ORIGINAL ARTICLE

Prognostic value of midregional proadrenomedullin in critically ill patients

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KEY WORDS

acute kidney injury, APACHE II, midregional proadrenomedullin, mortality, SOFA

ABSTRACT

INTRODUCTION Scoring systems can be used to predict the risk of mortality and outcomes in critically ill patients. Acute kidney injury (AKI) is one of the strongest factors negatively influencing patient outcomes. Midregional proadrenomedullin (MR-proADM) shows promising results as an outcome predictor in patients with sepsis.

OBJECTIVES We aimed to evaluate the value of MR-proADM in incident AKI and mortality prognostication among patients admitted to the intensive care unit (ICU) in comparison with commonly used scoring systems.

PATIENTS AND METHODS Our study included a single-center cohort of 77 patients admitted to the ICU. Plasma MR-proADM levels were measured within 24 h of admission. The Acute Physiology and Chronic Health Evaluation II (APACHE II) and the Sequential Organ Failure Assessment (SOFA) scores were used as a reference. The primary endpoints were incident AKI and in-hospital mortality.

RESULTS Patients who died during hospitalization period had a higher MR-proADM concentrations as compared with patients who survived (2592.5 pg/ml vs 995.3 pg/ml; $P < 0.001$). The levels of MR-proADM correlated positively with the APACHE II or SOFA score ($r = 0.3$; $P = 0.004$ and $r = 0.3$; $P = 0.008$, respectively). In the receiver operating characteristics analysis, MR-proADM concentration was superior to both scoring systems ($P = 0.002$ and $P = 0.001$, respectively). In univariate logistic regression, MR-proADM was associated with in-hospital mortality (odds ratio [OR], 1.22; 95% CI, 1.11–1.35 per 100 pg/ml increase of MR-proADM) and after adjusting for multiple variables remained an independent predictor of death (OR, 1.35; 95% CI, 1.22–1.49 per 100 pg/ml increase of MR-proADM). MR-proADM was not useful in predicting incident AKI.

CONCLUSIONS MR-proADM can be applied in clinical practice as a prognostic tool for mortality but not incident AKI in the general ICU population with at least similar accuracy as APACHE II and SOFA scores.

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INTRODUCTION In patients admitted to intensive care units (ICUs), early diagnosis and stratification is essential for the initiation of appropriate treatment. A shorter time to effective intervention is an important outcome predictor for severely ill patients. Time is pivotal in the management of sepsis, pneumonia, stroke, and myocardial infarction. Possible delay may result in unfavorable outcomes. With growing position of ICUs in hospitals worldwide, it is important to embrace early support measures that improve patient outcomes. Stratification of patients in the ICU is crucial, hence the introduction of various triage tools. They stratify patients based on physiological measurements, vital signs, and routine blood tests. Commonly used scales are Sequential Organ Failure Assessment (SOFA) to establish the presence of organ damage and to identify patients with sepsis,[1] and Acute Physiology and Chronic Health Evaluation II (APACHE II) to determine the severity of the disease and adverse outcomes in patients requiring intensive care.[2] Noteworthy, acute kidney injury (AKI) is one of the strongest factors negatively influencing patient outcomes. It occurs in up to 30% of critically ill patients[3,4] and is associated with 50% to 80% mortality rate.[5-7]

Proadrenomedullin is a precursor for adrenomedullin (ADM), a member of the calcitonin

WHAT'S NEW?

A universal marker of multiorgan dysfunction is the "holy grail" of intensivists, since patients admitted to the intensive care unit (ICU) present a wide range of disorders. Midregional proadrenomedullin (MR-proADM) shows promising results as an outcome predictor in patients with sepsis. In our study, we evaluated the value of MR-proADM in incident acute kidney injury and mortality prognostication among patients admitted to the ICU in comparison with commonly used scoring systems. Our study revealed the utility of MR-proADM in prognostication of mortality in critically ill patients extending the scope of its application to the whole ICU population. A single measurement of MR-proADM assessed within 24 h of admission allowed early detection of patients at risk for unfavorable outcome, which may enable appropriate utilization of resources to improve the outcome.

peptide family similar to procalcitonin. Adrenomedullin is widely expressed in tissues, including bone, adrenal cortex, kidney, lung, heart, blood vessels, adipose, anterior pituitary, thalamus, and hypothalamus tissues.[8] In the kidneys, ADM was detected in glomeruli as well as cortical, distal, and medullary collecting tubules.[8] Its biological effects include vasodilatation, immune modulation, and metabolic regulation (ie, diuretic, natriuretic impact).[9] Tissues release ADM in response to physiological stress or infection[10] and its high levels have been described in sepsis, hypertension, renal failure, respiratory failure, and cancer.[11-13] Unfortunately, detecting ADM by a standard immunoassay is cumbersome due to its very short half-life of 22 minutes[14] and its binding to complement factor H.[15] Therefore, its more stable midregional fragment is determined in clinical practice. Midregional proadrenomedullin (MR-proADM) reflects ADM concentration in blood as it is cleaved from the precursor molecule in equimolar amounts.[15]

Several studies found that elevated MR-proADM levels are associated with disease severity and outcome in patients with community-acquired pneumonia,[16] sepsis,[17] heart failure,[18,19] and myocardial infarction.[20] Moreover, ADM is elevated in the early stages of chronic kidney disease (CKD) and is highly predictive of its progression in patients without diabetes,[12] suggesting that plasma levels may depend largely on renal function. Also, MR-proADM levels rise up in patients with CKD (both nondialyzed[21] and dialyzed)[22] and decrease significantly after kidney transplantation.[23] The responsible mechanism is not clear. Both increased secretion of MR-proADM in cardiac ventricles and the vascular endothelium in patients with CKD and cardiovascular disease[22] as well as decreased clearance[23] are suggested. Up to now, there is scarce data regarding utility of MR-proADM in predicting incident AKI.

The present study was designed to evaluate the value of MR-proADM in incident AKI and mortality prognostication among patients admitted to the ICU. Additionally, we compared the effectiveness of MR-proADM measurements and other commonly used scoring systems in predicting patient outcomes.

PATIENTS AND METHODS

Study design and population The present study is a secondary analysis of the frozen blood samples from a previously reported single-center cohort study performed in patients admitted to the ICU.[24]

Patients were recruited from consecutive individuals admitted to the ICU. Patients younger than 18 years of age, dialyzed, or pregnant were excluded. Moreover, patients with serum creatinine levels higher than 1.5 mg/dl at the moment of admission were also excluded because our aim was to focus on incident AKI, and data from patients with CKD might cause possible misinterpretation of the results. All study participants were treated in accordance with relevant guidelines and literature.

Test methods Blood samples were collected at baseline (within 24 h of admission to the ICU), centrifuged, aliquoted, and frozen at –70°C until assayed. The plasma MR-proADM level, which was our index test, was measured using the enzyme-linked immunosorbent assay (ELISA) kit (Human midregional proadrenomedullin ELISA Kit, Mybiosource Inc., San Diego, California, United States; intra-assay coefficient of variability <8%) according to the manufacturer's recommendations. All other parameters were determined with standard laboratory methods.

SOFA and APACHE II scales, both utilized in the evaluation of organ damage in critically ill patients, were used as a reference. The scales were chosen due to their worldwide recognition and good accuracy for predicting in-hospital mortality.

Definitions and clinical outcomes Patients were followed until hospital discharge. The primary endpoints were incident AKI and in-hospital mortality during the ICU stay.

APACHE II and SOFA scores were calculated for each patient enrolled in the study. Incident AKI was defined according to the Kidney Disease Improving Global Outcomes Work Group guidelines.[25]

The study protocol adhered to the principles of the Declaration of Helsinki and was approved by the local ethics committee (approval no. R-I-002/84/2019). Written informed consent was obtained from all patients or their legal representatives.

Statistical analysis Statistical computations were performed with Statistica 13.1 (Dell Inc., Round Rock, Texas, United States) and R version 3.3.3 (Vienna, Austria). Continuous data are reported as median and interquartile range (IQR). Frequency and percentage are provided for discrete variables. Data between survivors and nonsurvivors were compared with the *t* test

TABLE 1 Baseline characteristic of the study population

Variable	All patients (n = 77)	Survivors (n = 51)	Nonsurvivors (n = 26)	*P* value
Age, y, median (IQR)	64 (47–78)	61 (46–72)	72 (53–86)	0.03
Sex (M/F), n (%)	48 (62)/29 (38)	35 (69)/16 (31)	13 (50)/13 (50)	0.11
Reason of admission to the ICU – infectious/noninfectious, n (%)	20 (26)/57 (74)	9 (18)/42 (82)	11 (42)/15 (58)	0.02
Illness severity, median (IQR)				
APACHE II	15 (11–21)	13 (10–19)	18 (14–21)	0.01
SOFA	9 (7–10)	9 (7–10)	9 (8–11)	0.02
Comorbidities, n (%)				
Diabetes mellitus	8 (10)	4 (8)	4 (15)	0.31
Chronic heart failure	20 (26)	10 (20)	11 (38)	0.08
Ischemic heart disease	11 (14)	5 (10)	6 (23)	0.12
Hypertension	31 (40)	18 (35)	13 (50)	0.21
COPD	13 (17)	10 (20)	3 (12)	0.36
Laboratory, median (IQR)				
Hemoglobin, g/dl	11.8 (10.1–13.0)	12.2 (10.1–13.1)	10.8 (9.9–12.5)	0.27
Creatinine, mg/dl	0.8 (0.7–1.0)	0.8 (0.6–1.0)	0.8 (0.7–1.0)	0.44
CRP, mg/l	55.0 (10.0–134.0)	45.3 (6.6–132.5)	69.0 (24.0–186.0)	0.85
Procalcitonin, μg/ml	0.26 (0.13–1.79)	0.23 (0.12–1.4)	0.62 (0.14–3.76)	0.87

SI conversion factors: to convert hemoglobin to g/l, multiply by 10.0; creatinine to μmol/l, by 88.4; CRP to nmol/l, by 9.524.

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; F, female; IQR, interquartile range; M, male; SOFA, Sequential Organ Failure Assessment

and Mann–Whitney test for continuous variables, and the χ^2 test for categorical variables. Associations between MR-proADM and outcome variables were evaluated with Pearson or Spearman correlation coefficient, depending on meeting the assumptions. Associations between the outcome and MR-proADM were evaluated with uni- and multivariate logistic regression analysis. Area under the receiver operator curve (ROC) was used to estimate the cut-off value of MR-proADM for in-hospital mortality prognostication. According to the cut-off level calculated with ROC, survival curves were plotted using the Kaplan–Meier method and compared with log-rank test. Patients with missing data were excluded from the analysis (2 patients were excluded as data on their MR-proADM level were missing due to results above the assay range). A 2-tailed *P* value of less than 0.05 was considered significant.

RESULTS A total of 77 white patients (29 women, 38%) admitted to a general ICU were prospectively followed until discharge or occurrence of an endpoint. The median age was 64 years, ranging from 19 to 94 years. The main cause of admission to the ICU was infectious in 20 patients and other (major trauma, complication after surgeries) in 57 patients. Detailed baseline characteristics of the population are presented in TABLE 1.

A total of 26 patients (34%) died during the study. Median (IQR) time to death was 26 (9–46) days. Patients required mechanical ventilation for a median (IQR) of 6 (2–17) days and the median length of hospitalization was 19 (4–32) days. Incident AKI was diagnosed in 8 patients (10%) after a median (IQR) of 2 (1–20) days.

Association between midregional proadrenomedullin level and other variables Patients who died during the hospitalization period had a higher MR-proADM concentration as compared with patients who survived (median [IQR], 2592.5 [1668.0–2998.0] pg/ml vs 995.3 [782.1–1256.0] pg/ml; $P < 0.001$). MR-proADM levels did not correlate with incident AKI. Concomitant chronic heart failure was associated with an elevated MR-proADM concentration (median [IQR], 1632.0 [871.5–3066.5] pg/ml vs 1155 [874.8–1563.0] pg/ml, $P = 0.010$). Patients admitted due to infection had higher levels of MR-proADM (median [IQR], 1632.00 [1132.15–2826.50] pg/ml vs 1094.00 [842.60–1559.00] pg/ml; $P = 0.008$) and procalcitonin (2.91 [0.14–16.00] ng/ml vs 0.21 [0.12–1.00] ng/ml; $P = 0.035$). Nevertheless, there was no correlation between MR-proADM and procalcitonin ($r = -0.036$; $P = 0.76$). Variables such as sex, diabetes mellitus, ischemic heart disease, hypertension, or chronic obstructive pulmonary disease did not have an influence on levels of MR-proADM.

Levels of MR-proADM correlated positively with APACHE II or SOFA score ($r = 0.3$; $P = 0.004$ and $r = 0.3$; $P = 0.008$, respectively) and negatively with phosphates ($r = -0.3$; $P = 0.008$). Other variables were not associated with MR-proADM levels.

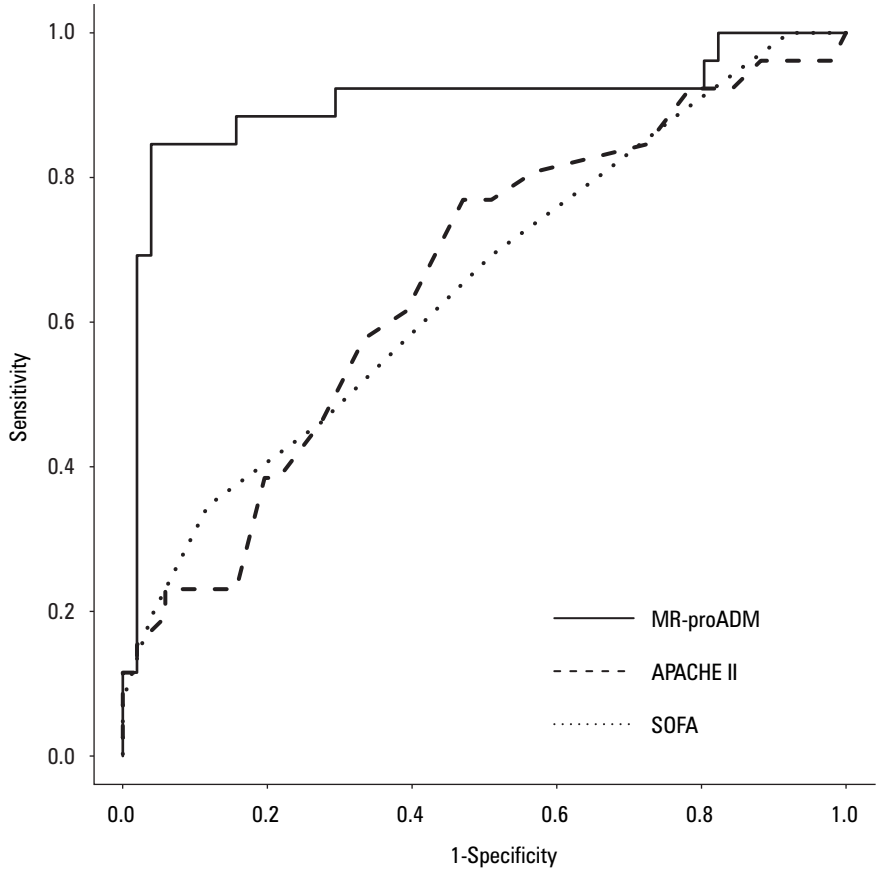

FIGURE 1 Receiver operator characteristic curves for the prognostic utility of midregional proadrenomedullin (MR-proADM), Acute Physiology and Chronic Health Evaluation II (APACHE II), and Sequential Organ Failure Assessment (SOFA) with regard to in-hospital mortality

MR-proADM in predicting mortality Firstly, the utility of MR-proADM was compared with APACHE II and SOFA in in-hospital mortality prediction. The ROC analysis revealed that the measurement of MR-proADM concentration was superior to both scoring systems (P = 0.002 and P = 0.001, respectively) (FIGURE 1).

Based on the ROC analysis, a MR-proADM concentration of 1616 pg/ml was chosen as a discriminative value, enabling prediction of death with the area under the ROC curve of 0.90. It corresponded to a sensitivity of 85% and specificity of 96%. Next, Kaplan–Meier curves were constructed based on the calculated cut-off level of MR-proADM and showed significant differences with regard to survival length (log-rank test, P <0.001) (FIGURE 2).

In univariate logistic regression, MR-proADM was associated with in-hospital mortality (odds ratio, 1.22; 95% confidence interval, 1.11–1.35 per 100 pg/ml increase of MR-proADM concentration). After adjustment for demographics (age and sex), comorbidities (diabetes mellitus, hypertension, ischemic heart disease, chronic heart failure, chronic obstructive pulmonary disease) and incident AKI, MR-proADM level remained an independent predictor of death (odds ratio, 1.35; 95% confidence interval, 1.22–1.49 per 100 pg/ml increase in the MR-proADM concentration).

Sepsis was added to the multivariable model as an independent variable to confirm whether MR-proADM was associated with the outcome irrespective of ongoing generalized infection. Inclusion of sepsis as an independent variable into multivariable model did not change the overall results.

DISCUSSION A universal marker of multiorgan dysfunction is the "holy grail" of intensivists, since patients admitted to the ICU present a wide range of disorders. Our study revealed that MR-proADM levels are useful in prognosing mortality in critically ill patients. A single measurement of MR-proADM assessed within 24 h of admission allowed early detection of patients at risk for unfavorable outcome, which may enable appropriate utilization of resources to improve their outcome. Prognostic utility of MR-proADM has been well described in patients with sepsis.[17,26,27] Our findings extend the scope of its application to the whole ICU population. Our data complement previous reports which suggested that MR-proADM could be applied more broadly than just in patients suffering from infectious diseases. To date, its value was proven in patients presenting to the hospital with dyspnea,[28] chest pain,[29] and undergoing elective cardiac surgery,[30] where MR-proADM proved to be a reliable predictor of poor survival. Our results point to the fact that MR-proADM might be a universal biomarker reflecting the mortality risk regardless of etiology. This is in agreement with a recently published study in nonselected ICU patients.[31] It is worth mentioning that in contrast to this study, we specifically excluded the impact of patients with sepsis on the overall results.

MR-proADM has potential to become a good biomarker: it gives accurate results, has a predictive

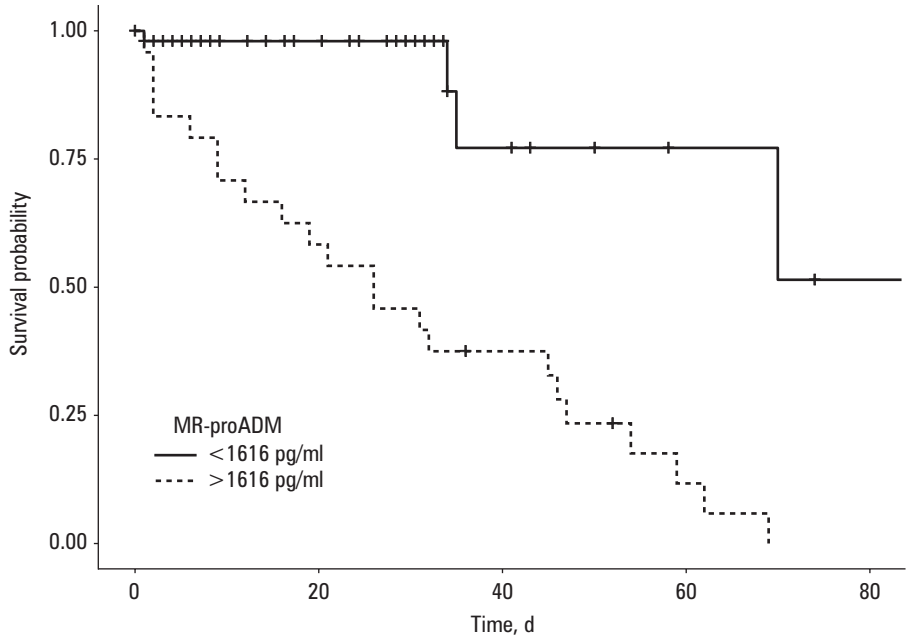

FIGURE 2
Kaplan–Meier survival curves regarding survival length. Cut-off level of midregional proadrenomedullin (MR-proADM) was calculated according to the receiver operator curve analysis. Log-rank test yielded $P < 0.0001$.

diagnostic and prognostic value, and an assay exists that measures the molecule objectively and precisely. Of note, MR-proADM seems to outperform commonly used ICU scales. Our study demonstrated that the prognostic value of MR-proADM in the general ICU population was superior to APACHE II and SOFA scales. Similar data were reported recently in patients with sepsis, as MR-proADM measurement performed equally to APACHE II score and Simplified Acute Physiology Score (SAPS).[17] Although these scales are used in everyday practice, they have several limitations. Firstly, multiple variables are required for the result computation, such as creatinine levels, platelet count, partial pressure of oxygen, and bilirubin levels. In addition, severity score systems, such as APACHE II, predict mortality after 24 h of ICU admission. Considering that a single MR-proADM measurement provides the prognostic information immediately, it can be considered as a good alternative for SOFA or APACHE II scales. Interestingly, MR-proADM might have even higher sensitivity than SOFA scale, which predicts mortality reliably when the score is high. Recently, it was shown that 25% of patients had high MR-proADM levels, and therefore a high mortality risk, despite having low scores on the SOFA scale.[32] The literature also demonstrated that incorporation of MR-proADM could improve the predictive capacity of other routine scales such as Pneumonia Severity Index (PSI)[33,34] or CURB-65 (confusion, urea, respiratory rate, blood pressure, age ≥65 years) score predicting mortality in community-acquired pneumonia.[35,36] Interestingly, a clinical study indicated that risk score–assisted decisions are less effective than those based on biomarkers.[37]

Although in clinical studies MR-proADM showed correlation with renal function,[12,21] we did not observe its value in incident AKI prediction. This is in agreement with previous observation in patients with heart failure that patients with renal disfunction had a higher MR-proADM concentration but its prognostic value was not affected by estimated glomerular filtration rate. This suggests potential utility of this biomarker in risk stratification independently of renal function.[38]

Our data raise the question whether MR-proADM is a causative factor influencing patient outcomes or just merely reflects the general patient condition. High concentrations in patients with sepsis are not surprising since MR-proADM is a member of calcitonin gene family that is extensively synthesized in response to infections.[15] Pleiotropic effects of ADM are implicated in antimicrobial action and thus participate in the defense mechanisms of the host.[39] Additionally, it pays a role in vascular permeability, endothelial barrier regulation, and stabilization of microcirculation,[8,40] all of which may contribute to organ failure and thus affect the outcome adversely. This association with vascular permeability was documented in ICU patients in whom MR-proADM predicted sodium[41] and extracellular fluid overload.[41,42] For the aforementioned reasons, increased expression of ADM as well as MR-proADM might reflect clinical condition of the patient as well as initiate and perpetuate vicious circle of the excessive systemic inflammatory response.

Our study has certain limitations. Firstly, it was a single-center observational study, thus center-specific bias must be taken into consideration. Secondly, our sample size was small so subtle differences might not be detected. Thirdly, we measured MR-proADM at a single time point, thus we cannot draw any conclusions on the behavior of the molecule over the course of the disease. Monitoring biomarker levels over time may further indicate the success of specific therapies and change in predicted outcome. Fourthly, due to the study design any conclusions regarding

causality between MR-proADM and patient outcomes cannot be drawn.

In conclusion, ICU patients are a heterogeneous group with poor survival which continues to have high mortality rates despite considerable efforts in treatment. Our results support the introduction of MR-proADM into clinical practice as a prognostic tool in ICU with accuracy at least similar or even better than that of APACHE II and SOFA severity scores. It seems that MR-proADM measurement does not provide any additional information with regard to predicting incident AKI.

ARTICLE INFORMATION

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CONTRIBUTION STATEMENT KK, AR-R, and TH conceived the concept for the study and contributed to the design of the research. KR and AS recruited the patients. All authors were involved in data collection. KK, AR-R, KR, AS, EK-Ż, EZ, and TH analyzed the data. KK, AR-R, and TH performed final revision of the manuscript. All authors edited and approved the final version of the manuscript.

CONFLICT OF INTEREST None declared.

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