Published in final edited form as:

Scand J Clin Lab Invest. 2013 December ; 73(8): 650–660. doi:10.3109/00365513.2013.849357.

Soluble receptor for advanced glycation end products predicts 28-day mortality in critically ill patients with sepsis

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Abstract

Objective—Multiple biomarkers are used to assess sepsis severity and prognosis. Increased levels of the soluble receptor for advanced glycation end products (sRAGE) were previously observed in sepsis but also in end-organ injury without sepsis. We evaluated associations between sRAGE and (i) 28-day mortality, (ii) sepsis severity, and (iii) individual organ failure. Traditional biomarkers procalcitonin (PCT), C-reactive protein (CRP) and lactate served as controls.

Methods—sRAGE, PCT, CRP, and lactate levels were observed on days 1 (D1) and 3 (D3) in 54 septic patients. We also assessed the correlation between the biomarkers and acute respiratory distress syndrome (ARDS), acute kidney injury (AKI) and acute heart failure.

Results—There were 38 survivors and 16 non-survivors. On D1, non-survivors had higher sRAGE levels than survivors ($p = 0.027$). On D3, sRAGE further increased only in non-survivors ($p < 0.0001$) but remained unchanged in survivors. Unadjusted odds ratio (OR) for 28-day mortality was 8.2 (95% CI: 1.02–60.64) for sRAGE, $p = 0.048$. Receiver operating characteristic analysis determined strong correlation with outcome on D3 (AUC = 0.906, $p < 0.001$), superior to other studied biomarkers. sRAGE correlated with sepsis severity ($p < 0.00001$). sRAGE showed a significant positive correlation with PCT and CRP on D3. In patients without ARDS, sRAGE was significantly higher in non-survivors ($p < 0.0001$) on D3.

Conclusion—Increased sRAGE was associated with 28-day mortality in patients with sepsis, and was superior compared to PCT, CRP and lactate. sRAGE correlated with sepsis severity.

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Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

sRAGE was increased in patients with individual organ failure. sRAGE could be used as an early biomarker in prognostication of outcome in septic patients.

Keywords

Soluble receptor for advanced glycation end products; sepsis; procalcitonin; C-reactive protein; biomarker

Introduction

Severe sepsis represents over 20% of admissions to the intensive care unit (ICU) and remains the leading cause of death, representing an important clinical and economical target. Multiple laboratory markers have been evaluated as a determinant of severity of organ failure in sepsis, and were used for prognostication of outcome [1]. Specific biomarkers with an established role in sepsis include C-reactive protein (CRP) [2], procalcitonin (PCT) [3], lactate, cytokines, coagulation parameters, and others. These markers are used both clinically and experimentally to diagnose sepsis and guide treatment [4–6].

Receptor for advanced glycation end products (RAGE) is a multiligand receptor of the immunoglobulin superfamily of cell surface molecules that acts as a pattern recognition receptor. RAGE was initially identified in the lung tissue which has the highest basal level of expression of RAGE under normal conditions [7]. RAGE activates pathways responsible for acute and chronic inflammation. The soluble type of this receptor, sRAGE, which acts as a decoy receptor, is a novel biomarker that has been linked to severity of sepsis and its outcome [8–11]. However, other studies linked sRAGE to chronic [12,13] or acute lung injury [10,14–18], coronary artery disease [19], cardiogenic shock [20], end-stage renal disease [21], severe trauma [22] or other diseases [11] without sepsis. Given the conflicting findings, the potential benefits of sRAGE as an independent biomarker in patients with sepsis are not yet fully elucidated.

In our study, we evaluated sRAGE as a novel marker of inflammation in septic patients with or without organ injury. We also assessed traditional biomarkers – CRP, PCT, lactate, creatinine – and their correlation with survival, severity of illness and organ injury, and with sRAGE. We hypothesized that sRAGE will have a positive correlation with severity of illness, and a negative correlation with survival. To test these hypotheses, we serially evaluated: (1) The association between plasmatic sRAGE levels early after admission and 28-day mortality, (2) the correlation between sRAGE and severity of illness, and (3) correlation of sRAGE with established biochemical markers of sepsis severity (PCT, CRP, lactate, creatinine) and organ injury.

Patients and methods

Ethical aspects

The study was approved by the Institutional Ethics Committee of the 1st Medical Faculty, Charles University and the General University Hospital in Prague, Czech Republic. A separate approval of the Institutional Review Board, University of Pittsburgh, was obtained

for an independent data analysis by the Clinical and Translational Research Institute, University of Pittsburgh School of Public Health.

The purpose and procedures of the study were explained to participants and/or their legal representatives, and signed informed consents were obtained. The study enrolled patients older than 18 years admitted for sepsis to mixed ICU of the General University Hospital in Prague, Czech Republic. The plasmatic levels of sRAGE, procalcitonin (PCT), C-reactive protein (CRP), lactate and creatinine were assessed on admission, which was considered day 1 (D1), and on day 3 (D3).

Patients

Fifty-four patients with the age of 54 ± 16 years (mean $\pm$ SD) admitted to the mixed population ICU with clinical symptoms of sepsis were enrolled in a prospective observational study. The diagnosis of sepsis was established with regard to the previously published clinical criteria [23,24]. The severity of illness was evaluated according to the Acute Physiologic and Chronic Health Evaluation (APACHE) II criteria. The presence of selected organ injury was determined based on generally accepted criteria for individual organs. For acute kidney injury (AKI), the criteria of Acute Kidney Injury Network were used [25]; for lung injury, criteria for acute respiratory distress syndrome were used [26]. Acute heart failure was defined as a need for inotropic support to maintain cardiac index > 2.0 L/min/m² monitored by a thermodilution method and systolic blood pressure > 90 mmHg in the absence of hypovolemia. These criteria were similar to those used in a study by Selejan et al. [20].

Laboratory analyses

All routine biochemical parameters such as creatinine, lactate, CRP were determined by standard clinical-chemistry methods. PCT was measured by enzyme-linked immunosorbent assay Vidas Brahms. sRAGE levels were measured by enzyme-linked immunosorbent assay (Quantikine, R&D Systems Europe Ltd, Abingdon, Oxfordshire, UK).

Reference ranges used were as follows: PCT 0.0–0.05 µg/L, CRP 0.0–7.0 mg/L, creatinine 44–110 mmol/L, lactate 0.5–2.0 mmol/L. For sRAGE, widely accepted reference range was not established; however, the reference range of plasma sRAGE declared by the manufacturer for 42 healthy subjects was 382–4329 pg/mL, mean 1655 ± 693 pg/mL. In a contemporaneous study from our center using the same methodology, a healthy control group ($n = 154$) had sRAGE levels 1723 ± 643 pg/mL [27]. The intra-assay coefficient of variation (means 571–3189) was 4.8–6.1%, while inter-assay coefficient of variation (means 519–2890) was 6.7–8.7%. Kit series number was DRG00.

Statistical analysis

Statistical analysis was performed using the Statistica CZ 7.0 software (StatSoft Inc, USA), Cutoff Finder freeware (<http://molpath.charite.de/cutoff/index.jsp>) or SPSS 20.0 (IBM SPSS Statistics, USA). Mann-Whitney *U* test was performed to compare continuous variables between two groups. Receiver operating characteristic (ROC) curves were used to determine the sensitivity and specificity of individual biomarkers to predict outcome. Comparison of

ROC curves was used to evaluate the diagnostic performance of individual biomarkers [28]. Logistic regression was used to test the independent association of sRAGE and 28-day mortality. Spearman's rank correlation coefficient was used as a measure of linear relationship between two sets of data. A p value less than 0.05 was considered significant.

Results

The baseline characteristics of the patient population are shown in Table I. There were 38 survivors and 16 non-survivors. The non-survivors tended to be older, but this trend did not reach statistical significance.

No patients died within the period of the three days when blood samples were collected. There were no patients lost to follow-up. There were no differences between different etiologic agents of sepsis (i.e. Gram-positive vs. Gram-negative vs. mycotic) in individual biomarkers (data not shown).

Survival and severity of illness

sRAGE levels were significantly higher in non-survivors vs. survivors on both D1 and D3. In non-survivors, the levels further increased between D1 and D3, while they remained similar in survivors (Figure 1). The ROC analysis of sRAGE for 28-day mortality revealed area under curve (AUC) greater than 0.5 on both D1 (AUC = 0.660; $p = 0.066$) and D3 (AUC = 0.913; $p < 0.001$), suggesting poor correlation with 28-day mortality on D1 but excellent correlation on D3 [29]. On both days, sRAGE was significantly better predictor of 28-day mortality than PCT (D1: AUC = 0.377, $p = 0.157$; D3: AUC = 0.669, $p = 0.053$) or CRP, respectively (D1: AUC = 0.444; $p = 0.523$; D3: AUC = 0.419, $p = 0.357$). Lactate was superior to sRAGE on D1 (AUC = 0.805, $p < 0.001$) but not on D3 (AUC = 0.747; $p = 0.005$) (Figure 2).

Using pooled sRAGE data from both D1 and D3, unadjusted odds ratio for 28-day survival was 8.250 (95% CI 1.017; 60.636), $p = 0.048$ for cutoff sRAGE level of 1721 pg/mL.

Logistic regression showed independent association of increased sRAGE on D3 with 28-day mortality (OR 1.002; 95% CI = 1.00004; 1.00396; $p = 0.014$), with best cut-off sensitivity 94% and specificity 79%, cut-off value 2003 pg/mL. No such statistically significant association was identified for D1.

sRAGE levels correlated well with the severity of the illness on D3 ($p < 0.0001$) but not on D1 when only a borderline significance was observed ($p = 0.059$) (Figure 3). We also dichotomized sRAGE levels on D3 in non-survivors to 'low' vs. 'high'. Kaplan-Meier log rank analysis did not show difference in survival time (5.5 ± 1.7 days vs. 5.9 ± 2.4 days; $p = 0.925$; See Supplementary Figures 1 and 2, available online at <http://informahealthcare.com/doi/abs/10.3109/21695717.2013.849357>). When the entire patient population, i.e. both survivors and non-survivors, was dichotomized around the median sRAGE level on D3 (940 pg/mL) to 'low' vs. 'high', the difference in survival time between the groups was significant ($p = 0.007$; Supplementary Figures 1 and 2, available online at <http://informahealthcare.com/doi/abs/10.3109/21695717.2013.849357>).

Lactate levels were significantly higher in non-survivors vs. survivors on D1 and D3 ($p = 0.0006$ and $p < 0.0001$, respectively). PCT was higher in non-survivors only on D3 ($p = 0.041$). CRP and creatinine did not differ between non-survivors and survivors at either time-point (Table II).

Correlation between biomarkers

As expected, sRAGE showed a significant positive correlation with serum creatinine ($r = 0.237$, $p = 0.037$ on D1; and $r = 0.397$, $p = 0.015$, on D3; respectively). A strong positive correlation was found in sRAGE and lactate at both D1 and D3 ($r = 0.453$ and $r = 0.529$, respectively, $p < 0.001$).

sRAGE values showed a significant positive correlation with CRP and PCT only on D3 (CRP: $r = 0.496$, $p = 0.016$; PCT: $r = 0.45$, $p = 0.007$, respectively). Strong positive correlation of sRAGE and PCT on D3 was observed both in survivors and non-survivors.

Pairwise comparison of ROC curves of individual biomarkers did not reveal any statistically significant differences on D1. However, the diagnostic ability of sRAGE was significantly superior to both PCT ($p = 0.0004$) and CRP ($p = 0.002$) on D3 but not lactate ($p = 0.19$). Lactate had better diagnostic ability than either PCT ($p = 0.038$) or CRP ($p = 0.014$).

Organ injury

There was a higher number of failing organs per patient in non-survivors (mean = 2; IQR 2–2) vs. survivors (mean = 1; IQR 0–1; $p < 0.001$; Table II). The number of organ failures in non-survivors did not affect survival time ($p = 0.719$, Supplementary Figures 1 and 2, available online). However, in the entire patient population, i.e. in both survivors and non-survivors, the survival time was significantly different depending on the number of organ failures ($p < 0.001$; Supplementary material, online).

ARDS

sRAGE levels were similar in septic patients with vs. without ARDS on D1, but were higher on D3 vs. D1 ($p = 0.027$). sRAGE levels also increased in patients with ARDS between D1 and D3 (Figure 4). In patients without ARDS, sRAGE was significantly higher in non-survivors vs. survivors on D3. Similar values were observed in non-survivors and survivors in patients with ARDS on D3, but the difference was not statistically significant (Table III). Lactate was higher in patients with vs. without ARDS on both D1 and D3, but the levels did not change over time in subgroups (Figure 5).

Acute kidney injury

sRAGE was higher in non-survivors vs. survivors in subgroups of patients with or without AKI. sRAGE was higher in survivors with AKI vs. without AKI (Table IV). Irrespective of survival, sRAGE, lactate and creatinine were higher in patients with vs. without AKI on both D1 and D3, while PCT was higher only on D3 (Table V).

Acute heart failure

sRAGE was higher in non-survivors vs. survivors in patients with acute heart failure, but not in patients without (Table IV). Irrespective of survival, on D1, patients with vs. without acute heart failure had higher CRP and creatinine. On D3, patients with vs. without acute heart failure had higher PCT, sRAGE and creatinine. Differences in other biomarkers did not reach statistical significance (Table VI).

Discussion

We serially investigated sRAGE, a novel biomarker, in patients with sepsis with or without organ failure. Our results document that early sRAGE levels correlated with the 28-day mortality from sepsis, and that sRAGE levels on D3 correlated with the severity of illness. Moreover, sRAGE correlated well with established biomarkers of sepsis, further strengthening its value. Only sRAGE and lactate had predictive value for 28-day mortality on D1 and D3; PCT was also able to predict mortality only on D3. sRAGE was superior in predicting outcome to PCT or CRP. CRP was unable to predict 28-day mortality in our study population.

sRAGE was also increased in non-survivors vs. survivors in patients without ARDS or acute heart failure. Non-surviving patients with ARDS or acute heart failure had also higher sRAGE levels compared to survivors. sRAGE was increased in non-survivors vs. survivors irrespective of the presence of AKI. Our findings support a valuable role of sRAGE in determining the prognosis early in the course of sepsis with or without organ failure.

None of the currently used biomarkers shows optimal sensitivity and specificity for sepsis [1]. Individual biomarkers have different characteristics. Clinically, it is advised to use a panel of biomarkers to increase the accuracy of the assessment of inflammatory disease, and to differentiate sepsis from systemic inflammatory response syndrome [30]. We explored the trends of multiple sepsis biomarkers over the first 48 hours of inflammatory response. Rather than absolute values, the increasing trend in sRAGE was characteristic for non-survivors in our cohort. Similar trend was observed also for PCT. Both of these parameters, or their trends, could be useful in predicting survival.

We observed an increasing PCT levels in non-survivors over the 48 hours. Karlsson et al. could not demonstrate a difference in PCT between survivors vs. non-survivors in sepsis, but mortality was significantly decreased in patients with decreasing PCT levels within the first 72 hours [31]. This underscores the importance of a serial assessment of biomarkers, with individual values being less informative than the trend over time.

A strong correlation of sRAGE with APACHE II scores, reflecting the severity of illness, was also demonstrated. This correlation was also tighter over time. We chose APACHE II scoring system over Sequential Organ Failure Assessment (SOFA), Multiple Organ Dysfunction Score (MODS) or others [32], because APACHE II was shown to correlate well with SOFA and it outperformed SOFA in predicting mortality in critically ill patients [33,34], the primary endpoint of our study.

Correlation between plasma levels of sRAGE with PCT or CRP was shown only on D3, i.e. after 48 hours, both in survivors and non-survivors, which is surprising, given the early onset of PCT production in sepsis.

The role of RAGE in sepsis has been explored only in a limited number of experimental and clinical studies so far that yielded controversial results. RAGE is expressed in high levels in lung tissue even under normal conditions whereas other tissues express RAGE at low levels, including immune system cells. RAGE binds variety of ligands actively participating in inflammation and immune responses. One of these ligands is high-mobility group box chromosomal protein 1 (HMBG-1). The interaction of HMBG-1 with cell-surface RAGE triggers inflammatory response due to activation of nuclear factor kappa B (NF- κ B), a potent pro-inflammatory cytokine. Increased NF- κ B activation has been demonstrated to be a predictor of outcome in septic patients [35].

The origin of circulating sRAGE is not yet fully explored. The evidence suggests that sRAGE is probably produced by ectodomain shedding [36,37]. Experimental models of sepsis using sRAGE as a therapy showed attenuation of inflammation-induced lung injury [38]. These findings are further corroborated by studies using knock-out mice (RAGE $^{-/-}$) that are protected from certain chronic inflammatory diseases. sRAGE administered to wild-type mice resulted in better protection from inflammation than observed in RAGE $^{-/-}$ mice, suggesting that sRAGE may also prevent other ligands from interacting with receptors other than RAGE [39]. Anti-RAGE antibody was efficient in improving survival from experimental sepsis in a dose-dependent fashion, even when the treatment was delayed. The survival achieved by blocking the receptor were similar to survival in RAGE $^{-/-}$ or RAGE $^{+/-}$ mice [40].

Specific studies assessed sRAGE in patients with ALI and/or sepsis with organ dysfunction. A separate body of literature explored the role of sRAGE in chronic inflammatory diseases, including diabetes mellitus and its complications, coronary artery disease or neuroinflammatory diseases.

First reports exploring the role of sRAGE in a clinical setting concluded that sRAGE is increased in sepsis and the magnitude of its increase correlates with sepsis severity. Higher levels were observed in non-survivors [9]. Given the fact that RAGE is primarily located in the basal surface of alveolar type I cells, there were concerns that sRAGE may be associated with lung injury rather than sepsis. This was based on experimental data supporting the role of sRAGE in lung injury [41]. Using sRAGE as therapeutic modality rather than a biomarker attenuated endotoxin-induced lung injury in a murine model [38]. Several clinical studies supported the role of RAGE in lung diseases. In COPD patients, sRAGE levels were higher than in healthy controls, but surprisingly lower values were seen in acute exacerbation of COPD compared to stable COPD [13]. In contrast, Miniati et al. showed opposite results, with lower sRAGE levels in COPD patients [12]. In lung transplant patients, higher plasma RAGE levels correlated with the duration of mechanical ventilation, and ICU length of stay [14]. Serum sRAGE was significantly decreased in lung cancer patients compared with healthy controls or patients with tuberculosis [16]. In ALI/ARDS patients, plasma and alveolar sRAGE correlated with lung injury and infection over time

[17]. sRAGE also correlated with impaired lung function in infants and young children undergoing cardiac surgery [18].

Most importantly, two studies focused on sRAGE in septic patients with or without ALI. Kikkawa et al. documented an increase in sRAGE on day 1 in septic patients who did not develop ALI vs. those with ALI [10]. These findings are in contradiction to a larger study by Jabaudon et al. who reported higher sRAGE levels in patients with ALI/ARDS, regardless of presence or absence of sepsis [15]. Nakamura et al. found in patients with ARDS with severe infection that higher sRAGE were associated with death in ARDS patients, but severity of illness was not. HBGB-1 correlated with sRAGE [42]. Narvaez-Rivera et al. showed a positive correlation between sRAGE, SOFA and mortality in patients with community-acquired pneumonia and ARDS [43].

In our study, all patients met the criteria for sepsis. Given the current conundrum germane to the role of sRAGE in sepsis and/or ARDS, we further explored the role of sRAGE and other biomarkers in dichotomized patient population with vs. without ARDS. On D1, there were no differences in sRAGE between these groups, while on D3, patients with ARDS had higher sRAGE levels. The lack of difference in sRAGE levels on D1 argues against a major effect of ALI/ARDS in our study population. On D3, the levels of sRAGE were higher in non-survivors vs. survivors in patients without ARDS. Similar values were observed in patients with ARDS. Thus, our results support the hypothesis that sRAGE in septic patients is more reflective of the severity of sepsis and ultimate outcome, irrespective of the presence of ARDS. However, these findings should be interpreted with caution since there were only nine patients with ARDS in our study, and only two patients survived. The hypothesis that sRAGE can reliably predict survival in septic patients with ARDS needs to be tested in a larger study in this specific population with high mortality.

In our study, sRAGE levels also correlated with AKI. Creatinine was used as a surrogate marker of renal function. We observed strong correlation between sRAGE and creatinine, which corroborates previously described correlation between sRAGE and renal function [21]. sRAGE levels in survivors were higher in patients with AKI vs. without AKI. This may represent either higher production of sRAGE with AKI, or delayed elimination. On the contrary, Nakashima et al showed inverse correlation between sRAGE and CRP, with no prognostic value of sRAGE for mortality in hemodialysis patients [44]. Of note, no patient received hemodialysis or a continuous renal replacement therapy within the first 48 h of treatment in our study, leaving the creatinine levels unaffected by this therapy.

Increased sRAGE levels were also previously linked to cardiovascular disease and chronic inflammation outside sepsis. In patients with congestive heart failure (CHF), high sRAGE levels were associated with higher incidence of cardiac death vs. low sRAGE levels [45]. sRAGE, but not AGE, was related to ischemic etiology independent of age, sex, diabetes, renal function, clinical severity, or other variables. Moreover, sRAGE was directly associated with the extent of coronary artery disease in patients with CHF [19]. We observed higher sRAGE levels in patients with acute heart failure on D1 and on D3 ($p = 0.02$). Also, sRAGE increased between D1 and D3 only in patients with heart failure. This may represent an effect of both CHF (the presence of which was not known to us) and acute heart failure

associated with sepsis. Our results are in contrast to the recent report by Selejan et al. that non-survivors of cardiogenic shock had lower sRAGE levels than survivors [20]. These conflicting results are difficult to directly compare and interpret. Our study enrolled septic patients with secondary organ complications, while Selejan et al. studied patients in cardiogenic shock without sepsis. They also observed a negative correlation of sRAGE and Simplified Acute Physiology Score (SAPS) II score, which is in striking contrast to our findings. Surprisingly, survivors in the study by Selejan et al. had similar sRAGE levels as patients with acute myocardial infarction or healthy controls. These conflicting reports may suggest that sRAGE may play a different role in the pathophysiology of sepsis vs. acute heart failure. In this regard, our findings support the dominant role of the sepsis on sRAGE levels, rather than the effect of heart failure.

We did not address the possible confounding effects of pre-existing diabetes, congestive heart failure, or corticosteroid treatment of sepsis on biomarkers evaluated in our study. We cannot rule out that other medical conditions and/or therapeutic interventions could also have an independent impact on outcome. Given the small sample size we cannot rule out the possibility of confounding through multiple organ failure. Future studies should examine large sample size to address this issue directly.

Conclusions

Early increased plasma sRAGE levels showed excellent correlation with 28-day mortality, and with severity of illness in patients with sepsis. In non-survivors, sRAGE levels were increasing over the first three days, underscoring the importance of serial measurements. Positive correlations of plasmatic levels of sRAGE with traditional markers of sepsis severity, i.e. CRP, PCT and lactate were observed. sRAGE was increased in patients with ARDS, AKI or acute heart failure. sRAGE could serve as an additional independent predictor of the 28-day mortality, being superior to the traditional biomarkers. The prognostic efficacy in septic patients with ARDS needs to be determined in a larger study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The project described was supported by the National Institutes of Health through Grant Numbers UL1 RR024153 and UL1 TR000005 to the Clinical and Translational Science Institute, University of Pittsburgh, and by the Research Program P25 of the Charles University in Prague.

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Figure 1. Differences in sRAGE levels between survivors and non-survivors on days 1 and 3. sRAGE, soluble receptor for advanced glycation end products.

Figure 2.

Receiver operating characteristics of individual biomarkers for predicting 28-day mortality. Left panel, day 1; right panel, day 3. sRAGE shows superior characteristics to other biomarkers on day 3. sRAGE, soluble receptor for advanced glycation end products; PCT, procalcitonin; CRP, C-reactive protein.

Figure 3. The correlation between soluble receptor for advanced glycation end products (sRAGE) levels and Acute Physiologic and Chronic Health Evaluation (APACHE) II score on days 1 and 3.

Figure 4. Differences in sRAGE levels between patients with vs. without ARDS on days 1 and 3. sRAGE, soluble receptor for advanced glycation end products; ARDS, acute respiratory distress syndrome.

Figure 5. Differences in lactate levels between patients with vs. without ARDS on days 1 and 3. ARDS, acute respiratory distress syndrome.

Table I

Baseline characteristics of the patient population.

Gender, <i>n</i> (%)	
Females	13 (24%)
Males	41 (76%)
Age (years), median (interquartile range)	64 (57; 76)
28-days survival, <i>n</i> (%)	
Yes	38 (70%)
No	16 (30%)
Blood culture, <i>n</i> (%)	
G+ bacteria	8 (15%)
G- bacteria	16 (30%)
Fungi	8 (15%)
Negative	22 (40%)
Acute respiratory distress syndrome, <i>n</i> (%)	
Yes	9 (17%)
No	45 (83%)
Acute renal failure, <i>n</i> (%)	
Yes	35 (65%)
No	19 (35%)
Heart failure, <i>n</i> (%)	
Yes	18 (33%)
No	36 (67%)
APACHE score, median (interquartile range)	27 (22; 36)

APACHE, Acute Physiologic and Chronic Health Evaluation.

Table II

Number of patients with individual organ failures.

	Number of failing organs			
	0	1	2	3
Survivors	18	12	7	1
Non-survivors	0	3	11	2

Non-survivors had a higher number of failing organs per patient vs. survivors ($p < 0.001$, Mann-Whitney test).

Table III

Biomarkers in survivors and non-survivors.

	Day 1			Day 3		
	non-survivors <i>n</i> = 16	survivors <i>n</i> = 38	<i>p</i> -value*	non-survivors <i>n</i> = 16	survivors <i>n</i> = 38	<i>p</i> -value*
CRP mg/L	183 (36;286)	195 (98;320)	0.55	190 (46;266)	196 (129;276)	0.54
PCT ng/mL	9.4 (0.82;13.05)	12.20 (4;36.60)	0.14	33.90 (12.95;74.51)	20 (5.10;51)	0.041
sRAGE pg/mL	2261 (895;3366)	1033.50 (605;1789)	0.037	5263 (2621;6091)	940 (561;1758)	< 0.0001
Lactate mmol/L	3.50 (2.20;8.50)	1.75 (1.10;2.90)	0.0006	3.90 (2.55;12.10)	1.45 (0.90;2.45)	< 0.0001
Creatinine, μ mol/L	172 (100;271.50)	151 (91;252)	0.51	201.50 (177;267)	155 (91;248)	0.10

Medians (IQR) of measured parameters on day 1 and day 3 in survivors and non-survivors.

sRAGE, soluble receptor for advanced glycation end products; PCT, procalcitonin; CRP, C-reactive protein.

Table IV

sRAGE levels in survivors and non-survivors with respect to organ injury.

	non-survivors	survivors
ARDS		
yes	7	2
sRAGE pg/mL	5328 (3664;5674)	1101 (783;1419)
no	36	9
sRAGE pg/mL	5197 (2305;7040)	940 ^a (542;1798)
AKI		
yes	14	21
sRAGE pg/mL	4693 (2341;5909)	1699 ^{c,d} (7650;3010)
no	2	17
sRAGE pg/mL	5901 (5328;6475)	607 ^b (487;976)
AHF		
yes	10	8
sRAGE pg/mL	5656 (2223;6516)	1436 (596;3047)
no	6	30
sRAGE pg/mL	4693 (2949;5406)	854 ^e (515;1755)

sRAGE levels in survivors and non-survivors based on the presence or absence of individual organ injury on day 3. Values represent median (IQR).

^a $p = 0.002$ between survivors and non-survivors;

^b $p = 0.012$ between survivors and non-survivors;

^c $p = 0.001$ between survivors and non-survivors;

^d $p = 0.008$ between survivors with AKI vs. without AKI;

^e $p = 0.025$ between survivors and non-survivors.

ARDS; acute respiratory distress syndrome; AKI; acute kidney injury; AHF, acute heart failure.

Table V

Differences in biomarkers in patients with or without acute kidney injury.

	sRAGE pg/mL	PCT ng/mL	CRP mg/L	Lactate mmol/L	Creatinine μ mol/L
D1/AKI no	742 (516;1714)	12.9 (1.8;25)	164 (38;320)	1.6 (1.1;2.3)	91 (66;124)
D1/AKI yes	1541 (987;3129)	11 (2.6;36.6)	238 (41;290)	2.4 (1.3;5.5)	224 (147;423)
<i>p</i> value	0.04	0.73	0.14	0.04	< 0.0001
D3/AKI no	710 (491;1281)	10.5 (4.3;32)	129 (50;214)	1.4 (0.9;2.5)	92 (66;172)
D3/AKI yes	2399 (1419;5011)	34 (12.8;75)	249 (129;284)	2.6 (1.2;4.5)	206 (160;342)
<i>p</i> value	0.001	0.01	0.17	0.01	< 0.0001

Differences in measured parameters on days 1 and 3 depending on the presence of acute kidney injury, irrespective of the survival. Values represent median (IQR). *p* values were determined by a Mann-Whitney test. sRAGE, soluble receptor for advanced glycation end products; PCT, procalcitonin; CRP, C-reactive protein.

Table VI

Differences in biomarkers in patients with or without acute heart failure.

	sRAGE pg/mL	PCT ng/mL	CRP mg/L	Lactate mmol/L	Creatinine μmol/L
D1/AHF no	1055 (560;1849)	13.5 (8.5;47.5)	226 (113;343)	1.9 (1.1;3.1)	124 (76;270)
D1/AHF yes	1960 (1011;3710)	5.6 (0.7;5.6)	52 (24;257)	2.4 (1.2;6.4)	180 (135;333)
<i>p</i> value	0.12	0.07	0.01	0.11	0.03
D3/AHF no	997 (581;2709)	20 (6.6;64.8)	197 (118;266)	1.8 (0.9;2.75)	155 (79;286)
D3/AHF yes	2863 (1436;6091)	27.8 (16.1;60.5)	177 (33;265)	3.8 (1.5;9.85)	205 (173;257)
<i>p</i> value	0.02	0.02	0.07	0.01	0.02

Differences in measured parameters on days 1 and 3 depending on the presence of acute heart failure, irrespective of the survival. Values represent median (IQR). *p* values were determined by a Mann-Whitney test. sRAGE, soluble receptor for advanced glycation end products; PCT, procalcitonin; CRP, C-reactive protein; AHF, acute heart failure.