Boletín Médico del
Hospital Infantil de México

PERMANYER

Check for updates

REVIEW ARTICLE

Multisystem inflammatory syndrome and COVID-19: a scoping review

Eduardo Tuta-Quintero[1], Camila Martínez-Ayala[1], Gabriela Mantilla-Beltrán[1], Alejandro Rueda-Rodríguez[1], and Juan Pimentel[2]*

[1]Facultad de Medicina; [2]Departamento de Medicina Familiar y Salud Pública. Universidad de La Sabana, Chía, Colombia

Abstract

Background: *Multisystem inflammatory syndrome temporally associated with COVID-19 presents with similar symptomatology and therapeutic approach to Kawasaki disease in the pediatric population. Given the novelty of the disease and the growing scientific literature on the subject, it is relevant to collect and report available scientific information. This review aimed to explore the medical evidence on multisystem inflammatory syndrome temporally associated with COVID-19 in a population under 18 years of age.* **Methods:** *We conducted a scoping review using Scopus and PubMed, including observational (cohort, case-control, and cross-sectional) studies and case series.* **Results:** *Of the total articles reviewed as of April 10, 2021, 45 articles met eligibility criteria: case series (n = 32), retrospective cohort studies (n = 6), prospective cohort studies (n = 4), case-control studies (n = 2), and cross-sectional studies (n = 1). Gastrointestinal and respiratory symptoms and myocardial dysfunction are the most commonly reported. The most relevant paraclinical markers were lymphopenia, thrombocytopenia, and elevated D-dimer levels.* **Conclusions:** *The multisystem inflammatory syndrome temporally associated with COVID-19 presents a broad spectrum of signs and symptoms. Aneurysms of the coronary arteries and myocarditis are usually present in the acute phases of the disease. The early diagnosis led by a multidisciplinary group of pediatric intensivists, infectious disease specialists, cardiologists, and rheumatologists allows adequate and effective medical management.*

Keywords: *Kawasaki Disease. Vasculitis. COVID-19. SARS-CoV-2. Systematic review.*

Síndrome inflamatorio multisistémico y COVID-19: una revisión exploratoria

Resumen

Introducción: *El síndrome inflamatorio multisistémico temporalmente asociado con COVID-19 se presenta con una sintomatología y un enfoque terapéutico similares a los de la enfermedad de Kawasaki en la población pediátrica. Dado lo novedoso de la enfermedad y la creciente literatura científica al respecto, resulta relevante recopilar y comunicar la información disponible. El objetivo fue explorar la evidencia médica sobre el síndrome inflamatorio multisistémico temporalmente asociado con COVID-19 en población menor de 18 años.* **Métodos:** *Se realizó una revisión exploratoria utilizando Scopus y PubMed, incluyendo estudios observacionales (estudios de cohorte, casos y controles, y transversales) y series de casos.* **Resultados:** *Del total de los artículos revisados hasta el 10 de abril de 2021, 45 cumplieron con los criterios de elegibilidad: series de casos (n = 32), estudios de cohorte retrospectiva (n = 6), estudios de cohorte prospectiva (n = 4), estudios de*

Correspondence:
Eduardo Tuta Quintero
E-mail: Eduardotuqu@unisabana.edu.co

Date of reception: 19-04-2021
Date of acceptance: 06-07-2021
DOI: 10.24875/BMHIM.21000073

Available online: 21-04-2022
Bol Med Hosp Infant Mex. 2022;79(2):69-82
www.bmhim.com

casos y controles (n = 2) y estudios transversales (n = 1). Los síntomas gastrointestinales, respiratorios y de disfunción miocárdica son los que más se reportan en la literatura. Por su parte, los marcadores paraclínicos más relevantes fueron linfocitopenia, trombocitopenia y valores elevados de dímero D. **Conclusiones:** *El síndrome inflamatorio multisistémico temporalmente asociado con COVID-19 se presenta con un amplio espectro de signos y síntomas. Las complicaciones más graves son el compromiso aneurismático de las arterias coronarias y la miocarditis. El diagnóstico temprano liderado por un grupo multidisciplinario de pediatras intensivistas, infectólogos, cardiólogos y reumatólogos permite un manejo médico adecuado y eficaz.*

Palabras clave: *Enfermedad de Kawasaki. Vasculitis. COVID-19. SARS-CoV-2. Revisión sistemática.*

Introduction

Severe acute respiratory syndrome type 2 coronavirus (SARS-CoV-2) infection was identified in December 2019 in Hubei province, Wuhan, China[1]. In January 2020, the World Health Organization (WHO) named COVID-19 the new disease caused by SARS-CoV-2 and officially declared a pandemic on March 11, 2020[1,2]. The virus belongs to the *Coronaviridae* family and has a positive-sense single-stranded ribonucleic acid genome surrounded by an extracellular membrane[2,3]. The clinical presentation of COVID-19 varies from an asymptomatic clinical presentation to acute respiratory distress syndrome (ARDS) and multiorgan failure[4]. In a systematic review, Cui et al.[5] reported that in the pediatric population, clinical manifestations such as fever and cough are less frequent when compared to the adult population.

Throughout the pandemic, a multisystem inflammatory syndrome temporally associated with COVID-19 (MIS-C) began to be identified in children with previous SARS-CoV-2 infection. This syndrome's clinical and paraclinical features are similar to Kawasaki disease (KD)[6,7]. MIS-C presents with an acute, self-limited, systemic vasculitis affecting the pediatric population under 5 years of age[7,8]. Its pathophysiology is mediated by monocytes, macrophages, T cells, and proinflammatory cytokines such as interleukin 6 (IL-6), promoting an inflammatory phenomenon that weakens the vascular wall and can lead to coronary artery aneurysms[7,9].

Vasculitis pathophysiology seems to be explained by the interaction between the infection, a genetic component of the individual, and a disproportionate immune response, with a marked tropism for the endothelium and vascular wall[8]. Countries such as Italy are a clear example of the high number of cases of MIS-C in children with previous SARS-CoV-2 infection, where early diagnosis allowed adequate management of the disease, preventing possible short- and medium-term cardiac complications[10,11]. Given the novelty of the disease and the growing scientific literature on the subject, it is relevant to collect and communicate the available scientific information that will help health professionals to make decisions in their clinical practice[6,7,10]. Therefore, the present review explored the current medical evidence up to April 10, 2021, on MIS-C and SARS-CoV-2 infection in the population under 18 years of age.

Methods

We followed the steps proposed by Arksey and O'Malley[12] and refined by Levac et al.[13] for the review: i) definition of the research question; ii) search for and identification of relevant studies; iii) selection of studies; iv) data collection; v) summary and reporting of results, and vi) review by the expert team. The review adhered to the preferred reporting elements for systematic reviews and meta-analyses PRISMA-ScR[14] (Table 1).

Our research questions were as follows:

– What is the current medical evidence on MIS-C and SARS-CoV-2 infection in the pediatric population (< 18 years)?
– What are the research gaps in the literature on MIS-C in the pediatric population with previous SARS-CoV-2 infection?

Eligibility criteria

Due to a large amount of medical literature available on the topic and the need to concisely analyze and describe the impact of SARS-CoV-2 infection in the pediatric population, this exploratory review included only analytical and descriptive observational studies (cohort, case-control, case series, and cross-sectional studies) on MIS-C. Only articles published in English and Spanish between 2019 and 2021 were included. Case reports, theoretical publications, or publications with no available abstract or full text were excluded.

Table 1. Characteristics of the publications included in the review

Author, year [reference]	Type of document	Target population characteristics	Objective	Country	Main finding/contribution
Whittaker et al., 2020[47]	Case series	58 patients Mean age of 9 years	To describe and compare clinical and paraclinical characteristics in pediatric patients who met criteria for MIS-C	United Kingdom	A total of 58 patients with a median age of 9 years were evaluated, of which 13 met the definition of MIS-C
Feldstein et al., 2020[45]	Case series	186 patients Mean age of 8.3 years	To report patients with MIS-C from March 15 to May 20, 2020, of whom 74 (40%) documented KD-like features	United States	MIS-C caused severe disease involving damage to multiple organs and systems in previously healthy pediatric and adolescent patients
Toubiana et al., 2020[21]	Prospective cohort	21 patients Mean age of 7.9 years	To describe the characteristics of the pediatric patients affected by MIS and KD, evaluating a possible association with SARS-CoV-2 infection	France	MIS-C could be related to COVID-19 in the pediatric population; in addition, it is associated with gastrointestinal symptoms and shock
Dufort et al., 2020[29]	Case series	99 patients	To describe the clinical manifestations of patients hospitalized for MIS-C	United States	MIS-C in pediatric patients coincided with the widespread transmission of SARS-CoV-2, whose dermatological, mucocutaneous, and gastrointestinal manifestations were associated with cardiac dysfunction
Verdoni et al., 2020[11]	Retrospective cohort	19 patients with KD before the pandemic 10 patients with MIS-C after the pandemic	To evaluate the incidence and clinical characteristics of MIS-C patients diagnosed during the COVID-19 pandemic	Italy	A 30-fold higher incidence of MIS-C was found in the pediatric population; in addition, a higher rate of cardiac involvement of a severe form of KD was reported
Pouletty et al., 2020[46]	Retrospective cohort	10 patients with KD before the pandemic 16 patients with MIS-C	To analyze the clinical and paraclinical characteristics in patients with a confirmed diagnosis of COVID-19 and MIS-C	France	MIS-C represents a new inflammatory syndrome associated with high morbidity and mortality in the pediatric population; prospective studies are needed to characterize this syndrome better
Chiotos et al., 2020[52]	Case series	6 children with MIS-C Treated in the PICU	To describe the clinical and paraclinical features in six children with MIS-C seen in a pediatric intensive care unit	United States	Patients received Ig and methylprednisolone therapies, achieving the reduction of systemic inflammation, resolution of fever, and improvement of cardiac function
Lee et al., 2020[26]	Retrospective cohort	28 patients with MIS-C Mean age of 9 years	To describe the clinical and paraclinical manifestations of pediatric patients diagnosed with MIS-C	United States	MIS-C encompasses a broad phenotypic spectrum with clinical and laboratory features distinct from KD
Ramcharan et al., 2020[15]	Case series	15 patients Mean age of 8.8 years	Description of short-term cardiovascular manifestations in a pediatric population with MIS-C in a tertiary children's hospital	United Kingdom	Cardiovascular involvement was reported to be greater than in other published series; it is necessary to emphasize pediatric cardiology assessment

(continues)

Table 1. Characteristics of the publications included in the review *(continued)*

Author, year [reference]	Type of document	Target population characteristics	Objective	Country	Main finding/contribution
Cheung et al., 2020[65]	Case series	17 patients Mean age of 8.8 years	To describe the clinical manifestations and therapeutic approaches in a previously healthy pediatric population infected with SARS-CoV-2 with an inflammatory phenotype	United Kingdom	Cytokine elevation via IFN, TNF-α, and IL-13 and abnormal cardiac findings suggest the need for surveillance regarding MIS-C-associated complications
Blondiaux et al., 2020[17]	Case series	4 patients Mean age of 9 years	To evaluate cardiac magnetic resonance imaging findings in a pediatric population admitted to the intensive care unit for MIS-C	France	Diffuse myocardial edema was evident on T2 and T1 sequences, with no evidence of late gadolinium enhancement suggestive of replacement fibrosis or focal necrosis; these findings suggest post-infectious myocarditis
Labé et al., 2020[22]	Case series	2 patients aged 3 and 6 years	To describe two cases with a clinical picture of fever and cutaneous eruptions with involvement of mucous membranes (erythema multiforme) associated with COVID-19	France	SARS-CoV-2 infection is a trigger for MIS-C; respiratory symptoms are evident as a typical clinical picture
Rostad et al., 2020[39]	Prospective cohort	10 patients with MIS-C 10 patients with symptomatic COVID-19 5 patients with KD 4 healthy controls	To evaluate the diagnostic capability of serological tests for MIS-C	United States	Quantitative SARS-CoV-2 serology may have a role in diagnosing MIS-C, distinguishing it from similar clinical entities, and stratifying the risk of adverse outcome
Ouldali et al., 2020[36]	Case series	230 patients with KD	To determine if SARS-CoV-2 infection is associated with an increased incidence of KD	France	An increase in MIS-C cases was evident, particularly in countries where the peak of COVID-19 had recently been reached
Capone et al., 2020[49]	Case series	33 patients Mean age of 8.6 years	To describe the presentation and clinical course of 33 children with MIS concomitant with SARS-CoV-2 infection	United States	MIS-C was related to COVID-19; furthermore, a large proportion of patients developed shock requiring vasoactive agents and anti-inflammatory therapy
Waltuch et al., 2020[16]	Case series	4 patients with MIS-C	To describe four pediatric patients with confirmed SARS-CoV-2 infection who presented to the emergency department with features associated with MIS-C	United States	Patients presented with prolonged fever, gastrointestinal symptoms with or without rash; in addition, these patients may decompensate rapidly and require specialized care
Toubiana et al., 2020[56]	Case-control	23 patients with MIS-C 102 controls	To evaluate the association between severe SARS-CoV-2 infection and MIS-C in pediatric patients in France.	France	SARS-CoV-2 infection was confirmed in 17/23 cases vs. 11/102 controls (95% CI: 6.0-116.9); suggesting a strong association between COVID-19 and systemic proinflammatory state

(continues)

Table 1. Characteristics of the publications included in the review *(continued)*

Author, year [reference]	Type of document	Target population characteristics	Objective	Country	Main finding/contribution
Corwin et al., 2020[66]	Retrospective cohort	33 patients Mean age of 10.9 years	To compare the presentation of clinical and paraclinical features in a pediatric population with MIS-C	United States	The initial pattern of lymphopenia, thrombocytopenia, hyponatremia and abnormal creatinine can help recognize patients with MIS-C
Lima-Setta et al., 2021[18]	Prospective cohort	56 patients with MIS-C Mean age of 6.2 years	To describe the clinical, laboratory, and radiological characteristics in a pediatric population diagnosed with MIS-C	Brazil	Diagnostic chest images with bilateral diffuse interstitial infiltrate. On echocardiogram, mild pericardial effusion, left ventricular dysfunction, and signs of coronary dilation. Laboratory tests: anemia, leukocytosis, lymphopenia, and thrombocytopenia, altered C-reactive protein, ESR, and fibrinogen levels
Toubiana et al., 2021[19]	Case-control	30 patients with KD onset after the pandemic 59 patients with KD onset before the pandemic	To analyze the clinical manifestations, therapeutic approaches, and clinical outcomes in a pediatric population diagnosed with MIS-C	France	Specific characteristics of MIS-C and classic KD are recognized; therefore, it is necessary to differentiate both pathologies, allowing an early and effective diagnosis
Heidemann et al., 2020[53]	Case series	3 patients aged 5, 6, and 7 years	To describe 3 cases of vasculitis associated with SARS-CoV-2 infection and their therapeutic approaches	United States	Partial response to intravenous Ig and ECMO therapy was evidenced; arrhythmias may be related to inflammation and myocardial ischemia
Falah et al., 2020[24]	Case series	10 patients Mean age of 6 years	To describe the clinical manifestations, paraclinical features, therapeutic approaches, and clinical outcomes in a pediatric population with MIS-C	United States	MIS-C in the pediatric population manifests with fever, rash, seizures, cough, tachypnea, and gastrointestinal symptoms due to the associated hyperinflammatory state
Bordet et al., 2021[28]	Case series	32 patients	To analyze the clinical features of MIS-C as a new disease between a spectrum of KD and viral myocarditis	France	The pediatric population with COVID-19 presented with mild to severe myocarditis and fever plus two to three KD-like symptoms
Carbajal et al., 2021[40]	Case series	7 patients with MIS-C 40 patients with KD	To determine the relationship between COVID 19 and MIS-C and compare it with the main characteristics of KD	France	The clinical manifestations of MIS-C are associated with a hyperinflammatory state, and its clinical features are different from those presented in KD
Del Greco et al., 2020[50]	Case series	4 patients	To present four cases of MIS-C in the emergency department and describe their therapeutic approach	United States	Patients with MIS-C have a good recovery with medical management with Ig and corticosteroids, and a low mortality rate
Fouriki et al., 2021[34]	Case series	6 patients	To report six cases of MIS-C in pediatric patients in Switzerland and to describe the therapeutic approach	Switzerland	The use of anakinra could be an alternative to corticosteroid treatment

(continues)

Table 1. Characteristics of the publications included in the review *(continued)*

Author, year [reference]	Type of document	Target population characteristics	Objective	Country	Main finding/contribution
Grimaud et al., 2020[51]	Case series	20 patients	To describe the clinical characteristics in a pediatric population with cardiogenic shock secondary to acute myocarditis and suspected SARS-CoV-2 infection	France	Early recognition and referral to a specialized center are required in MIS-C patients
Gruber et al., 2020[41]	Case series	9 patients with MIS-C	To determine possible autoantibodies linked to target organs in SARS-CoV-2 and MIS-C	United States	The profile revealed known disease-associated autoantibodies (anti-La), which recognize endothelial, gastrointestinal, and immune cell antigens
Iio et al., 2021[27]	Case series	30 patients with KD onset before the pandemic 14 patients with KD onset after the pandemic	To analyze the clinical manifestations in a pediatric population with an initial diagnosis of COVID-19 in order to determine the relationship between the infection and a systemic inflammatory response	Japan	There was no evidence of an increase in the incidence of KD; instead, MIS-C with a different profile of clinical manifestations than KD was described
Matsubara et al., 2020[30]	Case series	28 patients with MIS-C 20 patients with KD 20 healthy controls	To describe the echocardiographic findings in MIS-C	United States	MIS-C presents aneurysmal dilatations in the coronary arteries, usually reverting to normal; the myocardial lesion is similar to that produced in KD
Ng et al., 2020[57]	Case series	3 patients	To describe the clinical presentations and outcomes of three adolescents with confirmed SARS-CoV-2 infection admitted to the pediatric intensive care unit	United Kingdom	Similarities were found between KD and MIS-C; the mechanism of MIS-C depends on macrophage activation. Further studies on MIS-C, including cytokine and immune profiles, are needed
Papadopoulou et al., 2021[58]	Case series	19 patients Mean age of 9.1 years	To describe the clinical presentation and therapeutic approach to MIS-C in the pediatric population and to highlight the role of the pediatric rheumatologist in this setting	United Kingdom	Nineteen children met MIS-C criteria, and nine also met diagnostic criteria for complete or incomplete KD; immunomodulatory therapy is necessary
Rekhtman et al., 2021[37]	Prospective cohort	31 patients with COVID-19 or MIS-C	To characterize the mucocutaneous disease and its relationship with the clinical course of hospitalized patients with MIS-C	United States	The mucocutaneous disease is common in children and adolescents with MIS-C
Sethurama et al., 2021[38]	Case series	34 patients with MIS-C Mean age of 8 years	To describe the clinical and paraclinical manifestations of 34 children with MIS-C who were evaluated within 12 weeks	United States	MIS-C starts at an older age than KD, with a predominance of gastrointestinal symptoms, presence of myocarditis, and shock
Shahbazneja et al., 2020[25]	Case series	10 patients Mean age of 5.37 years	To examine the association between exposure to COVID-19 and MIS-C	Iran	MIS-C in the pediatric population is present with fever, rash, seizures, cough, tachypnea, and gastrointestinal symptoms due to the associated hyperinflammatory state

(continues)

Table 1. Characteristics of the publications included in the review *(continued)*

Author, year [reference]	Type of document	Target population characteristics	Objective	Country	Main finding/contribution
To et al., 2020[42]	Case series	3 patients with KD	To describe three patients with KD and false-positive COVID-19 serology	China	Neutralizing antibody screening is recommended to confirm previous SARS-CoV-2 infection in patients who are positive by serology but negative for RT-PCR
Vergnano et al., 2020[55]	Case series	7 patients with MIS-C Younger than one year	To describe seven cases who presented MIS-C in five hospital centers	United Kingdom	Pediatricians must consider early and aggressive treatment and close cardiac monitoring in patients with MIS-C and SARS-CoV-2 infection
Fabi et al., 2021[20]	Cross-sectional study	8 patients with KD 1 patient with myocarditis 4 patients with MIS-C	To compare patients with diagnoses of KD, myocarditis, and MIS-C from February to April 2020 versus patients diagnosed before the pandemic	Italy	MIS-C and myocarditis responded rapidly to treatment without cardiac sequelae; it is necessary to differentiate KD and MIS-C despite their diagnostic and therapeutic similarities
Plebani et al., 2020[67]	Case series	9 patients Mean age of 8.9 years	To report nine previously healthy children (six males and three females) admitted for MIS-C and SARS-CoV-2 infection	Italy	*Mycoplasma pneumoniae* co-infection in pediatric patients with MIS-C may contribute to a more severe clinical course
Vukomanovic et al., 2020[70]	Case series	3 patients with MIS-C	To present three male adolescents with MIS-C and myocardial injury admitted to hospital.	Serbia	Clinical presentation, laboratory and echocardiographic findings pointing to MIS-C with a cardiac lesion
Shikhare et al., 2021[32]	Case series	6 patients with MIS-C with a mean age of 8 years	To report six children with MIS-C who were admitted to the hospital between May 5, 2020, and June 25, 2020.	United States	Two children with complete KD, three with incomplete KD, and one with terminal ileitis with late-onset circulatory shock were managed with Ig, corticosteroids, and aspirin.
Esteve et al., 2021[60]	Case-control	14 patients with MIS-C 9 patients with COVID-19 with no MIS-C 14 patients with pre-pandemic KD 37 healthy controls	Hypothesize that pre-pandemic MIS-C patient profiles are different from the clinical manifestations observed in MIS-C	Spain	An essential role for IFN-γ in MIS-C pathogenesis is evidenced, which may be relevant for therapeutic management
Cattalini et al., 2021[59]	Retrospective cohort	149 patients: 96 patients with KD and 53 patients with MIS-C	To collect data from patients diagnosed with MIS-C by surveying between February 1, 2020, and May 31, 2020	Italy	The clinical characteristics and treatment response of MIS-C and its relationship with KD were better characterized
Niño-Taravilla et al., 2021[54]	Case series	26 patients with MIS-C Mean age of 6.5 years	To describe pediatric population with MIS-C in the pediatric intensive care unit	Chile	Most patients had echocardiographic abnormalities, and half required treatment with vasoactive drugs and immunomodulatory therapy

(continues)

Table 1. Characteristics of the publications included in the review *(continued)*

Author, year [reference]	Type of document	Target population characteristics	Objective	Country	Main finding/contribution
Coll-Vela et al., 2020[63]	Case series	8 patients with MIS-C Mean age of 5.1 years	To present a series of 8 cases with clinical presentation of fever, acute gastrointestinal problems, and ocular and mucocutaneous involvement	Peru	All patients received Ig, corticosteroids, and aspirin. Only two cases received a second dose of Ig, and only one patient presented myocarditis, shock, and required ventilatory support

CI, confidence interval; ECMO, extracorporeal membrane oxygenation; ESR, erythrocyte sedimentation rate; IFN, interferon; Ig, immunoglobulin; IL, interleukin; KD, Kawasaki disease; MIS, multisystem inflammatory syndrome; MIS-C, multisystem inflammatory syndrome temporally associated with COVID-19; NT-proBNP, N-terminal brain natriuretic peptide; PICU, pediatric intensive care unit; RT-PCR, real-time polymerase chain reaction; TNF-α, tumor necrosis factor-alpha

Search strategy

The search strategy was developed with the guidance of a research librarian from the Universidad de La Sabana, Colombia, to identify relevant references. We used Boolean operators and key terms according to each electronic database: PubMed and Scopus were included (Table 2). References cited in the selected papers were added, and, additionally, papers provided by experts were incorporated if they met the inclusion criteria and had not been previously identified. The last update of the search was performed on April 10, 2021.

Selection of studies

The titles and abstracts of the references were reviewed independently by three authors (CM, GM, AR), following the eligibility criteria. At regular meetings of these three authors, a consensus was reached on the full-text documents included, which were finally reviewed independently by all the other authors. Publication data were extracted as follows: authors, country, type of document, type of study, number of participants, objective, and main findings.

Data extraction

Data from the included articles were extracted by four independent reviewers (ET, CM, AR, GM) in the scoping review. We present the results in a table with an overview of the studies, followed by a narrative synthesis of the most important findings.

Results

We selected 45 papers that met the eligibility criteria (Figure 1). We further divided them according to study type: case series (n = 32), retrospective cohort studies (n = 6), prospective cohort studies (n = 4), case-control studies (n = 2), and cross-sectional study (n = 1). The countries of origin of these studies were as follows: United States (n = 16), France (n = 10), United Kingdom (n = 6), Italy (n = 4), Brazil (n = 1), Iran (n = 1), Serbia (n = 1), Japan (n = 1), Spain (n = 1), China (n = 1), Chile (n = 1), Switzerland (n = 1), and Peru (n = 1). The general characteristics of the included studies are presented in Table 1.

Case series

Ramcharan et al.[15] described the short-term cardiovascular manifestations, therapeutic approaches, and clinical outcomes in 15 patients under 18 years of age with a confirmed diagnosis of MIS-C based on the Royal College of Paediatrics and Child Health definition. The patients were African, Afro-Caribbean, or South Asian, with a median age of 8.8 years (interquartile range (IR): 6.4-11.2 years). All patients presented with fever, 13 patients with gastrointestinal symptoms, and eight patients with features of Kawasaki disease (KD) that did not meet diagnostic criteria. Two patients manifested symptoms typical of SARS-CoV-2 infection, and three patients had family members with symptoms of COVID-19 in the two months prior to the study. Twelve patients were positive for enzyme-linked immunosorbent assay (ELISA) combined immunoglobulins (IgG, IgA, and IgM). In addition, elevated levels of C-reactive protein (CRP), ferritin, troponin I, and pro-B-type natriuretic peptide (proBNP) were found. At the structural level, seven patients had normal coronary arteries, six had ectatic dilated coronary arteries, and one showed a fusiform aneurysm. Ten patients had mitral insufficiency, eight had pericardial effusion, and

Table 2. Search strategy

PubMed
((“Mucocutaneous Lymph Node Syndrome”[Mesh] OR “Kawasaki Disease” OR “Kawasaki Syndrome” [Title]) AND (“pediatric multisystem inflammatory disease, COVID-19 related” [Supplementary Concept] OR “MIS-C”[Title] OR “PIMS-TS”[Title]) AND ((“coronavirus”[MeSH]) OR (“coronavirus infections”[MeSH Terms]) OR (“coronavirus”) OR (“covid 2019”) OR (“SARS2”) OR (“SARS-CoV-2”) OR (“SARS-CoV-19”) OR (“severe acute respiratory syndrome coronavirus 2”[supplementary concept]) OR (“severe acute respiratory” AND “pneumonia outbreak”) OR (“novel cov”) OR (2019ncov) OR (“sars cov2”) OR (cov2) OR (ncov) OR (“covid19”) OR (“coronaviridae”) OR (“corona virus”))
Scopus
(TITLE-ABS-KEY (kawasaki AND disease) OR ALL (kawasaki AND disease) AND ALL (mucocutaneous AND lymph AND node AND syndrome) AND ALL (pediatric AND multisystem AND inflammatory AND disease) OR TITLE-ABS-KEY (pims-ts) OR TITLE-ABS-KEY (mis-c) AND TITLE-ABS-KEY (sars-cov-2) OR TITLE-ABS-KEY (covid-19) OR ALL (covid-19) OR ALL (2019-ncov))

twelve had altered left ventricular ejection fraction. Ten patients required medical assistance in intensive care with inotropic and vasopressors for a median of 3 days, and only four patients were mechanically ventilated. Medical treatment with immunoglobulin was administered in ten patients, of whom only two required a second dose, and only five patients received a course of methylprednisolone. Hospital discharge occurred on day 12 (RI: 9-13 days) with normal clinical and paraclinical parameters. Although the diagnostic and therapeutic approach is similar to KD patients, the authors concluded that early medical treatment is necessary to reduce inflammation and associated complications.

Waltuch et al.[16] described four pediatric patients with MIS-C and associated SARS-CoV-2 infection confirmed by IgG testing serologic but negative nasopharyngeal reverse transcriptase-polymerase chain reaction (RT-PCR) swab. Two patients had no significant history, one had asthma, and the last patient had hypothyroidism. All patients had symptoms in common: fever, cough, fatigue, and rash; in addition, two patients reported gastrointestinal symptoms such as nausea, vomiting, and diarrhea. On physical examination, three patients showed a diffuse non-pruritic erythematous rash on the chest, abdomen, back, and extremities (including palms and soles) and conjunctival injection; one patient had pain on palpation in the epigastrium and both iliac fossae with no signs of peritoneal irritation. Medical management was performed in the intensive care unit (ICU) with hydration support and broad-spectrum antibiotics coverage. Three patients were treated with immunoglobulin and tocilizumab. One patient who presented ARDS required mechanical ventilation and administration of anakinra. After an echocardiogram, coronary dilatation and left ventricular ejection fraction (LVEF) of 47% were found. The authors reported that patients with MIS-C presented fever and gastrointestinal symptoms with or without exanthema and features similar to KD. However, it is necessary to differentiate this disease, manage it medically, and immediately admit patients to the ICU because they may deteriorate rapidly.

Blondiaux et al.[17] reported the most common findings on cardiac magnetic resonance imaging, and transthoracic echocardiography in the pediatric population admitted to the ICU for tachycardia and inflammatory shock syndrome with acute myocarditis. All patients had a diffuse non-pruritic erythematous rash, lymphopenia, and elevated brain natriuretic peptide levels, troponin I, and CRP. Transthoracic echocardiography showed LVEF < 30% in one patient and > 50% in three patients. Septal hypokinesia was found in three patients, mitral insufficiency in two patients, and diffuse myocardial hyperintensity of the left ventricle in T2 sequences suggestive of interstitial edema in three patients. No late gadolinium enhancement—suggestive of replacement fibrosis or focal necrosis, findings indicative of transient post-infective myocarditis—was observed in any patient.

Retrospective cohorts

Verdoni et al.[11] evaluated the incidence, clinical and paraclinical characteristics in a cohort of 19 patients diagnosed with Kawasaki-like disease before the onset of the COVID-19 pandemic (group 1) and ten patients diagnosed between February and April 2020 (group 2). The mean age of disease onset in group 1 was 3 years (standard deviation (SD):2.5) versus 7.5 years (SD:3.5) in group 2 (p = 0.003). Patients diagnosed with Kawasaki-like disease during the pandemic showed more pronounced leukopenia and thrombocytopenia than those in group 1 (p = 0.017 and p = 0.001, respectively). In addition, an abnormal echocardiogram with LVEF < 50% was observed in five patients, pericardial effusion in four patients, and coronary aneurysm > 4 mm in two patients in group 2 (p = 0.089). Elevated proBNP levels were observed in the ten patients diagnosed with Kawasaki-like disease during the pandemic, hypertriglyceridemia in seven, and eight

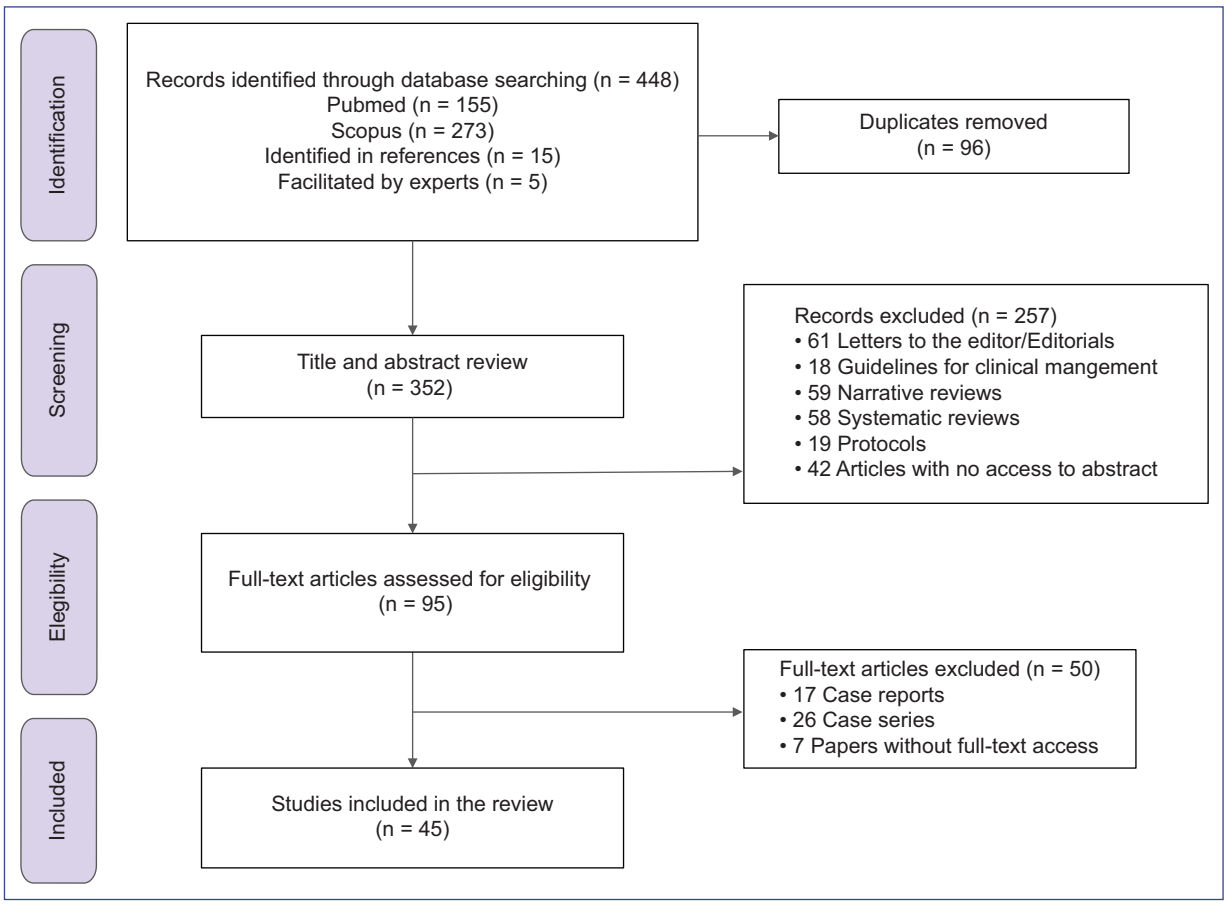

Figure 1. Flow chart for the scoping review process (PRISMA).

required supplemental corticosteroid therapy (p = 0.045). The authors reported a monthly incidence at least 30 times higher during the pandemic than the incidence prior to the first case of COVID-19, with positive seroconversion to the virus in most patients.

Prospective cohorts

Lima-Setta et al.[18] analyzed the clinical manifestations, inflammatory and respiratory markers, and diagnostic imaging of 56 patients younger than 18 years diagnosed with MIS-C in Brazil. The median age was 6.2 years, and all confirmed SARS-CoV-2 cases were positive by RT-PCR or serologic testing. Gastrointestinal symptoms, such as abdominal pain, diarrhea, and vomiting, were present in 71% of patients. Skin rash, headache, or irritability were also common symptoms. Inflammation markers (CRP) and cardiac dysfunction markers (troponin and proBNT peptide) were elevated in most patients. Among the diagnostic imaging findings, chest radiographs showed a bilateral diffuse interstitial infiltrate, computed tomography showed ground-glass opacities, and echocardiography showed mild pericardial effusion, left ventricular dysfunction, and signs of coronary dilatation. The most commonly used medical treatment was intravenous Ig in 89% of patients, broad-spectrum antibiotics in 59%, corticosteroids in more than 50%, and aspirin in 45%. Only 11% of patients required invasive mechanical ventilation with a mean duration of five days. The authors emphasized the importance of serology and clinical manifestations in establishing an early diagnosis and an effective therapeutic scheme for MIS-C.

Case-control studies

Toubiana et al.19 compared 30 patients with a suspected diagnosis of MIS-C versus a control group of 59 patients diagnosed with KD according to American Heart Association criteria before the pandemic in a pediatric population in France. Of the case group, 23 patients had positive SARS-CoV-2 IgG antibodies, and 9 had positive RT-PCR tests. The mean age in this group was 8.2 years versus 4 years in the control group (p < 0.001). Gastrointestinal symptoms such as abdominal pain,

vomiting, and diarrhea (odds ratio (OR): 84 [4.9-1456]), myocarditis (OR: 387 [38-3933]), and pericardial effusion (OR: 11.6 [3.7-36.5]) were frequent in patients with MIS-C, along with higher ICU admission (OR:196 [31-1257]). Higher CRP levels, lymphopenia, and severe anemia were observed in this group compared to the control group. Two KD patients developed coronary artery aneurysms. Both groups were treated with intravenous Ig with an adequate clinical and paraclinical response.

Cross-sectional study

Fabi et al.[20] described cardiovascular manifestations during the increase in cases of SARS-CoV-2 infections in the Emilia-Romagna region (Italy), including the pediatric population with diagnoses of KD, myocarditis, and MIS-C. Eight patients were diagnosed with KD, of whom three showed transient coronary lesions, and all were negative for SARS-CoV-2. One 5-year-old patient positive for parvovirus B19 and negative for SARS-CoV-2 was diagnosed with myocarditis. Lastly, four patients positive for SARS-CoV-2 were diagnosed with MIS-C, of whom three showed myocardial dysfunction and pericardial effusion, and one case developed multi-coronary aneurysms and mitral and aortic insufficiency. Finally, all responded to medical therapy with Ig with no cardiac sequelae.

Discussion

This study reviewed the available medical evidence on the clinical, paraclinical, and therapeutic aspects of MIS-C in the pediatric population. The most common clinical manifestations were fever, gastrointestinal symptoms (abdominal pain, diarrhea, and vomiting), diffuse non-pruritic erythematous rash on the chest, abdomen, back, and extremities (including the palmar and dorsal regions of the hands and feet), and conjunctival injection[15-18,21-28]. Cardiac manifestations are the most dangerous presentation of the disease. Due to transient post-infectious myocarditis, patients may present reduced LVEF, septal hypokinesia, atrioventricular or aortic insufficiency, and interstitial edema with no signs of fibrosis or focal necrosis[11,17,18,29]. Markers of inflammation and myocardial injury justify close cardiac and vascular structural follow-up to diagnose coronary artery aneurysms during the acute phase[30], the most severe complication. Most patients are treated with intravenous Ig, aspirin, corticosteroids, and immunomodulatory agents such as tocilizumab and anakinra[16,31-34]. Hydration support and broad-spectrum antibiotic therapy are also widely used[15,18].

WHO defined MIS-C as a syndrome in patients younger than 18 years characterized by a fever of three or more days and at least two of the following criteria: i) rash or bilateral nonpurulent conjunctivitis or signs of mucocutaneous inflammation; ii) hypotension or shock; iii) features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiographic signs or elevated troponin or proBNP values); iv) suggestive evidence of coagulopathy; v) acute gastrointestinal symptoms (diarrhea, vomiting, or abdominal pain); vi) elevated levels of inflammatory markers without an apparent microbial cause of inflammation in patients with previous SARS-CoV-2 infection[35-38].

The pathophysiologic mechanisms of MIS-C are still unknown. However, resembling systemic inflammatory diseases in pediatrics, a humoral and cellular immune response secondary to SARS-CoV-2 infection is suggested[39]. The recognition of autoantigens by antibodies or T cells results in autoantibodies and immune complexes by viral mimicry; these activate an inflammatory cascade that promotes tissue injury with tropism at the cardiovascular level[40-42]. Similarly, damage-associated molecular patterns and pathogen-associated molecular patterns lead to the formation of inflammasomes and precipitate cell death by pyroptosis and cytokine storm, mainly involving interleukin-1 (IL-1), which has inflammatory effects on the endothelial cells of the coronary arteries[43].

Unlike adult patients, the pediatric population experiences a transient type of myocardial and vascular injury, with troponin elevation in patients without underlying chronic pathologies, which decreases the associated mortality rate[44-46]. Inflammatory or cardiac injury markers are associated with the development of myocarditis, allowing the initial clinical suspicion. However, follow-up by echocardiography, CT angiography, magnetic resonance imaging, or electrocardiography (because some patients also develop arrhythmias) is essential in all cases of MIS-C[47,38]. In addition, the absence of paraclinical markers that identify the development of aneurysms requires strict follow-up during the hospital stay and for 2 to 6 weeks after discharge[17,48].

The conventional medical treatment for patients with MIS-C is based on the protocol used for KD, consisting of the administration of intravenous Ig with or without aspirin, corticosteroids, immunomodulatory agents such as infliximab (tumor necrosis factor-alpha neutralizer)[49,50], tocilizumab (IL-6 signal transduction inhibitor)[51], and anakinra (IL-1 receptor antagonist)[52-55], which are

effective in diseases with a similar systemic inflammatory load[56,57]. The use of early immunotherapy with tocilizumab in patients without cardiac complications or infliximab in patients with positive echocardiographic findings avoided the need for extracorporeal membrane support therapy, demonstrating that immunotherapy prevents further supportive interventions in patients with MIS-C[54]. However, clinical trials with a more extensive study population and study time are needed to elucidate the mechanisms of this therapy and its possible effects on survival[58-60].

Currently, antiviral (lopinavir and interferon) and non-antiviral (colchicine) treatments do not positively impact mortality, mechanical ventilation requirements, or length of hospital stay[61-63]; only remdesivir has shown clinical improvement in hospitalized adults with severe COVID-19 symptoms[64]. However, its use is limited in the pediatric population with clinical manifestations of MIS-C because the clinical picture presented in the acute phase of the disease is associated with undetectable viral loads by RT-PCR[35]. To date, the dose of anticoagulant and antiplatelet therapy in critically ill pediatric patients is guided by elevated D-dimer and fibrinogen, a decision made in conjunction with pediatric hematologists[65-67].

This review evaluated the available medical evidence on MIS-C in the pediatric population regarding clinical manifestations, treatments used, and overall prognosis, demonstrating the gaps that still exist in epidemiological, clinical, and immunological research on this new disease. Therefore, this review allows establishing new research questions and guiding the development of long-term follow-up clinical studies[68].

Strengths and limitations

A librarian guided our review strategy to ensure its adequacy. Only publications from PubMed and Scopus in English and Spanish were included. We did not perform a quality assessment of the included studies because this does not correspond to an objective of scoping reviews[12,13].

The small sample size of patients with MIS-C is an important limitation for studying this new and complex disease. More observational studies and clinical trials are needed to establish the pathophysiology and therapeutic schemes focused on immunomodulation, cardiovascular myocardial injury, mechanical ventilation, and renal replacement therapy[69,70].

In conclusion, patients with MIS-C experience a broad spectrum of signs and symptoms, including gastrointestinal, cutaneous, and conjunctival injection manifestations. Aneurysmal involvement of the coronary arteries and myocarditis are the most severe complications and frequently appear in the acute phases of the disease, along with electrocardiographic and imaging alterations. Early diagnosis allows the initiation of appropriate and effective medical treatment using Ig, corticosteroids, antiplatelet agents, anticoagulants, and other immune system modulators. The potential severity of MIS-C requires multidisciplinary care with pediatric intensivists, infectious disease specialists, cardiologists, and rheumatologists.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on patient data publication.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Conflicts of interest

The authors declare no conflict of interest.

Funding

None.

References

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382:727-33.
2. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395:507-13.
3. Pollard CA, Morran MP, Nestor-Kalinoski AL. The COVID-19 pandemic: a global health crisis. Physiol Genomics. 2020;52:549-57.
4. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020;323:1239-42.
5. Cui X, Zhao Z, Zhang T, Guo W, Guo W, Zheng J, et al. A systematic review and meta-analysis of children with coronavirus disease 2019 (COVID-19). J Med Virol. 2021;93:1057-69.
6. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet. 2020;395:1607-8.
7. Viner RM, Whittaker E. Kawasaki-like disease: emerging complication during the COVID-19 pandemic. Lancet. 2020;395:1741-3.
8. Cavallo F, Chiarelli F. An outbreak of Kawasaki-like disease in children during SARS-CoV- 2 epidemic: no surprise? Acta Biomed. 2020;91:e2020015.
9. Kanegaye JT, Wilder MS, Molkara D, Frazer JR, Pancheri J, Tremoulet AH, et al. Recognition of a Kawasaki disease shock syndrome. Pediatrics. 2009;123:e783-9.

10. Yonker LM, Shen K, Kinane TB. Lessons unfolding from pediatric cases of COVID-19 disease caused by SARS-CoV-2 infection. Pediatr Pulmonol. 2020;55:1085-6.
11. Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet. 2020;395:1771-8.
12. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. Int J Soc Res Methodol. 2005;8:19-32.
13. Levac D, Colquhoun H, O'Brien KK. Scoping studies: advancing the methodology. Implement Sci. 2010;5:69.
14. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. Ann Intern Med 2018;169:467-73.
15. Ramcharan T, Nolan O, Lai CY, Prabhu N, Krishnamurthy R, Richter AG, et al. Paediatric inflammatory multisystem syndrome: temporally associated with SARS-CoV-2 (PIMS-TS): cardiac features, management and short-term outcomes at a UK tertiary paediatric hospital. Pediatr Cardiol. 2020;41:1391-401.
16. Waltuch T, Gill P, Zinns LE, Whitney R, Tokarski J, Tsung JW, et al. Features of COVID-19 post-infectious cytokine release syndrome in children presenting to the emergency department. Am J Emerg Med. 2020;38:2246.e3-6.
17. Blondiaux E, Parisot P, Redheuil A, Tzaroukian L, Levy Y, Sileo C, et al. Cardiac MRI in children with multisystem inflammatory syndrome associated with COVID-19. Radiology. 2020;297:E283-8.
18. Lima-Setta F, Magalhães-Barbosa MC, Rodrigues-Santos G, Figueiredo EADN, Jacques ML, Zeitel RS, et al. Multisystem inflammatory syndrome in children (MIS-C) during SARS-CoV-2 pandemic in Brazil: a multicenter, prospective cohort study. J Pediatr (Rio J). 2021;97:354-61.
19. Toubiana J, Cohen JF, Brice J, Poirault C, Bajolle F, Curtis W, et al. Distinctive features of Kawasaki disease following SARS-CoV-2 infection: a controlled study in Paris, France. J Clin Immunol. 2021;41:526-35.
20. Fabi M, Filice E, Andreozzi L, Conti F, Gabrielli L, Balducci A, et al. Spectrum of cardiovascular diseases in children during high peak COVID-19 period infection in Northern Italy: is there a link? J Pediatric Infect Dis Soc. 2021;10:714-21.
21. Toubiana J, Poirault C, Corsia A, Bajolle F, Fourgeaud J, Angoulvant F, et al. Kawasaki-like multisystem inflammatory syndrome in children during the COVID-19 pandemic in Paris, France: prospective observational study. BMJ. 2020;369:m2094.
22. Labé P, Ly A, Sin C, Nasser M, Chapelon-Fromont E, Ben Saïd P, et al. Erythema multiforme and Kawasaki disease associated with COVID-19 infection in children. J Eur Acad Dermatol Venereol. 2020;34:e539-41.
23. Dursun R, Temiz SA. The clinics of HHV-6 infection in COVID-19 pandemic: Pityriasis rosea and Kawasaki disease. Dermatol Ther. 2020;33:e13730.
24. Falah NU, Hashmi S, Ahmed Z, Jaan A, Akhtar A, Khalid F, et al. Kawasaki disease-like features in 10 pediatric COVID-19 cases: a retrospective study. Cureus. 2020;12:e11035.
25. Shahbaznejad L, Navaeifar MR, Abbaskhanian A, Hosseinzadeh F, Rahimzadeh G, Rezai MS. Clinical characteristics of 10 children with a pediatric inflammatory multisystem syndrome associated with COVID-19 in Iran. BMC Pediatr. 2020;20:513.
26. Lee PY, Day-Lewis M, Henderson LA, Friedman KG, Lo J, Roberts JE, et al. Distinct clinical and immunological features of SARS-CoV-2-induced multisystem inflammatory syndrome in children. J Clin Invest. 2020;130:5942-50.
27. Iio K, Uda K, Hataya H, Yasui F, Honda T, Sanada T, et al. Kawasaki disease or Kawasaki-like disease: influence of SARS-CoV-2 infections in Japan. Acta Paediatr. 2021;110:600-1.
28. Bordet J, Perrier S, Olexa C, Gerout AC, Billaud P, Bonnemains L. Paediatric multisystem inflammatory syndrome associated with COVID-19: filling the gap between myocarditis and Kawasaki? Eur J Pediatr. 2021;180:877-84.
29. Dufort EM, Koumans EH, Chow EJ, Rosenthal EM, Muse A, Rowlands J, et al. Multisystem inflammatory syndrome in children in New York State. N Engl J Med. 2020;383:347-58.
30. Matsubara D, Kauffman HL, Wang Y, Calderon-Anyosa R, Nadaraj S, Elias MD, et al. Echocardiographic findings in pediatric multisystem inflammatory syndrome associated with COVID-19 in the United States. J Am Coll Cardiol. 2020;76:1947-61.
31. Elias MD, McCrindle BW, Larios G, Choueiter NF, Dahdah N, Harahsheh AS, et al. Management of multisystem inflammatory syndrome in children associated with COVID-19: a survey from the International Kawasaki Disease Registry. CJC Open. 2020;2:632-40.
32. Shikhare AR, Iqbal RM, Tariq R, Turner DR, Gebara BM, Freij BJ. l. Glob Pediatr Health. 2021;8:2333794X21996613.
33. Dove ML, Jaggi P, Kelleman M, Abuali M, Ang JY, Ballan W, et al. Multisystem inflammatory syndrome in children: survey of protocols for early hospital evaluation and management. J Pediatr. 2021;229:33-40.
34. Fouriki A, Fougère Y, De Camaret C, Blanchard Rohner G, Grazioli S, Wagner N, et al. Case report: case series of children with multisystem inflammatory syndrome following SARS-CoV-2 infection in Switzerland. Front Pediatr. 2021;8:594127.
35. World Health Organization. Multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19. Scientific Brief. Geneva: World Health Organization; 2020. Available from: https://www.who.int/news-room/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19
36. Ouldali N, Pouletty M, Mariani P, Beyler C, Blachier A, Bonacorsi S, et al. Emergence of Kawasaki disease related to SARS-CoV-2 infection in an epicentre of the French COVID-19 epidemic: a time-series analysis. Lancet Child Adolesc Health. 2020;4:662-8.
37. Rekhtman S, Tannenbaum R, Strunk A, Birabaharan M, Wright S, Garg A. Mucocutaneous disease and related clinical characteristics in hospitalized children and adolescents with COVID-19 and multisystem inflammatory syndrome in children. J Am Acad Dermatol. 2021;84:408-14.
38. Sethuraman U, Kannikeswaran N, Ang J, Singer A, Miller J, Haddad R, et al. Multisystem inflammatory syndrome in children associated with novel coronavirus SARS-CoV-2: presentations to a pediatric emergency department in Michigan. Am J Emerg Med. 2021;39:164-7.
39. Rostad CA, Chahroudi A, Mantus G, Lapp SA, Teherani M, Macoy L, et al. Quantitative SARS-CoV-2 serology in children with multisystem inflammatory syndrome (MIS-C). Pediatrics. 2020;146:e2020018242.
40. Carbajal R, Lorrot M, Levy Y, Grimprel E, Lecarpentier T, Heritier S, et al. Multisystem inflammatory syndrome in children rose and fell with the first wave of the COVID-19 pandemic in France. Acta Paediatr. 2021;110:922-32.
41. Gruber CN, Patel RS, Trachtman R, Lepow L, Amanat F, Krammer F, et al. Mapping systemic inflammation and antibody responses in multisystem inflammatory syndrome in children (MIS-C). Cell. 2020;183:982-95.e14.
42. To KK, Chua GT, Kwok KL, Wong JS, Au DCY, Lam YY, et al. False-positive SARS-CoV-2 serology in 3 children with Kawasaki disease. Diagn Microbiol Infect Dis. 2020;98:115141.
43. Jiang L, Tang K, Levin M, Irfan O, Morris SK, Wilson K, et al. COVID-19 and multisystem inflammatory syndrome in children and adolescents. Lancet Infect Dis. 2020;20:e276-88.
44. Lala A, Johnson KW, Januzzi JL, Russak AJ, Paranjpe I, Richter F, et al. Prevalence and impact of myocardial injury in patients hospitalized with COVID-19 infection. J Am Coll Cardiol. 2020;76:533-46.
45. Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MBF, et al. Multisystem inflammatory syndrome in U.S. children and adolescents. N Engl J Med. 2020;383:334-46.
46. Pouletty M, Borocco C, Ouldali N, Caseris M, Basmaci R, Lachaume N, et al. Paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 mimicking Kawasaki disease (Kawa-COVID-19): a multicentre cohort. Ann Rheum Dis. 2020;79:999-1006.
47. Whittaker E, Bamford A, Kenny J, Kaforou M, Jones CE, Shah P, et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. JAMA. 2020;324:259-69.
48. Sperotto F, Friedman KG, Son MBF, VanderPluym CJ, Newburger JW, Dionne A. Cardiac manifestations in SARS-CoV-2-associated multisystem inflammatory syndrome in children: a comprehensive review and proposed clinical approach. Eur J Pediatr. 2021;180:307-22.
49. Capone CA, Subramony A, Sweberg T, Schneider J, Shah S, Rubin L, et al. Characteristics, cardiac involvement, and outcomes of multisystem inflammatory syndrome of childhood associated with severe acute respiratory syndrome coronavirus 2 infection. J Pediatr. 2020;224:141-5.
50. Del Greco G, Brady KA, Clark B, Park H. A Novel pediatric multisystem inflammatory syndrome during the COVID-19 pandemic. Pediatr Emerg Care. 2020;36:500-4.
51. Grimaud M, Starck J, Levy M, Marais C, Chareyre J, Khraiche D, et al. Acute myocarditis and multisystem inflammatory emerging disease following SARS-CoV-2 infection in critically ill children. Ann Intensive Care. 2020;10:69.
52. Chiotos K, Bassiri H, Behrens EM, Blatz AM, Chang J, Diorio C, et al. Multisystem inflammatory syndrome in children during the coronavirus 2019 pandemic: a case series. J Pediatric Infect Dis Soc. 2020;9:393-8.
53. Heidemann SM, Tilford B, Bauerfeld C, Martin A, Garcia RU, Yagiela L, et al. Three cases of pediatric multisystem inflammatory syndrome associated with COVID-19 due to SARS-CoV-2. Am J Case Rep. 2020;21:e925779.
54. Niño-Taravilla C, Otaola-Arca H, Lara-Aguilera N, Zuleta-Morales Y, Ortiz-Fritz P. Multisystem inflammatory syndrome in children, Chile, May-August 2020. Emerg Infect Dis. 2021;27:1457-61.
55. Vergnano S, Alders N, Armstrong C, Bamber AR, Bandi S, Evans JA, et al. Severe refractory Kawasaki disease in seven infants in the COVID-19 era. Lancet Rheumatol. 2020;2:e520.
56. Toubiana J, Levy C, Allali S, Jung C, Leruez-Ville M, Varon E, et al. Association between SARS-CoV-2 infection and Kawasaki-like multisystem inflammatory syndrome: a retrospective matched case-control study, Paris, France, April to May 2020. Euro Surveill. 2020;25:2001813.

57. Ng KF, Kothari T, Bandi S, Bird PW, Goyal K, Zoha M, et al. COVID-19 multisystem inflammatory syndrome in three teenagers with confirmed SARS-CoV-2 infection. J Med Virol. 2020;92:2880-6.
58. Papadopoulou C, Al Obaidi M, Moraitis E, Compeyrot-Lacassagne S, Eleftheriou D, Brogan P. Management of severe hyperinflammation in the COVID-19 era: the role of the rheumatologist. Rheumatology. 2021;60:911-7.
59. Cattalini M, Della Paolera S, Zunica F, Bracaglia C, Giangreco M, Verdoni L, et al. Defining Kawasaki disease and pediatric inflammatory multisystem syndrome-temporally associated to SARS-CoV-2 infection during SARS-CoV-2 epidemic in Italy: results from a national, multicenter survey. Pediatr Rheumatol Online J. 2021;19:29.
60. Esteve-Sole A, Anton J, Pino-Ramirez RM, Sanchez-Manubens J, Fumadó V, Fortuny C, et al. Similarities and differences between the immunopathogenesis of COVID-19-related pediatric multisystem inflammatory syndrome and Kawasaki disease. J Clin Invest. 2021;131:e144554.
61. WHO Solidarity Trial Consortium; Pan H, Peto R, Henao-Restrepo AM, Preziosi MP, Sathiyamoorthy V, Abdool Karim Q, et al. Repurposed antiviral drugs for COVID-19—Interim WHO Solidarity Trial results. N Engl J Med. 2021;384:497-511.
62. Tuta-Quintero E, Vega-Corredor MC, Perdomo-Rodríguez LS, Pimentel J. Colchicina, perspectivas de un viejo amigo para la reumatología en la COVID-19: una revisión exploratoria. Rev Colomb Reumatol. 2021. [Epub ahead of print].
63. Coll-Vela LE, Zamudio-Aquise MK, Nuñez-Paucar H, Bernal-Mancilla RR, Schult-Montoya SC, Ccorahua-De La Paz M, et al. Síndrome inflamatorio multisistémico asociado con COVID-19 en niños: serie de casos en un hospital pediátrico de Perú. Rev Perú Med Exp Salud Publica. 2020;37:559-65.
64. Pimentel J, Laurie C, Cockcroft A, Andersson N. Clinical studies assessing the efficacy, effectiveness and safety of remdesivir in management of COVID-19: a scoping review. Br J Clin Pharmacol. 2021;87:2663-84.
65. Cheung EW, Zachariah P, Gorelik M, Boneparth A, Kernie SG, Orange JS, et al. Multisystem inflammatory syndrome related to COVID-19 in previously healthy children and adolescents in New York City. JAMA. 2020;324:294-6.
66. Corwin DJ, Sartori LF, Chiotos K, Odom John AR, Cohn K, Bassiri H, et al. Distinguishing multisystem inflammatory syndrome in children from Kawasaki disease and benign inflammatory illnesses in the SARS-CoV-2 pandemic. Pediatr Emerg Care. 2020;36:554-8.
67. Plebani A, Meini A, Cattalini M, Lougaris V, Bugatti A, Caccuri F, et al. Mycoplasma infection may complicate the clinical course of SARS-CoV-2 associated Kawasaki-like disease in children. Clin Immunol. 2020;221:108613.
68. Hoste L, Van Paemel R, Haerynck F. Multisystem inflammatory syndrome in children related to COVID-19: a systematic review. Eur J Pediatr. 2021;180:2019-34.
69. Belhadjer Z, Méot M, Bajolle F, Khraiche D, Legendre A, Abakka S, et al.Acute heart failure in multisystem inflammatory syndrome in children inthe context of global SARS-CoV-2 pandemic. Circulation. 2020;142:429-36.
70. Vukomanovic V, Krasic S, Minic P, Petrovic G, Nesic D, Paripovic A, et al. Kawasaki-like disease and acute myocarditis in the SARS-CoV-2 pandemic - reports of three adolescents. Bosn J Basic Med Sci. 2021;21(2):252.