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Usefulness of midregional pro-adrenomedullin as a marker of organ damage and predictor of mortality in patients with sepsis

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Abstract *Background:* Midregional proadrenomedullin (MR-proADM) is a prognostic biomarker in patients with community-acquired pneumonia (CAP) and sepsis. In this paper, we examined the ability of MR-proADM to predict organ damage and long-term mortality in sepsis patients, compared to that of procalcitonin, C-reactive protein and lactate.
Methods: This was a prospective observational cohort, enrolling severe sepsis or septic shock patients admitted to internal service department. The association between biomarkers and 90-day mortality was assessed by Cox regression analysis and Kaplan–Meier curves. The accuracy of biomarkers for mortality was determined by area under the receiver operating characteristic curve (AUROC) analysis.

All authors contributed equally to this work.

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Results: A total of 148 patients with severe sepsis, according to the criteria of the campaign to survive sepsis, were enrolled. Eighty-five (57.4%) had sepsis according to the new criteria of Sepsis-3. MR-proADM showed the best AUROC to predict sepsis as defined by the Sepsis-3 criteria (AUROC of 0.771, 95% CI 0.692–0.850, p <0.001) and was the only marker independently associated with Sepsis-3 criteria (OR = 4.78, 95% CI 2.25–10.14; p < 0.001) in multivariate analysis.MR-proADM was the biomarker with the best AUROC to predict mortality in 90 days (AUROC of 0.731, CI 95% 0.612–0.850, p <0.001) and was the only marker that kept its independence [hazard ratio (HR) of 1.4, 95% CI 1.2-1.64, p <0.001] in multivariate analysis. The cut-off point of MR-proADM of 1.8 nmol/L (HR of 4.65, 95% CI 6.79–10.1, p < 0.001) was the one that had greater discriminative capacity to predict 90 days mortality. All patients with MR-proADM concentrations ≤0.60 nmol/L survived up to 90 days. In patients with SOFA ≤ 6, the addition of MR-proADM to SOFA score increased the ability of SOFA to identify non-survivors, AUROC of 0.65 (CI 95% 0.537–0.764) and AUROC of 0.700 (CI 95% 0.594–0.800), respectively (p < 0.05 for both).
Conclusions: MR-proADM is a good biomarker in the early identification of high risk septic patients and may contribute to improve the predictive capacity of SOFA scale, especially when scores are low.
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Introduction

Sepsis continues to be a very important cause of mortality in the emergency department, internal medicine and intensive care units (ICU), despite the early administration of antibiotics and hemodynamic management.[1] In Europe, it causes mortality ranging from 27% to 54% depending on severity. In the US, CDC estimates that 500,000 patients develop sepsis and 200,000 die every year.[2,3] For this reason, it is necessary to find tools that can help the clinician to recognize these patients early, especially those at high risk, and thus be able to initiate specific treatment as soon as possible.

At present, the third international consensus for sepsis and septic shock (Sepsis-3)[4] defines sepsis as an organic dysfunction caused by a deregulated response of the host to an infection. The use of SOFA ("Sequential Organ Failure Assessment") scale as the tool to establish the presence of organic damage and to identify patients with sepsis has been approved. However, this scale has a number of limitations to be used in the emergency or internal medicine department. First, cut-off points were established by consensus in patients admitted to the ICU and it is unknown what their role may be outside this service.[4] It needs the determination of multiple analytical variables such as PaO2, platelet count, creatinine and bilirubin levels. In addition, it uses variables associated with treatment (doses of vasopressors). This is not ideal since treatment protocols vary depending on institutions, on patients and over time.[5] Finally, it is a good test to predict mortality when giving high scores. Thus, a score greater than 15 point has been correlated with a mortality of 90%,[6] but not so much when the scores are lower. For this reason, it would be pertinent to have a standardized evaluation tool for the identification of patients with sepsis, especially the most serious ones, and thus help in clinical decision-making and to optimize the use of health care resources. Consequently, a number of prognostic biomarkers have emerged in recent years, such as hormones, cytokines, and inflammation-related proteins that attempt to identify these patients.

Adrenomedullin (ADM) is a peptide that is released from multiple tissues in response to physiological stress or after infection where it performs vasodilation, anti-inflammatory and antimicrobial activity reinforced by the regulation it exerts on the complement system.[7] Also, it is released from multiple tissues in response to other diseases such as hypertension, heart failure, respiratory failure, renal failure, cirrhosis, and cancer. ADM has a dual behavior, "hormokine" function, i.e. it behaves as a hormone when expressed only in endocrine cells, and as a cytokine when released in other locations. In addition, exogenous ADM administration has been shown to reduce acute lung injury, vascular permeability, and cell death in animal models with sepsis, while endogenous overexpression reduces sepsis damage.[8,9]

The measurement of circulating ADM is complicated due to its rapid degradation and clearance from circulation. In addition, it is hidden by binding to a binding protein (complement factor H), avoiding its detection by standard immunoassay. The midregional fragment of proadrenomedullin (MR-proADM), comprising amino acids 45–92, is more stable and directly translates the levels of the active ADM peptide.[10]

An increase in mean of plasma concentrations of MR-proADM has been identified in patients with community-acquired pneumonia and has been widely studied in the assessment of risk and severity of this disease.[11–13]

It has also been associated with increased mortality in patients with sepsis, but most studies have been performed in patients with severe sepsis or septic shock admitted to the ICU[14] and not in internal medicine or emergency departments.

For this reason, the aims of this study is to evaluate the ability of MR-proADM levels to predict the presence of organic damage assessed by SOFA, as well as to predict mortality during hospitalization and later (in 90 days) in patients with sepsis from the emergency and internal medicine department, compared to other standard biomarkers (procalcitonin (PCT), C-reactive protein (CRP) and lactate).

Methods

Patient selection, inclusion and exclusion criteria

A prospective observational study of hospitalized patients with sepsis in the internal medicine service at Reina Sofía Hospital in Murcia (Spain) has been carried out. This hospital

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has 350 beds, serves a population of 250,000 people and treats about 1600 cases of annual sepsis. The study was approved by the local ethics committee.

Consecutive signs and symptoms consistent with the sepsis survival campaign were included from January 14, 2014 to April 14, 2014.[15]

The following variables have been collected: demographic (age and sex), presence of comorbidity (ischemic heart disease, heart failure, peripheral vascular disease, dementia, stroke, hemiplegia, chronic lung disease, renal failure, liver disease, peptic ulcus, connective tissue disease, neoplasia or infection), predisposing factors for infection (vascular catheter, bladder catheter, transfusion, dialysis, pressure ulcer, previous ICU hospitalization, use of pacemakers or other devices, infections, use of antibiotics and hospitalization in the previous month), focus of sepsis, bacteremia, levels of biomarkers (C-reactive protein, procalcitonin, MR-proADM, lactate, NT-proBNP) and days of hospitalization.

Patients younger than 14 years old, pregnant women, those with no blood sample to determine biomarkers and those with no informed consent were excluded.

Patients were followed up from admission to 90 days after discharge or until death.

Subsequently, a retrospective analysis was carried out and two groups were established according to whether or not they presented sepsis following the new definition of Sepsis-3.[4] Therefore, patients were considered to have sepsis if infection was suspected and if were graded 2 or more points on the SOFA ("Sequential Organ Failure Assessment") scale.

Determination of biomarkers

The determination of biomarkers was performed in the first 72 hours, most of them (86%) in the first 24 hours.

Measurement of MR-proADM in plasma was performed using the TRACE (Extended Cryptate Emission Resolution Time) technology using a new sandwich immunoassay (Kryptor Compact Plus Analyzer, BRAHMS, Hennigsdorf, Germany); detection limit 0.05 nmol/l. PCT measurement was performed by electrochemiluminescent immunoassay (ECLIA) on a chemical analyzer (Cobas 6000, Roche Diagnostics, Meylan, France); limit of detection 0.02 ng/ml. Serum CRP and lactate were measured by immunoturbidimetric and particle intensified colorimetric assay, respectively (e501 Module Analyzer, Roche Diagnostics, Meylan, France); detection limit of 0.15 mg/dl and 0.2 mmol/l, respectively.

Statistical analysis

Differences in demographic and clinical characteristics among patients with and without sepsis according to Sepsis-3 were assessed using the Chi-square test for categorical variables. Student's t-test and Mann–Whitney U-test were used, respectively, to compare continuous variables based on the presence or absence of normal distribution.

The accuracy and predictive values of the biomarkers for the presence of organic damage according to SOFA were evaluated by calculating the area under the receiver operating characteristic curve (AUROC).

Cut-off points of different biomarkers were sought to predict in a more accurate way both organ damage and mortality during admission and after 90 days.

The association between biomarkers and the risk of sepsis were assessed by binary logistic regression analysis, adjusted for confounding variables.

The time was censored 90 days after admission to the hospital. The first 24 hours of hospital admission were considered as day 1 in the analysis.

Variables with $p < 0.05$ in the univariate regression analysis were additionally included in the multivariate analysis. The impact of biomarkers on mean survival time was assessed using Kaplan–Meier curves and the Mantel–Haenszel log-rank test.

Data were analyzed using the IBM SPSS 24.0 software (SPSS, Chicago, IL).

To compare the AUROC curves, the free software "R" and the "pROC" library have been used. A p value < 0.05 has been considered as significative.

Results

Characteristics of patients and concentrations of biomarkers

A total of 148 patients with sepsis were included according to the criteria of the definition of the campaign to survive sepsis, of which 85 (57.4%) had sepsis according to the new criteria of Sepsis-3. The majority of them were male (60.13%) with an average age of 72 ± 15 years. The most frequent sepsis focus was respiratory (66.9%), followed by several foci (12.8%) and urinary (10.8%). The majority had a SOFA score of ≤6 points (96%) and, therefore, a low probability of death. During the admission, 13 patients died (8.7%) and in 90 days, 27 patients died (18.24%).

Table 1 shows the distribution of patients admitted according to the presence or absence of sepsis defined by the Sepsis-3 criteria. Patients with sepsis according to the Sepsis-3 criteria had higher CRP, PCT, and proADM levels and were more likely to be women (all with $p < 0.05$). In addition, they were more likely to die at admission, but not in 90 days.

Depending on the focus, MR-proADM levels [median (interquartile range)] were as follows: respiratory [1.08 nmol/l (0.9)], urinary [1.3 nmol/l (1.27)], [1.16 nmol/l (1.01)], cutaneous [1.16 nmol/l (1.73)] and several foci [1.82 nmol/l (0.87)].

Prediction of organ failure according to the Sepsis-3 criteria with markers

Fig. 1 shows the ROC curve and the area under the curve of the different markers to discriminate between patients with and without organ failure according to the Sepsis-3 criteria (2 or more points in SOFA score). MR-proADM showed the best AUROC to determine the presence of organ failure, followed by PCR and PCT.

Cut-off points were established to evaluate biomarkers independently associated with the presence of organ failure and therefore sepsis. The MR-proADM cut-off point of 1.8 nmol/l showed a sensitivity of 40%, specificity of 93%, negative pre-

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Table 1 Distribution of patients according to the presence of sepsis defined by the Sepsis-3 criteria.

	No sepsis	Sepsis according to Sepsis-3 criteria	p
n	63	85	
Male (%)	45 (71.4)	44 (51.8)	0.025
Age, years	70.00 (15.42)	74.48 (15.39)	0.082
Hypertension (%)	21 (33.3)	20 (23.5)	0.258
Diabetes (%)	32 (50.8)	48 (56.5)	0.257
Dyslipidemia (%)	39 (61.9)	52 (61.2)	1.000
Smoker (%)	51 (81.0)	73 (85.9)	0.563
Alcohol (%)	52 (82.5)	76 (89.4)	0.334
Comorbidity (%)	9 (14.3)	6 (7.1)	0.244
Acute renal failure (%)	0 (0)	5 (5.9)	0.134
Predisposing factors (%)	22 (34.9)	32 (37.6)	0.867
Previous stay in ICU (%)	0 (0)	1 (1.8)	1.000
Previous infections (%)	36 (57.1)	49 (57.6)	1.000
Previous use of antibiotics (%)	35 (55.6)	47 (55.3)	1.000
Previous hospital admissions (%)	37 (58.7)	44 (51.8)	0.500
Infectious focus (%)			0.311
Respiratory	46 (73.0)	53 (62.4)	
Urinary	6 (9.5)	7 (8.2)	
Abdominal	3 (4.8)	5 (5.9)	
Central nervous system	1 (1.6)	0 (0.0)	
Catheter	0 (0.0)	2 (2.4)	
Bone	1 (1.6)	0 (0.0)	
Skin	2 (3.2)	2 (2.4)	
Several focus	4 (6.3)	15 (17.6)	
Organ failure (%)			0.003
Hypotension	5 (7.9)	7 (8.2)	
pO2/Fio2 < 250 without pneumonia	1 (1.6)	2 (2.4)	
Oliguria	1 (1.6)	0 (0.0)	
Creatinine > 2 mg/dl	0 (0.0)	4 (4.7)	
Lactic acid elevated	51 (81.0)	45 (52.9)	
Several criteria	5 (7.9)	27 (31.8)	
Septic shock (%)	0 (0)	4 (4.7)	0.218
CRP, mg/dl	6.37 (8.36)	9.75 (8.78)	0.020
PCT, mg/dl	1.76 (6.58)	6.86 (14.38)	0.010
Lactic acid, mg/dl	1.97 (0.92)	1.90 (0.75)	0.616
MR-proADM, nmol/l	0.97 (0.47)	2.36 (2.32)	<0.001
MR-proADM > 1.8 nmol/l (%)	4 (6.3)	34 (40.0)	<0.001
Days of stay	10.83 (12.99)	12.14 (8.57)	0.460
ICU admission (%)	4 (6.3)	13 (14.3)	0.207
Intra hospital mortality	1 (1.58)	12 (14.11)	0.018
Global mortality	7 (11.1)	20 (23.52)	0.086

Data are presented as mean (SD) and number (%).
CRP: C-reactive protein; PCT: procalcitonin; MR-proADM: pro-adrenomedullin; ICU: intensive care unit.

dictive value of 54%, and positive predictive value of 90%. On the other hand, the cut-off point of 0.6 nmol/l showed a sensitivity of 95%, specificity of 17%, negative predictive value of 74%, and positive predictive value of 61%.

A binary logistic regression analysis was performed to evaluate which variables were independently associated with the presence of organ failure and therefore sepsis, which included age, respiratory focus, comorbidity, concentrations of PCR, PCT, lactate, MR-proADM and MR-proADM > 1.8 nmol/l. The variables that were independently associated were MR-proADM (OR = 4.78, 95% CI 2.25–10.14; p < 0.001) and MR-proADM> 1.8 nmol/l (OR = 7.69, 95% CI 5.17–23.25; <0.001).

Prediction of mortality

Table 2 shows the distribution of patients admitted according to survival in 90 days. A Cox regression analysis was performed to evaluate variables independently associated with early mortality and in 90 days. PCR, PCT, proADM,

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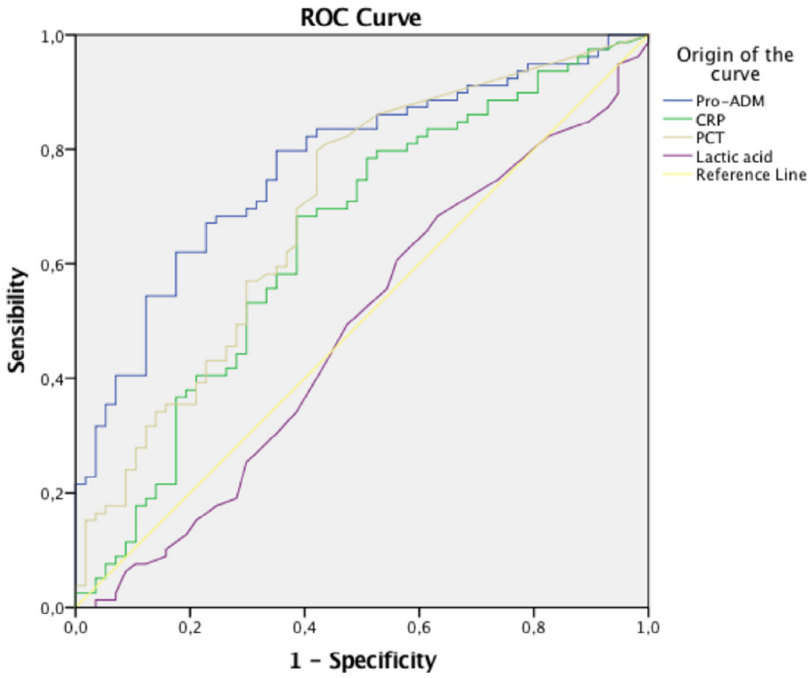

Fig. 1. ROC curve and AUROC analysis of sepsis defined by the Sepsis-3 criteria.

	AUROC (95% CI)	p
MR-proADM	0.771 (0.692–0.850)	<0.001
CRP	0.643 (0.547–0.739)	0.004
PCT	0.695 (0.604–0.786)	<0.001
Lactic acid	0.483 (0.383–0.583)	0.736

Comparing AUROC: MR-proADM vs CRP (p = 0.01); MR-proADM vs PCT (p = 0.09); MR-proADM vs Lactic acid (p < 0.001); CRP vs PCT (p = 0.14); CRP vs Lactic acid (p = 0.03); PCT vs Lactic acid (p = 0.005).
CRP: C-reactive protein; PCT: procalcitonin; MR-proADM: pro-adrenomedullin; AUROC: area under curve ROC; ROC: receiver operating curve.

presence of sepsis according to SOFA, comorbidity, age and infectious focus were included. The only variable that kept its independence was MR-proADM for early mortality [HR 1.39 (95% CI 1.15–1.68); p < 0.001) and MR-proADM for mortality in 90 days [HR 1.4 (95% CI 1.2–1.64); p < 0.001). Taking into account the cut-off point of MR-proADM of 1.8 nmol/l, the adjusted HR was 6.17 (95% CI 2.3–16.6; p < 0.001) for early mortality and HR 4.65 (95% CI 6.79–10.1; p < 0.001) for mortality in 90 days.

Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for early mortality and final mortality together with the cut-off point for MR-proADM 1.8 mmol/l and 0.6 mmol/l appear in Table 3.

Fig. 2 shows the ROC curve of the different biomarkers to predict mortality in 90 days. The MR-proADM demonstrated the greater AUROC.

The survival curve of the proADM for mortality in 90 days is shown in Fig. 3, the difference between the groups being verified by the log-rank test, X2 = 29.45, p < 0.001.

Improvement of prediction of mortality

The combination of MR-proADM and SOFA scale has been evaluated in predicting mortality, so that patients who had MR-proADM levels >1.8 mmol/l were increased at one point on the SOFA scale. This combination was already used by Andaluz-Ojeda et al.[14] in a cohort of patients admitted to the ICU. Thus, we found an improvement in mortality prediction than the isolated SOFA. For early mortality, the AUROC (95% CI) for SOFA was 0.656 (0.525–0.787) and for ADM-SOFA was 0.695 (0.573–0.818) (p = 0.05). For 90-day mortality the AUROC (95% CI) for SOFA was 0.65 (0.537–0.764) and for ADM-SOFA was 0.700 (0.594–0.800) (p = 0.011).

Discussion

Sepsis continues to be a major cause of mortality and is directly related to the severity of organ damage it produces that can be assessed using the SOFA scale.[4] However, performing the SOFA score requires the determination of multiple analytical variables; it needs several parameters associated with the treatment that may be different among institutions, and their results predict mortality with high reliability when scores are high, but not when they are low. In this sense, the appearance of an increasing number of biomarkers may provide a new pathway with which we can improve diagnostic and prognostic accuracy in a simple and rapid manner.

The most notable findings of our study in patients admitted to an internal medicine department have been that MR-proADM has a high discriminative capacity to detect organic

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Table 2 Distribution of patients according to survival in 90 days.

	Survivors	Non-survivors	p
n	121	27	
Male (%)	77 (63.6)	12 (44.4)	0.104
Age, years	70.80 (15.44)	80.52 (13.41)	0.003
Hypertension (%)	34 (28.1)	7 (25.9)	1.000
Diabetes (%)	68 (56.2)	12 (44.4)	0.185
Dyslipidemia (%)	72 (59.5)	19 (70.4)	0.406
Smoker (%)	100 (82.6)	24 (88.9)	0.612
Alcohol (%)	102 (84.3)	26 (96.3)	0.181
Comorbidity (%)	13 (10.7)	2 (7.4)	0.868
Acute renal failure (%)	4 (3.3)	1 (3.3)	1.000
Predisposing factors (%)	42 (34.7)	12 (44.4)	0.466
Previous stay in ICU (%)	1 (0.8)	0 (0)	1.000
Previous use of antibiotics (%)	66 (54.5)	16 (59.3)	0.817
Previous hospital admissions (%)	64 (52.9)	17 (63.0)	0.461
SOFA [mean (SD)]	2.18 (2.10)	3.26 (2.54)	0.022
Infectious focus (%)			0.575
Respiratory	81 (66.9)	18 (66.7)	
Urinary	13 (10.7)	0 (0.0)	
Abdominal	6 (5.0)	2 (7.4)	
Central nervous system	1 (0.8)	0 (0.0)	
Catheter	2 (1.7)	0 (0.0)	
Bone	1 (0.8)	0 (0.0)	
Skin	3 (2.5)	1 (3.7)	
Several focus	13 (10.7)	6 (22.2)	
Organ failure (%)			0.011
Hypotension	12 (9.9)	0 (0.0)	
pO2/Fio2 < 250 without pneumonia	2 (1.7)	1 (3.7)	
Oliguria	1 (0.8)	0 (0.0)	
Creatinine > 2 mg/dl	1 (0.8)	3 (11.1)	
Lactic acid elevated	82 (67.8)	14 (51.9)	
Several criteria	23 (19.0)	9 (33.3)	
Septic shock (%)	118 (97.5)	26 (96.3)	1.000
CRP, mg/dl	7.88 (8.50)	10.26 (9.65)	0.203
PCT, mg/dl	4.47 (11.47)	5.75 (14.21)	0.619
Lactic acid, mg/dl	1.92 (0.83)	1.97 (0.82)	0.795
MR-proADM, nmol/l	1.48 (1.42)	3.07 (3.02)	<0.001
MR-proADM > 1.8 nmol/l (%)	22 (18.2)	16 (59.3)	<0.001
MR-proADM < 0.6 nmol/l (%)	15 (12.4)	0 (0.0)	0.115
Days of stay	11.60 (11.20)	11.52 (7.96)	0.973
ICU admission (%)	13 (10.7)	3 (11.1)	0.893

Data are presented as mean (SD) and number (%).
CRP: C-reactive protein; PCT: procalcitonin; MR-proADM: pro-adrenomedullin; ICU: intensive care unit.

damage according to the Sepsis-3 criteria (2 or more point in SOFA score), so that patients with MR-proADM > 1.8 mmol/l had a risk of organic damage of 7.6 times more than patients with lower values, with a specificity of 93% and a positive predictive value of 90%. On the other hand, when the short-term and long-term mortality were analyzed, MR-proADM was the only marker that demonstrated its independence in the Cox regression analysis showing a higher risk than other

Table 3 Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for early mortality and final mortality together with the cut off point for MR-proADM 1.8 mmol/l and 0.6 mmol/.

		Sensitivity	Specificity	PPV	NPV
MR-proADM 1.8 mmol/l	Early mortality	65%	80%	29%	94.5%
	Final mortality	60%	81.8%	42.1%	90%
MR-proADM 0.6 mmol/l	Early mortality	100%	11.5%	12.8%	100%
	Final mortality	100%	12.5%	20.3%	100%

MR-proADM: pro-adrenomedullin; PPV, positive predictive value; NPV, negative predictive value.

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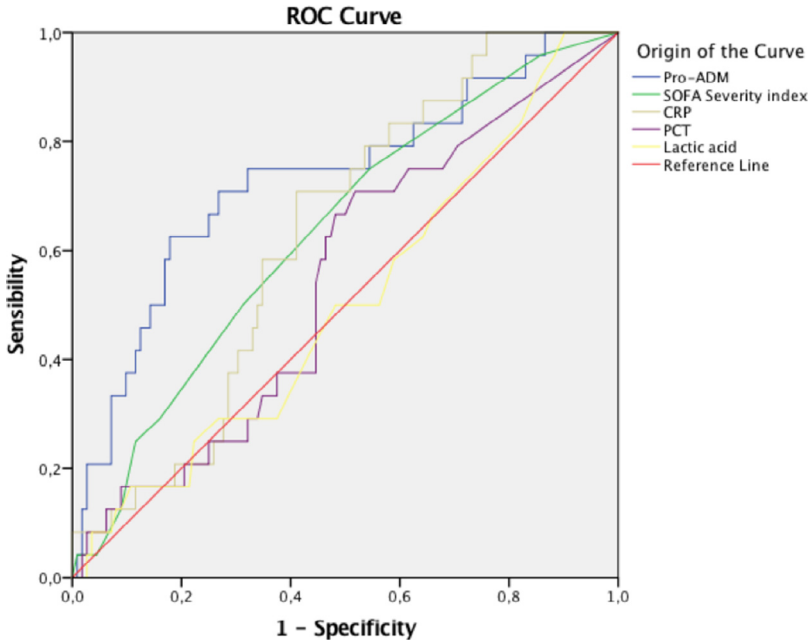

Fig. 2. ROC curve and AUROC analysis of mortality in 90 days (entire cohort).

	AUROC (95% CI)	p
MR-proADM	0.771 (0.692–0.850	<0.001
CRP	0.643 (0.547–0.739)	0.004
PCT	0.695 (0.604–0.786)	<0.001
Lactic acid	0.483 (0.383–0.583)	0.736

Comparing AUROC: MR-proADM vs CRP ($p = 0.03$); MR-proADM vs PCT ($p < 0.001$); MR-proADM vs Lactic acid ($p = 0.008$); CRP vs PCT ($p = 0.07$); CRP vs Lactic acid ($p = 0.102$); PCT vs Lactic acid ($p = 0.62$).
CRP: C-reactive protein; PCT: procalcitonin; MR-proADM: pro-adrenomedullin; AUROC: area under curve ROC; ROC: receiver operating curve.

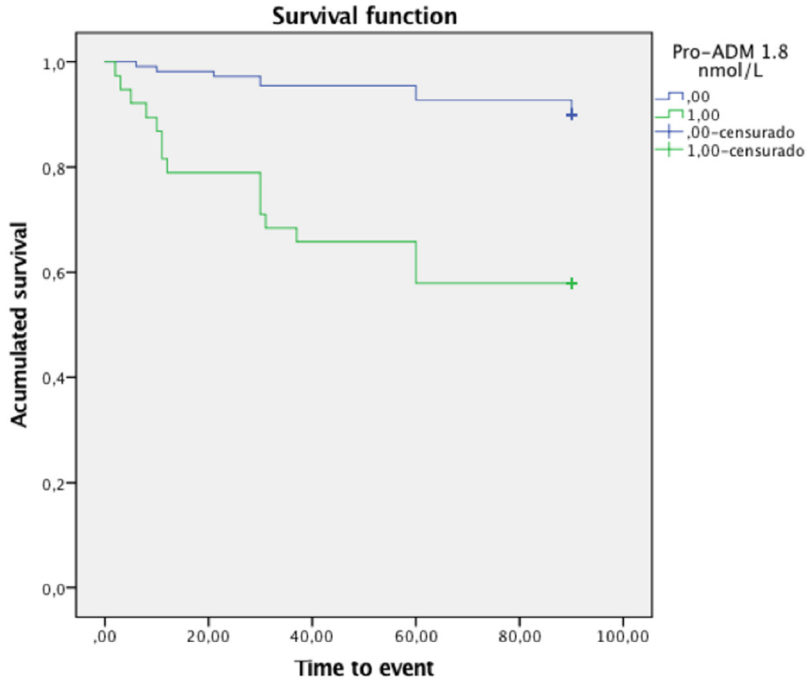

Fig. 3. Survival function according to MR-proADM levels higher and lower than 1.8 nmol/l.

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markers and the SOFA itself, so for each mmol/l elevation of MR-proADM, the risk of death increased by 40% compared to the pre-existing and long-term previous value.

The MR-proADM has already been evaluated as a marker of sepsis. In this regard, Christ-Crain et al.,[16] in a study performed in 101 critical patients, 53 with sepsis and 48 with non-septic, observed that the levels of MR-proADM were increasingly dependent on whether subjects were healthy, patients with SIRS, septic patients, severe sepsis, septic shock or if they required noradrenaline. Another study by Angeletti et al.[17] compared MR-proADM levels in septic and non-septic patients, obtaining similar results with an AUC to determine the presence of sepsis of 0.977 and an optimal cut-off of 1 nmol/l.

With respect to the predictive capacity of mortality, the results have been contradictory. Thus, Christ-Crain et al[16] found that MR-proADM had an AUROC of 0.81 to detect ICU mortality. Marino et al.[18] demonstrated that in 101 patients with sepsis, severe sepsis, or septic shock, plasma levels of MR-proADM were strongly associated with disease severity, vasopressor requirement, and mortality in 28 days. Another study,[14] performed in 326 ICU patients with severe sepsis (21.7%) and septic shock (79.3%), showed that MR-proADM was the most discriminatory marker for mortality in 28 days (AUROC 0.79). When patients were stratified by the degree of organ failure, MR-proADM was the only marker capable of predicting mortality in all established severity groups. In contrast, Suberviola et al.[19] found that MR-proADM had a limited value for predicting mortality in 137 septic patients with an AUROC of 0.62. These different results could be explained by the characteristics of the patients included, the severity of the disease, the infectious focus, the treatments received and the small sample sizes.

In contrast to most studies conducted to evaluate MR-proADM prognostic capacity, our study has not been performed in the ICU, but in the internal medicine department. In addition, the great majority of patients included had low severity (SOFA score less than 6). This group of patients is especially important because they correspond to the earliest presentation during the course of sepsis or are the least severe form of the disease. Detecting those patients with poor prognosis at this stage of the disease is really interesting. In this way the clinician can be alerted to take more aggressive measures to avoid the fatal outcome. Our results are in line with those reported by Andaluz-Ojeda et al.[14] They showed that MR-proADM was the most discriminative marker in patients admitted to the ICU compared to other biomarkers (lactic acid, CRP and PTC) in all groups of SOFA risk, included in patients with SOFA less than 6 (AUROC 0.75). In our study, 25% of patients had high MR-proADM levels and therefore had a high risk of dying despite having low scores on the SOFA scale. Therefore, MR-proADM could be a good candidate, after validation in subsequent studies, to be incorporated into an early sepsis treatment protocol, as it can provide a rapid prognosis and help guide diagnostic interventions and treatment decisions. The cut-off point for MR-proADM identified for this group of patients (1.8 nmol/l) could be very useful in this regard. MR-proADM showed a higher predictive value for mortality than other commonly used markers such as lactate, PTC or CRP.

On the other hand, we observed that having an MR-proADM value below 0.6 nmol/l allows us to rule out early and long-term mortality. In this way, we can recognize patients with low mortality risk who could benefit from less intensive treatment and even receive outpatient management. These results are similar to those found by Albrich et al.[12] They observed in patients with respiratory tract infections that levels of MR-proADM <0.75 nmol/l had a mortality lower than 0.5%.

In addition, we have demonstrated that the use of MR-proADM could improve the predictive capacity of SOFA by increasing at one point those patients with high MR-proADM values. Our results are in consonance with those found by Andaluz-Ojeda et al.,[14] who observed that adding MR-proADM (>1.70 nmol/l) in patients with SOFA ≤ 6 improved AUROC (from 0.70 to 0.77). Other studies have also pointed out that the combination of MR-proADM with classic scores such as PSI or CURB-65 improved their predictive ability in patients with respiratory infections.[12,20] Therefore, the incorporation of MR-proADM into routine clinical practice could improve the predictive capacity of routine scales and help the decision-making.

The main limitation of this study has been that, to establish the prognostic value of the markers, a single determination has been used, as well as the effect that variable change has over time. However, with this single determination, it has been sufficient to reliably predict the evolution of these patients in both the short- and long-term. On the other hand, the new sepsis criteria have appeared after the study was completed and, when applied, it would imply a retrospective analysis at this point, which could reduce the value of the study. However, the data collection, including SOFA and mortality assessment, has been prospective from the beginning, so as a whole it should be considered as prospective.

Although more prospective studies that include the new sepsis criteria from the beginning of the assessment are needed to verify these results, our findings are robust enough to confirm that MR-proADM can be a good marker to detect high-risk patients with sepsis.

In conclusion, we can affirm that patients with elevated levels of MR-proADM have a high probability of presenting organic damage evaluated by SOFA. In addition, their levels are associated with an increased likelihood of earlier and longer term mortality. On the other hand, MR-proADM may contribute to improve the predictive capacity of the SOFA scale, especially when the scores are low, and therefore help to detect at an early stage those high-risk patients that should be considered with special attention and administered a more intensive treatment.

Conflict of interest

The authors declare to have no conflicts of interest.

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Transparency declarations

None to declare.

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