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Prognostic role of adrenomedullin in sepsis

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Abstract

Objective: Adrenomedullin (ADM) has been found to be elevated in plasma of septic patients. Our study aim was to explore the prognostic role of ADM in septic patients. Design A prospective observational study. Setting Intensive Care Department of Alexandria University Hospitals. **Patients:** 100 patients with proved sepsis in need for ICU admission. **Methods:** Patients were followed up for 5 days. APACHE II score was calculated on admission. SOFA score, CRP, serum lactate, PCT, and serum ADM were measured twice. Primary end-point was development of septic shock, and secondary end-point was 28 days mortality. **Results:** SOFA score and serum ADM on admission could predict progression to septic shock. ADM prediction power was significantly higher than SOFA. Day 5 readings of all tested parameters could predict occurrence of septic shock. ADM with a cut-off value of 35.9 pg/ml showed the highest sensitivity and specificity (100% & 93.8% respectively). SOFA score with a cut-off value of 2 and serum ADM with a cut-off value of 40 pg/ml were early predictors of mortality. ADM prediction power was significantly higher than SOFA. **Conclusion:** ADM in septic patients may serve as an early predictor of outcome.

Keywords: sepsis, adrenomedullin, septic shock, mortality.

Introduction

The high mortality recorded in sepsis is in many cases due to multi-organ hypo-perfusion and hypotension associated with the development of septic shock. As the clinical and laboratory findings of sepsis are nonspecific and culture results are not readily available, the diagnosis and risk stratification of patients is often delayed (Vincent; 2002). Serum biomarkers such as C-reactive protein (CRP), lactate, and procalcitonin (PCT) are often used to verify different stages of sepsis and patient risk stratification (Dellinger et al; 2013, Travaglino et al; 2012).

Adrenomedullin (ADM) is a peptide which was first isolated from a human pheochromocytoma (Kitamura et al; 1993). Its serum level has been found to be elevated in septic patients (Beltowski and Jamroz; 2004). The mechanism of secretion of ADM in large part relates to the effects of lipopolysaccharide (LPS) stimulation (Wong et al; 2005). Previous studies indicate that ADM plays a major role in initiating the hyperdynamic response during the early stages of polymicrobial sepsis (Koo et al; 2001, Wang et al; 1998, Ueda et al; 1999, Ehlenz et al; 1997, Nishio et al; 1997). Our study aim was to explore the prognostic role of adrenomedullin in patients hospitalized for sepsis.

Patients and Methods

100 patients, according to sample size calculation, were presented to the Emergency Room of Alexandria University Hospitals with sepsis according to the Surviving sepsis Campaign guidelines (Dellinger et al; 2013) and in need for ICU admission.

Exclusion criteria:

Those under 18 years old, patients with chronic renal or liver disease, conditions influencing adrenomedullin level; (chronic heart failure & acute coronary syndrome, acquired immune deficiency syndrome, malignancy, and immunosuppressive status) were excluded from the study (Ehlenz et al; 1997).

Informed written consent was taken from all patients' next of kin according to the Helsinki declaration. The study was approved by the local ethical committee of Alexandria Faculty of Medicine. Patients enrolled into the study were subjected to collection of demographic data, associated co-morbidities, routine ICU investigations, culture from suspected sites of infection (and/or automated blood culture), and APACHE II score calculation on admission.

SOFA score, CRP, serum lactate level, PCT level, and serum ADM were measured on admission and at day 5. Adrenomedullin was analyzed using enzyme-linked immunosorbent assay (ELISA) using double antibody sandwich method (Di Somma et al; 2013). The ELISA assay included a purified human anti-ADM antibody as the capture antibody, and perborate /3, 3, 5, 5-tetramethylbenzidine as the substrate.

Patients were followed up for 5 days. Primary end-point was development of septic shock, and secondary end-point of the study was 28 days mortality. Survival was recorded daily by in- hospital observation and later by phone call. Septic shock was defined as the presence of sepsis induced organ dysfunction accompanied by a sustained arterial hypotension (mean arterial pressure < 65mmHg) requiring vasopressor therapy despite adequate volume resuscitation (Dellinger et al; 2013).

Statistical Analysis:

Data were analyzed using SPSS program version 13.0 (SPSS Inc., Chicago, IL, USA). Normal distributed data were expressed as mean ± standard deviation and compared by Kruskal- Wallis one-way analysis of variance. Skewed distributed data were expressed as median and quartiles and analyzed by Mann-Whitney U test. Comparison of frequencies was done using the χ^2 test. Receiver operating characteristic (ROC) curve was constructed, and the area under the ROC curve (AUC) was determined to assess the predictive value of AM. On the basis of optimal threshold determined by ROC curve, prognostic parameters (sensitivity, specificity, and positive and negative predictive values) were also calculated. All statistical tests were two-tailed, and $P < 0.05$ was considered statistically significant.

Results

The present study enrolled 100 patients with an age range of 53-71 years, 61% of them were males. The most common site of infection was the respiratory tract (42%), followed by intra-abdominal (25%), and urosepsis (20%). Positive cultures were obtained in 68 patients. APACHE II score of the studied population ranged between 10 and 16, (table 1).

On admission and day 5 readings of SOFA score and different biomarkers including ADM were presented in table (1). Out of 100 studied patients, 35 developed septic shock. Mortality rate in the present study was 23%, (table 1).

According to the present study, only SOFA score and serum ADM on admission could predict occurrence of septic shock as both showed significant AUC. In addition, ADM AUC was significantly higher than SOFA ($p < 0.0001$). On the other hand, day 5 readings of the all tested parameters could predict incidence of septic shock. ADM with a cut-off value of 35.9 pg/ml showed the highest sensitivity and specificity (100% & 93.8% respectively) when compared to SOFA score ($p= 0.0001$), lactate ($p= 0.0001$), CRP ($p < 0.0001$), and procalcitonin ($p= 0.0003$) (table 2, figure 1).

SOFA score with a cut-off value of 2 and serum ADM with a cut-off value of 40 pg/ml were early predictors of mortality in septic patients. Both showed significant AUC when measured on admission. Adrenomedullin AUC was significantly higher than SOFA ($p = 0.0005$). When testing the validity of SOFA score, lactate, CRP, Procalcitonin, and ADM, to predict mortality after 5 days of admission all tested parameters could predict mortality but the difference between AUCs of these variables was not statistically significant, (table 3, figure 2).

Discussion

The recent report, which appeared in the February 23 issue of JAMA, was released to coincide with its presentation at the Society of Critical Care Medicine's 45th Critical Care Congress. They declared new definitions for sepsis and septic shock. Sepsis was defined as life-threatening organ dysfunction caused by a dys-regulated host response to infection. Septic shock was defined as a subset of sepsis in which

Table 1: Baseline characteristics of patients:

Study variables	Median (IQR) / Frequency (%)
Age (years)	63 (53 – 71)
Male sex	61 (61)
Site of infection	
Pulmonary	42 (42)
Urinary	20 (20)
Blood stream	13 (13)
Abdominal	25 (25)
Culture positive	68 (68)
APACHE II score (0-71)	13 (10 – 16)
On admission:	
SOFA score (0-24)	2 (2 – 3)
Lactate (mg/dl)	22.5 (17 – 28)
CRP (mg/dl)	29 (18 – 38)
Procalcitonin (ng/ml)	3.9 (2.3 – 6.1)
Adrenomedullin (pg/ml)	36 (28 – 45)
Day 5:	
SOFA score (0-24)	5 (4 – 7)
Lactate (mg/dl)	19 (15 – 29)
CRP (mg/dl)	29 (19 – 39)
Procalcitonin (ng/ml)	4.9 (2 – 6.7)
Adrenomedullin (pg/ml)	31 (26 –52)
Septic shock	35 (35)
Mortality	23 (23)

Table 2: Areas under the receiver operating characteristic curves (AUC) in predicting septic shock:

	AUC (95% CI)	Cut-off point	Sens	Spec	PPV	NPV
On admission:						
SOFA score	0.694(0.594– 0.782)	3	42.9	86.1	62.5	73.7
Lactate	0.341 (0.219 – 0.464)	----	----	----	----	----
CRP	0.401 (0.279 – 0.523)	----	----	----	----	----
Procalcitonin	0.507 (0.384 – 0.630)	----	----	----	----	----
Adrenomedullin	0.952 (0.890 – 0.985)	37.9	94.3	83	75	96.4
Day 5:						
SOFA score	0.793(0.700– 0.868)	5	77.1	67.7	56.2	84.6
Lactate	0.799 (0.707– 0.873)	21.7	77.1	80	67.5	86.7
CRP	0.819 (0.730 – 0.889)	32	74.3	81.5	68.4	85.5
Procalcitonin	0.854 (0.769 – 0.917)	4.5	80	80	68.3	88.1
Adrenomedullin	0.979 (0.928 – 0.997)	35.9	100	93.8	89.7	100

Table 3: Areas under the receiver operating characteristic curves (AUC) in predicting mortality:

	AUC (95% CI)	Cut-off point	Sens	Spec	PPV	NPV
On admission:						
SOFA score	0.765(0.670– 0.844)	2	78.3	61	37.5	90.4
Lactate	0.578 (0.439 – 0.717)	----	----	----	----	----
CRP	0.427 (0.272 – 0.582)	----	----	----	----	----
Procalcitonin	0.552 (0.408 – 0.696)	----	----	----	----	----
Adrenomedullin	0.964 (0.906 – 0.991)	40	91.3	87	67.7	97.1
Day 5:						
SOFA score	0.886(0.806– 0.941)	7	78.3	98.7	94.7	93.8
Lactate	0.992 (0.949– 1)	31.4	95.6	100	100	98.7
CRP	0.944 (0.879– 0.980)	32	95.6	79.2	57.9	98.4
Procalcitonin	0.928 (0.858– 0.970)	7.2	78.2	39.5	78.3	93.5
Adrenomedullin	0.982 (0.933–0.998)	41	100	84.4	65.7	100

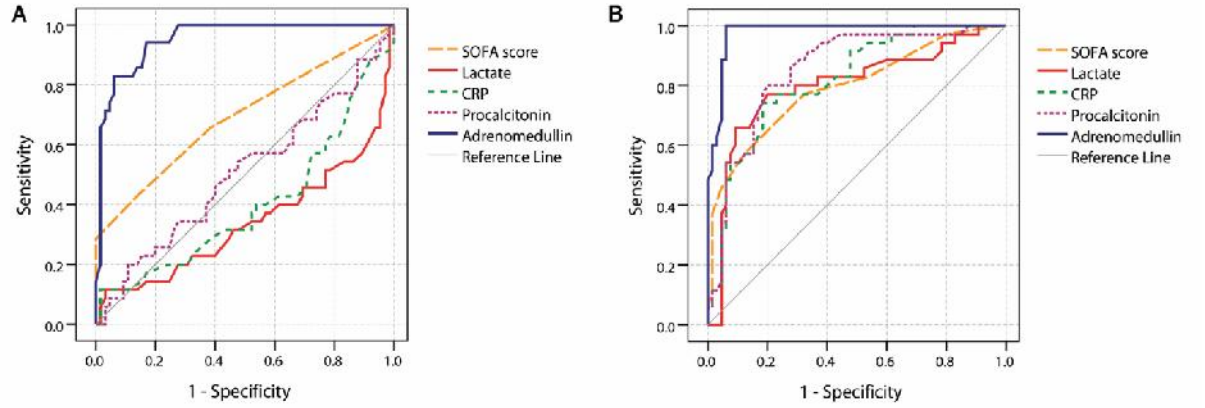

Fig 1: ROC curves in predicting septic shock from **(A)** on admission measurements and **(B)** day 5 measurements:

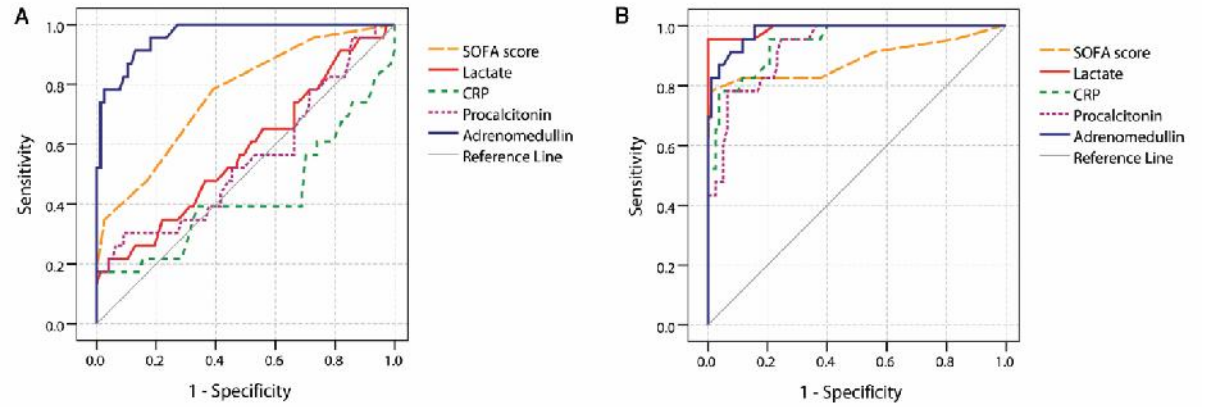

Fig 2: ROC curves in predicting mortality from **(A)** on admission measurements and **(B)** day 5 measurements:

particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone (Mervyn et al; 2016).

This consensus process will take full advantage of the rapidly advancing understanding of molecular processes that lead from infection to organ failure and death so that sepsis and septic shock will no longer need to be defined as a syndrome but rather as a group of identifiable diseases, each characterized by specific cellular alterations and linked biomarkers (Mervyn et al; 2016).

The ability to choose which is more ideal from the most widely used biomarkers such as lactate, PCT, and CRP, to early diagnose sepsis and guide its management is limited. Still the role of these biomarkers in prognosis of septic patients is questionable. Techniques that integrate data from various combinations of biomarkers with information already available at the bedside are promising but require further evaluation (Khan and Rajendrum 2015).

In the present study, the role of ADM as one of the promising septic biomarkers in prognosis of septic patients was evaluated in conjunction with some other biomarkers and SOFA score hoping to find out which of them could predict incidence of septic shock and mortality. The choice of SOFA score in this study has been more reinforced after its inclusion in the new clinical criteria defining sepsis.

The present work revealed that admitting SOFA score and ADM were the only early predictors of occurrence of septic shock and mortality. SOFA score was an early predictor for septic shock with sensitivity, specificity, positive, and negative predictive values of 42.9%, 86.1%, 62.5, & 73.7 respectively. For predicting mortality it showed sensitivity, specificity, positive, and negative predictive values of 78.3%, 61%, 37.5, & 90.4 respectively. ADM showed superiority over SOFA score in predicting both outcomes ($p = 0.0005$). For predicting septic shock, ADM with a cut-off value of 37.9 showed sensitivity, specificity, positive, and negative predictive values of 94.3%, 83%, 75, & 96.4 respectively. In predicting mortality, ADM with a cut-off value of 40 showed sensitivity, specificity, positive, and negative predictive values of 91.3%, 87%, 67.7, &97.1 respectively.

Regarding the values of SOFA score, serum lactate, CRP, serum PCT, and ADM obtained at day 5 of the study, our results proved that all fore-mentioned variables could predict prognosis of septic patients (septic shock and mortality) at this particular time of the study. However ADM showed statistical significance over other parameters in predicting septic shock with highest sensitivity and specificity (100% & 93.8% respectively) but did not reach significance over the other parameters in predicting mortality (sensitivity: 100% & specificity: 84.4%), $p < 0.05$.

The role of SOFA score for predicting outcome in 248 severe sepsis patients was studied by Alan E. Jones et al (2009). This score was measured on admission and after 72 hours. They concluded that SOFA score was potentially valuable prognostic parameter in predicting in-hospital mortality in septic patients.

Another study done by Bale et al (2013), they evaluated the role of SOFA score as a prognostic marker in critically ill septic patients, SOFA was calculated twice, (on admission and 48 hours later), they found that SOFA score was a good predictor of mortality.

Yun-Xia Chen and Chun-Sheng Li (2013) studied the predictive value of ADM for development of severe sepsis and septic shock in ER. This research enrolled 372 septic patients, 71 of them (19%) deteriorated to severe sepsis and septic shock. They measured ADM level only on admission and they concluded that ADM was the only independent predictor of development of severe sepsis and septic shock in those patients. However, they did not evaluate the role of ADM in predicting mortality.

In another study done by Rossella Marino et al (2014), about the role of ADM in predicting 28-days mortality of 101 septic patients, they concluded that plasma ADM is strongly associated with short-term mortality.

Conclusion

Serum adrenomedullin when measured on admission in septic patients may serve as an early predictor of outcome including deterioration to septic shock and 28-days mortality.

Conflict of interests:

The authors declare that they have no conflict of interests.

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