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REVIEW ARTICLE

Multisystem inflammatory syndrome in children: an Umbrella review

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Abstract

We conducted an Umbrella review of eligible studies to evaluate what patient features have been investigated in the multisystem inflammatory syndrome in children (MIS-C) population, in order to guide future investigations. We comprehensively searched MEDLINE, EMBASE, and Cochrane Database of Systematic Reviews from December 1, 2019 to the May 6, 2022. The time period was limited to cover the coronavirus disease-2019 (COVID-19) pandemic period. The protocol was registered in the PROSPERO registry (CRD42022340228). Eligible studies included (1) a study population of pediatric patients ≤21 years of age diagnosed with MIS-C; (2) an original Systematic review or Mata-analysis; (3) published 2020 afterward; and (4) was published in English. A total of 41 studies met inclusion criteria and underwent qualitative analysis. 28 studies reported outcome data of MIS-C. 22 studies selected clinical features of MIS-C, and 6 studies chose demographic data as a main topic. The mortality rate for children with MIS-C was 1.9% (interquartile range (IQR) 0.48), the ICU admission rate was 72.6% (IQR 8.3), and the extracorporeal membrane oxygenation rate was 4.7% (IQR 2.0). A meta-analysis of eligible studies found that cerebral natriuretic peptide in children with MIS-C was higher than that in children with COVID-19, and that the use of intravenous immunoglobulin (IVIG) in combination with glucocorticoids to treat MIS-C compared to IVIG alone was associated with lower treatment failure. In the future, for patients with MIS-C, studies focused on safety of surgery requiring general anesthesia, risk factors, treatment, and long-term outcomes are warranted.

Keywords MIS-C · COVID-19 · Umbrella review

Introduction

Multisystem inflammatory syndrome in children (MIS-C) is a severe condition associated with coronavirus disease-2019 (COVID-19).The syndrome consists of a collection of primarily hyperinflammatory pathologies that can involve multiple organs [1]. The United States Centers for Disease Control and Prevention (CDC) officially defined case of MIS-C as follows: Any illness in a person aged less than 21 years that meets: The clinical and the laboratory criteria (Confirmed), or the clinical criteria and epidemiologic linkage criteria (Probable), or the vital records criteria (Suspect). Based on a study population from New York State in 2020, the total incidence of MIS-C was low at 2 per 100,000 children, far lower than the overall laboratory-diagnosed COVID-19 rate in children of 322 per 100,000 children [2]. Most patients who developed MIS-C required ICU admission (21–80%) [1–6]. Consequently, the impact of COVID-19 and MIS-C on healthcare systems is enormous [7, 8]. In the early phase of the

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COVID-19 pandemic, most pediatric hospitals in North America canceled or delayed elective surgeries to preserve medical resources and prevent the spread of the disease in hospitals. Although significantly investigated, the precise pathophysiology and optimal treatment are not yet wholly established [9]. Furthermore, safety of anesthesia and surgery for these children with MIS-C remain unclear.

There are an increasing number of evidence synthesis studies (e.g., systematic review (SR), meta-analysis (MA)) which focus on MIS-C. However, there has been no systematic assessment of the quality of published evidence. The purpose of the current study is to conduct an Umbrella review to reveal what patient characteristics of MIS-C eligible studies have investigated and to assess the methodological quality of these studies in order to provide information for perioperative management.

Methods

Systematic literature search

This Umbrella review followed the framework described by the Cochrane Handbook citation [10], Institute of Medicine(IOM) Finding What Works in Health Care [11], the Centre for Reviews and Dissemination (CRD) CRD's Guidance on Systematic Reviews [12], and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13]. The protocol was registered in the PROSPERO registry (CRD42022340228).

We conducted comprehensive searches for published SRs and MAs from the following three databases (MEDLINE (Ovid), Embase (Ovid), and Cochrane Database of Systematic Reviews (Ovid)) from December 1, 2019, to May 6, 2022, and restricted to manuscripts written in English. The details of the database search strategy are provided as online only supplement 1.

Study selection

Duplicate studies retrieved from more than one database were removed. Two independent reviewers (N.S, M.S.) investigated titles and abstracts of relevant studies to remove any that did not meet eligibility criteria. SRs and MAs that featured MIS-C were identified. For those that fulfilled the eligibility criteria, the full article was obtained. Disagreement between reviewers regarding study eligibility for inclusion in the Umbrella review was resolved through consensus of a third reviewer (K.A.).

Inclusion and exclusion criteria

The inclusion criteria of this Umbrella review were as follows: (1) study population of pediatric patients ≤21 years of age diagnosed MIS-C utilizing one of the following definitions: the World Health Organization (WHO) [14], CDC [15], the Canadian Paediatric Surveillance Program (CPSP)[16] and the Royal College of Pediatrics and Child Health (RCPCH, UK) [17]; (2) type of publication original SR or MA; (3) published 2020 or later; and (4) published in English.

Exclusion criteria included any randomized controlled trials, controlled, cohort, or case-controlled studies, case series/case report, animal studies, conference abstracts, or narrative reviews.

Data extraction

Each eligible study was retrieved, and data extracted into DistillerSR by one reviewer (N.S.) and comprehensively cross-checked by a second reviewer (M.S.). Any uncertainty was resolved with a third reviewer (K.A.).

The following data was extracted from eligible papers: (1) first author; (2) study title; (3) journal; (4) publication year; (5) study design (SRs/MAs); (6) MA model; (7) included studies and participants; (8) main topic/subtopic (demographic data, clinical features, laboratory findings, diagnostic tests, radiological data, treatment/management, outcome data); and (9) outcomes (e.g., mortality, ICU admission, ICU length of stay, need for mechanical ventilation, inotropes or vasopressors, and need for extracorporeal membrane oxygenation (ECMO)).

Quality assessments

The quality of SRs and MAs was assessed using AMSTAR-2 [18]. Overall risk of bias was evaluated using ROBIS [19]. Both quality assessments were conducted by one reviewer (N.S) and entirely validated by a second reviewer (M.S). Any uncertainty was resolved with a third reviewer (K.A.).

Data synthesis

A narrative synthesis was applied to summarize the rate of the primary outcome and secondary outcomes. We described the basic characteristics of eligible studies, including patient factors related to MIS-C (e.g., prognoses, risk factors, treatment/management) and methodological quality based on ROBIS and AMSTER-2. Descriptive statistics were summarized, including mortality, ICU admission rate, ICU length of stay, need for mechanical ventilation, inotropes,

or vasopressors, and need for ECMO. The characteristics and statistically significant variables of eligible MAs were summarized. Publication timing was broken into four six-month epochs encompassing the years 2021 and 2022. Trends of ROBIS and AMSTER-2 were assessed using the Mann Kendall Trend test, with the null hypothesis positing no existence of monotonic trends in the given series and the alternate hypothesis setting the presence of a trend, be it positive, negative, or non-null. An advantage of this test is that it is non-parametric, handling any data distribution and bypassing the requirement for data normality, particularly beneficial for limited data sets. We analyzed the trends, and the resulting *P* values were computed to determine the statistical significance.

Results

The overall systematic literature search identified 5244 studies, of which 1648 were removed due to duplication. The resultant 3596 articles underwent title and abstract screening and 50 studies were subsequently retrieved for full text article assessments. Of the 50 studies, 41 (29 SRs and 12 SRs + MAs) met the inclusion criteria and underwent qualitative analysis (Fig. 1).

Table 1 and online supplement 2 summarizes the eligible studies. The 41 studies originated from 19 different countries for the corresponding authors, with the most common countries represented being United States of America ($n=8$) and China ($n=7$). The number of studies included in each review ranged from 3 to 328, and the total number of MIS-C cases ranged from 17 to 2290. Twenty-eight studies reported outcome data of MIS-C, including mortality, ICU admission rate, ICU length of stay, need for mechanical ventilation, inotropes or vasopressors, and the need for ECMO (Table 2). Twelve reviews conducted MAs, of which one applied individual patient data [20]. Characteristics and statistically significant variables from eligible MAs were summarized in Table 3 and 4, respectively. Twenty-two studies selected clinical features of MIS-C as a main topic, of which 3 studies focused topic on cardiac manifestations [21–23], 1 on neurological manifestations [24], 1 on gastrointestinal complications [25], 1 on ocular manifestation [26], and 1 on oral manifestations [27]. Six studies chose demographic data [28–33], 3 studies laboratory findings [34–36], and 2 treatment paradigms [37, 38] as their focus. The other studies investigated the difference between Kawasaki disease (KD) and MIS-C [39], MIS-C in neonates and infants [40], pre-existing factors associated with severe disease, primary admission to critical care, death [20], pooled prevalence estimates of pediatric hyperinflammatory conditions in hospitalized patients admitted for treatment due to COVID-19 [41], echocardiographic findings [42], severe neurological issues and a coexisting positive SARS-CoV-2 test [43], and thrombotic complications [44].

Seventeen studies (41%) were assessed as having a low risk of bias, 13 studies (32%) were rated as having a high risk of bias, and eleven studies (27%) assessed as having an unclear risk of bias according to their ROBIS assessment. Forty studies (98%) were appraised as critical low-quality studies according to the AMSTER-2 assessment, and 1 study (2%) was rated as low quality. The detailed result of AMSTER-2 and ROBIS were presented in online only supplement 3 and 4. No statistically significant trend over time was observed in AMSTER-2 and ROBIS. (Online only supplement 5, 6).

Clinical features

Seven studies that selected clinical features as a main topic conducted single-arm MAs. Nepal et al. [24] investigated neurological manifestations of MIS-C patients in their study, in which they found that 27.1% of children with MIS-C developed neurological manifestations, of which 27% were

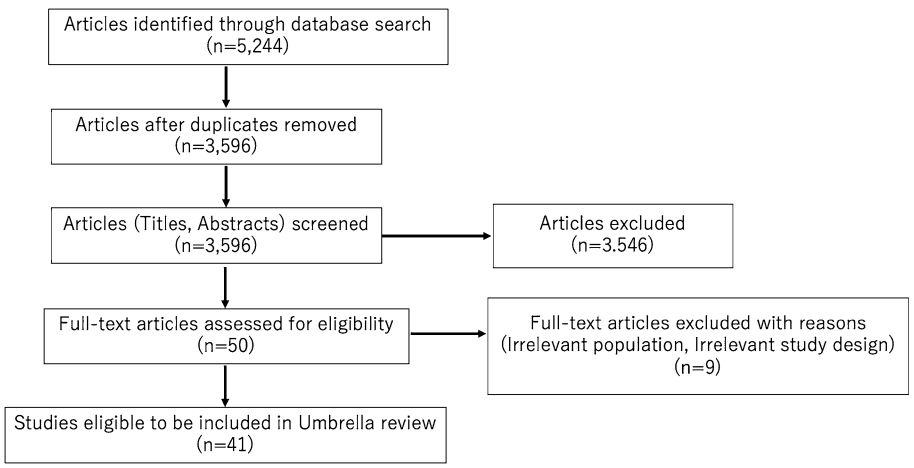

Fig. 1 PRISMA diagram

Table 1 Basic characteristics of eligible studies

First author's last name	Publication year	Country of the corresponding author	Study design	Number of included studies	Number of included MISC cases	Main topic	Subtopic report [Yes/No]	Clinical outcome report [Yes/No]	ROBIS	AMSTAR2
Zhao	2021/2022	China	SR + MA	24	1613	Laboratory findings (cardiac makers)	No	No	Unclear	Critically low
Guimaraes	2021/2022	Portugal	SR	31	1415	Demographic data	Yes	Yes	Unclear	Critically low
Kornitzer	2021/2022	United States of America (USA)	SR	54	543	Clinical features	Yes	Yes	Unclear	Critically low
Keshavarz	2021/2022	Iran	SR	45	47	The relationship between MIS-C and COVID-19	Yes	Yes	Unclear	Critically low
Zhao	2020/2021	China	SR + MA	21	787	Laboratory findings (inflammatory makers)	Yes	No	Low	Critically low
Toraih	2020/2021	United States of America (USA)	SR + MA	15	318	Clinical features	Yes	Yes	High	Critically low
Hoste	2020/2021	Belgium	SR	68	953	Demographic data	Yes	Yes	Unclear	Critically low
Radia	2021/2022	United Kingdom (UK)	SR	35	783	Clinical features	Yes	Yes	High	Critically low
Yasuhara	2020/2021	United States of America (USA)	SR + MA	27	917	Demographic data	Yes	Yes	High	Critically low
Nepal	2020/2021	Nepal	SR + MA	15	785	Clinical features (neurological manifestations)	No	No	High	Critically low
Zou	2020/2021	China	SR + MA	6	182	Clinical features	Yes	Yes	Low	Critically low
Bustos	2020/2021	Chile	SR + MA	11	468	Clinical features	Yes	Yes	High	Critically low
Abrams	2020/2021	United States of America (USA)	SR	8	440	Demographic data	Yes	Yes	High	Critically low
Aronoff	2020/2021	United States of America (USA)	SR	16	505	Clinical features	Yes	Yes	High	Critically low
Baradaran	2020/2021	Iran	SR + MA	16	600	Clinical features	No	Yes	Low	Critically low
Yasuhara	2020/2021	United States of America (USA)	SR	46	17	Clinical features	Yes	Yes	Low	Critically low
Kaushik	2020/2021	United States of America (USA)	SR	328	655	Clinical features	Yes	Yes	Low	Critically low
Nascimento	2020/2021	Brazil	SR	25	624	Clinical features (oral manifestations)	No	No	Low	Critically low
Rouva	2020/2021	Greece	SR	38	385	Clinical features (gastrointestinal complications)	No	No	High	Critically low

Table 1 (continued)

First author's last name	Publication year	Country of the corresponding author	Study design	Number of included studies	Number of included MISC cases	Main topic	Subtopic report [Yes/No]	Clinical outcome report [Yes/No]	ROBIS	AMSTAR2
Dhar	2021/2022	India	SR	18	833	Demographic data	Yes	Yes	Low	Low
Henrina	2020/2021	Indonesia	SR	26	1228	Clinical features (cardiac manifestations)	Yes	Yes	High	Critically low
Sood	2020/2021	India	SR	17	992	Clinical features	Yes	Yes	High	Critically low
Zhou	2021/2022	China	SR	12	969	Laboratory findings (differences in laboratory parameters between MIS-C and KD)	No	No	High	Critically low
Wang	2021/2022	China	SR	57	2290	Clinical features	Yes	Yes	High	Critically low
Lo	2021/2022	Taiwan	SR + MA	32	1458	Clinical features (ocular manifestation)	Yes	No	Unclear	Critically low
Haghighi	2020/2021	Iran	SR	21	916	Clinical features (cardiac manifestations)	No	No	Low	Critically low
Mardi	2020/2021	Iran	SR	25	599	Demographic data	Yes	Yes	Low	Critically low
Tang	2020/2021	China	SR	24	270	Clinical features	Yes	Yes	Low	Critically low
Ahmed	2020/2021	United States of America (USA)	SR	39	662	Clinical features	Yes	Yes	Low	Critically low
Rodriguez-Gonzalez	2020/2021	Spain	SR	193	688	Clinical features (cardiac manifestations)	Yes	Yes	Unclear	Critically low
Llinas-Caballero	2020/2021	Colombia	SR	17	961	Comparison between KD and MIS-C	No	Yes	Unclear	Critically low
Williams	2020/2021	India	SR	18	833	Clinical features	Yes	Yes	Low	Critically low
Wang	2021/2022	China	SR	10	-	Treatment/management	No	No	Low	Critically low
De Rose	2021/2022	Italy	SR	48	32	MIS-C in neonates and infants	Yes	Yes	Unclear	Critically low

Table 1 (continued)

First author's last name	Publication year	Country of the corresponding author	Study design	Number of included studies	Number of included MISC cases	Main topic	Subtopic report [Yes/No]	Clinical outcome report [Yes/No]	ROBIS	AMSTAR2
Sharma	2021/2022	Austria	SR	14	780	To determine a pooled prevalence estimate of these paediatric hyperinflammatory conditions in hospitalized patients admitted for treatment due to COVID-19	No	Yes	Low	Critically low
Harwood	2021/2022	United Kingdom (UK)	SR + MA	-	-	Pre-existing factors associated with severe disease, primarily admission to critical care, and death	No	Yes	Low	Critically low
Rauniyar	2021/2022	Nepal	SR + MA	3	756	Treatment (IVIG alone versus IVIG plus glucocorticoids)	No	No	Low	Critically low
Santos	2021/2022	Brazil	SR + MA	98	2275	Clinical features	Yes	Yes	Low	Critically low
Karimi	2021/2022	Iran	SR	33	1392	Echocardiographic findings	No	No	Low	Critically low
O'Loughlin	2021/2022	Grenada	SR	41	65	Severe neurological issues and a coexisting positive SARS-CoV-2 test	No	No	High	Critically low
Zaffanello	2021/2022	Italy	SR	14	-	Thrombotic complications	No	No	Unclear	Critically low

MIS-C multisystem inflammatory syndrome in children, *COVID-19* coronavirus disease 2019, *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2, *KD* Kawasaki disease, *SR* systematic review, *MA* meta-analysis, *IVIG* intravenous immunoglobulin

Table 2 Descriptive statistics of eligible studies

Clinical outcome	Number of studies reporting outcome	Range [minimum–maximum]	Median	Interquartile range
Mortality (%)	20	0.17–12.5	1.9	0.48
ICU admission rate (%)	22	40.6–82	72.4	8.3
ICU length of stay (days)	3	4–6	4.8	1.0
Mechanical ventilation rate (%)	18	17.6–37.9	26.6	7.7
Inotrope & pressor rate (%)	18	15.6–63	54.7	14.7
ECMO rate (%)	12	0.48–11.2	4.7	2.0

ECMO extracorporeal membrane oxygenation

Table 3 Summary of characteristics from eligible meta-analyses

First author's last name	Main topic	Model of meta-analysis	Number of included studies	Number of included MIS-C cases	Number of explored variables	Number of statistically significant variables (number vs. single arm)
Zhao	Laboratory findings	FEM/REM	24	1613	12	2
Zhao	Laboratory findings	FEM/REM	21	787	32	15
Toraih	Clinical features	REM	15	318	80	Single arm meta-analysis
Yasuhara	Demographic data	REM	27	917	59	Single arm meta-analysis
Nepal	Clinical features (neurological manifestations)	FEM/REM	15	785	4	Single arm meta-analysis
Zou	Clinical features	FEM/REM	6	182	58	Single arm meta-analysis
Bustos	Clinical features	Not applicable	11	468	28	Single arm meta-analysis
Baradaran	Clinical features	REM	16	600	34	Single arm meta-analysis
Lo	Clinical features (ocular manifestation)	REM	32	1458	3	Single arm meta-analysis
Harwood	Pre-existing factors associated with severe disease, primarily admission to critical care, and death	REM/Multilevel mixed effect models	0	0	43	5
Rauniyar	Treatment (IVIG alone versus IVIG plus glucocorticoids)	FEM/REM	3	756	4	2
Santos	Clinical features	FEM/REM	98	2275	38	Single arm meta-analysis

FEM fixed effect model, *REM* random effect model, *IVIG* intravenous immunoglobulin

headaches, 17.1% were meningism/meningitis, and 7.6% were encephalopathy.

Lo and Chen [26] investigated the ocular and systemic manifestations of children with MIS-C. Their MA revealed that around half of the children had conjunctivitis, and the five most common systemic manifestations were fever (96.4%), gastrointestinal symptoms (76.7%), shock (61.5%), rash (57.1%), and neurological symptoms (36.8%).

Demographic data

Six studies focused on demographic data in their study, of which 1 conducted a single-arm MA. Yasuhara et al. reported that the mean age of children with MIS-C was 9.3 (95% CI 8.4–10.1), and males constituted 56.8% (95% CI 52.1–61.5; $I^2 = 41.6$) of the patients. The pooled proportions of Hispanic and Black cases were 34.6% (95%CI 28.3–40.9; $I^2 = 41.6\%$) and 31.5% (95%CI 24.8–38.1; I2 = 63.4), respectively [28].

Laboratory finding

Two studies investigated laboratory findings by conducting MAs. Zhao et al. [35] compared cardiac markers (brain natriuretic peptide (BNP), troponin, aspartate aminotransferase (AST)) between MIS-C vs. COVID-19, severe MIS-C vs. non-severe MIS-C, and MIS-C with coronary artery abnormality (CAA) vs. MIS-C without CAA. They reported that MIS-C patients exhibited higher BNP levels than patients with COVID-19. In a comparison between

Table 4 Summary of statistically significant variables from eligible meta-analyses

First author's last name	Statistically significant variables	Effect size of each variables	Statistical heterogeneity
Zhao	MIS-C vs. COVID-19	SMD (95% CI)	I^2 (%)
	BNP[a]	0.49 (0.17, 0.80)	27.9
	MIS-C vs. non-severe COVID-19		
	BNP[a]	1.13 (0.48, 1.77)	0
	Severe MIS-C vs. non-severe MIS-C		
	BNP[a]	0.26 (0.04, 0.48)	58.6
Zhao	MIS-C vs. severe/non-severe COVID-19	WMD/SMD (95% CI)	I^2 (%)
	PLT ($\times 10^9$/L)	−95.16 (−112.15, −78.17)	17.1
	ANC ($\times 10^6$/L)	1976.79 (1116.09, 2837.49)	26.5
	CRP (mg/L)	0.68 (0.36, 1.00)	67.7
	MIS-C vs. severe COVID-19		
	LDH[a]	−0.91 (−1.39, −0.43)	32.9
	ESR (mm/h)	34.52 (14.23, 54.80)	0
	MIS-C vs. non-severe COVID-19		
	ALC ($\times 10^6$/L)	−1110.43 (−1477.75, −743.11)	68
	ANC ($\times 10^6$/L)	2392.68 (1636.71, 3148.64)	0
	CRP (mg/L)	1.09 (0.70, 1.48)	67.9
	D-dimer (μg/ml)	1.61 (−1.39, −0.43)	2
	Severe MIS-C vs. non-severe MIS-C		
	ALC ($\times 10^6$/L)	−0.60 (−0.91, −0.30)	41.5
	ANC ($\times 10^6$/L)	3.28 (2.01, 4.55)	48.9
	CRP (mg/L)	68.64 (46.19, 91.09)	27.9
	D-dimer (μg/ml)	2.50 (1.78, 3.21)	10.8
	Ferritin (ng/ml)	362.50 (130.25, 594.76)	0
	Age groups of MIS-C (younger vs. older age)		
	CRP (mg/dl)	−88.75 (−122.67, −54.84)	0
Harwood	Critical care admission vs. non-critical care admission	Odds ratio (95% CI)	I^2 (%)
	Age 5–9 years	1.81 (1.51, 2.16)	0
	10–14 years	2.65 (1.48, 4.74)	21.32
	>14 years	2.56 (2.03, 3.21)	0
	Metabolic including obesity	1.45 (1.10, 1.92)	0
	Any co-morbidity[b]	12.44 (9.74, 15.87)	(No data available)
Rauniyar	IVIG + Glucocorticoids vs. IVIG	Odds Ratio (95% CI)	I^2 (%)
	Persistence of fever/treatment failure[c]	0.57 (0.42, 0.79)	45.36
	Need of adjunctive therapy[d]	0.27 (0.20, 0.37)	0

MIS-C multisystem inflammatory syndrome in children, *COVID-19* coronavirus disease 2019, SMD standardised mean difference, *WMD* weighted mean difference, CI confidence interval, *BNP*: brain natriuretic peptide, *PLT platelet* ANC absolute neutrophil count, *CRP* C-reactive protein, *LDH* lactate dehydrogenase, *ESR* erythrocyte sedimentation rate, *ALC* absolute lymphocyte count, *IVIG* intravenous immunoglobulin

[a] No units provided

[b] Any co-morbidity (pre-existing factors) includes cardiovascular, respiratory, asthma, gastrointestinal/Liver, neurological, malignancy, haematological, immunosuppression, trisomy 21 (Down's Syndrome), chronic kidney disease, endocrine including diabetes, and metabolic conditions including obesity

[c] Persistence of fever was taken as presence of fever at any point from day two or recrudescence after seven days of initial therapy

[d] The need for adjunctive therapy was defined as the addition of a separate immunomodulator or an increment of 5 mg/kg or equivalent in the daily dose of prednisolone

MIS-C with and without CAA, no difference was detected in the BNP and troponin levels.

In a separate manuscript, the same author group compared inflammatory markers of MIS-C by severity and age [34]. They found that severe MIS-C patients had higher white blood cell counts (WBC), absolute neutrophil counts (ANC), C-reactive protein (CRP), D-dimer, and ferritin levels, in comparison with non-severe MIS-C patients. Younger children (0–5 years) with MIS-C had lower CRP and ferritin levels than middle-aged/older children/adolescents.

Treatment

One paper that selected treatment as a main topic conducted a MA. In the study, Rauniyar et al. [38] compared the effect of combination therapy (intravenous immunoglobulin (IVIG) plus glucocorticoids) versus IVIG alone for the treatment of MIS-C, using individual patient data (IPD). The results of the MA showed that the incidence of persistence of fever/treatment failure (OR 0.57, 95%CI (0.42, 0.79), $I^2 = 45.36\%$) and need of adjunctive therapy (OR 0.27, 95%CI (0.20, 0.37), $I^2 = 0.0$) were lower in children treated with combination therapy, but did not show a significant reduction in the rate of left ventricular dysfunction (OR 0.79, 95% CI (0.34, 1.87), $I^2 = 58.44\%$) or the need for inotropic support (OR 0.83, 95% CI (0.35, 1.99), $I^2 = 75.40\%$).

Discussion

This Umbrella review was conducted to reveal what patient and clinical characteristics of pediatric patients with MIS-C have been investigated, to assess the methodological quality of these included studies and to guide future investigations. The results of our research indicate that most of the studies selected clinical features of MIS-C as a main topic. The other topics included demographic data, laboratory findings, treatment paradigms, differences the between KD and MIS-C, MIS-C in neonates and infants, pre-existing factors, pooled prevalence estimates of MIS-C in hospitalized patients admitted for treatment due to COVID-19, echocardiographic findings, neurological issues, a coexisting positive SARS-CoV-2 test, and thrombotic complications. Most of the studies included were appraised as critical low-quality studies according to the AMSTER-2 assessment. The result of the AMSTER-2 assessment inherently influences the result of our study. The time to publication was generally short due to clinical urgency, which often means that the quality of evidence may be sacrificed.

The current study findings in the context of prior literature

An Umbrella review is a type of novel methodology that aims to summarize and appraise a broad scope of literature and provide a comprehensive view of a specific topic. Several Umbrella reviews on COVID-19 patients have been published. Harrison et al. [45] investigated the association between cardiovascular risk factors and health outcomes with COVID-19 and the impact of COVID-19 on cardiovascular health. Treskova-Schwarzbach et al. [46] explored pre-existing conditions and outcomes across geographical regions. Yang et al. [47] investigated the impact of COVID-19 on kidney health and the associations between kidney diseases and clinical outcomes in COVID-19 patients, including children. There are no prior Umbrella reviews focused explicitly on pediatric COVID-19 or on MIS-C, in part due to the rarity of the latter disease and it's very recent emergence. This Umbrella review is the first study to summarize the broad aspects of evidence in pediatric patients with MIS-C, including outcomes, assessing the methodological quality of these studies. Three prior Umbrella reviews assessed COVID-19 study quality or risk of bias with AMSTER-2 or ROBIS, while our review assessed both metrics. Harrison et al. [45] assessed the quality of 84 reviews on COVID-19 with AMSTAR-2, in which 28 reviews (33%) were appraised as critically low, 24 reviews (29%) were low quality, and 31 reviews (37%) were moderate quality.

Treskova-Schwarzbach et al. [46] used AMSTER-2 to evaluate the methodological quality of 120 included studies. Of these, 114 studies (95%) were rated as critically low quality, and 6 studies (5%) were rated as low quality. Yang et al. [47] assessed the methodological quality of 103 included reviews with ROBIS. Their result illustrated that 30 reviews (29.1%) were rated as low risk of bias, 73 reviews (70.9%) were rated as high risk of bias. Our result with AMSTER-2 assessment was similar to the findings of Treskova-Schwarzbach et al. [46], with most included reviews rated as critically low-quality studies, significantly higher than the findings by Harrison et al. [45]. The rate of the studies assessed as low risk of bias with ROBIS in our review was 41%, higher than that reported by Yang et al. [47]. This might come from the difference in study population and number of studies published.

Generally, the quality of the SRs and MAs conducted during the COVID-19 outbreak appeared to be low. Possible reasons for this are that the authors might have considered that time to publication outweighing the quality of the study in an emergent situation, overwhelming clinical work due to a large number of critically ill patients with COVID-19 negating the time to conduct SRs and MAs, and reviewers might have eased the quality of studies for publication.

Also, not enough studies due to new disease might have not allowed to conduct SRs and MAs.

Strengths and limitations

The current study is the first Umbrella review to investigate what patient specific features have been explored in the literature for pediatric patients with MIS-C. The strengths of our Umbrella review include the comprehensive search strategy and the rigorous appraisal of the risk of bias and study quality with AMSTER-2 and ROBIS. There are several limitations of our study. Due to the novelty of the disease, and its recent emergence as a clinical entity, data on long-term outcomes was and still generally is limited. However, we comprehensively evaluated and summarized the outcome data available. The time period was limited from December 1, 2019 to May 6, 2022. However, this period covers the COVID-19 pandemic period. In order to answer our research question, we did not update the search.

Research and clinical implications

Clinical data including poor outcome risk factors, treatment, and long-term outcomes related to MIS-C is limited at this point. Studies focused on these topics are warranted to improve the evidence used to guide clinical treatment strategies. Clinician experience with the related disease of KD facilitated educated treatment paradigms. Given the lack of predictability for future waves of COVID-19 and MIS-C, it is important to consolidate evidence and guide future studies to enhance the therapeutic decisions by clinicians. For anesthesiologist, perioperative differential diagnosis should encompass MIS-C. The safety of surgery requiring general anesthesia for these MIS-C patients cannot be answered based on the results of the Umbrella review, perhaps because of the rarity of this disease or the limited number of studies on this topic. Therefore, at this time, surgery requiring general anesthesia for these MIS-C patients should be planned based on individual risk, severity of organ involvement, and whether surgery is urgent or not [48]. The optimal timing of surgery should be discussed with the multidisciplinary team.

Conclusion

Our Umbrella review found that most studies selected clinical features of MIS-C as a main topic. In the future, for patients with MIS-C, studies focused on safety of surgery requiring general anesthesia, risk factors, treatment, and long-term outcomes are warranted.

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Author contribution KA and NS conceived this paper. KA and NS developed the protocol. ME performed the systematic literature searches, managed database results and documentation. NS, MS and KA performed the systematic review and data extraction. NS and KA performed the analysis on the result of the literature search and extracted data. NS and KA wrote the initial draft of the manuscript, and MS, GE and MJ helped draft the final version, which was approved by all authors.

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Data availability The data supporting this study are all available from the main text and online-only supplements.

Declarations

Conflict of interest All authors are disclosed appropriately that they have no competing interests related to this publication.

References

1. Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MBF, Newburger JW, Kleinman LC, Heidemann SM, Martin AA, Singh AR, Li S, Tarquinio KM, Jaggi P, Oster ME, Zackai SP, Gillen J, Ratner AJ, Walsh RF, Fitzgerald JC, Keenaghan MA, Alharash H, Doymaz S, Clouser KN, Giuliano JS Jr, Gupta A, Parker RM, Maddux AB, Havalad V, Ramsingh S, Bukulmez H, Bradford TT, Smith LS, Tenforde MW, Carroll CL, Riggs BJ, Gertz SJ, Daube A, Lansell A, Coronado Munoz A, Hobbs CV, Marohn KL, Halasa NB, Patel MM, Randolph AG, Overcoming COVID-19 Investigators, CDC COVID-19 Response Team. Multisystem inflammatory syndrome in us children and adolescents. N Engl J Med. 2020;383:334–46.
2. Dufort EM, Koumans EH, Chow EJ, Rosenthal EM, Muse A, Rowlands J, Barranco MA, Maxted AM, Rosenberg ES, Easton D, Udo T, Kumar J, Pulver W, Smith L, Hutton B, Blog D, Zucker H, New York State and Centers for Disease Control and Prevention Multisystem Inflammatory Syndrome in Children Investigation Team. Multisystem inflammatory syndrome in children in New York State. N Engl J Med. 2020;383:347–58.
3. Davies P, Evans C, Kanthimathinathan HK, Lillie J, Brierley J, Waters G, Johnson M, Griffiths B, du Pré P, Mohammad Z, Deep A, Playfor S, Singh D, Inwald D, Jardine M, Ross O, Shetty N, Worrall M, Sinha R, Koul A, Whittaker E, Vyas H, Scholefield BR, Ramnarayan P. 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.
4. Whittaker E, Bamford A, Kenny J, Kaforou M, Jones CE, Shah P, Ramnarayan P, Fraisse A, Miller O, Davies P, Kucera F, Brierley J, McDougall M, Carter M, Tremoulet A, Shimizu C, Herberg J, Burns JC, Lyall H, Levin M, PIMS-TS Study Group and EUCLIDS and PERFORM Consortia. Clinical characteristics

of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. JAMA. 2020;21(324):259–69.
5. Fernandes DM, Oliveira CR, Guerguis S, Eisenberg R, Choi J, Kim M, Abdelhemid A, Agha R, Agarwal S, Aschner JL, Avner JR, Ballance C, Bock J, Bhavsar SM, Campbell M, Clouser KN, Gesner M, Goldman DL, Hammerschlag MR, Hymes S, Howard A, Jung HJ, Kohlhoff S, Kojaoghlanian T, Lewis R, Nachman S, Naganathan S, Paintsil E, Pall H, Sy S, Wadowski S, Zirinsky E, Cabana MD, Herold BC, Tri-State Pediatric COVID-19 Research Consortium. Severe acute respiratory syndrome coronavirus 2 clinical syndromes and predictors of disease severity in hospitalized children and youth. J Pediatr. 2021;230:23–31.
6. Antúnez-Montes OY, Escamilla MI, Figueroa-Uribe AF, Arteaga-Menchaca E, Lavariega-Saráchaga M, Salcedo-Lozada P, Melchior P, de Oliveira RB, Tirado Caballero JC, Redondo HP, Montes Fontalvo LV, Hernandez R, Chavez C, Campos F, Uribe F, Del Aguila O, Rios Aida JA, Buitrago AP, Betancur Londoño LM, Mendoza Vega LF, Hernández CA, Sali M, Higuita Palacio JE, Gomez-Vargas J, Yock-Corrales A, Buonsenso D. COVID-19 and multisystem inflammatory syndrome in Latin American children: a multinational study. Pediatr Infect Dis J. 2021;40:e1–6.
7. Gai N, Maynes JT, Aoyama K. Unique challenges in pediatric anesthesia created by COVID-19. J Anesth. 2021;35:345–50.
8. Aoyama K, Heath A, Yang A, Maynes JT, Petroz G, Robertson J, Mc Donnell C, Velummailum R, Bond E, Pechlivanoglou P. Estimating the risk of SARS-CoV-2 transmission to pediatric anesthesiologists: a microsimulation model. Can J Anaesth. 2020;67:1694–6.
9. Shioji N, Aoyama K, Englesakis M, Annich G, Maynes JT. Multisystem inflammatory syndrome in children during the coronavirus disease pandemic of 2019: a review of clinical features and acute phase management. J Anesth. 2021;35:563–70.
10. Cochrane handbook for systematic reviews of interventions | cochrane training. Available from: https://training.cochrane.org/handbook. Cited 14 May 2022.
11. Eden J, Levit L, Berg A, Morton S. Finding what works in health care: standards for systematic reviews. 2011. Available from: http://www.nap.edu/catalog.php?record_id=13059. Cited 14 May 2022.
12. Centre for Reviews and Dissemination U of Y. CRD's guidance on systematic reviews. Centre for Reviews Dissemination, University of York, 2008. 2009. p 294. Available from: https://gate2.library.lse.ac.uk/login?url=http://onlinelibrary.wiley.com. Cited 21 Apr 2023.
13. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372: n71.
14. Multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19. Available from: https://www.who.int/news-room/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19. Cited 21 Apr 2023.
15. Information for healthcare providers about multisystem inflammatory syndrome in children (MIS-C) | CDC. Available from: https://www.cdc.gov/mis-c/hcp/. Cited 12 Jan 2021.
16. Paediatric inflammatory multisystem syndrome temporally associated with COVID-19 (spring 2021 update) | Canadian Paediatric Society. Available from: https://cps.ca/en/documents/position/pims. Cited 21 Apr 2023.
17. Paediatric multisystem inflammatory syndrome temporally associated with COVID-19 (PIMS)—guidance for clinicians | RCPCH. Available from: https://www.rcpch.ac.uk/resources/paediatric-multisystem-inflammatory-syndrome-temporally-associated-covid-19-pims-guidance. Cited 12 Jan 2021.
18. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017;358: j4008.
19. Whiting P, Savović J, Higgins JP, Caldwell DM, Reeves BC, Shea B, Davies P, Kleijnen J, Churchill R. ROBIS: a new tool to assess risk of bias in systematic reviews was developed. J Clin Epidemiol. 2016;69:225–34.
20. Harwood R, Yan H, Talawila Da Camara N, Smith C, Ward J, Tudur-Smith C, Linney M, Clark M, Whittaker E, Saatci D, Davis PJ, Luyt K, Draper ES, Kenny SE, Fraser LK, Viner RM. Which children and young people are at higher risk of severe disease and death after hospitalisation with SARS-CoV-2 infection in children and young people: a systematic review and individual patient meta-analysis. eClinicalMedicine. 2022;44:101287.
21. 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.
22. Haghighi Aski B, Manafi Anari A, Abolhasan Choobdar F, Zareh Mahmoudabadi R, Sakhaei M. Cardiac abnormalities due to multisystem inflammatory syndrome temporally associated with Covid-19 among children: a systematic review and meta-analysis. Int J Cardiol Heart Vasc. 2021;33: 100764.
23. Henrina J, Putra ICS, Lawrensia S, Marta DS, Wijaya E, Saboe A, Cool CJ, Suciadi LP. Cardiac manifestations, treatment characteristics, and outcomes of paediatric inflammatory multisystem syndrome temporally associated with severe acute respiratory syndrome coronavirus-2: a systematic review. Prog Pediatr Cardiol. 2021;63: 101365.
24. Nepal G, Shrestha GS, Rehrig JH, Gajurel BP, Ojha R, Agrawal A, Panthi S, Khatri B, Adhikari I. Neurological Manifestations of COVID-19 Associated multi-system inflammatory syndrome in children: a systematic review and meta-analysis. J Nepal Health Res Counc. 2021;19:10–8.
25. Rouva G, Vergadi E, Galanakis E. Acute abdomen in multisystem inflammatory syndrome in children: a systematic review. Acta Paediatr. 2022;111:467–72.
26. Lo TC, Chen YY. Ocular and systemic manifestations in paediatric multisystem inflammatory syndrome associated with COVID-19. J Clin Med. 2021;10:2953.
27. Nascimento RB, Araujo NS, Silva JC, Xavier FCA. Oral manifestations of multisystemic inflammatory syndrome in children (MIS-C) and Kawasaki disease associated to COVID-19: a systematic review. Spec Care Dentist. 2022;42:266–80.
28. Yasuhara J, Watanabe K, Takagi H, Sumitomo N, Kuno T. COVID-19 and multisystem inflammatory syndrome in children: a systematic review and meta-analysis. Pediatr Pulmonol. 2021;56:837–48.
29. Abrams JY, Godfred-Cato SE, Oster ME, Chow EJ, Koumans EH, Bryant B, Leung JW, Belay ED. Multisystem inflammatory syndrome in children associated with severe acute respiratory syndrome coronavirus 2: a systematic review. J Pediatr. 2020;226:45–54.
30. Guimarães D, Pissarra R, Reis-Melo A, Guimarães H. Multisystem inflammatory syndrome in children (MISC): a systematic review. Int J Clin Pract. 2021;75: e14450.
31. 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.
32. Dhar D, Dey T, Samim MM, Padmanabha H, Chatterjee A, Naznin P, Chandra SR, Mallesh K, Shah R, Siddiqui S, Pratik

K, Ameya P, Abhishek G. Systemic inflammatory syndrome in COVID-19-SISCoV study: systematic review and meta-analysis. Pediatr Res. 2022;91:1334–49.
33. Mardi P, Esmaeili M, Iravani P, Abdar ME, Pourrostami K, Qorbani M. Characteristics of children With Kawasaki disease-like signs in COVID-19 pandemic: a systematic review. Front Pediatr. 2021;9: 625377.
34. Zhao Y, Yin L, Patel J, Tang L, Huang Y. The inflammatory markers of multisystem inflammatory syndrome in children (MIS-C) and adolescents associated with COVID-19: a meta-analysis. J Med Virol. 2021;93:4358–69.
35. Zhao Y, Patel J, Huang Y, Yin L, Tang L. Cardiac markers of multisystem inflammatory syndrome in children (MIS-C) in COVID-19 patients: a meta-analysis. Am J Emerg Med. 2021;49:62–70.
36. Zhou C, Zhao Y, Wang X, Huang Y, Tang X, Tang L. Laboratory parameters between multisystem inflammatory syndrome in children and Kawasaki disease. Pediatr Pulmonol. 2021;56:3688–98.
37. Wang Z, Zhao S, Tang Y, Wang Z, Shi Q, Dang X, Gan L, Peng S, Li W, Zhou Q, Li Q, Mafiana JJ, Cortés RG, Luo Z, Liu E, Chen Y. Potentially effective drugs for the treatment of COVID-19 or MIS-C in children: a systematic review. Eur J Pediatr. 2022;181:2135–46.
38. Rauniyar R, Mishra A, Kharel S, Giri S, Rauniyar R, Yadav S, Chaudhary G. IVIG plus glucocorticoids versus IVIG alone in multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19: a systematic review and meta-analysis. Can J Infect Dis Med Microbiol. 2022;2022:9458653.
39. Llinás-Caballero K, Rodríguez Y, Fernández-Sarmiento J, Rodríguez-Jiménez M, Anaya JM. Kawasaki disease in Colombia: a systematic review and contrast with multisystem inflammatory syndrome in children associated with COVID-19. Rev Colomb Reumatol. 2022;29:S66–76.
40. De Rose DU, Pugnaloni F, Calì M, Ronci S, Caoci S, Maddaloni C, Martini L, Santisi A, Dotta A, Auriti C. Multisystem inflammatory syndrome in neonates born to mothers with SARS-CoV-2 infection (MIS-N) and in neonates and infants younger than 6 months with acquired COVID-19 (MIS-C): a systematic review. Viruses. 2022;14:750.
41. Sharma D, Bhaskar SMM. Prevalence of paediatric hyperinflammatory conditions in paediatric and adolescent hospitalized COVID-19 patients: a systematic review and meta-analysis. APMIS. 2022;130:101–10.
42. Karimi A, Ghafouri P, Alilou S, Rezaei N, Talesh SA, Ashraf H. Echocardiographic findings in multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19: a systematic review. Iran J Pediatr. 2022;32:e119001.
43. O'loughlin L, Toledo NA, Budrie L, Waechter R, Rayner J. A systematic review of severe neurological manifestations in pediatric patients with coexisting sars-cov-2 infection. Neurol Int. 2021;13:410–27.
44. Zaffanello M, Piacentini G, Nosetti L, Ganzarolli S, Franchini M. Thrombotic risk in children with COVID-19 infection: a systematic review of the literature. Thromb Res. 2021;205:92–8.
45. Harrison SL, Buckley BJR, Rivera-Caravaca JM, Zhang J, Lip GYH. Cardiovascular risk factors, cardiovascular disease, and COVID-19: an umbrella review of systematic reviews. Eur Hear J Qual Care Clin Outcomes. 2021;7:330–9.
46. Treskova-Schwarzbach M, Haas L, Reda S, Pilic A, Borodova A, Karimi K, Koch J, Nygren T, Scholz S, Schönfeld V, Vygen-Bonnet S, Wichmann O, Harder T. Pre-existing health conditions and severe COVID-19 outcomes: an umbrella review approach and meta-analysis of global evidence. BMC Med. 2021;19:212.
47. Yang L, Li J, Wei W, Yi C, Pu Y, Zhang L, Cui T, Ma L, Zhang J, Koyner J, Zhao Y, Fu P. Kidney health in the COVID-19 pandemic: an umbrella review of meta-analyses and systematic reviews. Front Public Health. 2022;10: 963667.
48. Shioji N, Sumie M, Aoyama K. How long elective surgery should be delayed from COVID-19 infection in pediatric patients? J Anesth. 2023. https://doi.org/10.1007/s00540-023-03284-3.