

Potential of Inflammatory Biomarkers as Diagnostic Tools for Paediatric Inflammatory Multisystemic Syndrome related to SARS-CoV-2: Literature Review

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ABSTRACT

The World Health Organization has named the enveloped RNA virus Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Clinical aspects and pathogenic mechanisms between hyperinflammatory disease and SARS-CoV-2 are triggering factor for the out brake of autoinflammation disease and autoimmune dysregulation. This condition is known as Paediatric Inflammatory Multisystem Syndrome Temporally (PIMS-TS) related to SARS-CoV-2 or Multisystem Inflammatory Syndrome in Children (MIS-C) related to COVID-19. There are similarities between MIS-C and other diseases, that is overlapping clinical manifestations that lead to delaying diagnosis. Therefore, whether inflammatory biomarkers could be used to distinguish between these conditions are needed to be investigated. In order to distinguish MIS-C from infection and other inflammatory condition, it will continue to be a challenge as the COVID-19 pandemic. Therefore, a study is needed to investigate whether inflammatory biomarkers could be used to distinguish between these conditions.

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INTRODUCTION

Corona Virus Disease-19 (COVID-19) is a global pandemic occurred in Wuhan, China on December 2019.¹ The World Health Organization named RNA viruses enveloped the outbreak from Wuhan, China with The 2019 Novel Coronavirus (2019-nCoV) or Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).² Regarding this case, the Indonesian government issued Presidential Decree (Keppres) No. 12 Year 2020 on the Determination of Non-natural Disasters Spread Corona Virus DiseaseE 2019 (COVID-19) as a National Disaster as of April 13, 2020.³

In Indonesia, until mid-April 2020, the number of patients had reached 5,923 positive virus. Based on data from the Ministry of Health, the most recovered patients are still in DKI Jakarta, which was the epicentre of COVID - 19 in Indonesia. The next largest are was East Java with a total of 94 patients recovered, then South Sulawesi with 43 patients recovered. Next area was West Java

with 41 patients recovered, then followed by Bali and Central Java respectively 33 patients recovered.⁴ Meanwhile, based on WHO reports, Europe had become the center of the coronavirus pandemic globally. Europe had more cases and mortality from COVID-19 than China, while the United States was the country with the largest number of infected patients in the world, approaching 700 thousand people. The accumulation of patients infected the coronavirus worldwide had reached 2.24 million people and at least 185 countries had infected and killed 153,822 people.⁵

SARS-CoV-2 is directly transmitted from person to person through respiratory droplets using ACE2 receptors to infect people. Children are considered to be marginally involved compared to adults with a significant percentage of asymptomatic carriers.⁶ A Chinese study evaluated COVID-19-affected infants under the age of one year in the period between December 6, 2019 and February 8, 2020.⁷ Research from the Center China Disease Control and Prevention Centre; published 72,314 cases classified as confirmed cases of positive COVID-19, suspected COVID-19, clinically diagnosed COVID - 19, or asymptomatic cases of COVID-19. Among the group of confirmed cases, there were 416 (0,93%) aged which less than 10 years and 549 (1,2%) were between 10 and 19 years old; the case mortality rate in children under 9 years old was 0%.⁸

Another study reported a COVID-19 positive neonate is born from a COVID-19 positive mother. Currently, there is controversial version for vertical transmission of mother to baby and there are not many studies that can be used as a reference. Other things that need more attention in this study is the sample was taken 36 hours after give birth. So, it is possible that the child can be infected through direct contact.⁹ Data from the Indonesian Pediatrician Association (IDAI) reported an increase in mortality for Indonesian children by 1,9% with the percentage of case fatality rate is 1,1% which led to the presence of more than 7,000 total cases of mortality in children. Reporting from the United Nations (PBB) page, it was reported that there were an additional 228,000 cases of mortality in children under five ages due to COVID-19 in the six largest countries in ASEAN and Indonesia has the second position.¹⁰

COVID-19 in childhood is usually with mild symptoms, such as symptoms of cough, fever, and fatigue. Some studies have mentioned a mild fever or even no fever at all.¹¹ It is usually accompanied by upper respiratory tract symptoms, such as nasal congestion and headache.¹² Children also experience with gastrointestinal manifestations, such as diarrhea, vomiting or flatulence.¹³ COVID - 19 has a good prognosis in children with most cases recovering after a mild course of the disease and very rarely progressing to severe.¹⁴ Dong et al. conducted a retrospective study of 2,141 pediatric patients confirmed COVID-19 or suspected of having COVID-19 in China. They found that most of the 1.091 patients (50.9%) had mild disease, while 831 (38.8%) children had moderate disease. These mean that about 90% of the children in this study had mild or moderate disease. Only 13 (0,6%) had critically ill patients and mostly 7 (0.3%) were infants (53.8%). The study explains that childhood illnesses are generally not severe. Besides, younger children with the one-year-old are the most vulnerable group to critical illness and are admitted to the ICU.¹⁵

Since April 2020, several countries in Europe and North America have reported young patients suffering severe multisystem inflammatory syndrome associated with SARS-CoV-2.¹⁶ These manifestations must be alerted and monitored intensively as a result of the COVID-19 pandemic due to their severity and especially due to the increasing number of cases reported worldwide.¹⁷ In early May 2020, the evidence was collected from the United Kingdom, the United States, and Europe regarding a different manifestation of COVID-19 in pediatric patients, namely hyperinflammatory shock with multi-organ involvement.¹⁸ Clinical aspects and pathogenic mechanisms between hyperinflammatory diseases and SARS-CoV-2 as a provoking factor in the outbreak from autoinflammation disease autoimmune dysregulation. This condition is referred as Paediatric Inflammatory Multisystem Syndrome Temporally (PIMS-TS) associated SARS-CoV-2 or Multisystem Inflammatory Syndrome in Children (MIS-C) related to COVID - 19.¹⁹

Early descriptions showed an important clinical heterogeneity, partially overlapping with Kawasaki disease (KD) or toxic shock syndrome (TSS). However, it is different from these known inflammatory conditions.²⁰ Through the advent of COVID-19, this comprehensive review was adapted to help review diagnostic tools in patients with MIS-C that display biomarker profiles with key differences from various clinically similar to hyperinflammatory condition

Multisystem Inflammatory Syndrome in Child (MIS-C)/Pediatric Inflammatory Multisystem Syndrome (PIMS) In the mid-April 2020 period, there was a report from The South Thames Retrieval Service in London UK, where the symptoms were found in an unprecedented group of pediatric patients in the form of hyperinflammatory shock involving multisystems of organs. Along with many case reports of hyperinflammatory shock, this disease is called as Multisystem inflammatory Syndrome in Child (MIS-C) or Pediatric Inflammatory Multisystem Syndrome. World organizations, such as The World Health Organization (WHO), The Centers for Disease Control and Prevention (CDC), The Royal College of Paediatrics and Child Health (RCPCH) and The European Centre for Disease Prevention and Control began to decide this syndrome as one of the inflammatory disorders that appeared in children most often during the COVID - 19 pandemic.²¹ This hyperinflammatory shock presents symptoms similar to those of Kawasaki Disease (KD) or Kawasaki Shock Syndrome, Kawasaki-like syndrome (KLS), Atypical Kawasaki Disease, Incomplete Kawasaki Disease, SARS-CoV-2- Kawasaki-Like Hyperinflammatory Syndrome (SCiKH Syndrome), Eve-COVID - 19, Toxic Shock Syndrome (TSS), and severe acute infection COVID-19.^{22,23}

Results of epidemiological data report by CDC on MIS-C cases on October 1, 2020, the number of patients who met the criteria of MIS-C in the United States exceeded 1000 cases. Continued in 2021, the number has increased to more than 2000, and the last report on June 2 was 4018 cases with 36 deaths. Cases of MIS-C patients based on ethnicity and race vary, with dark skin and hispanic children have a very high number of cases and Asian children are also accounting for a number of cases. In the three big series of cases, 25% -45% occurred in dark skin children, 30% -40% in hispanic children, 15% -25% in light skin children, and 3% -28% in children of Asian race/ethnicity.²³ In terms of gender, it was obtained that 40% in women and 60% in men with an average age of 9 years and the rest between 5-13 years.²⁴ A report from the New York stated that the incidence rate of SARS-CoV-2 infection in individuals <21 years of age is 322 per 100,000 with the incidence of MIS-C being 2 per 100,000.²³

Multisystem inflammatory Syndrome in Child (MIS-C) or Pediatric Inflammatory Multisystem Syndrome is a condition in which more than one organ of the body has an inflammatory condition, such as the heart, lungs, kidneys, brain, skin, eyes, or gastrointestinal tract.²⁴ The definition of SARS-CoV-2-related MIS-C has been established by The Centers for Disease Control and Prevention (CDC) in several criteria, namely (1) patients with aged <21 years; (2) patients have fever and increased inflammatory markers; (3) the presence of severe clinical history with indications requiring hospitalization and attack two or more organs (heart, kidney, lungs, hematologist, gastrointestinal, dermatologists, or neurological); (4) shows a positive test result for SARS-CoV - 2 by reaction of Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) within four weeks before the onset of symptoms[25]. Multisystem inflammatory Syndrome in Child (MIS-C) and Kawasaki Disease (KD)

Related to COVID-19 cases, there are the health reports describing the incidence of hyperinflammation due to infection from COVID-19, with marked changes in coronary arteries similar to KD. The correlation between Kawasaki Disease (KD) and MIS-C has the similarity in symptoms. Kawasaki Disease (KD) or Kawasaki Shock Syndrome has a definition as acute vasculitis that has high fever and inflammation symptoms with unknown causes and mostly affects children under 5 years of age, and rarely in children under 6 months of age.²⁶ A study from Bergamo, Italy, which was heavily affected by COVID-19, found a 30-fold increase in the incidence of Kawasaki Disease after the start of the COVID-19 epidemic, patients diagnosed in that period

exhibited immune response reactions to the virus, high cardiac involvement, macrophage activation, and required steroid adjuvants in treatment [27]. Clinical symptoms in KD that have similarities to MIS - C include, the presence of signs of prolonged fever, lymphadenopathy, diarrhea, inflammation of the multisystem, and a high increase in inflammatory biomarkers. This leads to an overlap of symptoms in MIS-C with KD, causing conflict that whether KD related to SARS-CoV-2 is a triggering agent that causes MIS - C or MIS-C itself as dependent syndrome. The existing of some symptoms in MIS-C that or rare happens in KD can be seen in Figure 1

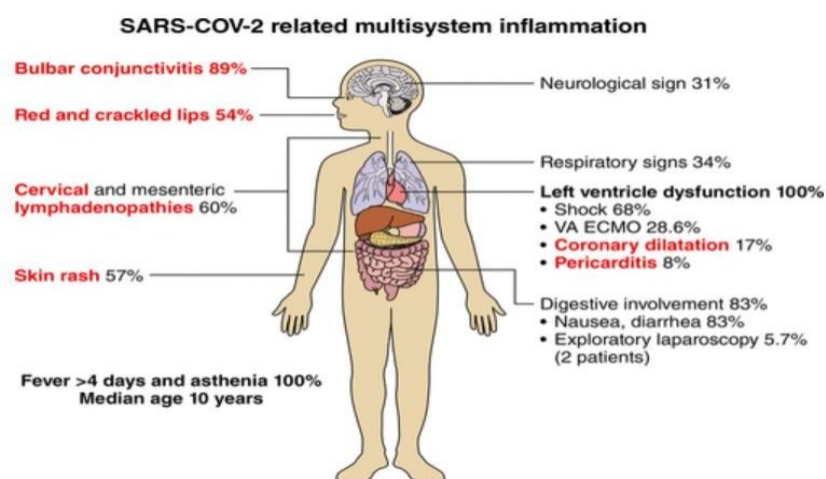


Figure 1. Schematic representation of clinical signs in severe forms of SARS-CoV-2 - 2-associated with multisystem inflammation, Red text indicates signs or symptoms corresponding to Kawasaki disease; Black text indicates signs that are rare in Kawasaki disease.

The difference between MIS-C and KD is seen in: (1) mis-C cases tend to be more common in older children / adolescents while KD affects infants and young children (with MIS - C 8-11 years, KD 3 years), (2) MIS-C that occurs in children who have dark skin and hispanic is affected disproportionately and only a small number of cases in Asian children. In contrast with the case of KD, the incidence was higher in Asian descent children. (3) In gastrointestinal symptoms (especially abdominal pain) were more likely to occur in MIS - C, while in KD these symptoms were less dominant. (4) Shok and myocardial dysfunction were less likely to occur in MIS-C than KD. (5) Then, in inflammatory biomarkers (CRP, D-dimer, and ferritin) the amount was much higher in MIS-C than KD. (6) In addition, the number of lymphocytes and platelets in the case of MIS-C has lower levels than KD [29] Multisystem inflammatory Syndrome in Child (MIS-C) and Toxic Shock Syndrome (TSS)

MIS-C also has similarities with Toxic Shock Syndrome (TSS). TSS is a syndrome with symptoms, such as hypotension, fever, the presence of rashes, such as sunburn as well as the existence of organ damage, especially clinical criteria that occur in TSS according to the Center for Disease Control (CDC).³⁰ Reported cases of TSS, related to COVID-19, the infection are still not obviously with the etiology of the TSS itself which comes from the mediation of toxins produced by streptococcal bacteria (*Streptococcus pyogenes*) or *Staphylococcus aureus*. This Antigen can activate T cells through normal pathways, resulting in excessive activation of cytokines and inflammatory cells.³¹ Symptoms that overlap between MIS-C and TSS are found in the inflammatory involvement in several organ systems (three or more). But, in TSS, there are typical symptoms of conjunctival inflammation. In addition, TSS also has a history in adult individuals so that it can be used as a distinction in MIS-C that occurs only in children.³²

Multisystem inflammatory Syndrome in Child (MIS-C) and Severe Acute Infection SARS-CoV - 2 Furthermore, the difference between SARS-CoV-2 severe acute infection with MIS-C, namely

(1) mis-C cases that mostly occur in children who previously had no history of other diseases (healthy). However, severe acute COVID-19 cases occur in children who have previous health problems. (2) Pulmonary disorders (such as pneumonia and acute respiratory distress syndrome) occur predominantly in severe acute COVID-19 infections. In MIS-C patients, respiratory symptoms occur due to shock / impaired heart function. The symptoms of myocardial dysfunction gastrointestinal, mucocutaneous, lymphopenia, and thrombocytopenia are more common in MIS-C than in severe acute COVID-19 infections. Then, if reviewed from laboratory tests, inflammatory biomarkers (CRP, ferritin, and D-dimer) tend to be more in MIS-C patients.³⁰ Pathophysiology of Multisystem inflammatory Syndrome in children (MIS-C)

On the pathophysiology of MIS-C currently reported still has unclear information. Symptoms of MIS-C usually arise after 4-6 weeks of infection with SARS-CoV-2. Some of the symptoms are, (1) immune dysregulation of the body. It is suspected that there is an abnormal immune response to the virus and based on existing studies, MIS-C has a distinctive immunophenotype. Early studies reported that patients with severe MIS-C had persistent immunoglobulin G (IgG) antibodies with the ability to activate monocytes, persistent cytopenia (T cell lymphopenia), and higher activation of CD8+T. (2) Myocardial injury, it is apparently trigger to be from of systemic inflammatory injury, hypoxia, acute viral myocarditis, cardiomyopathy, and ischemia involved in the coronary arteries. Meanwhile, the mechanism of how the SARS-CoV-2 virus itself triggers abnormalities of the immune system and the mechanism of myocardial injury in MIS-C patients is still unclear due to variability in clinical presentation. Then, the visible clinical manifestations are (1) persistent fever (4-6 days) 100%, (2) gastrointestinal disorders (vomiting,

diarrhea, abdominal pain) 60% -100%, (3) Rash 45% - 76%, (4) Congjunctivist 30% -81%, (5) Lip membranes (swollen, red, or strawberry tongue) 27%-76%, (6) neurocognitive (confused, lethargic, headache) 29% -58%, (7) respiratory disorder 21%-65%, (8) sore throat 10% -16%, (9) myalgia 8% - 17%, (10) Lymphadenopathy 6% -16%, and (11) swelling of the feet/hands 9% -16%. The long-term end result of MIS-C also has unclear information because it is a kind of new syndrome. Some reports of MIS-C mortality rates in hospitals are very diverse with different centers. Some studies reported no mortality and other studies reported it up to 18%.

RESEARCH METHOD

The method used in this study was a qualitative method by literature review . Through this literature review, the interpretation of various libraries is carried out optimally by summarizing, analyzing, evaluating, and synthesizing a document. The material used a literature in the form of journals issued by institutions with recognized credibility. Information discovery used keywords, namely Inflammatory Biomarkers, Paediatric Inflammatory Multisystemic Syndrome, and SARS-CoV-2. Keywords were used to extract documents into the database in the form Google Scholar, Pubmed, Ovid, and ScienceDirect using Boolean operators (AND, or, NOT).³⁵ The number of literatures used as a reference as many as 40 within the last 10 years:

RESULTS AND DISCUSSIONS

In MIS-C Immunopathology, the results of the data are presented in Table 1. Based on the literature studies, it is said that there is an increase in systemic regulation of inflammatory cytokines, namely the cytokine storm syndrome caused inflammation on gastrointestinal (92%), cardiovascular (80%), hematology (76%), mucocutaneous (74%), and respiratory involvement (70%).

Leukosit	Jumlah Sel Limfosit CD4+	Hemoglobin	Initial Platelet
Neutrophil	Peak Platelet	Ferritin	C-Reactive Protein
ESR	Procalcitonin	D-dimer	Creatinin
IL-6	IL-17	IL-8	IL-10
CXCL10	Pro-BNP	BNP	HD MB-C
NT-ProBNP	LDH	AST	Troponin I
Albumin	BUN	Fibrinogen	PTT

Table 2. Consensation of biomarkers, cardiac markers, hematology, and laboratory results in COVID-19 patients with MIS-C.

In MIS-C patients, there is a serum profile that has an increase in interleukin-1 β (IL-1 β), IL-6, IL-8, IL-10, IL-17, and interferon-gamma (IFN- γ) with an increase in IL-6, IL-17A, and CXCL10 have the most contribution to the cytokine storm. On the report of Consiglio et al. also found an increase in antiendoglin (excreted into endothelial cells), anti MAP2K2 (Mitogen-Activated Protein Kinase 2), proteins of the anti-casein kinase family (activated into SARS-CoV-infected cells- 2), and antibodies that react with protein antigens. The schematic of the cytokine storm can be seen in Figure 2.

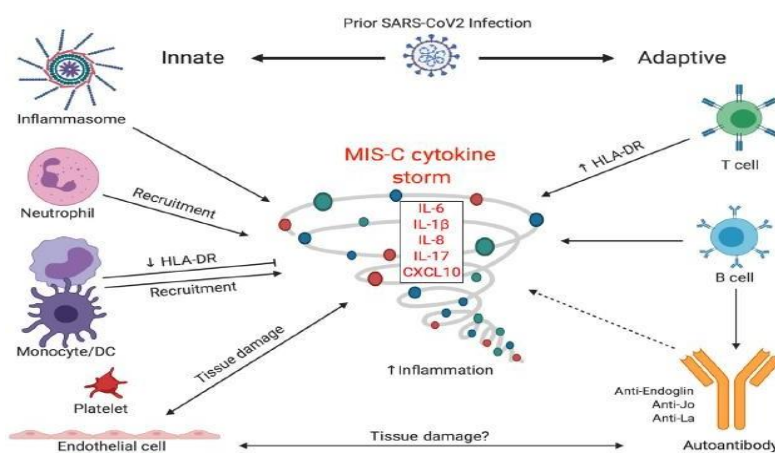


Figure 3: Systematics of cytokine storms in MIS-C involving immune cells. Abbreviations: DC, dendritic cells; HLA-DR, human leukocyte antigen-DR; IL, interleukin, MIS-C, multisystem inflammatory syndrome in children; SARSCoV-2, severe acute respiratory syndrome coronavirus

Detection of autoantibodies in MIS-C patients, it is reported that there are target antigens for autoantibodies excreted in mucous tissues, heart, cytokine molecules, and endothelial cells. Patients infected SARS-CoV-2 will trigger immunological mechanisms derived from the production of virus-specific antibodies and cross-reactive antibodies that bind to host antigens. These antibodies can bind with FCY receptors expressed by neutrophils and monocytes resulting

in the formation of immune complexes. Based on this, it is suspected that autoantibodies or antibodies to SARS-CoV-2 have a role in the pathogenesis of the disease in MIS-C, with a systematic scheme in Figure 3.

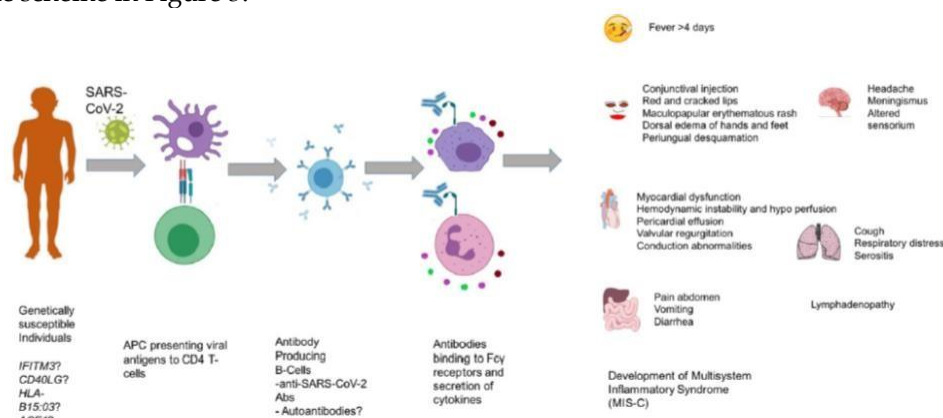


Figure 4. Mechanism of Antibody Production in MIS-C related SARS-CoV-2. Abbreviations: IFITM3 interferon-induced transmembrane protein-3, CD40LG cluster of differentiation 40 (CD40) ligand, HLA-B15:03 human leukocyte antigen (HLA) B15: 03, ACE1 angiotensin-converting enzyme 138

Laboratory Test of MIS-C related to SARS CoV-2 showed some changes ranging from indicating the presence of abnormal blood cell counts (Lymphocytopenia 80% - 95%, Neutrophilia 68% - 90%, mild Anemia 70%, and Thrombocytopenia 31% - 80%), increase of Inflammation Markers (C-reactive Protein 90% - 100%, Erythrocyte sedimentation rate 75% - 80%, D-dimer 67% - 100%, Fibrinogen 80% -100%, Ferritin 55% -76%, Procalcitonin 80% -95%, and Interleukin-6 80% - 100%), elevated cardiac markers (Troponin 50% - 90% and BNP or NT-pro-BNP 73% - 90%), hypoalbuminemia 48% - 95%, elevated liver enzymes 62% - 70%, elevated lactate dehydrogenase 10% - 60%, and hypertriglyceridemia 70%. The ESR phase reactants did not show a significant increase in MIS-C. In patients with moderate to severe symptoms, it is recommended to have a complete blood test (CBC) with differential, C-reactive Protein (CRP), and erythrocyte sedimentation rate, liver function and lactate dehydrogenase tests, serum electrolytes and kidney function, urinalysis, coagulation tests, troponin and Brain Natriuretic Peptide (BNP) or N-terminal pro-BNP (NT-pro-BNP). Meanwhile, if the patient has mild symptoms (fever ≥ 3 days and normal measured vital signs) can be done with 3 initial examinations, namely CBC with differential, CRP, and serum electrolytes and kidney function.[32]

MIS-C has MAS-like features with the possibility that it may represent a Kawasaki disease-like post-infection process complicated by cytokine storms similar to MAS. $IFN\gamma$ plays a central role in both familial HLH that are also characterized by cytokine storms. CXCL9 and IL-18 were slightly elevated in patients with MIS-C, but significantly lower concentrations than in patients with MAS or secondary HLH. MIS-C has significantly higher concentrations of fibrinogen and lactate dehydrogenase, while triglyceride concentrations did not differ significantly. Cut off CXCL9 optimally to differentiate MIS-C from Kawasaki disease was determined to be 535 pg/mL with a sensitivity of 93% and a specificity of 100%. One patient with MIS-C had a bone marrow biopsy as part of their diagnostic evaluation. These patients had an increase in CXCL9 with biopsy results showing an increase in histiocytes and scattered hemophagocytosis. Previous studies have suggested that $IFN\gamma$, CXCL9, CXCL10, or combinations may be elevated in MIS-C. A 2021 report showed that a subset of patients with MIS-C showed significant upregulation of $IFN\gamma$ and CXCL10 compared to patients with Kawasaki disease. These findings highlight the role of changes in interferon response and immunity moved by Th1, which was well described in MAS and in the pathogenesis of MIS - C. In addition, that activation of $IFN\gamma$ can have the same key role in clinical

and biochemical dysfunction in MIS-C. Through stratifying patients with MIS-C based on high and low CXCL9 concentrations, it was found that the high CXCL9 group had multi-organ dysfunction, systemic inflammatory markers, and cytopenia. Meanwhile, the low CXCL9 group had a lower frequency of shock and myocardial dysfunction. The low CXCL9 of MIS-C group was more similar to the Kawasaki disease group, including the frequency of coronary involvement [39].

S100A8/A9 and S100A12 are alarmin proteins produced by myeloid cells that strengthen the innate immune response where overproduction of these proteins can cause apoptosis and organ damage. S100A8/A9 and S100A12 are diagnostic biomarkers and sensitive disease activity in various autoimmune and autoinflammatory diseases. MIS-C showed simple increases in S100 and IL-18 proteins, reflecting activation of innate immune effectors. This is in line with previous studies which showed increased IL-18 concentrations in patients with MIS-C, and increased regulation of the S100A8/A9 and S100A12 genes in neutrophils and monocytes in six patients with MIS-C. Although there was no significant difference between the concentrations of S100, IL-6, or IL-18 proteins, in patients with MIS-C had high concentrations of CXCL9 by having increased concentrations of several physiological markers of MAS, including ferritin, D - dimer, aspartate aminotransferase, alanine aminotransferase, triglycerides, and decreased platelet count. In addition, although MIS-C and Kawasaki diseases have similar elevations of S100 and IL-18. These disease entities can be distinguished by higher elevations of CXCL9 in patients with MIS-C.

CONCLUSION

PIMS/MIS-C is a new disease entity found in children after a few weeks of SARS-CoV-2 infection. MIS-C has a typical biomarker profile consisting of highly elevated inflammatory markers, such as CRP, IL-6, leukocyte count, ferritin, and LDH, along with anemia, hyponatremia and elevated NT-ProBNP are differentiating from the disease of other autoimmune. As for inflammatory markers which have been studied in the form of WBC, ALC, ANC, PLT, CRP, PCT, ferritin, D-dimer, LDH, fibrinogen, ESR, S100A8/A9, S100A12, and CXCL9. Therefore, the use of inflammatory biomarkers, especially CXCL9 (Gamma Interferon / MIG) is the marker that has the most potential as a diagnostic tool to distinguish MIS-C from other hyperinflammatory diseases because it shows high production of IFN-related chemokines in COVID-19 pediatric patients with MIS-C. Marker CXCL9 with ROC analysis of 0.96, 93% sensitivity, and 100% specificity also has the potential to identify the degree of severity of MIS-C in SARS-CoV-2.

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