

COVID-19 and multisystem inflammatory syndrome in children: A systematic review and meta-analysis

Jun Yasuhara MD¹  | Kae Watanabe MD² | Hisato Takagi MD, PhD³ | Naokata Sumitomo MD, PhD⁴ | Toshiki Kuno MD, PhD⁵

¹Center for Cardiovascular Research, The Abigail Wexner Research Institute and The Heart Center, Nationwide Children's Hospital, Columbus, Ohio, USA

²Division of Pediatric Cardiology, Ann & Robert H. Lurie Children's Hospital of Chicago, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA

³Division of Cardiovascular Surgery, Shizuoka Medical Center, Shizuoka, Japan

⁴Department of Pediatric Cardiology, Saitama Medical University International Medical Center, Saitama, Japan

⁵Department of Medicine, Icahn School of Medicine at Mount Sinai, Mount Sinai Beth Israel, New York, New York, USA

Correspondence

Jun Yasuhara, MD, Center for Cardiovascular Research, The Abigail Wexner Research Institute and The Heart Center, Nationwide Children's Hospital, 700 Children's Dr Room WB4237, Columbus, OH 43205.
Email: jun.yasuhara@nationwidechildrens.org

Abstract

Background: Multisystem inflammatory syndrome in children (MIS C) associated with coronavirus disease 2019 has been increasingly recognized. However, the clinical features of MIS C and the differences from Kawasaki disease remain unknown. The study aims to investigate the epidemiology and clinical course of MIS C.

Methods: PubMed and EMBASE were searched through August 30, 2020. Observational studies describing MIS C were included. Data regarding demographic features, clinical symptoms, laboratory, echocardiography and radiology findings, treatments, and outcomes were extracted. Study specific estimates were combined using one group meta analysis in a random effects model.

Results: A total of 27 studies were identified including 917 MIS C patients. The mean age was 9.3 (95% confidence interval [CI], 8.4–10.1). The pooled proportions of Hispanic and Black cases were 34.6% (95% CI, 28.3–40.9) and 31.5% (95% CI, 24.8–38.1), respectively. The common manifestations were gastrointestinal symptoms (87.3%; 95% CI, 82.9–91.6) and cardiovascular involvement such as myocardial dysfunction (55.3%; 95% CI, 42.4–68.2), coronary artery aneurysms (21.7%; 95% CI, 12.8–30.1) and shock (65.8%; 95% CI, 51.1–80.4), with marked elevated inflammatory and cardiac markers. The majority of patients received intravenous immunoglobulin (81.0%; 95% CI, 75.0–86.9), aspirin (67.3%; 95% CI, 48.8–85.7), and corticosteroids (63.6%; 95% CI, 53.4–73.8) with a variety of anti inflammatory agents. Although myocardial dysfunction improved in 55.1% (95% CI, 33.4–76.8) at discharge, the rate of extracorporeal membrane oxygenation use was 6.3% (95% CI, 2.8–9.8) and the mortality was 1.9% (95% CI, 1.0–2.8).

Conclusion: Our findings suggest that MIS C leads to multiple organ failure, including gastrointestinal manifestations, myocardial dysfunction and coronary abnormalities, and has distinct features from Kawasaki disease.

KEYWORDS

hyperinflammatory shock, Kawasaki disease, MIS-C, myocarditis, PIMS-TS

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by a novel coronavirus, called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in a global pandemic since December 2019. Initial studies indicated that children with SARS-CoV-2 infection generally present with mild symptoms or are asymptomatic.¹⁻³ However, in late April 2020, the United Kingdom reported a newly recognized syndrome related to SARS-CoV-2 infection characterized by hyperinflammation and multiorgan involvement in children, presenting with clinical features similar to Kawasaki disease (KD) and toxic shock syndrome.⁴ This syndrome has been named multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19 by the Centers for Disease Control and Prevention⁵ and pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 in Europe.

Since this new syndrome was identified, several reports have revealed the clinical features of MIS-C, however, there is no large study to date which can clarify the nature and course of MIS-C, including the epidemiology, pathogenesis, clinical spectrum, laboratory features, potential optimal management, and long-term outcomes. Therefore, we conducted a systematic review and meta-analysis aimed to investigate the characteristics of MIS-C, to provide insights into further understanding and the clinical practice of MIS-C.

2 | METHODS

2.1 | Search strategy

All observational studies and case series reporting patients with MIS-C were searched using a two-level search strategy. First, PubMed, and EMBASE were searched through August 10, 2020. Second, relevant studies were identified through a manual search of secondary sources including references of initially identified articles, reviews, and commentaries. All references were downloaded for consolidation, elimination of duplicates, and further analyses (Figure 1).

The search terms included "COVID-19" OR "SARS-CoV-2" OR "coronavirus", "MIS-C" OR "multisystem inflammatory syndrome in children" OR "multisystem", "inflammatory" OR "Kawasaki disease", "pediatrics" OR "child" OR "children". Two independent and blinded authors (J.Y. and T.K.) reviewed the search results separately to select the studies based on the inclusion and exclusion criteria. Any discrepancies were resolved by discussion and consensus. There were no language restrictions. This study was conducted in accordance with the preferred reporting items for systematic reviews and meta-analyses reporting guidelines.⁶

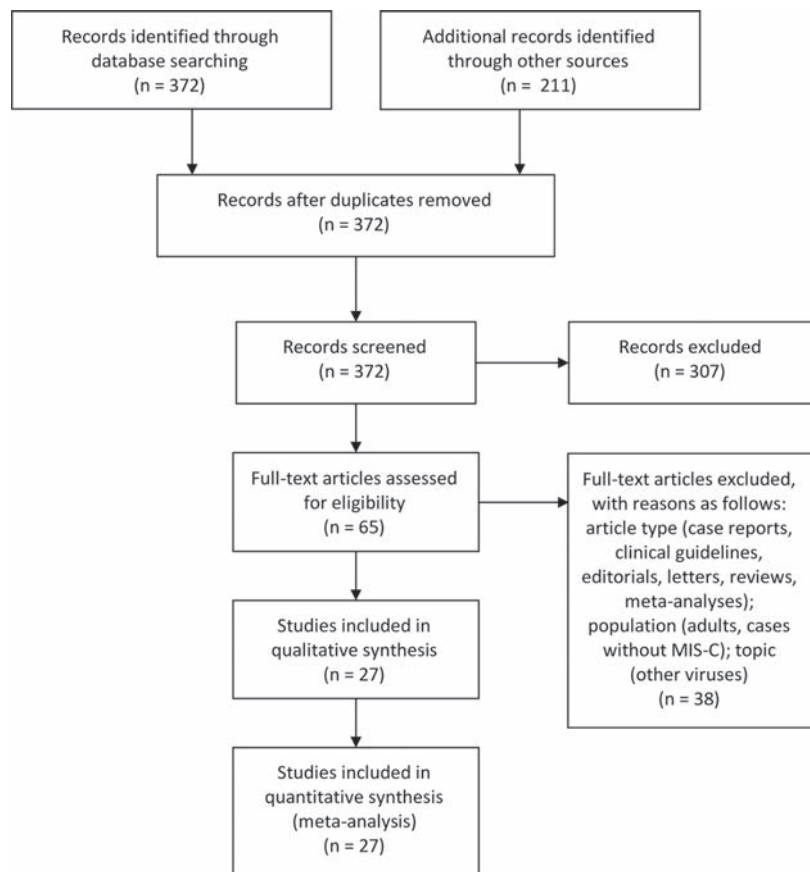


FIGURE 1 PRISMA flow diagram for the study selection. MIS-C, multisystem inflammatory syndrome in children. PRISMA, preferred reporting items for systematic reviews and meta-analyses

2.2 | Study selection and risk of bias assessment

Studies which met the following criteria were included: (1) the study design was an observational study or a case series, (2) the study population included children and adolescents (age <21 years old) who met the diagnostic criteria for MIS-C with confirmed SARS-CoV-2 infection through a reverse transcriptase-polymerase chain reaction or serological tests. The diagnosis of MIS-C was confirmed using the case definition established by the Centers for Disease Control and Prevention and World Health Organization.^{5,7} Case reports including one patient, studies not containing original data of the patients such as clinical guidelines, consensus documents, clinical trials, editorials, letters, reviews, systematic reviews and meta-analyses, and articles on other types of coronavirus were excluded from the secondary review. The risk of bias in the individual studies was reviewed using an assessment of the risk of bias in prevalence studies.⁸

2.3 | Data extraction

The following information was extracted: author, year of publication, country of the study, sample size, age, sex, race/ethnicity, comorbidities, clinical symptoms, laboratory data, echocardiography, and chest X-ray findings, treatments, and outcomes. Disagreements regarding the extracted data were resolved through discussion and consensus of a third author (H.T.).

2.4 | Statistical analysis

We performed one-group meta-analysis in a random effects model using the DerSimonian-Laird method for continuous values and Wald method for discrete values with the OpenMetaAnalyst version 12.11.14 (available from <http://www.cebm.brown.edu/openmeta/>). Continuous variables are expressed as the means \pm standard deviations or medians (interquartile range), as appropriate for the data distribution. Categorical variables are expressed as frequencies and percentages.

3 | RESULTS

3.1 | Study characteristics

Our search identified 372 articles that were reviewed based on the title and abstract, and of those, 307 articles were excluded. Sixty-five full texts were assessed for eligibility and 38 articles were excluded based on the article type (case reports, clinical guidelines, consensus documents, clinical trials, editorials, letters, reviews, systematic reviews, and meta-analyses), population (adult patients with COVID-19, cases without meeting the case definition for MIS-C) and topic (other viruses). Twenty-seven articles met the inclusion and exclusion criteria and were analyzed for the systemic review and

meta-analysis (Figure 1).^{4,9–34} The study and patient characteristics of the included studies are shown in Table S1 and Table S2. The results of the pooled analysis are summarized in Table 1. A summary of the risk of bias assessment for the prevalence studies for each retrospective cohort study is shown in Table S3.

All the included articles were published between May 2020 and July 2020. Twelve studies were conducted in the United States,^{11,12,15,17,21,22,24,27–29,32,33} 7 in the United Kingdom,^{4,16,20,23,26,30,31} 6 in France,^{10,13,14,18,19,25} and 1 each in Italy⁹ and Spain.³⁴ Overall, the studies included 917 patients with MIS-C associated with SARS-CoV-2 infections.

3.2 | Demographic features

The mean age was 9.3 (95% confidence interval [CI], 8.4–10.1; I^2 77.6%) and males were 56.8% (95% CI, 52.1–61.5; I^2 41.6%) (Figure 2). 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; I^2 63.4%), respectively, which was higher compared to the other race/ethnicities. In addition, at least one comorbidity was present in 30.7% (95% CI, 24.7–36.7; I^2 48.1%) of the population, including obesity and asthma or chronic lung disease (Table 1).

3.3 | Clinical symptoms

The most common symptom was fever (99.3%; 95% CI, 98.8–99.9; 804/809 patients; I^2 0%), followed by gastrointestinal symptoms (87.3%; 95% CI, 82.9–91.6; 564/653 patients; I^2 84.2%) and abdominal pain (70.1%; 95% CI, 58.4–81.7; 245/378 patients; I^2 65.3%). The pooled prevalence of respiratory symptoms was 40.7% (95% CI, 23.1–58.1; 259/488 patients; I^2 94.2%), however, only 7 studies reported respiratory symptoms. The pooled prevalence of neurologic symptoms was 36.0% (95% CI, 22.8–49.2; 98/459 patients; I^2 90.2%). Commonly reported symptoms similar to KD were conjunctivitis (57.0%; 95% CI, 47.3–66.6; 405/766 patients; I^2 87.2%), rash (59.0%; 95% CI, 52.8–65.2; 436/770 patients; I^2 62.3%), and oral mucosal changes (42.3%; 95% CI, 31.7–53.0; 235/595 patients; I^2 42.3%) (Table 1).

3.4 | Laboratory findings

Laboratory findings are shown in Figure 3, Table 1, and Figure S1. Inflammatory biomarkers, such as C-reactive protein, procalcitonin, ferritin, erythrocyte sedimentation rate, interleukin-6 (IL-6) and fibrinogen, were significantly elevated (Figure 3 and Figure S1). In addition, cardiac markers were elevated with marked elevations in B-type natriuretic peptide, N-terminal pro-B-type natriuretic peptide, and troponin (Figure 3). The majority of patients had elevated levels of D-dimer, elevated neutrophils, reduced lymphocytes, and low albumin (Figure 3 and Figure S1).

TABLE 1 Random-effects estimate (95% confidence interval [CI]) of the demographics, clinical characteristics, treatment, outcomes, laboratory, echocardiogram, and imaging findings of the patients with MIS-C

	Random-effects estimate (95% CI)
Demographics	
Age, years	9.3 (8.4 10.1)
BMI, kg/m ²	19.2 (17.7 20.6)
Male, %	
Race/ethnicity	56.8 (52.1 61.5)
Hispanic, %	34.6 (28.3 40.9)
Black, %	31.5 (24.8 38.1)
White, %	18.9 (14.3 23.6)
Asian, %	18.7 (8.6 28.9)
Other, %	19.0 (10.0 28.0)
Comorbidity	
Total, %	30.7 (24.7 36.7)
Obesity, %	18.0 (11.0 24.9)
Asthma/CLD, %	14.4 (11.2 17.5)
Symptoms	
Fever, %	99.3 (98.8 99.9)
Any respiratory symptoms, %	40.7 (23.1 58.4)
Cough, %	35.2 (22.2 48.1)
Dyspnea, %	37.6 (22.2 53.0)
Sore throat, %	18.5 (10.6 26.3)
Any neurologic symptoms, %	36.0 (22.8 49.2)
Headache, %	25.3 (19.6 31.0)
Meningeal signs, %	14.8 (5.8 23.8)
Any gastrointestinal symptoms, %	87.3 (82.9 91.6)
Diarrhea, %	57.0 (49.3 64.7)
Vomiting, %	60.0 (52.6 67.4)
Abdominal pain, %	70.1 (58.4 81.7)
Conjunctivitis, %	57.0 (47.3 66.6)
Rash, %	59.0 (52.8 65.2)
Peripheral extremity changes, %	32.9 (20.6 45.1)
Cervical lymphadenopathy, %	25.2 (15.0 35.3)
Oral mucosal changes, %	42.3 (31.7 53.0)
Myalgia, %	14.2 (8.3 20.0)
Laboratory values	
Hematology	
White blood cell, × 10 ⁹ /L	11.8 (10.5 13.2)
Neutrophil count, × 10 ⁹ /L	10.8 (9.3 12.4)
Lymphocyte count, × 10 ⁹ /L	0.8 (0.7 1.0)
Platelet count, × 10 ⁹ /L	155.1 (143.2 167.1)
Hemoglobin, g/dl	10.7 (9.9 11.5)
Inflammatory markers	
C-reactive protein, mg/L	235.5 (215.8 255.5)
Procalcitonin, ng/ml	8.5 (5.3 11.7)
Ferritin, ng/ml	711.0 (599.5 822.4)

TABLE 1 (Continued)

	Random-effects estimate (95% CI)
ESR, mm/h	62.8 (58.9 66.6)
Interleukin-6, pg/ml	172.2 (137.9 206.5)
Biochemistry	
Albumin, g/dl	2.7 (2.4 2.9)
Serum sodium, mEq/L	131.7 (129.6 133.8)
Serum creatinine, mg/dl	0.8 (0.7 1.0)
AST, U/L	49.1 (35.5 62.7)
ALT, U/L	44.6 (32.9 60.4)
Lactate dehydrogenase, U/L	347.7 (292.5 403.0)
Coagulation	
D-Dimer, µg/ml	3.5 (2.9 4.1)
Fibrinogen, mg/dl	643.0 (598.6 687.5)
Cardiac markers	
Troponin, ng/L	100.8 (55.2 146.3)
BNP, pg/ml	2191.5 (1334.2 3048.7)
NT-proBNP, pg/ml	14072.0 (7975.1 20168.9)
Echocardiography findings	
LV systolic dysfunction or myocarditis, %	55.3 (42.4 68.2)
LVEF, %	41.7 (36.1 47.4)
LVEF < 30%, %	7.9 (2.6 13.2)
LVEF 30-50%, %	53.8 (37.0 70.5)
Coronary artery dilation or aneurysm, %	21.4 (12.8 30.1)
Pericardial effusion, %	31.7 (23.5 40.0)
Chest X-ray findings	
infiltrates or Opacities, %	38.3 (29.7 46.9)
Treatment	
Intravenous immunoglobulin, %	81.0 (75.0 86.9)
Corticosteroids, %	63.6 (53.4 73.8)
Tocilizumab (IL-6 receptor antagonist), %	27.7 (15.2 40.3)
Anakinra (IL-1 receptor antagonist), %	10.8 (8.2 13.4)
Infliximab (TNF-α antagonist), %	8.0 (2.9 13.1)
Remdesivir, %	8.3 (0.0 16.7)
Aspirin, %	67.3 (48.8 85.7)
Anticoagulation, %	56.5 (41.8 71.1)
Inotropes, %	62.9 (53.2 72.6)
High-flow nasal cannula, %	16.8 (10.4 23.3)
Noninvasive ventilation, %	24.6 (14.4 34.7)
Mechanical ventilation, %	33.0 (24.5 41.5)
ECMO, %	6.3 (2.8 9.8)
Outcomes	
ICU admission, %	79.1 (71.6 86.7)
Kawasaki Disease, %	44.3 (34.7 53.9)
Shock, %	65.8 (51.1 80.4)

TABLE 1 (Continued)

	Random-effects estimate (95% CI)
Recovery of LV systolic dysfunction at discharge, %	55.1 (33.4 76.8)
Death, %	1.9 (1.0 2.8)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BNP, B-type natriuretic peptide; CLD, chronic lung disease; ECMO, extracorporeal membrane oxygenation; ESR, erythrocyte sedimentation rate; ICU, intensive care unit; IL, interleukin; LV left ventricular; LVEF, left ventricular ejection fraction; MIS-C, multisystem inflammatory syndrome in children; NA, not available; NT-proBNP, N-terminal proBNP; TNF- α , tumor necrosis factor- α .

3.5 | Echocardiography and radiology findings

According to the echocardiography findings, cardiovascular involvement was common (Table 1). Left ventricular (LV) systolic dysfunction, defined as a depressed LV ejection fraction (<50%) or myocarditis was identified in 55.3% (95% CI, 42.4 68.2; 410/773 patients; I^2 94.6%). The mean LV ejection fraction at admission was 41.7% (95% CI, 36.1 47.4; I^2 91.4%). The pooled

prevalence of coronary artery dilation or aneurysms was 21.7% (95% CI, 12.8 30.1). Finally, the proportion of chest X-ray findings, such as infiltrates or opacities was 38.3% (95% CI, 29.7 46.9; 133/341 patients; I^2 46.6%) (Table 1).

3.6 | Treatment and outcomes

The pooled proportions of the therapeutic management and outcomes are shown in Table 1. Overall, 79.1% (95% CI, 71.6 86.7; 550/725 patients; I^2 89.4%) required admission to the intensive care unit. The most common therapy was intravenous immunoglobulin (IVIG) (81.0%; 95% CI, 75.0 86.9; 608/787 patients; I^2 84.7%), followed by aspirin (67.3%; 95% CI, 48.8 85.7; 147/235 patients; I^2 93.7%), systemic corticosteroids (63.6%; 95% CI, 53.4 73.8; 434/714 patients; I^2 88.6%), inotropes (62.9%; 95% CI, 53.2 72.6; 469/770 patients; I^2 87.8%), and anticoagulation (56.5%; 95% CI, 41.8 71.1; 261/466 patients; I^2 91.1%). A range of anti-inflammatory biologics and antiviral agents were used including tocilizumab, anakinra, infliximab, and remdesivir (Table 1). Overall, 33.0% (95% CI, 24.5 41.5; 252/891 patients; I^2 91.5%) required mechanical ventilation. The rate of extracorporeal membrane oxygenation

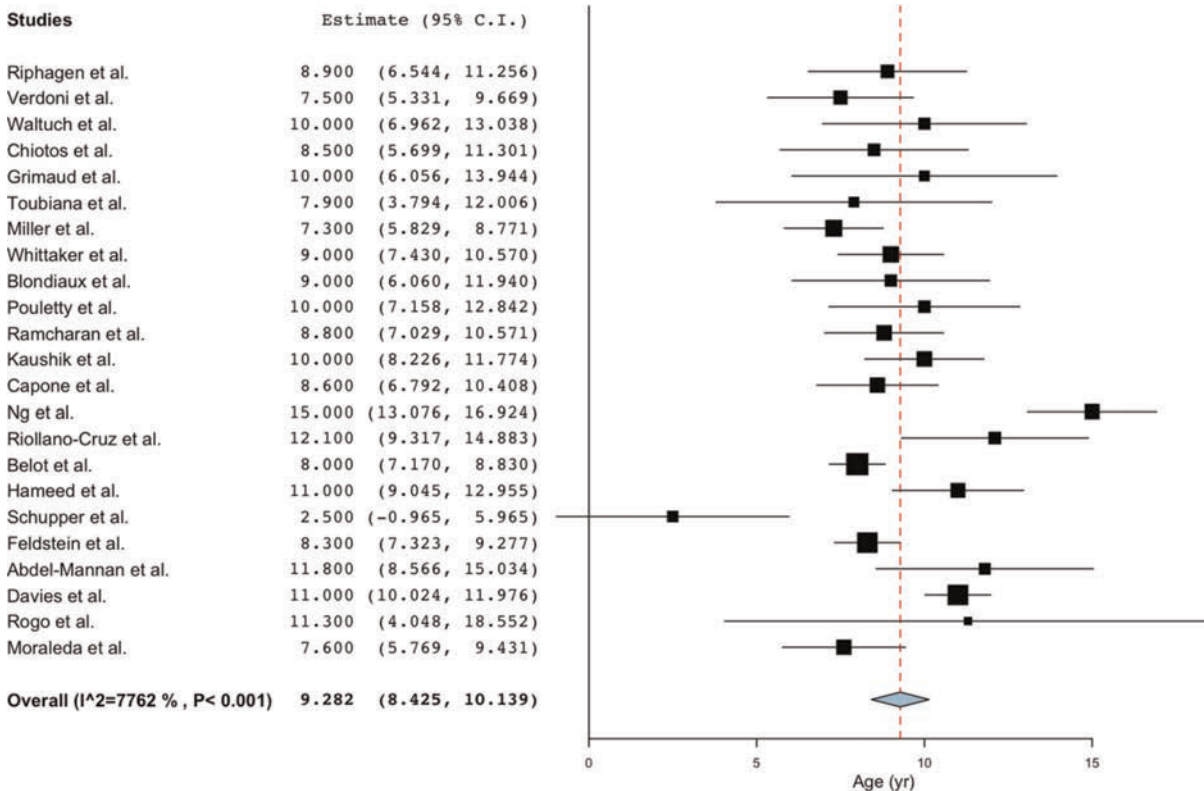


FIGURE 2 Forrest plots of the included studies showing the pooled estimate of the age [Color figure can be viewed at wileyonlinelibrary.com]

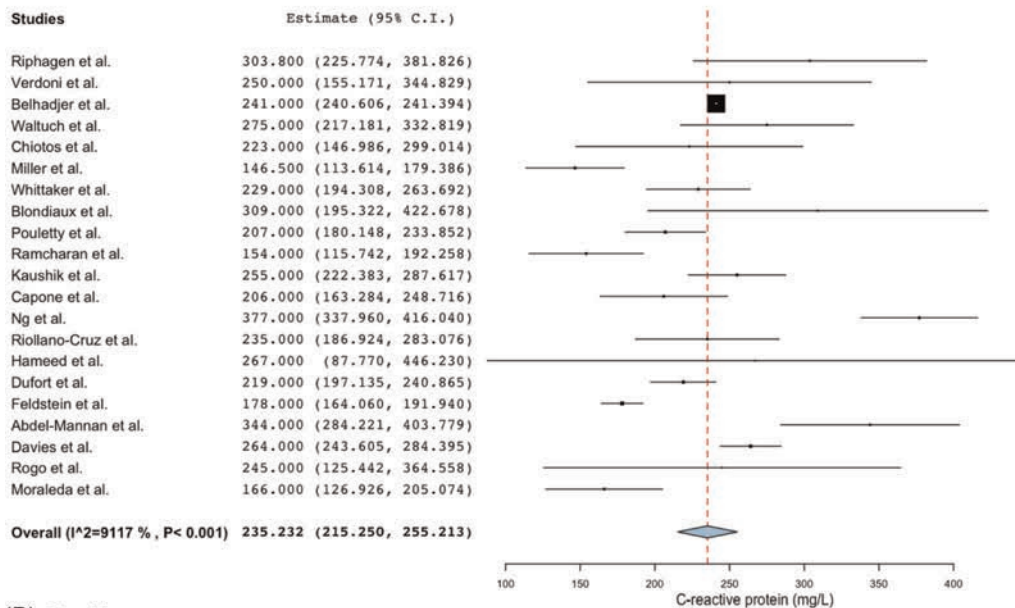
090177e1981d3439\Final\Final On: 20-Sep-2021 19:30 (GMT)

(ECMO) use was 6.3% (95% CI, 2.8–9.8; 36/553 patients; I^2 60.4%). Overall, 44.3% (95% CI, 34.7–53.9; 256/590 patients; I^2 80.5%) received a diagnosis of KD or atypical KD and 65.8% (95% CI, 51.1–80.4; 357/615 patients; I^2 95.8%) developed shock. At time of hospital discharge, recovery of LV systolic function, which was defined as an LV ejection fraction of more than 60%, was observed in 55.1% (95% CI, 33.4–76.8; 79/145 patients; I^2 88.3%). The mortality rate was 1.9% (95% CI, 1.0–2.8; 16/917 patients; I^2 0%) (Table 1).

4 | DISCUSSION

This systematic review and meta-analysis comprehensively summarized the available published literature and assessed the clinical characteristics and management of MIS-C associated with COVID-19. The salient findings of our study can be summarized as follows: (1) the mean age was 9.3 years; (2) the majority of MIS-C cases were Hispanic and Black children; (3) the common symptoms were fever, gastrointestinal symptoms, and dermatologic or

(A) C-reactive protein



(B) Ferritin

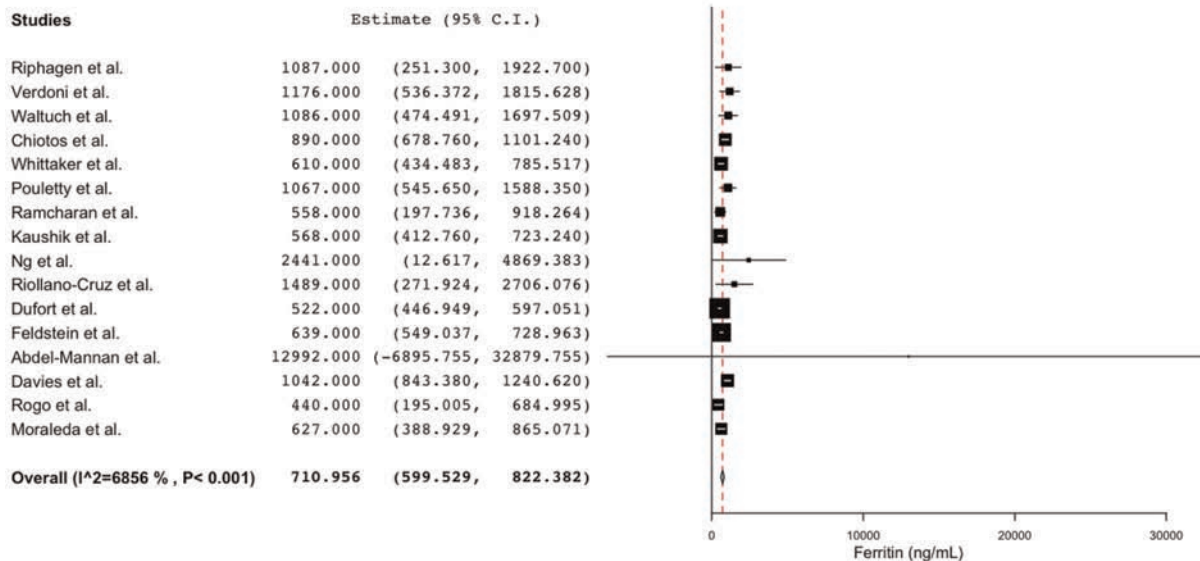
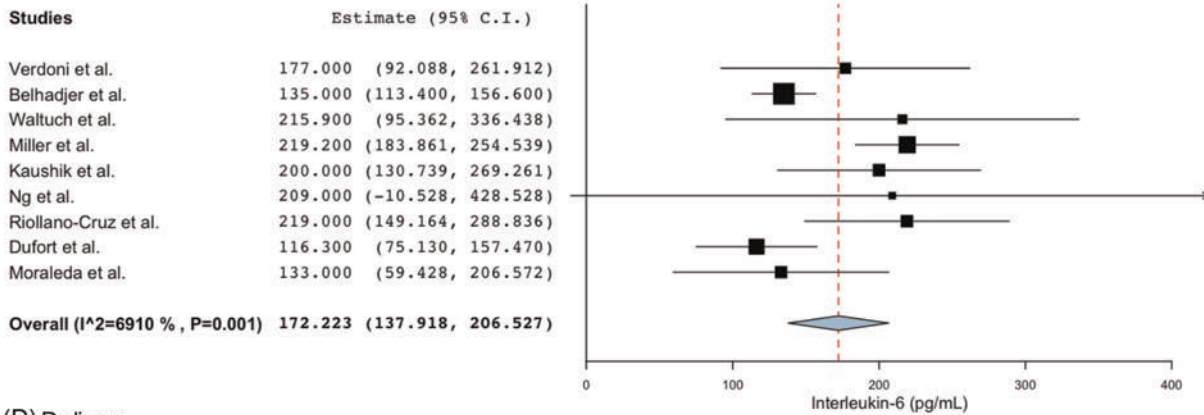


FIGURE 3 Forrest plots of the included studies showing the pooled estimate of the laboratory findings. (A) C reactive protein. (B) Ferritin. (C) Interleukin 6. (D) D dimer. (E) Troponin. (F) B type natriuretic peptide. (G) N terminal proB type natriuretic peptide [Color figure can be viewed at wileyonlinelibrary.com]

(C) Interleukin-6



(D) D-dimer

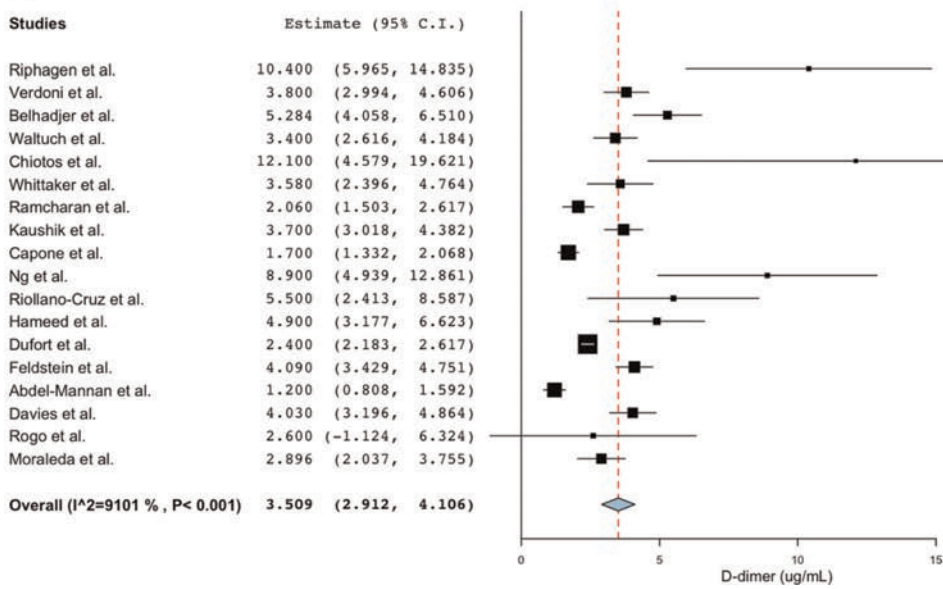
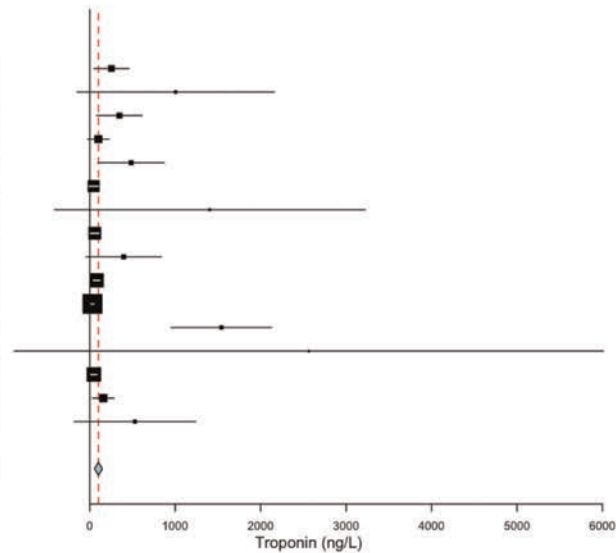


FIGURE 3 Continued

090177e1981d3439\Final\Final On: 20-Sep-2021 19:30 (GMT)

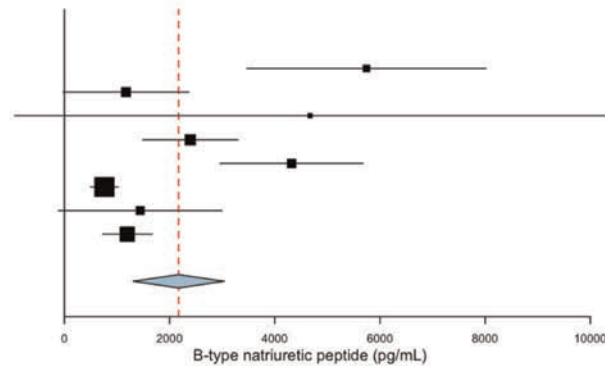
(E) Troponin

Studies	Estimate (95% C.I.)
Riphagen et al.	253.000 (49.272, 456.728)
Verdoni et al.	1004.000 (-150.058, 2158.058)
Belhadjer et al.	347.000 (81.633, 612.367)
Waltuch et al.	100.000 (-26.418, 226.418)
Chiotos et al.	484.000 (95.126, 872.874)
Whittaker et al.	45.000 (-9.559, 99.559)
Blondiaux et al.	1404.000 (-413.867, 3221.867)
Pouletty et al.	58.000 (10.961, 105.039)
Ramcharan et al.	396.000 (-46.297, 838.297)
Kaushik et al.	80.000 (42.128, 117.872)
Capone et al.	31.000 (12.815, 49.185)
Ng et al.	1541.000 (952.575, 2129.425)
Riollano-Cruz et al.	2563.000 (-884.284, 6010.284)
Hameed et al.	47.000 (11.220, 82.780)
Davies et al.	157.000 (30.948, 283.052)
Rogo et al.	528.000 (-183.467, 1239.467)
Overall (I²=7461 %, P< 0.001)	101.222 (55.292, 147.151)



(F) B-type natriuretic peptide

Studies	Estimate (95% C.I.)
Belhadjer et al.	5743.000 (3470.321, 8015.679)
Waltuch et al.	1171.000 (-23.598, 2365.598)
Chiotos et al.	4671.000 (-945.267, 10287.267)
Blondiaux et al.	2394.000 (1488.497, 3299.503)
Pouletty et al.	4319.000 (2959.275, 5678.725)
Kaushik et al.	760.000 (495.581, 1024.419)
Riollano-Cruz et al.	1440.000 (-114.618, 2994.618)
Feldstein et al.	1194.700 (721.745, 1667.655)
Overall (I²=8696 %, P< 0.001)	2172.470 (1303.056, 3041.883)



(G) N-terminal proB-type natriuretic peptide

Studies	Estimate (95% C.I.)
Riphagen et al.	18701.400 (9049.827, 28352.973)
Verdoni et al.	1255.000 (679.210, 1830.790)
Belhadjer et al.	41484.000 (37394.833, 45573.167)
Whittaker et al.	788.000 (-1189.523, 2765.523)
Ramcharan et al.	24470.000 (20930.107, 28009.893)
Kaushik et al.	15000.000 (13566.678, 16433.322)
Capone et al.	3325.000 (1713.579, 4936.421)
Ng et al.	18228.000 (13772.947, 22683.053)
Rogo et al.	10208.000 (514.998, 19901.002)
Moraleda et al.	8918.000 (6279.259, 11556.741)
Overall (I²=9892 %, P< 0.001)	14072.011 (7975.080, 20168.941)

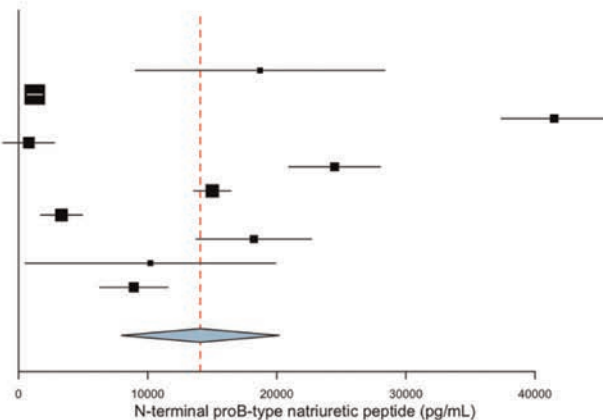


FIGURE 3 Continued

mucocutaneous symptoms; (4) the inflammatory markers, *D*-dimer, and cardiac markers were significantly elevated; (5) cardiovascular involvement was common, including shock and myocardial dysfunction; (6) MIS-C patients were commonly treated with IVIG, aspirin, and systemic corticosteroid; and (7) myocardial dysfunction

improved in many cases but the rate of ECMO use and the mortality rate were high.

Identification of MIS-C is crucial as it can result in severe organ dysfunction, including myocardial dysfunction, even leading to death.^{28,29} MIS-C has been reported to occur approximately

2–4 weeks after infection with SARS-CoV-2.³⁵ The interval between SARS-CoV-2 infection and MIS-C which may result from immune response to infection with SARS-CoV-2. Although both the Centers for Disease Control and Prevention and World Health Organization case definitions may apply to patients with other infectious and inflammatory conditions, such as KD, viral infections, and juvenile idiopathic arthritis, the findings of our study are consistent with the current diagnostic guidelines.^{5,7,36} Our data indicated that MIS-C patients commonly present with gastrointestinal, dermatologic, or mucocutaneous symptoms, and cardiovascular manifestations, as well as elevated inflammatory and cardiac marker levels. Furthermore, compared to acute COVID-19, we found that the prevalence of neurological symptoms was higher in MIS-C, with a lower prevalence of respiratory symptoms.^{30,37–39} Interestingly, our study also showed that infiltrates or opacities were less frequent in MIS-C, whereas these are common findings in acute COVID-19.^{40–44} These findings can be useful clues to the development of an accurate diagnosis and case definition of MIS-C.

MIS-C and KD have clinical similarities and there is no definitive diagnostic test for either MIS-C or KD, resulting in diagnostic difficulty. Although MIS-C shares clinical features with KD, we demonstrated that these syndromes have important distinct features. As previously reported, we confirmed that MIS-C affects older children and adolescents, which is in a marked contrast to the epidemiology of KD, occurring predominantly in children 5 years of age or younger and with a peak incidence at 9–11 months of age.⁴⁵ Interestingly, the proportions of Hispanic and Black cases were high for MIS-C with few cases reported in children of Asian descent or in Asian countries in contrast to KD.⁴⁶ This might be associated with the socioeconomic disparities as the rates of COVID-19 were shown to be higher among racial/ethnic minorities and socioeconomically disadvantaged children.⁴⁷ In addition, we noted that MIS-C manifests with a higher incidence of myocardial dysfunction and gastrointestinal symptoms compared to KD.¹⁶ Furthermore, the extent of the elevation of inflammatory biomarkers and cardiac markers in MIS-C are significantly higher than in KD.^{9,16} These marked differences in the epidemiology and clinical and laboratory findings suggest that MIS-C and KD are two distinct diseases with overlapping clinical characteristics.

Kawasaki disease shock syndrome (KDSS), a rare form of KD, has many similarities to MIS-C. The incidence of KDSS is 1.5% to 7.0% of KD patients and is higher in Western countries than Asian countries.⁴⁸ KDSS is previously found to be associated with an older age and is characterized as hyperinflammation with higher C-reactive protein, procalcitonin, erythrocyte sedimentation rate, IL-6, and D-dimer as compared to KD.⁴⁸ In addition, KDSS is often associated with myocarditis and prolonged myocardial dysfunction.^{49,50} Patients with KDSS often require intensive care in the acute phase such as intravenous fluid resuscitation and inotropes. These features of KDSS are consistent with our findings of MIS-C. However, resistance to IVIG and coronary artery abnormalities are more common in KDSS and gastrointestinal symptoms are more common in MIS-C. A great uncertainty still exists regarding the link between MIS-C and KDSS

related to COVID-19, and further research is needed to better understand MIS-C, KD, and KDSS.

Patients with MIS-C are currently managed in different ways based on symptoms, using standard protocol for KD, or COVID-19 treatment for adult patients. In this study, we report that the most common treatments were IVIG, aspirin, and corticosteroids, extrapolated from KD management. These standard treatments for KD were primarily used based on the known efficacy in preventing coronary aneurysms in this population. In addition, several MIS-C patients received anti-inflammatory biologics and antiviral therapies. Tocilizumab, an IL-6 receptor antagonist, and Anakinra, an IL-1 receptor antagonist, have been used for the treatment of severe COVID-19 in adults, although safety and efficacy has been controversial.^{51–54} Infliximab, an anti-human tumor necrosis factor- α (TNF- α) monoclonal antibody, is effective against several inflammatory diseases including KD thus maybe an interesting agent in the MIS-C population.^{55,56} Furthermore, remdesivir, which is a nucleoside analogue that inhibits viral RNA polymerases, has been shown to be associated with the clinical improvement in adults with COVID-19.^{57–59} Given the presentation of shock, MIS-C cases required inotropes and intensive care, including mechanical ventilation and ECMO. The rate of ECMO use and the mortality rate in MIS-C were extremely higher than that in children with acute COVID-19 or KD.^{60,61} Our findings demonstrated heterogeneity in management of MIS-C. Further studies including randomized clinical trials or global registries are required to determine what treatments are beneficial against distinct manifestations of MIS-C, such as shock and myocardial dysfunction, hopefully improving the high mortality rate.

Myocardial dysfunction is a more common cardiovascular complication in MIS-C than coronary artery dilation or aneurysms, unlike in KD. We revealed that the majority of MIS-C patients recovered successfully with a relatively high rate of improvement in myocardial dysfunction, however, the underlying mechanism of myocardial dysfunction in MIS-C has not been fully elucidated. The pathogenesis of myocardial injury characterized by the elevation of cardiac troponin in acute COVID-19 can be direct damage of myocardial cells by the virus or a severe cytokine storm induced by inflammatory responses, leading to myocarditis.^{62–66} Recent studies have identified that IL-6 is elevated in COVID-19 patients with myocarditis⁶⁷ and IL-6 plays a crucial role in a cytokine storm associated with COVID-19 by forming hyperinflammation and promoting the production of the coagulation cascade activator plasminogen activator inhibitor-1.⁶⁸ In addition, they found that the inhibition of IL-6 signaling by tocilizumab treatment decreased plasminogen activator inhibitor-1 production and resolved clinical manifestations in severe COVID-19. Therefore, a potential mechanism for myocardial injury in MIS-C may be a cytokine storm induced by IL-6, leading to the development of fulminant myocarditis. In contrast, immunological activation accompanied by secretion of TNF- α is an essential predisposing factor to exacerbate vascular damage in KD, resulting in coronary artery aneurysms.⁶⁹ Given the differences in cytokines,

anti-IL-6 treatment might be a potential therapeutic option for MIS-C in addition to IVIG and steroids as opposed to anti-TNF- α therapy for KD. To date, the long-term morbidity and outcomes of MIS-C, such as sequelae of myocardial dysfunction and coronary artery aneurysm formation remain unknown. Future research is needed to understand which treatment could prevent myocarditis and coronary artery aneurysms as well as tracking long-term cardiac comorbidities.

Radia et al. reported a systematic review of MIS-C.⁷⁰ They summarized the clinical, biochemical, radiological, and microbiological features of 783 cases of MIS-C between March to June, 2020. Compared to this systematic review, the novelty of our study lies on the examination of the pooled estimates across published observational studies on MIS-C using one-group meta-analysis in a random-effects model. We identified more cases of MIS-C through a longer-term literature search and examined more variables. The pooled estimates of a variety of clinical findings would provide novel insights into understanding the full spectrum of MIS-C. In particular, more detailed and specific data such as on the race/ethnicity, inflammatory and cardiac markers, infiltrates or opacities, myocardial dysfunction, coronary artery abnormalities, and treatment would be useful for a diagnosis and management of MIS-C as well as the exploration of the risk factors and susceptibility for MIS-C and COVID-19.

This study had several limitations to be noted. First, the available studies were observational studies or case series, which are subject to methodological biases or publication biases. However, only observational studies are currently available describing the clinical features of MIS-C patients, and our study is crucial to assess the current data on MIS-C. Second, the data on some variables were not available in all studies or were not reported consistently. Third, the lack of a universal case inclusion criteria or diagnostic test could lead to a misdiagnosis or underreporting of MIS-C cases. Finally, the studies were from the United States and European countries, which limit generalizability of findings.

5 | CONCLUSION

Our findings demonstrated MIS-C could lead to severe multisystem dysfunction, including myocardial dysfunction and coronary artery dilation or aneurysms. MIS-C has distinct features from KD, including an older age at onset and higher incidence of gastrointestinal symptoms and myocardial dysfunction with elevated inflammatory and cardiac markers. Most cases of MIS-C are treated by extrapolating from standard protocols for KD with a variety of anti-inflammatory agents. Although myocardial injury improved in many cases at discharge, the rate of ECMO use and the mortality rate were higher than that in children with acute COVID-19 or KD. These findings provide insights into understanding the clinical characteristics and establishing specific diagnostic criteria and management of MIS-C. Further studies with large cohorts of MIS-C patients are

necessary to investigate the pathophysiology, full spectrum of the clinical features, optimal treatment and long-term outcomes of this population.


CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Jun Yasuhara: conceptualization (lead); data curation (lead); formal analysis (lead); investigation (lead); methodology (lead); project administration (lead); resources (lead); software (lead); validation (lead); visualization (lead); writing original draft (lead); writing review & editing (lead). Kae Watanabe: formal analysis (supporting); investigation (supporting); validation (supporting); writing review & editing (supporting). Hisato Takagi: investigation (supporting); supervision (supporting); validation (supporting); writing review & editing (supporting). Naokata Sumitomo: investigation (supporting); supervision (equal); validation (supporting); writing review & editing (supporting). Toshiki Kuno: conceptualization (supporting); data curation (supporting); formal analysis (supporting); investigation (supporting); methodology (supporting); supervision (equal); validation (supporting); writing review & editing (supporting).

ORCID

Jun Yasuhara  <https://orcid.org/0000-0002-7937-3699>

REFERENCES

- Castagnoli R, Votto M, Licari A, et al. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children and adolescents: a systematic review. *JAMA pediatrics*. 2020;174(9):882-889.
- Yasuhara J, Kuno T, Takagi H, Sumitomo N. Clinical characteristics of COVID-19 in children: a systematic review. *Pediatr Pulmonol*. 2020;55:2565-2575.
- de Souza TH, Nadal JA, Nogueira RJN, Pereira RM, Brandão MB. Clinical manifestations of children with COVID-19: a systematic review. *Pediatr Pulmonol*. 2020;55(8):1892-1899.
- Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet (London, England)*. 2020;395(10237):1607-1608.
- Centers for Disease Control and Prevention. Multisystem inflammatory syndrome in children (MIS-C) associated with coronavirus disease 2019 (COVID-19). 2020. <https://emergency.cdc.gov/han/2020/han00432.asp>. Accessed June 20, 2020.
- Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6(7):e1000097.
- World Health Organization. Multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19. 2020. <https://www.who.int/news-room/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19>. Accessed August 15, 2020.
- Kim SY, Park JE, Lee YJ, et al. Testing a tool for assessing the risk of bias for nonrandomized studies showed moderate reliability and promising validity. *J Clin Epidemiol*. 2013;66(4):408-414.
- Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *Lancet (London, England)*. 2020;395(10239):1771-1778.

10. Belhadjer Z, Méot M, Bajolle F, et al. Acute heart failure in multi system inflammatory syndrome in children (MIS-C) in the context of global SARS-CoV-2 pandemic. *Circulation*. 2020;142(5):429-436.
11. Waltuch T, Gill P, Zinns LE, et al. Features of COVID-19 post-infectious cytokine release syndrome in children presenting to the emergency department. *Am J Emerg Med*. 2020;38:2246.e3-2246.e6.
12. Chiotos K, Bassiri H, Behrens EM, et al. Multisystem inflammatory syndrome in children during the COVID-19 pandemic: a case series. *J Pediatric Infect Dis Soc*. 2020;9(3):393-398.
13. Grimaud M, Starck J, Levy M, et al. Acute myocarditis and multi system inflammatory emerging disease following SARS-CoV-2 infection in critically ill children. *Ann Intensive Care*. 2020;10(1):69.
14. Toubiana J, Poirault C, Corsia A, et al. Kawasaki-like multisystem inflammatory syndrome in children during the COVID-19 pandemic in Paris, France: prospective observational study. *BMJ*. 2020;369:m2094.
15. Miller J, Cantor A, Zachariah P, Ahn D, Martinez M, Margolis K. Gastrointestinal symptoms as a major presentation component of a novel multisystem inflammatory syndrome in children (MIS-C) that is related to COVID-19: a single center experience of 44 cases. *Gastroenterology*. 2020;159(4):1571-1574.
16. Whittaker E, Bamford A, Kenny J, et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. *JAMA*. 2020;324(3):259-269.
17. Cheung EW, Zachariah P, Gorelik M, et al. Multisystem inflammatory syndrome related to COVID-19 in previously healthy children and adolescents in New York City. *JAMA*. 2020;24(3):294-296.
18. Blondiaux E, Parisot P, Redheuil A, et al. Cardiac MRI of children with multisystem inflammatory syndrome (MIS-C) associated with COVID-19: case series. *Radiology*. 2020:202288.
19. Pouletty M, Borocco C, Ouldali N, et al. Paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 mimicking Kawasaki disease (Kawa-COVID-19): a multicentre cohort. *Ann Rheum Dis*. 2020;79(8):999-1006.
20. Ramcharan T, Nolan O, Lai CY, et al. Paediatric inflammatory multi system syndrome: temporally associated with SARS-CoV-2 (PIMS-TS): cardiac features, management and short-term outcomes at a UK Tertiary Paediatric Hospital. *Pediatr Cardiol*. 2020;41(7):1391-1401.
21. Kaushik S, Aydin SI, Derespina KR, et al. Multisystem inflammatory syndrome in children (MIS-C) associated with SARS-CoV-2 infection: a multi-institutional study from New York City. *J Pediatr*. 2020;224:24-29.
22. Capone CA, Subramony A, Sweberg T, et al. Characteristics, cardiac involvement, and outcomes of multisystem inflammatory disease of childhood (MIS-C) associated with SARS-CoV-2 infection. *J Pediatr*. 2020;224:141-145.
23. Ng KF, Kothari T, Bandi S, et al. COVID-19 multisystem inflammatory syndrome in three teenagers with confirmed SARS-CoV-2 infection. *J Med Virol*. 2020;92:2880-2886.
24. Riollano-Cruz M, Akkoyun E, Briceno-Brito E, et al. Multisystem inflammatory syndrome in children (MIS-C) related to COVID-19: a New York City experience. *J Med Virol*. 2020;jmv.26224.
25. Belot A, Antona D, Renolleau S, et al. SARS-CoV-2-related paediatric inflammatory multisystem syndrome, an epidemiological study, France, 1 March to 17 May 2020. *Euro Surveill*. 2020;25(22):2001010.
26. Hameed S, Elbaaly H, Reid CEL, et al. Spectrum of imaging findings on chest radiographs, US, CT, and MRI images in multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19. *Radiology*. 2020;298:202543-E10.
27. Schupper AJ, Yaeger KA, Morgenstern PF. Neurological manifestations of pediatric multi-system inflammatory syndrome potentially associated with COVID-19. *Child's Nervous System: ChNS: Official Journal of the International Society for Pediatric Neurosurgery*. 2020;36(8):1579-1580.
28. Dufort EM, Koumans EH, Chow EJ, et al. Multisystem inflammatory syndrome in children in New York State. *N Engl J Med*. 2020;383(4):347-358.
29. Feldstein LR, Rose EB, Horwitz SM, et al. Multisystem inflammatory syndrome in U.S. children and adolescents. *N Engl J Med*. 2020;383(4):334-346.
30. Abdel-Mannan O, Eyre M, Löbel U, et al. Neurologic and radiographic findings associated with COVID-19 infection in children. *JAMA neurology*. 2020;77:e202687.
31. Davies P, Evans C, Kanthimathinathan HK, et al. Intensive care admissions of children with paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) in the UK: a multicentre observational study. *The Lancet Child & Adolescent Health*. 2020;4(9):669-677.
32. Rogo T, Mathur K, Purswani M. Systemic inflammation with cardiac involvement in pediatric patients with evidence of COVID-19 in a community hospital in the Bronx, NY. *J Pediatric Infect Dis Soc*. 2020;9(4):502-503.
33. Lee PY, Day-Lewis M, Henderson LA, et al. Distinct clinical and immunological features of SARS-CoV-2-induced multisystem inflammatory syndrome in children. *J Clin Invest*. 2020;130(11):5942-5950.
34. Moraleda C, Serna-Pascual M, Soriano-Arandes A, et al. Multi-inflammatory syndrome in children related to SARS-CoV-2 in Spain. *Clin Infect Dis*. 2020.
35. Godfred-Cato S, Bryant B, Leung J, et al. COVID-19-associated multisystem inflammatory syndrome in children United States, March-July 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(32):1074-1080.
36. Abrams JY, Godfred-Cato SE, Oster ME, et al. Multisystem inflammatory syndrome in children associated with severe acute respiratory syndrome coronavirus 2: a systematic review. *J Pediatr*. 2020;226:45-54.e41.
37. Lu X, Zhang L, Du H, et al. SARS-CoV-2 infection in Children. *N Engl J Med*. 2020;382(17):1663-1665.
38. Dong Y, Mo X, Hu Y, et al. Epidemiology of COVID-19 among children in China. *Pediatrics*. 2020;145(6):e20200702.
39. Shekerdemian LS, Mahmood NR, Wolfe KK, et al. Characteristics and outcomes of children with coronavirus disease 2019 (COVID-19) infection admitted to US and Canadian pediatric intensive care units. *JAMA pediatrics*. 2020;174(9):868-873.
40. Zachariah P, Johnson CL, Halabi KC, et al. Epidemiology, clinical features, and disease severity in patients with coronavirus disease 2019 (COVID-19) in a Children's Hospital in New York City, New York. *JAMA Pediatrics*. 2020;174:e202430.
41. Arentz M, Yim E, Klaff L, et al. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State. *JAMA*. 2020;323(16):1612-1614.
42. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054-1062.
43. Chao JY, Derespina KR, Herold BC, et al. Clinical characteristics and outcomes of hospitalized and critically ill children and adolescents with coronavirus disease 2019 at a Tertiary Care Medical Center in New York City. *J Pediatr*. 2020;223:14-19.e12.
44. Nino G, Zember J, Sanchez-Jacob R, Gutierrez MJ, Sharma K, Linguraru MG. Pediatric lung imaging features of COVID-19: a systematic review and meta-analysis. *Pediatr Pulmonol*. 2020;56:252-263.
45. Ae R, Makino N, Kosami K, Kuwabara M, Matsubara Y, Nakamura Y. Epidemiology, treatments, and cardiac complications in patients with Kawasaki disease: the nationwide survey in Japan, 2017-2018. *J Pediatr*. 2020;225:23-29.

46. Shulman ST. Pediatric coronavirus disease-2019-associated multi system inflammatory syndrome. *J Pediatric Infect Dis Soc.* 2020;9(3): 285-286.
47. Goyal MK, Simpson JN, Boyle MD, et al. Racial/ethnic and socio economic disparities of SARS-CoV-2 infection among children. *Pediatrics.* 2020;146(4):e2020009951.
48. Li Y, Zheng Q, Zou L, et al. Kawasaki disease shock syndrome: clinical characteristics and possible use of IL-6, IL-10 and IFN- γ as biomarkers for early recognition. *Pediatr Rheumatol Online J.* 2019;17(1):1.
49. Kanegaye JT, Wilder MS, Molkara D, et al. Recognition of a Kawasaki disease shock syndrome. *Pediatrics.* 2009;123(5):e783-e789.
50. Gámez-González LB, Murata C, Muñoz-Ramírez M, Yamazaki-Nakashimada M. Clinical manifestations associated with Kawasaki disease shock syndrome in Mexican children. *Eur J Pediatr.* 2013; 172(3):337-342.
51. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review. *JAMA.* 2020;323(18):1824-1836.
52. Cavalli G, De Luca G, Campochiaro C, et al. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. *The Lancet Rheumatology.* 2020;2(6):e325-e331.
53. Luo P, Liu Y, Qiu L, Liu X, Liu D, Li J. Tocilizumab treatment in COVID-19: a single center experience. *J Med Virol.* 2020;92(7): 814-818.
54. Toniati P, Piva S, Cattalini M, et al. Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: a single center study of 100 patients in Brescia, Italy. *Autoimmun Rev.* 2020;19(7):102568.
55. Miura M, Kobayashi T, Igarashi T, et al. Real-world safety and effectiveness of infliximab in pediatric patients with acute Kawasaki disease: a postmarketing surveillance in Japan (SAKURA study). *Pediatr Infect Dis J.* 2020;39(1):41-47.
56. Burns JC, Mason WH, Hauger SB, et al. Infliximab treatment for refractory Kawasaki syndrome. *J Pediatr.* 2005;146(5):662-667.
57. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of COVID-19 - preliminary report. *N Engl J Med.* 2020;383: 1813-1826.
58. Grein J, Ohmagari N, Shin D, et al. Compassionate use of remdesivir for patients with severe COVID-19. *N Engl J Med.* 2020;382(24): 2327-2336.
59. Yokoyama Y, Briasoulis A, Takagi H, Kuno T. Effect of remdesivir on patients with COVID-19: a network meta-analysis of randomized control trials. *Virus Res.* 2020;288:198137.
60. Nakamura Y, Yanagawa H, Harada K, Kato H, Kawasaki T. Mortality among persons with a history of Kawasaki disease in Japan: the fifth look. *Arch Pediatr Adolesc Med.* 2002;156(2):162-165.
61. McCrindle BW, Manlhiot C, Newburger JW, et al. Medium-term complications associated with coronary artery aneurysms after Kawasaki disease: a study From the International Kawasaki Disease Registry. *J Am Heart Assoc.* 2020;9(15):e016440.
62. Inciardi RM, Lupi L, Zaccone G, et al. Cardiac involvement in a patient with coronavirus disease 2019 (COVID-19). *JAMA cardiology.* 2020;5(7):1-6.
63. Aikawa T, Takagi H, Ishikawa K, Kuno T. Myocardial injury characterized by elevated cardiac troponin and in-hospital mortality of COVID-19: An insight from a meta-analysis. *J Med Virol.* 2020; jmv.26108.
64. Kuno T, Takahashi M, Obata R, Maeda T. Cardiovascular comorbidities, cardiac injury, and prognosis of COVID-19 in New York City. *Am Heart J.* 2020;226:24-25.
65. Shi S, Qin M, Shen B, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA cardiology.* 2020;5(7):802-810.
66. Guo T, Fan Y, Chen M, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA cardiology* (2020;5(7):811-818.
67. Chen C, Zhou Y, Wang DW. SARS-CoV-2: a potential novel etiology of fulminant myocarditis. *Herz.* 2020;45(3):230-232.
68. Kang S, Tanaka T, Inoue H, et al. IL-6 trans-signaling induces plasminogen activator inhibitor-1 from vascular endothelial cells in cytokine release syndrome. *Proc Natl Acad Sci USA.* 2020;117(36): 22351-22356.
69. Furukawa S, Matsubara T, Juhoh K, et al. Peripheral blood monocyte/macrophages and serum tumor necrosis factor in Kawasaki disease. *Clin Immunol Immunopathol.* 1988;48(2):247-251.
70. Radia T, Williams N, Agrawal P, et al. Multi-system inflammatory syndrome in children & adolescents (MIS-C): a systematic review of clinical features and presentation. *Paediatr Respir Rev.* 2020.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Yasuhara J, Watanabe K, Takagi H, Sumitomo N, Kuno T. COVID-19 and multisystem inflammatory syndrome in children: A systematic review and meta-analysis. *Pediatric Pulmonology.* 2021;56:837-848. <https://doi.org/10.1002/ppul.25245>