patients with SAB stratified by serum suPAR levels using a cut-off value of 9.25 ng/mL on day three after the first positive blood culture

Characteristics	suPAR<9.25 ng/mL, *n*=31	suPAR>9.25 ng/mL, *n*=28	OR (95% CI)	*p*-value
Male sex	58%	61%	1.1 (0.4–3.2)	1.000
Age >65 years	32%	64%	3.8 (1.3–11.1)	0.019
Male sex	58%	61%	1.1 (0.4–3.2)	1.000
Predisposing factors				
Hospital-acquired	58%	79%	2.6 (0.8–8.4)	0.105
Prosthetic or intravascular device	45%	36%	0.7 (0.2–1.9)	0.597
Central intravenous catheter	10%	36%	5.2 (1.2–21.4)	0.026
Previous surgery[a]	23%	14%	0.6 (0.1–2.2)	0.513
Corticosteroid use ≥1 month	7%	21%	4.0 (0.7–22)	0.134
Alcohol abuse	7%	21%	4.0 (0.7–22)	0.134
Intravenous drug abuse[b]	23%	0%	0.8 (0.6–0.9)	0.011
Immunosuppressive therapy	10%	11%	1.1 (0.2–6.1)	1.000
Underlying diseases				
Coronary artery disease	29%	43%	1.8 (0.6–5.4)	0.291
Chronic renal failure	7%	46%	12.6 (2.5–63)	0.001
Diabetes	16%	32%	2.5 (0.7–8.5)	0.221
Chronic lung disease[c]	19%	25%	1.4 (0.4–4.8)	0.755
Malignancy	16%	21%	1.4 (0.4–5.3)	0.741
Autoimmune disease	7%	21%	4.0 (0.7–21.5)	0.134
Hepatic cirrhosis	0	7%	–	–
HIV	7%	–	–	0.493
McCabe's classification				
Ultimately or rapidly fatal	26%	64%	5.2 (1.7–15.8)	0.004
Deep infection focus[d]	71%	78%	0.7 (0.2–2.2)	0.561

[a] During the 3 months preceding the positive blood culture

[b] During the 6 months preceding the positive blood culture

[c] Chronic obstructive pulmonary disease, bronchial asthma, or other pulmonary disease

[d] Presence of deep infection focus in the beginning of the SAB

In the multivariate binary logistic regression analysis for the one-month mortality, covariates tested in the same model were suPAR dichotomized at 9.25 ng/mL and the presence of cerebral symptoms on the first three days (Table 3). In this analysis, suPAR was found to be independently associated with the increased mortality (OR, 8.0; 95% CI, 2.1–30.5; $p=0.002$), while presence of cerebral symptoms was not (OR, 4.3; 95% CI, 1.3–13.9; $p=0.059$). Other factors showing an association with the one-month mortality were age >65 years and ultimately or rapidly fatal underlying disease according to McCabe's classification. However, both age and fatal underlying diseases were collinear with dichotomized suPAR, and to avoid confounding in the analysis, they were not analyzed together with the suPAR. Due to the limited number of cases, the need for treatment for hypotension in the beginning of the SAB was omitted from the multivariate analysis.

Discussion

In the present study, serum suPAR levels were evaluated for the first time in SAB. Serum suPAR concentrations at the beginning of SAB were found to be significantly higher in fatalities than in survivors. This difference remained significant in repeated measurements on days three, four, and ten after the first positive blood culture. However, a deep infection focus was not associated with elevated suPAR levels on any day. Only elevated suPAR level significantly predicted mortality and it showed higher sensitivity and specificity than the CRP level.

Our findings are in accordance with the two previous studies on pneumococcal bacteremia which showed that suPAR concentrations were significantly higher in patients with fatal outcome as compared to surviving patients [29, 35]. In one of these studies, the CRP level had no predictive value for mortality [29], whereas in the other study, CRP

also predicted fatal outcome [35]. In these studies, suPAR levels were measured only once either on admission or 12–36 h after the positive blood culture was achieved. Our results clearly indicate that the predictive value of suPAR is not affected by the time point of measurement. Elevated suPAR levels during the first 10 days of SAB could, at any time, predict fatal outcome. The predictive value of suPAR measurement in gram-negative bacteria is still not known, but suPAR levels have been reported to be elevated approximately to the same level as in our study [28]. Together with this data, it indicates that high suPAR concentrations are predictive for fatal outcome in bacteremic gram-positive infections.

It was surprising that high suPAR levels were not associated with deep infection foci. This has not been investigated previously. In one study of pneumococcal bacteremia, patients with multiple infection sites were excluded [29] and in another study including patients with either pneumonia or meningitis, the possible impact of multiple infection sites to suPAR levels was not analyzed [35]. Deep infection foci seem to be very common in SAB and they were found in 84% of the patients in our study and with equally high occurrence in other studies as well [4, 6, 28]. The high prevalence of deep infection foci might be one reason why suPAR levels did not differ in patients with a deep infection focus or without. However, suPAR might not be diagnostic in finding deep infection foci and it has been claimed to be a more prognostic than diagnostic marker in infections [29, 31].

Elevated suPAR levels have been found to reflect the level of inflammation and immune activation [21, 22], but the mechanisms behind predicting effect for the mortality are not clarified. The fact is that high suPAR levels have been associated with poor prognosis also in more slowly progressing infections like HIV [23] and tuberculosis [24], or even in certain cancers [24–26]. The suPAR levels that discern the risk of mortality seem to be variable in different infections. In HIV, higher two-year mortality was attributed to values of suPAR >6 ng/mL [36]. In a large patient cohort from West Africa without any observed infection, a log-linear relationship was found between suPAR levels <15 ng/mL and increased mortality [37]. In SAB, we found that suPAR with a cut-off value of 9.25 ng/mL was predictive for mortality. This value is comparable to cut-off values in earlier pneumococcal studies, where cut-off values of 10 ng/mL and 10.3 ng/mL were presented [29, 35]. In our material, suPAR concentrations above 9.25 ng/mL had a specificity of 0.68 and a sensitivity of 0.79 for mortality, which lie within the acceptable range for a clinical measurement. suPAR concentrations below this had a negative predictive value (NPV) of 0.87, but levels above this limit had a positive predictive value (PPV) of only 0.54. We presented that individual variation in suPAR concentrations was quite wide, as evidenced by Fig. 1. Although high suPAR levels were predictive for mortality, many surviving patients also had high suPAR concentrations above the cut-off level, suggesting that high levels should be interpreted with caution in an individual patient. In our study, the patient samples were serum instead of plasma, which was used in previous studies. Serum has been shown to have slightly higher suPAR concentrations compared to plasma [38]. However, serum and plasma suPAR levels are strongly correlated, but the use of serum can partly explain the detected individual variations in suPAR levels.

suPAR measurements are shown to be higher in older persons [39] and this correlation was confirmed in the present study. Patients over 65 years of age had significantly higher suPAR levels than younger patients. We found that advanced age >65 years and, also, the presence of fatal underlying diseases were strongly correlated to higher mortality. Both of these factors have also previously been related to higher mortality in SAB [3, 5]. However, we could not clarify the relationship between age and underlying diseases on suPAR levels as predictors for mortality because these parameters could not be analyzed together in a multivariate analysis due to linkage. Females have been shown to have slightly higher suPAR concentrations as compared to males, which was not observed in our study [40].

In conclusion, we demonstrated that the new promising biomarker, serum suPAR concentration, was able to predict mortality in SAB. The results encourage future studies where the mechanism of this association could be clarified and the mortality predictive association confirmed in a larger patient cohort.

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