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REVIEW

Multisystem inflammatory syndrome in children related to COVID-19: a systematic review

Levi Hoste[1,2] · Ruben Van Paemel[3,4,5] · Filomeen Haerynck[1,2]

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Abstract

An association between a novel pediatric hyperinflammatory condition and SARS-CoV-2 was recently published and termed pediatric inflammatory multisystem syndrome, temporally associated with SARS-CoV-2 (PIMS-TS) or multisystem inflammatory syndrome (in children) (MIS(-C)). We performed a systematic review and describe the epidemiological, clinical, and prognostic characteristics of 953 PIMS-TS/MIS(-C) cases in 68 records. Additionally, we studied the sensitivity of different case definitions that are currently applied. PIMS-TS/MIS(-C) presents at a median age of 8 years. Epidemiological enrichment for males (58.9%) and ethnic minorities (37.0% Black) is present. Apart from obesity (25.3%), comorbidities are rare. PIMS-TS/MIS(-C) is characterized by fever (99.4%), gastrointestinal (85.6%) and cardiocirculatory manifestations (79.3%), and increased inflammatory biomarkers. Nevertheless, 50.3% present respiratory symptoms as well. Over half of patients (56.3%) present with shock. The majority of the patients (73.3%) need intensive care treatment, including extracorporal membrane oxygenation (ECMO) in 3.8%. Despite severe disease, mortality is rather low (1.9%). Of the currently used case definitions, the WHO definition is preferred, as it is more precise, while encompassing most cases.

Conclusion: PIMS-TS/MIS(-C) is a severe, heterogeneous disease with epidemiological enrichment for males, adolescents, and racial and ethnic minorities. However, mortality rate is low and short-term outcome favorable. Long-term follow-up of chronic complications and additional clinical research to elucidate the underlying pathogenesis is crucial.

Hoste Levi and Van Paemel Ruben contributed equally to this work.

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✉ Levi Hoste
levi.hoste@ugent.be

Ruben Van Paemel
ruben.vanpaemel@ugent.be

Filomeen Haerynck
filomeen.haerynck@ugent.be

[1] Department of Pediatric Pulmonology, Infectious Diseases and Immunology, Ghent University Hospital, Ghent, Belgium

[2] Primary Immunodeficiency Research Lab, Center for Primary Immunodeficiency Ghent, Jeffrey Modell Diagnosis and Research Center, Ghent University Hospital, Ghent, Belgium

[3] Center for Medical Genetics, Ghent University Hospital, Ghent, Belgium

[4] Cancer Research Institute Ghent (CRIG), Ghent, Belgium

[5] Department of Pediatric Hematology, Oncology and Stem Cell Transplantation, Ghent University Hospital, Ghent, Belgium

What is Known:
- *A novel pediatric inflammatory syndrome with multisystem involvement has been described in association with SARS-CoV-2.*
- *To date, the scattered reporting of cases and use of different case definitions provides insufficient insight in the full clinical spectrum, epidemiological and immunological features, and prognosis.*

What is New:
- *This systematic review illustrates the heterogeneous spectrum of PIMS-TS/MIS(-C) and its epidemiological enrichment for males, adolescents, and racial and ethnic minorities.*
- *Despite its severe presentation, overall short-term outcome is good.*
- *The WHO MIS definition is preferred, as it is more precise, while encompassing most cases.*

Keywords PIMS-TS · MIS-C · COVID-19 · SARS-CoV-2

Abbreviations

ARDS	Acute respiratory distress syndrome
COVID-19	Coronavirus disease 2019
ECMO	Extracorporal membrane oxygenation
IVIG	Intravenous immunoglobulins
KD	Kawasaki disease
KDSS	Kawasaki disease shock syndrome
LVEF	Left ventricular ejection fraction
MAS	Macrophage activation syndrome
MIS(-C)	Multisystem inflammatory syndrome (in children)
PIMS-TS	Pediatric inflammatory multisystem syndrome temporally associated with COVID-19
RT-PCR	Reverse transcriptase-polymerase chain reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
TSS	Toxic shock syndrome

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing coronavirus disease 2019 (COVID-19), led to a pandemic health crisis within a few months' time [1–3]. Severe COVID-19 and associated mortality has been highest in elderly and patients with comorbidities, such as cardiovascular disease, diabetes mellitus, and chronic lung disease [4–6]. Since the outbreak, COVID-19 was generally described as asymptomatic or mild in children, causing few pediatric hospitalizations and minimal mortality [7–10].

Since April 2020, several countries from Europe and North America reported on young patients with a severe multisystem inflammatory syndrome associated with SARS-CoV-2. The initial descriptions exposed important clinical heterogeneity, partially overlapping with features of Kawasaki disease (KD) or toxic shock syndrome (TSS), but nevertheless distinct from these known inflammatory conditions [11, 12]. In contrast with (acute) COVID-19 respiratory disease, a significant proportion of children were reported with severe or fatal disease [11, 13–17]. Since its description, this novel disease is mostly referred to as pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 infection (PIMS-TS) [18, 19] or multisystem inflammatory syndrome in children (MIS(-C)) [18, 19].

At present, it is pivotal to optimize the characterization and the diagnostic criteria of this inflammatory syndrome related to COVID-19. To date, the scattered case reporting provides insufficient insight in the full clinical, epidemiological, immunological, and prognostic spectrum. Hence, we performed a systematic review, the most extensive to date to our knowledge, to describe the diagnostic criteria and clinical manifestations of this novel pediatric COVID-19-associated phenotype.

Methods

Original studies describing cases meeting the definition of PIMS-TS or MIS(-C) by the Royal College of Paediatrics and Child Health (RCPCH) [20], World Health Organization (WHO) [19], or Centers for Disease Control and Prevention (CDC) [18], were eligible for inclusion (Supplementary information 1). Primary outcome analysis focused on epidemiological, clinical, and outcome parameters.

A search strategy was designed with keywords combining the pediatric population, COVID-19, and hyperinflammatory presentations (Table 1), including articles published from December 31, 2019, to August 13, 2020. Electronic databases were searched (PubMed, Embase), including pre-print (bioRxiv, medRxiv) and COVID-19-specific repositories (Cochrane COVID-19 Study Register and WHO COVID-19 Global Research Database). The reference lists of included studies were considered additional sources.

After duplicate removal, two reviewers (LH/RVP) independently applied the inclusion and exclusion criteria, first, by screening titles and abstracts and, second, by examining

Table 1 Search strategy criteria

Inclusion criteria
1 Study population: hyperinflammatory syndrome meeting the case definitions of PIMS-TS [19] or MIS(-C) [20, 21] in children (0–21 years of age) with a temporal association with confirmed or probable COVID-19
2 Outcome: clinical, epidemiological, and immunological descriptions; therapeutic management and clinical effect; and prognosis of individuals or cohorts of patients.
3 Types of study designs: RCT, observational studies, case-control studies, cross-sectional studies, case reports, and case series
Exclusion criteria
1 Studies on adult patients with SARS-CoV-2 infection and/or SARS-CoV-2 associated hyperinflammatory syndromes
2 Studies on pediatric patients with other coronavirus infections (SARS-CoV-1 and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infection or other respiratory infections.
3 Studies with incomplete or lacking necessary data
4 Duplicate studies
5 Studies without accessible full-text versions
6 Studies not in English language

full texts. LH extracted data using a standardized form, while RVP cross-checked for correctness and completeness. Any disagreement was resolved by FH. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist guided study selection and extraction. Risk for bias [21] and levels of evidence [22] were assessed (LH) with verification (RVP). Prior to conducting the review, the protocol was published (PROSPERO CRD42020189248). Data was analyzed with R v3.6.3 (Supplementary information 4).

Cohort studies and studies reporting single-case data were analyzed separately. To report on most variables, we used the sum of cases of only the records reporting on the variable. As such, the denominator in the proportions varies depending on the publications reporting on a given variable. Rare conditions (e.g., death), however, were calculated on the total group of cases. "Severe course" was defined as the presence of one or more of following conditions: coronary dilatation/aneurysm, shock, death, need for mechanical ventilation, extracorporeal membrane oxygenation (ECMO), renal replacement therapy, inotropes, or PICU admission. Data was extracted from pre-print publications for 4 records [23–26]. During the process of conducting this systematic review, 3 of these manuscripts [27–29] were published in peer-reviewed literature. The data extracted in this review was left unchanged and is thus based on the pre-print publications.

Results

Study characteristics

The search strategy yielded 918 records. After removing duplicates, 567 unique publications were screened on title and abstract of which 409 were excluded, mostly because it concerned editorial or review articles (n = 139), non-clinical case studies (n = 84), or articles on PIMS-TS/MIS(-C) diagnostics, epidemiology, or management (n = 70). One hundred and fifty-eight full-text articles were assessed for eligibility. Finally, 68 studies were included (Fig. 1). In general, risk of bias was low (Supplementary information 2), despite short follow-up in all studies.

All studies were published after May 9, 2020, and presented observational data from single case reports [24, 30–57] or case series (2–186 cases per publication) [11–17, 23, 25, 26, 58–86] (Fig. 2 - Supplementary 3). Four manuscript published on pre-print servers were included [23–26]. Most studies were non-controlled, although three publications used historical KD [15, 64, 81], MAS [81], or TSS [15] cohorts as a reference population. Limited studies prospectively included control cohorts of non-PIMS-TS/MIS(-C) pediatric COVID-19 [23, 26, 83], KD [26], (adult) COVID-19-associated acute respiratory distress syndrome (ARDS) [25], or convalescent plasma donors [25]. Studies were mostly conducted in the USA (n = 28), the UK (n = 10), or France (n = 6) and India (n = 6).

Demographics

In total, 953 patients with PIMS-TS/MIS(-C) were reported, with individual patient information (single-case data) available for 138 patients (14.5%). Fifty-five patients (5.8%) were reported in duplicate, although the corresponding manuscripts [13, 16, 17, 78, 83] did not provide sufficient information to filter for unique data.

Among single cases, a median age of 8.4 years (IQR 5–12.6) was found (Fig. 3a), corresponding with a median age of at least 8 years noted in 14/20 cohorts (586/716 cohort patients) [13, 14, 16, 17, 23, 25, 26, 59, 63–65, 78, 81, 86]. Remarkably, age was substantially higher compared to non-COVID-19 KD cases (median age 2.0–2.7y) [15, 64] or non-PIMS-TS/MIS(-C) pediatric COVID-19 (median age 2.0 years) [23]. Additionally, a male predominance (561/953; 58.9%; Fig. 3b) was found, comparable to historic KD groups [64] and non-PIMS-TS/MIS(-C) pediatric COVID-19 [23].

PIMS-TS/MIS(-C) cases were frequent Black (240/647; 37.0%), followed by patients of Caucasian (189/647; 29.2%) or Asian origin (56/647; 8.7%) [11, 13–15, 17, 23–26, 30, 35, 58, 61, 63, 65–67, 70, 71, 76, 78–81, 83, 86]. However, many mixed/other/unknown origins (144/647; 22.3%) were reported. Hispanic/Latino was reported in 97/332 (29.2%). Overweight (BMI > 25 kg/m^2 or >85th percentile for age/sex) was found in 147/581 (25.34%). Other comorbidities were infrequent, and mainly consisted of respiratory diseases, including asthma (39/953; 4.1%) or chronic lung disease (14/953; 1.5%), cardiovascular diseases (12/953; 1.3%) and immunodeficiencies (10/953; 1.0%) [13–15, 17, 23, 25, 55, 59, 60, 63, 64, 66, 68, 70, 81, 82, 86].

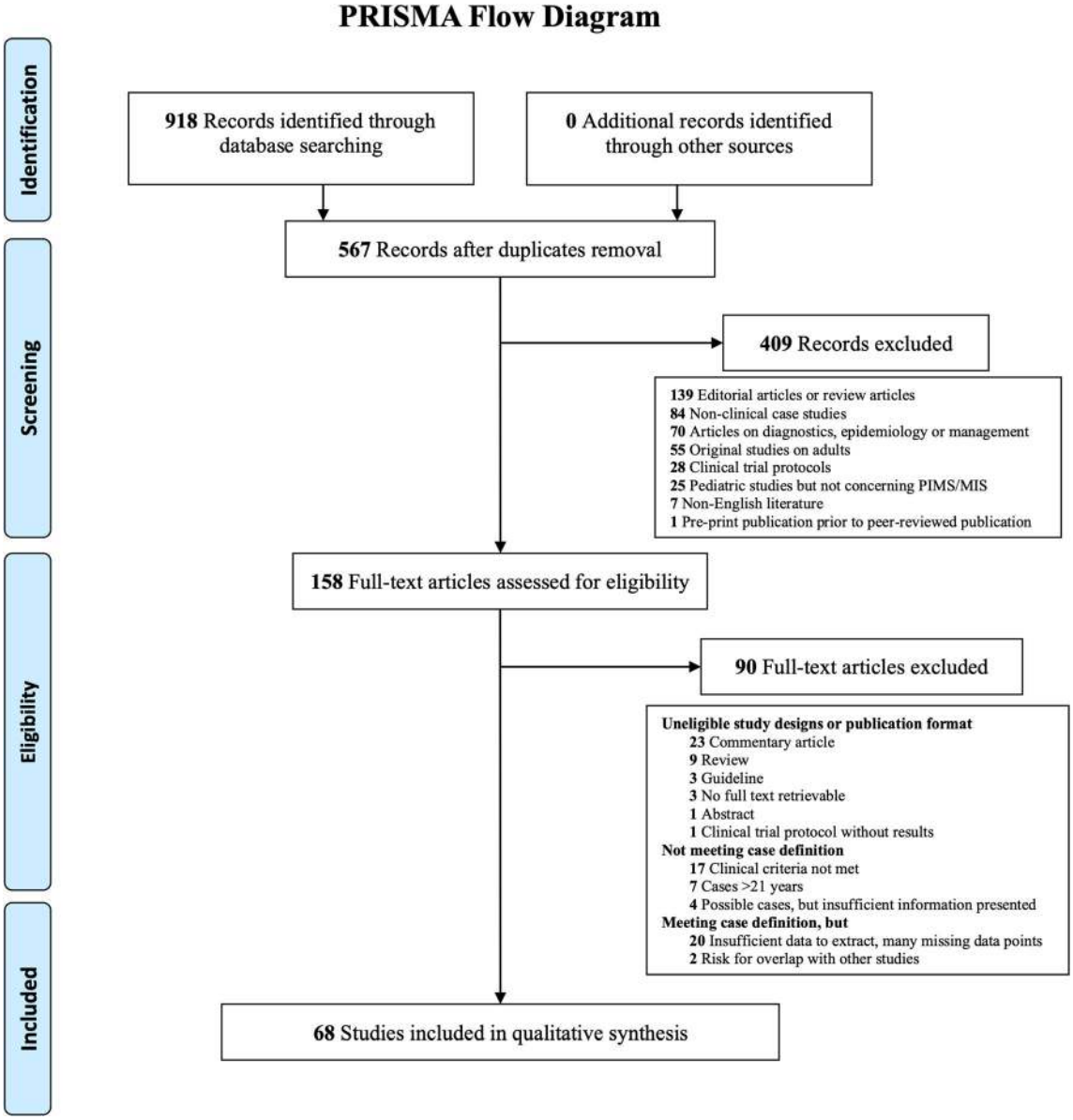


Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram

Clinical presentation

Fever was documented in nearly all patients (922/928; 99.4%) [11–17, 23, 24, 30–85], commonly during at least 5 days (258/928; 27.0%). The majority (598/699; 85.6%) presented gastrointestinal symptoms, mostly abdominal pain (315/539; 58.4%), vomiting (306/532; 57.5%), and diarrhea (268/532; 50.4%) [11–14, 16, 24, 26, 30–37, 39, 40, 43–45, 47, 49–52, 54–77, 79, 80, 82, 84–86]. Cardiovascular manifestations were found in 79.3% of patients (307/387) [11–17, 24, 30–37, 39–41, 44–49, 51–86]. Tachycardia (194/253; 76.7%), hemodynamic shock or hypotension (416/695; 59.9%), myocarditis (128/309; 41.4%) and mild or moderate decreased left ventricular ejection fraction (LVEF between 30 and 55%; 211/522; 40.4%) were frequently observed cardiovascular abnormalities. Severe complications such as LVEF less than 30% (36/506; 7.1%), coronary dilatation (z-score between 2.0 and 2.5; 74/638; 11.6%) or aneurysms (z-score above 2.5; 59/572; 10.3%) were found in a minority of cases. Pericardial effusion was frequently found (114/511; 22.3%). Half of cases (295/587; 50.3%) showed respiratory symptoms, including upper respiratory tract symptoms (95/397; 23.9%), dyspnea (101/378; 26.7%) and (multiple) radiological infiltrates (114/321; 35.5%) [14, 15, 23, 33, 35, 37, 38, 40, 44, 45, 47, 52, 59, 60, 66, 68, 71, 73, 77, 82]. Thirteen cases (1.4%) revealed thrombotic complications [11, 13, 16, 17, 74, 78], including 2 splenic infarctions [16]. (Hemorrhagic) Cerebral strokes during ECMO (n = 5), a recognized complication, contributed substantially to thrombotic complications [11, 16, 17, 74, 75].

A quarter of patients (130/557; 23.3%) fulfilled criteria for complete KD [12, 13, 15, 30, 35, 37, 41, 45, 46, 50, 53, 56, 59,

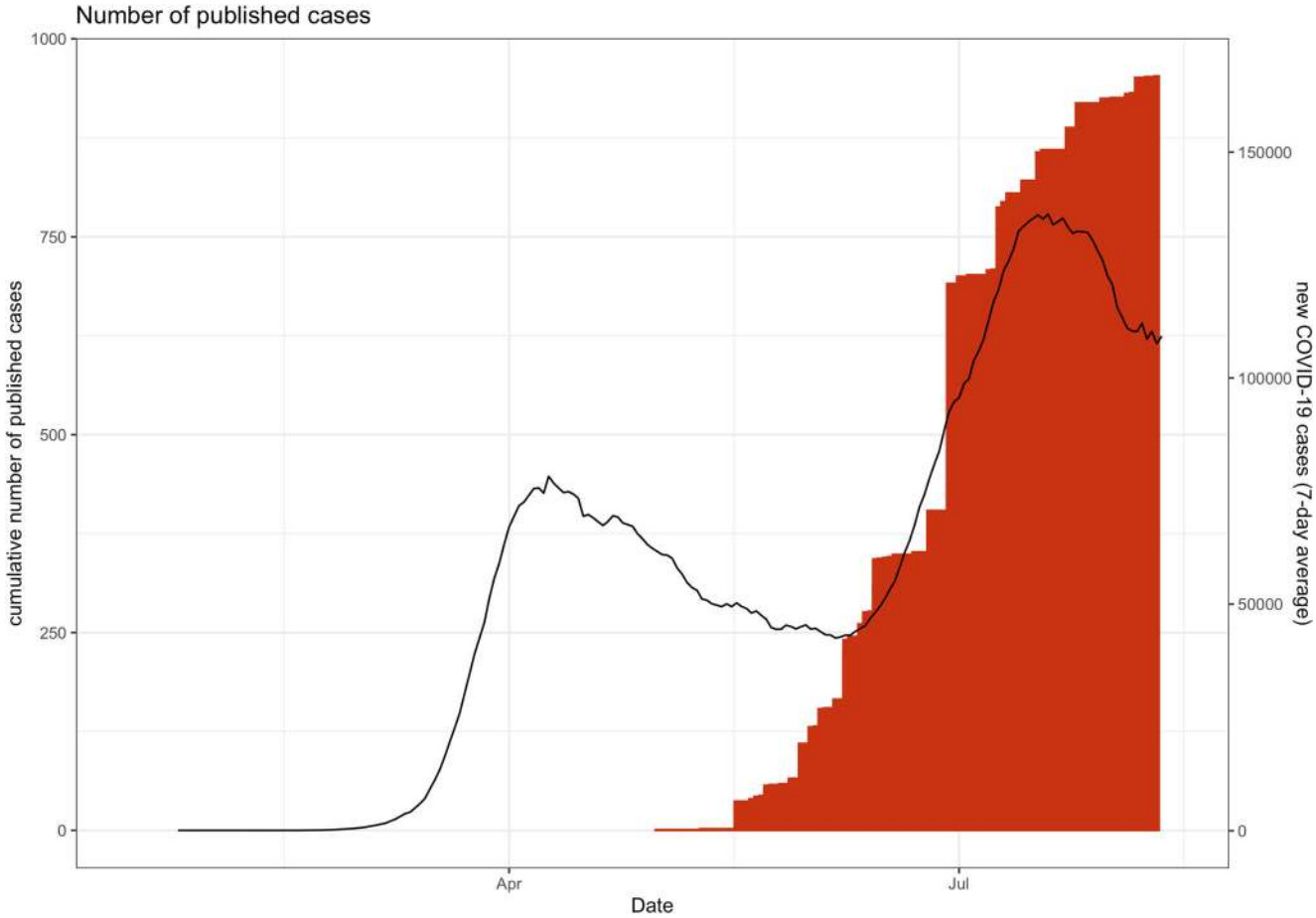


Fig. 2 Cumulative number of published PIMS-TS/MIS(-C) cases (bars) in relation to total worldwide reported COVID-19 cases, according to data from Johns Hopkins Coronavirus Resource Center (lines; 7-day rolling average)

61, 63, 64, 68, 69, 72, 73, 77, 79, 81, 83, 85, 86] (criteria in Supplementary information 1). A similar proportion (99/411; 24.1%) fulfilled 2 or 3 of the KD criteria in combination with prolonged fever, resembling incomplete KD [11–13, 32, 36, 39, 44, 47, 48, 52, 54, 57, 61–63, 65–69, 77, 79, 81, 83]. Polymorphous exanthema (466/849; 54.9%) and non-purulent conjunctivitis (423/849; 49.8%) occurred the most. Although shock was frequently reported in single cases (103/138; 74.6%), shock only presented in half of single cases with complete KD (11/24; 45.8%) [12, 30, 35, 41, 45, 46, 53, 68, 69, 72, 77].

Biological markers

Increased inflammatory markers were frequently documented (Fig. 4) [11, 12, 24, 30–57, 60, 62, 64, 66–73, 75–77, 80, 84], including C-reactive protein (CRP; median 249 mg/l [IQR 173–322] in single cases), ferritin (910 µg/l [457–1521]), and interleukin-6 (244.5 pg/ml [107–379]). Notably, patients exhibited substantially higher inflammation compared to historical KD [15, 64] or non-PIMS-TS/MIS(-C) [23] cohorts.

Although white blood cell counts were frequently increased (12,800/µl [9150–20,075]), lymphocytopenia was common (831.5/µl [510–1157.5]) [12, 24, 30–36, 39–41, 43–46, 48–50, 52–57, 60, 62, 67–73, 75, 77, 80, 84], contrasting with historical KD cohorts [15, 64] (median lymphocytes 2800–3080/µl) or non-PIMS-TS/MIS(-C) (median 2100/µl) [23]. Most PIMS-TS/MIS(-C) presented reduced to normal thrombocytes (platelets below 150,000/µl in 44/104; 42.3%) [11, 12, 24, 30, 32–36, 38, 40, 41, 43–46, 48, 50, 52–56, 62, 66–68, 70, 71, 77, 80, 84]. Thrombocytosis (platelets above 450,000/µl), a typical KD sign and a laboratory criterium for incomplete KD [87], occurred in only 5/104 (4.8%).

Besides inflammatory parameters, coagulation markers were substantially upregulated, including D-dimers (3750 ng/ml [1946–6896]) and fibrinogen (640 mg/dl [504–800]) [11, 12, 31–35, 38, 40, 43–47, 49, 51, 55–57, 60, 62, 66–68, 70, 71, 75–77, 80, 84]. Furthermore, myocardial injury markers such as troponins (188 ng/l [60–614]) and brain natriuretic peptide (BNP) (median 1619 pg/ml [424–3325]) were often elevated [11, 12, 30, 32–36, 39, 40, 46–49, 54–57, 60, 62, 66–71, 75, 77, 80, 84, 87, 88]. Hyponatremia (130 mmol/l [128–133]) [12, 24, 30, 32, 35, 37, 41, 44–46, 48–50, 52, 54,

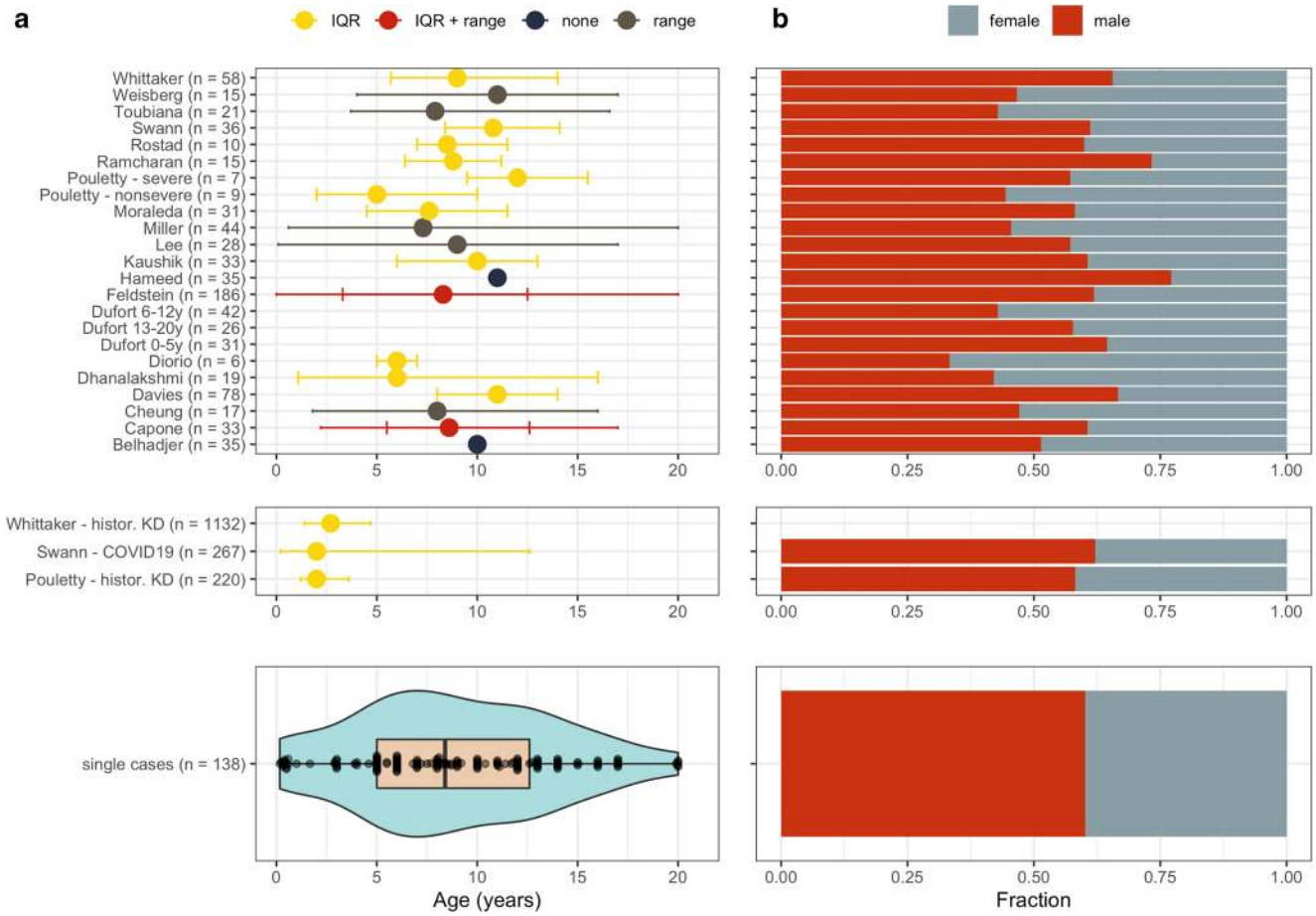


Fig. 3 Demographic characteristics of all included studies. **a** Age distribution. **b** Fraction of males and females in each study. *IQR*, interquartile range. "Control" corresponds to the control populations with Kawasaki disease as described by Pouletty et al. [64] and Whittaker et al. [15] and non-PIMS-TS/MIS(-C) pediatric COVID-19 by Swann et al. [23]. Data from Swann et al. [23], Rostad et al. [26], and Weisberg et al. [25] was extracted from pre-print publications and these references and have subsequently been published in the peer-reviewed literature [27–29]

55, 62, 67, 69, 76, 84] was frequent, contrasting with KD controls (135 mmol/l [134–137]) [64] or non-PIMS-TS/MIS(-C) COVID-19 (137 mmol/l [136–139]) [23].

SARS-CoV-2 testing and diagnostic criteria

Current or recent SARS-CoV-2 infection was assessed with RT-PCR (nasopharyngeal or fecal swab) and/or serological assays (IgG/IgM/IgA) [12–17, 25, 26, 30–34, 36–53, 55, 57–72, 75–82, 84–86]. Two-thirds of patients were IgG-positive (362/569; 63.6%). IgM (substantial variation between 5.7 and 100%) [16, 26, 59, 82] and IgA positivity (25/35; 71.4%) [59] were documented in only four and one cohort(s), respectively. All single patients being IgA-positive (19/138; 13.8%) [36, 62, 70] or IgM-positive (8/138; 5.8%) [12, 34, 46, 47, 69, 72], had detectable IgG as well. Only 338/901 (37.5%) had positive respiratory RT-PCR. Positive fecal RT-PCR was rare (7/268; 2.6%) [16, 39, 40, 45, 58, 59, 62, 64, 79]. Close contacts with COVID-19 were registered in 168/598 (28.1%) [11–13, 17, 24, 34, 36, 40, 44, 47, 48, 53, 59, 61, 63–65, 70, 72, 73, 75, 77, 78, 80–82]. Of single cases, 115/138 (83.3%) had a microbiologically confirmed SARS-CoV-2 infection (PCR and/or serology-positive). Of the 23 cases negative (or missing) for both techniques [11, 12, 24, 35, 50, 54, 56, 62, 73, 77, 79], 15 additionally had no known COVID-19 contact [11, 12, 35, 50, 54, 56, 62, 79].

As an inclusion criterium, all cases in this review corresponded to at least one of the recognized case definitions [18–20]. The RCPCH definition, not requiring proven or probable SARS-CoV-2 infection, was most comprehensive, and subsequently comprised all single cases. Although more stringent concerning clinical manifestations and the relationship with SARS-CoV-2, the WHO definition nevertheless included 97% (18 not assessable), missing only 4 mild cases that did not present multisystem dysfunction (criterium 3). In contrast, the CDC definition comprised only 62% (8 not assessable) of single cases and neglected on 31 cases with severe course, all failing to achieve the CDC criterium concerning the multi-organ (≥2 organ systems) dysfunction. Of single cases, the WHO definition missed 1 out of 5 patients needing ECMO

because of insufficient data reported to assess [74], while the CDC definition not included 2/5 ECMO cases [11, 52, 66, 74, 75] and 2/6 deaths [11, 24, 66, 74, 75, 79].

Therapeutic management

Three quarter of patients (662/872; 75.9%) received intravenous immunoglobulins (IVIG) [11–15, 17, 25, 30, 35, 37, 39, 41, 43–48, 50, 52–54, 56–69, 71–73, 75–86]. Only few papers report IVIG dosages, which were mainly immunomodulatory. Multiple IVIG doses were needed in 73/662 (11.0%). Systemic corticosteroids were prescribed in 516/908 (56.8%) [11–15, 17, 23, 25, 31, 33–35, 43, 46, 47, 50, 54, 57–67, 69, 71, 72, 76–86]. Acetylsalicylic acid was reported in 171/327 (52.3%) of which 39/171 (22.8%) received high, anti-inflammatory dosages (80–100mg/kg/day) [11, 12, 30, 35, 37, 39, 44, 45, 47, 48, 50, 52–54, 56, 61, 63–67, 69, 71, 77–79, 81, 85, 86]. Heparin (259/563; 46.0%) was a frequent anti-thrombotic [11, 13, 17, 33, 34, 43, 51, 52, 55, 59, 60, 63, 65, 66, 68, 74, 75, 78, 80, 81, 84, 86].

One hundred and fifty-five cases (155/953; 16.3%) were treated with biopharmaceuticals, including IL-1R antagonist (anakinra) (72/953; 7.6%), interleukin-6 inhibitors (tocilizumab/siltuximab; 64/953; 6.7%), and to a lesser extent, TNFα-inhibitors (infliximab) (22/953; 2.3%) [11, 13, 15, 17, 25, 33, 38, 41–43, 45, 46, 51, 57–60, 63, 64, 66–68, 70, 75, 76, 78–81, 84–86]. Remdesivir (22/953; 2.3%) was rarely prescribed [17, 25, 57, 60, 66, 78, 81, 82].

Inotropics were given to 477/863 (55.3%) [11–17, 23, 26, 31–33, 35, 39, 45–47, 52, 54, 57, 59–72, 75, 77, 78, 80, 81, 83–86]. Mechanical and non-invasive ventilation was initiated in 219/928 (23.6%) and 130/503 (25.8%), respectively [11, 13–17, 23, 30, 31, 33, 39, 41, 46, 47, 52, 54, 58–62, 64–72, 74, 75, 78, 80–86]. A relative high rate of ECMO (36/953; 3.8%) [11, 13–17, 52, 59, 66, 74, 75, 78] was reported.

Prognosis and outcomes

Intensive care admission was common (564/769; 73.3%) with median duration of 4 days (IQR 3.75–8) in single cases and 4–7 days in cohorts [11, 13, 14, 16, 17, 23, 26, 33, 45, 47, 54, 59–67, 70, 71, 79, 81–83, 85, 86]. The median time of hospitalization was 8 days (IQR 7–12) in single cases and 4–12 days in cohorts [13, 17, 30, 54, 55, 59, 63, 65–67, 70, 71, 86]. A majority of single cases (118/138; 86%) experienced severe course. Such patients were substantially older and presented more gastrointestinal and cardiovascular symptoms as compared to mild PIMS-TS/MIS(-C) (Table 2). They presented however less respiratory symptoms, exanthema, or complete KD. Laboratory measurements in patients with severe disease showed lower WBC counts and more lymphopenia, higher CRP, and ferritin (but lower IL-6), and higher platelet counts, D-dimer, and troponin. There were no differences in sex, microbiology, or medical treatment.

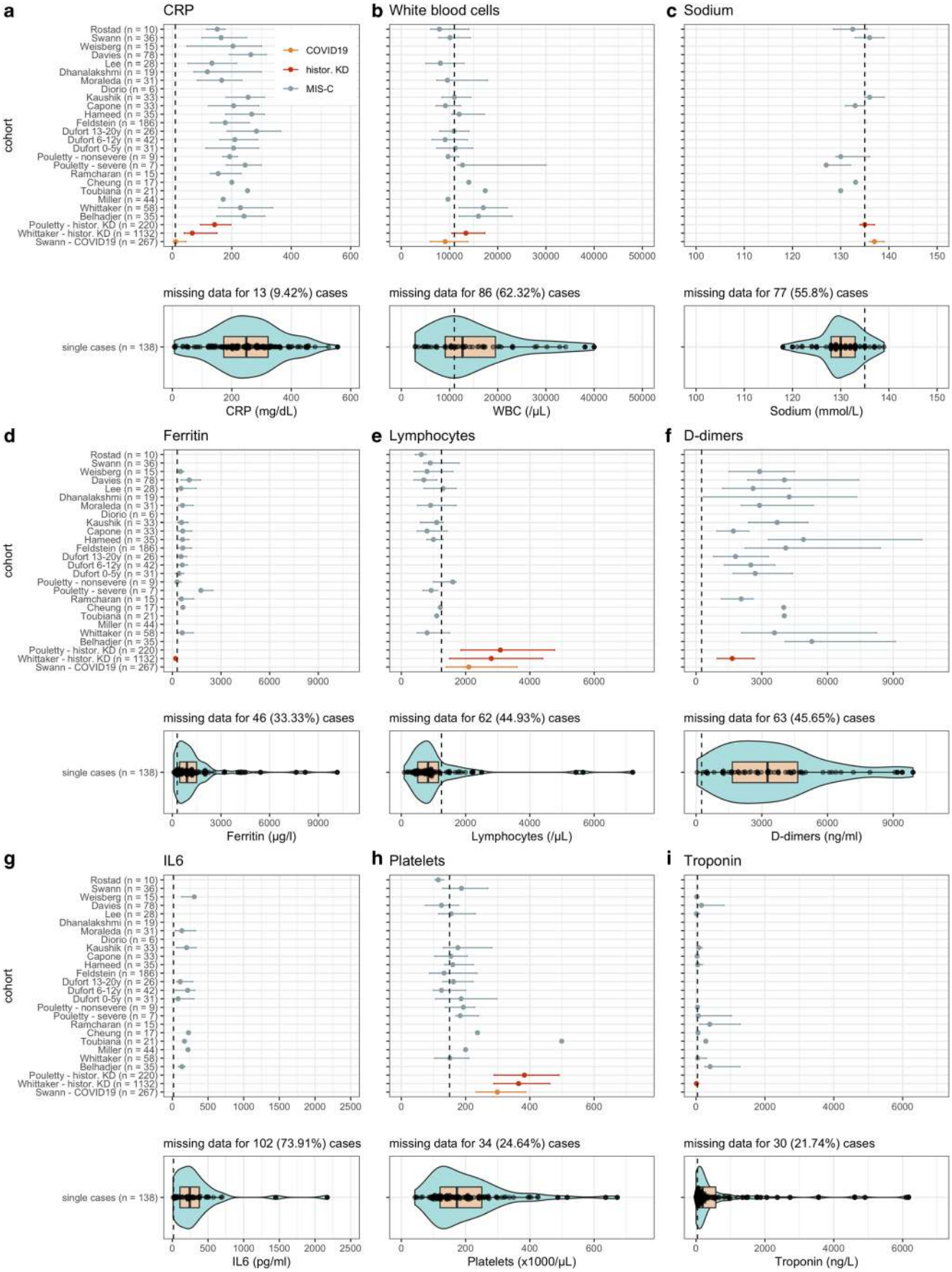
Eighteen deaths were described (18/953; 1.9%) [11, 13–17, 24, 66, 74, 75, 78, 79, 82]. Of deaths with reported ages, 2/12 (16.7%) patients were less than 1 year old [14, 79], 6/12 (50%) were aged 5–12 [13, 14, 17, 66, 74, 75], and 4/12 (33.3%) were older than 13 years [11, 13]. The majority was male (8/11; 72.3%) and Black (5/8; 62.5%), although race/ethnicity was underreported. All reported deaths but one [79] presented with shock and/or myocardial dysfunction, needing inotropics, and/or mechanical circulatory support [11, 13–17, 24, 66, 74, 75]. ECMO was initiated in 10/15 (66.7%) of fatal cases, of which 5 died of (hemorrhagic) cerebral infarction [11, 16, 17, 74, 75]. Comorbidities among fatal cases were obesity (n = 4) [11, 13], acute leukemia (n = 1) [82], glucose-6-phosphate dehydrogenase deficiency (n = 1) [24], asthma (n = 1) [13], and multiple neurological conditions (n = 1) [13]. Residual cardiac dysfunction, often reported as decreased LVEF at discharge or follow-up, was present in 21/287 (7.3%) [17, 59, 63–65, 75, 86]. Two patients showed persistent neurological damage after PIMS-TS/MIS(-C) [76]. No other residual morbidity was reported.

Discussion

Overall, children with COVID-19 exhibit mild or asymptomatic disease. Only limited reports of complicated or fatal COVID-19 in children are published [7, 10, 89, 90]. Although some immunological hypotheses are presented [91–94], hitherto, obvious elucidation on why children display a milder COVID-19 phenotype is lacking.

At the end of April 2020, while over 3 million SARS-CoV-2 infections were reported worldwide, a relative sudden emerge of children presenting a severe hyperinflammatory disorder with multisystem involvement, prompted an international alert. Noteworthy, during the first 4 months after the initial reports, more than 950 individual cases with PIMS-TS/MIS(-C) have been reported in scientific literature, and, subsequently, systematically reviewed herein. Currently, several countries are still struggling with widespread SARS-CoV-2, requiring continuous and evidence-based updates on the COVID-19 spectrum, in particular concerning complicated disease courses. In this context, we performed the most extensive PIMS-TS/MIS(-C) systematic review to appropriately characterize its presentation and prognosis.

The findings in this review confirm the heterogeneous clinical spectrum. The majority of PIMS-TS/MIS(-C) patients present gastrointestinal symptoms. Despite SARS-CoV-2 displaying respiratory tract tropism [95], a large proportion of cases does not exhibit respiratory symptoms, as typically seen in adults. Eventually, in 50.3% respiratory manifestations are noted, although critical illness might have contributed to


a
CRP
b White blood cells
c Sodium
cohort
Rostad (n = 10)
Swann (n = 36)
Weisberg (n = 15)
Davies (n = 78)
Lee (n = 28)
Dhanalakshmi (n = 19)
Moraleda (n = 31)
Diorio (n = 6)
Kaushik (n = 33)
Capone (n = 33)
Hameed (n = 35)
Feldstein (n = 186)
Dufort 13-20y (n = 26)
Dufort 6-12y (n = 42)
Dufort 0-5y (n = 31)
Pouletty - nonsevere (n = 9)
Pouletty - severe (n = 7)
Ramcharan (n = 15)
Cheung (n = 17)
Toubiana (n = 21)
Miller (n = 44)
Whittaker (n = 58)
Belhadjer (n = 35)
Pouletty - histor. KD (n = 220)
Whittaker - histor. KD (n = 1132)
Swann - COVID19 (n = 267)
COVID19
histor. KD
MIS-C
missing data for 13 (9.42%) cases
missing data for 86 (62.32%) cases
missing data for 77 (55.8%) cases
single cases (n = 138)
CRP (mg/dL)
WBC (/µL)
Sodium (mmol/L)
d Ferritin
e Lymphocytes
f D-dimers
missing data for 46 (33.33%) cases
missing data for 62 (44.93%) cases
missing data for 63 (45.65%) cases
Ferritin (µg/l)
Lymphocytes (/µL)
D-dimers (ng/ml)
g IL6
h Platelets
i Troponin
missing data for 102 (73.91%) cases
missing data for 34 (24.64%) cases
missing data for 30 (21.74%) cases
IL6 (pg/ml)
Platelets (x1000/µL)
Troponin (ng/L)

◀ **Fig. 4** Laboratory tests values and distribution for each study. Error bars correspond to the interquartile range. Dashed vertical line equals the upper limit of normal (CRP, white blood cells, ferritin, D-dimers, IL6, and troponin) or the lower limit of normal (sodium, lymphocytes, and platelets). For studies that report multiple values for the same test, the maximum (CRP, white blood cells, ferritin, D-dimers, IL6, and troponin) or the minimum (sodium, lymphocytes, platelets) was used. "Covid" (red line) equals values corresponding to the COVID-19-related hyperinflammatory syndrome; "control" (gray line) equal values corresponding to the control populations with Kawasaki disease described by Pouletty et al. [64] and Whittaker et al. [15] and (orange line) non-PIMS-TS/MIS(-C) pediatric COVID-19 by Swann et al. [23]. Data from Swann et al. [23], Rostad et al. [26], and Weisberg et al [25]. was extracted from pre-print publications and these references have subsequently been published in the peer-reviewed literature [27–29]

secondary respiratory failure and ventilator-associated pneumonia. Considering the high rate of ICU admission (73.3%), we conclude that a relevant proportion of critical cases does not exhibit initial respiratory manifestations. In contrast with typical adult COVID-19, PIMS-TS/MIS(-C) predominantly affects cardiovascular, gastrointestinal, and/or neurological organ systems and only occasionally the respiratory system. Cardiovascular manifestations, including severe circulatory failure and myocardial involvement requiring intensive care, burdens PIMS-TS/MIS(-C) substantially, and was dominantly present in all deceased patients. Nevertheless, the majority of patients (98.1%) survived the acute phase of PIMS-TS/MIS(-C). Noteworthy, an overrepresentation of males and minorities (Black, Hispanic/Latino), as well as the paucity of reports from Asian countries, is observed in this review. Apart from obesity, significant co-morbidities are missing, also among fatal cases. So far, underlying factors such as genetic predisposition, prior infections, or immunizations contributing to PIMS-TS/MIS(-C) vulnerability are unclear.

Comparing with historical KD cohorts [15, 64] or non-PIMS-TS/MIS(-C) COVID-19 children [23], PIMS-TS/MIS(-C) patients are substantially older, and represent more systemic inflammation (higher WBC counts and drastically increased CRP and IL-6), more lymphocytopenia and thrombocytopenia, and higher markers of myocardial injury (troponin and NT-pro-BNP) and coagulopathy (D-dimers). Of the PIMS-TS/MIS(-C) cases fulfilling complete KD criteria, half presented with shock, contrasting with non-COVID-19-associated KD shock syndrome with an incidence rate of only 3.3–7% of KD cases [96, 97]. Moreover, coronary dilatation (11.6%) and aneurysm formation (10.3%) are more prevalent than in appropriately treated KD (~5%), as well as mortality rates, typically less than 0.1% in KD (1.9% in PIMS-TS/MIS(-C)) [98]. Despite some overlapping features, this review confirms that PIMS-TS/MIS(-C) is a distinct entity from KD, KD shock syndrome, or (acute) COVID-19 in children. Epidemiological enrichment for adolescents is present, but clinicians should remain vigilant with other age categories as similar disease also presents in series of infants [33, 37, 48, 53, 79], and recently, even in a 36-year-old [99]. Despite the international recognition of this novel disease entity, none of the clinical variables presented in this review seems to be neither sensitive nor specific for PIMS-TS/MIS(-C). Thus, it remains challenging to recognize this heterogeneous disease in daily clinical practice. Prompt recognition is pivotal to insure a good individual prognosis. Knowledge of the disease spectrum (summarized in Fig. 5) and the combination of a detailed medical history, clinical examination, and routine laboratory markers in a child presenting with prolonged fever should allow an experienced clinician to differentiate against diseases with overlapping presentations. In either case, its frequent association with end-organ damage requires the accessibility of a pediatric intensive care unit.

Severe COVID-19 might be related to host immune overdrive and unbounded cytokine release [100, 101]. In contrast with adult COVID-19, respiratory symptoms are less common in PIMS-TS/MIS(-C), and primary respiratory failure does not seem a dominant cause for ICU admission. Moreover, the clinical presentation of PIMS-TS/MIS(-C) is mainly characterized by systemic vasculitis, multisystem involvement, and hypercoagulation. However, although abnormal coagulation parameters are frequently reported, thrombotic or embolic events were rare, in contrast with adult COVID-19 [102]. To date, the molecular pathophysiological mechanisms in PIMS-TS/MIS(-C) are insufficiently studied, although publications measuring serological and inflammatory responses have shown some initial insights [28, 103, 104]. Further research efforts are however required as understanding of the involved pathways might contribute to appropriate therapeutics that interfere with these dysregulated immune responses.

With a seroconversion rate of two-thirds, this review confirms the probable association with recent SARS-CoV-2 infection and possibility of antibody-driven pathogenesis in PIMS-TS/MIS(-C). In this review, a proportion of patients are, however, included without microbiological evidence for (past) SARS-CoV-2 infection, which is an important caveat in the current case definitions. The true incidence of PIMS-TS/MIS(-C) remains moreover unknown and a notification bias might be present. In absence of comprehensive pediatric surveillance studies, the proportion of SARS-CoV-2-infected children subsequently suffering from PIMS-TS/MIS(-C) can only be estimated. A better understanding of affected age groups and associated risk factors is thus necessary.

The appropriate use of case definitions should prospectively be assessed. This review currently favors the WHO MIS definition. In contrast with the RCPCH definition, both CDC and WHO case descriptions are more precise (e.g., requiring a proven association with SARS-CoV-2 and multisystem involvement), while the WHO definition comprised 97% of cases, and CDC only 62%.

Table 2 Characteristics of patients with mild versus severe PIMS-TS/MIS(-C) of reported single cases (n = 138). Severe course was defined as presence of coronary dilatation/aneurysm, shock, death, need for mechanical ventilation, extracorporal membrane oxygenation (ECMO), renal replacement therapy, inotropes, or PICU admission. Abbreviations used: *ECMO*, extracorporal membrane oxygenation; *IL*, interleukin; *IVIG*, intravenous immunoglobulins; *KD*, Kawasaki disease; *RRT*, renal replacement therapy; *WBC*, white blood cells

	PIMS-TS/MIS(-C)	
Variable	Severe course	Mild course
Count, *n* (%)	118 (100)	20 (100)
Age (year), median (IQR)	9 (6–12.7)	6.5 (3–9.75)
Male, *n* (%)	70 (59)	13 (65)
Symptoms, *n* (%)		
Respiratory	56 (47)	12 (60)
Gastrointestinal	103 (87)	10 (50)
Cardiovascular	117 (99)	7 (35)
Shock	103 (87)	NA
Coronary dilatation	13 (11)	NA
Aneurysm formation	12 (10)	NA
Neurological	38 (32)	9 (45)
Dermatological	59 (50)	14 (70)
Fever ≥ 5 days	64 (54)	12 (60)
Complete KD	16 (14)	8 (40)
Incomplete KD	29 (25)	4 (20)
SARS-CoV-2, *n* (%)		
RT-PCR-positive	54 (45)	9 (45)
Serology-positive	65 (55)	11 (55)
Critical care interventions, *n* (%)		
PICU admission	64 (54)	NA
Inotropics	77 (65)	NA
Mechanical ventilation	35 (30)	NA
ECMO	5 (4)	NA
RRT	2 (2)	NA
Medical treatment, *n* (%)		
IVIG once	90 (76)	14 (70)
IVIG multiple	9 (8)	2 (10)
Systemic corticoids	49 (42)	9 (45)
Anakinra	8 (7)	1 (5)
Tocilizumab	22 (19)	3 (15)
Infliximab	9 (8)	1 (5)
Laboratory markers, median (IQR)		
WBC (/μl)	12,735 (8602.5–20,075)	14,950 (10025–18,827.5)
Lymphocytes (/μl)	800 (510–1190)	920 (700–1030)
Platelets (/μl)	181,000 (123,000–254,000)	121,000 (104000–151,000)
CRP (mg/l)	251 (183–328)	197 (132.25–258.7)
Ferritin (ng/ml)	966.5 (482.5–1569.25)	752.5 (343–1286.5)
IL-6 (pg/ml)	2197.15 (23.125–9927.5)	3689 (0.75–12,193.75)
Sodium (mmol/l)	130 (128–133)	132 (129.35–133)
D-Dimer (ng/ml)	3917 (2105.75–8218)	2818 (633.5–4379)
Troponin (ng/l)	2020.5 (111–9660)	193.5 (19–10,949.2)
Outcome, *n* (%)		
Death	6 (5)	NA

Ultimately, this review has some limitations. In particular, we were unable to collect individual data of all patients. We did not contact authors of included studies for insights in their data as we believed this would significantly delay the reporting of this pressing data. Due to the nature of included studies, these reports are moreover enriched for severe disease

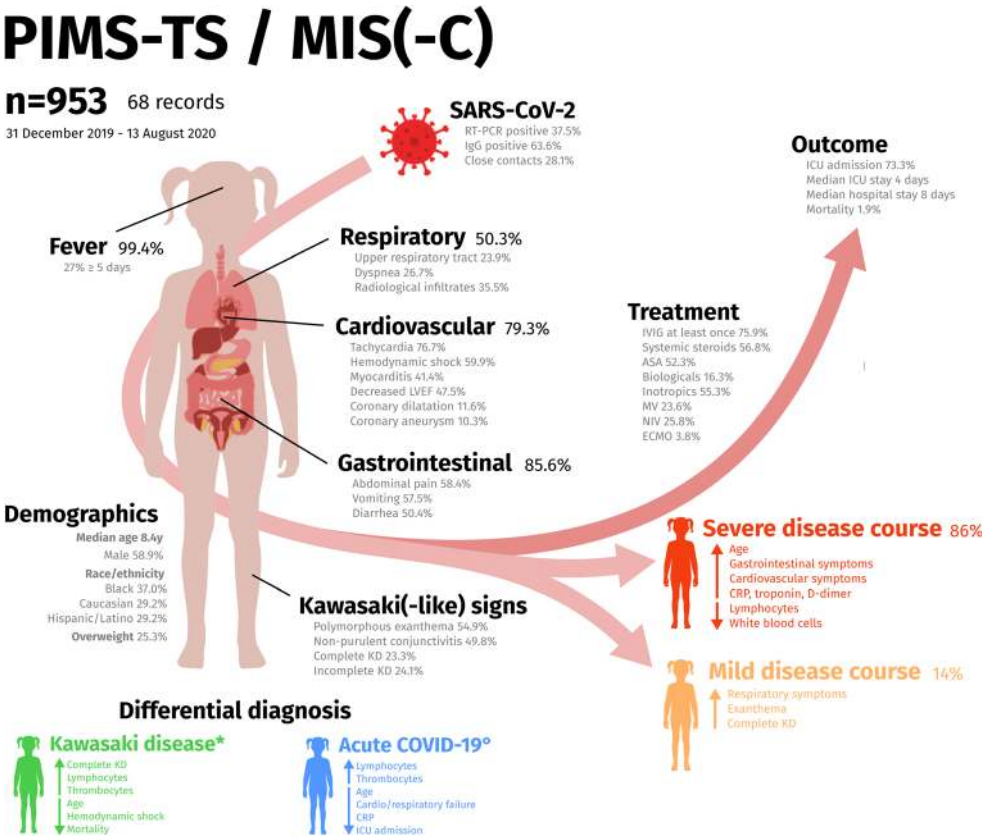


Fig. 5 Summary figure presenting the findings of this systematic review on the clinical spectrum of PIMS-TS/MIS(-C). Comparison of the clinical picture is made, based on relevant differences with control populations such as published on Kawasaki disease (KD) by Pouletty et al. [64] and Whittaker et al. [15] (*), and non-PIMS-TS/MIS(-C) pediatric COVID-19 by Swann et al. [23] (°). For each variable, the percentage denoting the fraction of included cases is displayed. PIMS-TS/MIS(-C) disease severity is assessed as described in the "Methods" section. Arrows pointing upwards mean that a higher proportion of cases display one of the mentioned symptoms or that higher values for the laboratory markers are found. Arrows pointing down denote lower values or frequencies

course. Furthermore, only 7 studies contain a control population, of which 3 use historical data [15, 64, 81], 1 uses an adult control population [25] and 2 others report on 15 or less control cases [26, 83]. Additionally, the association with COVID-19 could have triggered a reporting bias, which might result in overdiagnosis of PIMS-TS/MIS(-C). This phenomenon could have affected the in-depth analysis of the case definitions as well, as the "true" false positivity rate remains unknown. To partly overcome this issue, we excluded cases with insufficient data in our sensitivity analysis. As this review was conducted while PIMS-TS/MIS(-C) has only been described since a few months, inevitably, delayed complications or long-term effects were not yet assessed.

Because the relatively small number in the single-case cohort and many lacking data in larger cohorts, formal statistical testing was not conducted. As such, the findings of this review should be interpreted as descriptive and exploratory. Due to the retrospective nature of included studies, and not all studies reporting all variables, we were unable to collect sufficient data for prediction modeling for disease course or treatment response. To date, there is lack of randomized controlled trials concerning PIMS-TS/MIS(-C) and additional prospective cohort studies including control populations are needed. As a surrogate, systematic reviewing of observational data might contribute to the expertise required and identify gaps in knowledge. Updating the dataset of this review, might consecutively provide answers to these ongoing needs.

Conclusions

A novel hyperinflammatory condition with severe multisystem involvement has been described in children and adolescents during the COVID-19 pandemic (PIMS-TS/MIS(-C)). This review systematically assesses this novel syndrome and, as such, illustrates an epidemiological enrichment for males, adolescents, and racial minorities; a clinical heterogeneous presentation with frequent gastrointestinal manifestations and circulatory failure including myocardial injury; and lastly, an overall good prognosis with absence of short-term complications despite frequent critical care interventions. Further epidemiological, clinical, immunological, and genetic research is needed, as well as long-term follow-up studies of PIMS-TS/MIS(-C) patients.

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Author's contributions LH contributed to study conception and design and drafted the review protocol. LH independently carried out the review selection process, extracted data from the included records, and assessed risk of bias and level of evidence. LH drafted the initial manuscript, and has read, contributed to and approved the final version of the manuscript. RVP contributed to study conception and design, independently carried out the review selection process. RVP cross-checked extracted data, verified risk of bias and level of evidence, and carried out the data analysis. RVP has read, contributed to and approved the final version of the manuscript.FH supervised the full study conception, design, data extraction, data analysis and interpretation, and manuscript drafting. FH resolved any disagreement in the record selection process. FH has read, contributed to and approved the final version of the manuscript.

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Data availability/Code availability All code, additional supporting data, and the full data analysis have been made publicly accessible (url provided in Supplementary information)

Code availability N/A

Declarations

Ethics approval/consent to participate/consent for publication This article does not contain any studies with human participants or animals performed by any of the authors.

Competing interests The authors declare no competing interests.

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