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Soluble urokinase plasminogen activator receptor (suPAR): Its relation to neurological outcome in patients with survived cardiac arrest☆

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ABSTRACT

Background: High serum levels of the inflammatory biomarker soluble urokinase plasminogen activator receptor (suPAR) have been associated with poor neurological outcome in patients after cardiac arrest (CA), but with inadequate and contradictive prediction values. The purpose of this study was to provide further evidence on the prognostic value of suPAR for the prediction of poor neurological outcome after initially survived CA.
Methods: A total of 177 patients were prospectively enrolled in this cohort study. 85 patients with survived CA were included and the neurological outcome was assessed after 6 months. 71 patients with ST-segmental elevation myocardial infarction (STEMI) and 21 healthy control patients served as comparative groups.
Results: The serum suPAR levels on admission and the subsequent serum course were significantly higher in patients with CA as compared to STEMI and control patients. Furthermore, patients with poor neurological outcome showed significantly higher serum suPAR levels as compared to patients with good neurological outcome. By the use of ROC-curves and setting the specificities to 100%, inadequate sensitivities and cut-off values were calculated (day 2: sensitivity 21.1%, cut-off 10.2 ng/dl, AUC 0.716). By setting the specificities to at least 80% the best prediction values could be calculated for day 2 with a sensitivity of 57.9% and a cut-off value of 5.3 ng/dl.
Conclusions: SuPAR serum levels in patients with poor neurological outcome were significantly higher as compared to patients with good neurological outcome. However, the prognostic value was low and inadequate because of a substantial overlap of serum suPAR levels between the outcome groups.

1. Introduction

Myocardial infarction and sudden cardiac arrest (CA) are the leading causes of death in Europe and the USA [1]. The improved rates of restoration of spontaneous circulation (ROSC) after cardiopulmonary resuscitation (CPR) resulted in an increasing number of patients suffering from various degrees of brain damage [2]. Furthermore, ROSC following CA causes a complex ischemia–reperfusion injury with activation of a complex systemic inflammation, coagulation and fibrinolysis resulting in increased levels of circulating plasma cytokines and endotoxins [3,4].

Urokinase plasminogen activator (uPA) is a serine protease that has been implicated in a variety of physiological and pathophysiological processes. For example, uPA is known to activate extracellular matrix degrading enzymes and induces intracellular signaling pathways regulating cell adhesion and migration [5]. In addition, the uPA system has been implicated in the pathogenesis of ischemia–reperfusion injury [6]. The uPA-receptor (uPAR) is expressed on different cell types including neutrophils, lymphocytes, monocytes, macrophages and vascular endothelial cells [7]. Through inflammatory stimulation uPAR is cleaved from the cell surface by proteases to the soluble form of the receptor (suPAR), which can be detected in the blood of patients [8]. Increased suPAR blood concentrations could be detected in various infectious diseases and tumors [9,10]. Moreover, suPAR has been identified as a biochemical marker to indicate poor outcome in patients with systemic inflammatory response syndrome (SIRS) and sepsis [11].

Recently, it has been demonstrated that high levels of suPAR were associated with poor outcome in patients with out-of-hospital CA, but

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their interpretation.

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with the restriction, that the predictive value of suPAR for poor outcome was low and inadequate [12,13]. Furthermore, the time points of blood sample collection for the measurement of suPAR were limited to the 3rd and 4th day after ICU admission, respectively [12,13]. Hence, the present study was conducted to provide further information on suPAR serum concentrations as a predictor for poor neurological outcome in patients after CA. The blood samples were collected on 5 different time points (on admission, 2nd day, 3rd day, 5th day and 7th day after admission) and the neurological outcome was assessed after 6 months. Additionally, and to serve as a comparison, suPAR serum concentrations were measured in a control cohort and in patients after ST-segment elevation myocardial infarction (STEMI).

2. Methods

2.1. Study design and patients

Patients were enrolled in this study between March 2009 and June 2011 at the intensive care unit (ICU) of the RWTH Aachen University Hospital Germany in a prospective manner. Approval for the study was obtained from the ethics committee at the RWTH Aachen University Hospital Germany in accordance with the international guidelines for Good Clinical Practice. The cohort data and serum samples of the patients with CA (n = 85) used in this study have previously been evaluated for the biochemical serum marker neurofilament light chain (NF-L) to predict poor neurological outcome in patients with CA [2]. Serum samples for the determination of suPAR levels in patients with CA were taken within 2 h (day 1) after admission, as well as on days 2, 3, 5 and 7 after admission. Accordingly, serum samples for the measurement of suPAR in patients with STEMI (n = 71) were collected before percutaneous coronary intervention (PCI, day 1), as well as on days 2, 3 and 5 after admission. As a control population we analyzed 21 healthy blood donors with normal blood values. The neurological outcome of patients with CA was assessed 6 months after CPR by employing the Glasgow Outcome Score (GOS) and the Modified Glasgow Outcome Score (MGOS) [14].

2.2. Standard care

All patients with STEMI and CA were admitted to the ICU, monitored and treated according to international standards. Patients with documented ST-segment elevation in the ECG underwent coronary angiography and PCI as soon as possible. All patients with CA were intubated and mechanically ventilated. Patients were sedated using midazolam and/or propofol and received adequate analgesia with fentanyl. The procedure of mild hypothermia was performed according to international standards with the CoolGard 3000 (Zoll®, USA) and Hilotherm Clinic (Hilotherm® GmbH, Germany) cooling systems [14,15]. Vasoactive or inotropic support, usually norepinephrine or dobutamine was administered if necessary.

2.3. Neurological outcome and assessment of brain damage

Cerebral function was evaluated 6 months after CA by employing the GOS as described by Jennett and Bond [16] and the modified GOS a described previously [14].

For statistical purposes, outcome categories of both scores were split into 2 to 3 groups:

GOS:

poor: consisted of patients who died of any cause or remained in a persistent vegetative state (GOS 1–2)

good: consisted of patients who regained consciousness (GOS 3–5)

MGOS:

unclear: consisted of patients who died of any cause without documented brain damage (MGOS 0)

poor: consisted of patients who died with certified brain damage or remained in a persistent vegetative state (MGOS 1–2)

good: consisted of patients who regained consciousness (MGOS 3–5 = GOS 3–5).

Brain damage was assessed as described previously [2,14,17].

2.4. suPAR measurements

Blood samples were taken from patients and collected in a standard serum tube on time points as described above. Samples were immediately centrifuged for 10 min at 1500 g and serum aliquots were frozen immediately at −20 °C. suPAR serum concentrations were analyzed using a commercial enzyme immunoassay (ViroGates, Birkeroed, Denmark) as described previously [11].

2.5. Statistical analysis

Data are presented as median and quartiles due to the skewed distribution of most of the parameters. Differences between 2 groups were assessed by the Mann–Whitney-U-test and comparisons between more than 2 groups have been conducted by the Kruskal–Wallis-H-test and Mann–Whitney-U-test for post-hoc analysis. Box plot graphics illustrate comparison between the groups and subgroups and they display a statistical summary of the median, quartiles, upper whiskers 95%, lower whiskers 5%, minimum/maximum values and the means. All values have been included for statistical analysis without excluding the outliers. Statistical analysis of longitudinal measurements of suPAR levels have been conducted by the Friedman test. The receiver operating characteristic (ROC) curve analysis and the derived area under the curve (AUC, c-statistic) were used to provide a global and standardized appreciation of the accuracy of suPAR for predicting poor neurological outcome [18]. ROC curves were generated by plotting the sensitivity against 1-specificity. A p value < 0.05 was considered as significant. Statistical analysis was performed with the IBM SPSS Statistics 20 Software for Windows.

3. Results

3.1. Baseline characteristics

The baseline characteristics of the patients enrolled in this study are shown in Table 1. The healthy control group was significantly younger as compared to the group of STEMI or CA. Furthermore, the O_2 and CO_2 partial pressure, lactate, pH, blood glucose and serum creatine kinase on admission were significantly higher in patients with CA as compared to STEMI patients. In addition, coronary heart disease in the past medical history was more frequently present in patients with CA as compared to the control group or patients with STEMI. No further significant differences were observed among the groups.

3.2. suPAR serum concentrations upon admission

Upon admission, patients with STEMI demonstrated significantly higher levels of suPAR as compared to control patients (median — min — max — range — mean (ng/ml): control 1.7 — 0.6 — 2.5 — 1.9 — 1.55, STEMI 2.7 — 0.8 — 13.8 — 13 — 3.42, $p < 0.001$) (Fig. 1). In analogy, patients that initially survived CA showed significantly higher values of suPAR as compared to control patients (median — min — max — range — mean (ng/ml): control 1.7 — 0.6 — 2.5 — 1.9 — 1.55, CA 4.1 — 0.7 — 19.4 — 18.7 — 5.24, $p < 0.001$). In addition, comparison of suPAR serum levels of patients with STEMI and CA revealed significantly higher levels of suPAR in patients with CA as compared to STEMI (median — min — max — range — mean (ng/ml): STEMI 2.7 — 0.8 — 13.8 — 13 — 3.42, CA 4.1 — 0.7 — 19.4 — 18.7 — 5.24, $p < 0.001$).

Table 1
Baseline characteristics of patients.

Parameters (unit) ± SD	Control (1) (n = 21)	STEMI (2) (n = 71)	CA (3) (n = 85)	*p* value 1 vs. 2	*p* value 2 vs. 3	*p* value 1 vs. 3
Sex (male/female)	15/6	54/17	72/13	0.816	0.913	0.871
Age (years)	45.2 ± 15.4	63.1 ± 11.3	65.6 ± 14.2	<0.001	0.945	<0.001
On admission						
O_2 partial pressure (mm Hg)		163.3 ± 96.2	234 ± 169.4		0.008	
CO_2 partial pressure (mm Hg)		38 ± 9.7	46.4 ± 19.2		0.002	
Lactate (mmol/l)		2 ± 1.6	6.2 ± 4.5		<0.001	
pH		7.38 ± 0.11	7.23 ± 0.2		<0.001	
Blood glucose (mmol/l)		9.2 ± 4.1	13.1 ± 5.9		<0.001	
Serum creatinine (mg/dl)		0.91 ± 0.54	1.39 ± 1.2		0.002	
APACHE II			31.9 ± 5.8			
Time of hypoxia (min)			8.8 ± 3.5			
Mean duration of CPR (min)			27.3 ± 27.8			
Bystander-initiated CPR (min)			1.3 ± 3			
Defibrillations before ROSC			2.5 ± 3.4			
Epinephrine dose before ROSC (mg)			3.7 ± 3			
Hypothermia — no./total no. (%)			63/85 (74)			
Days of mechanical ventilation			9.5 ± 10.1			
First ECG no./total no. (%)						
Ventricular fibrillation			51/85 (60)			
Ventricular tachycardia			2/85 (2)			
Asystole			23/85 (27)			
Other rhythm			9/85 (11)			
Past medical history no./total no. (%)						
Diabetes	3/21 (14)	9/71 (13)	20/85 (24)	0.985	0.163	0.552
Coronary heart disease	2/21 (10)	14/71 (20)	34/85 (40)	0.544	0.012	0.009
Cerebrovascular disease	0/21 (0)	3/71 (4)	8/85 (9)	0.763	0.353	0.237
Peripheral artery disease	0/21 (0)	6/20 (30)	9/85 (11)	0.550	0.662	0.234

CA: cardiac arrest, APACHE: Acute Physiology and Chronic Health Evaluation, CPR: cardiopulmonary resuscitation, ROSC: restoration of spontaneous circulation.

Next, we subdivided the STEMI patients into ramus interventricularis anterior (RIVA), ramus circumflexus (RCX) and right coronary artery (RCA) associated STEMI and analyzed the serum concentrations of suPAR on admission. Although patients with RCA- and RCX-STEMI demonstrated higher serum suPAR levels as compared to RIVA-STEMI patients, the elevation did not reach statistical significance when compared to RIVA-STEMI patients (median — min — max — range — mean (ng/ml): RCA 3.1 — 0.8 — 13.8 — 13 — 4.04, RIVA 2.4 — 1.3 — 4.9 — 3.6 — 2.54, RCX 3.1 — 1.6 — 7.2 — 5.6 — 3.58, *p* n.s.) (Fig. 2).

In addition, on admission suPAR serum levels were measured in patients with CA, and the neurological outcome was evaluated after 6 months according to the Glasgow Outcome Score (GOS) and the Modified Glasgow Outcome Score (MGOS) as described in the method section. Patients with poor neurological outcome, either assessed by the GOS or the MGOS, demonstrated significantly higher suPAR levels as compared to patients with good neurological outcome (median — min — max — range — mean (ng/ml): GOS/MGOS good 3.9 — 0.7 — 10.9 — 10.2 — 4.18, GOS poor 5.2 — 0.9 — 19.4 — 18.5 — 6.29, MGOS poor 5.9 — 2 — 12.7 — 10.7 — 6.41) (Fig. 3). However, in contrast to

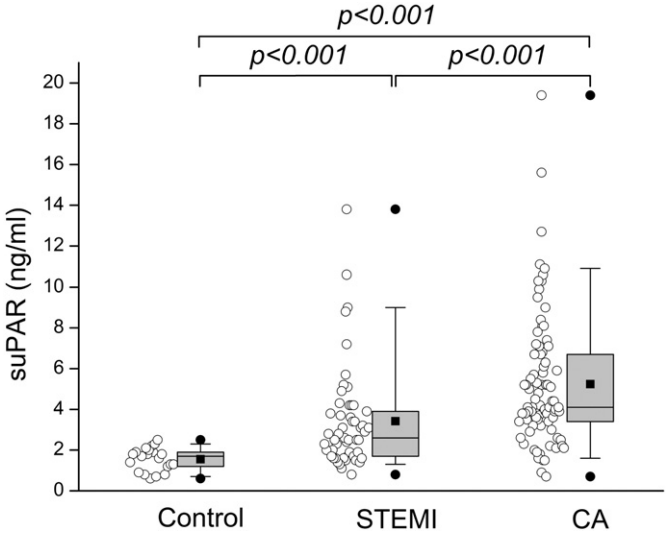

Fig. 1. suPAR serum levels in patients with CA, STEMI and healthy subjects. Box plots showing suPAR serum levels on admission in healthy subjects (n = 21), patients with STEMI (n = 52) and CA (n = 84). Serum suPAR levels were significantly elevated ($p < 0.001$, Mann–Whitney-U-test) in patients with STEMI and CA as compared to healthy controls. Furthermore, patients with CA demonstrated significantly higher suPAR levels as compared to STEMI patients ($p < 0.001$, Mann–Whitney-U-test). □ body of box with range from first to third quartile, - horizontal line in the box represents the median, ┬ upper whisker with 95%, ┴ lower whisker with 5%, ■ mean of all data, ● minimum/maximum data point, ○ data points.

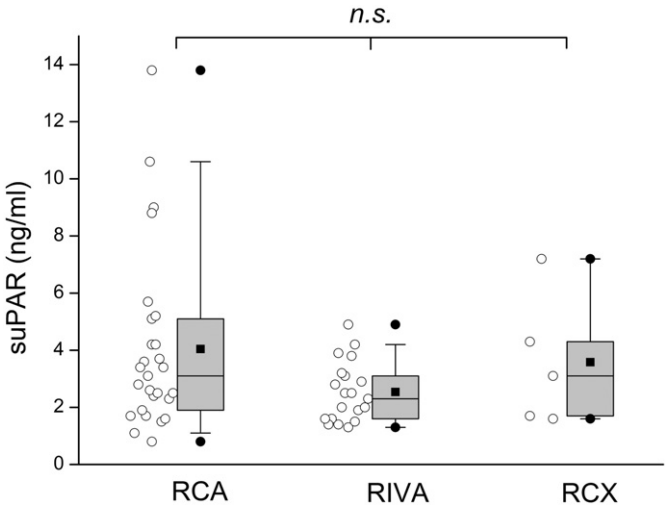

Fig. 2. suPAR serum levels in patients with STEMI. Box plots demonstrating patients with RCA (n = 27), RIVA (n = 20) and RCX (n = 5) associated STEMI on admission. No statistical significance was observed among the groups. □ body of box with range from first to third quartile, - horizontal line in the box represents the median, ┬ upper whisker with 95%, ┴ lower whisker with 5%, ■ mean of all data, ● minimum/maximum data point, ○ data points.

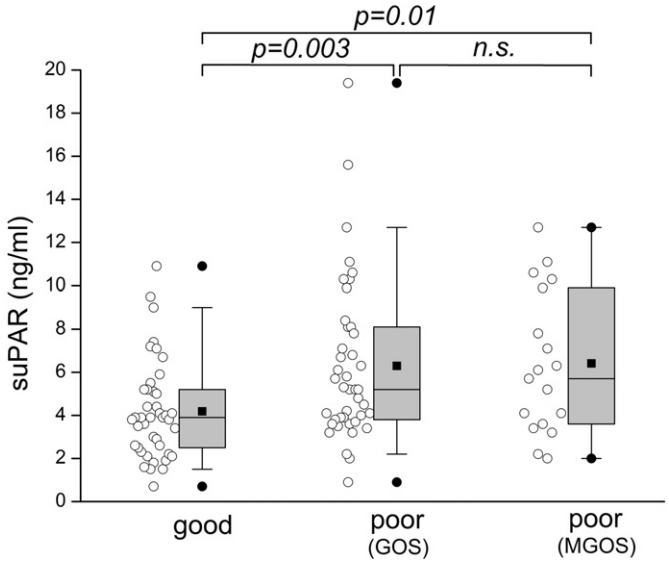

Fig. 3. suPAR serum levels in patients with CA. Box plots illustrating suPAR levels on admission in patients with good (n = 42) and poor neurological outcome as assessed 6 months after CA by the use of the GOS (n = 42) and MGOS (n = 18). Patients with poor neurological outcome demonstrated significantly higher serum suPAR levels as compared to patients with good neurological outcome. However, no significant differences were found when comparing both poor outcome groups to each other. □ body of box with range from first to third quartile, - horizontal line in the box represents the median, ┬ upper whisker with 95%, ┴ lower whisker with 5%, ■ mean of all data, ● minimum/maximum data point, ○ data points.

our findings of neuron-specific enolase (NSE), S100B and neurofilament light chain (NF-L) [2,14], no significant differences in suPAR serum levels were found among the patients with poor neurological outcome when compared GOS with MGOS.

3.3. suPAR serum course in patients with STEMI and CA

We next investigated whether suPAR levels changed in patients with STEMI during the first 5 days after admission and in patients with CA within the first week of ICU treatment. We found a tendency towards rising suPAR levels in patients with STEMI in longitudinal measurements, but serum suPAR levels did not significantly change within the first 5 days (Friedman test, $p = 0.092$) (Fig. 4A). This observation was made for the total cohort of patients with STEMI, as well for their subgroups (data not shown).

In contrast, the suPAR serum levels of patients with CA demonstrated a significant increase in longitudinal measurements during the first week after ICU admission (Friedman test, $p < 0.001$). This time-dependent elevation of suPAR could also be confirmed for the subgroups of patients with CA (Fig. 4B). These data show that the initial serum suPAR elevation in patients with STEMI and CA remains stable elevated during the studied time course with a significant increase in patients with CA.

3.4. Prediction power of suPAR for poor neurological outcome

Next, we measured cut-off values, sensitivities and AUC by the use of ROC analysis. Initially, the specificity was set to 100% for the prediction of poor outcome of suPAR for each day, respectively. The group of poor outcome comprised patients who died of any reason, either with documented brain damage or without, and patients who remained in the vegetative status (GOS 1 + 2). All other patients were categorized in the group of patients with good neurological outcome (GOS 3 + 4 + 5).

The calculated sensitivities for the prediction of poor outcome remained below 20% for all measured time points with the exception of suPAR levels of day 1 (sensitivity 21.1%) (Table 2). In order to

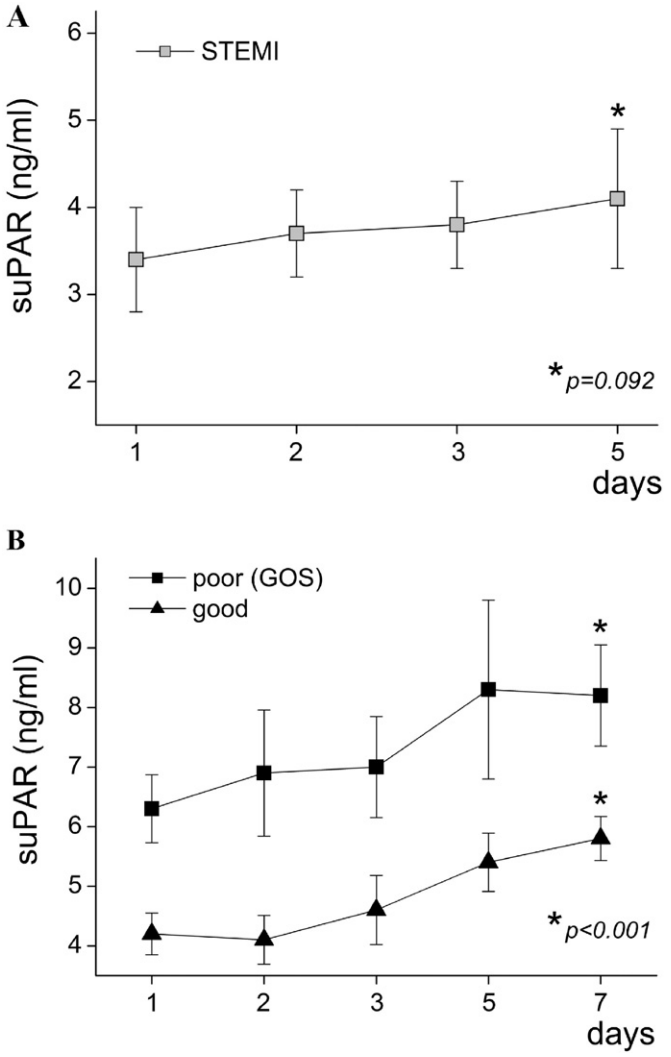

Fig. 4. suPAR serum course of patients with STEMI and CA. A) Demonstrates the serum course of suPAR in patients with STEMI over a time period of 5 days. There was a tendency towards rising suPAR levels in longitudinal measurements, but serum suPAR concentrations did not significantly change within the first 5 days after STEMI (Friedman test, $p = 0.092$). B) In contrast, the serum suPAR levels in patients with CA, either the total cohort (not shown) or their subgroups, significantly increased during the course of disease within the first week (Friedman test, $p < 0.001$). ■/▲ mean of values, ┬/┴ SEM.

calculate best prediction values for suPAR the specificity was set to at least 80% and the sensitivities were calculated again. Hereby, the calculated sensitivities rose up to 57.9% (day 2) (Table 3). The ROC curve of suPAR for day 2 is depicted in Fig. 5.

4. Discussion

The major findings of the present study are 1) after CA, serum suPAR levels are significantly increased in patients with poor neurological outcome as compared to patients with good neurological outcome, 2) suPAR could be confirmed as an early serum prediction marker for long-term neurological outcome in patients after CA, but with inadequate predictive values, 3) suPAR serum levels in patients with STEMI are significantly higher as compared to control patients and significantly lower as compared to patients with CA, 4) the suPAR serum course remains stable in patients with STEMI and increases significantly in patients with CA over a period of 7 days.

In analogy to previous studies investigating the role of suPAR as a predictive marker for the neurological outcome in patients surviving

Table 2
Cut-off points, sensitivities and AUC values of suPAR serum levels predicting poor outcome with 100% specificity.

	Cut-off value	Specificity	Sensitivity	AUC	95% CI of AUC	*p* value
suPAR day 1	11	100	9.5	0.690	0.578–0.803	0.003
suPAR day 2	10.2	100	21.1	0.716	0.565–0.867	0.012
suPAR day 3	12.5	100	13.3	0.733	0.570–0.897	0.015
suPAR day 5	12.7	100	13.3	0.693	0.524–0.862	0.041
suPAR day 7	11.8	100	18.8	0.748	0.593–0.903	0.006

AUC: area under the curve; CI: confidence interval.

CA [12,13], we found significantly increased serum suPAR levels in patients with poor neurological outcome as compared to patients with good neurological outcome. In line with the studies of Jalkanen et al. [12] and Rundgren et al. [13], we could calculate fair prediction values for suPAR to predict poor outcome in our cohort of patients with CA (suPAR serum level day 2: sensitivity 58%, specificity 80%, AUC 0.716, n = 85).

Jalkanen et al. demonstrated that high suPAR concentrations were associated with poor outcome in patients with CA. However, they concluded that suPAR alone had inadequate predictive value for poor outcome and did not associate with 12 month neurological outcome according the GP-CPC [5]. Jalkanen et al. reported of a sensitivity of 65%, specificity of 76% and an AUC of 0.75 for the prediction of poor outcome (GP-CPC 3–5) of baseline suPAR. Details of the sensitivities and specificities of the other days (day 1, day 2 and day 4) were not provided. However, the best AUC value which Jalkanen et al. reported was for baseline suPAR with 0.75. This is in line with our findings with a best calculated AUC of 0.748 on day 7.

Rundgren et al. performed a study with 55 CA patients in which they demonstrated that suPAR levels were significantly higher in nonsurviving patients compared with survivors at 6 and 36 h, but not at 72 h. Furthermore, they reported that suPAR levels significantly increased from 6 to 72 h, which is in line with our findings. They reported of an AUC of 0.76 at 6 h by the use of ROC curve analyses.

Our group could demonstrate that with the use of the GOS or the GP-CPC the calculated prediction power of the neurological markers NSE and S100B with respect to sensitivities and AUC values is underestimated as compared with the modified outcome score, which we termed as MGOS [14]. This bias is mainly created, because patients who died with an unclear neurological status were not excluded from the group of patients with poor outcome in the GOS and GP-CPC. However, in this study, we could found no significant difference in suPAR levels when comparing both groups with poor outcome (GOS 1–2 vs. MGOS 1–2, Fig. 3). This is mainly because suPAR is a more ubiquitous inflammatory marker rather than a more selective brain damage marker, as it is the case with NSE, S100B and NF-L.

To be an ideal predictive marker for global hypoxic brain damage or injury in patients with CA, a marker should be specifically and exclusively expressed and proved to be released from neurons. However, up to now, this exclusive criteria for an ideal marker is only present in NF-L and neurofilament heavy chain (NF-H) [2,19]. For NF-L on admission, we could demonstrate excellent predictive values with an AUC of 0.93, a sensitivity of 79% and a specificity of 100% [2]. However, Rundgren et al. demonstrated lower prediction values for NF-H in their cohort of patients with CA (serum NF-H at 2 h: AUC 0.72) [19].

Table 3
Cut-off points, sensitivities and AUC values of suPAR serum levels predicting poor outcome with at least 80% specificity.

	Cut-off value	Specificity	Sensitivity
suPAR day 1	5.6	81	45.2
suPAR day 2	5.3	80	57.9
suPAR day 3	6.7	84	33.3
suPAR day 5	7.7	81.5	40
suPAR day 7	7.3	80	50

Shinozaki et al. emphasized to set the specificity to 100% when investigating biochemical markers for the prediction of poor outcome in patients with CA [20]. By following this recommendation, the calculated average sensitivities of suPAR were extremely low and thereby not applicable for clinical utility. In analogy, the calculated cut-off values with 100% specificities were extremely high because of a substantial overlap of suPAR levels in numerous patients with good (range 10.2 ng/ml) and poor (range 18.5 ng/ml) neurological outcome. Because suPAR is not a specific brain damage marker rather an inflammatory marker, the authors of this study recommend to set the specificity to at least 80% to calculate clinically applicable cut-off values with fair sensitivities. Hence, the calculated sensitivity rose up to 58% for suPAR serum levels on day 2 with a calculated cut-off value of 5.3 ng/ml, which is, to our opinion, a representative cut-off value for the prediction of poor outcome in patients after CA. However, its reclusive application as a biomarker to predict poor outcome in CA patients had inadequate predictive values with sensitivities far below 50%. Thus, suPAR is a drawback for the exclusive use in clinical routine. However, suPAR serum levels below the cut-off values may indicate favorable neurological outcome (>80% specificity) and could be used, certainly with involvement of clinical representation of the patient and combined with other biochemical markers such as NSE or S100B, not to withdraw from further therapy. However, these findings and suggestions require independent verification in a multicenter prospective cohort study.

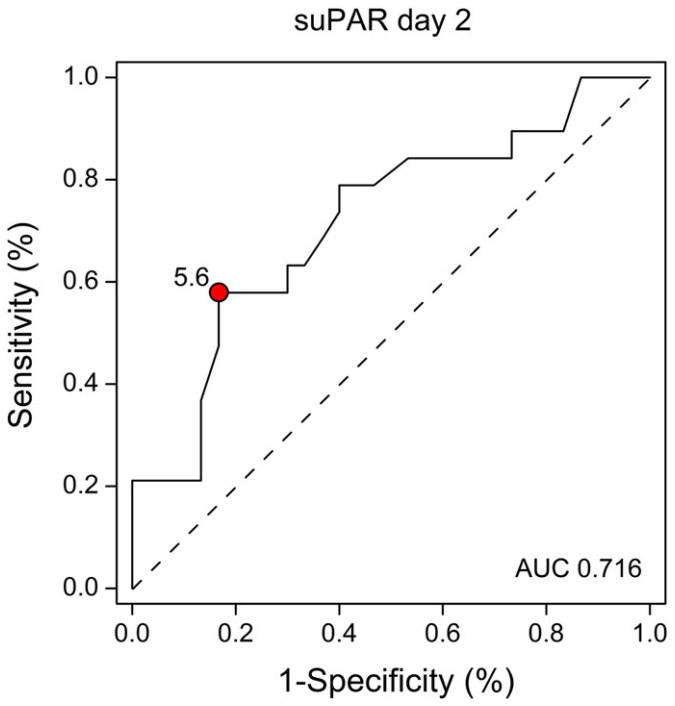

Fig. 5. ROC curve analysis of serum suPAR levels on day 2 for the prediction of poor neurological outcome assessed by the GOS. The red solid circle marks the serum suPAR cut-off point with 80% specificity and 57.9% sensitivity. suPAR cut-off values are given in ng/ml. AUC denotes area under the curve.

5. Conclusions

suPAR could be confirmed as an early serum prediction marker for the long-term neurological outcome in patients after CA. The suPAR serum levels in patients with poor neurological outcome were significantly higher as compared to patients with good neurological outcome. However, the prognostic value was low and inadequate because of a substantial overlap of suPAR levels between the outcome groups.

Competing interests

The authors declare that they have no competing interests.

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None.

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