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Original article

Demographic, clinical, and laboratory characteristics of children with confirmed Coronavirus disease 2019 (COVID-19) in Bali

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Abstract

Introduction: The Coronavirus disease 2019 (COVID-19) has become a global issue since the disease was first reported in Wuhan, China, in December 2019. The proportion of COVID-19 cases in children is less than in adults, with highly variable incidence rates. Milder clinical manifestations occur in children than adults. Children with comorbidities are more likely to develop more severe symptoms and require hospitalization. Monitoring of laboratory results in confirmed cases of COVID-19 is crucial.

Methods: This study was a retrospective study on data collected from the Bali Branch of Indonesia Pediatric Society COVID-19 Team and the Bali Provincial Government Health Department, Indonesia, from March 2020 until February 2021. The study population included children aged 0-18 years with laboratory-confirmed COVID-19. Subjects were selected using the total sampling method.

Results: During the study period, 3,674 children were confirmed to have COVID-19. In this study, the majority of age was 12-18 years. Nineteen (0.5%) were neonates with a vertical transmission source. The most prevalent source of transmission was living in the same house, which was found in 1,811 cases (49.3%). Out of 181 confirmed cases of COVID-19 treated at Sanglah Hospital, Denpasar, 49 (27.1%) had comorbidities. In 2,701 (73.5%) cases, the subjects were found to be asymptomatic. 652 (17.7%) subjects had fever, 771 (21%) had cough, and only 17 (0.5%) had anosmia.

A total of 139 (3.8%) subjects had symptoms of shortness of breath, and only 4 subjects required treatment with a ventilator. Regarding the infection markers, lactate dehydrogenase (LDH), C-reactive protein (CRP), D-dimer, and procalcitonin showed higher levels in the critical group compared to other groups.

Conclusion: The highest incidence of COVID-19 occurs in children aged 12-18 years, and the most frequent sources of close contact come from household contacts. Most children who have confirmed COVID-19 have asymptomatic clinical manifestation. The most common clinical manifestation was cough (21%). Increased infection markers such as LDH, CRP, procalcitonin and D-dimer occur in critically ill COVID-19 patients.

Keywords

Children, COVID-19, demographic, clinical, laboratory.

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Introduction

In December 2019, a novel Coronavirus emerged in Wuhan, China, which was linked to animal-to-human transmission at a local market. Furthermore, there was a human-to-human transmission of the virus that resulted in widespread respiratory disease in Wuhan and other urban areas in Hubei Province, China. The Coronavirus then spread throughout China and at least 20 other countries. On February 11, 2020, the World Health Organization (WHO) named the virus SARS-CoV-2, and the disease is known as Coronavirus disease 2019 (COVID-19). Although it is not as lethal as the severe acute respiratory syndrome (SARS) outbreak in 2003, COVID-19 remains a serious respiratory disease [1, 2].

Several studies have reported that the proportion of COVID-19 in children is less than in adults, with the incidence rates being highly variable. The reported incidence rates were approximately 2% in the Chinese study, 1.2% in the Italian study, 4.8% in the South Korean study, and 1.7% in the United States study [3, 4]. The latest data from the Ministry of Health of the Republic of Indonesia until February 2021 shows 1,334,634 confirmed cases of COVID-19 with a mortality rate of 2.7%, and Bali is included in the 10 provinces with the highest number of confirmed cases of COVID-19 in Indonesia [5].

A retrospective study of 2,142 confirmed and suspected cases of COVID-19 infection in children reported by the Chinese Center for Disease Control and Prevention showed milder clinical manifestations in children than adults. The clinical manifestations of COVID-19 cases vary widely from asymptomatic, fever, cough, fatigue, anorexia, shortness of breath, myalgia, sore throat, nasal congestion, headache, diarrhea, nausea and vomiting, loss of smell (anosmia), loss of taste (ageusia), shortness of breath to severe symptoms such as acute respiratory distress syndrome (ARDS), sepsis, and septic shock. Children with comorbidities such as chronic lung disease, asthma, heart disease, malignancy, diabetes mellitus, autoimmune disease, kidney disease, hypertension, tuberculosis, and others have the possibility to have more severe clinical manifestations and require hospitalization [6].

Monitoring of the laboratory results in confirmed cases of COVID-19 is important. The laboratory indicators include levels of leukocytes, neutrophils, lymphocytes, platelets, neutrophil-lymphocyte ratio (NLR), lactate dehydrogenase (LDH), D-dimer, C-reactive protein (CRP), and procalcitonin [7]. Currently, there is not much data showing the laboratory characteristics of confirmed cases of COVID-19 in children. Based on this background, the researchers conducted a study to determine the demographic characteristics, clinical manifestations, and laboratory profile of confirmed cases of COVID-19 in children in Bali.

Methods

This study was conducted with a retrospective study design. The data was secondary data obtained from the Bali Branch of Indonesia Pediatric Society COVID-19 Team and the Bali Provincial Government Health Department, Indonesia, from

March 2020 to February 2021. The inclusion criteria were children aged 0-18 years with confirmed COVID-19. Subjects with incomplete medical records were excluded from the study. The sample was determined using a total sampling method, which implies that the subjects were taken by including the total number of confirmed COVID-19 patients in Bali Province during the study period.

The collected data includes demographic characteristics (gender, age, source of transmission, outcomes and comorbidities), clinical manifestations (fever, cough, sore throat, anosmia, diarrhea, dyspnea, and severity), and laboratory data (leukocytes, lymphocytes, neutrophils, platelets, NLR, LDH, D-dimer, CRP, and procalcitonin).

Source of transmission is defined as a source of close contact acquired through: vertical transmission (obtained from pregnant women), living in the same house, public places, religious ceremonies (traditional Balinese ceremonies), or unknown.

The severity was divided into 5 groups:

1. asymptomatic: no symptoms;
2. mild: symptoms without evidence of viral pneumonia or without hypoxia;
3. moderate: patients with clinical signs of pneumonia (fever, cough, shortness of breath, tachypnea) but no signs of severe pneumonia;
4. severe: patients with clinical signs of pneumonia plus one of the criteria from severe pneumonia (nasal flare, cyanosis, subcostal retraction or SpO_2 < 92% on room air);
5. critical: patients with ARDS, sepsis and septic shock.

Tachypnea was defined as respiratory rate > 60 times/minute (< 2 months), > 50 times/minute (2-11 months), > 40 times/minute (1-5 years), and > 30 times/minute (> 5 years).

Laboratory data were obtained from medical records, and the laboratory results used were the results obtained when the subjects were first diagnosed, without serial examinations.

After the data was collected, data tabulation, data entry, and data cleaning were performed. Data analysis was performed using computer software to describe the characteristics of the subjects and variables studied. Categorical variables were presented in the form of number (n) and percentage (%). Numerical variables were tested for normality; if the data distribution was normal, the data was stated by mean and standard deviation, but if the data was not normally distributed, the data was expressed by median (range).

This research has obtained an ethical feasibility permit from the Research Ethics Commission of the Faculty of Medicine, Udayana University, Sanglah Hospital, Denpasar, and a research permit from the Bali Provincial Government Health Department, Indonesia.

Results

During the study period, 3,674 children were confirmed to have COVID-19. The first confirmed cases of COVID-19 in children in Bali occurred in March 2020. The number of confirmed cases increased sharply in January and February 2021. The monthly incidence of COVID-19 cases can be seen in **Fig. 1**.

In this study, the proportion of males was slightly higher than females (51.8%). The most common age was 12-18 years, with a median age of 12 years (range 0-18 years). Nineteen (0.5%) were neonates with a vertical transmission source. The biggest source of transmission was living in the same house, accounting for 1,811 (49.3%) subjects. Only 10 (0.3%) subjects with a confirmed case of COVID-19 had an outcome of death, with 2 subjects with comorbidities, which were systemic lupus erythematosus disease and acute leukemia. Most subjects with the outcome of death were 12-18 years old (6 out of 10 subjects). The demographic characteristics of the subjects can be seen in **Tab. 1**.

In 2,701 (73.5%) cases, subjects were found to be asymptomatic. The most common clinical manifestations were cough (21%) and fever (17.7%). A total of 139 (3.8%) subjects had symptoms of shortness of breath, and only 4 subjects required treatment with a ventilator. Only 17 (0.5%) subjects had anosmia. Subjects who were asymptomatic and had mild symptoms were not hospitalized but were self-isolating at home or in self-isolation facilities provided by the government. The characteristics of the clinical manifestations of the subject can be seen in **Tab. 2**.

During this study period, there were 181 confirmed cases of COVID-19 children being treated at Sanglah Hospital, Denpasar. There were 49 (27.1%) subjects who had comorbidities. Thalassemia was the most frequent comorbidity (7.2%). Characteristics of comorbidities can be seen in **Fig. 2**.

During the study period, there were 37 subjects who were treated at Sanglah Hospital and underwent laboratory examinations. Laboratory

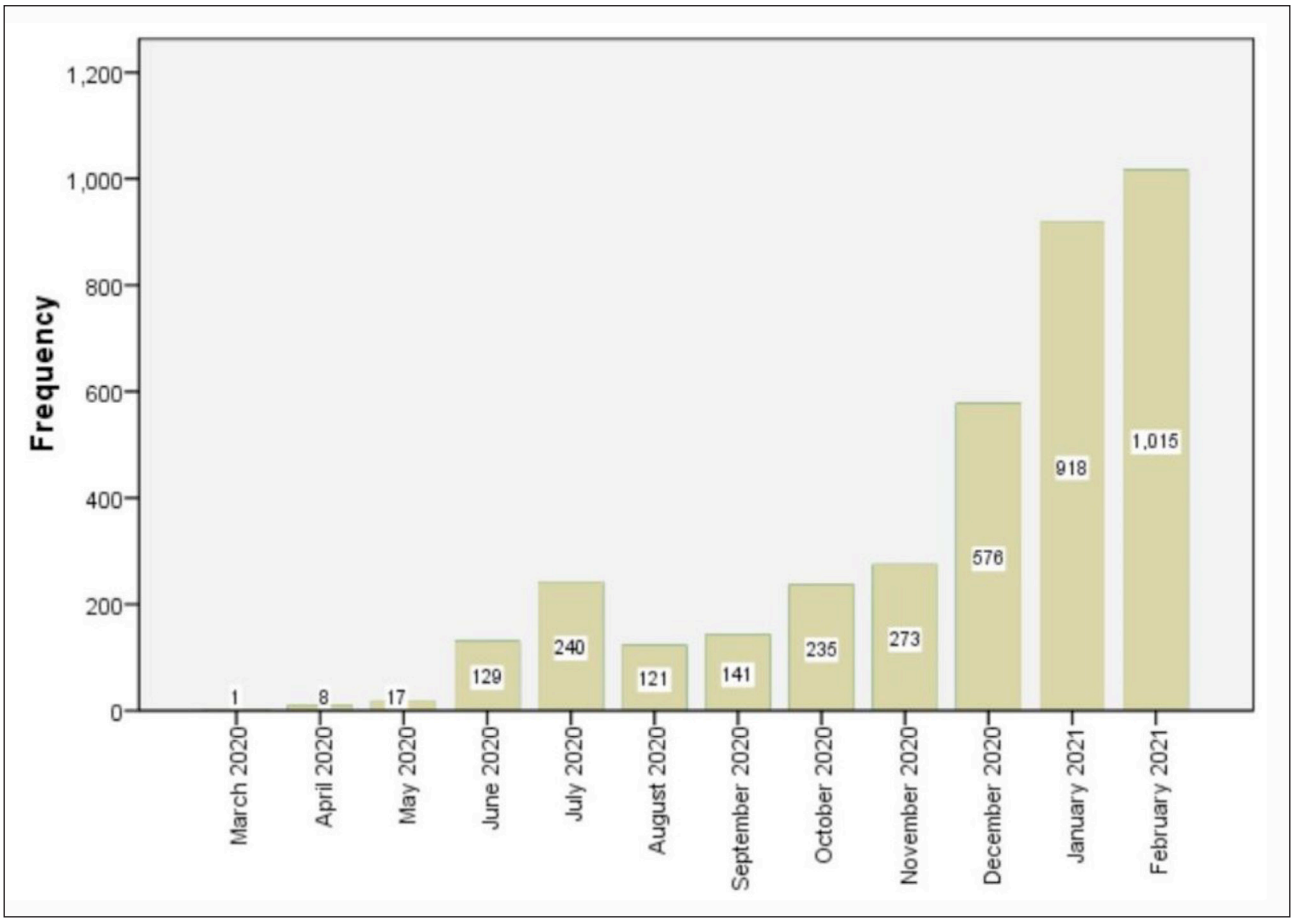

Figure 1. Monthly incidence of COVID-19 pediatric cases in Bali.

Table 1. Demographic characteristics of COVID-19 pediatric cases in Bali (n = 3,674).

Variable		No.	%
Gender	Male	1,904	51.8
	Female	1,770	48.2
Age	Neonates	19	0.5
	1-24 months	302	8.2
	2-5 years	462	12.6
	6-11 years	1,010	27.5
	12-18 years	1,881	51.2
Souce of transmission	Vertical transmission	19	0.5
	Living in the same house	1,811	49.3
	Public places	113	3.1
	Religious ceremony	12	0.3
	Unknown	1,719	46.8
Degree of severity	Asymptomatic	2,701	73.5
	Mild	834	22.7
	Moderate	129	3.5
	Severe	6	0.2
	Critical	4	0.1
Outcome	Alive	3,664	99.7
	Death	10	0.3

Table 2. Clinical manifestations of COVID-19 pediatric cases in Bali (n = 3,674).

Variable		No.	%
Fever	Yes	652	17.7
	No	3,022	82.3
Sore throat	Yes	199	5.4
	No	3,475	94.6
Cough	Yes	771	21
	No	2,903	79
Shortness of breath	Yes	139	3.8
	No	3,535	96.2
Anosmia	Yes	17	0.5
	No	3,657	99.5
Diarrhea	Yes	14	0.4
	No	3,660	99.6

characteristics of confirmed COVID-19 children treated at Sanglah Hospital based on severity can be seen in **Tab. 3**. Several variables, including NLR, LDH, CRP, D-dimer, and procalcitonin, were not normally distributed. The critical group had the highest range of biomarker levels compared to other groups, specifically, LDH

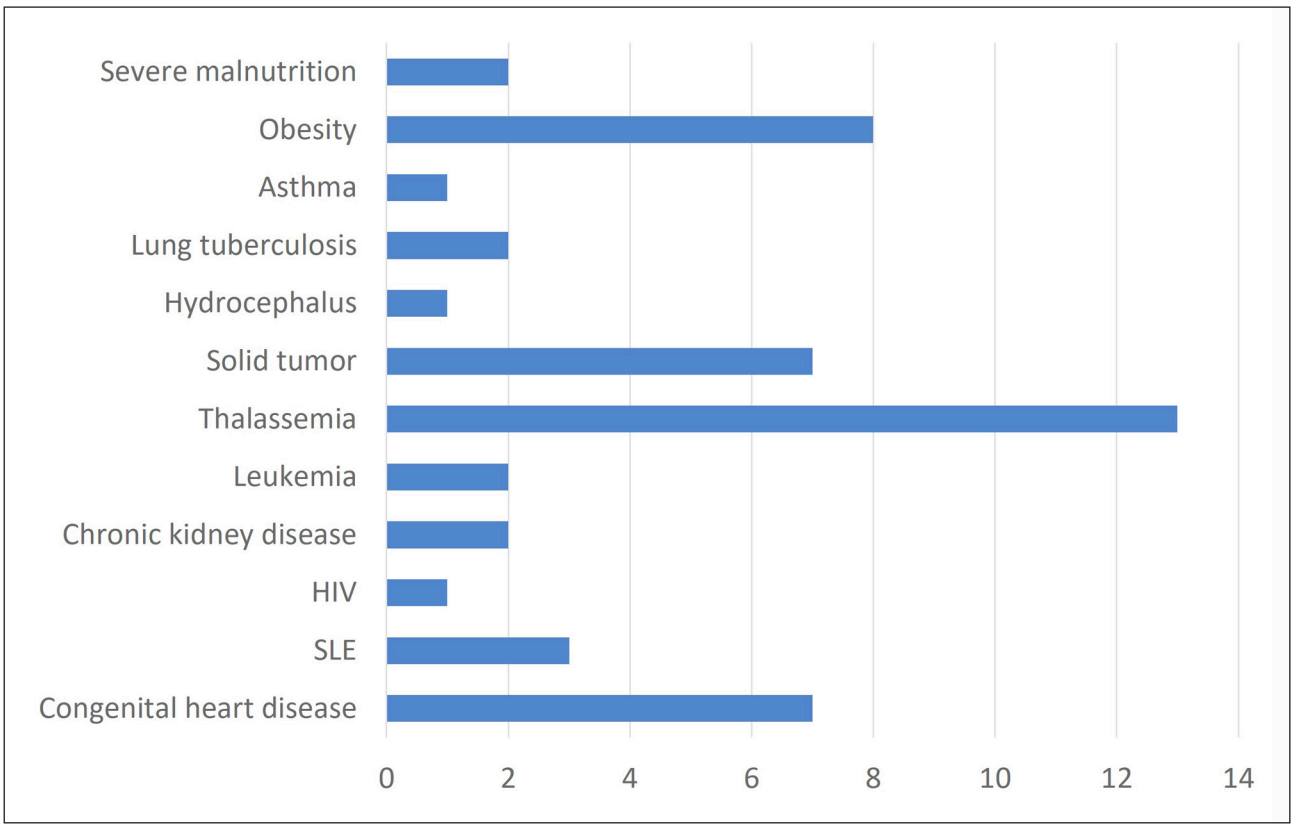

Figure 2. Characteristics of comorbidities of children with confirmed COVID-19 treated at Sanglah Hospital, Denpasar (n = 49 [a]).
[a] Out of 181 confirmed cases of COVID-19 treated at Sanglah Hospital, Denpasar, 49 (27.1%) subjects had comorbidities.
HIV: human immunodeficiency virus; SLE: systemic lupus erythematosus.

Table 3. Laboratory characteristics of children with confirmed COVID-19 treated at Sanglah Hospital, Denpasar, based on the degree of disease (n = 37 [a]).

Variable	Mild (n = 13)	Moderate (n = 18)	Severe (n = 3)	Critical (n = 3)
Leukocytes, $10^3/\mu L$, mean (SD)	9.1 (5.7)	7.2 (4.7)	13.4 (5.1)	7.1 (4.7)
Neutrophils, $10^3/\mu L$, mean (SD)	5.5 (4.3)	4.1 (3.8)	10.5 (3.3)	3.5 (1)
Lymphocytes, $10^3/\mu L$, mean (SD)	2.7 (1.6)	2.2 (1.7)	1.9 (1.3)	2.4 (2.3)
Platelets,$10^3/\mu L$, mean (SD)	343.3 (143.1)	214.5 (166.1)	415.6 (134.7)	268.4 (84.1)
NLR, median (range)	1.7 (0.2-10)	1.4 (0.1-24.3)	7.5 (3.9-8.9)	1.8 (0.9-5.9)
LDH, U/L, median (range)	462 (33.5-5,778)	573 (0.5-1,964)	535 (472-743)	965 (766-2,992)
CRP, mg/L, median (range)	3 (0.3-83.2)	6.8 (0.5-423.6)	4.9 (2.4-9)	69.7 (60-74.9)
D-dimer, ng/mL, median (range)	0.7 (0.2-4)	1.1 (0.4-11.2)	0.8 (0.2-1.4)	4.7 (4.4-17.9)
Procalcitonin, ng/mL, median (range)	0.1 (0.1-1.4)	0.2 (0.1-467.8)	0.2 (0.3-0.1)	22.7 (0.5-70.3)

[a] Out of 181 confirmed cases of COVID-19 treated at Sanglah Hospital, Denpasar, 37 subjects underwent laboratory examinations.
CRP: C-reactive protein; LDH: lactate dehydrogenase; NLR: neutrophil-lymphocyte ratio; SD: standard deviation.

range of 766.0-2,992.0 U/L, CRP range of 60.0-74.9 mg/L, D-dimer range of 4.4-17.9 ng/mL, and procalcitonin range of 0.5-70.3 ng/mL.

Discussion

Epidemiology

This study is the first study to describe the demographic characteristics, clinical manifestations, and laboratory profile of children with a confirmed case of COVID-19 in Bali. COVID-19 is a global problem with highly variable incidence rates around the world. In this study, there were 10.74% of children with confirmed COVID-19 (3,674 out of 34,215 total cases confirmed COVID-19). Around the world, children have made up a lower number of confirmed cases of COVID-19 during the first wave of the pandemic, usually between 1% and 5% of total case numbers. This is almost

certainly because some studies undercounted the total case numbers as many countries have tested only the most unwell children [8]. The disease can affect all ages, including children. In this study, the highest incidence of COVID-19 occurred in the age range of 12-18 years (51.2%) and slightly more in males (51.8%). This is similar to a study conducted by Dong et al. [9]. in China, which stated that the highest incidence of COVID-19 was at the age of 11-18 years (34.9%), and the incidence in males was 56.6%. Bellino et al. [10] stated that the incidence of COVID-19 in children in Italy was highest in adolescents aged 13-17 years (40.1%) and only 13.8% in children aged 0-1 years.

Transmission

Sheth et al. [11] reviewed 39 published studies and reported that of 326 pregnant women with confirmed COVID-19, 23 newborns (7.05%) were confirmed positive. Another study conducted by Etika et al. [12] stated that only 1.8% of infants were tested positive for COVID-19. This is similar to the results of this study, which found that only 0.5% of the children confirmed to have COVID-19 were neonates. In this study, a PCR swab was examined less than 48 hours postpartum. Very few SARS-CoV-2 infections are acquired through vertical transmission. Several studies have suggested the possibility of vertical transmission in neonates with confirmed COVID-19 who underwent RT-PCR swab examination at 48 hours postpartum with a delivery process that was in accordance with COVID-19 prevention protocol. Recent data suggest that angiotensin-2 receptor levels are very low in the placenta, so that vertical transmission does not occur. Chen et al. [13] reported that there were no changes in the morphological features of placentas from COVID-19-infected mothers, and no nucleic acids were found.

Tracing close contacts is very important to determine the spread of COVID-19 infection in the community. The transmission of COVID-19 infection is reported to come significantly from close contact with family members. The transmission of COVID-19 in children is thought to be mostly from family members who live at home [14]. Tracing close contacts was obtained from tracking epidemiology officers. In this study, the transmission in children came mainly from family clusters, which was 49.3%. This is similar to a study in China that stated that 50.8% of COVID-19 transmissions came from family clusters. Household studies with children as index cases have so far been difficult to interpret due to bias from shared exposure that means children and their contacts becoming infected simultaneously, increased exposure of caregivers to their symptomatic children post-infection, and underrepresentation of asymptomatic cases. A study in Korea stated that the potential for children as the main source of transmission for COVID-19 infection at home is very small. A study mentioned that only 0.4% of children is the main source of transmission in the family cluster [15]. This is presumably because children have less interaction outside of home than adults. In addition, school closures during the pandemic in various countries are also a strategy for controlling the COVID-19 outbreak in children [16, 17]. This is similar in Bali, school closed during the pandemic to reduce contact between children.

In this study, there were 12 confirmed cases of COVID-19 in children with the source of transmission from religious ceremonies. Since the first case in Indonesia was announced in March 2020, the provincial government of Bali has made an appeal to improve clean and healthy living behaviors by promoting social and physical distancing. In Bali, the tradition of religious ceremonies (such as "Ngaben") involving large numbers of people is very risky for the transmission of COVID-19. A special strategy was issued by the Government of Bali regarding the implementation of Hindu ceremonies during COVID-19 in Bali. Limiting the number of participants in every religious ceremony in Bali is carried out to prevent transmission. The other strategy to prevent COVID-19 transmission was the prohibition of the Ogoh-ogoh festival (annual parade on the night before Balinese Nyepi, a day of silence in Bali where all people are obliged to stay home) and adding another day of prohibition of going out after Nyepi [18].

Clinical manifestations

A meta-analysis study states that children have milder clinical manifestations of COVID-19 than adults, but children with confirmed COVID-19 who have comorbidities are reported to have worse clinical manifestations. In this study, only 49 (27.1%) out of 181 confirmed COVID-19 children treated at Sanglah Hospital had comorbidities. A similar study conducted by Bellino et al. [10] stated that only 5.4% of children with confirmed COVID-19 had comorbidities, and 4 of them died. In contrast to Bixler et al. [19], it was stated that

75% (91 out of 121 children) of children with confirmed COVID-19 had at least 1 comorbidity. Comorbid conditions in these patients include asthma, obesity, neurological disorders and cardiovascular disorders. In this study, the most common comorbidities were hematological-oncological disorders and obesity. A study in Madrid showed that the prevalence of COVID-19 infection in children with malignancy was 1.3% in the first 2 months of the pandemic. It is generally known that pediatric patients with malignancy who use immunosuppressant therapy have a higher risk of developing COVID-19. Tsankov et al. [20] stated that obese children were associated with a poorer prognosis of COVID-19 infection. The presence of high visceral adipose in obese children induces systemic inflammatory cytokines such as IL-6 and CRP. The increase in these cytokines correlates with the severity of COVID-19 infection. In this study, there were 2 subjects with obesity who had mild symptoms.

In this study, 10 (0.3%) children with confirmed COVID-19 died. Sepsis was the most common cause of death in this study. In general, children with confirmed COVID-19 have a better prognosis than the adult population. This is in accordance with the research results by Bellino et al. [10], which states that the mortality rate in children is only 0.1%, with causes of death including cardiomyopathy, multisystemic genetic disease (Williams syndrome), malignancy, and heart failure. A similar study conducted in the United States stated that the mortality rate for children with COVID-19 was very low (0.08%) [20].

Children with COVID-19 usually have mild symptoms, and 15-35% can be asymptomatic [21]. In this study, 73.5% of children were asymptomatic. Subjects in this study did not follow up to determine if they later developed symptoms, so the true proportion of asymptomatic children is unknown. Mild symptoms or asymptomatic cases are thought to be related to exposure and host factors. During this pandemic, children tend to stay at home and have little chance of being exposed to pathogens or other people infected with COVID-19. Angiotensin-converting enzyme II (ACE2) is known as the receptor for SARS-CoV-2. A study revealed that children are less sensitive to SARS-CoV-2 because the maturity and amount of ACE2 receptors in children are lower than in adults. In addition, children more often have a history of respiratory syncytial virus (RSV) infection and are thought to have higher antibodies to fight the virus than adults [9]. In this study, only 17 (0.5%) children had anosmia; this result is related to the fact that anosmia can only be assessed in older children.

In this study, only 4 children experienced critical COVID-19. This is similar to the study conducted by Dong et al. [9], which showed that severe and critical COVID-19 cases were only 5.2% and 0.6%. They also found that severe and critical manifestations were most commonly found in the < 1-year age group [9, 22]. Several previous studies have stated that children aged < 1 year have a higher risk of experiencing severe COVID-19 infection. As in adults, children with severe COVID-19 can develop respiratory failure, myocarditis, shock, acute renal failure, coagulopathy, and multi-organ failure [23].

Children with confirmed COVID-19 who required hospital treatment were being subjected to laboratory tests. In this study, laboratory data came from children with confirmed COVID-19 who were being treated at Sanglah Hospital, Denpasar, as a tertiary hospital in Bali. Some subjects were treated at regional and private hospitals in Bali. For subjects admitted to regional and private hospitals, several laboratory examinations could not be performed because they were not available. Laboratory parameters used include complete blood count and inflammatory markers (CRP, LDH, D-dimer, and procalcitonin). In this study, the results of the examination of leukocytes, neutrophils, lymphocytes, platelets, and NLR did not differ between the mild and severe degree groups. This is similar to the results of a study by Zachariah et al. [24], which stated that the leukocyte count during the first day of treatment was generally normal (median, 7.6×10^3/μL; IQR, 4.6-11.4 $\times 10^3$/μL). They also found that there was no significant difference between lymphocytes levels at the time of the first treatment between the non-severe and severe groups (median 1,201/μL and 1,199.5/μL). Thrombocytopenia occurred in only 14% of cases (median, 248×10^3/μL; IQR, 18-733 $\times 10^3$/μL). Lymphopenia is a consistent laboratory finding in COVID-19 cases but has no prognostic value [24].

A significant increase in inflammatory markers indicates the presence of hyperinflammation in critically ill patients [25]. In this study, inflammatory markers such as CRP, LDH, D-dimer and procalcitonin were higher in the critically ill group than in other groups. This is in accordance with the study conducted by Zachariah et al. [24], which stated that procalcitonin and CRP

were significantly increased on the first day of treatment in the severe COVID-19 group ($p < 0.001$) [24]. A meta-analysis study by Henrya et al. [25] also mentioned an increase in CRP, LDH, procalcitonin and D-dimer in severe COVID-19 children. Children with severe COVID-19 showed a consistent trend of elevated levels of LDH, CRP and procalcitonin, similar to studies that have been reported in adult COVID-19 patients. In addition, an increase in D-dimer has also been reported in pediatric patients with severe COVID-19. The increase in procalcitonin is thought to be due to secondary bacterial infection in children hospitalized with pneumonia. Bacterial and viral coinfection at the time of treatment has been reported frequently in children with COVID-19. Therefore, serial monitoring of procalcitonin is needed as a biomarker of lung and systemic bacterial infection [25].

The limitation of this study is that this study is a retrospective study and does not analyze the relationship between variables. Therefore, this study was not able to determine risk factors. This study also did not mention any Multisystem Inflammatory Syndrome in Children (MIS-C) or Long COVID. The laboratory data was only obtained from children with confirmed COVID-19 who were being treated at Sanglah Hospital without including laboratory results from other hospitals. Thus, the amount of laboratory data that it was possible to collect was very small.

Conclusion

From this research, we can conclude that 10.74% of children confirmed COVID-19, with the highest incidence of COVID-19 occurring in children aged 12-18 years, few neonates confirmed COVID-19, and the main source of transmission was household contacts. Our data showed a number of confirmed cases of COVID-19 in children with transmission from religious ceremonies. Most children with confirmed COVID-19 were asymptomatic. The most common clinical manifestations were cough and fever. Inflammatory markers such as CRP, LDH, D-dimer and procalcitonin were higher in the critical group compared to other groups.

Ethical clearance

Ethical approval was obtained in this case, and protocols were approved by the Ethical Committee of the Medical Faculty of Udayana University/Sanglah General Hospital.

Declaration of interest

The Authors have nothing to disclose. The Authors have no support or funding to report.

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