RESEARCH PAPER

Mid-Regional Pro-Adrenomedullin as A Predictor of Mortality and Respiratory Failure in Paediatric Community-Acquired Pneumonia: A Prospective Cohort Study

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Received: 24th April, 2026; Revised: 20th May 2026; Accepted: 30th June, 2026; Available Online: 10th July, 2026

ABSTRACT

Introduction: Community-acquired pneumonia (CAP) is a major cause of morbidity and mortality in young children worldwide. Early recognition of patients at risk of severe outcomes is essential. Conventional biomarkers such as C-reactive protein and procalcitonin have limited prognostic performance. Mid-regional pro-adrenomedullin (MR-proADM) has been proposed as a potential marker of severity, but evidence in paediatric populations, particularly in Indonesia, remains scarce. This research to assess the prognostic value of MR-proADM for predicting mortality and respiratory failure in children with CAP.

Material and Methods: Children aged 2 months to 18 years with CAP were enrolled. MR-proADM levels were measured at admission. Outcomes included in-hospital mortality and respiratory failure. Reporting followed STROBE guidelines. A prospective cohort study was performed at a tertiary hospital in Makassar, Indonesia, from August 2025 to January 2026. Data were analyzed using Chi-square, Mann–Whitney U test, logistic regression, and ROC curve analysis.

Results: A total of 64 patients were analyzed. Higher MR-proADM levels were observed in patients who developed mortality and respiratory failure ($p = 0.001$ and $p < 0.001$). MR-proADM was significantly associated with mortality ($p = 0.011$) and respiratory failure ($p < 0.001$). ROC analysis demonstrated good predictive ability for mortality (AUC = 0.815) and excellent performance for respiratory failure (AUC = 0.967), with a cut-off value of 0.459.

Conclusions: MR-proADM shows strong prognostic potential in paediatric CAP and may be useful for early identification of high-risk patients.

Keywords: MR-proADM, paediatric pneumonia, CAP, prognosis, biomarker

How to cite this article: Purnamamulya R, Lawang SA, Rahimi R, Artati RD, Amiruddin L, Mid-Regional Pro-Adrenomedullin as A Predictor of Mortality and Respiratory Failure in Paediatric Community-Acquired Pneumonia: A Prospective Cohort Study Int J Drug Deliv Technol. 2026;16(7): 1125-1131; DOI: 10.25258/ijddt.16.7.119
Source of support: Nil.
Conflict of interest: None

INTRODUCTION

Community-acquired pneumonia (CAP) remains a major contributor to morbidity and mortality among children under five years of age worldwide. Despite advances in clinical management, severe forms of pneumonia continue to account for a substantial proportion of paediatric deaths, particularly in low- and middle-income countries. The World Health Organization (WHO) highlights that early detection, rapid referral, and access to appropriate levels of care are essential strategies to reduce pneumonia-related mortality in children.[1]

On a global scale, pneumonia was responsible for approximately 740,180 deaths among children under five in 2019, representing around 14% of all deaths in this age group. The burden of disease is disproportionately higher in developing regions, especially in Southeast Asia and Africa, which together contribute a large share of global cases. Indonesia is included among the countries with the highest burden of under-five mortality due to pneumonia.[2–4]

At the national level, pneumonia continues to represent a significant public health concern in Indonesia. Reported cases in children under five increased from 278,261 in 2021 to 386,724 in 2022, indicating an upward trend in case detection. Although the reported mortality proportion appears relatively low high number of cases reflects a persistent and substantial disease burden. In addition, data from the 2023 Indonesia Health Survey showed a pneumonia prevalence of 0.9% among children under five in South Sulawesi.[5–7]

From a clinical perspective, paediatric pneumonia often presents with nonspecific symptoms such as fever, cough, and increased respiratory rate. Among these, tachypnea is frequently the most reliable early clinical indicator in infants and young children. However, reliance on clinical features alone is often insufficient to accurately predict

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disease severity, emphasizing the importance of early risk assessment to prevent progression and complications.[2,8]

The pathogenesis of pneumonia is closely linked to host inflammatory responses triggered by infectious agents. Activation of immune cells leads to the release of cytokines and chemokines, which promote further immune cell recruitment to the site of infection. While this response is essential for pathogen clearance, excessive inflammation may result in tissue damage, impaired organ function, and in severe cases, multi-organ failure. This inflammatory cascade plays a central role in the development of severe pneumonia and respiratory failure, and therefore inflammatory biomarkers may assist in identifying patients at higher risk of deterioration.[9,10]

However, commonly used biomarkers such as C-reactive protein (CRP) and procalcitonin (PCT) have demonstrated limited performance in accurately predicting disease severity and clinical outcomes in paediatric CAP.[11] These limitations highlight the need for more reliable biomarkers that better reflect the underlying pathophysiological processes of severe infection.

Mid-regional pro-adrenomedullin (MR-proADM) is a stable fragment derived from the precursor of adrenomedullin, a vasoactive peptide released in response to inflammatory stress and endothelial activation. MR-proADM has gained attention as a potential biomarker because it reflects both systemic inflammation and endothelial dysfunction, two key mechanisms involved in severe infectious diseases. Previous studies have suggested that MR-proADM may provide superior prognostic performance compared to conventional biomarkers in patients with CAP.[10]

In paediatric populations, available evidence also supports its prognostic value. Florin et al. demonstrated that MR-proADM levels measured at emergency department presentation were associated with increased risk of severe outcomes in children with CAP, and showed better predictive accuracy compared with CRP and procalcitonin.[12] Nevertheless, studies in children remain limited, particularly in resource-limited settings.

Considering this gap, further investigation is needed to evaluate the clinical utility of MR-proADM in paediatric CAP across different populations. In Indonesia, evidence regarding the prognostic role of MR-proADM in children with CAP is still lacking. Therefore, this study was conducted to assess the ability of MR-proADM to predict mortality and respiratory failure in paediatric patients with community-acquired pneumonia.

The results of this study are expected to contribute to improved early risk stratification and support clinical decision-making in paediatric CAP, potentially leading to better outcomes through timely and appropriate management.

MATERIAL AND METHODS

Ethical approval was obtained from the institutional ethics committee (approval number: 1081/UN4.6.4.5.31/PP 36/2025). Informed consent was obtained from the parents or legal guardians of all participants prior to study inclusion. The study was reported in accordance with the STROBE guidelines for observational studies.

This study employed a prospective cohort design to investigate the prognostic role of mid-regional pro-adrenomedullin (MR-proADM) in predicting clinical outcomes among paediatric patients diagnosed with community-acquired pneumonia (CAP). The study was conducted in the paediatric inpatient ward of Dr. Wahidin Sudirohusodo Hospital, Makassar, Indonesia. Laboratory analysis of MR-proADM samples was performed at the Research Laboratory Unit of (hospital name blinded for peer review). The study was carried out between August 2025 and January 2026.

The study population consisted of paediatric patients aged 2 months to 18 years who were hospitalized with a clinical diagnosis of CAP. Diagnosis was established by attending paediatricians based on clinical evaluation and documented medical records. Consecutive sampling was applied to recruit all eligible patients during the study period.

Sample size determination was based on a cohort sample size formula using an estimated relative risk of 2, an expected proportion of 0.15 in the control group, a two-sided significance level of 5%, and a statistical power of 80%, resulting in a minimum required sample size of 53 participants. Sample size formula : (based on Fleiss (1981)).[13]

$$n = \frac{(z\alpha\sqrt{2PQ} + z\beta\sqrt{P1Q1+P2Q2})^2}{P1-P2}$$

Description:

N: Minimum sample size

P : ½ (P1+P2) = 0,2

P1 : 0,22

P_2 : 0,1875

zα : 1,96

zβ : 0,84

Q : 1 — P = 0,8

Q1 : 1 — P1 = 0,78

Q2 : 1 — P2 = 0,83

$n = (1,96\sqrt{2x0,2x0,8}+0,84\sqrt{0,22x0,78+0,1875x0,8})^2$

0,03

$n = (1,96 \text{ x } 0,56 + 0,84 \text{ x } 0,55)^2$

0,03

$n = (1,097+0,48)^2$

0,0325

$n = 52{,}5 \approx 53$

Eligibility criteria included paediatric patients diagnosed with CAP by a paediatric specialist, aged between 2 months and 18 years, and with complete clinical and laboratory data available. Patients with incomplete records were excluded from the study.

Potential selection and measurement bias were minimized by consecutive sampling and standardized laboratory procedures.

Serum MR-proADM levels were measured at hospital admission using a commercially available human MR-proADM enzyme-linked immunosorbent assay (ELISA) kit based on the double-antibody sandwich ELISA principle. The assay employed two monoclonal antibodies recognizing different epitopes of human MR-proADM. Microplate wells were pre-coated with a monoclonal anti-MR-proADM antibody to specifically capture MR-proADM present in the serum samples. All assays were performed according to the manufacturer's instructions. The primary outcomes assessed were in-hospital mortality and respiratory failure during hospitalization.

Respiratory failure was defined as the need for mechanical ventilation (invasive or non-invasive) or admission to the intensive care unit.

Data analysis was conducted using the Chi-square test, Mann–Whitney U test, logistic regression, and receiver operating characteristic (ROC) curve analysis. Statistical significance was set at a p-value of less than 0.05.

No multivariable adjustment was applied for potential confounders due to the relatively small sample size. Subgroup and interaction analyses were not undertaken. The final dataset contained no missing values. Because this was an in-hospital cohort study, there was no loss to follow-up. In addition, no sensitivity analyses were carried out.

Quantitative data were presented as median with interquartile range (IQR) because the distribution was not normal. Age was grouped into predefined categories (<5 years, 5–12 years, and >12 years) for clinical relevance. MR-proADM was evaluated as both a continuous measure and a dichotomized variable using an ROC-derived optimal cut-off point (0.459) to determine its prognostic value.

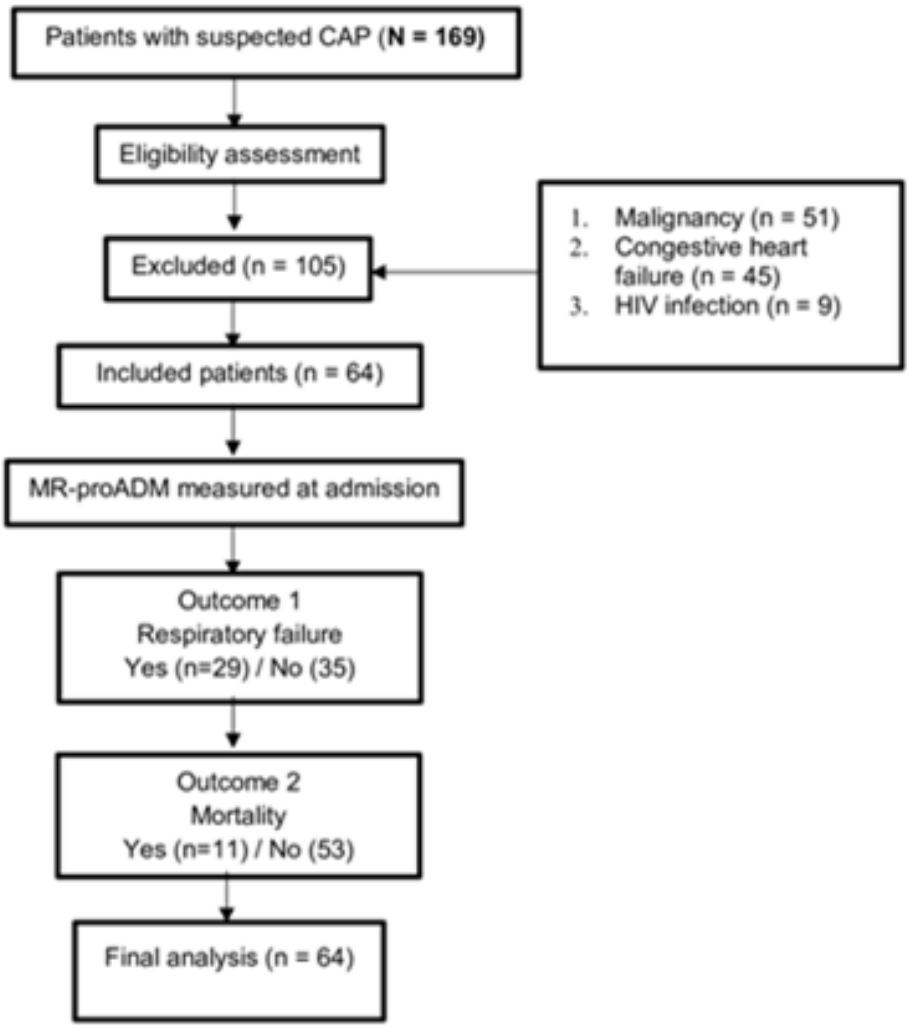

Figure 1. Study Flow of Participants

RESULTS:

A total of 64 paediatric patients diagnosed with community-acquired pneumonia (CAP) were included in the final statistical analysis.

Table 1. Baseline Characteristics

Characteristics Frequency	F (n=64)	(%)
Gender		
Male	36	56.3
Female	28	43.8
Age (years)		
<5 years	41	64.0
5-12 years	11	17.2
>12 years	12	18.8
Nutritional Status		
Severely malnourished Undernourished	35	54.7
Well-nourished	6	9.4
	23	35.9
Outcome Mortality		
Alive	53	82.8
Dead	11	17.2
Incidence of Respiratory Failure		
Respiratory Failure	29	45.3
No Respiratory Failure	35	54.7

Most participants were male, accounting for 56.3% of the study population. The majority of patients were under 5 years of age (64.0%). In terms of nutritional status, more than half of the patients were categorized as having poor nutrition (54.7%). Regarding clinical outcomes, in-hospital mortality occurred in 17.2% of patients, while 45.3% developed respiratory failure during hospitalization.

Table 2. Association Between Baseline Characteristics and Outcomes

Variable	Category	Death n (%)	*p-value*	Respiratory Failure n (%)	*p-value*
Age	< 5 years	6 (14.6%)	**0.622***	24 (58.5%)	**0.573***
	5 –12 years	3 (27.3%)		4 (36.4 %)	
	>12–18 years	2 (16.7%)		7 (58.3%)	
Gender	Male	8 (22.2%)	**0.226***	18 (50.0%)	**0.393***
	Female	3 (10.7%)		17 (60.7%)	
Nutritional Status	Well-nourished	5 (21.7%)	**0.762***	13 (56.5%)	**0.280***
	Severely malnourished	5 (14.3%)		17 (48.6%)	
	Undernourished	1 (16.7%)		5 (83.3%)	

*Chi-Square

Analysis revealed that age group, sex, and nutritional status were not significantly associated with either mortality or respiratory failure (all p-values > 0.05), as summarized in Table 2. Although some differences in proportions were observed among subgroups, these did not reach statistical significance.

Table 3. MR-proADM Levels in Relation to Clinical Outcomes

Variable	Group	n	Mean Rank	Median (IQR)	*p-value*
Death	Alive	53	29.04	0.45 (0.35 – 0.58)	**0.001***
	Deaths	11	49.18	0.67 (0.67 – 0.69)	
Respiratory Failure	No	29	16.17	0.40 (0.30 – 0.52)	**<0.001***
	Yes	35	46.03	0.65 (0.58 – 0.69)	

*Mann–Whitney

MR-proADM concentrations were significantly higher among patients who died compared with those who survived (p = 0.001). A similar pattern was observed for respiratory failure, where patients with this complication had significantly elevated MR-proADM levels compared to those without respiratory failure (p < 0.001), as shown in Table 3.

Tabel 4. Univariate Logistic Regression Analysis of MR-proADM

Outcome	Variable	B	S.E.	OR (Exp(B))	p-value
Death	MR-proADM	13.035	5.121	458.382	**0.011**
Respiratory Failure	MR-proADM	24.245	6.069	3.38×10^{10}	**<0.001**

**Logistic Regression*

Univariate logistic regression analysis demonstrated that higher MR-proADM levels were significantly associated with mortality ($p = 0.011$) and respiratory failure ($p < 0.001$).

Table 5. Predictive Accuracy of MR-proADM

Outcome	AUC	95% CI	Cut-off	Sensitivity (%)	Specificity (%)	Youden Index
Death	0.815	0.69 – 0.94	0.632	81.8	73.6	0.554
Respiratory Failure	0.967	0.92 – 1.00	0.459	94.3	79.3	0.763

Receiver operating characteristic (ROC) analysis demonstrated that MR-proADM had good discriminatory performance for predicting mortality (AUC = 0.815; 95% CI: 0.69–0.94) and excellent performance for predicting respiratory failure (AUC = 0.967; 95% CI: 0.92–1.00). The optimal cut-off value was determined to be 0.459, yielding a sensitivity of 94.3% and specificity of 79.3%.

MR-proADM showed good discriminatory ability for mortality prediction (AUC = 0.815; 95% CI: 0.69–0.94) and excellent performance in predicting respiratory failure (AUC = 0.967; 95% CI: 0.92–1.00). The optimal cut-off value of 0.459 provided a sensitivity of 94.3% and specificity of 79.3%, with a corresponding Youden index of 0.736.

DISCUSSION

This study demonstrated that MR-proADM is an associated of both mortality and respiratory failure in paediatric patients with community-acquired pneumonia (CAP). The extremely large odds ratios may reflect the small sample size and possible quasi-complete separation in the logistic regression model. Elevated concentrations of this biomarker were significantly associated with worse clinical outcomes, indicating its potential role as an indicator of disease severity and systemic inflammatory burden. These findings are consistent with previous reports showing that increased MR-proADM levels correlate with adverse outcomes in patients with CAP.(14)

In paediatric populations, earlier studies have similarly reported that higher MR-proADM levels are associated with more severe disease presentations, including increased rates of hospitalization, need for respiratory support, and admission to intensive care units. These findings support its potential utility as an early risk stratification tool for identifying children at higher risk of clinical deterioration.(15)

Evidence from adult and mixed populations further strengthens these observations, showing that MR-proADM levels rise in proportion to CAP severity and are strongly associated with both short- and long-term mortality. Notably, MR-proADM has been shown to improve prognostic accuracy when combined with established clinical severity scores such as PSI and CURB-65, suggesting additive value beyond conventional clinical assessment tools.(16)

Recent evidence from contemporary meta-analyses also confirms that elevated MR-proADM levels are consistently observed in patients with poor outcomes, particularly in severe respiratory infections and sepsis. These findings reinforce its role as a biomarker reflecting systemic disease severity and endothelial dysfunction across different infectious conditions.(17)

In children, recent literature has highlighted MR-proADM as an emerging biomarker for severity assessment in respiratory infections, including pneumonia. A recent paediatric-focused review reported that MR-proADM reflects both inflammatory activation and endothelial response, and may offer superior prognostic performance compared with traditional inflammatory markers in predicting severe outcomes.(18)

Moreover, studies in paediatric invasive bacterial infections suggest that MR-proADM may contribute to early risk stratification, although its diagnostic performance varies across populations and clinical settings. Despite this variability, higher concentrations are generally associated with more severe clinical manifestations and increased risk of complications in children with infection.(19)

From a mechanistic perspective, MR-proADM represents a stable surrogate of adrenomedullin, a vasoactive peptide involved in vascular tone regulation and endothelial barrier function. During severe infection, pro-inflammatory mediators and endotoxins stimulate adrenomedullin release, resulting in vasodilation, increased vascular permeability, and impaired microcirculatory perfusion. These pathophysiological changes may contribute to tissue hypoxia and organ dysfunction, particularly in the lungs, ultimately leading to respiratory failure.(20)

In current clinical practice, severity assessment of paediatric CAP still relies predominantly on clinical evaluation and basic laboratory parameters, which have limited accuracy in predicting early deterioration. Emerging evidence suggests that MR-proADM may enhance risk stratification when used in conjunction with conventional tools, thereby supporting earlier identification of high-risk patients and potentially improving clinical decision-making.(21)

However, despite its promising prognostic performance, the clinical application of MR-proADM remains limited by several factors, including variability in cutoff values, limited assay availability, and cost constraints, particularly in resource-limited settings. Therefore, further large-scale multicenter studies are required to validate its clinical utility and establish standardized reference thresholds in paediatric populations.

Several limitations of this study should be considered. The single-center design may restrict the applicability of the findings to wider populations. In addition, the limited sample size could reduce statistical power and may affect the reliability of subgroup analyses. Some potential confounding variables, such as prior antibiotic administration, timing of therapeutic intervention, and the underlying infectious etiology, were not fully adjusted for and might have influenced the clinical outcomes. Furthermore, MR-proADM levels were assessed only at admission, which did not allow evaluation of their temporal changes during disease progression. Lastly, the study only evaluated short-term in-hospital outcomes and did not include long-term follow-up after discharge.

Finally, it should be noted that single time-point measurement of MR-proADM may not fully reflect the dynamic nature of disease progression. Serial measurements during hospitalization may provide additional prognostic information by capturing temporal changes in endothelial injury and inflammatory response, which was not evaluated in the present study.(16)

Acknowledgement
The authors used AI-based tools for language editing and proofreading. The authors are fully responsible for the content of the manuscript.

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

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