Predictors of Mortality of Pediatric Patients with COVID-19 in Dr. Moewardi General Hospital, Surakarta

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ABSTRACT

Background: COVID-19 has spread all over the world and became a global pandemic. In Indonesia, COVID-19 has officially defined the non-natural disaster of COVID-19 spread as national disaster in April 13th 2020. COVID-19 cases are predominant in adult population with higher severity particularly if accompanied with comorbidities resulting in a relatively high mortality rate. However, some recent studies showed that children are at a similar or higher risk to COVID-19 compared to adults. This study aims to evaluate the predictors of mortality in pediatric COVID-19 cases.

Subjects and Method: This study used a cross-sectional design using data from medical records of pediatric patients with confirmed COVID-19 who were hospitalized in the isolation ward of Dr Moewardi General Hospital from March 2020 to August 2021. All variables with significant result in the bivariate analysis were analyzed using multivariate logistic regression. Data were analyzed using SPSS (IBM SPSS Statistics version 25) with significance of p value of < 0.05.

Results: Results of this study showed that age 10-17 years (OR= 16.26; 95% CI= 1.47 to 179.56; p= 0.023), the use of oxygen mask (OR= 45.89; 95% CI = 5.39 to 390.58; p <0.001), and the use of continued oxygen therapy (OR= 181.48; 95% CI=11.25 to 2927.80; p <0.001) are predictors of mortality in pediatric patients with confirmed COVID-19.

Conclusion: Age 10-17 years, use of oxygen mask and advanced oxygen therapy are predictors of mortality in pediatric patients with COVID-19 hospitalized in Dr Moewardi General Hospital Surakarta.

Keywords: mortality, COVID-19, pediatric.

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BACKGROUND

COVID-19 first occurred in Wuhan, China, in December 2019 and currently COVID-19 has spread all over the world and became a global pandemic. In Indonesia, COVID-19 was first detected in the beginning of 2020. According to the Decree of President of Republic of Indonesia No. 12 Year 2020, this condition has officially defined the non-natural disaster of COVID-19 spread as national disaster in April 13th 2020 (Wanti et al, 2021; Kemenkes, 2020).

In the early days of its occurrence, COVID-19 cases are predominant in adult population with higher severity particularly if accompanied with comorbidities resulting in a relatively high mortality rate. However, some recent studies showed that children are

at a similar or higher risk to COVID-19 compared to adults. Therefore, COVID-19 control should not only be by providing adequate high quality resources to hospitals, but also by paying more attention to the health care system including health care services, health care workers, information system, funding of health care services, workers, and management of health care. (Mahrous ES, Mokbel RA, 2021). Mother and children are at a higher risk for severe disease, morbidity and mortality compared to the general population (Rahmi et al., 2020).

Many studies have evaluated the severity and mortality rate in cases of COVID-19 in adult population. However, there are very limited studies that evaluated the mortality of COVID-19 in pediatric patients. This study aimed to evaluate the predictors of mortality in COVID-19 cases in pediatric patients hospitalized in Dr Moewardi General Hospital Surakarta.

SUBJECTS AND METHOD

1. Study Design
This study is an analytic observational study with cross-sectional design. This study was conducted by collecting data from the medical records of pediatric patients with COVID-19 in Dr Moewardi General Hospital Surakarta from March 2020 to August 2021.

2. Population and samples
The population data were all pediatric patients diagnosed with confirmed COVID-19 with moderate, severe, and critical severity hospitalized in the isolation ward in Dr Moewardi General Hospital Surakarta from March 2020 to August 2021. The exclusion criteria were patients who died or discharge from hospital with no laboratory or X-ray data.

3. Study variable
The independent variable were pediatric patients diagnosed with confirmed COVID-19 with moderate, severe, and critical severity.

The Dependent variable were epidemiology finding, nutritional status, immunization status, radiology finding, laboratorium finding, comorbid and oxygen therapy.

4. Operational Definition of Variables
COVID-19 infection by the SARS-CoV-2 virus characterized by fever (≥ 38°C) or a history of fever and cough; or there are 3 or more of the following symptoms such as fever or a history of fever, cough, fatigue, headache, myalgia, sore throat, runny nose, nasal congestion, shortness of breath, anorexia, nausea, vomiting, diarrhea, decreased consciousness and confirmed by RT-PCR confirmed positive. (Burhan et al, 2020).

Age length of time lived or existed since born. Based on the Regulation of the Minister of Health no. 25 of 2014, age categories are: infants aged 0 to <1 years, toddlers 0 to <5 years, adolescents 10 to 18 years, school-aged children 6 to <18 years (Kemenkes, 2014).

Gender was differentiated to male and female.

Immunization status was history of immunization based on the Ministry of Health immunization schedule.

Epidemiology finding was epidemiological investigations to seek close contacts.

Laboratory finding was laboratory examinations conducted on research subjects.

Radiology finding was radiological examination conducted on research subjects.

Comorbid was other diseases experienced apart from the main disease, such as congenital or acquired heart disease, autoimmune disease, malignancy, kidney disease, liver disease, hematological disease, and others.

Length of stay was number of days calculated from the time the patient was admitted in to the time when the patient was discharged from hospital or died.

Oxygen therapy was medical intervention by giving oxygen support (O2) to prevent or improve tissue hypoxia and maintain adequate tissue oxygenation.

5. Study instrument

The basic characteristics of study subjects were age, gender, chest X-ray finding, hospital's length of stay, immunization status, clinical symptoms, nutritional status, and epidemiological findings of the patients was acquired from the medical records.

6. Data Analysis

The numerical demographic data were presented as mean + SD (standard deviation), while categorical data were presented as frequency distribution (%). Categorical variables were presented as numbers (percentage) and compared using Chi-square test. Categorical data were analyzed using Chi-square or Fisher's exact test, while numerical data were analyzed using independent t-test. All parameters with significant results in bivariate analysis were continued to multivariate analysis using logistic regression.

Data analysis was using SPSS program (IBM SPSS Statistics version 25) and a p value of less than 0.05 is considered statistically significant.

7. Research ethics

This study was approved by the Health Research Ethics Committee of Dr. Moewardi Hospital, Surakarta.

RESULTS

1. Sample of characteristics

This study used data from the medical records of 67 pediatric patients aged 0 – 17 years old. According to the results of the study, there were 48 patients who were alive at the end of the study period and 19 patients with mortality. The general description of the study subjects is presented on Table 1.

Table 1. Characteristics of subjects

Variables	Results (n= 67)
Gender	
Male	32 (47.8%)
Female	x5 (52.2%)
Age	
$\leq$ 5 years old	31 (46.3%)
6-9 years old	7 (1.4%)
10-17 years old	29 (43.3%)
Length of stay (days)	
<7 days	18 (26.9%)
>7 days	49 (73.1%)
Nutritional status	
Normal	23 (34.3%)
Underweight	34 (50.7%)
Overweight	10 (14.9%)
Immunization status	
Complete	59 (88.1%)
Incomplete	8 (11.9%)
Radiological finding	
Local patchy shadowing	14 (20.9%)
Bilateral patchy shadowing	40 (59.7%)
Others	8 (11.9%)
Comorbidities	46 (68.7%)
Malignancy	14 (20.9%)

Variables	Results (n= 67)
CHD (Congenital Heart Disease)	9 (13.4%)
Oxygen Therapy	
Nasal cannula	45 (67.2%)
Oxygen mask	11 (16.4%)
Advanced	11 (16.4%)
Laboratory finding	
Hb (n=67)	11.16, SD=3.20
Leukocyte (n=67)	22.91, SD=51.56
Platelets (n=67)	254.66, SD=174.75
NLR (n=59)	4.94, SD=7.51
Lymphocyte (n=60)	32.06, SD=21.85
Neutrophil (n=60)	59.28, SD=23.67
Sodium (n=45)	131.51, SD=8.25
Clinical finding	
Cough	48 (71.6%)
Fever	44 (65.7%)
Dyspnea	41 (61.2%)
Gastrointestinal disturbance	18 (26.9%)
Contact	
None	41 (61.2%)
Present	26 (38.8%)
Disease severity	
Moderate	50 (74.6%)
Severe / critical	17 (25.4%)
Outcome	
Alive	48 (71.6%)
Deceased	19 (28.4%)

2. Bivariate analysis

According to the bivariate analysis, there were several variables with significant result, including age (p 0.001), radiological finding (p < 0.036), and oxygen therapy (p < 0.010). The results are presented in Table 2.

Table 2. Bivariate analysis characteristics of pediatric patients based on mortality

Variables	Alive (n=48)	Deceased (n=19)	OR (95% CI)	P
Gender[a]				0.968
Male	23 (47.9%)	9 (47.4%)		
Female	25 (52.1%)	10 (52.6%)	1.02 (0.35-2.96)	
Age[a]				0.001*
< 5 years old	28 (58.3%)	3 (15.8%)		
6-9 years old	6 (12.5%)	1 (5.3%)	1.56 (0.14-17.65)	
10-17 years old	14 (29.2%)	15 (78.9%)	10.00 (2.48-40.38)	
Length of stay (days) [a]				0.949
<7 days	13 (27.1%)	5 (26.3%)		
≥7 days	35 (72.9%)	14 (73.7%)	1.04 (0.31-3.46)	
Nutritional status[a]				0.814

Variables	Alive (n=48)	Deceased (n=19)	OR (95% CI)	P
Normal	16 (33.3%)	7 (36.8%)		
Underweight	24 (50.0%)	10 (52.6%)	0.95 (0.30-3.02)	
Overweight	8 (16.7%)	2 (10.5%)	0.571 (0.09-3.41)	
Immunization status[a]				1.000
Complete	42 (87.5%)	17 (89.5%)		
Incomplete	6 (12.5%)	2 (10.5%)	0.82 (0.15-4.49)	
Radiological finding				
local patchy shadowing[a]	12 (25.0%)	2 (10.5%)	0.35 (0.07-1.75)	0.189
bilateral patchy shadowing[a]	29 (60.4%)	11 (57.9%)	0 .90 (0.31- 2.65)	0.850
others[a]	3 (6.3%)	5 (26.3%)	5.36 (1.14- 25.29)	0.036*
Comorbidities[a]	29 (60.4%)	17 (89.5%)	5.57 (1.15- 26.91)	0.021*
Malignancy[a]	8 (16.7%)	6 (31.6%)	2.31 (0.67- 7.89)	0.196
CHD[a]	8 (16.7%)	1 (5.3%)	0.28 (0.03- 2.39)	0.427
Oxygen therapy			0.01 (0.02-0 .08)	
Nasal cannula[a]	43 (89.6%)	2 (10.5%)		<0.001*
Oxygen mask[a]	3 (6.3%)	8 (42.1%)	10.91 (2.48- 48.02)	0.001*
Advanced[a]	2 (4.2%)	9 (47.4%)	20.70 (3.87- 110.83)	<0.001*
Laboratory finding				
Hb (n=67) [b]	11.27, SD=2.81	10.90, SD=4.12	0.964 (0.814-1.142)	0.676
Leukocyte (n=67) [c]	16.15, SD=25.68	39.96, SD=87.15	1.009 (0.996-1.023)	0.126
Platelet (n=67) [c]	261.35, SD=124.99	237.74, SD=266.01	0.99 (0.99- 1.00)	0.146
NLR (n=59) [c]	5.57, SD=8.41	3.38, SD=4.45	0.95 (0.86 - 1.05)	0.543
Lymphocyte (n=60) [c]	31.02, SD=21.93	34.71, SD=22.09	1.01 (0 .98- 1.03)	0.528
Neutrophil (n=60) [b]	60.08, SD=23.09	57.26, SD=25.69	0.99 (0.97- 1.019)	0.681
Sodium (n=45) [b]	131.00, SD=7.80	132.77, SD=9.50	1.027 (0 .948- 1.11)	0.521
Clinical finding				
Cough[a]	36 (75.0%)	12 (63.2%)	0 .57 (0.18- 1.78)	0.367
Fever[a]	34 (70.8%)	10 (52.6%)	0.458 (0.15- 1.37)	0.157
Dyspnea[a]	28 (58.3%)	13 (68.4%)	1.55 (0 .50- 4.77)	0.445
Gastrointestinal disturbance[a]	12 (25.0%)	6 (31.6%)	1.39 (0.43- 4.45)	0.584
Contact[a]				0.187
None	27 (56.3%)	14 (73.7%)		
Present	21 (43.8%)	5 (26.3%)	0.46 (0.14- 1.48)	
Disease severity[a]				<0.001*
Moderate	44 (91.7%)	6 (31.6%)		
Severe/Critical	4 (8.3%)	13 (68.4%)	23.83 (5.83-97.46)	

Note: [a]categorical data using Chi-square/ Fisher's exact test; [b]numerical data that did not meet the normality assumption, using Mann-Whitney test; [c]numerical data that met the normality assumption, using independent t-test; *significant at α= 5%.

3. Multivariate analysis

From Table 3, it can be seen that Age 10-17 years old (OR= 16.27; 95% CI= 1.47 to 179.56 p=0.023) significantly affect the outcome of

COVID-19 in pediatric patients with a p value of <0.05. Meaning that pediatric patients aged 10-17 years old had 16.27 times more risk for mortality outcome compared to those aged <5 years old.

Oxygen mask (OR= 45.89; 95% CI = 5.39 to 390.58; p < 0.001) significantly affect the outcome of COVID-19 in pediatric patients with a p value of < 0.05. Meaning that pediatric patients with oxygen mask use had 45.89 times more risk for mortality outcome compared to those with no oxygen mask use.

The use of advanced oxygen therapy (OR= 181.48; 95% CI= 11.24 to 2927.80; p< 0.001) significantly affect the outcome of COVID-19 in pediatric patients with a p value of <0.05. Meaning that pediatric patients with advanced oxygen therapy had 181.43 times more risk for mortality outcome compared to those without. While other radiologic findings, comorbidities, nasal cannula use, and disease severity had less significant effect than age, oxygen mask use and advanced oxygen therapy as predictors of COVID-19 outcome.

Table 3. Multivariate analysis of variables that affect the outcome of COVID-19

Variables	OR	CI 95%		p
		Lower limit	Upper limit	
Age 10-17 years old	16.265	1.473	179.558	0.023*
Oxygen mask	45.890	5.392	390.577	<0.001*
Advanced oxygen therapy	181.482	11.249	2927.800	<0.001*
N observation= 67				
Adj R-Squared= 0.73				
p < 0.001*				

Note: Backward Logistic Regression Method; *significant for α=5%

DISCUSSION

From the general description of this study, it is known that the majority of pediatric patients were female which were 35 patients (52.2%) and mostly were <5 years old which were 31 patients (46.3%). This result is in contrast to the most recent national data which showed that the percentage of COVID-19 patients were dominated by male which was 51.3% and 48.7% female, while based on age, the 2.9% were 0-5 years old and 10.5% were 6-18 years old (Satgas Penanganan COVID-19, 2020). Accordancing to a study by Wong in 2021 which found that COVID-19 patients in Indonesia and Japan were dominated by female (75% and 67%), in contrast to in Malaysia, India, and Pakistan which were slightly dominated by male with a percentage of 50-60% (Wong et al, 2021). In the multivariate analysis, patients who were deceased was found at age 10-17 years old had a significant value (risk p= 0.023) with OR= 16.265, meaning that in this study, patients aged 10-17 years old were at 16.265 times more risk to die from COVID-19. However, this result has been discussed several times in other studies regarding the expression of ACE-2. Expression of ACE-2 in the epithelial cells of the nose and lungs are increased during childhood and then during adulthood. The number and affinity of ACE-2 receptors in the epithelial cells increases with age (Mancia et al, 2020; Wang et al, 2020).

From the general description was found that the majority of subject's nutritional status were dominated underweight, followed by normal and overweight (50.7%, 34.3%, and 14.9%, respectively). In the multivariate analysis of patient outcome, there was no significant result. According to studies which reported that malnutrition or obesity are

associated with more severe COVID-19. The suspected underlying mechanisms are abnormality in leptin production, atrophy of thymus in malnourished patients, and chronic inflammation in patients with obesity (Tsankov et al, 2020; Kurtz A et al, 2021).

The majority of patients in this study had a complete immunization status which were 59 patients (88.1%). In the multivariate analysis, there was no significant result in the outcome of patients. There were limited studies that correlate immunization status to the severity of COVID-19. Several vaccines which were reported to have strong correlation to COVID-19 severity are BCG, MMR and hepatitis A. However, those studies have universally conflicting results, therefore further studies are necessary (Beric-Stojsic et al, 2020; Saad and Elsalamony, 2020).

A total of 46 patients (68.7%) had a comorbidity recorded in the medical records, and malignancy was the most common comorbidity with 14 patients (20.9%), followed by congenital heart disease with 9 patients (13.4%). According to the national COVID-19 distribution pattern in October 2021, malignancy has 1.8% percentage as a comorbidity in COVID-19 patients of all ages (Satgas penanganan COVID-19, 2021). Congenital heart disease is one of the most common comorbidity in several studies, including in Pakistan and North America which studies the association between pediatric patients with COVID-19 indicated for PICU admission (Shekerdemian et al, 2019; González-Dambrauskas et al, 2020). Malnutrition and malignancy are the two most common comorbidity, which were 18% and 17% (Pudjiaji et al, 2020). Children with malnutrition and malignancy are at an increased risk due to the decreased immunity compared to healthy individuals. Patients with malignancy are also more at risk for COVID-19 exposure since they have to visit the hospital to receive treatments (Akseer et al, 2020). From this study, there was no significant result of the multivariate analysis of patient outcome.

Clinical findings of patients in this study were dominated by cough, which were 48 patients (71.6%), followed by fever which were 41 patients (61.2%) and gastrointestinal disturbance. According to the national COVID-19 distribution pattern in October 2021, cough and fever were the most common symptom of COVID-19 patients of all ages (64.6% and 43.7%, respectively) (Satgas penanganan COVID-19, 2021). In this study, there was no significant result from the multivariate analysis of patient outcome.

Laboratory findings showed that the mean value of Hemoglobin profile was 11.16; SD= 3.20, leukocyte count was 22.91; SD= 51.56, platelet count was 254.66; SD= 174.75, NLR was 4.94, SD=7.51, lymphocyte count was 32.06; SD=1.85, neutrophil count was 59.28; SD= 23.67, and sodium was 131.51, SD=8.25. The reported laboratory findings that can be a predictor for diseases severity in COVID-19 infection were lymphopenia and NLR. A high neutrophil-to-lymphocyte ratio (>9.8) had a higher incidence of acute respiratory distress syndrome (ARDS) (p= 0.005) and higher number of non-mechanical and mechanical ventilation (p= 0.002 and p= 0.048, respectively) (Ma et al, 2020). Radiological finding was mostly bilateral patchy shadowing which was found in 40 patients (73.1%). According to the Diagnosis and Care Protocol of COVID-19 in China, radiological findings are divided in to 4 stages: early stage, continued stage, critical stage, and recovery stage (National Health Commission of Cina, 2020). The finding of bilateral patchy shadowing are more commonly found in early stage radiological finding. However, from the laboratory and radiological findings, there were no significant result from the multivariate analysis of patient outcome.

The most common oxygen therapy

used was nasal cannula were 45 patients (67.2%), followed by oxygen mask 11 patients (16.4%). In the mortality outcome, oxygen mask and advanced oxygen therapy showed a significant value. Oxygen mask had a p value of <0.001 with OR = 45.89 and continued oxygen therapy had a p value of <0.001 with OR= 181.482. This result can be appre-hended since the risk of mortality is directly proportional to the severity of COVID-19. As of now, the authors have not yet found another study that correlates oxygen therapy with mortality risk in COVID-19.

AUTHOR CONTRIBUTION
Dwi Suryaning Ayu Aprilizia was the main author who conducted the study, processed data analysis, and wrote the manuscript. Is-miranti Andarini examined the background and discussion of the study Yulidar Hafidh formulated the framework of study.

FUNDING AND SPONSORSHIP
None.

CONFLICT OF INTERESTS
There is no conflict of interest in this study.

ACKNOWLEDGMENT
The author gratefully acknowledged to Medi-cal Records department in Dr. Moewardi General Hospital and the helpful comments and suggestions of several anonymous revie-wers.

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