Clinicolaboratory Profile, Treatment, Intensive Care Needs, and Outcome of Pediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2: A Systematic Review and Meta-analysis

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Abstract

This study was aimed to summarize the current data on clinicolaboratory features, treatment, intensive care needs, and outcome of pediatric inflammatory multisystem syndrome temporally associated with severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2; PIMS-TS) or multisystem inflammatory syndrome in children (MIS-C). Articles published in PubMed, Web of Science, Scopus, Google Scholar, and novel coronavirus disease 2019 (COVID-19) research database of World Health Organization (WHO), Centers for Disease Control and Prevention (CDC) database, and Cochrane COVID-19 study register between December 1, 2019 and July 10, 2020. Observational studies involving patients <21 years with PIMS-TS or MIS-C were reported the clinicolaboratory features, treatment, intensive care needs, and outcome. The search identified 422 citations and finally 18 studies with 833 participants that were included in this study, and pooled estimate was calculated for parameters of interest utilizing random effect model. The median age was 9 (range: 8–11) years. Fever, gastrointestinal symptoms, rash, conjunctival injection, and respiratory symptoms were common clinical features. Majority (84%) had positive SARS-CoV-2 antibody test and only one-third had positive reverse transcript polymerase chain reaction (RT-PCR). The most common laboratory abnormalities noted were elevated C-reactive protein (CRP), D-dimer, procalcitonin, brain natriuretic peptide (BNP), fibrinogen, ferritin, troponin, interleukin 6 (IL-6), lymphopenia, hypoalbuminemia, and thrombocytopenia. Cardiovascular complications included shock (65%), myocardial dysfunction (61%),

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myocarditis (65%), and coronary artery abnormalities (39%). Three-fourths of children required admission to pediatric intensive care unit (PICU) where they received vasoactive medications (61%) and mechanical ventilation (25%). Treatment strategies used included intravenous immunoglobulin (IVIg; 82%), steroids (54%), antiplatelet drugs (64%), and anticoagulation (51%). Mortality for patients with PIMS-TS or MIS-C was low ($n = 13$). In this systematic review, we highlight key clinical features, laboratory findings, therapeutic strategies, intensive care needs, and observed outcomes for patients with PIMS-TS or MIS-C. Commonly observed clinical manifestations include fever, gastrointestinal symptoms, mucocutaneous findings, cardiac dysfunction, shock, and evidence of hyperinflammation. The majority of children required PICU admission, received immunomodulatory treatment, and had good outcome with low mortality.

Introduction

The novel coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) affected almost all continents and countries, overwhelmed the health care system, and caused significant mortality.[1–6] Severe COVID-19 typically presents in the second week of illness coinciding with decreases in viral load and increases in inflammatory markers. Host-tissue damage occurs and is thought to be mediated by dysregulated and aberrant innate and adaptive immune responses.[7–11] Acute respiratory failure is the most common organ dysfunction observed in severe COVID-19, although other organ systems including the cardiovascular system are also involved.[7–9] In comparison to adults, children are less frequently affected and the majority of children present with mild symptoms.[1–3]

In April 2020, clinicians from the United Kingdom (UK) reported a cluster of eight previously healthy children who presented with hyperinflammatory shock syndrome temporally associated with COVID-19.[12] The Royal College of Pediatric and Child Health (RCPCH; May 1, 2020), Centers for Disease Control and Prevention (CDC; May 2020), and World Health Organization (WHO; May 2020) issued health advisories and criteria for reporting children presenting with evidence of hyperinflammation and multisystem involvement. Thereafter, multiple reports of pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS), multisystem inflammatory syndrome in children (MIS-C), Kawasaki's disease (KD), and Kawasaki's-like syndrome were published from countries with high caseloads of COVID-19 (UK, France, Italy, and the United States), describing the patient demographic details, clinical features, investigations, treatment details, and outcomes.[12–33] The case fatality of COVID-19 in children with PIMS-TS or MIS-C is higher than those without.

To reduce the morbidity and mortality associated with PIMS-TS or MIS-C, timely and appropriate information on epidemiology, spectrum of disease, clinical features and course, treatment details, and outcome is needed. This will facilitate development of effective interventions for early diagnosis and treatment, as well as scaling up adequate hospital and intensive care facilities. Therefore, in this systematic review and meta-analysis, we describe the demographic details, clinical features, laboratory investigations, management modalities, intensive care needs, and outcome of children with PIMS-TS or MIS-C.

Methodology

This systematic review was conducted as per the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[34] The review was registered in PROSPERO (CRD42020198231).

Search Strategy

Three investigators (K.N., V.W., and S.K.A.) performed independent literature searches in electronic databases including PubMed, Web of Science, Scopus, Google Scholar, WHO COVID-19 research database, CDC database, and Cochrane COVID-19 study register for original articles published between December 1, 2019 and July 10, 2020 using a predefined search strategy targeting children and adolescents <21 years with PIMS-TS or MIS-C. In addition, preprints from MedRxiv and BioRxiv were also screened.

The combination of the following keywords was used as the search strategy for literature search:

- Age group (infants, children, adolescents) with an age <21 years.

  AND

- Virus (COVID-19, novel coronavirus, SARS-CoV-2, 2019-nCoV, severe acute respiratory syndrome coronavirus 2).

  AND

- Condition (PIMS-TS, PIMS, MIS-C, KD, Kawasaki's-like syndrome, toxic shock syndrome [TSS], hyperinflammation, hyperinflammatory shock, vasculitis, macrophage activation syndrome [MAS], hemophagocytic lymphohistiocytosis [HLH]].

The references of included studies and review articles were retrieved and screened. Articles published in the English

language were included. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were followed.[35]

Study Selection

The studies were considered eligible for this systematic review based in following inclusion and exclusion criteria.

- Inclusion criteria: studies meeting only the following criteria were included:
  - Age group: infants, children, and adolescents <21 years with PIMS-TS or MIS-C in association with COVID-19.
  - Article types: observational (prospective or retrospective) studies, case series correspondences, brief communications, or letters with data fulfilling data items criteria.
  - Data items: studies reporting demographical details, clinical features, laboratory investigations, treatment modalities, intensive care needs, and outcome.
- Exclusion criteria: the following study types were excluded:
  - Case reports.
  - Case series reporting <10 cases (case reports and case series with <10 cases were excluded as these might be part of large studies).
  - Narrative or systematic review.
  - Editorials, letter to editors, correspondences, viewpoints, and opinion letters without original data.
  - Dissertations and conference reports.
  - Other studies that do not meet the inclusion criteria or lack enough data on patient characteristics.

Three investigators (V.W., K.N., and S.K.A.) independently screened the titles and abstracts for the eligibility. Later on, all the authors examined the full articles and supplementary contents, if any for inclusion and exclusion criteria.

Data Extraction

A predesigned standardized proforma was used for data extraction. Three investigators (V.W., K.N., and S.K.A.) extracted the data independently from the full-text articles and supplementary contents. The data collected included first author's name, journal name, year of publication, country, study design, number of centers, number of cases, study population, age and sex distribution, methods of SARS-CoV-2 infection confirmation, criteria used to define PIMS-TS or MIS-C, clinical features, laboratory investigations, treatment details, intensive care needs (pediatric intensive care unit [PICU] admission, mechanical ventilation, vasoactive medications, renal replacement therapy [RRT], and extracorporeal membrane oxygenation [ECMO]), and outcomes (mortality).

Any disagreement between the three investigators was sorted out through discussion and consensus with two other investigators (R.S. and V.M.). The data extracted were rechecked by independent researchers for accuracy and completeness (N.D., K.T.K., and N.J.). To avoid duplicity of the data, efforts were made to screen full texts of all included studies for author names, setting, location, date and duration of study, number of participants, and baseline data.

Quality Assessment

The quality of included studies was assessed using the National Institutes of Health Study Quality Assessment Tools for case series and observational cohort and cross-sectional studies. The overall risk of bias for each study was independently assessed by three investigators (V.W., K.N., and S.K.A.). The studies were rated as either having low- or high-risk of bias.

Main Outcome

The outcome of this systematic review and meta-analysis was to provide pooled estimates of demographic details, clinical features, laboratory investigations, treatment details, intensive care needs, and outcome (mortality) of children and adolescents (<21 years) with PIMS-TS or MIS-C.

Data Synthesis

The initial data entry was done using Microsoft Excel 2013 (Microsoft, Redmond, Washington, United States). The descriptive analysis was performed using SPSS version 23 (IBM Corp. 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY, United States: IBM Corp.). The data were presented as number and percentages for categorical variables and median (interquartile range [IQR]) for continuous variables.

Meta-analysis was performed by using STATA version 14 (Stata Corp LLC, College Station, Texas, United States). Individual parameters were presented as pooled estimates with a 95% confidence interval (CI) using Metaprop command. The data were pooled from individual studies utilizing the random effects model with the assumption that variance exists across studies. The statistical heterogeneity among studies was assessed by Chi-squared test and I^2 statistics. The heterogeneity was considered to be present if I^2 >50% and $p < 0.1$.

The subgroup analysis was performed between studies published from the United States and European countries.

Results

The search identified 422 articles, from which 233 duplicate articles and 69 irrelevant articles were removed. Out of 120 full-text articles assessed, 102 articles were removed as per exclusion criteria. Ultimately, 18 articles with 833 children were included in the final analysis (►**Fig. 1**). On quality assessment, eight studies were judged to have had low risk of bias,[13,15–17,21,22,27,28] while 10 had high risk of bias[14,18–20,23–26,29,30] (►**Table 1**).

Study Characteristics

All studies were conducted between March 1 and May 23, 2020, with median (IQR) length of study duration being 39 (24–56) days. Seven studies were from the United States,[13,15,18,21,22,25,27] 11 were from Europe,[14,16,17,19,20,23,24,26,28–30] and almost 50% cases were from each region. The studies from Europe included four studies from the United Kingdom,[16,17,19,28] five from France,[14,23,24,26,29] one from France and Switzerland,[20] and one from Italy.[30] Nine studies were single center,[18,19,21,23,25,27–30] and nine were multicenter studies.[13–17,20,22,24,26] The study design was retrospective

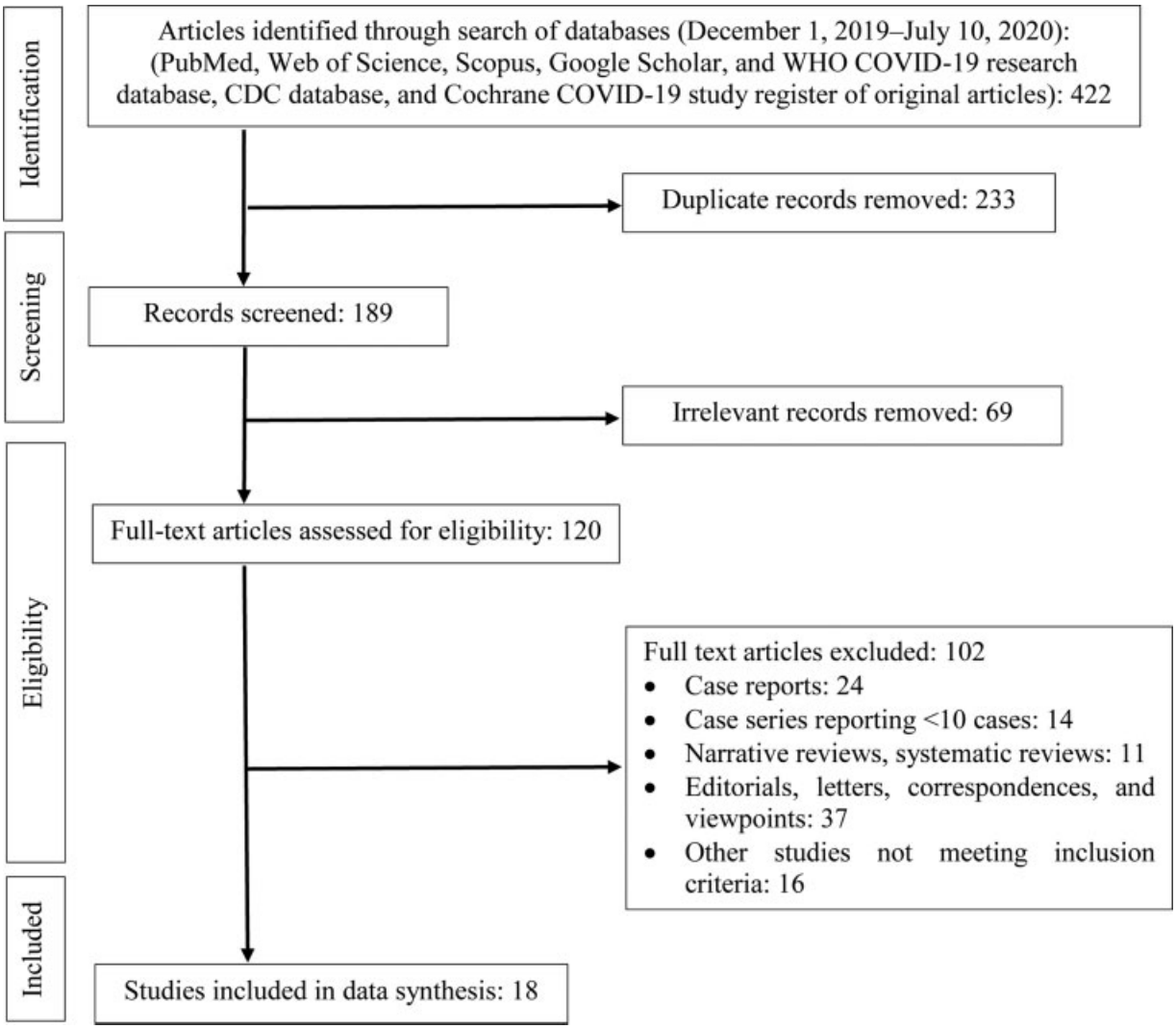

Fig.1 Flow diagram of the study selection. COVID-19, novel coronavirus 2019; WHO, World Health Organization.

in 14 studies,[15,17–22,24–30] retrospective and prospective in 3,[13,14,16] and prospective in 1 study.[23] The criteria used to define the inflammatory syndrome in temporal relation with COVID-19 was CDC or New York State Department of Health (NYSDOH) criteria in six studies,[13,15,18,21,22,27] RCPCH criteria in five studies,[14,16,17,19,28] and American Heart Association (AHA) KD criteria in five studies.[23,25,26,29,30] Two studies enrolled cases with fever, shock, acute myocarditis/left ventricular (LV) dysfunction, and evidence of inflammation (►**Table 2**).[20,24]

There was overlap of few cases in studies from the United Kingdom,[16,17,19,28] France,[26,29] and the United States.[22,27] As the information to identify overlapping cases could not be derived, after discussion among 3 authors (V.W., K.N., and S. K.A.), consensus was reached to include all these studies in the systematic review.

Clinical Features

All except one study (15) reported median (IQR) age observed as 9 (8–11) years. All studies reported gender and 57% of patients were male. The median (IQR) duration of illness/fever was 5 (4–6) days as reported in 11 studies.[13,16,20–26,28,30] Race was reported in 12 studies,[13,15–18,21–23,25,26,28,30] and the most commonly reported races included black (35%), white (27%), Asian (10%), and others (14%). All except four studies[14,19,28,29] reported comorbidities (29%); commonly reported comorbidities include underlying respiratory, cardiac, immunocompromised state, autoimmune disease, and obesity (►**Table 3**).

Fever was the most commonly reported symptom (96%) in all except one study.[14] Gastrointestinal (GI) symptoms (abdominal pain, nausea/vomiting, and diarrhea) were noted in 86% of patients in all except two studies.[14,29] Other common clinical features noted were rash (58%), conjunctival injection (52%), respiratory symptoms (43%), oral mucosal changes (42%), peripheral extremity changes (39%), neurological symptoms (32%), cervical lymphadenopathy (24%), and musculoskeletal symptoms (17%; ►**Table 3**).

The results of SARS-CoV-2 antibody and reverse transcript polymerase chain reaction (RT-PCR) testing were reported by all studies and these were positive in 84 and 37% of children, respectively (►**Table 3**).

Table 1 Details of studies included in the systematic review

S. no	Author	Country	No. of centers	No. of cases	Study design	Age group (y)	Criteria used	Study period during 2020	Risk of bias[a]
1	Feldstein et al[13]	USA	53	186	Retrospective and Prospective	0–21	CDC	March 15–May 20	Low
2	Belot et al[14]	France	7	108	Retrospective and Prospective	0–15	RCPCH	March 1–May 17	High
3	Dufort et al[15]	USA	106	99	Retrospective	0–21years	NYSDOH	March 1–May 10	Low
4	Davies et al[16]	UK	21	78	Retrospective and prospective	0–18	RCPCH	April 1–May 10	Low
5	Whittaker et al[17]	UK	8	58	Retrospective	0–18	RCPCH	March 23–May 16	Low
6	Miller et al[18]	USA	1	44	Retrospective	0–21	CDC	April 18–May 22	High
7	Hameed et al[19]	UK	1	35	Retrospective	4–14	RCPCH	April 14–May 9	High
8	Belhadjer et al[20]	France and Switzerland	13	35	Retrospective	2–16	Fever, cardiogenic shock, or acute left ventricular dysfunction with inflammatory state	March 22–April 30	High
9	Capone et al[21]	USA	1	33	Retrospective	0–21	CDC	April 17–May 13	Low
10	Kaushik et al[22]	USA	3	33	Retrospective	0–21	CDC	April 3–May 23	Low
11	Toubiana et al[23]	France	1	21	Prospective	0–18	AHA KD	April 27–May 11	High
12	Grimaud et al[24]	France	4	20	Retrospective	0–18	Fever, shock, acute myocarditis	April 15–April 27	High
13	Cheung et al[25]	USA	1	17	Retrospective	0–21	AHA KD	April 18–May 5	High
14	Pouletty et al[26]	France	7	16	Retrospective	0–18	AHA KD	April 1–April 30	High
15	Riollano-Cruz et al[27]	USA	1	15	Retrospective	0–21	CDC and NYSDOH	April 24–May 14	Low
16	Ramcharan et al[28]	UK	1	15	Retrospective		RCPCH	April 10–May 9	Low
17	Ouldali et al[29]	France	1	10	Retrospective	1.5–15.8	AHA KD	April 28–May 4	High
18	Verdoni et al[30]	Italy	1	10	Retrospective	3–16	AHA KD	February 18–April 20	High

Abbreviations: AHA, American Heart Association, CDC, Centers for Disease Control and Prevention, KD, Kawasaki Disease, NYSDOH, New York State Department of Health, RCPCH, Royal College of Pediatric and Child Health, UK, the United Kingdom, USA, the United States of America.

[a]Study quality was assessed using National Institute of Health Study Quality Assessment Tools for case series studies and observational cohort and cross-sectional studies.

Table 2 Characteristics of the included studies

Study characteristics	Studies *n* (%)	Cases *n* (%)
Included in review	18 (100)	833 (100)
Region		
USA	7 (38.9)	427 (51.3)
Europe	11 (61.1)	406 (48.7)
Country		
USA	7 (38.9)	427 (51.3)
UK	4 (22.2)	186 (22.3)
France	5 (27.8)	175 (21)
France and Switzerland	1 (5.6)	35 (4.2)
Italy	1 (5.6)	10 (1.2)
Number of centers		
Single center	9 (50)	200 (24)
Multiple centers	9 (50)	633 (76)
Study design		
Retrospective	14 (77.8)	440 (52.8)
Retrospective and prospective	3 (16.7)	372 (44.7)
Prospective	1 (5.6)	21 (2.5)
Study duration in days Median (IQR)	39 (24–56)	
Criteria used		
CDC and/or NYSDOH	6 (33.3)	410 (49.2)
RCPCH	5 (27.8)	294 (35.5)
Kawasaki's disease (AHA)	5 (27.8)	74 (8.9)
Fever, shock, acute myocarditis/LV dysfunction, and inflammation	2 (11.1)	55 (6.6)

Abbreviations: AHA, American Heart association; CDC, Centers for Disease Control and Prevention; IQR, interquartile range; LV, left ventricular; NYSDOH, New York State Department of Health; RCPCH, Royal College of Pediatric and Child Health; UK, the United Kingdom, USA, the United States of America.

Laboratory Investigations

The laboratory investigations are shown in ►**Supplementary Table S1** (available in the online version). Radiological investigations were reported in 11 studies[13,15,18,19,22,23,25–28,30] and the findings are described in ►**Supplementary Table S2** (available in the online version). Inflammatory markers observed to be abnormally elevated include C-reactive protein (CRP; 98%), procalcitonin (90%), fibrinogen (86%), ferritin (82%), and interleukin (IL)-6 (68%). Other laboratory abnormalities noted were elevation of D-dimer (92%), lymphopenia (85%), hypoalbuminemia (71%), thrombocytopenia (53%), and elevated alanine transaminase (ALT) (40%). Among cardiac markers, 89% children had elevated brain natriuretic peptide (BNP) or N-terminal pro-hormone BNP (NT-proBNP) and 78% had elevated troponin (►**Table 4**).

Echocardiography Findings

Sixteen studies reported data on echocardiography which was done in 94% of children.[13,15–18,20–30] Commonly observed echocardiography abnormalities include LV dysfunction or ejection fraction <55% (61%), myocarditis as defined by clinical and/or biochemical and/or echocardiographic diagnosis (65%), coronary artery abnormality (39%), pericardial effusion (35%), coronary artery dilatation or aneurysm (16%), and coronary artery diameter >2.5 *z*-score (8%). Approximately 10% of children had residual LV dysfunction at discharge as reported in eight studies (►**Table 4**).[20–22,24–26,28,30]

Intensive Care Needs

All studies reported intensive care admission and 76% of children were managed in a PICU where they received supplemental oxygen via high-flow nasal cannula (18%), noninvasive ventilation (22%), and invasive ventilation (25%). Shock was noted in 65% of children and 61% required vasoactive/inotropic medication. Acute kidney injury was noted in 35% of children and 2% underwent RRT. The requirement of ECMO was reported in all except three studies[14,26,30] in 4% children ($n = 32$; ►**Table 5**).

Treatment Details

All except two studies[14,19] reported data on intravenous immunoglobulin (IVIg) and steroid use, and these were given to 82 and 54% of children, respectively. A second dose of IVIg was administered in 25% of children who did not show improvement after the first dose.[13,20,21,23,26,28–30] The combination of steroid plus IVIg was used in 50% children.[13,15,23,30] Other biological and immunomodulator agents used were IL-6 inhibitors (12.6%), IL-1Ra inhibitor (8.6%), infliximab ($n = 16$), convalescent plasma therapy ($n = 5$), and rituximab ($n = 1$). Anticoagulation (prophylactic or therapeutic) and antiplatelet agents (any dose) were used in 51 and 64% of children, respectively (►**Table 5**). Three studies reported the use of remdesivir in 7.9% of children.[16,22,27]

Outcome

There were 13 deaths with a pooled estimate percentage (95% CI) of 2 (1–3). Data on hospital discharge was provided in all except one study.[14] The majority of children (95%) were ultimately discharged, and 3.6% of children were still hospitalized the time of reporting. The median (IQR) duration of hospital stay was 7.8 (5–10) days (►**Table 5**).

Subgroup Analysis

We compared studies from the United States and European regions. Significant differences were noted to exist between the two regions including differences in criteria used (the United States: CDC and/or NYSDOH criteria; Europe: RCPCH and AHA KD criteria), proportion of children with comorbidities (36% in the United States vs. 19% in European regions, $p = 0.04$), frequency of treatment with IL-6 inhibitors (27% in the United States vs. 4% in European regions, $p = 0.02$) and frequency of treatment with IL-1Ra inhibitors (13% in the United States vs. 5% in European regions, $p = 0.004$).

Table 3 Clinical features in children with inflammatory syndrome in association with SARS-CoV-2 infection

Characteristics	Number of studies	Number of cases	Pooled estimate % (95% CI)	Heterogeneity (I^2 %)
Age (y) Median (IQR)	17	734	9 (8–11)	
Duration of illness i(d) Median (IQR)	11	725	5 (4–6)	
Male gender	18	833	57 (51–62)	88[a]
Race	12	610		
Black			35 (28–42)	69[a]
White			27 (10–35)	83[a]
Other			14 (6–22)	84[a]
Asian			10 (5–15)	76[a]
Comorbidity	14	665	29 (22–36)	74[a]
Clinical features				
Fever	17	725	96 (89–100)	89[a]
Gastrointestinal symptoms	16	715	86 (82–90)	51[a]
Rash	14	667	58 (52–65)	63[a]
Conjunctival injection	13	632	52 (40–63)	89[a]
Respiratory symptoms	8	445	43 (27–59)	91[a]
Oral mucosal changes	10	504	42 (29–55)	78[a]
Peripheral extremity changes	6	306	39 (24–52)	82[a]
Neurological symptoms	11	529	32 (10–42)	82[a]
Cervical adenopathy	9	462	24 (14–34)	88[a]
Musculoskeletal symptoms	5	337	17 (10–24)	55[a]
Confirmation of exposure				
SARS-CoV-2 RT-PCR and/or antibody positive	14	722	85 (74–91)	89[a]
SARS-CoV-2 antibody test positive	18	833	84 (72–93)	89[a]
SARS-CoV-2 RT-PCR positive	18	833	37 (28–46)	89[a]

Abbreviations: IQR, interquartile range; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2; RT-PCR, reverse transcript polymerase chain reaction.
[a]*p*-Value for $I^2 < 0.1$.

In addition, the need for mechanical ventilation was noted to be higher in studies from Europe than in studies from the United States (33% vs. 12%, $p = 0.03$; ►**Supplementary Table S3**; available in the online version).

Discussion

PIMS-TS or MIS-C is characterized by a febrile hyperinflammatory state with GI, mucocutaneous, dermatological, and cardiac manifestations. The peak incidence occurred approximately 2 to 4 weeks following the April 2020 peak of the COVID-19 pandemic (►**Fig. 2**) when the rate of new COVID-19 cases was declining.[13–16,30] As several countries progress toward the peak of the COVID-19 pandemic, the number of children presenting with PIMS-TS or MIS-C may potentially increase. There is urgent need to make appropriate preparations, so that the surge in cases of children with this syndrome may be adequately managed. In this context, this systematic review and meta-analysis which summarizes the epidemiological and clinical features, investigations, treatment details, intensive care needs, and outcomes of children with PIMS-TS or MIS-C is significant and expands upon the currently available knowledge and understanding of this delayed but life-threatening complication of SARS-CoV-2 infection.

The possible pathogenesis suggested for the development of PIMS-TS or MIS-C involves immune-mediated injury and inflammatory vasculopathy triggered by SARS-CoV-2 infection rather than active viral infection itself.[11,13,15] Facts supporting this hypothesis include the onset of symptoms 2 to 4 weeks after SARS-CoV-2 infection, laboratory evidence that the majority of children have had recent or concurrent SARS-CoV-2 infection in the form of positive SARS-CoV-2 antibody testing or RT-PCR, and suggestions of a temporal association between SARS-CoV-2 and PIMS-TS or MIS-C. These patients also exhibit an exuberant host inflammatory response and show potential benefit from treatment with immunomodulator therapy from IVIg and/or steroids.

Table 4 Laboratory abnormalities, echocardiographic findings, and other cardiovascular manifestations

Characteristics	Number of studies	Number of cases	Pooled estimate % (95% CI)	Heterogeneity ($I^{2\%}$)
Lymphopenia	10	514	85 (76–93)	50[a]
Thrombocytopenia	4	330	53 (43–98)	96[a]
Elevated CRP	13	603	98 (79–100)	93[a]
Elevated procalcitonin	7	221	90 (76–100)	82[a]
Elevated fibrinogen	5	330	86 (73–96)	85[a]
Elevated ferritin	8	477	82 (67–98)	88[a]
Elevated IL-6	6	178	68 (32–98)	74[a]
Elevated D-dimer	8	477	92 (82–100)	97[a]
Hypoalbuminemia	7	401	71 (50–93)	91[a]
Elevated ALT	7	330	40 (23–56)	86[a]
Elevated BNP (any)	11	510	89 (82–96)	90[a]
Elevated troponin	12	371	78 (63–93)	86[a]
Thrombosis	3	297	2 (2–7)	25[a]
Arrhythmia	7	347	7.2 (2.5–13.3)	30
Echocardiography performed	16	681	94 (91–96)	44
Myocardial dysfunction or ejection fraction <55%	15	603	61 (50–72)	77[a]
Myocarditis (clinical and/or biochemical and/or echocardiography)	12	588	65 (49–80)	87[a]
Any coronary artery abnormality	9	248	39 (25–63)	90[a]
Coronary artery dilatation or aneurysm	16	681	16 (12–20)	51[a]
Coronary artery diameter $> +2.5$ *z*-score	12	551	8 (6–11)	16
Pericardial effusion	12	477	35 (24–46)	74[a]
Residual myocardial dysfunction at discharge	8	179	10.4 (2.5–18.3)	20

Abbreviations: BNP, brain natriuretic peptide; CI, confidence interval; CRP, C-reactive protein; IL, interleukin.
[a]*p*-Value for $I^2 < 0.1$.

We noted that most children were older (median age, 9 years) and previously healthy. The proportion of black children (35%) were higher than other races and is a finding similarly noted in adults with severe COVID-19 for which a possible genetic predisposition needs to be further explored.[36] The most commonly presenting symptoms were fever, GI symptoms, rash, conjunctival injection, respiratory symptoms, and oral mucosal changes. The GI symptoms (86%) were strikingly prominent[13,15–22,24–26,28,30] mimicking GI infection, acute abdomen, or inflammatory bowel disease.[18,19,37] The possible mechanisms for the GI symptoms could be bowel wall edema or ischemia due to vasculitis, cardiac dysfunction and/or shock, mesenteric inflammation, and mesenteric lymphadenitis.[19,23,37]

The symptom complex of fever, GI symptoms, and rash in children with preceding symptomatic or asymptomatic SARS-CoV-2 infection, in the 2 to 4 weeks prior to presentation, should prompt clinicians to recognize this syndrome early. We recommend prompt investigation for evidence of hyperinflammation and organ dysfunction, close monitoring (e.g., hemodynamic monitoring, electrocardiography, and echocardiography), and aggressive treatment with supportive and specific therapy.

The majority of children had elevated inflammatory markers (CRP, procalcitonin, fibrinogen, ferritin, D-dimer, and IL-6), lymphopenia, hypoalbuminemia, and thrombocytopenia. These manifestations of hyperinflammation were similar to what has been noted in adults with severe COVID-19.[38,39] Cardiac involvement was a predominant feature in the form of myocarditis, LV dysfunction, and coronary dilatation or aneurysm. In adults with COVID-19, myocardial dysfunction has been observed to be a prominent extrapulmonary manifestation associated with increased mortality.[40,41]

The most common chest radiographic abnormalities noted in children with COVID-19 are bronchial thickening, ground-glass opacities, and inflammatory pulmonary infiltrates suggestive of pneumonia. These pulmonary findings were also noted in asymptomatic children and those with mild symptoms, suggesting that SARS-CoV-2 infection induces a primary inflammation of lung parenchyma and lower respiratory tract.[42,43] Of note, the reporting of radiographic features was not uniform in included studies.

Most children with acute SARS-CoV-2 infections are asymptomatic or have mild symptoms,[1–4] while the majority of children with PIMS-TS or MIS-C were noted to have severe disease requiring PICU admission (76%), vasoactive medications

Table 5 Intensive care needs, treatment details, and outcome

Characteristics	Number of studies	Number of cases	Pooled estimate % (95% CI)	Heterogeneity ($I^{2\%}$)
Admission in PICU	18	833	76 (65–88)	80[a]
HFNC	5	389	18 (7–29)	73[a]
Noninvasive ventilation	9	497	22 (13–31)	84[a]
Invasive ventilation	18	833	25 (19–37)	92[a]
Shock	18	833	65 (54–73)	88[a]
Vasoactive drugs	18	833	61 (53–70)	86[a]
Acute kidney injury	8	477	35 (21–50)	95[a]
Renal replacement therapy	5	363	2 (1–4)	65[a]
ECMO	15	699	4 (1–8)	33
IVIg	16	690	82 (74–89)	65[a]
2nd dose IVIg (among those who received 1st dose)	8	326	25 (11–33)	83[a]
Steroids	16	690	54 (41–67)	94[a]
Steroids + IVIg	4	306	50 (39–62)	67[a]
IL-6 inhibitors (tocilizumab or siltuximab)	13	533	12.6 (1–26)	88[a]
IL-1Ra inhibitor (anakinra)	12	549	8.6 (5–12)	0.00
Infliximab	9	469	2.9 (0.1–6.8)	54[a]
Rituximab	6	210	0.2 (0–0.8)	43
Plasma therapy	7	333	2 (0–4)	24
Anticoagulation	11	487	51 (25–77)	93[a]
Antiplatelets (any dose)	9	238	64 (30–78)	95[a]
Discharged at the time of reporting	17	725	95 (91–100)	92[a]
Still hospitalized at the time of reporting	17	725	3.6 (0.5–7.8)	88[a]
Deaths at the time of reporting	18	833	2 (1–3)	44
Duration of stay, median (IQR)	11	376	7.8 (5–10)	

Abbreviations: CI, confidence interval; ECMO, extracorporeal membrane oxygenation; HFNC, high flow nasal cannula; IL, interleukin; IQR, interquartile range; IVIg, intravenous immunoglobulin; PICU, pediatric intensive care unit.
[a]*p*-Value for $I^2 < 0.1$.

(61%), and invasive mechanical ventilation (25%). The most common treatment strategies used were IVIg and steroids. A small proportion of children also received IL-6 inhibitors, an IL-1Ra inhibitor, infliximab, rituximab, and/or convalescent plasma therapy. The short-term morbidity was high in terms of requiring intensive care interventions but the overall mortality was low.

The presentation of PIMS-TS or MIS-C shared overlapping features with KD, TSS, HLH, or MAS.[15,16] However, it differed from KD on following accounts: older age at presentation (older children and adolescents), higher proportion of children with GI and respiratory symptoms, predominance of severe cardiovascular system involvement in the form of shock, LV dysfunction, or myocarditis, higher proportion of children with lymphopenia, thrombocytopenia, elevated CRP and procalcitonin, and a higher percentage of children being admitted to the PICU, requiring vasoactive medications, and supported with mechanical ventilation.[11–13,15,16,20,30]

Based on available data, PIMS-TS or MIS-C seems to be an uncommon manifestation of SARS-CoV-2 infection reported at a greater frequency among specific age groups, race (i.e., blacks), and region as there is a scarcity of reports from Asia including China. These differences could be due to differential

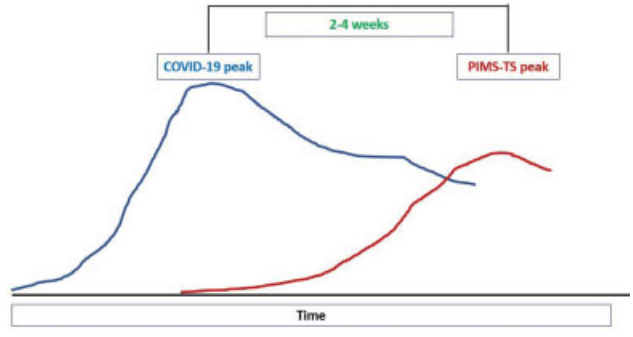

Fig. 2 Figure demonstrating that the peak of PIMS-TS or MIS-C occurs 2 to 4 weeks after the peak of COVID-19. COVID-19, novel coronavirus disease 2019. MIS-C, multisystem inflammatory syndrome in children; PIMS-TS, pediatric inflammatory multisystem syndrome temporally associated with severe acute respiratory syndrome-coronavirus-2.

Table 6 Proposed case definition for PIMS-TS or MIS-C

Sl. no.	Criteria	Description
1	Children and adolescents aged <21 years presenting with fever >24 hours	
2	Severe illness requiring hospitalization with ≥1 organ dysfunction	Shock: tachycardia, prolonged capillary refill time, poor perfusion, weak pulses, hypotension
		Cardiac: myocardial dysfunction, pericarditis, valvulitis, coronary artery abnormality, arrhythmia, or elevated troponin or NT-proBNP
		Respiratory: respiratory distress or failure, pneumonia, effusion, radiological opacities or consolidation
		Gastrointestinal: diarrhea, vomiting, or abdominal pain
		Kidney: oliguria, acute kidney injury
		Hematological: evidence of coagulopathy (elevated PT, aPTT, D-dimers, fibrinogen)
		Neurological: lethargy, encephalopathy, or seizure
		Mucocutaneous: rash, bilateral conjunctivitis, mucocutaneous inflammation, cervical lymphadenopathy, or peripheral extremity changes
3	Elevated markers of inflammation (≥1)	CRP, procalcitonin, ESR, fibrinogen, D-dimer, ferritin, lactate dehydrogenase, triglycerides, IL-6, or neutrophils; lymphopenia; thrombocytopenia; or hypoalbuminemia
4	Evidence of current or recent SARS-CoV-2 infection	Positive RT-PCR, antigen test, or antibody test; or contact with proven or suspected COVID-19 patient within 4 weeks prior to onset of symptoms
5	Exclusion of other alternative causes	Bacterial sepsis, toxic shock syndrome (Staphylococcal or Streptococcal), infection associated myocarditis (e.g., enterovirus)
	This syndrome may be considered in children with of typical or atypical features of Kawasaki's disease or toxic shock syndrome	

Abbreviations: aPTT, activated partial thromboplastin time; BNP, brain natriuretic peptide; COVID-19, novel coronavirus disease 2019; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IL, interleukin; MIS-C, multisystem inflammatory syndrome in children; NT-proBNP, N-terminal pro-hormone brain natriuretic peptide; PIMS-TS, pediatric inflammatory multisystem syndrome temporally associated with severe acute respiratory syndrome-coronavirus-2; PT, prothrombin time; RT-PCR, reverse transcript polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2.
Note: The case definition needs all the criteria (1–5) to be fulfilled.
Adapted and modified based on Royal College of Pediatric and Child Health (RCPCH), Centers for Disease Control and Prevention (CDC), New York State Department of Health (NYSDOH), and World Health Organization (WHO) case definitions.

exposure to SARS-CoV-2 infection, incomplete reporting, predominance of SARS-CoV-2 infection among black patients, differential nasal expression of angiotensin-converting enzyme 2 (ACE2) receptors impacting SARS-CoV-2 cell entry, variability in host immune response, socioeconomic status, and existing comorbidities. Patient susceptibility to inflammatory disease and subsequent response to treatment may be influenced by differences in the gut microbiome, signaling pathways, genetic variations, other host factors, and early treatment with immunomodulator therapy.[9,13,16,44,45]

There is great variation among clinicians in the use of immunomodulatory therapy for PIMS-TS or MIS-C. IVIg and steroids were the most commonly used treatments; however, high-quality evidence from well-designed clinical trials are required to establish treatment guidelines. In the absence of definitive evidence, we believe that it is crucial to provide clinical management inclusive of specific treatment, supportive care, and a multidisciplinary approach involving intensivists, infectious disease specialists, cardiologists, hematologists, immunologists/rheumatologists, and pharmacologists.

Strengths and Limitations

This systematic review has several strengths. To the best of our knowledge, this is the first review that summarizes the available literature on epidemiology, clinical features, investigations, treatment, intensive care needs, and outcomes of children with PIMS-TS or MIS-C. The search strategy was rigorous to include all studies that reported children with hyperinflammatory syndrome associated with COVID-19 irrespective of the description (PIMS-TS, MIS-C, KD, cardiac involvement, acute heart failure, acute myocarditis, GI manifestations, or imaging findings). We also performed a subgroup analysis to compare studies from two continents, North America and Europe, which did not demonstrate significant differences in characteristics despite racial differences.

This systematic review has several limitations. All included studies were conducted over a short period of time. Most studies were retrospective with small sample sizes. More than half of the studies had high-risk of bias. The criteria used were different across regions. There was a small overlap of a few cases in a few studies which could not be delineated. Long-

term follow-up data were not available which is needed to identify long-term health issues, especially those patients with myocardial dysfunction and coronary artery abnormalities. Studies from other countries (Brazil, India, Russia, South Africa, Mexico, Spain, etc.) with high burden of COVID-19 were not available when this review was performed.

A case definition has been proposed by the authors for uniform evaluation and reporting of PIMS-TS or MIS-C based on the case definitions provided by RCPCH, CDC, NYSDOH, and WHO (►**Table 6**).

Conclusion

In this systematic review, we summarized current evidence and highlight clinical features, laboratory parameters, treatment details, intensive care needs, and outcomes of PIMS-TS or MIS-C. Fever, GI symptoms, rash, and mucocutaneous manifestations were the most commonly observed clinical features. The majority of children showed evidence of systemic inflammation, exhibited cardiovascular involvement, required PICU admission, and were treated with vasoactive medications and immunomodulator therapy including IVIg and/or steroids. Overall short-term outcomes were good with low-observed mortality.

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Conflict of Interest
None declared.

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