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Biomarkers in Shock Patients and Their Value as A Prognostic Tool; A Prospective Multi-Center Cohort Study

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ABSTRACT

Objective: To investigate the prognostic value of clinical and laboratory tests in prediction of outcome in patients at day 30 post presentation to hospital with shock and to determine the prognostic value of mid regional pro-adrenomedullin (MR-proADM) on mortality prediction at 30 days in the same patient cohort.
Method: This prospective multicenter cohort study analyzed data from patients who had presenting with shock to the emergency departments of eleven urban, tertiary-care University hospitals in Spain between March, 2011 and May, 2011. Recruitment of patients was via convenience sampling. Inclusion criteria included age between 14 and 100 years with clinical diagnostic criteria of shock on admission. Various patient parameters were analysed, such as age, sex, past medical history. Other clinical variables were measured on arrival to hospital, including sequential organ failure assessment score (score SOFA), blood pressure, oxygen saturations, capillary refill time and shock index (SI). Laboratory variables investigated included base excess, MR-proADM, lactate, C-Reactive Protein (CRP) and procalcitonin (PCT).
Results: There were 212 patients included in the study from the eleven hospitals involved. The mean age was 72.2 years old and 60.4% of the patients were men. In the discriminant analysis only age, MR-proADM and PCT remained in the final discriminant equation. The separate analysis of MR-proADM showed that, in the non-survivors group, MR-proADM levels are significantly higher than those found in the group of survivors (p<0.001).
Conclusion: Age, PCT and MR-proADM were useful to predict short-term mortality in patients presenting to the emergency department shock. This suggests that PCT and MR-proADM in combination with the most common prediction models will improve prognostic value.

Keywords: Biomarkers; Shock; Patients; Prognostic tool.

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Introduction

Shock is an urgent and life-threatening clinical condition in which there is a failure of the circulatory system to adequately perfuse and, therefore, oxygenate and provide nutrients to bodily tissues [1, 2]. The effects of shock are initially reversible, however, if the cause is not adequately resolved, it can progress to a situation of irreversible multi-organ failure and death in patients. Sepsis is the main cause of shock, with a global estimated incidence of more than 30 million people worldwide annually, leading to a potential 6 million deaths per year [3]. In Europe, sepsis represents 62% of total cases of shock, followed by cardiogenic and hypovolemic shock (which represent 17% and 16% of cases, respectively) [1]. According to the Spanish Shock Registry, of the Spanish Society of Emergency Medicine (RESH) study [4], in Spain, septic shock represents 64% of total shock cases, followed by hypovolemic (20%), cardiogenic (12%), anaphylactic (2%) and other causes (2%). Mortality in septic shock is believed to be around 40-50%, but some estimate it being as high as 80% [1].

In patients presenting to the emergency department (ED) with undifferentiated hypotension or shock, the emergency physician should stratify the patient according to the severity of shock and the need for immediate or early intervention. Several medical scoring systems, such as early warning scores and the Sequential Organ Failure Assessment (SOFA) Score tool, assist clinical decision-making and aid the practitioner to predict outcome and stratify risk [5]. There are many different tools commonly used in the emergency department to stratify patients presenting in shock based on severity. The Shock Index and Modified Shock Index are good predictors of massive haemorrhage in hypovolemic shock [6]. The Predisposition Insult Response and Organ failure (PIRO) scoring system, the SOFA score and the Mortality in Emergency Department Sepsis (MEDS) score predict mortality in ED patients with features suggesting severe sepsis or septic shock [7]. The goal of the study was to identify the prognostic value of clinical, physiological and laboratory tests to predict 30-day mortality in patients with shock.

Materials and Methods

Study Population and Endpoints

A prospective multicenter cohort study was conducted using patients presenting with shock to the emergency department (Figure 1). Convenience sampling was used to recruit patients. The study took place between March 16th, 2011 and May 16th, 2011 in eleven Spanish urbans, tertiary-care university hospitals. The inclusion criteria were patients aged between 14 and 100 years with clinical diagnostic criteria of shock. Criteria of shock consisted of hypotension (systolic blood pressure <90 mm Hg) or a 30-mmHg fall in baseline blood pressure) with one or more signs of organ hypoperfusion; cool extremities,

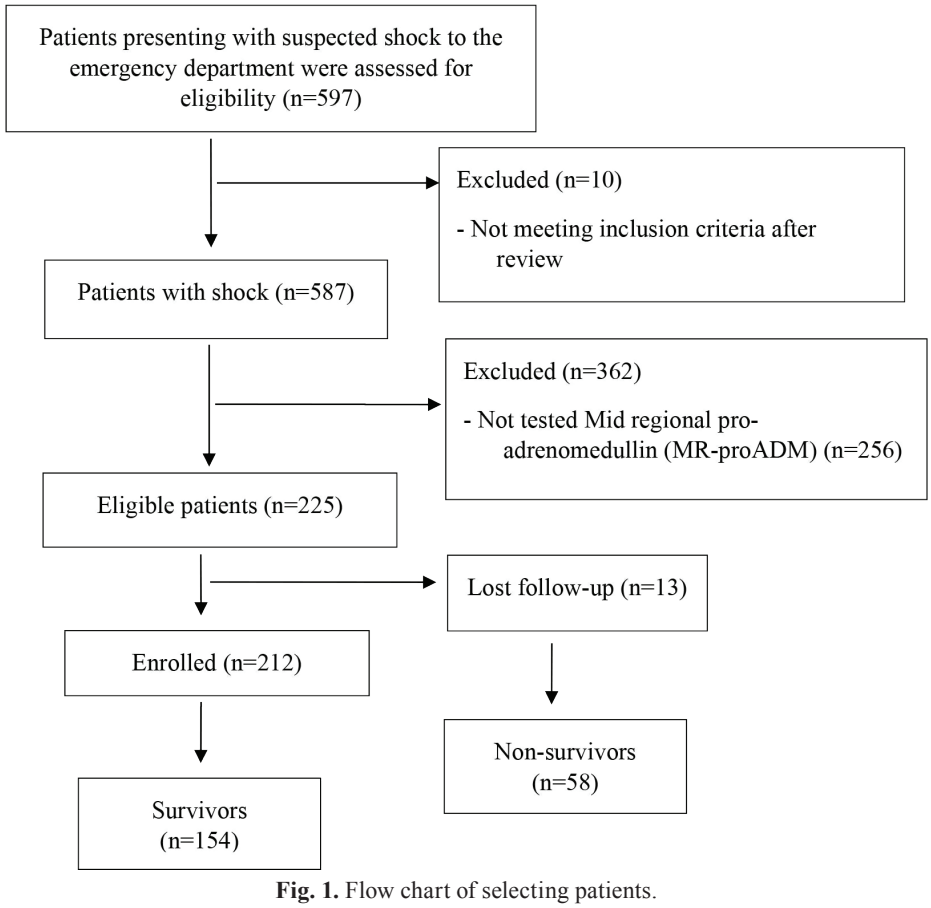

Fig. 1. Flow chart of selecting patients.

confusion or altered mental status, heart rate >100, respiratory rate >22. urine output <0.5 mL/kg/h for the previous 6 h, or blood lactate >2 mmol/l). Further laboratory findings that supported the diagnosis of shock included lactate >2 mmol/L, base deficit <4 mEq/L, and Paco2<32 mm Hg. Exclusion criteria were pregnancy and patients declining to participate in the study. The study protocol was approved by the local ethics committees of all participating sites and is in compliance with the Helsinki Declaration. Written informed consent was obtained from each participant or family member if patients were unable to provide consent due to clinical condition.

The parameters recorded on hospital arrival included age, sex, past medical history (i.e. congestive heart failure (CHF), renal failure, chronic obstructive pulmonary disease (COPD) and liver disease). Other clinical parameters recorded included SOFA score, systolic blood pressure, arterial oxygen saturation (SaO2), capillary refill time and Shock INDEX score. Laboratory variables included base excess, mid regional pro-adrenomedullin (MR-proADM), lactate, C-reactive protein (CRP) and procalcitonin (PCT). The primary endpoint of the study was to identify the prognostic value of clinical, physiologic and laboratory tests for outcome prediction at 30 days in patients in shock. The secondary endpoint was to determine the prognostic value of MR-proADM on mortality prediction at 30 days.

MR-proADM Measurement

Blood testing was performed in all study participants. A blood specimen was frozen at –80°C for the estimation of biomarker levels. MR-proADM was measured using a fully automated chemiluminescence immunoassay on the KRYPTOR system (Thermo Scientific Biomarkers, Hennigsdorf, Germany). The BRAHMS MR-proADM KRYPTOR has a detection range of 0.05 to 100 nmol/L and a functional assay sensitivity of 0.25 nmol/L.

Statistical Analysis

Recorded data was entered into an Excel support application and processed by the statistical program SPSS 18.0. Multivariate discriminant analysis was performed from all the quantitative covariates and the outcome variable (dichotomous) was mortality status at day 30. In addition, Box's Test was used to test the null hypothesis of equality of variances/covariance's of the groups, the Wilks's lambda distribution was used to test the discriminant capacity of the covariates in the equation and the goodness of fit of the model was determined via Canonical correlation analysis. A classification table was constructed to determine the sensitivity, specificity and index of validity of the discriminant function.

Results

There were 212 patients included in the study from the eleven hospitals involved. The mean age was 72.2 years old and 60.4% of the patients were men. Of the 212 patients, 58 patients died at the 30-day follow-up. The overall mortality at 30-day follow-up was 27.4% (n=58). According to the shock classification, 158 patients (74.5%) presented with distributed shock. Diagnosis of distributive shock was establishing in patients who were hypotensive without signs of reduced preload, fluid overload or a hyperdynamic left ventricle on echocardiography. Among patients with distributive shock, clinical features help distinguish the aetiology. Hypotension in association with an infectious source points to septic shock being the most common in the distributive shock subgroup 91.1% and in general 67.9%. Anaphylaxis (anaphylactic shock) was diagnosed in eight patients (3.8%) and brain or spinal trauma (neurogenic shock) was diagnosed in two patients (0.9%). Drug and toxin-induced shock was diagnosed in three patients and Endocrine shock (adrenal failure due to mineralocorticoid deficiency in one patient.

Hypovolemic shock was distinguished by the presence of reduced preload in the context of a suspected or known cause, these patients presented with signs of reduced skin turgor, dry mucous membranes, and a collapsible inferior vena cava on Point-of-care ultrasound (POCUS). The aetiology was varied including traumatic haemorrhage, rupture aortic abdominal aneurism, diarrhoea and vomiting, upper and lower gastrointestinal bleeding and heat exposure. This group represented the second aetiology of shock with 25 patients (11.8%). Patients were diagnosed with cardiogenic shock if they demonstrated evidence of hypotension in association with: (1) clinical or radiological manifestations of pulmonary edema and poor left ventricular function; or (2) a proven valvular/septal abnormality on echocardiography.

The main aetiologies of cardiogenic shock observed included myocardial infarction, arrhythmias and myocarditis, representing a total of 14 (6.6%) patients in the study. Obstructive shock was diagnosed in five (2.4%) patients. Diagnosis was based on presence of hypotension associated with distended neck veins in absence of clinical signs of fluid overload or reduced preload. One patient presented with pericardial tamponade (diagnosed with POCUS), another patient with pneumothorax and three patients with massive pulmonary embolism.

The treatment and management of the patients was based upon protocol; septic shock was managed with the activation of the "codigo sepsis" and the use of the sepsis bundle. In patients with poor response to the initial load of fluids (defined as increase in mean arterial pressure <65mmHg following administration of two litres of crystalloid fluid), vasopressor drugs were started. Hypovolemic shock was managed with fluid resuscitation, blood transfusion and/or surgical treatment. The Interventions in cardiogenic shock included administration of pharmacologic agents,

coronary revascularization procedures, vasopressors and intraaortic balloon pumps. Vasopressors were administered in 46.2%% of patients diagnosed with cardiogenic shock. In this cohort, dopamine was the most frequently used drug (It was used in 46.9% of cases), followed by noradrenaline (26.2%), epinephrine (adrenaline; 15.3%) and dobutamine (11.2%).

Compared to survivors, non-survivors were older and presented with higher serum base excess, lactate, PCT and MR-proADM (all $p<0.05$) (Table 1). Table 2 shows the results of the discriminant analysis where only raised age, MR-proADM and PCT remained in the final discriminant equation. As for the goodness of fit of the model, the canonical correlation coefficient obtained was 0.406. The classification table showed a sensitivity of 66.7%, specificity of 72.7%, with a diagnostic validity index of 71.1%. Cut-off values for each variable were: age (77.5 years), MR-proADM (4,003) and PCT (1,295). Separate analysis of MR-proADM showed that, in the non-survivors group, results are significantly higher than those found in the group of survivors ($p<0.001$) (Figure 2).

Discussion

We included 11 University Hospitals in different geographical areas of Spain. Results indicate that

Table 1. Characteristics of 30-day survivors and non-survivors

	Survivors (n=154)	Non-survivors (n=58)	*p* value
Age (years) (mean, SD)	69,3 (16,2)	80,1 (12,8)	<0.001
Male (%)	98 (63,6%)	30 (51,7%)	
Female (%)	56 (36,4%)	28 (46.3%)	0.155
Medical history			
CHF	34 (22.1%)	17 (29.3%)	0.359
Renal failure	22 (14.3%)	8 (13.8%)	0.591
COPD	35 (22.7%)	14 (24.1%)	0.828
Liver disease	13 (8.4%)	4 (6.9%)	0.481
Clinical variables			
SOFA (mean, SD)	3.25 (3.77)	4.75 (4.71)	0.183
Shock INDEX	1.24 (0.41)	1.31 (0.37)	0.248
MR-proADM (nmol/L) (median, IQR)	3.78 (2.7)	7.56 (11.3)	<0.001
Lactate (mmol/L) (median, IQR)	1.84 (1)	2.33 (1)	<0.001
CRP (mg/dl) (median, IQR)	83.20 (117)	96.57 (116)	0.382
PCT (ng/ml) (median, IQR)	16.74 (39.3)	30.70 (49.5)	0.043
Capillary refill time			0.228
<2	39 (25.3%)	10 (17.2%)	
3-4.5	78 (50.6%)	28 (48.3%)	
4.6-5	29 (18.8%)	13 (22.4%)	
>5	8 (5.2%)	7 (12.1%)	
Systolic blood pressure			0.226
<90	103 (66.9%)	44 (75.9%)	
91-100	27 (17.5%)	11 (19.0%)	
101-109	13 (8.4%)	1 (1.7%)	
>110	11 (7.1%)	2 (3.4%)	
SaO2			0.043
<60%	50 (44.2%)	26 (57.8%)	
60-85%	37 (32.7%)	16 (35.6%)	
>85%	26 (23.0%)	3 (6.7%)	
Base excess			<0.001
<3	75 (48.7%)	15 (25.9%)	
4-9	55 (35.7%)	11 (19.0%)	
10-14	18 (11.7%)	20 (34.5%)	
>15	6 (3.9%)	12 (20.7%)	
PaO2/FiO2 Ratio			0.085
<199	32 (20.8%)	17 (29.3%)	
199-200	35 (22.7%)	18 (31.0%)	
201-299	50 (32.5%)	14(24.1%)	
>300	37 (24.0%)	9 (15.6%)	

Continuous variables expressed as mean (standard deviation) or median (interquartile range), as appropriate; categorical variables expressed as number (percentage). Shock index defined as heart rate/systolic blood pressure, CHF chronic heart failure, COPD chronic obstructive pulmonary disease, SOFA Sequential Organ Failure Assessment, MR-proADM Mid regional pro-adrenomedullin, CRP C-reactive protein, PCT procalcitonin, PaO2/FiO2 ratio of arterial oxygen partial pressure to fractional inspired oxygen

Table 2. Results of the discriminant analysis (Lambda method of Wilks F> = 3.84). Variable result: non-survivors

Covariable	Box's M Test	*p*	Wilks' Lambda	*p*	Canonical analysis	Sensitivity	Specificity	Youden's J statistic	Validity index
Age	36,3	<0.001	21,39	<0.001	0,045	66,7%	72,7%	0,394	71,1%
MR-proADM			17,53	<0.001	0,118				
Procalcitonin			13,61	<0.001	0,009				
Constant					-4,011				

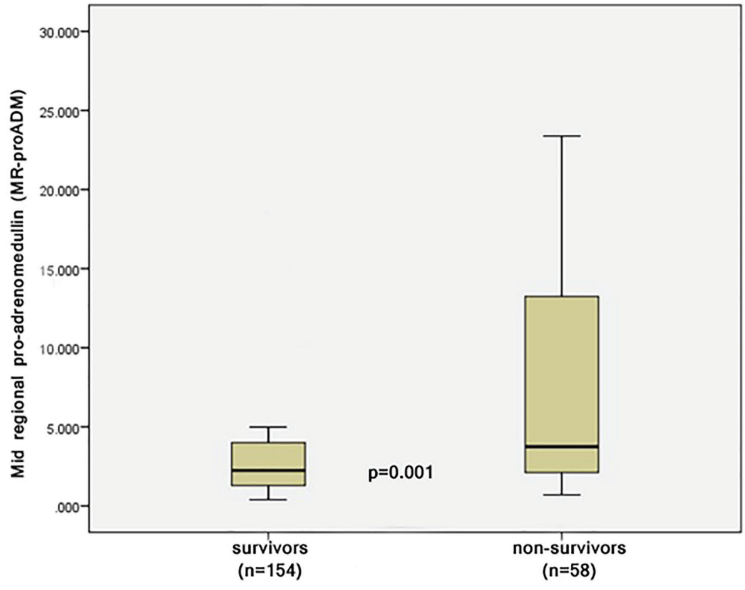

Fig. 2. The mean levels of MR-proADM in patients who survive at 30 days and patient who did not survive at 30 days.

increased age and raised serum MR-proADM and PCT correlate best with increased mortality rate. Although, all aetiologies of shock were considered, septic shock was the most prevalent with 144 cases (67.9%). The lower respiratory tract was the most common site of infection (27.7%), followed by the urinary tract and digestive tract respectively. Disease severity can be quantified by measuring a simple combination of physiological parameters and biomarkers. Based on these simple physiological measurements, there are now many widely known track and trigger systems that have low sensitivity, low positive predictive values, and high specificity. Therefore, they often fail to identify patients needing additional care and have not been shown to improve patient outcomes, at present, few track and trigger systems meet these standards [8].

The quick Sequential related Organ Failure Assessment (qSOFA score) has been recently proposed as a useful tool in assessment of organ failure. This risk stratification system is believed to assist in identification of the need to initiate or escalate treatment in patients by highlighting cases of potentially life threatening sepsis [9, 10]. qSOFA is a new, simpler adaptation of the SOFA score. The SOFA tool calculates the number and severity of dysfunction in six organ systems; pulmonary, coagulation, hepatobiliary, cardiovascular, renal, and neurologic [11]. Due to its increased simplicity, qSOFA is more suited than the older SOFA tool to emergency medicine as it can be obtained immediately at the head of the patient's bed without any need for further laboratory testing. However, the qSOFA recommendation was based upon retrospective analysis of data and critics of its clinical usefulness have emerged [12, 13]. Our study predates the latest guidance and, therefore, SOFA scores were calculated for patients rather than qSOFA. Several studies suggest that the qSOFA tool has a greater prognostic accuracy for in-hospital mortality than the systemic inflammatory response syndrome (SIRS) or severe sepsis criteria [14-16], although, it does not help with screening for those less obviously septic patients in the ED. However, other studies have established different conclusions. McDonald *et al*., [17] compared of PIRO, SOFA, and MEDS scores for predicting mortality in ED patients with severe sepsis and septic shock. The paper concluded that the PIRO model, which considers comorbidities, source of sepsis and physiologic status, performed better than the SOFA score and similarly to the MEDS score for predicting mortality in ED patients with severe sepsis and septic shock. A Norwiegan observational cohort study [18] found that qSOFA failed to identify two thirds of the patients admitted to ED with severe sepsis and, due to this low sensitivity, was poor at predicting of seven and 30-day mortality. A Spanish study by García-Villalba [19] showed that a high percentage of patients predicted to be at low risk of organ failure had poor outcomes, associated with SOFA score. In our study (which had a similar population to that in the Garcia-Villalba paper) the SOFA score by itself was an inadequate prognostic tool in patients at low

risk of organ damage. More recently, a single-centre retrospective study [20] reviewed the use of the National Early Warning Score (NEWS) as an early sepsis screening score and compare it to SIRS and qSOFA systems in an ED triage setting. The authors found NEWS to be more accurate when compared with both SIRS and qSOFA for the early detection of severe sepsis and septic shock, septic shock alone and sepsis-related mortality. Our study did not find a significant (p=0.183) relationship between SOFA and mortality. We cannot exclude that the performance of the SOFA scoring system may be different in other study populations; however, our results agree with these previous studies. We, however, appreciate that other clinical and analytical variables are required to complement the SOFA score in clinical practice. Laboratory tests in the stratification risk of shock.

CRP has been used in many hospitals across Europe as a screening tool for inflammation and infection. It is commonly used to screen early onset sepsis because it is a sensitive early infection marker. However, the low specificity of CRP is a handicap as biomarker of sepsis in adults. A Spanish study compared PCT and CRP levels in febrile patients admitted to a medical ward and found that CRP was not able to discriminate between infections and inflammatory diseases [21]. In addition, its prognostic accuracy has been found to be inferior to other commonly used markers of infection [22]. A recent meta-analysis [23] concluded that CRP was moderately useful in the diagnosis of sepsis in adult patients. Whilst it was found that raised CRP was more common in patients in septic shock, this was not specifically associated with increased mortality.

It is accepted that lactate rises in critically ill patients. When oxygen delivery fails to meet oxygen demand, an oxygen debt with global tissue hypoxia and lactate production ensues [24, 25]. Jansen demonstrated that lactate reduction during the first 24 hours of ICU stay is associated with improved outcome in septic patients, but not in patients with haemorrhage or other conditions generally associated with low-oxygen transport [26]. They hypothesise that in this other group; a reduction in lactate is not associated with improved outcome due to irreversible tissue damage. More recently, Marik [27] suggested that the degree of elevation of serum lactate reflects disease severity and degree of activation of the stress response. The paper suggests that, rather than being solely a marker of anaerobic metabolism, an increased lactate may be an important adaptive survival response during critical illness. In our study, lactate did not remain in the final discriminant equation as a marker of mortality.

PCT has emerged as an inflammatory blood marker which is specific to bacterial infections and has a use in guiding antibiotic therapy. A combination of elevated PCT levels and systemic inflammatory response syndrome criteria seems to be more accurate for the diagnosis of early and uncomplicated sepsis in ED patients, compared to either measure taken alone [28]. The diagnosis accuracy and specificity of PCT are higher than those of CRP as demonstrated in a recent systematic review and meta-analysis [23].

Increased serum MR-proADM concentrations have been identified in patients with community acquired pneumonia and are commonly used in the risk and severity assessment [29]. However, there are few publications on the usefulness of MR-proADM in the diagnosis and prognostication of patients with sepsis [30-34]. Most the studies analysed isolated MR-proADM levels in ED at admission; very few studies analysed levels during evolution of the disease [35]. Other studies have evaluated MR-proADM in combination with other biomarkers, such as CRP and PCT [30-34]. For example, The TRIAGE study [36] included consecutive medical patients presenting with a medical emergency at three tertiary-care hospitals. Three biomarkers were studied, including MR-proADM, copeptin and PCT. This study found a high precision for predicting adverse outcome and requirement of high priority treatment by measuring initial levels of the biomarkers. MR-proADM was the best biomarker, especially for mortality prediction. In our study age, procalcitonin levels and MR-proADM levels were found as the most important predictors of 30-day mortality; specifically, MR-proADM has been identified as the most accurate predictor of mortality.

Our study has several limitations that must be considered. Most importantly, despite being a multicentre study, sample size was not large enough to completely exclude type I error. Results must be validated, in the near future, by conduction of further multi-centre studies, with a larger sample size to predict mortality. To establish the prognostic value of the markers, a single determination was used and the effect of the prediction tools on other outcome variables were not considered. It is necessary to design studies with a greater number of patients that allow us to confirm the current findings and perhaps assess longer term mortality or consider analysing other markers of morbidity.

In conclusion, increased age and elevation of serum levels of PCT and MR-proADM were found to correlate with 30-day mortality in patients presenting to ED in shock. These values could, therefore, help clinicians in predicting short-term mortality in patients in shock. It is also possible that, procalcitonin and MR-proADM, in combination with the most common prediction models will improve prognostic value of these prognostic tools. The combination of clinical information on admission to ED with the added value of biomarkers may also allow early risk stratification of individual patients and guide treatment. Compared to PCT, MR-proADM is a better biomarker in enabling mortality prediction.

Conflicts of Interest: None declared.

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