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Circulating soluble urokinase plasminogen receptor is reduced by - and predicts early treatment response to therapeutic plasma exchange in septic shock

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Sepsis is a life-threatening organ dysfunction caused by a dysregulated host-response to infection affecting immune and endothelial function and coagulation (1). Circulating soluble urokinase plasminogen activator receptor (suPAR) can attract inflammatory cells into organs (2,3) and correlates with organ injury and mortality. Targeting suPAR may hold promise in modulating the dysregulated host response.

We have recently reported hemodynamic stabilization upon therapeutic plasma exchange (TPE) in early (<24 h) and severe (norepinephrine-tartrate (NE) >0.4 μg/kg/min) septic shock (4,5). However, the underlying immunological effects are poorly understood and it remains unclear which subset of patients benefit most. Here, the effect of TPE on circulating suPAR-levels was investigated in a post-hoc biobank-analysis of the EXCHANGE study-program. Further, longitudinal change of suPAR was used to predict subsequent clinical response, indicated by reduction of lactate during the first 24 h.

Serum suPAR-levels from 49 patients with septic shock were measured by ELISA (suPARnostic assay, ViroGates) at baseline and after 6 h. Fourteen patients were initially assigned to standard of care (SOC) and 35 patients to the intervention group (SOC +1× TPE). Median (IQR) SOFA score at inclusion was 17 (15–20), NE dose was 0.660 (0.483–0.887) μg/kg/min and lactate was 4.2 (2.6–6.9) mmol/l. Ninety-two percent were mechanically ventilated and 63 % required renal replacement therapy (RRT) (Table 1).

Baseline suPAR correlated with SOFA-score ($r = 0.425, p = 0.002$) and lactate ($r = 0.294, p = 0.04$) and patients on RRT had higher suPAR-levels (RRT: 15.9 (11.7–25.2) ng/ml vs. no RRT: 10.7 (7.2–13.8) ng/ml, $p = 0.005$). Interestingly, suPAR-levels further correlated with indicators of endothelial activation (Fig. 1A, B). Initial suPAR-concentrations were comparably high in both groups (12.3 vs. 13.8 ng/ml, $p = 0.887$, Fig. 1C). However, after 6 h, suPAR was lower in the TPE group ($p = 0.01$, Fig. 1C). While longitudinal suPAR even increased in the SOC group within 6 h (+3.7 (−6 to +14.4) %, $p = 0.135$), they significantly decreased in the TPE group (−32.3 (−42.7 to −24) %, $p < 0.001$) (Fig. 1D). This corresponded to an absolute change of +0.6 (−1 to +2.1) ng/ml in the SOC and − 5.3 (−7.5 to −2.1) ng/ml in the TPE group (Fig. 1E), respectively. A linear mixed-effects model showed a triple interaction of time, study-intervention and delta-suPAR on longitudinal lactate concentrations over the first 24 h. TPE patients with a reduction of suPAR within 6 h also experienced a lactate reduction during the following 24 h, while TPE patients with increasing suPAR experienced diminishing lactate reductions over 24 h in contrast to patients under SOC ($p = 0.006$, Fig. 1F).

This study supports the association of suPAR with severity of illness (2,3). The median suPAR concentration of 13.8 ng/ml was higher than the recently identified cut-off for the highest risk of RRT and death in septic shock patients (3). Importantly, this study highlights a potential therapeutic intervention to reduce suPAR. Of interest, early longitudinal change of suPAR-levels predicted subsequent clinical response to TPE, suggested by reduction of lactate during the first 24 h. While a reduction in suPAR within 6 h was associated with a sustained lactate reduction with TPE (indicating potential benefit over SOC), an early increase of suPAR despite TPE was associated with impaired lactate clearance.

Sample size and bicentric setting are limitations of this study. Repeated measurements at preselected timepoints including the days following treatment will be implemented in follow-up trials (NCT05726825) to capture the variability due to biomarker assessment time.

In summary, this post-hoc analysis of two septic shock trials found that suPAR-levels correlated with disease severity, organ dysfunction and endothelial activation. TPE reduced levels of suPAR by more than one-third. In a multivariate mixed-effects model, only reduced suPAR concentrations following the study intervention predicted early treatment response, as indicated by sustained longitudinal lactate reduction.

Abbreviations: AKI, Acute kidney injury; Angpt-1, Angiopoietin-1; FFP, Fresh frozen plasma; IQR, Interquartile range; RCT, Randomized controlled trial; RRT, Renal replacement therapy; SOC, Standard of care; SOFA, Sequential Organ Failure Assessment; suPAR, soluble urokinase plasminogen receptor; TPE, Therapeutic plasma exchange; vWF:Ag, von-Willebrand-factor-antigen.

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Table 1
Demographic and clinical characteristics at study inclusion.

Category	All $n = 49$	SOC $n = 14$	TPE $n = 35$	p
Age - years (median, [IQR])	53 [43–59]	54 [43–63]	53 [42–58]	0.838
Sex - n (%)				0.162
Female	14 (28.6)	2 (14.3)	12 (34.3)	
Male	35 (71.4)	12 (85.7)	23 (65.7)	
BMI - kg/m^2 (median, [IQR])	25.4 [22–31.1]	25.4 [22.8–34.3]	25 [21–31.1]	0.153
Sepsis onset - n (%)				
Ambulatory	30 (61.2)	9 (64.3)	21 (60)	0.781
Hospital	19 (38.8)	5 (35.7)	14 (40)	1
Side of infection - n (%)				
Pulmonary	31 (63.3)	9 (64.3)	22 (62.9)	0.925
Abdominal	12 (24.5)	4 (28.6)	8 (22.9)	0.674
Soft tissue	4 (8.2)	1 (7.1)	3 (8.6)	0.869
Endocarditis	2 (4.1)	0 (0)	2 (5.7)	0.361
Identified pathogen - n (%)				
Gram+	10 (20.4)	4 (28.6)	6 (17.1)	0.370
Gram-	15 (30.6)	4 (28.6)	11 (31.4)	0.845
Fungal	4 (8.2)	1 (7.1)	3 (8.6)	0.869
Viral	4 (8.2)	2 (14.3)	2 (5.7)	0.322
Mixed	4 (8.2)	0 (0)	4 (11.4)	0.187
Non-identified	12 (24.5)	3 (21.4)	9 (25.7)	0.753
SOFA score - points (median, [IQR])	17 (15–20)	17 [14–19]	17 [15–20]	0.645
Norepinephrine dose - µg/kg/min (median [IQR])	0.660 [0.483–0.887]	0.483 [0.443–0.624]	0.792 [0.561–1.037]	0.071
Lactate concentration - mmol/l (median, [IQR])	4.2 (2.6–6.9)	3.9 [2.9–5.5]	4.3 [2.5–9.1]	0.098
RRT - n (%)	31 (63.3)	8 (57.1)	23 (65.7)	0.574
Mechanical ventilation - n (%)	45 (91.8)	12 (85.7)	33 (94.3)	0.322
Oxygenation index (PaO_2/FiO_2) - mmHg (median [IQR])	135 [94–233]	167 [89–249]	128 [93–223]	0.740

Given are demographic and clinical characteristics at the time of study inclusion for patients receiving standard of care treatment (SOC) as well as for patients receiving additive therapeutic plasma exchange (TPE). Values are presented as median (25 % to 75 % interquartile range) or if categorical as numbers and percentages.
BMI - Body mass index, IQR - Interquartile range, RRT - Renal replacement therapy, SOFA - Sequential Organ Failure Assessment.

Ethics approval and consent to participate

The ethical committee of Hannover Medical School (No. 2786–2015 and No. 8852_MPG_23b_2020) and University Medicine Bonn (No. 024/20) approved protocols of both studies, and written informed consent was obtained from participants or authorized representatives. The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Consent of publication

Not applicable.

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Authors contributions

KS and AS collected clinical data from the PDMS and generated the figures for publication. PDWG performed mixed effect modelling. BMWS was the leading nephrology consultant coordinating and performing the plasma-exchange on our unit. CN and MW performed the laboratory experiments. KS, AS, JJS, BS, TP, HS, LW, KP, CB and SD recruited patients. KS, CN, PDWG, CB, MAW and SD interpreted data. KS, CN, PDWG, CB, MAW and SD wrote the manuscript. KS, CB and SD had the original idea for both trials and wrote the proposals. All authors read an approved the final manuscript.

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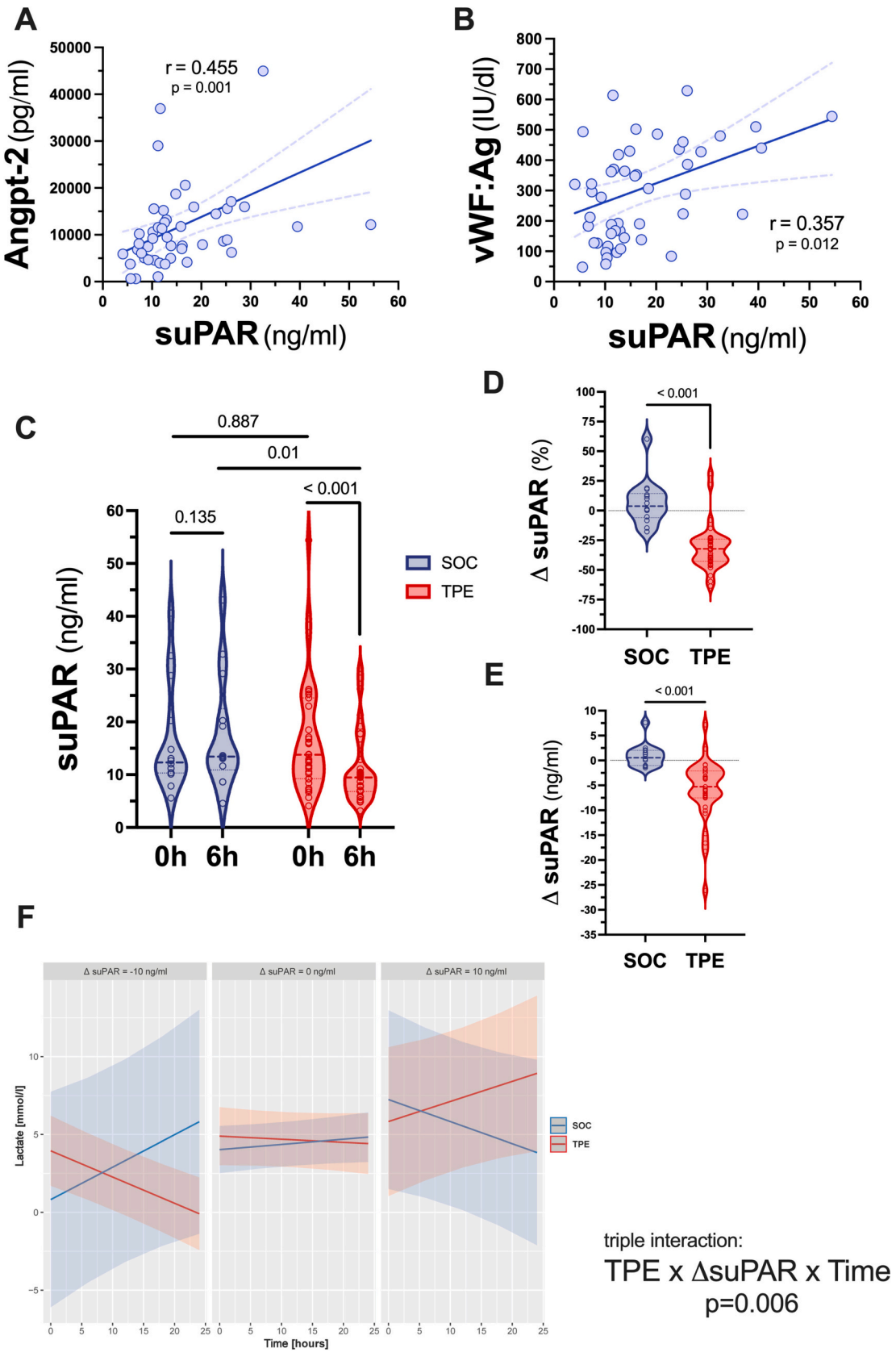

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Fig. 1. Effect of therapeutic plasma exchange on circulating levels of soluble urokinase plasminogen receptor activator and prediction of early treatment response.
Correlation of soluble urokinase plasminogen receptor activator (suPAR) serum concentrations with circulating levels of angiopoietin-2 (Angpt-2) (**A**) and von-Willebrand-factor-antigen (vWF:Ag) (**B**) at study inclusion.
Violin plots showing suPAR serum concentrations at study inclusion and 6 h after study inclusion in patients with septic shock who received either standard of care (SOC) alone or SOC in combination with therapeutic plasma exchange (TPE) (**C**). Both relative (**D**) and absolute (**E**) change of suPAR concentrations over time are shown for SOC and TPE groups.
Longitudinal lactate concentration response TPE was stratified by delta-suPAR concentrations (delta calculated as concentration at 6 h after study inclusion minus concentration at study inclusion). Shown are estimated longitudinal lactate concentrations for both the standard of care (SOC) and therapeutic plasma exchange (TPE) group stratified by different delta-suPAR concentrations. Estimated values were calculated using a triple interaction model with TPE/SOC and time, as well as all simple interactions terms between fixed effects. The model indicates that TPE patients with reduced suPAR levels over time experienced a lactate concentration reduction, while TPE patients with increasing suPAR concentrations experienced diminishing lactate concentration reductions over 24 h in contrast to patients under SOC ($p = 0.006$). With decreasing longitudinal suPAR (delta-suPAR of −10 ng/ml), patients in the TPE exhibited a reduction in lactate concentrations while the SOC group showed increasing lactate concentrations (**F**, **left panel**). At stabile longitudinal suPAR (delta-suPAR = 0) both TPE and SOC groups showed no longitudinal change of lactate concentrations (**F, middle panel**). With increasing longitudinal suPAR (delta-suPAR of +10 ng/ml), patients in the TPE exhibited an increase in lactate concentrations while the SOC group showed decreasing lactate concentrations (**F**, **left panel**). The thresholds for delta-suPAR levels employed, were chosen post hoc in order to best illustrate the continuous effect of TF concentrations within the model.
Data were presented as median with interquartile range (IQR). Normality of data distribution was assessed prior with the D'Agostino-Pearson omnibus normality test and the Shapiro-Wilk normality test. Within-group effects between the chosen two time points (randomization, 6 h after randomization) were analyzed via paired-*t*-test or Wilcoxon signed-rank test as appropriate. Comparisons between groups were analyzed by means of Mann-Whitney *U* test.
Modelling of the effect of TPE on repeated-measures of lactate levels was approached by means of a linear mixed-effects model. Lactate measures were entered as outcome variable into the model, whereas TPE or SOC and time were entered as independent fixed effects including the interaction between both, finally per patient random intercepts were entered into the model. *P* values for individual fixed effects were obtained by Satterthwaite's degrees of freedom method. In order to explore predictor variables for TPE effect, delta-suPAR levels were entered as additional fixed effects including a triple interaction term with TPE/ SOC and time, as well as all simple interaction terms between fixed effects. Model fit was assessed using a likelihood ratio test of the full model with the effects in question against a "null model". Interaction terms were retained only if they were found to contribute to the model. For all statistical analyses a two-tailed p- value <0.05 was considered statistically significant. GraphPad Prism 7 (Graph Pad, La Jolla, CA, USA), SPSS Statistics Version 25 (SPSS Inc., Chicago, IL, USA) and the R environment for statistical computing version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria) were used for data analysis and graph generation.

Conceptualization.

Declaration of competing interest

The authors declare that they have no competing interest.

Data availability

The datasets used and analyzed are during the current study are available from the corresponding author on reasonable request.

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Not applicable.

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