A Systematic Review of Multisystem Inflammatory Syndrome in Children Associated With SARS-CoV-2 Infection

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Background: Recently, severe manifestations associated with coronavirus disease 2019 (COVID-19) called multisystem inflammatory syndrome in children (MIS-C) have been recognized. Analysis of studies for this novel syndrome is needed for a better understanding of effective management among affected children.

Methods: An extensive search strategy was conducted by combining the terms multisystem inflammatory syndrome in children and coronavirus infection or using the term multisystem inflammatory syndrome in children in bibliographic electronic databases (PubMed, EMBASE, and CINAHL) and in preprint servers (BioRxiv.org and MedRxiv.org) following the Preferred Reporting Items for Systematic Reviews and Metaanalyses guidelines to retrieve all articles published from January 1, 2020, to July 31, 2020. Observational cross-sectional, cohort, case series, and case reports were included.

Results: A total of 328 articles were identified. Sixteen studies with 655 participants (3 months–20 years of age) were included in the final analysis. Most of the children in reported studies presented with fever, gastrointestinal symptoms, and Kawasaki Disease-like symptoms. Sixty-eight percent of the patients required critical care; 40% needed inotropes; 34% received anticoagulation; and 15% required mechanical ventilation. More than two-thirds of the patients received intravenous immunoglobulin and 49% received corticosteroids. Remdesivir and convalescent plasma were the least commonly utilized therapies. Left ventricular dysfunction was reported in 32% of patients. Among patients presenting with KD-like symptoms, 23% developed coronary abnormalities and 26% had circulatory shock. The majority recovered; 11 (1.7%) children died.

Conclusions: This systematic review delineates and summarizes clinical features, management, and outcomes of MIS-C associated with SARS-CoV-2 infection. Although most children required intensive care and immunomodulatory therapies, favorable outcomes were reported in the majority with low-mortality rates.

Accepted for publication August 23, 2020.

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The authors have no funding or conflicts of interest to disclose.

A.K. and S.G. have contributed equally as cofirst authors. M.S. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors participated in concept and design. A.K., S.G., M.S., S.S., and S.V. did acquisition, analysis, or interpretation of data. A.K., S.G., M.S., and S.V. did drafting of the article. A.K., S.G., M.S., and S.S. participated in critical revision of the manuscript for important intellectual content. A.K., S.G., M.S., S.S., and S.V. did statistical analysis. A.K. and S.G. participated in administrative, technical, or material support. A.K., M.S., and S.G. participated in supervision.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (www.pidj.com)

ISSN: 0891-3668/20/3911-e340
DOI: 10.1097/INF.0000000000002888

Key Words: multisystem inflammatory syndrome, children, SARS-CoV-2, COVID-19

(*Pediatr Infect Dis J* 2020;39:e340–e346)

Multisystem inflammatory syndrome in children is a novel spectrum of pediatric illness that has been recently recognized in association with SARS-CoV-2 infection. As of July 2020, children and adolescents constitute a small proportion (1%–5%) of the total 12,274,654 laboratory-confirmed COVID-19 cases reported worldwide.[1,2] Although early reports of COVID-19 showed mild or asymptomatic disease in the majority of children,[1] since late April, reports from Europe and North America have described clusters of children and adolescents with a multisystem inflammatory condition leading to multiorgan failure with a temporal association with SARS-CoV-2 infection.[3,4] Kawasaki Disease (KD) like illness with COVID-19 was first described in late April in United Kingdom in 8 children of whom 1 died[5] and variable presentations of MIS with features resembling macrophage activation syndrome, Kawasaki shock syndrome, and toxic shock syndrome, with markedly elevated inflammatory markers have since been recognized.[6–9] On May 14, 2020, the United States Centers for Disease Control (CDC) named this entity Multisystem Inflammatory Syndrome in Children (MIS-C) associated with COVID-19 and introduced a case definition.[3] The understanding of this novel syndrome is evolving and the clinical spectrum and optimal treatment regimens for MIS-C are not fully understood. We aim to analyze the literature to clarify the clinical spectrum, treatment modalities, and outcomes of this novel syndrome by means of systematic review of studies on MIS-C. This can further help define the appropriate management approach and therapeutic strategies for these children.

METHODS

Outcome

The primary outcome of this study was the systematic evaluation and characterization of currently reported cases of multiple inflammatory syndromes in pediatric patients associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

Search Strategy

We conducted an extensive literature search in several electronic bibliographic databases (PubMed, EMBASE, CINAHL) and in preprint servers (BioRxiv.org and MedRxiv.org) and retrieved all articles published from January 1, 2020, to July 31, 2020, using the search terms "multisystem inflammatory syndrome in children" OR combining "COVID-19" OR "Coronavirus" OR "SARS-CoV-2" AND "MIS-C" OR "Multisystem inflammatory syndrome" OR "pediatric hyperinflammatory syndrome" OR "pediatric inflammatory multisystem syndrome" OR "pediatric multisystem inflammatory syndrome."

Observational cross-sectional and cohort studies, case reports/series reporting MIS-C were screened. The Preferred Reporting

Items for Systematic Reviews and Metaanalyses (PRISMA) reporting guideline was followed,[10] and available full texts and the reference lists of all the relevant studies were screened. There was no language restriction in our search. Search results were compiled in accordance with the quality standards for reporting systematic reviews and metaanalysis of observational studies,[11] and the retrieved articles were screened by 2 independent investigators (M.S. and S.S.) who also independently studied full texts of records considered eligible for inclusion, resolving any discrepancies by discussion and consensus.

Study Selection and Risk of Bias Assessment

We assessed the risk of bias for all eligible observational studies according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.[12]

The risk was evaluated using a question tool explicitly designed for this review, which asked questions regarding (1) Selection criteria of patients: Do all the patients meet inclusion criteria (0- to 21-year-old participants affected by SARS-CoV-2 and having fever and laboratory evidence of inflammation meeting published definitions for MIS-C)? (2) Adequate ascertainment of exposure and the outcome (3) Causality: was follow-up long enough for outcomes to occur? (4) Reporting: were the case(s) described with sufficient detail to allow other investigators to replicate the research or to allow practitioners to make inferences?

Possible item rankings were yes (2 stars), partial (1 star), and no (0 star).[13] An overall risk of bias was independently assigned to each eligible study by 2 researchers (M.S. and S.S.), and a third reviewer (A.K.) was consulted for any disagreement. No studies rated below 3 were included in the systematic review (see Table, Supplemental Digital Content 1, http://links.lww.com/INF/E106, which illustrates risk of bias assessment).

The inclusion and exclusion criteria for studies are shown in Table 1.

Data Extraction

Data from each eligible study were extracted by 2 independent reviewers (M.S. and S.S.) using a standardized data extraction sheet followed by cross-checking of the results. We extracted the following information: first author name, country, type of study (retrospective/prospective, case report, case series, single center, or multicenter), age (0–21 years), and gender of affected children, clinical presentation, diagnostic tests [SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR), SARS-CoV-2 serology], inflammatory markers, cardiac evaluation including biomarkers and echocardiography, chest radiograph, chest computed tomography/magnetic resonance imaging, therapeutic agents and prognosis (hospitalization, intensive care unit admission, complications, or death).

RESULTS

The search found 328 articles [182 records from Medline PubMed, 27 records from EMBASE, 4 records from CINAHL, and 115 records identified through search of other databases (unpublished preprints in BioRxiv.org and MedRxiv.org)]. After removing 198 unrelated and duplicate articles, 130 records were reviewed based on the title and abstract, and, of those, 101 articles were excluded based on article topic (pathogenesis and molecular aspects, other serotypes of coronavirus, other viral agents), article type (reviews, editorials, comments, guidelines), and population (adult patients with COVID-19). Twenty-nine full texts were assessed for eligibility with 13 records excluded based on article type (editorials, reviews, systematic reviews, guidelines). Sixteen articles met the inclusion criteria and were analyzed for the systematic review (see Figure, Supplemental Digital Content 2, http://links.lww.com/INF/E107).

Study Characteristics and Demographic Features

All included studies reported data from March to July, 2020, except 1 study from Italy that included data from February 2020.[6] The included articles represented global disease burden of MIS-C with data from the United States, Europe (France, United Kingdom, Italy, and Spain), and South Asia (India) (Table 2).[6,9,14–27]

We found a total of 655 patients with MIS-C associated with SARS-CoV-2 infection. All included articles reported the age of affected children (Table 2). Children were 3 months to 20 years of age, and the median age was 8 years in most of the studies. Three studies had infants 3, 4, and 7 months of age.[20,23,27] All studies described gender of the affected children. Three hundred and sixty-one (55%) children were male (male: female ratio 1.2:1). Eight studies reported high proportions of patients affected by MIS-C to be Black, Hispanic, or South Asian.[9,14–16,18–20,23]

One hundred and fifty-three (23.3%) children had comorbidities (87 were obese/overweight; 39 had respiratory, 6 had cardiac, and 21 had other comorbid conditions including acute lymphoblastic leukemia, epilepsy, neurodisability, and alopecia).[9,14,16,18–21,23,24]

Clinical Features

Clinical symptoms were reported in all studies. The median duration from symptom onset to hospital admission was 4 days (interquartile range, 3–6 days). Fever was the most common presenting symptom followed by gastrointestinal (GI) manifestations.

Gastrointestinal manifestations were reported in all studies except 1,[27] and seen in 458 (70%) patients, with presentation mimicking viral gastroenteritis or inflammatory bowel disease with nausea, vomiting, diarrhea, and abdominal pain (Table 2).

Cardiovascular symptoms at presentation were reported in 332 (51%) patients. One hundred and eighty-six (28%) patients presented with hypotension. KD like symptoms were seen in 235 (36%) patients of whom 41 had features of classic/typical KD and 194 had atypical presentation. Among patients presenting with KD like symptoms, 62 (26%) patients had circulatory shock.[6,16,18,23,25–27]

Involvement of central nervous system was reported in 12 studies with 145 (22%) of children presenting with aseptic

TABLE 1. Selection Criteria for Studies

Inclusion criteria
1. Population: Children and adolescents (0–21 yr of age) with MIS associated with SARS-CoV-2 infection.
2. Study design: Observational cross-sectional and cohort studies, case reports/series, reporting multisystem inflammatory syndrome in children.
3. Outcome: Evaluation of age, clinical presentation, diagnosis, therapeutic management, associated cardiac morbidity, and prognosis of children with MIS with COVID-19.

Exclusion criteria
1. Clinical guidelines, consensus documents, clinical trials, reviews, systematic reviews, webinars, and conference proceedings
2. Studies about other serotypes of severe acute respiratory syndrome coronavirus and Middle East respiratory syndrome coronavirus infection
3. Studies of MIS unrelated to SARS-CoV-2 infection

MIS, multisystem inflammatory syndrome; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

TABLE 2. Clinical Characteristics of Patients With MIS-C

Study No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Country	United States	United States	United States	United States	United States	United States	United States	United States	United States	France	United Kingdom	Italy	Spain	India	India	India
Author	Kaushik S et al	Riollano-Cruz M et al	Chiotos K et al	Capone C A et al	Greene A G et al	Dufort E M et al	Feldstein L R et al	Miller J et al	Y Pui et al	Belot A et al	Whittaker E et al	Verdoni L et al	Moraleda C et al	Balasubramanian et al	Rauf A et al	Acharyya B C et al
Time Period	April 23 to May 23, 2020	April 24 to May 15, 2020.	ns	April 17, to May 13, 2020	May 2020	March 1 to May 10, 2020	March 15 to May 20, 2020	April 18 to May 22, 2020	March 17 to June 6, 2020	March 1 to May 17, 2020	March 23 to May 16, 2020	Feb 18 to April 20, 2020	March 1 to June 1, 2020	May 2020	May 2020	May 2020
Type of study	Multicenter, retrospective cohort	Single center retrospective cohort	Single center case series	Single center case series	Single center case report	Multicenter case series	Multicenter case series	Single center case series	Single center case series	Multicenter case series	Multicenter case series	Single center case series	Multicenter case series	Case report	Case report	Case report
Number of children (n)	33	15	6	33	1	99	186	44	28	108	58	10	31	1	1	1
Age (yr)	Median 10 (IQR, 6–13)	Median 12 (IQR, 3–20)	Range 5–14	Median 8.6 (IQR, 5.5–12.6)	11	Range 6–12 yrs	Median 8.3 (IQR, 3.3–12.5)	Median 7.3 (IQR, 7 mo–20 yr)	Median 9 (IQR, 5.7–14)	Median 8 (IQR, 5–11)	Median 9 (IQR, 3 mo–17 yr)	Median 7.5 (IQR, 2.9–16)	Median 7.6 (IQR, 4.5–11.5)	8	5	4 mo
Clinical symptoms:																
Fever n (%)	31 (93)	15 (100)	6 (100)	33 (100)	1 (100)	99 (100)	186 (100)	44 (100)	28 (100)	20 (100)	23 (40)	10 (100)	30 (97)	1 (100)	1 (100)	1 (100)
Gastrointestinal symptoms n (%)	21 (63)	13 (87)	4 (67)	32 (97)	1 (100)	79 (80)	171 (92)	37 (84.1)	15 (54)	20 (100)	31 (53)	6 (60)	27 (87)	1 (100)	1 (100)	NR
Cardiovascular n (%)	21 (63)	13 (87)	6 (100)	25 (76)	1 (100)	11 (11)	149 (80)	22 (50)	15 (54)	20 (100)	29 (50)	2 (20)	15 (48)	1 (100)	1 (100)	1 (100)
Neurologic symptoms n (%)	4 (12)	4 (26)	3 (50)	19 (58)	NR	30 (30)	22 (12)	13 (29.5)	NR	NR	15 (26)	4 (40)	6 (21)	NR	NR	1 (100)
Skin Rash n (%)	14 (42)	7 (47)	2 (33)	21 (64)	1 (100)	59 (60)	110 (59)	31 (70.5)	10 (36)	66 (61)	30 (52)	5 (50)	21 (67)	1 (100)	NR	1 (100)
Conjunctival injection n (%)	12 (36)	4 (27)	2 (33)	NR	NR	55 (56)	103 (55)	23 (52.3)	16 (57)	NR	26 (45)	NR	21 (67)	NR	1 (100)	NR
Respiratory symptoms n (%)	11 (33)	NR	4 (66)	17 (52)	NR	40 (40)	NR	NR	14 (50)	NR	12 (21)	NR	11 (36)	NR	NR	1 (100)

IQR, interquartile range; NR, not reported; NS, not specified.

TABLE 3. Geographic Variation in Presenting Symptoms of MIS-C

	United States (n = 445)	Europe (n = 207)	India (n = 3)
Presenting symptoms (% of patients)			
Fever	100	80	100
Rash	57	59	67
Conjunctival injection	48	23	33
Gastrointestinal symptoms	84	74	67
Cardiovascular symptoms	59	74	67
Neurologic symptoms	21	12	33
Respiratory symptoms	19	11	33

meningitis, headache, or altered mental status.[6,9,14–16,18–21,23,24,27] Only 8 studies reported respiratory symptoms like cough and congestion.[14–16,18,21,23,24,27]

Rash was reported in 379 (58%) patients, edema over hands and feet in 83 (13%), conjunctival injection in 263 (40%), red cracked lips in 148 (23%), strawberry tongue in 29 (4.5%); and cervical lymphadenitis was reported in 27(4%) patients. The presenting features reported in studies from different geographical regions are shown in Table 3. Conjunctival injection and GI manifestations were seen most commonly in children at presentation in studies from the United States, while rash was commonly reported in cases from India, and cardiovascular involvement at presentation was most commonly seen in studies from Europe, respectively.

Laboratory Evaluation and Imaging Findings

Increased levels of C-reactive protein, troponin, and B-type natriuretic peptide (BNP) were reported in all studies. Troponin was increased in 234 (36%) patients and BNP in 263 (40%) patients. Lymphopenia was seen in 380 (58%) patients and reported in all except 4 studies.[20,22,26,27]

Other hematologic abnormalities including anemia, thrombocytopenia, neutrophilia was seen in 142 (22%) patients. Increased interleukin (IL)-6 and IL-8 levels were reported by 5[9,14,17,18,24] and 2 studies, respectively,[9,14] while normal levels of IL-1 was reported in 2 studies.[9,14]

Raised ferritin levels (>500 ng/mL) were reported in all except 5 studies,[15,20,25–27] while 10 studies reported elevation of D-dimers (>2.5 ng/mL).[9,14–19,21,23,24] Fibrinogen elevation was reported in 10 studies.[6,9,14,16–19,21–23]

Ten studies reported chest imaging abnormalities including opacities/infiltrates noted on chest radiograph/chest computed tomography in 90 (13.7%) patients.[6,9,14–16,18,20,21,25,26]

Echocardiography was obtained in 482 (73%) patients and decreased left ventricular ejection fraction of <55% was reported in 211 (32%) patients of whom 23 (11%) had an ejection fraction below 30%.[14,16,19,21,24] Myocarditis was present in 150 (23%) patients.[14,18,22,26] Among patients presenting with KD like symptoms, 55 (23.4%) patients had coronary artery dilatation/aneurysms.[6,9,15,16,18,19,21,23,24]

SARS-CoV-2 Test Results

In all included studies, patients were tested for SARS-CoV-2 RT-PCR and serology. A total of 218 (33%) patients tested positive for SARS-CoV-2 by RT-PCR, while 352 (54%) patients had antibodies against SARS-CoV-2. Forty-four (7%) patients had both antibodies as well as a positive SARS-CoV-2 RT-PCR testing.[14,18,24] Recent exposure to COVID-19-positive family members was mentioned in 8 studies for 99 (15%) patients.[15–17,21–25]

Therapeutic Management

All patients were hospitalized, and the majority (447, 68%) of patients with MIS-C required intensive care with a median duration of intensive care unit stay of 5 days (IQR, 4–8 days). All of the studies reported therapeutic agents used for the treatment of MIS-C. Intravenous immunoglobulin (IVIG) was used for treatment in 15 studies, and corticosteroid use was reported in 12 studies with 13 and 10 studies reporting the use of inotropic support and anticoagulation, respectively (Table 4).

For treatment of MIS-C, IVIG was used in 410 (63%) patients, corticosteroids in 321 (49%), anakinra in 51 (8%), tocilizumab in 43 (6.5%), remdesivir in 19 (3%), infliximab in 8 (1.2%), and plasma therapy used in 3 children. One patient received hydroxychloroquine.[21] Forty-one (7%) patients required a second dose of IVIG, due to ongoing fever.[15,19]

Inotropes were required in 261 (40%), anticoagulant therapy in 224 (34%), mechanical ventilation in 96 (15%), extracorporeal membrane oxygenation in 18 (2.7%) patients. One patient received intraaortic balloon pumping.[14] Thirty-four percentage of patients received aspirin and low molecular–weight heparin was administered to patients with significantly elevated D-dimer and fibrinogen levels with left ventricular dysfunction, coronary artery involvement, or echocardiographic changes.[16,17] Use of empiric broad-spectrum antibiotics for possible sepsis was reported in all studies.

Outcome

A total of 570 patients (87%) were discharged, and 74 (11%) were still hospitalized till the time of publication of studies; 11 children (1.7%) died in the hospital.[9,14,18,19,22–24] Six patients died while on extracorporeal membrane oxygenation,[9,14,18,19] and the other fatalities were reported to be possibly related to complications of inflammatory, coagulopathic, or neurologic processes. Compared with reports from the United States with 8/445 (1.7%) fatalities, there were 3/207 (1.4%) deaths reported in studies from Europe. Duration of hospitalization ranged from 4 to 13 days with a median of 7 days in most studies.

In the studies that reported outcomes at discharge[14,16,17] or during follow-up[9,15] majority of the patients with cardiac involvement had full recovery of left ventricular dysfunction and normalization of cardiac inflammatory markers except for mild cardiac dysfunction seen in 9 patients in 1 study at discharge.[16] One patient was noted to have right coronary artery dilatation 14-day postdischarge.[15]

DISCUSSION

This systematic review of multisystem inflammatory syndrome in children analyzes and summarizes available data including the epidemiology, clinical course, and outcomes of MIS-C globally from 16 published studies till July 31, 2020. All included studies reflect reported data from the United States, France, United Kingdom, Italy, Spain, and India. Surprisingly, China, from where the pandemic had originated has not reported any cases of MIS-C, and most reports of hospitalized children with COVID-19 from China have indicated mild disease in affected children.[1,28,29] Reasons for this observation are unclear and may involve differences in rates of infection in children, host factors, or incomplete reporting.

Clinical definitions for MIS-C have been provided by the Centers for Disease Control and Prevention (US CDC),[3] the World Health Organization,[4] and the Royal College of Paediatrics and Child Health.[30] In this review, clinical presentation of MIS-C resembled features of other pediatric inflammatory conditions such as KD, toxic shock syndrome, sepsis, and macrophage activation syndrome.[6,8,22,23] Most of the affected children were previously healthy. MIS was noted to affect children of all ages; however, occurrence in infants was reported in 3 studies. Notably, several studies reported

TABLE 4. Therapeutic Management of Patients With MIS-C

Study no.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
IVIG n (%)	18 (54)	12 (80)	6 (100)	33 (100)	1 (100)	69 (70)	144 (77)	36 (81.8)	20 (71)	NR	41 (71)	10 (100)	20 (65)	1 (100)	1 (100)	1 (100)
Corticosteroids n (%)	17 (51)	3 (20)	5 (84)	23 (70)	1 (100)	63 (64)	91 (49)	42 (95.5)	17 (61)	NR	37 (64)	NR	21 (68)	NR	1 (100)	NR
Tocilizumab n (%)	12 (36)	12 (80)	NR	3 (9)	1 (100)	NR	14 (8)	NR	NR	NR	NR	NR	NR	1 (100)	NR	NR
Remdesivir n (%)	7 (21)	2 (13)	NR	NR	1 (100)	NR	NR	NR	7 (25)	NR	NR	NR	2 (6)	NR	NR	NR
Anakinra n (%)	4 (12)	2 (13)	1 (16)	4 (12)	NR	NR	24 (13)	8 (18.2)	5 (18)	NR	3 (5)	NR	NR	NR	NR	NR
Convalescent plasma n (%)	1 (3)	1 (7)	NR	NR	1 (100)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Hydroxychloroquine n (%)	NR	NR	NR	NR	NR	NR	NR	NR	1 (0.4)	NR	NR	NR	NR	NR	NR	NR
Inotropic support n (%)	17 (51)	8 (53)	5 (84)	10 (30)	1 (100)	61 (62)	48 (25)	NR	7 (25)	79 (73)	27 (47)	2 (20)	NR	1 (100)	1 (100)	NR
Anticoagulation n (%)	33 (100)	15 (100)	3 (50)	29 (88)	1 (100)	NR	87 (47)	40 (90)	13 (46)	NR	NR	2 (20)	NR	NR	NR	1 (100)
Invasive mechanical ventilation n (%)	5 (15)	3 (20)	3 (50)	6 (18)	NR	10 (10)	37 (20)	1 (2.3)	NR	NR	25 (43)	NR	6 (19)	NR	NR	NR
ECMO n (%)	1 (3)	1 (7)	1 (16)	NR	NR	4 (4)	8 (4)	NR	NR	NR	3 (5)	NR	NR	NR	NR	NR

ECMO, extracorporeal membrane oxygenation; IVIG, intravenous immunoglobulin; NR, not reported.

high incidence of MIS-C among Blacks, Hispanics, and South Asi ans,[9,14–16,18–20,23] which emphasizes the critical importance of measures to prevent virus transmission in these groups.[31]

GI manifestations were reported to be one of the main presenting clinical features. This is in contrast to adults with COVID-19, who commonly present with respiratory symptoms, and report GI symptoms in <10%–15% of cases.[6] Pulmonary involvement was not noted to be a prominent feature in most of the reported studies.

Among patients presenting with KD like symptoms, more than 20% of the patients had coronary artery dilatation/aneurysms[6,9,15,16,18,21,23,24] and hypotension.[6,16,18,23,25–27] Although similar to KD, there were several notable differences between MIS-C in this systematic review and KD. MIS-C tended to affect older children and adolescents, as supported by the median age in most of the studies in this review. A higher proportion of MIS-C patients with KD-like symptoms presented with shock (28%) compared with less than 3% rates of shock known with KD.[32] Moreover, patients with MIS-C had higher rates of coronary artery abnormalities as noted above. Another difference was the markedly elevated markers of inflammation and moderate to severe myocardial involvement (as shown by the echocardiographic findings and the elevated BNP and troponin levels) seen in patients with MIS-C. Moreover, the cytokine profile leading to the inflammatory process was distinct in patients with MIS-C. Although interleukin levels were rarely obtained, a few studies reported elevated levels of IL-6 and IL-8 and showed a noteworthy discordance between IL-6 and IL-1.[9,15] In patients with KD, IL-1 appears to be the main mediator of coronary artery inflammation,[32] while the inflammatory process in MIS-C appears to be driven predominantly by IL-6 and IL-8, which may play a role in myocardial injury/dysfunction.[33,34] Myocardial dysfunction could be due to direct viral invasion of myocytes, systemic inflammatory response triggering myocyte injury compounded by myocardial ischemia secondary to hypotension, or secondary to inflammatory mediators; however, further studies are needed to elucidate disease mechanisms.[14]

The pathogenesis of MIS-C is not well understood, and it is thought to be a postinfectious immune-mediated phenomenon, as seen from a lag of 2–4 weeks between occurrence of peak incidence of COVID-19 cases in communities and the recognition of MIS-C.[3] Moreover, the high percentage of seropositivity for SARS-CoV-2 with MIS-C, as also seen in this review, also supports this hypothesis. Overall, a third of the patients tested positive for SARS-CoV-2 by RT-PCR, while more than a half had antibodies against SARS-CoV-2. However, prior COVID-19 exposure was reported only for 15% of patients in studies and most of the children developed MIS-C without prior history of exposure, suggesting that asymptomatic spread of SARS-Co-V-2 could have led to MIS-C in a sizable proportion of patients.

Most children with MIS-C in the studies were severely ill needing critical care. Although most patients with MIS-C required intensive care and immunomodulatory therapies, and a large proportion also needed inotropes and anticoagulation, favorable outcomes were observed with low mortality (<2%). Mortality rates in studies from the United States and Europe were comparable. Because of biochemical and clinical similarities with KD, principles of therapy for KD were successfully used in the majority of patients and treatment was associated with rapid clinical improvement and reduction in inflammatory markers in most patients. IVIG and steroids were used in the majority and less than 20% of the patients received other immunomodulators like interleukin-1, interleukin-6, and tumor necrosis factor alpha inhibiting agents. Remdesivir and convalescent plasma were the least commonly utilized therapies reported. Interestingly, in adults with COVID-19, remdesivir is the preferred agent in critically ill patients per guidelines

from the National Institutes of Health, and plasma is being increasingly utilized, in contrast to pediatric patients with MIS-C thus far.[35–37] One of the studies reported using hydroxychloroquine.[21]

Only a few studies have reported posthospital discharge follow-up data, and most cardiac abnormalities were reported to have resolved at discharge or on follow-up except for a few patients.[15,16] However, the long-term outcomes of MIS-C, such as the squeal of coronary artery aneurysm formation, remain unknown. Follow-up studies and long-term cardiac surveillance are needed to monitor late effects on cardiac function and ascertain development of coronary abnormalities.

According to the World Health Organization, management of MIS should involve multidisciplinary care with intensive care, pediatric cardiology, infectious disease, and rheumatology specialists. Recently, American College of Rheumatology has published clinical guidance for diagnostic and therapeutic management for MIS-C.[38] The guidelines recommend immunomodulatory therapy for all critically ill patients with shock, significant respiratory distress, severe neurologic involvement or features of KD. IVIG and glucocorticoid remain first-line therapies either alone or in combination with other agents.

The true incidence of MIS-C remains unknown. Because children often present with mild symptoms of COVID-19[1] and are less frequently tested than adults, the incidence of MIS-C among children infected with SARS-CoV-2 is unclear. It is crucial to establish surveillance for MIS-C cases, particularly in communities with higher levels of SARS-CoV-2 transmission.

STRENGTHS AND LIMITATIONS

This systematic review summarizes the clinical features, management, and outcomes of patients with MIS-C from 16 studies globally. Another key strength is the lack of population bias since most patients had evidence of current or recent SARS-CoV-2 infection and were nucleic acid and serology positive.

This study has several limitations. First, the included studies were observational, and all of the data was collected retrospectively. No randomized control trial on MIS-C has been conducted thus far, and many studies were simple case series or case reports. Second, the research occurred over a short 5-month period. Third, this being a very novel disease, very few postdischarge outcomes studies are available, and the incidence of coronary artery aneurysms and cardiac function in convalescence could not be ascertained due to lack of follow-up evaluations. The available data also cannot address the mechanisms underlying MIS-C. Fourth, we presume that the numbers in our systematic review may be an underestimation, possibly due to mild cases of MIS-C not being hospitalized, and possible underreporting of cases due to lack of recognition of an emerging syndrome. Some patients may have been excluded due to not being fully investigated. In addition, the lack of molecular or serologic testing early in the outbreak among asymptomatic or mildly symptomatic children and clinician testing practices in children may have led to underrecognition.

CONCLUSIONS

This systematic review assesses and summarizes the current evidence on MIS-C associated with SARS-CoV-2 infection. The data include studies from the United States, Europe, and South Asia and delineate clinical presentation, therapeutic management, and outcomes in patients with MIS-C. Fever, GI symptoms, and KD-like symptoms were the main presenting symptoms. Most patients were critically ill, requiring intensive care and immunomodulatory therapies; however, the majority recovered with low mortality. In the context of MIS-C, several unanswered questions remain, including pathogenesis, long-term complications, and immunity for which more studies are needed. It is likely that long-term prognosis will become clearer as more scientific data becomes available.

ACKNOWLEDGMENTS

None.

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