Gastrointestinal Manifestations in Hospitalized Children With Acute SARS-CoV-2 Infection and Multisystem Inflammatory Condition: An Analysis of the VIRUS COVID-19 Registry

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Background: Describe the incidence and associated outcomes of gastrointestinal (GI) manifestations of acute coronavirus disease 2019 (COVID-19) and multisystem inflammatory syndrome in hospitalized children (MIS-C).

Methods: Retrospective review of the Viral Infection and Respiratory Illness Universal Study registry, a prospective observational, multicenter international cohort study of hospitalized children with acute COVID-19 or MIS-C from March 2020 to November 2020. The primary outcome measure was critical COVID-19 illness. Multivariable models were performed to assess for associations of GI involvement with the primary composite outcome in the entire cohort and a subpopulation of patients with MIS-C. Secondary outcomes included prolonged hospital length of stay defined as being >75th percentile and mortality.

Results: Of the 789 patients, GI involvement was present in 500 (63.3%). Critical illness occurred in 392 (49.6%), and 18 (2.3%) died. Those with GI involvement were older (median age of 8 yr), and 18.2% had an underlying GI comorbidity. GI symptoms and liver derangements were more common among patients with MIS-C. In the adjusted multivariable models, acute COVID-19 was no associated with the primary or secondary outcomes. Similarly, despite the preponderance of GI involvement in patients with MIS-C, it was also not associated with the primary or secondary outcomes.

Conclusions: GI involvement is common in hospitalized children with acute COVID-19 and MIS-C. GI involvement is not associated with critical illness, hospital length of stay or mortality in acute COVID-19 or MIS-C.

Key Words: gastrointestinal, coronavirus disease 2019, pediatric, critical illness

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Coronavirus disease 2019 (COVID-19) has resulted in a modern pandemic. A subset of children infected with SARS-CoV-2 become critically ill, including those with multisystem inflammatory syndrome in children (MIS-C).[1] While COVID-19 was initially viewed as a respiratory illness early during the pandemic, our understanding of this novel virus and its clinical manifestations has drastically shifted.[2] The receptor of SARS-CoV-2, angiotensin converting enzyme 2, has been found to be highly expressed both in gastrointestinal (GI) epithelial cells and liver, possibly contributing to GI disease.[3] GI involvement in patients with COVID-19 is widespread, ranging from nausea, vomiting and loss of appetite, to acute severe manifestations such as appendicitis, mesenteric adenitis, hepatitis and ascites.[4,5] Patients with other viruses such as influenza may also present with GI involvement. A recent meta-analysis described significant heterogeneity in the type and frequency of symptoms across the 10 studies included such that no comparison

of the occurrence of GI symptoms among patient type and influenza subtype could be performed.[6,7]

Several studies have investigated GI involvement of COVID-19 in adults,[8–10] but comparable pediatric data are scarce. A small multicenter pediatric study in Spain reported that more than half of children experienced GI symptoms and that GI symptoms portended a high risk for intensive care unit (ICU) admission.[11]

The purpose of this study was to determine the incidence of GI involvement among hospitalized children with acute COVID-19 and a subset of patients with MIS-C and determine the impact of GI involvement on disease severity, hospital length of stay (LOS) and mortality. We hypothesized that hospitalized pediatric patients with GI involvement would have greater disease severity and higher hospital resource utilization defined by prolonged hospital LOS.

MATERIALS AND METHODS

Study Design

We conducted a retrospective review of the Society of Critical Care Medicine Discovery Network's Viral Infection and Respiratory Illness Universal Study (VIRUS) registry from March 2020 to November 2020. VIRUS registry is a prospective, observational, multinational registry of hospitalized patients with COVID-19.[12] Ethical oversight was obtained at each participating center with a waiver of informed consent and data submitted to a centralized REDCap database hosted by the Mayo Clinic.[13] The reporting of this study confirms to the "Strengthening the reporting of observational studies in epidemiology" statement (Supplemental Document, Supplemental Digital Content 1, http://links.lww.com/INF/E743).

Population, Settings, and Data collection

Hospitalized children <18 years with suspected or confirmed COVID-19 or MIS-C at 53 participating sites were included. Patients readmitted within 90 days and non-COVID-19 related admission were excluded. Patients who had incomplete outcome variables (hospital LOS and discharge status), missing demographic data (age, weight or sex) and unknown MIS-C status were also excluded.

Measurements

Demographic and clinical characteristics, severity of illness and outcomes data for each patient's entire hospital admission were extracted from the VIRUS database. Variables collected on the day of hospital admission included age, sex, race and ethnicity, initial signs and symptoms, preexisting comorbidities and admission diagnosis. Variables collected throughout the entire duration of hospitalization included the following: alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin and international normalized ratio (INR); administered medications (corticosteroids, vasopressors/inotropes, neuromuscular blocking agents, remdesivir, azithromycin, hydroxychloroquine and tocilizumab); therapeutic interventions [nasal cannula (NC), high-flow NC (HFNC), invasive and noninvasive ventilation, extracorporeal membrane oxygenation (ECMO), continuous renal replacement therapy (CRRT) and inhaled nitric oxide therapy]; duration of NC, HFNC, noninvasive and invasive ventilation and ECMO; hospital LOS and ICU LOS and mortality.

The VIRUS registry includes 41 pediatric comorbidities, which were categorized into organ system groups and compared independently and as organ systems. Patients were grouped as having 1 comorbidity if there was one organ system involved and up to 4 comorbidities from 4 different organ systems. We also specifically compared asthma, obesity, developmental delay, and seizures separately since these comorbidities have been previously identified to impact outcomes of the disease.[14]

GI involvement was defined by one or more of the following characteristics present on the day of admission: symptoms (abdominal pain, nausea or vomiting, diarrhea, loss of appetite, constipation, hematochezia, hematemesis and jaundice); a diagnosis of appendicitis, pancreatitis, or mesenteric adenitis; or hepatic manifestations even in the absence of symptoms determined by elevated total bilirubin or INR levels and liver enzymes measured within the first full day of hospitalization. Elevated total bilirubin included values >1.2 mg/dL and elevated INR included values >1.1.

The primary outcome was critical illness. Critical illness was defined as a composite outcome of invasive hospital therapeutic interventions including invasive or noninvasive ventilation, HFNC, ECMO, inhaled nitric oxide, inotropes, vasopressors, renal support therapy (CRRT or hemodialysis) and mortality, which was adapted from the National Institute of Health without the use of laboratory assessments.[15] All other patients were classified as having moderate disease. Secondary outcomes included prolonged hospital LOS and mortality. Prolonged hospital LOS was defined as >75th percentile (9.8 days) of the entire population and assessed as a dichotomous outcome. Mortality was defined as death in the hospital. Adjudication of MIS-C was made by individual sites using the Center for Disease Control definition.[16]

Statistical Analysis

All analyses were performed using the entire cohort and separately in patients with MIS-C. Descriptive statistics were performed for continuous variables and were reported as median with interquartile range (IQR). Categorical variables are reported as count with percentages. Continuous variables were compared using the Mann-Whitney *U* tests, and categorical variables were compared using the χ^2 or Fisher exact test, as appropriate. Multivariable logistic regression was performed to analyze associations between GI involvement and hospital outcomes; stepwise selection was performed to assess relevant demographic and clinical characteristics for inclusion in the multivariable models, and goodness of fit was assessed using Akaike Information Criterion. Since MIS-C was hypothesized to confound the relationship between GI involvement and hospital outcomes, additional multivariable models with MIS-C included as a covariate were performed for each outcome (critical illness, prolonged hospital LOS and mortality). Additional univariate and multivariable models were performed with only MIS-C patients. Relative risk was estimated and were reported with 95% confidence intervals (CI). Statistical significance was determined by a *P*-value <0.05. All analyses were performed in SAS 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

A total of 955 patients were assessed for eligibility. Among these, a total of 166 patients were excluded: 59 due to missing age data and 107 due to missing MIS-C categorization and vital demographic elements. The final sample included 789 patients.

The median age was 6 years (IQR, 1, 13 yr); 54.1% of patients were male, 44% (n = 328) identified as White, 33.1% (n = 249) identified as Hispanic of any race and 43.4% (n = 320) reported having at least one comorbidity. The most common comorbidities were: asthma (n = 93; 11.8%), seizures/epilepsy (n = 66; 8.4%), obesity (n = 53; 6.7%) and developmental delay (n = 50; 6.3%). Three hundred ninety-two patients (49.7%) were classified as having critical illness, and 18 patients (2.3%) died. Of the patients who survived, 195 (25.3%) had a prolonged hospital LOS. Demographic and clinical data of the entire cohort are summarized in Table 1.

TABLE 1. Descriptive Patient Demographics, Clinical Characteristics, Treatments and Outcomes of Study Population

Variable	All Patients (N = 789)	Patients Without GI Involvement (N = 289)	Patients With GI Involvement (N = 500)	*P*
Age in yr, median (IQR)	6.0 (1, 14)	2.0 (0, 13)	8.0 (1.5, 14)	<0.0001
Age group, n (%)				
<2	259 (32.8)	134 (46.4)	125 (25.0)	<0.0001
2–10	240 (30.4)	64 (22.1)		
>10	290 (36.8)	91 (31.5)		
Sex, n (%)				
Male	427 (54.1)	150 (51.9)	277 (55.4)	0.34
Race, n (%)				
White	347 (44.0)	117 (40.5)	230 (46.0)	0.01
Black	184 (23.3)	63 (21.8)	121 (24.2)	
Other	79 (10.0)	42 (14.5)	37 (7.4)	
Missing/not specified	179 (22.7)	67 (23.2)	112 (22.4)	
Ethnicity, n (%)				
Hispanic	261 (33.1)	87 (30.1)	174 (34.8)	0.18
Comorbidities, n (%)				
Any comorbidity	342 (43.4)	117 (40.5)	225 (45.0)	0.22
Any pulmonary comorbidity	140 (17.7)	55 (19.0)	85 (17.0)	0.47
Any central nervous system comorbidity	131 (16.6)	54 (18.7)	77 (15.4)	0.23
Any rheumatology/immunology/endocrine/oncology comorbidity	118 (15.0)	40 (13.8)	78 (15.6)	0.50
Any GI/liver comorbidity	112 (14.2)	21 (7.3)	91 (18.2)	<0.0001
Any cardiac comorbidity	56 (7.1)	21 (7.3)	35 (7.0)	0.89
Any kidney comorbidity	41 (5.2)	20 (6.9)	21 (4.2)	0.10
Any previous transplant	14 (1.8)	5 (1.7)	9 (1.8)	0.94
Asthma	93 (11.8)	30 (10.4)	63 (12.6)	0.35
Seizures/epilepsy	66 (8.4)	32 (11.1)	34 (6.8)	0.04
Obesity	53 (6.7)	5 (1.7)	48 (9.6)	<0.0001
Developmental delay	50 (6.3)	22 (7.6)	28 (5.6)	0.26
Treatments, n (%)				
High flow nasal cannula	108 (13.7)	22 (7.6)	86 (17.2)	0.0002
Vasopressor/inotrope use	89 (11.3)	15 (5.2)	74 (14.8)	<0.0001
Invasive ventilation	90 (11.4)	37 (12.8)	53 (10.6)	0.35
Non-invasive ventilation	68 (8.6)	20 (6.9)	48 (9.6)	0.20
Neuromuscular blocking agents	43 (5.5)	18 (6.2)	25 (5.0)	0.46
Nitric oxide	15 (1.9)	3 (1.0)	12 (2.4)	0.18
ECMO	7 (0.9)	1 (0.4)	6 (1.2)	0.43
CRRT	1 (0.1)	0 (0)	1 (0.2)	>0.99
Treatment duration in days, median (IQR)				
Hospital length of stay	3.8 (1.9, 8)	3.0 (1.6, 6.9)	4.3 (2, 8.1)	0.002
N missing (%)	6 (0.8)	4 (1.4)	2 (0.4)	
ICU length of stay	3.8 (2, 8)	3.3 (1.4, 8.7)	3.9 (2, 7.5)	0.42
N missing (%)	2 (0.6)	1 (1.0)	1 (0.4)	
High flow nasal cannula	2.2 (0.9, 4.3)	3.3 (2.2, 5)	2.0 (0.8, 3)	0.04
N missing (%)	21 (20.6)	11 (52.4)	10 (12.3)	
Invasive ventilation	5.0 (2, 7)	3.0 (1.2, 6.7)	5.1 (2.6, 8.6)	0.45
N missing (%)	9 (12.0)	5 (15.6)	4 (9.3)	
Non-invasive ventilation	2.1 (1, 4.5)	2.5 (0.7, 6.7)	2.1 (1, 3.3)	0.93
N missing (%)	5 (7.8)	1 (5.3)	4 (8.9)	
ECMO	5.4 (1.2, 8.5)	5.4 (5.4, 5.4)	6.5 (1.2, 8.5)	0.39
N missing (%)	0 (0)	0 (0)	0 (0)	
Outcomes, n (%)				
Critical illness	392 (49.7)	121 (41.9)	271 (54.2)	0.001
MIS-C incidence	217 (27.5)	24 (8.3)	193 (38.6)	<0.0001
Prolonged hospital length of stay	195 (25.3)	59 (20.9)	136 (27.8)	0.03
Mortality	18 (2.3)	7 (2.4)	11 (2.2)	0.84

N indicates number of patients.

GI involvement was present in 500 patients (61.4%). The median age was 8 years (IQR, 12.5 yr) compared with 2 years (IQR, 13 yr) in those without GI involvement ($P < 0.0001$). There were no sex differences in patients with versus without GI involvement, but there was a difference across race categories (Table 1). In the GI involvement group, the most common GI symptoms were nausea/vomiting (52.6%), abdominal pain (39.2%), loss of appetite (31%) and diarrhea (29%). INR and total bilirubin measured within the first full day of hospitalization were elevated in 120 (24%) and 67 (13.4%) patients, respectively. AST and ALT were elevated in 31.6% and 24.2% patients, respectively (Table 2). A greater proportion of patients with GI involvement were classified as having critical illness (54.2% vs. 41.9%; $P = 0.001$). Hospital LOS was prolonged in 27.8% patients with GI involvement, compared with 20.9% of those without ($P = 0.03$). Mortality was not different between those with and without GI involvement ($P = 0.84$). A comparison of other symptoms and hospital medications comparing those with and without GI involvement is summarized in

TABLE 2. Gastrointestinal and Hepatic Characteristics Among Patients With Acute COVID-19 and MIS-C

Variable	All Patients With GI Involvement (N = 500)	Acute COVID-19 Patients With GI Involvement (N = 307)	MIS-C Patients With GI Involvement (N = 193)	*P*
GI symptoms, n (%)				
Any GI symptom	411 (82.2)	239 (77.9)	172 (89.1)	0.001
Nausea/vomiting	263 (52.6)	142 (46.3)	121 (62.7)	0.0003
Abdominal pain	196 (39.2)	101 (32.9)	95 (49.2)	0.0003
Loss of appetite	155 (31.0)	89 (29.0)	66 (34.2)	0.22
Diarrhea	145 (29.0)	64 (20.8)	81 (42.0)	<0.0001
Constipation	10 (2.0)	10 (3.3)	0 (0)	0.01
Hematochezia	7 (1.4)	5 (1.6)	2 (1.0)	0.71
Hematemesis	2 (0.4)	2 (0.7)	0 (0)	0.53
Jaundice	1 (0.2)	1 (0.3)	0 (0)	>0.99
Admission diagnosis, n (%)				
Appendicitis	29 (5.8)	27 (8.8)	2 (1.0)	0.0003
Mesenteric adenitis	4 (0.8)	2 (0.7)	2 (1.0)	0.64
Pancreatitis	3 (0.6)	3 (1.0)	0 (0)	0.29
Elevated liver enzymes, n (%)				
AST	158 (31.6)	77 (25.1)	81 (42.0)	<0.0001
ALT	121 (24.2)	59 (19.2)	62 (32.1)	0.001
INR	120 (24.0)	34 (11.1)	86 (44.6)	<0.0001
Total bilirubin	67 (13.4)	42 (13.7)	25 (13.0)	0.82

Supplemental Table 1, Supplemental Digital Content 1 (http://links.lww.com/INF/E743).

GI Involvement in Acute COVID-19 and MIS-C

Descriptive statistics comparing demographics clinical characteristics and outcomes between patients with acute COVID-19 and MIS-C are summarized in Table 3. Of the 500 patients with GI manifestations, 307 (61.4%) had acute COVID-19 and 193 (38.6%) had MIS-C.

Acute COVID-19

In the entire cohort of patients with acute COVID-19 (n = 572), 307 (53.7%) had GI involvement. Among patients with acute COVID-19, those with GI involvement were a median of 5 years older ($P = 0.004$), and a greater proportion had a comorbidity (54.1% vs. 41.5%; $P = 0.003$). There was no significant difference in critical illness, prolonged hospital length of stay (HLOS) or mortality between those with and without GI involvement (Supplemental Table 2, Supplemental Digital Content 1, http://links.lww.com/INF/E743).

In adjusted multivariable models assessing the association of critical illness in acute COVID-19, only older age was associated with critical illness (adjusted relative risk: 1.02; 95% CI: 1.01–1.04, $P = 0.01$). GI involvement was not associated with critical illness in acute COVID-19. Similarly, GI involvement was not associated with prolonged HLOS or mortality in patients with acute COVID-19 (Table 4).

Multisystem Inflammatory Syndrome in Children

In the entire cohort of patients with MIS-C (n = 217), 193 (88.9%) had GI involvement. Among patients with MIS-C, those with GI involvement were a median of 8 years younger than those without GI involvement ($P = 0.05$). Among MIS-C patients, critical illness (77.2% vs. 50%; $P = 0.01$) was more common among those with GI involvement. There was a greater proportion of patients with GI involvement who had a prolonged HLOS (41.2% vs. 2,5%; $P = 0.01$). Of the 6 patients with MIS-C who died, all had GI involvement (Supplemental Table 3, Supplemental Digital Content 1, http://links.lww.com/INF/E743).

In the adjusted multivariable models assessing the associations of with outcomes among patients with MIS-C, GI involvement was not associated with critical illness or prolonged hospital LOS. The association with mortality could not be assessed since all MIS-C who died had GI involvement (Table 4).

Comparison of Acute COVIID-19 and MIS-C

The presence of any comorbidity was significantly more common among patients with acute COVID-19 compared with MIS-C (54.1% vs. 30.6%; $P < 0.0001$). The proportion of patients with critical illness and prolonged HLOS was significantly greater in MIS-C compared with acute COVID-19 (both $P < 0.0001$). A comparison of the types of GI symptoms, admission diagnosis for a GI complaint and liver laboratory abnormalities is summarized in Table 2. Any GI symptom was more common among MIS-C patients, as were the proportion of patients with elevated AST, ALT and INR.

DISCUSSION

In this study focusing on GI involvement in hospitalized children with acute COVID-19 or MIS-C, predominantly from the United States, GI involvement was present in just over 60% of children at initial presentation. The presence of GI involvement appears to be more important in patients with MIS-C, particularly as it relates to prolongation of HLOS, although this did not reach statistical significance in multivariable analysis. GI involvement was not associated with any outcomes in acute COVID-19 infection.

The presence of GI symptoms has been reported with variable incidence in other pediatric COVID-19 studies.[11,17,18] Similarly, GI symptoms can manifest in other common coronavirus infections. In one study, the incidence of GI symptoms in COVID-19 parallels the incidence in this report.[19] This study is in agreement with the systematic review and meta-analysis from Mao et al[20] and Dong et al[9] who reported that pediatric patients hospitalized with COVID-19 had a higher prevalence of GI symptoms compared with adult patients. Our study findings are also similar to Giacomet et al[21] who reported that GI symptoms were more frequent with severe and critical phenotype of COVID-19 in children, although this did not hold true in the multivariable analysis of our study. Moreover, in their study, having GI symptoms was more frequently reported in patients who developed cardiac impairment. It is plausible that the differential diagnosis of patients with GI symptoms and cardiac impairment

TABLE 3. Comparison of Demographics, Clinical Characteristics, Treatments and Outcomes of Patients With GI Involvement Due to Acute COVID-19 and MIS-C

Variable	Acute COVID-19 Patients With GI Involvement (N = 307)	MIS-C Patients With GI Involvement (N = 193)	*P*
Age in yr, median (IQR)	7.0 (1, 14)	8.0 (4, 13)	0.37
Age group, n (%)			
<2	99 (32.2)	26 (13.5)	<0.0001
2–10	80 (26.1)	96 (49.7)	
>10	128 (41.7)	71 (36.8)	
Sex, n (%)			
Male	164 (53.4)	113 (58.6)	0.26
Race, n (%)			
White	146 (47.5)	84 (43.5)	0.09
Black	64 (20.9)	57 (29.5)	
Other	21 (6.8)	16 (8.3)	
Missing/not specified	76 (24.8)	36 (18.7)	
Ethnicity, n (%)			
Hispanic	119 (38.8)	55 (28.5)	0.02
Comorbidities, n (%)			
Any comorbidity	166 (54.1)	59 (30.6)	<0.0001
Any pulmonary comorbidity	60 (19.5)	25 (13.0)	0.06
Any central nervous system comorbidity	56 (18.2)	21 (10.9)	0.03
Any rheumatology/immunology/endocrine/oncology comorbidity	68 (22.2)	10 (5.2)	<0.0001
Any GI/liver comorbidity	68 (22.2)	23 (11.9)	0.004
Any cardiac comorbidity	25 (8.1)	10 (5.2)	0.21
Any kidney comorbidity	18 (5.9)	3 (1.6)	0.02
Any previous transplant	9 (2.9)	0 (0)	0.01
Asthma	41 (13.4)	22 (11.4)	0.52
Seizures/epilepsy	26 (8.5)	8 (4.2)	0.06
Obesity	31 (10.1)	17 (8.8)	0.63
Developmental delay	20 (6.5)	8 (4.2)	0.26
Treatments, n (%)			
High flow nasal cannula	45 (14.7)	41 (21.2)	0.06
Vasopressor/inotrope use	10 (3.3)	64 (33.2)	<0.0001
Invasive ventilation	19 (6.2)	34 (17.6)	<0.0001
Non-invasive ventilation	15 (4.9)	33 (17.1)	<0.0001
Neuromuscular blocking agents	11 (3.6)	14 (7.3)	0.07
Nitric oxide	2 (0.7)	10 (5.2)	0.002
ECMO	2 (0.7)	4 (2.1)	0.21
CRRT	0 (0)	1 (0.5)	0.39
Treatment duration in days, median (IQR)			
Hospital length of stay	3.0 (1.7, 6)	6.6 (4, 10)	<0.0001
N missing (%)	2 (0.7)	0 (0)	
ICU length of stay	3.4 (1.7, 8.3)	4.3 (2.8, 7)	0.01
N missing (%)	1 (0.9)	0 (0)	
High flow nasal cannula	2.6 (0.9, 5.8)	1.8 (0.7, 2.8)	0.11
N missing (%)	4 (9.1)	6 (16.2)	
Invasive ventilation	6.0 (3.5, 13)	4.9 (2.6, 7)	0.26
N missing (%)	1 (7.1)	3 (10.3)	
Non-invasive ventilation	2.6 (1, 5.6)	1.9 (1, 3.2)	0.45
N missing (%)	1 (6.7)	3 (10.0)	
ECMO	3.1 (1.2, 4.9)	8.3 (4.4, 8.8)	0.11
N missing (%)	0 (0)	0 (0)	
Outcomes, n (%)			
Critical illness	122 (39.7)	149 (77.2)	<0.0001
Prolonged hospital length of stay	59 (19.5)	77 (41.2)	<0.0001
Mortality	5 (1.6)	6 (3.1)	0.35

N indicates number of patients.

would include MIS-C, but this report was published within the first 6 months of the pandemic when we were just beginning to understand MIS-C as a disease entity. In our report, however, we did not separately evaluate cardiac dysfunction in MIS-C patients.

Feldstein et al[18] compared clinical characteristics and outcomes of children and adolescents with MIS-C versus those with severe COVID-19. GI involvement was common, but the authors did not specifically evaluate the contribution of GI manifestations to illness severity and outcomes. This is especially relevant because GI involvement in our study was associated with, although not significantly so with prolonged HLOS in patients with MIS-C. It is possible that this lack of association is confounded by the fact that we also included patients with abnormal liver function but without GI symptoms, although one has to acknowledge that there is selection bias as it relates to age and symptom reporting. However, we postulate that the patients with GI involvement could have direct viral invasion of the GI mucosa and liver. However, our current understanding of MIS-C

TABLE 4. Associations Between GI Involvement and Outcomes Stratified by Acute COVID-19 and MIS-C

	GI Involvement vs. No GI Involvement in Acute COVID-19 Patients		GI Involvement vs. No GI Involvement in MIS-C Patients	
Variables	RR (95% CI)	*P*	RR (95% CI)	*P*
Critical illness				
Age	1.02 (1.01–1.04)	0.01	1.01 (0.98–1.04)	0.43
Black vs. White	—	—	0.99 (0.54–1.83)	0.98
Hispanic vs. non-Hispanic	0.89 (0.72–1.10)	0.29	0.86 (0.57–1.30)	0.47
GI involvement	0.95 (0.78–1.16)	0.60	1.52 (0.84–2.76)	0.17
Prolonged hospital length of stay				
Age	1.03 (1.004–1.05)	0.02	1.04 (1.001–1.09)	0.05
Male vs. female	—	—	1.12 (0.72–1.74)	0.63
Black vs. White	1.91 (1.18–3.07)	0.01	0.88 (0.34–2.26)	0.79
Hispanic vs. non-Hispanic	0.63 (0.40–0.97)	0.03	—	—
Any comorbidity	—	—	1.23 (0.77–1.96)	0.38
GI involvement	0.93 (0.67–1.28)	0.65	3.08 (0.97–9.80)	0.06
Mortality*				
GI involvement	0.62 (0.20–1.92)	0.40	—	—

*All MIS-C patients who died had GI involvement; a mortality analysis between MIS-C patients with GI involvement vs. no GI involvement could not be performed.

— denotes variables not included in the multivariable analysis.

is limited with respect to the pathophysiology of the inciting pathogen, the hyperinflammatory process and organ hypoperfusion and how those influence GI symptoms/clinical presentation and outcomes.

Our study findings are similar to Miller et al[22] who in their single-center experience of 44 cases with MIS-C reported that GI symptoms were a presenting symptom in 84.1% of cases, and majority had a markedly elevated inflammatory markers upon admission. Our study findings are also consistent with the most recently published systematic reviews and meta-analysis of MIS-C associated with COVID-19.[23–26] All these reviews consistently reported the higher prevalence of GI symptoms in this subgroup of patients, the need for higher level of care including ventilatory support and vasoactive therapies in this group. Our study further adds to our understanding of the impact of GI involvement toward to outcomes, specifically HLOS.

A recent study published by Sahn et al[27] reported that the GI tract of children with MIS-C appears especially prone to inflammatory damage reflected by >95% of children in their cohort presenting with GI symptoms and >50% of those with CT imaging having terminal ileitis with bowel wall thickening. However, it is unknown whether the inflammatory disease in these areas of bowel is due to direct virus-induced cellular damage or is the end organ damage of a systemic inflammatory process. The histopathologic findings among those with intestinal resection evaluated in the study by Sahn et al[27] case series were notable for absence of viral cytopathic effect or detectable viral particles. Further translational studies are needed to improve our understanding of the mechanisms underlying GI involvement and outcomes in pediatric patients with MIS-C.

Our study has several strengths. It is a multicenter study, including 53 centers in USA, one of the most impacted countries during the pandemic. Therefore, our sample is probably the largest published in hospitalized pediatric patients with GI involvement in COVID-19, separating those with acute disease and those with MIS-C. Our study also has the unique finding of greater MIS-C incidence and need for invasive and noninvasive mechanical ventilations in pediatric patients with COVID-19 who had GI involvement at presentation.

This study was limited by the fact that we were only able to evaluate the contribution of GI involvement at the time of initial presentation and were not able to assess development through the course of hospitalization. Since we included patients with suspected COVID-19, it may bias the results because of the lower sensitivity and specificity of the test early on in the course of the pandemic. Further limitations to our study include those that are related to large registries; the results and data obtained from the participating hospitals in this study may not be generalizable and could possibly be overrepresenting patients seeking care at tertiary-care centers. The data collection process through abstraction of routine clinical documentation may result in incomplete reporting of data. Despite excluding patients who were missing essential data from our study population, there were still some patients who were missing data for specific variables. Since a complete case analysis assumes data missing at random, the missing data were not imputed, and it might be nonrandom and subject to bias.[28] In addition, there is bias in symptom reporting toward older patients. The number of patients per hospital in our study population varied significantly, ranging from 1 to 126 patients. This limited our ability to assess if meaningful differences existed in GI involvement and outcomes between hospitals. Specific GI-related problems such as colitis and/or inflammatory bowel disease were not captured as a separate comorbidity that could confound findings. Finally, since MIS-C is thought to be delayed in onset after SARS-CoV-2 infection, this patient characterization was made by individual centers based on the existing Center for Disease Control criteria, and it is, therefore, possible that patients were misclassified.

CONCLUSIONS

In conclusion, GI involvement is common among hospitalized pediatric patients with COVID-19. These manifestations appear to be part of a more severe course in both acute COVID-19 and MIS-C, although this did not maintain significance in multivariable analysis. An improved understanding of the pathophysiology of COVID-19 and MIS-C may allow for improved risk stratification and identification of patients who will experience a complicated course.

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