



REVIEW ARTICLE

Multisystem inflammatory syndrome (MIS-C): a systematic review and meta-analysis of clinical characteristics, treatment, and outcomes

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Abstract

Objective: The clinical cases of patients with multisystem inflammatory syndrome (MIS-C) were analyzed via a systematic review and meta-analysis of the clinical findings, treatments, and possible outcomes of articles retrieved via database searches.

Sources: The authors searched the PubMed, Scielo, Web of Science, Science Direct, EMBASA, EBSCO, and Scopus databases for articles containing the keywords “multisystem inflammatory syndrome in children” or “MIS-C” or “PIMS-TS” or “SIMP” and “COVID-19” or “SARS-CoV-2” published between December 1st, 2019 and July 10th, 2021. Patient characteristics, tissue and organ comorbidities, the incidence of symptoms after COVID-19 infection, treatment, and patient evolution in the articles found were evaluated. The data were abstracted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and Newcastle-Ottawa Scale (NOS).

Findings: In total, 98 articles (2275 patients) were selected for demographics, clinical treatment, and outcomes of patients diagnosed with MIS-C. The average age of children with MIS-C, 56.8% of whom were male, was of nine years. Fever (100%), gastrointestinal (GI) (82%), and abdominal pain (68%) were the decisive symptoms for the diagnosis of MIS-C. Shock and/or hypotension were common in patients with MIS-C. Cardiac symptoms (66%) predominated over respiratory (39%) and neurological (28%) symptoms. MIS-C treatment followed the common guidelines for treating children with septic shock and Kawasaki disease (KD) and proved to be effective.

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Conclusions: This meta-analysis highlights the main clinical symptoms used for the diagnosis of MIS-C, the differences between MIS-C and KD, and the severity of the inflammatory process and urgency for hospital care.

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Introduction

In April 2020, during the peak of the coronavirus disease (COVID-19) pandemic in Europe, reports on children in England with hyperinflammatory shock, the characteristics of which are similar to those of Kawasaki disease (KD) and toxic shock syndrome (TSS), were published. The Royal College of Pediatrics and Child Health referred to this acute condition as pediatric multisystem inflammatory syndrome temporally associated with COVID-19 (PIMS-TS).¹ As more cases emerged worldwide, the disease was called multisystem inflammatory syndrome in children (MIS-C) by the U.S. Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO).^{2,3}

An initial challenge faced by physicians was differentiating patients with MIS-C due to KD and TSS from patients with MIS-C related to COVID-19. Several questions about the symptoms and the possibilities of treatment have been raised.¹⁻³

At the beginning of the pandemic, children were not at high risk for serious manifestations of COVID-19, such as severe acute respiratory syndrome (SARS). However, as the pandemic evolved, more serious complications, including thrombotic events, myocardial dysfunction, and coronary artery disease or aneurysms, manifested in the pediatric age group with MIS-C.

The aim of this systematic review was to describe the main symptoms of MIS-C and characterize its treatment and possible outcomes.

Methods

Literature search and selection criteria

The authors conducted an online search of the PubMed (<http://www.ncbi.nlm.nih.gov/pubmed>), Scielo (<http://www.scielo.br/>), Web of Science (<https://clarivate.com/products/web-of-science/>), Science Direct (<https://www.sciencedirect.com/>), Embase (www.elsevier.com/embase), EBSCO (<https://www.ebscohost.com>), and Scopus (<https://www.scopus.com/>) databases using the keywords “multisystem inflammatory syndrome in children” or “MIS-C” or “PIMS-TS” (pediatric inflammatory multisystem syndrome temporally associated with COVID-19) or “SIMP” (síndrome inflamatória multissistêmica pediátrica) and “COVID-19” or “SARS-CoV-2” to identify relevant studies published between December 1st, 2019 and July 10th, 2021. Before starting our search, the authors searched the Cochrane Library (<https://www.cochranelibrary.com>) and the National Institute for Health Research database (<https://www.crd.york.ac.uk/prospero/>) for systematic reviews and

meta-analyses on a similar subject, but no articles were found (registration: PROSPERO CRD42020204774).

The risk of bias and the quality of the systematic review was assessed using a quality assessment tool published by the National Institutes of Health. The items included in this systematic review (Supplemental information) were evaluated using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist and the Newcastle-

Ottawa scale (NOS)

To find additional eligible studies, the authors checked the reference lists of the papers found by our search. Additional studies were included in our review if they presented (1) systemic inflammatory syndrome in children or adolescents with COVID-19 and (2) clinical information and outcomes for children and adolescents.

Studies were included in our quantitative analysis if they had a sample size ≥ 6 . The authors did not exclude any article because of language. The series of cases and studies that investigated the pathological characteristics of tissues and organs were evaluated using qualitative analysis.

Some retrieved articles were excluded from this systematic review because (1) the author of the study made the diagnosis of KD and did not consider the possibility of MIS-C related to COVID-19 or PIMS-TS. (2) The study did not present any confirmation that the patient had contact with people infected with COVID-19 or that the RT-PCR test for SARS-CoV-2 and the serological tests were negative. (3) The study was on children who required intensive care before MIS-C and PIMS were identified; however, if the study did not meet the inclusion criteria, it was excluded to avoid bias. (4) The study used the same patient database as another study, so the information overlapped. (5) The article was opinion, editorial, or comment; review article; or health guidelines. These articles were excluded because they did not contain basic patient data.

Data selection was in accordance with the PRISMA and NOS guidelines.

Statistical analysis

The present research is characterized as a systematic review and meta-analysis. Research of this type is carried out by systematically selecting data and later applying statistical tests. The systematic review was carried out in accordance with the PRISMA guidelines.⁴

Determination of heterogeneity

To assess the heterogeneity of our meta-analysis, the authors used the Higgins and Thompson test (I^2), with the

following interpretation of the results: 25% = low heterogeneity, 50% = moderate heterogeneity, and $\geq 75\%$ = high heterogeneity. A heterogeneity of $\geq 50\%$ indicates significant differences among the results of the studies used in the meta-analysis; thus, the randomized effect was used. On the other hand, when the heterogeneity was $< 50\%$, the fixed effect was used, which considers the heterogeneity as insignificant. This interpretation and statistical application are extremely important for assertive results.⁵

Proportion transformation models and methods

When the heterogeneity among the survey data showed results without significance, the inverse model was used, allowing for the return of the transformation of proportions. This model is associated with the Freeman-Tukey double sine transformation (PFT) for the exact probability transformation. However, when the surveys plotted on the graph had several similar, and some discrepant data, the inverse model, associated with the arcsine transformation (PAS) was used for approximate likelihood transformations. When the heterogeneity among the survey data was significant, the mixed generalized linear model (GLMM), associated with the logistic transformation (PLOGIT), was used for the approximate likelihood transformations.

Determination of bias

The bias in our search results was determined by analyzing funnel plot graphs, which was feasible only when the

number of plotted surveys was ≥ 10 . This takes into account the inefficiency of the graph when the sample size is small.⁶

Sample significance

For all statistical analyses, an alpha level of 5% was previously defined as significant; thus, $P < 0.05$ was considered statistically significant. Statistical analyses were performed using the RStudio® version 4.0.2, and STATA® statistical software ver. 16.0 (StataCorp LLC, College Station, TX, USA).

Results

Study selection and characteristics

The inclusion and exclusion criteria for articles followed the guidelines of the Royal College of Pediatrics and Child Health (RCPCH), the CDC, and the WHO (Supplementary Table 1). The search of the databases yielded 1312 articles, of which 252 were examined in full, and 98 were selected for systematic review (Figure 1 and Supplementary Tables 2 and 3).

The articles included in the systematic review included 26 case series, 35 observational cohort studies, and 37 case reports (Table 1). The authors divided the analysis into qualitative studies with five or fewer patients and quantitative studies with six or more patients (Figure 1 and Supplementary Table 2). The number of patients in the quantitative meta-analysis articles was 2197 children, adolescents, and

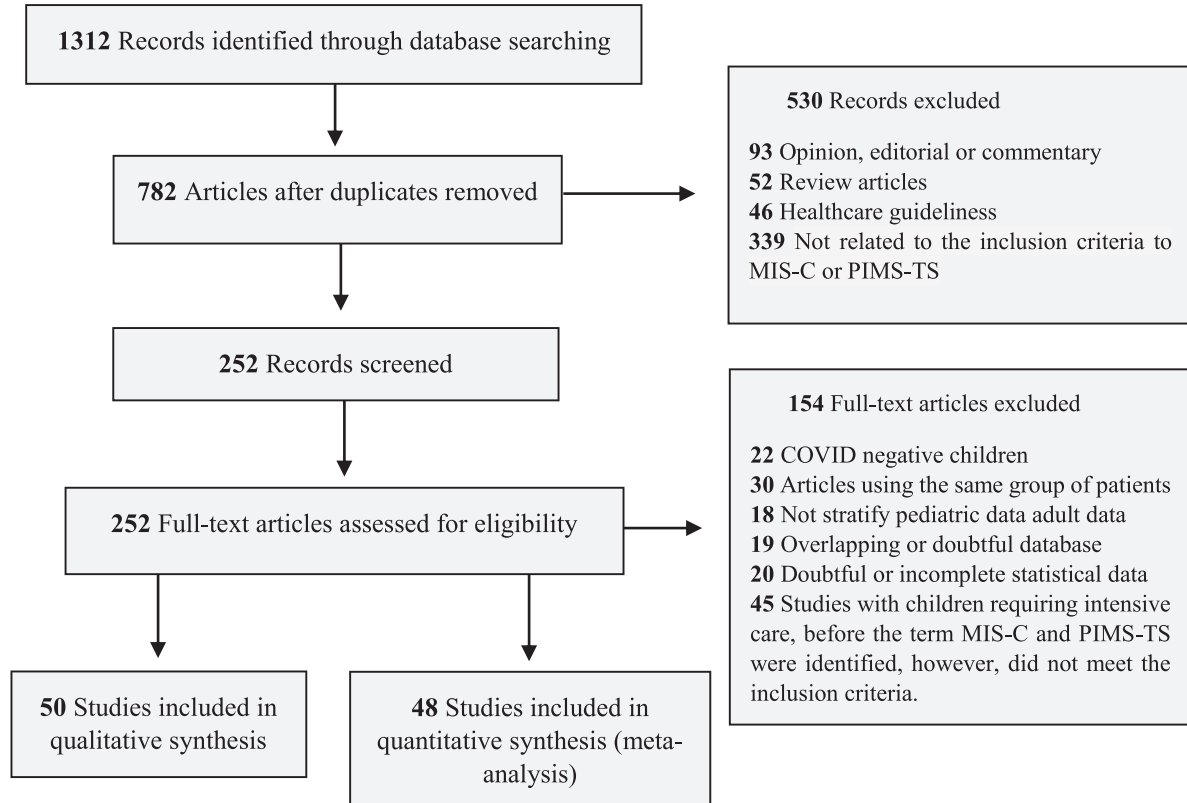


Figure 1 PRISMA flow diagram of the search of databases. The diagram contains the steps of identification, screening, eligibility, and inclusion.

Table 1 Characteristics of the studies selected in the systematic review and meta-analysis.

Articles (2020/2021)	Country	Study	Total cases	Age in years	Total male
Abdel-Haq et al. 2021 ⁷	USA	Observational	33	6 (0.3-17)	15
Abdel-Mannan et al. 2020 ⁸	UK	Case series	4	12 (8-15)	2
Acharya et al. 2020 ⁹	India	Case report	1	0.3	1
Alkan et al. 2021 ¹⁰	Turkey	Observational	36	7.8 (1.7-17)	19
Bahrami et al. 2020 ¹¹	Iran	Case report	1	5	0
Balasubramanian et al. 2020 ¹²	India	Case report	1	8	1
Bapst et al. 2020 ¹³	Switzerland	Case report	1	13	1
Bektaş et al. 2021 ¹⁴	Turkey	Case report	2	10.5	1
Belhadjer et al. 2020 ¹⁵	France/Switzerland	Observational	35	10 (2–16)	18
Belot et al. 2020 ¹⁶	France	Observational	108	8 (5–11)	53
Blondiaux et al. 2020 ¹⁷	France	Case series	4	9 (6–12)	1
Blumfield et al. 2021 ¹⁸	USA	Observational	16	10 (1-20)	10
Buonsenso et al. 2020 ¹⁹	Italy	Case report	1	11	0
Capone et al. 2020 ²⁰	USA	Observational	33	8.6 (5.5–12.6)	20
Carter et al. 2020 ²¹	UK	Observational	25	12.5 (7.7-14.4)	15
Cattalini et al. 2021 ²²	Italy	Observational	53	7 (4.5-11)	31
Cheung et al. 2020 ²³	USA	Observational	17	8 (1.8–16)	8
Chiotos et al. 2020 ²⁴	USA	Case series	6	7.5 (5–14)	1
Cogan et al. 2020 ²⁵	Belgium	Case report	1	19	0
Dallan et al. 2020 ²⁶	Switzerland	Case series	3	11 (10-12)	2
Dasgupta and Finch 2020 ²⁷	USA	Case report	1	8	0
Davies et al. 2020 ²⁸	UK	Observational	78	11 (8-14)	52
De Paulis et al. 2020 ²⁹	Brazil	Case report	1	4	0
Deza Leon et al. 2020 ³⁰	USA	Case report	1	6	0
Dhanalakshmi et al. 2020 ³¹	India	Case series	19	6 (1-16)	8
Dionne et al. 2020 ³²	USA	Observational	25	9.5 (2.7 – 15)	15
Diorio et al. 2020 ³³	USA	Case series	6	6 (5-7)	2
Dolhnikoff et al. 2020 ³⁴	Brazil	Case report	1	11	0
Dolinger et al. 2020 ³⁵	USA	Case report	1	14	1
Domico et al. 2020 ³⁶	USA	Case report	1	11	1
Dufort et al. 2020 ³⁷	USA	Observational	99	(0–20)	53
Farias et al. 2020 ³⁸	Brazil	Case series	11	4.9 (0.7-11)	9
Farias et al. 2020 ³⁹	Brazil	Case report	1	0.7	0
Feldstein et al. 2020 ⁴⁰	USA	Observational	186	8.3 (3.3–12.5)	115
Flood et al. 2021 ⁴¹	UK and Ireland	Observational	268	8.2 (4-12.1)	161
Giannattasio et al. 2021 ⁴²	Italy	Case report	1	9	1
Godfred-Cato et al. 2020 ⁴³	USA	Observational	570	8 (4-12)	316
Greene et al. 2020 ⁴⁴	USA	Case report	1	11	0
Grimaud et al. 2020 ⁴⁵	France	Observational	20	10 (2.9–15)	10
Gruber et al. 2020 ⁴⁶	USA	Case series	8	11.5 (3-20)	4
Gupta et al. 2020 ⁴⁷	India	Case report	1	7	0
Hameed et al. 2020 ⁴⁸	UK	Observational	35	11	27
Heidemann et al. 2020 ⁴⁹	USA	Case series	3	6 (5-7)	2
Hutchison et al. 2020 ⁵⁰	USA	Case report	1	14	1
Jain et al. 2020 ⁵¹	India	Observational	23	7.2 (0.8-14)	11
Joshi et al. 2020 ⁵²	USA	Case series	3	10.6 (6-13)	2
Kashyap et al. 2021 ⁵³	India	Observational	12	6.5	9
Kaushik et al. 2020 ⁵⁴	USA	Observational	33	10 (6–13)	20
Kest et al. 2020 ⁵⁵	USA	Case series	3	8 (6-10)	1
Khesrani et al. 2020 ⁵⁶	Algeria	Case report	1	9	0
Klocperk et al. 2020 ⁵⁷	Czechia	Case report	1	8	0
Lang et al. 2020 ⁵⁸	Germany	Case report	2	(10-13)	0
Lee and Margolskee 2020 ⁵⁹	USA	Case report	1	5	0
Lee et al. 2020 ⁶⁰	USA	Observational	28	9 (0.1-17)	15
Lee et al. 2020 ⁶¹	USA	Case report	1	17	1
Licciardi et al. 2020 ⁶²	Italy	Case series	2	12, 7	1
Lin et al. 2020 ⁶³	USA	Case report	1	13	0
Mamishi et al. 2020 ⁶⁴	Iran	Observational	45	7 (4–9.9)	24

Table 1 (Continued)

Articles (2020/2021)	Country	Study	Total cases	Age in years	Total male
Mehler et al. 2021 ⁶⁵	Germany	Case series	9	12.1 (1-16)	6
Meredith et al. 2021 ⁶⁶	UK	Case report	1	10	0
Miller et al. 2020 ⁶⁷	USA	Observational	44	7.3 (0.6–20)	20
Mills et al. 2021 ⁶⁸	USA	Case series	2	9.5	0
Moghadam et al. 2020 ⁶⁹	France	Case report	1	21	1
Moraleda et al. 2020 ⁷⁰	Spain	Observational	31	7.6 (4.5-11.5)	18
Nathan et al. 2020 ⁷¹	France	Case series	2	5.5 (5-11)	0
Ng et al. 2020 ⁷²	UK	Case series	3	16, 17, 13	2
Nguyen et al. 2020 ⁷³	USA	Case report	1	10	0
Okarska-Napierala et al. 2020 ⁷⁴	Poland	Case report	1	14	1
Paolino and Wllillians 2020 ⁷⁵	USA	Case series	3	7.6 (6-9)	2
Patnaik et al. 2021 ⁷⁶	India	Observational	21	8.5 (2-16)	13
Penner et al. 2021 ⁷⁷	UK	Observational	46	10.2 (8.8-13.3)	30
Pereira et al. 2020 ⁷⁸	Brazil	Case series	6	7.78 (0.01-17.6)	5
Perez-Toledo et al. 2020 ⁷⁹	UK	Case series	8	9 (7–14)	5
Pouletty et al. 2020 ⁸⁰	France	Observational	16	10 (4.7–12.5)	8
Prata-Barbosa et al. 2020 ⁸¹	Brazil	Case series	10	5.2 (1.5–8.4)	8
Prieto et al. 2021 ⁸²	Spain	Case series	5	7 (5-12)	3
Ramcharan et al. 2020 ⁸³	UK	Observational	15	8.8 (6.4–11.2)	11
Rauf et al. 2020 ⁸⁴	India	Case report	1	5	1
Regev et al. 2020 ⁸⁵	Israel	Case report	1	16	0
Riollano-Cruz et al. 2020 ⁸⁶	USA	Observational	15	12 (3–20)	11
Riphagen et al. 2020 ⁸⁷	UK	Case series	8	8.9 (4–14)	5
Roberts et al. 2021 ⁸⁸	USA	Observational	50	9.6 (6.2-14)	33
Rodriguez-Gonzalez 2020 ⁸⁹	Spain	Case report	1	0.6	1
Rogo et al. 2020 ⁹⁰	USA	Case series	4	11.2 (3-20)	3
Sadiq et al. 2020 ⁹¹	Pakistan	Case series	8	9.5 (8-10.5)	7
Saeed and Shorafa 2020 ⁹²	Iran	Case report	1	3	1
Sandoval et al. 2021 ⁹³	Chile	Case series	8	5.4 (1.5-12)	3
Schupper et al. 2020 ⁹⁴	Germany	Case report	1	5	1
Shenker et al. 2020 ⁹⁵	USA	Case report	1	12	1
Torres et al. 2020 ⁹⁶	Chile	Observational	27	6 (0-14)	14
Toubiana et al. 2020 ⁹⁷	France	Observational	21	7.9 (3.7–16.6)	9
Vari et al. 2020 ⁹⁸	USA	Case report	1	14	1
Verdoni et al. 2020 ⁹⁹	Italy	Case series	10	7.5 (2.9–16)	7
Verkuil et al. 2020 ¹⁰⁰	USA	Case report	1	14	0
Webb et al. 2020 ¹⁰¹	South Africa	Observational	23	6.6 (4.7-8.4)	17
Whittaker et al. 2020 ¹⁰²	UK	Observational	58	9 (5.7–14)	25
Yonker et al. 2020 ¹⁰³	USA	Observational	18	7.7	14
Yozgat et al. 2020 ¹⁰⁴	Turkey	Case report	1	3	0

young adults. All data, forest plot graphs, and bias analysis (funnel plot) are provided in the Supplementary Figures.

Demographic characteristics and comorbidities

Meta-analysis showed that 0.58 (0.55 - 0.61) of the children with MIS-C were male, and the median age of all children was 8.9 years (range = 0.1 days to 20 years old).

Only 23 articles included in the meta-analysis reported the race/ethnicity of the patients. Approximately 0.33 (0.26–0.42) of the children were Hispanic, 0.29 (0.24–0.34) were Black, 0.32 (0.24–0.40) were White, 0.05 (0.02–0.13) were Asian, 0.11 (0.07–0.16) were multiracial or other, and 0.13 (0.07–0.21) had no ethnicity specified in the study (Table 2).

Only 41 studies reported specific comorbidities and were included in the meta-analysis. Of the 1973 children and adolescents in whom MIS-C was diagnosed, approximately 0.33 (0.27 ± 0.40) had a comorbidity. Several comorbidities were mentioned in the articles evaluated in the qualitative analysis. The most cited comorbidities were asthma, obesity and diabetes. Other less frequent comorbidities were associated with cardiac, renal, neurological, dermatological, and hematological disorders.⁷⁻¹⁰⁴ The analysis of some comorbidities was discussed in specific studies.¹⁰⁵⁻¹¹⁷

Clinical manifestations

The analysis of the symptom data and clinical characteristics of all patients with MIS-C (Table 2 and Figure 2) showed that the most common symptoms were fever, 1.00 (0.98–1.00);

Table 2 Meta-analysis of pooled demographic and clinical characteristics of MIS-C or PIMS-TS patients.

Characteristics	Total	Events	Pooled mean proportion %(95%CI)	Heterogeneity I ² (%)	Combined
Demographics			Prop CI95%		
Sex Male	2.144	1.234	0.58 [0.55-0.61]	31%, p = 0.03	Random
Ethnicity					
White	1627	338	0.19 [0.13-0.26]	84%, p < 0.01	Random
Multiracial or others	1.514	139	0.11 [0.07-0.16]	77%, p < 0.01	Random
Black or Afrodescendents	1.627	477	0.32 [0.24-0.40]	74%, p < 0.01	Random
Asian	1.627	158	0.05 [0.02-0.13]	79%, p < 0.01	Random
Hipanic	1.043	340	0.33 [0.26-0.42]	55%, p < 0.02	Random
Not declared	1.134	175	0.13 [0.07-0.21]	82%, p < 0.01	Random
Clinical features					
Fever	2.144	2.067	1.00 [0.98-1.00]	78%, p < 0.01	Random
Cough	1.388	535	0.41 [0.28-0.55]	93%, p < 0.01	Random
Headache	1.173	280	0.28 [0.21-0.37]	70%, p < 0.01	Random
Dyspnea	874	235	0.29 [0.21-0.38]	65%, p < 0.01	Random
Conjunctivitis	978	541	0.54 [0.47-0.61]	58%, p < 0.01	Random
Sore throat	279	57	0.20 [0.12-0.31]	71%, p < 0.01	Random
Diarrhoea	1.542	655	0.58 [0.49-0.67]	76%, p < 0.01	Random
Vomiting	1.541	736	0.66 [0.56-0.75]	73%, p < 0.01	Random
Abdominal pain	1.598	763	0.68 [0.62-0.74]	24%, p < 0.12	Random
GI symptoms (not specifics)	1.228	986	0.82 [0.71-0.89]	87%, p < 0.01	Random
Erythema	1.724	814	0.59 [0.53-0.65]	51%, p < 0.01	Random
Shock	1.544	675	0.60 [0.51-0.69]	84%, p < 0.01	Random
Hypotension	1.697	890	0.59 [0.53-0.65]	62%, p < 0.01	Random
Cardiac symptoms	1.837	1.251	0.66 [0.58-0.74]	87%, p < 0.01	Random
Neurologic symptoms	1.494	488	0.28 [0.20-0.38]	83%, p < 0.01	Random
Respiratory symptoms	1.695	869	0.39 [0.30-0.49]	88%, p < 0.01	Random
Comorbidity	1.805	604	0.33 [0.27-0.40]	80%, p < 0.01	Random
Laboratory features					
Serological test confirmation	2.044	2.102	0.69 [0.60-0.77]	84%, p < 0.01	Random
RT-PCR	2.102	588	0.31 [0.24-0.38]	76%, p < 0.01	Random
Treatment					
Inotropics	1.965	913	0.54 [0.47-0.60]	77%, p < 0.01	Random
Steroids	1.973	1.145	0.64 [0.52-0.74]	68%, p < 0.01	Random
Antibiotics	777	395	0.77 [0.54-0.95]	97%, p < 0.01	Random
IVIG	1.963	1.501	0.84 [0.79-0.88]	79%, p < 0.01	Random
Antiplatelet	1.625	1.116	0.78 [0.63-0.89]	97%, p < 0.01	Random
Biological Immunodulation	1.401	355	0.27 [0.16-0.42]	77%, p < 0.01	Random
Antiviral therapy	295	45	0.16 [0.08-0.29]	67%, p < 0.01	Random
ICU	1.973	1.294	0.76 [0.67-0.84]	77%, p < 0.01	Random
(MV/NIV/ HFNC)	1.919	731	0.50 [0.39-0.62]	82%, p < 0.01	Random
ECMO	641	36	0.06 [0.03-0.10]	65%, p < 0.01	Random
Outcomes					
Recoverd	1.973	1.935	1.00 [0.99-1.00]	13%, p < 0.24	Random
Death	1.973	38	0.01 [0.01-0.03]	22%, p = 0.11	Random

PICU, pediatric intensive care unit; MV, mechanical ventilation; NIV, noninvasive ventilation; HFNC, high-flow nasal cannula; ECMO, extra-corporeal membrane oxygenation.

gastrointestinal symptoms, 0.82 (0.71–0.89); abdominal pain, 0.68 (0.62–0.74); erythema and rash, 0.59 (0.53–0.65); and non-purulent conjunctivitis, 0.54 (0.47–0.61). Cough [0.41 (0.28–0.55)], dyspnea [0.29 (0.21–0.38)], and sore throat [0.20 (0.12–0.31)] also were reported. In contrast with adults, respiratory symptoms in children [0.39 (0.30–0.49)] were less prevalent. Cardiac comorbidities were commonly observed in children with MIS-C [0.66 (0.58–0.74)].

Treatment of patients with MIS-C

Thirty-three articles that met the inclusion criteria presented clinical characteristics and the complete outcome of the treatment of patients with MIS-C (Table 2). The treatment offered to these patients involved the WHO protocols for treating patients with septic shock and KD.²

Of the 1294 patients with MIS-C, 0.76 (0.67–0.84) needed intensive hospitalization. Because of the rapid and progressive

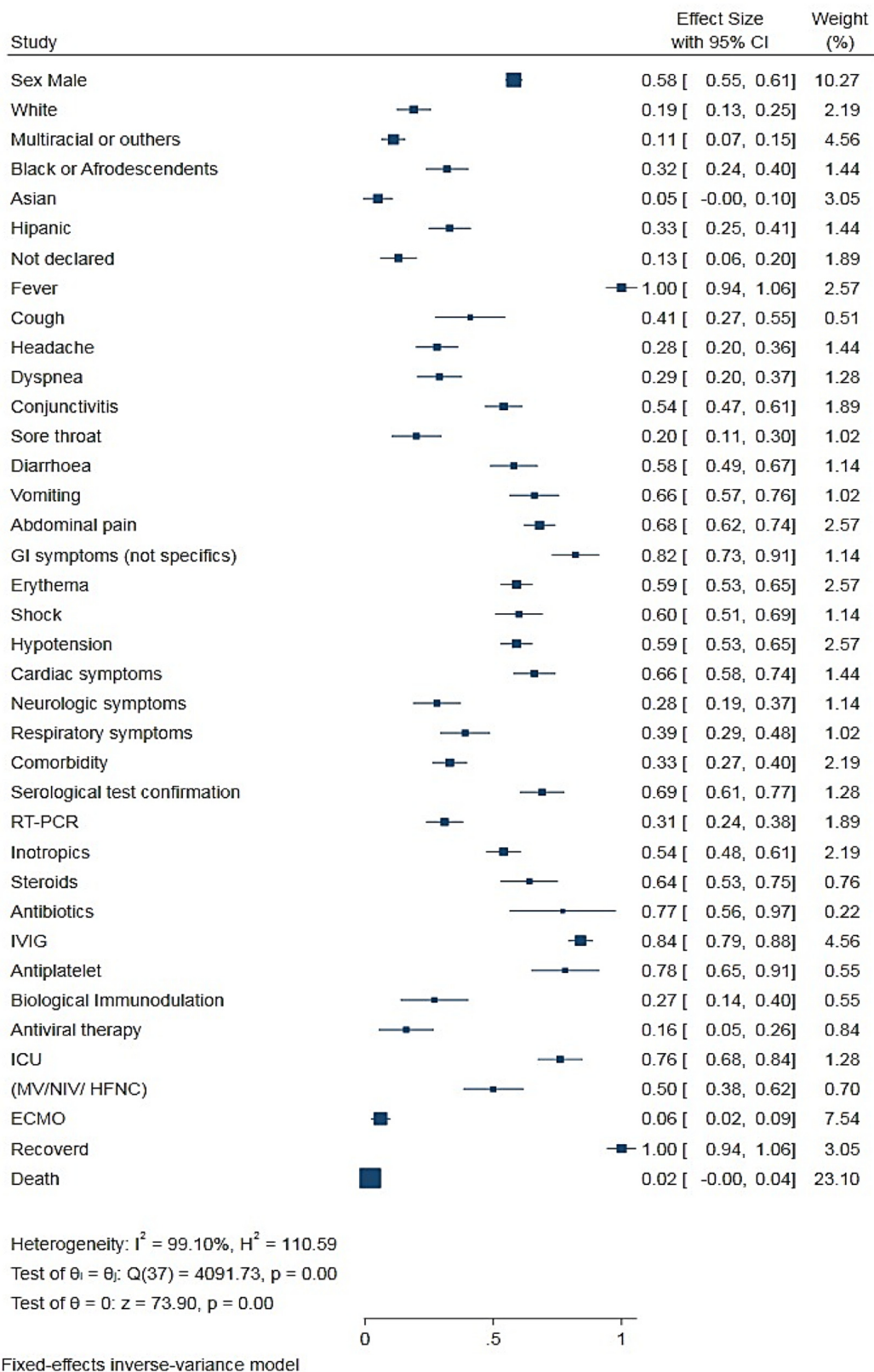


Figure 2 Summary of the size of the effect of proportions on all the variables studied in the meta-analysis.

instability caused by the inflammatory process, 0.54 (0.47–0.60) of the patients needed stabilization and inotropic agents. Shock or hypotension was reported in 0.60 (0.51–0.69) and 0.59 (0.53–0.65) of the patients, respectively.

The authors observed the following variations in the treatment of patients with MIS-C: intravenous immunoglobulin (IVIG), 0.84 (0.79–0.88); antiplatelet or anticoagulant, 0.78 (0.63–0.89); steroid, 0.64 (0.52–0.74); biological immunomodulator, 0.27 (0.16–0.42); and antiviral, 0.16 (0.08–0.29). Approximately 0.50 (0.39–0.62) of the patients with COVID-19-related MIS-C required some respiratory support, and 0.06 (0.03–0.10) eventually needed membrane oxygenation cardiopulmonary bypass (extracorporeal membrane oxygenation [ECMO]).

Some studies reported the use of broad-spectrum antibiotics in the first days of hospitalization; however, once the diagnosis of MIS-C was confirmed, the antibiotics were suspended. Only 0.02 (0.01–0.05) of the patients died despite the severity of the clinical symptoms of MIS-C.

To determine the statistical significance of all the characteristics studied, the authors performed a size test on the effect of proportions on all the variables studied in the meta-analysis (Figure 2).

Discussion

This systematic review analyzed and summarized 98 publications that included case reports, case series, and broader observational studies of patients with MIS-C. All the criteria were followed, and all information was noted for statistical analysis and evaluation. The results of this review confirm that there is a new multisystem inflammatory syndrome related to SARS-CoV-2.

In April 2020, alarming news emerged about children with evidence of recent SARS-CoV-2 infection and who developed a severe multisystem disease with fever, severe abdominal pain, hypotension and/or shock, and myocardial dysfunction with markedly elevated damage markers. This syndrome is called pediatric multisystem inflammatory syndrome temporally associated with COVID-19 (PIMS-TS) in Europe and multisystem inflammatory syndrome in children (MIS-C) by the CDC.² Although the symptoms and characteristics of MIS-C are similar to those of KD, several studies have presented significant differences that distinguish the two diseases.^{1,2,3,87,88,95,105} Studies have shown that MIS-C occurs in children and adolescents, where the average age of those studied was 08–11 years.^{11,14-24,32,36,41,46,52,85-87} In our systematic review, the mean age of the children with MIS-C was nine years. This contrasts with studies on the incidence of KD in children with an average age of 5 years.^{8,21,24,61,79,83,96,98,105,107,108,116}

Despite the incidence of COVID-19 in Asian countries, the prevalence of MIS-C there is lower, although cases have been registered worldwide according to the WHO (2020). Our systematic review, which included studies from 18 countries, found there was no statistically significant difference in the incidence of MIS-C in Asian children. This contrasts with studies that showed a predominance of KD in children of Asian origin.¹⁰⁵⁻¹⁰⁸ In addition, children with MIS-C had significant abdominal pain that required advanced imaging and surgical consultation, whereas abdominal pain rarely occurs with KD.^{95-98,105,108,109}

Children with MIS-C have gastrointestinal symptoms more often than do adults with COVID-19.^{93,108,109} As most children with gastrointestinal symptoms are not severely ill, the authors can conclude that children are more vulnerable to gastrointestinal involvement than to respiratory involvement than are adults.^{73,93,94,108-110} Some children had abdominal pain so severe that they underwent surgery for suspected peritonitis or appendicitis that resulted in the diagnosis of MIS-C.^{50,60,107-109} The most common conditions associated with abdominal pain include ascites and mesenteric lymphadenitis.^{13,65,73,107-109}

Cardiac involvement was commonly observed in children with MIS-C (Table 2). Fever, skin rashes, and gastrointestinal symptoms also were common. Case report studies showed that the symptoms of patients hospitalized with MIS-C quickly became acute. Placement in the intensive care unit, treatment for shock and hypotension, fluid resuscitation, and ventilatory support were necessary in most cases. Many patients with MIS-C develop cardiac symptoms, including mild coronary artery dilation or, rarely, aneurysms.^{11,16,26,28,32,36,55,81,82,89,111-117}

That mild transient coronary artery dilation can develop as a result of a cytokine storm with high IL-6 levels has been demonstrated in systemic-onset juvenile idiopathic arthritis, and it could result from a similar cytokine storm in MIS-C.^{86,96,97,111-113} However, persistent coronary artery aneurysms and their complications have been previously attributed to only KD in pediatric patients.^{83,98,104-110,112-117}

Another theory about the cause of cardiac injury is that a direct viral infection causes myocarditis. SARS-CoV-2 may directly cause myocardial damage by entering cardiomyocytes via the angiotensin-converting enzyme 2 (ACE2) receptor. The virus is also capable of activating CD8+ T lymphocyte migration to cardiomyocytes and causing myocardial inflammation through cell-mediated cytotoxicity.¹¹³⁻¹¹⁶ Endomyocardial biopsies from patients with COVID-19 have shown viral particles, and inflammatory infiltrates in the myocardium.¹¹¹⁻¹¹⁷ All patients in the articles reviewed who had cardiac symptoms were followed up for a longer period, and the total regression of their cardiac symptoms was observed.

Our systematic review found that the immediate medical support offered to patients with MIS-C that was associated with treatment proved effective toward their recovery [1.00 (0.99–1.00)]. In addition, the treatment of patients with MIS-C correlated with that of patients with KD and with the control of the systemic inflammatory process and cardiac injury as reported in other studies.^{45,100,101,102}

The successful use of steroids, in addition to IL-1 receptor antagonists (Anakinra) and IVIG, to control KD has been described. The anti-IL-6 receptor monoclonal antibody tocilizumab has been used successfully in treating chronic inflammatory processes such as juvenile idiopathic arthritis.⁶⁷ The authors observed the use of preventive treatment that included the use of antiplatelet drugs or anticoagulants as well as broad-spectrum antibiotics initially until severe inflammation was contained, and then the diagnosis of MIS-C was confirmed.

Limitations

This systematic review has some limitations. Because the authors are still working within the situation of a global

pandemic, we believe that patient overload and the need for urgent care have prevented hospitals and researchers from providing more detailed information about symptoms, examinations, and outcomes. In addition, several studies included in this review have points of bias resulting from the type of case, the absence of statistical analysis, patient data in more than one article, or difficulty in separating the data of children from that of adults. The authors believe that the inclusion and exclusion criteria used to obtain articles for this review, as well as the attention paid in analyzing the data and statistics, minimized the observed biases.

Conclusions

The results of this systematic review show MIS-C as a severe inflammatory syndrome that affects older children, in contrast to DK. Many organs are affected, and children need hospitalization and fluid and respiratory support. The treatments proposed by the health guidelines (WHO and RCPCH) were followed and proved to be effective in the total recovery of patients.

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Conflicts of interest

The authors declare no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.jpeds.2021.08.006](https://doi.org/10.1016/j.jpeds.2021.08.006).

References

1. RCPCH. Paediatric multisystem inflammatory syndrome temporally associated with COVID-19 (PIMS) - guidance for clinicians. 2020;178:379-85. [Cited 2020 Nov 23]. Available from: <https://www.rcpch.ac.uk/resources/paediatric-multisystem-inflammatory-syndrome-temporally-associated-covid-19-pims-guidance>.
2. CDC. Centers for disease control and prevention. Emergency Preparedness and Response: Multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19. May 14.
3. WHO. Organization World Health. Multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19. Geneva: WHO; 2020.
4. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535.
5. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557-60.
6. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics*. 2000;56:455-63.
7. Abdel-Haq N, Asmar BI, Deza Leon MP, McGrath EJ, Arora HS, Cashen K, et al. SARS-CoV-2-associated multisystem inflammatory syndrome in children: clinical manifestations and the role of infliximab treatment. *Eur J Pediatr*. 2021;180:1581-91.
8. Abdel-Mannan O, Eyre M, Löbel U, Bamford A, Eltze C, Hameed B, et al. Neurologic and radiographic findings associated with COVID-19 infection in children. *JAMA Neurol*. 2020;77:1440-5.
9. Acharyya BC, Acharyya S, Das D. Novel Coronavirus mimicking Kawasaki disease in an infant. *Indian Pediatr*. 2020;57:753-4.
10. Alkan G, Sert A, Oz SK, Emiroglu M, Yılmaz R. Clinical features and outcome of MIS-C patients: an experience from Central Anatolia. *Clin Rheumatol*. 2021;40:4179-89.
11. Bahrami A, Vafapour M, Moazzami B, Rezaei N. Hyperinflammatory shock related to COVID-19 in a patient presenting with multisystem inflammatory syndrome in children: First case from Iran. *J Paediatr Child Health*. 2021;57:922-5.
12. Balasubramanian S, Nagendran TM, Ramachandran B, Ramanan AV. Hyper-inflammatory syndrome in a child with COVID-19 treated successfully with intravenous Immunoglobulin and Tocilizumab. *Indian Pediatr*. 2020;57:681-3.
13. Bapst T, Romano F, Muller M, Rohr M. Special dermatological presentation of paediatric multisystem inflammatory syndrome related to COVID-19: erythema multiforme. *BMJ Case Rep*. 2020;13:e236986.
14. Bektaş G, Nihal A, Kübra B, Esra Ş. Reversible splenic lesion syndrome associated with SARS-CoV-2 infection in two children. *Brain Dev*. 2021;43:230-3.
15. Belhadj Z, Meot M, Bajolle F, Khraiche D, Legendre A, Abakka S, et al. Acute heart failure in multisystem inflammatory syndrome in children in the context of global SARS-CoV-2 pandemic. *Circulation*. 2020;142:429-36.
16. Belot A, Antona D, Renolleau S, Javouhey E, Hentgen V, Angoulvant F, et al. SARS-CoV-2-related paediatric inflammatory multisystem syndrome, an epidemiological study, France 1 March to 17 May 2020 *Euro Surveill*. 2020;25:2001010.
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. Blumfield E, Levin TL, Kurian J, Lee EY, Liszewski MC. Imaging findings in multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19. *AJR Am J Roentgenol*. 2021;216:507-17.
19. Buonsenso D, Di Sante G, Sali M, Group CC-S. Cytokine profile in an adolescent with pediatric multisystem inflammatory syndrome temporally related to COVID-19. *Pediatr Infect Dis J*. 2020;39:e213-5.
20. 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.
21. Carter MJ, Fish M, Jennings A, Doores KJ, Wellman P, Seow J, et al. Peripheral immunophenotypes in children with multisystem inflammatory syndrome associated with SARS-CoV-2 infection. *Nat Med*. 2020;26:1701-17.
22. Cattalini M, Della Paolera S, Zunica F, Bracaglia C, Giangreco M, Verdoni L, et al. Rheumatology Study Group of the Italian Pediatric Society. 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:e29.

23. 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.
24. 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.
25. Cogan E, Foulon P, Cappelliez O, Dolle N, Vanfraechem G, De Backer D. multisystem inflammatory syndrome with complete Kawasaki disease features associated with SARS-CoV-2 infection in a young adult. A case report. *Front Med*. 2020;7:428.
26. Dallon C, Romano F, Siebert J, Politi S, Lacroix L, Sahyoun C. Septic shock presentation in adolescents with COVID-19. *Lancet Child Adolesc Health*. 2020;4:e21–3.
27. Dasgupta K, Finch SE. A case of pediatric multisystem inflammatory syndrome temporally associated with COVID-19 in South Dakota. *S D Med*. 2020;73:246–51.
28. Davies P, Evans C, Kanthimathinathan HK, Lillie J, Brierley J, Waters G, et al. Intensive care admissions of children with paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) in the UK: a multicentre observational study. *Lancet Child Adolesc Health*. 2020;4:669–77.
29. De Paulis M, Oliveira DB, Vieira RP, Pinto IC, Machado RR, Cavalcanti MP, et al. Multisystem inflammatory syndrome associated with COVID-19 with neurologic manifestations in a child: a brief report. *Pediatr Infect Dis J*. 2020;39:e321–4.
30. Deza Leon MP, Redzepi A, McGrath E, Abdel-Haq N, Shawaqfeh A, Sethuraman U, et al. COVID-19-associated pediatric multisystem inflammatory syndrome. *J Pediatric Infect Dis Soc*. 2020;9:407–8.
31. Dhanalakshmi K, Venkataraman A, Balasubramanian S, Madhusudan M, Amperayani S, Putilibai S, et al. Epidemiological and clinical profile of pediatric inflammatory multisystem syndrome - temporally associated with SARS-CoV-2 (PIMS-TS) in Indian children. *Indian Pediatr*. 2020;57:1010–4.
32. Dionne A, Mah DY, Son MBF, Lee PY, Henderson L, Baker AL, et al. atrioventricular block in children with multisystem inflammatory syndrome. *Pediatrics*. 2020; e146.
33. Diorio C, Henrickson SE, Vella LA, McNERney KO, Chase J, Burudpakdee C, et al. Multisystem inflammatory syndrome in children and COVID-19 are distinct presentations of SARS-CoV-2. *J Clin Invest*. 2020;130:5967–75.
34. Dolhnikoff M, Ferreira Ferranti J, de Almeida Monteiro RA, Duarte-Neto AN, Soares Gomes-Gouveia M, Viu Degaspere N, et al. SARS-CoV-2 in cardiac tissue of a child with COVID-19-related multisystem inflammatory syndrome. *Lancet Child Adolesc Health*. 2020;4:790–4.
35. Dolinger MT, Person H, Smith R, Jarchin L, Pittman N, Dubinsky MC, et al. Pediatric crohn disease and multisystem inflammatory syndrome in children (MIS-C) and COVID-19 treated with infliximab. *J Pediatr Gastroenterol Nutr*. 2020;71:153–5.
36. Domico M, McCanta AC, Hunt JL, Ashouri N, Nugent D, Kelly RB. High-grade heart block requiring transvenous pacing associated with multisystem inflammatory syndrome in children during the COVID-19 pandemic. *HeartRhythm Case Rep*. 2020;6:811–4.
37. 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.
38. Farias EC, Piva JP, de Mello M, do Nascimento L, Costa CC, Machado MM, et al. Multisystem inflammatory syndrome associated with coronavirus disease in children: a multi-centered study in Belem, Para, Brazil. *Pediatr Infect Dis J*. 2020;39:e374–6.
39. Farias EC, Justino MC, Ferraz ML, Mello MF. Multisystem inflammatory syndrome in a child associated with coronavirus disease 19 in the Brazilian Amazon: fatal outcome in an infant. *Rev Paul Pediatr*. 2020;38:e2020165.
40. Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MB, et al. Multisystem inflammatory syndrome in U.S. children and adolescents. *N Engl J Med*. 2020;383:334–46.
41. Flood J, Shingleton J, Bennett E, Walker B, Amin-Chowdhury Z, Oligbu G, et al. Paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 (PIMS-TS): prospective, national surveillance, United Kingdom and Ireland, 2020. *Lancet Reg Health Eur*. 2021;3:e100075.
42. Giannattasio A, Maglione M, Zenzeri L, Mauro A, Di Mita O, Iodice RM, Tipo V. A child with a severe multisystem inflammatory syndrome following an asymptomatic COVID-19 infection: A novel management for a new disease? *J Med Virol*. 2021;93:112–4.
43. Godfred-Cato S, Bryant B, Leung J, Oster ME, Conklin L, Abrams J, et al. COVID-19- Associated multisystem inflammatory syndrome in children - United States, March-July 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69:1074–80.
44. Greene AG, Saleh M, Roseman E, Sinert R. Toxic shock-like syndrome and COVID-19: Multisystem inflammatory syndrome in children (MIS-C). *Am J Emerg Med*. 2020;38:2492.e5-2492.e6.
45. 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.
46. 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.
47. Gupta N, Richter R, Robert S, Kong M. Viral sepsis in children. *Front Pediatr*. 2018;6:252.
48. Hameed S, Elbaaly H, Reid CE, Santos RM, Shivamurthy V, Wong J, et al. Spectrum of imaging findings on chest radiographs, US, CT, and MRI images in multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19. *Radiology*. 2020; e202543.
49. 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 Repor*. 2020;21:e925779.
50. Hutchison L, Plichta AM, Lerea Y, Madora M, Ushay HM. Neuropsychiatric symptoms in an adolescent boy with multisystem inflammatory syndrome in children. *Psychosomatics*. 2020;61:739–44.
51. Jain S, Sen S, Lakshmivenkateshiah S, Bobhate P, Venkatesh S, Udani S, et al. Multisystem inflammatory syndrome in children with COVID-19 in Mumbai, India. *Indian Pediatr*. 2020;57:1015–9.
52. Joshi K, Kaplan D, Bakar A, Jennings JF, Hayes DA, Mahajan S, et al. Cardiac dysfunction and shock in pediatric patients with COVID-19. *JACC Case Rep*. 2020;2:1267–70.
53. Kashyap H, Kumar RN, Gautam S, Gupta A, Gupta S, Tiwari PK. Multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19 infection. *Indian J Pediatr*. 2021;88:e1053.
54. Kaushik S, Aydin SI, Derespina KR, Bansal PB, Kowalsky S, Trachtman R, et al. Multisystem inflammatory syndrome in children associated with severe acute respiratory syndrome Coronavirus 2 infection (MIS-C): a multi-institutional study from New York city. *J Pediatr*. 2020;224:24–9.
55. Kest H, Kaushik A, DeBruin W, Colletti M, Goldberg D. Multisystem inflammatory syndrome in children (MIS-C) associated with 2019 novel Coronavirus (SARS-CoV-2) infection. *Case Rep Pediatr*. 2020;2020:8875987.
56. Khesrani LS, Chana K, Sadar FZ, Dahdouh A, Ladjadj Y, Bouguermouh D. Intestinal ischemia secondary to Covid-19. *J Pediatr Surg Case Rep*. 2020;61:e101604.

57. Klocperk A, Parackova Z, Dissou J, Malcova H, Pavlicek P, Vymazal T, et al. Case report: systemic inflammatory response and fast recovery in a pediatric patient with COVID-19. *Front Immunol.* 2020;11:1665.
58. Lang P, Eichholz T, Bakchoul T, Streiter M, Petrasch M, Bosmuller H, et al. Defibrotide for the treatment of pediatric inflammatory multisystem syndrome temporally associated with severe acute respiratory syndrome Coronavirus 2 infection in 2 pediatric patients. *J Pediatric Infect Dis Soc.* 2020;9:622–5.
59. Lee WS, Margolskee E. Leukoerythroblastosis and plasmacytoid lymphocytes in a child with SARS-CoV-2-associated multisystem inflammatory syndrome. *Blood.* 2020;136:914.
60. Lee PY, Platt CD, Weeks S, Grace RF, Maher G, Gauthier K, et al. Immune dysregulation and multisystem inflammatory syndrome in children (MIS-C) in individuals with haploinsufficiency of SOCS1. *J Allergy Clin Immunol.* 2020;146:1194–200.
61. 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.
62. Licciardi F, Pruccoli G, Denina M, Parodi E, Taglietto M, Rosati S, et al. SARS-CoV-2-Induced Kawasaki-Like hyperinflammatory syndrome: a novel COVID phenotype in children. *Pediatrics.* 2020;146:e20201711.
63. Lin J, Lawson EC, Verma S, Peterson RB, Sidhu R. Cytotoxic lesion of the corpus callosum in an adolescent with multisystem inflammatory syndrome and SARS-CoV-2 infection. *AJNR Am J Neuroradiol.* 2020;41:2017–9.
64. Mamishi S, Movahedi Z, Mohammadi M, Ziaee V, Khodabandeh M, Abdolsalehi MR, et al. Multisystem inflammatory syndrome associated with SARS-CoV-2 infection in 45 children: a first report from Iran. *Epidemiol Infect.* 2020;148:e196.
65. Mehler K, Jung N, Oberthuer A. Is it all MIS-C? Unusual findings in a series of nine German patients with multisystem inflammatory syndrome in children after SARS-CoV-2 infection. *I J of Infect Dis.* 2021;106:405–8.
66. Meredith J, Khedim CA, Henderson P, Wilson DC, Russell RK. Paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 [PIMS-TS] in a patient receiving infliximab therapy for inflammatory bowel disease. *J Crohns Colitis.* 2021;15:687–91.
67. Miller J, Cantor A, Zachariah P, Ahn D, Martinez M, Margolis KG. Gastrointestinal symptoms as a major presentation component of a novel multisystem inflammatory syndrome in children that is related to Coronavirus disease 2019: a single center experience of 44 cases. *Gastroenterology.* 2020;159:1571–4. e2.
68. Mills T, Trivedi A, Tremoulet AH, Hershey D, Burns JC. Hyponatremia in patients with multisystem inflammatory syndrome in children. *Pediatr Infect Dis J.* 2021;40:e344–6.
69. Moghadam P, Blum L, Ahouach B, Radjou A, Lambert C, Scanvic A, et al. Multisystem inflammatory syndrome with particular cutaneous lesions related to COVID-19 in a young adult. *Am J Med.* 2020;134:e36–7.
70. Moraleda C, Serna-Pascual M, Soriano-Arandes A, Simó S, Epalza C, Santos M, et al. Multi-inflammatory syndrome in children related to severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) in Spain. *Clin Infect Dis.* 2020;72:e397–401.
71. Nathan N, Prevost B, Sileo C, Richard N, Berdah L, Thouvenin G, et al. The wide spectrum of COVID-19 clinical presentation in children. *J Clin Med.* 2020;9:e2950.
72. 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.
73. Nguyen DC, Haydar H, Pace ER, Zhang XS, Dobbs KR. Pediatric case of severe COVID-19 with shock and multisystem inflammation. *Cureus.* 2020;12:e8915.
74. Okarska-Napierala M, Zalewska E, Kuchar E. Fever and diarrhea as the only symptoms of Multisystem Inflammatory Syndrome in Children (MIS-C). *Gastroenterology.* 2020;160:968–9.
75. Paolino J, Williams DA. Peripheral blood smears of children with multisystem inflammatory syndrome demonstrate prominence of early myeloid forms with morphologic evidence of toxic change. *Pediatr Blood Cancer.* 2020;68:e28551.
76. Patnaik S, Jain MK, Ahmed S, Dash AK, RK P, Sahoo B, et al. Short-term outcomes in children recovered from multisystem inflammatory syndrome associated with SARS-CoV-2 infection. *Rheumatol Int.* 2021;14:1957–62.
77. Penner J, Abdel-Mannan O, Grant K, Maillard S, Kucera F, Hassell J, et al. 6-month multidisciplinary follow-up and outcomes of patients with paediatric inflammatory multisystem syndrome (PIMS-TS) at a UK tertiary paediatric hospital: a retrospective cohort study. *Lancet Child Adolesc Health.* 2021;5:473–82.
78. Pereira MF, Litvinov N, Farhat SC, Eisencraft AP, Gibelli M, Carvalho WB, et al. Severe clinical spectrum with high mortality in pediatric patients with COVID-19 and multisystem inflammatory syndrome. *Clinics.* 2020;75:e2209.
79. Perez-Toledo M, Faustini SE, Jossi SE, Shields AM, Kanthimathinathan HK, Allen JD, et al. Serology confirms SARS-CoV-2 infection in PCR-negative children presenting with Paediatric Inflammatory Multi-System Syndrome. *medRxiv.* 2020: e20123117.
80. 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.
81. Prata-Barbosa A, Lima-Setta F, Santos GRD, Lanziotti VS, de Castro REV, de Souza DC, et al. Pediatric patients with COVID-19 admitted to intensive care units in Brazil: a prospective multicenter study. *J Pediatr (Rio J).* 2020;96:582–92.
82. Prieto LM, Toral B, Llorente A, Coca D, Blázquez-Gamero D. Cardiovascular magnetic resonance imaging in children with pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 and heart dysfunction. *Clin Microbiol Infect.* 2021;27:648–50.
83. 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.
84. Rauf A, Vijayan A, John ST, Krishnan R, Latheef A. Multisystem inflammatory syndrome with features of atypical Kawasaki disease during COVID-19 Pandemic. *Indian J Pediatr.* 2020;87:745–7.
85. Regev T, Antebi M, Eytan D, Shachor-Meyouhas Y, Ilivitzki A, Aviel YB, et al. Pediatric inflammatory multisystem syndrome with central nervous system involvement and hypocomplementemia following SARS-COV-2 Infection. *Pediatr Infect Dis J.* 2020;39:e206–7.
86. Riollano-Cruz M, Akkoyun E, Briceno-Brito E, Kowalsky S, Reed J, Posada R, et al. Multisystem inflammatory syndrome in children related to COVID-19: a New York city experience. *J Med Virol.* 2020;93:424–33.
87. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet.* 2020;395:1607–8.
88. Roberts JE, Campbell JI, Gauvreau K, Lamb GS, Newburger J, Son MB, et al. Differentiating multisystem inflammatory syndrome in children: a single-centre retrospective cohort study. *Arch Dis Child.* 2021;8. archdischild-2021-322290. [Epub ahead of print].

89. Rodriguez-Gonzalez M, Castellano-Martinez A, Cascales-Poyatos HM, Perez-Reviriego AA. Cardiovascular impact of COVID-19 with a focus on children: a systematic review. *World J Clin Cases*. 2020;8:5250–83.
90. Rogo T, Mathur K, Purswani M. Systemic inflammation with cardiac involvement in pediatric patients with evidence of COVID-19 in a community hospital in the Bronx, New York. *J Pediatr Infect Dis Soc*. 2020;9:502–3.
91. Sadiq M, Aziz OA, Kazmi U, Hyder N, Sarwar M, Sultana N, et al. Multisystem inflammatory syndrome associated with COVID-19 in children in Pakistan. *Lancet Child Adolesc Health*. 2020;4:e36–7.
92. Saeed A, Shorafa E. Status epilepticus as a first presentation of COVID-19 infection in a 3 years old boy; Case report and review the literature. *IDCases*. 2020;22:e00942.
93. Sandoval F, Julio K, Méndez G, Valderas C, Echeverría AC, Perinette MJ, et al. Neurologic features associated with SARS-CoV-2 infection in children: a case series. Report. *J Child Neurol*. 2021;36:853–66.
94. Schupper AJ, Yaeger KA, Morgenstern PF. Neurological manifestations of pediatric multi-system inflammatory syndrome potentially associated with COVID-19. *Childs Nerv Syst*. 2020;36:1579–80.
95. Shenker J, Trogen B, Schroeder L, Ratner AJ, Kahn P. Multisystem inflammatory syndrome in children associated with status epilepticus. *J Pediatr*. 2020;227:300–1.
96. Torres JP, Izquierdo G, Acuna M, Pavez D, Reyes F, Fritis A, et al. Multisystem inflammatory syndrome in children (MIS-C): report of the clinical and epidemiological characteristics of cases in Santiago de Chile during the SARS-CoV-2 pandemic. *Int J Infect Dis*. 2020;100:75–81.
97. 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.
98. Vari D, Miller JM, Rellosa N, Srivastava S, Frizzola M, Thacker D. Severe cardiac dysfunction in a patient with multisystem inflammatory syndrome in children associated with COVID-19: Retrospective diagnosis of a puzzling presentation. A case report. *Prog Pediatr Cardiol*. 2020;58:101270.
99. 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.
100. Verkuil LD, Liu GT, Brahma VL, Avery RA. Pseudotumor cerebri syndrome associated with MIS-C: a case report. *Lancet*. 2020;396:532.
101. Webb K, Abraham DR, Faleye A, McCulloch M, Rabie H, Scott C. Cape Town MIS-C-Team. Multisystem inflammatory syndrome in children in South Africa. *Lancet Child Adolesc Health*. 2020;4:e38.
102. 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.
103. Yonker LM, Neilan AM, Bartsch Y, Patel AB, Regan J, Arya P, et al. Pediatric severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2): clinical presentation, infectivity, and immune responses. *J Pediatr*. 2020;227:45–52. e5.
104. Yozgat CY, Uzuner S, Bursal Duramaz B, Yozgat Y, Erenberk U, Iscan A, et al. Dermatological manifestation of pediatrics multisystem inflammatory syndrome associated with COVID-19 in a 3-year-old girl. *Dermatol Ther*. 2020;33:e13770.
105. Burns JC. The riddle of Kawasaki disease. *N Engl J Med*. 2007;356:659–61.
106. Jenco M. AAP provides guidance on diagnosing, treating MIS-C. *Am Acad Pediatr*. 2020; 2. [Cited Oct 28] Available from <https://publications.aap.org/aapnews/news/7007?autologin-check=redirected>.
107. Makino N, Nakamura Y, Yashiro M, Kosami K, Matsubara Y, Ae R, et al. Nationwide epidemiologic survey of Kawasaki disease in Japan 2015-2016. *Pediatr Int*. 2019;61:397–403.
108. Colomba C, La Placa S, Saporito L, Corsello G, Ciccio F, Medaglia A, et al. Intestinal involvement in Kawasaki disease. *J Pediatr*. 2018;202:186–93.
109. Oba J, Carvalho WB, Silva CA, Delgado AF. Gastrointestinal manifestations and nutritional therapy during COVID-19 pandemic: a practical guide for pediatricians. *Einstein*. 2020;18:eRW5774.
110. Xia W, Shao J, Guo Y, Peng X, Li Z, Hu D. Clinical and CT features in pediatric patients with COVID-19 infection: different points from adults. *Pediatr Pulmonol*. 2020;55:1169–74.
111. Binstadt BA, Levine JC, Nigrovic PA, Gauvreau K, Dedeoglu F, Fuhlbrigge RC, et al. Coronary artery dilation among patients presenting with systemic-onset juvenile idiopathic arthritis. *Pediatrics*. 2005;116:e89–93.
112. Akhmerov A, Marban E. COVID-19 and the Heart. *Circ Res*. 2020;126:1443–55.
113. Tissières P, Teboul JL. SARS-CoV-2 post-infective myocarditis: the tip of COVID-19 immune complications? *Ann Intensive Care*. 2020;10:98.
114. Wei X, Fang Y, Hu H. Immune-mediated mechanism in coronavirus fulminant myocarditis. *Eur Heart J*. 2020;41:1855–8.
115. Tavazzi G, Pellegrini C, Maurelli M, Belliato M, Sciutti F, Bottazzi A, et al. Myocardial localization of coronavirus in COVID-19 cardiogenic shock. *Eur J Heart Fail*. 2020;22:911–5.
116. Gordon JB, Kahn AM, Burns JC. When children with Kawasaki disease grow up: myocardial and vascular complications in adulthood. *J Am Coll Cardiol*. 2009;54:1911–20.
117. Inciardi RM, Lupi L, Zacccone G, Italia L, Raffo M, Tomasoni D, et al. Cardiac involvement in a patient with coronavirus disease 2019 (COVID-19). *JAMA Cardiol*. 2020;5:819–24.