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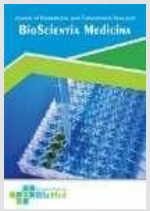

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SARS-CoV-2 Serology Antibody in Children with MIS-C (Multiple Inflammatory Syndrome in Children) Suspected

Finny Fitry Yani[1,2*], Indra Ihsan[1,2], Efrida[2,3]

[1]Departement of Child Health, Faculty of Medicine, Universitas Andalas, Padang, Indonesia

[2]Dr. M. Djamil General Hospital, Padang, Indonesia

[2]Departement of Clinical Pathology, Faculty of Medicine, Universitas Andalas, Padang, Indonesia

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***Corresponding author:**
Finny Fitry Yani

E-mail address:
finny@med.unand.ac.id

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A B S T R A C T

Background: Multiple inflammatory syndromes in children (MIS-C) relate to COVID-19 severity in children. SARS-CoV-2 serology antibody is one of the diagnostic tools of MIS-C. The study aimed to describe the yield of serology antibodies of MIS-C and some characteristics found in hospitalized children with MIS-C suspects. **Methods:** This research was an analytic observational study. The data were collected retrospectively from some children who were hospitalized in Dr. M. Djamil General Hospital, Padang, West Sumatra, Indonesia, from April - June 2021. The inclusion criteria were children aged 1 month to 18 years, with or without contact history with the person who probable or confirmed COVID-19 and have signs and symptoms as MIS-C base on WHO criteria. **Results:** About eight out of 44 children showed positive serology antibodies and were diagnosed as MISC (18,2%). Based on demographic characteristics, children aged 11-15 years (27.3%) and boys were more affected (52.3%) as MIS-C suspected. Most of them were referred from a 2nd-level hospital outside Padang City (70.4%), but only 13.6% had a history of contact with COVID-19 confirmation patients. There was a significant difference in cardiovascular signs and symptoms between positive and negative serology antibody SARS-CoV-2 among children with MIS-C suspected ($p<0.05$), but not in fever, respiratory distress, gastrointestinal, neurology symptoms, either in laboratory results such as leukocytes, CRP and D-dimmer. Intravenous immunoglobulin, steroid, and PICU admitted showed no significant differences between the 2 groups, but more death prevalence in positive than negative. However, no significant differences (12.5% vs. 11.1%, $p>0.05$). **Conclusion:** Cardiovascular signs and symptoms could be proposed to be one of the significant differences in clinical conditions to differentiated children with MIS-C suspected and MIS-C due to serology antibody results.

1. Introduction

COVID-19 cases still exist in several countries globally. According to the American Academy of Paediatrics, for the week ending November 18, 2020, there were 141.905 new cases of COVID-19 in children in New York.[1] Children have represented 16.9% of all cases, or approximately 6.767.762, until November 18, 2021. In Indonesia, COVID-19 has been confirmed at 2.9% and 10.2% in children aged 0-5 years and 6-18 years.[2] Mostly, COVID-19 symptoms in children are mild to moderate. However, in April 2020, England found some symptoms similar to Kawasaki disease and toxic shock syndrome in children with confirmed real-time polymerase chain reaction (RT-PCR) COVID-19 test. These syndromes were defined as multiple

inflammatory syndromes in children (MIS-C) or pediatric inflammatory multisystem syndrome-temporally associated SARS-CoV-2 (PIM-TS).[3]

The differences between pathophysiology and immune response in children and adults lead to extending an acute COVID-19 become MIS-C. MIS-C occurs 2-6 weeks after COVID-19 infection. According to Yasuhara's study on 917 MIS-C patients, some have found organ failures such as in the gastrointestinal system, myocardium dysfunction, and coronary abnormality. MIS-C inflammatory response is different from cytokine storm in severe COVID-19 patients. A few immunological conditions have similarities to Kawasaki Disease. Still, they differ in a low level of T cell and IL-17 and elevated levels of biomarkers related to artery defects in MISC patients.[4]

MIS-C was diagnosed from several criteria, such as the presence of fever with minimal one following symptom and abnormal laboratory findings, and also confirmed positive in the COVID-19 test.[5] On the other hand, WHO establishes MIS-C diagnosis based on (1) aged 0-19 years with fever for more than three days; (2) and two of the following: rash or bilateral non-purulent conjunctivitis or mucocutaneous inflammation signs (oral, hands, or feet), hypotension or shock, features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated Troponin/NT-proBNP), evidence of coagulopathy (by PT, PTT, elevated D-dimmers), acute gastrointestinal problems (diarrhea, vomiting, or abdominal pain); (3) and elevated markers of inflammation such as ESR, C-reactive protein, or procalcitonin; (4) no other apparent microbial cause of inflammation including bacterial sepsis, staphylococcal or streptococcal shock syndromes; (5) and evidence of COVID-19 (RT-PCR), antigen test or serology positive), or likely contact with patients with COVID-19.[6]

Some children with MIS-C have a negative result for the acute COVID-19 test. This condition means that when they are diagnosed, they do not get an acute infection at that time. Still, they have a history of COVID infection as evidenced by positive antibody SARS-CoV-2.[7] In Indonesia, the first MISC case was reported in September 2020 with shock and positive IgM antibody, but no evidence of acute infection on COVID-19.[8] Early detection of MIS-C based on serology antibodies is urgent to explore. It is because MIS-C can cause Mortality in children. The study aimed to describe the yield of serology antibodies of MIS-C and some characteristics found in hospitalized children with MIS-C suspects in Dr. M.Djamil General Hospital, Padang, Indonesia.

2. Methods

This research was an analytic observational study. The data were collected retrospectively from some children who were hospitalized in Dr. M.Djamil General Hospital, Padang City, West Sumatra, Indonesia, from April - June 2021. The inclusion criteria were children aged 1 month to 18 years, with or without contact history with the person who probable or confirmed COVID-19 and have signs and symptoms as MIS-C base on WHO criteria.

The demographic data, including age, gender, address, the origin of referral, and history of contact with a person who is probable or confirmed COVID-19, have been collected, as well as clinical data about fever and cough, cardiac abnormality, gastrointestinal tract abnormality, neurology deficit, laboratory findings (including CBC, D-dimer, NLR, CRP, ferritin, and serology antibody test for COVID-19), treatment, and outcome.

Children were categorized as having MIS-C suspected if they had fever ≥3 days and followed by minimal two organ dysfunction (dermatologic, respiratory, hypotension or shock, cardiovascular, coagulopathy, and gastrointestinal), elevated marker inflammation, without microbial cause inflammation, and positive SARS-CoV-2 infection, based on WHO case definition of MIS-C.[6]

Clinical symptoms measured in this study were the presence of fever and multiple organ dysfunction. There were dermatologic, respiratory, hypotension or shock, cardiovascular, neurology, coagulopathy, and gastrointestinal. Dermatological disorders included

rash, bilateral non-purulent conjunctivitis, or signs of mucocutaneous inflammation of the mouth, hands, or feet. Then, respiratory disorders are assessed in the form of a cough, runny nose, or other disorders that are included in upper respiratory tract infections. Cardiovascular disorders were assessed by the presence of pericarditis, valvulitis, coronary abnormalities such as abnormal findings on echocardiography, and elevated Troponin/NT-proBNP. Furthermore, coagulopathy was assessed by finding an increased level in PT, PTT, and D-dimmer examinations. Lastly, gastrointestinal disorders assessed in this study were nausea, vomiting, and abdominal pain.

The references of normal value on laboratory tests are measured by age. All samples were evaluated for serology antibody test for COVID-19. Children with MIS-C suspected will be considered and treated as MIS-C if they have positive serology antibodies for COVID-19. This study has received approval from the ethical committee of Dr. M.Djamil Hospital (Reference Num. 300/KPK/2021)

Data analysis was carried out with the help of SPSS software version 25. Univariate analysis is performed to display the frequency distribution data of each variable. Next, a bivariate analysis was performed with a chi-square test. P-value is set at 5% or 0.05, meaning that if the p-value of < 0.05 indicates that there is a difference between the test variables.

3. Results

A total of 44 patients with clinically MIS-C suspected were included in this study. Eight patients showed positive serology antibodies for COVID-19. Therefore yield of the positivity rate is 18.2% (Table 1). Table 2 showed that more suspected MIS-C is experienced by children aged 11-15 years (27.3%), and boys were more affected (52.3%). Most of them were referred from a district-level hospital outside Padang City (70.4%). Only 13.6% had a history of contact with COVID-19 confirmation patients.

Table 1. The yield of positivity rate of serology antibody of children with MIS-C suspected (n=44).

Serology antibody among children MIS-C suspected	f	%
Positive	36	81.8
Negative	8	18.2

Table 2. Demographic characteristics of children with MIS-C suspected (n=44).

Characteristics		f	%
Age (year old)	1 month - < 1	8	18.2
	1-5	10	22.7
	6-10	8	18.2
	11-15	12	27.3
	>15-18	6	13.6
Gender	Females	21	47.7
	Males	23	52.3
Address	Padang city	13	29.5
	others	31	70.4
Refer by	Self-reported	11	25.0
	District hospital	27	71.5
History of COVID-19 contact	Yes No	6 38	13.6 86.3

Table 3. Clinical & laboratory characteristics of children with MIS-C suspected based on serology antibody SARS-CoV-2 results.

Symptoms & Signs	Serology antibody SARS-CoV-2		p-value
	Positive (n=8) f (%)	Negative (n=36) f (%)	
Fever			
• Yes	8 (100)	25 (69.4)	0.071
• No	0 (0)	11 (30,6)	
Respiratory distress			
• Yes	7 (87.5)	17 (47.2)	0.038
• No	1 (12.5)	19 (52.8)	
Gastrointestinal			
• Yes	7 (87.5)	20 (55.6)	0.093
• No	1 (12,5)	16 (44,4)	
Neurology			
• Yes	2 (25.0)	20 (55.6)	0.118
• No	6 (75.0)	16 (44.4)	
Cardiovascular			
• Yes	6 (75)	13 (36.1)	0.045
• No	2 (25)	23 (63.9)	
Leukocyte			
• Increase	4 (50)	18 (50)	1.000
• Normal	4 (50)	18 (50)	
Laboratory Examinations C-Reactive Protein (CRP)*			
• Abnormal	1 (16%)	3 (15.8)	0.959
• Normal	5 (83.3%)	16 (48.2)	
D-dimmer *			
• Abnormal	6 (23.1)	20 (83.3)	0.283
• Normal	0 (0)	4 (16.7)	

*incomplete data; ** Chi-square, p=0,05

There was a significant difference in cardiovascular signs and symptoms between positive and negative serology antibody SARS-CoV-2 among children with MIS-C suspected ($p<0.05$), but not in fever, respiratory distress, gastrointestinal, neurology symptoms. Also no significant differences in laboratory results such as leukocytes, CRP, and D-dimmer (Table 3).

Table 4. Management and outcome of children with MIS-C suspected based on serology antibody SARS-CoV-2 results

Variable	Serology antibody SARS-CoV-2		p-value
	Positive (n=8) f(%)	Negative (n=36) f(%)	
Immunoglobulin			
• Yes	6 (74)	3 (8.3)	0.179
• No	2 (25)	33 (91,7)	
Steroid			
• Yes	5 (62.5)	15 (41.7)	0.284
• No	3 (37.5)	21(58.3)	
PICU			
• Yes	1 (12.5)	31 (86.1)	0.918
• No	7 (87.5)	5 (13.9)	
Outcome			
• Survive	7 (87.5)	32 (88.9)	0.911
• Death	1 (12.5)	4 (11.1)	

Intravenous immunoglobulin, steroid, and PICU admitted showed no significant differences between positive and negative serology antibody SARS-CoV-2. There was more death prevalence in positive than negative, but no significant differences (12.5% vs. 11.1%, p>0.05).

4. Discussion

This study showed that 18.2% of children with MIS-C were suspected of having positive serology antibodies, thus confirming the diagnosis of MIS-C based on WHO criteria. A study told that MIS-C incidence was 5.1 per 1.000.000 person-months and 316 persons per 1 000 000 SARSS-CoV-2 infections in persons younger than 21 years. Incidence was higher among Black, Hispanic or Latino, and Asian or Pacific Islander compared with White and in younger compared with the older.[9] Then, the finding of reactive antibody results in patients with MISC was found in 80-90% of patients. Positive results on the COVID-19 test in the form of RT-PCR and gen-X-pert for SARS-CoV-2 are also supporting evidence for MISC enforcement.[5]

Children with MIS-C suspected were more in children aged 11-15 years (27.3%) than in other age groups, and girls were more affected (52.3%). These results are not much different from the study of Kaushik et al., where the average MISC patient was ten years old; however, more affected in boys.[10] Most of them refer from 2nd level hospital (71.5%) due to the severe condition that needs more complete facilities to manage the disease as we know that MIS-C is one of the extreme forms of COVID-19.

The history of COVID contacts influences the prevalence of MISC. Based on the contact history of COVID-19, many patients with suspected MISC have no clear history of close contact. In this study, only 13.6% have a history of close contact with COVID-19 patients. The MISC case was first published in mid-May 2020 at New York Hospital, coinciding with the high number of COVID cases one month earlier. This is the basis for suspicions of a relationship between COVID-19 and MISC.[10,11]

Some literature showed that fever is a common clinical symptom found in MISC patients and in this study. The clinical signs of MIS-C were (1) mucocutaneous disorders such as a rash (81%), conjunctivitis (93%), and chapped lips (87%); (2) gastrointestinal disorders as much as 81%; (3) hemodynamic disturbances such as tachycardia, decreased peripheral pulses, cold extremities, CRT>3 seconds as much as 69%; (4) neurological disorders such as headache and aseptic meningitis in 37% and 17%; and (5) respiratory disorders such as cough and dyspnoea in 12%.[11,12] However, this study did not find all of the signs and symptoms of MIS-C completely.

Leukocytes, C-reactive protein, and D-dimmer has been at an abnormal level in this study. However, they did not show significant differences between the two groups. This finding is consistent with other similar studies. A study showed a significant increase in the CRP value of 450 mg/L (83% vs 25%, p=0.008) and D-dimer 41000 ng/mL (100% vs 40%, p=0.007) in MISC patients compared to other patients who did not MISC.[13] In one study in the USA, the inflammatory biomarkers studied in his study (CRP, ESR, leukocyte, procalcitonin, IL-6, D-dimer, and ferritin) were elevated in almost all MISC patients.[14] Other similar studies also showed the same results that there was an increase in the value of CRP, procalcitonin, D-dimer, and pro-B-type natriuretic peptide (BNP) in all MISC patients treated at the PICU in New York City.[10] Unfortunately, not all patients have been examined for those markers in referral hospitals, sometimes due to limited resources.

Intravenous immunoglobulin (IVIG) and steroids are recommended in patients with moderate-to-severe clinical or poor prognosis. Similar to our finding, a study has reported that IVIG was administered in 5 of 16 patients (36%) and gave good results or remission in the inflammatory phase.[12] Due to the severe condition of children with MIS-C suspected, in our study, most of them need to PICU admitted (86.4%); these results are similar to previous studies that

declared about 80% of patients with MISC are admitted to PICU, and 23% of them require a ventilator.[15,16]

In general, the patients in this study with MIS-C suspected survived, but Mortality in MIS-C suspected with positive serology antibodies was higher than negative serology group. This finding is in line with the previous studies that 4 of 186 patients treated with MISC died.[17,18] The patients' ages ranged from 10 to 16 years, and two had co-morbidities. However, a limitation was found in this study. MIS-C definitions were not established during the initial assessment due to the lack of inflammatory markers examination and limited access to laboratory evaluation.

5. Conclusion

Cardiovascular signs and symptoms could be proposed to be one of the significant differences in clinical conditions to differentiated children with MIS-C suspected and MIS-C.

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