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The use of mid-regional proadrenomedullin to identify disease severity and treatment response to sepsis - a secondary analysis of a large randomised controlled trial

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Abstract

Background: This study assessed the ability of mid-regional proadrenomedullin (MR-proADM) in comparison to conventional biomarkers (procalcitonin (PCT), lactate, C-reactive protein) and clinical scores to identify disease severity in patients with sepsis.

Methods: This is a secondary analysis of a randomised controlled trial in patients with severe sepsis or septic shock across 33 German intensive care units. The association between biomarkers and clinical scores with mortality was assessed by Cox regression analysis, area under the receiver operating characteristic and Kaplan-Meier curves. Patients were stratified into three severity groups (low, intermediate, high) for all biomarkers and scores based on cutoffs with either a 90% sensitivity or specificity.

Results: 1089 patients with a 28-day mortality rate of 26.9% were analysed. According to the Sepsis-3 definition, 41.2% and 58.8% fulfilled the criteria for sepsis and septic shock, with respective mortality rates of 20.0% and 32.1%. MR-proADM had the strongest association with mortality across all Sepsis-1 and Sepsis-3 subgroups and could facilitate a more accurate classification of low (e.g. MR-proADM vs. SOFA: $N = 265$ vs. 232 ; 9.8% vs. 13.8% mortality) and high (e.g. MR-proADM vs. SOFA: $N = 161$ vs. 155 ; 55.9% vs. 41.3% mortality) disease severity. Patients with decreasing PCT concentrations of either $\geq 20\%$ (baseline to day 1) or $\geq 50\%$ (baseline to day 4) but continuously high MR-proADM concentrations had a significantly increased mortality risk (HR (95% CI): 19.1 (8.0–45.9) and 43.1 (10.1–184.0)).

Conclusions: MR-proADM identifies disease severity and treatment response more accurately than established biomarkers and scores, adding additional information to facilitate rapid clinical decision-making and improve personalised sepsis treatment.

Keywords: MR-proADM, Biomarkers, Sepsis, Mortality, SOFA, Septic shock

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Background

The incidence of sepsis has continued to escalate rapidly in hospitalized patients [1], with mortality rates of between 10% and 54%, depending on disease severity [2, 3]. A prompt assessment of the infectious load and disease severity in the early stages of sepsis is therefore crucial in order to provide a rapid diagnostic and therapeutic response [4]. In addition, an accurate assessment of disease severity may help to guide physicians in making efficient intensive care unit (ICU) discharge decisions. However, to date, no diagnostic markers allow for a reliable severity assessment to be made [4]. Clinical scores such as the Sequential Organ Failure Assessment (SOFA) score, Acute Physiological and Chronic Health Evaluation (APACHE) II, and the Simplified Acute Physiological Score (SAPS) II have previously been developed for this purpose [5]. However, such scores may not promptly capture individual organ system dysfunction [4], and incorporation into daily routine is hampered by their relative complexity. The use of biomarkers might therefore satisfy this unmet clinical need.

Mid-regional proadrenomedullin (MR-proADM) is a peptide generated by multiple tissues in order to stabilise the microcirculation and protect against endothelial permeability [6–11], both of which are widely acknowledged to play a significant role in the pathophysiological host response to sepsis [12, 13]. Indeed, MR-proADM levels are rapidly induced during the initial stages of sepsis development following burns [14] and neurological disorders [15], in response to invasive fungal infections in patients with septic shock [16], and in other conditions such as lower respiratory tract infections [17–19], lung transplantation [20] and thoracic surgery [21]. Thus, MR-proADM may be of significant clinical utility in the early risk stratification of patients with sepsis. However, supporting data from large patient populations are rare.

In this secondary analysis of a previous randomised controlled trial [22], we aimed to investigate MR-proADM performance in comparison to a range of biomarkers (procalcitonin, lactate, C-reactive protein) and clinical scores (SOFA, APACHE II and SAPS II) in order to (i) make an accurate assessment of disease severity at diagnosis and throughout ICU therapy, (ii) aid in the early assessment of treatment response, and (iii) identify low-risk patients eligible for an early ICU discharge to a step-down unit.

Methods

Study design and patients

This is a secondary analysis of the randomised *Placebo-Controlled Trial of Sodium Selenite and Procalcitonin Guided Antimicrobial Therapy in Severe Sepsis (SISPCT)* trial, performed across 33 German multidisciplinary ICUs from November 2009 until February 2013 [22]. Inclusion criteria were adults ≥ 18 years of age presenting

with new-onset severe sepsis or septic shock (≤ 24 h), according to the Sepsis-1 definition [23]. The study protocol was approved by the ethics board of Jena University Hospital. Written informed consent was obtained from all patients or their legal representatives. For the purpose of this analysis, patients were further classified according to the Sepsis-3 definitions [4]. Details of the SISPCT study design, data collection and management were described previously [22].

Biomarker measurements

Patients were enrolled up to 24 h after diagnosis of severe sepsis or septic shock, and serum C-reactive protein (CRP) and lactate concentrations measured immediately thereafter. Additional blood samples were collected at baseline and on days 1, 4, 7 and 10 and stored at the central study laboratory in Jena, Germany, at -80 °C. MR-proADM and procalcitonin (PCT) plasma concentrations were measured retrospectively (Kryptor®, Thermo Fisher Scientific, Germany) with a limit of detection of 0.05 nmol/L and 0.02 ng/ml, respectively. APACHE II and SAPS II scores were calculated at baseline, whilst SOFA scores were calculated at all time points.

Statistical analysis

The onset of either severe sepsis or septic shock was considered as day 0 (baseline), irrespective of the prior duration of hospital or ICU length of stay (LOS). Differences in demographic and clinical characteristics with regards to 28-day mortality were assessed at baseline using the chi-square (χ^2) test for categorical variables, and Student's *t* test or the Mann-Whitney U test for continuous variables, depending on distribution normality. Normally and non-normally distributed variables were expressed as mean (standard deviation) and median (first quartile to third quartile), respectively. The association between mortality and each biomarker and clinical score was assessed using area under the receiver operating characteristic curves (AUROC) and Cox regression analysis, with multivariate analysis corrected for age, the presence of comorbidities and septic shock. Net reclassification improvement (NRI) was used to evaluate the additional performance of MR-proADM to individual markers or scores across the total population and surviving and non-surviving patient groups [24]. For each biomarker and clinical score at each time point, two cutoffs with a predefined sensitivity or specificity close to 90% were derived from the AUROCs, allowing patients to be classified into three severity subgroups (low, intermediate and high). A subgroup of clinically stable patients was subsequently identified with an absence of any ICU-associated procedures or complications, which included focus eradication procedures, emergency surgery, new infections, transfusion of blood products, infusion of

colloids, invasive mechanical ventilation, renal/liver replacement or vasopressor therapy, and a deterioration in the patient's general clinical signs. Patients within this group with low MR-proADM concentrations (which had not increased since the previous measurement) were further analysed. Mortality rates and average LOS were calculated in both groups and compared to the patient group discharged at each specific time point.

Finally, the response to ICU treatment was investigated by constructing models of PCT, MR-proADM and SOFA kinetics over time. Multivariate logistic regression was used to assess the relationship of biomarkers and their interactions at baseline, day 1 and day 4 with mortality, considering both absolute concentrations and the delta change between time points. Accordingly, two models stratifying patients based on PCT decreases of $\geq 20\%$ or $< 20\%$ from baseline to day 1 and $\geq 50\%$ or $< 50\%$ from baseline to day 4 (based on a previous model [22]), and three models stratifying patients with either decreasing (≥ 2 points), stable (< 2 point change) or increasing (≥ 2 points) SOFA scores from baseline to day 1, were constructed. Patient subgroups were subsequently identified according to MR-proADM concentrations, and respective mortality rates calculated. The risk of mortality within each subgroup in comparison to other subgroups was calculated by Cox regression analysis and illustrated by Kaplan-Meier curves. The predicted risk of developing new infections and the requirement for focus control procedures and emergency surgery over days 4 to 7 was subsequently investigated. All data were analysed using the statistics software R (version 3.1.2).

Results

A total of 1089 patients with either severe sepsis (number (N) = 142; 13.0%) or septic shock (N = 947; 87.0%) were analysed. The 28-day all-cause mortality rate was 26.9% with a hospital mortality rate of 33.4%. Of these patients, 439 (41.2%) and 627 (58.8%) fulfilled the criteria for sepsis and septic shock according to the Sepsis-3 definition, with 28-day and hospital mortality rates of 20.0% and 24.4% (sepsis) and 32.1% and 40.4% (septic shock), respectively. Patient characteristics upon study enrollment for 28-day mortality are summarized in Table 1. The most common causes of mortality included sepsis-induced multiple organ failure (N = 132; 45.7%), refractory septic shock (N = 54; 18.7%), death due to pre-existing illness (N = 35; 12.1%) and acute respiratory insufficiency (N = 17; 5.9%). Other causes not directly related to sepsis accounted for a mortality rate of 8.6%. A limitation of therapy was applied in 3.4% of patients. Supplementary results on infectious foci and microbial identification are reported in Additional file 1. In general, non-surviving patients had significantly higher concentrations of MR-proADM, PCT and lactate, as well as higher SOFA, APACHE II and SAPS II scores than survivors. CRP concentrations were not significantly different.

Association between biomarkers and clinical scores with mortality at baseline

AUROC, univariate and multivariate Cox regression analyses indicated that MR-proADM had the strongest association with 28-day mortality across the total patient population, and within the Sepsis-1 (severe sepsis and septic shock hazard ratio (HR) and interquartile range (IQR) (95% confidence interval (CI)): 2.46 (1.45–4.15) and 3.02 (2.48–3.69)) and Sepsis-3 (sepsis and septic shock HR IQR (95% CI): 2.80 (2.04–3.84)) and 2.41 (1.97–2.96); Fig. 1) subgroups. Similar results were found for 7-day, 90-day, ICU and hospital mortality prediction in the total patient population (Table 2). The addition of MR-proADM to all possible biomarker and clinical score combinations (N = 63) significantly increased prognostic performance according to likelihood ratio (LR) χ^2 analysis within the bivariate and multivariate models (Additional file 1: Table S1). There were also significant increases in the AUROCs for individual biomarkers and scores (Additional file 1: Table S2). Finally, net reclassification improvement analysis resulted in a more accurate classification following the addition of MR-proADM to all biomarkers and scores (Additional file 1: Table S3), and to an existing model of PCT and SOFA in the total population (NRI (95% CI): 0.72 (0.58–0.83)), surviving (NRI (95% CI): 0.32 (0.25–0.39)) and non-surviving (NRI (95% CI): 0.40 (0.29–0.47)) patient subgroups.

Identification of high-risk patients at baseline

All patients were further stratified into low, intermediate and high SOFA severity levels, and biomarker and clinical score performance in predicting 28-day mortality was assessed in each subgroup. MR-proADM had the highest accuracy among all parameters in the low (SOFA ≤ 7) and moderate (SOFA 8–13) severity SOFA subgroups (Fig. 2; Additional file 1: Table S4). Two corresponding MR-proADM cutoffs were subsequently calculated to identify low (≤ 2.75 nmol/L) and high (> 10.9 nmol/L) severity patient populations at baseline (Additional file 1: Table S5). Compared to SOFA, a more accurate classification could be made in identifying low (MR-proADM vs. SOFA, N = 265 vs. 232; 9.8% vs. 13.8% mortality) and high (MR-proADM vs. SOFA, N = 161 vs. 155; 55.9% vs. 41.3% mortality) disease severity patients (Additional file 1: Table S6). A subgroup of 94 patients (9.3%) with high MR-proADM concentrations and corresponding low/intermediate SOFA values had respective 28 and 90-day mortality rates of 57.4% and 68.9%, compared to 19.8% and 30.8% in the remaining low/intermediate SOFA patient population. There were similar patterns for MR-proADM performance in relation to SAPS II, APACHE II and lactate, respectively (Additional file 1: Supplementary results and Tables S7–S9).

Table 1 Clinical patient characteristics at baseline with regards to survival up to 28 days

	Total (N = 1076)	Survivors (N = 787)	Non-Survivors (N = 289)	p value
Age (years) (mean, SD)	65.7 (13.7)	64.3 (14.0)	69.5 (12.0)	<0.001
Male gender (N, %)	681 (63.3%)	510 (64.8%)	171 (59.2%)	0.091
Definitions of sepsis and length of stay				
Sepsis-1, severe sepsis (N, %)	139 (12.9%)	109 (13.9%)	30 (10.4%)	0.125
Sepsis-1, septic shock (N, %)	937 (87.1%)	678 (86.2%)	259 (89.6%)	0.125
Sepsis-3, sepsis (N, %)	439 (41.2%)	351 (45.2%)	88 (30.4%)	<0.001
Sepsis-3, septic shock (N, %)	627 (58.8%)	426 (54.8%)	201 (69.6%)	<0.001
ICU length of stay (days) (median, IQR)	12 (6 - 23)	13 (7 - 26)	8 (4 - 15)	<0.001
Hospital length of stay (days) (median, IQR)	28 (17 - 45)	34 (22 - 51)	14 (7 - 23)	<0.001
Pre-existing comorbidities				
History of diabetes mellitus (N, %)	280 (26.0%)	188 (23.9%)	92 (31.8%)	0.009
Heart failure (N, %)	230 (21.4%)	150 (19.1%)	80 (27.7%)	0.003
Renal dysfunction (N, %)	217 (20.2%)	135 (17.2%)	82 (28.4%)	<0.001
COPD (N, %)	131 (12.2%)	90 (11.4%)	41 (14.2%)	0.228
Liver cirrhosis (N, %)	50 (4.7%)	27 (3.4%)	23 (8.0%)	0.003
History of cancer (N, %)	319 (29.7%)	224 (28.5%)	95 (32.9%)	0.163
Immunosuppression (N, %)	46 (4.3%)	30 (3.8%)	16 (5.5%)	0.227
Microbiology				
Gram positive (N, %)	146 (13.6%)	113 (14.4%)	33 (11.4%)	0.205
Gram negative (N, %)	132 (12.3%)	95 (12.1%)	37 (12.8%)	0.747
Fungal (N, %)	51 (4.7%)	37 (4.7%)	14 (4.8%)	0.922
Gram positive and negative (N, %)	183 (17.0%)	133 (16.9%)	50 (17.3%)	0.877
Gram positive and fungal (N, %)	92 (8.6%)	68 (8.6%)	24 (8.3%)	0.861
Gram negative and fungal (N, %)	51 (4.7%)	35 (4.5%)	16 (5.5%)	0.463
Gram positive and negative and fungal (N, %)	115 (10.7%)	81 (10.3%)	34 (11.8%)	0.492
Origin of infection				
Pneumonia (N, %)	453 (43.7%)	327 (42.9%)	126 (46.0%)	0.380
Upper or lower respiratory (N, %)	44 (4.3%)	29 (3.8%)	15 (5.5%)	0.252
Thoracic (N, %)	44 (4.3%)	35 (4.6%)	9 (3.3%)	0.344
Bones/soft tissue (N, %)	78 (7.5%)	56 (7.4%)	22 (8.0%)	0.716
Gastrointestinal (N, %)	80 (7.7%)	68 (8.9%)	12 (4.4%)	0.011
Catheter associated (N, %)	30 (2.9%)	18 (2.4%)	12 (4.4%)	0.102
Surgical wound (N, %)	41 (4.0%)	31 (4.1%)	10 (3.7%)	0.759
Intraabdominal (N, %)	375 (36.2%)	276 (36.2%)	99 (36.1%)	0.979
Cardiovascular (N, %)	6 (0.6%)	4 (0.5%)	2 (0.7%)	0.708
Urogenital (N, %)	99 (9.6%)	70 (9.2%)	29 (10.6%)	0.503
Central nervous system (N, %)	3 (0.3%)	2 (0.3%)	1 (0.4%)	0.792
Bacteraemia (N, %)	31 (3.0%)	20 (2.6%)	11 (4.0%)	0.261
Organ dysfunction				
Neurological (N, %)	348 (32.3%)	240 (30.5%)	108 (37.4%)	0.034
Respiratory (N, %)	486 (45.2%)	350 (44.5%)	136 (47.1%)	0.450
Cardiovascular (N, %)	829 (77.0%)	584 (74.2%)	245 (84.8%)	<0.001
Renal (N, %)	382 (35.5%)	249 (31.6%)	133 (46.0%)	<0.001

Table 1 Clinical patient characteristics at baseline with regards to survival up to 28 days (*Continued*)

	Total (N = 1076)	Survivors (N = 787)	Non-Survivors (N = 289)	p value
Haematological (N, %)	156 (14.5%)	89 (11.3%)	67 (23.2%)	<0.001
Gastrointestinal (N, %)	387 (36.0%)	271 (34.4%)	116 (40.1%)	0.086
Metabolic (N, %)	718 (66.7%)	504 (64.0%)	214 (74.1%)	0.002
Other organ dysfunction (N, %)	499 (46.4%)	380 (48.3%)	119 (41.2%)	0.038
Treatment upon sepsis diagnosis				
Invasive mechanical ventilation (N, %)	789 (73.3%)	567 (72.1%)	222 (76.8%)	0.113
Non-invasive mechanical ventilation (N, %)	64 (5.9%)	46 (5.8%)	18 (6.2%)	0.815
Renal replacement therapy (N, %)	326 (30.8%)	158 (20.5%)	168 (58.1%)	<0.001
Vasopressor use (N, %)	980 (91.1%)	712 (90.5%)	268 (92.7%)	0.239
Biomarker and severity scores				
MR-proADM (nmol/L) (median, IQR)	5.0 (2.6–8.8)	4.0 (2.3–7.2)	8.2 (5.2–12.6)	<0.001
PCT (ng/mL) (median, IQR)	7.4 (1.6–26.9)	6.6 (1.4–25.1)	9.3 (2.6–31.8)	0.033
Lactate (mmol/L) (median, IQR)	2.7 (1.6–4.7)	2.4 (1.5–4.0)	3.7 (2.1–7.2)	<0.001
CRP (mg/L) (median, IQR)	188 (120.9–282)	189 (120.5–277.4)	188 (122–287)	0.773
SOFA (points) (mean, SD)	10.02 (3.33)	9.58 (3.18)	11.22 (3.43)	<0.001
SAPS II (points) (mean, SD)	63.27 (14.18)	61.08 (13.71)	69.24 (13.74)	<0.001
APACHE II (points) (mean, SD)	24.24 (7.60)	23.05 (7.37)	27.49 (7.28)	<0.001

Data are presented as absolute numbers with percentages in brackets, indicating the proportion of surviving and non-surviving patients at 28 days
APACHE II Acute Physiological and Chronic Health Evaluation II score, *COPD* chronic obstructive pulmonary disease, *CRP* C-reactive protein, *ICU* intensive care unit, *MR-proADM* mid-regional proadrenomedullin, *N* number, *PCT* procalcitonin, *SAPS II* Simplified Acute Physiological Score II, *SOFA* Sequential Organ Failure Assessment score

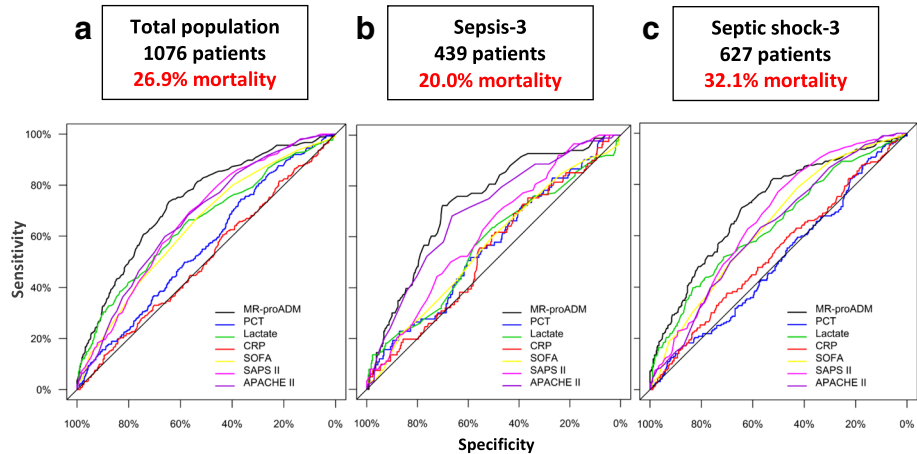
Identification of low-risk patients throughout ICU stay

MR-proADM had the strongest association with 28-day mortality across all subsequent time points (Additional file 1: Table S10). Across days 4–10, a cutoff of ≤ 2.25 nmol/L identified more patients with a lower mortality rate than the other biomarkers and clinical scores (Additional file 1: Tables S11–S12). Accordingly, 290 low MR-proADM severity patients were identified on day 4, of which 79 (27.2%) were deemed as clinically stable with no increase in MR-proADM concentration from the previous measurement (Table 3). A continuously low MR-proADM concentration from day 1 was identified in 51 (64.6%) patients, whilst a decrease from an intermediate to low severity level was observed in 28 (35.4%) patients. Conversely, patients who maintained MR-proADM concentrations > 2.25 nmol/L at all time points had a significantly higher 28-day mortality risk (Additional file 1: Table S13). The average ICU LOS was 8 (7–10) days, with a 28 and 90-day mortality rate of 0.0% and 1.4%, respectively. In comparison, only 43 patients were actually discharged from the ICU on day 4, with a 28 and 90-day mortality rate of 2.3% and 10.0%, respectively. MR-proADM concentration analysis within this patient group indicated that 52.6%, 42.1% and 5.3% of patients were discharged with low, intermediate and high-severity concentrations, respectively. The results were similar on ICU days 7 and 10.

Additional value of MR-proADM in the early identification of treatment response

Multivariate logistic regression for all mortality periods analysed indicated that MR-proADM performance at baseline and day 1 was independent of absolute PCT concentrations or change in PCT between each time point. Results were similar on day 4, with MR-proADM performance independent of delta PCT change. Absolute MR-proADM values had the strongest predictive value for mortality, with delta change in MR-proADM having no significant effect on mortality.

Accordingly, patients with decreasing PCT concentrations of $\geq 20\%$ from baseline to day 1 (Fig. 3 and Additional file 1: Table S14) or $\geq 50\%$ from baseline to day 4 (Additional file 1: Figure S1 and Table S15) had a 28-day mortality rate of 18.3% ($N = 458$) and 17.1% ($N = 557$), respectively. This decreased to 5.6% ($N = 125$) and 1.8% ($N = 111$) when patients had continuously low levels of MR-proADM, and increased to 66.7% ($N = 27$) and 53.8% ($N = 39$) in the presence of continuously high concentrations (HR (95% CI): 19.1 (8.0–45.9) and 43.1 (10.1–184.0)). A similar model of PCT and SOFA kinetics identified fewer low severity patients who had a higher 28-day mortality rate between baseline and day 1 ($N = 102$; 10.8% mortality) or day 4 ($N = 64$; 4.7% mortality), and identified fewer high severity patients with lower mortality rates between baseline and day 1 ($N = 16$; 50.0% mortality) or day 4 ($N = 31$; 41.9% mortality).



	Biomarker or clinical score	Patients (N)	Mortality (N)	AUROC	Univariate Cox regression				Multivariate Cox regression		
					LR χ^2	C-index	HR	IQR [95% CI]	p-value	LR χ^2	C-index
Total population	MR-proADM	1030	275	0.73	142.7	0.71	3.2 [2.6 - 3.9]	<0.001	161.7	0.72	2.9 [2.4 - 3.6]
	PCT	1031	275	0.56	12.2	0.56	1.4 [1.2 - 1.7]	0.001	70.3	0.64	1.4 [1.1 - 1.7]
	CRP	936	251	0.49	0.1	0.51	1.0 [0.9 - 1.2]	0.730	50.5	0.62	1.1 [0.9 - 1.2]
	Lactate	1066	289	0.65	78.3	0.64	2.2 [1.8 - 2.5]	<0.001	122.7	0.69	2.1 [1.7 - 2.5]
	SOFA	1051	282	0.64	47.3	0.62	1.6 [1.4 - 1.8]	<0.001	96.1	0.67	1.6 [1.4 - 1.8]
	SAPS II	1076	289	0.67	70.5	0.65	1.8 [1.6 - 2.0]	<0.001	100.3	0.67	1.6 [1.4 - 1.9]
	APACHE II	1076	289	0.67	69.9	0.65	1.9 [1.6 - 2.2]	<0.001	99.2	0.67	1.7 [1.4 - 2.0]
Sepsis-3	MR-proADM	425	83	0.73	40.9	0.71	2.8 [2.0 - 3.8]	<0.001	61.4	0.74	2.6 [1.8 - 3.7]
	PCT	425	83	0.56	4.6	0.56	1.4 [1.0 - 1.9]	0.031	40.6	0.70	1.5 [1.1 - 2.1]
	CRP	382	81	0.55	2.1	0.54	0.9 [0.7 - 1.1]	0.151	36.7	0.69	0.9 [0.7 - 1.1]
	Lactate	439	88	0.57	7.7	0.56	1.3 [1.1 - 1.6]	0.006	45.0	0.69	1.3 [1.1 - 1.7]
	SOFA	428	86	0.58	3.2	0.56	1.2 [1.0 - 1.5]	0.075	40.8	0.69	1.2 [1.0 - 1.5]
	SAPS II	439	88	0.62	14.5	0.61	1.7 [1.3 - 2.3]	0.001	45.0	0.69	1.5 [1.1 - 2.0]
	APACHE II	439	88	0.70	30.8	0.68	2.1 [1.6 - 2.6]	<0.001	52.6	0.71	1.7 [1.3 - 2.3]
Septic shock-3	MR-proADM	597	192	0.72	77.4	0.69	2.4 [2.0 - 3.0]	<0.001	93.5	0.71	2.3 [1.8 - 2.9]
	PCT	597	192	0.50	0.4	0.51	1.1 [0.9 - 1.3]	0.526	35.7	0.62	1.1 [0.9 - 1.4]
	CRP	545	170	0.53	2.1	0.53	1.1 [1.0 - 1.3]	0.150	31.7	0.63	1.1 [1.0 - 1.4]
	Lactate	627	201	0.64	52.2	0.64	2.0 [1.7 - 2.4]	<0.001	79.4	0.68	2.0 [1.7 - 2.4]
	SOFA	616	196	0.65	31.1	0.62	1.6 [1.4 - 1.9]	<0.001	56.5	0.66	1.6 [1.3 - 1.9]
	SAPS II	627	201	0.67	42.2	0.65	1.7 [1.4 - 1.9]	<0.001	59.8	0.66	1.6 [1.3 - 1.8]
	APACHE II	627	201	0.63	28.3	0.61	1.6 [1.3 - 1.9]	<0.001	50.7	0.65	1.5 [1.3 - 1.8]

Fig. 1 Prediction of 28-day mortality at baseline. Association between biomarkers and clinical scores with mortality at baseline, with respective AUROC and Cox regression analyses across the total patient population (a), Sepsis-3 (b) and Septic shock-3 (c) subgroups. All multivariate analyses for 28-day mortality were significant ($p < 0.001$). APACHE II Acute Physiological and Chronic Health Evaluation II score, AUROC area under the receiver operating characteristic curve, CI confidence interval, CRP C-reactive protein, HR hazard ratio, IQR interquartile range, MR-proADM mid-regional proadrenomedullin, N number, PCT procalcitonin, SAPS II, Simplified Acute Physiological Score II, SOFA Sequential Organ Failure Assessment

Furthermore, patients with decreasing PCT values of $\geq 50\%$ (baseline to day 4) had a significantly higher risk of developing subsequent nosocomial infections if corresponding MR-proADM concentrations were either continuously high (HR (95% CI): 3.9 (1.5–10.5)) or intermediate (HR (95% CI): 2.4 (1.2–6.8)). In addition, patients with decreasing PCT values of $\geq 50\%$ but increasing intermediate to high MR-proADM concentrations were subsequently more likely to require focus control procedures compared to those with either continuously intermediate (HR (95% CI): 3.2 (1.3–7.6)), intermediate to low (HR (95% CI): 8.7 (3.1–24.8)) or high to intermediate (HR (95% CI): 4.6 (1.4–14.5)) values. When PCT levels failed to decrease by $\geq 50\%$ over the first 4 days of ICU treatment, the risk of requiring emergency surgery was significantly increased if MR-proADM concentrations were either at a continuously high (HR (95% CI): 5.7 (1.5–21.9)) or intermediate (HR (95% CI): 4.2 (1.3–13.2)) level.

Finally, despite undergoing ICU treatment, a stable intermediate SOFA severity level persisted in 260 (26.6%) patients from baseline to day 1, resulting in a 28-day mortality rate of 26.2%. Of these patients, those with continuously low or decreasing MR-proADM concentrations ($N = 80$; 13.8% mortality) had a significantly lower mortality rate compared to those with continuously high or increasing concentrations ($N = 40$; 47.5% mortality; HR (95% CI): 0.1 (0.0–0.4)). Similar MR-proADM subgroups were also identified within the populations with stable low, increasing and decreasing SOFA.

Discussion

Sepsis remains a major public health concern with high rates of morbidity, mortality and resource use worldwide [25]. Although considerable advances have been made to better define the host response to infection, there is still a lack of specific tools to identify

Table 2 Survival analysis for 7-day, 90-day, ICU and hospital mortality

	Biomarker or clinical score	Patients (N)	Mortality (N)	AUROC	Univariate Cox regression				Multivariate Cox regression		
					LR χ^2	C-index	HR IQR (95% CI)	p value	LR χ^2	C-index	HR IQR (95% CI)
7-day mortality	MR-proADM	1037	131	0.72	71.6	0.71	3.3 (2.4–4.3)	<0.001	82.1	0.73	3.4 (2.5–4.6)
	PCT	1038	131	0.58	9.7	0.58	1.5 (1.2–2.0)	0.002	28.4	0.64	1.6 (1.2–2.1)
	CRP	943	111	0.55	1.2	0.55	1.1 (0.9–1.4)	0.284	16.6	0.62	1.2 (0.9–1.4)
	Lactate	1074	135	0.72	86.0	0.71	3.1 (2.4–3.9)	<0.001	99.1	0.73	3.1 (2.4–4.0)
	SOFA	1059	130	0.63	25.5	0.63	1.7 (1.4–2.0)	<0.001	41.0	0.67	1.7 (1.4–2.1)
	SAPS II	1085	135	0.66	38.5	0.66	1.8 (1.5–2.2)	<0.001	50.1	0.67	1.8 (1.5–2.2)
	APACHE II	1085	135	0.63	24.4	0.63	1.7 (1.4–2.1)	<0.001	37.8	0.65	1.7 (1.4–2.1)
90-day mortality	MR-proADM	1000	379	0.71	146.2	0.68	2.7 (2.3–3.2)	<0.001	194.1	0.71	2.4 (2.0–2.8)
	PCT	1000	379	0.55	11.8	0.55	1.3 (1.1–1.5)	0.001	113.5	0.65	1.3 (1.1–1.5)
	CRP	909	348	0.51	0.2	0.51	1.0 (0.9–1.2)	0.664	92.3	0.64	1.1 (0.9–1.2)
	Lactate	1037	399	0.64	83.2	0.63	2.0 (1.7–2.3)	<0.001	168.8	0.68	1.9 (1.6–2.2)
	SOFA	1021	388	0.62	48.1	0.61	1.5 (1.4–1.7)	<0.001	143.7	0.67	1.5 (1.3–1.7)
	SAPS II	1045	399	0.66	81.1	0.64	1.7 (1.5–1.9)	<0.001	144.4	0.67	1.5 (1.3–1.7)
	APACHE II	1045	399	0.67	86.4	0.64	1.8 (1.6–2.1)	<0.001	146.8	0.67	1.6 (1.4–1.8)
ICU mortality	MR-proADM	1023	264	0.73	136.4	0.73	4.0 (3.1–5.2)	<0.001	158.3	0.75	3.7 (2.8–4.9)
	PCT	1024	264	0.58	18.0	0.58	1.6 (1.3–2.0)	<0.001	73.0	0.67	1.6 (1.3–2.1)
	CRP	928	237	0.54	2.5	0.54	1.1 (1.0–1.3)	0.111	51.4	0.65	1.2 (1.0–1.4)
	Lactate	1059	277	0.66	75.2	0.66	2.4 (2.0–3.0)	<0.001	115.5	0.71	2.4 (1.9–2.9)
	SOFA	1044	270	0.64	48.6	0.64	1.8 (1.5–2.2)	<0.001	95.2	0.69	1.8 (1.5–2.2)
	SAPS II	1070	277	0.65	58.7	0.65	1.9 (1.6–2.3)	<0.001	91.2	0.68	1.8 (1.5–2.2)
	APACHE II	1070	277	0.66	62.5	0.66	2.1 (1.7–2.6)	<0.001	91.6	0.69	1.9 (1.5–2.3)
Hospital mortality	MR-proADM	980	323	0.73	152.0	0.74	4.0 (3.1–5.2)	<0.001	186.8	0.76	3.6 (2.7–4.6)
	PCT	981	323	0.57	15.0	0.57	1.5 (1.2–1.9)	<0.001	96.2	0.68	1.5 (1.2–1.9)
	CRP	891	299	0.52	0.9	0.52	1.1 (0.9–1.3)	0.348	76.0	0.67	1.1 (1.0–1.3)
	Lactate	1016	342	0.66	77.8	0.66	2.4 (2.0–2.9)	<0.001	146.2	0.72	2.3 (1.9–2.9)
	SOFA	1001	333	0.63	41.3	0.63	1.7 (1.4–2.0)	<0.001	118.9	0.70	1.7 (1.4–2.0)
	SAPS II	1027	342	0.65	59.1	0.65	1.9 (1.6–2.2)	<0.001	115.9	0.69	1.7 (1.4–2.0)
	APACHE II	1027	342	0.67	76.7	0.67	2.2 (1.9–2.7)	<0.001	127.1	0.71	1.9 (1.6–2.4)

All multivariate *p* values <0.001, apart from PCT and CRP for 7-day mortality (0.002 and 0.084, respectively)

APACHE II Acute Physiological and Chronic Health Evaluation II score, CI confidence interval, CRP C-reactive protein, HR hazard ratio, IQR interquartile range, MR-proADM mid-regional proadrenomedullin, N number, PCT procalcitonin, SAPS II Simplified Acute Physiological Score II, SOFA Sequential Organ Failure Assessment score, LR likelihood ratio

patients at risk of a poor outcome. Accordingly, numerous biomarkers and clinical severity scores have been proposed to fulfil such a requirement, with the SOFA score (representing sepsis-related organ dysfunction) and serum lactate (indicating a deterioration in tissue perfusion) both playing a central role in the recent definition of sepsis [4]. Nevertheless, earlier indicators of developing organ dysfunction or a deteriorating host response are essential in order to guide the most appropriate therapeutic intervention at the earliest opportunity [26, 27].

The novel biomarker, MR-proADM, may fulfil this clinical unmet need, with previous experimental studies

showing adrenomedullin to play a significant role in vascular permeability [6], inflammatory mediator and endothelial barrier regulation, and stabilisation of the microcirculation [9, 28, 29] - all of which contribute to the development of organ dysfunction and failure. Accordingly, this secondary analysis of the SISPECT trial [22], for the first time, compared sequential measurements of conventional biomarkers and clinical scores, such as lactate, PCT and SOFA, with those of MR-proADM.

Our results indicate that the initial use of MR-proADM within the first 24 h after sepsis diagnosis resulted in the strongest association with short-term, mid-term and long-term mortality compared to all

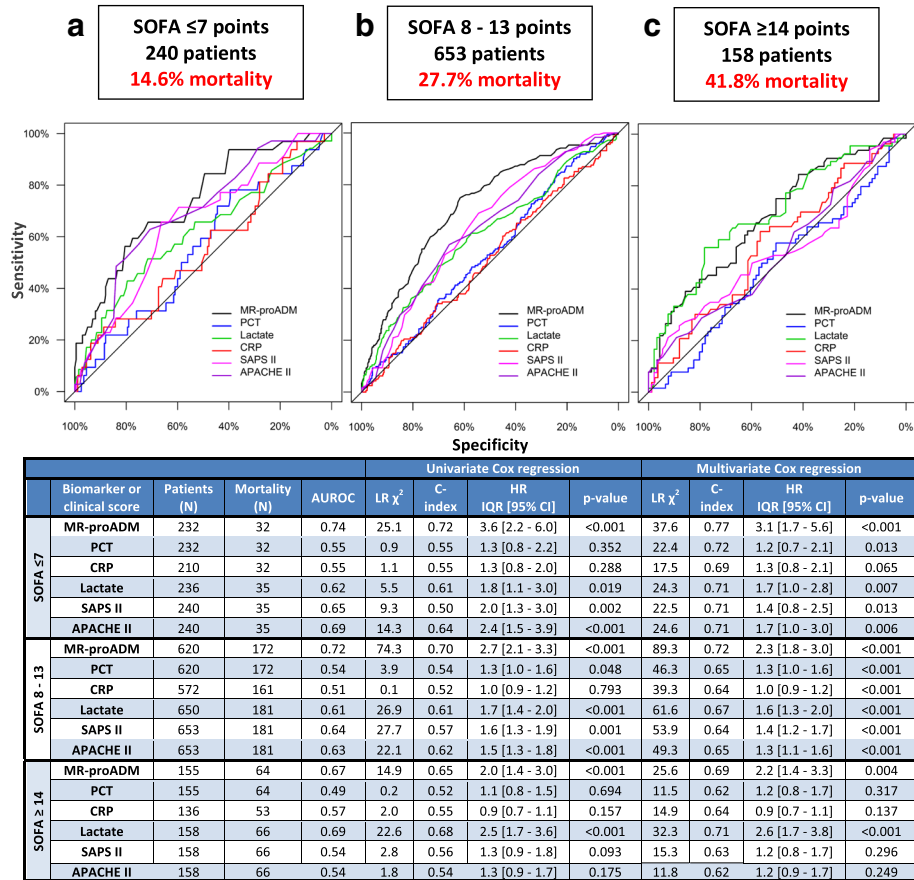
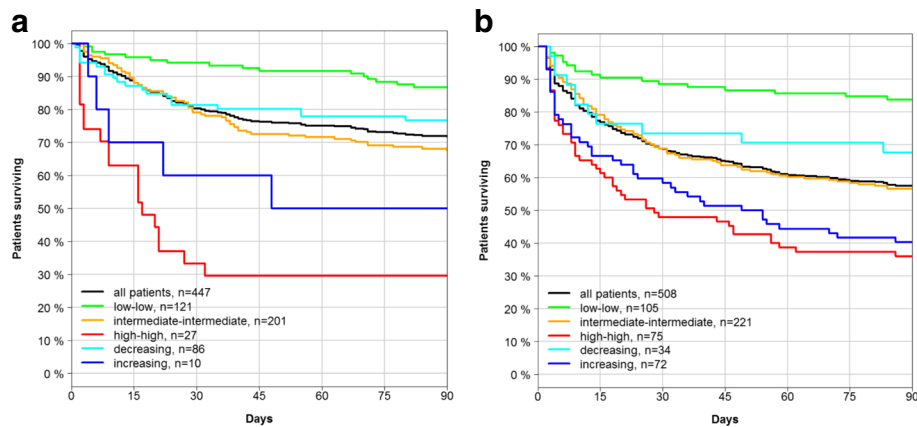


Fig. 2 Cox regression and AUROC analysis for 28-day mortality prediction based on SOFA severity levels. Biomarker and clinical score performance in predicting 28-day mortality with respective AUROC and Cox regression analyses in the low (SOFA ≤ 7) (a), moderate (SOFA 8–13) (b) and high (SOFA ≥ 14) (c) severity SOFA subgroups. APACHE II Acute Physiological and Chronic Health Evaluation II score, AUROC area under the receiver operating characteristic curve, CI confidence interval, CRP C-reactive protein, HR hazard ratio, IQR interquartile range, MR-proADM mid-regional proadrenomedullin, N number, PCT procalcitonin, SAPS II Simplified Acute Physiological Score II, SOFA Sequential Organ Failure Assessment

Table 3 Mortality and duration of ICU therapy at different time points

Patient severity group		Patients (N)	SOFA (points)	Length of stay (days)	28-day mortality (N, %)	90-day mortality (N, %)
Day 4	Total patient population	777	8.4 (4.3)	16 (10–27)	158 (20.3%)	256 (33.9%)
	Clinically stable population	145	4.5 (2.4)	8 (6–11)	10 (6.9%)	22 (15.8%)
	Clinically stable and low MR-proADM population	79	3.6 (1.5)	8 (7–10)	0 (0.0%)	1 (1.4%)
	Actual day-4 discharges	43	3.6 (2.1)	–	1 (2.3%)	4 (10.0%)
Day 7	Total patient population	630	8.0 (4.2)	19 (13–31)	127 (20.2%)	214 (34.9%)
	Clinically stable population	124	3.9 (1.7)	11.5 (9–16)	9 (7.3%)	17 (13.9%)
	Clinically stable and low MR-proADM population	78	3.4 (1.6)	11 (9–14)	1 (1.3%)	4 (5.3%)
	Actual day-7 discharges	36	3.6 (2.6)	–	2 (5.6%)	5 (13.9%)
Day 10	Total patient population	503	7.6 (4.0)	23.5 (17–34.25)	82 (16.3%)	159 (32.6%)
	Clinically stable population	85	3.5 (1.8)	15 (13–22)	9 (10.6%)	14 (17.3%)
	Clinically stable and low MR-proADM population	57	3.2 (1.3)	14 (12.25–19)	1 (1.8%)	2 (3.8%)
	Actual day-10 discharges	29	4.0 (2.6)	–	5 (17.2%)	7 (24.1%)

N number, MR-proADM mid-regional proadrenomedullin, SOFA Sequential Organ Failure Assessment score



	Biomarker Kinetics		28 day mortality			90 day mortality		
	Baseline	Day 1	N	%	HR [95% CI]	N	%	HR [95% CI]
PCT decrease ≥20%			458	18.3%		447	28.2%	
MR-proADM severity level	Low	Low	125	5.6%	3.6 [1.6 - 8.1]*	121	13.2%	2.7 [1.6 - 4.8]*
	Intermediate	Intermediate	204	19.1%	5.3 [3.0 - 9.3]**	201	32.3%	3.8 [2.3 - 6.3]**
	High	High	27	66.7%	19.1 [8.0 - 45.9]***	27	70.4%	10.4 [5.3 - 20.2]***
	Increasing							
	Low	Intermediate	2	50.0%	-	2	50.0%	-
	Intermediate	High	10	40.0%	2.5 [0.9 - 7.0]††	10	50.0%	1.9 [0.8 - 4.8]††
	Decreasing							
	High	Intermediate	30	36.7%	0.4 [0.2 - 0.9]‡	29	44.8%	0.5 [0.2 - 0.9]‡
	Intermediate	Low	60	8.3%	0.4 [0.2 - 1.0]‡‡	57	12.3%	0.3 [0.2 - 0.7]‡‡
	PCT decrease <20%			522	29.7%		508	42.5%
MR-proADM severity level	Low	Low	106	10.4%	3.1 [1.7 - 5.9]*	105	16.2%	3.2 [1.9 - 5.3]*
	Intermediate	Intermediate	229	29.7%	2.0 [1.3 - 2.9]**	221	43.4%	1.9 [1.3 - 2.6]**
	High	High	77	49.4%	6.2 [3.2 - 12.2]***	75	64.0%	5.9 [3.4 - 10.3]***
	Increasing							
	Low	Intermediate	29	17.2%	1.8 [0.6 - 5.2]†	27	44.4%	3.2 [1.5 - 6.7]†
	Intermediate	High	45	53.3%	2.3 [1.4 - 3.6]††	45	68.9%	2.1 [1.4 - 3.2]††
	Decreasing							
	High	Intermediate	11	54.5%	-	11	72.7%	-
	High	Low	1	0.0%	-	1	100.0%	-
	Intermediate	Low	24	12.5%	0.4 [0.1 - 1.2]‡‡	23	13.0%	0.2 [0.1 - 0.8]‡‡

Fig. 3 Mortality rates at 28 and 90 days following PCT and MR-proADM kinetics between baseline and day 1. Kaplan-Meier plots illustrate patient subgroups stratified by MR-proADM severity levels for 90-day mortality, based on corresponding PCT concentrations from baseline to day 1, decreasing either by ≥ 20% (a) or by <20% (b). Severity levels are grouped as continuously low, intermediate or high, or as a composite for increasing or decreasing MR-proADM levels. Individual hazard ratios for comparisons between patient subgroups are indicated: *continuously intermediate vs. low values; **continuously high vs. intermediate values; ***continuously high vs. low values; †increasing low to intermediate vs. continuously low values; ††increasing intermediate to high vs. continuously intermediate values; ‡decreasing high to intermediate vs. continuously high values; ‡‡decreasing intermediate to low vs. continuously intermediate values. HR hazard ratio, IQR interquartile range, MR-proADM mid-regional proadrenomedullin, N number, PCT procalcitonin

other biomarkers or clinical scores. Previous studies confirm our findings [30–32], whereas conflicting results [33] may be explained in part by the smaller sample sizes analysed and by other factors highlighted within this study, such as microbial species, origin of infection and previous surgical history, all of which may influence biomarker performance, thus adding to the potential variability of results. Furthermore, our study confirms the results of a previous investigation highlighting the superior performance of MR-proADM in low and intermediate severity organ dysfunction patients with severe sepsis or septic shock [34]. Indeed, Andaluz-Ojeda et al. placed significant importance on patients with low levels of organ dysfunction, since “this group represents either the

earliest presentation in the clinical course of sepsis and/or the less severe form of the disease” [34]. The incorporation of MR-proADM into an early sepsis management protocol may therefore help guide early diagnostic interventions and facilitate more intensive treatment in these patient groups before development of any further organ dysfunction. In addition, a reasonable performance across all organ dysfunction, Sepsis-1 and Sepsis-3 subgroups with respect to disease severity further strengthens its clinical utility irrespective of changing definitions or population heterogeneity.

Further analysis of biomarker measurements throughout ICU stay allowed for the effects of therapy to be visualised, resulting in the discrimination of specific

patient groups according to host response. Based on the results of this study, two further clinically important uses for MR-proADM can be proposed: (i) the early escalation of therapy in patients at risk of treatment failure and (ii) the de-escalation of treatment and early discharge of low-risk patients.

First, our results revealed a significant benefit in the addition of MR-proADM measurements in the early identification of non-responding patients in order to initiate alternative targeted treatment strategies. Whilst decreasing PCT concentrations are known to indicate the initiation of successful antimicrobial therapy [35, 36], and adherence to a PCT-guided algorithm has been shown to facilitate a reduction in antibiotic use [22, 37, 38], our results revealed a significant benefit in the addition of MR-proADM measurements. The presence of continuously elevated or increasing MR-proADM concentrations in relation to the high sensitivity cutoffs (2.75 and 10.9 nmol/L) identified within this study - despite decreasing PCT concentrations - may provide a prompt indication as to a likely subsequent failure in treatment, and a poor overall outcome. Similar results have been previously found in critically ill febrile patients with cancer, where MR-proADM concentrations were uniquely increased in patients who did not respond to therapy or antibiotic treatment [39]. Such a biomarker constellation may therefore be useful at an early stage of ICU therapy in order to facilitate the earlier initiation of specific interventions, such as focus control and surgical procedures [16], or may potentially aid in the streamlining of antimicrobial agents in patients with sepsis or septic shock [40].

Second, the identification of a population with low disease severity who may be eligible for an early discharge to a step-down setting may be of additional clinical and economic interest [41]. A prompt discharge of patients no longer at risk is essential in maintaining an efficient bed-management workflow as well as being of a likely clinical benefit [42]. Our results suggest that the identification of low levels of microcirculatory or vascular damage, as indicated by low MR-proADM concentrations, identifies patients with a very low risk of death in whom early ICU discharge might be possible, and may potentially prevent unnecessary additional diagnostic or interventional procedures [39, 43, 44]. Indeed, similarities have been shown in an earlier randomised controlled trial of 313 patients with suspected lower respiratory tract infections [19]. A non-significant decrease in hospitalization of 0.5 days was identified at the 30-day follow up, although overruling of the MR-proADM algorithm in 34.5% of cases after medical stabilisation resulted in delayed discharge, primarily due to organisational criteria such as further consultant examinations, imaging studies or laboratory results. Such factors should therefore be considered when designing further interventional studies to confirm the results of this analysis.

Interestingly, the discharge of patients with varying MR-proADM concentrations within our study potentially indicated either an incomplete or insufficient treatment, which was consequently reflected in an increased 28 and 90-day mortality rate. Whilst it is unknown whether further ICU treatment for non-microcirculatory, non-life-threatening issues was required, or if beds in a step down-unit were available, such a biomarker-driven approach to ICU discharge in addition to clinician judgement may reduce ICU LOS and improve patient disposition stratification, with accompanied clinical benefits and potential cost savings.

Our analysis has strengths and weaknesses. Biomarker measurements were not collected on a daily basis and were not available earlier than day 1. Given the secondary analysis design of the study, our results should be viewed as exploratory and hypothesis-generating. Admittedly, some of the subgroups analyses involved small patient numbers, revealing the need for future studies to confirm the hypotheses generated. Strengths include the thorough examination of several different subgroups with varying disease severity from a randomised trial database with a high internal validity, and the largest sample size of sepsis patients with MR-proADM measurements to date.

Conclusions

MR-proADM provides a more accurate disease severity and mortality risk stratification compared to clinically established biomarkers and scores, both on initial diagnosis and over the course of treatment. Changes in MR-proADM kinetics, despite ongoing antimicrobial treatment, may be used to identify patients at risk of treatment failure who may require alternative diagnostic and therapeutic interventions, as well as low severity patients eligible for an early ICU discharge in conjunction with an absence of ICU-specific therapies. Interventional studies to confirm these hypotheses are essential and should be viewed as mandatory before incorporation into routine clinical use.

Additional file

Additional file 1: Supplementary results. (PDF 5376 kb)

Abbreviations

APACHE II: Acute Physiological and Chronic Health Evaluation II; AUROC: Area under the receiver operating characteristic curve; CI: Confidence interval; CRP: C-reactive protein; HR: Hazard ratio; ICU: Intensive care unit; IQR: Interquartile range; LOS: Length of stay; LR: Likelihood ratio; MR-proADM: Mid-regional proadrenomedullin; N: Number; NRI: Net reclassification improvement; PCT: Procalcitonin; SAPS II: Simplified Acute Physiological Score II; SISPCT: Placebo-Controlled Trial of Sodium Selenite and Procalcitonin Guided Antimicrobial Therapy in Severe Sepsis; SOFA: Sequential Organ Failure Assessment

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Availability of data and materials

The datasets used and/or analysed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

GE, FB, KR and PM conceived the design of the study. GE was the primary author and editor of the manuscript. FB was the principal investigator for the SISPECT trial. GE, FB, DCW, FMB, JB, KR, ML, SK, AN, UJ, OM, AW and PM collected the study data and contributed to the evaluation and interpretation of data and writing and editing of all drafts of the manuscript. GE, FB, DCW and PM performed and ML assisted in and supervised the statistical analysis of data. All authors critically reviewed and approved the final manuscript.

Ethics approval and consent to participate

The study protocol of the SISPECT trial was approved by the ethics board of Jena University Hospital (Internal File No. 2242-03/08). Written informed consent was obtained from all patients or their legal representatives.

Consent for publication

No individual participant data are reported that would require consent from the participant (or legal parent or guardian for children) to publish.

Competing interests

All authors have provided information on potential conflicts of interests directly or indirectly related to the work submitted in the journal's disclosure forms. FB reported receiving lecture honoraria from biosyn, Gilead, and CSL Behring and public funding for the SISPECT trial to his department by the German Federal Ministry of Education and Research, and unrestricted research grants for the SISPECT trial from biosyn and Thermo Fisher Scientific. DCW is an employee of BRAHMS GmbH. KR reported receiving personal fees from Adrenomed and being a shareholder of InflaRx Jena. SK reported receiving lecture fees from Astellas, Basilea, biotest, CSL Behring, CytoSorbents, Fresenius, Gilead, MSD, Pfizer and Thermo Fisher Scientific and being a member of advisory boards for Astellas, Fresenius, Gilead, MSD, Novartis and Pfizer. AN reported receiving lecture honoraria from Thermo Fisher Scientific. All other authors declared that they have no conflict of interest.

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