Proadrenomedullin in Sepsis/Septic Shock

Subjects: Pharmacology & Pharmacy

Contributor: Andrea Piccioni

Sepsis and septic shock represent a leading cause of mortality in the Emergency Department (ED) and in the Intensive Care Unit (ICU). For these life-threating conditions, different diagnostic and prognostic biomarkers have been studied. Proadrenomedullin (MR-proADM) is a biomarker that can predict organ damage and the risk of imminent death in patients with septic shock.

sepsis septic shock proadrenomedullin MR-proADM procalcitonin emergency department

1. Introduction

Sepsis and septic shock are life-threatening medical emergencies characterized by severe systemic inflammation and organ dysfunction due to an excessive response to infections that may lead to death [1][2][3][4][5][6]. The definition of sepsis includes a dysregulated systemic inflammation, acute multi-organ dysfunction (i.e., cardiovascular, respiratory, and renal systems), and a deregulated immune response to a microbial invasion of the blood that is responsible of organ failure [7][8][9][10]. The mortality rate ranges from 15–25% [7]. Septic shock is sepsis characterized by a state of hypotension and hyperlactatemia, refractory to adequate fluid volume resuscitation that leads to hypoperfusion abnormalities, oliguria, and the alteration of mental status [7]. Septic shock has a mortality rate that ranges from 30–50% [7]. The early identification of sepsis and septic shock is essential for immediate treatment [1][2] and for the reduction of the patient mortality rate [10][11]. Sepsis can affect people of all ages [2][3][4]. Therapy for sepsis should be personalized and tailored according to the patient's needs. Many biomarkers such as procalcitonin (PCT) or interleukin (IL)-6 or IL-18 are used in clinical practice to facilitate the diagnosis of sepsis [5][6]. Novel biomarkers such as proadrenomedullin (MR-proADM), kallistatin, testican-1, and presepsin have been introduced to assess the severity of sepsis and to predict the organ damage and the risk of imminent death [5].

2. Role of MR-proADM in ICU and in ED

Several authors have investigated the role of MR-proADM in patients with sepsis and septic shock. MR-proADM is a stable and detectable fragment of 48-amino acids derived from ADM (a 52-amino acid peptide and member of the calcitonin family) that is mainly produced by vascular endothelial cells and smooth muscle cells. ADM and MR-proADM have effects on vasodilatation (on artery and vein), natriuresis, bronchodilatation, and they have influences on cardiac contractility and glomerular filtration [11], which are involved in some clinical manifestations of

sepsis and septic shock as refractory hypotension. MR-proADM has a half-life that is longer than ADM and can be more easily detected in blood compared to ADM, which is rapidly cleared from the circulation.

Most of the reported studies found that MR-proADM was a reliable biomarker that could serve as an early predictor of high mortality risk. In fact, levels of MR-proADM can potentially reflect the severity of organ dysfunction, even in the first stages of the disease, in the progression of systemic inflammatory response, in the movement from sepsis to septic shock, and in the mortality risk of septic patients [11][12]. A prospective observational study conducted with 213 septic patients showed that MR-proADM was able to predict system dysfunction (respiratory, coagulation, renal, neurological, and cardiovascular) and was well-correlated with Sequential Organ Failure Assessment (SOFA) score components [13]. The same results were obtained by Onal et al. [11], who concluded that MR-proADM could be a good alternative to SOFA score. L. Buendgens and his team [14] designed a prospective study to assess the role of MR-proADM in a cohort of 203 ICU patients and 66 healthy controls that they followed for a period of 26 months. They demonstrated that MR-proADM values were higher in critically ill patients—especially in those with sepsis progression—with a close correlation with other markers of systemic inflammation and endothelial dysfunction. Moreover, MR-proADM levels correlated with scores for disease severity (Acute Physiology and Chronic Health Disease Classification System (APACHE II), SOFA, and Simplified Acute Physiology Score (SAPS2)). The best cut-off value that was found by these authors to identify patients at high mortality risk was of 1.4 nmol/L [14]. Similar results were also reported by Gonzales Del Castillo et al. [15] in a larger study of 684 patients admitted to the ED for a suspected infection.

The abovementioned authors found that MR-proADM was able to identify those hiding an underlying severe condition and who were at high risk for delayed or insufficient initial treatment. In addition, authors compared several biomarkers (MR-proADM, C-reactive protein (CRP), PCT, and lactate) and clinical scores (SOFA, quick SOFA, and National early warning score (NEWS)), concluding that MR-proADM could help identify patients with low NEWS or quick SOFA values but who were at high risk for sepsis progression, helping in the initial treatment choices [15]. A prospective observational study of 657 patients with an acute infection conducted by Haang et al. [16] reported that the combination of MR-proADM and SOFA-score would better improve the stratification risk of patients for 30-day mortality (area under the curve (AUC) 0.87) than the SOFA-score alone (AUC 0.81). The authors defined a MR-proADM threshold value of 1.75 nmol/L as a prognostic value for 30-day mortality (sensitivity 81%, specificity 75%, and negative predictive value 98%) [16]. The summary of studies exploring the role of MR-proADM can be seen in **Table 1**.

Table 1. Summary of studies exploring the role of proadrenomedullin (MR-proADM).

Authors	Type of Study	Number of Patients and Time of Enrollment	Evidence	Cut-Off (nmol/L)
Spoto S [2] et al.	Retrospective observational study	571	MR-proADM has a strong correlation with 90-day	3.39 (for sepsis) and

Authors	Type of Study	Number of Patients and Time of Enrollment	Evidence	Cut-Off (nmol/L)
Microb Pathog 2019	in adults	(2012–2018)	mortality	4.33 (for septic shock)
Li [3] et al. Med Intensiva 2018	Systematic review and meta-analysis of thirteen studies in adults	2556 (1999–-2017)	MR-proADM might predict the prognosis of septic patients	unknown
Fahmey [4] et al. Korean J Pediatr 2018	Prospective observational pediatric study	60 septic newborns vs. 30 healthy neonates (May 2016–January 2017)	MR-proADM: valid biomarker for neonatal sepsis. High levels were associated with mortality and the disease's outcome.	4.3
Enguix-Armada [12] et al. Clin Chem Lab Med 2016	Prospective observational study in adults	388 (2015)	MR-proADM is useful in the management of septic patients (measured in the first 24 h after ICU admission)	unknown
Andrés C [13] et al. Eur J Clin Invest 2020	Prospective observational study in adults	213 (2019–2020)	MR-proADM correlates with the largest number of Sequential Organ Failure Assessment (SOFA) score components and with organ dysfunction	1.4
Buendgens L [14] et al.	Prospective observational study in adults	269 (2018–2020)	MR-proAMD values are higher in critical septic patients and correlates with other markers of	0.05

Authors	Type of Study	Number of Patients and Time of Enrollment	Evidence	Cut-Off (nmol/L)
Mediators Inflamm 2020			systemic inflammation and severity scores	
Gonzalez Del Castillo J [15] et al. Crit Care 2019	Prospective observational study in adults	684 (May–July 2018)	MR-proADM identifies patients hiding an underlying severe condition and who are at high risk for delayed or insufficient initial treatment	1.77
Haag E [16] et al. Clin Chem Lab Med 2021	Prospective observational study in adults	657 (2019)	MR-proADM plus SOFA-score provide a better risk stratification than SOFA alone	1.75
Spoto S [17] et al. Sci Rep 2020	Prospective observational study in adults	209 (May 2014–June 2018)	MR-proADM anticipates organ failure in septic patients	1
Andaluz-Ojeda D [18] et al. Ann Intensive Care 2017	Prospective observational study in adults	326 (April 2013–January 2016)	MR-proADM predicts mortality in patients with sepsis at an early clinical stage	0.8
Schuetz [19] et al.	Review in adult patients	4 studies (March 2013–October 2014)	MR-proADM: prognostic marker that may improve site of	unknown

Authors	Type of Study	Number of Patients and Time of Enrollment	Evidence	Cut-Off (nmol/L)
Crit Care 2015			care decisions	
Kim [20] et al. Infect Chemother 2020	Review in adult patients	9 studies (1985–2020)	MR-proADM predicts 28-day mortality in septic patients	unknown
Al Shuaibi [21] et al. Clin Infect Dis 2013	Control observational study in adults	340 (June 2009–December 2010)	MR-proADM is useful in the management of febrile patients with hematologic malignancies. It localized bacterial infection and differentiated sepsis from SIRS	0.91 median level in septic patients (range: 0.05–8.78) 0.79 median level in non-septic patients (range: 0.05–6.48)
Valenzuela-Sánchez [22] et al. Minerva Anestesiol 2019	Prospective observational single-center study in adults	20 ICU-patients (June 2011–January 2013)	MR-proADM helped to identify sepsis in patients admitted to ICU. After 48 h of admission, it was associated with death risk	1.425 (before ICU admission) 5.626 (48 hours after)
Viaggi [23] et al.	Prospective	64	MR-proADM anticipates the modification of several scores	1.1

ient.

rinoni, A.; Caputo, D.; Constantino, S.; et al. Procalcitonin and MR-proAdrenomedullin combination in the etiological diagnosis and prognosis of sepsis and septic shock. Microb. Pathog. 2019, 137, 103763.

Authors	Type of Study	Number of Patients and Time of Enrollment	Evidence	Cut-Off (nmol/L)
PLoS One 2018	observational study in adults	(12 March–25 June 2016)	(SOFA, Pitt, and CPIS) related to organ dysfunction	
De La Torre-Prados [24] et al. Minerva Anestesiol 2016	Prospective observational study in adults	100 (January–December 2011)	MR-proADM correlates with 28-day mortality in septic shock patients	unknown

septic shock. Nat. Rev. Dis. Prim. 2016, 2, 16045.

8. Evans, T. Diagnosis and management of sepsis. Clin. Med. 2018, 18, 146–149.
9. Angus, D.C.; Van der Poll, T. Severe sepsis and septic shock. N. Engl. J. Med. 2013, 369, 2063.
10. Zhang, Z.; Smischney, N.J.; Zhang, H.; Poucke, S.V.; Argaud, L.; Kim, W.Y.; Spapen, H.D.; Rocco, J.R. AME evidence series 001-The Society for Translational Medicine: Clinical practice guidelines for diagnosis and early identification of sepsis in the hospital. J. Thorac. Dis. 2016, 8, 2654–2665.
11. Önal, U.; Valenzuela-Sánchez, F.; Vandana, K.E.; Rello, J. Mid-Regional Pro-Adrenomedullin (MR-proADM) as a Biomarker for Sepsis and Septic Shock: Narrative Review. Healthcare 2018, 6, 110.
12. Enguix-Armada, A.; Escobar-Conesa, R.; García-De La Torre, A.; De La Torre-Prados, M.V. Usefulness of several biomarkers in the management of septic patients: C-reactive protein, procalcitonin, presepsin and mid-regional pro-adrenomedullin. Clin. Chem. Lab. Med. 2016, 54, 163–168.
13. Andrés, C.; Andaluz-Ojeda, D.; Cicuendez, R.; Munoz-Bellvis, L.; Aldecoa, C.; Bermejo-Martin, J.F. MR-proADM to detect specific types of organ failure in infection. Eur. J. Clin. Investig. 2020, 50, e13246.
14. Buendgens, L.; Yagmur, E.; Ginsberg, A.; Weiskirchen, R.; Wirtz, T.; Jhaisha, S.A.; Eisert, A.; Luedde, T.; Trautwein, C.; Tacke, F.; et al. Midregional Proadrenomedullin (MRproADM) Serum Levels in Critically Ill Patients Are Associated with Short-Term and Overall Mortality during a Two-Year Follow-Up. Mediat. Inflamm. 2020, 2020, 7184803.

15. Gonzalez Del Castillo, J.; Wilson, D.C.; Clemente-Callejo, C.; Gonzales, V.; Llopis-Roca, F. On behalf of the INFURG-SEMES investigators. Biomarkers and clinical scores to identify patient populations at risk of delayed antibiotic administration or intensive care admission. Crit. Care 2019, 23, 335.
16. Haag, E.; Gregoriano, C.; Molitor, A.; Kloter, M.; Kutz, A.; Mueller, B.; Schuetz, P. Does mid-regional pro-adrenomedullin (MR-proADM) improve the sequential organ failure assessment-score (SOFA score) for mortality-prediction in patients with acute infections? Results of a prospective observational study. Clin. Chem. Lab. Med. 2021, 59, 1165–1176.
17. Spoto, S.; Nobile, E.; Carnà, E.P.R.; Fogolari, M.; Caputo, D.; De Florio, L.; Valeriani, E.; Benvenuto, D.; Constantino, S.; Ciccozzi, M.; et al. Best diagnostic accuracy of sepsis combining SIRS criteria or qSOFA score with Procalcitonin and Mid-Regional pro-Adrenomedullin outside ICU. Sci. Rep. 2020, 10, 16605.
18. Andaluz-Ojeda, D.; Nguyen, H.B.; Meunier-Beillard, N.; Gandia, F.; Bermejo-Martin, J.F.; Charles, P.E. Superior accuracy of mid-regional proadrenomedullin for mortality prediction in sepsis with varying levels of illness severity. Ann. Intensiv. Care 2017, 7, 15.
19. Schuetz, P.; Hausfater, P.; Amin, D.; Amin, A.; Haubitz, S.; Faessler, L.; Kutz, A.; Conca, A.; Reutlinger, B.; Canavaggio, P.; et al. TRIAGE Study group. Biomarkers from distinct biological pathways improve early risk stratification in medical emergency patients: The multinational, prospective, observational TRIAGE study. Crit. Care 2015, 19, 377.
20. Kim, M.H.; Choi, J.H. An Update on Sepsis Biomarkers. Infect. Chemother. 2020, 52, 1–18.
21. Al Shuaibi, M.; Bahu, R.R.; Chaftari, A.M.; Chaftari, A.M.; Wohoush, I.A.; Shomali, W.; Jiang, Y.; Debiane, L.; Raad, S.; Jabbour, J.; et al. Pro-adrenomedullin as a novel biomarker for predicting infections and response to antimicrobials in febrile patients with hematologic malignancies. Clin. Infect. Dis. 2013, 56, 943–950.
22. Valenzuela-Sánchez, F.; Valenzuela-Méndez, B.; Bohollo de Austria, R.; Rodriguez-Gutierrez, J.F.; Estella-Garcia, A.; Fernandez-Ruiz, L.; Gonzalez-Garcia, M.; Rello, J. Plasma levels of mid-regional pro-adrenomedullin in sepsis are associated with risk of death. Minerva Anestesiol. 2019, 85, 366–375.
23. Viaggi, B.; Poole, D.; Tujjar, O.; Marchiani, S.; Ognibene, A.; Finazzi, S. Mid regional pro-adrenomedullin for the prediction of organ failure in infection. Results from a single centre study. PLoS ONE 2018, 13, e0201491.
24. DE LA Torre-Prados, M.V.; Garcia-DE LA Torre, A.; Enguix, A.; Mayor-Reyes, M.; Nieto-González, M.; Garcia-Alcantara, A. Mid-regional pro-adrenomedullin as prognostic biomarker in septic shock. Minerva Anestesiol. 2016, 82, 760–766.