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Sustained value of proadrenomedullin as mortality predictor in severe sepsis

KEYWORDS
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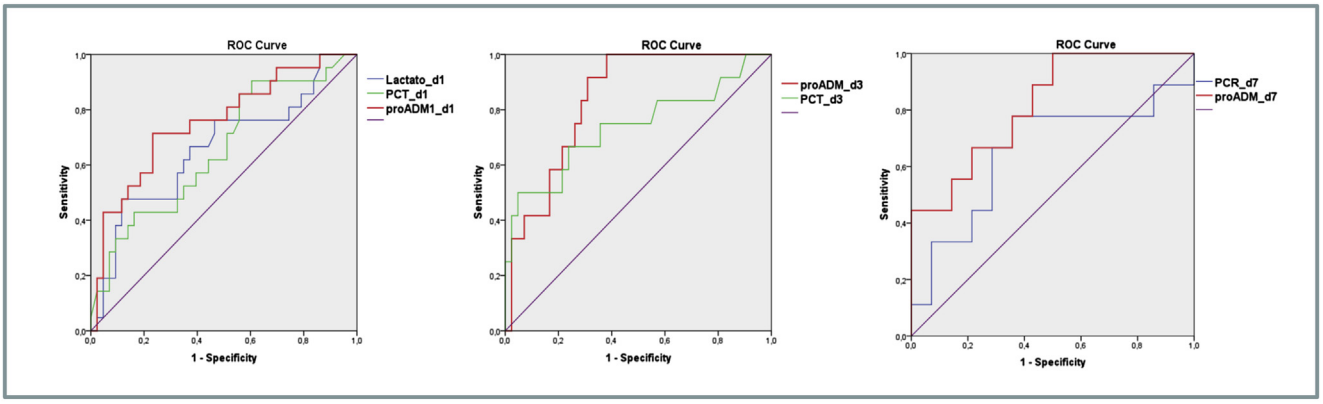
In a recent article published in Journal of Infection, España P et al. demonstrate the value of pro-adrenomedullin (ProADM) levels in plasma to identify those patients developing adverse outcomes following community acquired pneumonia (CAP).[1] While proADM has been widely assessed as prognostic biomarker in CAP (alone or in combination with severity scores),[2–7] there is limited evidence on its potential clinical role in sepsis. We sought to evaluate the prognostic role of proADM in patients with this disease compared to that showed by other biomarkers commonly employed for the management of septic patients. Patients (>18 years old) admitted to the intensive care unit (ICU) of Hospital Clínico Universitario de Valladolid from October 2013 to July 2014 with a diagnosis of severe sepsis or septic shock were prospectively recruited. Written informed consent was obtained directly from all patients, or their legal representative before enrolment and study protocol was approved by the local scientific and ethics committees.

Levels of procalcitonin (PCT), lactate, C-reactive protein (CRP) and proADM in plasma were measured in the first 24 h following admission to the ICU, and again by day 3 and day 7. PCT measurement was performed by electrochemiluminescence immunoassay (ECLIA) in a chemistry analyzer (Cobas 6000, Roche Diagnostics Meylan, France). The limit of detection for PCT was 0.5 ng/ml. Serum CRP and lactate levels were measured by particle-enhanced immunoturbidimetric and colorimetric assay respectively by using the e501 module analyser from Roche Diagnostics, Meylan, France. Reference limit were 0–5 mg/dl and 0.5–2.2 mmol/L respectively. Finally, proADM measurement was performed by TRACE (Time Resolved Amplified Cryptate Emission) using a new sandwich immunoassay on a Brahms Kryptor Compact Plus analyzer (BRAHMS; Hennigsdorf, Germany). The reference limit for this method was 0.55 nmol/L.

Seventy one patients with severe sepsis (29.6%) or septic shock (70.4%) were included in the study with a median age at admission of 63 years. The median values for SOFA (Sequential Organ Failure Assessment) and APACHE II (Acute Physiology and Chronic Health Evaluation II) scores at day 1 were 8.3 and 21.3 respectively. The majority of the patients in our cohort were male. The most common co-morbidities were arterial hypertension and diabetes while the subgroup of patients who ultimately died during hospitalization at the ICU showed more frequently some degree of immunosupression. Septic shock was the most frequent cause of admission to the ICU in the group who eventually died. Origin of sepsis was the



	Day 1 (n = 71)			Day 3 (n = 63)			Day 7 (n = 62)		
	AUROC	CI 95%	*p*	AUROC	CI 95%	*p*	AUROC	CI 95%	*p*
CRP	0.45	[0.42 - 0.62]	n.s	0.60	[0.40 - 0.80]	n.s	**0.70**	**[0.50 - 0.93]**	**0.048**
Lactate	**0.67**	**[0.53 - 0.81]**	**0.02**	0.66	[0.47 - 0.84]	n.s	0.64	[0.43 - 0.86]	n.s
PCT	**0.66**	**[0.52 - 0.79]**	**0.03**	**0.73**	**[0.54 - 0.91]**	**0.01**	0.69	[0.49 - 0.88]	n.s
proADM	**0.75**	**[0.62 - 0.87]**	**0.01**	**0.83**	**[0.72 - 0.94]**	**<0.001**	**0.84**	**[0.67 – 0.99]**	**0.006**

Figure 1 Receiver Operating Characteristic (ROC) curves of biomarkers for prediction of mortality at the ICU. Only those biomarkers showing statistically significant areas under the curve were represented each time point.

community in the vast majority of cases. In turn, the principal suspected source of infection was the lower respiratory tract. The presence of a microorganism was documented in 74% of the cases, with a balanced proportion of Gram-positive and Gram-negative bacteria. The most frequent cause of death was multi-organ dysfunction syndrome (n = 23, 32.3%) (full description of patients' clinical characteristics is showed in supp data 1). ProADM was the only biomarker showing significant differences between survivors and non survivors for concentration in plasma in the three time points analysed (supp data 2). In addition, it was the biomarker showing the best diagnostic accuracy for predicting mortality at the ICU in the area under the receiver operating curve analysis (Fig. 1). Interestingly, the diagnostic accuracy of proADM was preserved in all the time points analysed (Fig. 1). Spearman–Karber test indicated that only PCT and proADM showed a significant association with organ failure extent at all the time points evaluated, assessed by SOFA score (supp data 3). Nonetheless, proADM showed the strongest association with SOFA score over time, principally in the first 72 h of the disease.

Christ-Chrain et al. and Suberbiola et al. had already described higher levels on admission of proADM in those septic patients who did not subsequently survive, with a significant AUROC of 0.81 and 0.63 for ICU and hospital mortality respectively.[8,9] In another recent interesting work Marino et al. report not only higher levels of adrenomedullin (ADM) in those septic patients who finally died but also show a positive correlation between ADM levels on admission and severity of disease as assessed by APACHE II score ($r = 0.46$; $p < 0.0001$).[10] These findings are in agreement with our results. However, proADM levels in these studies were analysed only at one temporal point during the course of sepsis (at ICU admission). In contrast, in our work, we assessed the prognostic value of ProADM along time. This way, ProADM showed a superior prognostic accuracy over time compared to other classical biomarkers evaluated in plasma. In consequence, we show for the first time that the prognostic value of ProADM is preserved throughout the first week following diagnosis of severe sepsis or septic shock. Moreover, we have identified a cut-

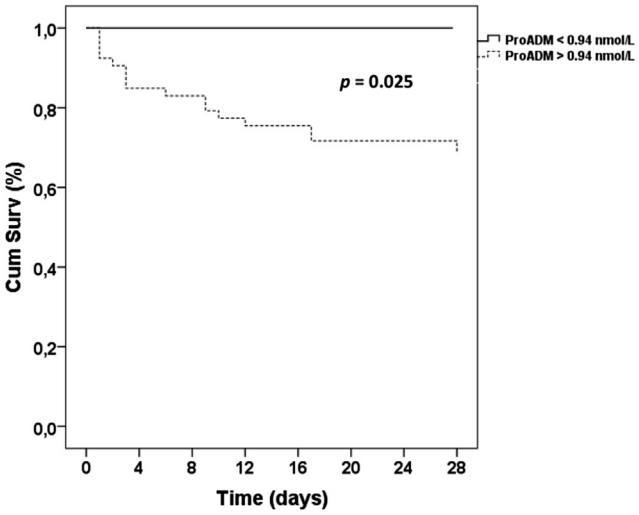


Figure 2 Kaplan Meier survival curves based on ProADM levels at day 1. Deciles from percentile 10 to percentile 90 of ProADM were calculated and used to compare survival times in those patients with low or high concentrations of this biomarker. The first decile showing significant differences between groups based upon the log-rank test (Mantel–Haenzel) was represented.