Critical Care

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Identification of developing multiple organ failure in sepsis patients with low or moderate SOFA scores

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An early identification of sepsis patients likely to progress towards multiple organ failure is crucial in order to initiate targeted therapeutic strategies to decrease mortality. Our recent publication highlighted the greater accuracy of mid-regional proadrenomedullin (MR-proADM) compared with conventional biomarkers and clinical scores in predicting 28-day mortality in patients with initially low ($\leq$7 points; $N = 240$) or moderate (8–13 points; $N = 653$) Sepsis-related Organ Failure Assessment (SOFA) scores [1], thus confirming results from smaller investigations [2, 3]. This additional post hoc analysis aimed to further describe the non-surviving patient population of both subgroups and identify those likely to progress towards sepsis-related multiple organ failure.

In our study, patients with low SOFA scores had a lower 28-day mortality rate ($N = 35$; 14.6% vs. $N = 181$; 27.7%) and incidence of septic shock [4] ($N = 87$; 36.7% vs. $N = 399$; 61.5%) compared to those with moderate values. Nevertheless, multiple organ failure was the most common cause of death irrespective of initial SOFA classification (low vs. moderate SOFA: $N = 16$; 45.7% vs. $N = 79$; 43.6%). Patients with low SOFA scores tended to take longer to progress towards multiple organ failure (10 [6–18] vs. 7 [3–11] days) and had an increasing number of dysfunctional organs (identified by organ-specific SOFA scores $\geq$2) and an increasing overall SOFA score (e.g. diagnosis to day 7: 2 [1–2]

vs. 4 [3–5] dysfunctional organs; $P < 0.01$; 6.3 ± 1.3 vs. 10.2 ± 4.7 points; $P < 0.01$).

Area under the receiver operating characteristic curve (AUROC) and Cox regression analysis indicated that MR-proADM had the highest accuracy in predicting progression towards sepsis-related multiple organ failure mortality in both groups (Fig. 1). High initial concentrations in non-surviving patients with low or moderate SOFA scores resulted in a high progression rate towards multiple organ failure ($N = 6$; 100.0% and $N = 25$; 52.1%), with similar results found in patients with increasing concentrations over the first 24 h (e.g. moderate SOFA population: $N = 15$; 57.8%). Conversely, mortality in patients with low MR-proADM concentrations was predominantly due to non-sepsis-related causes ($N = 14$; 60.9%), with a low subsequent progression rate towards sepsis-related multiple organ failure in the total patient population with continuously low concentrations over the first 24 h ($N = 3$; 1.4%).

Results suggest that initially high or increasing MR-proADM concentrations may help to identify patients with a high risk of progression towards sepsis-related multiple organ failure. Elevated microcirculation dysfunction and endothelial permeability may therefore play a significant role in driving the development of further organ dysfunction, as described previously [5]. Further studies in larger patient populations are essential to confirm these hypotheses.

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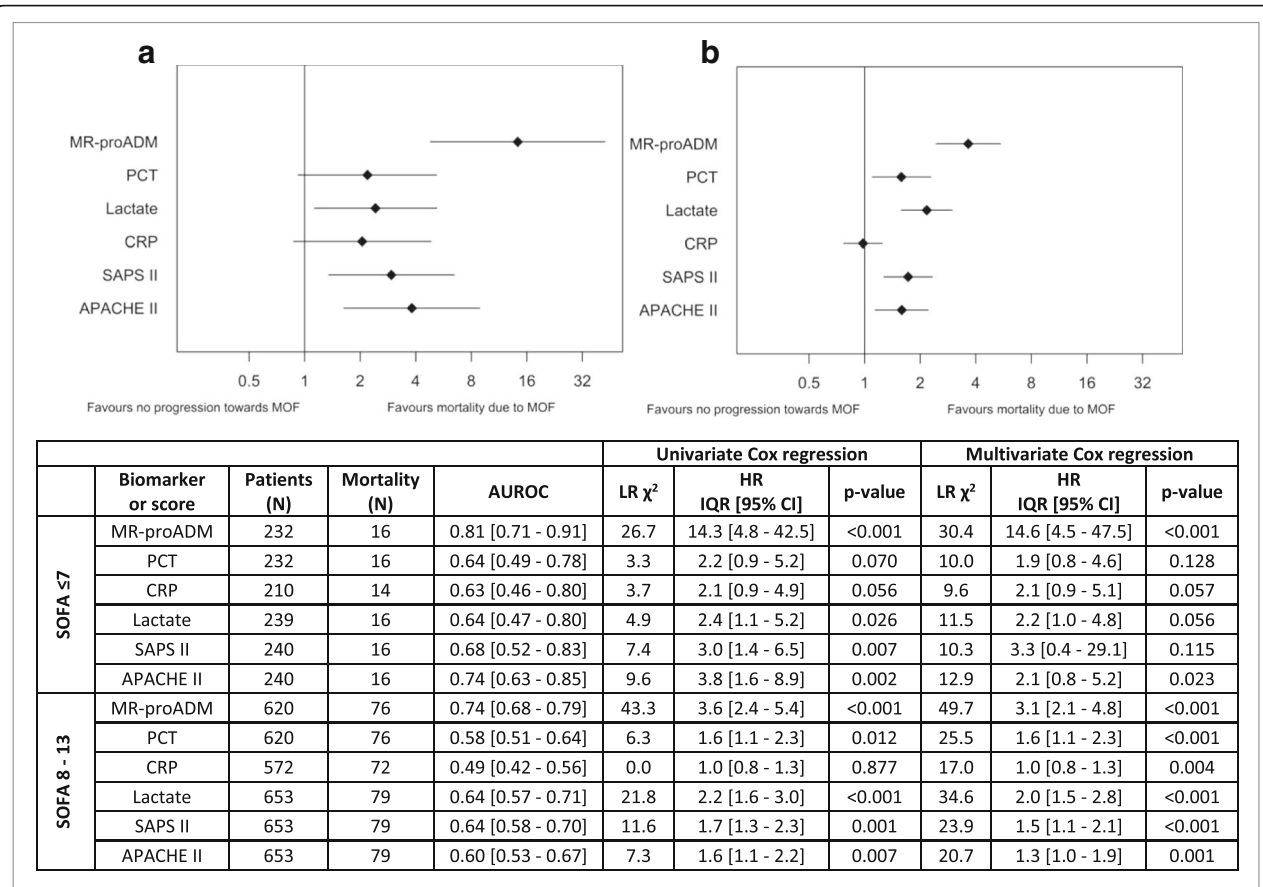Full list of author information is available at the end of the article

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	Biomarker or score	Patients (N)	Mortality (N)	AUROC	Univariate Cox regression			Multivariate Cox regression		
					LR χ^2	HR IQR [95% CI]	p-value	LR χ^2	HR IQR [95% CI]	p-value
SOFA ≤7	MR-proADM	232	16	0.81 [0.71 - 0.91]	26.7	14.3 [4.8 - 42.5]	<0.001	30.4	14.6 [4.5 - 47.5]	<0.001
	PCT	232	16	0.64 [0.49 - 0.78]	3.3	2.2 [0.9 - 5.2]	0.070	10.0	1.9 [0.8 - 4.6]	0.128
	CRP	210	14	0.63 [0.46 - 0.80]	3.7	2.1 [0.9 - 4.9]	0.056	9.6	2.1 [0.9 - 5.1]	0.057
	Lactate	239	16	0.64 [0.47 - 0.80]	4.9	2.4 [1.1 - 5.2]	0.026	11.5	2.2 [1.0 - 4.8]	0.056
	SAPS II	240	16	0.68 [0.52 - 0.83]	7.4	3.0 [1.4 - 6.5]	0.007	10.3	3.3 [0.4 - 29.1]	0.115
	APACHE II	240	16	0.74 [0.63 - 0.85]	9.6	3.8 [1.6 - 8.9]	0.002	12.9	2.1 [0.8 - 5.2]	0.023
SOFA 8 - 13	MR-proADM	620	76	0.74 [0.68 - 0.79]	43.3	3.6 [2.4 - 5.4]	<0.001	49.7	3.1 [2.1 - 4.8]	<0.001
	PCT	620	76	0.58 [0.51 - 0.64]	6.3	1.6 [1.1 - 2.3]	0.012	25.5	1.6 [1.1 - 2.3]	<0.001
	CRP	572	72	0.49 [0.42 - 0.56]	0.0	1.0 [0.8 - 1.3]	0.877	17.0	1.0 [0.8 - 1.3]	0.004
	Lactate	653	79	0.64 [0.57 - 0.71]	21.8	2.2 [1.6 - 3.0]	<0.001	34.6	2.0 [1.5 - 2.8]	<0.001
	SAPS II	653	79	0.64 [0.58 - 0.70]	11.6	1.7 [1.3 - 2.3]	0.001	23.9	1.5 [1.1 - 2.1]	<0.001
	APACHE II	653	79	0.60 [0.53 - 0.67]	7.3	1.6 [1.1 - 2.2]	0.007	20.7	1.3 [1.0 - 1.9]	0.001

Fig. 1 Prediction of sepsis-related multiple organ failure in low (≤7 points) and moderate (8–13 points) SOFA severity patient populations. Cox regression and AUROC analysis for 28-day mortality due to sepsis-related multiple organ failure. Univariate Cox regression was compared for each biomarker and clinical score in the (**a**) low (≤7 points) and (**b**) moderate (8–13 points) SOFA severity subgroups. Multivariate Cox regression analysis was corrected for age and the presence of comorbidities. *Abbreviations*: *APACHE II* Acute Physiology 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, *LR* likelihood ratio, *MOF* multiple organ failure, *MR-proADM* mid-regional proadrenomedullin, *N* number, *PCT* procalcitonin, *SAPS II* Simplified Acute Physiology Score II, *SOFA* Sepsis-related Organ Failure Assessment

Authors' contributions
GE was the primary author and editor of the manuscript. FB was the principal investigator for the SISPCT trial. All authors collected the study data and contributed to the evaluation and interpretation of data as well as writing and editing of the manuscript, performing the statistical analysis of data, and critically reviewing and approving the final manuscript.

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