Health Impairments in Children and Adolescents After Hospitalization for Acute COVID-19 or MIS-C

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abstract

OBJECTIVES: To evaluate risk factors for postdischarge sequelae in children and adolescents hospitalized for acute coronavirus disease 2019 (COVID-19) or multisystem inflammatory syndrome in children (MIS-C).

METHODS: Multicenter prospective cohort study conducted in 25 United States pediatric hospitals. Patients <21-years-old, hospitalized May 2020 to May 2021 for acute COVID-19 or MIS-C with follow-up 2 to 4 months after admission. We assessed readmissions, persistent symptoms or activity impairment, and new morbidities. Multivariable regression was used to calculate adjusted risk ratios (aRR) and 95% confidence intervals (CI).

RESULTS: Of 358 eligible patients, 2 to 4 month survey data were available for 119 of 155 (76.8%) with acute COVID-19 and 160 of 203 (78.8%) with MIS-C. Thirteen (11%) patients with acute COVID-19 and 12 (8%) with MIS-C had a readmission. Thirty-two (26.9%) patients with acute COVID-19 had persistent symptoms (22.7%) or activity impairment (14.3%) and 48 (30.0%) with MIS-C had persistent symptoms (20.0%) or activity impairment (21.3%). For patients with acute COVID-19, persistent symptoms (aRR, 1.29 [95% CI, 1.04–1.59]) and activity impairment (aRR, 1.37 [95% CI, 1.06–1.78]) were associated with more organ systems involved. Patients with MIS-C and pre-existing respiratory conditions more frequently had persistent symptoms (aRR, 3.09 [95% CI, 1.55–6.14]) and those with obesity more frequently had activity impairment (aRR, 2.52 [95% CI, 1.35–4.69]). New morbidities were infrequent (9% COVID-19, 1% MIS-C).

CONCLUSIONS: Over 1 in 4 children hospitalized with acute COVID-19 or MIS-C experienced persistent symptoms or activity impairment for at least 2 months. Patients with MIS-C and respiratory conditions or obesity are at higher risk of prolonged recovery.

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WHAT'S KNOWN ON THIS SUBJECT: Many adults hospitalized with coronavirus disease 2019 (COVID) experience post-COVID conditions. Research evaluating postdischarge outcomes of children and adolescents hospitalized for acute COVID-19 or multisystem inflammatory syndrome in children (MIS-C) are limited, especially for children who became critically ill.

WHAT THIS STUDY ADDS: Over 1 in 4 children and adolescents hospitalized with COVID-19 or MIS-C had sequelae beyond 2 months posthospitalization. Patients with COVID-19 and more organ system involvement and patients with MIS-C and underlying respiratory conditions or obesity were at increased risk.

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Since severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged globally in 2020, it infected over 59 million United States persons, including over 10.2 million children and adolescents.[1] As of March 27, 2022, over 975 000 of them, including 1374 children, died of coronavirus disease 2019 (COVID-19).[1] Although hospitalization is less common in the very young than in the elderly, ~118 058 children in the United States were hospitalized for severe COVID-August 19, 2020 to March 2022.[2] Additional hospitalizations occurred because of a postinfectious complication of SARS-CoV-2, termed multisystem inflammatory syndrome in children (MIS-C).[3] As of March 1, 2022, 7459 cases of MIS-C were reported in the United States.[2] Acute COVID-19 and MIS-C can lead to need for life-supporting interventions in children.[4]

Some adults infected with SARS-CoV-2 report prolonged symptoms with inability to return to their baseline health for months after a sometimes minimal initial illness.[5] Post-COVID conditions (PCC) were evaluated across 16 studies of mostly hospitalized adults and identified persistent symptoms in a median of 72.5% of patients.[6] Research evaluating PCC in children hospitalized for acute COVID-19 is limited.[7] Pediatric studies of hospitalized children are limited to postdischarge outcomes identified by administrative data,[8] a multicenter study from Iran with follow-up 3 months postdischarge,[9] and a single-center study from Russia with follow-up 5 months postdischarge.[10] Other than cardiac outcomes, data delineating posthospitalization outcomes for patients with MIS-C are sparse, including 1 single-center study conducted in the United Kingdom[11] and 1 population-based study in Sweden.[12] The objectives of this study were to characterize the sequelae and recovery of United States children hospitalized with acute severe COVID-19 or MIS-C 2 or more months after hospital admission, and identify factors associated with ongoing symptoms or activity impairment.

METHODS

We conducted a multicenter prospective observational cohort study in children and adolescents admitted for acute COVID-19 or MIS-C at 25 sites across the Overcoming COVID-19 network (Supplemental Information). We evaluated posthospitalization outcomes and illness-associated complications. Informed consent was obtained by trained study staff from the patient's legal guardian. Patient assent was also obtained, when possible, based on age, developmental capacity, and illness severity. This study was approved centrally by Boston Children's Hospital's Institutional Review Board and was reviewed by the Centers for Disease Control and Prevention.

We enrolled children and adolescents (<21-years-old) hospitalized for acute COVID-19 (SARS-CoV-2 reverse transcriptase polymerase chain reaction or antigen test positive and admitted with symptoms suspected to be related to COVID-19) or MIS-C (fever, evidence of inflammation, multisystem [≥2] involvement (Supplemental Table 2), positive SARS-CoV-2 respiratory or antibody test results, and without another etiology) between May 12, 2020, and May 4, 2021.[4] We excluded patients suspected of a nosocomial SARS-CoV-2 infection and in-hospital deaths. After October 27, 2020, we excluded patients with acute COVID-19 and pre-existing acquired immune compromise (Supplemental Table 2), limitations of life support because of poor prognosis, end-stage lung disease awaiting transplant, or requiring chronic mechanical ventilation support.

Patient and hospitalization characteristics were collected by chart review and interview. Patient data included demographics, acute symptoms, and comorbidities. Obesity was defined by national reference standards for body mass index if aged >2 years and was considered separately from other pre-existing conditions.[13] Race and ethnicity data were collected by parental or patient report. Hospitalization data included organ system involvement based on the Centers for Disease Control and Prevention MIS-C organ system involvement criteria (Supplemental Table 2), ICU admission and duration, pediatric logistic organ dysfunction score (PELOD-2), organ failure support (invasive mechanical ventilation, vasopressor support, extracorporeal membrane oxygenation), impaired left ventricular ejection fraction defined as <55%, and hospital length of stay.[14] A pre-illness Functional Status Scale (FSS) score was collected by patient or family interview.[15]

Clinical Outcomes

Primary outcomes included persistent symptoms or activity intolerance 2 to 4 months (50 to 120 days) after hospitalization. For patients missing 2 to 4 month survey data, we reported 1-month (30 to 41 days) survey data, when available. Secondary outcomes were hospital readmission and new morbidity at hospital discharge and follow-up relative to preillness baseline. Data delineating ongoing symptoms and activity impairments were collected by telephone interview or online surveys at approximately 1 month and 3 months after enrollment. Because of variability in time of enrollment and follow-up interview(s), follow-up durations were reported relative

to hospital admission. Caregivers were asked to respond based on their child's symptoms during the 7 days before survey completion. Questionnaires were based on symptoms and activity impairments previously reported in adult studies.[16] New morbidity was defined as an increase of ≥3 points in the total FSS score or ≥2 points in a domain-specific score compared with preillness FSS.[15] FSS and hospital readmission data were collected by caregiver interview and electronic health record review. All data were entered using standardized forms by trained study personnel into Boston Children's Hospital's REDCap database.[17]

Statistical Analyses

Descriptive statistics included frequency (proportion) for categorical variables and median (interquartile range [IQR]) for continuous variables. Fisher's exact and Wilcoxon rank sum tests were used to compare variables between patients with acute COVID-19 and MIS-C. We conducted univariate analyses to identify variables associated with the 2 outcomes: persistent symptoms or impaired activity 2 to 4 months after hospitalization. Pre-existing respiratory disease and obesity were evaluated separately in the models because of prior reports of their association with PCC.[10,18] Based on univariate results, variables associated ($P < .09$) with 2 to 4 months outcomes were included in multivariable Poisson regression models using robust variance estimates to determine risk ratios. We conducted sensitivity analyses including 30-day survey data for patients with resolution of symptoms and activity impairments at 30-days but missing 60 day outcomes. We report adjusted risk ratios (aRR) and risk differences and 95% confidence intervals (CI).

P values less than .05 were considered statistically significant. All analyses were conducted using R software, version 4.0.2 (R Project for Statistical Computing, Vienna).

RESULTS

We enrolled 373 children. Fifteen patients were excluded including 2 in-hospital deaths and 1 that remained hospitalized (Fig 1). Of 358 patients eligible for follow up, 155 (43.3%) had acute COVID-19 and 203 (56.7%) had MIS-C. At 2 to 4 month follow-up, 7 patients were readmitted, for whom outpatient survey data were unavailable. We report 2 to 4 month outcomes for the 279 of 351 (79.5%) patients who were not readmitted and had 2 to 4 month survey data available including 119 of 150 (79.3%) patients with acute COVID-19 and 160 of 201 (79.6%) with MIS-C. Patient demographics did not differ between patients with and without 2 to 4 month follow-up data (Supplemental Table 3). Patients with acute COVID-19 and missing 2 to 4 month survey data were more frequently admitted to the ICU, supported with invasive mechanical ventilation, and had more significant organ dysfunction than those with 2 to 4 month survey data. For patients with MIS-C requiring mechanical ventilation ($n = 41$), mechanical ventilation duration was shorter in patients without versus with 2 to 4 month survey data.

Patients With Acute COVID-19

Patients with acute COVID-19 and 2 to 4 month survey data ($n = 119$) demonstrated a bimodal age distribution with more patients in the <2 and ≥13 years old age groups, 59 (49.6%) were male, 79 (66.4%) had pre-existing conditions, and 39 (32.8%) were obese (Table 1). Median duration of hospitalization was 4 days (IQR 2–10).

By 2 to 4 months after hospitalization, 32 of 119 (26.9%) patients with acute COVID-19 had persistent symptoms or activity impairment; with 27 of 119 (22.7%) having persistent symptoms (Fig 2A) and 17 of 119 (14.3%) having activity impairments (Fig 2B). Fever and respiratory symptoms, which were common upon admission, had resolved at follow-up, but fatigue or weakness persisted in 14.3% of patients (Supplemental Fig 4). Patients with persistent symptoms or activity impairment most frequently had respiratory, hematologic, or gastrointestinal organ system involvement during hospitalization (Supplemental Fig 5). Patients with impaired activity had longer ICU stays compared with those without impaired activity (11.0 days [IQR 4.0–26.5] versus 4.0 days [IQR 2.0–7.0], $P = .01$), whereas there was no difference in length of ICU stay among patients with and without persistent symptoms (Supplemental Table 4). Patients reporting persistent symptoms or cactivity impairments had longer hospitalizations compared with those without persistent symptoms or activity impairments. Of the 31 patients with acute COVID-19 without 2 to 4 month outcomes, 9 (29%) had survey data available at 1 month and 7 of 9 (78%) reported symptom resolution and normalized activity.

Preillness and hospital discharge FSS scores were available for 115 of 119 patients with acute COVID-19. New morbidities were present at hospital discharge in 10 of 115 (9%) patients. The most frequently affected domains were respiratory ($n = 6$; 5%), communication ($n = 3$; 3%), motor ($n = 3$; 3%), and feeding ($n = 3$; 3%). Three of the 10 patients with new morbidities at discharge had persistent morbidities at 2 to 4 months, whereas 7 patients' morbidities had resolved. An additional 6 patients had new morbidities that were not present at hospital discharge (data not shown). Thirteen (11.0%)

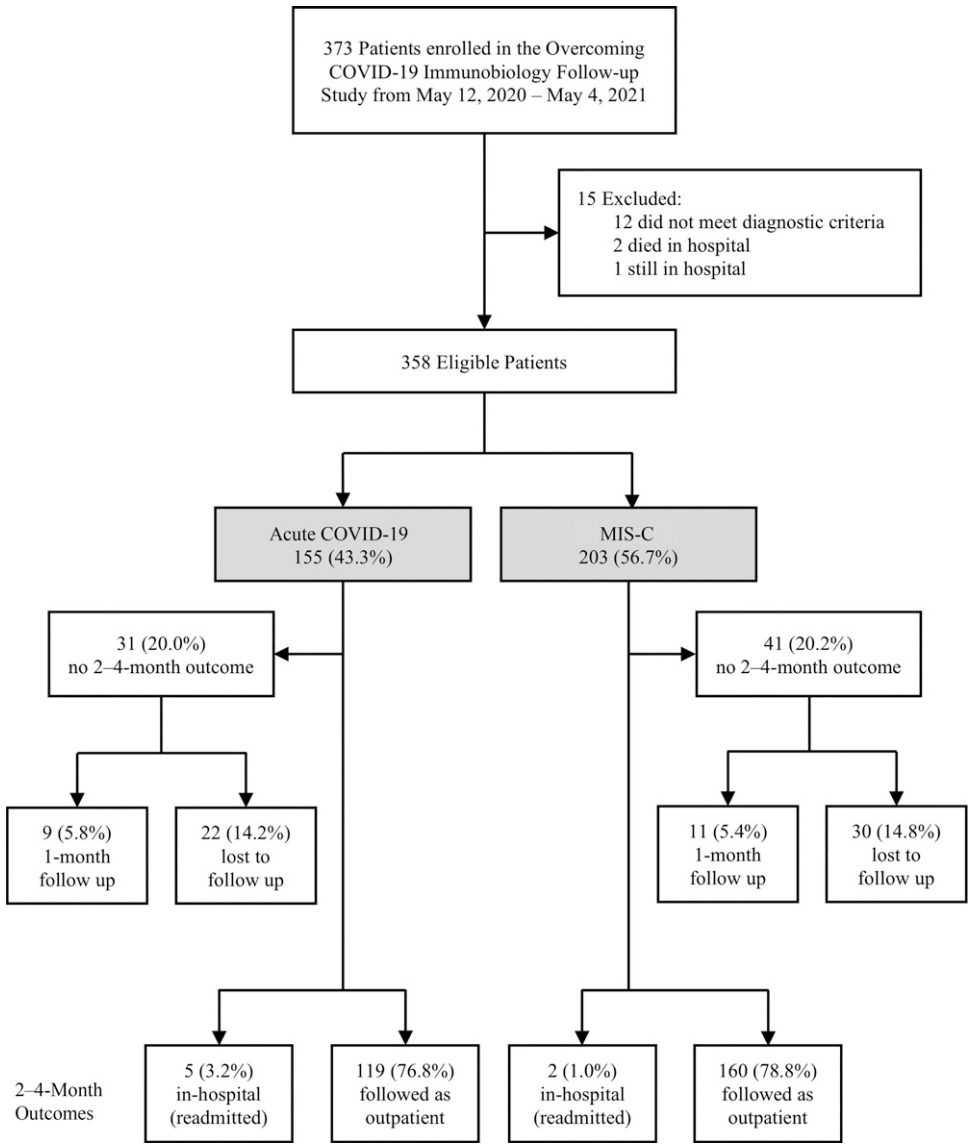

FIGURE 1
Enrollment and follow-up of patients hospitalized for acute COVID-19 or MIS-C across 25 United States sites in the Overcoming COVID-19 network.

patients with acute COVID-19 were readmitted within 2 to 4 months (Supplemental Table 5). Of the patients who were readmitted, 1 was previously healthy and was readmitted for epistaxis and the other 12 patients had pre-existing conditions that were commonly associated with their reason for readmission.

Patient and hospitalization characteristics associated with persistent symptoms and impaired activity in the univariate analyses are included in Supplemental Table 6. In the adjusted model for patients with acute COVID-19, number of organ systems involved was independently associated with persistent symptoms (aRR 1.29 [95% CI, 1.04–1.59]) and activity impairment (aRR 1.37 [95% CI, 1.06–1.78]) (Fig 3). A sensitivity analysis including 30-day survey data for patients with missing 2 to 4 month outcomes but resolution of symptoms and without activity impairment at 1 month had similar results (Supplemental Table 7).

Patients With MIS-C

Patients with MIS-C and 2 to 4 month survey data ($n = 160$) were most frequently 5 years or older, 93 (58.1%) were male, 111 (69.4%) were previously healthy, 19 (11.9%) had a pre-existing respiratory condition which was most frequently asthma (17 of 19; 89%), and 50 (31.2%) were obese (Table 1). During hospitalization, 153 (95.6%) patients with MIS-C received steroids. Median duration of hospitalization was 6 days (IQR 5–9).

TABLE 1 Patient and Hospitalization Characteristics of Patients With 2 to 4 Month Survey Data

	Acute COVID-19 (n = 119)	MIS-C (n = 160)	P[a]
Age group, y			
<2	29 (24.4)	7 (4.4)	<.001
≥2 and <5	8 (6.7)	20 (12.5)	
≥5 and <13	24 (20.2)	74 (46.2)	
≥13 and <21	58 (48.7)	59 (36.9)	
Sex, male	59 (49.6)	93 (58.1)	.18
Race			
White	64 (53.8)	68 (42.5)	.17
Black	28 (23.5)	59 (36.9)	
Asian	3 (2.5)	2 (1.2)	
Other or unknown	24 (20.2)	31 (19.4)	
Ethnic Group			
Not Hispanic	78 (65.5)	115 (71.9)	.12
Hispanic	38 (31.9)	36 (22.5)	
Unknown	3 (2.5)	9 (5.6)	
Underlying conditions			
Previously healthy	40 (33.6)	111 (69.4)	<.001
Pre-existing respiratory condition[b]	36 (30.3)	19 (11.9)	
Other pre-existing condition[c]	43 (36.1)	30 (18.8)	
Obesity[d]	39 (32.8)	50 (31.2)	.13
Hospitalization characteristics			
Admission PELOD-2 score, median (IQR)	0 (0, 2)	2 (0, 3)	<.001
Maximum PELOD-2 score, median (IQR)	1 (0, 1)	3 (1, 5)	<.001
Organ systems involved, median (IQR)	2 (2, 3)	5 (4, 6)	<.001
ICU admission	60 (50.4)	137 (85.6)	<.001
Invasive mechanical ventilation	21 (17.6)	33 (20.6)	.65
Length of invasive mechanical ventilation, median (IQR)[e]	7 (3, 15)	5 (2, 8)	.17
Left ventricular ejection fraction <55%	NA	86 (53.8)	NA
Vasopressor-dependent shock	19 (16.0)	104 (65.0)	<.001
Extracorporeal membrane oxygenation	5 (4.2)	10 (6.2)	.59
Hospitalization outcomes			
ICU length of stay, median (IQR)[e]	5 (2–11)	4 (2–5)	.07
Hospital length of stay, median (IQR)	4 (2–10)	6 (5–9)	<.001

Data are presented as n (%) unless otherwise indicated. IQR, interquartile range; NA, not applicable; PELOD-2, pediatric logistic organ dysfunction score version 2.

[a] Compares patients admitted with acute coronavirus disease (COVID-19) to patients admitted with multisystem inflammatory disease in children (MIS-C).

[b] Of the 36 patients with acute COVID-19 and a pre-existing respiratory condition, 15 (42%) had isolated asthma or reactive airways disease, whereas 17 of 19 (89%) patients with MIS-C and a pre-existing respiratory condition had isolated asthma.

[c] Other pre-existing conditions categorized as (not mutually exclusive): Acute COVID-19 (gastrointestinal or hepatic n = 31 [26%], neurologic or neuromuscular n = 29 [24%], endocrine or metabolic excluding obesity n = 24 [20%], cardiovascular n = 11 [9%], hematologic n = 13 [11%], oncologic or immunosuppressive n = 7 [6%], renal or urologic n = 6 [5%]) and MIS-C (gastrointestinal or hepatic n = 3 [2%], neurologic or neuromuscular n = 6 [4%], endocrine or metabolic excluding obesity n = 8 [5%], cardiovascular n = 3 [2%], hematologic n = 2 [1%], oncologic or immunosuppressive n = 1 [<1%], renal or urologic n = 2 [1%]).

[d] Only patients older than 2 y were eligible to be categorized as obese. Patients younger than 2 y old were categorized as not obese.

[e] In patients supported by invasive mechanical ventilation or admitted to the ICU, respectively.

At 2 to 4 month follow up, 48 (30.0%) patients with MIS-C had persistent symptoms or activity impairment; 32 (20.0%) had persistent symptoms (Fig 2A) and 34 (21.3%) had activity impairments (Fig 2B). Signs or symptoms common at presentation, including fever and gastrointestinal illness, resolved in most, but fatigue and weakness persisted in 18 (11.3%) patients and headache in 12 (7.5%) (Supplemental Fig 4). Length of ICU stay among those admitted to the ICU did not differ in patients with and without persistent symptoms or impaired activity (Supplemental Table 4). Hospital lengths of stay were longer in patients with persistent symptoms or activity impairments compared with those without persistent symptoms or activity impairments. Of the 41 patients with MIS-C without 2 to 4 month outcomes, 11 (27%) had 1-month survey data available and 5 of 11 (45%) reported symptom resolution and normalized activity.

Preillness baseline and hospital discharge FSS scores were available for 141 of the 160 patients with MIS-C. New morbidities at hospital discharge occurred in 2 (1%) patients with both resolving the morbidity before the 2 to 4 month follow-up. At 2 to 4 month follow-up, 5 of 136 (4%) patients with MIS-C had a new morbidity with domain-specific morbidities in the mental status (n = 4) and motor (n = 1) domains (data not shown). By 2 to 4 month follow-up, 12 of 160 (7.5%)

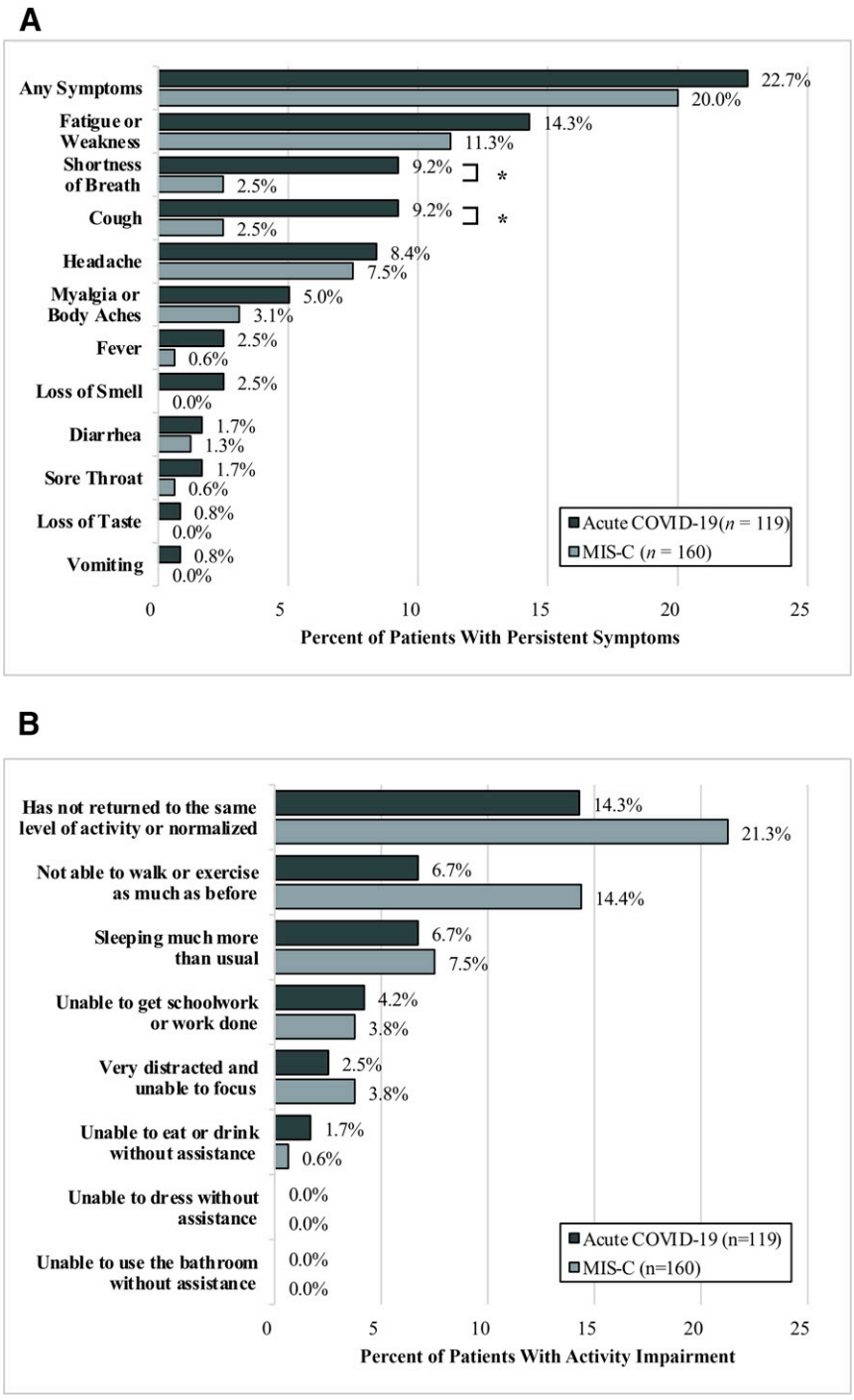

FIGURE 2

Outcomes of patients hospitalized for acute COVID-19 or MIS-C with (A) persistent symptoms and (B) ongoing activity impairment 2 to 4 months after hospitalization. *Denotes significant difference ($p<.05$) between patients with acute COVID-19 and MIS-C.

patients with MIS-C had been readmitted (Supplemental Table 5). Of the 12 readmitted patients, 8 did not have pre-existing conditions, although 2 met criteria for obesity. Readmissions among these 8 patients were for fever or infection, MIS-C flare up, memory loss or psychosis, gastrointestinal bleed, hyperglycemia, catheter site infection, and a non-COVID lower respiratory tract infection. Duration of readmission was determined in 7 of the 8 patients without pre-existing conditions and, excepting the patient readmitted for a gastrointestinal bleed, the durations were 3 days or shorter.

In multivariable analyses, having a pre-existing respiratory condition (17 of 19 had isolated asthma) was associated with persistent symptoms (aRR 3.09 [95% CI, 1.55–6.14]) and obesity was associated with ongoing activity impairment (aRR 2.52 [95% CI, 1.35–4.69]) (Fig 3). There was also an association between number of organ systems involved and activity impairment (aRR 1.27 [95% CI, 1.02–1.57]). A sensitivity analysis including 1-month survey data for patients with missing 2 to 4 month outcomes, but resolution of symptoms and activity impairment at 1 month had similar results (Supplemental Table 7).

DISCUSSION

In this multicenter follow-up study of United States children and adolescents hospitalized with acute COVID-19 or MIS-C, more than 1 in 4 patients had persistent symptoms or activity impairment after having 2 to 4 months to recover from their illness. Fatigue or weakness were the most common symptoms in both children with acute COVID-19 and MIS-C, followed by cough and shortness of breath in the acute COVID-19 group, and headache in the MIS-C group. More than 1 in 5 patients with MIS-C were not able to walk or exercise at their prior level. Factors associated with persistent symptoms or activity impairment differed between children hospitalized for acute COVID-19 and MIS-C. Most children with acute COVID-19 had underlying conditions, and the number of organ systems affected during the index hospitalization predicted persistent symptoms and activity impairment.

	Number With Outcome/Total (%)		Adjusted Risk Difference % (95% CI)	Adjusted Risk Ratio (95% CI)	*P*-value
Acute COVID-19 Persistent Symptoms	**Variable Group[a]**	**Reference Group[a]**			
Number of Organ Systems Involved			8 (2 to 14)	1.29 (1.04 to 1.59)	.02
Pre-Existing Condition	23/79 (29.1)	4/40 (10.0)	13 (0 to 26)	2.22 (0.82 to 5.96)	.12
Invasive Mechanical Ventilation	7/21 (33.3)	20/98 (20.4)	-25 (- to 0)	0.58 (0.25 to 1.31)	.19
Vasopressor-Dependent Shock	9/19 (47.4)	18/100 (18.0)	28 (-3 to 59)	1.81 (0.67 to 4.87)	.24
Acute COVID-19 Impaired Activity					
Number of Organ Systems Involved			6 (1 to 12)	1.37 (1.06 to 1.78)	.02
Pre-Existing Condition	16/79 (20.3)	1/40 (2.5)	12 (3 to 22)	5.62 (0.79 to 40.16)	.09
Invasive Mechanical Ventilation	6/21 (28.6)	11/98 (11.2)	-9(-49 to 0)	0.87 (0.30 to 2.50)	.80
Vasopressor-Dependent Shock	7/19 (36.8)	10/100 (10.0)	28 (-3 to 59)	1.50 (0.45 to 5.06)	.51
MIS-C Persistent Symptoms					
Number of Organ Systems Involved			3 (-2 to 8)	1.18 (0.90 to 1.56)	.23
Pre-Existing Respiratory Condition	10/19 (52.6)	19/111 (17.1)	35 (11 to 59)	3.09 (1.55 to 6.14)	.001
Other Pre-Existing Condition	3/30 (10.0)	19/111 (17.1)	-10 (-23 to 3)	0.51 (0.17 to 1.54)	.23
Obesity	12/50 (24.0)	20/101 (19.8)	6 (-8 to 20)	1.29 (0.68 to 2.46)	.44
Invasive Mechanical Ventilation	9/33 (27.3)	23/127 (18.1)	2 (-15 to 19)	0.98 (0.43 to 2.27)	.97
MIS-C Impaired Activity					
Number of Organ Systems Involved			5 (0 to 9)	1.27 (1.02 to 1.57)	.03
Pre-Existing Respiratory Condition	4/19 (21.1)	21/111 (18.9)	0 (-18 to 18)	0.98 (0.39 to 2.46)	.97
Other Pre-Existing Condition	9/30 (30.0)	21/111 (18.9)	0 (-17 to 18)	1.03 (0.55 to 1.94)	.93
Obesity	20/50 (40.0)	13/101 (12.9)	23 (7 to 38)	2.52 (1.35 to 4.69)	.004
Invasive Mechanical Ventilation	11/33 (33.3)	23/127 (18.1)	4 (-13 to 21)	1.14 (0.62 to 2.10)	.67

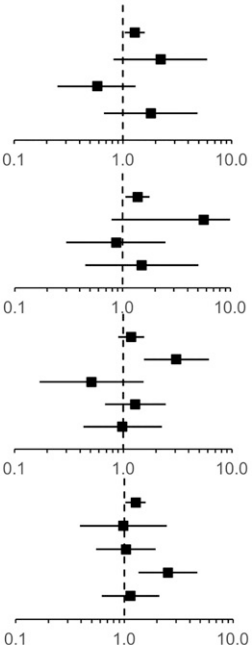

FIGURE 3

Multivariable models evaluating factors associated with persistent symptoms or impaired activity 2 to 4 months after hospitalization for COVID-19 or MIS-C. [a]Variable versus Reference Group corresponds to proportion of subjects with the outcome in "No" versus "Yes" for each variable. Organ system involvement is a continuous variable.

In contrast, most patients with MIS-C were previously healthy, but pre-existing respiratory conditions (mostly asthma) were associated with persistent symptoms and obesity was associated with ongoing activity impairment. Few patients with MIS-C reported major functional deficits, but hospital readmissions related to their prior illness did occur within the assessment period. Our study highlights that, although most children recover, many children with both acute COVID-19 and MIS-C have persistent sequelae and further follow-up to determine if these sequelae persist is warranted.

The frequency of persistent symptoms in these United States children and adolescents after hospitalization for acute COVID-19 is similar to a prospective follow-up study by Osmanov et al, from Russia describing 518 children hospitalized for acute COVID-19 followed to 5 months postdischarge where 1 in 4 had persistent symptoms.[10] These authors identified fatigue and sleep disturbance as common ongoing symptoms, reporting that older children and those with pre-existing allergic conditions were at higher risk of PCC. Despite these similarities, 51% of our patients versus 3% of the patients in the Russian cohort were admitted to the ICU. A smaller Iranian study of 58 children hospitalized for acute COVID-19, including 10 admitted to the ICU, reported prolonged symptoms in 45% of patients at 3 months.[9] Similar to our study, fatigue, shortness of breath, and activity intolerance were the most common symptoms and ICU admission was a risk factor for prolonged symptoms. Taken together, these studies suggest that children hospitalized with acute COVID-19, particularly critically ill children, are at an increased risk of PCC relative to nonhospitalized cohorts where rates of PCC are reported as less than 2%.[19]

We report that nearly one in three patients with MIS-C had persistent symptoms or activity impairment 2 to 4 months after hospitalization. This frequency is similar to a single center report of 46 pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 patients from London.[11] Those investigators conducted comprehensive direct patient assessments 6 weeks and 6 months after hospitalization, reporting that 1 in 3 participants had impairments in physical, emotional, or psychosocial domains 6 weeks after illness despite normalization of laboratory data.[11] Unlike our study, they followed these children until 6 months where 45% of them did very poorly on the 6-minute walk test. Congruent with their findings, walking and exercise limitations were the most common ongoing impairment in this United States cohort with MIS-C.

In our cohort, most patients were admitted to the ICU and, thus, at risk for developing postintensive care syndrome, including functional impairment.[20,21] New functional impairment after pediatric critical illness varies across cohorts but is estimated to be 5% at discharge in general PICU populations and 20% at 6 months postdischarge in children with acute respiratory failure.[22,23] Although it is prohibitively challenging to separate the relative contributions of the direct effects of SARS-CoV-2 infection from ICU-specific sequelae, ICU interventions were not predictive of ongoing symptoms or activity impairment in the multivariable models. For patients with MIS-C, where a higher proportion required ICU-level support, pre-existing factors such as asthma and obesity were more predictive of future outcomes than critical illness factors. Although there is some overlap, the pathobiology driving persistent symptoms in patients with MIS-C likely differs from that in patients with acute COVID-19. The often-prolonged immunomodulatory treatments used for MIS-C, including glucocorticoids, could contribute to long-term sequelae such as fatigue and weakness.[24]

This study has important limitations. Most of our patients were admitted to the ICU, and intentionally our outcomes represent those of severely ill hospitalized patients. Some patients (14%) were lost to follow-up, introducing a potential for selection bias as those with symptoms may be more likely to participate. We did not assess social vulnerability. We also did not have a control group of patients with negative SARS-CoV-2 testing for comparison because of enrollment limitations. We relied on caregiver report of symptoms and activity impairments and did not conduct objective assessments of the child's functional limitations. Although the FSS is a validated assessment to identify new morbidities, our questionnaire to delineate symptomatology and activity intolerance was modified from other validated instruments and abbreviated, leading to potential under-assessment of sequelae.[16,25] Patients were enrolled before the emergence of the B.1.617.2 (Δ) and B.1.1.529 (*o*) SARS-CoV-2 variants, which may differ in their longer term impacts.[2] We did not evaluate the association between practices aimed at preventing morbidities (eg, early mobility) or treatments for acute COVID-19 or MIS-C and outcomes. Finally, at the time of this study, no patients were vaccinated. Across these sites there is evidence that vaccination effectively prevents severe acute COVID-19 and MIS-C and therefore may also decrease the risk of postdischarge sequelae.[26,27]

CONCLUSIONS

Over 1 in 4 children and adolescents in this study developed sequelae after hospitalization for acute COVID-19 or MIS-C. Acute COVID-19, especially when it impacts multiple organ systems, can precipitate ongoing symptoms and activity impairments. These findings highlight the importance of postdischarge follow-up of these severely ill patients. In patients with MIS-C, underlying respiratory conditions, most frequently asthma, were associated with ongoing symptoms and obesity was associated with activity impairment. Additional interventions (eg, occupational or physical therapy) and clinical follow up of these high-risk cohorts may mitigate long-term sequelae. Most children hospitalized for MIS-C or acute COVID-19 recovered and were back to baseline within two months, which is reassuring.

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ABBREVIATIONS

aRD: adjusted risk difference
MIS-C: multisystem inflammatory syndrome in children
aRR: adjusted risk ratios
CI: confidence intervals
COVID-19: coronavirus disease 2019
FSS: Functional Status Scale
IQR: interquartile range
PCC: post-corona virus disease 2019 conditions
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

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A complete list of study group members appears at the end of this article.

Dr Maddux participated in acquisition of data, design of statistical analyses, interpretation of data, and drafting and revision of the article; Mr Young, Ms Newhams, Ms FitzGerald, Ms Chen, and Dr Kucukak participated in acquisition of data, interpretation of data, development of figures, and critically reviewed the manuscript for important intellectual content; Dr Randolph conceptualized and designed the study, coordinated and supervised data collection, participated in interpretation of the data, and critically reviewed the manuscript for important intellectual content; Drs Campbell, Feldstein, Zambrano, Patel, and Tenforde participated in interpretation of the data and critically reviewed the manuscript for important intellectual content; Ms Berbert, Dr Weller, Ms Jie, and Ms Miller conducted the analyses and critically reviewed the manuscript for important intellectual content; Drs Halasa, Cvijanovich, Loftis, Walker, Schwartz, Gertz, Tarquinio, Fitzgerald, Kong, Schuster, Mack, Hobbs, Rowan, Staat, Zinter, Irby, Crandall, Flori, Cullimore, Nofziger, Shein, Gaspers, Hume, and Levy participated in acquisition of data and critical review of the manuscript for important intellectual content; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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