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The value of midregional proadrenomedullin to predict mortality in intensive care unit

Luisa Agnello [a,1], Fabio Del Ben [b,1], Andrea Cortegiani [c], Giuseppe Biundo [d], Aurora Giglia [d], Caterina Maria Gambino [a,d], Marcello Ciaccio [a,d,*]

[a] Department of Biomedicine, Neurosciences and Advanced Diagnostics, Institute of Clinical Biochemistry, Clinical Molecular Medicine, and Clinical Laboratory Medicine, University of Palermo, Palermo, Italy
[b] Immunopathology and Cancer Biomarkers, Centro di Riferimento Oncologico (CRO)-IRCCS, Aviano, Italy
[c] Department of Anesthesia, Intensive Care and Emergency, University Hospital "P. Giaccone", Palermo, Italy
[d] Department of Laboratory Medicine, University Hospital Paolo Giaccone, Palermo, Italy

A B S T R A C T

Aim: This study explores the value of midregional proadrenomedullin (mr-proADM), C-reactive protein (CRP), procalcitonin (PCT), and presepsin (PSP) in predicting mortality, considering both their absolute values at different time points and their dynamic kinetics.
Methods: We conducted a retrospective observational study including all consecutive adult ICU admissions. Biomarkers were measured at admission (T0), day 3 (T3), and day 5 (T5). We assessed absolute values, relative variations, and categorized changes (≥50 % increase or decrease).
Results: A total of 99 patients were included. mr-proADM at T3 had the highest predictive value for ICU mortality (AUC = 0.77), followed by PSP at T3 (AUC = 0.70). Cox regression identified mr-proADM at T3 as an independent predictor of mortality (HR: 1.16, $p < 0.001$), with a ≥ 50 % increase in mr-proADM from T0 to T3 significantly associated with mortality risk (HR: 4.15, $p < 0.001$). In patients with low baseline mr-proADM levels, a ≥ 50 % increase at T3 was significantly associated with mortality (HR: 4.43, $p = 0.04$), while in those with high baseline levels, the absolute value at T3 was more predictive.
Conclusion: Our findings suggest that mr-proADM at T3 is the most informative biomarker for predicting ICU mortality, with its absolute value and dynamic increase providing valuable prognostic insights. Importantly, stratified analysis highlights that different risk stratification approaches may be necessary based on baseline mr-proADM levels.

1. Introduction

Mortality in intensive care unit (ICU) represents a global public health problem, ranging from 20 % to 40 % [1–3]. Assessing the prognosis of these patients is essential for guiding clinical decisions, optimizing resource utilization, and improving patient outcomes. Traditional scoring systems, such as the Acute Physiology and Chronic Health Evaluation (APACHE-II) and the Sequential Organ Failure Assessment (SOFA), are widely used for mortality prediction [4,5]. However, these systems have several limitations, including complexity, delayed assessment, and dependence on extensive clinical and laboratory evaluation. Indeed, APACHE-II requires 14 clinical variables, including physiological parameters, laboratory results, and chronic health conditions, all of which must be collected within the first 24 h of ICU admission. This process is time-consuming and requires trained personnel to ensure accurate data collection, making it challenging to implement in resource-limited settings or hospitals with high patient turnover. Similarly, SOFA, while less complex than APACHE-II, still requires repeated evaluation of six organ systems (respiratory, cardiovascular, liver, coagulation, renal, and neurological function). Additionally, both scoring systems have limitations in generalizability across different patient populations. APACHE-II was primarily developed using data from Western ICUs, and its performance may be less reliable in low- and middle-income countries, where resource availability and patient demographics differ significantly [6]. Thus, while APACHE-II and SOFA remain valuable tools for prognostic assessment in ICU patients, they have significant limitations. In the last decades, the value of biomarkers as powerful tools for real-time and individualized prognosis assessment in critically ill patients has emerged. Biomarkers offer dynamic insights into disease progression and may provide more timely and individualized risk assessments than traditional scoring systems.

In this study, we evaluated the predictive value of midregional

* Corresponding author at: Department of Biomedicine, Neurosciences and Advanced Diagnostics, Institute of Clinical Biochemistry, Clinical Molecular Medicine, and Clinical Laboratory Medicine, University of Palermo, Palermo, Italy.
E-mail address: marcello.ciaccio@unipa.it (M. Ciaccio).
[1] These authors contributed equally.

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proadrenomedullin (mr-proADM), C-reactive protein (CRP), procalcitonin (PCT), and presepsin (PSP), as absolute value at different time points during ICU stay and their dynamic kinetics, in forecasting mortality among critically ill patients in ICU. By analyzing the absolute value at different time points and temporal changes, we seek to determine the most reliable indicators of patient outcomes and improve prognostic capabilities in critical care settings.

2. Materials and Methods

2.1. Study design

This observational, retrospective, monocentric cohort study was performed at the University Hospital "P. Giaccone" of Palermo, Italy. The study protocol was approved by the Ethics Committee of the University Hospital of Palermo (nr 07/2019) and was performed in accordance with the current revision of the Helsinki Declaration. Each patient provided informed consent.

2.2. Study population

We included all consecutive adult patients admitted to the ICU of the University Hospital "P. Giaccone" of Palermo for any cause from February 2023 to July 2023. Sepsis was diagnosed according to the Sepsis-3 criteria [7]. Briefly, sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction is identified as an acute change in total SOFA score ≥ 2 points consequent to the infection [7]. The infection was defined according to clinical, imaging, and laboratory test findings. Exclusion criteria were: i) age < 18 years; ii) incomplete data collection; iii) < 5 days hospital stay.

Patients' demographic and clinical characteristics were retrospectively recorded from ICU admission to discharge.

2.3. Biochemical analysis

For each patient, we measured mr-proADM, CRP, PCT, and PSP at the following time points: T0 (at admission), T3 (3 days after admission), and T5 (5 days after admission). CRP and PCT were measured as part of the routine, while mr-proADM and PSP were measured for research purposes on stored samples.

mr-proADM and PCT levels were measured in plasma by the time-resolved amplified cryptate emission (TRACE) technology on the Brahms KRYPTOR fully automated analyzer (BRAHMS AG, Hennings-dorf, Germany). We chose a threshold of 2.75 nmol/L to discriminate patients into low and high group [8].

Plasma PSP levels were measured by a commercially available non-competitive chemiluminescent enzyme immunoassay combined with Magtration® technology using a point-of-care device. The method is optimized on an automated immunoassay analyzer (PATHFAST, Mitsubishi, Tokyo, Japan). Briefly, the sample is incubated with alkaline phosphatase labeled anti-presepsin polyclonal and monoclonal antibodies coated magnetic particles; after removing the unbound substances by Magtration® technology, a chemiluminescent substrate is added.

Serum CRP levels were measured by the latex-enhanced immunoturbidimetric assay on the fully automated platform Cobas 8000 (Roche Diagnostics International Ltd, Rotkreuz, Switzerland), according to the manufacturer.

2.4. Statistical analysis

Statistical analyses were performed by R Language v.4.0.3 (R Foundation for Statistical Computing, Vienna, Austria). Normality distribution was assessed preliminarily by q-q plot and Shapiro–Wilk test. Most variables were not normal, so descriptive statistics are shown as median (IQR). To analyze changes over time, we calculated the relative variation between a given time point (Tx) and baseline (T0) as (Tx − T0)/T0. We evaluated both the absolute values of these changes and categorized them as "increased" or "decreased" based on whether there was at least a 50 % change in either direction. The area under the curve (AUC) was calculated to evaluate the accuracy of biomarkers to predict ICU mortality. In the survival analysis, we adapted the scaling of biomarkers to account for their varying ranges, reporting hazard ratios (HRs) for CRP and PSP per 100-unit. The significance level was set to $p < 0.05$. Univariate and multivariate cox regression analysis were performed: due to the limited sample size, a multivariate analysis including all considered covariates would have resulted in low statistical power and potential overfitting. Therefore, we performed bivariate analyses for each pair of variables to explore their individual associations. Kaplan-Meier survival curves with patients at risk table are provided as a complement to survival analysis.

3. Results

3.1. Study population

We enrolled 99 patients with a median age of 70 years; 37 had sepsis at admission, 25 developed sepsis during ICU hospitalization, and 37 did not have sepsis (neither after admission nor during hospitalization). 41 patients died during ICU stay. The study population's demographic, clinical, and biochemical characteristics are described in Table 1.

3.2. Mortality prediction

An analysis of the AUC for ICU mortality revealed that several biomarkers measured at T5 exhibited the strongest predictive power. However, the clinical utility of T5 may be limited due to its late timing in the disease course. Among earlier time points, mrpro-ADM at T3 demonstrated the highest predictive value (AUC = 0.77), followed by

Table 1
Demographic, clinic, and biochemical characteristic of the study population. ICU, intensive care unit; CRP, C-reactive protein; PCT, procalcitonin; PSP, presepsin; mrpro-ADM, midregional-proadrenomedullin.

Variable	
Nr.	99
Sex, M	57 %
Admission	
Medical admission	63 %
Planned surgery	22 %
Unplanned surgery	12 %
Trauma	9 %
Coma or neurological diseases	6 %
Sepsis at admission	37 %
Sepsis during hospitalization	26 %
ICU stays, days	12
ICU mortality	42 %
APACHEII score	27 (16–29)
SOFA score	10 (8–12)
Biomarkers at T0	
CRP, mg/L	140 (181.25)
PCT, ng/mL	1.66 (9.49)
PSP, pg/mL	982 (1256)
mrpro-ADM, nmol/L	2.90 (4.05)
Biomarkers at T3	
CRP, mg/L	131 (125.80)
PCT, ng/mL	1.27 (4.50)
PSP, pg/mL	1044 (1944)
mrpro-ADM, nmol/L	2.45 (4.10)

PSP at T3 (AUC = 0.70).

In survival analysis, biomarkers were scaled to account for their varying ranges, with hazard ratios (HRs) reported per 100-unit increase for CRP and PSP. Univariate Cox regression identified T3 as the time point with the highest HR for mrpro-ADM, CRP, and PSP, while PCT showed similar HRs at T0 and T3 (Table 2 shows only statistically significant data).

Among dynamic measurements assessing biomarker changes, mrpro-ADM increase at T3 exhibited the highest HR, followed by PCT increase at T3. Conversely, a PCT decrease at T3 was associated with a strongly protective HR, highlighting its potential relevance as a prognostic indicator.

These findings underscore that T3 is the most informative time point for predicting mortality, with both mrpro-ADM level and its increase potentially providing valuable prognostic information. Interestingly, the presence of sepsis at ICU admission was not associated with survival.

3.3. Multivariate analysis

A Cox proportional hazards model was employed to assess the independent prognostic value of mr-proADM measurements in various scenarios: baseline (T0), follow-up (T3), and the presence of a significant increase (≥50 %). The analysis controlled for age, PCT, CRP, and PSP.

At baseline, mr-proADM levels were found to be significantly and independently associated with mortality when adjusted for age and creatinine, with an HR of 1.05 (95 % CI: 1.00–1.10, p = 0.03), indicating a 5 % increase in mortality risk per unit increase in mr-proADM. Age was also independently associated with mortality, with an HR of 1.03 (95 % CI: 1.00–1.07, p = 0.03). Associations with other covariates, including PCT, CRP, and PSP did not reach statistical thresholds (Table 3).

At T3, mr-proADM demonstrated a stronger independent association with mortality, with an HR of 1.15 (95 % CI: 1.08–1.21, p < 0.001). Notably, at this time point, mr-proADM absorbed the information provided by other variables (age, PCT, and PSP) with only CRP maintaining an independent association (HR: 1.45, 95 % CI: 1.04–2.02, p = 0.03).

Testing the prognostic value of a ≥ 50 % increase in mr-proADM did not yield additional predictive information, as the increase itself was not independently associated with mortality (HR: 1.85, 95 % CI: 0.71–4.86, p = 0.21). This could potentially be attributed to heterogeneity between individuals with low and high baseline mr-proADM levels, necessitating further stratified analysis (Table 4).

3.4. Stratified analysis by baseline mr-proADM levels

To account for differences in baseline mr-proADM levels, the cohort was stratified into two groups: individuals with low baseline mr-proADM (<2.75 nmol/L) and those with higher levels (≥2.75 nmol/L).

In the low baseline group (<2.75 nmol/L), a ≥ 50 % increase in mr-proADM was significantly associated with mortality (HR: 4.43, 95 % CI: 1.10–17.9, p = 0.04). However, the absolute value of mr-proADM at T3 was not significantly associated with outcomes (HR: 1.06, 95 % CI: 0.94–1.19, p = 0.34).

In the high baseline group (≥2.75 nmol/L), for individuals with higher baseline mr-proADM, the absolute value at T3 was significantly associated with mortality (HR: 1.15, 95 % CI: 1.02–1.30, p = 0.02). Conversely, a ≥ 50 % increase in mr-proADM did not demonstrate a significant association with mortality (HR: 1.71, 95 % CI: 0.43–6.80, p = 0.44). Results are shown in Table 5.

To summarize findings, baseline mr-proADM levels provide an initial stratification for mortality risk. mr-proADM at T3 provides an additional, improved stratification, irrespectively of baseline levels; however, in stratified analysis emerges as a meaningful marker only in patients starting with high baseline mr-proADM values. At the same time, in patients starting with low baseline mr-proADM values, a ≥ 50 % increase of mr-proADM at T3, rather than the absolute level of mr-proADM at T3, is more meaningful for assessing mortality risk.

3.5. Kaplan-Meier survival analysis

Complementing the multivariate Cox proportional hazards model, Kaplan-Meier survival curves were constructed to evaluate the visual impact of mr-proADM levels on mortality.

Survival curves were generated for individuals stratified into low (<2.75 nmol/L) and high baseline mr-proADM (≥2.75 nmol/L) (Fig. 1). The curves demonstrate significantly reduced survival for patients with high baseline levels (log-rank test, p < 0.01).

Survival curves based on mr-proADM values at T3 highlighted that also patients with high T3 values exhibited significantly worse survival outcomes (log-rank test, p < 0.001) (Fig. 2). For patients with baseline

Table 2
Univariate analysis. *Statistically significant values are indicated with asterisks (* p < 0.05, ** p < 0.001).

	HR (95 % CI)	pValue
mr-proADM T0	1.06 (1.01 – 1.11)	0.010*
mr-proADM T3	1.16 (1.10 – 1.23)	<0.0001**
mr-proADM T0-T3 increase	4.15 (1.97 – 8.75)	<0.0001**
PCT T0	1.01 (1 – 1.02)	0.037*
PCT T3	1.01 (1 – 1.02)	0.022*
PCT T0 – T3 increase	1.87 (1.01 – 3.5)	0.048*
PCT T0 – T3 decrease	0.35 (0.17 – 0.73)	0.005*
PSP T3	1.02 (1.01 – 1.06)	<0.0001**
PSP T5	1.02 (1.01 – 1.03)	<0.0001**
CRP T3	1.69 (1.27 – 2.25)	<0.0001**
CRP T5	1.67 (1.27 – 2.18)	<0.0001**
Age	1.03 (1.01 – 1.06)	0.018*

Table 3
Cox Regression analysis at baseline (T0). *Statistically significant values are indicated with asterisks (* p < 0.05, ** p < 0.001).

	HR (95 % CI)	p-value
mr-proADM	1.05 (1.00–1.10)	0.03*
Age	1.03 (1.00–1.07)	0.03*
PCT	1.01 (1.00–1.02)	0.24
CRP	1.10 (0.80–1.50)	0.55
PSP	1.00 (0.97–1.02)	0.82

Table 4
Cox Regression analysis at follow-up (T3).

	HR (95 % CI)	p-value
mr-proADM	1.14 (1.08–1.21)	<0.001**
Age	1.02 (0.99–1.06)	0.12
PCT	1.00 (0.99–1.01)	0.96
CRP	1.45 (1.04–2.02)	0.03*
PSP	1.01 (0.99–1.03)	0.13
50 % Increase	1.85 (0.71–4.86)	0.21

Statistically significant values are indicated with asterisks (p < 0.05, ** p < 0.001).

Table 5
Stratified Analysis by Baseline mr-proADM Levels.

Group	Variable	HR (95 % CI)	p-value
Low Baseline T0 (<2.75 nmol/L)	mr-proADM T3	1.06 (0.94–1.19)	0.34
	50 % Increase	4.43 (1.10–17.9)	0.04*
High Baseline T0 (≥2.75 nmol/L)	mr-proADM T3	1.15 (1.02–1.30)	0.02*
	50 % Increase	1.71 (0.43–6.80)	0.44

* Statistically significant values are indicated with asterisks (* p < 0.05).

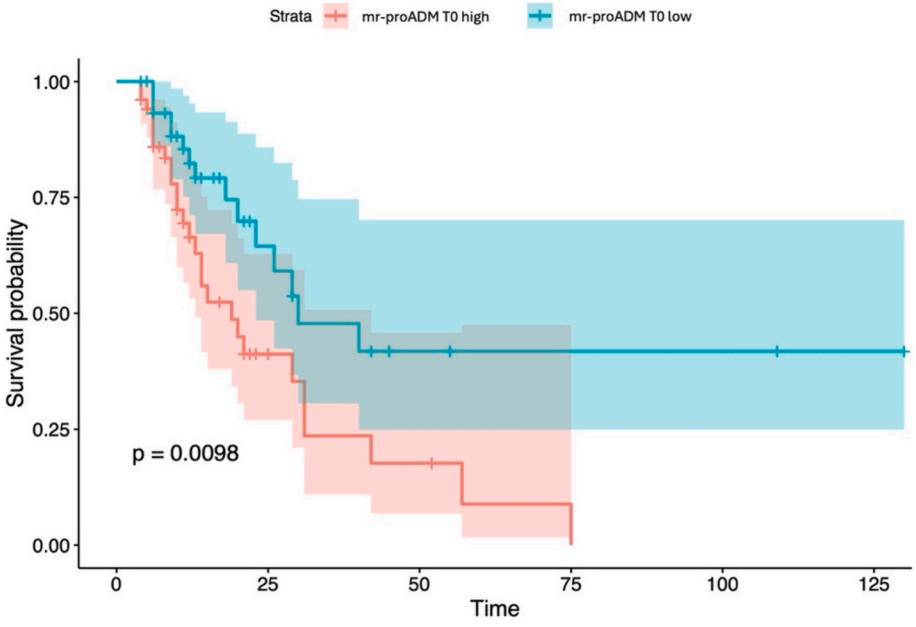

Fig. 1. Kaplan-Meier curve stratified according to mr-proADM at T0.

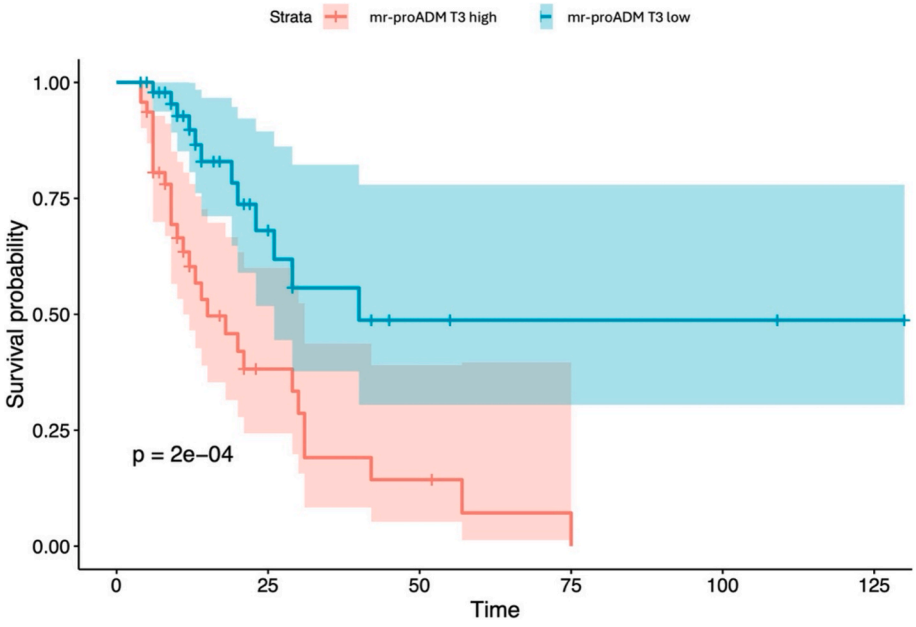

Fig. 2. Kaplan-Meier curve stratified according to mr-proADM at T3.

mr-proADM < 2.75 nmol/L, a significant association between a ≥ 50 % increase in mr-proADM and reduced survival can be appreciated (log-rank test, $p < 0.0001$) (Fig. 3).

4. Discussion

In this study, we evaluated the performance of different biomarkers as absolute values and their kinetic to predict mortality in critically ill patients. The main findings of our study can be summarized as follows: i) at baseline, mr-proADM levels were significantly and independently associated with mortality, with a 5% increase in mortality risk per unit increase in mr-proADM levels; ii) at T3, mr-proADM demonstrated the highest predictive value, with an AUC of 0.77, followed by PSP, with AUC of 0.70; iii) when stratifying patients in low and high mr-proADM levels at baseline, using 2.75 nmol/L as cut point, in patients with low levels of mr-proADM, a ≥ 50 % increase in mr-proADM was significantly associated with mortality (HR: 4.43). Thus, our findings suggest that baseline mr-proADM levels provide an initial stratification for mortality risk in critically ill patients. T3 is the most informative time point for predicting mortality, with both mrpro-ADM level and its increase providing valuable prognostic information. Noteworthy, in patients with low baseline mr-proADM values, a ≥ 50 % increase of mr-proADM at T3, rather than the absolute level of mr-proADM at T3, is more meaningful for assessing mortality risk.

This is the first study that shows the value of assessing the temporal change in mr-proADM levels during hospitalization in predicting mortality in critically ill patients. Elke et al. explored the value of mr-proADM to identify disease severity in patients with sepsis considering both absolute concentrations and dynamic variation of mr-proADM during ICU hospitalization [9]. They found that the presence of

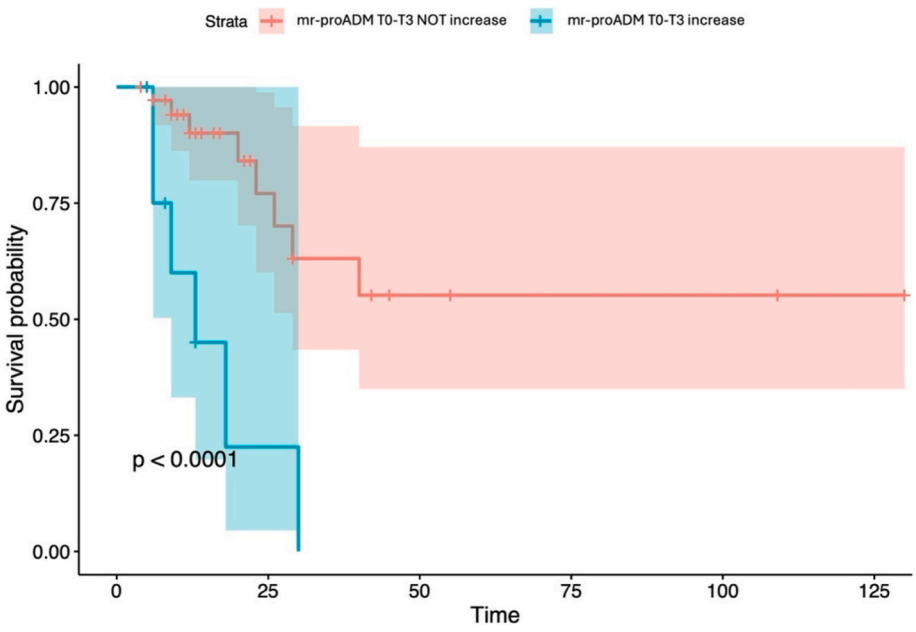

Fig. 3. Kaplan-Meier curve stratified for mr-proADM increase from T0 to T3.

continuously elevated or increasing mr-proADM concentration were indicative of poor overall outcome. Julián-Villaverde et al. analyzed the time variation of mature adrenomedullin in intracerebral hemorrhage patients [10]. The authors showed that the dynamic changes in adrenomedullin levels over time have prognostic implications, with an initial increase followed by a return to baseline being associated with favorable outcomes. These studies highlights the potential importance of temporal dynamics in biomarker interpretation, in accordance with our findings.

mr-proADM is a surrogate biomarker of adrenomedullin, which is a peptide hormone with vasodilatory, anti-inflammatory, and anti-apoptotic properties, playing a critical role in maintaining vascular integrity and homeostasis [11–16]. However, due to its short half-life and rapid clearance, direct measurement of ADM is challenging. Instead, mr-proADM is a stable fragment derived from the precursor molecule proadrenomedullin, released in 1:1 ratio with adrenomedullin. Thus, mr-proADM represents a valuable biomarker for assessing vascular integrity. Increased levels indicate endothelial dysfunction, a key determinant of disease severity in critically ill patients. Several authors described the prognostic value of mr-proADM in different clinical conditions, including pneumonia, myocardial infarction, and sepsis [17–19]. Nevertheless, only a few authors have explored the potential of mr-proADM as a prognostic tool in critically ill patients, independently of the underpinning disease.

In this study, we also evaluated the performance of CRP and PCT, which are widely used in the ICU to monitor critically ill patients and the emerging biomarker PSP.

CRP is an acute-phase protein synthesized primarily in the liver in response to infection, tissue injury, or chronic disease conditions, whose levels increase during several physiological and pathological conditions [20]. PCT is the precursor of the hormone calcitonin produced systemically in response to bacterial infection. Guidelines recommend its use in antibiotic stewardship and differentiating bacterial and viral infections [21,22]. In this study, CRP and PCT were independently associated with mortality at T3. However, compared to mr-proADM, their predictive power was relatively lower. This is consistent with prior studies suggesting that CRP and PCT alone may not be sufficient for mortality prediction in critically ill patients, but their value is strongest only in patients with sepsis [23–25].

PSP, also known as soluble CD14 subtype (sCD14-ST), was discovered about 20 years ago in Japan [26]. CD14 is a Toll-like receptor (TLR) family member expressed on the surface of myeloid-derived cells, including monocytes, macrophages, and dendritic cells. It plays a vital role in recognizing Gram-positive and Gram-negative bacteria ligands, thus initiating the inflammatory response [27]. Recent studies indicate that CD14 is involved in the phagocytic clearance of apoptotic cells [28]. CD14 exists in two forms: (i) anchored to the membrane of monocytes/macrophages (mCD14), and (ii) soluble in plasma/serum (sCD14) [29]. The soluble form results from the shedding of mCD14 from immune cells. Membrane CD14 functions as a receptor for lipopolysaccharides (LPS), transferring LPS to the cell surface receptor CD14 in conjunction with LPS-binding protein (LBP), ultimately triggering monocyte activation through proinflammatory signaling pathways. sCD14 also mediates immune responses in CD14-negative endothelial and epithelial cells. Under inflammatory conditions, sCD14 is cleaved in plasma, producing PSP (sCD14-ST), a 13kDa N-terminal fragment. PSP is generated when phagocytes engulf bacteria during sepsis, leading to the internalization and degradation of CD14 by neutrophil elastase. Due to its high specificity as a sepsis biomarker and its short half-life (~4 h), PSP is useful for the early detection of sepsis [30]. Beyond its role as a biomarker of bacterial sepsis, Ikegame et al. have recently hypothesized a mechanism of production that does not involve bacterial phagocytosis. [28,31]. In an *in vitro* study, the authors showed that neutrophil extracellular traps (NETs) induce PSP production in monocytes/macrophages. NETs are web-like structures composed of DNA, histones, and antimicrobial proteins released by neutrophils as part of the innate immune response. This unique defense mechanism, known as NETosis, helps trap and neutralize invading pathogens such as bacteria, fungi, and viruses. Notably, an imbalance in immune responses can lead to the uncontrolled release of NETs, causing excessive inflammation and damage to host tissues beyond their antimicrobial role, thereby contributing to the development of various diseases [32]. NETs have been independently associated with disseminated intravascular coagulation and mortality in critically ill patients [33]. To date, most authors have focused on the role of PSP as a biomarker of sepsis in different clinical scenarios. Based on the recent discovery of the role of PSP, we tested the hypothesis that it could serve as a biomarker of mortality prediction in critically ill patients, independently of sepsis [34,35]. We found that PSP measured after 72hr of ICU admission was associated with an increased mortality.

This study provides significant insights into biomarkers' prognostic

utility contributing to the growing body of literature exploring biomarker-driven approaches in critical care.

Some limitations of the study should be mentioned. First, this was a single-center retrospective study, which may limit generalizability to other ICU populations. Second, although we identified significant associations between biomarker kinetics and mortality, larger multicenter prospective studies are needed to validate these findings and determine optimal cut-off values for clinical application. Additionally, integrating biomarker-based prognostic models with machine learning algorithms could further refine risk stratification and enhance real-time clinical decision-making. Finally, we did not record the body mass index (BMI) and diabetes of patients, thus, we cannot exclude the influence of these conditions on mr-proADM levels. However, only 10 % of patients admitted in ICU are obese and 25 % have diabetes.

CRediT authorship contribution statement

Luisa Agnello: Writing – original draft, Data curation, Conceptualization. **Fabio Del Ben:** Writing – original draft, Investigation, Data curation. **Andrea Cortegiani:** Validation, Investigation, Conceptualization. **Giuseppe Biundo:** Formal analysis, Data curation. **Aurora Giglia:** Formal analysis, Data curation. **Caterina Maria Gambino:** Writing – review & editing, Formal analysis. **Marcello Ciaccio:** Writing – review & editing, Validation, Supervision, Conceptualization.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

References

[1] A. Oliveira, T. Vieira, A. Rodrigues, N. Jorge, L. Tavares, L. Costa, et al., Critically ill patients with high predicted mortality: Incidence and outcome, Med Intensiva (engl Ed). 48 (2024) 85–91, https://doi.org/10.1016/j.medine.2023.11.001.

[2] H. Vallet, B. Guidet, A. Boumendil, D.W. De Lange, S. Leaver, W. Szczeklik, et al., The impact of age-related syndromes on ICU process and outcomes in very old patients, Ann Intensive Care. 13 (2023) 68, https://doi.org/10.1186/s13613-023-01160-7.

[3] T.B. Demass, A.G. Guadie, T.B. Mengistu, Z.A. Belay, A.A. Melese, A.A. Berneh, et al., The magnitude of mortality and its predictors among adult patients admitted to the Intensive care unit in Amhara Regional State, Northwest Ethiopia, Sci Rep. 13 (2023) 12010, https://doi.org/10.1038/s41598-023-39190-7.

[4] H. Mumtaz, M.K. Ejaz, M. Tayyab, L.I. Vohra, S. Sapkota, M. Hasan, et al., APACHE scoring as an indicator of mortality rate in ICU patients: a cohort study, Ann Med Surg (lond). 85 (2023) 416–421, https://doi.org/10.1097/MS9.0000000000000264.

[5] K. Aggrawal, S. Verma, M.T. Stoltzfus, B. Singh, F. Anamika, R. Jain, Tools for Screening, Predicting, and Evaluating Sepsis and Septic Shock: A Comprehensive Review, Cureus. 16 (2024) e67137, https://doi.org/10.7759/cureus.67137.

[6] R. Haniffa, A. Pubudu De Silva, P. Weerathunga, M. Mukaka, P. Athapattu, S. Munasinghe, et al., Applicability of the APACHE II model to a lower middle income country, J Crit Care. 42 (2017) 178–183, https://doi.org/10.1016/j.jcrc.2017.07.022.

[7] M. Singer, C.S. Deutschman, C.W. Seymour, M. Shankar-Hari, D. Annane, M. Bauer, et al., The Third international consensus definitions for sepsis and septic shock (sepsis-3), JAMA 315 (2016) 801–810, https://doi.org/10.1001/jama.2016.0287.

[8] P. Bima, G. Montrucchio, V. Caramello, F. Rumbolo, S. Dutto, S. Boasso, A. Ferraro, L. Brazzi, E. Lupia, A. Boccuzzi, G. Mengozzi, F. Morello, S. Battista, et al., Prognostic value of mid-regional proadrenomedullin sampled at presentation and after 72 hours in septic patients presenting to the emergency department: an observational two-center study, Biomedicines. 10 (2022) 719, https://doi.org/10.3390/biomedicines10030719.

[9] G. Elke, F. Bloos, D.C. Wilson, F.M. Brunkhorst, J. Briegel, K. Reinhart, M. Loeffler, S. Kluge, A. Nierhaus, U. Jaschinski, O. Moerer, A. Weyland, P. Meybohm, et al., The use of mid-regional proadrenomedullin to identify disease severity and treatment response to sepsis - a secondary analysis of a large randomised controlled trial, Crit Care. 22 (2018) 79, https://doi.org/10.1186/s13054-018-2001-5.

[10] F.J. Julián-Villaverde, L. Ochoa-Callejero, E. Siles, E. Martínez-Lara, A. Martínez, Adrenomedullin is a diagnostic and prognostic biomarker for acute intracerebral hemorrhage, Curr Issues Mol Biol. 43 (2021) 324–334, https://doi.org/10.3390/cimb43010027.

[11] B. Lo Sasso, C.M. Gambino, N. Scichilone, R.V. Giglio, G. Bivona, C. Scazzone, et al., Clinical Utility of Midregional Proadrenomedullin in Patients with COVID-19, Lab Med. 52 (2021) 493–498, https://doi.org/10.1093/labmed/lmab032.

[12] A. Erriquez, G. Campo, V. Guiducci, J. Escaned, R. Moreno, G. Casella, et al., Complete vs Culprit-Only Revascularization in Older Patients With Myocardial Infarction and High Bleeding Risk: A Randomized Clinical Trial, JAMA Cardiol. 9 (2024) 565–573, https://doi.org/10.1001/jamacardio.2024.0804.

[13] L. Agnello, G. Bivona, E. Parisi, G.D. Lucido, A. Iacona, A.M. Ciaccio, et al., Presepsin and Midregional Proadrenomedullin in Pediatric Oncologic Patients with Febrile Neutropenia, Lab Med. 51 (2020) 585–591, https://doi.org/10.1093/labmed/lmaa011.

[14] C. Bellia, L. Agnello, B. Lo Sasso, G. Bivona, M.S. Raineri, A. Giarratano, et al., Mid-regional pro-adrenomedullin predicts poor outcome in non-selected patients admitted to an intensive care unit, Clin Chem Lab Med. 57 (2019) 549–555, https://doi.org/10.1515/cclm-2018-0645.

[15] S. Martínez-Herrero, A. Martínez, Adrenomedullin: Not Just Another Gastrointestinal Peptide, Biomolecules 12 (2022) 156, https://doi.org/10.3390/biom12020156.

[16] L. Bálint, N.P. Nelson-Maney, Y. Tian, S.D. Serafin, K.M. Caron, Clinical Potential of Adrenomedullin Signaling in the Cardiovascular System, Circ Res. 132 (2023) 1185–1202, https://doi.org/10.1161/CIRCRESAHA.123.321673.

[17] E. Valeriani, A. Falletta, D. Pastori, A. Porfidia, C.M. Mastroianni, S. Di Bari, et al., Midregional-proAdrenomedullin as a prognostic tool in sepsis and septic shock: A systematic review and meta-analysis, Eur J Clin Invest. 54 (2024) e14225, https://doi.org/10.1111/eci.14225.

[18] M.F. Yuyun, H.K. Narayan, L.L. Ng, Prognostic significance of adrenomedullin in patients with heart failure and with myocardial infarction, Am J Cardiol. 115 (2015) 986–991, https://doi.org/10.1016/j.amjcard.2015.01.027.

[19] D. Liu, L. Xie, H. Zhao, X. Liu, J. Cao, Prognostic value of mid-regional pro-adrenomedullin (MR-proADM) in patients with community-acquired pneumonia: a systematic review and meta-analysis, BMC Infect Dis. 16 (2016) 232, https://doi.org/10.1186/s12879-016-1566-3.

[20] S. Bhattacharya, C. Munshi, Biological significance of C-reactive protein, the ancient acute phase functionary, Front Immunol. 14 (2023) 1238411, https://doi.org/10.3389/fimmu.2023.1238411.

[21] A.B. Chambliss, K. Patel, J.M. Colón-Franco, J. Hayden, S.E. Katz, E. Minejima, et al., AACC Guidance Document on the Clinical Use of Procalcitonin, J Appl Lab Med. 8 (2023) 598–634, https://doi.org/10.1093/jalm/jfad007.

[22] C. Lelubre, S. Anselin, K. Zouaoui Boudjeltia, P. Biston, M. Piagnerelli, Interpretation of C-reactive protein concentrations in critically ill patients, Biomed Res Int. (2013) 124021, https://doi.org/10.1155/2013/124021.

[23] R. Qu, L. Hu, Y. Ling, Y. Hou, H. Fang, H. Zhang, et al., C-reactive protein concentration as a risk predictor of mortality in intensive care unit: a multicenter, prospective, observational study, BMC Anesthesiol. 20 (2020) 292, https://doi.org/10.1186/s12871-020-01207-3.

[24] I. Kılınç Toker, A. Çelik, H. Turunç Özdemir, D. Sağlam, M. Koçer, M. Eşlik, I. Toker, The value of C-reactive protein velocity (CRPv) on mortality in sepsis patients who are emergently hospitalized in the ICU: A retrospective single-center study, Heliyon. 10 (2024) e38797, https://doi.org/10.1016/j.heliyon.2024.e38797.

[25] Y.H. Huang, C.J. Chen, S.C. Shao, C.H. Li, C.H. Hsiao, K.Y. Niu, C.C. Yen, Comparison of the Diagnostic Accuracies of Monocyte Distribution Width, Procalcitonin, and C-Reactive Protein for Sepsis: A Systematic Review and Meta-Analysis, Crit Care Med. 51 (2023) e106–e114, https://doi.org/10.1097/CCM.0000000000005820.

[26] Y. Yaegashi, S. Endo, H.T. Inada, et al., Soluble CD14 subtype as a new diagnostic marker of sepsis, Shock 21 (2004) 108.

[27] A. Ciesielska, M. Matyjek, K. Kwiatkowska, TLR4 and CD14 Trafficking and Its Influence on LPS-Induced pro-Inflammatory Signaling, Cell Mol Life Sci. 78 (2021) 1233–1261.

[28] A. Ikegame, A. Kondo, K. Kitaguchi, K. Sasa, M. Miyoshi, Presepsin production in monocyte/macrophage-mediated phagocytosis of neutrophil extracellular traps, Sci Rep. 12 (2022) 5978, https://doi.org/10.1038/s41598-022-09926-y.

[29] M.O. Labeta, R. Landmann, J.P. Obrecht, R. Obrist, Human B cells express membrane-bound and soluble forms of the CD14 myeloid antigen, Mol Immunol. 28 (1991) 115–122, https://doi.org/10.1016/0161-5890(91)90094-z.

[30] P. Formenti, M. Gotti, F. Palmieri, S. Pastori, V. Roccaforte, A. Menozzi, et al., Presepsin in Critical Illness: Current Knowledge and Future Perspectives, Diagnostics (basel). 14 (2024) 1311, https://doi.org/10.3390/diagnostics14121311.

[31] T. Paraskevas, C. Chourpiliadi, S. Demiri, C. Micahilides, E. Karanikolas, M. Lagadinou, et al., Presepsin in the diagnosis of sepsis, Clin Chim Acta. 550 (2023) 117588, https://doi.org/10.1016/j.cca.2023.117588.

[32] A. Hidalgo, P. Libby, O. Soehnlein, I.V. Aramburu, V. Papayannopoulos, C. Silvestre-Roig, Neutrophil extracellular traps: from physiology to pathology, Cardiovasc Res. 118 (2022) 2737–2753, https://doi.org/10.1093/cvr/cvab329.

[33] S.T. Abrams, B. Morton, Y. Alhamdi, M. Alsabani, S. Lane, I.D. Welters, et al., A Novel Assay for Neutrophil Extracellular Trap Formation Independently Predicts Disseminated Intravascular Coagulation and Mortality in Critically Ill Patients, Am J Respir Crit Care Med. 200 (2019) 869–880, https://doi.org/10.1164/rccm.201811-2111OC.

[34] H.S. Yang, M. Hur, A. Yi, H. Kim, S. Lee, S.N. Kim, Prognostic value of presepsin in adult patients with sepsis: Systematic review and meta-analysis, PLoS One 13 (2018) e0191486, https://doi.org/10.1371/journal.pone.0191486.

[35] J. Zhang, Z.D. Hu, J. Song, J. Shao, Diagnostic Value of Presepsin for Sepsis: A Systematic Review and Meta-Analysis, Medicine (Baltimore) 94 (2015) e2158.