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Mid-regional proadrenomedullin is a good prognostic marker for patients in the Intensive Care Unit with sepsis

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Abstract

***Objectives*: In the current study, we aimed to evaluate the prognostic value of measuring C-reactive protein (CRP), procalcitonin (PCT), and mid-regional proadrenomedullin (MR-ProADM) at 2-time points (i.e., day 1 and day 5) in predicting 28-day mortality.**

***Design*: This was a cohort, cross-sectional study.**

***Setting*: In Zagazig University Hospitals from June 2019 to June 2020 as a collaboration between Clinical Pathology Department and the Intensive Care Unit.**

***Patients and participants*: The study included 32 septic intensive care unit (ICU) patients.**

***Measurements and results*: Blood samples (for serum separation) were collected from each patient on the first day of sepsis diagnosis (day 1) and then 5 days later (day 5). The serum was analyzed for CRP, PCT, and MR-ProADM. At the end of 28 days of observation, patients were classified as survivors or non-survivors. Comparing the level of each biomarker between survivors and non-survivors on day 1 and day 5 showed that only MR-ProADM was significantly different between groups at both measuring points. Meanwhile, PCT showed a significant difference only on day 5. On day 1, using 245.9 pg/ml as a cutoff point, MR-ProADM had 75% sensitivity and 85.7% specificity. Meanwhile on day 5, using 124.4 pg/ml as the cutoff for MR-ProADM, it had 80% sensitivity and 85.2% specificity.**

***Conclusion*: Based upon our findings in our study setting, MR-ProADM was a good mortality predictor for ICU patients with sepsis on both the first and fifth day of sepsis detection.**

Key words: MR-ProADM, sepsis, ICU mortality.

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Introduction

As a response to microorganism invasion of the body in sepsis, multiple body systems are affected by the activation of many immune response pathways. This overwhelming activation may ultimately result in multiorgan failure characteristic of sepsis. (1)

Sepsis as a life-threatening condition may worsen into septic shock. The subsequent circulatory and cell failure may increase the patient death rate. To avoid such sequel, sensible detection and management of sepsis is a must. (2)

Identification of the causative organism of sepsis should begin before starting antibiotic therapy. The standard procedure is microbiological culture for samples collected from any suspected site e.g.,

blood, other body fluid, wound swab, etc. (3)
Due to the unavoidable delay in culture results, introducing biomarkers in management protocols is a must. Biomarkers could provide guidance to clinicians for rapid, and accurate diagnosis, in addition to provide insight about the prognosis, and so direct the treatment regimen. (4)
Among the biomarkers that are largely studied in sepsis are lactate, procalcitonin (PCT), C-reactive protein (CRP), and mid-regional proadrenomedullin (MR-proADM). (5)
MR-proADM is a 48 amino acids fragment produced by a series of a proteolytic breakdowns of adrenomedullin (ADM) and so its level is indirectly representative of ADM level. MR-proADM has a longer half-life than both ADM and proADM and its level can be easily measured in the circulation. (6)
Some studies have highlighted the value of MR-proADM in cases of sepsis, especially as a disease severity and a death predictor. They even raised its value above that of PCT and CRP. (7-9)
In the current study, we aimed to evaluate the prognostic value of measuring CRP, PCT, and MR-ProADM at 2-time points (i.e., day 1 and day 5) in predicting 28-day mortality.

Materials and methods

Ethical principle

The study's protocol was approved by the Zagazig Medical Institutional Review Board (IRB#:5419-9-6-2019) in accordance with the ethical standards of the 1964 Helsinki declaration. Preinclusion informed consent was obtained from each subject or his legal health representative.

Study design

This was a cohort, cross-sectional study that was carried out in Zagazig University Hospital as a collaboration between Clinical Pathology Department and the Intensive Care Unit. The study included 32 septic intensive care unit (ICU) patients. All patients had at least one positive culture (blood, urine, sputum, pus on swabs) and fulfilled the criteria of sepsis diagnosis as classified by Lambden and colleagues. (10)
Blood samples (for serum separation) were collected from each patient on the first day of sepsis diagnosis (day 1) and then 5 days later (day 5). The serum was analyzed immediately for PCT (using Cobas E411 analyzer, Roche Diagnostics, Germany) and CRP quantitation (using Cobas 8000 analyzer, Roche Diagnostics, Germany). An aliquot was preserved at -80 ºC for later MR-ProADM quantification using Human MR-ProADM ELISA kit (Sunred Biological Technology Co., Shanghai, China). At the end of 28 days of observation, patients were classified as survivors or non-survivors.

Statistical analysis

A test of normality (Shapiro-Wilk test) was performed. Parametric data were expressed as mean±standard deviation (SD) and non-parametric data was expressed as median (min-max). Wilcoxon sign test was used to test the difference between paired quantitative variables. Mann-Whitney U test was used to test the difference between non-parametric variables. Receiver operating characteristic (ROC) curve analysis was done to determine the best cutoff for biomarkers as a predictor of 28-day mortality. A significance level of p-value was set at ≤0.05.

Results

Thirty-two septic ICU patients, aged 38.4±4.6 years, were enrolled in this study. They were 19 males and 13 females (59.7 and 40.6% of cases, respectively). Multi-trauma was the main cause of admission (11 [34.4%] cases), followed by neurological cases (7 [21.8%] cases). Orthopedic, gastrointestinal tract (GIT), and gynecological cases constituted the remaining.
The most frequently isolated organisms from the obtained biological samples were Klebsiella pneumonia (37.5%), followed by Staphylococcus aureus (25.0%) and Escherichia coli (18.8%). Pseudomonas aeruginosa and Acinetobacter baumanii each represented 9.3% of isolates.
We summarize and study the difference between levels of septic biomarkers on day1 and day 5 of sepsis diagnosis in **Table 1**. All biomarkers were significantly different between day 1 and day 5.
Comparing the level of each biomarker between survivors and non-survivors on day 1 and day 5 showed that only MR-ProADM was significantly different between groups at both measuring points. Meanwhile, PCT showed a significant difference only on day 5 (**Table 2**).
Table 3 and **Figure 1** show ROC curve analysis for the prognostic performance of different biomarkers in predicting 28-day mortality. MR-ProADM was a good mortality predictor on day 1 and day 5, while PCT showed the same predicting ability on day 5 only.

Discussion

None of the current septic biomarkers is an ideal one. The ideal one should increase rapidly following sepsis development then decline rapidly following efficient therapy and has a validated method of

assay. (11)
The circulating level of MR-ProADM was evaluated and found helpful in many conditions- in addition to sepsis- such as systemic inflammation, heart failure, respiratory failure, and coronary ischemia. (8,12-15)
Isolates from microbiological cultures differ between studies according to the site of infection and the population studied as well. Consequently, the antibiotic protocol shall differ from patient to patient. It is of utmost importance to obtain samples for culture before starting antibiotic treatment. (3)
Our patient's groups showed Klebsiella pneumoniae was the most common cause of sepsis followed by Staphylococcus aureus then Escherichia coli. Fay and his colleagues (16) reported different results. In their study, Escherichia coli was the commonest isolated organism followed by Klebsiella pneumonia and Staphylococcus aureus.
A characteristic sequel of sepsis is organ failure involving different body systems. Quantification of the degree of declining function is achievable using the Sequential Organ Failure Assessment (SOFA) score. (1)
In our study, the SOFA score was calculated for day 1 and day 5. A statistically significant difference was found between the two measuring time points with a higher median on day 1. Additionally, on both days 1 and 5, there was a significant difference between 28 days of survivors and non-survivors.
A previous study by Karakike and his colleagues (17) exhibited a significant change in SOFA score at the 7 measuring time points and SOFA score at day 7 was the best predictor of 28-day mortality. Using 5 as a cutoff point on day 1 had 60% sensitivity, 77.8% specificity, 33.3% positive predictive value, 91.3% negative predictive value, and 75% accuracy. While using 4 as a cutoff point on the 5th day had higher sensitivity (80%), but lower specificity and accuracy (59.3% and 62.5%, respectively), and comparable positive predictive value, and negative predictive value (26.7% and 94.1%, respectively).
The three sepsis markers (i.e., CRP, PCT, MR-proADM) were also measured on day 1 and day 5. A statistically significant difference in all markers was found between both measurements. The three markers had significantly decreased after 5 days compared to their levels on day 1. Other studies addressed the same markers. One study reported that CRP level between admission and day 4 was the best predictor for recovery and so of mortality. (18)
Others studied PCT and MR-ProADM and found a significant difference between day 1 and day 5. (19)
On day 1, only MR-ProADM (among septic biomarkers) was different between 28 days of survivors and non-survivors ($p=0.027$). At 245.9 pg/ml cutoff point, it had 75% sensitivity, 85.7% specificity, 42.9% positive predictive value, 96% negative predictive value, and 84.38% accuracy. Other studies agreed with our findings regarding the superiority of MR-ProADM on day 1 as a mortality predictor over other septic biomarkers. (19,20) However, Elke and colleagues added to that a good prognostic value of PCT as well. (21)
On day 5 MR-ProADM and PCT were significantly different between 28 days of survivors and non-survivors ($p=0.002$ and 0.011, respectively). At the chosen cutoff points (124.43 pg/ml for MR-ProADM and 27.5 ng/ml for PCT), MR-ProADM has the same sensitivity as PCT (80%) but superior performance than PCT in other parameters (i.e., 85.2% specificity vs. 74.1%, 50% positive predictive value vs. 36.4%, 95.8% negative predictive value vs. 95.2%, and 84.4% accuracy vs. 75 %). For the three parameters that were significant predictors of mortality on day 5 (i.e., SOFA, MR-ProADM, and PCT), MR-ProADM has a higher area under the ROC curve (AUC) (0.933) compared to PCT (0.862) and SOFA (0.822). Both Valenzula-Sanchez and colleagues (7) and Charles and colleagues (19) reported the better performance of MR-ProADM as a mortality predictor on day 5. Although in the study of Andaluz-Ojeda and colleagues, (22) different time measuring points were evaluated (i.e., day 1, 3, and 7), they reached the same conclusion about the mortality predictability of MR-ProADM. The studies on the role of MR-ProADM were not restricted to ICU patients. A recent systemic review highlighted its prognostic role for septic patients in the emergency department as well. (23)
We should note that the small number of our patient group was a major limitation of the study.

Conclusion

Based upon our findings in our study setting, MR-ProADM was a good mortality predictor for ICU patients with sepsis on both the first and fifth day of sepsis detection. We recommend further extended studies with the same setting to validate the usefulness of incorporating MR-ProADM in the assessment protocols in the ICU.

Acknowledgment

The authors declare the absence of any conflict of interest.

Table 1. Septic biomarkers on day 1 and day 5 after the diagnosis of sepsis

Variables	Day 1	Day 5	WS	p
CRP (mg/l), median (min-max)	88 (30-135)	64.5 (15-112)	-4.249	<0.001
PCT (ng/ml), median (min-max)	36 (23-58)	18 (10-45)	-4.042	<0.001
MR-ProADM (pg/ml), median (min-max)	163.21 (77.98-327.24)	83.014 (10.60-320.33)	-3.628	<0.001

Legend: CRP=C-reactive protein; PCT=procalcitonin; MR-ProADM=mid-regional proadrenomedullin; WS=Wilcoxon sign test.

Table 2. Association between CRP, PCT, and MR-ProADM levels and 28-day mortality

	Day 1				Day 5			
	Non-survivors (n=5)	Survivors (n=27)	MW	p	Non-survivors (n=5)	Survivors (n=27)	MW	p
CRP (mg/l), median (min-max)	89 (30-129)	87 (45-135)	-0.130	0.896	80 (46-112)	56 (15-112)	-1.406	0.160
PCT (ng/ml), median (min-max)	33 (28-46)	37 (23-58)	-0.494	0.621	36 (27-45)	18 (10-40)	-2.578	0.010
MR-ProADM (pg/ml), median (min-max)	260.1 (170.1-327.2)	137.8 (78-319)	-2.210	0.027	312.1 (118.1-320.3)	65.9 (10.6-301)	-3.038	0.002

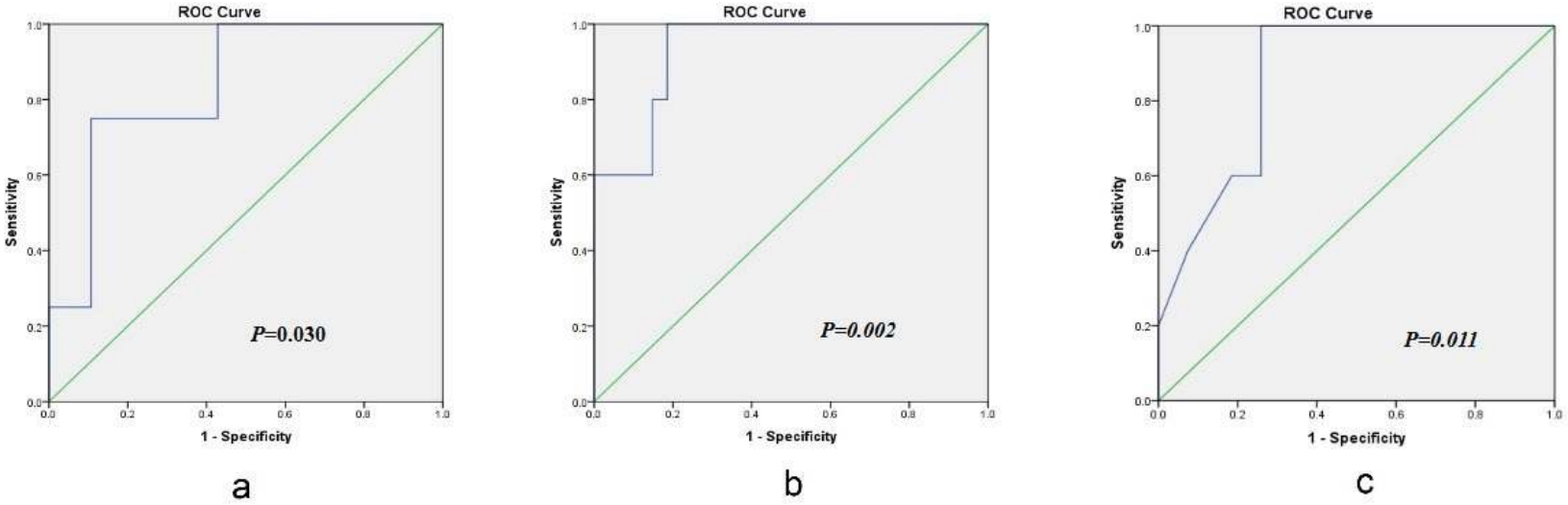
Legend: CRP=C-reactive protein; PCT=procalcitonin, MR-ProADM=mid-regional proadrenomedullin; MW=Mann-Whitney U test.

Table 3. Prognostic performance of PCT and MR-ProADM in the prediction of 28 mortality

	MR-ProADM		PCT
	Day 1	Day 5	Day 5
Cutoff point	246 pg/ml	124.4 pg/ml	27.5 ng/ml
AUC (95% CI)	0.839 (0.654-1.00)	0.933 (0.838-1.00)	0.863 (0.726-1.00)
Sensitivity	75%	80%	80%
Specificity	85.7%	85.2%	74.1%
Positive predictive value	42.9%	50%	36.4%
Negative predictive value	96%	95.8%	95.2%
Accuracy	84.38%	84.4%	75%
p	0.030	0.002	0.011

Legend: PCT=procalcitonin; MR-ProADM=mid-regional proadrenomedullin; AUC=area under the ROC curve; CI=confidence interval;

Figure 1. ROC curve for the prognostic performance of septic biomarkers in predicting 28-day mortality



Legend: a=MR-ProADM on day 1; b=MR-ProADM on day 5; c=PCT on day 5; ROC=receiver operating characteristic; MR-ProADM=mid-regional proadrenomedullin; PCT=procalcitonin.

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