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META-ANALYSIS

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Midregional-proAdrenomedullin as a prognostic tool in sepsis and septic shock: A systematic review and meta-analysis

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Abstract

Background: Midregional-proAdrenomedullin (MR-proADM) has been recently proposed as a tool in patients with sepsis and septic shock. Our aim was to evaluate the prognostic role of MR-proADM in hospitalized patients with sepsis and septic shock.

Methods: PRISMA guideline was followed. MEDLINE and EMBASE were searched up to June 2023. Primary outcome was mean difference in MR-proADM among survivors and nonsurvivors, secondary outcome mean difference in MR-proADM according to infection severity and type. Risk of bias was evaluated using Newcastle–Ottawa scale for observational studies and Cochrane tool for randomized trials. Pooled mean differences (MD) with corresponding 95% confidence intervals (CIs) were calculated in a random-effects model.

Results: Twenty-four studies included 6730 adult patients (1208 nonsurvivors and 5522 survivors) and three studies included 195 paediatric patients (30 nonsurvivors and 165 survivors). A total of 10, 4 and 13 studies included, respectively, patients with sepsis (3602 patients), septic shock (386 patients) and a mixed population (2937 patients). Twenty-one studies included patients with different source of infection, three with pneumonia and one with a catheter-related infection. Most studies ($n = 12$) had a follow-up of 28 days. In adult cohort, pooled mean difference between nonsurvivors and survivors of MR-proADM was 2.55 mmol/L (95% CI: 1.95–3.15) with higher values in patients with septic shock (4.25 mmol/L; 95% CI, 2.23–6.26 mmol/L) than in patients with sepsis (1.77 mmol/L; 95% CI: 1.11–2.44 mmol/L). In paediatric cohort, pooled mean difference was 3.11 mmol/L (95% CI: −0.02-6.24 mmol/L).

Conclusions: Higher values of MR-proADM are detectable in nonsurvivors adult and paediatric-hospitalized patients with sepsis or septic shock.

KEYWORDS
adrenomedullin, infections, mortality, prognosis, sepsis, septic shock

1 | BACKGROUND

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection,[1] and represents, along with septic shock, a frequent cause of death in critically ill patients. Worldwide, sepsis is estimated to affect more than 30 million people every year, potentially leading to 6 million deaths.[2]

Despite a trend towards lower mortality rate in patients with sepsis recorded over the past decade, sepsis and septic shock still remain a global health challenge as drivers for mortality, warranting an implementation of strategies for early recognition, risk stratification and prognosis evaluation.[3] Among available laboratory biomarkers, procalcitonin (PCT) represents the most validated diagnostic parameter used in medical wards, intensive care units and in the Emergency Department.[4] Despite its wide use, PCT is far from being the ideal biomarker. As a matter of fact, different clinical settings as well as various PCT cut off levels used can be misleading to medical interpretation due to falsely low or high PCT serum levels.[5]

However, commonly available laboratory diagnostic tools are of limited value in the identification of patients at risk of a poor outcome.[6] Because of that, novel biomarkers have been investigated and adrenomedullin (ADM) is among the most promising ones.[7,8] ADM and its precursor Midregional-proADM (MR-proADM) are hormones synthetized in different tissues, including heart, lungs, kidneys and vascular endothelium.[7,8] It has homeostatic and regulating roles, affecting physiological functions of cardiovascular system and kidneys as controlling blood pressure and vascular tone, increasing cardiac output and promoting natriuresis and diuresis.[7] ADM also acts as modulating agent on immune system by regulating the activity of complement, thus assuring its increased serum levels during sepsis.[7,8] Despite that, circulating ADM is extremely difficult to be detected in blood samples since it rapidly degrades from circulation. For this reason, MR-proADM, which directly reflects the serum level of ADM, has been recently proposed to endorse sepsis and septic shock-related organ damage and mortality risk.[9]

We conducted a systematic review and meta-analysis to provide pooled data on the levels of serum MR-proADM in hospitalized patients with sepsis and septic shock, in relation with mortality.

2 | METHODS

This study-level systematic review and meta-analysis was performed following the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) guidelines.[10]

The protocol was registered in the PROSPERO database on 17 April 2022 (registration number CRD42022317955).

2.1 | Databases search and study selection

MEDLINE and EMBASE were searched from inception up to June 2023 for studies evaluating the prognostic role in terms of mortality of MR-proADM in hospitalized patients with sepsis and septic shock. Neither language nor study type restrictions were applied. The complete search strategy is given in Tables S1 and S2.

Two authors (AO and AF) independently reviewed titles and abstracts identified from the databases search to select studies which met the following inclusion criteria: (i) inclusion of both adult and paediatric-hospitalized patients with sepsis and septic shock, (ii) inclusion of ≥10 patients, (iii) availability of data for MR-proADM and (iv) availability of data on outcomes of interest. Exclusion criteria were any of the following: (i) inclusion of <10 patients; (ii) lack of data on relevant variables or outcomes of interest and (iii) inclusion of patients with COVID-19.

Any disagreement was resolved through discussion or involving a third review author (EV).

2.2 | Data extraction and quality assessment

Two review authors (AO and AF) independently extracted data from the included studies onto a standardized electronic data set. The following data were extracted: methodological quality, study design, patient characteristics (e.g. age, sex category), site of infection, mean values of prognostic score (e.g. Sequential Organ Failure Assessment—SOFA, acute physiology and chronic health evaluation—APACHE—II), duration of follow-up and outcomes. Published supplementary materials were searched for data of interest, when needed and available.

A consensus between the two review authors or a discussion with a third review author (EV) resolved any disagreement.

The risk of bias of the included studies and the summary of the risk of bias were evaluated using the Newcastle–Ottawa scale for observational studies (scores of 7–9, 4–6 and <4 classified a study as having a low, moderate, or high risk of bias respectively) and the Cochrane tool for randomized controlled trials.[11,12]

2.3 | Study outcomes

The primary outcome included the difference in MR-proADM values among survivors and nonsurvivors in the overall population. The secondary outcome included the difference in MR-proADM values among survivors and nonsurvivors according to the severity of infection (i.e. sepsis or septic shock) and source of infections.

2.4 | Statistical analysis

The logit-transformed mean values and corresponding sampling variances were calculated. Pooled mean differences (MD) with corresponding 95% confidence intervals (CIs) were calculated in a random-effects model through the inverse variance method. DerSimonian–Laird method was used for $\tau 2$ estimation and Jackson method for confidence intervals estimation. When median and interquartile ranges were provided by the authors, means and corresponding sampling variances were approximated using the method by Luo.[13] Heterogeneity was evaluated by visual inspection of forest plot and classified as follows according to the I^2 values: (i) 0%–40% I^2 values indicate an heterogeneity that might not be important, (ii) 30%–60% I^2 values may represent moderate heterogeneity, (iii) 50%–90% I^2 values may represent substantial heterogeneity and (iv) 75%–100% I^2 values indicate a considerable heterogeneity.

A subgroup analyses was performed sorting patients by the severity of infection (i.e. sepsis, septic shock and mixed population). Furthermore, included studies were sorted by the source of infection and duration of follow-up.

The presence of publication bias was assessed by funnel plot of logit-transformed proportion versus standard error. Funnel plot symmetry was tested by performing the Egger's test.

Statistical analyses were performed using R studio version 1.2.5001, 'meta' and 'forest' packages.

3 | RESULTS

PRISMA flow diagram is reported in Figure 1. A total of 639 records were identified by the combined strategy search. After removing 112 duplicates, 429 items were

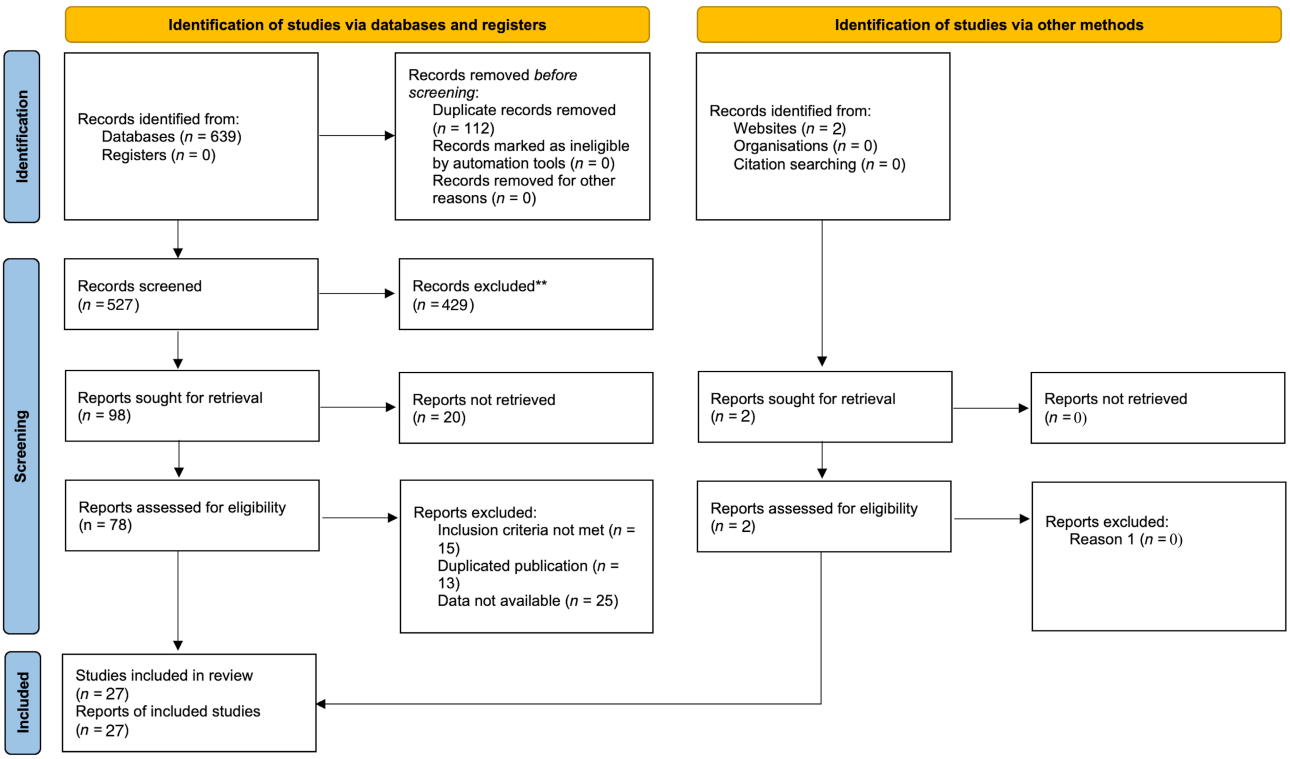

FIGURE 1 PRISMA flow diagram.

excluded by title and abstract screening and 98 full texts were evaluated. Two further studies were identified from websites. Finally, 24 studies with 6730 adult patients (1208 nonsurvivors and 5522 survivors)[6,14–36] and three studies with 195 paediatric patients (30 nonsurvivors and 165 survivors) were included in the analysis.[37–39]

3.1 | Characteristics of included studies and patients

Table 1 reported the characteristics of included studies. Twenty-five and two studies were, respectively, prospective and retrospective cohort studies. No randomized controlled trials have been included. Study size ranged from 25 to 2071 patients. Ten studies included patients with sepsis (3602 patients), 4 studies patients with septic shock (386 patients) and 13 a mixed population (2937 patients). Patients from 17 studies (62.9%) were included in intensive care unit. The majority of studies ($n=21$) included patients with different source of infection, three patients with pneumonia and one study patients with a catheter-related bloodstream infection. MR-proADM was detected at admission in 22 studies (81.5%) and most studies (n = 12) have a follow-up of 28 days (Table 1). The quality of the included studies is reported in Table S3 and varied from intermediate to high. Overall, 11.1%, 88.9% and 0% of studies were considered at low, intermediate and high risk of bias respectively. The results of publication bias are reported in Figure S1.

Specific patients' characteristics were reported only in studies including adult patients (Table 2). The mean age of nonsurvivors and survivors were 72 and 65 years, respectively, and 59.6% and 56.7% were, respectively, men (Table 2). Mean SOFA, APACHE II scores were higher in nonsurvivors than survivors. Similarly, mean C-reactive protein (CRP), PCT and lactate values were higher in nonsurvivors than in survivors (Table 2).

3.2 | Pooled mean values and differences in MR-proADM values

In adult patients, overall mean baseline values of MR-proADM were higher in nonsurvivors than survivors patients (5.52 mmol/L [95% CI: 4.51–6.54] vs. 2.76 mmol/L [95% CI: 2.20–3.32]).

This difference was evident also in patients with sepsis (3.54 mmol/L [95% CI: 2.13–.94] vs. 1.67 mmol/L [95% CI: 0.93–2.41]) and in those with septic shock (7.74 mmol/L [95% CI: 5.78–9.69] vs. 3.08 mmol/L [95% CI: 1.94–4.23]).

The pooled mean difference of MR-proADM values between nonsurvivors and survivors was 2.55 mmol/L (95% CI: 1.95–3.15) with higher values in patients with septic shock (4.25 mmol/L; 95% CI: 2.23–6.26 mmol/L) than in patients with sepsis (1.77 mmol/L; 95% CI: 1.11–2.44 mmol/L) (Figure 2).

The paediatric cohort included only patients with sepsis. Mean value of MR-proADM was higher in nonsurvivors than survivors (10.20 mmol/L [95% CI: 3.80–16.60] vs. 6.86 mmol/L [95% CI: −3.16 to 16.89]) with a pooled mean difference between nonsurvivors and survivors of 3.11 mmol/L (95% CI: −0.02-6.24 mmol/L) (Figure 2). These three studies included patients with different source of infection and no studies reported the length of follow-up.

4 | DISCUSSION

The results of our study showed higher MR-proADM values in nonsurvivors group with respect to survivor comparators in both adult and paediatric-hospitalized patients with sepsis or septic shock. Furthermore, in adult patients, mean values and mean difference of MR-proADM values appeared to be higher in hospitalized patient with septic shock than in those with sepsis.

Among biomarkers under evaluation (e.g. presepsin and interleukin-6), increasingly consistent data in the literature are identifying MR-proADM as a valid tool in hospitalized patients with sepsis and septic shock due to its vasodilator and antibacterial properties.[7–9,40,41] Along with its role as a predictor marker of disease severity, MR-proADM also showed a high accuracy in identifying patients upon arrival at the emergency department, providing clinicians with additional tool for assessing the appropriateness of intensive care unit admission and thus facilitate an early treatment strategy in case of sepsis and septic shock.[17] An early prognostic prediction is crucial in these patients and may guarantee a targeted therapeutic and clinical management including a safe home discharge from the emergency department or admission to unmonitored hospital beds.[42] Despite several studies performed during the last years, data are heterogeneous in terms of included patients, type and severity of infection, and duration of follow-up. Pooling these results, our meta-analysis appeared to corroborate the role of baseline MR-proADM in identifying patients at high risk of mortality. Whether change in MR-proADM values during the first days of hospitalization instead of a single baseline measurement may have a higher prognostic power is of clinical interest.[36] Regarding this matter, in a prospective observational study, mean change in MR-proADM values upon admission and after 72 h

TABLE 1 Characteristics of included studies.

Author name, year	Design of the study	Cohort of patients	Hospital ward	Nonsurvivors N	Survivors N	Disease severity	Site of infection	MR-proADM determination	Duration of follow-up
Akpinar S, 2014[14]	Prospective	Adult	Not specified	18	39	Mixed	Pneumonia	Not specified	28
Andaluz-Ojeda D, 2017[15]	Prospective	Adult	ICU	101	225	Mixed	Mixed	At admission	28
Badia Tejero AM, 2017[16]	Prospective	Adult	ICU	9	24	Mixed	Mixed	At admission	Not reported
Baldirà J, 2020[17]	Prospective	Adult	Mixed	28	102	Mixed	Mixed	Not specified	28
Bernal-Morell E, 2018[18]	Prospective	Adult	Not specified	27	121	Sepsis	Mixed	At admission	90
Bima P, 2022[35]	Prospective	Adult	Emergency	19	128	Mixed	Mixed	At admission	28
Charles P, 2017[19]	Prospective	Adult	ICU	63	110	Sepsis	Mixed	At admission	28
Christ-Crain M, 2006[20]	Prospective	Adult	Medical ward	38	264	Sepsis	Pneumonia	At admission	Not reported
De La Torre-Prados MV, 2016[21]	Prospective	Adult	ICU	36	64	Septic shock	Mixed	At admission	28
Elke G, 2018[22]	Prospective	Adult	ICU	289	787	Mixed	Mixed	At admission	28
Fahmey SS, 2018[37]	Prospective	Child	ICU	12	48	Sepsis	Mixed	At sepsis diagnosis	Not reported
Fahmy AA, 2022[23]	Retrospective	Adult	ICU	5	27	Sepsis	Not reported	At sepsis diagnosis	28
Haag E, 2021[24]	Prospective	Adult	Emergency	47	610	Mixed	Mixed	At admission	30
Hagag A, 2011[38]	Retrospective	Child	ICU	8	32	Sepsis	Mixed	At admission	Not reported
Helan M, 2022[36]	Prospective	Adult	ICU	9	12	Septic shock	Mixed	At admission	90
Hoeboer S, 2012[25]	Prospective	Adult	ICU	26	75	Mixed	Mixed	At admission	28
Jordan I, 2014[39]	Prospective	Child	ICU	10	85	Sepsis	Mixed	At admission	Not reported
Julián-Jiménez A, 2019[26]	Prospective	Adult	Emergency	13	123	Sepsis	Not reported	Not specified	30
Lundberg O, 2016[27]	Prospective	Adult	ICU	15	38	Septic shock	Mixed	At admission	28
Mearelli F, 2020[28]	Prospective	Adult	Emergency	122	423	Sepsis	Mixed	At admission	30
Ni J, 2018[29]	Prospective	Adult	ICU	11	14	Mixed	CRBSI	At admission	28
Saeed K, 2019[30]	Prospective	Adult	Emergency	129	1942	Sepsis	Mixed	At admission	28
Schuetz P, 2007[31]	Retrospective	Adult	ICU	21	74	Mixed	Mixed	At admission	Not reported
Serano A, 2019[32]	Prospective	Adult	Emergency	58	154	Septic shock	Mixed	At admission	30
Suberviola B, 2012[6]	Prospective	Adult	ICU	17	32	Mixed	Pneumonia	At admission	Not reported
Suberviola B, 2013[33]	Prospective	Adult	ICU	41	96	Mixed	Mixed	At admission	Not reported
Valenzuela-Sanchez F, 2019[34]	Prospective	Adult	ICU	66	38	Mixed	Mixed	At admission	90

Abbreviations: CRBSI, catheter-related blood stream infection; ICU, Intensive care unit.

contributed to a deeper understanding of patient mortality risk stratification.[35] Similarly, MR-proADM measurement some days after hospital admission (e.g. 3 or 7 days) appeared to maintain the capability of mortality prediction.[43]

Our data also showed that mean values and mean differences of MR-proADM appear to increase with the severity of the infection, showing high values in case of sepsis and even higher values in septic shock. This finding is of outmost importance, since early antimicrobial treatment is one of the major drivers of outcome in patients with septic shock. In this setting, whether MR-proADM is able to differentiate causative pathogens (i.e. Gram-positives from Gram-negatives and, among the latter, those resistant from those susceptible to antibiotics) or type of micro-organisms (e.g. virus or fungi) is still an unresolved issue and surely deserves further investigations.[44] The few available data, however, showed as MR-proADM values appear to be high in patients with severe viral infection (e.g. SARS-CoV2 or Dengue infections).[45–47] More specifically, MR-proADM is able to predict disease severity, adverse events development and mortality risk in patients with COVID-19.[43,48–53]

Likewise, whether MR-proADM is capable to identify specific organ failure or have prognostic value also in noninfectious inflammatory conditions is debatable and yet under investigation.[54] For example, plasma levels of MR-proADM upon admission were associated with a higher risk of hospitalization and overall mortality in individuals with acute myocardial infarction or

TABLE 2 Baselines patients' characteristic and laboratory values of adults hospitalized patients with sepsis and septic shock.

Variables	Nonsurvivors	Survivors
Mean age, years	72	65
Male sex, *n* (%)	588 (59.6)	2714 (56.7)
Prognostic scores		
Mean SOFA score	9	7
Mean APACHE II score	28	22
Laboratory markers		
Mean CRP values, mg/dL	16.3	13.4
Mean PCT values, ng/mL	6.4	5.3
Mean lactate values, mmol/L	3.6	2.1

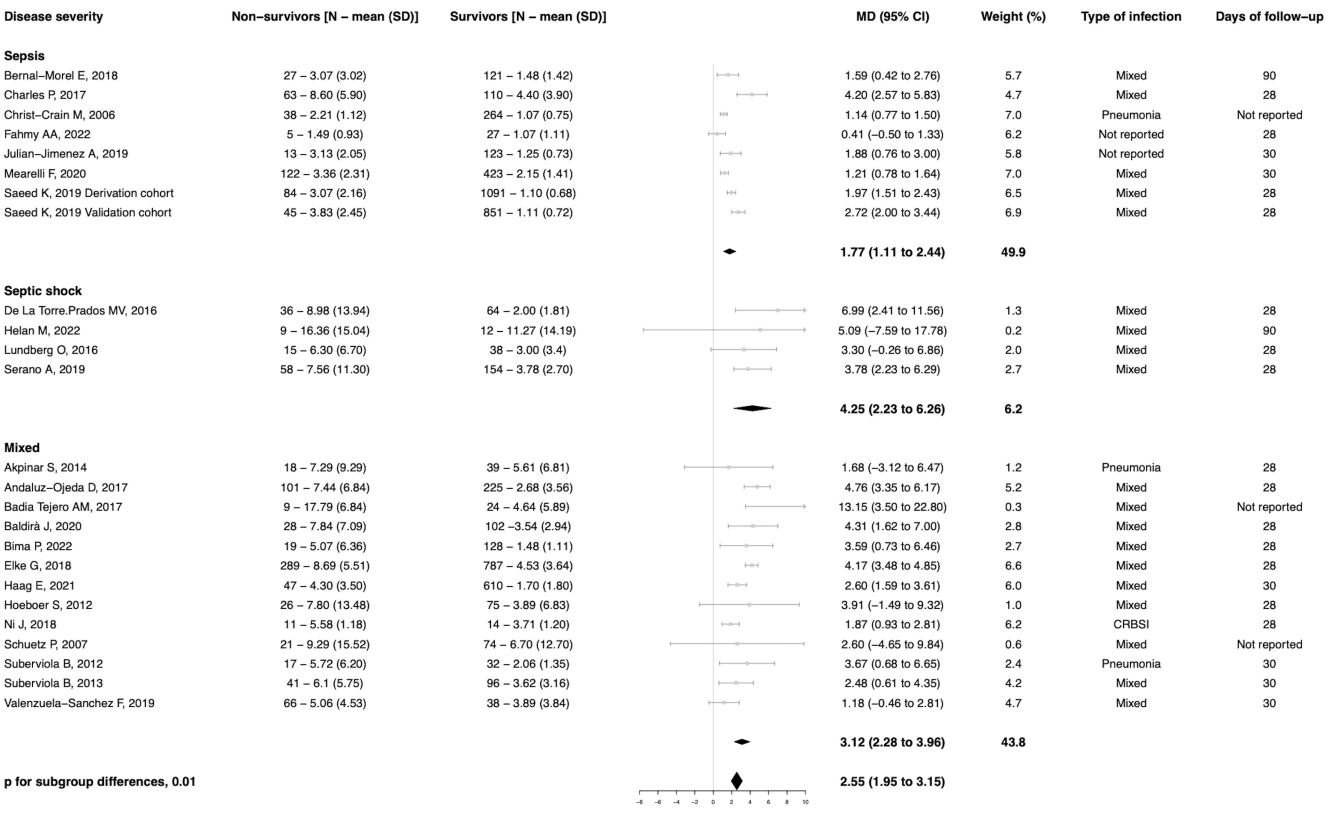

FIGURE 2 Mean differences in MR-proADM between nonsurvivors and survivors in adult cohort. Grey squares indicate individual study mean differences of MR-proADM, grey horizontal lines indicate 95% CIs of the individual studies and diamonds indicate summary estimates with 95% CI. CI, confidence interval; MD, mean difference; MR-proADM, Midregional-proAdrenomedullin; SD, standard deviation.

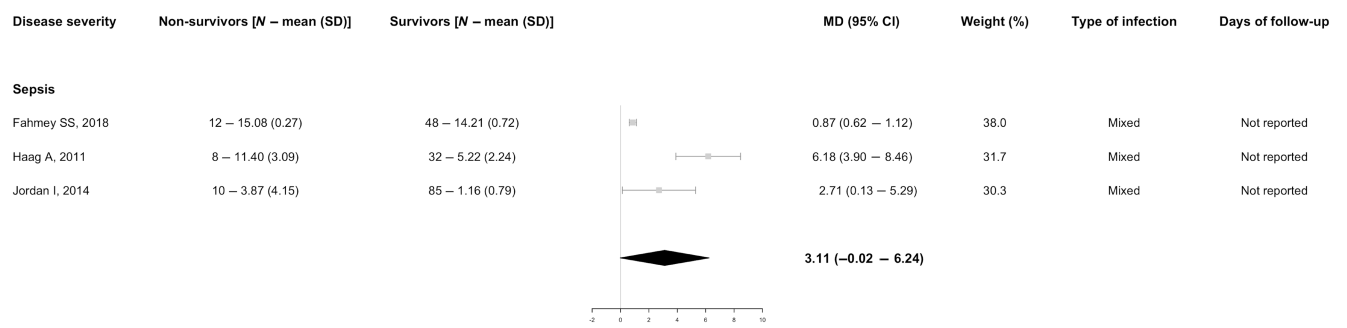

FIGURE 3 Mean differences of MR-proADM between nonsurvivors and survivors in paediatric cohort. Grey squares indicate individual study mean differences of MR-proADM, grey horizontal lines indicate 95% confidence intervals of the individual studies and diamonds indicate summary estimates with 95% confidence intervals. CI, confidence interval; MD, mean difference; MR-proADM, Midregional-proAdrenomedullin; SD, standard deviation.

with acute and chronic heart failure as well as higher MR-proADM values has been detected during specific cardiologic treatments (e.g. sacubitril/valsartan).[55–61] Similarly, MR-proADM appeared to be a useful biomarker of chronic kidney disease progression in non-diabetic patients and of acute decompensation and short-term survival in patients with liver disease.[62,63] If confirmed in future studies, all this properties of MR-proADM may provide further patients' stratification and therapeutic implications.

The comprehensiveness of the systematic search and the rigorous evaluation of study quality according to standard methodological assessment tools are the major strengths of our work. However, several limitations have to be discussed. First of all, included studies were heterogenous in terms of underlying patients' characteristics, site and severity of infection and duration of follow-up. Trying to reduce this heterogeneity, we performed a subgroup analysis according to disease severity and sorted patients by the type of infection and duration of follow-up (Figures 2 and 3). Second, the evaluation of data on a study-level basis represents an intrinsic limitation of a study-level meta-analysis and did not allow any further analysis evaluating the impact of specific patients' characteristics (e.g. presence of specific comorbidities) on the outcomes of interest. Similarly, available data allowed to evaluate MR-proADM levels with no direct comparison with other biomarkers (e.g. PCT, CRP and lactate values). Third, all included studies were at some risk of bias, which potentially limits the external validity of the results and emphasizes the urgent need for high-level evidence in this field. Fourth, there was evidence of significant publication bias in adult cohorts that is consistent with the possibility that small studies with large effect size were not published. However, it is unlikely that the latter were missed by our comprehensive and systematic databases' search. Finally, it would be interesting to investigate MR-proADM values in infections from different sites and according to different pathogens.

5 | CONCLUSIONS

In conclusion, our meta-analysis shows higher MR-proADM values in nonsurvivors than survivors patients with sepsis and septic shock, with its values increasing with the severity of the disease.

AUTHOR CONTRIBUTION

Study conception and design: E. Valeriani and A. Oliva; Data acquisition: E. Valeriani, A. Falletta and A. Oliva; Statistical analysis: E. Valeriani; Interpretation of the data: All authors; Drafting of the article: E. Valeriani, A. Falletta and A. Oliva; Critical revision of the article for important intellectual content: All authors; Final approval of the article: All authors.

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None.

CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

All data generated or analysed during this study are included in this published article (and its Supporting Information files).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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