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Hongisto, Mari

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Soluble urokinase-type plasminogen activator receptor improves early risk stratification in cardiogenic shock

Mari Hongisto [1],*, Johan Lassus[2], Tuukka Tarvasmäki [2], Jordi Sans-Roselló[3],
Heli Tolppanen[2], Anu Kataja[1], Toni Jäntti[2], Tuija Sabell[2], Marek Banaszewski[4],
Jose Silva-Cardoso[5], John Parissis[6], Raija Jurkko[2], Jindrich Spinar[7],
Maaret Castrén [1], Alexandre Mebazaa[8], Josep Masip[9], and Veli-Pekka Harjola[1]
for the CardShock Study Investigators and the GREAT Network

[1]Emergency Medicine, University of Helsinki, Department of Emergency Medicine and Services, Helsinki University Hospital, Helsinki, Finland; [2]Cardiology, University of Helsinki and Heart and Lung Centre, Helsinki University Hospital, Helsinki, Finland; [3]Cardiology Department, Hospital de la Santa Creu I Sant Pau, Universitat Autònoma de Barcelona, Biomedical Research Institute IIB-Sant Pau, CIBER-CV, Spain; [4]National Institute of Cardiology, Warsaw, Poland; [5]CINTESIS—Center for Health Technology and Services Research, Faculty of Medicine, University of Porto, São João University Medical Center, Faculty of Medicine, University of Porto, Porto, Portugal; [6]ER and Heart Failure Unit, Attikon University Hospital, National and Kapodestrian University of Athens, Athens, Greece; [7]St. Ann university hospital and Medical faculty Masaryk University, Brno, Czech Republic; [8]Université de Paris, Inserm 942—MASCOT, Paris, France; and [9]Research Direction, Consorci Sanitari Integral, University of Barcelona, Barcelona, Spain

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Aims	Soluble urokinase–type plasminogen activator receptor (suPAR) is a biomarker reflecting the level of immune activation. It has been shown to have prognostic value in acute coronary syndrome and heart failure as well as in critical illness. Considering the complex pathophysiology of cardiogenic shock (CS), we hypothesized suPAR might have prognostic properties in CS as well. The aim of this study was to assess the kinetics and prognostic utility of suPAR in CS.
Methods and results	SuPAR levels were determined in serial plasma samples (0–96 h) from 161 CS patients in the prospective, observational, multicentre CardShock study. Kinetics of suPAR, its association with 90-day mortality, and additional value in risk-stratification were investigated. The median suPAR-level at baseline was 4.4 [interquartile range (IQR) 3.2–6.6)] ng/mL. SuPAR levels above median were associated with underlying comorbidities, biomarkers reflecting renal and cardiac dysfunction, and higher 90-day mortality (49% vs. 31%; $P = 0.02$). Serial measurements showed that survivors had significantly lower suPAR levels at all time points compared with nonsurvivors. For risk stratification, suPAR at 12 h (suPAR$_{12h}$) with a cut-off of 4.4 ng/mL was strongly associated with mortality independently of established risk factors in CS: OR 5.6 (95% CI 2.0–15.5); $P = 0.001$) for death by 90 days. Adding suPAR$_{12h} > 4.4$ ng/mL to the CardShock risk score improved discrimination identifying high-risk patients originally categorized in the intermediate-risk category.
Conclusion	SuPAR associates with mortality and improves risk stratification independently of other previously known risk factors in CS patients.

* Corresponding author. Tel: +358 40 586 3263, Fax: +358 9 471 66650, Email: mari.hongisto@hus.fi

Graphical Abstract
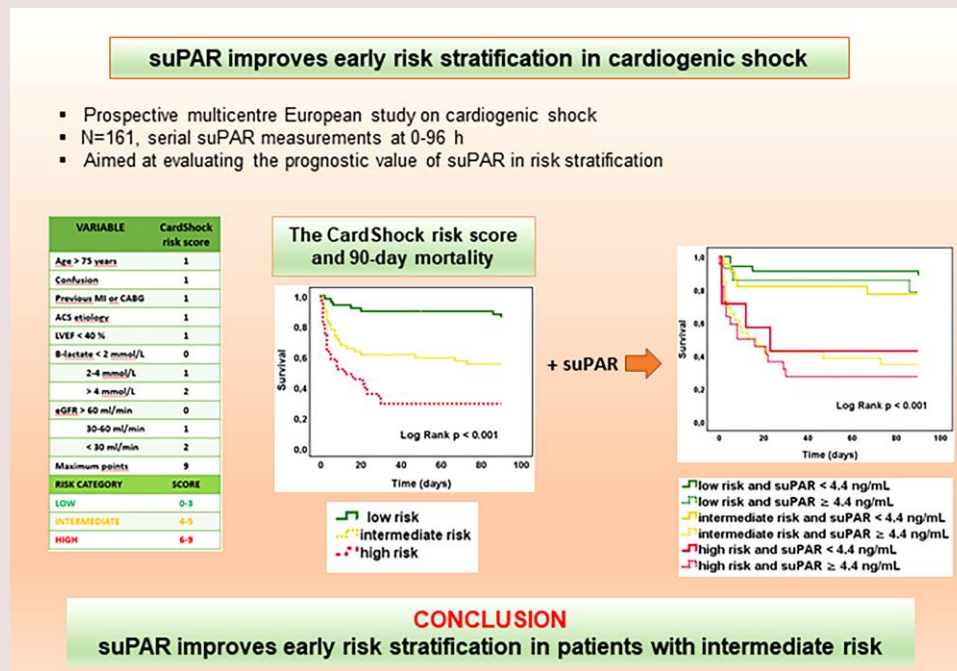
Soluble urokinase-type plasminogen activator receptor (suPAR) improves early risk stratification in cardiogenic shock spesifically in patients with intermediate risk.

Introduction

Cardiogenic shock (CS) is the most life-threating manifestation of acute heart failure (HF) characterized by systemic hypoperfusion due to severe cardiac dysfunction, often leading to multi-organ failure. In addition, the activation of systemic inflammatory responses plays a central role in the complex pathogenesis of CS.[1]

Soluble urokinase–type plasminogen activator receptor (suPAR) is the soluble form of the membrane-bound urokinase plasminogen activator receptor.[2,3] SuPAR is thought to reflect the level of immune activation. It has been shown to have excellent prognostic properties in several acute and chronic inflammatory states, including infectious diseases, cancer, organ failures, critical illnesses, and cardiovascular diseases.[4–9] High suPAR levels are known to associate with worse outcome in acute and chronic kidney disease, as well as in HF.[7,9,10]

Biomarkers have proved to be helpful in risk stratification and prognostication in cardiovascular diseases. We hypothesized that suPAR could serve as a biomarker reflecting multi-organ dysfunction as well as the severity of the systemic inflammatory response involved in CS pathogenesis, and be valuable in risk prediction in CS.

The aim of this study was to investigate the role of suPAR in CS using serial measurements, to assess its association with organ dysfunction, and to evaluate the prognostic ability and value of suPAR in early risk stratification in CS.

Methods

This was a biomarker substudy of the CardShock study. The CardShock study (ClinicalTrials.gov identifier: NCT01374867) was a prospective, observational, multicentre study on CS conducted in nine tertiary centres in eight European countries between October 2010 and December 2012. A detailed description of the study design and main results have been previously published.[11]

Inclusion criteria and data collection

Patients (n = 219) aged over 18 years were included within 6 hours from the detection of shock. In addition to an acute cardiac cause, the inclusion criteria required a systolic blood pressure (SBP) of < 90 mmHg for 30 min (despite adequate fluid administration), *or* the need for a vasopressor to maintain SBP > 90 mmHg *and* at least one sign of hypoperfusion (altered mental status, cold periphery, oliguria < 0.5 mL/kg/h for the previous 6 h, or blood lactate > 2 mmol/L). Exclusion criteria included shock caused by ongoing haemodynamically significant arrhythmia and shock after cardiac or non-cardiac surgery. The aetiology of CS [acute coronary syndrome (ACS) or non-ACS] was defined by the local investigators, and the patients were treated according to local clinical practice. Medical history, baseline characteristics, clinical signs, and treatment and procedures were recorded. The primary endpoint was 90-day all-cause mortality. Written informed consent was obtained from each patient or next of kin if the patient was unable to give the consent on admission. The study was approved by local ethics committees and conducted in accordance with the Declaration of Helsinki.

Blood sampling and laboratory analyses

Serial plasma samples were collected at seven pre-specified time points: at baseline (0 h), 12, 24, 36, 48, 72, and at 96 h. Plasma aliquots were immediately frozen and stored at −70°C until assayed. Patients with available study plasma samples at baseline were included in this substudy (n = 161); two centres did not participate in the biomarker substudy. Creatinine, C-reactive protein, alanine aminotransferase, high-sensitivity troponin T

(hsTnT), and n-terminal pro–B-type natriuretic peptide (NT-proBNP) were analysed using assays from Roche Diagnostics (Basel, Switzerland), whereas suPAR was analysed using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (suPARnostic®, ViroGates, Denmark). SuPAR was analysed by ViroGates in Denmark, whereas rest of the biomarkers were analysed at a central accredited laboratory (ISLAB, Kuopio, Finland). Arterial blood lactate and pH were analysed locally. Estimated glomerular filtration rate (eGFR) was calculated from creatinine values using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation.[12]

Statistical analyses

Results are presented as numbers (n) and percentages (%) for categorical variables, and as means and standard deviations (SD), or as medians and interquartile ranges (IQRs) for continuous variables, as appropriate. Patients were categorized by the baseline median suPAR into two groups: (i) above median and (ii) median or less. Between-group comparisons were performed using Chi-squared tests or Fisher's exact tests for categorical variables and Student's t-tests or Mann–Whitney U tests for continuous variables, as appropriate. Wilcoxon signed rank tests were used to determine differences in serial suPAR measurements. Spearman tests were used to assess the correlation of suPAR with other biomarkers. The correlation analyses were performed on samples taken at 12 h. Differences in suPAR levels between survivors and non-survivors over time were analysed with linear mixed modelling; due to skewed distribution, suPAR values were log-transformed to normalize the distribution and the residuals. The primary endpoint was all-cause 90-day mortality; three patients were lost to follow-up.

Kaplan–Meier curves were used to examine the 90-day survival and log-rank tests were used for group comparisons. A multivariate logistic regression model was used to evaluate the association of suPAR with 90-day mortality. The model was adjusted with the CardShock risk score, a nine-point risk prediction tool for in-hospital mortality consisting of seven clinical parameters: age, eGFR, blood lactate, confusion on admission, left ventricular ejection fraction (LVEF), previous myocardial infarction or coronary artery bypass grafting, and ACS aetiology.[11] Results from the regression analyses are presented as odds ratios (ORs) with 95% confidence intervals (CIs).

To evaluate the prognostic value of suPAR and its capability to improve discrimination beyond the CardShock risk score, receiver operating characteristic (ROC) curves were generated and the areas under the curves (AUC) were calculated. The Youden index was used to determine the optimal cut-off value for suPAR at 12 h ($suPAR_{12h}$) from the ROC curve. The additional value of suPAR in the risk prediction model was assessed using the likelihood ratio test for nested models. A two-sided P value <0.05 was regarded as statistically significant. All statistical analyses were performed with SPSS 25.0 software (IBM, Armonk, NY).

Results

This study included 161 patients with a mean age of 66 (12) years; 26% were women, and ACS was the main cause of shock (79%). All-cause mortality at 90 days was 40%. The clinical characteristics of the study population are presented in Table 1.

SuPAR levels in CS

Baseline suPAR level measurements were available from 161 patients, with a median of 4.4 (IQR 3.2–6.6) ng/mL. In serial sampling, the median level of the biomarker remained relatively stable during the first 12 h [4.4 (IQR 3.3–7.5) ng/mL at 12 h] but tended to increase from then on, reaching a maximum at 96 h with a median of 5.6 (IQR 4.1–9.4) ng/mL.

Table 1 outlines the clinical characteristics and presentation, biochemistry at baseline, and treatment, stratified by the baseline median suPAR level. The prevalence of comorbidities, particularly HF, atrial fibrillation, and renal failure, was significantly higher among those with a baseline suPAR above median, as were the levels of creatinine, NT-proBNP, and CRP. ACS aetiology was more common in patients with suPAR ≤ median. The treatment did not differ with respect to the suPAR level (Table 1). The use of mechanical assist devices was infrequent in this study, only few patients were treated with temporary mechanical circulatory support, except for the use of intra-aortic balloon pump, which was used in 87 (46%) patients.

Correlation of suPAR with other biomarkers

SuPAR correlated moderately with markers reflecting renal function (creatinine ρ = 0.44, P < 0.001; and estimated GFR ρ = –0.46; P < 0.001), congestion/cardiac stress (NT-proBNP ρ = 0.41, P < 0.001), and CRP (ρ = 0.38; P < 0.001). Conversely, suPAR did not correlate with hs-TnT, neutrophil-to-lymphocyte ratio (NLR) or with pH, and its correlation with age (ρ = 0.26; P = 0.003), lactate (ρ = 0,30; P = 0.001), and Alat (ρ = 0.22; P = 0.008) was modest.

Outcome and serial sampling of suPAR

Clinical outcomes, stratified by the baseline median suPAR level, are presented in Table 1. Mortality at 90 days was significantly higher in those having baseline suPAR above median (49% vs. 31%; P = 0.02). According to serial measurements, survivors had significantly lower suPAR levels at all time points compared with non-survivors (Figure 1; P < 0.001 for between-group, and P < 0.001 for all pairwise comparisons). Furthermore, suPAR levels remained fairly stable during the first 24 h among survivors 4.15 (IQR 2.85–5.95) ng/mL at baseline vs. 3.84 (IQR 2.80–5.46) ng/mL at 24 h; P = 0.84. In contrast, in non-survivors suPAR levels increased from 5.11 (IQR 3.36–7.13) ng/mL at baseline to 5.90 (IQR 4.49–9.32) ng/mL at 24 h; P < 0.001. Changes in suPAR levels differed significantly between survivors and non-survivors during the whole study period ($P_{interaction}$ < 0.001) (Figure 1).

SuPAR in risk prediction

To assess the ability of suPAR for early risk stratification in CS, we selected $suPAR_{12h}$ for further analysis (n = 138). When analysed as a continuous variable, $SuPAR_{12h}$ had an AUC of 0.72 for 90-day mortality. According to the Youden index, the optimal cut-off value for $suPAR_{12h}$ to predict outcome was 4.4 ng/mL. Patients with $suPAR_{12h}$ > 4.4 ng/mL had a 90-day mortality of 56% compared with 19% for those with $suPAR_{12h}$ ≤ the cut-off (P < 0.001). After adjustment for the CardShock risk score variables, $suPAR_{12h}$ remained an independent predictor for 90-day mortality, OR 5.6 (2.0–15.5); P = 0.001. We analysed the predictive role of NLR as well. Although NLR was an independent predictor for 90-day mortality when adjusted for the CardShock variables (OR 0.94 [0.89–0.996]; P = 0.04), after adjusting this model further with $suPAR_{12h}$ ≥ 4.4 ng/mL, NLR lost its predictive role, but suPAR associated independently with the outcome.

As a binary variable partitioned by the cut-off value, $SuPAR_{12h}$ improved discrimination compared to CardShock risk score alone (AUC 0.87 vs. 0.84; χ2 = 14.2 for 90-day mortality prediction; P < 0.001 for comparison of nested models) (Figure 2) as well as when added on top of the CardShock risk score and NLR (AUC 0.81 vs. 0.86; P = 0.004) (see Supplementary material online, Figure S1).

Kaplan-Meier analysis showed that, by dividing each CardShock risk category by the $suPAR_{12h}$ cut-off into two subgroups (low/intermediate/high risk category + $suPAR_{12h}$ above or below cut-off), risk stratification improved, especially in the intermediate risk group (Figure 3).

Table 1 Clinical characteristics and presentation, biochemistry, treatment of the shock, and outcome

|	All *n* = 161	suPAR ≤ median *n* = 81	suPAR > median *n* = 80	*P*-value
Age, years (SD)	66 (12)	66 (11)	66 (12)	1.0
Female, *n* (%)	41 (26)	21 (26)	20 (25)	0.9
BMI, kg/m² (SD)	27 (4)	27 (4)	27 (4)	0.8
Aetiology of shock, *n* (%)				
ACS	127 (79)	71 (88)	56 (70)	0.006
STEMI	106 (66)	65 (80)	41 (53)	<0.001
Medical history, *n* (%)				
Hypertension	100 (62)	47 (58)	53 (66)	0.3
Diabetes	48 (30)	21 (26)	27 (34)	0.3
Coronary artery disease	53 (33)	21 (26)	32 (40)	0.06
Heart failure	27 (17)	7 (9)	20 (25)	0.005
Atrial fibrillation	25 (16)	6 (7)	19 (24)	0.004
Renal insufficiency	19 (12)	1 (1)	18 (23)	<0.001
Clinical presentation (at baseline)				
Systolic BP; mmHg	77 (14)	75 (12)	80 (15)	0.05
HR, beats/min	88 (28)	86 (26)	90 (29)	0.4
LVEF; %	32 (14)	35 (14)	29 (13)	0.006
CardShock risk score	4.3 (1.9)	3.9 (1.9)	4.7 (1.9)	0.008
Biochemistry (at baseline)				
Hemoglobin; g/L	129 (24)	132 (20)	125 (26)	0.05
CRP; mg/L	16 (2–75)	6 (2–25)	41 (9–89)	<0.001
Creatinine; μmol/L	101 (77–139)	88 (69–114)	127 (91–168)	<0.001
eGFR; mL/min/1.73 m²	62 (41-–87)	71 (55–96)	48 (30–70)	<0.001
ALT; U/L	46 (21–96)	44 (23–79)	50 (20–141)	0.2
pH	7.32 (7.20–7.40)	7.34 (7.21–7.43)	7.30 (7.19–7.38)	0.3
Lactate; mmol/L	2.7 (1.6–5.9)	2.6 (1.5–4.9)	3.0 (1.7–6.8)	0.1
Peak lactate; mmol/L	3.0 (2.0–6.6)	2.7 (1.7–5.5)	3.2 (2.3–8.2)	0.6
NT-proBNP; ng/L	2450 (565–9172)	1077 (253–3589)	6726 (2088–16786)	<0.001
hs-TnT; ng/L	1857 (365–5279)	1885 (446–5365)	1733 (208–5110)	0.6
NLR (*n* = 122)	6.5 (3.7–10.7)	7.0 (3.9–11.7)	5.9 (3.1–10.2)	0.6
Treatment, *n* (%)				
Coronary angiogram	132 (82)	75 (93)	57 (71)	<0.001
PCI[a]	109 (83)	66 (88)	43 (75)	0.1
CABG[a]	6 (5)	2 (3)	4 (7)	0.4
Use of norepinephrine	127 (79)	64 (79)	63 (79)	0.90
Use of dobutamine	92 (57)	45 (56)	47 (59)	0.80
Invasive mechanical ventilation	105 (65)	52 (64)	53 (66)	0.60
Renal replacement therapy	18 (11)	7 (9)	11 (14)	0.30
In-hospital mortality, *n* (%)	59 (37)	23 (28)	36 (45)	0.03
90-day mortality, *n* (%)	64 (40)	25 (31)	39 (49)	0.02

Data are presented as numbers and percentages (%), means (with SD), or medians (with interquartile range), as appropriate.

ACS, acute coronary syndrome; ALT, alanine aminotransferase; BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass surgery ;CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HR, heart rate; LVEF, left ventricular ejection fraction; NLR, neutrophil-to-lymphocyte ratio; PCI, percutaneous coronary intervention; SD, standard deviation; STEMI, ST-elevation myocardial infarction.

[a]Proportion of those who underwent angiogram.
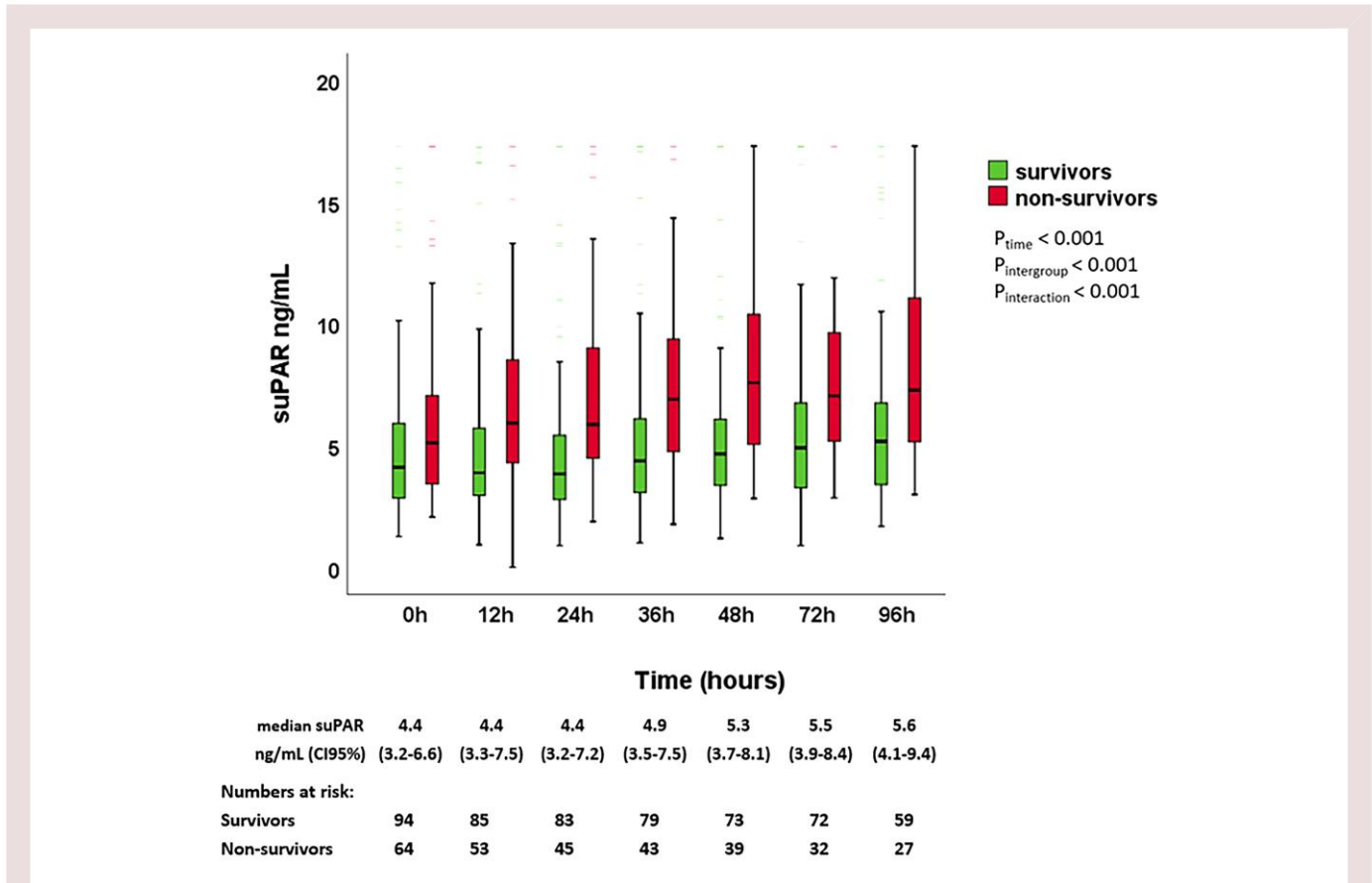
Figure 1 Soluble urokinase–type plasminogen activator receptor 0–96 h levels in survivors vs. non-survivors. Soluble urokinase–type plasminogen activator receptor levels during 0–96 h in survivors and non-survivors. Soluble urokinase–type plasminogen activator receptor median levels at each time point are presented below the figure.
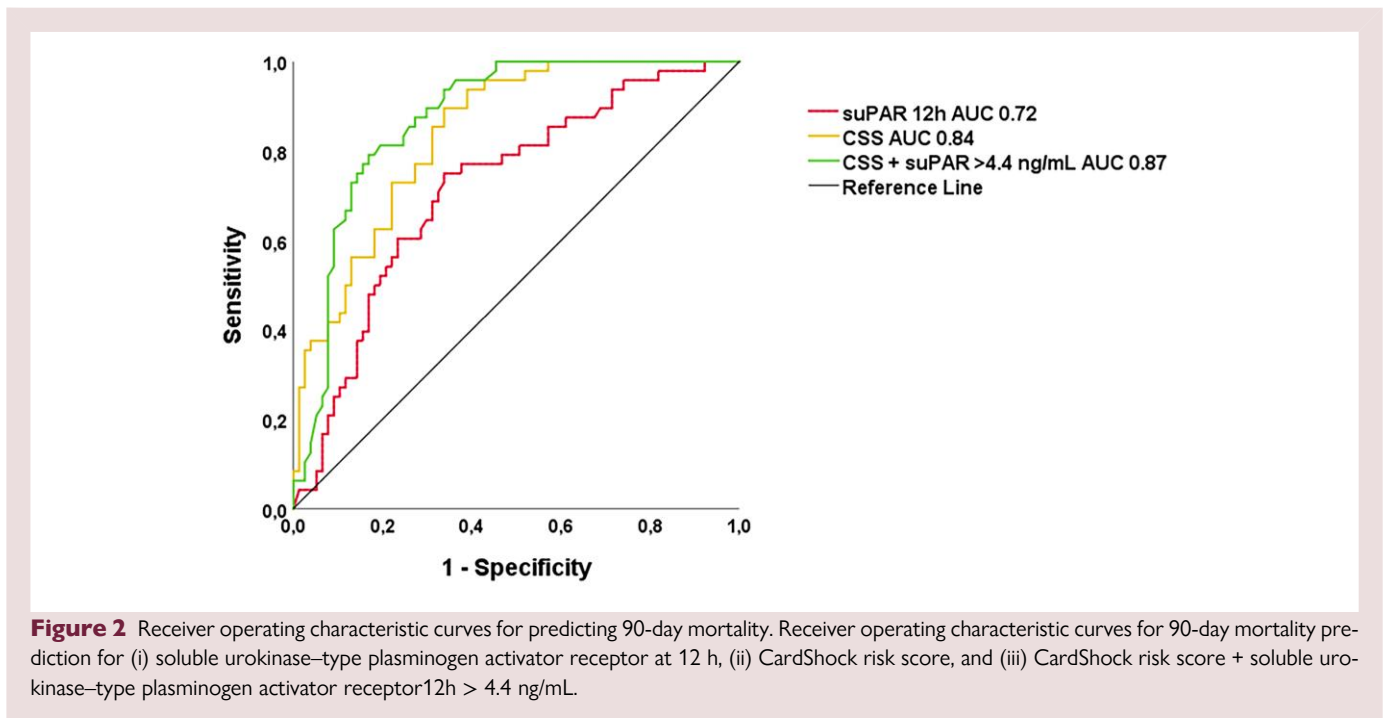
Figure 2 Receiver operating characteristic curves for predicting 90-day mortality. Receiver operating characteristic curves for 90-day mortality prediction for (i) soluble urokinase–type plasminogen activator receptor at 12 h, (ii) CardShock risk score, and (iii) CardShock risk score + soluble urokinase–type plasminogen activator receptor12h > 4.4 ng/mL.
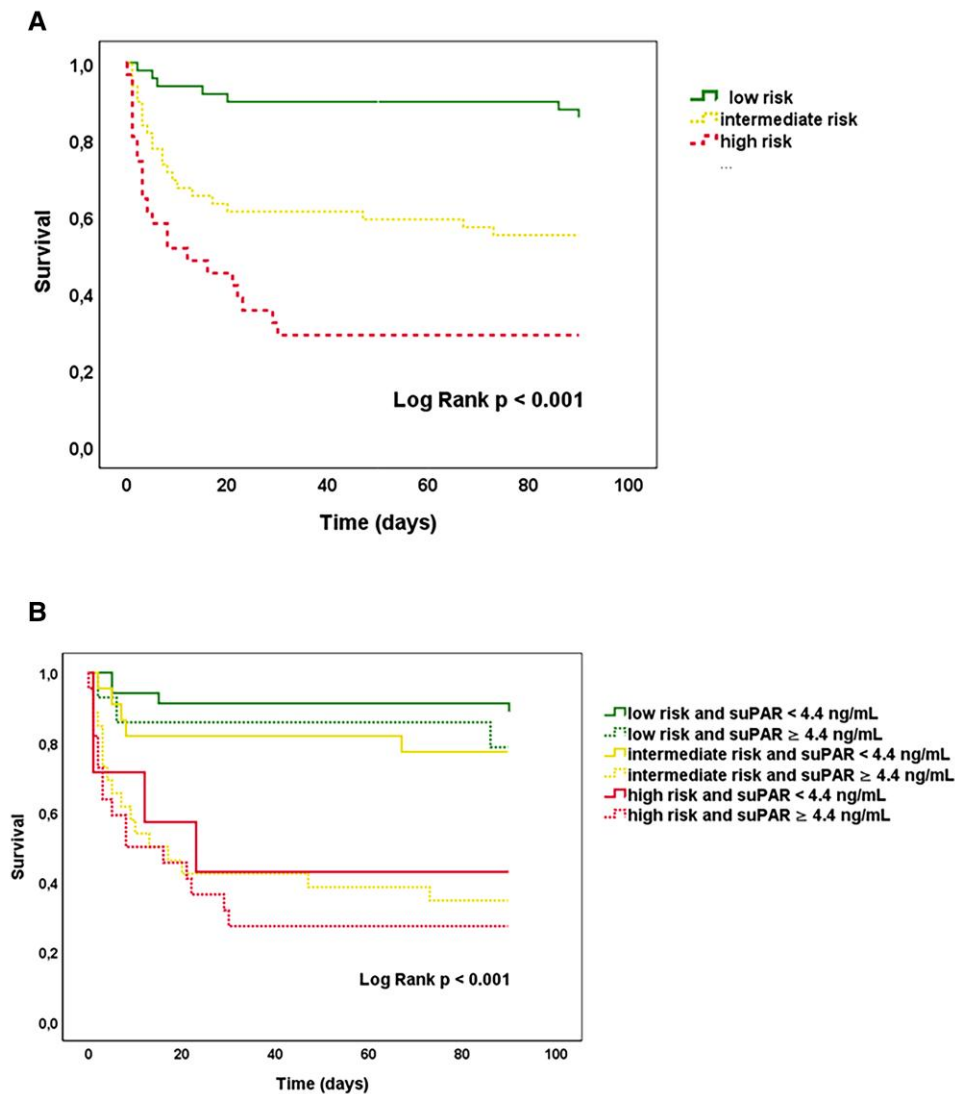
Figure 3 Kaplan–Meier survival curves for 90-day mortality stratified by the CardShock risk score categories and soluble urokinase–type plasminogen activator receptor above or below the cut-off-value 4.4 ng/mL at 12 h. Panel (*A*) comparison of survival curves according to the CardShock risk score categories (low/intermediate/high risk), (*B*) comparison of survival curves according to the CardShock risk score categories (low/intermediate/high risk) divided by the soluble urokinase–type plasminogen activator receptor cut-off 4.4 ng/mL at 12 h into two subgroups.

Discussion

This is the first study to assess suPAR in the context of CS and its association with outcome. We report three main findings. First, suPAR levels in CS are elevated and associate with comorbidities and acute organ dysfunctions. Secondly, higher suPAR levels are associated with worse outcomes, and suPAR is a strong and independent predictor of mortality in CS. Finally, measuring $suPAR_{12h}$ from baseline with a cut-off of 4.4 ng/mL improves early risk stratification.

The suPAR levels in our study were markedly lower than suPAR levels reported in other critically ill patients. In sepsis, suPAR has been reported to be as high as 9–11 ng/mL, and, in acute severe pancreatitis, the biomarker has been shown even to reach 17 ng/mL.[5,13,14] In contrast, the suPAR levels in this study more closely resemble those reported in populations with ST-elevation myocardial infarction and chronic HF (3.5–4 ng/mL).[9,15] The differences in suPAR

concentrations between CS and sepsis or pancreatitis may be due to a higher degree of inflammation and a greater amount of inflammatory cells observed in the latter critical illnesses. This can be related to two findings. First, shedding of urokinase-type plasminogen activation receptor (uPAR) from activated neutrophils has been shown to represent a main source of suPAR in serum and plasma in systemic inflammation and in patients with sepsis[16] Secondly, although inflammation has a remarkable role in the complex pathophysiology in CS, the degree of inflammation has shown to be much lower in CS than in septic shock.[17] However, systemic inflammatory response syndrome (SIRS) complicates approximately 20% of CS cases and is associated with increased mortality.[1] Biomarkers could help to identify different phenotypes of CS, such as those with SIRS, and help with the risk assessment.

SuPAR was associated with a previous history of renal insufficiency and HF, and it correlated positively with markers reflecting these

derangements. This is not surprising, considering that suPAR is known to be related to the pathogenesis and development of chronic kidney disease, and it was recently shown to be associated with a risk of acute kidney injury as well.[7,10] In addition, suPAR has been shown to predict mortality in chronic HF.[9] It remains unclear whether suPAR is a specific, prognostic biomarker for CS or merely reflects the severity of underlying chronic as well as acute renal dysfunction and HF, both related to worse prognosis in CS. However, SuPAR was shown to be a strong and independent predictor of mortality in CS. The underlying pathophysiological mechanisms behind the incremental prognostic ability of suPAR are not fully understood. The causes may be multifactorial and relate to the close correlation of suPAR with existing co-morbidities and incident acute organ failures as well as with the complex pathophysiology of CS itself.

NLR, another biomarker of inflammation, did not correlate with suPAR in our study. SuPAR outperformed NLR in prognostication and discrimination. Interestingly, higher NLR levels associated with a better outcome. Our results are somewhat contradictory compared with a study by Jentzer et al.,[18] who found high NLR levels to associate with a worse outcome. However, the association was seen in milder shock states but not in more severe cases reflecting probably diminished role of inflammation and NLR or exhaustion of the immune system in severe shock. The patient population in the study by Jentzer et al.[18] is quite different from our study—only 6% had CS as an admission diagnosis and in-hospital mortality in this study was low (8%). The patients in our study suffered from more severe CS which probably explains the controversial observations.

We found that an optimal cut-off of 4.4 ng/mL for $suPAR_{12h}$ strongly predicted mortality and improved early risk stratification when added to the CardShock risk score, especially in the patients with intermediate risk. This is an important finding, considering the acute setting of CS and the importance of identifying high-risk patients who would benefit most from further intensive and costly treatment options, such as mechanical circulatory support. Evaluation of the patients with intermediate risk with traditional clinical tools may remain imprecise and potentially delay implication of further life-saving interventions. Using suPAR as a 'warning bell', in combination with mainly clinical variables in the CardShock risk score, could identify patients at high risk more accurately, and thus guide the treatment intensity after the initial phase of CS.

When a novel biomarker is considered to be applied in clinical use, the costs and usefulness are carefully assessed. Considering suPAR, there is a commercially available kit with a rapid turnaround time. SuPAR can be analysed on automated analyser platforms routinely used in laboratories with short (1–2 h) turn-over times so the test results will be available in a time frame comparable to that of other routinely used biomarkers. Furthermore, there is a point-of-care -test available for suPAR increasing its attractiveness and applicability from a clinical point of view. The costs of suPAR testing are comparable to other commonly used biomarkers.

Limitations

This study has some limitations to be acknowledged. First, blood samples were not available from all the 219 patients of CardShock study and at all time points. However, this is one of the largest biomarker cohorts in CS. Secondly, since this was the first study to explore the prognostic role of suPAR in CS, the determined cut-off value needs to be validated in further studies. Thirdly, as with other observational studies, there may be residual unidentified confounders which could have led to an overestimation of the independent association of suPAR with mortality. Finally, even though the aetiology of CS in the CardShock study was unselected, the number of the patients presenting with non-ACS-CS was limited, and most of the patients (up to 80%)

presented with ACS-CS. In more recent studies non-ACS aetiology has been more common and in contrast to our study, the prognosis has been better in patients with ACS-CS.[19]

Conclusions

Circulating suPAR levels are elevated in CS and associate with multiple acute and chronic organ impairments. Higher suPAR levels are independently associated with mortality in CS patients. Finally, suPAR improves early risk stratification, especially in patients initially categorized into intermediate risk class by the CardShock risk score.

Supplementary material

Supplementary material is available at European Heart Journal: Acute Cardiovascular Care online.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author. The data that support the findings of this study are available from the corresponding author (M.H.) upon reasonable request.

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