Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Clinical aspects and presumed etiology of multisystem inflammatory syndrome in children (MIS-C): A review

Anusrita Kundu, Swagata Maji, Suchismita Kumar, Shreya Bhattacharya, Pallab Chakraborty, Joy Sarkar

Keywords: MIS-C, Pediatric patient, SARS-CoV-2, Kawasaki disease, Multiorgan failure, Macrophage and antibody-dependent enhancement (ADE)

1. Introduction

The COVID-19 pandemic generated by Severe acute respiratory syndrome coronavirus 2 has swiftly expanded globally with about 18 million confirmed reports by August 2020, after a multitude of pneumonia occurrences resulting from unexplained causes was formerly detected in Wuhan (China) in December 2019. Children generally account for a tiny percentage of COVID-19 instances. However, there is confusion regarding the real disease risk of adolescents and children, due to asymptomatic illness, inadequate examination of diagnostically quiet or moderate cases, or doubts about the accuracy of existing testing protocols. In children, COVID-19 hospitalization was uncommon, contributing to only 0.1% of all fatalities. But between April 2020, and July 2020, there has been an upsurge in the incidence of a Kawasaki-like disease in youngsters by 30 times. Pediatricians in the United Kingdom initially declared a group of children having fever, cardiovascular shock, and hyper inflammation in April 2020, with symptoms that were identical to those of Kawasaki Disease, cytokine storm, or toxic shock syndrome on the grounds of clinical studies recorded from United States, United Kingdom, Italy, Switzerland, and France. The ailment was named “pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2” by the Royal College of Pediatrics & Child Health. Next, the Centers for Disease Control and Prevention in the United States and the World Health Organization issued their separate case definitions for the ailment, renaming it as a multisystem inflammatory syndrome in children. Scientists have named it profusely like “Kawashocky”, “Coronasacki”, “hyperinflammatory shock in children with COVID-19”, “pediatric COVID-19”, “Pediatric COVID-19 Associated Inflammatory Disorder” and many more because it’s a novel illness. Reports have been identified where, 15 children, 2–15 years old in the...
2. Patient demographics

The demographic analysis deals with the assessment of the population, based on variables such as age, race, and sex. Several studies under the present body of knowledge and close monitoring of MIS-C patients have led to a subjective result of the appearance of this syndrome in children.

- Patients with MIS-C had a median age of 9 years. Between the ages of 5 and 13, half of the children with MIS-C were diagnosed. In other studies, the range of age is from 7 months to 20 years, with the highest proportion occurring in youths under the age of 21. It remains evident whether it is a post-sepsis or delayed infectious consequence or is chiefly connected with SARS-CoV-2 infection, although the recent epidemiologic accounts are extremely provocative of a relationship.

- Early findings showed males may be highly represented, same as KD. MIS-C has yet to demonstrate a definite gender preference, but only a small male preponderance is found in six investigations. Sixty percent of reported patients were male, according to instances reported to the CDC on or before June 28, 2021.

- Many studies have found that MIS-C has a significant impact on African American, African/Afro-Caribbean, and Hispanic youngsters. African/Afro-Caribbean children constituted the largest fraction of the cases in European research with relevant race/ethnicity data, ranging from 38% to 62% of MIS-C patients. The African American and Hispanic were around 18–40% and 24–45% respectively among the MIS-C affected children, in one of the U.S. reports. And, till June 2020, 62% of all cases confirmed to the CDC consisted of Hispanic or Latino (1246 cases) or Black, Non-Hispanic (1175 cases).

- Cases recorded at CDC till June 2020 show that 99% of MIS-C sufferers tested positive for SARS-CoV-2, the rest 1% of patients might have gotten into touch with a COVID-19 infected patient. 3

- Out of 29 patients in a finding, SARS-CoV-2 Polymerase Chain Reaction tests yielded positive results in 10 cases, while SARS-CoV-2 Real Time-Polymerase Chain Reaction test result, 45% were solely SARS-CoV-2 antibody positive, 31% were positive for both, and an antibody test was not conducted in 19% of the cases. 4

- In these children, the initial COVID-19 infection is nearly often moderate or asymptomatic. 5

- Feldstein et al. spotted that 73% of MIS-C affected patients were priory healthy in case reports of 186 individuals. A vast majority of studies found almost no comorbidities. Obesity and a history of asthma have been the most frequent comorbidities in individuals who did possess past medical issues across studies, with autoimmune illness, long-term lung ailment, diabetes, cancer, congenital heart disease, and neurological disorders as fundamental detections.

2.1. Case definition of MIS-C

The WHO has published the case-definition MIS-C, where the following six criteria are to be fulfilled.

1. Age 0–19 years
2. Fever for ≥3 days
3. The clinical indication of the involvement of multiple organ systems (At least 2 of the mentioned manifestations)
   i. Erythema, bilateral non-purulent conjunctivitis, or mucocutaneous or dermatological inflammation signs on mouth, hands, or feet.
   ii. Hypotension or shock
   iii. Cardiac disability, pericardial inflammation, coronary anomalies, or valvulitis (including echocardiographic findings or elevated troponin/brain natriuretic peptide)
   iv. Presence of coagulopathy (prolonged prothrombin time; amplified D-dimer)
   v. Acute gastrointestinal symptoms (diarrhea, vomiting, or abdominal pain)
4. Inflammation markers that are elevated (namely, erythrocyte sedimentation rate, C-reactive protein, or procalcitonin).
5. Other microbiological causes of inflammation, like bacterial sepsis and staphylococcal/streptococcal toxic shock syndromes are not identified.
6. Reports testing positive for present or past SARS-CoV-2 pathogenesis by RT-PCR, antibody, or antigen test; or interaction with a person infected with COVID-19.

3. Clinical manifestation

Knowledge revolving around the clinical condition of MIS-C patients is unfolding day by day. As a significant percentage of SARS-CoV-2 infections has escaped diagnosis, the overall population of children residing in the danger for MIS-C is unclear, owing to the possibility of asymptomatic or pauciymptoms.

3.1. Cardiovascular symptoms and image finding

Patients initially felt chest pain, with an average delay of 6 days between the onset of clinical symptoms and the onset of heart failure symptoms. They experienced cardiogenic shock upon their entry to the pediatric intensive care unit and were provided with inotropic support. All of the investigations found cardiac abnormalities using echocardiography or electrocardiography, highlighting the appearance of myocardial dysfunction. Echocardiography revealed depressed systolic function, with left ventricular ejection fraction of <55% (moderate dysfunction) and sometimes <30% (severe dysfunction), peri-carditis (pericardial effusion) and myocarditis, atrioventricular valve regurgitation, cardiac dysrhythmia, coronary dilation, or aneurysms with a medial z score range of 2.0–2.8 indicating small aneurysm and rarely giant aneurysm were reported.

In adolescents with vasodilatory shock, cardiac magnetic resonance imaging (MRI) revealed signs of myocardial edema, necessitating fluid resuscitation. Cardiac involvement is an extensive factor to differentiate MIS-C from COVID-19.

3.2. Respiratory symptoms and image findings

Though COVID-19-like respiratory complaints are not often
associated with MIS-C, difficulties in breathing like tachypnoea, cough, hypoxia, have been disclosed so far. Chest radiographs showed pulmonary edema, basilar opacities suggestive of atelectasis, either dependent or coercive as a consequence of pleural effusion, pneumothorax, pulmonary hemorrhage, and bronchospasm, requiring the utility of bronchodilators continuously. Critical pulmonary infection, such as acute respiratory distress syndrome, was uncommon in children who needed supplemented oxygen or a ventilator for breathing support.

3.3. Neurological symptoms and image findings

The youngsters have been observed with various neurologic issues. Headaches, hearing & visual problems, amnesia, meningitis, irritability, apathy, and lassitude are some of the symptoms. Encephalopathy, stroke or abrupt intracranial hemorrhage, uveitis, coma, seizures, demyelinating disease, aseptic meningoencephalitis (strengthening proinflammatory Central nervous system feedback),\textsuperscript{31} and brain death were among the profound neurologic findings seen in specific cases. Rare instances reported ischemic brain infarction, acute cerebral edema, and Guillain-Barre syndrome.\textsuperscript{4,6,10,11,21,27,29,31,32}

3.4. Gastrointestinal symptoms and image finding

Gastrointestinal involvement was usually the most apparent attribute of MIS-C, reported in maximum patients often resembling abdominal infections.\textsuperscript{4,11,12} Abdominal cramps, diarrhoea, and vomiting were among the prominent symptoms.\textsuperscript{4,11,12,14,27,29} Abdominal ultrasonography and computed tomography of the abdomen and pelvis disclosed grave results like appendicitis, gall bladder hydrops, ascites, mesenteric adenopathy, pleural effusions, enterocolitis, in certain cases terminal ileitis and colitis, all leading to hypovolemia. The pancreatic images reported pancreatomegaly, and those of the liver reported hepatomegaly, and biliary sludge, while increased renal echogenicity, lead to acute kidney failure.\textsuperscript{4,9,10,21,29,32}

3.5. Mucocutaneous and dermatological symptoms

The mucocutaneous results were heterogeneous. Morbilliform, urticarial, scarlatiniform, and reticulated forms were among the morphologic features of exanthemas.\textsuperscript{26} The area of the skin affected also differed where certain individuals were with restricted acrofacial inclusion while others harbored more extensive outbreaks.\textsuperscript{26} Some studies have also revealed a strong age bias in the advent of symptoms.\textsuperscript{26} The prevailing cutaneous records were conjunctivitis, hyperemia, periorbital swelling and erythema, and strawberry tongue. A few dermatological findings were whereas malar rashes, facial edema, palmar erythema, lip cracks, and lip hyperemia causing redness and swelling.\textsuperscript{4,10,11,21,26,29,32} In a special case, a skin biopsy presented lymphocytic infiltrate as the root of skin lesion.\textsuperscript{26}

3.6. Hematological findings

MIS-C patients were found with several thrombotic events where activation of coagulation lead to deep vein thrombosis, intracardiac thrombosis, cerebral venous sinus thrombosis, subarachnoid hemorrhage bringing about ischemic brain death.\textsuperscript{10,13,20,27,31} A prothrombotic coagulopathy may be enhanced by MIS-C’s hyperinflammatory
condition in conjunction with COVID-19 triggering pulmonary embolism. Additional hematologic abnormalities comprise lymphopenia, neutrophilia, haematolysis, hypoxemia, ischemia, anaemia, pancytopenia, and hemolytic uremic syndrome.

3.7. Lymphatic findings

Swollen lymph node often called adenopathy has been noted as a common sign of inflammation in MIS-C-affected children encompassing distinct organs like mesenteric lymphadenitis and mediastinal and hilar lymphadenopathy which have been observed through thoracic imaging.

3.8. Laboratory findings

The common feature found in every MIS-C patient is an extremely elevated level of inflammatory and cardiac indicators. Inflammatory indicators like C-reactive protein, Serum interleukin-6, Ferritin, Procalcitonin are significantly raised. The elevated values of CRP, Ferritin and Procalcitonin vary as 11.98–27.62 mg/dL, 370.7–1032.5 mg/mL and 8.41–31.96 mg/mL, respectively. The values of cardiac indicators like Troponin I and Brain natriuretic peptide vary as 0.03–2.17 mg/mL, 229.5–1778.5 pg/mL, respectively. Another characteristic feature of MIS-C is raised levels of D-dimer, Fibrinogen, Factor VIII. The value varies as 2.42–3.79 μg/mL for D-dimer and 468.5–629 mg/mL for Fibrinogen. The low percentage of Antithrombin III causes several types of thrombosis in patients. Cytokines like Tumour necrosis factor, Interleukin-6, IL-1β are synthesized in excess amounts, which upregulate the inflammatory reaction. MIS-C patients show abnormal Liver function test results having elevated Alanine transaminase and Aspartate transaminase. The values of ALT and AST vary as 27.73–73.6 U/L and 36.25–56.75 U/L, respectively. MIS-C patients show a comparatively lower value of Lactate dehydrogenase enzyme than patients having severe COVID-19. A higher Erythrocyte sedimentation rate value is also very common in MIS-C patients. ESR value varies as 38–58 mm/hr. Low blood Sodium and Albumin and high Creatinine value are revealed by laboratory examination in MIS-C patients. According to a recent study, severe COVID-19 instances have a greater neutrophil to lymphocyte ratio.

4. Comparing MIS-C with other associated diseases

Following the past COVID-19 infection, new publications have revealed that MIS-C possesses symptoms of an array of different disorders namely KD that had originated in Japan in 1967, Toxic Shock Syndrome that had originated in 1978, Secondary Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome, and Severe COVID-19 (Table 1).

5. A plausible course of patient management

There exist no definitive therapeutic guidelines for the treatment of MIS-C at this time, but few current administration and therapy options are available. Most of these treatment strategies have yielded a positive result. Intravenous immunoglobulin and corticosteroids have been proven to be effective in various studies as a remedy for inflammation, leading to a quick recovery. Use of IVIG similar to normal KD therapy and corticosteroids has been encountered in MIS-C patients. Patients with a low index of suspicion present with some but not all of the MIS-C symptoms should be examined for inflammatory screening, including a complete blood count and CRP, along with SARS-CoV-2 PCR and antibody testing.

5.1. Hospital treatment

Empiric antibiotic coverage is prescribed in children, who have been assessed for having MIS-C and have been admitted to the hospital, with initial broad-spectrum antibiotics, since symptoms overlap with severe bacterial infections. Ceftriaxone is generally suggested if they are sick to a moderate extent. In cases of severe illness or shock, vancomycin, clindamycin, and cefepime, or vancomycin, meropenem, and gentamicin are recommended. If redeem (an antiviral drug with activity against SARS-CoV-2 approved for compassionate use in young children and restricted clinical trials) is available, it must be evaluated, especially for individuals who have been PCR positive and/or have a characteristic COVID-19 presentation.

For children, the current recommended dose is 5 mg/kg IV once (max dose 200 mg) on day 1, then 2.5 mg/kg IV daily for nine days (max dose 100 mg). In case of all children exhibiting KD-like illness and evidence of significant inflammation (CRP >30 g/dL, ferritin >700 ng/mL), cardiac involvement, or multi-fold organ failure, 20–25 mg/kg/dose every 6 h (80–100 mg/kg/day) of aspirin is advised as a medication. However, individual health centers may use different amounts of aspirin. When a patient has been afebrile for 24 h or more, the aspirin dose typically reduces to 3–5 mg/kg as a single daily dose, which will be continued after discharge. Anakinra is prescribed at a dose of 2–6 mg/kg/day IV/SQ, with the period of treatment determined with the help of a pediatric rheumatologist or immunologist.

A major percentage of patients got intravenous steroids, Infliximab, and IL-6 inhibitors (Tocilizumab or Siltuximab) as anti-inflammatory therapy. Owing to the involvement of TNF-α in MIS-C, anti-TNF-α medication is useful for the control of auto-inflammatory disorders in which many cytokines are high, implying that anti-TNF-α therapy may stop a cytokine cascade on its own.

5.2. ICU treatment

A significant percentage of MIS-C patients are referred to the ICU, frequently requiring respiratory and cardiac assistance. Several studies indicated that about 44–100% of the children were sent to the ICU. A major proportion of children also required routine ventilation. Mild to medium doses of vasoactive medicines, like vasopressors and inotropes, were regularly administered to MIS-C ICU patients due to shock-induced myocardial dysfunction (e.g., acute myocarditis) and/or intense vasoplegia.

5.3. Discharge norms

Studies have revealed several guidelines that are to be taken care of before patients are discharged off. Some of them include two days without fever, two days out of vasopressors and supplemented oxygen, two to four days of declining inflammatory markers like ferritin, D-dimer, CRP, lowers levels of troponin, standard Electrocardiogram (the German spelling- Elektrokardiogramm) with stable blood pressure. Patients released from the emergency unit must receive particular discharge manuals including a follow-up clinic or telemedicine consultation within 72 h. A repetition of the laboratory tests must be conducted within one week. The interval between the initial echocardiography and the cardiology follow-up should be at least two weeks.

6. Case study

COVID-19 instances (after COVID as well as current COVID) linked to MIS-C have been discovered all over the world. Some of the occurrences from various nations have been summarised in Table 2 and Table 3 simultaneously.
Table 1
Comparison between multisystem inflammatory syndrome in children (MIS-C), Kawasaki disease (KD), toxic shock syndrome (TSS), secondary hemophagocytic lymphohistiocytosis/macrophage activation syndrome (SHLH/MAS), and severe COVID-19.

| Sl. No. | Characters | Multisystem inflammatory syndrome in children (MIS-C) | Other diseases associated with MIS-C | Secondary Hemophagocytic lymphohistiocytosis/ Macrophage activation syndrome (SHLH/MAS) | Severe COVID-19 in children without MIS-C | Severe COVID-19 in adults | References |
|---------|------------|-------------------------------------------------------|------------------------------------|--------------------------------------------------------------------------------|------------------------------------------|--------------------------------|------------|
| 1.      | Age of affected persons | Children of age range 8–10 are mostly affected. | Usually in youngsters of less than five years of age. | Mostly found in adults. | Adolescents are most commonly affected. | Death rates are increasing as people get older. | 5,4,10,11,29,37 |
| 2.      | Differences in gender | Males are mostly affected. | Females are mostly affected. | Occurs in males as well as females | There is no such differentiation. Both the genders are affected equally. | Males are mostly affected. | 11,37 |
| 3.      | Affected Ethnicity | Hispanic/Latino/African American | East Asian | No ethnic variation known | No difference | No difference | 4,10,11,29,37 |
| 4.      | Symptoms | A. Hypotension | May be present or absent. | Generally present | Generally present | Generally present | May be present or absent. | 4,11,29 |
|         | B. Rash | Generally absent | Generally present | Almost always present | Bleeding from the skin is noted in some cases. | Present | Present | 2,4,38 |
|         | C. Fever | Present | Present | General present | May be present or absent. | Present | Present | 4,10,11,29,37,39 |
|         | D. Vomiting, Diarrhoea, or abdominal pain | Present | Rare | General present | Generally present | Generally present | Present | Present | 11,37 |
|         | E. Respiratory distress | Generally present | Rare | Almost always present | Generally present | Generally present | Generally present | 11,38 |
|         | F. Mucous Membrane Involvement | May be present or absent. | Generally present | May be present or absent. | Noted in some cases | Generally present | Generally present | 11,38 |
| 5.      | Underlying etiology | Assumed to be a post-infectious syndrome; the SARS-CoV-2 antibody test is frequently positive; in seronegative individuals, there is generally a history of exposure to a covid-19 positive individual. | No identifiable cause. | An infection caused by streptococcus or staphylococcus is a regular occurrence. | T-cells and macrophages possess hemophagocytic activity to expand and become highly activated. | There may be underlying comorbidity; SARS-CoV-2 RT-PCR is frequently positive; Extreme sickness is frequently caused by pre-existing comorbidity. | 4,20,37,404 |
| 6.      | T Cells | Lymphopenia | Involvement of cytotoxic T cells | Lymphopenia | Activation and proliferation of CD8⁺ T cells and NK cells, including secretion of IFNγ | Usually, unaltered | Lymphopenia in severe disease | 37,60 |
| 7.      | Comorbidity as risk factors | Immune deficiency states may be present. | Rarely observed when it comes to original immunodeficiency and occasionally in case of acquired immunodeficiency. | Normally, nothing noteworthy | The cytokine storm plays a role in coronavirus infection. COVID-19-associated pneumonia. Some people have minimal or mild lung manifestations, with others having severe pulmonary dysfunction. | Comorbidity like malignancy, chronic lung disease and neurological disorder is linked to a more severe form of the disease. | Comorbidity like hypertension, diabetes mellitus, chronic heart disease is linked to a more severe form of the disease. | 37,40,41 |

(continued on next page)
7. The most feasible mechanism of the build-out of MIS-C

Pediatric patients distressed with MIS-C exhibit large amounts of SARS-CoV-2 antibodies in their serum but test negative for the virus through RT-PCR, indicating that certified reports of COVID-19 are relatively few in children or they might have had a prior infection.1,3 The feedback from antibodies in children was unique from those of the adults stating that the induction of adaptive immune reaction to SARS-CoV-2 virus in the former corresponds with the onset of inflammatory symptoms and is not influenced by viral attack.1

The cellular damage thus instigates the surrounding macrophages to generate chemokines and cytokines3,41,75 which contribute to the reduced prevalence and extremity of COVID-19 related inflammation in pediatric patients.3,41,54,55,60,66 Thereupon, adrenarche is an essential milestone that describes the reason for the greater vulnerability of children 10–12 years or above, to MIS-C, signifying that those children have entered the adrenarche stage that enhances androgen output. This age-dependent revelation of ACE2 and TMPRSS2 eases viral entry in adolescents causing pronounced pathogenesis and MIS-C symptoms, while curbing viral access in pre-adolescents minimizing their symptoms.3,41,54,55,60,66

Moreover, the higher concentration of serum antibodies in pediatric patients portrays the possible operation of antibody-dependent enhancement mechanism in provoking MIS-C, which is more certain to arise as an outcome of acquired immune response and not due to enhanced multiplication of virus.1,2,69 Certain viral disorders, like dengue and Zika virus infections, have well-documented ADE pathways.69 Reports on MIS-C patients producing neutralizing2 and non-neutralizing (binding) antibodies’ as feedback to the spike protein of SARS-CoV-2 have been obtained. Neutralizing antibodies confers sterilizing immunity by negating the pathogenic effect of the virus while the non-neutralizing one attaches to the virus but doesn’t possess the potential to nullify its virulence.2,41,70,71 It is thought that when children are first exposed to the SARS-CoV-2 virus, their immune system produces both of these antibodies. Later on, the youngsters overridden with neutralizing antibodies are likely to suffer from asymptomatic sickness but, virus attack and critical multisystem inflammation are boosted in them with prevalent binding antibodies via ADE.3 Non-neutralizing antibodies or inadequate quantities of neutralizing antibodies bound to the epitopes of SARS-CoV-2, in the patient’s blood, promote its intake inside the host tissue which is described as ADE. This machinery is un-associated with the ACE2 pathway and involves uniting of the complex virus epitope and virus-specific non-neutralizing antibody by dint of the Fc domain of immunoglobulin to the immune cell’s membrane harboring IgG Fc receptor (F,R).3,70 This interaction activates macrophages, natural killer cells, lymphocytes, and monocytes causing cellular endocytosis.3,41 (Fig. 2B). Endocytic Toll-like receptors such as TLR3, TLR7 detect the viral RNA and thus make the macrophages operational, inducing a surge of pro-inflammatory cytokines like TNF-α, IL-6, IL-1β occasionally by the NF-κB route.3,41,71–73 This originates a cytokine storm mimicking the provocation of macrophages as seen in hemophagocytic lymphohistiocytosis.3,41 CD68+, CD169+ macrophages aid in viral dispersion and induce pyroptosis via inflammation41,70 (Fig. 2A). Pyroptosis indicates cell death linked to the NLR family pyrin domain containing 3 inflammasome activation systems. The cellular damage thus instigates the surrounding macrophages to generate chemokines and cytokines3 furthermore indicators of inflammation can also help macrophages to engage T-cells in the infection area.41,72,76,77 Elevated levels of IL-1β in blood serum evince the occurrence of pyroptosis.77 A probable role of non-specific antibodies has been put forward that justifies the genesis of MIS-C through ADE, in seropositive patients where non-specific antibodies unite with the virus aiding its intake by the immune cells. Gruber et al. (2020)78 have also studied the role of auto-antibodies found against endothelial and gastrointestinal cells in MIS-C patients, which fails to distinguish

| SL No. | Characters Multisystem inflammatory syndrome in children (MIS-C) | Kawasaki disease (KD) | Toxic Shock Syndrome (TSS) | Secondary Hemophagocytic lymphohistiocytosis/ Macrophage activation syndrome (SILH/MAS) | Severe COVID-19 in children without MIS-C | Severe COVID-19 in adults |
|--------|---------------------------------------------------------------|------------------------|-----------------------------|---------------------------------------------------------------|------------------------------------------|---------------------------|
| 8.     | Predominant manifestation                                    | Gastrointestinal signs (abdominal discomfort, diarrhea) are common, with more than 80% of patients experiencing them. | Symptoms of the gastrointestinal tract are rarely noticeable. | Rash, hypotension. | Unrelenting fevers, cytopenia, splenomegaly, hepatitis, coagulopathy, lymphadenitis, and hepatosplenomegaly multisystem organ failure, and death in its most severe form. | Cough, respiratory distress may be present, gastrointestinal symptoms are less common. | Cough, respiratory distress is common. |
| 9.     | Management                                                   | IVIG; steroids; IL-6 inhibitors; IL-1 impedes. | Antibiotics, IVIG | Involvement of particular cytokines in this phenomenon, especially TNF-α, IL-6, and IL-1β | Antibiotics, antiviral medication, steroids, IVIG, IL-6 inhibitors | HCQs; steroids; IL-6 inhibitors, plasma in remission; antiviral therapies. |

References: 1, 3, 54, 55, 58, 61, 62
between self and non-self cells, ultimately attacking a patient’s native tissues.\(^7,8\) Thus, it can be inferred that localized inflammation and the build-up of pathogenic macrophage congregations in body tissues are two especially common factors that cause MIS-C syndrome and more analysis is needed to illustrate the role of macrophages further.\(^3\)}
| Study | Region          | Schedule of patient admission | Description of patients (number, age/interquartile range [IQR]) | Number of Patients detected positive | Symptoms and Image findings | Laboratory findings | Similarities with | Treatment | Reference |
|-------|----------------|-------------------------------|--------------------------------------------------------------|--------------------------------------|-------------------------------|---------------------|-------------------|-----------|-----------|
| Trevor K. Young et al. (2020) | New York | April 1 to July 14, 2020 | A cohort of a patient (total = 56) IQR = 0.7–17 years | PCR: 10/56 IgG Tests: 19/56 Mucocutaneous findings: 27/56 | Fever for 1–2 days, mild cough. Major mucocutaneous findings (in 21) included strawberry tongue (in 8), lip crack (in 13), conjunctivitis (in 21), erythematous hands and feets (in 13), cheek (in 6) and orbit of the eye (in 7). Eruptions of several types, i.e., mobiliform (in 3), reticulate (in 3), scarlatiniform (in 5) and urtecarial (in 5). Gastrointestinal and cardiac trouble. | D-dimer, BNP, and troponin levels were all enhanced. | KD | Injectable immunoglobulin, corticosteroids, Aspirin, Remdesivir, Anakinra. |
| Blumfield et al. (2020) | New York | April 21–May 22, 2020 | A cohort of patients (total = 16) IQR = 20 months to 20 years. | RT-PCR: 3/16 IgG Tests: 10/16 Both RT-PCR and IgG Tests: 1/16 | Fever (in 16), erythema (in 10), emesis (in 12), diarrhoea (in 7), abdominal discomfort (in 11), conjunctivitis (in 8), headache (in 6), and hoarseness (in 5) were the first symptoms, followed by breathing issues and congestion (in 1), hypotension (in 10), and ischemia (in 7). Echocardiography: Systolic myocardial abnormality (in 10), ectatic coronary arteries (in 4), and pericardial effusion (in 2) were discovered on echocardiography. Chest radiography: Megalocardia (in 10), cardiogenic pulmonary edema (in 9), and a modest pleural discharge (in 7) were seen on chest radiographs, with only a few patients developing pneumonia (in 1) and acute respiratory distress syndrome (in 2). CT scan of abdomen and pelvis: Abdominal fluid build-up (in 6), hepatomegaly (in 6), mesenteric lymphadenitis (in 2), and thickening of the urinary (in 1) and gall bladder (in 3) walls were all seen on abdominal radiography. | Erythrocyte sedimentation rate (in 12), CRP (in 16), D-dimer (in 16), troponin (in six), and pro-BNP (in 15) values were all raised. High white blood cell count (in 13) leading to leucocytos and hypoalbuminaemia (in 16) were encountered too. | Kawasaki Disease (KD) | Intravenous corticosteroids Intravenous immunoglobulin and Anakinra |
| Belhadjer et al. (2020) | France and Switzerland | March 22 to April 30, 2020. | A cohort of a patient (total = 35) IQR = 2–16 years. | Nasopharyngeal swab PCR: 12/35 Fecal PCR: 2/35 Antibody Tests: 30/35 | All of the children had a fever and weakness, and 80% of them had gastrointestinal issues (in 29) such as abdominalache, diarrhoea, and vomiting. Runny | Heightened IL-6, D-dimer, troponin, CRP and BNP. | KD | Inotropic support, Immunoglobulin infusion, Intravenous corticosteroids, IL-1 inhibitor and therapeutic dose of heparin. |

(continued on next page)
| Study                  | Region         | Schedule of patient admission | Description of patients (number, age/interquartile range [IQR]) | Number of Patients detected positive | Symptoms and Image findings                                                                 | Laboratory findings                                                                 | Similarities with               | Treatment                                                                  | Reference |
|-----------------------|----------------|-----------------------------|-----------------------------------------------------------------|-------------------------------------|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|--------------------------------|---------------------------------------------------------------------------|-----------|
| Whittekar E. et al.   | England        | March 23 to May 16, 2020    | A cohort of a patient (total = 58) IQR – 3 months-17 years.    | PCR: 15/58 IgG Test: 40/58          | nose (in 15), skin rashes (in 20), meningism (in 11), angina (in 6) mesenteric and cervical lymphadenopathy (in 21) were among the additional symptomatology. Echocardiography: It denoted impaired left ventricular systolic activity, with an EF of 30-50%, resulting in left ventricular hypokinesia (EF<45%) in 31 individuals. | All of the patients exhibited a significant inflammatory response in terms of elevated levels of CRP, troponin, ferritin, N-terminal pro-BNP and neutrophilia. | PIMS-TS and Kawasaki Disease (KD) shock syndrome. | Intravenous immunoglobulin (in 41), Corticosteroids (in 37), Anakinra (in 3) and Infliximab (in 8). | 21        |
| Kaushik et al. (2020) | New York       | April 23 to May 23, 2020     | A cohort of a patient (total = 33) IQR – 6–13 years.            | RT-PCR: 11/33 Antibody Test: 27/33 Both test: 6/33                  | Major portion of the patients had fever (Avg. temperature of about 39.4°C) (in 31) and other symptoms like uneasiness of the stomach/vomiting (in 23), diarrhoea (in 16), dyspnoea (in 11), vertigo (in 3), low blood pressure (in 21), peritoneal pain (in 21), mucocutaneous involvement (in 7) like conjunctivitis (in 12) and dermatological symptoms like rashes (in 14), and also neurological involvement (in 4). Echocardiogram: Depressed LVEF with various range of EF was observed (in 21). Chest Radiograph: Megacardia (in 10) and in addition bilateral pulmonary opacities were noted (in 11). | Inflammatory indicators like CRP, procalcitonin, D-dimer, ferritin, ESR, and fibrinogen were found to be increased. There were also heightened markers of aberrant cardiac state like, troponin, N-proBNP, and BNP. | Toxic shock                      | Intravenous immunoglobulin (in 18), Corticosteroids (in 17), Tocilizumab (in 12), Remdesivir (in 7), Anakinra (in 4), Convalescent plasma therapy (in1), Norepinephrine (in 10) and Dopamine (in 9). | 3,4       |
8. Conclusion

MIS-C is generally curable and rarely happens, but a certain lack of knowledge could make it severe in the long term aspect. As it is a rare condition, most children who have it improve with medical treatment. However, some children swiftly deteriorate to the point where their lives are jeopardized. As the number of MIS-C cases related to COVID-19 is increasing incessantly, it can be clearly stated that COVID-19 is not only a respiratory disease, further elaborate research is needed to know more about the etiology of MIS-C associated with COVID-19, as it is still unknown how the risk factor for MIS-C varies among child community.

Children develop COVID-19, unlike adults, by ADE due to a lack of androgens, which directly regulates the TMPRSS2 receptor. Therefore, to prevent the transmission of COVID-19 in this age group, parents should be more careful of their children in surroundings with a high population density. Precautions and safety measures such as social distancing, use of face masks, frequent washing of hands, use of alcohol-based disinfectants, should be followed in places like schools, parks, crèche, etc. Parents, babysitters, teachers, and school officials should primarily be cognizant of the indications and signs of both COVID-19 and MIS-C so that proper treatment is provided before its late.

Authors’ contributions

Conceptualization: [Joy Sarkar, Suchismita Kumar]; Formal analysis and investigation: [Anusrita Kundu, Joy Sarkar]; Writing – original draft preparation: [Anusrita Kundu], [Swagata Maji], [Suchismita Kumar], [Shreya Bhattacharya], [Pallab Chakraborty]; Image Preparation: [Pallab Chakraborty]; Writing – review and editing: [Joy Sarkar]; Funding acquisition: [N/A]; Resources: [N/A]; Supervision: [Joy Sarkar].

Availability of data and material

Not applicable.

Code availability

Not applicable.

Ethics approval

Not applicable.

Funding

We don’t have any funding support from any organizational or institutional level.

Permission to reproduce material from other sources

Not applicable.

Consent to participate

All the authors mutually agree to participate in this work.

Consent for publication

All the authors mutually agree to submit the manuscript for publication.

Declaration of competing interest

On behalf of all listed authors, the corresponding author declares that there is not any sort of financial and non-financial conflict of interest in the subject materials mentioned in this manuscript.

Acknowledgments

We do not have any funding support from any organizational or institutional level. The authors acknowledge the immense help received from the scholars whose articles are cited and included in references of this manuscript. The authors are also grateful to authors/editors/publishers of all those articles, journals, and books from where the literature for this article has been reviewed and discussed.

References

1. Jiang L, Tang K, Levin M, et al. COVID-19 and multisystem inflammatory syndrome in children and adolescents. Lancet Infect Dis. 2020;20(11):e276–e288. https://doi.org/10.1016/S1473-3099(20)30651-4.
2. Vella LA, Giles JR, Baxter AE, et al. Deep immune profiling of MIS-C demonstrates marked but transient immune activation compared to adult and pediatric COVID-19. Science Immunology. 2021;6(57):1–19. https://doi.org/10.1126/sciimmunol. abf7570.
3. Rothan HA, Byrareddy SN. The potential threat of multisystem inflammatory syndrome in children during the COVID-19 pandemic. Pediatr Allergy Immunol. 2021;32(1):17–22. https://doi.org/10.1111/pai.13361.
4. Rafferty MS, Burrows H, Joseph JP, Leveille J, N ihtianova S, Amri an ES. Multisystem inflammatory syndrome in children (MIS-C) and the coronavirus...
Yu J, Yu J, Mani RS, et al. An integrated network of androgen receptor, polycomb, Mikkonen L, Pihlajamaa P, Sahu B, Zhang FP, J
Rahman F, Christian HC. Non-classical actions of testosterone: an update. Glowacka I, Bertram S, Muller MA, et al. Evidence that TMPRSS2 activates the severe
Mihalopoulos M, Levine AC, Marayati NF, et al. The resilient child: sex-steroid hormones and COVID-19 incidence in pediatric patients. J Endocr Soc. 2020;4(9). https://doi.org/10.1210/jendos/bva2106.

Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by the novel coronavirus from wuhan: an analysis based on decade-long structural studies of SARS coronavirus. J Virol. 2020;94(7). https://doi.org/10.1128/vi.01172-20.

Zhou P, Lou Yang X, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798):270–273. https://doi. org/10.1038/s41586-020-2012-7.

Lucas JM, Heinlein C, Kim T, et al. The androgen-regulated protease TMPRSS2 activates a proteolytic cascade involving components of the tumor microenvironment and promotes prostate cancer metastasis. Cancer Discov. 2014;4(11):1310–1225. https://doi.org/10.1158/2159-8290.CD-13-1010.

Glowacka I, Bertram S, Muller MA, et al. Evidence that TMPRSS2 activates the severe acute respiratory syndrome coronavirus spike protein for membrane fusion and reduces viral control by the humoral immune response. J Virol. 2011;85(9):4122–4134. https://doi.org/10.1128/jvi.02232-10.

Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020;181(2):271–286. https://doi.org/10.1016/j.cell.2020.02.052. e8.

Rahman F, Christian HC. Non-classical actions of testosterone: an update. Trends Endocrinol Metabol. 2007;18(10):371–378. https://doi.org/10.1016/j.tem.2007.09.004.

Mikkonen I, Pihlajamaa P, Sahu B, Zhang FP, Jänne OA. Androgen receptor and androgen-dependent gene expression in lung. Mol Cell Endocrinol. 2015;317(1-2):14–24. https://doi.org/10.1016/j.mce.2009.12.022.

Yu J, Yu J, Mani RS, et al. An integrated network of androgen receptor, polycomb, and TMPRSS2-ERG gene fusion in prostate cancer progression. Cancer Cell. 2010;17(5):443–454. https://doi.org/10.1016/j.ccr.2010.03.018.

McCrohan JA, Death AK, Nakhla S, et al. Androgen receptor expression is greater in macrophages from male than from female donors. Circulation. 2000;101(3):224–226. https://doi.org/10.1161/01.CIR.101.3.224.

Kim JB, Lee JJ, Park JC, et al. Integrated analyses of single-cell atlases reveal age, gender, and smoking status associations with cell type-specific expression of mediators of SARS-CoV-2 viral entry and highlight inflammatory programs in putative target cells. Angew Chem Int Ed. 2018;6(11):951–952, 12(3):351-376.

Kashon ML, Hayes MJ, Shek PP, Sisk GL. Regulation of brain androgen receptor immunoreactivity by androgen in prepubertal male ferrets. Biol Reprod. 1995;52(5):1198–1205. https://doi.org/10.1095/biolreprod52.5.1198.

Denison MR. Severe acute respiratory syndrome coronavirus pathogenesis, disease and vaccines: an update. Pediatr Infect Dis J. 2004;23(11 SUPPL):207–214. https://doi.org/10.1097/01.inf.0000146666.95284.05.

Liu Y, Yan LM, Wan L, et al. Viral dynamics in mild and severe cases of COVID-19. Lancet Infect Dis. 2020;20(6):656–657. https://doi.org/10.1016/S1473-3099(20)30232-2.

Rothan HA, Bidokhti MR, Byrareddy SN. Current concerns and perspectives on Zika virus co-infection with arboviruses and HIV. J Autoimmun. 2018;89:11–20. https://doi.org/10.1016/j.jauto.2018.01.002.

Ho MS, Chen WJ, Chen HY, et al. Neutralizing antibody response and SARS severity. Emerg Infect Dis. 2005;11(11):1730–1737. https://doi.org/10.3201/ eid1111.040659.

Wang SF, Tseng SP, Yen CH, et al. Antibody-dependent SARS coronavirus infection is mediated by antibodies against spike proteins. Biochem Biophys Res Commun. 2014;451(2):208–214. https://doi.org/10.1001/j.bbr.2014.07.090.

Feng Z, Dao B, Wang R, et al. The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) directly decimates human spleens and lymph nodes. medRxiv. 2020;2020.21–18. https://doi.org/10.1101/2020.03.27.20042477.

Santoro MG, Rossi A, Amici C. NF-kB and virus infection: who controls whom. EMBO J. 2003;22(11):2552–2560. https://doi.org/10.1093/emboj/cdg267.

D’Antiga L. Coronaviruses and immunosuppressed patients: the facts during the third epidemic. Liver Transplant. 2020;26(6):832–834. https://doi.org/10.1002/lt.24756.

Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun. 2020;109(Febuary), 102433. https://doi.org/10.1016/j.jauto.2020.102433.

Yang M. Cell Pyroptosis, a Potential Pathogenic Mechanism of 2019-nCoV Infection. SSRN Electronic Journal. 2020. https://doi.org/10.2139/ssrn.3527425. Published online.

Malmgaard L, Melchjorsen J, Bowie AG, Mogensen SC, Paludan SR. Viral activation of macrophages through TLR-dependent and -independent pathways. J Immunol. 2004;173(11):6890–6898. https://doi.org/10.4049/jimmunol.173.11.6890.

Gruber CN, Patel RS, Trachtman R, et al. Mapping systemic inflammation and antibody responses in multisystem inflammatory syndrome in children (MIS-C). Cell. 2020;183(4):982–995. https://doi.org/10.1016/j.cell.2020.09.034. e14.