



Pooled analysis of mid-regional pro-adrenomedullin values in COVID-19 patients with critical illness

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Received: 2 March 2021 / Accepted: 29 April 2021 / Published online: 7 May 2021
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Keywords Coronavirus · COVID-19 · Mid-regional pro-adrenomedullin · MR-proADM

Dear Editor,

Adrenomedullin (ADM), a potent vasodilatory peptide hormone produced by endothelial cells and several other mammalian tissues (heart, lung, kidney, bone, adrenals, etc.) exerts a vast array of angiogenic, anti-inflammatory, antioxidant and anti-apoptotic activities, thus playing a crucial role in inflammatory diseases and influencing the progression from sepsis to septic shock [1]. Recent evidence suggests that the measurement of the mid-regional pro-adrenomedullin (MR-proADM), a 48 amino acid mostly inert fragment split from the final ADM, which is secreted in 1:1 ratio and which has a significantly longer half-life than ADM, may offer considerable clinical prognostic value for predicting the risk of developing critical illness in patients with overt sepsis [1, 2], as well as in those with severe localized infections, such as community-acquired pneumonias [3], including those of viral origin [4]. As interstitial pneumonia is the leading pathological manifestation of coronavirus disease 2019 (COVID-19), and given that patients with COVID-19 are at extremely high risk of developing bacterial superinfections, especially those needing intensive care [5], we performed a critical literature review and meta-analysis to explore as to whether MR-proADM assessment may help predicting unfavorable disease progression in COVID-9 patients.

An electronic search was carried out in PubMed, Scopus, and Web of Science, using the keywords “adrenomedullin” OR “proadrenomedullin” OR “Mid-regional

proAdrenomedullin” OR “MR-proADM” AND “coronavirus disease 2019” OR “COVID-19” within all fields, and without language or date limits (i.e., up to April 20, 2021). The two authors reviewed title, abstract and full text of all documents identified with these search criteria, selecting studies which described MR-proADM values in COVID-19 patients with different degrees of illness severity. The references list of each of these articles was also scrutinized for identifying other eligible documents. Mean and standard deviation (SD) of MR-proADM values were included in a pooled analysis, with estimation of weighted mean difference (WMD) and 95% confidence interval (95% CI) in COVID-19 patients with or without critical illness. When mean value and SD were unavailable, they were estimated from sample size, median and interquartile range (IQR), as suggested by Hozo et al. [6]. When multiple MR-proADM values were shown, those corresponding to COVID-19 peak severity were selected. A quality effects model was used for pooled analysis, whilst a second random effects model was also calculated to adjust for heterogeneity emerging across different studies. Heterogeneity was evaluated with the χ^2 test and I^2 statistic. The statistical analysis was performed using MetaXL, software Version 5.3 (EpiGear International Pty Ltd., Sunrise Beach, Australia). The study was conducted in agreement with the declaration of Helsinki and within the terms of local legislation.

The electronic search carried out in accordance the above-mentioned criteria identified 34 documents after elimination of duplicates. Among these, 28 were excluded as they were review articles ($n = 13$), editorial material ($n = 1$) or correspondence without original data ($n = 2$), did not specifically deal with COVID-19 ($n = 6$), did not provide MR-proADM values ($n = 2$), lack of complete information on MR-proADM values ($n = 1$), or MR-proADM values were not stratified according to COVID-19 severity ($n = 3$). No significant disagreement emerged between

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Table 1 Summary of clinical studies which explored mid-regional pro-adrenomedullin (MR-proADM) levels in coronavirus disease 2019 (COVID-19) patients with or without critical illness

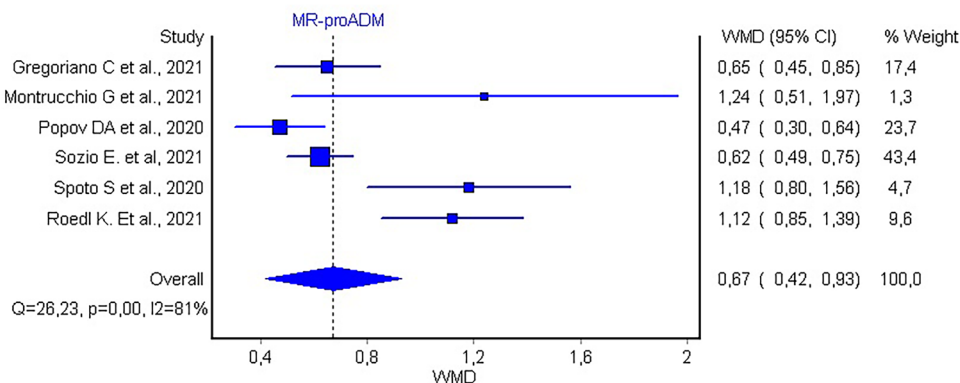
Authors	Setting	Sample size	Endpoint	Values (severe vs. non-severe; nmol/L)
Gregoriano C et al. (2021) [7]	Switzerland	89 (19% severe)	Death	1.50±0.40 vs. 0.85±0.23
Montrucchio G et al. (2021) [8]	Italy	57 (54% severe)	ICU admission or death	2.37±1.63 vs. 1.13±1.16
Popov DA et al. (2020) [9]	Russia	97 (14% severe)	Death	1.25±0.31 vs. 0.78±0.22
Roedl K. et al. (2021) [10]	Germany	64 (45% severe)	RRT	2.46±0.64 vs. 1.34±0.39
Sozio E et al. (2021) [11]	Italy	111 (25% severe)	Death or intubation	1.36±0.31 vs. 0.74±0.23
Spoto S et al. (2021) [12]	Italy	69 (58% severe)	ARDS	2.30±1.11 vs. 1.12±0.45

ARDS acute respiratory distress syndrome, ICU intensive care unit, RRT renal replacement therapy

the two reviewers. Six studies were thus finally included in pooled analysis, totaling 487 COVID-19 patients, 159 (32.6%) with critical illness, as summarized in Table 1 [7–12]. All included studies were cross sectional investigations, three conducted in Italy, while the others were located in Germany, Russia and Switzerland. The clinical endpoints used for characterizing critical illness of COVID-19 were cumulative mortality in two studies, as opposed to intensive care unit (ICU) admission or death, need for renal replacement therapy (RRT), death or intubation, and acute respiratory distress syndrome (ARDS) in the remaining investigations (Table 1). The pooled analysis of these six studies is shown in Fig. 1, demonstrating a positive difference of MR-proADM values between patients with or without critical COVID-19 in each individual study. The WMD of MR-proADM values in COVID-19 patients with critical illness versus those without was 0.67 (95% CI 0.42–0.93) nmol/L in the quality effects model (with high heterogeneity, $I^2 = 81%$) (Fig. 1), further increasing to 0.80 (95% CI 0.58–1.02) nmol/L in the random effects model. Overall, MR-proADM values were found to be increased by 74% (95% CI 46–103%) in COVID-19 patients with critical illness compared to those without.

Notably, two studies among those excluded deserve special mention. Hupf et al. assayed ADM gene expression rather than the circulating hormone concentration in 21 COVID-19 patients and, in agreement with our findings on MR-proADM levels, they reported significantly higher values in subjects who died than in those who survived [13]. In a subsequent investigation, which could not be included in the pooled analysis due to lack of complete information on MR-proADM values, Benedetti et al. found that the median concentration of this biomarker was significantly higher in COVID-19 patients who died (11/21; 52%) than in those who survived (3.5 vs. 0.8 nmol/L; $p = 0.006$) [14]. As concerns the possible mechanisms underpinning the negative effect of MR-proADM on infectious diseases course, including COVID-19, this molecule is deeply involved in the inflammatory response and in progression from sepsis to septic shock [1]. In both conditions, vascular endothelium represent the most predominant source of MR-proADM, although other organs may contribute to its production. Since endothelial injury is commonplace in patients with COVID-19, and progression to critical illness is always associated with multiple organ failure [15], MR-proADM assessments may hence represent a valuable tool for monitoring disease severity and stratifying the risk of critical illness or death.

Fig. 1 Weighted mean difference (WMD) and 95% confidence interval (95% CI) of mid-regional pro-adrenomedullin (MR-proADM) in patients with coronavirus disease 2019 (COVID-19) with or without critical illness



Funding No financial support was provided relevant to this article.

Declarations

Conflict of interest All authors report no conflicts of interest relevant to this article.

Ethical approval Not applicable.

Human and animal rights Not applicable.

Informed consent Not applicable.

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