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ORIGINAL ARTICLE

The Role of Mid-Regional Proadrenomedullin in Diagnosis of Sepsis in Intensive Care Unit Patients

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ABSTRACT

Background: As a major health problem, mortality due to sepsis accounts for about 42% in intensive care deaths. This high mortality rate necessitates rapid and accurate diagnosis of sepsis, differentiating it from other confusing conditions. Rapid and evidence-based management is expected to follow. The use of biomarkers gained high attention in the scientific community for sepsis diagnosis. In the current study, we aim to evaluate the diagnostic accuracy of measuring C-reactive protein (CRP), Procalcitonin (PCT), and Mid-Regional Proadrenomedullin (MR-proADM) in differentiation between septic and non-septic patients within intensive care unit.

Methods: A total of 64 subjects were enrolled. They were divided into: (1) control group: 32 Non-septic ICU patients, and (2) case group: 32 septic ICU patients. CBC, CRP, PCT, MR-proADM quantification was done at day 1 of sepsis suspension for case group and randomly for control group.
At a cut-off 78.479 pg/ml, MR-proADM has 93.8 % sensitivity, 90.6 % specificity, 90.9 % positive predictive value, 93.5% negative predictive value and 92.18 % accuracy.

Conclusions: Based upon our findings, MR-proADM could be useful as a diagnostic marker in sepsis patients admitted to ICU. It had diagnostic criteria comparable to that of PCT and better than that of CRP.

Key words: Sepsis, ICU, MR-proADM, CRP, PCT

INTRODUCTION

As a major health problem, sepsis accounts for about 20% of all mortalities worldwide annually. It also accounts for about 27% of hospital mortality rate and this percentage increases to 42% in intensive care patients with sepsis. In Egypt, death related to sepsis is estimated to be about 15% of cases. However, due to lack of solid epidemiological data, it's expected to be even higher [1].

This high mortality rate necessitates rapid and accurate diagnosis of sepsis, differentiating it from other confusing conditions. Rapid and evidence-based management is expected to follow [2].

Management of sepsis includes administration of empirical antibiotics preceded by obtaining biological samples (particularly blood) for microbiological culture to isolate the causative organism and its sensitivity to antibiotics for later tailoring of the treatment plan [3]. However, due to the impact of antibiotic administration on microbial growth, culture results in sepsis patients are occasionally false-negative. Since standard culture-based microbiology diagnosis frequently produces results within 48–96 hours, physician can't rely on culture results in diagnosis of sepsis. Consequently, the use of rapid identification techniques may have both clinical and financial advantages, allowing clinicians to quickly and accurately diagnose cases and select a proper therapy [4].

As an alternative approach for sepsis diagnosis, the use of biomarkers gained high attention in the scientific community. Lactate is the most common biomarker used in sepsis shock diagnosis [5]. Procalcitonin (PCT), C-reactive protein (CRP) and mid-regional proadrenomedullin (MR-proADM) are some of the biomarkers most extensively studied in sepsis [6].

MR-proADM is a 48 amino acids fragment, split from the final proADM molecule. It proportionally represents the levels and activity of adrenomedullin (ADM), its half-life is longer (i.e. several hours), and its plasma concentrations can be easily measured in the serum [7]. ADM levels have been measured in various pathophysiological

conditions, and interestingly, the highest concentrations were found in patients with septic shock. In sepsis patients, circulating ADM levels , and hence MR-proADM, correlated with disease severity and mortality [8].

Recently, studies on corona pandemic have found measuring the level of MR-proADM valuable to differentiate Covid-19 patients who need intensive therapeutic approach [9, 10].

In the current study, we aim to evaluate the diagnostic accuracy of measuring CRP, PCT and MR-proADM in differentiation between septic and non-septic patients within intensive care unit (ICU).

METHODS

Study design

This is a case-control study that was carried out in Clinical Pathology department, Intensive Care Units (surgical ICU, emergency ICU) of Zagazig University Hospitals.

A total of 64 subjects were enrolled. They were divided into: (1) control group: 32 Non-septic ICU patients (i.e., they were age, sex and cause of admission matched to case group), and (2) case group: 32 septic ICU patients from whom samples were obtained at first day of sepsis suspension. Patients were classified as septic if they had ≥2 SIRS (Systemic Inflammatory Response Syndrome) criteria and a clinical suspicion of infection. SIRS criteria are: (a) temperature of >38ºC or < 36 ºC , (b) heart rate of >90 beats/min, (c) respiratory rate of >20 breaths/min. or partial CO2 pressure (pCO2) of <32 mm hg , (d) white blood cell (WBC) count of >12,000 (12K)/µl or 10% immature forms (i.e. bands) [11].

All septic patients had positive cultures (blood, urine, sputum, pus, and swabs). Subjects (either case or control) with cardiovascular diseases, malignant tumors, immunodeficiency diseases, focal segmental glomerulosclerosis, and type II diabetes were excluded.

Laboratory tests:

Blood samples were collected from every participant (i.e., at day 1 of sepsis suspension for case group and randomly for control group). An EDTA whole blood sample was used for measuring parameters of complete blood picture (CBC) using Sysmex XN automated hemocytometer (Siemens, Germany). Serum samples were used for immediate measurement of PCT using Cobas E411 analyzer (Roche diagnostics, Germany), and CRP quantitation using Cobas 8000 analyzer (Roche diagnostics, Germany). Serum aliquots were stored frozen at -80ºC for later MR-proADM quantification using Boster human MR-proADM (Sunred, China-Catalogue No. 201-12-7275) kit by ELISA technique according to manufacture protocol. The kit has a sensitivity of 2.839pg/ml, an assay range of 3pg/ml to 900pg/ml, an intra-assay CV <10%, and an inter-assay CV <12%.

Ethical Approvals

The study was approved by "Institutional Review Board" (IRB) committee at Faculty of Medicine, Zagazig University (IRP No.5419-9-6-2019). A written informed consent was taken from all subjects for ethical consideration. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis:

Quantitative data were presented as mean and standard deviation. Qualitative data was presented as frequencies and percentage. Chi-square test was used to test differences for categorical variables. Independent samples Student's t-test or Mann-Whitney U test was used, as appropriate, to test differences for continuous variables between two groups. Receivers operating characteristic (ROC) curves were plotted for the optimal cut-off value of MR-proADM that was diagnostic of sepsis as well as the sensitivity, specificity, accuracy, and predictive values. In all the tests, p value of ≤0.05 was taken as significant.

RESULTS

Differences between case and control groups regarding the demographic and clinical characteristics of the patients, laboratory parameters were assessed statistically and presented in table (1). The studied groups were statistically age, sex, location, and cause of admission matched. The most common cause of admission in both groups was multi-trauma (34.4 % in case and 37.5 % in control), followed by neurological causes (21.8% in case and 18.8% in control). All SIRS criteria showed statistically significant differences between groups (p <0.001). Sepsis markers (i.e., CRP, PCT, Mr pro-ADM), as well, showed statistically significant differences between groups (p <0.001).

Table 1 Demographic characteristics of the studied groups

Variables	Case group (*n*=32)	Control group (*n*=32)	Test of sig.	*p*
Age (years):			T	
Mean ± SD	38.4 ± 4.6	40.1 ± 6.3	1.2	0.2
Sex:	*n*(%)	*n*(%)	χ^2	
Male	19 (59.4%)	17 (53.1%)	0.6	0.4
Female	13 (40.6%)	15 (46.9%)		
Type of ICU:	*n*(%)	*n*(%)	χ^2	
Surgical ICU	17 (53.1%)	16 (50.0%)	0.1	0.8
Emergency ICU	15 (46.9%)	16 (50.0%)		
Cause of admission:	*n*(%)	*n*(%)	χ^2	
Multi-trauma	11 (34.4%)	12 (37.5%)	1.6	0.8
Neurological cases	7 (21.8%)	6 (18.8%)		
Orthopedic cases	4 (12.5%)	6 (18.8%)		
GIT cases	4 (12.5%)	5 (15.6%)		
Gynecological cases	6 (18.8%)	3 (9.3%)		
SIRS Criteria:				
Temperature (ºC):			T	
Mean ± SD	38.5 ± 1.6	37.1 ± 0.8	4.4	<0.001
Heart rate (beat/min.):			T	
Mean ± SD	109.3 ± 17.4	88.9 ± 4.6	6.4	<0.001
Respiratory rate (breath/min.):			T	
Mean ± SD	26.2 ± 4.7	18.8 ± 3.5	7.1	<0.001
WBCs (cells/µl):	13384.38±	7453.13± 1553.76	T	<0.001
Mean ± SD	4467.31		7.09	
Sepsis biomarkers of the studied groups on admission to ICU:				
CRP (mg/l):			MW	
Median (Range)	88 (30– 135)	17.5 (2– 48)	-6.719	<0.001
PCT (ng/ml):			MW	
Median (Range)	36 (23– 58)	0.17 (0.10 – 0.30)	-6.882	<0.001
Mr pro-ADM (pg/ml):			MW	
Median	163.21	11.28	-6.876	<0.001
(Range)	(77.98– 327.24)	(1.43 –46.68)		

WBCs: white blood cells count, CRP: C-reactive protein, PCT: procalcitonin and MR pro-ADM: Mid Regional Pro-Adrenomedullin, T: Student's t-test, χ2: Pearson's chi-squared test, MW: Mann-Whitney U test

Table 2 and figure (1) summarizes the diagnostic performance of the 3 sepsis markers assessed by Receiver Operating Characteristic (ROC).

Table 2 Diagnostic performance criteria of sepsis markers

	CRP	PCT	MR pro-ADM
Cutoff point	46 (mg/l)	25.5 (ng/ml)	78.48 (pg/ml)
AUC (95% CI)	0.95 (90-1.00)	0.96 (0.92-1.00)	0.95 (0.89-1.00)
Sensitivity	90.6%	93.8%	93.8%
Specificity	84.4%	90.6%	90.6%
Positive predictive value	85.3%	90.9%	90.9%
Negative predictive value	90.0%	93.5%	93.5%
Accuracy	87.5%	92.18%	92.18%
***p*-value**	0.001**	0.001**	0.001**

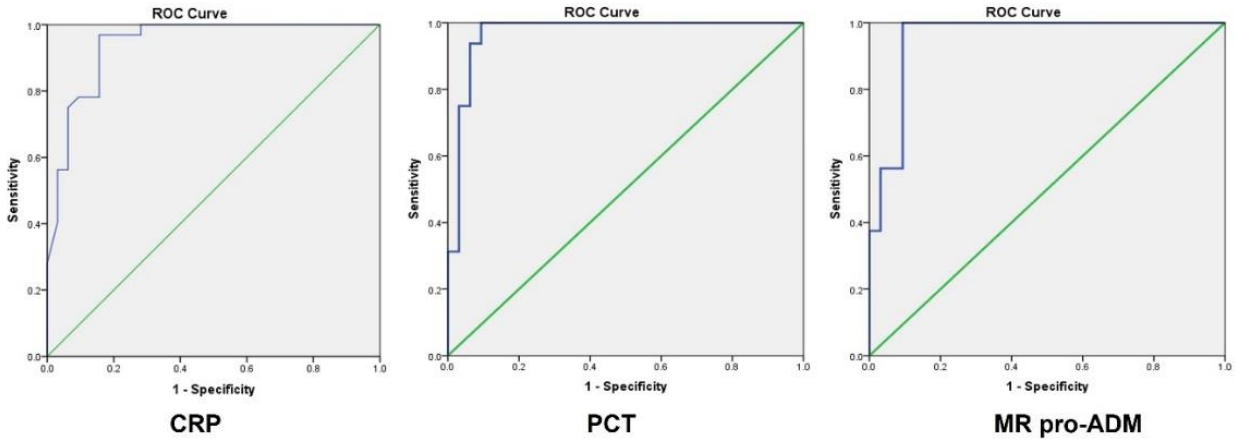

Figure 1 ROC curve showing performance of sepsis markers in the diagnosis of septic cases

DISCUSSION

An ideal sepsis biomarker would have a quick and distinct onset of sepsis, a quick decline following efficient treatment, a short half-life, and a quick, accessible, and trustworthy means of detection. However, none of the available biomarkers adequately demonstrates all of these qualities [12]. The two biomarkers that are utilized and researched the most are CRP and PCT. Both temporarily rise during sepsis, but for a long enough period that their detection is possible, indicating a real-time reaction. In spite of the fact that numerous studies have found PCT to be more accurate than CRP in detecting sepsis, data suggests that it may be increased in a wide range of diseases even in the absence of infection, particularly after trauma. Both PCT and CRP may be more helpful in excluding sepsis than in diagnosing it, and the combination of these two biomarkers may increase this effect [13].

In our study, we found a significant difference between septic and non-septic groups in levels of CRP and PCT, being higher in septic groups. This highlights the value of both CRP and PCT as diagnostic biomarkers for sepsis. Pierrakos and his co-workers in 2020 had similar conclusion regarding CRP [12]. But in the study of Spoto and his co-workers in 2019, they found no difference in CRP levels between septic and non-septic groups. Meanwhile , their study showed high PCT level in septic versus non-septic patients [14].

On another study by fan and his co-workers in 2016, patients with PCT levels in the intermediate range, it was not particularly helpful in determining the ultimate diagnosis. Additionally, the study advised that PCT should always be carefully interpreted considering medical history and other clinical data as per the recommendation of the Surviving Sepsis Campaign [15].

MR-proADM is an emerging biomarker in sepsis management. Its level was studied in different conditions and found to be potentially useful for evaluating patients with acute kidney injury [16], heart failure [17], and respiratory failure [18]. In our study, the level of MR-proADM was also statistically difference between septic patients to non-septic patients, being higher in septic group. In the study of Valenzuela-Sánchez and his coworkers in 2016, they stated that the initial levels of MR-proADM helped in the diagnosis of infectious origin of patients with SIRS and organ dysfunction [19].

We run ROC curve analysis for evaluation of MR-proADM diagnostic performance and found that at a cut-off 78.48 pg/ml, it had 93.8 % sensitivity, 90.6% specificity, 90.9% positive predictive value, 93.5% negative predictive value and 92.18% accuracy. These findings highlight the significance of MR-proADM as a diagnostic biomarker for sepsis. Similar significant results were found by Spoto and his coworkers in 2019 , with cutoff 0.05 (nmol/L) [14]and Al Shuaibi and his coworkers in 2013 with 0.91 nmol/L median level in septic patients (range: 0.05–8.78) [20]. CRP and PCT, as well, had a good diagnostic ability with CRP having lower diagnostic criteria than PCT (i.e., AUC 0.95 vs 0.96, sensitivity 90.6% vs 93.8%, specificity 84.4% vs 90.6%, +ve predictive value 85.3% vs 90.9%, -ve predictive value 90% vs 93.5% and accuracy 87.5% vs 92.18%). Among the 3 sepsis markers, PCT and MR-pro ADM had comparable diagnostic performance, while CRP was inferior to them. In earlier study by Buendgens and his coworkers in 2020, they reported similar finding regarding the diagnostic significance of the 3 sepsis markers. Meanwhile, they reported different diagnostic performance noting that PCT and CRP had better performance criteria than MR-pro ADM (AUCs of 0.767, 0.840, and 0.731 respectively) [21]. Later to this study, Spoto and his coworkers in 2020 reported that MR-proADM values > 1

nmol/L had the ability to identify septic patients when SIRS, SOFA and PCT were still negative. They reported the diagnostic performance of MR-proADM and PCT as (AUC 0.85, 0.93, sensitivity 83.0%, 67.94%, and specificity 83.0%, 98.04%) [22].

CONCLUSIONS

Based upon our findings, MR-proADM could be useful as a diagnostic marker in sepsis patients admitted to ICU. It had diagnostic criteria comparable to that of PCT and better than that of CRP.

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