JAMA | Original Investigation

Characteristics and Outcomes of US Children and Adolescents With Multisystem Inflammatory Syndrome in Children (MIS-C) Compared With Severe Acute COVID-19

Leora R. Feldstein, PhD; Mark W. Tenforde, MD; Kevin G. Friedman, MD; Margaret Newhams, MPH; Erica Billig Rose, PhD; Heda Dapul, MD; Vijaya L. Soma, MD; Aline B. Maddux, MD; Peter M. Mourani, MD; Cindy Bowens, MD; Mia Maamari, MD; Mark W. Hall, MD; Becky J. Riggs, MD; John S. Giuliano Jr, MD; Aalok R. Singh, MD; Simon Li, MD; Michele Kong, MD; Jennifer E. Schuster, MD; Gwenn E. McLaughlin, MD; Stephanie P. Schwartz, MD; Tracie C. Walker, MD; Laura L. Loftis, MD; Charlotte V. Hobbs, MD; Natasha B. Halasa, MD; Sule Doymaz, MD; Christopher J. Babbitt, MD; Janet R. Hume, MD; Shira J. Gertz, MD; Katherine Irby, MD; Katharine N. Clouser, MD; Natalie Z. Cvijanovich, MD; Tamara T. Bradford, MD; Lincoln S. Smith, MD; Sabrina M. Heidemann, MD; Sheemon P. Zackai, MD; Kari Wellnitz, MD; Ryan A. Nofziger, MD; Steven M. Horwitz, MD; Ryan W. Carroll, MD; Courtney M. Rowan, MD; Keiko M. Tarquinio, MD; Elizabeth H. Mack, MD; Julie C. Fitzgerald, MD; Bria M. Coates, MD; Ashley M. Jackson, MPH; Cameron C. Young; Mary Beth F. Son, MD; Manish M. Patel, MD; Jane W. Newburger, MD; Adrienne G. Randolph, MD; for the Overcoming COVID-19 Investigators

IMPORTANCE Refinement of criteria for multisystem inflammatory syndrome in children (MIS-C) may inform efforts to improve health outcomes.

OBJECTIVE To compare clinical characteristics and outcomes of children and adolescents with MIS-C vs those with severe coronavirus disease 2019 (COVID-19).

SETTING, DESIGN, AND PARTICIPANTS Case series of 1116 patients aged younger than 21 years hospitalized between March 15 and October 31, 2020, at 66 US hospitals in 31 states. Final date of follow-up was January 5, 2021. Patients with MIS-C had fever, inflammation, multisystem involvement, and positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) reverse transcriptase–polymerase chain reaction (RT-PCR) or antibody test results or recent exposure with no alternate diagnosis. Patients with COVID-19 had positive RT-PCR test results and severe organ system involvement.

EXPOSURE SARS-CoV-2.

MAIN OUTCOMES AND MEASURES Presenting symptoms, organ system complications, laboratory biomarkers, interventions, and clinical outcomes. Multivariable regression was used to compute adjusted risk ratios (aRRs) of factors associated with MIS-C vs COVID-19.

RESULTS Of 1116 patients (median age, 9.7 years; 45% female), 539 (48%) were diagnosed with MIS-C and 577 (52%) with COVID-19. Compared with patients with COVID-19, patients with MIS-C were more likely to be 6 to 12 years old (40.8% vs 19.4%; absolute risk difference [RD], 21.4% [95% CI, 16.1%-26.7%]; aRR, 1.51 [95% CI, 1.33-1.72] vs 0-5 years) and non-Hispanic Black (32.3% vs 21.5%; RD, 10.8% [95% CI, 5.6%-16.0%]; aRR, 1.43 [95% CI, 1.17-1.76] vs White). Compared with patients with COVID-19, patients with MIS-C were more likely to have cardiorespiratory involvement (56.0% vs 8.8%; RD, 47.2% [95% CI, 42.4%-52.0%]; aRR, 2.99 [95% CI, 2.55-3.50] vs respiratory involvement), cardiovascular without respiratory involvement (10.6% vs 2.9%; RD, 7.7% [95% CI, 4.7%-10.6%]; aRR, 2.49 [95% CI, 2.05-3.02] vs respiratory involvement), and mucocutaneous without cardiorespiratory involvement (7.1% vs 2.3%; RD, 4.8% [95% CI, 2.3%-7.3%]; aRR, 2.29 [95% CI, 1.84-2.85] vs respiratory involvement). Patients with MIS-C had higher neutrophil to lymphocyte ratio (median, 6.4 vs 2.7, $P < .001$), higher C-reactive protein level (median, 152 mg/L vs 33 mg/L; $P < .001$), and lower platelet count (<150 $\times 10^3$ cells/μL [212/523 {41%} vs 84/486 {17%}, $P < .001$]). A total of 398 patients (73.8%) with MIS-C and 253 (43.8%) with COVID-19 were admitted to the intensive care unit, and 10 (1.9%) with MIS-C and 8 (1.4%) with COVID-19 died during hospitalization. Among patients with MIS-C with reduced left ventricular systolic function (172/503, 34.2%) and coronary artery aneurysm (57/424, 13.4%), an estimated 91.0% (95% CI, 86.0%-94.7%) and 79.1% (95% CI, 67.1%-89.1%), respectively, normalized within 30 days.

CONCLUSIONS AND RELEVANCE This case series of patients with MIS-C and with COVID-19 identified patterns of clinical presentation and organ system involvement. These patterns may help differentiate between MIS-C and COVID-19.

JAMA. doi:10.1001/jama.2021.2091
Published online February 24, 2021.

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: A complete list of the Overcoming COVID-19 Investigators is provided in the eAppendix in the Supplement.

Corresponding Author: Adrienne G. Randolph, MD, Boston Children's Hospital, 300 Longwood Ave, Bader 634, Boston, MA 02115 (adrienne.randolph@childrens.harvard.edu).

International reports of coronavirus disease 2019 (COVID-19)–related severe complications in children began in April 2020 when predominantly healthy children were hospitalized with cardiogenic shock or Kawasaki disease–like presentations temporally associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.[1-3] In mid-May 2020, the Centers for Disease Control and Prevention (CDC) published a case definition for multisystem inflammatory syndrome in children (MIS-C) for disease surveillance.[4] Criteria were intentionally broad to facilitate data capture for diagnostic refinement. MIS-C was hypothesized to be mostly postinfectious and distinct from COVID-19 because many patients' respiratory specimens were SARS-CoV-2 negative and MIS-C peaked after reported COVID-19 cases.[5,6] Cardiovascular complications, such as ventricular dysfunction and coronary artery aneurysms, triggered recommendations for immunomodulatory treatments, including intravenous immunoglobulin (IVIG), corticosteroids, and biologics, and recommendations for intensive cardiac observation.[5-9]

Data on hospitalized children and adolescents with severe acute COVID-19 are sparse, with few reports including more than 100 severe cases,[5,8,10-15] and even fewer of these comparing COVID-19 with MIS-C.[8,11] As disease surveillance captured more patients with MIS-C, phenotypes within MIS-C emerged, including a predominantly respiratory phenotype with frequent SARS-CoV-2–positive respiratory testing that potentially overlapped with severe acute COVID-19.[8,14] A comparison of organ involvement in MIS-C with severe acute COVID-19 in children and adolescents, including the timing of resolution of cardiorespiratory dysfunction, could help refine the MIS-C case definition to improve specificity for guiding use of immune therapies, diagnostic testing, and follow-up.

Sentinel surveillance data captured on US patients hospitalized for 8 months were used to compare children and adolescents diagnosed with MIS-C vs those with severe acute COVID-19. Differences in the epidemiology, clinical characteristics, types of complications, as well as hospital and postdischarge outcomes were compared between these groups to identify features distinguishing MIS-C from COVID-19.

Key Points

Question How do the characteristics and outcomes of children and adolescents with multisystem inflammatory syndrome in children (MIS-C) compare with severe coronavirus disease 2019 (COVID-19)?

Findings In this case series that included 539 patients with MIS-C and 577 patients with severe COVID-19, patients with MIS-C were more likely than those with severe COVID-19 to be 6 to 12 years old, be non-Hispanic Black, and have severe cardiovascular or mucocutaneous involvement and more extreme inflammation.

Meaning The study findings suggest patterns of clinical presentation and organ involvement that distinguish between patients with MIS-C and severe acute COVID-19.

Methods

Study Design and Participants

For this case series, active surveillance was performed in the Overcoming COVID-19 network to identify children, adolescents, and young adults (<21 years of age) with SARS-CoV-2–related illness hospitalized during March 15 to October 31, 2020, from 31 states.[5] The last date of follow-up for outcomes was January 5, 2021. The study was approved by the central institutional review board at Boston Children's Hospital. The study was reviewed by the CDC and was conducted consistent with applicable federal law and CDC policy, which included a waiver of consent.[16]

Case Ascertainment and Definitions

Patients from the registry were included if they were hospitalized for acute illness at a participating site, were younger than 21 years old, and met criteria for MIS-C or severe acute COVID-19 (henceforth referred to as COVID-19), after adjudication by site and coordinating center principal investigators. MIS-C criteria were consistent with the CDC definition[17] (**Box 1**). Patients with COVID-19 had evidence of recent infection with SARS-CoV-2 based on having a positive RT-PCR test result and severe involvement of 1 or more organ systems (**Box 2**). Sites that included patients in other reports comparing COVID-19 and MIS-C or reporting cardiac outcomes (n ≤191) are listed in eTable 1 in the Supplement and include 168 patients with MIS-C we previously reported.[5]

We collected race and ethnicity information from hospital medical records as reported by the site clinicians who cared for the patients. Obesity was classified either by clinician diagnosis or, given underreporting,[5] based on national reference standards for body mass index if aged at least 2 years.[20] We classified nonobese patients without chronic diagnoses or use of prescription medications as having no underlying conditions. Mucocutaneous involvement was defined as presence of any of the following: rash, inflammation of the oral mucosa, conjunctivitis, and extremity findings, including erythema or edema of the hands or feet, or periungual peeling. Echocardiographic findings during hospitalization and postdischarge were obtained from medical records. Left ventricular (LV) ejection fraction (EF) was categorized as normal if EF was 55% or greater or noted to be qualitatively normal, or as depressed if EF was less than 55% or, in cases where EF was unavailable, based on the qualitative grade of dysfunction. LV systolic function was further classified based on lowest EF as mildly depressed if 45% to 54%, moderately depressed if 35% to 44%, and severely depressed if less than 35%.[21] Patients were classified as having no coronary artery aneurysm if the largest body surface area–adjusted *z* scores in the proximal right coronary artery and proximal left anterior descending coronary artery both were less than 2.5 or were reported as qualitatively normal. Patients were classified as having coronary artery aneurysms if either the right coronary artery or left anterior descending *z* score was 2.5 or greater or they were described as having an aneurysm qualitatively.[22] Aneurysms were categorized as small if the *z* score was 2.5 to less than 5.0, medium if the *z* score was 5.0 to less than 10.0, and large or giant if the *z* score was 10.0 or greater or an absolute dimension of 8 mm or more.[22] Each unique patient with 1 or more echocardiogram reports that could be evaluated was classified on the

basis of their worst-ever LVEF and highest coronary *z* score during the illness. Respiratory support and cardiovascular pediatric Severe Organ Failure Assessment scores based on vasoactive agent support were also documented throughout hospitalization (eTable 2 in the Supplement).[23]

Outcomes

We compared demographics (age, sex, race/ethnicity), underlying medical conditions, presenting symptoms and signs, laboratory values within 48 hours of admission, severe complications, and clinical outcomes and interventions between patients in the registry diagnosed with MIS-C vs COVID-19. We selected commonly tested laboratory values with values on at least 70% of patients (absolute lymphocyte count, absolute neutrophil count, neutrophil to lymphocyte ratio [NLR], platelet count, hemoglobin level, alanine aminotransferase level, C-reactive protein [CRP] level, and albumin level) or of relevance to MIS-C (B-type natriuretic peptide [BNP] or N-terminal-proBNP) based on past studies.[10,14] Initial measurements of inflammatory or hematologic biomarkers (NLR, CRP, and platelets) within the first 2 days of admission were used. Laboratory cutoffs were dichotomized based on the cutoff for thrombocytopenia or around median baseline values in the full cohort (CRP and NLR).[24] We were unable to conduct a planned comparison of RT-PCR and antibody testing differences between patients with MIS-C and COVID-19 because few patients (12%) with acute COVID-19 received antibody testing. Based on emerging evidence from small case series and 1 latent class analysis,[8,11,14] we evaluated differences in 5 mutually exclusive severe organ involvement subcategories of MIS-C and COVID-19: (1) cardiorespiratory involvement, (2) cardiovascular without respiratory involvement, (3) respiratory without cardiovascular involvement, (4) mucocutaneous without cardiovascular or respiratory involvement, and (5) other organ system involvement without cardiovascular, respiratory, or mucocutaneous involvement. We compared invasive mechanical ventilator support and vasoactive agent scores by day of hospitalization among patients with MIS-C vs COVID-19. Among patients with MIS-C, we evaluated the resolution of cardiac dysfunction over time among those with reduced LVEF or coronary artery aneurysms.

Statistical Analysis

For univariate comparisons between patients with MIS-C and COVID-19, we used the χ^2 test for categorical variables, Fisher exact test for variables with small sample sizes (n <5), or Kruskal-Wallis test for continuous variables. We used bivariable analysis to evaluate differences in the 5 mutually exclusive severe organ involvement subcategories of MIS-C and COVID-19.

We compared the association of selected baseline patient demographic and clinical characteristics with the diagnosis of MIS-C vs COVID-19 by fitting a Poisson regression with robust variance estimates to generate risk ratios.[25] Patient baseline demographic and clinical characteristics were selected based on whether there were meaningful differences in bivariable analyses between MIS-C and COVID-19 diagnoses.[5,11,14] To evaluate whether clinicians were ascribing a diagnosis of MIS-C vs COVID-19 based on clinical syndrome or laboratory features, we also evaluated the association between described severe organ involvement subcategories and laboratory markers of inflammation or hematologic dysfunction with less than 30% overall missingness within the first 2 days of admission.[14] Models were adjusted for age (0-5 years, 6-12 years, and 13-20 years), race/ethnicity (non-Hispanic White, non-Hispanic Black, other non-Hispanic, or Hispanic of any race), sex, US Census region to account for between-region differences, and presence of 1 or more vs no underlying conditions. Model convergence was evaluated using the GENMOD function in SAS. Risk differences were calculated using the adjrr command in Stata.[26]

We assessed cardiac outcomes using Kaplan-Meier estimates up to 90 days after hospital admission (when available) among patients with MIS-C and cardiac involvement. For patients with MIS-C and a diagnosis of coronary artery aneurysm or reduced LVEF, resolution was plotted using Kaplan-Meier curves. Patients were censored when resolution was documented or, if resolution was not confirmed, by date of last echocardiographic evaluation. For patients with MIS-C and COVID-19, the percentages receiving invasive mechanical ventilation and vasoactive agents were plotted graphically throughout the hospitalization. Missing data were not imputed for common laboratory markers of interest. Statistical significance was designated as $P < .05$ (2-sided). Because of the potential for type I error due to multiple comparisons, findings for analyses should be interpreted as exploratory. Analyses were conducted in R version 3.6.1 (R Project for Statistical Computing), Stata version 16.0 (StataCorp), and SAS version 9.4 (SAS Institute).

Box 1. Centers for Disease Control and Prevention Case-Definition for MIS-C[a]

- Age <21 y
- Fever ≥38.0 °C for ≥24 h or report of subjective fever lasting ≥24 h
- Laboratory evidence of inflammation[b]
- Evidence of clinically severe illness requiring hospitalization with multisystem (≥2) organ involvement (cardiac, kidney, respiratory, hematologic, gastrointestinal, dermatologic, or neurological)
- No alternative plausible diagnoses
- Positive for current or recent SARS-CoV-2 infection by RT-PCR, antibody, or antigen test; or exposure to a suspected or confirmed COVID-19 case within the 4 wk prior to the onset of symptoms[c]

Abbreviations: COVID-19, coronavirus disease 2019; MIS-C, multisystem inflammatory syndrome in children; RT-PCR, reverse transcriptase–polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a] Must meet all criteria after adjudication by site and coordinating center principal investigators.

[b] Including, but not limited to, 1 or more of the following: an elevated C-reactive protein, erythrocyte sedimentation rate, fibrinogen, procalcitonin, D-dimer, ferritin, lactate dehydrogenase, interleukin 6, elevated neutrophils, reduced lymphocytes, and low albumin level.

[c] Patients without a positive SARS-CoV-2 test result were excluded after May 31, 2020, when site RT-PCR and antibody testing was more available.

Results

Demographics and Clinical Characteristics Among All Patients

From March 15 to October 31, 2020, 1314 hospitalized children and adolescents younger than 21 years of age with

Box 2. Case-Definition for Severe Acute COVID-19[a,b]

- Admitted to the hospital with symptoms suspected to be related to COVID-19
- Evidence of infection with SARS-CoV-2 based on a positive RT-PCR test result during current illness
- Severe organ system involvement including at least 1 of the following:

Respiratory
- Receipt of mechanical ventilation or any type of supplemental oxygen (or increased support for patients receiving respiratory support at baseline)
- Severe bronchospasm requiring continuous bronchodilators
- Pulmonary infiltrates on chest radiograph
- Lower respiratory infection
- Pleural effusion
- Pneumothorax or other signs of barotrauma
- Pulmonary hemorrhage
- Chest tube or drainage required

Cardiovascular
- Cardiac dysrhythmia or arrhythmia
- Ejection fraction <55%
- Pulmonary edema due to left heart failure
- Coronary artery aneurysm (LAD or RCA *z* score ≥2.5)
- B-type natriuretic peptide ≥1000 pg/mL[2]
- Elevated troponin-based on the upper limit of normal for the site laboratory
- Receipt of vasopressor or vasoactive support
- Receipt of cardiopulmonary resuscitation or ECMO support

Kidney
- Receipt of dialysis (for patients without chronic kidney failure)
- Acute kidney injury[c] (in patients without prior kidney disease)

Neurologic
- Stroke or acute intracranial hemorrhage
- Seizures
- Coma
- Encephalitis, aseptic meningitis, or demyelinating disorder (eg, acute disseminated encephalomyelitis) diagnosed by a neurologist
- Decreased hearing or vision
- Iritis or uveitis

Gastrointestinal
- Appendicitis
- Pancreatitis
- Hepatitis or hepatomegaly
- Gallbladder hydrops or edema
- Other complications as determined by site clinicians included ileitis, colitis, or mesenteric adenitis

Hematologic
- Absolute lymphocyte count <1 ×10^3 cells/μL
- Absolute neutrophil count <0.5 ×10^3 cells/μL excluding chemotherapy patients[3]
- Severe anemia[d]
- Platelet count <50 000/μL[4]
- Deep vein thrombosis
- Pulmonary embolism
- Hemolysis
- Bleeding
- Ischemia of an extremity
- Other complications as determined by site clinicians included hemolytic uremic syndrome, anemia requiring transfusion, and pancytopenia

Abbreviations: COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; LAD, left anterior descending; MIS-C, multisystem inflammatory syndrome in children; RCA, right coronary artery; RT-PCR, reverse transcriptase–polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a] Must meet all criteria. On August 13, 2020, the registry was restricted to patients admitted to the intensive care unit or high-acuity stepdown unit for patients without MIS-C.

[b] Case definition was created by clinical consensus among the Overcoming COVID-19 steering committee principal investigators.

[c] Acute kidney injury was defined as a creatinine level equal to or above the following values by age[18]: less than 4 weeks: 1.59 mg/dL; 4 weeks to less than 1 year: 0.62 mg/dL; 1 to 10 years: 1.13 mg/dL; and ≥11 years: >1.59 mg/dL.

[d] Severe anemia was defined as hemoglobin level less than 7 g/dL among children younger than 59 months of age, otherwise hemoglobin level less than 8 g/dL.[19]

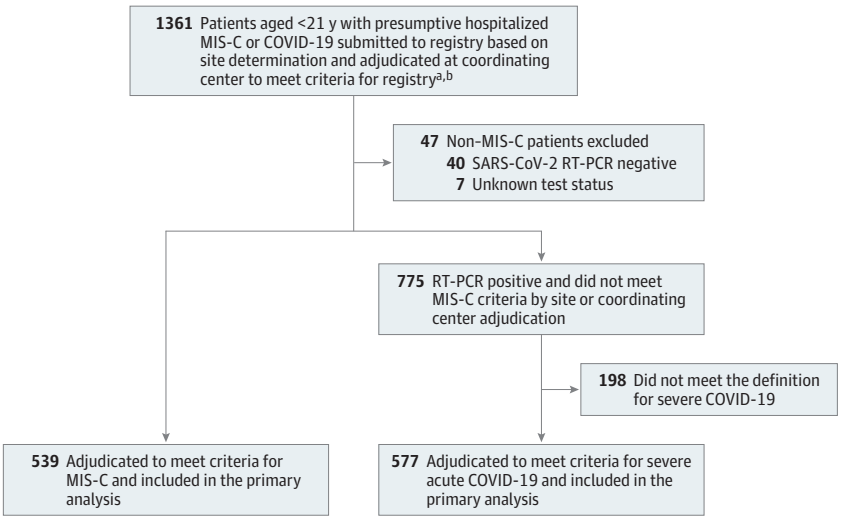
COVID-19-related illness were reported from 66 hospitals in 31 states (eTable 3 in the Supplement). Of 775 children and adolescents (59%) without a diagnosis of MIS-C, 198 were excluded because they did not meet prespecified criteria for severe COVID-19 (**Figure 1**). Of the 1116 cases included in the final analysis, 539 (48%) were classified as MIS-C and 577 (52%) as acute COVID-19 (Figure 1). In patients with MIS-C, 52% had a positive SARS-CoV-2 RT-PCR test result, 45% were SARS-CoV-2 antibody positive only, 31% were positive for both, and 19% did not have an antibody test performed (eTable 4 in the Supplement). By definition, results of all patients with COVID-19 were SARS-CoV-2 RT-PCR positive but only 12% received antibody testing (60% [43/72] positive).

Compared with patients with COVID-19, those with MIS-C were younger, more likely to be non-Hispanic Black, and less likely to have 1 or more chronic medical conditions (**Table 1**). Presenting symptoms and signs were similar among patients with MIS-C and COVID-19 with the exception of mucocutaneous findings (66.8% [95% CI, 63%-71%] vs 10.2% [95% CI, 8%-13%]; $P < .001$), which were uncommon in patients with COVID-19 and prevalent in those with MIS-C (Table 1). IVIG was administered to 77% of patients with MIS-C (78% of whom also received systemic steroids; 9% received steroids alone) compared with 4% of patients with COVID-19 (**Table 2**). Ten patients (1.9%) with MIS-C vs 8 (1.4%) with COVID-19 died during hospitalization (described in eTable 5 in the Supplement).

Inflammation and Severe Organ System Involvement

Eighty percent of patients with MIS-C and COVID-19 each had severe respiratory involvement; however, more patients with MIS-C had cardiac involvement (66.7% [95% CI, 63%-71%]) compared with patients with COVID-19 (11.8% [95% CI,

Figure 1. Eligibility Flowchart of Hospitalized Patients With COVID-19–Related Illness, March 15-October 31, 2020



COVID-19 indicates coronavirus disease 2019; RT-PCR, reverse transcriptase–polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; and MIS-C, multisystem inflammatory syndrome in children.

[a] Registry data was based on voluntary case reporting by participating sentinel surveillance sites.

[b] Criteria for registry: meet case definition for MIS-C (Box 1) or evidence of infection with SARS-CoV-2 based on a positive RT-PCR test result during current illness with clinical suspicion for acute COVID-19.

9%-15%]) (Table 2). On laboratory testing within 48 hours of admission, patients with MIS-C had a higher median NLR (6.4 vs 2.7, $P < .001$) and CRP level (152 mg/L vs 33 mg/L, $P < .001$) and more thrombocytopenia (platelets <150 $\times 10^3$ cells/μL) than patients with COVID-19 (41% vs 17%, $P < .001$).

Factors Distinguishing MIS-C vs Severe Acute COVID-19 in Multivariable Model

Compared with patients with COVID-19, patients diagnosed with MIS-C were more likely to be 6 to 12 years old (40.8% vs 19.4%; absolute risk difference [RD], 21.4% [95% CI, 16.1%-26.7%]), be non-Hispanic Black (32.3% vs 21.5%; RD, 10.8% [95% CI, 5.6%-16.0%]), and have no underlying conditions (69.0% vs 37.9%; RD, 31.1% [95% CI, 25.5%-36.6%]) (**Figure 2**A). Adjusting for other covariates, risk of MIS-C diagnosis was higher for patients aged 6 to 12 years vs 0 to 5 years (aRR, 1.51 [95% CI, 1.33-1.72]) and patients who were non-Hispanic Black vs White (aRR, 1.43 [95% CI, 1.17-1.76]). Certain clinical syndromes and laboratory features were also associated with diagnosis of MIS-C vs COVID-19 (Figure 2B). Compared with COVID-19, patients with MIS-C were more likely to have cardiorespiratory involvement (56.0% vs 8.8%; RD, 47.2% [95% CI, 42.4%-52.0%]), cardiovascular without respiratory involvement (10.6% vs 2.9%; RD, 7.7% [95% CI, 4.7%-10.6%]), and mucocutaneous without cardiorespiratory involvement (7.1% vs 2.3%; RD, 4.8% [95% CI, 2.3%-7.3%]). Compared with patients with respiratory involvement alone, MIS-C diagnosis was more likely in patients with cardiorespiratory involvement (aRR, 2.99 [95% CI, 2.55-3.50]), cardiovascular without respiratory involvement (aRR, 2.49 [95% CI, 2.05-3.02]), and mucocutaneous without cardiorespiratory involvement (aRR, 2.29 [95% CI, 1.84-2.85]).

Additionally, patients with an NLR greater than 5, platelet count less than 150 $\times 10^3$/μL, and CRP level greater than 100 mg/L within 48 hours of admission were more likely to be diagnosed with MIS-C. In contrast, patients with COVID-19 were more likely to have 1 or more underlying conditions; respiratory without cardiovascular involvement; or hematologic, neurologic, or gastrointestinal involvement without cardiovascular, respiratory, or mucocutaneous involvement. The regression model RDs are shown in eTable 6 in the Supplement. The number of patients excluded from the regression analyses varied based on the variables included in the model and ranged from 0 to 340 (depending on the laboratory marker of interest).

RT-PCR and Antibody Status by Clinical Subphenotype

The results of 92% of patients with severe respiratory involvement without cardiovascular involvement and 95% with hematologic, neurologic, or gastrointestinal severe involvement without severe respiratory or cardiovascular involvement were RT-PCR positive. Antibody positivity within these groups was 21% and 10%, respectively; however, 74% and 86% were not tested (details in eTable 7 in the Supplement). RT-PCR positivity was observed in fewer patients with severe cardiovascular involvement (range, 57%-58%) and mucocutaneous involvement without cardiovascular or respiratory involvement (45%) (details in eTable 7 in the Supplement).

The results from most patients with severe cardiorespiratory involvement, severe cardiovascular without respiratory involvement, and mucocutaneous without cardiorespiratory involvement were antibody positive (69%, 74%, and 61%, respectively, with 74%, 77%, and 71% tested). Comparing only patients with MIS-C by SARS-CoV-2 status, RT-PCR–positive and –negative patients with positive SARS-CoV-2 antibody results had similar demographic and clinical characteristics and outcomes (eTable 8 in the Supplement).

Respiratory Support and Vasoactive Agent Utilization

For patients who had data available on respiratory support, 9% of patients with MIS-C vs 10% with COVID-19 received invasive mechanical ventilation on admission day 1 (**Figure 3**A). The percentage of patients requiring ventilator support peaked on day 4 for patients with MIS-C (17%) and day 3 for those with COVID-19 (13%). Fifty patients (9%) with COVID-19, compared

Table 1. Baseline Characteristics of Patients With MIS-C and Severe Acute COVID-19 and Initial Laboratory Values Within 48 Hours of Admission[a,b,c]

Characteristic	Study cohort from the Overcoming COVID-19 registry (N = 1116)	
	MIS-C (n = 539)	Severe acute COVID-19 (n = 577)
Age, median (IQR), y	8.9 (4.7-13.2)	11.7 (1.2-16.6)
Sex, No. (%)		
Male	312 (57.7)	307 (53.2)
Female	227 (42.1)	270 (47.8)
Race/ethnicity, No. (%)[d]		
No.	421	529
White, non-Hispanic (n = 174)	66 (13.3)	108 (19.0)
Black, non-Hispanic (n = 310)	181 (34.7)	129 (22.7)
Hispanic or Latino (n = 455)	193 (35.9)	262 (45.5)
Other, non-Hispanic (n = 67)	27 (5.5)	40 (7.1)
Underlying medical conditions, No. (%)		
At least 1 underlying condition[e]	167 (30.9)	358 (62.1)
Obesity[f]	176 (36.2)	176 (41.8)
Respiratory	72 (13.4)	151 (26.2)
Other[g]	52 (9.6)	223 (38.6)
Neurological/neuromuscular	30 (5.6)	104 (18.0)
Cardiovascular	17 (3.2)	57 (9.8)
Clinical presentation on hospital admission		
Duration of symptoms/signs prehospitalization, d		
No.	503	516
Median (IQR)	4.0 (3.0-6.0)	3.0 (1.0-5.0)
Organ systems involved, median (IQR)[h]	4.0 (3.0-5.0)	2.0 (1.0-3.0)
Symptoms and signs on presentation, No. (%)[i]		
Constitutional	536 (99.4)	472 (81.8)
Gastrointestinal	486 (90.2)	332 (57.5)
Mucocutaneous	360 (66.8)	59 (10.2)
Lower respiratory	232 (43.0)	359 (62.2)
Upper respiratory	184 (34.1)	185 (32.1)
Neurologic	218 (40.4)	186 (32.2)
Initial laboratory value within 48 h of admission[j]		
Absolute lymphocyte count, $\times 10^3$ cells/μL (normal range, 1-5.6 $\times 10^3$ cells/μL, depending on age and sex)		
No.	505	459
Median (IQR)	1.3 (0.7-3.1)	1.75 (1.0-3.5)
Absolute neutrophil count, $\times 10^3$ cells /μL (normal range, 2.2-9.4 $\times 10^3$ cells/μL, depending on age and sex)		
No.	515	481
Median (IQR)	8.0 (5.0-13.0)	5.2 (2.8-9.2)
Neutrophil to lymphocyte ratio (normal range not established)		
No.	515	464
Median (IQR)	6.4 (3.4-12.4)	2.7 (1.1-6.5)
Platelet count <150 $\times 10^3$ cells/μL (n = 1009)	212 (41)	84 (17)
Hemoglobin level, g/dL (normal range, 10.2-11.4 g/dL, depending on age and sex)		
No.	483	449
Median (IQR)	11.3 (10.2-12.3)	12.3 (10.7-14.0)
Alanine aminotransferase level, U/L (normal range, 3-54 U/L, depending on age and sex)		
No.	458	335
Median (IQR)	34.5 (21.0-67.9)	30.0 (18.0-55.0)

(continued)

Table 1. Baseline Characteristics of Patients With MIS-C and Severe Acute COVID-19 and Initial Laboratory Values Within 48 Hours of Admission[a,b,c] (continued)

Characteristic	Study cohort from the Overcoming COVID-19 registry (N = 1116)	
	MIS-C (n = 539)	Severe acute COVID-19 (n = 577)
C-reactive protein level, mg/L (normal range ≤5 mg/L)		
No.	491	285
Median (IQR)	152.0 (69.4-231.0)	33.0 (10.1-90.0)
Albumin level ≤3 g/dL (n = 793)	146 (32.0)	43 (12.8)

Abbreviations: COVID-19, coronavirus disease 2019; IQR, interquartile range; MIS-C, multisystem inflammatory syndrome in children; RT-PCR, reverse transcriptase–polymerase chain reaction.

SI conversion factor: To convert to alanine aminotransferase, multiply by 0.0167.

[a] MIS-C is defined in Box 1.

[b] Severe acute COVID-19 was defined as severe complications involving 1 organ system or more and evidence of infection with severe acute respiratory syndrome coronavirus 2 based on having a positive RT-PCR test result (Box 2). Complications categorized as severe are listed in Box 2 by organ system.

[c] Included children and adolescents younger than 21 years of age from 66 hospitals in 31 states from March 15 to October 31, 2020.

[d] Race and ethnicity were recorded from hospital medical records as reported by the site clinicians or in the medical record; categories are not mutually exclusive.

[e] Underlying conditions excluded body mass index (BMI, calculated as weight in kilograms divided by height in meters squared)–estimated obesity (defined as BMI >95th percentile for age and sex based on national reference standards).

[f] A patient was considered to have obesity by either clinician-diagnosed obesity or BMI-based obesity and is only calculated in children aged 2 years or older; thus, the denominator is 893.

[g] Other category included oncologic, immunosuppressive, rheumatologic, autoimmune, hematologic, kidney, urologic, gastrointestinal, hepatic, endocrine, and metabolic conditions.

[h] Organ systems involved includes cardiovascular, respiratory, kidney, neurologic, gastrointestinal, hematologic, mucocutaneous, and musculoskeletal.

[i] Presenting signs and symptoms were recorded from hospital medical records and included constitutional symptoms (fever, fatigue, muscle aches/joint pain), gastrointestinal symptoms (nausea/refusal to eat, vomiting, abdominal pain, diarrhea), upper respiratory (rhinorrhea, congestion, and sore throat), lower respiratory (cough, shortness of breath, chest pain, wheezing, lower chest wall indrawing), mucocutaneous findings (rash, inflammation of the oral mucosa, conjunctivitis, and extremity findings, including erythema or edema of the hands or feet, or periungual peeling), hematological signs (abnormal cell counts or clotting function), and neurologic symptoms (headache, altered mental status/confusion).

[j] Clinically significant laboratory values that were commonly tested are presented here.

with 244 (45%) with MIS-C, received vasoactive agents (Table 2); the MIS-C and COVID-19 groups showed similar decreases in the percentage receiving vasoactive agent support over time (Figure 3B).

Cardiac Complications

In patients with MIS-C, among 503 (93.3%) in whom LVEF could be evaluated on 1 or more echocardiograms, 331 (65.8%) had preserved LVEF throughout the illness. Of the 172 patients (34.2%) with MIS-C and depressed LVEF, the lowest EF was mildly depressed in 95 (55.2%), moderately depressed in 39 (22.7%), and severely depressed in 38 (22.1%). By Kaplan-Meier analysis with censoring at the last echocardiogram, 91.0% (95% CI, 86.0%-94.7%) had a normal LVEF by 30 days (**Figure 4**A), and, based on a small number of patients with available follow-up, 99.4% (95% CI, 96.9%-99.9%) had normal LVEF by 90 days. The 1 patient without normalization documented within 90 days who had further echocardiographic analysis had a normal LVEF at 142 days. The severity of initial systolic dysfunction did not affect the likelihood of EF recovery (log-rank test, $P = .88$). Coronary arteries were evaluated in 424 of 504 patients (84.1%) with MIS-C who had echocardiograms (eTable 9 in the Supplement). Among these, 57 patients (13.4%) had coronary aneurysms, of which 53 (93.0%) were mild, 4 (7.0%) were moderate, and none were large/giant. Aneurysms regressed to normal internal lumen diameter (z score <2.5) in 79.1% (95% CI, 67.1%-89.1%) of patients by 30 days (Figure 4B) and, based on small numbers, 100% by 90 days. Fewer patients with COVID-19 (111/578, 19.2%) underwent echocardiographic assessment; depressed EF (6/111, 5.4%) and coronary aneurysms (1/111, 0.9%) were infrequent in those evaluated.

Discussion

In this case series comparing children and adolescents with MIS-C vs those with severe COVID-19, MIS-C was distinguished by certain demographic features and clinical presentations including being aged 6 to 12 years, being of non-Hispanic Black race, having severe cardiovascular or mucocutaneous involvement, and having more extreme inflammation. Patients from both groups commonly presented with a variety of constitutional, gastrointestinal, and upper or lower respiratory signs or symptoms on admission. Both groups often required intensive care unit support, more commonly in the MIS-C group. Although the results for most patients with MIS-C were SARS-CoV-2 antibody positive, most patients with COVID-19 were not antibody tested. Most severe cardiovascular involvement from MIS-C, including left ventricular dysfunction and coronary artery aneurysms, resolved within 30 days.

Previous studies have reported that a large proportion of pediatric patients with COVID-19–related disease were of Black race or Hispanic ethnicity, but these studies were limited in their ability to establish an association between race/ethnicity as a potential risk factor for MIS-C.[8,14,27] This case series found that non-Hispanic Black children and adolescents were more likely than non-Hispanic White patients to have MIS-C than COVID-19, after adjusting for age, sex, geographic

Table 2. Clinical Course of Patients With MIS-C and Severe Acute COVID-19[a,b]

Characteristic	Study cohort from the Overcoming COVID-19 registry (n = 1116)		
	No. (%)		
	MIS-C (n = 539 [48%])	Severe acute COVID-19 (n = 577 [52%])	Difference (95% CI)[c]
Treatments			
Intravenous immunoglobulin	415 (77.0)	24 (4.2)	72.8 (68.9 to 76.7)
Systemic steroids	374 (69.4)	141 (24.4)	45.0 (39.7 to 50.2)
Anticoagulation therapy	337 (62.5)	162 (28.1)	34.4 (29.0 to 39.9)
Antiplatelet therapy	308 (57.1)	23 (4.0)	53.1 (49.0 to 57.6)
Remdesivir	76 (14.1)	93 (16.1)	−2.0 (−2.2 to 6.2)
Tocilizumab	32 (5.9)	13 (2.3)	3.6 (1.4 to 6.0)
Hydroxychloroquine	14 (2.6)	41 (7.1)	−4.5 (2.0 to 7.0)
Convalescent plasma	10 (1.9)	20 (3.5)	−1.6 (−0.3 to 3.5)
Severe organ involvement[d]			
Respiratory	432 (80.1)	459 (79.5)	0.6 (−5.3 to 4.1)
Infiltrates on chest radiography	197 (36.5)	220 (38.1)	−1.6 (−4.1 to 7.3)
Lower respiratory infection	94 (17.4)	207 (35.9)	−18.5 (−13.4 to −23.5)
Asthma exacerbation	301 (55.8)	132 (22.9)	32.9 (27.6 to 38.4)
Pleural effusion	170 (31.5)	86 (14.9)	16.6 (11.8 to 21.5)
Pediatric ARDS	57 (10.6)	57 (9.9)	0.7 (−4.3 to 2.9)
Cardiovascular[e]	359 (66.7)	68 (11.8)	54.9 (50.1 to 59.6)
Pericardial effusion	125 (24.9)	5 (4.5)	20.4 (15.0 to 25.8)
Ejection fraction			
<35%	38 (7.6)	6 (5.4)	2.2 (−2.6 to 7.0)
35%-<45%	39 (7.8)	1 (0.9)	6.9 (4.0 to 9.8)
45%-<55%	95 (18.9)	6 (5.4)	13.5 (1.2 to 18.9)
Coronary artery aneurysm	57 (13.4)	1 (0.9)	12.5 (8.8 to 16.2)
Arrhythmia	46 (8.5)	4 (0.7)	7.8 (5.3 to 10.3)
Hematologic	256 (47.5)	129 (22.4)	25.1 (14.4 to 25.5)
Neurologic	66 (12.2)	115 (19.9)	−7.7 (3.4 to 12.0)
Gastrointestinal	50 (9.3)	41 (7.1)	2.2 (−5.2 to 1.2)
Severe organ involvement subcategories[d]			
Severe cardiorespiratory involvement	302 (56.0)	51 (8.8)	47.2 (42.4 to 52.0)
Severe respiratory without cardiovascular involvement	130 (24.1)	408 (70.7)	−46.6 (−51.8 to −41.4)
Severe cardiovascular without respiratory involvement	57 (10.6)	17 (2.9)	7.7 (4.7 to 10.6)
Mucocutaneous without severe cardiorespiratory involvement	38 (7.1)	13 (2.3)	4.8 (2.3 to 7.3)
Hematologic, neurologic, or gastrointestinal severe involvement only	12 (2.2)	88 (15.3)	−13.1 (−16.2 to −9.8)

(continued)

Table 2. Clinical Course of Patients With MIS-C and Severe Acute COVID-19[a,b] (continued)

Characteristic	Study cohort from the Overcoming COVID-19 registry (n = 1116)		
	No. (%)		
	MIS-C (n = 539 [48%])	Severe acute COVID-19 (n = 577 [52%])	Difference (95% CI)[c]
Critical care interventions			
Any respiratory support	303 (56.2)	292 (50.6)	5.6 (−0.2 to 11.5)
Noninvasive positive pressure ventilation	192 (35.6)	188 (32.6)	0.7 (−3.2 to 7.3)
Invasive mechanical ventilation	95 (17.6)	84 (14.6)	3.0 (1.2 to 7.4)
Vasopressor use	244 (45.3)	50 (8.7)	36.6 (31.8 to 41.4)
Extracorporeal membrane oxygenation	18 (3.3)	8 (1.4)	1.9 (0.2 to 3.7)
Clinical outcomes			
Length of admission, d (n = 1083)[f]			
No.	523	560	
Median (IQR)	7.0 (5.0 to 11.0)	3.0 (2.0 to 8.0)	
Intensive care unit admission[g]	398 (73.8)	253 (43.8)	30.0 (24.5 to 35.5)
Length of ICU stay, d (n = 639)			
No.	388	251	
Median (IQR)	4.0 (2.0 to 7.0)	4.0 (2.0 to 8.0)	
Died	10 (1.9)	8 (1.4)	0.5 (−2.0 to 1.0)

Abbreviation: ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; ICU, intensive care unit; IQR, interquartile range; MIS-C, multisystem inflammatory syndrome in children; RT-PCR, reverse transcriptase–polymerase chain reaction.

[a] Severe acute COVID-19 was defined as severe complications involving 1 organ system or more and evidence of infection with severe acute respiratory syndrome coronavirus 2 based on having a positive RT-PCR test result. Complications categorized as severe are listed in Box 2 by organ system.

[b] Included children and adolescents younger than 21 years of age from 66 hospitals in 31 states from March 15 to October 31, 2020.

[c] Differences calculated as the percentage with MIS-C minus the percentage with severe acute COVID-19. Negative values represent a higher proportion of patients with COVID-19 for the given characteristic.

[d] Severe organ involvement was diagnosed on presentation with the exception of ejection fractions and coronary artery aneurysms. Criteria for severe organ involvement are listed in Box 2.

[e] Ejection fraction and pericardial effusion denominators are patients with echocardiograms (MIS-C: n = 503; severe acute COVID-19: n = 111); coronary artery aneurysm denominators are any patient with an evaluable echocardiogram for MIS-C (n = 424) and any patient with an echocardiogram for severe acute COVID-19 (n = 111).

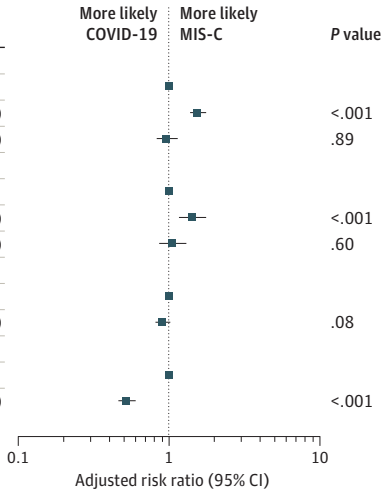
[f] Length of admission excluded patients who died during hospitalization (n = 18) and those still admitted to the hospital (n = 15).

[g] Inclusion of severe acute COVID-19 cases was restricted to the intensive care unit and high-acuity stepdown unit settings beginning August 13, 2020.

Figure 2. Multivariable Analyses of MIS-C vs COVID-19

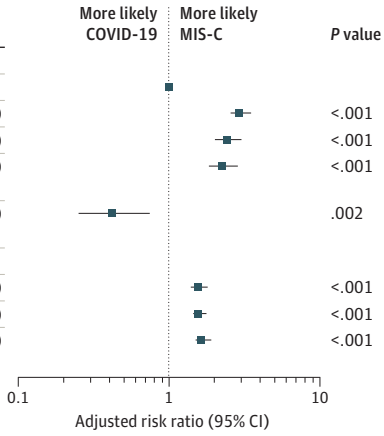
A Comparison of baseline demographic and clinical characteristics[a]

	No. (%)					
	MIS-C (n = 539)	Severe acute COVID-19 (n = 577)	Absolute risk difference, % (95% CI)[b]	Adjusted risk ratio (95% CI)[c]	More likely COVID-19 / More likely MIS-C	*P* value
Age, y						
0-5	178 (33.0)	211 (36.6)	-3.5 (-9.1 to 2.0)	1 [Reference]		
6-12	220 (40.8)	112 (19.4)	21.4 (16.1 to 26.7)	1.51 (1.33 to 1.72)		<.001
13-20	141 (26.2)	254 (44.0)	-17.9 (-23.4 to -12.4)	0.99 (0.84 to 1.17)		.89
Race/ethnicity[d]						
White, non-Hispanic	63 (11.7)	106 (18.4)	-6.7 (-10.8 to -2.5)	1 [Reference]		
Black, non-Hispanic	174 (32.3)	124 (21.5)	10.8 (5.6 to 16.0)	1.43 (1.17 to 1.76)		<.001
Hispanic or Latino	193 (35.8)	262 (45.4)	-9.6 (-15.3 to -3.9)	1.06 (0.86 to 1.30)		.60
Sex						
Male	312 (57.9)	307 (53.2)	4.7 (-1.1 to 10.5)	1 [Reference]		
Female	227 (42.1)	270 (46.8)	-4.7 (-10.5 to 1.1)	0.90 (0.81 to 1.01)		.08
≥1 Underlying medical conditions						
No	372 (69.0)	219 (37.9)	31.1 (25.5 to 36.6)	1 [Reference]		
Yes	167 (31.0)	358 (62.1)	-31.1 (-36.6 to -25.5)	0.52 (0.45 to 0.60)		<.001



B Comparison of clinical phenotypes and laboratory values[a]

	No./total No. (%)					
	MIS-C (n = 539)	Severe acute COVID-19 (n = 577)	Absolute risk difference, % (95% CI)[b]	Adjusted risk ratio (95% CI)[c]	More likely COVID-19 / More likely MIS-C	*P* value
Clinical group by complication						
Respiratory without cardiovascular	130/539 (24.1)	408/577 (70.7)	-46.6 (-51.8 to -41.4)	1 [Reference]		
Cardiorespiratory	302/539 (56.0)	51/577 (8.8)	47.2 (42.4 to 52.0)	2.99 (2.55 to 3.50)		<.001
Cardiovascular without respiratory	57/539 (10.6)	17/577 (2.9)	7.7 (4.7 to 10.6)	2.49 (2.05 to 3.02)		<.001
Mucocutaneous without respiratory or cardiovascular	38/539 (7.1)	13/577 (2.3)	4.8 (2.3 to 7.3)	2.29 (1.84 to 2.85)		<.001
Other without respiratory, cardiovascular, or mucocutaneous	12/539 (2.2)	88/577 (15.3)	-13.1 (-16.2 to -9.8)	0.43 (0.25 to 0.74)		.002
Laboratory value within first 48 h						
Neutrophil to lymphocyte ratio >5	321/515 (62.3)	154/464 (33.2)	29.1 (23.2 to 35.1)	1.59 (1.40 to 1.80)		<.001
Platelets <150 × 10^3/μL	212/523 (40.5)	84/486 (17.3)	23.2 (17.9 to 28.6)	1.58 (1.43 to 1.75)		<.001
C-reactive protein level >100 mg/L	325/491 (66.2)	67/285 (23.5)	42.7 (36.2 to 49.1)	1.70 (1.51 to 1.92)		<.001



COVID-19 indicates coronavirus disease 2019 and MIS-C, multisystem inflammatory syndrome in children.

[a] Included children and adolescents younger than 21 years of age from 66 hospitals in 31 states from March 15 to October 31, 2020.

[b] Absolute row differences in characteristic between patients with MIS-C and COVID-19 with exact confidence intervals; a positive value indicates that the characteristic was more common in children and adolescents diagnosed with MIS-C.

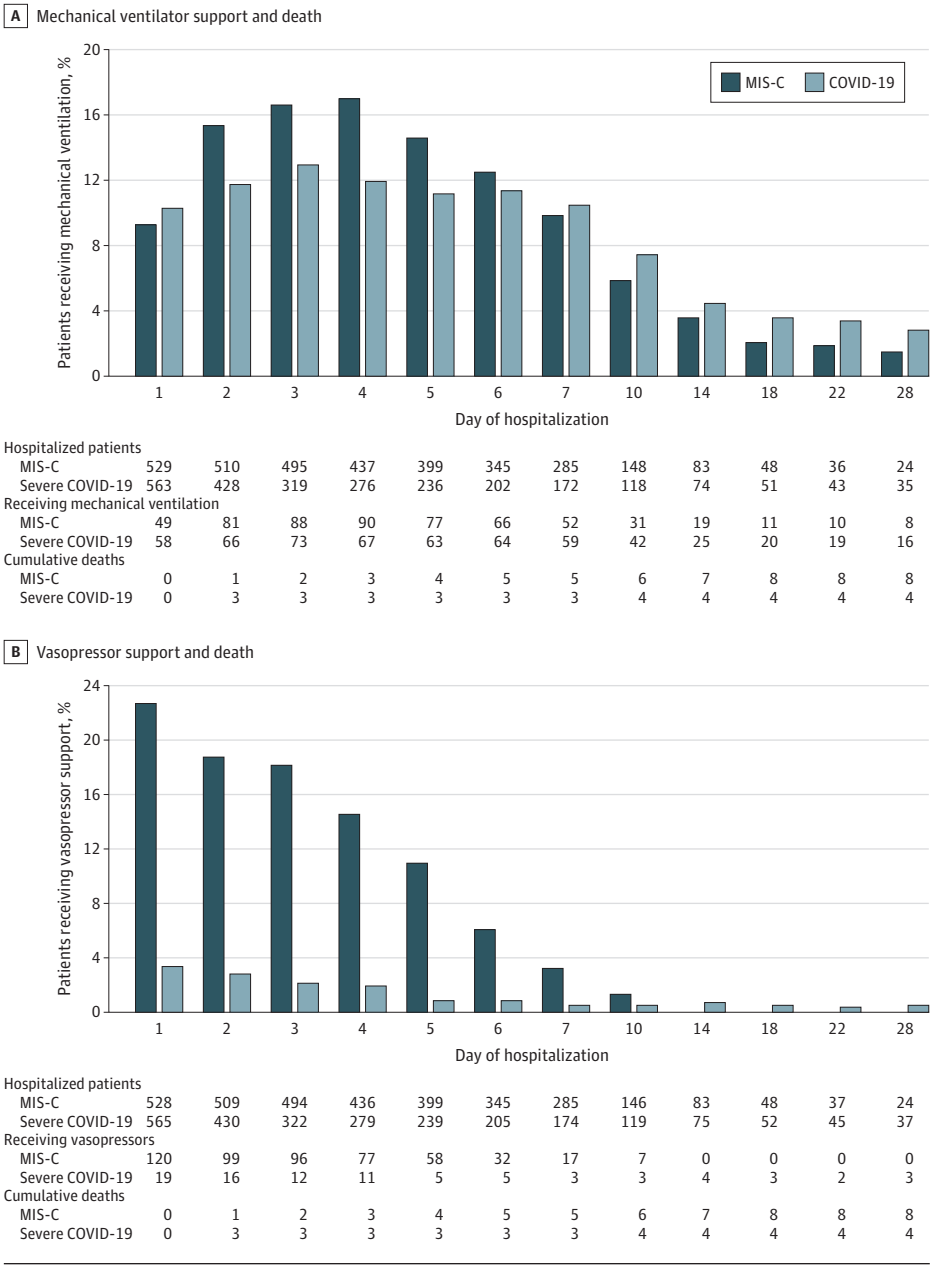
[c] The primary outcome is diagnosis of MIS-C vs COVID-19. A risk ratio greater than 1 represents a higher relative risk of MIS-C in the respective row relative to the referent group within that category. Associations were adjusted for age group (0-5 years, 6-12 years, 13-20 years), race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic of any race, other non-Hispanic), sex, 1 or more vs no underlying medical conditions, and US Census region (Northeast, South, Midwest, West).

[d] Other non-Hispanic race/ethnicity, which included patients documented as having other, unknown, or mixed race, not shown in the table.

region, and underlying conditions, whereas Hispanic patients did not appear to be at a higher risk for MIS-C than COVID-19.[14] In Kawasaki disease, Black race is a risk factor for nonresponse to IVIG treatment and increased frequency of coronary abnormalities.[28,29]

Similar to prior single-center studies, LVEF was found to normalize in most patients with MIS-C within 1 to 2 weeks.[30-32] Patients with severely depressed EF had a similar likelihood and temporal trajectory of recovery to those with mild dysfunction. The recovery of LVEF within a few weeks of diagnosis in most patients with MIS-C suggests that LV dysfunction likely results from severe systemic inflammation and acute stress more often than from ischemia or direct virus-mediated myocardial damage. However, Matsubara et al[30] demonstrated persistent abnormalities in strain and diastolic function in patients with MIS-C and normal EF. These data, together with literature in adult patients with COVID-19,[33] suggest that subclinical myocardial injury may persist even when

Figure 3. Clinical Outcomes by Day of Hospitalization for Patients With MIS-C and Severe COVID-19



	1	2	3	4	5	6	7	10	14	18	22	28
Hospitalized patients												
MIS-C	529	510	495	437	399	345	285	148	83	48	36	24
Severe COVID-19	563	428	319	276	236	202	172	118	74	51	43	35
Receiving mechanical ventilation												
MIS-C	49	81	88	90	77	66	52	31	19	11	10	8
Severe COVID-19	58	66	73	67	63	64	59	42	25	20	19	16
Cumulative deaths												
MIS-C	0	1	2	3	4	5	5	6	7	8	8	8
Severe COVID-19	0	3	3	3	3	3	3	4	4	4	4	4

	1	2	3	4	5	6	7	10	14	18	22	28
Hospitalized patients												
MIS-C	528	509	494	436	399	345	285	146	83	48	37	24
Severe COVID-19	565	430	322	279	239	205	174	119	75	52	45	37
Receiving vasopressors												
MIS-C	120	99	96	77	58	32	17	7	0	0	0	0
Severe COVID-19	19	16	12	11	5	5	3	3	4	3	2	3
Cumulative deaths												
MIS-C	0	1	2	3	4	5	5	6	7	8	8	8
Severe COVID-19	0	3	3	3	3	3	3	4	4	4	4	4

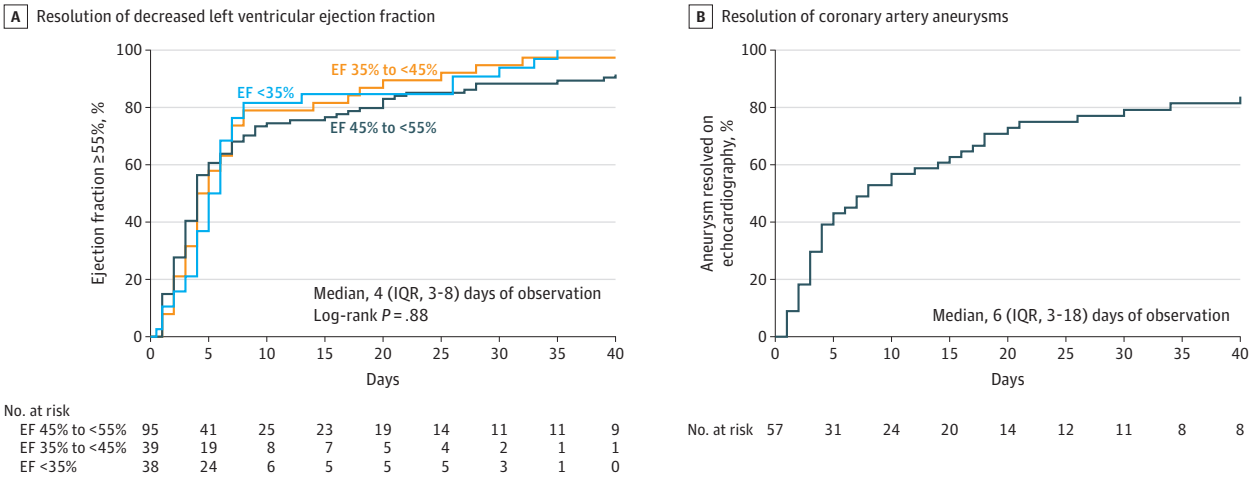
A, Graph shows mechanical ventilator support and death among patients with MIS-C (n = 529 with respiratory support data available) and patients with severe acute COVID-19 (n = 563 with respiratory support data available). B, Graph shows vasopressor support and death among patients with MIS-C (n = 528 with vasopressor support data available) and patients with severe acute COVID-19 (n = 565 with vasopressor support data available).

Percentages receiving mechanical ventilator or vasopressor support by day of admission use the full denominators specified at day 1 (the initial day of hospitalization). Some patients had missing information on mechanical ventilator or vasopressor use and are excluded. Tables below the x-axis present the number of patients with MIS-C and COVID-19 still hospitalized by admission day, the number on mechanical ventilation or receiving vasopressor support, and the cumulative deaths during index hospitalization. Cardiovascular pediatric Severe Organ Failure Assessment (pSOFA) scores range from 0 to 4 and were documented daily through 7 days, twice weekly through day 22, then at day 28. Details of pSOFA score criteria are included in eTable 2 in the Supplement. Scores of 2 to 4, indicating vasopressor use, are presented in the figure. COVID-19 indicates coronavirus disease 2019; MIS-C, multisystem inflammatory syndrome in children.

traditional measures of LV systolic function are normal. To understand the longer-term implications for myocardial health, including risk for myocardial fibrosis and diastolic dysfunction, it is critical to have comprehensive assessment of LV systolic and diastolic function in a large, multicenter cohort followed up longitudinally with centralized review of cardiac imaging. Cardiac magnetic resonance imaging and the rare endomyocardial biopsy or postmortem specimen may further help to clarify the underlying pathology and mechanisms of myocardial involvement in MIS-C.

Coronary artery aneurysms were generally small in size and regressed to normal internal lumen diameter within several weeks in a population that was often treated with IVIG, an effective therapy for reduction of prevalence of aneurysms in Kawasaki disease.[22] The pathophysiology of coronary enlargement in MIS-C has not been elucidated. However, the mild severity and rapid resolution may suggest that coronary enlargement in MIS-C more often results from vasodilation in the setting of a highly proinflammatory milieu,[34] rather than from destruction of the arterial wall by inflammatory cells.[35] Coronary imaging results were abstracted from reports of echocardiograms performed at varying times after hospital discharge, using inconsistent *z* score calculators, and of uncertain imaging quality. Future studies using standardized protocols and core laboratory interpretation will build on the results of this study and others.[36]

Figure 4. Cardiovascular Outcomes of Patients With MIS-C[a]



A. Graph shows resolution of decreased left ventricular ejection fraction (EF) on echocardiogram with mild (EF, 45% to <55%), moderate (EF, 35% to <45%), and severe (EF<35%) impairment with days to normalization (EF ≥55%). B, Graph shows resolution of coronary artery aneurysms defined as *z* score ≥2.5 for left anterior descending or right coronary artery.

Patients were evaluated from the day of first echocardiographic evaluation and censored on the day when repeat echocardiograph showed recovery or on the day of their last repeat echocardiogram if they had not recovered through 40 days. IQR indicates interquartile range and MIS-C, multisystem inflammatory syndrome in children.

[a] Kaplan-Meier curves shown up to 40 days from admission given early resolution of cardiac dysfunction in most patients with few uncensored by 40 days. Five patients were censored before documented resolution of reduced left ventricular EF at a median time of 2 days (range, 0-8 days); all other patients had resolution documented by 142 days. Nine patients were censored before documented resolution of coronary artery aneurysms at a median time of 4 days (range, 0-30 days); all other patients had resolution documented by 76 days.

Most patients classified as having MIS-C and COVID-19 experienced severe respiratory involvement and it is possible that some patients may have had COVID-19 with cardiovascular involvement, as has been described in adult patients, rather than MIS-C.[37] Current criteria for MIS-C may also capture a spectrum of hyperinflammation and cardiovascular involvement occurring acutely and during the postinfectious phase. Misclassification of these patients might impede optimal treatment if the pathogenesis differs between MIS-C and COVID-19; however, it is possible that anti-inflammatory agents like steroids could be beneficial for both.[38,39] Although longer-term follow-up is needed to assess outcomes and sequelae, most children with MIS-C with severe cardiac manifestations experienced clinical recovery within 30 days.

Limitations

This study has several limitations. First, data collection through in-depth abstraction of routine clinical documentation is subject to incomplete reporting. Research personnel at each site abstracted data and were part of a large research network with extensive data collection experience and intensive data clarification procedures. Second, missing data were not imputed and missingness might be nonrandom. Third, participating hospitals may not be generalizable and likely overrepresented patients seeking care at tertiary care centers. Fourth, although 93% of patients with MIS-C had echocardiograms, most patients with severe COVID-19 did not have detailed cardiac assessments. Among patients with COVID-19, only 19% had echocardiograms, and although LV dysfunction and coronary aneurysms were rare, they could have been underappreciated. Fifth, the efficacies of different immunomodulatory regimens on recovery of LV function in the current study were not examined.[40] Sixth, because MIS-C is thought to be delayed in onset after SARS-CoV-2 infection,[5,38] its distinction from acute COVID-19 could be improved by elucidating the temporal progression from viral exposure to disease onset.

Conclusions

This case series of patients with MIS-C and with COVID-19 identified patterns of clinical presentation and organ system involvement. These patterns may help differentiate between MIS-C and COVID-19.

ARTICLE INFORMATION

Accepted for Publication: February 8, 2021.

Published Online: February 24, 2021. doi:10.1001/jama.2021.2091

Author Affiliations: COVID-19 Response Team, Centers for Disease Control and Prevention, Atlanta, Georgia (Feldstein, Tenforde, Rose, Jackson, Patel); Public Health Service Commissioned Corps, Rockville, Maryland (Feldstein, Rose, Patel); Department of Cardiology, Boston Children's Hospital, Department of Pediatrics, Harvard Medical School, Boston, Massachusetts (Friedman, Newburger); Department of Anesthesiology, Critical Care, and Pain Medicine, Boston Children's Hospital, Boston, Massachusetts (Newhams, Young, Randolph); Division of Pediatric Critical Care Medicine, Department of Pediatrics, New York University Grossman School of Medicine, New York (Dapul); Division of Pediatric Infectious Diseases, Department of Pediatrics, New York University Grossman School of Medicine, New York (Soma); Department of Pediatrics, Section of Critical Care Medicine, University of Colorado School of Medicine and Children's Hospital Colorado, Aurora (Maddux, Mourani); Division of Critical Care

Medicine, Department of Pediatrics, University of Texas Southwestern, Children's Medical Center Dallas, Dallas (Bowens, Maamari); Division of Critical Care Medicine, Department of Pediatrics, Nationwide Children's Hospital, Columbus, Ohio (Hall); Department of Anesthesiology and Critical Care Medicine, Division of Pediatric Anesthesiology & Critical Care Medicine, Johns Hopkins School of Medicine, Baltimore, Maryland (Riggs); Division of Critical Care, Department of Pediatrics, Yale University School of Medicine, New Haven, Connecticut (Giuliano); Pediatric Critical Care Division, Maria Fareri Children's Hospital at Westchester Medical Center and New York Medical College, Valhalla (Singh); Department of Pediatrics, Division of Pediatric Critical Care, Bristol-Myers Squibb Children's Hospital, Robert Wood Johnson Medical School, Rutgers University, New Brunswick, New Jersey (Li); Division of Pediatric Critical Care Medicine, Department of Pediatrics, University of Alabama at Birmingham (Kong); Division of Pediatric Infectious Disease, Department of Pediatrics, Children's Mercy Kansas City, Kansas City, Missouri (Schuster); Division of Pediatric Critical Care Medicine, Department of Pediatrics, University of Miami Miller School of Medicine, Miami, Florida (McLaughlin); Department of Pediatrics, University of North Carolina at Chapel Hill Children's Hospital (Schwartz, Walker); Section of Critical Care Medicine, Department of Pediatrics, Baylor College of Medicine, Houston, Texas (Loftis); Division of Infectious Diseases, Department of Pediatrics, Department of Microbiology, University of Mississippi Medical Center, Jackson (Hobbs); Division of Pediatric Infectious Diseases, Department of Pediatrics, Vanderbilt University Medical Center, Nashville, Tennessee (Halasa); Division of Pediatric Critical Care, Department of Pediatrics, SUNY Downstate Health Sciences University, Brooklyn, New York (Doymaz); Division of Pediatric Critical Care, Miller Children's and Women's Hospital of Long Beach, Long Beach, California (Babbitt); Division of Pediatric Critical Care, University of Minnesota Masonic Children's Hospital, Minneapolis (Hume); Division of Pediatric Critical Care, Department of Pediatrics, Saint Barnabas Medical Center, Livingston, New Jersey (Gertz); Section of Pediatric Critical Care, Department of Pediatrics, Arkansas Children's Hospital, Little Rock (Irby); Division of Hospital Medicine, Department of Pediatrics, Hackensack University Medical Center, Hackensack, New Jersey (Clouser); Division of Critical Care Medicine, UCSF Benioff Children's Hospital Oakland, Oakland, California (Cvijanovich); Division of Cardiology, Department of Pediatrics, Louisiana State University Health Sciences Center and Children's Hospital of New Orleans, New Orleans (Bradford); Division of Pediatric Critical Care Medicine, Department of Pediatrics, University of Washington, Seattle (Smith); Division of Pediatric Critical Care Medicine, Department of Pediatrics, Central Michigan University, Detroit (Heidemann); Pediatric Critical Care Medicine, Department of Pediatrics, Icahn School of Medicine at the Mount Sinai Kravis Children's Hospital, New York, New York (Zackai); Division of Pediatric Critical Care, Stead Family Department of Pediatrics, University of Iowa Carver College of Medicine, Iowa City (Wellnitz); Division of Critical Care Medicine, Department of Pediatrics, Akron Children's Hospital, Akron, Ohio (Nofziger); Department of Pediatrics, Division of Critical Care, Rutgers Robert Wood Johnson Medical School, New Brunswick, New Jersey (Horwitz); Division of Pediatric Critical Care Medicine, MassGeneral Hospital for Children, Harvard Medical School, Boston, Massachusetts (Carroll); Division of Pediatric Critical Care Medicine, Department of Pediatrics, Indiana University School of Medicine, Riley Hospital for Children, Indianapolis (Rowan); Division of Critical Care Medicine, Department of Pediatrics, Emory University School of Medicine, Children's Healthcare of Atlanta, Atlanta, Georgia (Tarquinio); Division of Pediatric Critical Care Medicine, Medical University of South Carolina, Charleston (Mack); Division of Critical Care, Department of Anesthesiology and Critical Care, The University of Pennsylvania Perelman School of Medicine, Philadelphia (Fitzgerald); Division of Critical Care Medicine, Department of Pediatrics, Northwestern University Feinberg School of Medicine, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois (Coates); Division of Immunology, Boston Children's Hospital, Department of Pediatrics, Harvard Medical School, Boston, Massachusetts (Son); Departments of Anesthesia and Pediatrics, Harvard Medical School, Boston, Massachusetts (Randolph).

Author Contributions: Dr Patel had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Feldstein, Tenforde, and Friedman contributed equally, as did Drs Patel, Newburger, and Randolph.
Concept and design: Feldstein, Li, Walker, Hobbs, Halasa, Doymaz, Horwitz, Patel, Randolph.
Acquisition, analysis, or interpretation of data: Feldstein, Tenforde, Friedman, Newhams, Rose, Dapul, Soma, Maddux, Mourani, Bowens, Maamari, Hall, Riggs, Giuliano, Singh, Li, Kong, Schuster, McLaughlin, Schwartz, Loftis, Hobbs, Halasa, Babbitt, Hume, Gertz, Irby, Clouser, Cvijanovich, Bradford, Smith, Heidemann, Zackai, Wellnitz, Nofziger, Horwitz, Carroll, Rowan, Tarquinio, Mack, Fitzgerald, Coates, Jackson, Young, Son, Patel, Newburger, Randolph.
Drafting of the manuscript: Feldstein, Tenforde, Friedman, Rose, Doymaz, Jackson, Young, Patel, Newburger, Randolph.
Critical revision of the manuscript for important intellectual content: Feldstein, Tenforde, Friedman, Newhams, Dapul, Soma, Maddux, Mourani, Bowens, Maamari, Hall, Riggs, Giuliano, Singh, Li, Kong, Schuster, McLaughlin, Schwartz, Walker, Loftis, Hobbs, Halasa, Doymaz, Babbitt, Hume, Gertz, Irby, Clouser, Cvijanovich, Bradford, Smith, Heidemann, Zackai, Wellnitz, Nofziger, Horwitz, Carroll, Rowan, Tarquinio, Mack, Fitzgerald, Coates, Son, Patel, Newburger, Randolph.
Statistical analysis: Feldstein, Tenforde, Rose, Giuliano, Zackai, Jackson, Young, Randolph.
Obtained funding: Patel, Randolph.
Administrative, technical, or material support: Feldstein, Tenforde, Newhams, Rose, Dapul, Maamari, Hall, Riggs, Kong, McLaughlin, Schwartz, Loftis, Hobbs, Doymaz, Babbitt, Hume, Gertz, Irby, Bradford, Zackai, Wellnitz, Carroll, Fitzgerald, Coates, Son, Randolph.
Supervision: Feldstein, Friedman, Newhams, Singh, Hobbs, Cvijanovich, Horwitz, Carroll, Coates, Patel, Randolph.

Conflict of Interest Disclosures: Dr Maddux reported receiving grants from National Institutes of Health (NIH) (K23HD096018) and Francis Family Foundation (Parker B. Francis Fellowship) during the conduct of the study. Dr Mourani reported receiving grants from the NIH. Dr Hall reported receiving personal fees from LaJolla Pharmaceuticals for service on a data safety and monitoring board outside the submitted work. Dr Schuster reported receiving grants from Merck outside the submitted work. Dr Halasa reported receiving grants from Sanofi, Quindell, and Quidel; personal fees from Genentech (educational grant); and hemagglutination inhibition and microneutralization testing and vaccine donation from Sanofi outside the submitted work. Dr Cvijanovich reported receiving grants from Cincinnati Children's Hospital Medical Center outside the submitted work. Dr Rowan reported receiving grants from the National Heart, Lung, and Blood Institute (K23HL150244-01A1) outside the submitted work. Dr Fitzgerald reported receiving grants from an NIH career development award outside the submitted work. Dr Newburger reported serving as chair of events adjudication committee for a trial on apixaban in children for Pfizer and Bristol-Myers Squibb, as chair of events adjudication committee for a trial of Entresto in children for Novartis, and as a steering committee member for a trial of endoxaban for Daiichi-Sankyo outside the submitted work. Dr Randolph reported receiving royalties from UpToDate and personal fees from LaJolla Pharma Inc outside the submitted work. No other disclosures were reported.

Funding/Support: This study was funded by the Centers for Disease Control and Prevention (CDC) under a contract to Boston Children's Hospital.

Role of the Funder/Sponsor: The CDC designed and conducted the study; collected, managed, analyzed, and interpreted the data; prepared, reviewed, and approved the manuscript; and had a role in the decision to submit the manuscript for publication and journal choice, and had the right to veto publication.

Group Information: The Overcoming COVID-19 Investigators are listed in the eAppendix in the Supplement.

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the CDC.

Additional Contributions: We appreciate and thank the many research coordinators at the Overcoming COVID-19 hospitals who assisted in data collection for this study. We thank the leadership of the Pediatric Acute Lung Injury and Sepsis Investigator's (PALISI) Network for their ongoing support.

REFERENCES

1. NYC Health. 2020 Health alert 13: pediatric multi-system inflammatory syndrome potentially associated with COVID-19. Published May 4, 2020. Accessed December 3, 2020. https://www1.nyc.gov/assets/doh/downloads/pdf/han/alert/2020/covid-19-pediatric-multi-system-inflammatory-syndrome.pdf

2. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet*. 2020;395(10237):1607-1608. doi:10.1016/S0140-6736(20)31094-1

3. 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*. 2020;395 (10239):1771-1778. doi:10.1016/S0140-6736(20)31103-X

4. Centers for Disease Control and Prevention. Emergency preparedness and response: HAN00432. Published May 14, 2020. Accessed December 3, 2020. https://emergency.cdc.gov/han/2020/han00432.asp

5. Feldstein LR, Rose EB, Horwitz SM, et al; Overcoming COVID-19 Investigators; CDC COVID-19 Response Team. Multisystem inflammatory syndrome in US children and adolescents. *N Engl J Med*. 2020;383(4):334-346. doi:10.1056/NEJMoa2021680

6. Dufort EM, Koumans EH, Chow EJ, et al; New York State and Centers for Disease Control and Prevention Multisystem Inflammatory Syndrome in Children Investigation Team. Multisystem inflammatory syndrome in children in New York state. *N Engl J Med*. 2020;383(4):347-358. doi:10.1056/NEJMoa2021756

7. Sperotto F, Friedman KG, Son MBF, VanderPluym CJ, Newburger JW, Dionne A. Cardiac manifestations in SARS-CoV-2-associated multisystem inflammatory syndrome in children: a comprehensive review and proposed clinical approach. *Eur J Pediatr*. 2021;180(2):307-322. doi:10.1007/s00431-020-03766-6

8. Swann OV, Holden KA, Turtle L, et al; ISARIC4C Investigators. Clinical characteristics of children and young people admitted to hospital with covid-19 in United Kingdom: prospective multicentre observational cohort study. *BMJ*. 2020;370:m3249. doi:10.1136/bmj.m3249

9. Henderson LA, Canna SW, Friedman KG, et al. American College of Rheumatology clinical guidance for pediatric patients with multisystem inflammatory syndrome in children (MIS-C) associated with SARS-CoV-2 and hyperinflammation in COVID-19: version 2. *Arthritis Rheumatol*. Published online December 5, 2020.

10. Valverde I, Singh Y, Sanchez-de-Toledo J, et al; AEPC COVID-19 Rapid Response Team. Acute cardiovascular manifestations in 286 children with multisystem inflammatory syndrome associated with COVID-19 infection in Europe. *Circulation*. 2021;143(1):21-32. doi:10.1161/CIRCULATIONAHA.120.050065

11. Fernandes DM, Oliveira CR, Guerguis S, et al; Tri-State Pediatric COVID-19 Research Consortium. SARS-CoV-2 clinical syndromes and predictors of disease severity in hospitalized children and youth. *J Pediatr*. Published online November 14, 2020. doi:10.1016/j.jpeds.2020.11.016

12. Lu X, Zhang L, Du H, et al; Chinese Pediatric Novel Coronavirus Study Team. SARS-CoV-2 infection in children. *N Engl J Med*. 2020;382(17):1663-1665. doi:10.1056/NEJMc2005073

13. Götzinger F, Santiago-García B, Noguera-Julián A, et al; ptbnet COVID-19 Study Group. COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study. *Lancet Child Adolesc Health*. 2020;4(9):653-661. doi:10.1016/S2352-4642(20)30177-2

14. Godfred-Cato S, Bryant B, Leung J, et al; California MIS-C Response Team. COVID-19-associated multisystem inflammatory syndrome in children: United States, March-July 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(32):1074-1080. doi:10.15585/mmwr.mm6932e2

15. 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 Pediatr*. 2020;174(9):882-889. doi:10.1001/jamapediatrics.2020.1467

16. Office of the Federal Register; Government Publishing Office. Electronic code of federal regulations. Accessed February 21, 2021. https://www.ecfr.gov/cgi-bin/text-idx?SID=fc043bd2812f0775fa80066558a6bbcf&mc=true&node=pt45.1.46&rgn=div5#se45.1.46_1102

17. Centers for Disease Control and Prevention. Partner updates: case definition for MISC-C. Accessed December 4, 2020. https://www.cdc.gov/mis-c/hcp/

18. Leteurtre S, Duhamel A, Grandbastien B, et al. Daily estimation of the severity of multiple organ dysfunction syndrome in critically ill children. *CMAJ*. 2010;182(11):1181-1187. doi:10.1503/cmaj.081715

19. World Health Organization. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Accessed February 4, 2021. https://www.who.int/vmnis/indicators/haemoglobin.pdf

20. Centers for Disease Control and Prevention. Defining childhood obesity: BMI for children and teens. Accessed September 21, 2020. https://www.cdc.gov/obesity/childhood/defining.html

21. Lopez L, Colan SD, Frommelt PC, et al. Recommendations for quantification methods during the performance of a pediatric echocardiogram: a report from the Pediatric Measurements Writing Group of the American Society of Echocardiography Pediatric and Congenital Heart Disease Council. *J Am Soc Echocardiogr*. 2010;23(5):465-495. doi:10.1016/j.echo.2010.03.019

22. McCrindle BW, Rowley AH, Newburger JW, et al; American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; Council on Cardiovascular Surgery and Anesthesia; and Council on Epidemiology and Prevention. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. *Circulation*. 2017;135(17):e927-e999. doi:10.1161/CIR.0000000000000484

23. Matics TJ, Sanchez-Pinto LN. Adaptation and validation of a pediatric Sequential Organ Failure Assessment Score and evaluation of the Sepsis-3 Definitions in Critically Ill Children. *JAMA Pediatr*. 2017;171(10):e172352. doi:10.1001/jamapediatrics.2017.2352

24. Linkins LA, Dans AL, Moores LK, et al. Treatment and prevention of heparin-induced thrombocytopenia: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2)(suppl):e495S-e530S. doi:10.1378/chest.11-2303

25. Spiegelman D, Hertzmark E. Easy SAS calculations for risk or prevalence ratios and differences. *Am J Epidemiol*. 2005;162(3):199-200. doi:10.1093/aje/kwi188

26. Norton EC, Miller MM, Kleinman LC. Computing adjusted risk ratios and risk differences in Stata. *The Stata Journal*. 2013;13(3):492-509.

27. Lee EH, Kepler KL, Geevarughese A, et al. Race/ethnicity among children with COVID-19-associated multisystem inflammatory syndrome. *JAMA Netw Open*. 2020;3(11):e2030280. doi:10.1001/jamanetworkopen.2020.30280

28. Portman MA, Dahdah NS, Slee A, et al; EATAK Investigators. Etanercept with IVIg for acute Kawasaki disease: a randomized controlled trial. *Pediatrics*. 2019;143(6):e20183675. doi:10.1542/peds.2018-3675

29. Clark DE, Denby KJ, Kaufman LM, et al. Predictors of intravenous immunoglobulin nonresponse and racial disparities in Kawasaki disease. *Pediatr Infect Dis J*. 2018;37(12):1227-1234. doi:10.1097/INF.0000000000002019

30. Matsubara D, Kauffman HL, Wang Y, et al. Echocardiographic findings in pediatric multisystem inflammatory syndrome associated with COVID-19 in the United States. *J Am Coll Cardiol*. 2020;76(17):1947-1961. doi:10.1016/j.jacc.2020.08.056

31. Belhadjer Z, Méot M, Bajolle F, et al. Acute heart failure in multisystem inflammatory syndrome in children in the context of global SARS-CoV-2 pandemic. *Circulation*. 2020;142(5):429-436. doi:10.1161/CIRCULATIONAHA.120.048360

32. Theocharis P, Wong J, Pushparajah K, et al. Multimodality cardiac evaluation in children and young adults with multisystem inflammation associated with COVID-19. *Eur Heart J Cardiovasc Imaging*. 2020;jeaa212. doi:10.1093/ehjci/jeaa212

33. Freaney PM, Shah SJ, Khan SS. COVID-19 and heart failure with preserved ejection fraction. *JAMA*. 2020. doi:10.1001/jama.2020.17445

34. Muniz JC, Dummer K, Gauvreau K, Colan SD, Fulton DR, Newburger JW. Coronary artery dimensions in febrile children without Kawasaki disease. *Circ Cardiovasc Imaging*. 2013;6(2):239-244. doi:10.1161/CIRCIMAGING.112.000159

35. Shulman ST, Rowley AH. Kawasaki disease: insights into pathogenesis and approaches to treatment. *Nat Rev Rheumatol*. 2015;11(8):475-482. doi:10.1038/nrrheum.2015.54

36. Alsaied T, Tremoulet AH, Burns JC, et al. Review of cardiac involvement in multisystem inflammatory syndrome in children. *Circulation*. 2021;143(1):78-88. doi:10.1161/CIRCULATIONAHA.120.049836

37. Guo T, Fan Y, Chen M, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiol*. 2020;5(7):811-818. doi:10.1001/jamacardio.2020.1017

38. Rowley AH. Understanding SARS-CoV-2-related multisystem inflammatory syndrome in children. *Nat Rev Immunol*. 2020;20(8):453-454. doi:10.1038/s41577-020-0367-5

39. 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. doi:10.1172/JCI141113

40. Belhadjer Z, Auriau J, Méot M, et al. Addition of corticosteroids to immunoglobulins is associated with recovery of cardiac function in multi-inflammatory syndrome in children. *Circulation*. 2020;142(23):2282-2284. doi:10.1161/CIRCULATIONAHA.120.050147