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Treatments and severe outcomes for patients diagnosed with MIS-C at four children's hospitals in the United States, March 16, 2020 – March 10, 2021

Ami B. Shah, MPH[1,2], **Joseph Y. Abrams, PhD**[1], **Shana Godfred-Cato, DO**[1], **Amber Kunkel, ScD**[1,3], **Teresa A. Hammett, MPH, MS**[1], **Maria A. Perez, BS**[4], **Hui-Mien Hsiao, MS**[4], **Nadine Baida, BS**[4], **Christina A. Rostad, MD**[4], **Wassim Ballan, MD**[5], **Kaleo Ede, MD**[5], **Federico R. Laham, MD, MSc**[6], **Carol M. Kao, MD**[7], **Matthew E. Oster, MD, MPH**[1,4], **Ermias D. Belay, MD**[1]

[1]CDC COVID-19 Response Team, Centers for Disease Control and Prevention, Atlanta, Georgia, USA

[2]General Dynamics Information Technology, Falls Church, Virginia, USA

[3]Epidemic Intelligence Service, Centers for Disease Control and Prevention, Atlanta, Georgia

[4]Department of Pediatrics, Emory University School of Medicine, Atlanta, Georgia and Children's Healthcare of Atlanta, Atlanta, Georgia, USA

[5]Phoenix Children's Hospital, Phoenix, Arizona, USA

[6]Division of Pediatric Infectious Diseases, Orlando Health Arnold Palmer Hospital for Children, Orlando, Florida, USA

[7]Department of Pediatrics, Washington University School of Medicine, St. Louis, Missouri, USA

Abstract

Background—Clinical management of multisystem inflammatory syndrome in children (MIS-C) has varied over time and by medical institution.

Methods—Data on patients with MIS-C were collected from four children's hospitals between March 16, 2020 – March 10, 2021. Relationships between MIS-C treatments and patient demographics, clinical characteristics, and outcomes were described. Propensity score matching

Address for correspondence: Ami B. Shah, MPH, CDC COVID-19 Response Team, Centers for Disease Control and Prevention, 1600 Clifton Road, Atlanta, GA 30333, hiz4@cdc.gov.

All authors contributed equally.

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was utilized to assess the relative risk of outcomes dependent on early treatment with intravenous immunoglobulin (IVIG) or low-dose steroids, controlling for potential confounding variables.

Results—Out of 233 patients diagnosed with MIS-C, the most commonly administered treatments were steroids (88.4%), aspirin (81.1%), IVIG (77.7%), and anticoagulants (71.2%). Compared with those patients without respiratory features, patients with respiratory features were less likely to receive IVIG and steroids on the same day (combination treatment) (44.1%). Controlling for confounding variables, patients receiving IVIG within one day of hospitalization were less likely to have hospital length of stay (LOS) ≥8 days (RR = 0.53, 95% CI = 0.31–0.88). Patients receiving low-dose steroids within one day of hospitalization were less likely to develop ventricular dysfunction (RR = 0.45, 95% CI = 0.26–0.77), have increasingly elevated troponin levels (RR = 0.55, 95% CI = 0.40–0.75), or have hospital LOS ≥8 days (RR = 0.46, 95% CI = 0.29–0.74).

Conclusion—Treatments for MIS-C differed by hospital, patient characteristics, and illness severity. When IVIG and low-dose steroids were administered in combination or low-dose steroids were administered alone within 1 day of hospitalization, risk of subsequent severe outcomes was decreased.

Keywords

MIS-C; multisystem inflammatory syndrome in children; PIMS; COVID-19; pediatric; treatments

Introduction

Since multisystem inflammatory syndrome in children (MIS-C) was first described among pediatric patients in April and May of 2020 [1, 2], treatment regimens and guidelines for MIS-C have evolved. Following the recognition of these first cases, the Centers for Disease Control and Prevention (CDC) released a Health Advisory about MIS-C and shared an initial case definition [3]. As details about MIS-C were still limited, public health organizations such as the American College of Rheumatology (ACR) [4], American Academy of Pediatrics [5] and others recommended a treatment regimen closely following that for Kawasaki disease (KD) [6]. Increased clinician experience and differing presentations in clinical manifestations or severity influenced when and what treatments MIS-C patients received, resulting in different treatments provided across institutions.

This manuscript describes treatments administered to patients with MIS-C at four children's hospitals in the United States during the first 12 months of the COVID-19 pandemic and compares the use of these treatments and subsequent outcomes among patients with varying demographic and clinical characteristics.

Methods

Data were derived from The Phenotype Initiative, a project that conducted both retrospective and prospective enrollment of patients admitted with MIS-C between March 16, 2020 – March 10, 2021. Enrollment sites included Arnold Palmer Hospital for Children in Orlando, Florida, Children's Healthcare of Atlanta in Georgia, Phoenix Children's Hospital in Arizona, and Saint Louis Children's Hospital—Washington University in Missouri.

Medical records from initial hospitalization and follow-up medical encounters were abstracted using a single case report form, which included patient demographics, underlying medical conditions, signs and symptoms, diagnostic and treatment information, and clinical outcomes.

Patient sample

All enrolled patients were less than 21 years at the time of MIS-C onset. To assess timing of treatment, patients were divided into two groups—those hospitalized between March 16, 2020 – October 22, 2020, and from October 23, 2020 – March 10, 2021. This date represents the median date of hospital admission within the study cohort. Each site began admitting patients in March, June, July, and August of 2020, and the last patient admission was recorded on March 10, 2021. Patients were classified into three disease severity categories: 1) patients who received intensive care unit (ICU)-level care; 2) non-ICU patients with cardiac complications; and 3) non-ICU patients without cardiac complications. Recipients of ICU-level care were classified as such if they were admitted to the ICU, received treatment with a vasoactive medication, were intubated or placed on mechanical ventilation, or were placed on extracorporeal membrane oxygenation (ECMO). Patients not meeting these criteria for ICU-level care were classified as non-ICU patients and divided into two groups based on the presence or absence of cardiac complications. Lastly, we assessed treatments administered by groups according to common organ system involvement of MIS-C. These included the presence of gastrointestinal (i.e., abdominal pain, vomiting, or diarrhea), hematologic (i.e., elevated d-dimer, lymphopenia, or thrombocytopenia), mucocutaneous (i.e., rash, lesions, or conjunctival injection), respiratory (i.e., cough, shortness of breath, chest pain or tightness, pneumonia, acute respiratory distress syndrome (ARDS), or pleural effusion), and cardiac involvement (i.e., shock, elevated brain natriuretic peptide (BNP) or N-terminal pro-hormone BNP (NT-proBNP), elevated troponin, congestive heart failure, cardiac dysfunction, myocarditis, coronary artery aneurysm or dilatation, hypotension, pericardial effusion, or any mitral regurgitation).

Guidelines and Treatments

Site-specific treatment guidelines for the management of patients with MIS-C were developed and updated throughout the study period as treatment standards changed. Day of hospital admission was considered day 0. Patient-level data regarding date of first and second administration of IVIG, start and end dates of steroid and aspirin administration, and peak dosing of each treatment were collected from medical record review. Given that different types of steroids (i.e., methylprednisolone, prednisone, prednisolone, hydrocortisone, dexamethasone) were administered to patients at different hospitals, a corticosteroid dosage equivalency chart [7] was used to standardize steroid dosage to methylprednisolone dosage in mg/kg/day. Steroids and aspirin were considered “high-dose” if the dosage was ≥10 mg/kg/day and low-dose if dosage was <10 mg/kg/day. Timing of administration and dosage were also collected for immune modulators (defined as anakinra, tocilizumab, rituximab, and sirolimus) and vasoactive or inotropic medications, when applicable. Lastly, details about discharge medications were also collected.

Patient Outcomes

Outcomes assessed were: LOS ≥8 days, receipt of ICU-level care, presence of shock or hypotension, treatment with immune modulators (a surrogate for refractory illness) [4], and the presence of certain cardiac complications defined as arrhythmia, pericarditis, myocarditis, congestive heart failure, elevated troponin, and additional complications observed on multiple echocardiograms conducted during or post-hospitalization (i.e., mitral regurgitation (mild, moderate, or severe), coronary artery abnormalities (dilatation or aneurysms), ventricular dysfunction (of left, right, or both ventricles), or a left ventricular ejection fraction <50%). Coronary artery dilatation and aneurysm were defined by z-score classification guidelines for aneurysms in patients with KD [6]. Patients with coronary artery dilatation had a z-score ≥2 and <2.5, whereas those with aneurysms were classified into three categories—small (z-score ≥2.5 and <5), medium (z-score ≥5 to <10 and absolute dimension <8mm), and large (or giant) (z-score ≥10 or absolute dimension ≥8mm). Elevated troponin was defined as >0.04 ng/ml. Shock or hypotension was defined as clinical diagnosis of shock or receipt of vasoactive or inotropic medications.

Propensity Score Matching

Treatment effectiveness was assessed for IVIG and low-dose steroids, as those were common first-line treatments for patients with MIS-C. Analyses were conducted to determine if receipt of these treatments within 1 day of hospitalization, separately or in combination, were associated with lower risk of subsequent severe outcomes at two or more days following hospitalization. Severe outcomes of interest were: ICU-level care, shock/hypotension, coronary artery abnormality, any ventricular dysfunction, any mitral regurgitation, increased troponin levels (troponin that was elevated and continued to increase up to or after day 2 of hospitalization), hospital LOS ≥8 days, and receipt of immune modulators. Propensity score matching was used to generate comparable analytic groups of patients by similar demographic and clinical presentations for each treatment comparison, using optimal full matching (incorporating both matching and weights for matched patients) with distance measured through logistic regression [8]. The variables used in the matching algorithm were determined in a prior study [9] to be associated with risk of ICU admission: patient age, presence of cough, shortness of breath, abdominal pain, elevated D-dimer, elevated BNP or NT-proBNP, elevated troponin, elevated C-reactive protein (CRP), elevated ferritin, elevated Interleukin-6 (IL-6), thrombocytopenia, lymphopenia, and date of MIS-C symptoms onset. Instead of date of MIS-C symptoms onset, we considered timing of hospital admission on or before and after the median date of admission (October 22, 2020) to be associated with risk of ICU admission because admissions early in the pandemic were known to be associated with more severe outcomes [9, 10]. Analyses assessing the use of IVIG within 1 day of hospitalization additionally matched for the use of low-dose steroids within 1 day of hospitalization, and vice versa. Patients receiving high-dose steroids or immune modulators within 1 day of hospitalization were excluded from these analyses, as these are not common first-line treatments. The estimated relative risk with 95% confidence interval of each outcome given the treatment group was calculated using quasi-Poisson generalized linear modeling, controlling for all variables used in the matching algorithm.

Statistics

Differences in categorical variables were computed using chi-square tests (or Fisher's exact tests for comparisons with expected cell sizes below 5). All data were stored in a secure REDCap database and data cleaning and analyses were conducted using R version 4.1.2, RStudio version 2022.02.3, and Microsoft Excel. This study was approved by each site's institutional review boards. This activity was reviewed by CDC and was conducted consistent with applicable federal law and CDC policy as defined in 45 CFR §46.102(I)(2).

Results

A total of 233 patients with MIS-C were enrolled in the study, 151 (64.8%) from Hospital A, 37 (15.9%) from Hospital B, 23 (9.9%) from Hospital C, and 22 (9.4%) from Hospital D (Table 1). The median age of patients at the time of MIS-C onset was 9 years (IQR, 5–13 years). Among all patients, the most frequently administered treatments were at least one dose of IVIG (77.7%), any dose of steroids (88.4%), and any dose of aspirin (81.1%). The least frequently administered treatments were immune modulators (8.2%), non-invasive ventilation (e.g., CPAP, BiPAP) (8.2%), mechanical ventilation or intubation (5.2%), and ECMO (1.7%) (Table 1). The proportion of patients at each hospital who received at least one dose of IVIG ranged from 67.5% to 100%. Similarly, the proportion of patients receiving low-dose steroids (45.9% to 84.8%) and high-dose steroids (5.3% to 45.9%) also varied between hospitals (Table 1).

Table 2 shows the demographic characteristics of patients who received standard treatments for MIS-C [6]. Patients age 13–20 years old (64.3%) were less likely to receive one dose of IVIG compared with patients age 0–5 (83.1%) and 6–12 years old (81.2%). Furthermore, males (83.1%) were more likely to receive one dose of IVIG compared to females (68.2%). Patients age 6–12 years were more likely to receive high-dose aspirin (30.4%), whereas patients age 13–20 years (10.7%) were least likely to receive high-dose aspirin. Non-Hispanic, black patients (39.8%) were least likely to receive IVIG and steroids in combination and patients with unknown race (81.8%) were most likely to receive combination treatment. High-dose steroids were more frequently administered to Hispanic or Latino patients (28.3%) compared with patients of other races and ethnicities. No statistically significant difference by age group, sex, or race/ethnicity was observed among patients who received two doses of IVIG or low-dose steroids (Table 2).

Patients admitted on or before October 22, 2020 were more likely to receive one dose of IVIG (83.9%) compared with patients admitted after this date (71.3%, Figure 1). Patients receiving ICU-level care were more likely to receive at least one dose of IVIG (87.2%), two doses of IVIG (14.3%), and high-dose steroids (19.5%) compared to non-ICU patients. Non-ICU patients with cardiac complications were most likely to receive high-dose aspirin (40.4%), whereas non-ICU patients without cardiac complications were least likely to receive at least one dose of IVIG (54.7%), two doses of IVIG (1.9%), IVIG and steroids in combination (35.8%), or high-dose steroids (5.7%). Among all patients in the sample who received ICU-level care, 77.4% had cardiac complications and 50.4% were age 6 to 12 years.

Treatments also differed among patients with and without clinical features by organ system. Patients with mucocutaneous features were more likely to receive at least one dose of IVIG (82.8%) or high-dose aspirin (28.4%) compared with patients without mucocutaneous features (64.1% received IVIG and 12.5% received high-dose aspirin) (Figure 1). Patients with respiratory features were less likely to receive IVIG and steroids on the same day (44.1%) compared with patients without respiratory features (59.7%). Lastly, patients with cardiac features more frequently received at least one dose of IVIG (79.6%) compared with patients without cardiac features (41.7%). Administration of treatments did not significantly differ among patients with or without gastrointestinal or hematologic features (Figure 1).

All treatments, excluding second dose IVIG, vasoactive medications, and immune modulators, had a median day of administration of day 1 following hospital admission (Table 3). The median day of treatment for second dose IVIG and immune modulators was day 3. Median duration of treatment for patients who received high-dose steroids was 5.5 days compared to 4 days for patients who received low-dose steroids. All patients who received high-dose steroids during hospitalization were discharged home with steroids. The median dose of low- and high-dose steroids administered to patients with MIS-C was 2 mg/kg/day and 22.4 mg/kg/day, respectively (Table 3).

The 181 patients who received at least one dose of IVIG were more likely to exhibit elevated troponin levels (72.9%), experience shock or hypotension (70.7%), and receive ICU-level care (64.1%) compared with patients who did not receive IVIG. The 24 patients who received two doses of IVIG were more likely to have experienced shock or hypotension (87.5%), received ICU-level care (79.2%), and had an LOS of ≥8 days (70.8%) compared with patients not receiving two doses of IVIG. Furthermore, 169 patients who received low-dose steroids were more likely to have elevated troponin values (72.2%) but less likely to have received immune modulators (3.6%) compared with patients not receiving low-dose steroids. Patients who received high-dose steroids (36 patients) were significantly more likely than patients not receiving high-dose steroids to experience shock or hypotension (83.3%), but less than half required a hospital LOS of ≥8 days (47.2%), and less than one-third required treatment with immune modulators (30.6%). Coronary artery abnormalities were more common for patients receiving high-dose aspirin (33.9%) (Figure 2, details of abnormalities in Supplemental Table 2). Additional data related to patient demographics and severe outcomes are found in Supplemental Table 1.

After propensity score matching to adjust for potential confounding, we observed that patients receiving IVIG within 1 day of hospitalization had a lower risk of having hospital LOS of ≥8 days (RR = 0.53, 95% CI = 0.31–0.88) and a borderline lower risk of subsequently receiving immune modulators (RR = 0.38, 95% CI = 0.14–1.02) compared with patients who did not receive IVIG within 1 day of hospitalization (Figure 3). Patients receiving low-dose steroids within 1 day of hospitalization were significantly less likely to have subsequent ventricular dysfunction (RR = 0.45, 95% CI = 0.26–0.77), increasing troponin levels (RR = 0.55, 95% CI = 0.40–0.75), or hospital LOS of ≥8 days (RR = 0.46, 95% CI = 0.29–0.74) compared with patients who did not receive low-dose steroids within 1 day of hospitalization (Figure 3). Similarly, Figure 4 shows the relative risk of severe outcomes given the administration of both IVIG and low-dose steroids within 1

day of hospitalization. Compared with patients receiving only low-dose steroids within 1 day of hospitalization, patients receiving IVIG and low-dose steroids within 1 day of hospitalization were less likely to experience subsequent coronary artery abnormalities (RR = 0.05, 95% CI = 0.01–0.20). Additionally, compared with patients receiving only IVIG within 1 day of hospitalization, patients receiving IVIG and low-dose steroids in that timeframe were less likely to have increasing troponin (RR = 0.53, 95% CI = 0.40–0.71). The number of patients included in each comparison and the comparison of risk ratios before and after propensity score matching are shown in Supplemental Tables 3 and 4, respectively.

Discussion

The present study highlights differences in treatment practice for patients with MIS-C during the first year of the pandemic by institution and by patient demographics and clinical characteristics. Importantly, when controlling for demographic and clinical characteristics, administration of IVIG and low-dose steroids within 1 day of hospitalization, separately or in combination, was associated with lower risk of certain severe outcomes.

Treatment practices varied greatly across hospitals. For example, some hospitals administered IVIG for more severe cases who experienced KD-like symptoms or cardiovascular involvement, whereas others preferred to treat all patients with IVIG, regardless of severity. It is also possible that infrequent use of IVIG as a first-line treatment in some hospitals was related to concerns about IVIG shortages during the initial phases of the pandemic. We also observed variations in the number of patients receiving two doses of IVIG and anticoagulants across hospitals. Higher rates of administration of both treatments may have been related to greater illness severity of patients. Lastly, as treatment guidelines continuously evolved during the study period, patients hospitalized at different times may have received different treatments.

Unadjusted analyses primarily showed that receipt of specific MIS-C treatments was largely driven by patient clinical profiles. Patients with more KD-like features such as young age, being male, and having mucocutaneous symptoms showed a significantly greater likelihood of receiving at least one dose of IVIG. Patients presenting with severe disease typically received high-dose steroids or a second dose of IVIG and were more likely to experience shock or hypotension, require intubation or mechanical ventilation, receive immune modulators, and have longer hospital stays. By using propensity score matching, adjusted analyses, and temporally distinct treatments and outcomes, we estimated the effects of treatments on risk of subsequent clinical outcomes. While some reports suggest that IVIG aids in clinical improvement and recovery of cardiac function from MIS-C [11], not all studies have shown a clear benefit of its use alone [12, 13]. Prior studies have demonstrated that patients who received IVIG and steroids in combination had lower risk of treatment failure, cardiovascular dysfunction, need for escalated treatment regimens, and shorter ICU stays [12–14]. Findings of our study showed that receipt of IVIG within day 1 of hospitalization could reduce the risk of having an LOS of ≥8 days and when administered alongside low-dose steroids, patients had significantly lower risk of coronary artery abnormalities and increased troponin levels.

Overlapping symptoms of KD and MIS-C are well-documented in the literature [15–18]. Coronary artery abnormalities (CAA), aneurysms in particular, are serious complications of both illnesses. In our study, 16% of patients developed an aneurysm or dilatation, which were typically detected within 1 day of admission. Patients who received IVIG in conjunction with steroids had significantly lower risk of CAAs compared to patients who received steroids alone; however, overall patients receiving IVIG did not have a lower risk of CAAs compared to patients not receiving IVIG. Patients received IVIG a median of 5 days after MIS-C symptom onset (IQR: 4–6 days); it is possible that earlier MIS-C diagnosis and treatment with IVIG could have shown a greater protective effect against CAAs. To avoid higher risk of developing aneurysms, some studies on KD recommend that IVIG and high-dose aspirin should be started immediately upon diagnosis [19, 20]. Patients in our study predominantly received both treatments within 1 day of hospitalization (Table 3) and patients with mucocutaneous features were significantly more likely to receive both treatments compared to patients without mucocutaneous features (Table 2). Use of high-dose aspirin was also most common in patients who had cardiac complications but did not require ICU-level care. It is possible that aspirin was not given in accordance with standard administration guidelines to some ICU patients with thrombocytopenia; however, we did not evaluate this for our study. Of 44 patients who received high-dose aspirin within 1 day of hospitalization, 43 were treated with IVIG in the same timeframe. A high degree of collinearity between the two treatments disallowed estimation of effects of high-dose aspirin separately from IVIG, leaving open the possibility that part of any observed beneficial effect of IVIG may be attributable to combined administration with high-dose aspirin.

The present study has several limitations. First, given that this is an observational study and patient management differed by clinical disease severity at time of presentation, we could not directly assess the effectiveness of any treatment. The use of propensity score matching and analyses controlling for matched variables allowed for estimation of the effect of treatments on subsequent risk of severe outcomes, but residual confounding could potentially affect these estimates. Second, we assessed how the receipt of treatments on day 0 or 1 of hospitalization affected the risk of severe outcomes on day 2 or later. However, if outcomes were already developing before treatments became fully effective, our results may underestimate the effect of treatments on subsequent outcomes. Third, criteria for ICU admission and hospital discharge could have differed across institutions. Given that these results are specific to MIS-C patients at four institutions over a specific timeframe and patient demographics and clinical characteristics varied over setting and time, the findings of the present study may not be generalizable. Furthermore, the majority of patients enrolled in the study came from a single hospital. Lastly, our study did not account for SARS-CoV-2 variant-specific changes in MIS-C or vaccination status. To properly gauge treatment practices and outcomes among patients with MIS-C, future studies should collect data on a larger sample from additional institutions and over study periods encompassing multiple predominant strains of COVID-19. Should MIS-C cases continue to occur, additional studies including clinical trials could be conducted to outline the best practices for treatment.

In conclusion, treatments for MIS-C differed by hospital, patient characteristics, and illness severity and standard treatments for MIS-C such as IVIG, steroids, and high-dose aspirin, were administered to patients within a median of 1 day from hospital admission. Patients

who received high-dose steroids and aspirin had increased rates of severe outcomes and longer duration of treatment, indicating that patients with severe illness may have been selected for these treatments. Furthermore, treatment with IVIG and low-dose steroids within 1 day of hospitalization lowered risk of severe outcomes, illustrating that prompt treatment is essential for better outcomes among patients with MIS-C.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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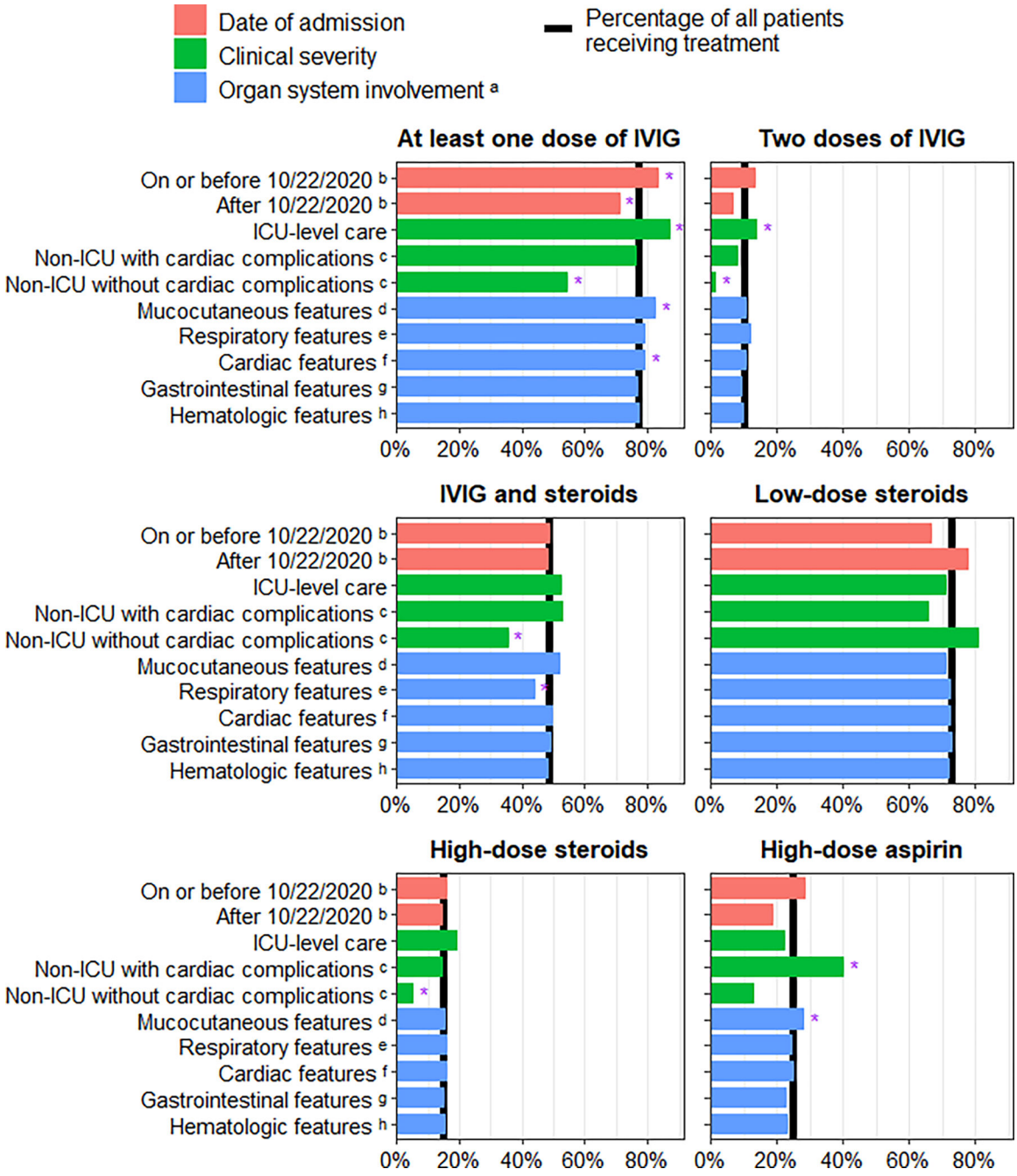

Figure 1.

Percentage of patients receiving treatments for MIS-C by date of admission and clinical characteristics

Abbreviations: MIS-C = Multisystem Inflammatory Syndrome in children; IVIG = Intravenous Immunoglobulin; ICU = Intensive Care Unit

* Percentage of patients in a demographic category receiving a specified treatment significantly differs from the percentage of patients in other demographic categories receiving the same treatment ($p<0.05$). For example, patients receiving ICU-level care were

compared to all non-ICU patients, regardless of the presence of cardiac complications. Chi square or Fisher's exact two-sided p-value if any expected cell counts were below 5.

[a] Organ system involvement categories are not mutually exclusive

[b] The cutoff date of October 22, 2020 for timing of hospitalization reflects the median date of hospital admissions among all patients.

[c] Cardiac complications are defined as arrhythmia, pericarditis, myocarditis, mitral regurgitation (mild, moderate, or severe), coronary artery abnormalities (dilatation or aneurysms), elevated troponin, congestive heart failure, ventricular dysfunction (left, right, or dysfunction in both ventricles), or a left ventricular ejection fraction <50%.

[d] Mucocutaneous features include the appearance of rash, mucocutaneous lesions, or conjunctival injection.

[e] Respiratory features include cough, shortness of breath, chest pain or tightness, pneumonia, acute respiratory distress syndrome (ARDS), or pleural effusion.

[f] Cardiac features include shock, elevated brain natriuretic peptide (BNP) or N-terminal pro-hormone BNP (NT-proBNP), elevated troponin.

[g] Gastrointestinal features include abdominal pain, vomiting, or diarrhea.

[h] Hematologic features include elevated d-dimer, lymphopenia, or thrombocytopenia. Lymphopenia was defined as a lymphocyte count of <4,500 cells per μl for infants aged <8 months, or less than 1,500 cells per ml for persons aged ≥8 months.

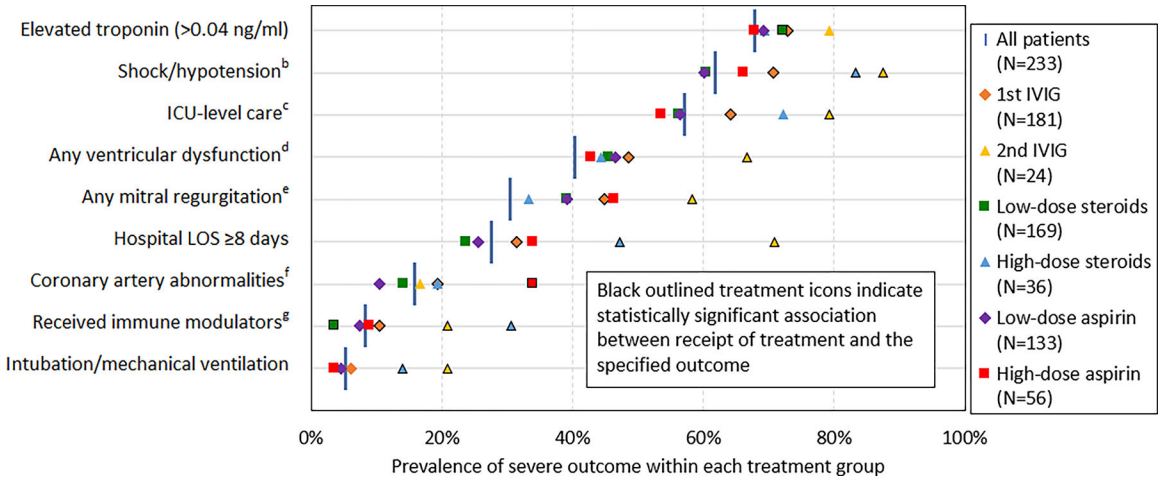

Figure 2.

Prevalence of severe outcomes of MIS-C by treatment regimen at day 2 or later of hospitalization[a]

Abbreviations: ICU = Intensive Care Unit; LOS = Length of Stay; IVIG = Intravenous Immunoglobulin

[a] Treatment regimens are not mutually exclusive. Percentages reflect the proportion of patients with severe outcomes within each treatment category.

[b] Patients with an outcome of Shock/Hypotension experienced shock, were hypotensive and received vasoactive medications, or received vasoactive medications regardless of shock or hypotension.

[c] Patients who were intubated or placed on mechanical ventilation are a subset of patients who received ICU-level care.

[d] Any ventricular dysfunction is defined as dysfunction of the left, right, or both ventricles.

[e] Any mitral regurgitation is defined as mild, moderate, or severe regurgitation.

[f] Coronary artery abnormalities are defined as dilatation or aneurysm indicated by z-score.

[g] Immune modulators administered included anakinra, tocilizumab, rituximab, or sirolimus.

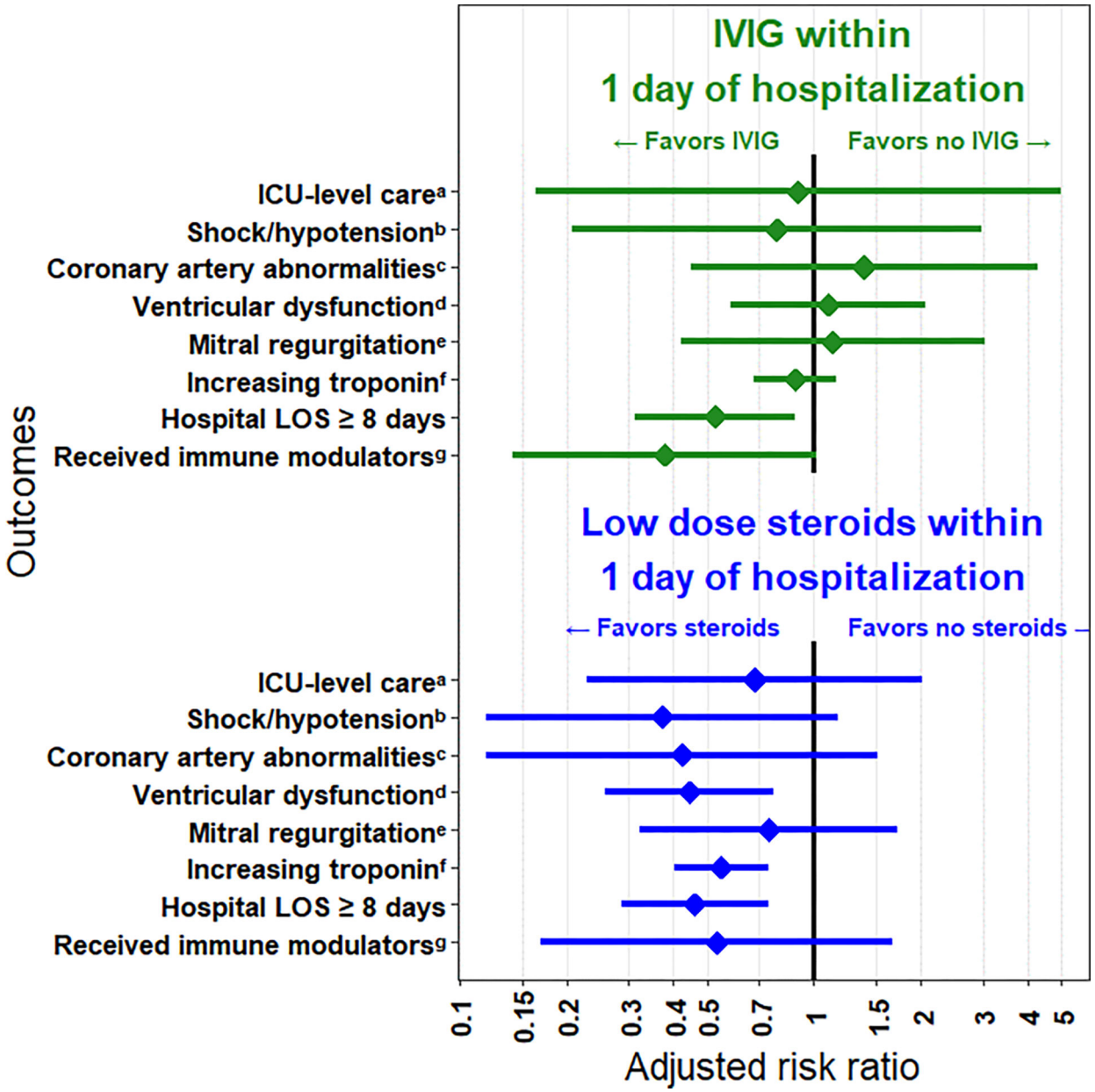

Figure 3.

Relative risk of subsequent outcomes for patients with MIS-C receiving IVIG or low-dose steroids within 1 day of hospitalization compared with patients not receiving these treatments within 1 day of hospitalization, using propensity score matching to account for demographic and clinical confounding variables

[a] Patients who received ICU-level care stayed in the ICU for one or more days, received treatment with a vasoactive medication, were intubated or placed on mechanical ventilation, or were placed on extracorporeal membrane oxygenation (ECMO).

[b] Patients with an outcome of Shock/Hypotension experienced shock, were hypotensive and received vasoactive medications, or received vasoactive medications regardless of shock or hypotension.

[c] Coronary artery abnormalities are defined as dilatation or aneurysm indicated by z-score.
[d] Ventricular dysfunction is defined as dysfunction of the left, right, or both ventricles.
[e] Mitral regurgitation is defined as mild, moderate, or severe regurgitation.
[f] Troponin that was elevated (>0.04 ng/ml) and peaked at two or more days following hospitalization
[g] Immune modulators administered included anakinra, tocilizumab, rituximab, or sirolimus.

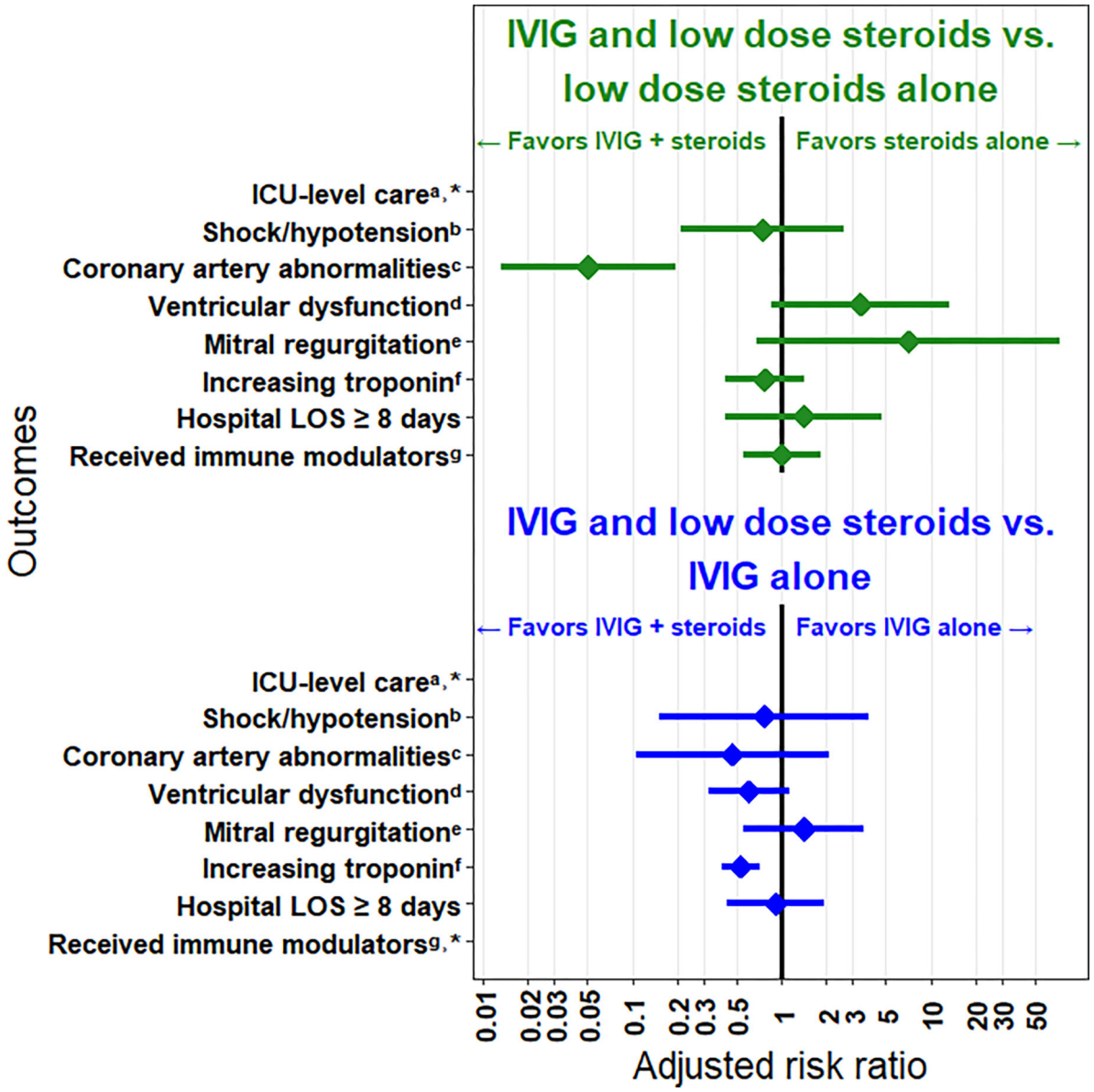

Figure 4.

Relative risk of subsequent outcomes for patients with MIS-C receiving both IVIG and low-dose steroids within 1 day of hospitalization compared with patients only receiving one of these treatments within 1 day of hospitalization, using propensity score matching to account for demographic and clinical confounding variables

* Calculation did not converge (risk ratio was not able to be estimated)

[a] Patients who received ICU-level care stayed in the ICU for one or more days, received treatment with a vasoactive medication, were intubated or placed on mechanical ventilation, or were placed on extracorporeal membrane oxygenation (ECMO).

[b] Patients with an outcome of Shock/Hypotension experienced shock, were hypotensive and received vasoactive medications, or received vasoactive medications regardless of shock or hypotension.

[c] Coronary artery abnormalities are defined as dilatation or aneurysm indicated by z-score.

[d] Ventricular dysfunction is defined as dysfunction of the left, right, or both ventricles.

[e] Mitral regurgitation is defined as mild, moderate, or severe regurgitation.

[f] Troponin that was elevated (>0.04 ng/ml) and peaked at two or more days following hospitalization

[g] Immune modulators administered included anakinra, tocilizumab, rituximab, or sirolimus.

Table 1.

All treatments administered to patients with MIS-C by institution, March 16, 2020 to March 10, 2021

Treatment	All patients (N=233) n (%)	Hospital A (N=151) n (%)	Hospital B (N=37) n (%)	Hospital C (N=23) n (%)	Hospital D (N=22) n (%)
At least one dose of IVIG	181 (77.7)	102 (67.5)	37 (100.0)	22 (95.7)	20 (90.9)
Two doses of IVIG	24 (10.3)	19 (12.6)	1 (2.7)	1 (4.3)	3 (13.6)
IVIG & Steroids[a]	114 (48.9)	57 (37.7)	27 (73.0)	14 (60.9)	16 (72.7)
Steroids[b]	206 (88.4)	136 (90.1)	34 (91.9)	21 (91.3)	15 (68.2)
Low-dose (< 10 mg/kg/day)	169 (72.5)	128 (84.8)	17 (45.9)	13 (56.5)	11 (50.0)
High-dose (≥ 10 mg/kg/day)	36 (17.4)	8 (5.3)	17 (45.9)	7 (30.4)	4 (18.2)
Aspirin[c]	189 (81.1)	130 (86.1)	33 (89.2)	16 (69.6)	10 (45.5)
Low-dose (< 10 mg/kg/day)	133 (70.4)	103 (68.2)	19 (51.4)	8 (34.8)	3 (13.6)
High-dose (≥ 10 mg/kg/day)	56 (24.0)	27 (17.9)	14 (37.8)	8 (34.8)	7 (31.8)
Anticoagulants[d]	166 (71.2)	129 (85.4)	9 (24.3)	13 (56.5)	15 (68.2)
Vasoactives or inotropes	99 (42.5)	65 (43.0)	15 (40.5)	9 (39.1)	10 (45.5)
Immune modulators[e]	19 (8.2)	8 (5.3)	7 (18.9)	2(8.7)	2 (9.1)
Low-flow nasal cannula	99 (42.5)	72 (47.7)	14 (37.8)	5 (21.7)	8 (36.4)
High-flow nasal cannula	66 (28.3)	49 (32.5)	5 (13.5)	7 (30.4)	5 (22.7)
Non-invasive ventilation[f]	19 (8.2)	15 (9.9)	2 (5.4)	1 (4.3)	1 (4.5)
Mechanical Ventilation or Intubation	12 (5.2)	8 (5.3)	1 (2.7)	1 (4.3)	2 (9.1)
ECMO	4 (1.7)	3 (2.0)	0 (0)	0 (0)	1 (4.5)

Abbreviations: IVIG = Intravenous immunoglobulin; ECMO = Extracorporeal Membrane Oxygenation

[a] IVIG and any dose of steroids administered on the same day.

[b] The category for Steroids is inclusive of all patients who received low- or high-dose steroids, which are presented in the two subsequent rows.

[c] The category for Aspirin is inclusive of all patients who received low- or high-dose aspirin, which are presented in the two subsequent rows.

[d] Anticoagulants administered included prophylactic and treatment doses but were not distinguished from each other for this study.

[e] Immune modulators are defined as anakinra, tocilizumab, rituximab, or sirolimus.

[f] Modes of non-invasive ventilation are defined as CPAP or BiPAP.

Table 2.

Number and percentage of patients receiving treatments for MIS-C by demographic characteristics (N=233)

	At least one dose of IVIG	Two doses of IVIG	IVIG & Steroids[a]	Low-dose Steroids	High-dose Steroids	High-dose Aspirin
Age (years)						
0–5 (n=65)	54 (83.1)	7 (10.8)	39 (60.0)	46 (70.8)	11 (16.9)	16 (24.6)
6–12 (n=112)	91 (81.2)	12 (10.7)	50 (44.6)	85 (75.9)	16 (14.3)	34 (30.4)*
13–20 (n=56)	36 (64.3)*	5 (8.9)	25 (44.6)	38 (67.9)	9 (16.1)	6 (10.7)*
Sex						
Male (n=148)	123 (83.1)*	12 (8.1)	77 (52.0)	102 (68.9)	28 (18.9)	37 (25.0)
Female (n=85)	58 (68.2)*	12 (14.1)	37 (43.5)	67 (78.8)	8 (9.4)	19 (22.4)
Race/Ethnicity						
Non-Hispanic, white (n=52)	39 (75.0)	5 (9.6)	28 (53.8)	40 (76.9)	5 (9.6)	11 (21.2)
Non-Hispanic, black (n=98)	73 (74.5)	11 (11.2)	39 (39.8)*	71 (72.4)	12 (12.2)	27 (27.6)
Hispanic or Latino (n=60)	48 (80.0)	6 (10.0)	33 (55.0)	39 (65.0)	17 (28.3)*	12 (20.0)
Other[b] (n=12)	11 (91.7)	1 (8.3)	5 (41.7)	10 (83.3)	1 (8.3)	3 (25.0)
Unknown[c] (n=11)	10 (90.9)	1 (9.1)	9 (81.8)*	9 (81.8)	1 (9.1)	3 (27.3)

Abbreviations: MIS-C = Multisystem Inflammatory Syndrome in children; IVIG = Intravenous Immunoglobulin

*Percentage of patients in a demographic category receiving a specified treatment significantly differs from the percentage of patients in other demographic categories receiving the same treatment ($p<0.05$). For example, patients of age 6–12 were compared to patients of ages 0–5 and 13–20. Chi square or Fisher's exact two-sided p-value if any expected cell counts were below 5.

[a]IVIG and Steroids administered on the same day.

[b]Patients identified as American Indian/Alaska Native (n=2), Asian (n=5), Multi-race (n=3), or Other (n=2).

[c]11 patients did not report their race or ethnicity.

Table 3.

Details of treatments administered to patients with MIS-C, March 16, 2020 to March 10, 2021 (N=233)

	Patients treated n (%)	First treatment day*, median (IQR)	Duration of treatment in hospital, median (IQR)	Discharged home with treatment, n (%)	Dosage mg/kg/day, median (IQR)
One dose IVIG	181 (77.7)	1 (0–1)	-	-	-
Two doses IVIG	24 (10.3)	3 (2–4.3)	-	-	-
Steroids	206 (88.4)	1 (0–2)	4 (3–6)	178 (86.4)	2 (1.6–3.9)
Low-dose	169 (72.5)	1 (0–2)	4 (3–5)	140 (82.8)	2 (1.4–2)
High-dose	36 (15.5)	1 (0–1)	5.5 (4–9.3)	36 (100.0)	22.4 (13.8–30)
Aspirin	189 (81.1)	1 (0–2)	4 (2–6)	183 (96.8)	3.6 (2.0–27.8)
Low-dose	133 (57.1)	1 (1–3)	4 (2–6)	129 (97.0)	2.7 (1.5–4.1)
High-dose	56 (24.0)	1 (0–1)	5 (3–6)	54 (96.4)	34.8 (30–54.2)
Vasoactive medications	99 (42.5)	0 (0–1)	2 (1–4)	-	-
Immune modulators [a]	19 (8.2)	3 (2–4)	7 (4–17.5)	4 (21.2)	-

Abbreviations: IQR = Interquartile range; IVIG = Intravenous Immunoglobulin

*Days from hospital admission (i.e., treatments given on the same day as hospitalization would be listed as 0)

[a]Patients who received immune modulators were administered anakinra, tocilizumab, rituximab, or sirolimus. Three patients were discharged home with anakinra and 1 patient was discharged home with sirolimus.