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ORIGINAL

SuPAR and PAI-1 in critically ill, mechanically ventilated patients

Ville Jalkanen
Runkuan Yang
Rita Linko
Heini Huhtala
Marjatta Okkonen
Tero Varpula
Ville Pettilä
Jyrki Tenhunen
The FINNALI Study Group

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V. Jalkanen · R. Yang · J. Tenhunen
Critical Care Medicine Research Group, Department of Intensive Care Medicine, Tampere University Hospital, PO BOX 2000, 33521 Tampere, Finland

V. Jalkanen
e-mail: ville.jalkanen@pshp.fi

R. Linko · M. Okkonen · T. Varpula · V. Pettilä
Division of Anaesthesia and Intensive Care Medicine, Department of Surgery, Meilahti Hospital, Helsinki University Central Hospital, PO BOX 340, 00029 Helsinki, Finland

H. Huhtala
School of Health Sciences, University of Tampere, 33014 Tampere, Finland

V. Pettilä
Department of Epidemiology and Preventive Medicine, Australian and New Zealand Intensive Care Research Centre, Monash University, Melbourne, VIC, Australia

J. Tenhunen (✉)
Department of Surgical Sciences, Anaesthesiology and Intensive Care, Uppsala University, 751 85 Uppsala, Sweden
e-mail: jyrki.tenhunen@surgsci.uu.se
Tel.: +46-76-9457195

Abstract *Purpose:* SuPAR (soluble urokinase plasminogen activator receptor) and PAI-1 (plasminogen activator inhibitor 1) are active in the coagulation-fibrinolysis pathway. Both have been suggested as biomarkers for disease severity. We evaluated them in prediction of mortality, acute lung injury (ALI)/acute respiratory distress syndrome (ARDS), sepsis and renal replacement therapy (RRT) in operative and non-operative ventilated patients. *Methods:* We conducted a prospective, multicenter, observational study. Blood samples and data of intensive care were collected. Mechanically ventilated patients with baseline suPAR and PAI-1 measurements were included in the analysis, and healthy volunteers were analysed for comparison. Receiver operating characteristics (ROC), logistic regression, likelihood ratios and Kaplan–Meier analysis were performed. *Results:* Baseline suPAR was 11.6 ng/ml (quartiles Q1–Q3, 9.6–14.0), compared to healthy volunteers with suPAR of 0.6 ng/ml (0.5–11.0). PAI-1 concentrations were 2.67 ng/ml (1.53–4.69) and 0.3 ng/ml (0.3–0.4), respectively. ROC analysis for suPAR 90-day mortality areas under receiver operating characteristic curves (AUC) 0.61 (95 % confidence interval (CI): 0.55–0.67), sepsis 0.68 (0.61–0.76), ALI/ARDS 0.64 (0.56–0.73) and RRT 0.65 (0.56–0.73). Patients with the highest quartile of suPAR concentrations had an odds ratio of 2.52 (1.37–4.64, $p = 0.003$) for 90-day mortality and 3.16 (1.19–8.41, $p = 0.02$) for ALI/ARDS. In non-operative patients, the AUC's for suPAR were 90-day mortality 0.61 (0.54–0.68), RRT 0.73 (0.64–0.83), sepsis 0.70 (0.60–0.80), ALI/ARDS 0.61 (0.51–0.71). Predictive value of PAI-1 was negligible. *Conclusions:* In non-operative patients, low concentrations of suPAR were predictive for survival and high concentrations for RRT and mortality. SuPAR may be used for screening for patients with potentially good survival. The association with RRT may supply an early warning sign for acute renal failure.

Keywords Plasminogen activator inhibitor 1 (PAI-1) · Soluble urokinase plasminogen activator receptor (suPAR) · Acute respiratory distress syndrome (ARDS) · Acute respiratory failure (ARF) · Biomarkers

Introduction

Urokinase plasminogen activator receptor (UPAR) and plasminogen activator inhibitor 1 (PAI-1) are both active in coagulation pathway [1]. The activation of coagulation and fibrinolysis pathways and local production of pro-inflammatory mediators are important innate reactions in acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) [2, 3], and biomarkers of coagulation, fibrinolysis and inflammation have been suggested for recognizing ALI/ARDS. Numerous studies on biomarkers for ALI/ARDS have resulted in promising results, but none of these have entered routine clinical practice [4–9]. In acute kidney injury (AKI), a novel biomarker neutrophil gelatinase-associated lipocalin (NGAL) has entered clinical use [10] and has shown prognostic value for renal recovery in AKI [11].

UPAR is involved in many immune functions like fibrinolysis, cell proliferation and angiogenesis [12–14]. UPAR is expressed in numerous different cells and is glycosyl phosphatidylinositol (GPI)-anchored to cell surface. Removal of the GPI anchor by phospholipases or extracellular proteolytic cleavage yields a soluble form: soluble urokinase plasminogen activator receptor (suPAR) [1, 15]. UPAR expression is induced under conditions that involve extra cellular matrix (ECM) remodelling, and also in stress, injury and inflammation. Elevated levels of suPAR in circulation are considered to be a marker for activation of immune and inflammatory systems [15]. In the acute setting, elevated levels of suPAR have been proposed to be predictive for disease severity in bacteraemia [16, 17], ventilator-associated pneumonia (VAP) with sepsis [18], and in intensive care unit (ICU) patients with or without sepsis [19]. Recently suPAR was discovered as a cause of chronic renal disease focal segmental glomerulosclerosis (FSGS). In addition, removing suPAR with plasmapheresis resulted in lowered suPAR concentrations and a disease-stabilizing effect [20].

PAI-1 (also known as SERPINE1) is the main inhibitor for tissue-type (tPA) and urokinase-type plasminogen activator (uPA). It is present during activation of the coagulation system in sepsis [21]. In ALI and ARDS, fibrin production is induced, but the activation of PAI-1 in pulmonary tissue inhibits fibrinolytic activity. It is suggested that higher levels of PAI-1 in alveoli or plasma are associated with higher mortality rate, increased risk of VAP, and fewer days of unassisted ventilation in adult [22, 23] and in paediatric patients [24]. PAI-1 levels in serum are suggested to be elevated in sepsis [25], to predict multiple organ failure (MOF), mortality [26] and AKI [27]. Increased levels of PAI-1 in bronchoalveolar lavage are suggested to differentiate patients developing VAP, before clinical signs are present in adult [22] and in paediatric patients [28].

Our primary hypothesis was that elevated serum levels of suPAR and PAI-1 in critically ill patients with acute respiratory failure (ARF) are associated with development of ALI/ARDS, sepsis, renal replacement therapy (RRT) and mortality. Accordingly, we analysed serum suPAR and PAI-1 concentrations at baseline and on day 2 in a large prospective nationwide multicenter cohort study. Our secondary hypothesis was that suPAR and PAI-1 act differently in different patient cohorts. In order to evaluate this, we also performed a subgroup analysis of operative and non-operative patients.

Methods

This was a predetermined substudy of the prospective observational FINNALI study, including 25 Finnish ICUs [29]. All adult patients admitted to participating ICUs and receiving ventilatory support for more than 6 h within an 8-week period in 2007 were included in the FINNALI-study.

The FINNALI study obtained approval from ethical committees in all participating hospitals. The routine quality data were collected in all participating ICUs (The Finnish Quality Consortium, Intensium Ltd, Kuopio, Finland). Routine data included information of critical illness severity by Sequential Organ Failure Assessment (SOFA), Acute Physiology and Chronic Health Evaluation (APACHE2) and Simplified Acute Physiology Score (SAPS II) points, age, gender, body mass index (BMI), survival and length of hospital stay. Ventilatory treatment strategies, need of RRT and presence of sepsis according to physicians' clinical evaluation were recorded on case report forms (CRFs). ALI or ARDS was defined according to American–European Consensus Conference (AECC) criteria [30]. We collected a written informed consent from the patient or his/her relative for blood samples. Baseline samples were collected within 6 h following ICU admission and on day 2 after ICU admission.

The sera were frozen until later analysed (after 32–34 months). SuPAR and PAI-1 levels in serum were measured as paired samples by enzyme linked immunosorbent assay (ELISA), according to the manufacturer's (suPAR suPARnostic®, ViroGates, Birkeroed, Denmark; PAI-1 BioVendor GmbH, Heidelberg, Germany) instructions. Samples from ten healthy volunteers were analysed for comparison.

All those patients with ventilatory support exceeding 6 h, with an informed consent and with blood samples, were included in this FINNALI sub study. In order to have comparable data between the two biomarkers, we only included patients with suPAR and PAI-1 blood

samples at baseline. The study flowchart is presented in the electronic supplemental material (Fig. 1 in ESM).

Statistical analysis

Data are presented as median and quartiles (Q1–Q3) or percentages. Nonparametric data were compared by Mann–Whitney *U* test and categorical variables with the Chi-square test or Fisher's exact test, as appropriate. Areas under receiver operating characteristic curves (AUCs) with 95 % confidence intervals (CIs) to determine the discrimination of suPAR and PAI-1 regarding different time-point mortality, sepsis, ALI/ARDS and RRT were calculated. Likelihood ratios (LR+ or LR−) with 95 % CIs were calculated. The Youden index with the highest sum of the sensitivity and specificity [sensitivity + (1-specificity)] was used to select the optimal cut-off point for calculating LR+ and LR−. SuPAR and PAI-1 levels were separately divided into quartiles, and Kaplan–Meier survival curves were produced. Two subgroups were identified and analysed according to patients being operative or non-operative, and Kaplan–Meier survival curves for subgroups were produced. Finally, a multivariate backward logistic regression analysis to evaluate the independent association of suPAR and PAI-1 and post hoc subgroups regarding the study primary endpoint of (1) 90-day mortality; (2) 12-month mortality; (3) ALI/ARDS; (4) sepsis; and (5) RRT. The following variables were first tested in a univariate analysis baseline: suPAR and PAI-1, SOFA- and SAPS II-points, baseline PaO_2:FiO_2 ratio, age, gender and body mass. Those with p value <0.10 were included in multivariate analysis. The level of $p < 0.05$ was considered statistically significant for all tests. PASW 18.0 software (SPSS, Chicago, IL) was used for the analyses.

Results

The characteristics of the 454 study patients and the remaining 504 FINNALI patients without laboratory samples are presented in Table 1.

SuPAR concentration was 11.6 ng/ml (9.6–14.0) at baseline and 12.8 ng/ml (10.8–15.1) on day 2. PAI-1 concentration was 2.67 ng/ml (1.53–4.69) at baseline and 1.62 ng/ml (1.26–2.62) on day 2. In healthy volunteers, the suPAR and PAI-1 concentrations were 0.6 ng/ml (0.5–11.0) and 0.3 ng/ml (0.3–0.4), respectively. SuPAR and PAI-1 concentrations were higher in critically ill patients compared to healthy volunteers ($p < 0.001$ for both groups and time points).

SuPAR: the whole patient cohort

The baseline and day 2 suPAR concentrations were higher in 90-day non-survivors compared to survivors, 13.2 ng/ml (10.3–15.8) versus 11.3 ng/ml (9.5–13.7), and 14.2 ng/ml (11.6–17.1) versus 12.5 ng/ml (10.7–14.5) ($p < 0.001$). SuPAR concentrations were higher in septic versus non-septic patients ($p < 0.001$).

AUC analyses for mortality, sepsis, ALI/ARDS and RRT are presented in Table 1 in ESM, and respective LR+ in Table 2. The highest of suPAR concentrations showed an independent effect on 90-day mortality and development of ALI/ARDS in a multivariate analysis adjusted to age, gender, SOFA and body mass. The univariate analysis showed no correlation between baseline suPAR and PAI-1 concentrations ($r = 0.041$, $p = 0.389$).

The binary logistic regression analysis showed that patients with the highest quartile of baseline suPAR concentrations had an odds ratio (OR) of 2.52 (95 % CI 1.37–4.64, $p = 0.003$) for 90-day mortality when compared to lowest quartile. Furthermore, the patients with

Table 1 Demographics and outcome of the study patients

	All patients with samples ($N = 454$)	The remaining FINNALI cohort without samples ($N = 504$)	p value	Non-operative ($N = 263$)	Operative ($N = 191$)	p value
Age (years)	64 (53–74)	62 (48.3–73.0)	0.157	61 (51–73)	67 (55–75)	0.080
Male (%)	68.5	64.7	0.211	68.1	69.1	0.079
Postoperative (%)	42.1	36.5	0.79	0	100	
BMI	26.2 (23.5–29.8)	25.9 (23.4–29.1)	0.107	26.3 (23.5–29.4)	26.0 (23.5–30.4)	0.966
SOFA at 24 h after admission	8 (6–10)	8 (6–10)	0.076	8 (5–10)	7 (6–9)	0.055
SAPS (score)	41 (29–53)	44 (33–57)	0.022	45 (35–60)	32 (26–46)	$p < 0.001$
Hospital LOS (days)	13 (7–23)	9 (4–19)	0.010	13 (7–23)	12 (8–22)	0.884
90-day mortality	26.2	34.9	0.003	32.7	17.3	$p < 0.001$
12-month mortality	31.5	38.7	0.020	38.8	21.5	$p < 0.001$

Continuous variables presented as median (Q1–Q3)

LOS length of stay, *BMI* body mass index, *APACHE* acute physiology and chronic health evaluation, *SOFA* sequential organ failure assessment, *SAPS* simplified acute physiology score, *ICU mortality* intensive care unit mortality

Table 2 Positive likelihood ratios (LR+) and 95 % confidence intervals (95 % CI) for baseline soluble urokinase plasminogen activator receptor (suPAR) concentrations

	Cut-off (according to Youden index)			Cut-off (9.7 ng/ml)	
	LR+	95 % CI	ng/ml	LR+	95 % CI
90-day mortality	1.75	1.40–2.19	12.8	1.17	1.05–1.30
12-month mortality	1.72	1.36–2.19	13.1	1.20	1.08–1.33
Sepsis	2.00	1.63–2.45	12.6	1.22	1.10–1.36
ALI/ARDS	1.45	1.21–1.75	11.3	1.19	1.05–1.36
RRT	1.79	1.35–2.37	13.0	1.15	1.00–1.33

The cut-off values are selected according to the Youden index and the lowest suPAR concentration quartile
ALI acute lung injury, *ARDS* acute respiratory distress syndrome, *RRT* renal replacement therapy

highest quartile of baseline suPAR concentration had an OR of 3.16 (95 % CI 1.19–8.41, $p = 0.021$) for developing ALI or ARDS.

The Kaplan–Meier analysis for the baseline suPAR concentration quartiles suggested a markedly increased risk of death in the highest suPAR concentration quartile ($p = 0.009$). The 12-month mortality in the lowest quartile of suPAR concentration was 20.8 %, and in the highest quartile, 41.4 % (Fig. 2 in ESM).

SuPAR: operative versus non-operative patient subgroups

In post hoc subgroup analyses relevant to clinical practice, Kaplan–Meier analysis for non-operative patients suggested high prognostic value for lower mortality with the lowest suPAR concentration quartile. Lowest baseline suPAR concentration quartile (below 9.7 ng/ml) was associated with 18.3 % 12-month mortality, while the three highest concentration quartiles had 41.3–47.7 % mortality. LR− for 90-day survival with a cut-off value of 9.7 ng/ml was 0.36 (0.18–0.70) and LR+ for 90-day mortality was 1.25 (1.11–1.40). In the subgroup of operative (surgical) admissions, the prognostic value was negligible (Fig. 1).

Non-operative patients belonging to the three highest suPAR concentration quartiles had an increased risk of death (90 days), with the OR varying from 2.2 to 2.6. OR for developing ALI or ARDS was insignificant in both subgroups. OR for sepsis in the highest concentration quartile of suPAR was 3.4 (95 % CI 1.2–9.6) in non-operative patients. In operative patients the highest two concentration quartiles had OR's of 6.6 (95 % CI 1.7–25.0) and 5.4 (95 % CI 1.3–22.9) for sepsis (Fig. 2).

ROC analysis in non-operative patients indicated suPAR as a moderate to good predictor for RRT at baseline and on day 2. The AUC's were 0.73 (0.64–0.83) and 0.78 (0.70–0.87), respectively with LR+ of 3.31 (2.06–5.32) and 2.38 (1.88–3.00). LR− for not needing RRT was 0.19 (0.07–0.49), with the cut off value of 13.4 ng/ml. In operative patients, suPAR had no predictive value for RRT [AUC 0.51 (0.37–0.65) and 0.62 (0.49–0.76)] (Table 1 in ESM). The binary logistic regression analysis for RRT in non-operative patients gave an OR 11.7 (2.6–53.4) for the highest baseline suPAR concentration quartile (Fig. 2).

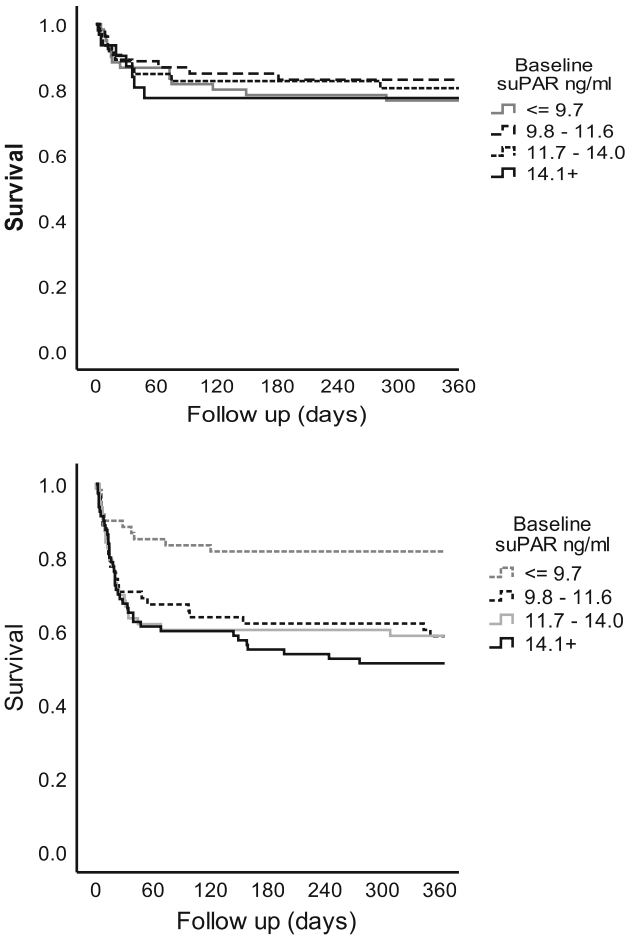

Fig. 1 Kaplan–Meier estimates of 12-month survival in operative (*upper*) and non-operative (*lower*) patients stratified in suPAR concentration quartiles. Log rank $p = 0.006$ for non-operative patients and $p = 0.86$ for operative patients

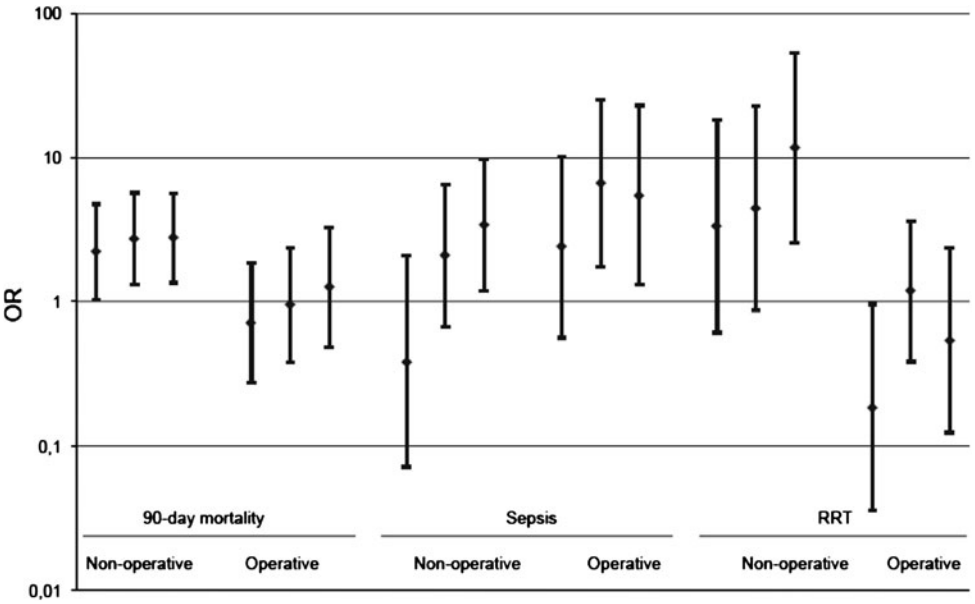

Fig. 2 Backward logistic regression for non-operative and operative subgroups of the whole patient cohort. Baseline suPAR concentration quartiles tested against the lowest quartile. The data are presented as odds ratios (OR) with 95 % confidence intervals (CIs) in logarithmic scale with 90-day mortality, presence of sepsis or renal replacement therapy (RRT) as outcomes. The lower limit thresholds for the three upper quartiles were 9.7 ng/ml, 11.7 ng/ml and 14.1 ng/ml

PAI-1: the whole cohort and the subgroups

Baseline PAI-1 levels were higher in in-hospital non-survivors [3.01 (2.28–5.34) vs. 2.62 ng/ml (1.51–4.47)] ($p = 0.006$). For the whole cohort and the subgroups, the AUC's in ROC analyses suggested insignificant or very weak prognostic value for PAI-1 to predict mortality, sepsis, ALI/ARDS or RRT (Table 1 in ESM). In the binary regression analysis, the highest PAI-1 concentration quartile was not prognostic for mortality, sepsis and ALI/ARDS, in the whole cohort or subgroups. OR for RRT in operative admissions when the PAI-1 concentration was in the highest quartile was 5.27 (1.05–26.41, $p = 0.04$) (Fig. 3 in ESM). Kaplan–Meier analysis revealed insignificant pattern between the PAI-1 quartiles in the whole cohort and the two subgroups (Figs. 4, 5 in ESM).

Discussion

Key findings of the present investigation were that in this cohort of critically ill patients receiving ventilatory support, suPAR was higher compared to healthy volunteers. The association between suPAR and 90-day mortality and secondary endpoints was only moderate. In post hoc subgroup analyses, high suPAR concentration was associated with high 90-day mortality and RRT in non-operative patients. In particular, LR− suggested that low suPAR at admission predicts high probability of survival.

Serum PAI-1 was higher in ICU patients compared to healthy volunteers. However, in the whole patient cohort and in the post hoc subgroups, no indication for prognostic value occurred.

In septic patients, suPAR concentrations were higher than in non-septic patients. This finding is in line with previous studies suggesting suPAR/uPAR activation in infection [16–19, 31]. Previous studies have suggested cut-off points of 8.0 ng/ml [19] and 11.0 ng/ml [17] for predicting 30-day and ICU mortality. In our study with a heterogeneous group of critically ill patients, a higher cut-off point than previously reported is more likely to be prognostic for mortality. The higher suggested cut-off point may be explained by the inclusion criteria in the study. In the work of Huttunen et al. [17], the patients were known to have positive blood culture and septicaemia. Our data represent a heterogeneous group of adult patients with a wide variety of etiology for respiratory failure. Although the low sensitivity in ROC analysis limits the use of suPAR, the increased risk of death and ALI/ARDS with the highest suPAR concentrations could be clinically relevant information. More importantly, in non-operative patients, low concentrations of suPAR were highly predictive for survival. The sensitivity for mortality was poor, but specificity was high, with the lowest quartile cut-off value of 9.7 ng/ml.

The activation of uPA–uPAR interaction is suggested to have a role in blocking fibrin accumulation and fibrin-associated inflammation [32]. Low concentrations of suPAR being predictive for survival may indicate that uPA–uPAR and fibrin-associated inflammation are not activated. Instead, high concentrations could indicate only activation of uPA–uPAR, but mechanistically this may also be required to block fibrin accumulation, and hence is a physiologically advantageous reaction to inflammation and fibrin accumulation.

In operative patients, prognostic value of suPAR is weaker than in non-operative patients. This is potentially

related to patient selection. Disease severity markers (SAPS, SOFA) indicate less organ failure and mortality in operative patients (Table 1). The low mortality rate and low disease severity suggest that operative patients recovered after single organ failure (e.g., head trauma) and hence had minor activation of uPA–uPAR.

In comparison to previously investigated biomarkers [5–9], suPAR was inferior to a combination of biomarkers and clinical evaluation [5] in predicting ALI, ARDS and mortality. Like other biomarkers, suPAR as a single biomarker is not strong enough for clinical decision-making. The combination of suPAR and disease severity scores as a clinical outcome prediction tool should be assessed in further studies.

Previous studies have suggested that PAI-1 is a marker for AKI [27]. In this study, we evaluated PAI-1 and suPAR on those with RRT, and found suPAR to be fairly prognostic for RRT. Based on the ROC analysis, risk of RRT was increased with higher concentrations of suPAR, especially on day 2. The indications for RRT in critically ill patients differ from those with AKI alone, and hence RRT cannot be used as a definition for AKI. A subgroup analysis revealed that in operative patients, PAI-1 was prognostic for RRT. In non-operative patients, suPAR was superior to PAI-1 in predicting RRT. A previous study [19] has reported an association between suPAR and renal dysfunction. A recent report on suPAR as a cause of kidney injury in chronic renal disease [20] suggests a tentative mechanistic role in acute kidney failure as well. NGAL is shown to have prognostic value for renal recovery in community-acquired pneumonia [11]. The reported AUC of 0.74 (0.66–0.81) for NGAL is the same level as suPAR-AUC for RRT in non-operative patients. A study involving suPAR and NGAL in prediction of AKI is strongly warranted.

There was a marked variation in suPAR in the healthy volunteers, in line with the previous report by Koch et al. [19]. The highest suPAR concentrations in healthy volunteers were lower than the concentrations of patients with an increased risk of poor outcome. PAI-1 levels in healthy volunteers were stable and low.

PAI-1 was a poor prognostic marker for mortality or development of sepsis. Previously, PAI-1 has been considered valuable in prognostication in patients with ARF [22–24]. Our data do not support this notion. Even the highest quartile of PAI-1, concentrations did not have predictive value for 90-day mortality or association with ALI/ARDS. Previous reports indicate that PAI-1 levels are elevated in sepsis and VAP, and predict mortality and MOF. We detected no statistically significant differences in PAI-1 levels at baseline or on day 2 in patients with ALI/ARDS or sepsis. Our findings suggest that PAI-1 is only weakly associated with 90-day mortality, sepsis and ALI/ARDS. The findings were similar in the subgroup analyses.

Strengths and limitations

Two major strengths of the present report are proposed: 1) the prospective design with national coverage for the cohort study; and 2) this study was an unselected group of consecutive patient admissions of critically ill patients with ventilatory support. Therefore, this study represented a real-life patient population for testing the prognostic markers. However, some important limitations need to be considered. First, in the FINNALI study [29] the ventilatory tidal volumes were higher than lung-protective strategy guidelines suggest, because due to the observational nature of the study, no strict guidelines were stipulated. This may have had an impact on our results, but again, this exemplifies real adherence to current guidelines, and therefore current clinical practice. Second, in comparison to the original FINNALI-study, the 90-day mortality in the whole FINNALI cohort was 30.8 %. Herein, amongst the patients with available laboratory samples, the 90-day mortality was slightly lower at 26.2 %. This could represent random chance variation. Alternatively, most severely ill patients and their next of kin may not have been approached for informed consent and blood sampling. Another indication towards informed consent procedure being the culprit is that operative patients with good prognosis were slightly over-represented in the patient cohort. Third, the sera were frozen for up to 2.5 years before analyses. However, long-term freezing, or even repeated thawing, should have minimal impact on suPAR or PAI-1 results [33, 34]. Finally, the data input on case report forms did not include administered anticoagulation. PAI-1 levels are known to decrease following low molecular weight heparin (LMWH) therapy [35]. To our knowledge, the impact of anticoagulation therapy on suPAR levels is unknown.

Conclusions

We found that suPAR and PAI-1 serum concentrations were increased in critically ill patients with ARF and need for ventilator support. In non-operative critically ill patients needing ventilator support, low concentrations of suPAR at baseline were predictive for survival, and high concentrations predicted RRT and to lesser extent, 90-day mortality. The association of high suPAR concentration with RRT and AKI needs to be further investigated, bearing in mind the potential for causality.

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Conflicts of interest Dr. Tenhunen was a member of international scientific advisory board for suPARnostic® (travel expenses and lodging) and Chief Medical Officer and shareholder of SenSem Technologies Ltd, Tampere, Finland.

The FINNALI Study Investigators

Participating hospitals and investigators

Satakunta Central Hospital: Dr. Vesa Lund, Päivi Tuominen, Pauliina Perkola; East Savo Central Hospital: Dr. Markku Suvela, Sirpa Kauppinen, Anne-Marja Turkulainen; Central Finland Central Hospital: Dr. Raili Laru-Sompa, Tiina Kirkhope, Sirpa Nykänen; South Savo Central Hospital: Dr. Heikki Laine, Kirsi Reponen, Pekka Kettunen; North Karelia Central Hospital: Dr. Matti Reinikainen, Tanja Eiserbeck, Helena Jyrkönen; Seinäjoki Central Hospital: Dr. Kari Saarinen, Dr. Matti Viitanen, Niina Siirilä, Johanna Soini; South Karelia Central Hospital: Dr. Seppo Hovilehto, Dr. Anne Kirsi, Dr. Pekka Tiainen, Sanna Asikainen; Päijät-Häme Central Hospital: Dr. Pekka Loisa; Vaasa Central Hospital: Dr. Pentti Kairi; Kanta-Häme Central Hospital: Dr. Risto Puolakka, Piia Laitinen, Tarja Heikkilä; Lappi Central Hospital: Dr. Outi Kiviniemi, Tarja Laurila, Tiina Pikkuhookana; Keski-Pohjanmaa Central Hospital: Dr. Samuli Forsström, Dr. Tadeusz Kaminski, Tuija Kuusela; Kymenlaakso Central Hospital: Dr. Jussi Pentti, Dr. Seija Alila, Reija Koskinen; Helsinki University Hospital-Jorvi Hospital: Dr. TeroVarpula, Mira Rahkonen; -Meilahti Hospital ICU: Dr. Ville Pettilä, Dr. Anne Kuitunen, Dr. Anna-Maija Korhonen, Dr. Rita Linko, Dr. Marjatta Okkonen, Janne Myller, Jarmo Pekkola, Leena Pettilä, Sari Sutinen; -Meilahti Hospital, Cardiac Surgical ICU: Dr. Raili Suojaranta-Ylinen, Dr. Sinikka Kukkonen, Elina Nurmi-Toivonen; -Meilahti Hospital, Department of Medicine: Dr. Tom Bäcklund, Dr. Juhani Rossinen, Riina Mäkelä; -Töölö Hospital: Dr. Janne Reitala, Dr. Jyrki Vuola, Raija Niemi, Marja-Leena Pihlajamaa, Aira Uusipaavalniemi; -Surgical Hospital: Dr. Anna-Maria Koivusalo, Pasi Kyllönen; Turku University Hospital: Dr. Juha Perttilä, Dr. Erkki Kentala, Dr. Olli Arola, Dr. Outi Inkinen, Jutta Kotamäki; Tampere University Hospital: Dr. Sari Karlsson, Dr. Jyrki Tenhunen, Minna-Liisa Peltola, Sanna Mäkinen, Anna-Liina Korkala, Samuli Kortelainen; Kuopio University Hospital: Dr. Esko Ruokonen, Dr. Ilkka Parviainen, Sari Rahikainen, Elina Halonen; Oulu University Hospital: Dr. Tero Ala-Kokko, Dr. Jouko Laurila, Sinikka Sälkiö, Tarja Lamberg.

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