Cardiac Manifestations of Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with SARS-CoV-2 Infection

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Abstract

Context: Multisystem inflammatory syndrome in children (MIS-C) is an emerging condition after the spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, termed COVID-19. This study aimed to describe the cardiac manifestations of children diagnosed with MIS-C.

Evidence Acquisition: This narrative review was conducted by searching the PubMed, Scopus, and Google Scholar databases to review MIS-C cardiac manifestations up to September 30, 2020. The demographic features, past medical history, clinical signs and symptoms, cardiac involvement, and the type of COVID-19 diagnosis confirmation were extracted.

Results: In many children, MIS-C seems to be a post-infectious complication of the COVID-19 infection. This syndrome affects multiple organs and has various clinical manifestations mimicking Kawasaki disease. Patients frequently present with persistent fever, kidney injury, gastrointestinal (GI) problems, neurologic symptoms, mucosal changes, conjunctivitis, and cardiac involvement. Children with MIS are more likely to present with hypotension, shock, and cardiac dysfunction, rather than coronary artery abnormalities and arrhythmia. Children with MIS need close observation; some need to be hospitalized, and a few may need a Pediatric Intensive Care Unit (PICU) admission. Treatment currently includes anticoagulants, IV immunoglobulin, and anti-inflammatory drugs.

Conclusions: As a novel syndrome associated with SARS-CoV-2 infection, MIS-C is potentially lethal. Cardiac manifestations, including coronary and myocardial involvement, are common and should be carefully identified. With prompt diagnosis and proper treatment, most children will survive, but the outcomes of the disease are unknown, so long-term follow-ups are required.

Keywords: Multisystem Inflammatory Syndrome in Children, COVID-19, SARS-CoV-2, Cardiac Involvement

1. Context

The SARS-CoV-2 infection, termed COVID-19, has spread very quickly and affected all ages, even newborns (1, 2). Initially, there was a misconception among the researchers believing that the virus does not affect children. However, it was then proposed that children are usually asymptomatic or present mild symptoms, but a complete immunity cannot be proposed for this age group (3). Since late April 2020, multiple studies from Europe and the United States showed that 2% - 6% of SARS-CoV-2-infected children exhibited a severe multi-system inflammatory syndrome with similarities to Kawasaki disease (4-6).

As there is no comprehensive testing, the true incidence of this severe condition in pediatrics has remained unclear. This significant hyper-inflammatory response can cause cardiovascular disorders, and some of these children may deteriorate faster and need admission to the Pediatric Intensive Care Unit (PICU) due to cardiogenic shock or acute left ventricular dysfunction (7). Apart from cardiac manifestations, various clinical symptoms have also been reported, including neurological, renal, significant gastrointestinal (GI), and mild respiratory symptoms, as well as rashes and stomatitis (8). Although it is still not fully understood whether this multisystem inflammatory syndrome in children (MIS-C) is a primary complication of COVID-19 infection or a post-infectious complication, a correlation is highly suggestive based on epidemiologic data (7).

There is little information about the cardiac involvement associated with COVID-19 in pediatric cases, and most of the studies on cardiac involvement are case reports or case series. It is also possible that children with an underlying cardiac disease are at a higher risk of experiencing
severe cardiac complications following the COVID-19 infection (9). Reports on MIS-C have shown coronary artery involvement, myocarditis, ventricular dysfunction, hemodynamic instability, and PICU admission, all of which suggest that cardiac dysfunction might be a notable risk factor for severe SARS-CoV-2 infection in pediatrics (10). Therefore, a literature review in this regard would be beneficial. This study aimed to review and summarize the available evidence on the potential cardiac clinical presentations in children with MIS to give a better perspective on management and care for these patients.

It should be noted that different terms have been used to refer to this novel condition, such as multisystem inflammatory syndrome in children (MIS-C), hyperinflammatory shock in children with COVID-19, "Coronasacki", "Kawashocky", Pediatric COVID-19-associated inflammatory disorder (PCAID), and pediatric multisystem inflammatory syndrome (PMIS) (7). In this review article, we continue to use the term MIS-C.

3. Definition of MIS-C

The three definitions of MIS-C, by the World Health Organization (WHO) (12), the Centers for disease control and prevention (CDC) (13), and the Royal College of Pediatrics and Child Health (RCPCH) (14), are presented in Table 1. The presence of fever, multisystem organ involvement without alternative plausible diagnoses, laboratory evidence of inflammation, and recent exposure to a COVID-19 case or evidence of COVID-19 infection are the key elements in all MIS-C cases. But, some signs, including fever duration and organ involvement, vary among these criteria.

4. Clinical Manifestation

The available information regarding the syndrome shows that the age of patients ranged from two months to 20 years, and the majority of cases were previously healthy (15, 16). Almost all affected children had a persistent fever for \( \geq 4 \) days and GI symptoms, including abdominal pain, diarrhea, and vomit. Other common clinical manifestations were mucocutaneous changes resembling Kawasaki disease (skin rash and conjunctivitis), extremity edema, lymphadenopathy, headache, mild respiratory distress, myalgia, fatigue, and cardiac symptoms (Table 2). Some patients presented with shock and hypotension requiring PICU admission (17, 18). The cardiac findings in MIS-C patients are divergent from Kawasaki disease’s manifestations. Children with this syndrome were more likely to present with hypotension, shock, and cardiac dysfunction, rather than coronary artery abnormalities (Figure 1) (19).

5. COVID-19 Infection

Epidemiological information indicates that SARS-CoV-2 is the possible cause of the syndrome, but the causality is unknown (1). Based on the studies mentioned in Table 2, the positivity percentage of the COVID-19 reverse-transcriptase protein chain reaction (RT-PCR) test varies from 0% to 100%. In most reports, it was positive in less than 50% of cases. On the other hand, the majority of the studies had evidence of positive immunoglobulin G (IgG) antibodies. These data suggest that a post-infectious disease is more likely to be responsible for this condition than an active infection (44).

6. Cardiac Involvement

6.1. Cardiac Dysfunction

In most cases diagnosed with MIS-C, left ventricular systolic dysfunction has been reported (Table 2). In the first
Fever

Elevated inflammatory factors (e.g., CRP, C-reactive protein, echocardiography; CXR, chest X-ray; ESR, erythrocyte sedimentation rate; GI, gastrointestinal; IL, interleukin; LDH, lactic acid dehydrogenase; MIS-C, multisystem inflammatory syndrome in children; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PT, prothrombin time; PTT, partial thromboplastin time; SARS-CoV-2 RT-PCR, reverse transcriptase-polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus.

Table 1. Case Definition of Multisystem Inflammatory Syndrome in Children

| WHO                        | CDC                                      | NHS-the Royal College of Pediatrics and Child Health |
|-----------------------------|------------------------------------------|-----------------------------------------------------|
| Age (years)                 | 0 - 19                                    | Children                                             |
| Fever                       | Fever ≥ 3 days                            | Subjective persistent fever ≥ 24 hours or documented fever > 38.0°C for ≥ 24 hours |
|                             |                                          | Persistent fever > 38.5°C                           |
| Clinical findings           | Mucocutaneous inflammation signs (e.g., stomatitis), bilateral non-purulent conjunctivitis or rash, shock or hypotension, ventricular dysfunction, valvulitis, pericarditis, or coronary involvement (including an increased level of NT-proBNP (troponin or echo findings), acute Gl manifestations, including abdominal pain, diarrhea, or vomiting |
|                             | Evidence of clinical deterioration requiring hospital admission, in addition to multiple (≥ 2) organ dysfunction (renal, dermatologic, cardiovascular, respiratory, GI, hematologic, or neurologic) |
|                             | Abnormal fibrinogen level, hypoalbuminemia, high D-dimer and ferritin amount Some: acute kidney injury, anemia, coagulopathy, thrombocytopenia, elevated IL-6, elevated IL-10, hypertransaminasemia, proteinuria, high troponin, increased creatine kinase level, elevated triglycerides, high LDH |
| Laboratory findings         | Elevated inflammatory factors (e.g., CRP, ESR, or procalcitonin) evidence of coagulopathy in laboratory data (PT, PTT, INR, and D-dimer) |
|                             | Elevated ESR, CRP, LDH, procalcitonin, fibrinogen, D-dimer, ferritin, IL-6, hypoalbuminemia neutrophilia; lymphocytopenia |
|                             | Abnormal fibrinogen level, hypoalbuminemia, high D-dimer and ferritin amount Some: acute kidney injury, anemia, coagulopathy, thrombocytopenia, elevated IL-6, elevated IL-10, hypertransaminasemia, proteinuria, high troponin, increased creatine kinase level, elevated triglycerides, high LDH |
| Evidence of COVID-19 infection | Positive for SARS-CoV-2 infection by serology, antigen test, or RT-PCR or exposure to patients with COVID-19 infection |
|                             | RT-PCR, or antigen test, or serology positive for COVID-19 or possible contact with COVID-19 patients within a month before the initiation of clinical features |
|                             | SARS-CoV-2 RT-PCR testing may be positive or negative |
| Exclusion of other microbial causes | Exclusion of any other infectious causes of inflammation, including toxic shock syndrome, bacterial sepsis, staphylococcal or streptococcal infections |
|                             | Exclusion of alternative plausible diagnoses |
|                             | Exclusion of any other microbial cause, including infectious myocarditis, bacterial sepsis, and staphylococcal/streptococcal toxic shock syndromes |
| Additional comments         | MIS-C must be considered in children with characteristics of toxic shock syndrome or typical or atypical Kawasaki disease |
|                             | Consider MIS-C in any pediatric death with evidence of COVID-19 infection. It should be considered in children with features of typical or atypical Kawasaki disease who meet the case definition for MIS-C |
|                             | Children may fulfill full or partial criteria for Kawasaki disease |

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6.2. Laboratory Findings

The elevated troponin and B-type natriuretic peptide (BNP)/pro-BNP levels have been reported in many patients with MIS-C. In most studies, the elevated BNP and troponin levels have been assessed as biomarkers to diagnose myocardial injury in the absence of cardiac magnetic resonance imaging (CMRI) or myocardial biopsies (15).

6.3. Coronary Involvement

Most reports have mentioned coronary involvement in 0-40% of cases (Table 2) (16, 21, 24, 26, 41). Mild coronary artery dilation with z-scores of 2 - 2.5 has been reported in most cases. However, large coronary artery aneurysm cases have also been mentioned. Some studies found the late development of coronary artery dilation, which necessitates an ongoing follow-up of MIS-C patients.

6.4. ECG Findings

Some case series reported rhythm abnormalities with variable severity in 4% - 58% of patients (Table 2) (18, 22). The most frequently reported arrhythmic manifestations were QTC prolongation, ST-segment changes, and premature atrial or ventricular beats, which all are non-specific. Whittaker et al. (18) reported first- and second-degree ativoventricular blocks, and two other studies mentioned atrial fibrillation (18, 33). Hemodynamic collapse and the need for extracorporeal membrane oxygenation (ECMO) support due to sustained dysrhythmias have also been reported in these patients (18, 24).

6.5. Management

This syndrome is a newly reported condition, and only a few studies have addressed it so far. Our knowledge about it is, therefore, limited, and the treatment of children with MIS has been based on the experts’ advice and the management of Kawasaki disease. Due to the similarity of the symptoms, the treatment method for adults with COVID-19 and other systemic inflammatory diseases can also be used in pediatrics. Management of these children requires a multidisciplinary care team comprising pediatric specialists in cardiology, infectious disease, critical care, and rheumatology.

Generally, the management is decided based on symptoms and their severity. Due to the potential shortage of drug supplies in a pandemic and considering side effects, pharmacotherapy is not recommended for non-hospitalized children. For children who present with mild symptoms, supportive care, including respiratory support and fluid resuscitation, is, therefore, recommended. However, children with hemodynamic instability and severe illness require PICU admission, mostly for inotropic support, which was reported in 20-100% of the cases (15-18, 20-22, 24-27, 30-35, 37, 38). Some of the PICU-admitted children required a veno-arterial (V-A) support (0% - 28%) (15, 17, 18, 20, 24, 30, 33).

Figure 1. Schematic representation of clinical signs of MIS-C patients (both CDC and WHO criteria are shown)
Various treatments have been suggested, but their effectiveness is still questionable. Furthermore, these treatments are based on experts’ opinions with no evidence to affirm them.

6.6. Cardiac Support

As mentioned above, a large proportion of children presenting with hemodynamic instability required acute resuscitation. Therefore, it is necessary to follow the pediatric resuscitation guidelines (51). Children suspicious of ventricular dysfunction and cardiogenic shock should receive smaller fluid blouses (e.g., 10 mg/kg), with an evaluation of the signs of fluid overload before each administration.

6.7. Immunomodulatory Therapy

The advantages of using immunomodulatory therapy in the treatment of Kawasaki disease, as well as other systemic inflammatory disorders, are well established (52, 53). An anti-inflammatory therapy, including intravenous immunoglobulins (IVIGs) and corticosteroids, was used in most patients, and a few cases also received an anti-inflammatory dosage of aspirin (15, 16, 18, 20-22, 24, 26, 31, 32, 34-38). It is critical to remember that the administration of IVIG in patients with cardiac dysfunction must be slower to reduce the risk of fluid overload. The dosage of corticosteroids is based on clinical judgment, but in more severe patients, using a low dosage is recommended.

The assessment of the pattern of cytokine storm in patients with MIS-C showed that an important component of this disorder is macrophage activation, as it is also observed in Kawasaki disease and other autoimmune disorders such as systemic lupus erythematosus (35, 54). Therefore, corticosteroids are another option in the treatment of MIS-C patients, as they can modulate this condition. However, corticosteroids may cause hypertension that can further exacerbate the underlying cardiac problem (45).

Two treatment protocols with corticosteroids have been proposed. The first method involves an intravenous injection of 0.8 mg/kg methylprednisolone, twice a day for 5 - 7 days or until achieving a normal CRP level and then continuing with oral treatment with 2 mg/kg/day for 2 - 3 weeks. The second protocol includes intravenous methylprednisolone 10 - 30 mg/kg/day for three days, followed by oral prednisone/prednisolone 2 mg/kg/day for four days or until achieving a normal CRP level and then tapering the treatment over 2 - 3 weeks. It is important to know that corticosteroids should not be administered in an active infection phase (1).

In some studies, cytokine blockers have been used as a supplemental therapy, for example, interleukin 1 receptor antagonist (e.g., anakinra), interleukin 6 (IL-6) inhibitors (e.g., tocilizumab), and tumor necrosis factor (TNF)-α inhibitors (e.g., infliximab) (16, 18, 20, 22-25, 27, 29-31, 34). These drugs can be prescribed for children who do not respond to routine treatments.

6.8. Antiplatelet Treatment and Anticoagulation

Hypercoagulable state, blood stasis due to immobilization, possible endothelial injury, and ventricular dysfunction are the proposed reasons for the increased risk of thrombotic complications. As a result, anticoagulant therapy should be considered based on coagulation tests and symptoms (55, 56).

6.9. Antiviral Therapy

The benefits of antiviral therapy, such as remdesivir, for children with this syndrome are still unknown (57, 58). The reports suggest that MIS-C is more likely a post-infectious complication in children rather than an active infection. Nonetheless, antiviral drugs could be considered in patients with a positive RT-PCR test, after consulting an infectious disease specialist.

7. Conclusions

In conclusion, children seem to proceed better with the novel coronavirus infection than adults. On the other hand, some children show signs and symptoms of MIS-C, which is a severe complication of the disease. Pediatricians should be aware of this syndrome and differentiate it from other differential diagnoses, including the Kawasaki disease. These children can quickly deteriorate and should closely be observed. The etiology of MIS-C is not yet fully understood, and treatment is mostly based on experts’ opinions. More studies are, therefore, required to define evidence-based management for this new syndrome, and our study played a part in this literature contribution.

Footnotes

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| Author          | Number of Cases | Age, y | Sex | Past Medical History                          | Ethnicity                  | Symptoms                                                                                                           | Cardiac Involvement | Ventricular Function | Arteritis/ECG Changes | Troponin | PostNP/NSP | HF-PCR | SARS-CoV-2 Test |
|-----------------|-----------------|--------|-----|-----------------------------------------------|----------------------------|-------------------------------------------------------------------------------------------------------------------|--------------------|----------------------|-----------------------|----------|------------|--------|-------------------|
| Belhadjer et al. | 16              | 1-16   |     | Previously healthy (13); asthmatic (2); overweight (BMI > 25) (5) | White (10); Black (1); Hispanic (1); Other (5) | Fever (3); cough (2); sore throat (5); decreased ventilation (3); conjunctivitis (3); rash (3); mouth sores (1); mental changes (1); nausea/vomiting (1); anxiety (2); tremors (1); dizziness (1) | Mild coronary dilatation (a score > 2.5) (4) (6); non-specific ST/T-wave abnormalities (9) | -                    | Elevated                  | Elevated                  | Elevated                  | Elevated                  | Elevated                  |                   |
| Toubiana et al.  | 21              | 4-17   | 9M, 12F |                                      | White (14); Black (3); Hispanic (1); Other (3) | Fever (21); cough (21); gastrointestinal symptoms (21); dilated coronary arteries (16); myocarditis (16); dysrhythmias (16); hypotension/shock (17); rhabdomyolysis (15); pericardial effusion (3); cervical lymphadenopathy (12); neurological features (16); rash (21); conjunctivitis (7) | Elevated                  | Elevated                  | Elevated                  | Elevated                  | Elevated                  |                   |
| Cheung et al.    | 17              | 2-16   | 8M, 4F | Mild asthma (3)                              | White (12); Black (1); Asian (1); Other (3) | Fever (5); cough (4); headache (1); rash (2); mouth sores (1); diarrhea (2); myalgia (5); cervical lymphadenopathy (2); neurological problems (6); limb changes (10); pericardial effusion (3); diffuse ST elevation or diffuse T-wave abnormalities (10) | Elevated                  | Elevated                  | Elevated                  | Elevated                  | Elevated                  | Elevated                  |                   |
| Whitaker et al.  | 30              | 6-14   | 8M, 22F | Congestive heart failure (7); dyspnea (1); rashes (2); rhabdomyolysis (1) | White (2); Black (1); Asian (1); Other (7) | Fever (5); cough (3); headache (1); rash (2); mouth sores (1); diarrhea (2); myalgia (5); cervical lymphadenopathy (2); neurological problems (6); limb changes (10); pericardial effusion (3); diffuse ST elevation or diffuse T-wave abnormalities (10) | Elevated                  | Elevated                  | Elevated                  | Elevated                  | Elevated                  | Elevated                  |                   |
| Dulingier et al. | 1               | 1-14   | M   | Child abuse                                 | Hispanic (1)                | Persistent fever; GI symptoms; subarachnoid hemorrhage | -                    | -                    | -                    | -                    | Positive                  | -                    | -                  |
| Feldstein et al. | 186             | 5-12   | 15M, 31F | Previously healthy (155); comorbidities (1); asthma (1); obesity (1); chronic obstructive pulmonary disease (1); chronic obstructive pulmonary disease (1); bronchitis (1); rashes (1); odynophagia (3); conjunctivitis (3); fatigue (2); rash (2); myalgia (1); cough (2) | White (156); Black (4); Hispanic (5) | Fever (15); cough (15); headache (5); rash (5); odynophagia (3); conjunctivitis (3); fatigue (2); rash (2); myalgia (1); cough (2); no coronary artery aneurysm (3); sputum (2); chest pain (1) | Anomalies (91) | Elevated                  | Elevated                  | Elevated                  | Elevated                  | Elevated                  | Elevated                  |                   |
| DeSant et al.    | 9/9             | 0-20   | 52M, 40F | Previous condition (19/19) | White (29); Black (3); Hispanic (15) | Persistent fever; GI symptoms; subarachnoid hemorrhage | -                    | -                    | -                    | -                    | Positive                  | -                    | -                  |
| Riphagen et al.  | 8               | 4-14   | 5M, 3F | Previously healthy (6); asthma (2); allergic rhinitis (1); atopic dermatitis (1); other (1) | Afro-Caribbean (8) | Fever (5); cough (5); rhinorrhea (15); headache (1); rash (1); myalgia (2); asthenia (1); fever (5); cough (5); rhinorrhea (15); headache (1); rash (1); myalgia (2); asthenia (1) | Elevated                  | Elevated                  | Elevated                  | Elevated                  | Elevated                  | Elevated                  |                   |
| Weisbuch et al.  | 4               | 5-15   | 1E, 3M | Previously healthy (2); hypothyroidism (1); asthma (1) | White (4) | Persistent fever; GI symptoms; subarachnoid hemorrhage | -                    | -                    | -                    | -                    | IgG positive (1) | -                    | -                  |

Table 2. Demographics, Clinical Manifestations, and Cardiac Involvement in Reports of Children WITH Multisystem Inflammatory Syndrome
| Authors | Year | Gender | Race | Age Range | Initial Symptoms | Findings | Antibody Status | Cardiac Abnormalities | Other Findings |
|---------|------|--------|------|------------|-----------------|----------|----------------|---------------------|--------------|
| Licciardi et al. (2) | 2021 | 10 M, 6 F | Caucasian, mixed race | 3 - 12 | Persistent fever, GI symptoms | Coronary dilation (3), myocarditis (7), LVEF 35% - Elevated (11) | Elevated (11) | 11 cases were IgG+ (7/8) |
| Borocco et al. (16) | 2021 | 5 - 12 M, 8 F | Previously healthy (10); Persistent fever, GI symptoms | Coronary dilation (3) | Myocarditis (7); LVEF 35% - Elevated (11) | Elevated (11) | - |
| Jones et al. (1) | 2021 | 1 F | Latino or Hispanic | - | Persistent fever, respiratory symptoms | Conjunctivitis (1); Pericarditis (4) | Positive cervical lymphadenopathy |
| Balasubramanian et al. (29) | 2021 | 5 - 16 M, 2 F | None; Persistent fever, GI symptoms, asthmatic (2); overweight (4); asthma (2); overweight (4); asthma (2); overweight (0.6 kg/m²); | Peripheral edema; conjunctivitis; hypotension; peripheral edema | Rash; Irritability; Respiratory distress; Mucosal changes; Conjunctivitis; Hypotension; Pericarditis (4); Coronary artery (z-score 3.15) (1); Proximal coronary artery (z-score 2.6) (1); Prominent coronary artery (z-score 3.1) (1); Moderate LV dysfunction; reduced LV fractional shortening (8) LVEF < 50% (21); LVEF < 30% (4) | Elevated Positive - Positive | Positive | Positive |
| Wolfler et al. (16) | 2021 | 5 - 12 M, 8 F | None; Persistent fever, GI symptoms | Coronary dilation (3) | Myocarditis (7); LVEF 35% - Elevated (11); Elevated (11) | Elevated (11) | Two cases were IgG+ (8) |
| Ghodsi A et al. (30) | 2021 | 5 - 12 M, 8 F | None; Persistent fever, GI symptoms, asthmatic (2); overweight (4); asthma (2); overweight (4); asthma (2); overweight (0.6 kg/m²); | Peripheral edema; conjunctivitis; hypotension; peripheral edema | Rash; Irritability; Respiratory distress; Mucosal changes; Conjunctivitis; Hypotension; Pericarditis (4); Coronary artery (z-score 3.15) (1); Proximal coronary artery (z-score 2.6) (1); Prominent coronary artery (z-score 3.1) (1); Moderate LV dysfunction; reduced LV fractional shortening (8) LVEF < 50% (21); LVEF < 30% (4) | Elevated Positive - Positive | Positive | Positive |
| Greene et al. (31) | 2021 | 11 F | None | Persistent fever, rash, GI symptoms | Rash; GI symptoms; hypotension; peripheral edema | Elevated | Positive | Positive |
| Rauf et al. (1) | 2021 | 15 - 16 M, 5 F | None; Persistent fever, rash, GI symptoms, asthmatic (2); overweight (4); asthma (2); overweight (4); asthma (2); overweight (0.6 kg/m²); | Peripheral edema; conjunctivitis; hypotension; peripheral edema | Rash; Irritability; Respiratory distress; Mucosal changes; Conjunctivitis; Hypotension; Pericarditis (4); Coronary artery (z-score 3.15) (1); Proximal coronary artery (z-score 2.6) (1); Prominent coronary artery (z-score 3.1) (1); Moderate LV dysfunction; reduced LV fractional shortening (8) LVEF < 50% (21); LVEF < 30% (4) | Elevated Positive - Positive | Positive | Positive |
| Deza Leon et al. (32) | 2021 | 6 F | None | Persistent fever, rash, GI symptoms | Rash; GI symptoms; hypotension; peripheral edema | Elevated | Positive | Positive |
| Chiotos et al. (34) | 2021 | 6 M, 3 F | None | Persistent fever, rash, GI symptoms | Rash; GI symptoms; hypotension; peripheral edema | Elevated | Positive | Positive |
| Blondiaux et al. (33) | 2021 | 6 M, 3 F | None | Persistent fever, rash, GI symptoms | Rash; GI symptoms; hypotension; peripheral edema | Elevated | Positive | Positive |

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| Authors               | n | Age | Sex | Race       | Symptoms                                                                 | Enzyme Activity | Echocardiographic Findings                                                                 | Other Lab Findings             | Other Findings |
|----------------------|---|-----|-----|------------|---------------------------------------------------------------------------|-----------------|--------------------------------------------------------------------------------------------|-------------------------------|----------------|
| Rivera-Figueroa et al. (13) | | 20 | 10 M, 10 F | African-American | Persistent fever, multi-organ failure, shock, conjunctivitis, peripheral edema, mucosal changes | No              | Elevated                                                                                  | Normal                        | -              |
| Grimaud et al. (38)   | | 20 | 3-15 | None      | Fever, abdominal pain, diarrhoea, conjunctivitis, lymphadenopathy, fatigue | No              | Elevated                                                                                  | Elevated                     | No cases were positive |
| Raymond et al. (54)   | | 1 | F | None      | Gastroenteritis, abdominal pain, rash, conjunctivitis, edema of hands and feet | No              | Elevated                                                                                  | Positive                      | -              |
| Jain et al. (138)     | | 1 | M | -          | Fever, tachycardia, diarrhea, abdominal pain, rash, conjunctivitis, lymphadenopathy | No              | Elevated                                                                                  | Normal                        | -              |
| Heidemann et al. (41) | | 5-7 | 2 M, 1 F | -          | Fever, conjunctivitis, dry and cracked lips, rash, abdominal pain, conjunctivitis | Dilation of the proximal left ventricle, decreased coronary artery size, left ventricular hypertrophy | Normal                        | Positive (1) |
| Alnashri et al. (41)  | | 16 | M | -          | Fever, diarrhea, vomiting, generalized abdominal pain, abdominal pain, conjunctivitis | No              | Hypokinesia of inferior wall with an ejection fraction of 45%                     | Elevated                     | -              |
| Torres et al. (42)    | | 27 | 14 M, 13 F | -          | Fever, abdominal pain, diarrhea, conjunctivitis, lymphadenopathy, fatigue | No              | Myocardial dysfunction detected           | 4.96                         | -              |
| Dolhnikoff et al. (43) | | 1 | F | None      | African-American | Fever, rash, conjunctivitis, lymphatic edema, fatigue | No              | Diffuse lymphopenia with lymphoid hyperplasia and perivascular inflammation | Positive                      | -              |

Abbreviations: AV, atrio-ventricular; BiV, biventricular; ECMO, extracorporeal membrane oxygenation; ECG, electrocardiograms; F, female; GI, gastrointestinal; IQR, interquartile range; LVEF, left ventricular ejection fraction; RV, right ventricle; SD, standard deviation; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VT, ventricular tachycardia.