Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
SARS-CoV-2 Clinical Syndromes and Predictors of Disease Severity in Hospitalized Children and Youth

Danielle M. Fernandes, MD, Carlos R. Oliveira, MD, PhD, Sandra Guerguis, MD, Ruth Eisenberg, MS, Jaeun Choi, PhD, Mimi Kim, ScD, Ashraf Abdelhemid, MBBS, Rabia Agha, MD, Saranga Agarwal, MD, Judy L. Aschner, MD, Jeffrey R. Avner, MD, Cathleen Ballance, MD, Joshua Bock, BA, Sejal M. Bhavsar, MD, Melissa Campbell, MD, Katharine N. Clouser, MD, Matthew Gesner, MD, David L. Goldman, MD, Margaret R. Hammerschlag, MD, Saul Hymes, MD, Ashley Howard, DO, Heejin Jung, MD, Stephan Kohlhoff, MD, Tsoline Kojaoghlanian, MD, Rachel Lewis, MD, Sharon Nachman, MD, Srividya Naganathan, MD, Elijah Paintsil, MD, Harpreet Pall, MD, Sharlene Sy, MD, Stephen Wadowski, MD, Elissa Zirinsky, MD, Michael D. Cabana, MD, MPH, Betsy C. Herold, MD, The Tri-State Pediatric COVID-19 Research Consortium Authors

PII: S0022-3476(20)31393-7
DOI: https://doi.org/10.1016/j.jpeds.2020.11.016
Reference: YMPD 11899

To appear in: The Journal of Pediatrics

Received Date: 10 October 2020
Revised Date: 2 November 2020
Accepted Date: 10 November 2020

Please cite this article as: Fernandes DM, Oliveira CR, Guerguis S, Eisenberg R, Choi J, Kim M, Abdelhemid A, Agha R, Agarwal S, Aschner JL, Avner JR, Ballance C, Bock J, Bhavsar SM, Campbell M, Clouser KN, Gesner M, Goldman DL, Hammerschlag MR, Hymes S, Howard A, Jung H-j, Kohlhoff S, Kojaoghlanian T, Lewis R, Nachman S, Naganathan S, Paintsil E, Pall H, Sy S, Wadowski S, Zirinsky E, Cabana MD, Herold BC, The Tri-State Pediatric COVID-19 Research Consortium Authors, SARS-CoV-2 Clinical Syndromes and Predictors of Disease Severity in Hospitalized Children and Youth, The Journal of Pediatrics (2020), doi: https://doi.org/10.1016/j.jpeds.2020.11.016.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of
Title: SARS-CoV-2 Clinical Syndromes and Predictors of Disease Severity in Hospitalized Children and Youth

The Tri-State Pediatric COVID-19 Research Consortium Authors: Danielle M. Fernandes, MD1*; Carlos R. Oliveira, MD, PhD*; Sandra Guerguis, MD1; Ruth Eisenberg, MS1; Jaeun Choi, PhD1; Mimi Kim, ScD1; Ashraf Abdelhemid3, MBBS; Rabia Agha MD4; Saranga Agarwal, MD5; Judy L. Aschner, MD5; Jeffrey R. Avner, MD4; Cathleen Ballance, MD5; Joshua Bock, BA1; Sejal M. Bhavsar, MD5; Melissa Campbell, MD5; Katharine N. Clouser, MD5; Matthew Gesner, MD5; David L. Goldman, MD1; Margaret R. Hammerschlag, MD5; Saul Hymes MD5; Ashley Howard, DO5; Hee-jin Jung, MD5; Stephan Kohlhoff, MD5; Tsoline Kojaoghlanian, MD5; Rachel Lewis, MD5; Sharon Nachman, MD5; Srividya Naganathan, MD6; Elijah Paintsil, MD5; Harpreet Pall, MD6; Sharlene Sy, MD1; Stephen Wadowski, MD1; Elissa Zirinsky, MD5; Michael D. Cabana, MD, MPH1; Betsy C. Herold, MD1

*Contributed equally

Affiliations: 1Department of Pediatrics, Albert Einstein College of Medicine, Children’s Hospital at Montefiore, Bronx, New York; 2Department of Pediatrics, Yale School of Medicine, New Haven, Connecticut; 3Department of Pediatrics, Kings County Hospital Center, Brooklyn, New York; 4Department of Pediatrics, Maimonides Children’s Hospital, Brooklyn, New York; 5Department of Pediatrics, Joseph M. Sanzari Children’s Hospital, Hackensack, New Jersey; 6Department of Pediatrics, K. Hovnanian Children’s Hospital, Neptune City, New Jersey; 7Department of Pediatrics, SUNY Downstate Medical Center University Hospital, Brooklyn, New York; 8Department of Pediatrics, Stony Brook University Renaissance Hospital, Stony Brook, New York

Corresponding Author: Danielle M. Fernandes, MD, Department of Pediatrics, The Children’s Hospital at Montefiore, 3411 Wayne Avenue, Room 851, Bronx NY, 10467, Phone: 718-741-2390, Fax: 718-920-6506, dffernandes@montefiore.org

M.C. serves on the Editorial Board for The Journal of Pediatrics and is a member of the United States Preventive Services Task Force (USPSTF). This manuscript does not necessarily reflect the views of the USPSTF. The other authors declare no conflicts of interest.

Data sharing statement: De-identified data that underlie the results reported in this article will be made available to investigators whose proposed use of the data has been approved by an independent review committee. Proposals may be submitted to the corresponding author up to 36 months following article publication. For access, data requestors will need to sign a data access agreement.

Key words: COVID-19, Biomarkers

Objective: To characterize the demographic and clinical features of pediatric SARS-CoV-2 syndromes and identify admission variables predictive of disease severity.
Study design: We conducted a multicenter, retrospective and prospective study of pediatric patients hospitalized with acute SARS-CoV-2 infections and multisystem inflammatory syndrome in children (MIS-C) at eight sites in New York, New Jersey, and Connecticut.

Results: We identified 281 hospitalized patients with SARS-CoV-2 infections and divided them into three groups based on clinical features. Overall, 143 (51%) had respiratory disease, 69 (25%) had MIS-C, and 69 (25%) had other manifestations including gastrointestinal illness or fever. Patients with MIS-C were more likely to identify as non-Hispanic black compared with patients with respiratory disease (35% versus 18%, \( P = .02 \)). Seven patients (2%) died and 114 (41%) were admitted to the ICU. In multivariable analyses, obesity (OR=3.39, 95% CI:1.26-9.10, \( P = .02 \)) and hypoxia on admission (OR=4.01; 95% CI:1.14-14.15; \( P = .03 \)) were predictive of severe respiratory disease. Lower absolute lymphocyte count (OR=8.33 per unit decrease in \( 10^9 \) cells/L, 95% CI:2.32-33.33, \( P = .001 \)) and higher C-reactive protein (OR=1.06 per unit increase in mg/dL, 95% CI:1.01-1.12, \( P = .017 \)) were predictive of severe MIS-C. Race/ethnicity or socioeconomic status were not predictive of disease severity.

Conclusions: We identified variables at the time of hospitalization that may help predict the development of severe SARS-CoV-2 disease manifestations in children and youth. These variables may have implications for future prognostic tools that inform hospital admission and clinical management.

Abbreviations:
MIS-C: multisystem inflammatory syndrome in children, COVID-19: coronavirus disease 2019, SES: socioeconomic status, CDC: Centers for Disease Control and Prevention, ICU: intensive care
The disease associated with SARS-CoV-2, COVID-19 (coronavirus disease 2019), predominantly affects adults, but case series have documented that SARS-CoV-2 also can cause severe disease in children and youth.\(^1\text{-}^3\) Manifestations of SARS-CoV-2 in children include a respiratory disease similar to what is described in adults, as well as a syndrome that was first described and appears to be more common in children designated as multisystem inflammatory syndrome in children (MIS-C).\(^1\text{-}^7\)

Although there is a growing body of research about COVID-19 in adults,\(^8\text{-}^{10}\) much is still unknown about the effects of this virus in the pediatric population. Most studies of COVID-19 in the pediatric population have been single-center, limited by size, or have focused on only one clinical manifestation. Thus, we still have a relatively limited understanding of the full spectrum of disease in children and youth.\(^1\text{-}^3, 5, 6, 11\) Furthermore, although it has been reported that COVID-19 disproportionately affects minorities and people of lower socioeconomic status (SES), this observation has not yet been examined formally in a large pediatric dataset of hospitalized patients.\(^12\text{-}^{14}\) Given the uncertainty around natural history and prognosis, there is a need to define the spectrum of disease and develop prognostic tools to identify children at risk for clinical decompensation.

As an important first step to addressing these gaps, this study aims to characterize the clinical course and outcomes of children and youth hospitalized with SARS-CoV-2 infections, and identify patient characteristics associated with an increased risk of becoming critically ill during hospitalization.
METHODS

Study Design and Data Collection

We conducted a retrospective and prospective multicenter cohort study of hospitalized pediatric patients, defined as children and youth ≤22 years of age, with laboratory-confirmed SARS-CoV-2 infection or MIS-C, at eight pediatric centers in New York (NY), New Jersey (NJ), and Connecticut (CT), an early epicenter of the pandemic in the United States. Data was collected retrospectively for patients admitted up until April 12, 2020 and prospectively thereafter for patients site. The hospitals, further described in Table I (available at www.jpeds.com), comprise the Tri-State Pediatric COVID-19 Consortium. Cases of patients in this study have been published previously at least in part (Appendix; available at www.jpeds.com).2, 3, 11, 15-23

Cases were identified at each participating site using active, hospital-based surveillance for COVID-19 and MIS-C using standardized inclusion criteria and case definitions. Patients were included if they were hospitalized between March 1, 2020, and May 22, 2020 for any reason, were ≤22 years of age at the time of admission, and ) had a positive diagnostic test for SARS-CoV-2 using reverse-transcriptase polymerase-chain-reaction (PCR) to detect the viral RNA, or met the MIS-C case definition as set by Centers for Disease Control and Prevention (CDC),24 which includes: age <21 years, reported or documented fever for more than 24 hours, laboratory markers of inflammation, multisystem (≥ 2) organ involvement, positive SARS-CoV-2 testing (PCR or serology) or exposure to a COVID-19 case within four weeks of symptom onset, and no plausible alternative diagnoses. Each site identified cases retrospectively and prospectively by reviewing COVID-19 test results (laboratory-based surveillance) and inpatient admission logs (MIS-C syndromic surveillance). Neonates who tested positive on the first day of
life and pregnant patients were excluded. In addition, patients who were admitted to the hospital with unrelated illnesses such as trauma, scheduled chemotherapy, or psychiatric disease and were found to be incidentally positive for SARS-CoV-2 by admission PCR screening were also excluded.

We reviewed the electronic medical records for demographic, clinical, laboratory, radiographic, and hospitalization outcome data from admission to discharge. Investigators at each site used a standardized data collection form and transmitted data to a central database using a web-based data capture program hosted at Albert Einstein College of Medicine (Bronx, NY). The study was approved by each center’s institutional review board, and each site was exempted from obtaining informed consent.

**Study Definitions**

Respiratory COVID-19 was defined based on the World Health Organization criteria and included patients having any of the following clinical features: cough, dyspnea, tachypnea, oxygen requirement, or imaging suggestive of pneumonia. Each MIS-C case was independently reviewed to ensure it met CDC criteria for MIS-C. Patients who did not meet the criteria for either respiratory COVID-19 or MIS-C were classified based on their primary reason for hospitalization. For the comparative analysis, non-respiratory, non-MIS-C SARS-CoV-2 infected hospitalized patients were broadly classified as “other.” Severe disease was defined as an intensive care unit (ICU) admission ≥48 hours.

Self-reported race and ethnicity were categorized into Hispanic, non-Hispanic white, non-Hispanic black, and non-Hispanic other. Patients were categorized as obese if they had a body mass index (BMI) or weight-for-age (if < 2 years old) that was ≥ 95th percentile for age and sex. Patients were considered medically complex if they had comorbidities that required
multiple services, were technology-dependent, were considered medically fragile (e.g., cancer), or had a severe disability (e.g., intellectual disability). Admission vital signs and relevant laboratory test results were described using age-adjusted standard values. Study definitions are detailed in Table 2 (available at www.jpeds.com). Socioeconomic measures at the zip code level were used to generate a composite index and proxy measure of individual-level SES. The selected area-level measures were based on previously described and validated instruments using data from the American Community Survey (2014–2018) and are further described in the Table 2. Patients were considered as low SES if they resided in a zip code that was ≥1 standard deviation below the mean area-level SES index.

**Statistical Analyses**

Descriptive statistics were used to summarize the clinical and sociodemographic characteristics of all patients for whom data were available. The clinical syndromes were collapsed into three groups: respiratory, MIS-C, and other. Differences in the distribution of the measured variables were compared using Fisher exact and Kruskal–Wallis tests for categorical and continuous variables, respectively. Results were adjusted for multiple comparisons with Tukey test.

Multivariable logistic regression models were fit for both respiratory and MIS-C groups separately to identify patient characteristics on admission that were predictive of developing severe disease. Potential predictor variables included: clinical manifestations, BMI, comorbidities, laboratory results, insurance status, race/ethnicity, age, sex, and SES. Categories of predictor variables with sparse data were combined before inclusion in the multivariable models. Specifically, insurance status was examined as Medicare/Medicaid versus all other types of payers, and race/ethnicity was examined as Hispanic, Non-Hispanic black, and Non-
Hispanic white or Non-Hispanic other. Only three patients with respiratory classification and six patients with MIS-C were classified as Non-Hispanic other.

For the severity models, adjusted odds ratios (aOR) were adjusted for hospital site using a fixed-effects approach given concerns about the performance and lack of convergence of random-effects models when the number of sites (clusters) is small.\textsuperscript{32} For the multivariable analyses, the initial model included variables with $P<.25$ in bivariate analyses, in addition to age and race, which were deemed \textit{a priori} to be important clinically (Model 1). An additional model also was fit using a stepwise backward selection strategy in which only those variables with $P<.05$ were retained (Model 2). Missing data rates in the predictor variables ranged from 0\% to 16\% and were handled using both list-wise deletion (i.e., available data) and multiple imputation (MI) using chained equations. C-reactive protein (CRP) level was not considered for inclusion in the respiratory specific model due to a high rate of missing data (28\%) and potential bias from non-random missingness because CRP likely was measured more frequently in patients with severe disease.

No sample-size calculations were performed \textit{a priori}. All tests of statistical significance were two-sided, and $P<.05$ were defined as statistically significant. Statistical analyses were performed using both Stata (V. 15, Stata Corp, Texas, USA) and SAS (V. 9.4, SAS Institute Inc, Cary, NC, USA) statistical software.

**RESULTS**

**Demographics and Clinical Characteristics**

We identified 315 hospitalized pediatric patients with laboratory-confirmed SARS-CoV-2 infection or MIS-C during the peak 3-month period of the pandemic in the Tri-State area. We
excluded 34 patients from the final cohort for analysis because review of the medical record indicated that they were hospitalized for unrelated problems deemed unlikely to be etiologically related to SARS-CoV-2, leaving a final cohort of 281 patients (Table 2). The majority of the cases came from hospitals in NY (192/281 [68%]) followed by NJ (68/281 [24%]) and CT (21/281 [7%]) (Table 1). The NY hospitals were located in Brooklyn, Bronx and Suffolk counties, which were among the hardest impacted areas. Hospitalizations for respiratory disease peaked during the third week of the study period and began to decline three weeks later, as MIS-C cases began to increase (Figure 1). Hospitalizations for other syndromes peaked during the fourth week of the pandemic and remained relatively constant throughout the study period.

The baseline characteristics of the overall cohort are detailed in Table 3. Patients were predominantly male (170/281 [60%]) with a median age of 10 years (IQR 1–17). The majority of patients were either Hispanic (125/245 [51%]) or non-Hispanic black (57/245 [23%]). Most of the patients had public insurance through Medicaid or Medicare (188/281 [67%]). Obesity and asthma were the most commonly reported preexisting comorbidities (85/250 [34%] and 40/281 [14%], respectively). Overall, 21% (59/281) of cases were considered medically complex.

Among the 281 patients, 143 (51%) presented with respiratory disease, 69 (25%) with MIS-C, and 69 (25%) with one of the other acute SARS-CoV-2 related clinical syndromes or conditions. The “other” group included 32 patients with gastrointestinal symptoms, 21 febrile infants, 6 with neurologic disease, 6 with diabetic ketoacidosis, and 4 patients hospitalized for other indications listed in Table 4 (available at www.jpeds.com). Additional details on the clinical features and outcomes of patients in this “other” group are shown in Table 5 (available at www.jpeds.com).

Differences in Demographics and Clinical Characteristics by Clinical Syndrome
The distribution of baseline patient characteristics varied significantly between the different clinical syndromes (Table 3). Patients with respiratory disease were older than those with MIS-C (median age: 14 [IQR:3–19] vs. 7 [IQR:3–11] years, respectively, P<.001). Compared with respiratory COVID-19, patients with MIS-C identified their race/ethnicity more commonly as non-Hispanic black (difference = 18%, 95%CI: 2%–33%, P=.02). Notably, the prevalence of obesity was 18% higher (95%CI: 2%–34%, P=.02) in the respiratory disease group compared with MIS-C. Similarly, the prevalence of medical complexity was 24% higher (95%CI: 10%–38%, P<.001) in the respiratory disease group compared with patients with MIS-C. Differences in other baseline characteristics by syndrome are shown in Table 6 (available at www.jpeds.com).

The most common signs and symptoms on admission are shown in Figure 2 (available at www.jpeds.com). Most patients had a fever (235/281 [84%]), and 58% (162/281) reported a respiratory symptom (ie, cough, wheezing, pharyngitis, or dyspnea). Anosmia and ageusia was reported in few patients (9/281 [3%]). Gastrointestinal symptoms, such as emesis, diarrhea, or abdominal pain, were common, particularly among children with MIS-C (52/69 [75%]). Several patients with MIS-C also manifested a rash (27/69 [39%]) and/or conjunctival injection (22/69 [32%]), which was rarely reported among the other clinical phenotypes.

Notable admission laboratory test results are shown in Table 3 and Table 6. Considering the entire cohort, admission CRP often was elevated (median 7.8 [IQR:1.7–27.2]) and absolute lymphocyte count (ALC) frequently was decreased (median 1.6 [0.9–2.7]). The highest CRP and lowest ALC were found in the patients with MIS-C (median 25.7 [IQR: 10.0–38.1] and 1.3 [IQR: 0.8–1.9], respectively). Other peak and nadir results are shown in Figure 3 (available at
Peak procalcitonin was greater in patients with MIS-C compared with respiratory illness (median 9.1 [IQR: 1.1-21.1]) vs. 0.2 [IQR: 0.1-0.9], \( P<.001 \).

Almost one half of the patients with respiratory symptoms had a chest radiograph with bilateral infiltrates on admission (63/143 [44%]), and 18% (25/143) required invasive mechanical ventilation (Table 7). Conversely, 64% (40/63) of the patients with MIS-C had a normal chest radiograph, and only 4% (3/69) were placed on a ventilator during hospitalization. Medical therapy varied considerably both between and within groups (Table 7). Patients with MIS-C were commonly prescribed methylprednisolone (32/69 [46%]) and/or intravenous immunoglobulin (41/69 [59%]), which were used infrequently in patients with respiratory disease (39/143 [27%] and 3/143 [2%], respectively). Remdesivir was given to 18% (26/143) of patients with respiratory disease and in 7% (5/69) of patients with MIS-C.

The two most common complications in the respiratory disease cohort were acute respiratory distress syndrome (24/143 [17%]) and acute kidney injury (15/143 [11%]). In contrast, cardiovascular complications such as shock (24/69 [35%]) and cardiac dysfunction (17/69 [25%]) were common in MIS-C. Although 12 patients with MIS-C (17%) had depressed ejection fractions on echocardiogram, none had a coronary artery aneurysm (z score dilation \( \geq 2.5 \)) identified during the study period.

**Outcome and Predictors of Disease Severity**

Nearly all patients (267/281 [95%]) recovered from their illness and were discharged home by the end of the study (Table 8; available at www.jpeds.com), with a median length of hospitalization of 4 days (IQR:2–8). Overall, 114/281 (41%) of the patients were admitted to the ICU: 16 were admitted for <48 hours. Patients with MIS-C were more likely than those with respiratory disease to be admitted to the ICU (44/69 [64%] vs. 64/143 [45%], \( P<.001 \)), but all
deaths (7/315 [2%]) occurred in the respiratory group. Four of the patients who died were considered medically complex; 2 had asthma as their only prior medical problem, and 1 had no previous medical conditions. Additional details on the deceased patients are provided in Table 9 (available at www.jpeds.com).

Overall, 40% (56/141) of patients with respiratory disease, 56% (38/68) with MIS-C, and 6% (4/69) with “other” phenotypes met our case definition of severe disease (i.e., ≥48 hours in the ICU). In multivariable analyses of the respiratory group (Table 10), younger age (aOR=1.09 per 1-year decrease, 95%CI: 1.02–1.16), obesity (aOR=3.39, 95%CI: 1.26–9.10), increasing white blood cell count (aOR=1.11 per unit increase in 10⁹/L, 95%CI: 1.03–1.20), hypoxia (aOR=4.01, 95%CI: 1.14–14.15), and bilateral infiltrates on chest radiograph (aOR=3.69, 95%CI: 1.46–9.32) at admission were independent predictors of severe disease (model 2); race adjusted results were similar (model 1). In the MIS-C group (Table 10), only lower ALC (aOR=8.33 per unit decrease in 10⁹ cells/L, 95%CI: 2.32–33.33) and increasing CRP (aOR=1.06 per unit increase in mg/dL, 95%CI: 1.01–1.12) at admission were independent predictors of severity (model 2). Insurance status, race/ethnicity, and SES were not significantly predictive of respiratory or MIS-C disease severity. Three patients were excluded from the analysis of disease severity (1 respiratory patient who died on the day of admission, 1 patient who was previously chronically ventilator-dependent and discharged on the same day of admission, and 1 MIS-C patient transferred to another facility on the day of admission). Results after conducting multiple imputation for missing data were similar to those estimated using available data (Table 11; available at www.jpeds.com).

In a separate analysis, laboratory variables measured during hospitalization (as opposed to at admission) also were compared between clinical syndromes. Compared with non-severe
cases, both severe respiratory disease and MIS-C were significantly associated with a higher peak CRP, procalcitonin, or troponin level, and a lower nadir ALC, platelet count, or serum sodium level (Table 12; available at www.jpeds.com). Although 78% (45/58) of patients with MIS-C had an elevated B-type natriuretic peptide (BNP), peak BNP did not differ significantly by severity status.

DISCUSSION

This multicenter cohort study describes a spectrum of clinical manifestations of SARS-CoV-2 in children and youth admitted to hospitals that serve racially and ethnically diverse regions of NY, NJ, and CT. Although the populations served by the hospitals vary in terms of sociodemographic diversity, with several having a predominantly non-Hispanic white population, nearly all sites reported that the majority of patients with SARS-CoV-2 were Hispanic and/or black. Notably, patients with MIS-C were more likely to be Non-Hispanic black, whereas children with respiratory illness were more likely to be Hispanic. Previous MIS-C case series also have shown that black children represent a significant percentage of MIS-C cases in the US, ranging from 25-40%.

These data reinforce the notion that minorities bear a disproportionate burden of disease.

There also have been reports that communities with a high proportion of lower-income individuals are experiencing a disproportionately higher rate of COVID-19. Consistent with these reports, we found that 31% of patients hospitalized with SARS-CoV-2 were of low SES. Poverty is associated with poor health outcomes and higher rates of pediatric ICU admissions in general. Importantly, however, children of lower SES in our study were not more likely to have severe outcomes following hospitalization.
Several features differentiated the various SARS-CoV-2 infection phenotypes. More than half of the patients with respiratory disease (similar to COVID-19 in adults) were older than 13 years on admission. Similar to what has been reported for adults, children and youth with respiratory COVID-19 commonly had obesity, preexisting pulmonary and neurologic disease, as well as medical complexity. In contrast, patients with MIS-C often had no comorbidities, and more than half were under 7 years of age. Although patients with MIS-C often were critically ill, requiring vasopressor and immunomodulatory therapy, their hospitalization outcomes generally were excellent.

There is little evidence-based guidance available to aid clinicians in the management of children and youth with acute COVID-19 or MIS-C. Predicting clinical decompensation has important ramifications in terms of resource utilization, hospital admission, and patient management. In terms of severity, close to one third of the hospitalized patients in our cohort spent ≥ 48 hours in the ICU, and 2% (7/281) died. Patients with respiratory COVID-19 were more likely to develop severe disease if, on admission, they had either an elevated white blood cell count, hypoxia, bilateral infiltrates on chest radiograph, were of younger age, or were obese. The association between weight and severe respiratory COVID-19 is consistent with the adult literature; however, the mechanisms of this association require further study. For MIS-C, only admission laboratory values of CRP and absolute lymphocyte count were predictive of severity. This study builds on the growing body of evidence showing that mortality in hospitalized pediatric patients is low compared with adults. However, it highlights that the young population is not universally spared from morbidity, and that even previously healthy children and youth can develop severe disease requiring supportive therapy.
We found a wide array of clinical manifestations in children and youth hospitalized with SARS-CoV-2. Although most of the clinical manifestations in children have also been reported in adults, the frequency of some differ considerably. For example, gastrointestinal symptoms such as abdominal pain, emesis and diarrhea, occur in less than a quarter of hospitalized adults, yet up to half of the patients in our cohort reported one of these symptoms\textsuperscript{39}. Ocular and dermatologic findings are also rarely reported in adults yet were observed in 32\% and 39\% of MIS-C cases, respectively. We also found that SARS-CoV-2 can be an incidental finding in a substantial number of hospitalized pediatric patients. As testing became more accessible and routine for all hospital admissions in late March, we documented a steady rate of incidental SARS-CoV-2 infections (i.e. not plausibly etiologically related). This observation has implications for infection control policies and for monitoring community prevalence of infection. Although data are limited, studies show that children can have high viral loads even when asymptomatic or affected with mild disease and some studies suggest that they can spread disease\textsuperscript{40}, making it important to screen hospitalized children to both limit potential transmission and track community prevalence of the virus.

Our study has limitations. The study population included patients within the Tri-State area but did not include patients hospitalized in all of the New York City boroughs and may not be generalizable to other geographic regions. Decisions to admit to the hospital and ICU may have varied by location. To date, children have been excluded from randomized controlled trials of antiviral drugs such as remdesivir\textsuperscript{41,42} and there have been no controlled studies on the optimal treatment of MIS-C. Therefore, approaches to treatment, and as a consequence, the clinical outcomes of the patients in this study, may have varied across sites.
Acknowledgments: We thank each of the COVID-19 treatment teams and healthcare providers at the sites involved in the care of patients with COVID-19 for their work and dedication to patient care.

References:

1. Shekerdemian LS, Mahmood NR, Wolfe KK, Riggs BJ, Ross CE, McKiernan CA, et al. Characteristics and Outcomes of Children With Coronavirus Disease 2019 (COVID-19)
Infection Admitted to US and Canadian Pediatric Intensive Care Units. JAMA Pediatr. 2020;174:868-73.

2. Dufort EM, Koumans EH, Chow EJ, Rosenthal EM, Muse A, Rowlands J, et al. Multisystem Inflammatory Syndrome in Children in New York State. N Engl J Med. 2020;383:347-58.

3. Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MBF, et al. Multisystem Inflammatory Syndrome in U.S. Children and Adolescents. New England Journal of Medicine. 2020;383:334-46.

4. Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, et al. Epidemiology of COVID-19 Among Children in China. Pediatrics. 2020;145.

5. Zachariah P, Johnson CL, Halabi KC, Ahn D, Sen AI, Fischer A, 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 Pediatr. 2020;174:e202430.

6. Kainth MK, Goenka PK, Williamson KA, Fishbein JS, Subramony A, Schleien C, et al. Early Experience of COVID-19 in a US Children' Hospital. Pediatrics. 2020;146:e2020003186.

7. Morris SB, Schwartz NG, Patel P, Abbo L, Beauchamps L, Balan S, et al. Case Series of Multisystem Inflammatory Syndrome in Adults Associated with SARS-CoV-2 Infection — United Kingdom and United States, March–August 2020. MMWR Morb Mortal Wkly Rep. 2020.

8. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. JAMA. 2020;323:2052-9.
9. Cummings MJ, Baldwin MR, Abrams D, Jacobson SD, Meyer BJ, Balough EM, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. Lancet. 2020;395:1763-70.

10. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395:1054-62.

11. Agha R, Kojaoghlanian T, Avner JR. Initial Observations of COVID-19 in US Children. Hosp Pediatr. 2020;10:902-5.

12. Azar KMJ, Shen Z, Romanelli RJ, Lockhart SH, Smits K, Robinson S, et al. Disparities In Outcomes Among COVID-19 Patients In A Large Health Care System In California. Health Aff (Millwood). 2020;39:1253-62.

13. Millett GA, Jones AT, Benkeser D, Baral S, Mercer L, Beyrer C, et al. Assessing differential impacts of COVID-19 on black communities. Ann Epidemiol. 2020;47:37-44.

14. Lieberman-Cribbin W, Tuminello S, Flores RM, Taioli E. Disparities in COVID-19 Testing and Positivity in New York City. Am J Prev Med. 2020;59:326-32.

15. Chao JY, Derespina KR, Herold BC, Goldman DL, Aldrich M, Weingarten J, et al. Clinical Characteristics and Outcomes of Hospitalized and Critically Ill Children and Adolescents with Coronavirus Disease 2019 (COVID-19) at a Tertiary Care Medical Center in New York City. J Pediatr. 2020;223:14-9.

16. Derespina KR, Kaushik S, Plichta A, Conway EE, Jr., Bercow A, Choi J, et al. Clinical Manifestations and Outcomes of Critically Ill Children and Adolescents with COVID-19 in New York City. J Pediatr. 2020;223:14-9.
17. Kaushik S, Aydin SI, Derespina KR, Bansal PB, Kowalsky S, Trachtman R, et al. 
Multisystem Inflammatory Syndrome in Children Associated with Severe Acute Respiratory 
Syndrome Coronavirus 2 Infection (MIS-C): A Multi-institutional Study from New York City. J 
Pediatr. 2020;224:24-9.

18. Clouser KN, Baer A, Bhavsar S, Gadhavi J, Li S, Schnall J, et al. MIS-C after ARDS 
Associated with SARS-COV-2. Pediatric Infectious Disease Journal. 2020.

19. Bhavsar SM, Clouser KN, Gadhavi J, Anene O, Kaur R, Lewis R, et al. COVID-19 in 
Pediatrics: Characteristics of hospitalized children in New Jersey. Hospital Pediatrics. 2020;In 
Revisions.

20. Perez A, Kogan-Liberman D, Sheflin-Findling S, Raizner A, Ahuja KL, Ovchinsky N. 
Presentation of Severe Acute Respiratory Syndrome-Coronavirus 2 Infection as Cholestatic 
Jaundice in Two Healthy Adolescents. J Pediatr. 2020.

21. Pierce CA, Preston-Hurlburt P, Dai Y, Aschner CB, Cheshenko N, Galen B, et al. Immune 
responses to SARS-CoV-2 infection in hospitalized pediatric and adult patients. Science 
Translational Medicine. 2020;12:eabd5487.

22. Godfred-Cato S, Bryant B, Leung J, Oster ME, Conklin L, Abrams J, et al. COVID-19- 
Associated Multisystem Inflammatory Syndrome in Children - United States, March-July 2020. 
MMWR Morb Mortal Wkly Rep. 2020;69:1074-80.

23. Bhavsar SM, Agarwal S, Lewis R, Ganta A, Roshchina YS, Clouser KN, et al. COVID-19 
infection associated with encephalitis in an adolescent. Neurology: Clinical Practice. 
2020:10.1212/CPJ.00000000000000911.
24. Centers for Disease Control and Prevention. Emergency preparedness and response: multisystem inflammatory syndrome in children (MIS-C) associated with coronavirus disease 2019 (COVID-19).

25. World Health Organization. Clinical management of COVID-19.

26. Centers for Disease Control and Prevention. Defining Childhood Obesity.

27. Cohen E, Kuo DZ, Agrawal R, Berry JG, Bhagat SK, Simon TD, et al. Children with medical complexity: an emerging population for clinical and research initiatives. Pediatrics. 2011;127:529-38.

28. Kuo DZ, Houtrow AJ, Council On Children With Disabilities. Recognition and Management of Medical Complexity. Pediatrics. 2016;138.

29. Hughes H, Kahl, LK. The Harriet Lane handbook: a manual for pediatric house officers. 21st ed2018.

30. U.S. Census Bureau. American Community Survey 2013-2018.

31. Martsolf GR, Barrett ML, Weiss AJ, Washington R, Steiner CA, Mehrotra A, et al. Impact of Race/Ethnicity and Socioeconomic Status on Risk-Adjusted Readmission Rates: Implications for the Hospital Readmissions Reduction Program. Inquiry. 2016;53:0046958016667596.

32. McNeish D, Stapleton LM. Modeling Clustered Data with Very Few Clusters. Multivariate Behav Res. 2016;51:495-518.

33. Hawkins D. Social Determinants of COVID-19 in Massachusetts, United States: An Ecological Study. J Prev Med Public Health. 2020;53:220-7.

34. Maroko AR, Nash D, Pavilonis BT. COVID-19 and Inequity: a Comparative Spatial Analysis of New York City and Chicago Hot Spots. J Urban Health. 2020;97:461-70.
35. Andrst E, Riley CL, Brokamp C, Taylor S, Beck AF. Neighborhood Poverty and Pediatric Intensive Care Use. Pediatrics. 2019;144.

36. Hajifathalian K, Kumar S, Newberry C, Shah S, Fortune B, Krisko T, et al. Obesity is associated with worse outcomes in COVID-19: Analysis of Early Data From New York City. Obesity (Silver Spring). 2020.

37. Kim L, Whitaker M, O’Halloran A, Kambhampati A, Chai SJ, Reingold A, et al. Hospitalization Rates and Characteristics of Children Aged <18 Years Hospitalized with Laboratory-Confirmed COVID-19 - COVID-NET, 14 States, March 1-July 25, 2020. MMWR Morb Mortal Wkly Rep. 2020;69:1081-8.

38. Gotzinger F, Santiago-Garcia B, Noguera-Julian A, Lanaspa M, Lancellia L, Calo Carducci FI, et al. COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study. Lancet Child Adolesc Health. 2020.

39. Goyal P, Choi JJ, Pinheiro LC, Schenck EJ, Chen R, Jabri A, et al. Clinical Characteristics of Covid-19 in New York City. N Engl J Med. 2020;382:2372-4.

40. Yonker LM, Neilan AM, Bartsch Y, Patel AB, Regan J, Arya P, et al. Pediatric SARS-CoV-2: Clinical Presentation, Infectivity, and Immune Responses. J Pediatr. 2020.

41. Beigel JH, Tomashek KM, Dodd LE. Remdesivir for the Treatment of Covid-19 - Preliminary Report. Reply. N Engl J Med. 2020;383.

42. Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet. 2020;395:1569-78.

43. Force ADT, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA. 2012;307:2526-33.
44. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney Int Suppl. 2012;2:1-138.

45. Bonafide CP, Brady PW, Keren R, Conway PH, Marsolo K, Daymont C. Development of heart and respiratory rate percentile curves for hospitalized children. Pediatrics. 2013;131:e1150-7.

Figure 1. Hospitalized Cases by Syndrome during the Study Period

Figure 2 (online only). Signs and Symptoms on Admission by Clinical Syndrome
Figure 3 (online only). Peak and Nadir Laboratory Results by Syndrome
### Table 1. Characteristics of Participating Hospitals

| Hospital                                                                 | Study Admissions No. (%) | Pediatric ED Visits No. in 2019 | Population Estimates: Race and Ethnicity in Hospital County<sup>a</sup> (%)<sup>b</sup> | Race and Ethnicity of Reported SARS-CoV-2 Infections by Hospital (%)<sup>b</sup> |
|------------------------------------------------------------------------|--------------------------|---------------------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| New York                                                              |                          |                                 | Hispanic Black White                                                              | Hispanic Black White |
| Children's Hospital at Montefiore<sup>c</sup>                         | 107 (38%)                | 51,284                          | 56% 44% 45% 52% 22% 5%                                                           |                                                                     |
| Maimonides Children's Hospital<sup>d</sup>                           | 31 (11%)                 | 32,006                          | 19% 34% 50% 16% 13% 55%                                                         |                                                                     |
| Stony Brook Children's Hospital<sup>e</sup>                          | 26 (9%)                  | 21,653                          | 20% 9% 84% 50% 12% 42%                                                         |                                                                     |
| Kings County Hospital Center<sup>d</sup>                             | 18 (6%)                  | 37,000                          | 19% 34% 50% 0% 78% 0%                                                          |                                                                     |
| The Children's Hospital at State University of New York (SUNY) Downstate<sup>d</sup> | 10 (4%)                  | 18,000                          | 19% 34% 50% 0% 90% 0%                                                          |                                                                     |
| New Jersey                                                           |                          |                                 |                                                                                  |                                                                     |
| Joseph M. Sanzari Children's Hospital<sup>f</sup>                     | 51 (18%)                 | 38,000                          | 21% 7% 73% 65% 8% 47%                                                          |                                                                     |
| K. Hovnanian Children's Hospital<sup>g</sup>                         | 17 (6%)                  | 20,300                          | 11% 8% 85% 29% 6% 64%                                                          |                                                                     |
| Connecticut                                                          |                          |                                 |                                                                                  |                                                                     |
| Yale New Haven Children’s Hospital<sup>h</sup>                       | 21 (7%)                  | 32,500                          | 19% 15% 77% 62% 10% 38%                                                         |                                                                     |

<sup>ED= Emergency Department</sup>

<sup>a</sup>Based on US Census data for the county of the pediatric hospital<sup>30</sup>

<sup>b</sup>For these estimates Hispanics could be of any race, so they are also included in applicable race categories. Other races were not included.

Hospital Counties: <sup>c</sup>Bronx County, <sup>d</sup>Kings County, <sup>e</sup>Suffolk County, <sup>f</sup>Bergen County, <sup>g</sup>Monmouth County, <sup>h</sup>New Haven County
Table 2. Study Definitions

| Variable | Definition |
|----------|------------|
| SARS-CoV-2 Infection | Respiratory: any one of the following reported or documented clinical features: cough, dyspnea, tachypnea, increased oxygen requirement, or imaging suggestive of pneumonia. MIS-C: aged <21 years, with fever for more than 24 hours, laboratory markers of inflammation, multisystem organ involvement, positive of SARS-CoV-2 testing or exposure to a suspected or confirmed COVID-19 case within four weeks of symptom onset, and no plausible alternative diagnoses. Other: Patients who did not meet the criteria for either respiratory COVID-19 or MIS-C. |
| Excluded cases | Patients with incidental SARS-CoV-2 included those hospitalized for psychiatric diseases (n=9), trauma (n=7), cancer treatment (n=2), gastrostomy tube malfunction (n=1), skin and soft tissue infection (n=8), urinary tract infection (n=3), bacteremia (n=2), otorrhoea (n=1), and Epstein-Barr virus infection (n=1). |
| Severe disease | Previous definitions for severe disease include any admission to the intensive care unit, need for supplemental oxygen or invasive mechanical ventilation and, for MIS-C, vasopressor support. We defined severe disease as ≥48 hours in the ICU. With the exception of 1 patient who was transferred on the day of admission, 1 patient who was chronically ventilator-dependent and discharged on hospital day one, and 1 patient who died on the day of admission, this definition included all children who were ventilated during hospitalization and/or required vaspressors. There were 16 patients (6%) who were admitted to the ICU for <48 hours and none of these required mechanical ventilation or vaspressors. |
| Multisystem organ involvement | Two or more of the following: Cardiovascular: require vaspressors, elevated troponins, arrhythmia, abnormal echocardiogram Renal: acute kidney injury, renal failure Pulmonary: need for supplemental respiratory support above baseline Hematologic: elevated d-dimer, thrombocytopenia, anemia for age, leukopenia, thrombotic event Gastrointestinal: nausea/vomiting, abdominal pain, diarrhea, elevated bilirubin or liver function tests Dermatologic: rash, oral mucosal changes, conjunctivitis, peripheral extremity changes Neurological: encephalopathy, aseptic meningitis, stroke Musculoskeletal: arthralgias, arthritis, myalgia, myositis |
| Thrombocytopenia | Defined as platelets count of <150,000/µL |
| Anemia for age | Defined as hemoglobin <10 g/dL if age <1 year, otherwise hemoglobin <9 g/dL |
| Lymphopenia | Defined as an absolute lymphocyte count of <1200/µL |
| Acute Respiratory Distress Syndrome | Based on the Berlin definition or a physician diagnosis |
| Acute Kidney Injury | Defined as: Increase in serum creatinine to 1.5 times baseline/age-appropriate standard |
| Carditis | Defined as patients with a physician-diagnosed myocarditis or cardiomyopathy |
| Shock | Defined as requiring vaspressors |
| Thrombotic event | Defined as patients with one of the following: deep vein thrombus, pulmonary embolus, intracranial thrombus, or atrial thrombus |
| Obesity | Defined as a body mass index or weight-for-age (if < 2 years old) ≥ 95th percentile for age and sex |
| Other Coexisting conditions | Respiratory: asthma, oxygen or tracheostomy dependent Neurologic: cerebral palsy or seizure disorder Cardiovascular: congenital heart disease, arrhythmia or hypertension Diabetes: Type 1 or Type 2 diabetes Gastrointestinal: gastrosotmy tube dependence, gastroesophageal reflux disease, or other gastrointestional chronic illness |
| Immunosuppressed | Defined as patients with immunosuppressive conditions or actively receiving immunosuppressant drugs |
| History of smoking | Defined as self-reported history of smoking (cigarettes or marijuana) or vaping |
| Medical complexity | Any one of the following: multiple comorbidities that require multiple services, technology-dependence, medical fragility (e.g., cancer, congenital heart disease), or severe disability (e.g., intellectual disability). |
| COVID-19 exposure | Given the high incidence of COVID-19 infection in the Tri-State area during the study period, all patients who met criteria for MIS-C were considered exposed. |
| Fever | Defined as having subjective fever or measured temperature of ≥38.0 degrees Celsius by any method |
| Hypoxia | Defined as oxygen saturation <90% |
| Tachypnea for age | Refers to a presenting respiratory rate (RR) per minute above the 95th percentile for age as follows: age <1 month & presenting RR > 60; age 1-12 months presenting RR > 50; age 1-4 years presenting RR > 40; age 4-12 years presenting RR > 30; age >12 years presenting RR >25 |
Table 2. Study Definitions (continued)

| Socioeconomic Status (SES) Index | Using data from the American Community Survey (2014-2018), we calculated a socioeconomic score index based on patient home addresses as previously described and validated. The index includes data from each patient’s home zip code using census-derived zip code tabulation areas and combines six variables to form a SES score for each geographic area. The variables are the percentage of 1) adults with less than a high school education; 2) families with income below the federal poverty level; 3) households receiving public assistance; 4) female-headed households with children; 5) male unemployment; and 6) median household income. These measures were standardized to a mean of 0 and a standard deviation of 1, with positive values associated with a higher socioeconomic status. The variables were then summed and re-standardized to a mean of 0 and a standard deviation of 1. |

Table 3. Baseline Characteristics of Patients Hospitalized with SARS-CoV-2

| Characteristic | Clinical Group |
|----------------|---------------|
| **Age, years** | Total, N=281 | Respiratory, N=143 | MIS-C, N=69 | Other, N=69 | *P* value |
| Median age, yr. (IQR) | 10 (1-17) | 14 (3-19) | 7 (3-11) | 7 (0-16) | <0.001 |
| **Sex** | | | | | |
| Male | 170/281 (60.5%) | 87/143 (60.8%) | 42/69 (60.9%) | 41/69 (59.4%) | 0.99 |
| **Race/Ethnicity** | | | | | |
| Hispanic | 125/245 (51.0%) | 70/120 (58.3%) | 27/65 (41.5%) | 28/60 (46.7%) | 0.040 |
| Non-Hispanic black | 57/245 (23.3%) | 21/120 (17.5%) | 23/65 (35.4%) | 13/60 (21.7%) | |
| Non-Hispanic white | 49/245 (20.0%) | 25/120 (20.8%) | 9/65 (13.8%) | 15/60 (25.0%) | |
| Non-Hispanic other | 14/245 (5.7%) | 4/120 (3.3%) | 6/65 (9.2%) | 4/60 (6.7%) | |
| **Insurance** | | | | | |
| Private | 72/281 (25.6%) | 32/143 (22.4%) | 28/69 (40.6%) | 12/69 (17.4%) | 0.039 |
| Medicaid/Medicare | 188/281 (66.9%) | 97/143 (67.8%) | 38/69 (55.1%) | 53/69 (76.8%) | |
| Uninsured/self-pay | 5/281 (1.8%) | 3/143 (2.1%) | 1/69 (1.4%) | 1/69 (1.4%) | |
| Other/unknown | 16/281 (5.7%) | 11/143 (7.7%) | 2/69 (2.9%) | 3/69 (4.3%) | |
| **SES by zip code** | | | | | |
| Low SES | 87/281 (31.0%) | 47/143 (32.9%) | 21/69 (30.4%) | 19/69 (27.5%) | 0.75 |
| **Coexisting conditions** | | | | | |
| Obesity* | 85/250 (34.0%) | 62/134 (46.3%) | 18/64 (28.1%) | 5/52 (9.6%) | <0.001 |
| Respiratory* | 49/281 (17.4%) | 39/143 (27.3%) | 6/69 (8.7%) | 4/69 (5.8%) | <0.001 |
| Neurologic* | 23/281 (8.2%) | 22/143 (15.4%) | 0/69 (0.0%) | 1/69 (1.4%) | <0.001 |
| Immunosuppressed* | 16/281 (5.7%) | 13/143 (9.1%) | 1/69 (1.4%) | 2/69 (2.9%) | 0.052 |
| Diabetes* | 11/281 (3.9%) | 8/143 (5.6%) | 0/69 (0.0%) | 3/69 (4.3%) | 0.14 |
| Sickle cell | 9/281 (3.2%) | 7/143 (4.9%) | 2/69 (2.9%) | 0/69 (0.0%) | 0.21 |
| Cardiovascular* | 18/281 (6.4%) | 12/143 (8.4%) | 2/69 (2.9%) | 4/69 (5.8%) | 0.30 |
| Gastrointestinal* | 10/281 (3.6%) | 10/143 (7.0%) | 0/69 (0.0%) | 0/69 (0.0%) | 0.005 |
| History of smoking* | 13/228 (5.7%) | 10/116 (8.6%) | 0/52 (0.0%) | 3/69 (5.0%) | 0.069 |
| Medical complexity* | 59/281 (21.0%) | 45/143 (31.5%) | 5/69 (7.2%) | 9/69 (13.0%) | <0.001 |
| **COVID Testing** | | | | | |
| Only RT-PCR+ | 204/281 (72.6%) | 133/143 (93.0%) | 10/69 (14.5%) | 61/69 (88.4%) | <0.001 |
| Only IgG+ | 44/281 (15.7%) | 3/143 (2.1%) | 36/69 (52.2%) | 5/69 (7.2%) | |
| Both PCR+ and IgG+ | 20/281 (7.1%) | 7/143 (4.9%) | 10/69 (14.5%) | 3/69 (4.3%) | |
| Only exposure | 13/281 (4.6%) | 0/143 (0.0%) | 13/69 (18.8%) | 0/69 (0.0%) | |
| **Vital signs on admission** | | | | | |
| O2 saturation <90% | 16/281 (5.7%) | 16/143 (11.2%) | 0/69 (0.0%) | 0/69 (0.0%) | <0.001 |
| Tachypnea for age† | 66/281 (23.5%) | 47/143 (32.9%) | 18/69 (26.1%) | 1/69 (1.4%) | <0.001 |
| **Admission laboratory test results, median (IQR)** | | | | | |
| Hemoglobin, g/dL | 12.1, n=270 (10.8-13.8) | 12.7, n=137 (10.9-14.5) | 11.4, n=69 (10.4-12.2) | 12.6, n=64 (11.5-13.95) | <0.001 |
| WBC, x10^9/L | 9.0, n=272 (6.2-14.2) | 8.5, n=138 (5.6-12.6) | 9.8, n=69 (7.4-14.6) | 9.8, n=65 (6.4-14.9) | 0.051 |
| Absolute neutrophil count, x10^9/L | 5.8, n=269 (3.3-9.6) | 5.1, n=137 (2.7-8.9) | 7.6, n=69 (5.6-11.1) | 5.1, n=63 (2.6-9.8) | <0.001 |
| Absolute lymphocyte count, x10^9/L | 1.6, n=269 (0.9-2.7) | 1.5, n=137 (0.9-2.65) | 1.3, n=69 (0.8-1.9) | 2.1, n=63 (1.4-3.4) | <0.001 |
| Platelets, x10^9/L | 231, n=270 (164-346) | 233, n=137 (178-342) | 164, n=69 (112-287) | 301, n=64 (215-412) | <0.001 |
| Alanine aminotransferase, U/L | 29.0, n=247 (18.5-55) | 31.5, n=128 (18.5-58) | 38.0, n=67 (22-64) | 20.0, n=52 (16-26) | <0.001 |
| CRP, mg/dL | 7.8, n=207 (1.73-27.2) | 4.5, n=104 (1.0-14.5) | 25.7, n=67 (10-38.1) | 3.5, n=36 (0.5-7.9) | <0.001 |
| **Co-infections** | | | | | |
| Viral infections | 12/281 (4.3%) | 6/143 (4.2%) | 3/69 (4.3%) | 3/69 (4.3%) | 1.00 |
| **Chest Radiograph Findings** | | | | | |
| Bilateral infiltrates | 71/215 (33.0%) | 63/143 (49.2%) | 8/69 (12.7%) | 0/24 (0.0%) | <0.001 |

Data are presented as n/total (%) for categorical measures and median (IQR) for continuous measures. Pairwise comparison between groups are shown in Table 6. Continuous variables are compared using ANOVA or Kruskal-Wallis based on normality test, categorical variables are compared using Fisher’s exact tests. *See definitions in Table 2.
**Table 4. Primary Reasons for Admission in Children and Youth with Other Clinical Syndromes**

| Description                  | No. |
|------------------------------|-----|
| **Gastrointestinal**         |     |
| Rule out appendicitis        | 17  |
| Gastroenteritis              | 7   |
| Gastrointestinal Bleed       | 3   |
| Appendicitis complication    | 1   |
| Ileitis                      | 1   |
| Intussusception              | 1   |
| Rule out pyloric stenosis    | 1   |
| Rule out cholangitis         | 1   |
| **Febrile Infant**           | 21  |
| **Neurologic**               |     |
| Seizures                     | 4   |
| Weakness/lethargy            | 1   |
| Irritability                 | 1   |
| **Endocrine**                | 7   |
| Diabetic Ketoacidosis        | 6   |
| New-onset hyperglycemia      | 1   |
| **Hematology/Oncology**      | 3   |
| Hemolytic anemia             | 1   |
| Thrombocytopenia             | 1   |
| Fever in patient with cancer | 1   |
Table 5. Baseline Characteristics of Patients Hospitalized with Other SARS-CoV-2 Infection (not Classified as Respiratory or MIS-C)

| Characteristic | Other Clinical Subgroups, N=69 |  |  |  |  |
|----------------|-------------------------------|---|---|---|---|
|                | Gastrointestinal | Febrile infant | Neurologic | Diabetes | Hematology or oncology |
| **Total**      | N=32 | N=21 | N=6 | N=7 | N=3 |
| **Age, years** | Median age (IQR) | 12 (6-17) | 0 (0-0) | 3 (1-11) | 15 (13-18) | 11 (1-18) | <0.001 |
| **Sex**        | Male | 20/32 (62%) | 11/21 (52%) | 5/6 (83%) | 3/7 (43%) | 2/3 (67%) | 0.61 |
| **Race/Ethnicity** | Hispanic | 17/30 (57%) | 7/17 (41%) | 1/5 (20%) | 2/6 (33%) | 1/2 (50%) | 0.21 |
|                | Non-Hispanic black | 7/30 (23%) | 2/17 (12%) | 1/5 (20%) | 3/6 (50%) | 0/2 (0%) |
|                | Non-Hispanic white | 5/30 (17%) | 6/17 (35%) | 3/5 (60%) | 1/6 (17%) | 0/2 (0%) |
|                | Non-Hispanic other | 1/30 (3%) | 2/17 (12%) | 0/5 (0%) | 0/6 (0%) | 1/2 (50%) |
| **Insurance**  | Private | 8/32 (25%) | 2/21 (10%) | 0/6 (0%) | 2/7 (29%) | 0/3 (0%) | 0.73 |
|                | Medicaid/Medicare | 22/32 (69%) | 17/21 (81%) | 6/6 (100%) | 5/7 (71%) | 3/3 (100%) |
|                | Uninsured/self-Pay | 1/32 (3%) | 0/21 (0%) | 0/6 (0%) | 0/7 (0%) | 0/3 (0%) |
|                | Other/unknown | 1/32 (3%) | 2/21 (10%) | 0/6 (0%) | 0/7 (0%) | 0/3 (0%) |
| **SES by zip code** | Low SES | 9/32 (28%) | 4/21 (19%) | 2/6 (33%) | 4/7 (57%) | 0/3 (0%) | 0.32 |
|                | Coexisting conditions | Obesity | 3/30 (10%) | 1/8 (12%) | 0/4 (0%) | 0/7 (0%) | 1/3 (33%) | 0.52 |
|                | Respiratory | 2/32 (6%) | 0/21 (0%) | 0/6 (0%) | 0/7 (0%) | 2/7 (29%) | 0/3 (0%) | 0.16 |
|                | Neurologic | 0/32 (0%) | 0/21 (0%) | 0/6 (0%) | 0/7 (0%) | 0/3 (0%) | 0.13 |
|                | Immunosuppressed | 1/32 (3%) | 0/21 (0%) | 0/6 (0%) | 0/7 (0%) | 1/3 (33%) | 0.12 |
|                | Diabetes | 1/32 (3%) | 0/21 (0%) | 0/6 (0%) | 0/7 (0%) | 0/3 (0%) | 0.19 |
|                | Cardiovascular | 3/32 (9%) | 1/21 (5%) | 0/6 (0%) | 0/7 (0%) | 0/3 (0%) | 1.00 |
|                | History of smoking | 3/27 (11%) | 0/21 (0%) | 0/6 (0%) | 0/4 (0%) | 0/2 (0%) | 0.52 |
|                | Medical complexity | 5/32 (16%) | 1/21 (5%) | 1/6 (17%) | 1/7 (14%) | 1/3 (33%) | 0.38 |
| **COVID Testing** | Only RT-PCR+ | 27/32 (84%) | 20/21 (95%) | 5/6 (83%) | 6/7 (86%) | 3/3 (100%) | 0.65 |
|                | Only IgG+ | 3/32 (9%) | 1/21 (5%) | 0/6 (0%) | 1/7 (14%) | 0/3 (0%) |
|                | Both PCR+ and IgG+ | 2/32 (6%) | 0/21 (0%) | 0/6 (0%) | 0/7 (0%) | 0/3 (0%) |
| **Admission laboratories, median (IQR)** | Hemoglobin, g/dL | 13, N=31 (12-14) | 12, N=19 (11-14) | 12, N=6 (12-12) | 14, N=5 (14-15) | 11, N=3 (6-12) | 0.017 |
|                | WBC, ×10^9/L | 11, N=32 (7-16) | 9, N=19 (6-13) | 9, N=6 (5-10) | 10, N=5 (9-14) | 4, N=3 (1-12) | 0.27 |
|                | Absolute Neutrophil Count, ×10^9/L | 7, N=31 (4-13) | 3, N=18 (2-5) | 4, N=6 (2-5) | 7, N=6 (6-11) | 3, N=3 (1-3) | 0.004 |
|                | Absolute Lymphocyte Count, ×10^9/L | 2, N=31 (1-2) | 3, N=18 (2-5) | 3, N=6 (3-3) | 2, N=5 (2-2) | 1, N=3 (0-7) | 0.010 |
|                | Platelets, ×10^9/L | 244, N=31 (213-411) | 341, N=19 (275-421) | 300, N=6 (204-416) | 334, N=5 (305-345) | 88, N=3 (4-160) | 0.036 |
|                | Alkaline aminotransferase, U/L | 19, N=26 (15-24) | 22, N=14 (18-26) | 17, N=4 (12-21) | 20, N=5 (17-26) | 55, N=3 (23-70) | 0.15 |
|                | CRP, mg/dL | 7, N=21 (2-17) | 0, N=10 (0-1) | 10, N=2 (5-14) | 2, N=2 (0-4) | 1, N=1 (1-1) | 0.073 |
| **Co-infections** | Viral infections | 1/32 (3%) | 0/21 (0%) | 1/6 (17%) | 1/7 (14%) | 0/3 (0%) | 0.19 |

Data are presented as median (IQR) for continuous measures, and n/total (%) for categorical measures. P values estimated using Fisher’s exact and Kruskal-Wallis tests for categorical and continuous variables, respectively. *See definitions in Table 2.
Table 6. Difference of Baseline Characteristics by Clinical Syndrome Using Tukey Multiple Comparison Test

| Characteristic | MIS-C versus Respiratory | Other vs Respiratory | Other versus MIS-C |
|----------------|--------------------------|---------------------|-------------------|
|                | RD (95% CI) | P value | RD (95% CI) | P value | RD (95% CI) | P value |
| Age, years     | -4.38      (-6.86,-1.90) | <0.001   | -4.34      (-6.84,-1.84) | <0.001   | 0.04      (-2.86,2.94) | 0.92    |
| Sex            |            |          |            |          |            |         |
| Male           | 0.01       (-0.17,0.17) | >0.99     | -0.01      (-0.18,0.16) | 0.98     | -0.01     (-0.21,0.18) | 0.89    |
| Race/Ethnicity |            |          |            |          |            |         |
| Hispanic       | -0.17      (-0.35,0.01) | 0.07      | -0.12      (-0.30,0.07) | 0.30     | 0.05      (-0.16,0.26) | 0.99    |
| Non-Hispanic black | 0.18   (0.02,0.33) | 0.02      | 0.04       (-0.11,0.2)  | 0.80     | -0.14     (-0.31,0.04) | 0.31    |
| Non-Hispanic white | -0.07  (-0.22,0.08) | 0.51      | 0.04       (-0.11,0.19) | 0.79     | 0.11      (-0.06,0.28) | 0.07    |
| Non-Hispanic other | 0.06   (-0.02,0.14) | 0.21      | 0.03       (-0.05,0.12) | 0.64     | -0.03     (-0.12,0.07) | 0.57    |
| Chest radiograph findings |            |          |            |          |            |         |
| Bilateral infiltrates | -0.32  (-0.45,-0.20) | <0.001    | -0.49      (-0.72,-0.27) | 0        | -0.13     (-0.37,0.12) | 0.11    |
| Co-infections |            |          |            |          |            |         |
| Viral infections | 0.01     (-0.07,0.07) | >0.99     | 0.01       (-0.07,0.07) | 0.99     | 0.01      (-0.08,0.08) | 0.99    |
| Coexisting Conditions |            |          |            |          |            |         |
| Obesity<sup>a</sup> | -0.18    (-0.34,-0.02) | 0.02      | -0.37      (-0.54,-0.19) | <0.001   | -0.19     (-0.38,0.01) | 0.10    |
| Respiratory<sup>a</sup> | -0.19    (-0.31,-0.06) | <0.001   | -0.21      (-0.34,-0.09) | <0.001   | -0.03     (-0.18,0.12) | 0.94    |
| Neurologic<sup>a</sup> | -0.15    (-0.25,-0.06) | <0.001   | -0.14      (-0.23,-0.05) | <0.001   | 0.01      (-0.09,0.12) | 0.62    |
| Immunosuppressed<sup>a</sup> | -0.08    (-0.16,0.00) | 0.06      | -0.06      (-0.14,0.02) | 0.16     | 0.01      (-0.08,0.11) | 0.78    |
| Diabetes<sup>a</sup> | -0.06    (-0.12,0.01) | 0.09      | -0.01      (-0.08,0.05) | 0.90     | 0.04      (-0.03,0.12) | 0.56    |
| Sickle Cell    | -0.02    (-0.08,0.04) | 0.04      | -0.05      (-0.11,0.01) | 0.14     | -0.03     (-0.10,0.04) | 0.76    |
| Cardiovascular<sup>a</sup> | -0.05    (-0.14,0.03) | 0.26      | -0.03      (-0.11,0.06) | 0.75     | 0.03      (-0.07,0.13) | 0.86    |
| Gastrointestinal<sup>a</sup> | -0.07    (-0.13,0.01) | 0.02      | -0.07      (-0.13,0.01) | 0.03     | 0.01      (-0.07,0.07) | 0.94    |
| History of smoking<sup>a</sup> | -0.09    (-0.17,0.00) | 0.06      | -0.04      (-0.12,0.05) | 0.59     | 0.05      (-0.05,0.15) | 0.50    |
| Medical complexity<sup>a</sup> | -0.24    (-0.38,-0.10) | <0.001   | -0.18      (-0.32,-0.05) | <0.001   | 0.06      (-0.10,0.22) | 0.18    |
| COVID-19 testing |            |          |            |          |            |         |
| Only RT-PCR+   | -0.79    (-0.89,-0.68) | <0.001   | -0.05      (-0.15,0.06) | 0.55     | 0.74      (0.62,0.86) | <0.001 |
| Only IgG+      | 0.50     (0.40,0.60) | <0.001   | 0.05       (-0.05,0.15) | 0.47     | -0.45     (-0.57,-0.33) | <0.001 |
| Both PCR+ and IgG+ | 0.10    (0.01,0.18) | 0.02      | -0.01      (-0.09,0.08) | 0.99     | -0.1      (-0.2,0.01) | 0.02    |
| Only exposure  | 0.19     (0.12,0.25) | <0.001   | 0.01       (-0.07,0.07) | 0.99     | -0.19     (-0.27,-0.11) | <0.001 |
| Vital signs on admission |            |          |            |          |            |         |
| O2 saturation of <90% | -0.11   (-0.19,-0.04) | <0.001   | -0.11      (-0.19,-0.03) | <0.001   | 0.01      (-0.09,0.09) | >0.99  |
| Tachypnea for age<sup>a</sup> | -0.07   (-0.02,0.06) | 0.45      | -0.31      (-0.45,-0.17) | <0.001   | -0.25     (-0.41,-0.08) | <0.001 |
| Admission laboratories, median (IQR) |            |          |            |          |            |         |
| Hemoglobin, g/dL | -1.18   (-1.98,-0.39) | <0.001   | -0.03      (-0.88,0.81) | 0.99     | 1.15      (0.18,2.12) | 0.01    |
| WBC, x10<sup>9</sup>/L | 1.45    (0.92,3.82) | 0.32      | 1.17       (-0.96,3.31) | 0.40     | -0.28     (-2.73,2.18) | >0.99  |
| Absolute neutrophil count, x10<sup>3</sup>/L | 2.43    (0.69,4.18) | <0.001   | 0.23       (-1.57,2.03) | 0.95     | -2        (-4.26,0.14) | 0.01    |
| Absolute lymphocyte count, x10<sup>3</sup>/L | -0.48   (-1.24,0.28) | 0.29      | 0.53       (-0.24,1.30) | 0.24     | 1.01      (0.13,1.89) | 0.01    |
| Platelets, x10<sup>9</sup>/L | -47.5    (-94.1,-0.99) | 0.04      | 53.1       (6.64,99.6) | 0.02     | 100.7     (47.4,154.0) | <0.001 |
| Alanine aminotransferase, U/L | -1.45   (-27.1,24.2) | 0.99      | -10.5      (-39.6,18.5) | 0.67     | -9.08     (-41.7,23.5) | 0.48    |
| CRP, mg/dL   | 26.3     (10.8,14.8) | <0.001   | -8.32      (-27.8,11.2) | 0.57     | -34.6     (-55.5,-13.8) | <0.001 |

Rate Difference (RD) is the difference in means of each characteristic across clinical syndromes. Pairwise comparisons were computed for each combination of clinical syndrome. Confidence intervals and P values were adjusted to account for multiple comparisons using Tukey’s. *See definitions in Table 2.
### Table 7: Clinical Characteristics during Hospital Admission

| Clinical Measure                              | Total, N=281 | Respiratory, N=143 | MIS-C, N=69 | Other, N=69 | P value |
|-----------------------------------------------|--------------|--------------------|-------------|-------------|---------|
| Maximum respiratory support                  |              |                    |             |             |         |
| Ambient air                                  | 169/281 (60.1%) | 60/143 (42.0%)    | 43/69 (62.3%) | 66/69 (95.7%) | <0.001  |
| Non-invasive respiratory support             |              |                    |             |             |         |
| Low-flow nasal cannula                       | 42/281 (14.9%) | 29/143 (20.3%)    | 11/69 (15.9%) | 2/69 (2.9%)  | 0.001   |
| High-flow nasal cannula                      | 24/281 (8.5%)  | 16/143 (11.2%)    | 8/69 (11.6%)  | 0/69 (0.0%)  | 0.004   |
| Noninvasive positive-pressure ventilation    | 8/281 (2.8%)  | 5/143 (3.5%)      | 3/69 (4.3%)   | 0/69 (0.0%)  | 0.24    |
| Invasive mechanical ventilation              | 29/281 (10.3%) | 25/143 (17.5%)   | 3/69 (4.3%)   | 1/69 (1.4%)  | <0.001  |
| Medical Therapy                              |              |                    |             |             |         |
| Hydroxychloroquine                           | 50/281 (17.8%) | 49/143 (34.3%)    | 0/69 (0.0%)  | 1/69 (1.4%)  | <0.001  |
| Remdesivir                                   | 31/281 (11.0%) | 26/143 (18.2%)    | 5/69 (7.2%)   | 0/69 (0.0%)  | <0.001  |
| Methylprednisolone                           | 72/281 (25.6%) | 39/143 (27.3%)    | 32/69 (46.4%) | 1/69 (1.4%)  | <0.001  |
| Interleukin inhibitor                        | 23/281 (8.2%)  | 10/143 (7.0%)     | 13/69 (18.8%) | 0/69 (0.0%)  | <0.001  |
| Azithromycin                                 | 38/281 (13.5%) | 34/143 (23.8%)    | 4/69 (5.8%)   | 0/69 (0.0%)  | <0.001  |
| Convalescent plasma                          | 4/281 (1.4%)  | 3/143 (2.1%)      | 1/69 (1.4%)   | 0/69 (0.0%)  | 0.81    |
| Intravenous immunoglobulin (IVIG)            | 47/281 (16.7%) | 3/143 (2.1%)      | 41/69 (59.4%) | 3/69 (4.3%)  | <0.001  |
| Empiric antibiotics (excluding azithromycin) | 178/281 (63.3%) | 93/143 (65.0%)    | 47/69 (68.1%) | 38/69 (55.1%) | 0.23    |
| Anticoagulant therapy                        | 98/281 (34.9%) | 55/143 (38.5%)    | 41/69 (59.4%) | 2/69 (2.9%)  | <0.001  |
| Complications                                |              |                    |             |             |         |
| Acute respiratory distress syndrome<sup>a</sup> | 27/281 (9.6%)  | 24/143 (16.8%)    | 3/69 (4.3%)   | 0/69 (0.0%)  | <0.001  |
| Acute kidney injury<sup>a</sup>               | 37/281 (13.2%) | 15/143 (10.5%)    | 17/69 (24.6%) | 5/69 (7.2%)  | 0.008   |
| Carditis<sup>a</sup>                         | 20/281 (7.1%)  | 3/143 (2.1%)      | 17/69 (24.6%) | 0/69 (0.0%)  | <0.001  |
| Shock<sup>a</sup>                            | 26/281 (9.3%)  | 2/143 (1.4%)      | 24/69 (34.8%) | 0/69 (0.0%)  | <0.001  |
| Thrombotic event<sup>a</sup>                 | 12/281 (4.3%)  | 11/143 (7.7%)     | 1/69 (1.4%)   | 0/69 (0.0%)  | 0.014   |
| Bacteremia                                   | 12/281 (4.3%)  | 10/143 (7.0%)     | 2/69 (2.9%)   | 0/69 (0.0%)  | 0.050   |
| Urinary tract infection                      | 10/281 (3.6%)  | 9/143 (6.3%)      | 0/69 (0.0%)   | 1/69 (1.4%)  | 0.037   |
| Outcomes                                     |              |                    |             |             |         |
| Discharged home                              | 267/281 (95.0%) | 133/143 (93.0%)   | 66/69 (95.7%) | 68/69 (98.6%) | 0.21    |
| Hospital length of stay, median days (IQR)<sup>b</sup> | 4 (2-8) | 5 (2-10) | 6 (3-8) | 2 (2-4) | <0.001  |
| Required intensive care unit (ICU) stay      | 114/281 (40.6%) | 64/143 (44.8%)    | 44/69 (63.8%) | 6/69 (8.7%)  | <0.001  |
| ICU length of stay, median days (IQR)<sup>c</sup> | 5 (2-10) | 6 (2-17) | 4 (2-7) | 2 (1-3) | <0.001  |

Data are presented as median (IQR) for continuous measures, and n/total (%) for categorical measures. 

*P* values estimated using Fisher’s exact and Kruskal-Wallis tests for categorical and continuous variables, respectively

<sup>a</sup>See definitions in Table 2

<sup>b</sup>Hospital length of stay excluding patients who were transferred to another facility

<sup>c</sup>ICU length of stay excluding patients who did not spend time in ICU
### Table 8. Patient Outcomes at Conclusion of Study

| Outcome                                      | No. (%)         |
|----------------------------------------------|-----------------|
| Discharged home                              | 267 (95%)       |
| Transferred to inpatient rehabilitation      | 3 (1%)          |
| Another acute care hospital\(^1\)            | 4 (1%)          |
| Death                                        | 7 (2%)          |

\(^1\) per parental request, 1 for cardiac surgery, 2 transferred to hospital for higher level of care
### Table 9. Narrative of Deaths

| Description                                                                 | Details                                                                                     |
|-----------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|
| An 11-year-old male with intermittent asthma, asthma, seizure disorder, developmental delay, and a gastrostomy tube, was admitted with a 3-day history of fever, cough, wheezing, dyspnea, and increased seizure frequency. He was started on high-flow nasal cannula, but by the first hospital day, he required intubation for mechanical ventilation. He was noted to have co-infection with Rhinovirus as well as SARS-CoV-2. He received methylprednisolone on admission and was on a steroid taper throughout this hospitalization. A 10-day course of Remdesivir and a single dose of Anakinra were also given. He developed line-associated *Enterococcus faecalis* bacteremia and was also noted to have a right femoral deep-vein-thrombosis for which he received antibiotics and anticoagulation, respectively. He died on hospital day 58. |
| An 11-year-old male with metastatic osteosarcoma on palliative chemotherapy with baseline nasal-cannula oxygen requirement presented with dyspnea and cough of 1-day duration. He was immediately intubated and mechanically ventilated for respiratory failure per the family's request. Care was withdrawn approximately 1 week later, and the patient died from respiratory failure due to a combination of lung metastases and SARS-CoV-2 infection. |
| A 3-month-old female with pulmonary hypertension, large atrial septum defect, and a moderate patent ductus arteriosus was admitted with a 1-day history of cough, fever, and dyspnea. She was initially started on nasal-cannula; however, soon after admission, she developed tachypnea and desaturations and was subsequently intubated for mechanical ventilation. She received a 10-day course of Remdesivir as well as intravenous immunoglobulin. She developed acute kidney injury, thrombocytopenia, and line-associated *Enterococcus faecalis* bacteremia. She remained mechanically ventilated and died on hospital day 30. |
| An 18-year-old female with morbid obesity, hypertension, and intermittent asthma presented with 8-day history of cough, fever, and dyspnea. She was immediately intubated and mechanically ventilated in the intensive care unit. She had evidence of acute kidney injury and acute respiratory distress syndrome. She was started on hydroxychloroquine and azithromycin, but these were discontinued after two days. She received a five-day course of methylprednisolone and a single dose of tocilizumab. However, she remained mechanically ventilated and died on hospital day 38. |
| A 20-year-old male with a medical history of intermittent asthma was admitted with respiratory distress. He had been ill for 21 days prior to hospital presentation with fever, cough, wheezing, myalgia, dyspnea, vomiting, fatigue, and neck swelling. He was immediately intubated and mechanically ventilated after arriving at the intensive care unit. He had evidence of thrombocytopenia, acute respiratory distress syndrome, and acute kidney injury. He received empiric antibiotic therapy, methylprednisolone, and convalescent plasma but died on hospital day 2. |
| A 5-month-old male with no medical history was admitted after he was found to be unresponsive and limp while at home. No preceding symptoms or known exposure to COVID-19 was reported. On hospital presentation, he was immediately intubated and started on mechanical ventilation as well as epinephrine, norepinephrine, and vasopressin. In addition to the SARS-CoV-2 infection, he was found to have *parainfluenza* infection. He received empiric antibiotic therapy with Ceftriaxone and Vancomycin. Five days into his hospitalization, he developed severe thrombocytopenia and acute kidney injury. At that time, he was started on a 6-day course of hydroxychloroquine. One week into his hospitalization, he was noted to have a *Staphylococcus epidermidis* line-associated bacteremia as well as *Stenotrophomonas maltophilia* pneumonia. Despite these interventions, he remained mechanically ventilated. He was given convalescent plasma on hospital day 29. He died shortly after a 31-day hospitalization. |
| A 10-year-old male with a medical history of intermittent asthma was admitted with fever, cough, wheezing, and dyspnea for seven days prior to presentation. The patient was noted to be in significant respiratory distress with hypoxia. He was admitted to the intensive care unit with ARDS and was mechanically ventilated and had L sided chest tube placement. He had evidence of acute kidney injury with elevated creatinine. He received methylprednisolone and empiric antibiotic therapy with Ceftaroline. He died on hospital day two due to respiratory distress. |
Table 10: Logistic Regression Models of Severe Disease

| Predictor                                | Bivariate OR (95% CI) | P value | Multivariable Model 1 (N=106) aOR (95% CI) | P value | Multivariable Model 2 (N=127) aOR (95% CI) | P value |
|------------------------------------------|------------------------|---------|---------------------------------------------|---------|---------------------------------------------|---------|
| Age (per 1 year decrease)                | 1.02 (0.98, 1.04)      | 0.29    | 1.09 (1.01, 1.18)                            | 0.02    | 1.09 (1.02, 1.16)                            | 0.01    |
| BMI (per unit increase in kg/m²)         | 1.01 (0.98, 1.04)      | 0.49    |                                             |         |                                             |         |
| Obesity (reference = no obesity)         | 1.78 (0.85, 3.73)      | 0.12    | 3.66 (1.14, 11.78)                          | 0.03    | 3.39 (1.26, 9.10)                            | 0.02    |
| Days of illness prior to admission       | 1.02 (0.94, 1.11)      | 0.64    |                                             |         |                                             |         |
| Admission WBC (per unit increase in 10⁹/L) | 1.07 (1.01, 1.14)    | 0.03    | 1.11 (1.01, 1.21)                            | 0.03    | 1.11 (1.03, 1.20)                            | 0.007   |
| Admission CRP level (per unit increase in mg/dL) | 0.92 (0.79, 1.08)    | 0.31    |                                             |         |                                             |         |
| Hispanic (reference = Non-Hispanic white/other) | 1.29 (0.49, 3.37)    | 0.61    | 0.88 (0.26, 2.98)                           | 0.84    |                                             |         |
| Non-Hispanic black (reference = Non-Hispanic White/Other) | 1.77 (0.50, 6.20) | 0.37    | 1.65 (0.31, 8.87)                           | 0.56    |                                             |         |
| Medicare/Medicaid (reference = private/other) | 0.95 (0.45, 2.04)   | 0.9     |                                             |         |                                             |         |
| Oxygen saturation <90% (reference = no)  | 3.55 (1.13, 11.20)    | 0.03    | 4.25 (1.10, 16.49)                          | 0.04    | 4.01 (1.14, 14.15)                           | 0.03    |
| Male (reference = female)                | 0.91 (0.45, 1.85)     | 0.79    |                                             |         |                                             |         |
| Medical complexity (reference = no)      | 1.99 (0.94, 4.21)     | 0.07    | 1.51 (0.51, 4.42)                           | 0.45    |                                             |         |
| Bilateral infiltrates on radiograph      | 3.14 (1.51, 6.53)     | 0.002   | 3.88 (1.36, 11.08)                          | 0.01    | 3.69 (1.46, 9.32)                            | 0.006   |
| Low SES (reference ≥-1)                  | 0.86 (0.31, 2.38)     | 0.77    |                                             |         |                                             |         |

**Respiratory illness: 56 events, N=141**

| Predictor                                | Bivariate OR (95% CI) | P value | Multivariable Model 1 (N=60) aOR (95% CI) | P value | Multivariable Model 2 (N=66) aOR (95% CI) | P value |
|------------------------------------------|------------------------|---------|---------------------------------------------|---------|---------------------------------------------|---------|
| Age (per 1-year decrease)                | 0.83 (0.74, 0.93)      | 0.002   | 1.00 (0.84, 1.19)                            | 0.98    |                                             |         |
| BMI (per unit increase in kg/m²)         | 1.02 (0.92, 1.14)      | 0.69    |                                             |         |                                             |         |
| Obesity (reference = no obesity)         | 1.16 (0.35, 3.91)      | 0.81    |                                             |         |                                             |         |
| Days of illness prior to admission       | 0.98 (0.77, 1.25)      | 0.87    |                                             |         |                                             |         |
| WBC (per unit increase in 10⁹/L)         | 0.95 (0.88, 1.04)      | 0.29    |                                             |         |                                             |         |
| Admission absolute lymphocyte count (per unit decrease in U/L) | 5.88 (2.13, 16.67)    | <0.001  | 12.50 (1.85, 100.0)                         | 0.009   | 8.33 (2.32, 33.33)                           | 0.001   |
| Admission CRP level (per unit increase in mg/dL) | 1.04 (1.00, 1.07)   | 0.03    | 1.05 (0.98, 1.12)                           | 0.14    | 1.06 (1.01, 1.12)                           | 0.02    |
| Hispanic (reference = Non-Hispanic white/other) | 1.09 (0.26, 4.55)    | 0.9     | 2.54 (0.23, 28.23)                          | 0.45    |                                             |         |
| Non-Hispanic black (reference = Non-Hispanic White/Other) | 4.05 (0.87,18.93) | 0.07    | 3.09 (0.22, 42.80)                          | 0.4     |                                             |         |
| Medicare/Medicaid (reference = private/other) | 0.39 (0.14, 1.12)   | 0.08    | 0.21 (0.04, 1.15)                           | 0.07    |                                             |         |
| Male (reference = female)                | 1.66 (0.60, 4.60)      | 0.33    |                                             |         |                                             |         |
| Medical complexity (reference = no)      | 0.51 (0.08, 3.37)      | 0.49    |                                             |         |                                             |         |
| Bilateral infiltrates on radiograph (reference = no) | 6.59 (0.73, 59.81)   | 0.09    |                                             |         |                                             |         |
| Low SES (reference ≥-1)                  | 0.78 (0.23, 2.62)      | 0.69    |                                             |         |                                             |         |

**MIS-C: 38 events, N=68**

P values for OR (odds ratio) and aOR (adjusted OR) estimated using logistic regression. All estimates are adjusted for site with fixed effects. Excluded 2 Respiratory cases (one who was chronically ventilator-dependent and discharged on hospital day one, and one who died on the day of admission) and 1 MIS-C case (transferred on the day of admission). Model 1 includes variables with \( P < 0.25 \) in bivariate analysis, age and race. Model 2 includes only variables with \( P < 0.05 \) using stepwise backward selection strategy. CRP level excluded in multivariable Respiratory models because 28% missing and data not missing at random. Bilateral infiltrates on radiograph not included in multivariable MIS-C due to limited number of MIS-C patients with this condition (N=7). *See definitions in Table 2.
Table 11. Sensitivity Analysis: Logistic Regression Models for Severe Outcome using Multiple Imputation for Missing Data

| Respiratory illness: 56 events, N=141 | Multivariable Model 1 | Multivariable Model 2 |
|---------------------------------------|------------------------|------------------------|
|                                       | aOR (95% CI)           | P value                | aOR (95% CI)           | P value                |
| Age (per 1 year decrease)             | 1.09 (1.02, 1.16)      | 0.01                   | 1.09 (1.02, 1.15)      | 0.01                   |
| Obesity* (reference = no)             | 3.48 (1.22, 9.96)      | 0.02                   | 2.84 (1.09, 7.39)      | 0.03                   |
| Admission WBC count (per unit increase in 10⁹/L) | 1.11 (1.02, 1.21) | 0.01                   | 1.10 (1.02, 1.19)      | 0.02                   |
| Hispanic (reference = Non-Hispanic white/other) | 0.93 (0.30, 2.90) | 0.90                   |                        |                        |
| Non-Hispanic black (reference = Non-Hispanic white/other) | 1.64 (0.34, 7.90) | 0.54                   |                        |                        |
| Oxygen saturation <90% (reference = no) | 3.56 (0.98, 12.95) | 0.05                   | 4.08 (1.17, 14.27)     | 0.03                   |
| Medical complexity* (reference = no)  | 2.34 (0.94, 5.81)      | 0.07                   |                        |                        |
| Bilateral infiltrates on radiograph (reference = no) | 4.05 (1.59, 10.30) | 0.003                  | 3.88 (1.59, 9.48)      | 0.003                  |

| MIS-C: 38 events, N=68 | Multivariable Model 1 |
|------------------------|------------------------|
| aOR (95% CI)           | P value                |
| Age (per 1 year decrease) | 0.98 (0.84, 1.16)      | 0.85                   |
| Admission absolute lymphocyte count (per unit decrease in U/L) | 6.25 (1.41, 25.0) | 0.02                   |
| Admission CRP level (per unit increase in mg/dL) | 1.03 (0.97, 1.09) | 0.33                   |
| Hispanic (reference = Non-Hispanic white/other) | 1.20 (0.14, 10.09) | 0.87                   |
| Non-Hispanic black (reference = Non-Hispanic white/other) | 2.86 (0.24, 33.71) | 0.40                   |
| Medicaid/Medicare (reference = private/other) | 0.40 (0.09, 1.68) | 0.21                   |

*See definitions in Table 2

P values for aOR (adjusted OR) estimated using logistic regression. All estimates are adjusted for site with fixed effects.

For Respiratory illness, excluded 2 Respiratory cases (one who was chronically ventilator-dependent and discharged on hospital day one, and one who died on the day of admission). Multiple imputation model included outcome, all predictor variables listed in Table 10 and hospital site. Results based on 40 imputed data sets.

For MIS-C, excluded 1 MIS-C case (transferred on the day of admission). Multiple imputation model included outcome, all predictor variables listed in Table 10 and hospital site. Results based on 40 imputed data sets. Model 1 includes variables with P<.25 in bivariate analysis, age and race. Model 2 had nearly complete data (2 missing values) so multiple imputation not performed.
Table 12. Patient Characteristics by Disease Severity Status

| Clinical Measure | Respiratory | MIS-C | Other |
|------------------|-------------|-------|-------|
|                  | Non-severe | Severe | P value* | Non-severe | Severe | P value* | Non-severe | Severe | P value* |
| N=85             | N=56       |       |         | N=30      | N=38    |         | N=65      | N=4    |         |
| Age, years       | 17 (2-20)  | 13 (3-16)| 0.12 | 3 (1-7)  | 10 (6-13)| <0.001 | 6 (0-16)  | 11 (4-17)| 0.32 |
| Male             | 53/85 (62%)| 33/56 (59%)| 0.73 | 17/30 (57%)| 25/38 (66%)| 0.46 | 38/65 (58%)| 3/4 (75%)| 0.64 |
| Race/Ethnicity   |            |        |       |           |         |         |           |        |       |
| Hispanic         | 44/70 (63%)| 26/48 (54%)| 0.37 | 15/28 (54%)| 12/36 (33%)| 0.09 | 26/56 (46%)| 2/4 (50%)| 0.25 |
| Non-Hispanic black| 9/70 (13%) | 11/48 (23%)| 0.62 | 6/28 (21%)| 17/36 (47%)| 0.11 | 11/56 (20%)| 2/4 (50%)|         |
| Non-Hispanic white/other | 17/70 (24%) | 11/48 (23%) | 0.72 | 7/28 (25%)| 7/36 (19%)|         | 19/56 (34%)| 0/4 (0%)|         |
| Insurance        |            |        |       |           |         |         |           |        |       |
| Medicaid/Medicare| 57/85 (67%)| 38/56 (68%)| >0.99| 21/30 (70%)| 17/38 (45%)| 0.05 | 50/65 (77%)| 3/4 (75%)| >0.99 |
| SES by zip code  |            |        |       |           |         |         |           |        |       |
| Low SES          | 32/85 (38%)| 15/56 (27%)| 0.20 | 11/30 (37%)| 10/38 (26%)| 0.43 | 16/65 (25%)| 3/4 (75%)| 0.061 |
| Coexisting conditions |    |        |       |           |         |         |           |        |       |
| Obesity*         | 34/81 (42%)| 27/51 (53%)| 0.28 | 6/25 (24%)| 12/38 (32%)| 0.58 | 5/49 (10%)| 0/3 (0%)| >0.99 |
| Medical complexity* | 22/85 (26%)| 22/56 (39%)| 0.099| 3/30 (10%)| 2/38 (5%)| 0.65 | 8/65 (12%)| 1/4 (25%)| 0.44 |
| Vital signs on admission | | | | | | | | | |
| O2 saturation of <90% | 6/85 (7%)| 10/56 (18%)| 0.06 | 0/30 (0%)| 0/38 (0%)| - | 0/65 (0%)| 0/4 (0%)| - |
| Tachypnea for age* | 19/85 (22%)| 28/56 (50%)| <0.001| 8/30 (27%)| 10/38 (26%)| >0.99 | 1/65 (2%)| 0/4 (0%)| >0.99 |
| Days of illness prior to admission | 3 (1-7) | 4 (2-7) | 0.33 | 5 (3-6) | 5 (4-6) | 0.95 | 1 (1-3) | 2 (1-4) | 0.65 |
| Laboratories and imaging | | | | | | | | | |
| Peak CRP >25, mg/dL | 4/57 (7%)| 14/45 (31%)| 0.003| 10/29 (34%)| 24/37 (65%)| 0.03 | 3/35 (9%)| 0/1 (0%)| >0.99 |
| Peak procalcitonin >0.5, ng/mL | 8/40 (20%)| 16/31 (52%)| 0.01 | 13/18 (72%)| 29/30 (97%)| 0.02 | 5/15 (33%)| 0/1 (0%)| >0.99 |
| Peak ESR >50, mm/hr | 7/17 (41%)| 15/23 (65%)| 0.20 | 16/23 (70%)| 18/26 (69%)| >0.99 | 2/13 (15%)| 0/1 (0%)| >0.99 |
| Peak ferritin >500, ng/mL | 21/43 (49%)| 23/43 (53%)| 0.83 | 10/25 (40%)| 2937 (78%)| 0.003 | 4/21 (19%)| 0/1 (0%)| >0.99 |
| Peak troponin >0.01, ng/mL | 5/43 (12%)| 11/30 (37%)| 0.02 | 6/22 (27%)| 27/35 (77%)| <0.001 | 2/17 (12%)| 1/2 (50%)| 0.30 |
| Peak BNP >500, ng/L | 5/31 (16%)| 10/24 (42%)| 0.07 | 16/22 (73%)| 29/36 (81%)| 0.53 | 3/12 (25%)| 0/1 (0%)| >0.99 |
| Nadir absolute lymphocyte count <1.0, ×10^9/L | 29/76 (38%)| 31/54 (57%)| 0.03 | 7/29 (24%)| 27/38 (71%)| <0.001 | 10/56 (18%)| 0/3 (0%)| >0.99 |
| Nadir platelets <100, ×10^9/L | 4/77 (5%)| 14/54 (26%)| 0.001 | 3/30 (10%)| 19/38 (50%)| <0.001 | 3/59 (5%)| 0/3 (0%)| >0.99 |
| Nadir sodium <130, mEq/L | 4/78 (5%)| 11/55 (20%)| 0.01 | 3/29 (10%)| 13/38 (34%)| 0.04 | 4/58 (7%)| 1/4 (25%)| 0.29 |
| Viral co-infection | 2/85 (2%)| 4/56 (7%)| 0.21 | 0/30 (0%)| 2/38 (5%)| 0.50 | 2/65 (3%)| 1/4 (25%)| 0.17 |

Data are presented as median (IQR) for continuous measures, and n/total (%) for categorical measures. *Continuous variables are compared using Wilcoxon rank-sum, categorical variables are compared using Fisher’s exact tests; Severity analysis excluded 1 MIS-C case (transferred on the day of admission) and 2 Respiratory cases (one who was chronically ventilator-dependent and discharged on hospital day one, and one who died on the day of admission). See definitions in Table 2.
FEVER

CONJUNCTIVAL INJECTION

MENTAL STATUS CHANGES

HEADACHE

EMESIS

DIARRHEA

ABDOMINAL PAIN

GASTROINTESTINAL

DYSPNEA

PHARYNGITIS

WHEEZING

COUGH

ANOSMIA/AGEUSIA

□ Respiratory

□ MIS-C

□ Other

0% 20% 40% 60% 80% 100%
