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by Diska Hanifah Nurhayati

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Risk Factors for Mortality in Children with Hospital-Acquired Pneumonia in Dr. Soetomo General Hospital Surabaya

Diska Hanifah Nurhayati^{1*}, Retno Asih Setyoningrum², Arie Utariani³, Ira Dharmawati²

¹ Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.

² Department of Pediatrics, Faculty of Medicine, Universitas Airlangga/Dr. Soetomo General Hospital, Surabaya, Indonesia.

³ Department of Anesthesiology and Reanimation, Faculty of Medicine, Universitas Airlangga/Dr. Soetomo General Hospital, Surabaya, Indonesia.

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ABSTRACT

Introduction: Hospital-Acquired Pneumonia (HAP) is a nosocomial pneumonia that brings negative impacts, such as prolonged hospital stay and increased cost. Previous studies often discussed about the risk factors of HAP mortality in adult patients rather than in children. This study aimed to analyze the risk factors of mortality in children with HAP.

Methods: This was a retrospective observational analytic study using cross sectional method with total sampling. A total of 73 children were enrolled in this study, consisted of inpatients at Pediatric Inpatient Room Dr. Soetomo General Hospital Surabaya who met the inclusion and exclusion criteria. Independent variables were gender, age, onset of HAP, length of stay (LOS), comorbidities, birth weight, type of breastfeeding, the use of mechanical ventilation (MV), and response to therapy. Dependent variable was mortality. The data were collected from medical records, which later were analyzed by bivariate and multivariate analysis.

Results: The mortality of children with HAP was 23.3%. Bivariate analysis showed that age ($p = 0.009$), the use of MV ($p = 0.029$), and response to therapy ($p = 0.036$) were proven to affect mortality in children with HAP in Dr. Soetomo General Hospital Surabaya. In addition, the use of MV was the significant risk factor ($p = 0.023$) given by the multivariate analysis. Gender, onset of HAP, LOS, comorbidities, and type of breastfeeding were not proven to be the risk factors for mortality.

Conclusion: Mortality in children with HAP in Dr. Soetomo General Hospital Surabaya was significantly affected by children's age, the use of MV, and response to therapy. This information might be used as early signs and treatment strategies for children with HAP which lead to the decrease of hospital mortality.

INTRODUCTION

Pneumonia is the leading cause of mortality in children around the world, it is responsible for 16% of deaths of children under 5 years old in 2015.¹ Hospital-Acquired Pneumonia (HAP) is one type of pneumonia which occurs after 48 hours of hospitalization, it does not include incubation phase and is not related to mechanical ventilation (MV).² The incidence of HAP in the United States was 1.6% and it was the most frequent infection taken place at the intensive care unit (ICU).³

As for pediatric patients, the incidence was 15-29%, around 10-15% of all nosocomial infections in children and 67% of all nosocomial infections happened in pediatric intensive care unit (PICU).⁴⁻⁶ HAP in critically ill children brought negative impacts on clinical outcomes and economy, prolonged the use of MV, extended the duration of ICU stay, and might increase the cost and hospital mortality rate.⁷ The mortality rate of adult patients with HAP was 14,4% until 48,5%.⁸

*Correspondence: diska.hanifah.nurhayati-2017@fk.unair.ac.id

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This increase of mortality and morbidity was associated with the risk of having multi-drug resistant (MDR) organism as causative pathogen.² According to previous study, other risk factors related to mortality of adult patients with HAP were the use of MV, duration of treatment, acute kidney injury, and hematologic disorders as comorbidities.⁸ Another study reported that inadequate empirical antibiotic therapy, Simplified Acute Physiology Score (SAPS), and more than one organs failure are also related to mortality of nosocomial pneumonia.⁹ Nevertheless, study about those risk factors are rarely observed in children although the incidence is quite high. Therefore, this study aimed to analyze the risk factors for mortality in children with HAP in Dr. Soetomo General Hospital Surabaya as the tertiary hospital.

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METHODS

This observational retrospective study used cross sectional method and total sampling of the patients at Dr. Soetomo General Hospital Surabaya. The sampling was conducted through medical records. All pediatric inpatients aged 1 month-18 years old with HAP were included among other pneumonia patients admitted between January 2016 and December 2019. Children who used the MV before HAP signs and symptoms appeared were excluded in the study. Medical records used were ones that met the inclusion and exclusion criteria.

Pneumonia was defined according to World Health Organization (WHO)¹⁰ by observing child's respiration rate, the presence of cough or breathing difficulty, chest indrawing, and fever. HAP diagnosis is done by the main doctor who consulted with pediatric respirologist if necessary. The risk factor variables studied were gender, age, onset of HAP, length of stay (LOS), comorbidities, birth weight, type of breastfeeding, the use of MV, and response to therapy. Gender was differentiated as male and female. Age was the child's lifetime from birth until HAP signs and symptoms emerged, it was classified into two groups of ≤ 5 years old and > 5 years old based on epidemiological findings of the pneumonia incidence. Onset of HAP was the time from admission to the presence of pneumonia clinical signs and symptoms. There were two types of the onset, early-onset if the signs and symptoms appear within 5 days of admission, and late-onset if it appears

after 5 days of admission or more.² LOS was the hospitalization duration from admission until hospital discharge or death, with the cutoff for prolonged hospital stay was > 25 days.

Comorbidities were the presence of other diseases at the same time along with HAP, including the initial diagnosis when admitted to hospital. They were grouped based on organ system disorder such as hematooncology, cardiology, neurology, gastrology, nephrology, and respiratory diseases. The number of diseases were counted in each group. Birth weight was child's weight measured right after birth and were written in medical record. Normal birth weight measured around 2,500-4,000 g, and low birth weight (less than 2,500 g) or macrosomia (above 4,000 g) indicated an abnormal birth weight.^{11,12} Type of breastfeeding was feeding practice which the child had received during its first 6 months. Exclusive breastfeeding meant the child only received breast milk without other food/drink/water for 6 months of life, and predominant breastfeeding meant the child also received other liquids beside breast milk.¹³ The use of MV was when the patient used mechanical breathing assistance because of decreased respiratory function during the time after HAP diagnosis. Response to therapy was clinical response that could be observed in 48-72 hours after initial treatment. The parameters were axillary temperature, respiration, and chest indrawing. Mortality was the outcome of hospital death of the pediatric patient.

Numerical and categorical variables were presented as median (IQR) and n (%). This study compared the risk factors between non-survivor and survivor and used X^2 -test or Fisher's exact test as bivariate analysis to find the correlation between independent and dependent variables. Significant variables performed in bivariate analysis was continued to be explored in multivariate analysis using logistic regression. Two-sided α of less than 0.05 was statistically significant and the statistical analysis was performed with IBM SPSS Statistic (version 25). The study had the ethical clearance published by Medical Research Ethics Committee of Dr. Soetomo General Hospital Surabaya.

RESULTS

From the total of 1,008 pediatric patients with pneumonia hospitalized in Dr. Soetomo General

Hospital Surabaya, 88 of them were HAP patients. After excluding patients that did not have required data, 73 inpatients were included in the study. There were 17 patients who died during hospitalization which was the non-survivor group and 56 were discharged with further outpatient setting, which was the survivor group. Mortality rate was 23.3% among children who developed HAP.

Median of age was 16.0 months (IQR 3.5 – 73.5) ranging from 1 month until 191 months (15 years) old. Most of the patients were males and almost all of the patients had comorbidities (Table 1). The three most frequent comorbidities were hematologic, cardiologic, and neurologic disorders, consecutively. Details for the type of diseases were presented in Table 2. 26 out of 34 patients had the signs and symptoms for pneumonia after 5 days of admission (late-onset), the median of onset duration for 34 patients was 15.5 days (IQR 5.5 – 29.3). There were 26 out of 72 patients who experienced prolonged LOS up to 25 days (Table 1).

The median of birth weight data of 69 patients was 3,000 g (IQR 2,600 – 3,235) and 57 of them had abnormal birth weight (<2,500 g or >4,000 g). There were only 32 out of 70 patients who had exclusive breastfeeding history. 9 patients were in need of MV and 5 of them (56%) died. Therefore, only 65 patients' response to therapy could be observed. 61.5% of the patients did not show clinical improvement (no response) and 86% of the non-survivor group were patients who did not respond to therapy.

In bivariate analysis, age ($p = 0.009$), the use of MV ($p = 0.029$), and response to therapy ($p = 0.036$) were risk factors associated to mortality in children with HAP. In the other hand, gender, onset of HAP, LOS, comorbidities (hematologic, cardiologic, and neurologic disorders), birth weight, and type of breastfeeding were not associated with mortality. The odds of hospital mortality were higher in patients who used MV and did not respond to therapy (Table 3).

Table 1. Patients' characteristics

Characteristics	Total (n=73)	Non-survivor (n=17)	Survivor (n=56)
Gender			
• Male	40 (55%)	7 (41%)	33 (59%)
• Female	33 (45%)	10 (59%)	23 (41%)
Age, month	16.0 (3.5 – 73.5)	72.0 (2.5 – 107.0)	12.0 (3.3 – 37.0)
• ≤5 years old	54 (74%)	8 (47%)	46 (82%)
• >5 years old	19 (26%)	9 (53%)	10 (18%)
Onset of HAP, day	15.5 (5.5 – 29.3)	17.0 (14.0 – 23.5)	15.0 (4.0 – 30.0)
• Late-onset	26/34 (76.5%)	8/9 (89%)	18/25 (72%)
• Early-onset	8/34 (23.5%)	1/9 (11%)	7/25 (28%)
LOS	16.0 (8.3 – 30.8)	18.0 (5.0 – 29.0)	16.0 (9.0 – 31.0)
• >25 days	26/72 (36%)	5 (29%)	21/55 (38%)
• ≤25 days	46/72 (64%)	12 (71%)	34/55 (62%)
Comorbidities	72 (99%)	16 (94%)	56 (100%)
• Hematooncology	40 (55%)	12 (71%)	28 (50%)
• Cardiology	27 (37%)	8 (47%)	19 (34%)
• Neurology	23 (32%)	3 (18%)	20 (36%)
• Gastrology	22 (30%)	2 (12%)	20 (36%)
• Nephrology	11 (15%)	2 (12%)	9 (16%)
• Respirology	14 (19%)	3 (18%)	11 (20%)
Birth weight, gram	3,000 (2,600 – 3,235)	2,950 (2,500 – 3,075)	3,000 (2,700 – 3,350)
• <2,500 and >4,000	57/69 (83%)	14/16 (87.5%)	43/53 (81%)
• 2,500-4,000	12/69 (17%)	2/16 (12.5%)	10/53 (19%)
Type of breastfeeding			
• Predominant breastfeeding	38/70 (54%)	9 (53%)	29/53 (55%)
• Exclusive breastfeeding	32/70 (46%)	8 (47%)	24 (45%)
The use of MV	9/72 (12.5%)	5 (29%)	4/55 (7%)
Response to therapy			
• Not responding	40/65 (61.5%)	12/14 (86%)	28/51 (55%)
• Responding	25/65 (38.5%)	2/14 (14%)	23/51 (45%)

Data were median (IQR), n (%), or n/N (%). HAP: Hospital-Acquired Pneumonia, LOS: length of stay, MV: mechanical ventilation.

Table 2. Patients' comorbidities

Group	Diseases
Hematooncology	Anemia (unspecified), anemia of iron deficiency, anemia of chronic disease, ALL, AML, leukocytosis, thrombocytopenia, febrile neutropenia, rhabdomyosarcoma, hemangioma, histiocytosis
Cardiology	ASD, VSD, TAPVD, valve disorders, PDA, TOF, MPA dilatation, endocarditis, PH, PFO, cardiomyopathy, pericardial abscess, pericardial effusion
Gastrology	Acute diarrhea, paralytic ileus, GERD, cholestasis, melena, anal fissure, post repair colon perforation
Neurology	Hydrocephalus, meningocele, brain edema, epilepsy, status epilepticus, febrile seizure, microcephaly, meningoencephalitis, encephalopathy, germinoma, hygroma, herpetic neuralgia
Nephrology	AKI, lupus nephritis, UTI, hydronephrosis, urolithiasis, Wilm's tumor
Respirology	Infant asthma, lung tuberculosis
Other	Developmental delay, Down syndrome, laryngomalacia, hypothyroid, electrolyte imbalance, malnutrition

ALL: acute lymphoblastic leukemia, AML: acute myeloblastic leukemia, ASD: atrial septal defect, VSD: ventricular septal defect, TAPVD: total anomalous pulmonary venous drainage, PDA: patent ductus arteriosus, TOF: tetralogy of Fallot, MPA: main pulmonary artery, PH: pulmonary hypertension, PFO: patent foramen ovale, GERD: gastroesophageal reflux disease, AKI: acute kidney injury, UTI: urinary tract infection

Table 3. Bivariate analysis

Risk Factors	OR	95% CI	P value
Gender			
• Male	0.49	0.16 – 1.47	0.198
• Female			
Age			
• ≤5 years old	0.19	0.60 – 0.62	0.009
• >5 years old			
Onset of HAP			
• Late-onset	3.11	0.36 – 29.7	0.403
• Early-onset			
LOS			
• >25 days	0.63	0.19 – 2.02	0.431
• ≤25 days			
Comorbidities			
• Hematooncology	2.40	0.75 – 7.71	0.135
• Cardiology	1.73	0.58 – 5.21	0.326
• Neurology	0.39	0.09 – 1.50	0.160
Birth weight, gram			
• <2,500 and >4,000	0.61	0.12 – 3.15	0.718
• 2,500-4,000			
Breastfeeding history			
• Predominant breastfeeding	0.93	0.31 – 2.78	0.898
• Exclusive breastfeeding			
The use of MV	5.31	1.24 – 22.81	0.029
Response to therapy			
• Not responding	4.93	1.00 – 24.30	0.036
• Responding			

P value obtained from χ^2 test or Fisher's exact test. OR: odds ratio, HAP: Hospital-Acquired Pneumonia, LOS: length of stay, MV: mechanical ventilation.

Multivariable analysis was performed in variables that had p value < 0.25 to see which variables significantly affected mortality. Five factors were included in logistic regression, namely gender, age, having hematooncologic and neurologic disorders as comorbidities, the use of MV, and response to therapy. The result can be seen in Table 3.

The logistic regression model was statistically significant, carrying χ^2 (6) = 17,113 with $p < 0.05$. This model explained 35.8% (Nagelkerke R^2) of the variance in mortality and correctly classified 83.1% cases. The use of MV was the significant risk factor which associated with mortality ($p = 0.023$). Children who used MV for breathing assistance were 11 times more likely to die compared to children who did not (Table 4).

Table 4. Multivariate analysis

Risk Factors	OR	95% CI	P value
Male (vs female)	0.41	0.10 – 1.72	0.223
Age ≤5 years old (vs >5 years old)	0.44	0.08 – 2.44	0.348
Comorbidities (vs no comorbidity)			
• Hematooncology	0.79	0.12 – 5.17	0.811
• Neurology	0.18	0.02 – 1.65	0.129
The use of MV (vs not using)	11.68	1.41 – 96.90	0.023
Did not respond to therapy (vs responded)	5.56	0.90 – 34.24	0.064

P value obtained from logistic regression. OR: odds ratio.

DISCUSSION

HAP doubled the duration of PICU stay, increased the length of MV usage, and increased mortality rate than in patients without HAP.⁷ The mortality in this study was 23.3% which corresponded with previous studies performed in adult and pediatric patients, ranging from 9.2% until 56%.^{7,8} This study found that there were more male patients than females. However, 10 (59%) females were in the non-survivor group, slightly higher than male that reached 7 (41%) patients. Gender had the possibility of affecting infectious disease incidence, including pneumonia.¹⁴ Arnold, *et al.* (2013) stated that adult females with Community-Associated Pneumonia (CAP) were more likely to have longer time to reach clinical improvement, but the difference of treatment between the two gender was still questionable.¹⁵ In this study, gender was not the risk factor associated with mortality in children with HAP. López-de-Andrés, *et al.* (2020) in their study also said that being female did not have association with mortality in CAP and HAP, but it did in patients with Ventilator-Associated Pneumonia (VAP).¹⁶ In CAP, there could be other factors correlated with gender which might result in the association with incidence and mortality, adult males tend to smoke more and develop respiratory disease.¹⁷

HAP was found mostly in children under 5 years old, about 74% of all patients in this study. 14.8% of them were in the non-survivor group and age was associated with mortality in children with HAP. It is known that pneumonia was the leading cause of death due to infection in children <5 years old.¹⁸ Age also influenced clinical overview in children, the disparity happened as consequence of anatomy and immunology immaturity in specific age groups.¹⁸ Ferdous, *et al.* (2018) said that younger infants (<6 months) had greater risk for mortality than the older group that was associated with weaker immune system in infants if they

did not have exclusive breastfeeding.^{19,20} Onset of HAP was not associated with mortality in children with HAP, although there were 89% of non-survivors who had late-onset HAP. Guidelines from American Thoracic Society and Infectious Diseases Society of America once stated that early-onset HAP had better prognosis than late-onset, because late-onset was reflected by multi-drug resistant causative pathogen.² This was feared to cause inadequate initial treatment.² Nevertheless, other study had similar finding with this study which stated that HAP onset did not statistically significant.⁸

Length of stay did not show association with mortality in children with HAP. From 17 non-survivors, 71% were patients hospitalized in <25 days. Mansour and Bendary (2012) reported that prolonged hospital stay was one of the risk factors for acquiring HAP.⁷ Almost all patients had comorbidities, 12 patients with hematooncologic disorders were in the non-survivor group. In immunocompromised adult patients with HAP, hematologic disorders and acute kidney injury were factors associated with mortality.⁸ Malignancy and shock were also in correlation with pneumonia mortality, especially VAP.^{21,22} In the contrary, this study did not find the association between comorbidities and mortality. The different results might be due to differences in sample group (child vs adult) and the comorbid impacts were varying on different age groups.

Around 83% of all patients had abnormal birth weight (<2,500 or >4,000 g) and 54% received predominant breastfeeding. According to Brown (1996), pneumonia mortality would decrease along with the increase of birth weight in children aged 1-5 years, but in different age group (6-11 months) the risk for mortality was the same in children with low birth weight (LBW) and >3,500 g.²³ Mortality were higher in predominant breastfeeding, because breast milk gave protective effect in infant <9 months against respiratory infection.²⁴ In this study, birth weight and type of

breastfeeding were not associated with mortality in children with HAP. In fact, LBW and predominant breastfeeding history were associated with the incidence of pneumonia.^{25,26} It might be caused by the treatment given after developing HAP that made this result, which more likely affected mortality and morbidity.

9 out of 72 patients were in need of MV and 5 of them died. MV was the significant factor associated with mortality in children with severe and more severe pneumonia.²⁷ MV dependence was also independent risk factor related to mortality in the study with CAP.²⁸ This study found the same result as previous studies, where the use of MV significantly associated with mortality in children with HAP. The risk of mortality increased until 11 times higher in patients who had MV. The dependence promoted barotrauma, volutrauma, or biotrauma, which lead to dangerous complication such as bronchopulmonary dysplasia (BPD).²⁹ The last, response to therapy was found to have association with mortality. The conditions that would likely lead to mortality were acting the same as deterioration factor that worsen patients' clinical state in early treatment.² Prolonged MV durations, respiratory failure, and other complications would hardly result in clinical improvement in adult.² In children with HAP, the conditions were respiration rate >70 x/min, lethargy/unconsciousness, and positive blood culture.³⁰ It was feared that there were lack information in correlation between response to therapy and mortality, because generally response to therapy was observed simultaneously with mortality as the outcome.

This study was the first to analyze risk factors for mortality in children with HAP in Indonesia. It gave information that could be used as early signs and treatment strategies for children with HAP. The limitations of this study were small sample size and there were some available data from medical records that could not be included.

CONCLUSION

There was an association between variables according to the *p* values. It is concluded that age, MV use, and response to therapy were the risk factors for mortality in children with HAP in Dr. Soetomo General Hospital Surabaya. On the other hand, gender, HAP

onset, LOS, comorbidities, and type of breastfeeding were not proven to be the risk factors for mortality. Multivariate analysis also found that MV use was the significant risk factor for mortality.

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