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Submission date: 12-Jan-2023 03:35PM (UTC+0800)
Submission ID: 1991654770
File name: in_pediatric_patients_with_suspected_and_confirmed_COVID-19.pdf (205.59K)
Word count: 4566
Character count: 23932

How to Cite:
Ermawati, Y., Setyoningrum, R. A., & Husada, D. (2022). The differences of clinical and supporting examinations in pediatric patients with suspected and confirmed COVID-19. *International Journal of Health Sciences*, *6*(S8), 4183–4193.
https://doi.org/10.53730/ijhs.v6nS8.13131

The differences of clinical and supporting examinations in pediatric patients with suspected and confirmed COVID-19

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***Abstract*---**Since most children's COVID-19 symptoms are asymptomatic, it might be challenging to diagnose severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection. This study aims to determine the differences in clinical features and supporting examinations of pediatric patients with suspected and confirmed COVID-19. A retrospective study was conducted using medical records from 120 eligible children with suspected COVID-19 from March to May 2022 in Surabaya. Incomplete medical records are excluded from the study. We divided them into two groups each 60 children with negative and positive SARS CoV-2 polymerase chain reaction (PCR) results. The Mann-Whitney U test and Chi-square tet were used for the analysis. Male children are more dominant than females (59.2% and 40.8%). The mean age of the children with negative SARS CoV-2 PCR results was 63.98 ± 59.508 months and the positive was 85.38 ± 69.071 months. There are no significant differences in laboratory examination. Only clinical symptoms of myalgia and bilateral diffuse radiological examinations were found to have a significant different in children with suspected and confirmed COVID-19. In conclusion, multiplying the SARS CoV-2 nasopharyngeal PCR swab test in patients with suspected COVID-19 accompanied by atypical symptoms were recommmended prevent poorer outcomes.

International Journal of Health Sciences ISSN 2550-6978 E-ISSN 2550-696X © 2022.
Manuscript submitted: 9 May 2022, Manuscript revised: 18 July 2022, Accepted for publication: 27 August 2022

Keywords---corona virus disease, pediatric patients, severe acute respiratory syndrome coronavirus-2.

Introduction

The symptoms of coronavirus disease 2019 (COVID-19) caused by the Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus vary widely from asymptomatic to cause acute respiratory distress syndrome (ARDS) and are life-threatening, especially in patients with comorbidities (Chen et al., 2020; World Health, 2020). However, cases in children are relatively rare, only around 25% of the total cases. Clinical symptoms in children are not typical, which often comes not with pneumonia symptoms, let alone laboratory and radiological features that are also non-specific. The antibody rapid test examination from peripheral blood is mostly false negatives and viruses are often not detected by polymerase chain reaction (PCR) examination of nasopharyngeal swabs even though clinically leads to COVID-19 in children with positive adult contacts. Data on cases of COVID-19 in children are also relatively limited so that evaluation of clinical, laboratory and radiological features needs to be done to determine the association with antibody rapid diagnostic test (RDT) and nasopharyngeal swab PCR results (Yuanyuan Dong et al., 2020).

Indonesia reported as many as 765,000 cases of COVID-19, the number of which is still growing (Indonesia Ministry of Health, 2020). COVID-19 cases are spread in all age groups, but are more common in adults, while the number of cases in children is relatively small, but there are no definitive data on COVID-19 case reports in children in the world (She et al., 2020). Acute respiratory distress including cough, fever, and dyspnea are the common signs and symptoms of COVID-19 infection. The longest incubation duration is 14 days, with an average of 5 to 6 days (DeBiasi et al., 2020). A study in May 2020 reported that children are less affected by SARS-CoV-2 than adults, according to a report in China that 72,314 cases were reported only 2% of individuals were under 19 years of age, as of February 11, 2020 (Zimmermann & Curtis, 2020). The results of a systematic review study, in 7,780 pediatric patients in 26 countries in the world from December 2019 to May 2020 showed symptoms of fever as much as 59.1%, and coughing as much as 55.9%, and as many as 19.3% were asymptomatic (Nogueira-de-Almeida et al., 2020).

In Europe, mild to moderate clinical manifestations of COVID-19 in children were found to be lymphopenia or neutropenia in 13% of patients and an increase in inflammatory markers in 31% of patients (Liguoro et al., 2020). In cases of pediatric COVID-19, normal leukocytes were 83% and lymphopenia was 3%. An increase in lactate dehydrogenase levels by 30% and an increase in C-reactive protein (CRP) and procalcitonin by only 3% (Zimmermann & Curtis, 2020). In China, radiological abnormalities in patients with symptomatic and asymptomatic COVID-19 were found ground-glass opacity and consolidation (Zhang et al., 2020). However, the nasopharyngeal swab PCR examination is the gold standard of examination to create the diagnosis of COVID-19 (Guo et al., 2020).

Most research has focused on symptomatic adult patients since the first case of COVID-19 was reported. The variety of symptoms and many children who are infected and have asymptomatic symptoms make it difficult to detect SARS-CoV-2 infection. Along with COVID-19 cases emerging rapidly, identification of the characteristic clinical and laboratory features in the pediatric population is critical for determining further treatment, predicting disease severity, and determining prognosis (Nogueira-de-Almeida et al., 2020). This study was conducted to analyze differences in clinical features and laboratory and radiological investigations in pediatric patients with suspected and confirmed COVID-19 in children in Surabaya.

Method

A retrospective case-control study was conducted in Isolation Rooms at the Department of Pediatrics, Dr. Soetomo Academic Hospital, Surabaya from March to May 2022. The inclusion criteria in this study were pediatric patients aged >1 month to 18 years who were indicated as suspected of COVID-19 and had a complete medical record. All pediatric patients were tested with a nasopharyngeal swab PCR test to see the results of COVID-19 confirmation. Incomplete medical records are excluded from this study. The research subjects will be divided into two groups, namely the group of pediatric patients who have positive SARS CoV-2 PCR swab results and groups who have negative SARS CoV-2 PCR swab results. The variables studied included clinical symptoms of fever, headache, myalgia, painful swallowing, rhinorrhea, anorexia, fatigue, and decreased consciousness. Furthermore, laboratory examinations (leukocytes, neutrophils, lymphocytes, platelets) and radiological examinations include peripheral basal, diffuse bilateral, and bilateral central. This research has received ethical clearance from the Clinical Research Unit of Dr. Soetomo General Academic Hospital Number 0797/LOE/301.4.2/II/2022. Confidentiality of research subjects is well maintained by not mentioning names, but writing with initials. The data from this study are only used for research purposes.

Data analysis

Microsoft Excel and IBM SPSS Statistical Version 25 were used for analyzing the data. Characteristics of pediatric patients were analyzed descriptively. The clinical symptoms and radiological examination used the Chi-Square test with a p-value of <0.05, which means the variables are statistically significant. Meanwhile, for laboratory examination variables, if the variables are normally distributed, then the difference test will be conducted using the T-test, whereas if the variables are not normally distributed, the difference test will be executed using the Mann-Whitney U-test. We also determine the value of the Odd Ratio (OR) and 95% Confidence Interval (CI) on the variables studied.

Discussion

A total of 120 pediatric patients with suspected COVID-19 who met the inclusion and exclusion criteria were included in this study. Each group consisted of 60 children with positive SARS CoV-2 PCR swab results and 60 children with negative SARS CoV-2 PCR swab results. There were more male children than

female patients (59.2% and 40.8%). The average age of children with negative SARS CoV-2 was 63.98 ± 59.51 months and for children with positive SARS CoV-2 was 85.38 ± 69.07 months. The most dominant comorbid was malignancy in both groups. The characteristics of the research subjects are presented more fully in Table 1. Table 2 shows that the symptoms of fever, headache, painful swallowing, rhinorrhea, anorexia, fatigue, and decreased consciousness were not significantly different in the two groups except for myalgia with a *p*-value of 0.034. OR 2.020 95% CI 0.998 – 4.091. Myalgia was found to be higher in the negative SARS CoV-2 PCR swab group (26.7%) than in the positive SARS CoV-2 PCR swab group (13.3%). On laboratory examination, no significant difference was found between the two groups. However, the negative SARS CoV-2 PCR swab group had leukocytes >10,000/µL (53.3%) compared to the positive SARS CoV-2 PCR swab group (36.7) (Table 3). Table 3 also shows that leukocytes, neutrophils, and platelets in the high category were more in the negative SARS CoV-2 PCR swab group than positive except for lymphocytes. On radiological examination, the results of the SARS CoV-2 PCR swab were negative in the bilateral and central diffuse categories. There was a significant relationship in bilateral diffuse between the two groups with *p* value 0.021, OR 5.364 95% CI 0.829-34,713. Meanwhile, on radiological examination of bilateral central and peripheral basal, no significant relationship was found between the two groups (Table 4).

Table 1
The characteristic of children

The characteristics	nasopharyngeal swab PCR results		Total
	Negative (N = 60)	Positive (N = 60)	
Sex			
Male	35 (58.3)	36 (60)	71 (59.2)
Female	25 (41.7)	24 (40)	49 (40.8)
Age (months)	63.98 ± 59.51	85.38 ± 69.07	74.68 ± 65.08
Comobidity			
None	30 (50)	26 (43.3)	56 (46.7)
Malignancy	13 (21.7)	19 (31.7)	32 (26.7)
Autoimmune	7 (11.7)	3 (5)	10 (8.3)
Obesity	0	2 (3.3)	2 (1.6)
Diabetes mellitus	0	2 (3.3)	2 (1.6)
Congenital Heart Disease	6 (10)	2 (3.3)	8 (6.7)
Chronic kidney disease	3 (5)	1 (1.7)	4 (3.3)
Others	1 (1.7)	5 (8.3)	6 (5)
Contact history			
No	59 (98.3)	55 (91.7)	114 (95)
Yes	1 (1.7)	5 (8.3)	6 (5)

In this study, male children were found to be more dominant than females. The results in this study are in line with the community-based study conducted by Karyono and Wicaksana (2020) in Indonesia that the proportion of men dominates as much as 54.6% compared to women (Karyono & Wicaksana, 2020).

In a study conducted in China, the number of males was 56.6%, but there was no statistically significant difference (Y. Dong et al., 2020). Several other studies also reported similar results, and in addition, it was found that men had a higher cure rate than women of 31.62% and 27.54%, respectively (Huang et al., 2020; Jutzeler et al., 2020; Wang et al., 2020). Sex-specific differences in disease susceptibility were associated with differences in the immune system, genetic polymorphisms, and lifestyle factors, including smoking habits, personal hygiene habits, and expression of angiotensin-converting enzyme 2 (ACE2) as a potential risk in males. Specific regulation of ACE2 was found to be influenced by sex hormones where its expression was found to be increased in ARDS patients (Jutzeler et al., 2020).

More than half of pediatric patients with confirmed COVID-19 had comorbidities in this study. This is in line with the meta-analysis of comorbidity studies showing hypertension has the highest prevalence (21.1%), followed by diabetes (9.7%), cardiovascular disease (8.4%) (Yang et al., 2020). Guan et al., (2020) also reported that hypertension (15%) and diabetes (7.4%) were the most common types of comorbidity found in 23.7% of patients who had comorbid diseases (Guan et al., 2020). It is not yet known whether patients with diabetes mellitus are more susceptible to COVID-19, but a study has reported a greater risk of severe COVID-19 in patients with diabetes. Diabetic patients are at high risk of developing respiratory tract infections due to impaired immune system, especially innate immunity (Huang et al., 2020)

Patients with comorbid malignancy are at high risk of contracting COVID-19 with a poorer prognosis. Research in China found that 18% of patients with malignancy (1% of 1590 people studied) had a higher risk of worsening the disease from COVID-19 as indicated by treatment in the Intensive Care Unit (ICU) and using a ventilator. The number of patients with malignancies in the study was relatively small (1% of 1590 cases) and only 4 of 18 patients with these malignancies were on chemotherapy (Liang et al., 2020). Malignancy and its treatment such as chemotherapy and radiation therapy or radiotherapy can cause the bone marrow of cancer patients to stop producing white blood cells that act as soldiers that protect the body against certain infections and diseases. So that patients with malignancy will experience a decrease in body resistance, so that their body is unable to fight infections, including COVID-19 virus infection. In another study, it was also found that 50 percent of the 928 patients with malignancy who recovered from COVID-19 after undergoing medical treatment, 13% died (Alsohime et al., 2020).

Most of the pediatric patients in this study had no contact history (95%). Contrary to this study, Guan et al. explained that the main transmission route for SARS-CoV-2 infection is close contact with infected patients with or without symptoms, especially in children. Another study also reported that partners had the highest attack rate (23.3%), followed by family members (10.6%), close relatives (7.0%), other relatives (4.1%), social contact (1.3%), transportation contacts (0.3%), health workers (0.3%), and others (0.0%) (Guan et al., 2020)

Clinical symptom analysis

The majority of children with confirmed COVID-19 do not experience worrying clinical symptoms, only 60% of them have a fever. This is supported by Alsohime et al. (2020) and Rehman et al., (2020) that pediatric patients are less symptomatic than the adult population. Children are less prone to develop serious COVID-19 illnesses, although they can also be asymptomatic carriers. Children infected with Compared to adult infections, COVID-19 often has far fewer fatalities and milder symptoms. The incidence of COVID-19 due to Angiotensin-converting enzyme 2 (ACE2) expression in the nasopharynx increases with age (Alsohime et al., 2020; Rehman et al., 2020; Yonker et al., 2020). In line with this study, the clinical symptom aspect was used to indicate an increase in IgM on the Rapid Diagnostic Test (RDT) for COVID-19 antibodies, with the most clinical symptomthat could be found being fever (Pollan et al., 2020). This study contradicts another study which found anosmia was found in 47% and 86% of subjects (Guan et al., 2020).

Table 2
The clinical symptoms of children

Characteristics	nasopharyngeal swab PCR results		*p*	OR	95% CI *Lower -Upper*
	Negative (N = 60)	Positive (N = 60)			
Fever			0.357	1.230	0.846 – 1.790
No	31 (51.7)	37 (61.7)			
Yes	29 (48.3)	23 (38.3)			
Headache			1.000	1.073	0.626 – 1.840
No	51 (85)	52 (86.7)			
Yes	9 (15)	8 (13.3)			
Myalgia			0.034	2.020	0.998 – 4.091
No	44 (73.3)	52 (86.7)	*		
Yes	16 (26.7)	6 (13.3)			
Painful swallowing			1.000		
No	60 (100)	59 (98.3)			
Yes	0 (0)	1 (1.7))			
Rhinorrhea			0.295	1.485	0.761 – 2..910
No	21 (35)	54 (90)			
Yes	39 (65)	6 (10)			
Anorexia			0.140	1.353	0.950 – 1.927
No	21 (35)	30 (50)			
Yes	39 (65)	30 (50)			
Fatigue			1.000	1.000	0.551 – 1.181
No	20 (41.7)	23 (47.9)			
Yes	28 (58.3)	25 (52.1)			
Loss of consciousness			0.179	1.459	0.990 – 2.151
No	54 (90)	54 (90)			
Yes	6 (10)	6 (10)			

*a *p*-value below 0.05 was significant.

Laboratory examination analysis

According to laboratory tests conducted for this study, pediatric patients with confirmed COVID-19 had higher leukocyte values >10,000/µL (36.7%) and higher platelet counts (48.3%). These results are supported by a meta-analysis study conducted by Pormohammadaa et al. which showed that of the 2,361 COVID-19 patients with available laboratory data, leukopenia was only found in about 28% of the subjects, but in addition, leukocytosis was found in as many as 18.3% of the subjects and the most infected patients had an increase in platelets of up to 61%. (95% CI 41–78, $p < 0.001$) (Pormohammad et al., 2020). These findings, however, conflict with a meta-analysis by Henry et al. (2020), which found that 69.6% of children had a normal leukocyte count while 15.2% had hyperleukocytosis and 15.2% had leukopenia, neutropenia, and lymphopenia. Patients with more severe symptoms had only mild increases in leukocyte count, whereas patients who died had more clinically significant increases in leukocyte parameters. Thus, in more severe patients, a significant increase in leukocytes may signal a worsening clinical course and an increased risk of poor outcomes. These data suggest that the increase in leukocytes was driven by an increase in neutrophils, as a downward trend was observed for lymphocytes, monocytes, and eosinophils. In the SARS virus, it is suspected that lymphocytes are essential for eliminating virus-infected cells (Henry, de Oliveira, et al., 2020; Henry, Lippi, et al., 2020).

Table 3
Laboratory examination of research subjects

Laboratory	nasopharyngeal swab PCR results		*p*
	Negative (N = 60)	Positive (N = 60)	
Leukocytes (µL)			0.061
< 5.000	13 (21.7)	20 (33.3)	
5.000 – 10.000	15 (25)	18 (30)	
> 10.000	32 (53.3)	22 (36.7)	
Neutrophils (%)			0.067
< 40	14 (23.3)	23 (38.3)	
40- 50	6 (10)	7 (11.7)	
51 – 60	11 (18.3)	9 (15)	
1-70	8 (13.3)	6 (10)	
> 70	21 (35)	15 (25)	
Lymphocytes (%)			0.209
< 25	31 (51.7)	25 (41.7)	
25-35	9 (15)	8 (13.3)	
35-40	3 (5)	4 (6)	
> 40	17 (28.3)	23 (33.3)	
Platelets (µL)			0.159
< 50.000	12 (20)	21 (35)	
50.000 – 100.000	9 (15)	5 (8.3)	
100.000 – 150.000	4 (6.7)	5 (8.3)	
> 150.0000	35 (58.3)	29 (48.3)	

CRP (mg/L)			0.519
< 1.0	6 (27.3)	9 (47.4)	
1.0 – 3.0	4 (18.2)	0 (0)	
>3	12 (54.5)	10 (52.6)	

Mann Whitney U test was used.

Radiological examination analysis

When it comes to detecting pulmonary involvement in COVID-19, chest X-ray is substantially less sensitive than chest CT; the majority of children with COVID-19 have no abnormalities on chest X-ray. The level of chest radiographic sensitivity increases during COVID-19 infection especially after 6 days of symptom onset, from as low as 55% at 2 days to 79% at 11 days after symptom onset, and serial chest X-rays are close to the 64 diagnostic accuracies of chest CT (Area Under the ROC Curve 0.875 vs. 0.916) (Stephanie et al., 2020). The most frequent finding in children referred to the ICU with more severe abnormalities is parenchymal consolidation or ground glass opacity, which can be multifocal, unilateral, or bilateral (Aguirre Pascual et al., 2021).

Table 4
Radiological examination of research subjects

The characteristics	nasopharyngeal swab PCR results		*p*	OR	95% CI *Lower - Upper*
	Negative (N = 60)	Positive (N = 60)			
Basal peripheral			1.000	1.261	0.424 – 3.745
No	31 (51.7)	37 (61.7)			
Yes	29 (48.3)	23 (38.3)			
Bilateral diffuse			0.021*	5.364	0.829 – 34.713
No	51 (85)	52 (86.7)			
Yes	9 (15)	8 (13.3)			
Bilateral central			0.369	1.316	0.785 – 2.206
No	44 (73.3)	52 (86.7)			
Yes	16 (26.7)	6 (13.3)			

*a *p*-value below 0.05 was significant.

Conclusion

Through clinical symptoms, only myalgia symptom factors have differences in pediatric patients with suspected and confirmed COVID-19. Meanwhile, for supporting examinations including laboratory and radiological examinations, there were no significant differences except in bilateral diffuse. Although this study incorporates data from medical records and needs to be re-confirmed the accuracy of the filling. However, we believe that this study contributes to assessing the different aspects of clinical and supportive examinations in pediatric COVID-19 patients. In this condition, we recommend multiplying the SARS CoV-2 nasopharyngeal PCR swab test in patients with suspected COVID-19 accompanied by atypical symptoms, laboratory and radiological examinations to save the patient and their family so as to reduce transmission. Further studies

such as cohort prospective also need to be conducted in order to see a definite picture of the differences in clinical features and investigations in patients with suspected and confirmed COVID-19.

Acknowledgments

Authors would like to express the gratitude for health workers who supported and helped during the study. We also would like to thank the Head of Department of Child Health for permitting us to do this research.

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