

Predictors of poor outcome severe pneumonia children in the paediatric intensive care unit

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Introduction

Severe pneumonia children frequently have poor outcome during hospitalization in PICU. However, the predicting of mortality is hampered by lacking evidence about the risk factors in Indonesia. This study aimed to determine risk factors that associated with mortality in children with severe pneumonia admitted to the pediatric intensive care unit (PICU).

Methods

This was a single-center case-control study in the PICU at Prof. Dr. I.G.N.G Ngoerah Hospital, Indonesia between January 2019 and December 2020. Children and adolescents who aged 28 days to 18 years old with severe pneumonia were included and divided into death and survivor groups. Patients with incomplete medical record data, history of perinatal lung disease, major congenital anomaly, or cyanotic congenital heart disease were excluded. Demographic, clinical, and laboratory data were obtained from medical records. Statistical analysis was conducted using χ^2 -test for bivariate and binary logistic regression for multivariate analysis.

Results

160 subjects were included with median age was 7 and 9 months in the death and survivor group respectively. Multivariate analysis showed $\text{SpO}_2 < 90\%$ at arrival, PELOD-2 score ≥ 7 , hemoglobin $< 8 \text{ g/dL}$, lymphopenia, and procalcitonin $\geq 0.5 \text{ ng/mL}$ were associated with mortality (adjusted odds ratio [aOR] 17.29, 95%CI 4.82-61.43; aOR 18.37, 95%CI 4.14-81.43; aOR 4.05, 95%CI 1.16-14.13; aOR 3.59, 95%CI 1.09-11.75; aOR 7.64, 95%CI 2.61-22.40, respectively). Invasive mechanical ventilation and malnutrition were not associated with mortality.

Conclusion

$\text{SpO}_2 < 90\%$ at arrival, PELOD-2 score ≥ 7 , hemoglobin $< 8 \text{ g/dL}$, lymphopenia, and procalcitonin $\geq 0.5 \text{ ng/mL}$ are risk factors for mortality in children with severe pneumonia.

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Pneumonia is a common infectious disease worldwide that can occur at any age, though can cause critical illness in children that requires intensive care.¹ The annual incidence of pediatric pneumonia varies geographically, ranging from 6.4 to 231 episodes per 1,000 children.²⁻⁴ Despite the decreasing mortality rate of pneumonia in developed countries, pneumonia continues to cause morbidity and hospitalization in developing countries⁴ and form substantial disease burden in healthcare settings.^{5,6} The disease is also the leading cause of death in children, with age-standardized mortality rates of 38.9 per 100,000 children and 80% of deaths occurring between the ages of 1 and 59 months.^{2,7}

It was estimated that 10.3% to 37.2% of children suffering from pneumonia would require admission to the pediatric intensive care unit (PICU)^{1,4} with the mortality rate of severe pneumonia in PICU ranged from 5.9% to 13.5%.⁷⁻¹⁰ This high rate of mortality in PICU warrants early and specific treatment through identification and classification of risk factors for mortality in patients admitted to PICU. Several studies have described some risk factors, ranging from clinical to laboratory characteristics, that associated with morbidity and mortality in patients with pneumonia in the PICU.^{9,11-14} The data about these risk factors for mortality of patients with severe pneumonia is important to clinician for recognizing high risk populations, establish appropriate early intervention, and reduce in-hospital complications and mortality^{7,15} especially in the area with scarce facilities.⁹

It is important to perceive the simple objective clinical signs and laboratory values as risk factors for mortality, as diagnosis and management of severe pneumonia in low-income settings rely on these parameters. Although many studies have identified risk factors for poor outcomes in patients with severe pneumonia in the PICU, data on these risk factors in Indonesia, particularly in Bali, are still limited. To our knowledge, there were only few studies in Indonesia that have described predictors of mortality in children and with only small sample size.¹⁶⁻¹⁸ Furthermore, the other limitations of evidence from previous studies also came from the population of samples were predominantly in less than five age group.⁸⁻¹⁰

Therefore, we sought to evaluate other demographic, clinical, and laboratory characteristics, including age, nutritional status, SpO₂ at arrival, invasive mechanical ventilation, Pediatric Logistic Organ Dysfunction (PELOD)-2 score, haemoglobin, lymphocyte count, and

procalcitonin level, and identify the association of these parameters with mortality in severe pneumonia children admitted into the PICU.

MATERIAL AND METHODS

Study design and population

This was a single-center unmatched case-control study conducted between January 2019 to December 2020 in the multidisciplinary care PICU of Prof Dr IGNG Ngoerah Hospital, Bali, Indonesia with maximum capacity of 9 beds and 9 mechanical ventilators. The inclusion criteria in this study were 1) pediatric patients between 28 days and 18 years of age when admitted to the PICU, 2) established diagnosis of severe pneumonia, and 3) were documented in the PICU's medical register. We excluded patients with history of perinatal lung disease, major congenital anomaly, presence of cyanotic congenital heart disease, and incomplete data in medical records.

The sample size was determined based on formula for study design to compare proportions of two populations. The degree of significance was 5%, the power was 80%, and proportion of risk factors based on previous studies.^{7,9} Therefore, total minimum sample in both case and control groups was determined to be 108 subjects (54 subjects each).

Data collections

The paper based PICU medical registry of all pediatric patients admitted during study period were screened retrospectively. The eligible patients who met the inclusion and exclusion criteria were included by consecutive sampling method. The subjects were assigned into two groups, the survivor and death groups, based on condition at the time discharge from PICU. Medical information data each subject was collected using a standard case report form and included demographic characteristics (age and gender), weight, height, nutritional status, comorbidities, mechanical ventilation type (invasive or noninvasive), duration of mechanical ventilation, ventilator-free days, PICU and hospital length of stay, and laboratory values (haemoglobin, lymphocyte, procalcitonin, and blood gas analysis) from electronic hospital data information system. We chose these variables based on the previous literature and were uncomplicated to be measured. Therefore, could be applied to our center and other limited-facilities healthcare.

Severe pneumonia was diagnosed by attending physicians as the presence of clinical signs (febrile

respiratory illness and lower respiratory tract infection signs), supported by radiological evidence, and accompanied by danger signs, such as chest indrawing, cyanosis, difficulties breastfeeding, or unconsciousness.^{3,19} This study included all pneumonia cases and did not differentiate by specific type (i.e., community- or hospital-acquired) during analysis.

Patient nutritional status was assessed on first day admitted in PICU based on actual subject weight compared to ideal body weight based on the World Health Organization (WHO) growth chart by Waterlow and further classified into well-nourished (above 80%) and moderate-severe malnourished (below 80%).

The lowest measured SpO₂ at arrival by portable pulse oximetry was recorded when the subjects were transferred to the PICU. The SpO₂ less than 90% at arrival was considered the hypoxemia state.

PELOD-2 score is continuous scale and indicates organ dysfunction, which consists of ten variables for five vital organs, namely the neurologic, cardiovascular, renal, respiratory, and hematologic organ systems. The higher score indicates poorer prognosis. The PELOD-2 score was measured in the first 24 hours of admission to the PICU. Organ dysfunction was determined when PELOD-2 score was equal or more than 7 without lactate examination.

Lymphocyte absolute count and haemoglobin level were obtained through routine complete blood count. Lymphocyte count was categorized into two categories: 1) below normal value (lymphopenia) and 2) normal, based on age-specific normal ranges from previous literature.²⁰ haemoglobin values were divided into two categories with a cutoff of 8 g/dL (< 8 g/dL and ≥ 8 g/dL).⁹ Procalcitonin levels were obtained through blood chemistry and divided into two categories, < 0.5 ng/mL and ≥ 0.5 ng/mL. The worst laboratory values were documented when more than one laboratory examinations were available.

Data Analysis

The collected data were analyzed using SPSS for windows version 25.0. Descriptive analysis described the baseline characteristics of subjects in each group. Continuous data were presented as mean and standard deviation (SD) if normally distributed, or median and interquartile range (IQR) if not normally distributed. Categorical data were presented as absolute numbers and percentages. Bivariate analysis was conducted to evaluate the association of mortality with each risk factor using χ^2 -test. Binary

logistic regression was used for multivariate analysis and included variables with p value less than 0.20 in bivariate analysis. P-value less than 0.05 was considered statistically significant.

Ethical Approval

This study was approved by Research Ethics Committee at Faculty of Medicine Udayana University Prof Dr IGNG Ngoerah Hospital, Denpasar (No. 295/UN14.2.2.VII.14/LT/ 2021).

RESULTS

Between January 2019 and December 2020, 1019 patients were admitted to PICU, and 192 patients met the inclusion criteria. Thirty-two subjects were excluded due to the presence of perinatal lung disease or cyanotic congenital heart disease or incomplete medical record data or multiple congenital anomalies. Therefore, 160 subjects with severe pneumonia were enrolled in this study. **Figure 1** illustrates the process of subject recruitment.

The median age of participants was 7 (IQR 2–47) months for the death group and 9 (IQR 3–48) months for the survivor group. The patients of both groups were predominantly male (58.9% and 57.5% in the death group and survivor group, respectively). Cardiovascular disease was the most common

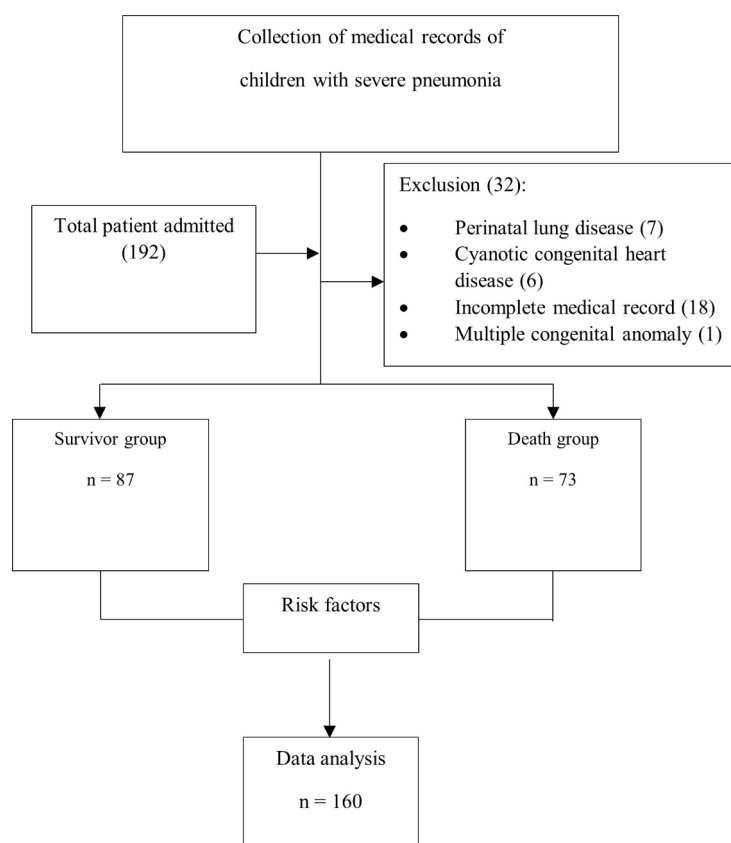


Figure 1 Study flow chart

Table 1 Baseline characteristics of subjects between groups

Characteristic	Outcome	
	Death (n=73)	Survivor (n=87)
Male n (%)	43 (58.9)	50 (57.5)
Age, months median (IQR)	7 (2-47)	9 (3-48)
Comorbidities n (%)	53 (72.6)	55 (63.2)
Cardiovascular n (%)	23 (31.5)	24 (27.6)
Neurology n (%)	12 (16.4)	15 (17.2)
Haematology-Oncology n (%)	6 (8.2)	5 (5.7)
Immunology n (%)	9 (12.3)	1 (1.1)
PICU LoS, days median (IQR)	4 (2-9)	9 (5-15)
Hospital LoS days median (IQR)	6 (3-15)	20 (12-30)
Ventilator-free days days median (IQR)	0 (0)	22 (15-25)
Length of MV days median (IQR)	4 (2-9)	6 (3-12)
PELOD-2 score median (IQR)	7 (5-8)	3 (1-4)
P/F ratio median (IQR)	171 (113-248.5)	305 (241-352)

Table 2 Bivariate analysis of some risk factors that associated with mortality

Risk Factors	Outcome		OR (95% CI)	p value
	Death	Survive		
Age < 60 months n, (%)	56 (76.7)	66 (75.9)	1.0 (0.50-2.17)	0.90
Invasive mechanical ventilation n, (%)	64 (87.7)	60 (69.0)	3.2 (1.39-7.35)	≤0.001*
SpO₂ < 90% at arrival n, (%)	41 (56.2)	7 (8.0)	14.6 (5.95-36.02)	≤0.001*
PELOD-2 score ≥ 7 n, (%)	40 (54.8)	4 (4.6)	25.1 (8.33-75.87)	≤0.001*
Moderate-severe malnutrition n (%)	29 (39.7)	20 (23.0)	2.2 (1.11-4.38)	0.02*
Haemoglobin < 8 g/dL n, (%)	26 (35.6)	9 (10.3)	4.7 (2.07-11.10)	≤0.001*
Lymphopenia n, (%)	26 (35.6)	20 (23.0)	1.8 (0.92-3.70)	0.07
Procalcitonin ≥ 0.2 ng/mL n, (%)	58 (79.5)	27 (31.0)	8.5 (4.15-17.77)	≤0.001*

*Significant $p < 0.05$ by x2-test

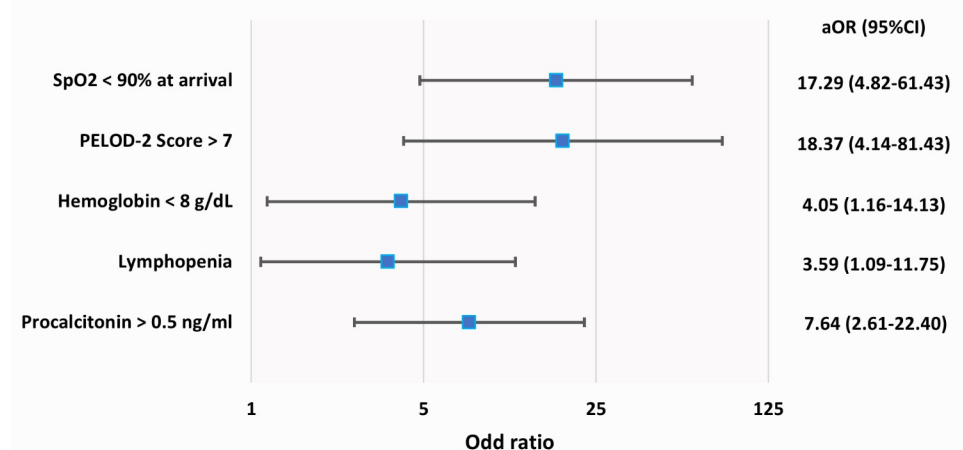


Figure 2 Multivariate analysis of risk factors of associated with mortality by logistic regression. The plot and error bars represent the odd ratio and confidence interval for each risk factors.

comorbidity found in both the survivor group (27.6%) and death group (31.5%), followed by neurological disorders, which had a prevalence of 17.2% and 16.4% for the survivor group and death group, hematology-oncology, and immunology disorders. Median PELOD-2 score was 7 (IQR 5–8) for the death group and 3 (IQR 1–4) for the survivor group, as detailed in [Table 1](#).

Bivariate analysis indicated that six risk factors were significantly associated with mortality. These factors were invasive mechanical ventilation, SpO₂ < 90% at arrival, PELOD-2 score ≥ 7, haemoglobin < 8 g/dL, moderate-severe malnutrition, and procalcitonin ≥ 0.5 ng/mL ([Table 2](#)). However, only five risk factors (SpO₂ < 90% at arrival, PELOD-2 score ≥ 7, haemoglobin < 8 g/dL, lymphopenia, and procalcitonin ≥ 0.5 ng/mL) were independently associated with severe pneumonia mortality in multivariate analysis, as detailed in [Figure 2](#).

DISCUSSION

Respiratory infections and illnesses, such as pneumonia, are significant causes of morbidity and mortality, particularly in developing countries. Early detection of severe clinical manifestations and well-timed admission to intensive care is crucial for lowering mortality⁵, and identification of risk factors for mortality at admission or during the clinical course is helpful to anticipate and observe treatment during hospitalization.²¹

The risk factors for severe pneumonia mortality vary between countries, regions, and communities. In Indonesia, only three studies have evaluated risk factors of mortality. Kisworini et al^{sup>17} found tachycardia and anemia and Meliyanti et al^{sup>16} found bacteremia and low weight as significant risk

factors for mortality. Valentania et al¹⁸ described modified PIRO score (malnutrition, complicated chest radiograph, hypoxemia, hypotension, CRP, procalcitonin, and organ dysfunction) could predict mortality of pneumonia. In this study, we found that SpO₂ < 90% at arrival, haemoglobin < 8 g/dL, PELOD-2 score ≥ 7, lymphopenia, and procalcitonin ≥ 0.5 ng/mL were associated independently with mortality.

This study was conducted in Prof Dr IGNG Ngoerah Hospital, as tertiary health center in Bali province, Indonesia. The diagnosis of patients admitted in PICU highly varied, consists of multidisciplinary care, and included pediatric patients who aged 28 days-18 years old. Therefore, the patients could represent all pediatric pneumonia patients that generally treated in PICU. This study was conducted at referral hospital for COVID-19 patients. However, because of small number (only 4) of pediatric patients required intensive care during study period, we decided to not include those patients into study.

Evaluation of SpO₂ is a simple, fast, and noninvasive method to measure arterial oxygenation. The WHO has recommended its clinical use to determine the requirement for oxygen administration for patients with hypoxemia, particularly in low-middle income countries,²² and states a threshold of < 90% as indicative of hypoxemia requiring immediate referral to the hospital.²³ An abnormal SpO₂ measured by pulse oximetry alone or ratio between SpO₂ / FiO₂ commonly indicates a ventilation–perfusion mismatch caused by a pulmonary illness in pediatric acute respiratory distress syndrome (ARDS).²³ In our PICU, pneumonia were found to be main cause of pulmonary ARDS with the median SpO₂/FiO₂ ratio were 165.²⁴ This study found that SpO₂ < 90% at arrival was associated with mortality, with an adjusted OR (odds ratio) of 17.29 (95%CI 4.82-61.43).

This result is consistent with previous studies by Shi et al^{sup>9} and Zhang et al^{sup>11} that found significant associations between $\text{SpO}_2 < 90\%$ and mortality, with an adjusted OR of 8.77 (95% CI 2.14–45.02). Colbourn et al also found that $\text{SpO}_2 < 90\%$ predicted death independently compared with $\text{SpO}_2 \geq 90\%$ (risk ratio 9.37; 95% CI 2.17–40.4; $p=0.003$).²³ In a study including 5,054 children in four hospitals in the Philippines, hypoxemia ($\text{SpO}_2 < 90\%$) was associated with death in children hospitalized with severe pneumonia in both < 2 months and 2–59 months age groups (aOR 4.69; 95%CI 2.23–9.56 and aOR 5.06; 95%CI 3.67–6.94, respectively).²⁵

The PELOD score is a frequently used scoring system that describes multiple organ dysfunction in pediatric patients. Different cutoff points have been reported in the literature and may be due to differences in patient characteristics, facilities, and staff capability at each center.²⁶ This study found a PELOD-2 score ≥ 7 without lactate measurement to be associated significantly with mortality in patients with severe pneumonia with an adjusted OR of 18.38 (95%CI 4.14–81.43). A similar result was found by Shi et al^{sup>9}, who showed that the proportion of multiple organ failure in the non-survivor group was significantly higher than that of the survivor group (21.5% versus 3.5%; $p = 0.040$). A higher PELOD-2 score indicates multiple organ dysfunction and poorer prognosis, and the most common organ dysfunction seen in sepsis patients is related to the respiratory system.²⁷ A previous study by Wati et al^{sup>28} found that most patients admitted to the PICU had three organ dysfunction (42.9%), with a median PELOD-2 score of 6 (IQR 8), and 58.3% of those who had three organ dysfunction died.

Of the complete blood count indices, mortality was associated with low lymphocyte count (aOR 3.59; 95%CI 1.09–11.75). These results are supported by the study by Wang et al^{sup>14} that found that lymphopenia increased mortality risk 7.68 times (95% CI 2.57–22.9) compared to normal lymphocyte values. Similarly, Chen et al^{sup>29} reported that abnormal lymphocyte count was significantly associated with more severe pneumonia and predicted further intensive care admission (OR 3.87; 95% CI 3.45–4.35). Significant lymphopenia has been recognized as a sign of blood lymphocyte dysfunction during infections.³⁰ Lymphopenia reflects impaired immune responses, especially among patients with severe infection and sepsis and may be the key factor in the inability to survive sepsis.³⁰ Therefore, this blood parameter could be used as a predictor of mortality in pneumonia patients as well. haemoglobin level < 8 g/dL was associated with mortality (aOR 4.05; 95%CI

1.16–14.13). Anemia as a predictor of mortality in patients with pneumonia has been consistently reported in previous studies^{9,11,17,21,25} and could be due to impaired oxygen transport in patients who have low haemoglobin levels. In addition, the presence of pneumonia concurrent with anemia could worsen hypoxic conditions and lead to a higher risk of death.¹⁷ Moschovis et al^{sup>31} stated that anemia was a predictor of worse prognosis and unresponsiveness to treatment among children with pneumonia, particularly when accompanied by anemia at high altitudes. Anemia and lymphopenia in this study was considered not only caused by severe infection but also the comorbidities, as the hematology and immunology disorders were prevalent in our settings.

Procalcitonin is an inflammatory biomarker that found to increase by several folds during inflammation, such as during a bacterial infection.³² Prior studies found as high as 16.1% of total patients and 21% of severe pneumonia patients had positive blood cultures.^{33,34} The bacterial etiology, represented by high procalcitonin level, could lead to more severe manifestations of pneumonia. This study found that procalcitonin levels ≥ 0.5 ng/mL increased risk of mortality (adjusted OR 7.64; 95%CI 2.61–22.4). This result is supported by Yadav et al^{sup>32}, who reported that procalcitonin level greater than 2 ng/mL was a predictor of more severe pneumonia manifestation and indicated a higher risk for complications including empyema, pneumothorax, septic shock, ARDS, and prolonged hospitalization. However, a contrary result was reported in the studies by Shi et al and Zhang et al which found no association between procalcitonin and mortality in patients with severe pneumonia.^{9,11} These conflicting results are expected due to variability in cutoffs for procalcitonin, analysis methods, populations, study settings, and outcomes. This suggests further study is necessary to evaluate optimum cutoff value to predict mortality in children with severe pneumonia.

Patient age has been considered as a risk factor for mortality among patients with pneumonia in previous studies. However, this study found that age was not associated with risk of mortality. This result is supported by Shi et al^{sup>9}, who reported no difference in fatal outcomes for patients aged 1–14 years old and those aged less than 1 years old. In contrast, Williams et al^{sup>13} found that age less than 2 months old and 10 years old significantly increased the risk of mortality compared to children aged 2 months old (OR 1.22 and 1.87, respectively), though children aged 5 years old had a lower risk of

mortality (OR 0.84). These contradictory results may be due to the large variations in age groups and cutoffs used in prior studies.^{9,11,13,21}

Invasive mechanical ventilation was associated significantly with mortality in bivariate analysis, though not in multivariate analysis. Similarly, a previous study by Shi et al⁹ showed that the requirement for mechanical ventilation was not associated significantly in multivariate analysis, despite it being associated significantly in bivariate analysis. In contrast, Sudarmadji et al³⁵ reported that intubated patients with severe pneumonia had a higher risk of death (OR 6.00; 95% CI 2.77–12.97), and Ramachandran et al⁸ stated that assisted ventilation was independently associated with fatal pneumonia cases.

Malnutrition is associated with altered metabolism, worsens the prognosis of severely ill children and contributes to higher mortality, longer length of hospital stay, and higher health cost.³⁶ In this study, moderate-severe malnutrition was not associated significantly with mortality in patients with severe pneumonia in multivariate analysis. A similar result was found by Shi et al⁹, who reported that the prevalence of malnutrition in the death and survivor groups was not significantly different. In contrast, Ramachandran et al⁸ showed that a weight-for-age Z score less than -3 SD had a 2.25 times higher risk of mortality. This result could be due to differences in anthropometric measurements of malnutrition. Previous studies primarily used weight-for-age as an indicator of malnutrition, while this study used the ratio of actual subject weight to ideal body weight based on the WHO growth chart.

This study had some limitations. First, it used a retrospective unmatched case-control design that is prone to biased patient selection due to incomplete previous data provided in medical records and unmatched in design. However, this study included only complete medical records confirmed with objective supporting examination to minimize selection bias and warranted further study with matching between case and control group. Second, the study sample size was relatively small, with resulting wide confidence intervals in certain

SUMMARY BOX

What is the already known about the subjects

- Prevalence of children with pneumonia who require admission to the pediatric intensive care unit (PICU) was high
- Anticipating of risk factors for mortality is important to establish appropriate early intervention, reduce in-hospital complications and mortality.

What are the new findings?

- Simple objective measurement and laboratory such as SpO₂ < 90% at arrival, haemoglobin < 8 g/dL, and lymphopenia were associated independently with mortality in pediatric patients with severe pneumonia.
- Invasive mechanical ventilation and malnutrition were not associated with mortality and warrants further study to reveal the association.
- These findings suggest that patients with SpO₂ < 90% at arrival should be treated and evaluated rigorously, and blood transfusion should be considered in patients who had haemoglobin < 8 g/dL, particularly in mechanically ventilated patients.

outcomes. Third, specific mechanical ventilation parameters were not included in the analysis, which could have provided more information for further analysis, research, and patient treatment. Fourth, this study did not mention socio-demographic factors (parental education, parental occupation, family income, geography, housing, number of family members) as the unavailability of these data in medical records. Finally, this study did not mention specific immunization history, such as history of measles, MMR, Hib, pneumococcal, and influenza vaccines, that may affect the severity of pneumonia in children.

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