

Prognostic Value of Bioactive Adrenomedullin in Critically Ill Patients

Osama El Minshawy*, Hager Gomaa Abd El Fatah*, Ali Omar Abdelaziz**, Ahmed Abdel Fadel Saedii***, Mohamed Omar Abd El Aziz*

*Internal Medicine Department, Faculty of Medicine, Minia University

** Chest Department, Faculty of Medicine, Minia University

*** Clinical Pathology Department, Faculty of Medicine, Minia University

*Corresponding author: Hager Gomaa Abd El Fatah, Mobile: (+20) 01142741126, E-Mail: hagerg1990@yahoo.com

Abstract:

Introduction: Sepsis can be identified and classified using biomarkers, which can aid in understanding critical illness. Vasoactive hormone adrenomedullin has been shown to have prognostic and maybe therapeutic value in sepsis. This study's objective is to assess the prognostic value of the serum level of admission bio-ADM in critically ill patients. **Patients & Methods:** In this observational prospective study, patients who were admitted to Minia University Hospitals' medical critical care unit (ICU) between December 2020 and November 2021 underwent a complete blood count, CRP as well as renal and liver function tests and blood culture. All patients had their bio-adrenomedullin levels evaluated by ELISA at the time of admission. **Results:** The work included 114 patients who were subdivided into 3 groups: non-septic group including SIRS patients with negative blood culture (n=44), mild sepsis group including patients with SOFA score ≥ 2 without organ dysfunction (n=26), and severe sepsis group including sepsis patients with organ dysfunction or refractory hypotension (n=44). There was a significant difference in distribution of the quartiles of bio-ADM between survivor and non-survivors.

Conclusion: measuring bio ADM levels in the blood enables the early diagnosis and warning of sepsis.

Keywords: bio active adrenomedullin; sepsis

Introduction

Sepsis can be recognized and classified using biomarkers, which can aid in understanding critical illness. Vasoactive hormone adrenomedullin has prognostic and maybe therapeutic effect in sepsis{1}. It is a 52-amino acid peptide hormone first discovered in human pheochromocytoma cells.{2}, but is produced by many different cell types {3}.Its plays a part in the homeostasis of cardiovascular, endocrine, renal and immunological systems and has a role in the electrolyte balance{4}.

More specifically, ADM has vasodilatory properties {5},by binding to receptors on both endothelial and smooth muscle cells. {6}. Further, ADM is capable of modulating the endothelial barrier, where it has a stabilizing effect. {7}.

Over the last fifteen years, the role of ADM in sepsis has been investigated. Several studies have reported an association of increased levels of ADM and poor outcomes among patients with sepsis and septic shock. {8}.A cut-off value of 70 pg/mL

bio-ADM has been used, which originates from Marino and colleagues [9]. It is not clear how this threshold was chosen, but the authors reported a 100% 28-day survival rate in a minimal subgroup ($n = 12$) where a reduction of bio-ADM levels to below 70 pg/ mL was observed.

Aim of the work

The primary aim of this study was to investigate the serum level of admission bio-ADM in critically ill patients and to compare its level between septic and non-septic patients. Also to evaluate the prognostic value of admission bio-ADM.

Ethical consent:

The study was approved by the Academic and Ethical Committee of Minia University. Acceptance of participation in the trial was contingent on the patient providing written informed permission. All procedures involving human subjects in this study have been performed in compliance with the principles outlined in the World Medical Association's Declaration of Helsinki on human research ethics.

Statistical analysis

Data collected and encoded using Microsoft Excel software. Data were then imported into Statistical Package for Social Sciences (SPSS version 20.0) software for analysis. Receiver operator characteristic (ROC) curve plots are used to show how the true positive and false positive values of various cut-off points relate to one another. P value < 0.05 was considered significant.

Patient & Methods

The current prospective study was conducted to all patients who were admitted to the medical intensive care unit (ICU) at Minia University Hospitals, between December 2020 and November 2021.

All patients were subjected to: complete history taking, full clinical examination, Measurement of vital signs (body temperature, pulse, blood pressure and respiratory rate). General examination with special emphasis on stigmata of dehydration, thyroid status, lower limb edema, and conscious level. Careful abdominal examination with special reference to the status of the liver and spleen as regards size, surface, edge, consistency and tenderness on examination.

All patients were subjected to the following investigations; Complete blood count, liver and renal function tests, serum electrolytes, CRP, and blood culture.

Chest X ray and abdominal ultrasound were done to all patients

The sepsis-3 criteria [10] were used to identify patients with sepsis, defined as a SOFA score ≥ 2 on ICU admission with a suspicion of infection within 24 h before or 24 h after ICU admission. A suspected infection was defined by blood culture sampling and concomitant administration of oral or intravenous antibiotics (24 h before to 72 h after blood culture), as suggested by the sepsis-3 task force [11].

Septic shock was defined as the need of a vasopressor, identified by either a cardiovascular SOFA score ≥ 3 or after a medical record review, and a lactate level of ≥ 2 mmol/L among those fulfilling sepsis criteria on ICU admission.

Blood Sampling Protocol

About 5 mls of venous blood were withdrawn from each subject by sterile venipuncture under complete aseptic conditions and then divided into two tubes as follow: 1st tube containing EDTA: 0.5 ml blood for complete blood count (CBC) by automated cell counter (SYSMEX KX-2iN, Japan), 2nd tube was a plain tube: the remaining blood left until clotted and then centrifuged for obtaining serum which used for assaying routine investigations as: CRP (latex, spinreact, Spain), renal function tests (blood urea and serum creatinine), liver function tests including (ALT, AST, albumin and bilirubin total & direct), serum electrolytes (Na^+ , K^+ , Ca^{++} , Mg^{++}) done using fully automated clinical chemistry auto-analyzer system Konelab 20i (Thermo-Electron Incorporation, Finland). The remaining serum was preserved at -20°C for assaying of adrenomedullin by ELISA (bioassay technology laboratory, China).

Blood culture was done using (BD™ BACTEC™ FX40 Automated Blood Culture System, Becton Dickinson, Ireland) and subcultures done for positive cases to identify the causative organism [identification and AST done by (VITEK-2, bioMérieux - USA)].

Results

The study included 114 patients who were subdivided into 3 groups: non-septic group including SIRS patients with negative blood culture and negative CRP (n=44), mild sepsis group including patients with SOFA score ≥ 2 without organ dysfunction (n=26), and severe sepsis group including sepsis patients with organ dysfunction or refractory hypotension (n=44).

Table (1): Distribution of bio-ADM quartiles in the studied groups

Bio-ADM quartiles	Non-septic (n=44)	Mild sepsis (n=26)	Severe sepsis (n=44)	P-value
<47 pg/ml	24(54.5%)	5(19.2%)	0(0%)	<0.001*
47-98 pg/ml	17(38.6%)	11(42.3%)	1(2.3%)	
99-215 pg/ml	3(6.8%)	10(38.5%)	15(34.1%)	
>215 pg/ml	0(0%)	0(0%)	28(63.6%)	

Data are expressed as number and percent.*Significant difference

Table (2): compares the four quartiles of bio-ADM in survivors and the Non-survivors groups

There was a significant difference in distribution of the quartiles of bio-ADM between survivor and non-survivors. Most of the non-survivors in our cohort were in the 4th quartile of bio-ADM (38.9%) while 45% of the survivors were in the 1st quartile of bio-

ADM.

Table (2): Distribution of bio-ADM quartiles in survivors and non-survivors

Bio-ADM quartiles	Survivors (n=60)	Non-survivors (n=54)	P-value
<47 pg/ml	27(45%)	2(3.7%)	<0.001*
47-98 pg/ml	14(23.3%)	15(27.8%)	
99-215 pg/ml	12(20%)	16(29.6%)	
>215 pg/ml	7(11.7%)	21(38.9%)	

Data are expressed as number and percent.*Significant difference

Fig. (1): Linear correlation of Bio-ADM with (A): CRP and (B): SOFA score. The levels of Bio-ADM were positively correlated with CRP (r-value: 0.65, p-value < 0.001) and SOFA score (r-value: 0.63, p-value < 0.001).

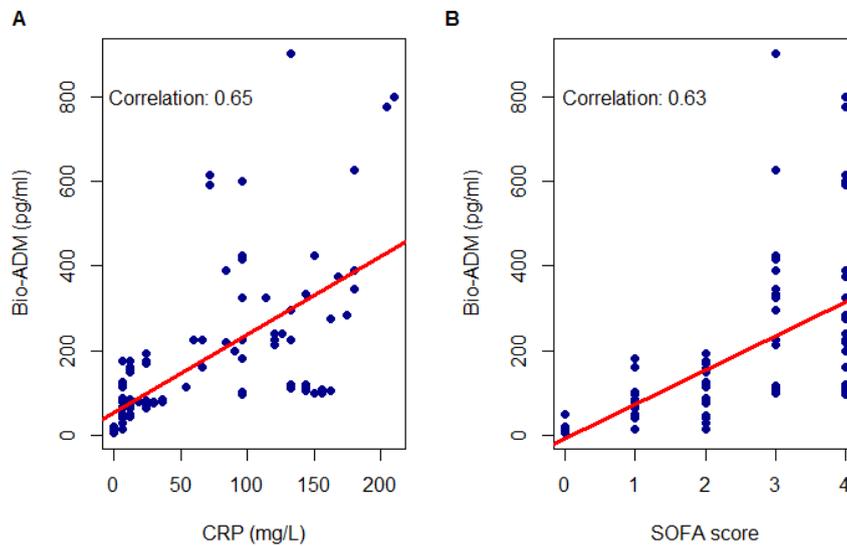


Fig.(2): Receiver operating characteristic (ROC) curve for the prognostic accuracy of bio-ADM, CRP, and SOFA score

Using receiver operating characteristic (ROC) curve to determine the prognostic accuracy of bio-ADM, CRP, and SOFA score (**Fig ; 2**) revealed higher area under curve (AUC) for bio-ADM (0.78, 95% CI: 0.69-0.86) followed by CRP (0.66, 95% CI: 0.56-0.76) and SOFA score (0.63, 95% CI: 0.52-0.73). The best cut-off for bio-ADM to predict ICU mortality in our cohort was 121.5 pg/ml with a sensitivity of 85% and a specificity of 61%.

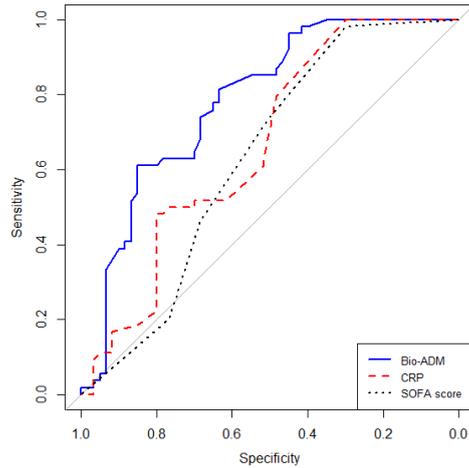


Fig.(3): Receiver operating characteristic (ROC) curve for the prognostic accuracy of bio-ADM, CRP, and SOFA score in the non- septic group.

In the control group, CRP had the best prognostic accuracy under ROC curve (AUC: 0.84) followed by bio-ADM (AUC: 0.83) and SOFA score (AUC: 0.76) (**Figure 3**).

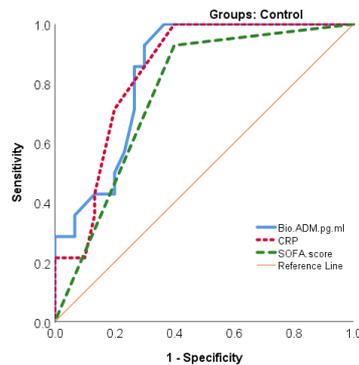


Fig.(4): Receiver operating characteristic (ROC) curve for the prognostic accuracy of bio-ADM, CRP, and SOFA score in mild sepsis group.

In the mild sepsis group, bio-ADM had the best prognostic accuracy under ROC curve (AUC: 0.97) followed by SOFA score (AUC: 0.50) and CRP (AUC: 0.39) (**Figure 4**).

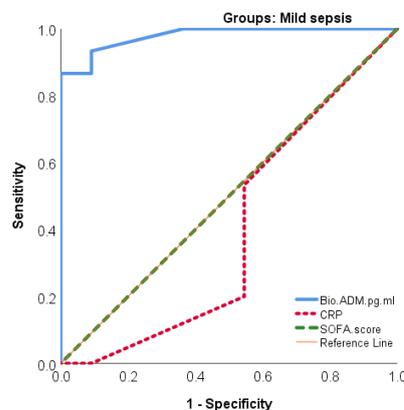
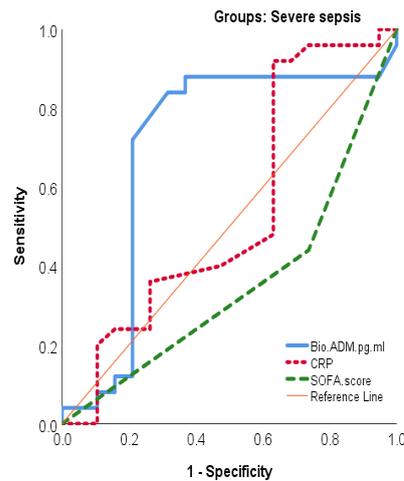


Fig.(5): Receiver operating characteristic (ROC) curve for the prognostic accuracy of bio-ADM, CRP, and SOFA score in severe sepsis group

In the severe sepsis group, bio-ADM had the best prognostic accuracy under ROC curve

(AUC: 0.69) followed by CRP (AUC: 0.53) and SOFA score (AUC: 0.35) (Figure 5).



Discussion

Sepsis is one of the most complex syndromes in medicine and it is one of the leading causes of mortality in critically ill patients to the tune of 20–40% in intensive care unit (ICU) with sepsis and 50% in septic shock.¹ (Angus DC)

The global incidence of severe sepsis is greater than of either cancer or myocardial infarction, with a mortality rate estimated at 40% [1-3 Angus DC, Martin GS, Vincent JL]. This high mortality is in many cases linked to multi-organ hypoperfusion 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 [4 Vincent JL]. Biomarkers such as C-reactive protein (CRP), leukocyte count, lactate and Procalcitonin (PCT) are often used to differentiate between systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis and septic shock as well as for patient risk stratification [5-7 Dellinger RP, Magrini L, Travaglini F].

In the last years, plasma biomarkers have been proposed as tools for a rapid diagnosis and good indicator of prognosis. Among these, PCT and MR-proADM showed the best diagnostic and prognostic accuracy for the complementary nature of given information. PCT was optimal for etiological diagnosis and antimicrobial therapy management¹² (Spoto, S. *et al* 2019), whereas MR-proADM was significantly correlated with organ failure and worse prognosis.

The combination of MR-proADM with other biomarkers, especially PCT, was proposed in previous studies^{21– 23,28} (Valenzuela-Sánchez, F).

The combined measurement of PCT and MR-proADM significantly improved sepsis diagnosis, mainly in case of Gram-positive or fungal sepsis where PCT alone could present a lower positive predictive value (PPV)¹²). Actually, the most significant approach to reduce sepsis-related mortality is based on early diagnosis by adequate microbiological cultures collection and administration of empirical antibiotic treatment within 3 h from clinical suspicion⁽¹²⁾

Adrenomedullin (ADM) is a molecule that was first isolated in 1993 from a pheochromocytoma.⁶ Adrenomedullin has anti-inflammatory, bactericidal, positive inotropic, and vasodilatory action (ADM may function as a hormone in circulation control). Adrenomedullin may also promote angiogenesis. The levels of ADM are high in patients with sepsis and its levels can predict the risk of mortality as well as the development of septic shock.^{7–9} (Marino R, Tamer A,) In the current study the overall average of bio-ADM in the studied group was 158.53 ± 176.30 pg/mL. It was 48.31 ± 40.7 pg/mL in control group, 100.9 ± 50.3 pg/mL in mild sepsis group, and 302.7 ± 206.9 pg/mL in severe sepsis group that reflects a significant step increase of bio-ADM with increased severity of sepsis ($P < 0.001$). Also, there was a significant difference in distribution of the quartiles of bio-ADM between the studied groups

Helmy et al studied 100 patients with proved sepsis who needed ICU admission, they found that SOFA score and serum ADM on admission could predict progression to septic shock. ADM prediction power was significantly higher than SOFA.

A previous study evaluated the predictive value of ADM for development of severe sepsis and septic shock in ER. That 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 (13).

Daga et al evaluated eighty patients of sepsis of which 36 were males and 44 were females, were taken in the study as per sepsis III guidelines. They were followed up for a period of 28 days. Serum ADM was measured on day 1 and day 5. They found that: Adrenomedullin is elevated in all patients with sepsis but the rise is more so in the female when compared with males and the ADM level on day 1 could effectively predict the need for inotropic use in patients with sepsis. (Mradul K Daga)

Marino¹ et al demonstrated a strong association of admission ADM levels with the severity of the disease, supporting an earlier report describing elevated ADM levels in those with severe sepsis and those with septic shock [14].

A correlation of plasma ADM in septic shock patients with the relaxation of vascular tone has been previously observed [15].

Sepsis patients were generally sicker and had significantly higher bio-ADM than the general ICU population. Further, patients with septic shock had significantly higher levels of bio-ADM, which is in agreement with previous reports [16].

Mid-regional pro-adrenomedullin (MR-proADM) has been recently proposed for sepsis diagnosis and prognosis, also providing etiological information (17). Its levels significantly relate with septic patients' outcomes showing good relation with prognosis and mortality rate (18)

The current study showed that, there was a significant difference in distribution of the quartiles of bio-ADM between survivor and non-survivors. Most of the non-survivors in our cohort were in the 4th quartile of bio-ADM (38.9%) while 45% of the survivors

were in the 1st quartile of bio-ADM. About 68% of the non survivors were in the third and fourth quartile of bio-ADM.

Our results are in agreement with Simon et al. Who studied 42 patients with sepsis in ICU and 14 patients who developed sepsis after major surgery. They found that higher ADM levels were associated with increased vasopressor need and mortality at 90 days.8 (Simon TP).

Also in accordance with our results, Marino1 et al studied 101 consecutive patients admitted to the emergency department with suspected sepsis, they found that In patients admitted with sepsis, severe sepsis or septic shock plasma ADM is strongly associated with severity of disease, vasopressor requirement and 28-day mortality.

Admission bio-ADM is associated with 30-day mortality and organ failure in sepsis patients as well as in a general ICU population. Bio-ADM may be a morbidity-independent sepsis biomarker (19). Lundberg et al evaluated Bio-ADM in 1867 consecutive patients; 632 patients fulfilled the sepsis-3 criteria of whom 267 had septic shock. They found that The median bio-ADM in the entire ICU population was 40 pg/mL, 74 pg/mL in sepsis patients, 107 pg/mL in septic shock and 29 pg/mL in non-septic patients. The association of elevated bio-ADM and mortality in sepsis patients and the ICU population resulted in ORs of 1.23 (95% CI 1.07–1.41) and 1.22 (95% CI 1.12–1.32), respectively. The association with mortality remained after additional adjustment for lactate in sepsis patients. Elevated bio-ADM was associated with an increased need for dialysis with ORs of 2.28 (95% CI 2.01–2.59) and 1.97 (95% CI 1.64–2.36) for the ICU population and sepsis patients, respectively, and with increased need of vasopressors, OR 1.33 (95% CI 1.23–1.42) (95% CI 1.17–1.50) for both populations. Sepsis was identified with an OR of 1.78 (95% CI 1.64–1.94) for bio-ADM, after additional adjustment for severity of disease. A bio-ADM cut-off of 70 pg/mL differentiated between survivors and non-survivors in sepsis, but a Youden's index derived threshold of 108 pg/mL performed better.

Lemasle and colleagues studied a large population of patients requiring vasopressor or invasive ventilation for more than 24 h and found an association of bio-ADM with mortality and need for organ support.

However ,in one study that investigated only 12 septic patients, admission ADM did not distinguish survivors from non-survivors and did not correlate with mean arterial pressure [20].

Interestingly, Mebazaa et al. reported Youden's index cut-off of 102 pg/mL from their sepsis cohort in a recent study [21]. For the entire ICU population, the Youden's index identified the cut-off 45 pg/mL, which is a novel finding for bio-ADM.

Spoto et al 2020 study using ROC analysis showed that besides clinical scores, PCT measurement represent the best diagnostic accuracy in sepsis, as previously described12 (Spoto, S. et al 2020),21– 24 (Angeletti, S. et al 2015, Angeletti, S. et al 2016) 41 (Spoto, S. et al 2018),42 (Vincenzi, B. et al. 2016) allowing early tailored antimicrobial therapy administration and daily follow-up (Silvia Spoto1) . It should be reliable to combine bedside SIRS criteria or qSOFA with PCT laboratory determination for early identification of sepsis, followed by SOFA score calculation for severity and

prognosis evaluation. In this study, about 35% of patients were negative for SIRS criteria or qSOFA, and SOFA score or for all, despite evidence of positive blood culture and documented microbiological isolate or clinical diagnosis of infection. In these patients, the use of MR-proADM was essential to provide early diagnosis and confirm the suspicion of sepsis (Silvia Spoto 2020) .

In the present study , using receiver operating characteristic (ROC) curve to determine the prognostic accuracy of bio-ADM, CRP, and SOFA score revealed higher area under curve (AUC) for bio-ADM (0.78, 95% CI: 0.69-0.86) followed by CRP (0.66, 95% CI: 0.56-0.76) and SOFA score (0.63, 95% CI: 0.52-0.73). The best cut-off for bio-ADM to predict ICU mortality in our cohort was 121.5 pg/ml with a sensitivity of 85% and a specificity of 61%. In the mild sepsis group, bio-ADM had the best prognostic accuracy under ROC curve (AUC: 0.97) followed by SOFA score (AUC: 0.50) and CRP (AUC: 0.39) .In the severe sepsis group, bio-ADM had the best prognostic accuracy under ROC curve (AUC: 0.69) followed by CRP (AUC: 0.53) and SOFA score (AUC: 0.35). The current study demonstrated a positive correlation between the levels of Bio-ADM with CRP (r-value: 0.65, p-value < 0.001) and SOFA score (r-value: 0.63, p-value < 0.001

In sepsis and septic shock, MR-proADM compared to other well-known biomarkers or clinical scores, showed a prognostic accuracy higher than those of PCT, IL-6, CRP or clinical scores as Acute Physiology and Chronic Health (APACHE) 23,24,26. (Spoto, S. *et al* 2018 ,Angeletti, S. *et al*,) .Christ-Crain et al. analyzed MR-proADM levels in septic patients admitted to intensive care unit (ICU) showing a significantly higher correlation with sepsis severity than PCT and CRP(26, . Christ-Crain, M. *et al*). Recently, Kim et al., reported a significant correlation between MR-proADM levels and septic shock, need for vasopressor, and 30-day mortality, suggesting its inclusion in the panel of biomarkers that may be useful for diagnosis and treatment management of critical patients in ICU 27 (Kim, H. *et al*).

Conclusion

Bio ADM is elevated in patients with sepsis and the elevation is more in patients with severe sepsis. The non-survivors patients Bio ADM was significantly higher than in the survivors group which implicate that Bio ADM could be used as diagnostic and prognostic markers in patients with sepsis.

References

1. Ashizuka S, Inatsu H, Kita T, Kitamura K(2016). Adrenomedullin therapy in patients with refractory ulcerative colitis. *Dig Dis Sci* 61(3):872–80.
2. Bell D, Campbell M, Harbinson MT(2016). Endothelium-derived intermedin/adrenomedullin-2 protects human ventricular cardiomyocytes from ischaemia-reoxygenation injury predominantly via the AM(1) receptor. *Peptides* 76:1–13.
3. Spoto, S. *et al*. Procalcitonin and MR-proAdrenomedullin combination in the etiological diagnosis and prognosis of sepsis and septic shock. *Microb. Pathog.* **137**, 103763 (2019).
4. Angeletti, S. *et al*. Diagnostic and prognostic role of procalcitonin (PCT) and MR-pro-Adrenomedullin (MR-proADM) in bacterial infections. *APMIS.* **123**, 740–748 (2015).
5. Angeletti, S. *et al*. Procalcitonin, MR-Proadrenomedullin, and cytokines measurement in sepsis

diagnosis: advantages from test combination. *Dis. Markers* **2015**, 951532 (2015).

6. Angeletti, S. *et al.* Procalcitonin and MR-proAdrenomedullin combined score in the diagnosis and prognosis of systemic and localized bacterial infections. *J. Infect.* **72**, 395–398 (2016).
7. Spoto, S. *et al.* Procalcitonin and MR-Proadrenomedullin combination with SOFA and qSOFA scores for sepsis diagnosis and prognosis: a diagnostic algorithm. *Shock* **50**, 44–52 (2018).
8. Önal, U., Valenzuela-Sánchez, F., Eshwara Vandana, K. & Rello, J. Mid-regional pro-adrenomedullin (MR-proADM) as a biomarker for sepsis and septic shock: narrative review. *Healthcare (Basel)*. **6**, 110 (2018).
8. Kim, H. *et al.* Circulating biologically active adrenomedullin predicts organ failure and mortality in sepsis. *Ann. Lab. Med.* **39**,454–463 (2019).
9. Valenzuela-Sánchez, F., Valenzuela-Méndez, B., Rodríguez-Gutiérrez, J. F., Estella-García, Á & González-García, M. Á. New role of biomarkers: mid-regional pro-adrenomedullin, the biomarker of organ failure. *Ann. Transl. Med.* **4**, 329 (2016).
10. Seymour, C. W. *et al.* Assessment of clinical criteria for sepsis: for the third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* **315**, 762–774 (2016).
11. Spoto, S. *et al.* The role of procalcitonin in the diagnosis of bacterial infection after major abdominal surgery: advantage from daily measurement. *Medicine (Baltimore)*. **97**, e9496 (2018).
12. Vincenzi, B. *et al.* Procalcitonin as diagnostic marker of infection in solid tumors patients with fever. *Sci. Rep.* **6**, 28090 (2016).
13. Silvia Spoto1*, Edoardo Nobile1, Emanuele Paolo Rafano C arnà1, Marta Fogolari2, Damiano C aputo3, Lucia De Florio2, Emanuele Valeriani1, Domenico Benvenuto4, Sebastiano C ostantino1, Massimo C iccozzi4 & Silvia Angeletti2. Best diagnostic accuracy of sepsis combining SIRS criteria or qSOFA score with Procalcitonin and Mid-Regional pro-Adrenomedullin outside ICU. *Scientific Reports* | (2020) 10:16605
14. Marino R, Struck J, Maisel AS, Magrini L, Bergmann A, Di Somma S. Plasma adrenomedullin is associated with short-term mortality and vasopressor requirement in patients admitted with sepsis. *Critical Care* 2014;18(1):R34. DOI: 10.1186/cc13731.
15. Simon TP, Martin L, Doemming S, Humbs A, Bruells C, Kopp R, et al. Plasma adrenomedullin in critically ill patients with sepsis after major surgery: a pilot study. *J Crit Care* 2017;38:68–72. DOI: 10.1016/j.jcrc.2016.10.017.
16. Tamer A, Bassem N. Prognostic role of adrenomedullin in sepsis. *Int J Adv Res Biol Sci* 2016;3(5):136–141.
17. Mradul K Dagal, Lalit Kumar2, Govind Mawari3, Naresh Kumar4, Shashank Singh5, Tarun Kumar Mishra6 .Adrenomedullin and Its Possible Role in Improved Survival in Female Patients with Sepsis: A Study in the South East Asian Region. *Indian Journal of Critical Care Medicine* (2020): 10.5005/jp-journals-10071-23672
- 18. Tamer Abdallah Helmy, Bassem Nashaat Beshey. Prognostic role of adrenomedullin in sepsis. Int. J. Adv. Res. Biol. Sci. (2016). 3(5): 136-141**
19. Yun-Xia Chen and Chun-Sheng Li (2013). The Predictive Value of Adrenomedullin for Development of Severe Sepsis and Septic Shock in Emergency Department. *BioMed Research International*, vol. 2013, Article ID 960101, 6 pages. doi:10.1155/2013/960101.
20. Marino R1, Joachim Struck2,3, Alan S Maisel4, Laura Magrini1, Andreas Bergmann2,3 and

Salvatore Di Somma¹. Plasma adrenomedullin is associated with short-term mortality and vasopressor requirement in patients admitted with sepsis. *Critical Care* 2014, 18:R34

21. Lundberg H. M. ^{1,2*}, Maria Lengquist^{1,2}, Martin Spångfors^{1,3}, Martin Annborn^{1,4}, Deborah Bergmann⁵, Janin Schulte⁵, Helena Levin¹, Olle Melander^{6,7}, Attila Frigyesi^{1,2} and Hans Friberg^{1,2}. Circulating bioactive adrenomedullin as a marker of sepsis, septic shock and critical illness. *Crit Care* (2020) 24:636
22. Mebazaa A, Geven C, Hollinger A, Wittebole X, Chousterman BG, Blet A, Gayat E, Hartmann O, Scigalla P, Struck J, Bergmann A, Antonelli M, Beishuizen A, Constantin JM, Damoiseil C, Deye N, Di Somma S, Dugernier T, Francois B, Gaudry S, Huberlant V, Lascarrou JB, Marx G, Mercier E, Oueslati H, Pickkers P, Sonnevile R, Legrand M, Laterre PF, AdrenOSSi. Circulating adrenomedullin estimates survival and reversibility of organ failure in sepsis: the prospective observational multinational adrenomedullin and outcome in sepsis and septic shock-1 (adrenoss-1) study. *Crit Care* 2018;22(1):354. <https://doi.org/10.1186/s13054-018-2243-2>
23. Kim H, Hur M, Struck J, Bergmann A, Di Somma S. Circulating biologically active adrenomedullin predicts organ failure and mortality in sepsis. *Ann Lab Med*. 2019;39(5):454–63
24. Lemasle L, Blet A, Geven C, Cherifa M, Deniau B, Hollinger A, Fournier MC, Monnet X, Rennuit I, Darmon M, Laterre PF, Struck J, Hartmann O, Bergmann A, Mebazaa A, Gayat E. Bioactive adrenomedullin, organ support therapies, and survival in the critically ill: results from the French and European outcome registry in ICU study. *Crit Care Med*. 2020;48(1):49–55.
25. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche J-D, Cooper Smith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, van der Poll T, Vincent J-L, Angus DC. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA*. 2016;315(8):801–10.