Multisystem Inflammatory Syndrome in Children (MISC): a systematic review

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Abstract

Context: Multisystem Inflammatory Syndrome in Children (MISC) is a newly and rising condition, particularly in SARS-CoV-2 high transmission communities. Objective: Analyze current literature and reported cases of MISC, concerning its clinical spectrum, complications associated, therapeutic strategies and distinguishing features of other clinical syndromes. Data Sources: Extensive literature research was performed in MEDLINE (trough PubMed), Scopus and Web of Science from December 2019 to December 2020.Study Selection: First analysis included all article titles and abstracts screening to identify relevant studies and second analysis included a full text screening of previous selected studies. Eligibility was assessed independently by two authors and disagreements were resolved by discussion and consensus. Data Extraction: Data were extracted on MISC definition, demographic data, clinical features, diagnostic tests, laboratory analysis andimaging, therapeutical approach and outcomes. Results: Common symptoms included: gastrointestinal (70%), rash (57%) and cardiovascular (52% with shock). Notable differences with Kawasaki Disease were identified including age, clinical presentation and cardiac involvement. 30% presented positive SARS-CoV-2 2 reverse transcription polymerase chain reaction and 51% positive serologies. 62% received intravenous immunoglobulin and 42% glucocorticoids. 62% required intensive care, 21 children died (<2%). Severe presentations were associated with neurological symptoms, hepatitis and acute kidney injury. Limitations: As a recently documented disease, there was limited prospective and follow-up studies, therefore disregarding long-term sequelae and prognosis. Conclusions: MISC raises concern on its severe cardiac involvement at presentation, with frequent intensive care and immunomodulatory therapy need. Short term outcomes seem to be favorable, with cardiac disfunction recovery and low mortality rates.

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Results: Common symptoms included: gastrointestinal (70%), rash (57%) and cardiovascular (52% with shock). Notable differences with Kawasaki Disease were identified including age, clinical presentation and cardiac involvement. 30% presented positive SARS-CoV-2 2 reverse transcription polymerase chain reaction

and 51% positive serologies. 62% received intravenous immunoglobulin and 42% glucocorticoids. 62% required intensive care, 21 children died (<2%). Severe presentations were associated with neurological symptoms, hepatitis and acute kidney injury.

Conclusions: MISC raises concern on its severe cardiac involvement at presentation, with frequent intensive care and immunomodulatory therapy need. Short term outcomes seem to be favorable, with cardiac disfunction recovery and low mortality rates.

Keywords: multisystem inflammatory disease COVID-19 related, child, SARS-CoV-2, COVID-19

Review criteria

References for this Review were performed in three electronic databases namely MEDLINE, Scopus and Web of Science and includes articles from December 2019 to December 2020. Other pertinent references were identified from key online sources (WHO). The search strategy was restricted to studies concerning human subject, with no language restriction

Message for the clinic

- MISC present notable differences with Kawasaki Disease, including age, clinical presentation and cardiac involvement.
- Severe presentations associated with neurological symptoms, hepatitis and acute kidney injury.
- Opposing to severe cardiac involvement and intensive care need, recovery appears favorable and mortality low.

Main body

INTRODUCTION

Coronavirus disease-2019 (COVID-19) is a respiratory tract infection caused by the recent identified severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). This viral infection emerged in late 2019 from an outbreak of unexplained pneumonia in Wuhan, China. Frequent reported symptoms include fever, dry cough and shortness of breath.[1-4]

Over the first months of 2020, SARS-CoV-2 infection has quickly spread worldwide through human populations, leading to a global health emergency. On 11 March 2020, the World Health Organization (WHO) officially declared COVID-19 as a global pandemic disease.[1,3,4] As of 1 March 2021, there are more than 100 million confirmed cases and over 2 million deaths.[5]

In comparison to adults, children were disproportionately spared from this infection.[6] Current evidence suggests that children's immune systems seems better prepared to eradicate SARS-CoV-2.[7] However, as most children are asymptomatic or present with only mild symptoms, the actual viral load and virus transmission among them remains unclear.

Notwithstanding that manifestations of the disease are usually milder, reports since April 2020 have described a subset of children with a multisystem inflammatory condition associated temporally and geographically with COVID-19, requiring hospitalization and intensive care.[8,9] This condition showed overlapping clinical features with previous known diseases such as Kawasaki disease (KD), toxic shock syndrome and macrophage activation syndrome, including abdominal pain, prolonged fever, cardiac dysfunction and multiple organ failure.[8-10] The condition has been termed Multisystem Inflammatory Syndrome in Children (MISC), also referred to as Pediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-CoV-2 or PIMS-TS. Case definitions for this syndrome were developed by WHO, Centers for Disease Control (CDC) and the Royal College of Paediatrics and Child Health (RCPCH).[8,10,11] Case definitions are presented in appendix (figure 1).

As much remains unknown of COVID-19, and particularly MISC, the aim of this systematic review was to analyze the current literature and reported cases of this newly unknown syndrome, in order to provide an overview of its clinical spectrum, complications associated, therapeutic strategies and distinguishing features

of other clinical syndromes, such as KD. Furthermore, this review's outcomes shall provide insights into current practice and suggestions for future research.

METHODS

Protocol

A review was conducted based on Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines.[12]

Eligibility criteria

Prospective and retrospective observational studies, cross-sectional studies and case series reporting MISC from December 2019 to December 2020 were considered. Only CDC, WHO or RCPCH case definition were included. The search strategy was restricted to studies concerning human subject, with no language restriction. Data concerning simultaneously MISC and other COVID-19 clinical presentations were included, unless the MISC group was not separated from the rest of the groups studied. Duplicate articles, comments, editorial letters, case reports, narrative or systematic reviews and clinical guidelines, as those not related with the purpose of the study were excluded. Reports with other coronavirus serotypes or pediatric inflammatory multisystem syndromes unrelated to SARS-CoV-2 infection were also excluded. Studies with patients included in larger studies were excluded to avoid duplicate results.

Search strategy and data sources

On January 1, 2021, an extensive literature research was performed in three electronic databases, namely: MEDLINE (trough PubMed), Scopus and Web of Science. The following search terms and equivalent British English terms were used: 'multisystem inflammatory disease' OR 'inflammatory multisystem syndrome' OR 'MISC' OR 'MIS-C' OR 'Kawasaki' OR 'Mucocutaneous Lymph Node Syndrome' AND 'infant' OR 'newborn' OR 'neonate' OR 'child' OR 'adolescent' AND 'severe acute respiratory syndrome coronavirus 2' OR 'SARS-CoV-2' OR 'nCov' OR 'COVID-19' OR '2019 novel coronavirus' OR '2019-nCoV' OR 'coronavirus disease 2019' OR 'Wuhan coronavirus' or 'Wuhan seafood market pneumonia virus'.

Study selection and Risk of Bias Assessment

First analysis included all article titles and abstracts screening to identify relevant studies with references crosschecked to identify articles missed by the initial search strategy. Second analysis included a full text screening of previous selected studies. Eligibility was assessed independently by two authors (D.G. and R.P.). Disagreements were resolved by discussion and consensus.

Risk of bias was assessed for all eligible studies according to the National Institutes of Health reporting guideline, using two study quality assessment tools: one for observational cohort and cross-sectional studies and another for case series studies. An overall risk of bias was independently assigned to each eligible study by two researchers and classified into good, fair and poor.

Data collection process

Data extraction from studies included were done using a standardized data extraction sheet followed by cross-checking and discussion of the results. Data were extracted on MISC definition, demographic data, including age, sex, ethnicity and past medical history, clinical features, diagnostic tests including SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) and serology, laboratory analysis and imaging, treatment and outcomes.

Synthesis of results

Categorical variables were presented as absolute and relative frequencies. When specific outcomes of interest were not reported in all studies, frequencies were evaluated considering only the patients included in the studies where it was reported. In case series without summary measures of their continuous variables,

including age, days of hospital admission or laboratory values, as there was an asymmetrical distribution, median was measured by the authors.

RESULTS

Study selection

Through database searching, 520 records were identified in MEDLINE, 421 in Scopus and 280 in Web of Science. After duplicates removed, 653 records were included in the first analysis, excluding a total of 535 articles. 117 full-text retrieved articles were carefully assessed in the second analysis. From these, 86 were excluded as followed: 24 for study design (comments, editorial letters, single case reports or reviews), 19 studies for presenting patients included in subsequent larger studies, 16 studies did not define or meet CDC, WHO or RCPCH case definitions, nine studies did not addressed a group of only MISC and 18 studies presented insufficient data on clinical features and laboratory markers. In the end, 31 studies were included in this systematic review to undergo data extraction, reporting a total of 1415 patients with MISC. A detailed flow diagram of the study design is presented in Figure 1.

All eligible studies were rated as good after risk of bias assessment, detailed in supplementary table 1.

Study characteristics

Studies characteristics are summarized in supplementary table 2. Almost half of the studies were multicenter, being the largest from 17 European countries with 286 patients.[13] Other studies reported mostly data from the United States of America or the United Kingdom, but also from Latin America (Brazil, Chile, Mexico, Colombia, Peru and Costa Rica) and Asia (India and Iran). Most reports included a study period of at least three months (range one-seven months), including data from January-August 2020. Six studies presented a prospective design.

Results of individual studies

Demographic characteristics and clinical features

26 studies[13-38] used CDC clinical definition for MISC, five studies[24,27,35,39,40] WHO definition (three of them including CDC or WHO) and six studies [13,27,29,31]RCPCH definition (including four with CDC or RCPCH).

The age at onset was reported in all included studies, except one.[32] Children were between one month to 21 years-old, including 24 infants and median age was nine years-old in most studies. 62% were male, with a male:female ratio of 1.6:1. Most studies reported Black or Hispanic/Latin ethnicity as the most frequent, globally present in 46%, followed by White ethnicity in 30%. Only five studies[13,14,19,26,29] reported white descent as the most frequent, being one of them the largest study included, an European one with 161 white children.[13] Regarding medical history, 73% children were previously healthy. The most stated comorbidity was obesity in 12%. Other reported comorbidities were asthma, cardiac disease and immunodeficiency.

The median duration from symptom onset to hospital admission ranged from two to nine days. Fever was present in all patients. Gastrointestinal symptoms were reported in 70%, including abdominal pain (64%), vomiting (63%) and diarrhea (60%). Dermatologic and mucocutaneous symptoms were commonly reported: skin rash in 57% and conjunctival injection in 48%. Oral mucosal changes and edema of hands or feet were also documented, in lower proportions.

Involvement of the cardiovascular system at presentation was reported in a significant number of children, 52% presenting with shock. A study comparing MISC presentation with and without shock, found that children with shock had a higher age, significantly more myocarditis with elevated troponin, pro b-type natriuretic peptide (BNP) and left ventricular dysfunction and significantly higher incidence of neutrophilia and lymphopenia.[40] The proportion of hypotension was not specified in most studies, but in those which it had, more than 50% presented it.[11,16,18,21,25,28,32]

Neurologic features were reported in ten studies, with aseptic meningitis being the most common and only two reported cases of seizures.[11,13,21,26,28,29,31,34-36]

Two studies addressed hepatitis and acute kidney injury related to MISC with a prevalence of 49% and 25%, respectively. Both conditions were associated with severe disease: increased length of stay and ventilation need, and hepatitis was also associated with shock at presentation. Nearly 40% of patients needing intensive care, developed severe acute kidney injury in the first 48 hours of intensive care unit stay. Hepatitis was associated with higher levels of inflammatory markers such as ferritin and interleukin (IL)-6 and biomarkers of cardiac injury such as troponin and BNP. Higher levels of ferritin were significantly associated with severe acute kidney injury.[36,41]

Table 1 resumes the demographic characteristics and clinical features of each individual study.

Features resembling KD were reported in 11 studies in a range from 25% to 67%, most of them not fulfilling the classic definition.[18,19,21,22,25,29-31,33,35,42] Notable differences between MISC and KD were identified.[20,24,35,43] Patients with MISC were older, as found in a case-control study [35] presenting with a median age of 8.6 years for MISC and 2.5 years for KD, and gastrointestinal symptoms were predominant. Also, children with MISC had higher neutrophil and C-reactive protein (CRP) levels but lower lymphocyte count. [44] Concerning echocardiogram findings, patients with MISC had a worse left ventricular systolic and diastolic functions and worse myocardial injury but lesser affection of coronary arteries (4% *versus* 20%).[24]Accordingly, MISC patients had a higher incidence of shock (76%) compared with less than 3% in patients with KD.[35]Concerning cytokines profile, MISC appears to be driven predominantly by IL-6 and IL-8 whereas IL-1 appears to be the main mediator in KD children.[25]

Besides six studies discussing clinical and laboratories features resembling toxic shock syndrome or macrophage activation syndrome, only one compared immunologic features of MISC and macrophage activation syndrome and found that children with MISC had lower levels of ferritin (median values of 4594ng/ml *versus* 537ng/ml) and lower levels of IL-2 receptor, IL-18 and CXCL9 (a surrogate marker for interferon).[24,25,31-33,45]

Four studies[19-21,25] compared children with MISC and with COVID-19 without MISC, and demonstrated that children with MISC had a predominance of male gender (80% *versus*51%)[25], higher prevalence of gastrointestinal symptoms (67% *versus* 22%)[21], and increased inflammatory markers such as CRP, ferritin and IL-6 and higher levels of D-dimers.[19-21,25]

Diagnostic testing: SARS-CoV-2 and laboratory evaluation

All included studies, except two [14,28], reported results of SARS-CoV-2 RT-PCR or serology tests. The proportion of children with positive RT-PCR test was 30%, while 51% had positive serology tests. One study found a correlation between IgG titers and hospital and intensive care unit lengths of stay.[17]Another study noted a strong IgG antibody response in RT-PCR-negative children, in agreement with SARS-CoV-2 infection having occurred weeks previously MISC onset.[35] Moreover, eight studies estimated that the onset and peak of MISC cases followed the peak of COVID-19 by approximately three to five weeks.[14,18,29,30,34,35,40,42]

COVID-19 exposure within the four weeks prior to the onset of symptoms was mentioned in 12 studies for 139 patients (26%).[11,14,18,19,26,29,30,32,37,40,42]

Table 2 summarizes SARS-CoV-2 testing results and exposure reported by each study.

Coinfection with other pathogens were reported in three studies: Epstein Barr-virus, Rhinovirus and Influenza virus were the most identified.[25,30,35]

Concerning laboratory evaluation, different inflammatory parameters have been assessed. Increased levels of CRP and ferritin were present in most studies. Median values of CRP ranged from 85-267mg/L and ferritin from 206-1893ng/ml. Few studies evaluated erythrocyte sedimentation rate and procalcitonin but in those where it was reported it was always increased, with minimum median values of 43mm/hour and 2.35ng/ul, respectively. IL-6 was increased in seven studies (median values ranged from 147-307pg/ml). In two studies addressing cytokines profiles, it was observed high levels of not only IL-6 but also IL-1B, IL-10 and IL-17.[20,46]

Hematologic abnormalities in MISC included lymphopenia and neutrophilia. Lymphopenia was reported on ten studies[14,16,19,21,24,25,30,31,34,37] and neutrophilia in five [13,15,30,31,37] out of ten reporting absolute count of neutrophils.

Several studies reported elevated levels of cardiac injury biomarkers including troponin, pro-BNP and BNP. Troponin median values were reported in 19 studies, with ten of them with values above the cut off of 0.1ng/ml. Nine studies reported pro-BNP and BNP values (lowest median value of 410pg/ml and 120pg/ml, respectively).[11,13,19,32,33,35,37,40,41]

Coagulation parameters as D-dimers and fibrinogen were reported in 27 studies with elevated median values in all patients. D-dimers median values were above 250ng/ml or 0.4mcg/ml and fibrinogen median values ranging from 503-931mg/dl.[13,15-26,28-32,34,35,37,38,40-42,45,46] On the other hand, PT and aPPT were not reported on most studies.

Hypoalbuminemia was reported in 11 studies with lowest median value of 2.6g/L.[11,16,18,26,30,31,34-37,45]

Imaging Findings

Chest imaging abnormalities were reported on 16 studies. For abnormal radiographs, the most common finding was pulmonary opacities/ infiltrates, present in 29%.[11,13,18,19,21,25-31,34,37,39,45]

Echocardiography alterations were reported in 21 studies. 36% showed cardiac dysfunction, of whom 46% presented an ejection ventricular fraction below 55%. Coronary artery dilatation or aneurysms were reported on 13%.[11,13,16,18,19,21-23,25-28,32-34,36,37,39,40,42,46]A study addressing cardiac findings, found an statistical association between an elevated level of BNP (>100pg/mL) or CRP (>50mg/L) and abnormal echocardiography, including left ventricular dysfunction.[22] Two studies reported electrophysiologic abnormalities (38% and 48%) including atrioventricular block, sinus tachycardia, ventricular tachycardia, non-specific T wave changes and abnormal QRS axis, associating arrhythmias with decreased left ventricular function.[22,33]

One study with 35 children focused on radiological alterations associated with MISC, performing chest and cardiac computed tomography and abdominal ultrasonography. Common findings included pulmonary basal consolidation with collapse (39%), pleural effusions (30%), coronary artery aneurysms (20%), and in abdominal ultrasonography, anechoic free fluid (53%) and localized inflammatory change within the right iliac fossa or multiple mildly enlarged lymph nodes (47%). Only 9% showed diffuse pulmonary ground-glass opacification on chest computed tomography.[27]

Treatment Approach and outcomes

Of registered therapies, intravenous immunoglobulin (IVIG) was the most commonly administered, in 62%, followed by glucocorticoids (49%), and IL-6 inhibitors such as Tocilizumab (16%). Anakinra (IL-1 receptor antagonist) was used in 50 children and remdesivir in 20. A second dose of IVIG was required in 29%. Not all studies stated the use of antibiotics, but when reported the proportion of usage ranged from 45% to 100%.[11,13,18,19,21,25,26,28,31,32,34]

Anticoagulant therapy was reported in 16 studies. Aspirin was used in 387 children while enoxaparin was used in 115.[11,13,18,21,24-26,28-32,35,42,45]

Convalescent plasma was given to 19 patients and extracorporeal membrane oxygenation support to six children.

Median duration of hospitalization ranged from four to ten days with a median of 6.5 days in most studies. Intensive care was required in 62%, with almost 20% requiring either noninvasive or invasive ventilation. Inotropic support was reported in 42%. Previous immunodeficiency, gastrointestinal symptoms, elevation in cardiac markers (higher pro-BNP and troponin), radiologic findings of pneumonia or acute respiratory distress syndrome and low socioeconomic conditions were associated with intensive care need.[33,38]

Most studies have not been capable of evaluating long term complication. One study[22] reported that at two-week outpatient follow-up, all electrocardiogram and echocardiogram abnormalities had resolved. Another

one[33] reported that two weeks after initial presentation, systolic function and electrocardiographic abnormalities had resolved, but coronary alterations, including aneurysms, had persisted. The only study with a longer follow-up period, noted that at two weeks most echocardiographic alterations had not completely resolved, but half of them showed significant improvement and at three-five months follow-up, it continued to improve, with normalization in some more.[29]

21 children, less than 2%, died in the hospital, including five of them while on extracorporeal membrane oxygenation support. Other reported deaths included mostly children with underlying conditions such as acute leukemia and other refractory malignancies, immunodeficiency, chronic kidney disease and cerebral palsy.

DISCUSSION

This systematic review of MISC summarizes available data from 31 published studies with a significant number of children (1415 patients) and a global representation (including American, European and Asian studies). Of the three case definitions, CDC was the most used. CDC definition probably includes a wider group of patients as it defines a smaller fever period as criteria (24 hours). Even though similarities have been firstly highlighted between MISC and KD, recent findings suggest that these conditions present several dissimilarities, including age, clinical presentation, echocardiographic abnormalities and cytokine profiles.[14,24]

Currently, more is known about MISC demographic and clinical spectrum. The majority of studies have shown that patients tend to be boys with five years-old or older. Despite this, some reports have identified it in a non-neglectable number of infants, making the diagnosis a bigger challenge in these fewer common ages. [11,26,30]Regarding ethnicity, our data further supports higher incidences of MISC among Hispanics or African descent, particularly in American and Latin studies. It has been hypothesized that these groups might be at increased risk for SARS-CoV-2 infection due to genetic/biologic factors or because of social and economic disparities, reflected on access to healthcare and workplace conditions, ultimately affecting children living in such households.[38,42]

Although the pathogenesis of MISC remains largely unclear, it has been hypothesized that it is an immune-mediated postinfectious process to SARS–CoV-2. This association is supported by its strong temporal association with COVID-19 (three to five weeks after peaks outbreaks) and the high percentage of IgG seropositivity, as shown in this review.[30,34,35,42] This highlights the importance of SARS-CoV-2 serology use for the diagnosis of MISC, especially with a negative RT-PCR. Accordingly, both serology and RT-PCR should be used to assess the epidemiologic link. Moreover, it is important to note that few children with MISC had formally reported previous COVID-19, raising awareness to asymptomatic spread of SARS-CoV-2 in children. For these previous reasons, to a proper diagnostic evaluation of MISC, the incidence and chronology of SARS-CoV-2 in a geographic area should be considered.

COVID-19 in adults is typically more severe in patients with underlying conditions such as hypertension, diabetes mellitus and other cardiovascular diseases, including cardiac and cerebrovascular disease.[14,47] In contrast, more than half of MISC children seemed to have been previously healthy. Notwithstanding, in cases of children with associated comorbidities, the most common one was obesity. Obesity in adult patients is associated with poor outcomes, including severe COVID-19 and intensive care need, being a greater risk factor in younger patients.[48]

Gastrointestinal signs and symptoms appear predominant as presenting features of MISC, with few respiratory signs and complications. Unlike adults with COVID-19 who presented as main clinical features respiratory symptoms, children appear to have less severe pulmonary manifestations, possibly because of the lower gene expression of the angiotensin converting enzyme-2 receptor (target of SARS-CoV-2).[6,14,28,49]

As a multisystem inflammatory syndrome, different inflammatory markers were evaluated, being elevated in all studies. The reasons for such an exaggerated inflammatory response to SARS-CoV-2 infection are still unclear, however some studies had identified cytokine-mediated storm as a trigger. Hypercytokinemia as a

response to the spread of a viral infection into the systemic circulation, causes an unregulated hyperinflammatory state with increased acute phase markers such as ferritin, CRP, and pro-coagulant factors, as seen in this review. This inflammatory response results in lymphocytes destruction, explaining the lymphopenia observed, particularly in severe cases.[50]It is crucial that all children under investigation for MISC should also be assessed for other causes that may explain their clinical and laboratory features.

Opposing to the frequent use of echocardiogram in MISC, for its cardiac involvement, there was a shortage in the literature about other radiologic findings. Other imaging studies may be requested in its differential diagnosis specially when gastrointestinal or respiratory symptoms are present. Further studies are needed to elucidate specific radiologic findings associated to MISC. Although rare, electrophysiologic abnormalities may have considerable clinical impact and require higher vigilance.[33] Regarding cardiac evaluation, recent guidelines recommended that children with MISC need, beside echocardiogram at diagnosis, close follow-up with cardiology.[25,27]

Probably because of overlapping features between MISC and KD, most children with MISC received therapies commonly used for the treatment of KD, including IVIG and glucocorticoids. It is known that IVIG prevents aneurisms in KD and have a potential role in SARS-CoV-2 associated myocarditis.[51-53] Currently, there is no universally standardized treatment for MISC.[25] Recent clinical guidance, recommend active monitoring in patients with mild symptoms and immunomodulatory therapy for critically ill, with IVIG considered first stage therapy and glucocorticoids as a complementary therapy for severe or refractory disease. Although a second dose of IVIG is not recommended for the risk of volume excess and hemolytic anemia, this review reported almost 30% use. Practical guidance also suggests anakinra for refractory MISC or if glucocorticoids are contraindicated.[54-56]

Less than half of the studies reported aspirin or anticoagulants use. Recent guidelines suggest low dose aspirin for all patients, that should be continued until platelet levels normalize and confirmation of normal coronary arteries four weeks after diagnosis. Anticoagulation with enoxaparin should be given to patients with documented thrombosis or with an ejection fraction below 35%.[55]

As MISC seems to overlap with severe bacterial infection, empiric broad spectrum of antibiotics should be considered in initial approach, as shown in this review.[18,34]

Illustrative of MISC's severity, most children needed intensive care or presented with shock. Despite severe cardiac involvement and shock presentation, recovery appears to be favorable with few cardiac sequelae. Long term sequelae and prognosis have hardly been evaluated, but myocardial fibrosis and scarring could result of the myocardial inflammation process. Also, mortality rates were low, below 2% and mostly occurred in children with severe comorbidities.

In this review, severe presentations or worse disease progression were associated with gastrointestinal and neurological symptoms, myocarditis, hepatitis and acute kidney injury. Certain laboratory abnormalities including, lymphopenia, neutrophilia, higher levels of CRP, ferritin, troponin, BNP, pro-BNP and IgG titers were also associated with these outcomes.[36,39,41] Besides systematic evaluation of the laboratory parameters mentioned above, mostly inflammatory or cardiac injury markers, there is also the need for systematic surveillance of renal and liver functions as neurological state monitoring.

As children frequently register no to mild symptoms of COVID-19, the incidence of MISC remains unclear. Fortunately, it appears to be a rare phenomenon (estimated incidence of 2/100000) with favorable outcomes.[8] It is crucial to establish universal surveillance mechanisms and implement most recent clinical guidance at hospital level, in order to attain prompt diagnosis and treatment, reducing potential, as yet unknown, sequelae especially in communities with higher SARS-CoV-2 transmission.

Strengths and limitations

This systematic review stands out from previous works due to its increased broadness. It is based on 31 studies featuring a significant number of children and geographically spread. Moreover, it benefits from being written one year after the first COVID-19 cases and several months after first MISC reports, including besides

multiple retrospective studies, six prospective ones. Another key of strength is that although overlapping features with KD, patients with only KD criteria and not fulfilling any of MISC definitions, were excluded.

However, as a recently documented disease, poses a limitation of follow-up studies, leading this review to disregard long-term sequelae and prognosis. As most studies were case series or observational, the reviewed data does not contain clear information on the mechanisms subjacent to the disease and the numbers reported are probably an underestimation of reality.

CONCLUSIONS

MISC is a newly and rising condition, particularly in high transmission communities with distinct features of KD. MISC raises concern on its severe cardiac involvement at presentation, with frequent intensive care and immunomodulatory therapy need. Short term outcomes seem to be favorable, with cardiac disfunction recovery and low mortality rates, besides a shortage in the literature to long-term complications. This review provides global insights into current diagnostic and therapeutical practice, pointing neurological symptoms, hepatis and acute kidney injury as factors associated with severe presentations and therefore needed to be systematical evaluated during acute phase. Further studies are needed to evaluate in particular pathogenesis and prognosis of MISC, and clinical trials are crucial to determine optimal clinical and therapeutical management.

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Table 1 Demographic characteristics and clinical features (continues on the next page)

Study reference	*30*	*34*	*11*	*18*	*25*	*14*	*15*	*35*	*20*	*24*	*39*	*21*	*27*
Age of the children in years median (IQR)	8[?]3 (3[?]3 - 12[?]5)	7[?]5 (7)	10 (6-13)	12 (11)	9(0[?]1-17)[a]	7[?]7(+-7)[b]	11 (4-17)	8[?]6 (5[?]5-12[?]6)	9.2 (+/-5[?]3)[b]	11[?]4 (8-13[?]7)	10[?]7 (8[?]3-14[?]1)	7[?]8(0-17[?]6)[c]	11 (6-14
Gender Male n(%)	115 (62)	1(17)	20(61)	11(73)	16(57)	14(78)	7(47)	20(61)	NR	14(50)	31(60)	5(83)	27(7
Ethnicity													
White, non-Hispanic n(%)	35 (19)	2(33)	3(9)	2	10(36)	9(50)	6(40)	3(9)	NR	7(25)	16(31)	NR	NR
Black, non-Hispanic n(%)	46 (25)	2(33)	13(39)	2	5(18)	2(11.1)	7(47)	8(24)	NR	13(46)	9(17)	NR	NR
Hispanic or Latino n(%)	57(31)	0	15(45)	10(66)	12(43)	6(33)	3(20)	9(27)	NR	4(14)	NR	NR	NR
Medical History													
Previous healthy n(%)	135(73)	6(100)	17(51)	11(73)	14(50)	NS	0	26(79)	NS	NR	37(71)	1(17)	NR
Obesity n(%)	12(8)	0	2(6)	2(13)	4(14)	2(11)	NR	13(39)	NR	14(50)	5(10)	NR	NR
Asthma n(%)	NR	0	5(15)	4(27)	3(11)	2(11)	3(23)	5(15)	NR	NR	4(8)	NR	NR
Cardiac disease n(%)	5(3)	0	2(6)	NR	1(4)	0	NR	NR	NR	NR	2(4)	NR	NR
Immunodeficiency n(%)	10(5)	0	NR	NR	NR	0	NR	NR	NR	NR	NR	1(17)	NR
Kawasaki disease n(%)	NR	NS	NS	NR	2(7)	NR	NR	NR	NR	NR	NR	NR	NR
Others	20(11)		6(18)	NR	4(14)	2(11)	0	2(6)	NR	NR	NR	5(83)	NR

Study reference	*30*	*34*	*11*	*18*	*25*	*14*	*15*	*35*	*20*	*24*	*39*	*21*	*27*
Duration in days from symptom onset to hospital admission median (IQR)	NR	NR	4[?]5 (3-6)	NR	5 (4-6)	NR	6 (4-7)	NR	4[?]1(+/-1[?]5)[b]	NR	NR	6(1-15)[c]	NR
Respiratory symptoms n(%)	131(70)	4(67)	NR	NR	NR	NS	NR	17(52)	NR	NR	NS	NS	NR
Cough or congestion n(%)	NS	NS	NA	3(20)	NA	4(22)	NA	NS	NR	NR	19(37)	5(83)	NA
Respiratory insufficiency n(%)	109(59)	4(67)	NA	NR	NA	NR	NA	NS	NR	NR	NR	NR	NA
Gastrointestinal symptoms n(%)	171(92)	6(100)	NS	13(87)	15(54)	NS	NR	32(97)	NR	NR	NS	4(67)	30(8
Abdominal pain n(%)	NS	5(83)	21(63)	NS	NS	NS	NR	NS	NR	NR	34(65)	NS	NS
Diarrhea n(%)	NS	4(67)	16(48)	NS	NS	3(17)	NR	NS	NR	NR	32(62)	NS	NS
Vomiting n(%)	NS	0	23(69)	NR	NS	5(28)	NR	NS	NR	NR	38(73)	NS	NS
Cardiovascular symptoms n(%)	149(80)	6 (100)	21(63)	13(87)	15(54)	NR	NR	25(76)	NR	NR	NR	5(83)	21(7

Study reference	*30*	*34*	*11*	*18*	*25*	*14*	*15*	*35*	*20*	*24*	*39*	*21*	*27*
Shock n(%)	NS	6(100)	NR	NR	15(54)	NR	NR	25(76)	NR	NR	NR	5(83)	21(7
Neurologic symptoms n(%)	NR	4(66)	4(12)	NR	NR	0	NR	19(58)	NR	NR	NR	1(17)	NR
Rash n(%)	110(59)	2(33)	14(42)	7(47)	10(36)	5(28)	NR	NR	NR	NR	28(54)	0(0)	13(3
Oral mucosal changes n(%)	78(42)	3(50)	7(21)	NR	7(25)	NR	NR	NR	NR	NR	NR	NR	NR
Edema of hands or feet n(%)	NS	2(33)	NR	4(27)	6(219)	NR	NR	NR	NR	NR	NR	NR	NR
Conjunctival injection n(%)	103(55)	2(33)	12(36)	4(27)	16(57)	NR	NR	NR	NR	NR	20(39)	0	9(26

IQR: Interquartile range; NR: Non reported; NS: Non specified; NA: Non appliable.

a result presented in median (range) b result presented in mean (+-standard deviation) c result presented in median (minimum-maximum values)

Study reference	*37*	*45*	*26*	*42*	*32*	*57*	*17*	*29*	*38*	*31*	*22*	*33*	*41*
Age of the children in years median (IQR)	9[?]2(+/-4[?]9)[b]	7 (4-9[?]9)	9	6(0-14)[a]	NR	6[?]2 (2[?]4-10[?]3)	8[?]5 (6[?]5-12)	6[?]0 (3[?]8-9[?]9)	7(0[?]1-17)[a]	6(0[?]13-16)[a]	2[?]8 (1[?]4-9)	7 (+/-5[?]2)[b]	11(7-14)
Gender Male n(%)	6(38)	24(53)	1(33)	14(52)	1(25)	39(70)	6(60)	20(69)	52(55)	8(42)	19(58)	31(56)	76(6

Study reference	*37*	*45*	*26*	*42*	*32*	*57*	*17*	*29*	*38*	*31*	*22*	*33*	*41*
Ethnicity													
White, non-Hispanic n(%)	NR	NR	2(66)	NR	NR	21(41)	3(30)	12(41)	0	NR	10(30)	13	24(2
Black, non-Hispanic n(%)	NR	NR	1(33)	NR	NR	9(18)	6(60)	4(14)	0	NR	7(21)	15	51(4
Hispanic or Latino n(%)	NR	NR	0	NR	NR	0	2(20)	NR	95	NR	12(36)	7(13)	NR
Medical History													
Previous healthy n(%)	7(44)	39(87)	3(100)	20(74)	3(75)	45(80)	7(70)	NR	84(88)	18	NR	55(100)	78(6
Obesity n(%)	4(25)	NR	NR	4(15)	NR	1(9)	NR	NR	NR	NR	7(21)	NR	5(4)
Asthma n(%)	3(19)	NR	NR	1(4)	1(25)	1(9)	NR	NR	NR	NR	5(15)	NR	NR
Cardiac disease n(%)	NR	NR	NR	NR	NR	2(18)	NR	NR	NR	NR	0	NR	NR
Immunodeficiency n(%)	NR	NR	NR	1(4)	NR	NR	0	NR	1(1)	NR	NR	NR	NR
Kawasaki disease n(%)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Others	3(19)	NR	NR	2(7)	NR	NR	3(30)	NR	NR	NR	1(3)	NR	15(1

Study reference	*37*	*45*	*26*	*42*	*32*	*57*	*17*	*29*	*38*	*31*	*22*	*33*	*41*
Duration in days from symptom onset to hospital admission median (IQR)	NR	5(3-7)	NR	4(2-9)	NR	5(3-7)	NR	NR	NR	NR	NR	NR	5(4-7)
Respiratory symptoms n(%)	NS	NS	NS	NS	NS	26(46)	5(50)	11(38)	23(50)	8(42)	NR	NR	NS
Cough or congestion n(%)	1(6)	16(36)	NR	7(26)	0	16(29)	NS	9(31)	NS	NR	NA	NA	NR
Respiratory insufficiency n(%)	NR	NR	2(66)	NR	NR	NR	NS	NS	NS	NR	NA	NA	23(2
Gastrointestinal symptoms n(%)	NS	NS	3(100)	NS	4 (100)	40(71)	10(100)	25(13)	43(45)	NS	NS	32(58)	NS
Abdominal pain n(%)	11(69)	26(58)	1(33)	17(63)	4(100)	30(54)	NS	13(45)	NS	8(42)	10(30)	NS	79(6
Diarrhea n(%)	7(44)	16(36)	3(100)	17(63)	4(100)	30(54)	NS	15(52)	NS	3(16)	12(36)	NS	67(5
Vomiting n(%)	12(75)	23(51)	1(33)	13(48)	4(100)	21(38)	NS	1(3)	NS	6(32)	11(33)	NS	NS

Study reference	*37*	*45*	*26*	*42*	*32*	*57*	*17*	*29*	*38*	*31*	*22*	*33*	*41*
Cardiovascular symptoms n(%)	10(63)	NR	3(100)	NR	3(75)	33(59)	10(100)	25(86)	11(12)	12(63)	NR	24(44)	64(5
Shock n(%)	10(63)	NR	3(100)	NR	NR	33(59)	10(100)	8(28)	NR	NR	3(9)	24(44)	57(4
Neurologic symptoms n(%)	NR	9(20)	1(33)	NR	NR	NR	NR	5(17)	NR	6(31)	NR	NR	NR
Rash n(%)	10(63)	24(53)	2(66)	14(52)	4(100)	38(68)	NR	21(72)	NR	12(63)	19(58)	27(49)	NR
Oral mucosal changes n(%)	1(6)		NR	11(41)	2(50)	17(30)	NR	18(62)	NR	9(47)	8(24)	16(29)	NR
Edema of hands or feet n(%)		18(40)	NR	NR	NR	NR	NR	15(52)	NR	10(53)	5(15)	12(22)	NR
Conjunctival injection n(%)	8(50)	23(51)	3(100)	13(48)	2(50)	26(46)	NR	20(69)	NR	9(47)	12(36)	18(33)	NR

Table 1 Demographic characteristics and clinical features (continues on the previous page)

IQR: Interquartile range; NR: Non reported; NS: Non specified; NA: Non appliable.

a result presented in median (range) b result presented in mean (+-standard deviation) c result presented in median (minimum-maximum values)

Table 2. SARS-CoV-2 testing results and exposure

Study reference	SARS-CoV-2 RT-PCR [a] positive n(%)	SARS-CoV-2 serology positive n(%)	COVID-19 exposure[b] n(%
30	73(39)	58(31)	55(30)
34	3(50)	5(83)	NR
11	11(33)	27(81)	5(15)
18	7(47)	15(100)	3(20)
25	17(61)	18(95)	NR
14	NS	NS	8(44)
15	7(47)	15(100)	NR
35	1(3)	30(91)	NR

Study reference	SARS-CoV-2 RT-PCR [a] positive n(%)	SARS-CoV-2 serology positive n(%)	COVID-19 exposure[b] n(%
[20]	NS	NS	NS
[24]	20(71)	28(100)	NR
[39]	28(56)	22(44)	NR
[21]	5(83)	1(17)	NR
[27]	0	27(90)	NR
[40]	9(39)	7(30)	8(35)
[36]	15(34)	31(97)	NR
[37]	3(19)	10(63)	NR
[45]	10(22)	35(78)	14(31)
[26]	2(66)	1(33)	1(33)
[42]	14(52)	10(77)	9(33)
[32]	1(25)	4(100)	1(25)
[57]	14(45)	19(61)	27(48)
[17]	2(20)	10(100)	NR
[29]	3(11)	14(48)	1(3)
[38]	NS	72(82)	NR
[31]	4(21)	8(42)	NR
[22]	11(33)	14(61)	NR
[33]	20(38)	19(35)	NR
[41]	19(16)	56(48)	NR
[16]	8(24)	18(72)	6(18)
[13]	90(34)	116(44)	NR
[28]	NS	18(45)	NR

RT-PCR: reverse transcription polymerase chain reaction;*NR:* Not reported; *NS* : Non specified

a nasopharyngeal swab *b* within the 4 weeks prior to the onset of symptoms

Table 3 Treatment approach and outcomes (continues bellow)

Study reference	*30*	*34*	*11*	*18*	*25*	*14*	*15*	*35*	*20*	*24*	*24*	*39*	*39*	*39*	*21*	*21*	*27*
IVIG n(%)	144(77)	6(100)	18(54)	12(0.8)	20(71)	NR	13(87)	33(100)	10(50)	10(50)	22(79)	22(79)	28(65)	4(67)	4(67)	35(100)	35(1
IVIG second dose n(%)	39(21)	2(33)	NR	NR	NR	NR	NR	11(33)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Corticosteroids n(%)	91(49)	5(83)	17(51)	3(20)	1(4)	NR	14(93)	23(70)	NS	NS	NR	NR	24(55)	2(33)	2(33)	35(100)	35(1
IL-6 inhibitor n(%)	38(20)	NR	12(36)	12(80)	17(61)	NR	NR	3(9)	NS	NS	NR	NR	1(1/52)	NR	NR	NR	NR

Study reference	*30*	*34*	*11*	*18*	*25*	*14*	*15*	*35*	*20*	*24*	*24*	*39*	*39*	*39*	*21*	*21*	*27*
Il-1 receptor antagonist n(%)	24(13)	NR	4(12)	2(13)	1(4)	NR	NR	4(12)	NS	NS	NR	NR	3(3/52)	NR	NR	NR	NR
Remdesivir n(%)	NR	NR	7(21)	2(13)	7(25)	NR	1(7)	NR	NS	NS	NR	NR	NR	NR	NR	NR	NR
Aspirin n(%)	NS	NR	8(24)	NR	19(68)	NR	NR	29(88)	NR	NR	24(86)	24(86)	NR	3(50)	3(50)	NR	NR
Enoxaparin n(%)	87(47)	NR	33(100)	15(100)	18(64)	NR	NR	14(42)	NR	NR	21(72)	21(72)	NR	2(33)	2(33)	NR	NR
Convalescent plasma n(%)	6(3)	NR	1(3)	1(66)	NR	NR	0	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
ECMO n(%)	8(4)	NR	1(3)	1(66)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	2(7)	2(7)
Duration of hospitalization in days median (IQR)	7 (4-10)	11	4.7 (4-8)	8	8	NR	NR	4 (4-8)	8[?]1(±4[?]1)[a]	8[?]1(±4[?]1)[a]	NR	NR	NR	NR	NR	NR	NR
ICU admission n(%)	148(80)	6(100)	33(100)	14	17(61)	NR	NR	26(79)	NR	NR	23(82)	23(82)	38(73)	6(100)	6(100)	24(69)	24(6
Death n(%)	4(2)	0	1(3)	0	0	0	0	0	0	0	0	0	0	4(67)	4(67)	1(3)	1(3)

IVIG: Intravenous Immunoglobulin; ECMO: Extracorporeal membrane oxygenation; ICU: Intensive Care Unit; NR: Non reported; NS: Non specified

a result presented in mean (+-standard deviation)

Table 3 Treatment approach and outcomes (continues above)

Study reference	*45*	*26*	*42*	*32*	*57*	*17*	*29*
IVIG n(%)	18(48)	2(66)	19(70)	2(50)	50(89)	10(100)	28(97)
IVIG second dose n(%)	NR	NR	NR	NR	NS	NR	17(61)
Corticosteroids n(%)	27(60)	3(100)	17(63)	4(100)	31(55)	5(50)	NS
IL-6 inhibitor n(%)	NR	1(33)	2(7)	1(50)	NR	NR	NR
Il-1 receptor antagonist n(%)	NR	NR	NR	NR	NR	1(10)	NR
Remdesivir n(%)	NR	NR	NR	NR	NR	1(10)	NR
Aspirin n(%)	NR	NR	17(63)	2(50)	25(45)	NR	22(91)
Enoxaparin n(%)	NR	3(100)	18(67)	1(25)	29(52)	NR	NR
Convalescent plasma n(%)	NR	NR	NR	NR	NR	1(10)	NR
ECMO n(%)	NR	NR	NR	NR	NR	NR	0
Duration of hospitalization in days median (IQR)	NR	6	9(6-13)	NR	6(4.8-11.3)	9(7.3-11.5)	NR
ICU admission n(%)	NR	3(100)	16(59)	1(25)	56(100)	10(100)	6(21)
Death n(%)	5(11)	0	0	0	1(2)	0	0

IVIG: Intravenous Immunoglobulin; ECMO: Extracorporeal membrane oxygenation; ICU: Intensive Care Unit; NR: Non reported; NS: Non specified

a result presented in mean (+-standard deviation)

Figures

Figure 1. Flow diagram of study selection

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