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Prognostic Value and Organ-Specific Correlations of Admission MR-proADM in Critically Ill Patients: A Retrospective Exploratory Study

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Abstract

Background: Acute organ dysfunction is a primary driver of ICU mortality. As clinical scores often act as lagging indicators, early recognition of subclinical endothelial stress may be essential for timely intervention. This exploratory study investigated the association of Mid-regional pro-adrenomedullin (MR-proADM)—a stable surrogate of the hormone adrenomedullin—as a potential early indicator of early organ failure.

Methods: This retrospective, single-center study analyzed a heterogeneous cohort of 26 critically ill patients. Plasma MR-proADM levels were assessed at admission (t0) and daily for five days. The primary outcome was the correlation between admission MR-proADM and the 24-hour SOFA score. Secondary outcomes included comparisons between septic and non-septic patients and between survivors and non-survivors.

Results: Admission MR-proADM showed a moderate correlation with the 24-hour SOFA score (rho = 0.488; p = 0.021), with the most prominent associations observed within the cardiovascular and renal SOFA domains. In the septic subgroup, MR-proADM levels were higher than in non-septic patients (10.90 [IQR 5.91–19.00] vs. 1.30 [IQR 0.74–2.53] nmol/L, p < 0.001); ROC analysis yielded an AUC of 0.88 (95% CI 0.73–1.00; p < 0.001), although this estimate should be interpreted descriptively given the small number of septic cases. Despite the low number of mortality events (n=4), higher admission MR-proADM values were observed in non-survivors than in survivors, although this finding remains preliminary. Furthermore, admission MR-proADM levels showed positive correlations with procalcitonin at each individual timepoint during the first five ICU days (p < 0.001 at each timepoint).

Conclusions: Within the limits of this small cohort, MR-proADM might provide a biological window into incipient organ dysfunction. Its possible role in supporting clinical assessment of sepsis and risk stratification—particularly regarding hemodynamic and renal dysfunction—remains strictly hypothesis-generating and requires validation in larger, prospective multicenter studies.

Keywords: biomarkers, MR-proADM, midregional proadrenomedullin, organ failure, SOFA, sepsis, critical care.

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BACKGROUND.

Acute organ failure is the primary driver of Intensive Care Unit (ICU) admission and remains the predominant determinant of morbidity and mortality in critically ill patients.[1,2] Consequently, a cornerstone of critical care management is the early and accurate recognition of organ dysfunction to guide timely therapeutic interventions. While traditional scoring systems, such as the Sequential Organ Failure Assessment (SOFA) score, remain essential for clinical monitoring, they often function as retrospective indicators, documenting physiological damage only after it has become clinically apparent. Furthermore, these scores possess inherent limitations, such as the limited ability to fully discriminate between acute exacerbations and pre-existing chronic organ dysfunction. [3-5] In this context, there is a growing need for sensitive biomarkers capable of identifying early subclinical organ stress before overt failure occurs.

Mid-regional pro-adrenomedullin (MR-proADM) has emerged as a reliable biomarker of endothelial activation, released into the systemic circulation as a stable fragment of the Adrenomedullin (ADM) precursor. ADM is a potent regulatory peptide with pleiotropic effects on the vascular and immune systems. From a pathophysiological standpoint, ADM acts as a vasodilator, positive inotrope, and diuretic hormone, playing a key role in maintaining hemodynamic homeostasis. Notably, it antagonizes the renin-angiotensin-aldosterone system by inhibiting aldosterone secretion, thereby counteracting excessive vasoconstriction. Beyond its hemodynamic profile, ADM exhibits significant immunoregulatory effects and antimicrobial properties, with its expression upregulated in response to bacterial infections and systemic inflammation. [6-8]

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While the active peptide, ADM, possesses a very short half-life that limits its clinical measurement, the mid-regional fragment exhibits superior plasma stability and directly reflects ADM production. As it is released by endothelial cells in response to increased vascular permeability and capillary leak, MR-proADM has emerged as a sensitive surrogate for endothelial stress—the common denominator unifying sepsis, trauma, and major surgical insults. [9-13]

The aim of this study was to evaluate the clinical utility of admission MR-proADM as a predictor of evolving organ dysfunction, with a specific focus on its ability to anticipate the 24-hour SOFA score and its exploratory ability to distinguish septic from non-septic patients within a heterogeneous ICU population.

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METHODS.

Study design, setting, participants, and ethics

This single-center, retrospective, exploratory, observational study was conducted at the ICU of the University Hospital "Azienda Ospedaliero-Universitaria delle Marche" of Ancona, Italy. We screened all adult patients admitted to the ICU over a three-month period from March to May 2024. Patients were eligible for inclusion if admission MR-proADM levels were measured. Exclusion criteria included age < 18 years, lack of informed consent, ICU length of stay < 48 hours, admission following elective surgery, moribund state, and legal interdiction.

The study was conducted in accordance with the principles of the Declaration of Helsinki (2024 revision). The study was approved by the Local Ethics Committee (Comitato Etico Territoriale Regione Marche; approval number: CET 2024 202, ID 272781). Informed consent for study participation and data processing were obtained from all participants or , where indicated, from their legal representatives.

Outcomes

The primary outcome of this study was to assess the correlation between admission MR-proADM and the 24-hour SOFA score (calculated at 24 hours post-admission in ICU)

Secondary outcomes included: the assessment of the correlation of admission MR-proADM with other clinical severity scores at entry; the association of MR-proADM levels with the total SOFA score and its individual components at admission and during the first five days and the correlation between MR-proADM and procalcitonin (PCT). Furthermore, we evaluated differences in MR-proADM levels between survivors and non-survivors and between septic and non-septic patients.

Data collection and MR-proADM assay

Upon ICU admission, we collected baseline demographic and clinical data, including age, sex, height, weight, body mass index (BMI), comorbidities, and the primary admission diagnosis. The presence of sepsis was defined according to the Sepsis-3 criteria [14]

Severity of illness was assessed using the SOFA score, the Simplified Acute Physiology Score (SAPS II) and the Acute Physiology Assessment and Chronic Health Evaluation (APACHE II) score.

The Sequential Organ Failure Assessment (SOFA) score was subsequently calculated daily, recording both total and organ-specific domain scores.

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At admission and for the first five days of ICU stay (from day 1 to 5), we recorded daily MR-proADM and procalcitonin (where available from clinical records). Clinical outcomes included the duration of vasopressor support and mechanical ventilation, all-cause ICU mortality, and length of stay (LOS).

MR-proADM levels were measured using the LIAISON® BRAHMS™ MR-proADM chemiluminescent immunoassay (DiaSorin LIAISON® analyzer) in ethylenediaminetetraacetic acid (EDTA) plasma. The reference limit for this method was 0.21 nmol/L.

Sample size and statistical analysis

Sample size was estimated based on the primary objective of identifying a clinically relevant correlation between admission MR-proADM (Day 0) and the 24-hour SOFA score (Day 1). Assuming an expected Spearman's correlation coefficient (rho = 0.60), a sample size of 28 patients was calculated to achieve a statistical power (1-beta) of over 85% (two-tailed alpha = 0.05). The final analyzed cohort included 26 patients. Given the exploratory and observational nature of this single-center study, this sample size was considered sufficient to provide preliminary 'proof-of-concept' data.

The statistical analysis was performed using IBM® SPSS (*Statistical Package for Social Science*) software version 21 (IBM Corp., Armonk, NY) and GraphPad Prism software version 6 (GraphPad Software, La Jolla, CA, USA).

Categorical data are expressed as absolute and relative frequencies; numerical data are presented as mean ± standard deviation for normally distributed variables, or as median [interquartile range, IQR], for non-normally distributed data. Normality was assessed using the Shapiro-Wilk test. The relationship between numerical variables was initially explored using scatter plots, and the strength of the association was assessed using Pearson's or Spearman's correlation coefficients, as appropriate.

Differences in MR-proADM levels between survivors and non-survivors, as well as between septic and non-septic patients, were compared using the Mann-Whitney U test. A receiver operating characteristic (ROC) curve model, with the y-axis being sensitivity, and the x-axis as 1-specificity, was constructed. The area under the curve (AUC) was calculated as part of an exploratory analysis to describe how admission MR-proADM values distinguished septic from non-septic patients. Statistical significance was defined as $p < 0.05$.

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RESULTS.

A total of 28 patients met the initial inclusion criteria for this exploratory study, based on the availability of plasma MR-proADM measurements. However, two patients were subsequently excluded due to incomplete data. Consequently, the final analysis cohort consisted of 26 patients.

Baseline Characteristics

The baseline characteristics of the study cohort are presented in *Table 1*. The mean age of the patients was 56 years (±17.6), and 50% (n=13) were male. Upon admission, the median APACHE II, SAPS II, and SOFA scores were 12 [7–19], 38 [24–43], and 8 [3–10], respectively.

Age, years	56 (±17.6)
Gender, male	13 (50%)
BMI, kg/m2	28 (±7.8)
APACHE II, AU	12 [7-19]
SAPS II, AU	38 [24-43]
SOFA score, AU	8 [3-10]

Table 1: Baseline Characteristics of the Study Cohort. Mean, (SD); median, (IQR). BMI= Body Mass Index; APACHE= Acute Physiology and Chronic Health Evaluation; SAPS= Simplified Acute Physiology Score; SOFA= Sequential Organ Failure Assessment

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The most frequent reasons of admission were sepsis and major trauma, each accounting for 26.9% of the cohort (*n*=7 each), followed by respiratory failure (19.2%, *n*=5). Other diagnoses included neurological events and non-traumatic hemorrhagic shock (7.7%, *n*=2 each), while hematological malignancies, isolated head trauma and emergent surgery each accounted for a smaller fraction (3.8%, r *n*=1 each). *(Table 2)*

DIAGNOSIS AT ADMISSION IN ICU		
	Sepsis and septic shock	7 (26.9%)
	Respiratory Failure	5 (19.2%)
	Neurological (ICH/SDH/SAH)	2 (7.7%)
	Major Trauma	7 (26.9%)
	Hematological Malignancy	1 (3.8%)
	Post-operative (emergency/urgency)	1 (3.8%)
	Head Trauma	1 (3.8%)
	Hemorrhagic Shock	2 (7.7%)

Table 2: Distribution of admission diagnoses. Data are expressed as n (%). Abbreviations: ICH= Intracerebral Hemorrhage, SDH=Subdural Hematoma, SAH=Subarachnoid Hemorrhage.

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At admission, the 42.3% of patients (n=11) presented with at least one established organ failure. Slightly more than half of the patients (53.8%; n=14) were admitted with an active infection; among these, 14.3% (n=2) were identified as carrying a multidrug-resistant (MDR) organism. The genitourinary system was the most frequent source of infection, accounting for 28.6% (n=4) of cases, while respiratory and abdominal sources were equally prevalent, each accounting for 21.4% (n=3). *(Table 3)*

Organ failure at admission in ICU		11 (42.3%)
Infections at admission in ICU		14 (53.8%)
MDR		2/14 (14.3%)
Source of infection		
	Respiratory	3 (21.4%)
	Abdominal	3 (21.4%)
	Genito-urinary	4 (28.6%)
	Bloodstream	1 (7.1%)
	Other (polydistrictual)	3 (21.4%)

Table 3: Organ failure and infection status at admission. Data are presented as n (%). Abbreviations: ICU= Intensive Care Unit; MDR= multidrug-resistance.

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The overall mortality rate was 15.4% (n=4). The median ICU length of stay (LOS) was 8 [4-16] days. The median duration of mechanical ventilation (MV) was 4 [3-11] days, while the median duration of vasoactive support and antibiotic therapy were 3 [1-6] days and 5 [3-15] days, respectively.

MR-proADM at admission in ICU

Figure 1 and Table 4 present the median [and IQR] plasma concentrations of MR-proADM (nmol/L) measured at admission (t0) and from Day 1 to Day 5 (t1-t5). The median value at admission was 2.88 nmol/L, with a wide IQR [0.87-7.74]. A comparable heterogeneity in the distribution of MR-proADM values was observed at all subsequent timepoints.

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	t0	t1	t2	t3	t4	t5
MR-proADM, *nmol/L*	2.9 [0.9-7.74]	2.21 [1.17-4.65]	1.88 [0.75-3.25]	3.47 [1.87-6.43]	3.55 [1.21-5.00]	2.40 [0.92-4.16]

Table 4: MR-proADM plasma concentrations (nmol/L) at each timepoint from admission to Day 5 (t0–t5). Data are presented as median [IQR].

At ICU admission, patients with at least one organ failure showed significantly higher median MR-proADM levels compared to those without organ failure (4.08 [2.17-16.20] vs. 1.26 [0.77-2.88] nmol/L; p=0.015)

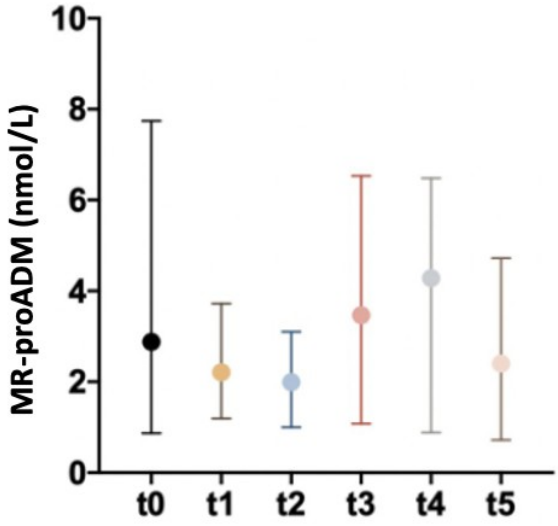

Figure 1: Admission MR-proADM plasma levels (nmol/L) from ICU admission to Day 5 (t5).

A significant moderate positive correlation was observed between admission MR-proADM and the 24-hour SOFA score (rho = 0.49; p = 0.021) Significant positive correlations were also found between admission MR-proADM and all the clinical severity scores upon ICU admission. These results are summarized in Table 5.

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	MR-proADM admission value (t0)	
	Rho di Spearman	p value
SAPS II SCORE, AU	0.55	*0.015*
APACHE II, AU	0.47	*0.015*
SOFA score, AU	0.55	*0.005*

Table 5: Spearman's Correlation (rho) of admission MR-proADM and admission severity scores. P<0.05. Abbreviations: SAPS= Simplified Acute Physiology Score; APACHE= Acute Physiology and Chronic Health Evaluation; SOFA= Sequential Organ Failure Assessment.

In addition to the total score, significant correlations were observed with individual SOFA sub-scores. Significant correlations between MR-proADM concentration and the cardiovascular SOFA score were observed at several timepoints (t0: rho = 0.57; p = 0.01; t1: rho = 0.70; p < 0.001; t2: rho = 0.65; p = 0.008; t3: rho = 0.51; p = 0.039). As each timepoint was analyzed independently, these findings describe cross-sectional associations rather than temporal changes.

The strongest correlation with the renal component of the SOFA score was found at admission (rho = 0.66; p = 0.002); the association between the admission MR-proADM and the 24-hour renal SOFA score was also strong (rho= 0.65; p = 0.002)

Admission MR-proADM also showed a positive correlation with the hepatic SOFA sub-score at t0 (rho = 0.47; p=0.011); however, this correlation was not observed at any of the subsequent individual timepoints (t1–t5).

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MR-proADM and PCT:

Admission MR-proADM showed positive correlations with PCT at each timepoint analyzed (t0–t5) with all associations being highly statistically significant (p<0.001). The correlation coefficients (rho) were 0.85 at t0, 0.83 at t1, 0.92 at t2, 0.85 at t3, 0.84 at t4 and 0.79 at t5.

MR-proADM in survivors and non-survivors:

Non-survivors exhibited significantly higher median admission MR-proADM concentrations compared to survivors (16.9 [IQR 5.00–23.45] vs. 1.85 [IQR (0.84-3.64) nmol/L; p =0.048) as shown in Figure 2. Given the very limited number of mortality events, mortality-related analyses were limited to descriptive comparisons between survivors and non-survivors.

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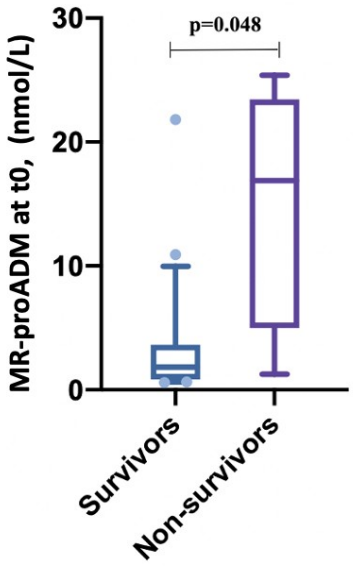

Figure 2: Admission MR-proADM (nmol/L) in survivors and Non-Survivors (p<0.05).

Admission MR-proADM did not correlate significantly with the ICU length of stay (LOS), the duration of the mechanical ventilation, or antibiotic therapy. It showed a weak positive correlation with the duration of vasoactive support (rho=0.39, p=0.049).

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MR-proADM in septic and non-septic patients

At admission, MR-proADM levels were significantly higher in septic patients (10.90 [5.91–19.00] nmol/L) compared to non-septic patients (1.30 [0.74–2.53] nmol/L); $p < 0.001$. (Table 6, Figure 3).

At Day 1(t1), the median in the septic group was 6.18 [3.72-11.40] nmol/L vs. 1.22 [0-67-1.92] nmol/L in non-septic patients ($p < 0.001$). At Day 2(t2), the septic group median was 3.71 [2.60-5.23] nmol/L vs. 1.15 [0.67-1.92] nmol/L in non-septic patients ($p = 0.002$).

The difference between the two groups was statistically non-significant at t3, t4 and t 5. (Table 6, Figure 3).

	Sepsis at admission in ICU		
	No	**Yes**	**p value**
MR-proADM at t0, nmol/L	1.30 [0.74-2.53]	10.90 [5.91-19.00]	*<0.001*
MR-proADM at t1, nmol/L	1.22 [0.67-1.92]	6.18 [3.72-11.40]	*<0.001*
MR-proADM at t2, nmol/L	1.15 [0.67-1.92]	3.71 [2.60-5.23]	*0.002*
MR-proADM at t3, nmol/L	2.54 [1.81-2.68]	6.26 [4.12-6.48]	0.143
MR-proADM at t4, nmol/L	1.57 [0.88-2.82]	5.19 [4.67-6.02]	0.10
MR-proADM at t5, nmol/L	1.76 [0.92-3.00]	5 [5.00-5.00]	0.40

Table 6: Median MR-proADM plasma concentrations (nmol/L) in septic and non-septic patients from admission (t0) to Day 5 (t5). Data are presented as median [IQR], p<0.05.

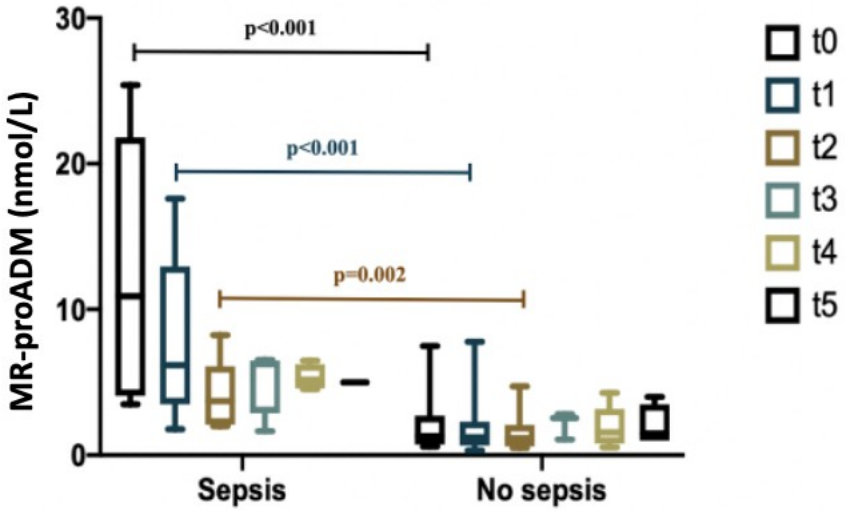

Figure 3: Comparison of admission MR-proADM levels between patients with and without sepsis from admission (t0) to Day 5 (t5).

An exploratory ROC analysis was performed to examine how well admission MR-proADM values distinguished septic from non-septic patients at ICU admission. Admission MR-proADM yielded an AUC of 0.88 (95% CI 0.73–1.00; $p < 0.001$). The cut-off identified by the Youden index was ≥3.28 nmol/L, corresponding to a sensitivity of 85.7%, a specificity of 88.9%, a positive likelihood ratio (LR+) of 7.72, and a negative likelihood ratio (LR–) of 0.16. Given the very small number of septic cases included in this analysis (n=6), these estimates should be interpreted with caution and considered descriptive rather than indicative of established diagnostic performance. The initial MR-proADM measurement was performed contextually or within a very short interval from the clinical diagnosis of sepsis.

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For the ROC analysis, one septic patient was excluded based on a strict temporal criterion, as the admission MR-proADM measurement occurred more than 4 hours after the clinical diagnosis. Consequently, this ROC analysis was performed on a total of 25 patients (6 septic cases and 19 non-septic controls).

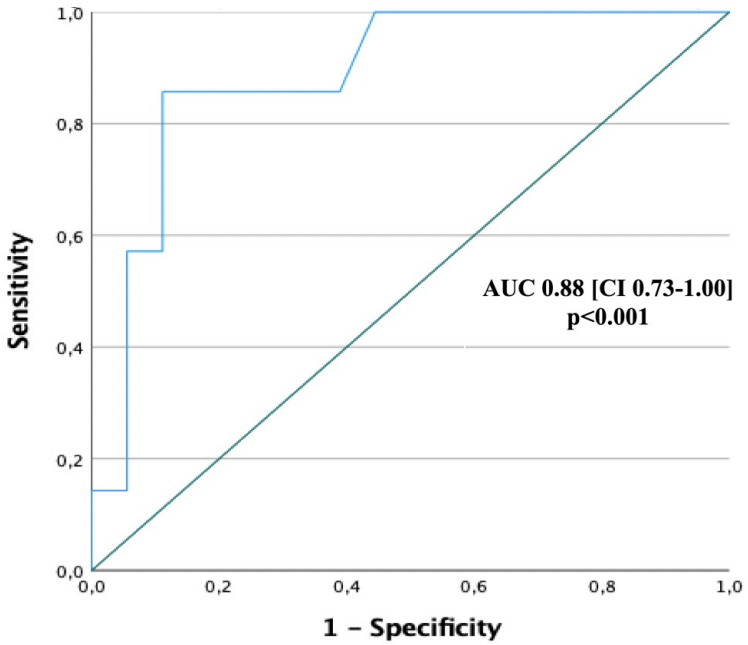

Figure 4: Exploratory receiver operating characteristic (ROC) curve analysis of admission MR-proADM values for distinguishing septic from non-septic patients at admission.

In septic patients, the correlation between admission MR-proADM and admission SOFA score was strong and statistically significant (rho=0.83; p=0.042). The correlation with the 24-hour SOFA score remained strong but did not reach the statistical significance (rho=0.75, p=0.084).

DISCUSSION.

This exploratory study investigated the clinical utility of admission MR-proADM as an early biomarker of organ dysfunction and prognosis within a heterogeneous in a cohort of critically ill patients.

The primary outcome revealed a moderate association between admission MR-proADM and the 24-hour SOFA score (rho = 0.488). However, secondary analyses showed associations between MR-proADM and organ dysfunction at several individual timepoints within the first 72 hours. This association was notably specific to cardiovascular and renal impairment. Admission MR-proADM

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levels showed timepoint-specific positive correlations with PCT during the first five ICU days together with a weak association with the duration of vasoactive support. Admission MR-proADM levels were significantly higher in non-survivors compared to survivors and in septic compared to non-septic patients. Higher MR-proADM values were observed in septic patients at early timepoints (t0–t2); beyond this interval, differences were no longer statistically significant. In our cohort, admission MR-proADM levels showed a potential role in supporting the clinical assessment of sepsis at the time of ICU entry.

As previously stated in the introduction, the decision to correlate admission MR-proADM with the 24-hour SOFA score was based on the hypothesis that this biomarker might serve as an early indicator of evolving organ dysfunction, given its equimolar release alongside ADM following endothelial damage [11-13, 15, 16]. Building on this premise, we aimed to explore the potential of MR-proADM to reflect the initial phases of organ impairment.

Our methodological focus on the timing of the SOFA score assessment was guided by two primary theoretical considerations. First, we reasoned that the 24-hour SOFA score might offer a more stabilized clinical picture compared to the admission score, which is often confounded by the variability of initial and pre-ICU resuscitation. Second, as the SOFA score often considered a lagging indicator, potentially requiring a sufficient time interval to manifest measurable changes, we hypothesized that it might not immediately reflect the full extent of an acute biological insult.

Within this framework, we hypothesized that an early biomarker such as MR-proADM might offer added value by signaling physiological and endothelial stress, before the derangement becomes clinically manifest through standard scoring systems. Therefore, early measurement of this biomarker might provide a 'biological window' into the initial phases of injury, potentially identifying risks before they are captured by conventional clinical tools.

Although the correlation observed did not reach the strength initially hypothesized, and the role of MR-proADM as an early indicator of subsequent dysfunction remains a preliminary observation in this cohort, further studies are warranted to provide definitive confirmation of these findings.

In this regard, it could be hypothesized that the heterogeneity of our study population partly contributed to these results. The inclusion of diverse clinical phenotypes—typical of a 'mixed' ICU setting, ranging from major trauma and neurological emergencies to hematological malignancies—may have introduced significant confounding variables. This clinical 'noise' might have diluted the overall statistical association compared to what could be observed in more homogeneous cohorts, potentially masking a stronger biological signal.

Notably, when analyzing the organ-specific components of the SOFA score, the most prominent cross-sectional correlations were identified within the cardiovascular and renal domains. These

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associations may find a clear pathophysiological correspondence in the expression of endothelial damage and impaired vascular integrity.

In critically ill patients, such microcirculatory distress often translates into hemodynamic instability and varying degrees of vasoplegia, alongside impaired glomerular filtration —pathophysiological hallmarks shared by sepsis, major surgical insult, systemic inflammation, and trauma.

As previously detailed, the elevation of ADM (and consequently its stable surrogate, MR-proADM) is biologically intuitive when considering the peptide's compensatory role in maintaining hemodynamic homeostasis. ADM functions to enhance vascular integrity and decrease permeability by stabilizing endothelial cell junctions. The widespread impact of this biological response is supported by the extensive distribution of ADM receptors across critical cell types—including endothelial cells, cardiomyocytes, macrophages, and dendritic cells—as well as within vital organs such as the heart, lungs, and kidneys [11, 17-19].

Within the renal microvasculature, ADM is expressed by glomerular endothelial cells during inflammatory states, potentially serving to preserve renal blood flow by dilating afferent arterioles and counteracting potent vasoconstrictors, such as endothelin-1.

Furthermore, as increased ADM expression has been associated with systemic cardioprotective and pro-angiogenic effects, its elevation could be hypothesized to reflect a compensatory homeostatic response aimed at mitigating the microvascular damage induced by systemic insults [17, 20].

From a hypothesis-generating perspective, these biological roles might provide a plausible framework to explain the correlations observed in our study between admission MR-proADM and the cardiovascular and renal components of the SOFA score [21, 22]. Our findings suggest the possibility that this biomarker could act as a surrogate for early-stage hemodynamic and filtration impairment; however, whether these correlations represent a direct clinical signal or a broader reflection of systemic stress is a question that remains to be addressed in larger, more homogeneous investigations.

Our analysis identified positive timepoint-specific associations between MR-proADM and PCT during the first five ICU days. These associations might suggest that both biomarkers reflect overlapping aspects of the systemic inflammatory response. However, their clinical roles may be read as complementary rather than redundant. While PCT is primarily influenced by bacterial load, MR-proADM levels should reflect more closely the degree of endothelial involvement, vascular permeability and microcirculatory impairment, which are key drivers of organ failure in sepsis.

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In this exploratory context, MR-proADM could offer additional insights into the patient's organ-level status, a dimension that may not be fully captured by PCT alone. [23,24] Nevertheless, given to the exploratory nature of this pilot study and the limited sample size, a formal comparative analysis of their diagnostic or predictive performance was not feasible. These comparative implications remain strictly hypothesis-generating and necessitate further validation to define their combined diagnostic or prognostic performance.

This potential physiological sensitivity of MR-proADM appears to align with preliminary prognostic findings observed in our cohort. Despite the low mortality rate (15.4%, n=4), which precludes any definitive prognostic conclusions, MR-proADM levels at admission were higher in non-survivors than in survivors. However, given the very limited number of mortality events (n=4), a reliable multivariable assessment of independent prognostic value was not feasible; therefore, these findings should be considered descriptive and no conclusion can be drawn regarding the independent prognostic value of MR-proADM beyond established clinical severity scores.

While the statistical power of this finding is critically limited by the small sample size and low event rate, the observed direction of the data tentatively parallels findings from larger multicenter studies. Such studies have proposed MR-proADM as a prognostic tool across various degrees of illness severity, including in emergency department settings. [25] In this context, our exploratory results could merely suggest the possibility that MR-proADM might offer a lead-time advantage on scores. However, given the substantial risk of statistical overestimation in our small sample, these prognostic implications remain speculative.

Our exploratory subgroup analysis further suggests the potential clinical utility of admission MR-proADM in septic patients. Within this small cohort, admission levels were notably higher in septic patients than in those with non-infectious systemic inflammation. These findings hint at the biomarker’s potential role as a supportive tool—when integrated with other clinical elements—for the early identification of sepsis during the critical initial hours of ICU admission. This could be particularly relevant in scenarios where differentiating sepsis from other forms of systemic inflammation remains a diagnostic challenge.

Nevertheless, these results must be interpreted with extreme caution. The limited subgroup size carries a substantial risk of statistical overestimation and mathematical overfitting. While the higher MR-proADM values observed in septic patients at early timepoints (t0–t2) might theoretically assist in risk stratification or clinical monitoring, these observations should be viewed as preliminary exploratory insights rather than definitive evidence. Our findings regarding the septic subgroup, although encouraging, necessitate validation to establish reliable diagnostic thresholds.

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This necessity aligns with current literature, which emphasizes that while MR-proADM is a promising tool, its optimal cut-off values may vary significantly depending on the clinical context and the patient's baseline endothelial reserve [25-28].

To provide a balanced interpretation of our findings, a comprehensive overview of the study's limitations—including those previously mentioned—is presented below.

The primary limitation of this study is the small sample size, which inherently carries a dual risk of statistical and mathematical error. First, as previously touched upon, there is a substantial risk of statistical overestimation and mathematical overfitting. In small cohorts, observed associations and effect sizes (such as ROC-AUC values or correlation coefficients) can be artificially inflated, potentially representing idiosyncratic features of this specific group rather than generalizable clinical truths. On the other hand, the limited number of subjects critically restricts the overall statistical power of our findings. This lack of power may account for the absence of statistical significance in certain cross-sectional correlation analyses. In addition, repeated measurements were analysed separately at each timepoint; therefore, these analyses should be interpreted as exploratory, timepoint-specific cross-sectional associations and do not allow conclusions regarding temporal evolution.

To ensure our findings reflect the everyday clinical reality of a mixed Intensive Care Unit, we intentionally opted for a heterogeneous study population encompassing sepsis, trauma, and neurological patients. However, we must acknowledge that this biological diversity represents a strong limitation of the study, as it introduces potential confounding factors: MR-proADM kinetics and baseline endothelial stress levels may indeed differ according to the primary underlying pathology. We considered performing additional subgroup analyses to explore these specific differences, however, the limited sample size rendered such stratification statistically unfeasible and prone to Type II errors. Consequently, while our mixed cohort provides a pragmatic overview of the biomarker, it limits our ability to draw isolated conclusions for distinct pathophysiological categories.

Furthermore, while our primary outcome focused on the correlation with the 24-hour SOFA score, we recognize that alternative endpoints, such as the progression of organ failure or specific requirements for organ support, might offer more direct clinical insights. Another constraint stemming from the retrospective nature of this work is the presence of missing data, particularly regarding serial PCT measurements at later time points. To maintain the integrity of the data and avoid introducing artificial bias, we chose not to apply any mathematical data imputation techniques. Consequently, analyses involving PCT were cautiously conducted only on the available

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cases. Moreover, the retrospective, single-center design of the study affects the generalizability of the data to different clinical settings and populations.

Lastly, a critical limitation resides in the low number of recorded events, especially regarding the mortality rate (4 events)—significantly restricts the statistical robustness of our prognostic findings. Although the difference in MR-proADM levels between survivors and non-survivors reached statistical significance this result must be interpreted with extreme caution.

Consequently, while our results provide interesting exploratory insights, they must be interpreted as preliminary and do not allow for definitive clinical recommendations at this stage.

CONCLUSION.

In conclusion, this exploratory study provides preliminary evidence suggesting that admission MR-proADM levels might serve as an early indicator of endothelial stress and early organ dysfunction in critically ill and septic patients. However, given the inherent limitations of our small cohort, the low number of mortality events and the exploratory nature of the analyses, these findings must be interpreted with extreme caution and should be regarded as strictly hypothesis-generating. The observed diagnostic and prognostic findings, while encouraging, require confirmation through larger, prospective, multicenter investigations.

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List of abbreviations:

- MR-proADM= Mid-regional pro-adrenomedullin
- *SOFA= Sequential Organ Failure Assessment*
- *APACHE= Acute Physiology and Chronic Health Evaluation*
- *SAPS= Simplified Acute Physiology Score*
- ICU=Intensive Care Unit
- PCT=Procalcitonin

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Declaration of interest statement:

The authors declare that they have no competing interests in relation to the submitted manuscript.

Ethics approval and consent to participate:

This retrospective observational study was approved by the local Ethics Committee (Comitato Etico Territoriale, approval number: CET 2024 202, ID 272781). Informed consent to participate in the study was obtained from all patients or, where indicated, from their legal representatives.

Consent for publication:

Not applicable. This manuscript does not contain any individual person's identifying data, details, or images.

Availability of data and material:

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest/Financial Disclosure:

The authors have nothing to disclose.

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Authors' contributions:

Domizi R, Donati A, Damiani E: study design.

Antolini R, Carsetti A, Moretti M, Calcinari A, Gabbanelli V, Compagnucci E, Adrario E: data collection and investigation

Domizi R, Damiani E: statistical analysis.

Domizi R, Damiani E, Casarotta E: manuscript preparation

All authors read and approved the final version.

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