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MR- proADM to detect specific types of organ failure in infection

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Abstract

Background: Following the SEPSIS-3 consensus, detection of organ failure as assessed by the SOFA (Sequential Organ Failure Assessment) score, is mandatory to detect sepsis. Calculating SOFA outside of the Intensive Care Unit (ICU) is challenging. The alternative in this scenario, the quick SOFA, is very specific but less sensible. Biomarkers could help to detect the presence of organ failure secondary to infection either in ICU and non-ICU settings.

Materials and methods: We evaluated the ability of four biomarkers (C-Reactive protein (CRP), lactate, mid-regional proadrenomedullin (MR-proADM) and procalcitonin (PCT)) to detect each kind of organ failure considered in the SOFA in 213 patients with infection, sepsis or septic shock, by using multivariate regression analysis and calculation of the area under the receiver operating curve (AUROC).

Results: In the multivariate analysis, MR-proADM was an independent predictor of five different failures (respiratory, coagulation, cardiovascular, neurological and renal). In turn, lactate predicted three (coagulation, cardiovascular and neurological) and PCT two (cardiovascular and renal). CRP did not predict any of the individual components of SOFA. The highest AUROCs were those of MR-proADM and PCT to detect cardiovascular (AUROC, CI95%): MR-proADM (0.82 [0.76-0.88]), PCT

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(0.81 [0.75-0.87] ($P < .05$) and renal failure: MR-proADM (0.87 [0.82-0.92]), PCT (0.81 [0.75-0.86]), ($P < .05$). None of the biomarkers tested was able to detect hepatic failure.

Conclusions: In patients with infection, MR-proADM was the biomarker detecting the largest number of SOFA score components, with the exception of hepatic failure.

KEYWORDS

biomarkers, infection, organ failure, sepsis

1 | INTRODUCTION

Following the SEPSIS-3 consensus, organ failure is the definitory event of sepsis. An increase in the Sequential Organ Failure Assessment (SOFA) score of 2 points or more is associated with an in-hospital mortality greater than 10%.[1] Identifying the presence of organ failure is mandatory thus to discriminate an uncomplicated infection from sepsis.[2] The SOFA score was developed in 1996 by the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine.[3] It includes six major items reflecting failure at the respiration, coagulation, liver, cardiovascular, central nervous system and renal level.[3] Calculating the SOFA score outside of the Intensive Care Unit (ICU) is challenging. The alternative to the SOFA score in this scenario, the quick SOFA (composed of three simple items: respiratory frequency, blood pressure and the Glasgow Coma Scale—GCS—score) is very specific but less sensitive to detect sepsis.[4]

Biomarkers could help to detect organ failure in a patient with infection, indicating the presence of sepsis, both in the ICU and also in non-ICU settings. To be clinically useful, biomarkers to detect sepsis should be accurate enough to detect all the components of the SOFA. Previous works have explored the correlation between the concentration of biomarkers in plasma or serum and the total SOFA score,[5-7] but so far, the ability of biomarkers to specifically detect each kind of organ failure considered in this score has not been studied.

Lactate, procalcitonin (PCT), C reactive protein (CRP) and mid-regional proadrenomedullin (MR-proADM) are some of the biomarkers most extensively studied in sepsis.[8-11] Lactate levels rise in those sepsis patients with decreased vascular perfusion leading to tissue or organic hypoxia, which then leads to anaerobic glycolysis.[8] PCT is a precursor of calcitonin which is physiologically synthesized by the C cells of the thyroid gland and pulmonary neuroendocrine cells in minute quantities.[12-14] In bacterial infections, systemic PCT secretion is a component of the inflammatory response. In this context, it is synthesized in various extrathyroidal neuroendocrine tissues[15,16]. CRP is an acute-phase protein released by the liver after the onset of inflammation or tissue damage.[17] MR-proADM directly reflects levels of adrenomedullin, a hormone synthesized by the endothelial cells but which is also widely distributed in tissues, including bone, adrenal cortex, kidney, lung, blood vessels and heart.[18,19] MR-proADM is considered a novel biomarker of microvascular endothelial dysfunction,[20] a key event in sepsis pathogenesis.[21] In this work, we have evaluated the performance of lactate, PCT, CRP and MR-proADM to independently detect each one of the six components of the SOFA score in patients with infection in the presence and absence of critical illness.

2 | MATERIALS AND METHODS

Reporting of the study conforms to STROBE statement along with references to STROBE statement and the broader EQUATOR guidelines [22]

2.1 | Inclusion criteria

This was a prospective observational study developed in three university hospitals in Spain. Adult patients (aged ≥ 18 years) admitted to the surgical, anaesthesiology or ICU departments participating in this study meeting criteria for infection, sepsis or septic shock were enrolled within 12 hours following diagnosis. Presence of infection was defined following the CDC/NHSN Surveillance Definitions for Specific Types of Infections.[23] Sepsis and septic shock were defined using the criteria proposed by the SEPSIS-3 consensus.[1,24] A specific standard survey was employed in the three participant hospitals to collect the clinical data, including medical history, physical examination and haematological, biochemical, radiological, microbiological investigations.

2.2 | Ethics approval

The study was approved by the respective Committees for Ethics in Clinical Research of the participating hospitals

(Hospital Clínico Universitario de Valladolid, CE-HCUV), (Hospital Universitario Río Hortega de Valladolid, CE-HURH) and (Hospital Clínico Universitario de Salamanca, CE-CAUSA). Written informed consent was obtained from the patients´ relatives or their legal representative before enrolment. The work fulfils the directives of the World Medical Association Declaration of Helsinki regarding ethical conduct of research involving human subjects.

2.3 | Microbiology

Standard cultures in biological samples guided by the presumptive source of the infection were performed to assess the presence of the causal pathogen. Potentially contaminant microorganisms were not considered.

2.4 | Biomarkers` quantification

Plasma MR-proADM measurement was performed by TRACE technology (Time-Resolved Amplified Cryptate Emission) using a new sandwich immunoassay (Kryptor Compact Plus Analyser, BRAHMS) limit of detection, as below 0.05 nmol/l. Procalcitonin (PCT) measurement in plasma was performed by electrochemiluminescence immunoassay on a chemistry analyzer (Cobas 6000, Roche Diagnostics) limit of detection, as below 0.02 ng/ml. Serum CRP and lactate were measured by particle enhanced immunoturbidimetric and colorimetric assay, respectively (e501 Module Analyser, Roche Diagnostics); limit of detection, as below 0.3 mg/L and 0.2 mmol/L, respectively. Biomarkers were profiled within 12 hours following diagnosis of infection, sepsis or septic shock.

2.5 | Statistical analysis

For the demographic and clinical characteristics of the patients, differences between groups were assessed using the chi-square test for categorical variables and the Mann-Whitney U test for continuous variables when appropriate. Each item of the SOFA scores 4 points as highest, preventing their use as dependent variable in a linear regression analysis. In consequence, SOFA scores for each kind of organ failure were transformed into dichotomic variables, distributing patients in two categories, those with "0" points (absence of failure) and those with at least one point in the specific organ score, which were assigned a "1." The ability of individual biomarkers to predict each specific kind of organ failure was assessed by using multivariate logistic regression analysis. In this analysis, adjustment for each type of organ failure was made compared with the five others. ORs of those biomarkers which were independent predictors of a specific organ failure in the multivariate analysis were represented by a heat map using the JColorGrid software (University of California San Francisco and University of California Berkeley).[25] In a further step, the accuracy of these biomarkers to identify each specific organ failure was assessed by using the area under the receiver operating characteristic curve analysis (AUROC), which was also employed to evaluate the biomarkers` accuracy to identify nonsurvivors. The optimal operating point in the area under the curve (AUC) analysis was identified as described previously.[26] Data were analysed by using the IBM SPSS 21.0 software (SPSS, Chicago, Ill). Significance was fixed at the level $P < .05$.

3 | RESULTS

3.1 | Clinical characteristics of the patients (Table 1)

Two hundred and thirteen patients (213) were enrolled. Thirty-seven presented infection, ninety-four sepsis and eighty-two septic shock. About 26.3% of the patients died during hospitalization (Table 1). The median age was 67 years, and 58.7% of patients were male. Compared to survivors, nonsurvivors presented with higher SOFA scores and APACHE. They presented a higher incidence of septic shock and renal replacement therapy ($P < .05$). Nonsurvivors were more likely to present prior immunosuppression. The most common kinds of organ failure at the time of inclusion were respiratory and cardiovascular (75.6% and 62.9%, respectively). The frequency of each specific organ failure was higher in nonsurvivors. The presence of an infection of respiratory origin was more common in the group of nonsurvivors. Microbiological findings did not differ between groups.

3.2 | Association between biomarkers and specific kinds of organ failure (Table 2 and Figure 1)

Multivariate regression analysis revealed that MR-proADM was the biomarker detecting the largest number of specific organ failures (respiratory, coagulation, cardiovascular, neurological and renal), followed by lactate, which detected three kinds of failure (coagulation, cardiovascular and neurological) (Table 2 and Figure 1). In turn, PCT was an independent marker of two kinds of failure (cardiovascular and renal). Finally, in the multivariate analysis, CRP failed to show any association with the different kinds of organ failures evaluated. In addition, MR-proADM was the biomarker

TABLE 1 Clinical characteristics of the patients (survivors and nonsurvivors during hospitalization)

	Total (n = 213)	Survivors (n = 157)	Nonsurvivors (n = 56)	*P* value
Age [years, median (IQR)]	67 (22)	64 (27)	68 (12)	NS
Male n (%)	125 (58.7)	89 (56.7)	36 (64.3)	NS
Diabetes mellitus n (%)	38 (17.8)	29 (18.5)	9 (16.1)	NS
Hypertension n (%)	91 (42.7)	65 (41.4)	26 (46.4)	NS
COPD n (%)	24 (11.3)	14 (8.9)	10 (17.9)	NS
Cardiovascular disease n (%)	39 (18.3)	25 (15.9)	14 (25.0)	NS
Chronic renal failure n (%)	14 (6.6)	9 (5.7)	5 (8.9)	NS
Immunosuppression n (%)	39 (18.3)	14 (8.9)	25 (44.6)	<.001
APACHE II (median, IQR)	18 (8)	16 (10)	23 (18)	<.001
SOFA (median, IQR)	6 (6)	5 (6)	10 (6)	<.001
SOFA ≥ 1 n (%)	194 (91.1)	138 (87.9)	56 (100)	.006
Respiratory n (%)	161 (75.6)	107 (68.2)	54 (96.4)	<.001
Coagulation n (%)	72 (33.8)	40 (25.5)	32 (57.1)	<.001
Hepatic n (%)	67 (31.5)	47 (29.9)	20 (35.7)	NS
Cardiovascular n (%)	134 (62.9)	84 (53.5)	50 (89.3)	<.001
Glasgow n (%)	51 (23.9)	25 (15.9)	26 (46.4)	<.001
Renal n (%)	101 (47.4)	66 (42.0)	35 (62.5)	.008
Vasopressor treatment n (%) at admission	120 (56.3)	74 (47.1)	46 (82.1)	<.001
Renal replacement therapy n (%)	27 (12.7)	9 (5.7)	18 (32.1)	<.001
Infection n (%)	37 (17.4)	36 (22.9)	1 (1.8)	<.001
Sepsis n (%)	94 (44.1)	75 (47.8.)	19 (33.9)	.07
Septic Shock n (%)	82 (38.5)	46 (29.3)	36 (64.3)	<.001
Length of hospital stay (days) (median, IQR)	26 (25)	19.5 (26)	20 (35)	NS
Length of ICU stay (days) (median, IQR)	10 (16.7)	4 (7)	12 (15)	<.001
Respiratory infection n (%)	62 (29.2)	36 (23.1)	26 (46.4)	.001
Urological infection n (%)	29 (13.6)	21 (13.4)	8 (14.3)	NS
Abdominal infection n (%)	74 (34.7)	60 (38.2)	14 (25)	NS
Gram – bacteria n (%)	76 (35.6)	52 (33.1)	24 (42.8)	NS
Gram + bacteria n (%)	60 (28.2)	46 (30.1)	14 (25.0)	NS
Fungi n (%)	17 (8.2)	13 (8.5)	4 (7.1)	NS
Glycemia (mg/dl) (median, IQR)	150 (72)	148 (66)	153 (92)	NS
Creatinine (mg/dl) (median, IQR)	1 (1.35)	1 (1.11)	1.54 (1.60)	.002
CRP (mg/L) (median, IQR)	190 (198)	190 (189)	196 (223)	NS
Lactate (mmol/L) (median, IQR)	1.87 (1.9)	1.72 (1.57)	2.51 (4.83)	<.001
Procalcitonine (PCT) (ng/ml) (median, IQR)	2.68 (23.31)	1.88 (14.4)	7.26 (29.20)	.005
MR-proADM (nmol/L) (median, IQR)	2.44 (4.18)	1.53 (2.88)	5.58 (6.72)	<.001
White Blood cells (cells/mm^3) median, IQR)	12 880 (10 165)	13 350 (8985)	11 000 (14 825)	.022
Monocytes (cells/ mm^3) (median, IQR)	570 (705)	635 (691)	442 (652)	.012
Lymphocytes (cells/ mm^3) (median, IQR)	874 (793)	885 (739)	838 (889)	NS
Neutrophils (cells/ mm^3) (median, IQR)	11 170 (9324)	11 551 (8386)	10 269 (13 575)	NS
Eosinophils (cells/ mm^3) (median, IQR)	11 (71)	15 (72)	0.00 (70)	.031
Basophils (cells/ mm^3) (median, IQR)	23 (52)	24 (50)	20 (64)	NS

TABLE 2 Clinical characteristics of the patients (survivors and nonsurvivors during hospitalization)

		Unadjusted			Adjusted		
Biomarker (ln)	**Organ failure**	**OR**	**IC (95%)**	***P*-value**	**OR**	**IC (95%)**	***P*-value**
CRP	Respiratory	1.3	0.99-1.70	.055	1.10	0.82-1.48	0.519
	Coagulation	1.13	0.86-1.48	.393	0.93	0.66-1.32	.700
	Hepatic	1.11	0.84-1.46	.466	1.03	0.74-1.42	.871
	Cardiovascular	1.53	1.16-2.00	**.002**	1.33	0.98-1.80	.069
	Glasgow	1.55	1.05-2.28	**.026**	1.37	0.91-2.06	.129
	Renal	1.55	1.16-2.08	**.003**	1.38	0.98-1.93	.066
PCT	Respiratory	1.23	1.07-1.41	**.003**	1.04	0.86-1.25	.691
	Coagulation	1.29	1.13-1.47	**.000**	1.02	0.85-1.23	.796
	Hepatic	1.26	1.11-1.44	**.000**	1.20	0.99-1.45	.062
	Cardiovascular	1.77	1.50-2.09	**.000**	1.64	1.35-1.98	**.000**
	Glasgow	1.33	1.15-1.54	**.000**	1.19	0.98-1.44	.076
	Renal	1.77	1.51-2.08	**.000**	1.58	1.32-1.89	**.000**
Lactate	Respiratory	2.37	1.39-4.06	**.002**	1.48	0.84-2.61	.172
	Coagulation	1.96	1.34-2.87	**.001**	1.55	1.04-2.33	**.033**
	Hepatic	1.43	1.01-2.01	**.041**	1.04	0.66-1.61	.877
	Cardiovascular	2.77	1.70-4.51	**.000**	1.83	1.09-3.08	**.022**
	Glasgow	2.30	1.52-3.48	**.000**	1.87	1.22-2.85	**.004**
	Renal	1.86	1.27-2.73	**.001**	1.11	0.74-1.67	.611
MR-proADM	Respiratory	2.41	1.67-3.50	**.000**	2.20	1.28-3.78	**.004**
	Coagulation	2.50	1.79-3.49	**.000**	2.12	1.31-3.44	**.002**
	Hepatic	1.56	1.16-2.09	**.003**	0.97	0.60-1.56	.903
	Cardiovascular	4.12	2.73-6.20	**.000**	3.19	1.94-5.25	**.000**
	Glasgow	2.13	1.51-3.01	**.000**	1.66	1.02-2.70	**.040**
	Renal	5.88	3.72-9.30	**.000**	4.91	2.93-8.24	**.000**

Association between biomarkers and specific kinds of organ failure. Logistic regression analysis for assessing the ability of each biomarker to detect specific organ failures. Both the results from the unadjusted and the multivariate analysis are shown. Multivariate analysis evaluates the association between each biomarker with the presence of each specific kind of organ failure considered in the SOFA, adjusted by the potential presence of the remaining five kinds of organ failures of this score.
OR: Odds ratio; **IC (95%)**: 95% Confidence Interval.

exhibiting the highest ORs, except in the case of neurological failure, for which lactate exhibited a slightly higher OR than that showed by MR-proADM.

3.3 | AUROC analysis (Figure 2)

Those biomarkers showing an association with each specific kind of organ failure in the multivariate analysis were further analysed by AUROC analysis. Since none of the biomarkers showed an association with hepatic failure, Figure 2 does not show a specific AUROC for this kind of failure. MR-proADM showed larger AUROCs than the other biomarkers, except in the comparison with lactate to detect neurological failure. The best balance between sensitivity and specificity was that for MR-proADM to detect renal failure (Appendix S1). MR-proADM showed also good positive predictive values for detecting respiratory, cardiovascular and renal failures (Appendix S1).

3.4 | AUROC analysis for hospital mortality (Figure 3)

Lactate, PCT and MR-proADM showed significant AUROCs for distinguishing nonsurvivors from survivors, with the later showing the largest AUROC (0.79), very close to that showed by SOFA (0.81) ($P < .001$) (Figure 3). In turn, CRP failed to predict mortality during hospital admission.

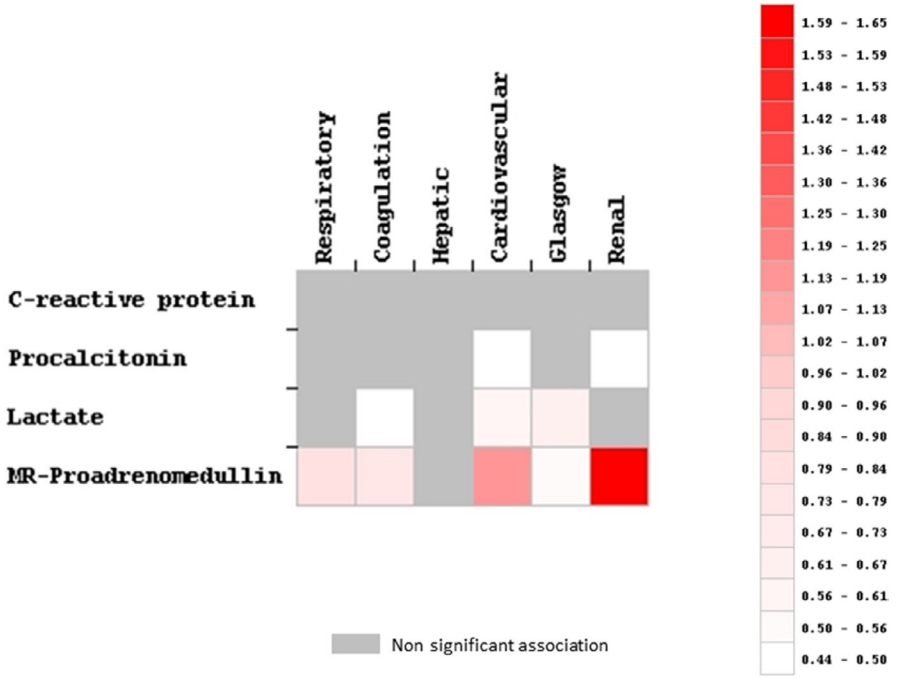
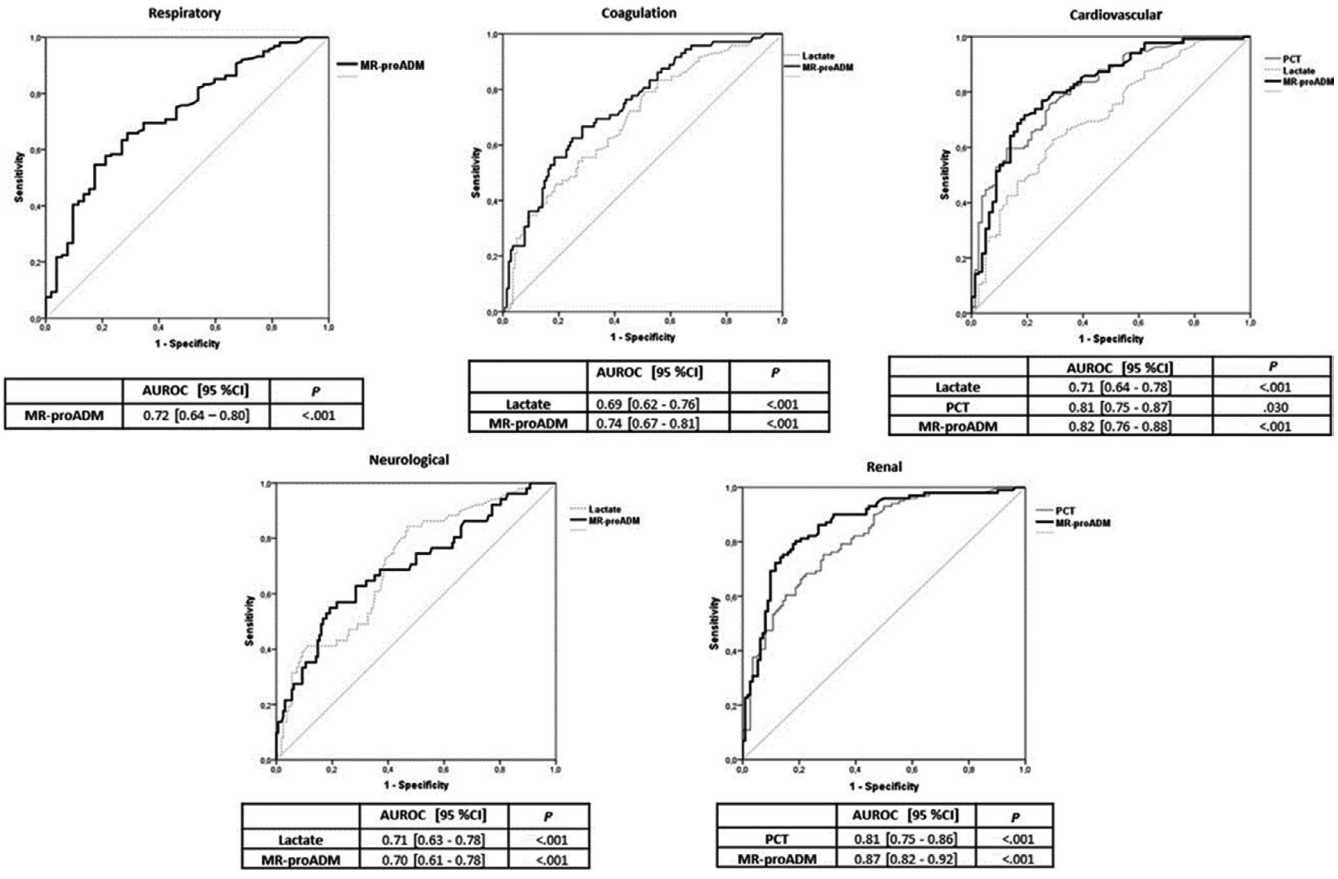


FIGURE 1 Heat map representing the odds ratios from the multivariate regression analysis. Red scale represents the magnitude of the association between biomarkers and types of organ failure. Grey squares represent absence of significant association



	AUROC [95 %CI]	P
MR-proADM	0.72 [0.64 – 0.80]	<.001

	AUROC [95 %CI]	P
Lactate	0.69 [0.62 - 0.76]	<.001
MR-proADM	0.74 [0.67 - 0.81]	<.001

	AUROC [95 %CI]	P
Lactate	0.71 [0.64 - 0.78]	<.001
PCT	0.81 [0.75 - 0.87]	.030
MR-proADM	0.82 [0.76 - 0.88]	<.001

	AUROC [95 %CI]	P
Lactate	0.71 [0.63 - 0.78]	<.001
MR-proADM	0.70 [0.61 - 0.78]	<.001

	AUROC [95 %CI]	P
PCT	0.81 [0.75 - 0.86]	<.001
MR-proADM	0.87 [0.82 - 0.92]	<.001

FIGURE 2 AUROC analysis to evaluate the accuracy of biomarkers to predict the specific kinds of organ failure evaluated in the SOFA score. In each box, only those biomarkers showing an independent association with each kind of organ failure in the multivariate regression analysis of Table 2 were represented

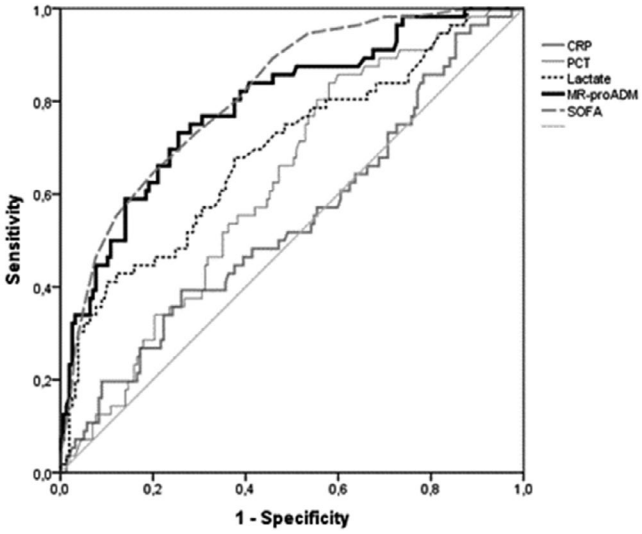


FIGURE 3 AUROC analysis for predicting hospital mortality. Accuracy of the four biomarkers considered in this work for differentiating between nonsurvivors and survivors during hospitalization was evaluated by calculating their corresponding AUROCs

	AUROC [95 %CI]	*P*
CRP	0.54 [0.45 - 0.63]	.372
Lactate	0.69 [0.61 - 0.78]	<.001
PCT	0.62 [0.54 - 0.70]	.007
MR-proADM	0.79 [0.72 - 0.86]	<.001
SOFA	0.81 [0.75 - 0.88]	<.001

4 | DISCUSSION

Biomarkers could add valuable information to clinical judgement to early detect the presence of organ failure during infection. Biomarkers could resume the information provided by the six items of the SOFA score. Some of these items are difficult to calculate in non-ICU settings (PaO_2/FiO_2). Calculation of others like GCS is affected by certain degree of subjectivity. Biomarkers provide quantitative and reproducible information in an easy manner. The emergence of point of care devices could increase the interest on biomarkers for the early detection of a complicated infection by making feasible their quantification outside of the hospital, in the community.[27]

Our results demonstrate that MR-proADM was the biomarker independently associated with the largest number of organ failure types (five out of the six considered in the SOFA score). This probably explains why MR-proADM was also the best biomarker predicting mortality, which is consistent with previous findings.[28] AUROC analysis evidenced that accuracy of MR-proADM was the highest to detect cardiovascular and renal failure (with areas > 0.80 in both cases).

In turn, lactate was an independent predictor of three kinds of failure: coagulation, cardiovascular and neurological, and performed slightly better to detect the presence of neurological failure than MR-proADM. In situations such as cardiac arrest or extracorporeal circulation, it has been observed a correlation between initial serum levels of lactate and the magnitude of neurological damage.[29-31]

PCT was able to detect the presence of cardiovascular and renal failure, with AUROCs > 0.80, but exhibited lower ORs in the multivariate analysis than those shown by MR-proADM. Some authors have studied the prognostic value of serum PCT levels in predicting sepsis, organ dysfunction and mortality among adults critically ill patients [32] with discordant results.[33,34] However, none of these studies analysed the relationship between PCT and specific organ failure.

Our analysis demonstrated that CRP was not an independent predictor of any of the specific components of the SOFA score. Following our results, this protein would not play a major role in the pathogenesis of the specific kinds of organ failure during sepsis.

None of the biomarkers tested were independently associated with the presence of hepatic failure, suggesting that these biomarkers have no relationship with the biological events leading to the increase in the bilirubin concentration observed in serum during sepsis. In light of these results, identifying biomarkers other than bilirubin to detect hepatic failure will represent a challenging task in the future.

As a limitation of our work, the patients of this cohort were recruited at the hospital. Further works should evaluate the performance of these biomarkers to detect specific kinds of organ failure in patients with infection in the community. In addition, the vast majority of the patients of our cohort had respiratory failure (75%). Works analysing cohorts with a lower frequency of this failure should confirm the performance of the biomarkers to detect it. Except in the case of

MR-proADM for detecting renal failure, sensitivity of the biomarkers tested to detect each specific failure was far to be optimal, in spite that specificity was > 70% in the vast majority of the cases (Appendix S1), indicating that we need to identify new biomarkers able to detect specific organ failures in sepsis. Finally, SOFA score is calculated by clinical and standardized biochemical measurements whereas the studied biomarkers were not. An effort to standardize the methods to quantify biomarkers is mandatory to make feasible their application in clinical practice.

Our study is the first in evaluating biomarkers' ability to detect the specific types of organ failure assessed by the SOFA score. Our work evidenced that, in patients with infection, MR-proADM was the biomarker detecting the largest number of SOFA score components. These results support the use of MR-proADM in combination with other biomarkers to improve early detection of organ failure in sepsis. Nonetheless, future studies with larger numbers of patients should confirm our findings.

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CONFLICT OF INTEREST

DAO and JFBM have received research grants from Thermo Fisher. The remaining authors declare no conflicts of interest regarding this work.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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