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Factors associated with severe childhood community-acquired pneumonia: a retrospective study from two hospitals

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Abstract

Background: Community-acquired pneumonia (CAP) is the leading cause of death in children globally. Indonesia is ranked 1st in South East Asia with the highest burden of pneumonia. Identification of risk factors is necessary for early intervention and better management. This study intended to describe CAP's clinical signs and laboratory findings and explore the risk factors of severe CAP among children in Indonesia.

Methods: This was a retrospective study of childhood hospitalizations in Siloam General Hospitals and Siloam Hospitals Lippo Village from December 2015 to December 2019. Demographic data, clinical signs, and laboratory findings were collected and processed using IBM SPSS 26.0.

Results: This study included 217 participants with 66 (30.4%) severe pneumonia cases. Multivariate analysis shows that fever that lasts more than 7 days ($OR_{adj} = 4.95$; 95%CI 1.61–15.21, $P_{adj} = 0.005$) and increase in respiratory rate ($OR_{adj} = 1.05$, 95%CI 1.01–1.08, $P_{adj} = 0.009$) are two predictors of severe pneumonia. Meanwhile, a normal hematocrit level ($OR_{adj} = 0.9$; 95%CI 0.83–0.98, $P_{adj} = 0.011$) and children with normal BMI ($OR_{adj} = 0.7$; 95%CI 0.57–0.84, $P_{adj} < 0.001$) are significant independent predictors of severe pneumonia. The Hosmer-Lemeshow test shows that this model is a good fit with a *P*-value of 0.281. The AUC for this model is 0.819 (95%CI = 0.746–0.891, *P*-value < 0.001) which shows that this model has good discrimination.

Conclusion: Pediatric CAP hospitalizations with fever lasting > 7 days and tachypnea were at higher risk for progressing to severe pneumonia. A normal hematocrit level and a normal BMI are protective factors for severe pneumonia.

Keywords: Childhood pneumonia, Severe pneumonia, Risk factors

Background

Pneumonia kills more children than other infectious diseases, especially in children under five. Although the implementation of safe, effective, and affordable interventions has reduced pneumonia mortality from four million in 1981 to just over one million in 2013, pneumonia still accounts for nearly one-fifth of childhood deaths worldwide. Almost 808,000 children died from pneumonia in 2017, accounting for 15% of child deaths globally, with more than 90% occurring in developing countries [1]. Based on Indonesia Health Profile Report in 2020, pneumonia, besides diarrhea, is one of the causes of high infant (14.5%) and toddler (5.05%) mortality in Indonesia [2].

The World Health Organization (WHO) has classified childhood community-acquired pneumonia (CAP) by clinical characteristics, dividing them into non-severe and severe pneumonia. WHO defines non-severe

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pneumonia in children as the presence of cough or difficulty breathing associated with fast breathing or chest indrawing in children 2–59 months of age. Severe pneumonia is defined as pneumonia plus the inability to drink, persistent vomiting, convulsions, lethargy, stridor, or severe malnutrition [1]. Studies show that clinical definitions of severity correlate with case fatality rates. Most childhood pneumonia deaths are due to severe pneumonia [3].

Case management is one of the cornerstones of CAP management strategies [4]. Early identification of cases using simple clinical signs and appropriate treatment is needed. Recognizing the risk for the severe outcome is essential to further morbidity and mortality. Identifying children at risk of pneumonia-related mortality could signal the need for closer monitoring, hospital admission, or more intensive therapy [5, 6].

Studies from low- and middle-income countries (LMICs) have tried to identify the risk factors for severe CAP. Four clinical prediction tools have been proposed to identify hospitalized children at risk of death due to acute respiratory illness: the Respiratory Index of Severity in Children (RISC), the Modified Respiratory Index of Severity in Children (mRISC) [7], the RISC-Malawi Score [8], and the Pneumonia Etiology Research for Child Health (PERCH) [9]. Studies of childhood CAP in Indonesia are lacking. While one study only looks at the risk factors of acquiring pneumonia [10], the other still uses the older childhood CAP classification, which is rarely used nowadays [11]. More clinical studies from Indonesia are needed because Indonesia is ranked 1st in Southeast Asia with the highest burden of CAP. Worldwide, Indonesia is placed seventh [12].

Hence, our study aims to compare the clinical signs and laboratory findings of children hospitalized with severe and non-severe CAP. We also identify the factors that contribute to the severity of childhood CAP.

Methods

The data were obtained retrospectively through medical records from two hospitals, Siloam General Hospital (SGH) and Siloam Hospital Lippo Village (SHLV), using consecutive methods from December 2015 to December 2019. Siloam General Hospital is a teaching hospital where patients can undergo treatment under national health insurance in Indonesia. Meanwhile, SHLV mainly comprises patients with private insurance or out-of-pocket payment. The inclusion criteria for this study include all hospitalized pediatric patients diagnosed with pneumonia with radiological confirmation as the reference diagnostic standard. This study's exclusion criteria include children who had another severe immunosuppression from chronic use of steroids or diseases such as human immunodeficiency virus (HIV) and primary immunodeficiency.

Childhood CAP cases were classified into two groups: non-severe and severe pneumonia, based on the World Health Organization (WHO) revised guidelines for classifying and treating childhood pneumonia at health facilities [1]. Pneumonia was diagnosed when a child had a cough and/or difficulty breathing, with or without fever with either lower chest wall indrawing (LCWI) or age-appropriate tachypnoea ($\geq$ 50 breaths per minute if the children were 2–12 months, $\geq$ 40 breaths per minute if $\geq$ 12 months). Severe pneumonia was defined as pneumonia with general danger signs: lethargic or unconscious, inability to drink, persistent vomiting, convulsions, stridor in a calm child, or severe malnutrition.

We collected demographic data such as age, gender, and nutritional status. Clinical signs such as temperature upon arrival, vital signs, clinical manifestations, duration of symptoms (fever, cough, shortness of breath, convulsions, decreased appetite, vomit), duration of hospitalization, and physical findings (cyanosis, nasal flaring, chest retraction, reduced vesicular breath sound, rhonchi, wheezing) were collected. Lastly, we collected laboratory findings such as full blood count, serum electrolytes, and inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).

Data collected was processed using IBM SPSS 26.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA). A normality test was done, and data with normal distribution will be presented as mean and standard deviation. Otherwise, the median and range will be used. Depending on the distribution of numerical data, the *T*-test will be used for normal distribution, while the Mann-Whitney *U* will be used when the data distribution is not normal. Bivariate analysis was analyzed using chi-square, and variables with *P*-values below 0.25 will be included in multivariate logistic regression analysis. The performance of the final prediction results would be checked for discrimination using the receiver operating curve (ROC) and calibration (goodness of fit) using the Hosmer-Lemeshow test. When the ROC curve corresponds to random chance, the area under the curve would be equal to 0.5, and when the ROC curve corresponds to good accuracy, AUC would be 1.0. A *P*-value of > 0.05 would measure a good calibration. The area under the curve was then calculated to analyze the sensitivity and specificity of the number of predictor variables in differentiating non-severe and severe pneumonia. The Ethics Committee of Universitas Pelita Harapan, Tangerang, Indonesia, approved this study with approval number 174/K-LKJ/ETIK/XII/2020.

Results

This study included 217 participants with 66 (30.4%) severe pneumonia cases (Table 1). The patients were mostly male in both groups. The median age is 2.4 years old (0.01–18 years old) in the non-severe group and 1.7 years old (0.2–17.4 years old) in the severe group. The majority of the patients in both groups had a good nutritional status. However, 22 patients (40%) with severe pneumonia are severely wasted. The median cough duration for both groups is 7 days, ranging from 1 to 90 days in non-severe pneumonia and 1 to 60 days in severe pneumonia. The median fever duration for both

Table 1 Characteristics of the study population

Characteristics	Frequency (%)		OR (95%CI)	*P*-value
	Non-severe ($n = 151$)	Severe ($n = 66$)		
Sex			1.14 (0.63–2.07)	0.77
Male	89 (58.9)	41 (63.1)		
Female	62 (41.1)	25 (37.9)		
Age (years), median (range)	2.4 (0.01–18)	1.7 (0.2–17.4)		
0–5	116 (76.8)	54 (81.8)	Ref	Ref
5–10	27 (17.9)	6 (9.1)	0.48 (0.19–1.22)	0.18
10–15	4 (2.65)	4 (6.1)	2.42 (0.52–8.91)	0.44
15–18	4 (2.65)	2 (3)	1.07 (0.19–6.05)	1
Body mass index (kg/m^2), median (range)	($n = 132$) 15.6 (12.9–76.2)	($n = 55$) 13.9 (6.4–24.8)		
Normoweight	100 (75.8)	24 (43.7)	Ref	Ref
Severely wasted	0 (0)	22 (40)	N/A	N/A
Wasted	21 (15.8)	7 (12.7)	1.39 (0.53–3.64)	0.68
Overweight	8 (6.1)	1 (1.8)	0.51 (0.06–4.37)	1
Obese	3 (2.3)	1 (1.8)	1.39 (0.15–13.95)	1
Duration of cough (days), median (range)	($n = 144$) 7 (1–90)	($n = 60$) 7 (1–60)	N/A	0.08
Duration of fever (days), median (range)	($n = 142$) 5 (1–15)	($n = 61$) 6 (1–18)	N/A	0.04
Temperature upon arrival (°C), median (range)	37.6 (35.7–41)	37.8 (35.5–40.1)	N/A	0.09
Respiratory rate (breaths per minute), median (range)	26 (13–88)	32 (20–97)	N/A	< 0.01
Heart rate (beats per unit) median (range)	124 (82–204)	130 (80–197)	N/A	0.05
Oxygen saturation (%), median (range)	($n = 92$) 97 (83–100)	($n = 58$) 96 (69–100)	N/A	0.08
Duration of hospitalization (days), median (range)	4 (1–14)	5 (1–37)	N/A	0.12
Clinical manifestations[a]				
Fever	142 (94)	61 (92.4)	0.77 (0.25–2.4)	0.88
Cough	144 (95.4)	60 (90.9)	0.49 (0.16–1.51)	0.34
Shortness of breath	53 (35.1)	25 (37.9)	1.13 (0.62–2.05)	0.81
Decreased appetite	59 (39.1)	33 (50)	1.56 (0.87–2.79)	0.18
Convulsion	0 (0)	17 (25.7)	N/A	N/A
Vomits	33 (21.9)	22 (33.3)	1.79 (0.94–3.39)	0.11
Physical findings[a]				
Tachypnea	20 (13.2)	20 (30.3)	2.85 (1.41–5.76)	0.003
Cyanosis	0 (0)	5 (7.6)	N/A	N/A
Nasal flaring	12 (7.9)	10 (15.2)	2.07 (0.85–5.06)	0.17
Chest retraction	34 (22.5)	32 (48.5)	3.239 (1.75–5.99)	< 0.001
Reduced vesicular breath sound	15 (9.9)	7 (10.6)	1.08 (0.42–2.78)	1
Rhonchi	116 (76.8)	54 (81.8)	1.36 (0.65–2.82)	0.52
Wheezing	22 (14.6)	11 (16.7)	1.17 (0.53–2.58)	0.85

[a] One patient can have more than one clinical manifestation and physical finding

groups is similar, with 5 days (1–15 days) among the non-severe group and 6 days (1–18 days) among the severe group. Patients with severe pneumonia had a higher respiratory rate (RR) compared to those in the non-severe group, with a median of 32 times/min (20–97 times/min) as compared to 26 times/min (13–88 times/min), respectively.

The median duration of hospitalization for non-severe and severe pneumonia is 4 days (1–14 days) and 5 days (1–37 days), respectively. Fever and cough are the most frequent clinical manifestations in both groups, followed by decreased appetite, shortness of breath, and vomiting. Seventeen patients (25.7%) with severe pneumonia experienced a seizure. Upon physical examination, 116 patients (76.8%) in the non-severe group and 54 patients (81.8%) in the severe group had rhonchi. Chest retractions were found in almost half of the patients with severe pneumonia, but only around 20% in patients with non-severe pneumonia. Around 30% of patients with severe pneumonia experienced tachypnea compared to 13% with non-severe pneumonia.

The hematological profile shows elevated ESR and CRP as the inflammatory markers in both categories. The median ESR in the non-severe and severe groups were 23.5 mm/h (3–120 mm/h) and 23 (2–105 mm/h), respectively. The median CRP was higher in the severe group with 15.3 mg/L (2–231 mg/L) compared to 13 mg/L (0.2–117.7 mg/L) in non-severe pneumonia patients (Table 2).

Multivariate logistic regression analysis adjusted for decreased appetite, chest retraction, temperature, length of stay, RR, hemoglobin, leukocyte, eosinophil, and mean corpuscular hemoglobin (MCH) is shown in Table 3. Multivariate analysis shows that fever that lasts more than 7 days ($OR_{adj} = 4.95$; 95%CI 1.61–15.21, $P_{adj} = 0.005$) and increase in RR ($OR_{adj} = 1.05$, 95%CI 1.01–1.08, $P_{adj} = 0.009$) are two predictors of severe pneumonia. Meanwhile, a normal hematocrit level ($OR_{adj} = 0.9$; 95%CI 0.83–0.98, $P_{adj} = 0.011$) and children with normal BMI ($OR_{adj} = 0.7$; 95%CI 0.57–0.84, $P_{adj} < 0.001$) are associated significantly with reduced risks of severe pneumonia. The Hosmer-Lemeshow test shows that this model is a good fit with a *P*-value of 0.281. The AUC for this model is 0.819 (95%CI = 0.746–0.891, *P*-value < 0.001), which shows that this model has good discrimination (Fig. 1).

Discussion

Childhood CAP is not easy to diagnose, and predicting complications is even more challenging [13]. Clinicians rely on their experience or "gestalt" to diagnose childhood pneumonia. However, it turns out that clinicians' gestalt may not be as reliable as we thought it was [14]. The unreliability in clinicians' gestalt is further compounded by poor agreement of examination findings between clinicians in diagnosing CAP [15]. Hence, our study seeks to evaluate the factors that contribute to the severity of childhood pneumonia.

Fever has been taught to medical students to be one of the cardinal signs of pneumonia [16]. However, a recent study has found that fever alone does not reliably differentiate pediatric CAP from other respiratory illnesses [13]. However, fever has been identified as a clinical marker to predict severe pneumonia [17]. In one study, an axillary temperature of $\geq$ 39 °C has an adjusted risk ratio of 1.9 for mortality in pediatric pneumonia [18]. Furthermore, the duration of illness, including fever, has been found as a factor that is associated with an adverse outcome in childhood pneumonia [19, 20]. A study from Bangladesh finds that symptoms that last more than 3 days increase the risk of adverse outcomes in pediatric CAP [21]. One explanation for this finding might be delayed presentation [22]. Children who receive medical intervention later than they should are associated with an increased mortality rate [23]. This finding bolsters our argument that it is imperative to correctly identify children with signs and symptoms suggestive of severe pneumonia so that they are not sent home immediately.

Hematocrit is a whole blood parameter that measures the ratio of red blood cells (RBC) to plasma. A lower hematocrit can be caused by a decrease in RBC volume and an increase in plasma volume. Hemodilution can occur in patients who are edematous, hypervolemic, or who appear to be euvolemic on clinical examination [24]. A low hematocrit, especially when compounded with true anemia, results in higher mortality in patients with congestive heart failure [24] and sepsis [25]. In our case, a normal hematocrit level is associated with a protective factor of severe CAP. Although anemia is only significant in bivariate and not multivariate analysis, we presume that the change in hematocrit level in our patients comes heavily from a decrease in RBC volume and not an increase in plasma volume. Although this assumption is theoretically based, children with severe pneumonia are usually dehydrated or refuse to drink [18, 26]. Anemia has been found to increase children's susceptibility to contracting pneumonia [27] and increases the risk of death [18, 28]. Although the biomolecular mechanism for a low hematocrit level contributing to increased death has yet to be fully elucidated, some theories exist [25]. Acute systemic infections cause inflammatory responses, which reduce the number of red blood cells entering circulation dramatically [29]. The production of reactive oxygen species may play a role in repressing red blood cell oxygen transport and red blood cell membrane deformities [30]. The number of red blood cells is reduced throughout the inflammatory response and oxidative stress process,

Table 2 Laboratory findings

Values	Reference range	Median (range)		*P*-value
		Non-severe	Severe	
Hemoglobin (g/dL)	9.5–14	(*n* = 147) 11.6 (5.4–16.8)	(*n* = 63) 11 (7.5–15)	0.008
Leukocyte (10^3 cells/mm^3)	6.2–17	(*n* = 147) 13.3 (1.67–36.9)	(*n* = 64) 14.7 (4–54.2)	0.16
Hematocrit (%)	30–40	(*n* = 147) 36 (4.62–51.1)	(*n* = 63) 33.2 (13.3–45.6)	0.03
Red blood cell count (10^6 cells/ µL)	4–5.5	(*n* = 147) 4.7 (1.87–16)	(*n* = 64) 4.6 (2.9–18.8)	0.59
Basophil (%)	0.5–1	(*n* = 144) 0 (0–1)	(*n* = 62) 0 (0–1)	0.95
Eosinophil (%)	1–4	(*n* = 144) 0 (0–9)	(*n* = 62) 0 (0–7)	0.04
Band neutrophil	3–5	(*n* = 144) 3 (2–3)	(*n* = 62) 3 (2–41)	0.96
Segmented neutrophil (%)	54–62	(*n* = 144) 54 (3–93)	(*n* = 62) 55 (18–88)	0.83
Lymphocyte (%)	20–40	(*n* = 144) 34 (2–79)	(*n* = 62) 35 (6–72)	0.66
Monocyte (%)	2–8	(*n* = 144) 7 (2–9)	(*n* = 62) 6.9 (2–9)	0.95
Monocyte lymphocyte ratio	N/A	(*n* = 144) 0.2 (0.06–1.54)	(*n* = 62) 0.2 (0.06–0.63)	0.62
Platelet (/mm^3)	150,000–400,000	(*n* = 145) 354 (26–1000)	(*n* = 64) 386 (102–989)	0.31
Platelet lymphocyte ratio	N/A	(*n* = 144) 11.37 (0–149)	(*n* = 62) 10.28 (2.74–103)	0.91
ESR (mm/h)	< 10	(*n* = 140) 23.5 (3–120)	(*n* = 59) 23 (2–105)	0.69
CRP (mg/L)	< 10	(*n* = 65) 13 (0.2–117.7)	(*n* = 8) 15.3 (2–231)	0.43
Neutrophil lymphocyte ratio	1–3	(*n* = 144) 1.68 (0.14–48)	(*n* = 62) 1.7 (0.3–15.2)	0.81
Mean corpuscular volume (fL)	80–95	(*n* = 145) 78.2 (7.4–104.7)	(*n* = 64) 75.4 (53.3–94.7)	0.06
Mean corpuscular hemoglobin (pg)	27–31	(*n* = 145) 25.8 (15.9–36.7)	(*n* = 64) 25.1 (16–31.3)	0.11
Mean corpuscular hemoglobin concentration (g/dL)	32–36	(*n* = 145) 32.7 (28.9–40.5)	(*n* = 64) 32.8 (29.7–36.4)	0.81
Random blood glucose (mg/dL)	60–100	(*n* = 50) 106 (63–240)	(*n* = 48) 104 (5–517)	0.22
Na (mEq/L)	136–145	(*n* = 60) 136 (123–148)	(*n* = 53) 136 (119–157)	0.98
K (mEq/L)	3.4–4.7	(*n* = 60) 4.45 (2.2–6.7)	(*n* = 53) 4.4 (2.3–6.2)	0.92
Cl (mEq/L)	96–106	(*n* = 60) 100 (85–111)	(*n* = 52) 99 (65–137)	0.19

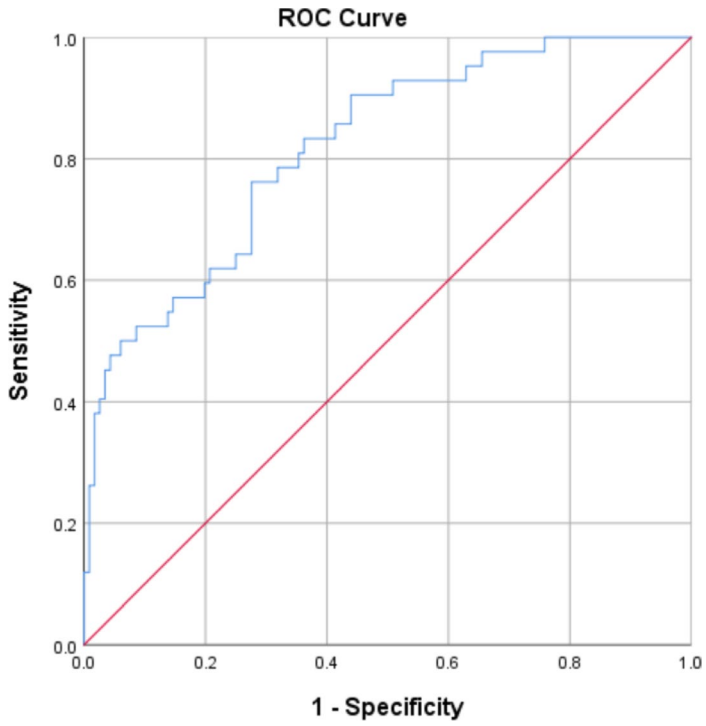
and blood dilution caused by liquid expansion lowers the hematocrit level [31, 32].

Age-associated tachypnea has been a criterion for diagnosing childhood CAP [1]. However, the revised WHO classification does not differentiate the severity of pneumonia based on the increased respiratory rate. Therefore, children with pneumonia of the same age as 2 years old who have a respiratory rate of 50 breaths per minute and 70 breaths per minute have the same prognosis, according to the revised WHO classification. Our finding indicates that an increase in respiratory rate contributes to the severity of pneumonia, and this finding

Table 3 Results from multivariate logistic regression analysis for severe pneumonia

Values	OR (95%CI)	*P*-value	OR_{adj} (95%CI)	$P\text{-value}_{adj}$
BMI, kg/m^2	10.21 (4.51–23.1)	< 0.001	0.7 (0.57–0.84)	< 0.001
Cough lasts > 7 days	0.78 (0.42–1.42)	0.08	0.38 (0.14–0.99)	0.05
Fever lasts > 7 days	1.9 (0.93–3.87)	0.11	4.95 (1.61–15.21)	0.005
Hematocrit	N/A	0.03	0.9 (0.83–0.98)	0.011
Vomits	1.79 (0.94–3.39)	0.11	2.4 (0.87–6.67)	0.09
Nasal flaring	2.07 (0.85–5.06)	0.17	5.17 (0.84–31.82)	0.077
Respiratory rate, breaths per minute	N//A	< 0.01	1.05 (1.01–1.08)	0.009

CI Confidence intervals, *OR* Odds ratio, OR_{adj} Adjusted odds ratio



Area	95% CI	*p-value*
0.819	0.746-0.891	<0.001

Fig. 1 The ROC curve analysis

has been replicated elsewhere [17, 19, 20, 22, 33]. For instance, Agweyu et al. [18] find that a respiratory rate of 70 breaths per minute or more is independently associated with death. The 1994 classification differentiates the severity of pneumonia according to different ranges of respiratory rates [34] and may be more appropriate for identifying children at risk of increased mortality.

Underweight or wasting are nutritional conditions associated with the severity of pneumonia [33]. Although the WHO classification does not include malnutrition, several risk scores to identify children at risk of hospitalized pneumonia-related mortality, such as the Respiratory Index of Severity in Children (RISC) [7], the RISC-Malawi [8], and the Pneumonia Etiology Research for Child Health (PERCH) [9], include malnutrition in their scoring systems. Agweyu et al. [18] find that children classified with non-severe pneumonia with a weight-for-age *Z* score of less than − 3 standard deviation are associated with a 3.8 times mortality risk.

There are several limitations to our study. Firstly, our study is a retrospective cohort study. Therefore, we could not control for some variables such as birth weight, parental smoking status, or immunization status, which may play a role in determining the severity status of childhood CAP. Secondly, our study is based on two hospitals where the catchment area of pneumonia cases may not be comprehensive. However, the nature of the two differing hospitals means that we could include children from various background demographics, ensuring that children from low- and middle-income parents and high-income parents are included in this study. Lastly, some variables are underpowered for analysis due to missing data (such as oxygen saturation) or laboratory data that were not analyzed. This reason may explain why some of the variables are insignificant, while other studies have identified hypoxemia [20] and CRP [35] as predictors of severe pneumonia.

Conclusion

Our study attempts to elucidate some of the factors associated with severe pneumonia. We find that fever lasting > 7 days and an increase in RR are predictors of severe pneumonia. At the same time, a normal hematocrit level and a normal BMI are protective factors for severe pneumonia. These findings suggest that an increase in RR should not be used only to diagnose pneumonia but should also determine the severity of pneumonia. While the revised WHO classification does not include fever duration as a component for severe pneumonia, clinicians should be wary of childhood CAP cases with fever lasting > 7 days.

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Authors' contributions
MP, GO, GH, and AJ have participated in the conception and design of the research. MP, GH, RH, FM, CB, MV, and AA contributed to the data collection, analysis, and interpretation. MP, GH, RH, FM, CB, MV, and AA drafted the article and revised it critically for important intellectual contents and based on the inputs from all authors. GO and AJ supervised the research. All authors approved the final version of the manuscript.

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Declarations

Ethics approval and consent to participate
Hereby, I, Michelle Patricia Muljono, consciously assure that for the manuscript *Factors associated with severe childhood community-acquired pneumonia: a retrospective study from two hospitals*, the following are fulfilled:
1) This material is the authors' own original work, which has not been previously published elsewhere.
2) The paper is not currently being considered for publication elsewhere.
3) The paper reflects the authors' own research and analysis in a truthful and complete manner.
4) The paper properly credits the meaningful contributions of co-authors and co-researchers.
5) The results are appropriately placed in the context of prior and existing research.
6) All sources used are properly disclosed (correct citation). Literal copying of text must be indicated as such by using quotation marks and giving proper references.
7) All authors have been personally and actively involved in the substantial work leading to the paper and will take public responsibility for its content.
The Ethics Committee of Universitas Pelita Harapan, Tangerang, Indonesia, approved this study with approval number 174/K-LKJ/ETIK/XII/2020.

Consent for publication
Not applicable

Competing interests
The authors declare that they have no competing interests.

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