

## Predictors of mortality in immunocompromised children with respiratory infections

Lea Sutrisna<sup>1</sup>, Rina Triasih<sup>2</sup>, Ida Safitri Laksanawati<sup>2</sup>

### Abstract

**Background** Respiratory infection is a common morbidity and a major cause of mortality in immunocompromised children. Hence, identification of clinical parameters that predict mortality among immunocompromised children with respiratory infections is of importance to provide timely and appropriate intervention.

**Objective** To determine predictors of mortality in immunocompromised children with respiratory infections.

**Methods** We conducted a prospective cohort study of immunocompromised children aged 18 years or younger with respiratory tract infections who were admitted to Dr. Sardjito Hospital, Yogyakarta, Indonesia. All eligible children were prospectively followed up until hospital discharge. Clinical and laboratory parameters during the first 24 hours of hospitalization were collected.

**Results** Of 79 eligible children, the overall mortality was 11 subjects (13.9%). Fever, tachycardia, tachypnea, cyanosis, leukopenia, neutropenia, thrombocytopenia, and pleural effusion were predictive factors of mortality in bivariate analysis ( $P < 0.25$ ). A logistic regression model showed that neutropenia (absolute neutrophil count  $< 125/\text{mm}^3$ ) and tachycardia were the best independent predictors of mortality in immunocompromised children with respiratory infections. The children with tachycardia had 15.8 times higher probability of mortality (95%CI 5.0 to 4.4) and those with neutropenia had 8.24 times higher probability of mortality. Cyanosis and pleural effusion were also independent mortality predictors.

**Conclusion** The risk of mortality is significantly increased in immunocompromised children with respiratory infection when tachycardia and neutropenia are also present. [Paediatr Indones. 2022;62:237-42 DOI: 10.14238/pi62.4.2022.237-42].

**Keywords:** mortality predictor; respiratory infection; immunocompromised

Respiratory infections are the most common cause of both morbidity and mortality in children. The *World Health Organization* (WHO) estimated that 150.7 million cases of acute respiratory infections in children under five occur each year, with pneumonia as the leading cause of death. Pneumonia accounted for nearly 7.6 million deaths in children younger than five years in 2010.<sup>1</sup> The incidence of pneumonia in the Southeast Asian region was 61 million cases yearly, of which the mortality rate was estimated at 0.6 million annually.<sup>2</sup> In 2013, Indonesia ranked 8<sup>th</sup> out of 15 countries with high pneumonia disease burden, with a mortality rate of 22,000 per year.<sup>1,3</sup> Of 174,000 children who died at  $< 5$  years of age in Indonesia, the leading cause of death was pneumonia (29%), followed by diarrhea (11%).<sup>3</sup>

Immunocompromised children are particularly vulnerable to upper and lower respiratory tract infections, which contribute to their morbidity and

From the Department of Child Health RSUD Melawi, Nanga Pinoh, Kalimantan Barat<sup>1</sup> and Universitas Gadjah Mada/Dr. Sardjito Hospital, Yogyakarta, Central Java<sup>2</sup>, Indonesia.

**Corresponding author:** Lea Sutrisna. RSUD Melawi. Kilometer 4, Desa Kelakik, Nanga Pinoh, 79672, Kalimantan Barat. Email: lea\_sutrisna@yahoo.com.

Submitted October 23, 2021. Accepted July 27, 2022.

mortality. The mortality rate in children with primary immunodeficiency was estimated to be between 13.6 to 17.5%. Lower respiratory tract infection was the leading cause of mortality (44%), and the most common pathogenic microorganisms were *Pseudomonas* and *Staphylococcus*.<sup>4</sup> The mortality rate among children with HIV infection in a Malawian study was 16.6%.<sup>5</sup> Respiratory tract infection in children with leukemia occurred in about 43% of children, and 26% of them demonstrated a complicated clinical course. The mortality rate related to viral lower respiratory infection in this population was 0.7%.<sup>6</sup>

Predictors of mortality in children with pneumonia have been identified, such as age <12 months,<sup>7</sup> malnutrition, tachycardia, anemia,<sup>8</sup> initial lymphocyte count  $\leq 800/\mu\text{L}$ ,<sup>9</sup> and hypoxemia.<sup>10</sup> Among HIV-infected children, the predictors of mortality were WHO clinical stages III and IV, whereas nutritional status, anemia (Hb less than 8 g/dL), and CD 4 level were not associated with mortality.<sup>11</sup> We aimed to identify factors which can be used as predictors of mortality in immunocompromised children with respiratory tract infections.

## Methods

We conducted a prospective cohort study, involving children who were aged  $\leq 18$  years, admitted to Dr. Sardjito Hospital, Yogyakarta, Indonesia, between September 2015 and August 2016, immunocompromised, and had at least one symptom of respiratory tract infections, i.e., cough, fever, or dyspnea. Immunocompromised patients in our study had malignancy, HIV infection, primary immunodeficiency, or were on long-term steroid treatment. Children with congenital heart disease and/or underlying lung disease were excluded. The diagnosis of respiratory tract infection was made by attending doctors, based on clinical symptoms and chest X-ray. Subjects' demographic, clinical, and laboratory parameters were documented during the first 24 hours, and subjects were followed up until hospital discharge.

Blood examinations were classified as follow: anemia (hemoglobin level less than -2SD by age, on admission), leukocytosis (leukocyte count above -2SD by age), leukopenia (leukocyte count less than -2SD by age, on admission), lymphopenia (absolute

limfocyte count less than -2SD by age), neutropenia (absolute neutrofil count less than -2SD by age), and thrombocytopenia (thrombocyte count less than 150.000/mcL).

The sample size was determined based on the formula for hypothesis testing of the population relative risk in cohort studies.<sup>14</sup> The minimum required sample size was calculated to be 60 children, based on the assumption of about 35% mortality,  $Z\alpha$  1.96,  $Z\beta$  0.84, 80% power, and relative risk (RR) of 1.75.

Bivariate analyses of potential associations with mortality were analyzed using relative risk with 95% confidence interval (RR; 95%CI) by Pearson's Chi-square and Fischer's tests. The variables with  $P < 0.25$  were included in a multivariate analysis using multiple logistic regression to identify independent factors associated with mortality. All hypothesis testing was two-tailed and P values  $\leq 0.05$  were considered to be statistically significant.

This study was approved by the Medical and Health Research Ethics Committee, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/Dr Sardjito Hospital, Yogyakarta. Medical record data were kept strictly confidential and anonymous.

## Results

A total of 84 immunocompromised children were admitted to the hospital with symptoms of respiratory infection (cough, fever, and/or dyspnea) during the study period. Two children were excluded because of lung metastasis and 3 children were excluded because of incomplete laboratory and radiologic examination results. The characteristics of the eligible children are presented in **Table 1**. Subjects' mean age was 6.5 (SD 5.1) years; more than half of subjects were aged >5 years. Subjects' hospital length of stay ranged from 1 to 61 days, with a mean of 13.8 days. The majority of subjects were immunocompromised due to malignancies, and the most common respiratory tract infection was pneumonia. Eleven children (13.9%) died during hospitalization.

The clinical, laboratory, and chest X-ray findings of subjects are presented in **Table 2**. Cyanosis and clubbed fingers were each found in 5 children (6.3%). The majority of children (80.2%) had anemia, with

**Table 1.** Baseline characteristics of the subjects

Characteristics	Total (N=79)
Males, n (%)	41 (51.9)
Mean age (SD), years	6.5 (5)
Age by group, n (%)	
0-1 years	7 (8.9)
1-5 years	26 (32.9)
>5 years	46 (58.2)
Malnutrition, n (%)	22 (27.8)
Underlying immunocompromising condition, n (%)	
HIV infection	13 (16.5)
Malignancy	56 (70.9)
Steroid treatment	6 (7.6)
Primary immunodeficiency	4 (5.1)
Respiratory tract infections, n (%)	
Pneumonia	63 (79.7)
Bronchitis	4 (5.1)
Pharyngitis	12 (15.2)

mean hemoglobin (Hb) level of 9.9 (SD 2.2) g/dL. Lymphopenia was also common (65.8%). Two children did not undergo chest X-ray examinations because it was not indicated. Of 77 children who had chest X-rays, the most common findings were infiltrates. Pleural effusions were found in six children.

**Table 3** shows the bivariate and multivariate analyses of possible predictors of mortality. Tachycardia (aRR 15.78; 95%CI 5.04 to 49.41), ANC < 125/mm<sup>3</sup> (aRR 8.24; 95%CI 2.58 to 26.29), cyanosis (aRR 6.88; 95%CI 1.06 to 44.57) and pleural effusion (P=0.006; aRR 4.79; 95%CI 1.56 to 14.77) were independent predictors for mortality in immunocompromised children with respiratory tract infections on multivariate analysis. We found a significant decrease of mortality risk in children with leukopenia.

**Table 2.** Clinical, laboratory, and chest X-ray findings

Variables	Died (n=11)	Survived (n=68)	Total (n=79)
Symptoms, n (%)			
Fever	9	40 (58.8)	49 (62.0)
Cough	7	48 (70.6)	55 (69.6)
Dyspnea	10	26 (38.2)	38 (46.9)
Stomatitis	5	21 (30.9)	26 (32.9)
Diarrhea	5	13 (19.1)	18 (22.8)
Physical findings, n (%)			
Cyanosis	2	3 (4.4)	5 (6.3)
Tachypnea	8	29 (42.6)	37 (46.8)
Chest retraction	4	19 (27.9)	23 (29.1)
Tachycardia	9	11 (16.2)	20 (25.3)
Rhonchi	5	26 (38.2)	32 (39.5)
Wheezing	2	5 (7.4)	7 (8.9)
Liver enlargement	5	16 (23.5)	22 (27.2)
Lymphadenopathy	1	10 (14.7)	11(13.9)
Clubbed fingers	1	4 (5.9)	5 (6.3)
Laboratory findings, n (%)			
Anemia	10	55 (80.9)	65 (82.3)
Leukocytosis	3	11 (27.3)	14 (17.7)
Leukopenia	2	37 (54.4)	39 (49.4)
Lymphopenia	8	44 (64.7)	52 (65.8)
TLC < 500/mm <sup>3</sup>	3	11 (16.2)	14 (17.7)
Neutropenia	4	30 (44.1)	34 (43.0)
ANC < 500/mm <sup>3</sup>	1	22 (32.4)	23 (29.1)
ANC < 125/mm <sup>3</sup>	4	4 (5.9)	8 (10.1)
Thrombocytopenia	7	29 (42.6)	36 (45.6)
Chest X-ray findings, n (%)			
Unilateral infiltrates	1	6 (9.1)	7 (9.1)
Bilateral infiltrates	7	48 (72.7)	55 (71.4)
Pleural effusions	3	3 (4.5)	6 (7.8)
Normal	0	9 (13.6)	9 (11.7)

TLC=total lymphocyte count; ANC=absolute neutrophil count

## Discussion

Respiratory tract infection is a common morbidity and cause of death in immunocompromised children. Our study documented mortality of 13.9% among immunocompromised children with respiratory symptoms. Of these children, the majority had pneumonia. The mortality rate in our study was in line with a report from Africa, which documented a mortality rate of 14% in children with pneumonia.<sup>1</sup> For children with HIV who were admitted to the hospital in the African region, mortality rate was 14%.<sup>12</sup>

In our subjects, tachycardia, cyanosis, ANC < 125/mm<sup>3</sup>, and pleural effusion were independent predictors of mortality. Tachycardia and cyanosis have been identified as predictors of hypoxemia, a common condition in children with acute respiratory tract infections and potentially increasing the risk of death.<sup>13,14</sup> A study of mortality risk among children with pneumonia in Bandung, West Java, showed that cyanosis was a significant risk factor of mortality.<sup>15</sup> A Yogyakarta study reported that tachycardia was a predictor of mortality in young children aged <5 years with pneumonia.<sup>8</sup> A study found that the combination of inability to cry, head nodding, or respiratory rate  $\geq$  90 breaths/min was the best predictor of hypoxemia

(sensitivity 70%, specificity 79%).<sup>16</sup> Along with another study which found that the clinical signs best predicting hypoxemia in children aged 1 month to 5 years with acute lower respiratory tract infection were cyanosis, respiratory rate >60x (OR 5; 95%CI 3.2 to 7.8), with 67% sensitivity, 71.1% specificity, and 74.4 positive predictive value.<sup>11</sup> A risk models study on predicting severe pneumonia outcomes in children showed that tachycardia was associated with severe pneumonia (aOR=1.59-2.90, depending on age).<sup>17</sup> Tachycardia reflects a hypoxemic condition, as it occurs in response to low oxygen supply, initiating activity of efferent chemosensory system to produce a cardiorespiratory adjustment in order to increase oxygen delivery.<sup>14,18</sup> Interestingly, tachypnea, which is also a typical response to hypoxemia, was not a good predictor of mortality in our study. Previous studies in children with pneumonia also found that tachypnea could not predict mortality.<sup>8,19,20</sup> This observation may have been because tachypnea is a hallmark of pneumonia in children, hence, all children with pneumonia have tachypnea regardless their level of hypoxemia.

Absolute neutrophil count <125/mm<sup>3</sup> was a significant predictor of mortality in our study. Similarly, previous studies have documented that neutropenia increased the risk of mortality in children

**Table 3.** Predictors of mortality in immunocompromised children with respiratory tract infection

Predictors	Bivariate analysis		Multivariate analysis	
	RR (95%CI)	P value	aRR (95%CI)	P value
Male	1.62 (0.55-5.11)	0.401		
Age < 1 year	2.29 (0.61-8.57)	0.250		
Malnutrition	0.97 (0.28-3.33)	0.637		
Fever	2.76 (0.64-11.90)	0.129	0.61 (0.156-2.39)	0.481
Cyanosis*	3.29 (0.96-11.32)	0.140	6.88 (1.06-44.57)	0.043
Tachypnea	3.03 (0.87-10.58)	0.064	0.48 (0.14-1.58)	0.224
Tachycardia**	13.28(3.13-56.36)	<0.001	15.78 (5.04-49.41)	<0.001
Chest retraction	1.39 (0.45-4.30)	0.402		
Liver enlargement	2.3 (0.78-6.76)	0.125	0.92 (0.24-3.56)	0.905
Lymphadenopathy	0.62 (0.09-4.36)	0.524		
Anemia	2.15 (0.30-15.49)	0.376		
Leukopenia	0.23 (0.05-0.99)	0.026	0.11 (0.04-0.35)	<0.001
TLC <500/mm <sup>3</sup>	1.74 (0.53-5.75)	0.302		
ANC <125/mm <sup>3</sup>	8.13 (1.69-38.99)	0.011	8.24 (2.58-26.29)	<0.001
Thrombocytopenia	2.09 (0.67-6.58)	0.195	0.68 (0.23-2.03)	0.485
Pneumonia	1.23 (0.29-5.18)	0.564		
Pleural effusion	4.56 (1.62-12.82)	0.033	4.74 (1.56-14.77)	0.006

with pneumonia (OR 9.53; 95%CI 1.69 to 53.8).<sup>17,21</sup> Neutrophils play an important role in the innate immune response to combat infection. A deficiency of neutrophils, as reflected by low ANC, may lead to an impaired immune system. Consequently, the infection may become more severe, resulting in increased risk of serious complications and death. Two studies of mortality predictors in children with pneumonia found that leukopenia was a significant risk factor of mortality.<sup>15,20</sup> However, a study in HIV-infected children showed no association between leukopenia and mortality in children with pneumonia.<sup>22</sup> We found a significant decrease of mortality risk in children with leukopenia.

Malnutrition also did not contribute as mortality predictor in our study, similar to a Brazilian study which included 871 children with pneumonia.<sup>23</sup> In contrast, a study of 150 malnourished children with pneumonia noted that malnutrition increased the risk of severe pneumonia by 4.6 times and the degree of malnutrition significantly contributed to mortality risk in children under 5 years.<sup>24</sup>

Anemia was reported to be a mortality predictor in children with pneumonia in 3 studies.<sup>8,20,22</sup> Anemia was not a mortality predictor in our subjects, possibly because malignancy was the major immunocompromising condition in our population.

A prospective cross-sectional study of 242 children with community-acquired pneumonia showed higher mortality among children with thrombocytopenia (OR 1.9; 95%CI 1.5 to 3.4; P=0.038).<sup>15</sup> The related finding showed in a study of fatality in community acquired pneumonia (OR=38.2; 95%CI 4.39 to 331.0; P=0.001).<sup>25</sup> The lack of an association in our subjects might have been influenced by the variety causes of thrombocytopenia in our population.

The children who were involved in this study were those with diseases or conditions postulated to suppress the immune system. We did not perform objective measurements of immunodeficiency, such as measurements of CD4, CD8, immunoglobulin or other parameters. Thus, this limitation of our study may not accurately represent true immunodeficiency. In conclusion, cyanosis, tachycardia, ANC <125/mm<sup>3</sup>, and pleural effusion are significant predictive factors for mortality in immunocompromised children with respiratory infection.

## Conflict of interest

None declared.

## Acknowledgements

We would like to acknowledge Labschool, Jakarta, for supporting this study.

## References

1. Liu L, Johnson HL, Cousens S, Perin J, Scott S, Lawn JE, *et al.* Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. *Lancet.* 2012;379:2151-61. DOI:10.1016/S0140-6736(12)60560-1.
2. Ghimire M, Battacharya SK, Narain JP. Pneumonia in South-East Asia region: public health perspective. *Indian J Med Res.* 2012;135:459-68.
3. Rudan I, O'Brien KL, Nair H, Liu L, Theodoratou E, Qazi S, *et al.* Epidemiology and etiology of childhood pneumonia in 2010: estimates of incidence, severe morbidity, mortality, underlying risk factors and causative pathogens for 192 countries. *J Glob Health.* 2013;3:010401. DOI: 10.7189/jogh.03.010401.
4. Ghazi BMS, Aghamohammadi A, Kouhi A, Farhoudi A, Moin M, Rezaei N, Doost PS, *et al.* Mortality in primary immunodeficient patients, registered in Iranian primary immunodeficiency registry. *Iran J Allergy Asthma Immunol.* 2004;3:31-6.
5. Preidis GA, McCollum ED, Mwansambo C, Kazembe PN, Schutze GE, Kline MW. Pneumonia and malnutrition are highly predictive of mortality among African children hospitalized with human immunodeficiency virus infection or exposure in the era of antiretroviral therapy. *J Pediatr.* 2011;159:484-9. DOI: 10.1016/j.jpeds.2011.02.033.
6. Hakim H, Dallas R, Zhou Y, Pei D, Cheng C, Flynn PM, *et al.* Acute respiratory infections in children and adolescents with acute lymphoblastic leukemia. *Cancer.* 2016;122:798-805. DOI: 10.1002/cncr.29833.
7. Arias Lopez MP, Fernández AL, Ratto ME, Saligari L, Serrate AS, Ko JJ, *et al.* Pediatric Index of Mortality 2 as a predictor

- of death risk in children admitted to pediatric intensive care units in Latin America: a prospective, multicenter study. *J Crit Care.* 2015;30:1324-30. DOI: 10.1016/j.jcrc.2015.08.001
8. Kisworini P, Setyati A. Mortality predictors of pneumonia in children. *Paediatr Indones.* 2010;50:149-53. DOI: 10.14238/pi50.3.2010.149-53
  9. Chien YS, Su CP, Tsai HT, Huang AS, Lien CE, Hung MN, et al. Predictors and outcomes of respiratory failure among hospitalized pneumonia patients with 2009 H1N1 influenza in Taiwan. *J Infect.* 2010;60:168-74. DOI: 10.1016/j.jinf.2009.12.012.
  10. Basnet S, Adhikari RK, Gurung CK. Hypoxemia in children with pneumonia and its clinical predictors. *Indian J Pediatr.* 2006;73:777-81. DOI: 10.1007/BF02790384
  11. Njom Nlend AE, Loussikila AB. Predictors of mortality among HIV-infected children receiving highly active antiretroviral therapy. *Med Mal Infect.* 2017;47:32-7. DOI: 10.1016/j.medmal.2016.07.003.
  12. Ford N, Shubber Z, Meintjes G, Grinsztejn B, Eholie S, Mills EJ, et al. Causes of hospital admission among people living with HIV worldwide: a systematic review and meta-analysis. *Lancet HIV.* 2015;2:e438-44. DOI: 10.1016/S2352-3018(15)00137-X.
  13. Duke T, Blaschke AJ, Sialis S, Bonkowsky JL. Hypoxaemia in acute respiratory and non-respiratory illnesses in neonates and children in a developing country. *Arch Dis Child.* 2002;86:108-12. DOI: 10.1136/adc.86.2.108.
  14. Lutz PL, Prentice HM. Sensing and responding to hypoxia, molecular and physiological mechanisms. *Integr Comp Biol.* 2002;42:463-8. DOI: 10.1093/icb/42.3.463.
  15. Fadlinda H, Utomo A, Djuhaeni H. Cyanosis as mortality risk among children with severe pneumonia. *AMJ.* 2016;3:186-9. DOI: 10.15850/amj.v3n2.799.
  16. Usen S, Weber M, Mulholland K, Jaffar S, Oparaugo A, Omosigho C, et al. Clinical predictors of hypoxaemia in Gambian children with acute lower respiratory tract infection: prospective cohort study. *BMJ.* 1999;318:86-91. DOI: 10.1136/bmj.318.7176.86.
  17. Aliberti S, Myers JA, Peyrani P, Blasi F, Menendez R, Rossi P, et al. The role of neutropenia on outcomes of cancer patients with community-acquired pneumonia. *Eur Respir J.* 2009;33:142-7. DOI: 10.1016/S0873-2159(15)30171-9.
  18. Michiels C. Physiological and pathological responses to hypoxia. *Am J Pathol.* 2004;164:1875-82. DOI: 10.1016/S0002-9440(10)63747-9.
  19. Djelantik IGG, Gessner BD, Sutanto A, Steinhoff M, Linehan M, Moulton LH, et al. Case fatality proportions and predictive factors for mortality among children hospitalized with severe pneumonia in a rural developing country setting. *J Trop Pediatr.* 2003;49:327-32. DOI: 10.1093/tropej/49.6.327.
  20. Atwa ZT. Usefulness of gender and abnormal blood count for predicting pneumonia outcome in children. *Egypt J Chest Dis Tuberc.* 2015;64:169-74. DOI: 10.1016/j.ejcdt.2014.11.022.
  21. Khanafer N, Sicot N, Vanhems P, Dumitrescu O, Meyssonier V, Tristan A, et al. Severe leukopenia in *Staphylococcus aureus*-necrotizing, community-acquired pneumonia: risk factors and impact on survival. *BMC Infect Dis.* 2013;13:359. DOI: 10.1186/1471-2334-13-359.
  22. Wang HW, Lin CC, Kuo CF, Liu CP, Lee CM. Mortality predictors of *Pneumocystis jirovecii* pneumonia in human immunodeficiency virus-infected patients at presentation: experience in a tertiary care hospital of northern Taiwan. *J Microbiol Immunol Infect.* 2011;44:274-81. DOI: 10.1016/j.jmii.2010.08.006.
  23. Ferreira S, Sant CC, March MF, Santos MA, Cunha AJ. Lethality by pneumonia and factors associated to death. *J Pediatr.* 2014;90:92-7. DOI: 10.1016/j.jpmed.2013.05.008.
  24. Arpitha G, Rehman M, Ashwita G. Effect of severity of malnutrition on pneumonia in children aged 2M-5Y at a tertiary care center in Khammam, Andhra Pradesh: a clinical study. *Sch J Appl Med Sci.* 2014;2:3199-203.
  25. Wang LJ, Mu SC, Lin CH, Lin MI, Sung TC. Fatal community-acquired pneumonia: 18 years in a medical center. *Pediatr Neonatol.* 2013;54:22-7. DOI: 10.1016/j.pedneo.2012.11.003.