The association of comorbidities with mortality and severity among children with COVID-19

Ni Made Dwi Angga Riani1*, Ni Putu Siadi Purniti1, Ida Bagus Subanada1

ABSTRACT

Background: Several case series have described the clinical characteristics of COVID-19 in pediatric patients and suggest milder illness severity in children compared with adults. However, some cases presented more severe diseases with small numbers of deaths have been documented. Some studies in developed countries demonstrated that the presence of comorbidities among COVID-19 patients could increase the severity of the disease. Therefore, this study aimed to identify the association of comorbidities with mortality and severity among children with COVID-19.

Methods: This was an analytic retrospective cross-sectional study conducted in Prof. Dr. IGNG Ngoerah Hospital, Denpasar, from May 2020 until March 2022. A total of 94 children aged 28 days-18 years old with confirmed COVID-19 were included in this study and divided into two groups, with comorbidities and without comorbidities. The chi-square test was used to determine the association between comorbidities and mortality and severity among children with COVID-19.

Results: Comorbidities significantly affect mortality and severity among children with COVID-19. A total of 33% children had preexisting comorbidities, with 22% had multiorgan failure. The similar result also showed by Biharie et al., which reported that preexisting comorbidities are more likely to have a higher risk of being admitted to the intensive care unit than subjects without comorbidities.

Conclusion: Comorbidities significantly affect mortality and severity among children with COVID-19.

Keywords: Comorbidities, mortality, children, severity, COVID-19.


INTRODUCTION

The coronavirus disease 19 (COVID-19) is a pathogenic viral infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).1 Children account for 9%–12% of patients diagnosed with COVID-19. On another side, some children have experienced severe clinical course and even death.2 A study in United Stated showed COVID-19 occurs more often among the 12 to 17 years age group compared to the 5 to 11-year age group.3 There were specifically 37.706 confirmed pediatric COVID-19 cases in Indonesia reported by the Indonesian Pediatric Society Data Registry in late 2020, with 175 death. The study from Purniti et al4 reported that the highest incidence of COVID-19 occurs in children aged 12-18 years; among them, 27.1% had comorbidities.

Hemato-oncological disorders and obesity are the most common comorbidities associated with the severity of COVID-19. A multicenter study involving 48 children with COVID-19 admitted to pediatric intensive care units in Canada and the United States reported that 83% of subjects had preexisting comorbidities and 38% had a multiorgan failure.5 The similar result also showed by Biharie et al., which reported that preexisting comorbidities are more likely to have a higher risk of being admitted to the intensive care unit than subjects without comorbidities.

There is a lack of studies regarding the spectrum of pediatric comorbidities and their outcome associated with COVID-19. Besides that, most of the studies were only conducted in developed countries. Data from developing countries are limited, and the published data may not reflect the global pattern of COVID-19 in children. Developing countries, including Indonesia, may face slight or significant differences in conditions compared to the results of the other studies and are particularly limited to children with comorbid conditions. This study aimed to show the association of comorbidities with mortality and severity among children with COVID-19.

MATERIAL AND METHODS

This study was an analytic retrospective cross-sectional study in Prof. Dr. IGNG Ngoerah Hospital, Denpasar, from May 2020 until March 2022. The inclusion criteria of this study were patients aged 28 days to 18 years old diagnosed with confirmed cases of COVID-19, admitted...
to the isolation ward, and documented in the medical registry. The exclusion criteria were incomplete data in medical records. The degree of significance and the power were set at 5% and 80%, respectively. The minimum sample required was 47 subjects for the comorbidities and non-comorbidities groups. The comorbidities were then analyzed to evaluate the association with mortality and severity.

Confirmed case COVID-19 was defined as subjects admitted in the isolation ward of Prof. Dr. IGNG Ngoerah Hospital Denpasar and had a positive result of COVID-19 RT-PCR evaluation of oropharyngeal and nasopharyngeal swabs. The nutritional status was classified into well-nourished and malnutrition (obesity or under-nourished). Length of stay was defined as the total amount of time spent by the patient from initial hospitalization until discharge or death.

Comorbidities were defined as a chronic disease(s) diagnosed concomitantly with a confirmed case of COVID-19. Comorbidities in this study included: (1) neurological disorders; (2) cardiovascular; (3) nephrology disorders; (4) gastro-hepatology; (5) malignancies; and (6) immunology.

Severity is the degree of the disease of COVID-19. It divides into: (a). Moderate symptoms if there are signs and symptoms of pneumonia like fever, cough, and tachypnea. It can be accompanied by rhonchi or wheezing without respiratory distress and hypoxemia in auscultation; (b). Severe symptoms if there are signs and symptoms of severe pneumonia, such as nostril breathing, cyanotic subcostal retraction, and there are warning signs and symptoms like seizure, a decrease of consciousness, profuse vomiting, oxygen desaturation (<95% room air); and (c). Critical symptoms if there is a decrease in condition, rapidly suffering from acute respiratory distress syndrome (ARDS) or respiratory failure or shock, encephalopathy, myocardial injury or heart failure, coagulopathy, acute renal disturbed and multiple organ dysfunction or other sepsis clinical features. Mortality is the number of deaths of patients admitted to the isolation ward.

All analyses were performed using SPSS for windows version 22.0. The chi-square test was used to determine the association between comorbidities with mortality and severity. Binary logistic regression was used for multivariate analysis. A p-value of less than 0.05 was considered statistically significant for this study data analysis.

Research Ethics Committee approved this study at Medical Faculty Universitas Udayana-Prof. Dr. IGNG Ngoerah Hospital, Denpasar (No. 124/UN14.2.2.V11/PD/2022).

RESULTS
From May 2020 until March 2022, there were 123 cases of COVID-19, 94 met the inclusion criteria, and 29 were excluded due to incomplete medical record data. Details of the characteristic subjects are described in Table 1.

Cardiovascular disorder was the most frequent comorbidity in our study (32%), followed by malignancies (25%), a neurological disorder (21%), immunology and nephrology (9%) respectively, and gastro-hepatology (4%). A significant association was found between comorbidities and mortality in children with COVID-19 (PR 3.21; 95%CI 1.04-9.90; p=0.036) and between comorbidities and severity (PR 10.71; 95%CI 4.12-27.83; p<0.001) (Table 2 and Table 3).

Multivariate analysis found aOR 3.74 (95%CI 1.14-12.25) for mortality and aOR 11.8 (95%CI 4.35-32.41) for severity after adjusting for age and nutritional status (Table 4 and Table 5).

DISCUSSION
This study enrolled 94 subjects of COVID-19 who were admitted to the isolation ward of Prof. Dr. IGNG Ngoerah Hospital Bali. In this study, the median age was 72 months (IQR 45-189) in with comorbidities group and 108 months (IQR 64-240) in the without comorbidities group, with predominantly male (51.1%) in the non-comorbid group. This result was consistent with a previous study by Graff, which reported that the subjects in the study were predominantly male (59.3%), and a study from Purniti et al. that reported the male was predominantly (51.3%) found in children with confirmed case COVID-19. The circulating concentration of ACE2 (a functional cellular receptor of SARS-CoV-2) is higher in males than females, which could increase the susceptibility to SARS-CoV-2, and the X chromosome in the female has encoded some immune regulatory genes which cause lower viral load levels.

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<th>Table 1. Characteristics of subjects.</th>
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<td>Length of stay, days</td>
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<th>Table 2. The association between comorbidities and mortality among children with COVID-19.</th>
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<td>Outcome</td>
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<td>Without Comorbidities</td>
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*Using the chi-square test
Malnutrition was predominantly found in a group with comorbidities (74.4%) and without comorbidities (61.8%). This result was similar to a previous study by Graff et al., which reported that obesity was found more often, and obesity was also associated with severe COVID-19 symptoms (OR, 4.7; p=0.04). Obesity leads to vascular abnormalities by various mechanisms, and the clinical presentation might be worse in obese patients with preexisting endothelial dysfunction and associated with activation of the renin-angiotensin-aldosterone system, which leads to increased levels of angiotensin II, with direct effects on the myocardium leads to dysfunction of myocardium and heart failure. Used of a mechanical ventilator was predominantly found in the group with comorbidities (40.4%). This result was consistent with a previous study by Barbosa et al., which reported that patients with comorbidities were associated with the need for invasive mechanical ventilation (OR 5.5; 95% CI 1.43 - 21.12; p=0.01). Patients with comorbidities are more likely to have a higher risk of deterioration related to hyper-inflammatory response and cytokine storm development during the third phase of the disease, immune disruption, and persistent inflammation, which leads to poor clinical outcomes.

Comorbidities that are chronic diseases are reported to increase the risk of death in children with COVID-19. This study found a significant association between comorbidities and mortality (PR 3.21; 95%CI 1.04 - 9.90 p=0.036). This study found that there is a significant association between comorbidities and severity of COVID-19 (PR 10.71; 95%CI 4.12 - 27.83; p<0.001), and this result was consistent with a previous study by Martin et al. in the United States that has been reported that comorbidities were associated with higher severity COVID-19 (OR, 1.19; 95%CI, 1.01 - 1.41. Multivariate analysis found comorbidities increasing the risk of mortality and severity with adjusted OR 3.74 (95%CI 1.14 - 12.25) and adjusted OR 11.8 (95%CI 4.35 - 32.41), respectively after adjusting for age and nutritional status. This result is consistent with a previous study by Biswas et al., which explained that comorbidities were also associated with a significant risk of mortality (RR 1.95; 95% CI 1.58 to 2.40; p<0.001). Comorbidities or some chronic diseases lead to reduced immune function, and natural immune function is reduced substantially, which may restrict the body from producing antibodies against any infection. Dysfunction of organs in COVID-19 patients can be caused by the body's reaction to the infection. It is known that there is an increase in troponin levels associated with disease severity during the disease. Comorbidities affect severity with different mechanisms during COVID-19. Autoimmune diseases like systemic lupus erythematosus with systemic glucocorticoids and immunosuppressants could be risk factors for developing severe COVID-19. Microangiopathic changes occurring in the respiratory tract of diabetic patients reduce gas exchange and lung compliance and cause a significant decrease in forced vital capacity (FVC) and forced expiratory volume in second (FEV1).

There are some limitations of this study. This study used a sample size that was relatively small and conducted in one-center research. This study only includes moderate to critical degrees of COVID-19 and did not include mild degrees of COVID-19, a multisystem inflammatory syndrome in children (MIS-C), and long COVID.

**CONCLUSION**
Comorbidities have a significant association with mortality and severity among children with COVID-19.

**DISCLOSURE**
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All author full contributed in the research and publication.

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**REFERENCES**


