LIUKOISEN UROKINAASITYYPPISEN PLASMINOGEENIAKTIVAATTORIN RESEPTORIN (SUPAR) PLASMAPITOISUUDEN MERKITYS ENSIAVUN INFEKTIOEPÄILYPOTILAILLA: PROSPEKTIIVINEN KOHORTTITUTKIMUS

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TARKKA MAIJA: LIUKOISEN UROKINAASITYYPPISEN PLASMINOGEENIAKTIVAATTORIN RESEPTORIN (SUPAR) PLASMAPITOISUUDEN MERKITYS ENSIAVUN INFEKTIOEPÄILYPOTILAILLA: PROSPEKTIIVINEN KOHORTTITUTKIMUS

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Avainsanat: bakteremia, suPAR, kuolleisuus

Tutkimuksen tarkoituksena oli selvittää millainen ennusteellinen merkkiaine plasman liukoinen urokinaasityyppisen plasminogeeniaktivaattorin reseptori (soluble urokinase-type plasminogen activator receptor, suPAR) on infektiopotilailla. Mielenkiinnon kohteena oli erityisesti suPAR:in yhteys baktereemisen infektion vaikeusasteeseen ja taudin ennusteeseen.

Tutkimusasetelmana oli prospektiivinen kohorttitutkimus. Potilasmateriaali kerättiin Satakunnan keskussairaalassa vuosina 2004-2005. Kohortti käsitti yhteensä 539 päivystyspotilasta, joille lääkäri oli asettanut työdiagnoosiksi jonkin infektiotaudin.

Kohortti jaettiin viiteen erilaiseen ryhmään: ryhmän 1 (n=59) potilailla ei ollut bakteeri-infektiota tai yleistynyttä tulehdusreaktio-oireyhtymää (systemic inflammatory response syndrome, SIRS), ryhmän 2 (n=68) potilailla oli bakteeri-infektio mutta ei SIRS:iä, ryhmän 3 (n=54) potilailla oli SIRS mutta ei bakteeri-infektiota, ryhmän 4 (n=309) potilailla oli sepsis (SIRS ja bakteeri-infektio, mutta ei elinvauriota) ja ryhmän 5 (n=49) potilailla oli vaikea sepsis (SIRS, bakteeri-infektio ja elinvaurio). Plasman suPAR-pitoisuus määritettiin kaupallisella entsyymi-immunologisella menetelmällä (enzyme-linked immunosorbent assay, ELISA; suPARnostic® Standard Kit; ViroGatesA/S, Birkerød, Denmark) sairaalaan tulovaiheessa otetusta ensimmäisestä näytteestä (1 näyte/potilas). Näytteistä olivat tiedossa myös prokalsitoniini (PCT), C-reaktiivinen proteiini (CRP) ja interleukiini-6 (IL-6) –pitoisuudet.

suPAR:in mediaanipitoisuudet ryhmissä 1-5 olivat 4,7; 5,0; 4,4; 4,8 ja 7,9 ng/ml ($p < 0.001$). Pitoisuudet olivat merkittävästi korkeampia seuranta-aikana menehtyneillä verrattuna selviytyneisiin (mediaani 8,3 vs. 4,9 ng/ml, $p < 0.001$). 28 päivän kuolleisuus oli 6,1%. suPAR:in herkkyys ja tarkkuus kuolleisuuden ennustamisessa olivat 76 % ja 69 % (raja-arvolla 6,4 ng/ml). Vaikean sepsiksen ennustamisessa vastaavat luvut olivat 67 % ja 72 % (raja-arvolla 6,6 ng/ml). suPAR oli tutkituista laboratoriomerkkiaineista paras

kuolleisuuden ennustaja kun taas vaikean sepsiksen ennakoimisessa PCT vaikutti olevan hieman suPAR:ia parempi. Muuttujien merkitsevyydet säilyivät myös erilaisissa monimuuttujamalleissa, joissa otettiin huomioon mahdolliset muut selittävät tekijät.

Tutkimus osoitti, että korkea suPAR-pitoisuus on riippumaton – ja mahdollisesti jopa kliinisesti käyttökelpoinen – taudin vaikeusastetta ja kuolleisuutta ennustava merkkiaine päivystyksen infektioepäilypotilailla. Jää nähtäväksi, voidaanko suPAR-määritystä käyttää yleisemminkin korkean riskin potilaiden tunnistamisessa.

Näiden syventävien opintojen tekijä on määrittänyt plasmanäytteistä suPAR-pitoisuudet, sekä osallistunut tulosten tilastolliseen analyysiin ja käsikirjoituksen kommentointiin. Tulokset on julkaistu Journal of Internal Medicine -lehdessä, ja yksi artikkelin kirjoittajista on Maija Tarkka.

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Soluble urokinase-type plasminogen activator receptor in patients with suspected infection in the emergency room: a prospective cohort study

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Abstract. Uusitalo-Seppälä R, Huttunen R, Tarkka M, Aittoniemi J, Koskinen P, Leino A, Vahlberg T, Rintala EM (Satakunta Central Hospital, Pori; Tampere University Hospital, Tampere; University of Tampere Medical School, University of Tampere, Tampere; Centre for Laboratory Medicine, Pirkanmaa Hospital District, Tampere; Turku University, Turku; Turku Univeristy Hospital, Hospital District of Southwest Finland, Turku; Turku University, Turku, Finland). Soluble urokinase-type plasminogen activator receptor in patients with suspected infection in the emergency room: a prospective cohort study. *J Intern Med* 2012; **272**: 247–256.

Objectives. The soluble form of urokinase-type plasminogen activator (suPAR) was evaluated as an early prognostic marker of sepsis in patients with suspected infection.

Design. A single-centre prospective cohort study.

Methods. The cohort comprised 539 patients in the emergency department with suspected infection: 59 without systemic inflammatory response syndrome (SIRS) and without bacterial infection (group 1), 68 with bacterial infection and without SIRS (group 2), 54 with SIRS and without bacterial infection (group 3), 309 with sepsis (SIRS and bacterial infection) and without organ failure (group 4) and 49 with severe sepsis (SIRS, bacterial infection and organ failure) (group 5). suPAR was measured on admission using a commercial solid-phase enzyme-linked immunosorbent assay.

Results. The median soluble form of the receptor (suPAR) concentrations in groups 1–5 were 4.7, 5.0, 4.4, 4.8 and 7.9 ng mL^{-1}, respectively ($P < 0.001$). The levels were significantly higher in nonsurvivors compared with survivors (8.3 vs. 4.9 ng mL^{-1}, $P < 0.001$) and in patients with severe sepsis (group 5) compared with those in the other groups (7.9 vs. 4.8 ng mL^{-1}, $P < 0.001$). Area under the receiver operating characteristics curve (AUC^{ROC}) for the prediction of case fatality was 0.79 (95% confidence interval [CI]: 0.72–0.86, $P < 0.0001$) and 0.75 for severe sepsis (95% CI: 0.68–0.81, $P < 0.0001$). At a cut-off level of 6.4 ng mL^{-1}, suPAR had 76% sensitivity and 69% specificity for fatal disease; at a cut-off level of 6.6 ng mL^{-1}, the sensitivity and specificity for severe sepsis were 67% and 72%, respectively. In multivariate models, high suPAR remained an independent predictor of case fatality and severe sepsis after adjusting for potential confounders.

Conclusions. A high suPAR level predicts case fatality and severe sepsis in patients with suspected infection.

Keywords: biomarker, case fatality, emergency room, infection, severe sepsis, suPAR.

Introduction

Early stratification of patients with suspected infection presents a serious clinical challenge in patients admitted to the emergency department. The definition of sepsis based on the criteria of systemic inflammatory response syndrome (SIRS) is internationally applied [1]; however, it has several limitations. SIRS criteria may be fulfilled in the case of nonbacterial conditions such as trauma, pancreatitis or viral infections. The range of useful prognostic biomarkers for the emergency department is narrow; therefore, further methods for the early aetiological and prognostic stratification of patients with suspected infection are eagerly awaited.

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Urokinase-type plasminogen activator receptor (uPAR) is a glycoprotein released during infection and inflammation [2]. It interacts with several molecules mediating immune system signals [2]. uPAR is upregulated in various cells, including neutrophils, macrophages, lymphocytes, endothelial cells and malignant cells in response to chemotaxis-inducing stimuli (e.g. interleukins) [2, 3]. uPAR and its ligand, urokinase plasminogen activator (uPA), promote the migration and adhesion of leucocytes by binding to β-integrins [2]. uPAR also has a pivotal role in cell proliferation, angiogenesis and fibrinolysis [4–6]. The soluble form of the receptor (suPAR) is formatted by proteases, which cleave uPAR from the cell surface [2]. Thus, plasma suPAR levels are believed to represent the degree of immunoactivation [7]. Elevated circulating suPAR levels have proved to be risk markers, even in the general population, of type 2 diabetes, cardiovascular disease, cancer and overall mortality, probably through low-grade inflammation [8].

In previous studies, plasma suPAR levels have been found to be increased in patients with bacteraemia [9], and high suPAR levels predict disease severity and outcome in various infections such as bacteraemia [10, 11], human immunodeficiency virus infection (HIV) [12, 13], bacterial meningitis [14] and active pulmonary tuberculosis [15]. High suPAR levels have been linked to admission to the intensive care unit (ICU) and overall survival in critically ill patients [7]. Plasma suPAR was found in a previous study to have only limited value for the diagnosis of bacterial infection [16].

The aim of this study was to assess the value of plasma suPAR in the stratification of patients admitted to the emergency department with suspected infection. We found that suPAR levels predicted outcome and severe sepsis in our large and unselected cohort.

Methods

Study population

Patients were recruited in Satakunta Central Hospital, a 350-bed secondary care hospital in western Finland serving the Satakunta Hospital District with a population of 240 000 inhabitants. This is the only hospital in the area with an emergency department and an ICU. We have published a previous study with data from this cohort [17]. The study was approved by the ethical review board of Satakunta Hospital District. Written consent was obtained from all patients or their close relatives.

The study included adult patients admitted to the emergency department with suspected infection, from whom a clinician decided to collect blood samples for blood culture. Enrolment took place over a 14-month period during 2004 and 2005. To ensure that written informed consent was obtained and interviews were conducted within 24–48 h, of admission, only patients admitted between 7.00 a.m. on a Sunday and 3.00 p.m. on a Wednesday were enrolled. Before initiating the study, a pre-evaluation of the target population was conducted to ensure the representativeness of the cohort. This assessment covered 1551 consecutive patients from whom blood had been collected in the emergency department for blood culture. The rate of positive blood culture in the pre-evaluation was 8.3% and of case fatality by day 28 after admission was 6.7%. No significant differences in age, gender, rate of positive blood culture or mortality were noted between patients admitted on study days and those admitted on other days, or between the study and the pre-evaluation populations.

Blood samples for the study were taken upon admission concurrently with the blood culture samples. Blood was collected into two 10-ml EDTA-containing tubes (plasma) and two 7-mL serum tubes (serum). The EDTA tubes were kept on ice until centrifugation. Plasma and serum were transferred in 1- to 2-mL aliquots to CryoPure® (Sarstedt, Germany) tubes. These were stored at −70 °C until required for assay.

A structured interview was carried out by the investigator or research nurse 24–48 h after admission. Highest body temperature, lowest blood pressure and highest pulse and respiratory rates were recorded daily on days 1–7. Symptoms and clinical signs, Glasgow coma scale, risk factors for sepsis, underlying diseases and diagnosis at admission were recorded, along with duration of stay in the ICU and in hospital. Potential organ failure (respiratory, cardiovascular, renal, haematological, hepatic or central nervous system), overall case fatality and sepsis-attributable case fatality were recorded. Final diagnoses, source of infection and trauma or other possible reasons for inflammation were obtained from medical records. Patients were followed up by telephone interview 3 months and 1 year after enrolment.

Blood samples for the study were collected from 609 patients. Fifty-five patients (or their close relatives) refused to participate, and their blood samples were destroyed. A further 15 were excluded from the analysis: one because of a missing blood sample at admission, 11 as a result of incomplete data and three had

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SIRS and organ dysfunction but no bacterial infection (one with epidemic nephropathy and two with myocardial infarction). The final study cohort consisted of 539 patients.

Laboratory methods

Plasma suPAR levels were determined using a commercial double monoclonal antibody sandwich enzyme immunoassay (suPARnostic® Standard Kit; ViroGates A/S, Birkerød, Denmark).

Procalcitonin (PCT) and interleukin-6 (IL-6) in plasma were measured with immunochemiluminometric assays in a Modular E170 automatic analyser (Roche Diagnostics GmbH, Mannheim, Germany). C-reactive protein (CRP) in plasma was measured with an immunoturbidimetric assay using a Modular P800 automatic analyser (Roche Diagnostics GmbH).

Statistical analysis

SPSS statistics for Windows software (IBM, Chicago, IL, USA version 15 and 20) was used for statistical analyses and a two-sided P-value <0.05 was considered statistically significant. Categorical data were analysed by chi-squared or Fisher's exact tests when appropriate and nonparametric continuous data by Mann–Whitney U or Kruskal–Wallis tests. A logistic regression model was used to study the independent effect of high suPAR activity on mortality and severe sepsis after adjusting for potential confounders. Odds ratios (ORs) were expressed with their 95% confidence intervals (CIs) when appropriate. The accuracy of the maximum suPAR value in predicting severe sepsis and case fatality was evaluated using receiver operating characteristic (ROC) curves [18]. According to this method, a perfect test has 100% sensitivity and no false-positives (1-specificity = 0) and an area under the curve (AUC) of 1.0, whereas a test of no diagnostic value has an AUC of 0.5. The Youden index with the highest sum of sensitivity and specificity was used to select the optimal cut-off values for analysis. Correlations between suPAR, CRP, PCT, and IL-6 levels and leucocyte and platelet counts were analysed using Spearman's rank analysis.

Results

Patients demographic characteristics and underlying diseases are shown in Table 1. The cohort was divided into five study groups on the basis of The American Collage of Chest Physicians/Society of Critical Care Medicine Consensus Conference

Table 1 *Patient demographic and clinical characteristics (n = 539)*

Characteristics	
Gender (female/male)	228/311
Age (years), median (range)	61 (18–100)
Obesity (BMI $\geq$ 30 kg m^{-2})[a]	120 (30.7%)
Alcohol abuse[b]	25 (4.6%)
Smoking (current smoker)	126 (23.4%)
Diabetes (types 1 and 2)	82 (15.2%)
Malignancy (solid or haematological)	95 (17.6%)
Rheumatic disease	50 (9.3%)
Chronic renal insufficiency[c]	18 (3.3%)
Cardiovascular disease[d]	289 (53.6%)
COPD or asthma[e]	108 (20.0%)
Surgery within previous 6 months	75 (13.9%)
Device[f]	82 (15.2%)
Continuous medication[g]	390 (72.4%)
Continuous cortisone treatment[h]	59 (11.0%)
Blood cultures[i]	
Positive (clinically significant)	47 (8.7%)
Positive (contamination)	4 (0.7%)
Blood cultures taken after antimicrobial treatment has started	136 (25.2%)
Infection focus (one patient may have more than one focus)	
Respiratory tract	235
Gastrointestinal and other visceral organs	105
Urinary	60
Skin and soft tissue	40
Postoperative infections	15
Bone and articular	10
Other focus	22

[a]Body mass index. Data available for 391 patients.
[b]Alcoholism was diagnosed or patient had previously been treated for alcohol-induced disease.
[c]Plasma creatinine concentration consistently more than 170 μmol L^{-1} (five patients had chronic dialysis treatment).
[d]Continuous medication for cardiovascular disease (including hypertension and arteriosclerosis).
[e]Continuous medication for asthma or chronic obstructive pulmonary disease (COPD).
[f]Joint or heart valve prosthesis or pacemaker (dental implants not included).
[g]Continuous medication for a chronic disease.
[h]Continuous systemic cortisone treatment (daily dose > 10 mg oral prednisolone).
[i]Blood for culture was collected from 538 patients.

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definitions [1], as shown in Table 2. Median suPAR concentration in all patients was 5.0 ng mL^{-1} (range 1.5–40.5 ng mL^{-1}). Median suPAR concentrations in groups 1–5 were 4.7, 5.0, 4.4, 4.8 and 7.9 ng mL^{-1}, respectively ($P < 0.001$). The focus of infection had no significant effect on suPAR levels (data not shown). Respiratory tract infection was diagnosed in 235 patients, 195 of whom had pneumonia. Median suPAR concentration in patients with and without pneumonia was 5.1 and 4.9 ng mL^{-1}, respectively ($P = 0.147$).

Soluble form of the receptor levels in patients stratified by demographic characteristics, underlying conditions and clinical parameters are shown in Table 3. Amongst patients admitted to the emergency department with suspected infection, median suPAR was significantly higher in patients with severe sepsis, compared to those without severe sepsis (7.9 vs. 4.8 ng mL^{-1}, $P < 0.0001$) and in nonsurvivors compared with survivors (8.3 vs. 4.9 ng mL^{-1}, $P < 0.0001$).

Soluble form of the receptor levels showed significant albeit weak positive correlations with PCT ($r = 0.376$, $P < 0.001$), IL-6 ($r = 0.255$, $P < 0.001$) and CRP ($r = 0.097$, $P = 0.024$). A weak positive correlation was also noted between suPAR and plasma creatinine concentrations ($r = 0.332$, $P < 0.001$). There were no significant associations between white blood cell (WBC) count and suPAR ($r = 0.038$, $P = 0.384$) or between platelet count and suPAR ($r = -0.044$, $P = 0.315$). Liver function tests were not systematically performed, and therefore, possible associations between liver function and suPAR levels could not be determined.

The optimal cut-off values for suPAR, PCT and IL-6 for predicting fatal disease or severe sepsis were estimated using ROC curves (Fig. 1) and Youden's index. AUC^{ROC} for case fatality was 0.79 (95% CI: 0.72–0.86, $P < 0.001$) for suPAR, 0.65 (95% CI: 0.57–0.74, $P = 0.003$) for PCT and 0.61 (95% CI: 0.51–0.72, $P = 0.030$) for IL-6. A cut-off level for suPAR $\geq$ 6.4 ng mL^{-1} showed a sensitivity of 76% and a specificity of 69% in predicting fatal disease (case fatality at day 28). This cut-off value was used to classify patients according to those with high or low suPAR values. High suPAR values were associated with several end-points indicative of severe disease (Table 4). For PCT, the optimal cut-off level for case fatality was 0.19 ng mL^{-1} (sensitivity 82% and specificity 53%); the corresponding level for IL-6 was 93.6 pg mL^{-1} (sensitivity 64% and specificity 60%).

Table 2 *Plasma soluble urokinase-type plasminogen activator receptor (suPAR) in patients in the emergency department with suspected infection stratified by diagnosis groups* (n = *539)*

Diagnosis group	Criteria	suPAR (ng mL^{-1})
1. No SIRS, no bacterial infection ($n = 59$)	Patients without SIRS[a] (less than two SIRS criteria at admission +/− 24 h), or documented[b] or probable[c] bacterial infection	4.7 (1.5–25.6)
2. Bacterial infection, no SIRS ($n = 68$)	Patients with documented or probable bacterial infection, but without SIRS (less than two SIRS criteria at admission +/− 24 h)	5.0 (1.5–23.6)
3. SIRS, no bacterial infection ($n = 54$)	Patients with SIRS (at least two SIRS criteria at admission +/− 24 h), but no documented or probable bacterial infection	4.4 (1.6–18.6)
4. Sepsis ($n = 309$)	Patients with sepsis (SIRS and documented or probable bacterial infection but no organ dysfunction as a result of sepsis)	4.8 (1.6–40.5)
5. Severe sepsis ($n = 49$)	Patients with severe sepsis (sepsiswith signs of organ failure, i.e.disturbed perfusion, metabolic acidosis, oliguria or neurological disorders)	7.9 (3.5–28.7)

Differences between the five groups were studied using the Kruskal–Wallis test ($P < 0.0001$).
[a]Systemic inflammatory response syndrome (SIRS): at least two of the following conditions. 1. Temperature > 38 °C or <36 °C; 2. Heart rate > 90 beats per min; 3. respiratory rate >20 breaths per min or partial pressure of carbon dioxide in arterial blood ($PaCO_2$) <32 mmHg (4.3 kPa). 4. White blood cell count >12 × 10^9 L^{-1} or <4.0% or >10% immature (band) forms).
[b]Documented bacterial infection: microbiologically confirmed bacterial infection (either pathogenic bacterial growth in blood culture or in normally sterile tissue or the same usually less pathogenic bacterium, for example, *Staphylococcus epidermidis*, in two different samples).
[c]Probable bacterial infection: a clinician suspected bacterial infection and either infection focus was confirmed or antimicrobial treatment was started and the response to treatment supported bacterial infection.

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Table 3 *Plasma soluble urokinase-type plasminogen activator receptor (suPAR) values stratified by demographic and clinical characteristics in patients admitted to the emergency department with suspected infection*

	suPAR (ng mL^{-1}) on admission; stratification by clinical parameter				
	Characteristics present		Characteristics absent		
	n	Median (quartiles)	*n*	Median (quartiles)	*P*-value
Characteristics					
Gender (male)	311	4.9 (3.4–7.3)	228	5.1 (3.8–7.6)	0.385
Age > 60 years	313	5.8 (4.1–8.1)	226	4.0 (2.9–5.9)	<0.001
Obesity (BMI[a] ≥ 30 kg m^{-2})	120	4.9 (3.6–7.3)	271	5.1 (3.5–7.8)	0.552
Alcohol abuse[b]	25	5.9 (3.8–9.7)	514	5.0 (3.6–7.3)	0.173
Smoking (current smoker)	126	4.4 (3.5–7.3)	413	5.2 (3.7–7.4)	0.229
Diabetes (types 1 and 2)	82	6.5 (4.4–9.4)	457	4.8 (3.5–7.0)	<0.001
Solid cancer	78	5.6 (3.9–7.4)	461	4.9 (3.5–7.4)	0.179
Rheumatic disease	50	6.3 (3.9–11.4)	489	4.9 (3.5–7.2)	0.004
Chronic renal insufficiency[c]	18	10.0 (7.2–13.7)	521	4.9 (3.6–7.2)	<0.001
Cardiovascular disease[d]	289	5.8 (3.9–8.3)	250	4.3 (3.2–6.2)	<0.001
Continuous cortisone treatment[e]	59	7.5 (4.4–11.5)	480	4.8 (3.5–7.0)	<0.001
Clinical parameters					
Case fatality (day 28)	33	8.3 (6.3–12.9)	506	4.9 (3.5–7.1)	<0.001
Case fatality (day 90)	58	8.2 (6.4–11.1)	481	4.7 (3.5–6.9)	<0.001
Case fatality (1 year)	112	7.2 (5.6–10.6)	427	4.5 (3.4–6.5)	<0.001
ICU[f] stay	42	8.1 (4.9–12.0)	497	4.9 (3.5–7.1)	<0.001
Hypotension[g]	28	8.1 (5.8–13.2)	511	4.9 (3.5–7.2)	<0.001
Vasopressors	19	8.0 (5.4–12.0)	520	4.9 (3.6–7.3)	<0.001
DIC[h]	8	16.2 (10.8–21.1)	531	5.0 (3.6–7.3)	<0.001
Decreased GCS[i]	26	7.1 (4.9–12.7)	513	4.9 (3.5–7.3)	<0.001
Mechanical ventilation	14	6.6 (4.6–12.4)	525	5.0 (3.6–7.3)	0.030
C-PAP/bi-PAP[j]	22	6.2 (4.7–10.0)	517	5.0 (3.6–7.3)	0.017
Sepsis + organ dysfunction	49	7.9 (5.2–12.9)	490	4.8 (3.5–7.0)	<0.001
MOF[k]	10	9.8 (6.2–15.5)	529	5.0 (3.6–7.3)	0.002

[a]Body mass index, data available on 391 patients.
[b]Alcoholism was diagnosed or patient had previously been treated for alcohol-induced disease.
[c]Plasma creatinine concentration continually more than 170 μmol L^{-1} (five patients underwent chronic dialysis treatment).
[d]Continuous medication for cardiovascular disease (including hypertension and arteriosclerosis).
[e]Continuous systemic cortisone treatment (daily dose > 10 mg oral prednisolone).
[f]Intensive care unit.
[g]Systolic blood pressure < 90 mmHg or a reduction of 40 mmHg from baseline. No response to 500 mL intravenous fluid replacement.
[h]Disseminated intravascular coagulation.
[i]Glasgow coma scale < 15.
[j]Continuous positive airway pressure/bilevel positive airway pressure.
[k]Multi-organ failure.

AUC^{ROC} for the prediction of severe sepsis was 0.75 (95% CI: 0.68–0.81, $P < 0.001$) for suPAR. ROC curves for PCT, IL-6 and CRP are presented in Fig. 1. The optimal cut-off value for suPAR for predicting severe sepsis was 6.6 ng mL^{-1} (specificity 72% and sensitivity 67%). Cut-off values for predicting severe sepsis were 0.30 ng mL^{-1} (sensitivity 82% and specificity 66%) for PCT, 172 pg mL^{-1} (sensitivity 69 and specificity 73%) for IL-6 and 158 mg L^{-1} (sensitivity 47% and specificity 70%) for CRP.

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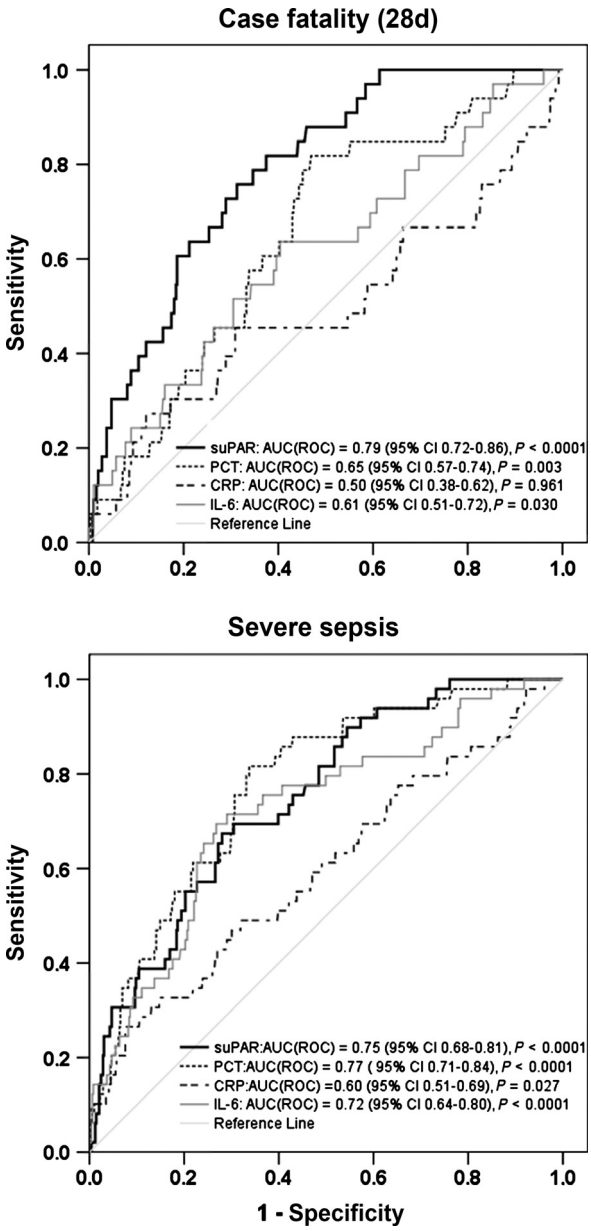

Fig. 1 *Receiver operating characteristic (ROC) curve for plasma levels of soluble urokinase-type plasminogen activator receptor (suPAR), procalcitonin (PCT), interleukin-6 (IL-6) and C-reactive protein (CRP) detected on admission in relation to severe sepsis and case fatality at day 28 (d28) in patients with suspected infection.*

In univariate analysis, high suPAR, PCT and IL-6 levels, age > 60 years, alcohol abuse, diabetes and continuous systemic cortisone treatment were associated with case fatality, whereas the levels of CRP and WBC count were not (data not shown).

A multivariate logistic regression analysis to assess the independent predictive value of suPAR, PCT and IL-6 in fatal disease is presented in Table 5. Laboratory parameters were included in the logistic model first without confounders and then with the demographic characteristics found to be significantly associated with case fatality in the univariate model.

High suPAR, PCT, IL-6 and CRP levels all predicted severe sepsis in the univariate model when included as continuous or grouping variables. Alcohol abuse and continuous systemic cortisone treatment were also associated with severe sepsis in the univariate model (data not shown). These parameters were studied together in the multivariate model first without and then with potential demographic confounders (Table 6).

Discussion

The present findings indicate that high plasma suPAR levels may be used to predict case fatality and severe sepsis in patients admitted to the emergency department with suspected infection. High levels of suPAR and PCT remained independent predictors of case fatality after adjustment for potential demographic confounders. SuPAR values were higher in nonsurvivors as compared to survivors, and in patients with compared to those without severe sepsis. By contrast, suPAR levels did not differ between the four other groups without severe sepsis. High levels of suPAR, PCT and IL-6 all remained independent predictors of severe sepsis. In AUC^{ROC} analysis, suPAR emerged as the best marker for case fatality and PCT was the optimum marker for severe sepsis.

In a recent study conducted in the ICU, it was shown that suPAR level predicts ICU admission and overall survival in critically ill patients [7]. Previous studies in patients with bacteraemia have demonstrated that suPAR can predict disease severity and case fatality [9–11]. In the present study, we showed that suPAR may be used to predict case fatality also in an unselected group of patents with suspected infection in an emergency department setting. In addition to a high suPAR concentration, a high PCT level was an independent predictor of case fatality; however, suPAR seemed to be superior to PCT as a predictor of death by day 28. In accordance with our findings, Kofoed *et al.* [19] showed that suPAR predicted outcome in patients with SIRS.

Table 4 *Clinical characteristics of patients stratified by soluble urokinase-type plasminogen activator receptor (suPAR) value detected on admission*

Clinical parameters	High suPAR ($\geq$6.4 ng mL^{-1}), n = 183	Low suPAR (<6.4 ng mL^{-1}), n = 356	OR (95% CI)	P-value
Grouping variables	n (%)	n (%)		
Case fatality (day 28)	25 (13.7)	8 (2.3)	6.89 (3.04–15.60)	<0.001
Case fatality (day 90)	44 (24.0)	14 (3.9)	7.73 (4.11–14.56)	<0.001
Case fatality (1 year)	73 (39.9)	39 (11.0)	5.39 (3.46–8.43)	<0.001
ICU[a] stay	26 (14.2)	16 (4.5)	3.52 (1.84–6.75)	<0.001
Hypotension[b]	21 (11.5)	7 (2.0)	6.46 (2.69–15.51)	<0.001
Vasopressors	13 (7.1)	6 (1.7)	4.46 (1.67–11.94)	0.003
Acute renal insufficiency[c]	13 (7.1)	3 (0.8)	9.00 (2.53–32.00)	0.001
Acute or chronic renal insufficiency[d]	25 (13.7)	7 (2.0)	7.89 (3.34–18.62)	<0.001
DIC[e]	8 (4.4)	0 (0.0)		<0.001
Decreased GCS[f]	17 (9.3)	9 (2.5)	3.95 (1.72–9.05)	0.001
Mechanical ventilation	8 (4.4)	6 (1.7)	2.67 (0.91–7.81)	0.073
C-PAP/bi-PAP[g]	11 (6.0)	11 (3.1)	2.01 (0.85–4.72)	0.111
Severe sepsis	34 (18.6)	15 (4.2)	5.19 (2.74–9.81)	<0.001
MOF[h]	8 (4.4)	2 (0.6)	8.09 (1.70–38.51)	0.009
Continuous variables on admission	Median (quartiles)	Median (quartiles)		
Plasma C-reactive protein (mg L^{-1})	114 (36–212)	110 (36–179)		0.239
Plasma procalcitonine (ng mL^{-1})	0.32 (0.12–1.63)	0.11 (0.04–0.42)		<0.001
Plasma interleukin-6 (pg mL^{-1})	115.0 (33.0–409.7)	57.2 (23.5–158.8)		<0.001
White cell count (10^9 L^{-1})	11.3 (8.2–14.8)	10.4 (7.4–13.5)		0.168
Platelet count (10^9 L^{-1})	259 (184–352)	249 (205–320)		0.983
Haemoglobin (g L^{-1})	121 (108–139)	132 (121–145)		0.239
Plasma creatinine (μmol L^{-1})	102 (74–148)	75 (62–92)		<0.001

[a]Intensive care unit.
[b]Systolic blood pressure < 90 mmHg or a reduction in 40 mmHg from baseline. No response to 500 mL intravenous fluid replacement.
[c]Diuresis < 30 mL h^{-1} at least 1 h, or continuous haemofiltration or acute dialysis treatment.
[d]Acute renal insufficiency (diuresis < 30 mL h^{-1} at least 1 h, or continuous haemofiltration or acute dialysis treatment) or chronic renal insufficiency (plasma creatinine concentration continuously >170 μmol L^{-1} previously (five patients underwent chronic dialysis treatment).
[e]Disseminated intravascular coagulation.
[f]Glasgow coma scale <15.
[g]Continuous positive airway pressure/bilevel positive airway pressure.
[h]Multi-organ failure.

Soluble form of the receptor is not a specific marker for bacterial infection or sepsis: an association has also been observed between high suPAR concentrations and mortality in patients with HIV [12, 13], tuberculosis [15] and malaria [20]. In a study including 151 patients with SIRS (96 with bacterial infection), it was found that CRP and PCT, but not suPAR, could be used in the diagnosis of bacterial sepsis [16]; AUC values for CRP, PCT and suPAR were 0.81, 0.72 and 0.50, respectively. However, in a recent study including 85 patients with SIRS and comparing the utility of suPAR, PCT and CRP, it was concluded that suPAR is useful in the differential diagnosis of bacterial infection amongst patients with SIRS [21]. In the present study, we found that groups 1–4 could not be differentiated from each other on the basis of suPAR, but levels of the receptor were significantly higher in patients with severe sepsis than in those without. High suPAR upon

Table 5 *Multivariate logistic regression analysis evaluating the independent predictive value of soluble urokinase-type plasminogen activator receptor (suPAR), procalcitonin (PCT) and interleukin-6 (IL-6) for 28-day case fatality*

Characteristics	Odds ratio	95% confidence interval	*P*-value
Parameters were included together in the logistic model without confounders (n = 538)			
suPAR $\geq$ 6.4 ng mL^{-1}	4.97	2.14–11.56	<0.001
PCT $\geq$ 0.19 ng mL^{-1}	2.90	1.09–7.70	0.033
IL-6 $\geq$ 93.6 pg mL^{-1}	1.37	0.62–3.04	0.433
Parameters were included in the analysis together with statistically significant confounders (n = 538)			
suPAR $\geq$ 6.4 ng mL^{-1}	3.86	1.63–9.11	0.002
PCT $\geq$ 0.19 ng mL^{-1}	3.21	1.20–8.62	0.020
IL-6 $\geq$ 93.6 pg mL^{-1}	1.22	0.54–2.77	0.635
Age > 60 years	2.56	0.94–6.97	0.067
Alcohol abuse[a]	5.37	1.39–20.76	0.015
Diabetes (types 1 and 2)	1.86	0.77–4.50	0.167
Continuous cortisone treatment[b]	1.82	0.73–4.56	0.200

The optimal cut-off values were estimated using ROC curve analysis and Youden's index.
[a]Alcoholism was diagnosed or patient had been treated for alcohol-induced disease previously.
[b]Continuous systemic cortisone treatment (daily dose > 10 mg oral prednisolone).

Table 6 *Multivariate logistic regression analysis evaluating the independent predictive value of soluble urokinase-type plasminogen activator receptor (suPAR), procalcitonin (PCT), interleukin-6 (IL-6) and C-reactive protein (CRP) for severe sepsis*

Characteristics	Odds ratio	95% confidence interval	*P*-value
Parameters were included together in the logistic model without confounders (n = 538)			
suPAR $\geq$ 6.6 ng mL^{-1}	3.38	1.74–6.57	<0.001
PCT $\geq$ 0.30 ng mL^{-1}	4.81	2.10–11.04	<0.001
IL-6 $\geq$ 72 pg mL^{-1}	2.99	1.48–6.04	0.002
CRP $\geq$ 158 mg L^{-1}	0.92	0.46–1.81	0.801
Parameters were included in the analysis together with statistically significant confounders (n = 538)			
suPAR $\geq$ 6.6 ng mL^{-1}	3.11	1.56–6.22	0.001
PCT $\geq$ 0.30 ng mL^{-1}	5.02	2.16–1.67	<0.001
IL-6 $\geq$ 172 pg mL^{-1}	2.56	1.24–5.26	0.011
CRP $\geq$ 158 mg L^{-1}	1.04	0.51–2.09	0.923
Alcohol abuse[a]	5.07	1.72–14.95	0.003
Continuous cortisone treatment[b]	2.76	1.19–6.43	0.019

The optimal cut-off values were determined using ROC curve analysis and Youden's index.
[a]Alcoholism was diagnosed or patient had previously been treated for alcohol-induced disease.
[b]Continuous systemic cortisone treatment (daily dose > 10 mg oral prednisolone).

admission was associated with severe sepsis, but so were high levels of PCT and IL-6. When comparing these factors with each other, PCT was the best marker of severe sepsis, followed by suPAR.

Soluble form of the receptor levels in the present study were significantly higher in patients over 60 years and in those with diabetes mellitus, rheumatic disease, chronic renal insufficiency or cardiovascular disease, but there were no differences in suPAR levels between patients stratified by history of alcohol abuse, smoking, obesity and malignancy. Furthermore, previously suPAR levels have been shown to be higher in the elderly [2]. It has also been reported that levels of suPAR are increased in patients with renal insufficiency, uraemia and rheumatic

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disease [22–24]. In contrast to our findings, suPAR levels have previously been reported to be increased in patients with a history of alcohol abuse or liver disease [9, 10]. Indeed, Zimmermann *et al.* [25] recently concluded that suPAR is a potential biomarker for the diagnosis of liver cirrhosis and alcohol-associated liver disease. We did not measure liver function tests systematically, and only 25 patients, in the present study, had a history of alcohol abuse.

We measured suPAR levels upon admission to the emergency department and did not conduct follow-up measurement of suPAR concentrations in those who survived. Previous studies have shown that suPAR levels are elevated in acute infection and decrease towards recovery [9, 10]. Our aim was to establish whether suPAR could be used as an early diagnostic and/or prognostic marker in patients with suspected infection in an emergency department setting. Furthermore, we did not include in this study either healthy controls or patients in the emergency department without suspected infection. In our previous study of suPAR levels in patients with bacteraemia [10], 91 patients provided a blood sample on recovery ($\geq$26 days after a positive blood culture result); in these patients, the median suPAR concentration at that time was 4 ng mL^{-1}. In a population of over 2000 apparently healthy Danish individuals aged 41–71 years, the median suPAR concentration using the same analytical method was recently reported to be 3.9 ng mL^{-1} [26]. Thus, suPAR levels on recovery appear to be similar to those of apparently healthy individuals.

The present cohort was ideal for studying unselected emergency department patients with suspicion of infection. A clinician unrelated to the study had made the decision to take blood for culture from all the study patients in the emergency department. In our protocol, patients were enrolled only from Sundays to Wednesdays. However, in a prior evaluation of 1551 consecutive patients, the rate of positive blood culture was 8.3%, compared with 8.7% in our cohort, which suggests that there was no selection bias in our study. As expected, the case fatality rate by day 28 was low (7.6%), corresponding to the proportion in the pre-evaluation cohort (6.7%). On the other hand, in the severe sepsis group, the mortality rate and distribution of infection foci were in accordance with the findings of a Finnish multicentre study of patients with sepsis [27].

The cut-off levels for case fatality in the present study were lower than in previous studies of patients with bacteraemia or sepsis [9–11]. In two studies, including SIRS patients [19, 21], the cut-off values were close to those in the present study. This may indicate that suPAR levels are dependent on the study cohort, including patient characteristics and the magnitude of immunoactivation.

We investigated the use of suPAR as a surrogate marker of severe sepsis and case fatality. The precise mechanisms underlying the high suPAR concentration and the role of suPAR in the inflammatory process are of great interest, as modifications of the inflammatory process could lead to potential therapeutic applications. It is temping to think that measurement of suPAR may be used for triage to determine which patients with sepsis may require more comprehensive monitoring, as high suPAR levels in the emergency department may predict the need for more intensive therapeutic intervention. Further interventional studies are needed, in which the cut-off levels are used in decision-making for triage.

Conclusions

In conclusion, we have shown here that the plasma suPAR level serves as a prognostic marker in patients with suspected infection admitted to the emergency department. suPAR was an independent predictor of case fatality and was also associated with severe sepsis. Of the four potential markers measured (suPAR, PCT, IL-6 and CRP), suPAR was the best marker for case fatality, whereas PCT was the best predictor of severe sepsis.

Conflict of interest statement

None of the authors has any conflicts of interest to declare.

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12. KIRJALLISUUSKATSAUS

12.1 Liukoisen urokinaasityyppisen plasminogeeniaktivaattorin reseptorin (suPAR) rakenne ja toiminta

Urokinaasityyppisen plasminogeeniaktivaattorin reseptori (urokinase-type plasminogen activator reseptor, uPAR) on solureseptori, joka on kiinnittyneenä solumembraanin pintaan glykofosfoinositoli (GPI)-ankkurilla. uPAR:ia ilmennetään useissa immuunijärjestelmän soluissa, kuten monosyyteissä, aktivoituneissa T-lymfosyyteissä ja makrofageissa. Reseptoria esiintyy myös endoteelisolujen, keratinosyyttien, fibroblastien, sileiden lihassolujen, megakaryosyyttien ja tiettyjen kasvainsolujen solumembraanilla. [Thuno ym. 2009.] uPAR:in primaarinen fysiologinen ligandi on urokinaasityyppinen plasminogeeniaktivaattori (urokinase-type plasminogen activator, uPA). Sekä uPAR että uPA ovat tärkeitä solumigraatiolle ja ekstrasellulaariselle proteolyysille [Nebuloni ym. 2009]. Lisäksi ne säätelevät syöpäsolujen metastasointia ja kasvua monissa syövissä. Eturauhassyövässä suPAR:in on havaittu estävän solujen kasvua, edistävän apoptoosia ja vähentävän migraatiota. [Piccolella ym. 2008.]

Liukoinen uPAR (soluble urokinase-type plasminogen activator reseptor, suPAR) syntyy, kun uPA kiinnittyy uPAR:iin ja proteaasientsyymit irrottavat uPAR:in solumembraanilta. suPAR:ia vapautuu erityisesti infektion ja inflammaation seurauksena. [Ossowski & Aguirre-Ghiso 2000.]

suPAR:ia esiintyy ainakin veressä, virtsassa sekä selkäydinnesteessä. Sen konsentraatio on riippuvainen immuunijärjestelmän senhetkisestä aktivaatiotasosta. Immuunijärjestelmän kohonnut aktivaatiotaso johtaa seerumin kohonneisiin suPAR-arvoihin. [Thuno ym. 2009.]

12.2 suPAR sepsisdiagnoosissa ja –prognoosissa

Viime vuosina suPAR on ollut erityisen kiinnostuksen kohteena taudinkuvan ennustajana sepsiksessä. Saksalaisessa tutkimuksessa seurattiin sairaalan

teho-osastolla (ICU) yhteensä 273 potilasta. Heistä 197:llä oli sepsis ja 76 oli sepsiksen suhteen verrokkeja. Kontrolliryhmässä oli 43 tervettä. Potilaiden suPAR-arvoja analysoitiin tulovaiheessa sekä 3. ja 7. päivänä tutkimuksen alusta. Kaikilta teho-osaston potilailta (n = 273) mitattiin korkeampia suPAR-arvoja kuin terveiltä kontrolleilta (mediaani 9,80 ng/ml vs. 2,44 ng/ml, $p < 0,001$). Iällä ja sukupuolella ei ollut vaikutusta suPAR-pitoisuuksiin. Korkea suPAR-pitoisuus tulovaiheessa sekä 3. päivänä olivat vahvoja itsenäisiä ennustetekijöitä sekä tehovalvonta- että myöhemmälle kuolleisuudelle. Matalat suPAR-pitoisuudet ennustivat positiivista kokonaisselviytymistä. Näin ollen tutkimuksen tekijät pitivät suPAR:ia vahvana markkerina infektiotaudin vakavuutta ja kuolleisuutta ennustettaessa. [Koch ym. 2011.]

Huttunen työryhmineen tarkasteli prospektiivisesti 132 bakteremiapotilaan plasman suPAR-pitoisuuksia. Bakteremian aiheuttajana oli *Staphylococcus aureus, Streptococcus pneumoniae*, β-hemolyyttinen streptokokki tai *Escherichia coli*. Taudin alkuvaiheessa suPAR-pitoisuudet olivat merkittävästi korkeampia niillä, jotka kuolivat seuranta-aikana verrattuna selvinneisiin (mediaani 15,8 ng/ml vs. 7,3 ng/ml). Mikäli taudin alkuvaiheessa suPAR-pitoisuus oli ≥ 11ng/ml, 30 päivän kuolleisuus oli 30%, kun taas pitoisuuden ollessa alle 11 ng/ml 30 päivän kuolleisuus oli vain 3 %. suPAR määritettiin sekä spesifiseksi (76%) että sensitiiviseksi (83%) fataalin taudin suhteen, kun sen pitoisuus oli ≥ 11 ng/ml. [Huttunen ym. 2011.]

Erään tutkimuksen mukaan suPAR on merkittävästi parempi kuolleisuutta ennustava markkeri yleistynyttä tulehdusreaktio-oireyhtymää (systemic inflammatory response syndrome, SIRS) sairastavilla potilailla kuin C-reaktiivinen proteiini (CRP) tai prokalsitoniini (PCT). Tutkimusaineistona oli yhteensä 85 SIRS-potilasta. Heistä 44:llä oli bakteremia, 20:llä virtsatieinfektio, 12:lla pneumonia ja 9:llä ei diagnosoitu mitään infektiota. Kontrolliryhmässä oli 53 tervettä verrokkia. Kaikilta määritettiin suPAR-, CRP- ja PCT-pitoisuudet heti tulovaiheessa sekä seurantanäytteistä. SIRS-ryhmän potilaista 10 kuoli tautiinsa (bakteremiaan 7, virtsatieinfektioon 1, pneumoniaan 2). Seuranta-aikana mitatut suPAR-pitoisuudet olivat

korkeampia niillä, jotka kuolivat verrattuna selvinneisiin (mediaani 17,8 ng/ml vs. 9,2 ng/ml, p = 0,001), mutta samaa tilastollisesti merkitsevää eroa ei voitu todeta CRP:n ja PCT:n suhteen. [Yilmaz ym. 2011.]

Vastaavanlaisia tutkimustuloksia on myöhemmin julkaistu muidenkin tutkimusryhmien toimesta. Esimerkiksi tehohoidon sepsispotilailla korkea veren suPAR-pitoisuus korreloi elinvaurioiden määrään [Donadello ym. 2014] ja ennustaa kuolleisuutta [Suberviola ym. 2013, Donadello ym. 2014]. Lisäksi *Staphylococcus aureus* –bakteremiassa korkean suPAR-pitoisuuden on todettu ennustavan kuolleisuutta [Mölkänen ym. 2011].

Mutta onko suPAR hyvä vain prognostisesta näkökulmasta vai onko sillä arvoa myös infektiotautien diagnostiikassa? Eräässä katsauksessa työryhmä kävi läpi kymmeniä tutkimusartikkeleita, joista tutkijat analysoivat suPAR:in kliinisen arvon sepsispotilailla prognoosin, diagnoosin ja terapeuttisen ohjeistuksen kannalta. suPAR ei eronnut CRP:stä tai PCT:stä sepsisdiagnoosin suhteen, mutta suPAR oli näistä markkereista silti ylivoimainen prognostisessa mielessä. Näin ollen suPAR-pitoisuuksien määrityksiä voisi käyttää apuna potilaita jaoteltaessa esimerkiksi triage-luokkiin – korkeat pitoisuudet olisivat selvä indikaatio siirtää potilas tehovalvontaan. [Donadello ym. 2012.]

Backes tutkimusryhmineen arvioi systemaattisessa katsauksessa suPAR:in kliinistä käytettävyyttä niillä potilailla, joilla oli todettu sepsis (SIRS ja bakteremia) – erityisesti diagnostinen ja prognostinen arvo olivat tutkimuksen kohteena. Systeemiset suPAR-pitoisuudet olivat selvästi korkeampia niillä potilailla, joilla veriviljely oli positiivinen verrattuna terveisiin verrokkeihin. Gramnegatiivisten ja –positiivisten bakteerien suhteen pitoisuudet eivät eronneet toisistaan. Bakteeri-, virus- tai parasiitti-infektioiden erotusdiagnostiikkaan suPAR ei tuonut lisäarvoa. Näin ollen helposti saatavilla olevat ja mitattavat CRP ja PCT olivat tutkijoiden mukaan edelleen tärkeimpiä biologisia markkereita nimenomaan diagnostiikan suhteen. [Backes ym. 2012.] Toisaalta on kuitenkin yhä selvittämättä suPAR:in diagnostinen arvo erityisryhmissä. Esimerkiksi Kaya työryhmineen osoitti, että suPAR voi olla käyttökelpoinen neutropeenisten

hematologisten potilaiden infektioiden varhaisdiagnostiikassa ja hoitovasteen seurannassa [Kaya ym. 2013]. Sen sijaan edellä mainitussa systemaattisessa katsauksessa suPAR:in prognostinen arvo yksinään kuolleisuuden ennustajana oli selvästi parempi verrattuna CRP:hen ja PCT:hen. Toisaalta prognostinen arvo kasvoi vielä enemmän mikäli suPAR-arvo yhdistettiin muihin biologisiin markkereihin (esim. CRP) tai ikään. Tehohoidossa käytetty simplifiled acute physiology score (SAPS) -pisteasteikko kuvaa potilaan sairauden vakavuutta ja se on käytössä maailmanlaajuisesti – myös Suomessa. Kun suPAR yhdistettiin SAPS-pisteisiin, pystyttiin potilaan kuolleisuutta arvioimaan kaikista parhaiten. Lisäksi korkeat plasman suPAR-pitoisuudet ennustivat siirtymistä tehovalvontaosastolle, tarvetta vasopressori-lääkitykselle sekä mekaaniselle ventilaatiolle. [Backes ym. 2012.]

12.3 suPAR ja *Streptococcus pneumoniae*

uPAR on tärkeä rakenne leukosyyttien adheesiolle ja migraatiolle. Erityisesti monosyyttien ja neutrofiilien transendoteliaalinen migraatio vaatii kyseisen rakenteen toimiakseen [Blasi 1997]. Endotoksiinien on osoitettu lisäävän uPAR:in ekspressiota erityisesti monosyyttien solumembraanilla. Samassa tutkimuksessa havaittiin myös suPAR:in lisääntyvän plasmassa endotoksiinin vaikutuksesta. *In vitro* –kokeilussa endotoksiini ja grampositiivisen bakteerin kaltainen stimulus lisäsi yhtä lailla monosyyttien uPAR-ekspressiota. [Dekkers ym. 2000.] uPAR:ia tarvitaan adekvaattiin immunipuolustukseen pneumokokkipneumoniaa vastaan – uPAR nimittäin houkuttelee keuhkoalveoleihin neutrofiilejä. Tämä voi osaltaan selittää sen, miksi uPAR:in suhteen poistogeenisillä hiirillä immuunipuolustus pneumokokkia vastaan on heikentynyt. [Rijneveld ym. 2002.]

Eräässä prospektiivisessa monikeskustutkimuksessa suPAR-pitoisuudet olivat merkittävästi kohonneet pneumokokkibakteremiaa sairastavilla potilailla (n=141) verrattuna terveisiin verrokkeihin (n=31) (mediaani 5,5; vaihteluväli 2,4 – 21,0 ng/ml vs. 2,6; 1,5 – 4,0 ng/ml). Mitatut suPAR-pitoisuudet olivat bakteremiaan kuolleilla lisäksi paljon korkeampia kuin siitä parantuneilla (mediaani 9,4 ng/ml vs. 5,0 ng/ml) ja tulos oli myös

tilastollisesti merkitsevä ($p < 0,001$). CRP:n ja suPAR:in välillä ei todettu olevan yhteyttä. Tutkijoiden mukaan suPAR-mittauksella oli prognostista arvoa niille potilaille, jotka olivat vaarassa kuolla pneumokokkibakteremiaan. [Wittenhagen ym. 2004.]

12.4 suPAR ja meningiitti

Oestergaard työryhmineen tutki suPAR-pitoisuuksia meningiitti-potilailla. Tulosten mukaan selkäydinnesteen suPAR-pitoisuus saattaa olla merkittävä ennustemarkkeri arvioitaessa kuolleisuutta purulenttiin meningiittiin. Heidän prospektiivinen tutkimusaineistonsa käsitti 183 potilasta, joille tulovaiheessa oli työdiagnoosiksi asetettu meningiitti. Potilaista lopulta 54:llä oli purulentti meningiitti, 63:lla lymfosyyttinen meningiitti, 12:lla enkefaliitti ja 54:llä mitään keskushermostoinfektiota ei myöhemmissä tutkimuksissa todettu. suPAR-pitoisuus erosi merkittävästi keskushermostoinfektioon sairastuneilla verrattuna niihin joilla sitä ei tarkemmissa tutkimuksissa todettu ($p < 0,05$). Niiltä potilailta, jotka lopulta kuolivat purulenttiin meningiittiin, mitattiin huomattavasti korkeampia suPAR-pitoisuuksia selkäydinnesteestä verrattuna taudista parantuneisiin (mediaani 4,9 µg/l (n=8) vs. 2,1 µg/l (n=46)) ja tulos oli myös tilastollisesti merkitsevä ($p = 0,046$). [Oestergaard ym. 2004.] Vastaavanlaisia tuloksia ovat raportoineet sittemmin myös muut tutkijat [Tzanakaki ym. 2012].

12.5 suPAR virusinfektioissa

Eräässä tutkimuksessa HIV-1-infektion on osoitettu lisäävän uPAR:in ekspressiota leukosyyttien solumembraanilla sekä *in vitro* että *in vivo*. Retrospektiivinen tutkimusaineisto käsitti 314 HIV-1-infektiota sairastavaa potilasta, joilta kaikilta mitattiin seerumin suPAR-pitoisuus. Tutkimus osoitti, että korkea pitoisuus oli yhteydessä huonoon tautiennusteeseen. Lisäksi kuolleisuus lisääntyi sitä enemmän mitä korkeampi suPAR-pitoisuus oli eli suPAR:in pääteltiin olevan hyvin vahva prognostinen markkeri HIV-1-infektiossa. [Sidenius ym. 2000.] Tulokset ovat saaneet edelleen vahvistusta myöhemmistä tutkimuksista [Ostrowski ym. 2005a, Schneider

ym. 2007]. Näin ollen suPAR on koholla myös kroonisissa infektioissa ja sillä on samanlainen prognostinen arvo verrattuna akuutteihin infektiotauteihin. Esimerkiksi hepatiitti C -virusinfektiossa korkean suPAR-pitoisuuden on todettu liittyvän nopeammin etenevään maksafibroosiin [Berres ym. 2012].

suPAR on yhteydessä myös Puumala-viruksen aiheuttamaan myyräkuumeen vaikeusasteeseen. Outinen työryhmineen tutki prospektiivisesti 97 myyräkuumepotilaalta suPAR-pitoisuuksia. Kaikkien diagnoosit olivat serologisesti varmistettuja. Tulosten mukaan suPAR-pitoisuudet olivat huomattavasti korkeampia taudin akuutin vaiheen aikana kuin kotiutumisen jälkeen (mediaani 8,7 ng/ml vs. 4,7 ng/ml). Lisäksi samassa tutkimuksessa havaittiin, että kohonnut suPAR-taso korreloi positiivisesti plasman kreatiniini-pitoisuuteen, potilaan painonvaihteluun osastohoidon aikana sekä koko hoitojakson pituuteen. [Outinen ym. 2013.]

12.6 suPAR ja malaria

Eräs tutkimusaineisto käsitti 645 afrikkalaislasta, jotka olivat hakeutuneet sairaalahoitoon malariaoireiden perusteella. Heistä 478 sai malariadiagnoosin, mutta 167:lla ei todettu veren sivelynäytteessä *Plasmodium*-parasiitteja. Kontrolliryhmässä oli 14 tervettä lasta. Plasman suPAR-pitoisuus oli korkeampi malariaa sairastavilla lapsilla (mediaani 7,90 ng/ml) verrattuna muihin oireileviin lapsiin, joilla verinäyte oli negatiivinen *Plasmodiumin* suhteen (mediaani 5,59 ng/ml). Kaikista matalin suPAR-arvo oli terveillä verrokeilla (mediaani 3,94 ng/ml). Korkeimmat suPAR-pitoisuudet mitattiin niiltä lapsilta, jotka kuolivat tai joiden tauti komplisoitui. [Ostrowski ym. 2005b.]

12.7. Yhteenveto

suPAR on erityisesti tulehdussolujen pinnalla ilmenevän uPAR:in liukoinen muoto, jonka pitoisuus kohoaa elimistössä immunologisen aktivaation seurauksena. suPAR on biologisesti merkittävä tekijä solumigraatiossa ja

esimerkiksi syöpätautien ilmenemisessä. Viime vuosina suPAR:in merkitys on todettu kliinisesti myös infektiotaudeissa ja tutkimusten mukaan se on infektiopotilailla erityisesti tautikuolleisuutta ennustava markkeri. Lisäksi suPAR:in kliinistä merkitystä on tutkittu myös mm. munuaissairauksissa. Nähtäväksi jää, vakiinnuttaako suPAR-määritys paikkansa tulevaisuudessa infektiotautien kliinisenä laboratoriomarkkerina.

13. LÄHTEET

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