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The emerging threat of multisystem inflammatory syndrome in adults (MIS-A) in COVID-19: A systematic review

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ABSTRACT

Background: The exact prevalence of Multisystem Inflammatory Syndrome in Adults (MIS-A) is largely unknown. Vague and multiple definitions and treatment options often add to the confusion on how to label the diagnosis with certainty.
Objectives: The objective of the study was to determine the demographic profile, clinical presentation, laboratory findings and outcomes of MIS-A in COVID-19.
Methods: A systematic review was conducted after registering with PROSPERO. Multiple databases were systematically searched to encompass studies characterizing MIS-A from 1st January 2020 up to 31st August 2021. The inclusion criteria were- to incorporate all published or in press peer-reviewed articles reporting cases of MIS-A. We accepted the following types of studies: case reports, case-control, case series, cross-sectional studies and letters to the editors that incorporated clinical, laboratory, imaging, as well as the hospital course of MIS-A patients. The exclusion criteria for the review were- articles not in English, only abstracts published, no data on MIS-A and articles which have focus on COVID-19, and not MIS-A. Two independent authors screened the articles, extracted the data, and assessed the risk of bias.
Results: A total of 53 articles were included in this review with a sample size of 79 cases. Majority of the patients were males (73.4%) with mean age of 31.67±10.02 years. Fever (100%) and skin rash (57.8%) were the two most common presenting symptoms. Echocardiographic data was available for 73 patients of whom 41 (73.2%) had reduced left ventricular ejection fraction. Cardiovascular system was most frequently involved (81%) followed by gastrointestinal (73.4%) and mucocutaneous (51.9%) involvement. Anti-inflammatory therapies used in treatment included steroids (60.2%), intravenous immunoglobulin (37.2%) and biologics (10.2%). Mean duration of the hospital stay was 11.67±8.08 days. Data regarding the outcomes was available for all 79 subjects of whom 4 (5.1%) died during course of hospital stay.
Conclusions: Emergence of MIS-A calls for further large-scale studies to establish standard case definitions and definite treatment guidelines.

Introduction

Coronavirus disease 2019 (COVID-19), caused by novel coronavirus SARS CoV-2, has rapidly evolved into a pandemic leading to widespread morbidity and mortality. Multisystemic involvement has been one of the defining features in COVID-19 with the respiratory system being the most commonly affected.[1] Systemic inflammation is the key pathophysiology of COVID-19 infection, especially in moderate and severe cases, with a host of pro-inflammatory cytokines being responsible for the cytokine surge.[2] This inflammatory state often subsided during the convalescent phase. However, a post infectious hyperinflammatory phase termed as multisystem inflammatory syndrome in children (MIS-C) was first reported in the pediatric population in April 2020.[3,4] This emerging clinical entity is usually seen among young children, weeks following infection with SARS-CoV-2, and tends to involve the cardiovascular and the gastrointestinal system.[3-5] A similar multisystem hyperinflammatory state with a temporal association with COVID-19 has recently been described in adults and is termed as the multisystem inflammatory syndrome in adults (MIS-A).[6]

The exact pathophysiology of MIS-A remains unclear and is thought to occur due to the dysregulated immune response involving both the innate and the adaptive immune system occurring weeks

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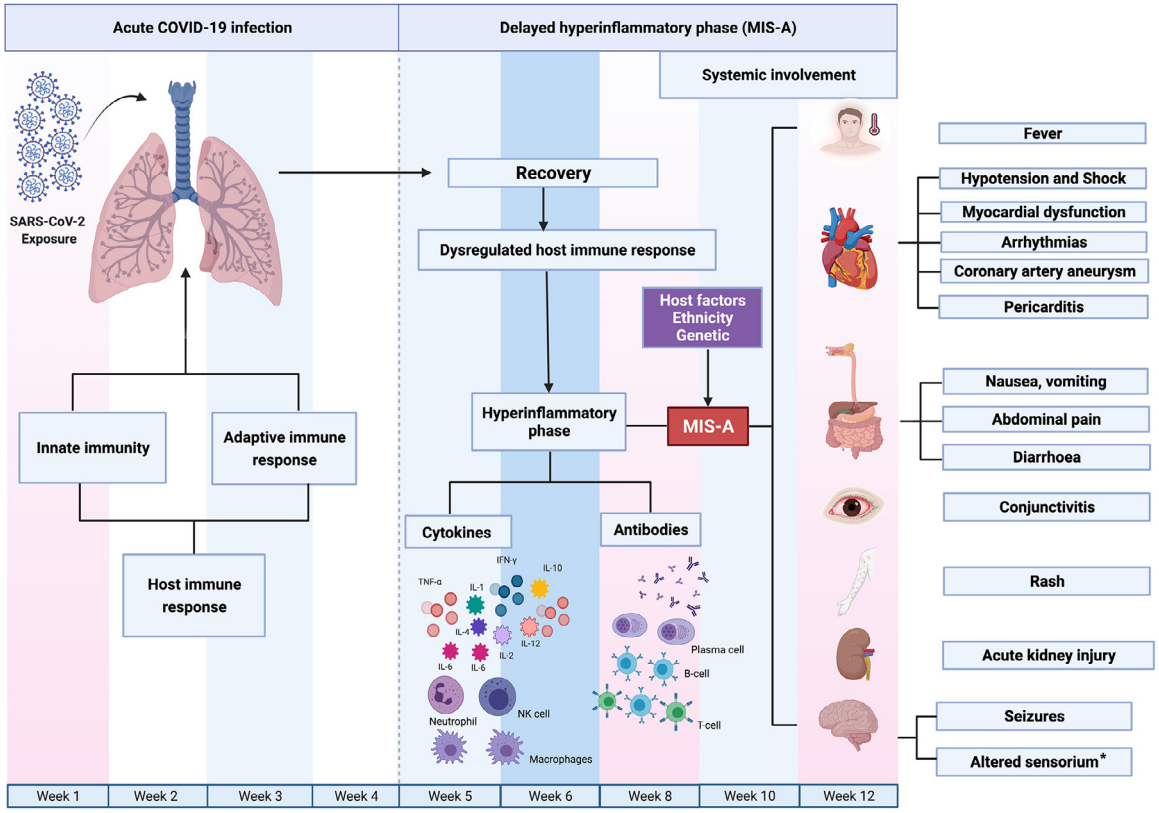

Fig. 1. Figure highlighting the pathophysiology of MIS-A. SARS-CoV-2 infection is characterized by an inflammatory immune response comprising both the innate as well as the adaptive immune system leading to recovery in majority of cases. However, in a fraction of cases following recovery, there develops a dysregulated immune response leading to a hyperinflammatory phase characterized by macrophage activation which leads to activation of innate as well as adaptive immune system comprising B-cells and T-cells with the production of inflammatory cytokines as well as antibodies. These inflammatory cytokines lead to multisystem inflammatory response and development of MIS-A. The exact cause for the dysregulated immune response following recovery is not known however, has been speculated to be due to super antigens or persistent viral antigens or even autoantibodies. Figure created by Biorender.com. * Altered sensorium implies decreased consciousness, altered mental status, altered awareness or confusion.

after recovery from COVID-19 infection. Possible pathophysiological mechanisms include (i) formation of autoantibodies, (ii) antibody recognition of persistent viral antigens on infected cells, and (iii) hyperinflammatory response due to the viral super antigens. Additionally, gender, genetic predisposition and ethnicity may play a defining role in occurrence of MIS-A (Fig. 1).[7] Case definitions for MIS-A have been put forth by the CDC which labels it as a hyper inflammatory syndrome with multiorgan (≥2) dysfunction in an adult (>21 years of age) having antecedent evidence of a SARS-CoV-2 infection.[8] The exact prevalence of MIS-A is largely unknown due to limited data in the form of case reports and series describing the occurrence, clinical features and outcomes of this novel clinical entity. This systematic review was carried out to evaluate the clinical signs and symptoms, laboratory findings, imaging results, and outcomes of individuals with MIS-A.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were adhered to while carrying out this systematic review (Fig. 2). The study protocol was registered with PROSPERO (International Prospective Register of Systematic Reviews) with the registration number CRD42021272912. A systematic search of the following databases viz. PubMed, Medline, Embase, Scopus, Cochrane Library, WHO Global COVID Literature Database and Google Scholar was carried out. Additionally, the references of included articles and reviews focusing on MIS-A were studied. All publications in the English language from 1st January 2020 up to 31st August 2021 were reviewed. The combination of the following keywords were used as the search strategy for literature search in the various databases: Age group [adults with age restriction (21 years)] AND Virus (COVID-19, novel coronavirus, SARS-CoV-2, 2019-nCoV, severe acute respiratory syndrome coronavirus 2) AND Condition [Adult inflammatory multisystem syndrome temporally associated with SARS-CoV-2 infection, multisystem inflammatory syndrome in adults (MIS-A), hyperinflammation, hyperinflammatory shock, macrophage activation syndrome, hemophagocytic lymphohistiocytosis (HLH)]. The diagnosis of MIS-A was based on the CDC case definition for MIS-A[8] which is enumerated in supplementary Table 1.

The inclusion criteria were to incorporate all published or in press peer-reviewed articles reporting cases of MIS-A. We accepted the following types of studies: case reports, case-control, case series, cross-sectional studies and letters to the editors that incorporated clinical, laboratory, imaging, as well as the hospital course of MIS-A patients. The exclusion criteria for the review were- articles not in English, only abstracts published, no data on MIS-A and articles which have focus on COVID-19 and not MIS-A.

Screening by the title and abstract was conducted independently by two investigators (NM, SK). A third investigator (PI) was consulted to resolve differences of opinion in either phase. Subsequent full-text review and data extraction was conducted by investigators (PI, SK, NM, PS, KG) using Google Sheets (Google, Mountain View, CA, USA). Our goals were to evaluate the clinical signs and symptoms, laboratory findings, imaging results, and outcomes of individuals with MIS-A.

The data collected from the studies included demographics, number of patients, clinical signs and symptoms, laboratory, hematological, inflammatory and cardiac markers, imaging in the form of echocardiography, cardiac magnetic resonance imaging (CMR), computed tomography (CT) of chest and abdomen, treatment modalities and outcomes. Only the initial laboratory values including

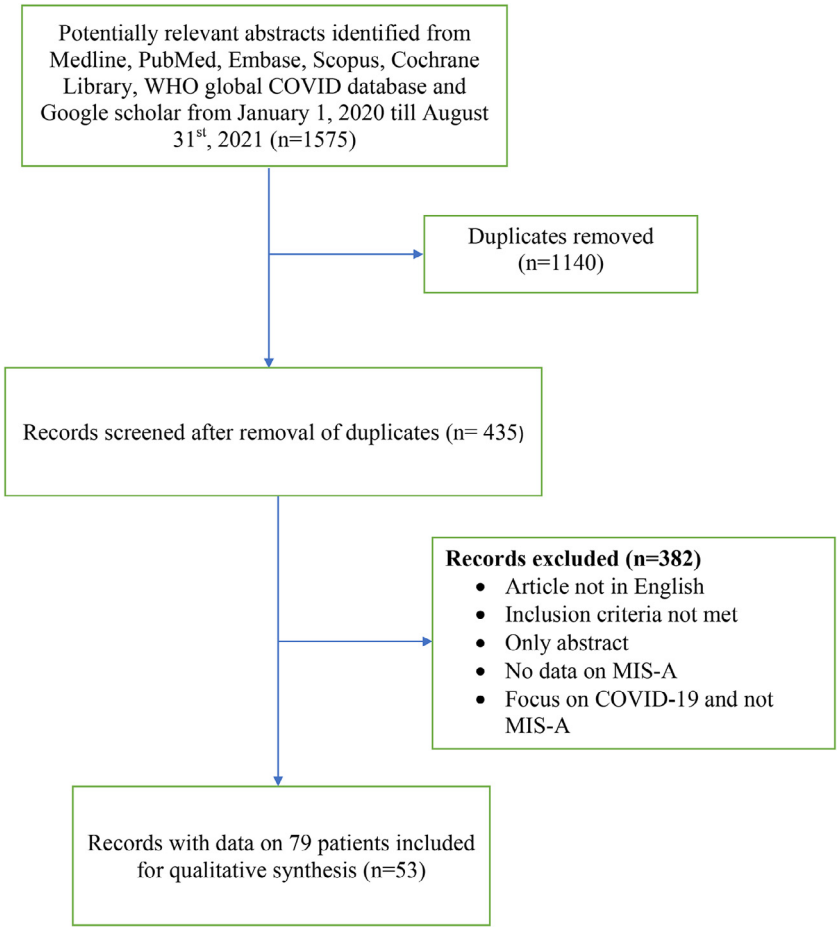

Fig. 2. PRISMA flow diagram of the systematic review.

inflammatory markers were recorded (e.g., at admission or first reported value). All signs and symptoms pre- hospitalization and during the patient's hospitalization were included. All echocardiograms were taken into consideration. Ejection fraction (EF), valvular dysfunction, pericardial effusion, coronary artery dilation, or aneurysm were recorded. Cardiac dysfunction was defined as an EF <50% and was categorized into mild (EF: 41–50%), moderate (EF: 31–40%) and severe (EF: ≤30%) left ventricular (LV) dysfunction.[9] In all these patients, evidence of SARS-CoV-2 infection was based on either (a) positivity on RT-PCR or (b) positive antibody or antigen test. Data regarding the outcomes were also evaluated including intensive care unit (ICU) stay, need for mechanical ventilation, inotropic support and mortality. Risk of bias for observational studies was assessed using the quality assessment tool published by the National Institutes of Health.[10] Risk of bias was assessed independently by two investigators (PI, SK) and disagreements were resolved by a third researcher (PI). Furthermore, the level of evidence was assessed according to Sackett.[11] Continuous data were summarized as mean with standard deviation. Categorical data were summarized as counts with percent. The means, standard deviations, counts and percent were calculated using SPSS, version 24.0 (IBM Corp) for Mac.

Results

A total of 1575 potentially relevant abstracts were identified from Medline, PubMed, Embase, Scopus, Cochrane Library, WHO global COVID database and Google scholar from 1st January 2020 till 31st August 2021. Out of these, 1140 were removed as they were duplicates. Out of the 435 studies left, 382 were excluded due to various reasons including articles not in English, inclusion criteria not met, only abstract, no data on MIS-A, focus on COVID-19 and not MIS-A, review article and scientific letter with no patient data. Ultimately, 53 articles were included in this review with a total sample size of 79 MIS-A cases (Fig. 2: PRISMA flow diagram). The summary of the included studies is summarized in Table 1.[6,12-63]

Demographic features and clinical characteristics

Of the 79 cases included, majority of them were males (73.4%), with a mean age of 31.67±10.02 years. The data regarding the race/ethnicity was available for 55 (69.6%) individuals with subjects most belonging to the Asian (25.4%), Caucasian (23.6%) and the Hispanic (21.8%) ethnicity. The mean duration from symptom onset to hospital admission was 5.84±8.01 days. Fever (100%) and skin rash (57.8%) were the two most common presenting symptoms. Diarrhea (51.6%) and abdominal pain (40.6%) were the most common gastrointestinal manifestations and mimicked viral gastroenteritis or inflammatory bowel disease. Twenty-six (32.9%) adults diagnosed with MIS-A, had comorbidities, with hypertension and obesity being the most frequent. In patients with a prior COVID-19 infection, the mean duration between prior infection and symptom onset was 31.61±14.34 days. The demographic and clinical characteristics of subjects with MIS-A has been listed in Table 2.

Laboratory and radiological investigations

The details of various laboratory and radiological investigations have been summarized in Table 3. Inflammatory markers were elevated in a majority of cases with leukocytosis reported in 36/44 (81.8%) and an elevated CRP in 56/57 (98.2%). Lymphopenia was

Table 1
Summary of the included MIS-A studies in the systematic review.

S.No	First author	Age (years)/ Gender	Publication type/ Number of cases	Symptoms	Laboratory/other system investigations	Inflammatory markers	Treatment	Outcome
1	Varadaraj G et al. [12]	21–30/ Male (3/3)	Case series (n = 3) Out of 4 reported, 3 included as the fourth one previously published by Dabas et al. [30]	Fever (3/3), skin rash (1/3), lymphadenopathy (1/3)	Thrombocytopenia (1/3), ↑ creatinine (2/3), ↑ troponin (3/3)	↑ Procalcitonin (3/3), ↑ CRP (3/3), ↑ LDH (3/3), ↑ ferritin (3/3), ↑ D-dimers (3/3)	Antibiotics (3/3), anticoagulants (3/3), inotropes (3/3)	Discharged (3/3)
2	Chung H et al. [13]	28/Male	Case report (n = 1)	Fever, nausea, vomiting, diarrhea	↑ BNP, Low EF	↑ CRP, ↑ Ferritin, ↑ Procalcitonin, ↑ Fibrinogen	Corticosteroid, IVIG, anticoagulant, antibiotic, inotrope	Discharged
3	Fiore M et al. [14]	42/Male	Case report (n = 1)	Fever, diarrhea, conjunctivitis, confusion	Lymphopenia, Low EF	↑ CRP	Corticosteroid, IVIG, antiplatelet, inotropes	Discharged
4	Razmi TM et al. [15]	40/Female	Case report (n = 1)	Fever, rash, lymphadenopathy	Lymphopenia	↑ ESR, ↑ CRP	Steroids	Discharged
5	Shaigany S et al. [16]	45/Male	Case report (n = 1)	Fever, cough, nausea, vomiting, abdominal pain, skin rash, conjunctivitis, cracking of lips	Lymphopenia, ↑ troponin, ↑ NT-Pro-BNP	↑ ESR, ↑ CRP, ↑ IL-6, ↑Ferritin, ↑D-dimer	Anticoagulant, IVIG, tocilizumab	Discharged
6	Kerkerian G et al. [17]	60/Male	Case report (n = 1)	Fever, skin rash, myalgia, lymphadenopathy, conjunctivitis, peripheral edema, glossitis	Lymphopenia, ↑ troponin, ↑NT-Pro-BNP	↑ CRP, ↑D-dimer, ↑Ferritin	Corticosteroid, IVIG, antiplatelet	Discharged
7	Ahmad F et al. [18]	26/Male	Case report (n = 1)	Fever, diarrhea, nausea, Abdominal pain, Skin rash	Severe LV dysfunction	↑ LDH, ↑ CRP, ↑ D-dimer, ↑Ferritin	Corticosteroid, IVIG, antiplatelet, anticoagulant, RRT, inotrope, anakinra	Discharged
8	Baruah R et al. [19]	22/Male	Case report (n = 1)	Fever, nausea, vomiting, diarrhea, skin rash, conjunctivitis	↑ NT-Pro-BNP, ↑ troponin	↑ Procalcitonin, ↑ CRP, ↑Ferritin, ↑ D-dimer	Corticosteroid, IVIG, antiplatelet, antibiotic, inotrope	Discharged
9	Yamada Y et al. [20]	51/Male	Case report (n = 1)	Fever, conjunctivitis, peripheral edema, cervical lymphadenopathy, fatigue	↑ NT-Pro-BNP	↑Procalcitonin, ↑CRP, ↑IL-6, ↑Ferritin, ↑D-dimer, ↑Fibrinogen	Corticosteroid, antibiotic, inotrope	Discharged
10	Razavi AC et al. [21]	23/Male	Case report (n = 1)	Dyspnea, fever, diarrhea, fatigue, conjunctivitis, headache	Lymphopenia, thrombocytopenia	↑ CRP, ↑ Ferritin, ↑ D-dimer, ↑ Fibrinogen	Corticosteroid, antiplatelet, anticoagulant, IVIG antibiotic	Discharged
11	Salzman MB et al. [22]	40/Male	Case report (n = 1)	Dyspnea, fever, abdominal pain, diarrhea, fatigue, headache	NR	↑ CRP, ↑ Ferritin, ↑ D-dimer, ↑ Fibrinogen	Corticosteroid, anticoagulant, antibiotic	Discharged
12	Bastug A et al. [23]	40/Male	Case report (n = 1)	Fever, abdominal pain, diarrhea	Lymphopenia, ↑troponin, ↑ BNP	↑ Procalcitonin, ↑ Ferritin, ↑ D-dimer	Corticosteroid, anticoagulant, IVIG, antibiotic	Discharged
13	Pombo F et al. [24]	24/Male	Case report (n = 1)	Dyspnea, fever, cough, abdominal pain, skin rash, diarrhea	↑ NT-Pro-BNP	↑ CRP, ↑Ferritin, ↑D-dimer, ↑Fibrinogen, ↑ESR	Corticosteroid	Discharged
14	Kofman AD et al. [25]	25/Female	Case report (n = 1)	Dyspnea, fever, cough, vomiting, abdominal pain, diarrhea, conjunctivitis, lymphadenopathy, fatigue	Neutrophilia	↑ CRP, ↑Ferritin, ↑D-dimer, ↑ ESR	IVIG, antiplatelet, antibiotic, inotrope	Discharged
15	Chau VQ et al. [26]	24–42/Male (5/5)	Case series (n = 5)	Dyspnea (4/5), fever (5/5), cough (1/5), chest pain (2/5), vomiting (1/5), diarrhea (2/5), skin rash (3/5), lymphadenopathy (1/5), fatigue (1/5)	↑ BNP (5/5)	↑ CRP (5/5), ↑ IL-6 (5/5), ↑ Ferritin (5/5), ↑ D-dimer (5/5)	Corticosteroid (5/5), anticoagulant (5/5), RRT (2/5), inotrope (5/5)	Discharged (5/5)
16	Ahsan T et al. [27]	28/Male	Case report (n = 1)	Fever, confusion, nausea, vomiting, skin rash, conjunctivitis, Myalgia	Anemia, lymphocytosis	↑ESR, ↑CRP	Corticosteroid	Discharged
17	Faller E et al. [28]	23/Male	Case report (n = 1)		Leukocytosis, ↑ Troponin		Anticoagulant, inotrope	Discharged

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Table 1 (*Continued*)

S.No	First author	Age (years)/ Gender	Publication type/ Number of cases	Symptoms	Laboratory/other system investigations	Inflammatory markers	Treatment	Outcome
				Fever, cough, vomiting, diarrhea, skin rash, conjunctivitis		↑ LDH, ↑ CRP, ↑ IL-6, ↑Ferritin, ↑D-dimer,		
18	Julius MA et al. [29]	59/Female	Case report (n = 1)	Fever, skin rash, lymphadenopathy, myalgia	↑ Troponin	↑LDH, ↑CRP	Corticosteroid, inotropes, RRT	Died due to multiorgan failure including shock, respiratory, renal and fulminant hepatic failure
19	Morris SB et al. [6]	21/Male 27/Male 42/Female	Case series (n = 3/9) Out of 9 reported, 3 fulfilled the CDC criteria for MIS-A	Fever (3/3), cough (1/3), nausea (1/3), vomiting (1/3), diarrhea (2/3), skin rash (1/3), myalgia (1/3), lymphadenopathy (1/3)	↑ Troponin (3/3), Reduced EF (3/3)	↑ CRP (3/3), ↑ IL-6 (1/3), ↑Ferritin (3/3) ↑D-dimer (3/3)	Steroids (3/3), anticoagulation (3/3), inotrope (3/3), antiplatelet (1/3)	Discharged (3/3)
20	Dabas R et al. [30]	22/Male	Case letter (n = 1)	Fever, nausea, abdominal pain, skin rash, conjunctivitis. Cracking of lips, myalgia, fatigue, joint pains	Transaminitis	↑ ESR, ↑ CRP, ↑ LDH, ↑ IL-6, ↑ Ferritin, ↑ Procalcitonin	Anticoagulant, antibiotic	Discharged
21	Veyseh M et al. [31]	43/Female	Case report (n = 1)	Fever, abdominal pain, diarrhea, skin rash	Leukocytosis, low EF	↑ CRP, ↑ LDH, ↑Ferritin, ↑ D-dimer	Steroids	Discharged
22	Hékimian G et al. [32]	22–37/ Male(2/4), Female (2/4)	Case series (n = 4/11) Out of 11 reported, 4 fulfilled the CDC criteria for MIS-A	Dyspnea (2/4), fever (4/4), cough (1/4), chest pain (1/4), abdominal pain (2/4), diarrhea (3/4), skin rash (1/4), conjunctivitis (1/4), lymphadenopathy (1/4), fatigue (4/4), joint pain (1/4), headache (2/4)	Lymphopenia (1/4), ↑creatinine (1/4), ↑ troponin (4/4), ↑ AST (2/4), ↑ ALT (3/4), ↑ NT-Pro-BNP (3/4)	↑Procalcitonin (3/4), ↑LDH (2/4), ↑CRP (3/4), ↑Ferritin (4/4), ↑ D-dimer (4/4), ↑ Fibrinogen (4/4)	Corticosteroid (1/4), IVIG (2/4), antibiotic (1/4), ECMO (1/4)	Discharged (4/4)
23	Bulut H et al. [33]	20/Male	Case report (n = 1)	Fever, abdominal pain, diarrhea, skin rash	Anemia, thrombocytopenia, ↑ NT-Pro-BNP, Low EF	↑ CRP, ↑ LDH, ↑ Ferritin	Corticosteroid, antiplatelet, anticoagulant, IVIG, antibiotic, inotrope	Discharged
24	Cogan E et al. [34]	19/Female	Case report (n = 1)	Fever, skin rash, conjunctivitis, cracking of lips, peripheral edema	Low EF, ↑ troponin	↑ CRP, ↑ LDH, ↑ IL-6, ↑ Ferritin, ↑ D-dimer	Corticosteroids, IVIG, tocilizumab, inotrope	Discharged
25	Brown LN et al. [35]	39/Male	Case report (n = 1)	Fever, dyspnea, vomiting, confusion, diarrhea, skin rash, Lymphadenopathy, myalgia	Thrombocytopenia	↑ CRP, ↑ LDH, ↑ Ferritin, ↑Procalcitonin, ↑Fibrinogen	Corticosteroid, IVIG, antiplatelet	Discharged
26	Gopalakrishnan M et al. [36]	28/Male	Case report (n = 1)	Fever, skin rash, odynophagia	Thrombocytopenia, ↑ troponin	↑ ESR, ↑ CRP, ↑ Ferritin	IVIG, antibiotic, inotropes	Died due to refractory shock and respiratory failure
27	Diakite S et al. [37]	33/Male	Case report (n = 1)	Fever, dyspnea, chest pain, diarrhea, conjunctivitis, cracking of lips	Anemia, leukocytosis, ↑ troponin	↑ CRP, ↑ D-dimer	Steroid, IVIG, antiplatelet, O_2, inotropes	Discharged
28	Alexandra OG et al. [38]	22/Male	Case report (n = 1)	Fever, cough, abdominal pain, diarrhea, skin rash, inguinal lymphadenopathy, myalgia, odynophagia	Leukocytosis	↑ CRP, ↑ D-dimer	Steroid, IVIG, Cyclophosphamide, Rituximab, Tocilizumab, inotrope, Ventilatory support, ECMO	Discharged
29	Kinter CW et al. [39]	32/Male	Case report (n = 1)	Fever, abdominal pain, skin rash, conjunctivitis, Lymphadenopathy, Neck pain	Leukocytosis, ↑ BNP, transaminitis, low EF	↑ CRP, ↑ IL-6, ↑ Ferritin	Steroid, antiplatelet, IVIG	Discharged
30	Shan Y et al. [40]	34/Male	Case report (n = 1)	Fever, vomiting abdominal pain, diarrhea, skin rash,	Leukocytosis, thrombocytopenia, ↑ troponin	↑ LDH, ↑ CRP, ↑ IL-6, ↑ Ferritin, ↑ D-dimer	Steroid, IVIG, RRT, O_2, ventilatory support, inotrope	Discharged

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Table 1 (*Continued*)

S.No	First author	Age (years)/ Gender	Publication type/ Number of cases	Symptoms	Laboratory/other system investigations	Inflammatory markers	Treatment	Outcome
				conjunctivitis, myalgia, headache				
31	Moghadam P et al. [41]	21/Male	Case letter (n = 1)	Fever, diarrhea, skin rash, conjunctivitis,	Leukocytosis, ↑ troponin	↑ CRP, ↑ Ferritin, ↑ Procalcitonin	Antibiotics, inotrope	Discharged
32	Aggarwal A et al. [42]	21/Male	Case report (n = 1)	Fever, abdominal pain, diarrhea, Headache	↑ D-dimer, ↑ BNP	↑ CRP, ↑ Ferritin, ↑ Procalcitonin	Steroid, IVIG, Anakinra	Discharged
33	Toplu SA et al. [43]	24/Female	Case report (n = 1)	Fever, abdominal pain, conjunctivitis, headache	Lymphopenia, thrombocytopenia, ↑ NT-Pro-BNP	↑ Procalcitonin, ↑ CRP, ↑ LDH, ↑ IL-6, ↑Ferritin, ↑ D-dimer	Corticosteroid, colchicine, antibiotic	Discharged
34	Chug L et al. [44]	25/Male	Case report (n = 1)	Fever, confusion, diarrhea, conjunctivitis	NR	↑ inflammatory markers (values not mentioned)	Corticosteroid, inotrope	Discharged
35	Brajkovic AV et al. [45]	22/Male	Case report (n = 1)	Fever, cough, headache, sore throat	↑ Troponin, ↑ NT-Pro-BNP, ↑AST, ↑ALT	↑ ESR, ↑ Procalcitonin, ↑ CRP, ↑ IL-6, ↑ Ferritin, ↑ D-dimer, ↑ LDH	Corticosteroid, antiplatelet, anticoagulant, IVIG, antibiotic, inotrope	Discharged
36	Mieczkowska K et al. [46]	32/Male 43/Female	Case series (n = 2)	Fever (2/2), cough (1/2), diarrhea (1/2), skin rash (2/2), conjunctivitis (1/2), peripheral edema (1/2), lymphadenopathy (1/2), fatigue (1/2), headache (1/2)	↑ Troponin (1/2), ↑ AST (2/2), ↑ ALT (1/2)	↑ ESR (2/2), ↑ Procalcitonin (1/2), ↑ CRP (2/2), ↑ IL-6 (2/2), ↑ Ferritin (2/2), ↑ D-dimer (2/2), ↑ Fibrinogen (1/2)	Corticosteroid (2/2), anticoagulant (2/2), antibiotic (2/2), inotrope (1/2)	Discharged
37	Uwaydah AK et al. [47]	22/Male	Case report (n = 1)	Fever, cough, nausea, vomiting, abdominal pain, diarrhea, skin rash, conjunctivitis, fatigue, headache	Thrombocytopenia, ↑ troponin, ↑ NT-Pro-BNP, ↑ AST, ↑ ALT	↑ Procalcitonin, ↑ CRP, ↑ IL-6, ↑ Ferritin, ↑ D-dimer	Corticosteroid, antibiotic	Discharged
38	Fox SE et al. [48]	31/Female	Case report (n = 1)	Fever, nausea, vomiting, conjunctivitis, lymphadenopathy	Anemia, ↑ serum creatinine, ↑ lactate, ↑ AST, ↑ ALT	↑ CRP, ↑ D-dimer, ↑ Ferritin	NR	Died due to shock and ventricular fibrillation. Autopsy revealed cardiac endothelitis and vasculitis.
39	Boudhabhay I et al. [49]	46/Male	Case report (n = 1)	Fever, skin rash	Thrombocytopenia, ↑ serum creatinine, ↑ troponin	↑ Ferritin, ↑ LDH, ↑ CRP	Hemodialysis, eculizumab, inotrope	Discharged
40	Pasara V et al. [50]	26/Male	Case report (n = 1)	Dyspnea, fever, cough, chest pain, diarrhea, headache,	↑ troponin, ↑ NT-Pro-BNP	NR	Corticosteroid, IVIG, antibiotic, inotrope	Discharged
41	Downing S et al. [51]	51/Male	Case report (n = 1)	Dyspnea, fever, cough, fatigue, headache,	NR	NR	Corticosteroid, antiplatelet, colchicine	Discharged
42	Malangu B et al. [52]	46/Male	Case report (n = 1)	Dyspnea, fever, cough, chest pain, skin rash, fatigue	Thrombocytopenia, ↑ serum creatinine, ↑ AST, ↑ ALT	↑Ferritin, ↑ CRP, ↑ LDH, ↑ D-dimer, ↑ Fibrinogen,	Anticoagulant, antibiotic	Discharged
43	Li M et al. [53]	28/Male	Case report (n = 1)	Fever, lymphadenopathy, fatigue	↑ troponin, ↑ BNP, ↑ AST, ↑ ALT	↑ CRP, ↑ ferritin,	Corticosteroid, IVIG, antibiotic,	Discharged
44	Lerner RK et al. [54]	26/Male	Case report (n = 1)	Fever, abdominal pain	Anemia, leukocytosis, thrombocytopenia, transaminitis, ↑ troponin, low EF	↑ LDH, ↑ Procalcitonin	Corticosteroid, RRT, IVIG, ECMO, inotrope	Died due to myocardial dysfunction and shock
45	Viana-Garcia A et al. [55]	24/Female	Case report (n = 1)	Fever, nausea, vomiting, abdominal pain, skin rash,	Anemia, ↑ NT Pro-BNP	↑ LDH, ↑ CRP, ↑ IL-6, ↑ Ferritin	Corticosteroid, IVIG	Discharged

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Table 1 (*Continued*)

S.No	First author	Age (years)/ Gender	Publication type/ Number of cases	Symptoms	Laboratory/other system investigations	Inflammatory markers	Treatment	Outcome
				lymphadenopathy, headache, odynophagia				
46	CattaneoP et al. [56]	27/Male	Case report (n = 1)	Fever, chest pain, skin rash, conjunctivitis, lymphadenopathy, bilateral leg pain, headache, cracking of lips,	Thrombocytopenia, ↑ troponin	↑ CRP, ↑ Ferritin, ↑ Procalcitonin	Corticosteroid, anakinra, antibiotic	Discharged
47	Gulseran M et al. [57]	31/Female	Case report (n = 1)	Pregnant lady with fever and chest pain	Leukocytosis, ↑ troponin, ↑ BNP, transaminitis, global left ventricular dysfunction	↑ CRP, ↑ IL-6, ↑ D-dimer, ↑ fibrinogen	Steroid, IVIG, anticoagulant, antibiotic, immunosuppressant, inotrope	Discharged
48	Choudary A et al. [58]	26/Male	Image (n = 1)	Fever, cough, abdominal pain, vomiting, diarrhea, myalgia	↑ Troponin, reduced LV function	↑ Ferritin, ↑ Procalcitonin, ↑ D-dimer	Antiplatelet, antibiotic, inotrope	Discharged
49	Davogustto GE et al. [59]	45 (mean)/Male (10/15), Female (5/15)	Case series (n = 15)	Symptoms: NR	Individual data: NR	Individual data: NR	Immunosuppressant n = 4; antibiotics n = 7; non-invasive ventilatory support n = 1	Discharged (n = 15)
50	Cherif MY et al. [60]	35/Female	Case report (n = 1)	Fever, cough, dyspnea, vomiting, diarrhea, skin rash, conjunctivitis, peripheral edema, cracking of lips, myalgia, hypogeusia	Lymphopenia, thrombocytopenia, ↑ troponin, ↑ NT Pro-BNP	↑ LDH, ↑ CRP, ↑ Ferritin	Hydroxychloroquine, antibiotics	Discharged
51	Jones I et al. [61]	26/Male	Correspondence (n = 1)	Fever, abdominal pain, skin rash, conjunctivitis, lymphadenopathy, cracking of lips, constipation, anorexia	Lymphopenia	↑ D-dimer, ↑ CRP, ↑ Ferritin	Corticosteroid, IVIG, antiplatelets	Discharged
52	Sokolovsky S et al. [62]	36/Female	Case report (n = 1)	Fever, vomiting, abdominal pain, diarrhea, skin rash, conjunctivitis, peripheral edema, lymphadenopathy, cracking of lips, joint pain	Anemia, leukocytosis	↑ ESR, ↑ D-dimer, ↑ CRP	Corticosteroid, IVIG., antiplatelets	Discharged
53	Lidder A et al. [63]	45/Male	Case report (n = 1)	Fever, diarrhea, skin rash, conjunctivitis,	Lymphopenia, ↑ troponin	↑ ESR, ↑ CRP, ↑ IL-6, ↑ Ferritin	Corticosteroid, IVIG, tocilizumab	Discharged

Abbreviations: BNP: B-type natriuretic peptide, CRP: C reactive protein, NT Pro-BNP: N terminal Pro-BNP, IL-6: Interleukin-6, IVIG: Intravenous Immunoglobulin, EF: Ejection fraction, ESR: Erythrocyte sedimentation rate, LDH: Lactate dehydrogenase, ALT: Alanine transaminase, AST: Aspartate transaminase, ↑: raised; RRT: renal replacement therapy, NR: not reported.

Table 2
Demographic and clinical characteristics of subjects with MIS-A.

Characteristics	Number of Patients (*N* = 79)	N (%)
Age [Mean ± SD]	Data available: 79	31.67±10.02 years
Gender	Data available: 79	Males: 58 (73.4%) Females: 21 (26.6%)
Ethnicity	Data available: 55/79	
Caucasian		13 (23.6%)
Hispanic		12 (21.8%)
Latin		1 (1.8%)
Asian		14 (25.4%)
African		4 (7.3%)
Afro-American		11 (20%)
Clinical features	Data available: 64/79	
Fever		64 (100%)
Dyspnea		20 (31.2%)
Cough		16 (25%)
Chest pain		8 (12.5%)
Nausea		10 (15.6%)
Vomiting		16 (25%)
Diarrhea		33 (51.6%)
Abdominal pain		26 (40.6%)
Skin rash		37 (57.8%)
Conjunctivitis		26 (40.6%)
Lymphadenopathy		22 (34.3%)
Confusion		4 (6.2%)
Peripheral Edema		5 (7.8%)
Myalgia		25 (39.1%)
Joint pain		4 (6.2%)
Headache		16 (25%)
Cracking of lips		9 (14.1%)
Sore throat		2 (3.1%)
Odynophagia		4 (6.2%)
Systemic involvement	Data available: 79/79	
Cardiovascular		64 (81%)
Muco-cutaneous		41 (51.9%)
Gastrointestinal		58 (73.4%)
Musculoskeletal		24 (30.4%)
Renal		34 (43.1%)
Hematological		33 (41.8%)
Neurological		13 (16.4%)
Pulmonary		23 (29.1%)
Comorbidities		26 (32.9%)
Hypertension		10
Diabetes		6
Dyslipidemia		2
Obesity		17
Coronary artery disease		1
Asthma		2
Malignancy		4
Chronic kidney disease		3
Duration of symptoms [Mean ± SD]	Data available: 58/79	5.84±8.01 days
Duration of hospital stay [Mean ± SD]	Data available: 59/79	11.67±8.08 days
Time between exposure and symptom onset [Mean ± SD]	Data available: 33/79	31.61±14.34 days
COVID-19 status		
Antibody positivity	Data available: 68/79	58 (85.3%)
RTPCR positivity	Data available: 77/79	28 (36.4%)
COVID-19 vaccination	Data available: 79/79	2 (2.5%)

Abbreviations: SD- Standard deviation, COVID-19- coronavirus disease, RTPCR-reverse transcriptase polymerase chain reaction.

observed in 27/40 (67.5%) of cases. Cardiac involvement was seen in a majority of cases where cardiac investigations and imaging were performed. An elevated cardiac troponin was reported in 43/50 (86%) while elevated Brain natriuretic peptide (BNP) and NT-pro BNP were observed in 16/17 (94.1%) and 14/15 (93.3%) patients each. Echocardiographic data was available for 73 patients of whom 41 (73.2%) had a reduced left ventricular ejection fraction (LVEF<50%) while 32 (43.8%) had a normal echocardiogram. Right ventricular dysfunction was present in one-fifth of the patients included in the study. Data regarding CMR was available for 18 patients of whom 6 (33.3%) had evidence of myocardial edema, 4 (22.2%) had late gadolinium enhancement and 2 (22.2%) had pericardial effusion. None of the patients had any evidence of coronary artery aneurysms on cardiac imaging. Evidence of current or past SARS-CoV-2 infection was based on RT-PCR positivity in 28/77 (36.4%) subjects and positive serology in 58/68 (85.3%) patients

Systemic involvement, treatment and outcomes

Cardiovascular system was the most frequently involved (81%) followed by gastrointestinal (73.4%) and mucocutaneous (51.9%) involvement (Table 2). On admission, 35/39 (89.7%) of cases had tachycardia while 43/72 (59.7%) were hypotensive. Forty-three (58.1%) of the adults diagnosed with MIS-A were admitted in the ICU. Shock was reported in 40/78 (51.3%) patients during the course of hospital stay mandating cardiovascular support in the form of inotropes (46.1%), intra-aortic balloon pump [IABP] (2.6%) or extracorporeal membrane oxygenation [ECMO] (3.8%). Acute kidney injury (AKI) requiring dialysis occurred in 6 (7.7%) patients. Respiratory dysfunction was reported in nearly one-third of patients with high flow humidified oxygen therapy used in 16 (20.5%), NIV support in 5 (6.4%) and mechanical ventilation in 12 (15.4%) patients Table 4. summarizes the information regarding the treatment administered and the outcomes. A variety of anti-inflammatory therapies were used for the treatment of MIS-A including steroids (60.2%), intravenous immunoglobulin (IVIG) [37.2%] and biologics (10.2%) such as Tocilizumab and Anakinra. Concomitant antibiotic therapy was administered in 60.2% patients while 32% of the subjects' received anticoagulants. The mean duration of the hospital stay was 11.67±8.08 days. Data regarding the outcomes was available for all the 79 subjects of whom 4 (5.1%) died during the course of hospital stay while 75 (94.9%) were discharged from the hospital. These deaths were due to myocardial dysfunction leading to refractory shock in three and multiorgan failure in one. Only one of these four cases underwent autopsy (Table 1) which revealed cardiac endothelitis and vasculitis.

Discussion

The exact incidence of MIS-A is largely unknown; however, MIS-A as a distinct clinical entity following COVID-19 infection is increasingly being recognized in the past few months.[64] This systematic review was carried out to determine the demographic profile, symptoms, systemic involvement, laboratory profile, treatment and outcome of patients diagnosed with MIS-A. MIS-C, a similar disease in the pediatric age group, is already a distinct entity with well-defined diagnostic criteria as well as treatment strategies.[65] However, in terms of MIS-A, the findings of our systematic review reveal that despite being reported globally among various ethnic groups, the clinical profile and treatment strategies are variable and often individualized. Additionally, there is a lack of a consistent criteria adopted for establishing a diagnosis of MIS-A. In our systematic review, the diagnostic criterion adopted was the CDC case definition for MIS-A which includes any individual ≥21 years of age presenting with fever and at least three other clinical criteria including either cardiovascular involvement or rash and non-purulent conjunctivitis in presence of laboratory evidence of inflammation and antecedent SARS-CoV-2 infection.[8] The other proposed criterion includes the Brighton Collaboration Case Definition for MIS-A, which classifies MIS-A cases into "definite", "probable", "possible", and "insufficient evidence".[66] However, the Brighton Collaboration Case Definition has certain limitations including (a) absence of an age-based cutoff as manifestations of MIS-C and MIS-A are quite different, (b) greater stress has been laid on the disease activity which is measured primarily by cardiac investigations besides hematological tests and c)

Table 3
Laboratory and radiological investigations in subjects with MIS-A.

Investigations	Number of Patients (*N* = 79)	N (%)
Hematology		
Hemoglobin (g/dl)	Data available: 26	11.58±2.17
Total leucocyte count (per mm^3)	Data available: 44	16,171.14±8288.58
Absolute lymphocyte count (per mm^3)	Data available: 35	1340.97±1685.32
Platelet count (per mm^3)	Data available: 32	185,062.5 ± 105,793.45
Thrombocytopenia	Data available: 35	18/35 (51.4%)
Lymphopenia	Data available: 40	27/40 (67.5%)
Organ functions:		
Serum creatinine (mg/dl)	Data available: 29	2.31±2.00
Cardiac troponin (ng/ml)	Data available: 50	287.06±1435.491
Serum BNP (pg/ml)	Data available: 17	3061.88±4738.37
Serum NT-pro BNP (pg/ml)	Data available: 15	13,400.27±12,843.65
Inflammatory markers		
LDH (U/L)	Data available: 28	676.49±1182.34
CRP (mg/dl)	Data available: 57	165.39±152.31
IL-6 (pg/ml)	Data available: 20	219.04±327.05
Ferritin (ng/ml)	Data available: 53	3062.83±4169.16
Procalcitonin (ng/ml)	Data available: 29	24.21±58.44
Positive procalcitonin (>0.5 ng/ml)	Data available: 45	43/45 (95.5%)
ESR (mm/hr)	Data available: 14	75.86±31.89
Coagulation profile		
D-Dimer (ng/ml)	Data available: 47	3268.16±4570.20
Fibrinogen (mg/dl)	Data available: 24	654.39±313.70
Imaging		
Echocardiogram	Data available: 73	
- Baseline EF (%)		39.09±14.12%
- Normal LVEF (≥50%)		32 (43.8%)
- Mild LV dysfunction (LVEF: 40–49%)		13 (37.1%)
- Moderate LV dysfunction (LVEF: 30–39%)		12 (34.2%) 10 (28.6%)
- Severe LV dysfunction (LVEF: <30%)		41 (73.2%)
- Reduced LVEF (<50%)		23/41 (56.1%)
- Improvement in LVEF		15 (20.5%)
- Right ventricular dysfunction		8 (10.9%)
- Pericardial effusion		
Cardiac MRI	Data available: 18	4 (22.2%)
- LGE		2 (11.1%)
- Pericardial effusion		6 (33.3%)
- Myocardial edema		
CT abdomen	Data available: 15	3 (20%)
- Terminal ileitis		2 (13.3%)
- Colitis		2 (13.3%)
- Hepatosplenomegaly		3 (20%)
- Mesenteric adenitis		
CT chest	Data available: 40	7 (17.5%)
- GGOs		1 (2.5%)
- Pulmonary embolism		11 (27.5%)
- Pleural effusion		8 (20%)
- Consolidation		2 (5%)
- Lymphadenopathy		

Abbreviations: BNP- B-terminal natriuretic peptide, CRP- C reactive protein, NT Pro-BNP- N terminal Pro-BNP, IL-6- Interleukin-6, IVIG- Intravenous Immunoglobulin, EF-Ejection fraction, ESR- Erythrocyte sedimentation rate, LDH- Lactate dehydrogenase, ALT- Alanine transaminase, AST- Aspartate transaminase, LVEF-. Left ventricular ejection fraction, LGE- Late Gadolinium Enhancement, CT- computed tomography, GGO-Ground glass opacities.

Table 4
Therapies administered for MIS-A and clinical outcomes.

Medications and Outcome	Number of Patients	N (%)
Medical treatment for MIS	Data available: 78	
Steroids		47 (60.2%)
Anti-inflammatory other than steroids		3 (3.8%)
- Colchicine		2 (2.6%)
- Cyclophosphamide		1 (1.3%)
Biologics		8 (10.2%)
- Tocilizumab		4 (5.1%)
- Anakinra		3 (3.8%)
- Rituximab		1 (1.3%)
- Eculizumab		1 (1.3%)
IVIG		29 (37.2%)
Antibiotics		47 (60.2%)
Antiplatelets		16 (20.5%)
Anticoagulants		25 (32%)
HCQs		1 (1.3%)
Shock	Data available: 78	40 (51.3%)
Inotropes	Data available: 78	36 (46.1%)
IABP	Data available: 78	2 (2.6%)
ECMO	Data available: 78	3 (3.8%)
Dialysis	Data available: 78	6 (7.7%)
Oxygen support	Data available: 78	16 (20.5%)
NIV	Data available: 78	5 (6.4%)
IMV	Data available: 78	12 (15.4%)
ICU stay	Data available: 74	43 (58.1%)
Outcome	Data available: 79	
Died		4 (5.1%)
Discharged		75 (94.9%)

MIS-Multisystem inflammatory syndrome, IVIG- Intravenous immunoglobulin, HCQs-Hydroxychloroquine, IABP-Intra Aortic balloon pump, ECMO-Extracorporeal membrane oxygenation, NIV- Noninvasive ventilation. IMV-Invasive mechanical ventilation, ICU-Intensive care unit.

creating sublevels of diagnosis with “probable” and “possible” cases leading to diagnostic confusion without any overt therapeutic benefits.[66]

Majority of the patients with MIS-A in our review were young (mean age of 31 years) with a male predisposition. In absence of large datasets, it is unclear whether this observation is due to a selection bias or MIS-A is truly a predominant clinical entity among younger age groups. MIS-A has been reported among various ethnic profiles however, in our review Asians, Caucasians and Hispanics had greater frequency of MIS-A. Though gender and ethnic variations have been reported in COVID-19,[67] it is still unclear whether this applies to MIS-A too. Additionally, one-third of our patients had comorbidities with hypertension and obesity being more common. Adults with MIS are more likely to have comorbidities with obesity being one of the possible risk factors for developing MIS-A as reported in patients with MIS-C too. Obesity often predisposes to a systemic inflammatory state due to accumulation of inflammatory cells within the fat tissue as well as the adipose tissue-associated cytokines which are often proinflammatory.[68] However, the currently available data is limited and there is a need for large scale studies to identify potential host factors as determinants for developing MIS-A.

Though the exact pathophysiology is not clear, evidence suggests MIS-A associated with COVID-19 is a post-infectious hyperinflammatory response triggered by a dysfunctional immune response leading to systemic inflammation, endothelial dysfunction and procoagulant state (Fig. 1). This hyperinflammatory response is evident in terms of elevated acute inflammatory markers such as CRP, IL-6, ferritin, and ESR. Fever and rash were the most common presenting symptoms in patients with MIS-A. Since the initial clinical presentation can be non-specific mimicking acute infection, a high index of suspicion for underlying MIS-A should be maintained for all patients presenting with similar complaints 4–6 weeks following recovery from COVID-19. A similar clinical presentation can be seen in patients with severe COVID-19 with elevated inflammatory markers and systemic involvement. In our review, in a majority of patients, symptoms of MIS-A usually occurred within four weeks of prior COVID-19 infection whereas MIS-C has been reported to occur within 1–6 weeks following COVID-19 in a recent systematic review.[69] The systemic involvement in MIS-A is often varied, with cardiovascular, gastrointestinal, mucocutaneous and musculoskeletal systems, being commonly affected. In our review of the 79 documented MIS-A cases, the cardiovascular system was most commonly affected followed by gastrointestinal and mucocutaneous involvement. Cardiac involvement in these patients often manifested as shock on initial presentation (51.3%) or left ventricular (LV) dysfunction (73.2%) on echocardiography. Cardiac imaging data revealed that a majority of patients had mild/moderate LV dysfunction which was reversible in 56.1% cases. Recovery of LVEF within a few weeks following MIS-A suggests that the LV dysfunction is usually a part of the systemic inflammatory response or acute stress rather than ischemic or a part of viral myocarditis. Cardiac MRI, an emerging imaging modality, was reported in a fraction of patients with diffuse myocardial edema and late gadolinium enhancement being predominant findings hereby suggesting

underlying myocardial inflammation. Similar findings too have been reported in patients with MIS-C[69,70] wherein the cardiovascular system was one of the most commonly affected organ systems. In contrast to MIS-C wherein 7.1% patients have been reported to have CAAs,[69] none of the patients reported in our review had CAAs. Clinical presentation in MIS-A varies with the majority of them (58.1%) requiring ICU admission, a finding previously reported in MIS-C cases.[69,70] Of the 79 included patients, 4 (5.1%) patients succumbed to the illness during index hospitalization. In comparison, a recent systematic review reported mortality in 1.7% of MIS-C cases[69] thereby highlighting that patient with MIS-A have a higher mortality than MIS-C cases.

There is a lack of uniform treatment strategy for MIS-A with supportive therapy being used in the majority of cases. Treatment largely focuses on immunosuppression using steroids or other immunomodulators. Supportive management strategies such as oxygen supplementation, mechanical ventilation, and even ECMO may be required in critically ill patients. In absence of large-scale clinical data and standard treatment protocols, treatment strategies in MIS-A are often based on therapies used for MIS-C. The American College of Rheumatology (ACR) guidelines on treatment of MIS-C recommends immunomodulatory therapies such as glucocorticoids and/or IVIG to be the first line treatment modality.[71] Findings from our review too revealed that the immunomodulatory therapies including steroids (60.2%) and IVIG were the most common therapeutic modalities used in MIS-A followed by other immuno-suppressants and biologics. A significant proportion of patients (60.2%) were also administered concomitant antibiotics as the majority of patients present with acute febrile illness with systemic involvement mimicking bacterial infection. Anticoagulants were administered in 32% of patients with MIS-A. The ACR guidelines for MIS-C recommend anticoagulation in patients with (a) documented thrombosis, (b) moderate-severe LV dysfunction and (c) CAAs.[71]These findings reinforce the urgent need for standard treatment guidelines for MIS-A.

A previous review article on MIS-A by Patel et al[72] in September 2021 included 221 patients from reported cases, voluntary reports to CDC of MIS-A and the patients aged 18−20 years in CDC surveillance for MIS-C. Our systematic review included all adults more than 21 years old as per the CDC definition for MIS-A. This is why the mean age in our systematic review was higher (31.67+10.02 years) along with 100% patients reporting fever (required as per CDC criteria for MIS-A) as compared to median age of 21 years and 96% patients having fever in review by Patel et al.

Around 73.2% in our systematic review had reduced left ventricular ejection fraction which was higher than the previous systematic review (54%). However, after excluding the CDC patients in the previous review, this incidence was nearly similar. Cardiac involvement was the most common followed by gastrointestinal manifestations in both the reviews. Steroids were most commonly used therapy in both. However, IVIG was more commonly used (55%) in the previous review as they included more younger patients many of whom had Kawasaki-like presentation (10 patients). The review by Patel et al. itself claims that none of the MIS-A reported to the CDC met the criteria for Kawasaki disease. Thus, the systematic review by Patel et al. had a few limitations including combining data from various sources and using cases from MIS-C surveillance system causing a reporting bias. The current review overcomes these limitations by strictly following the CDC case definition for MIS-A.

Limitations

Our systematic review on MIS-A had a few limitations. This study is mainly descriptive including primarily case reports and case series due to which the level of evidence is low. Additionally, due to inclusion of multiple studies, there is a risk of reporting bias. We stringently followed the CDC case definition of MIS-A and excluded reports which did not describe patients presenting with fever, a cardinal characteristic of MIS-A.

Conclusion

MIS-A was previously an unknown clinical entity in the early half of 2020 and has recently assumed a greater recognition following multiple waves of COVID-19 infection. There is a need for prompt recognition of MIS-A in order to limit the hyperinflammatory response and prevent development of severe organ dysfunction and poor outcomes. Though MIS-A is a rare clinical entity, its long-term sequelae is largely unknown. The emergence of MIS-A calls for harmonizing case definitions for establishing a correct diagnosis as well as definite treatment guidelines. This would largely be possible through wider research, collaborative efforts and development of data registries and clinical cohorts.

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No conflict of interests declared.

Informed consent

Not applicable

Contributors

SK, PI, NM involved in Conceptualization, literature search, writing the original draft of manuscript, literature search, planning, conduct and editing. SK, PI, NM, PS, KG involved in review and editing. All the authors have read and agreed with the submitted manuscript

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.hrtlng.2022.03.007.

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