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

Imran A. Sayed, MD,* Upal Bhala, MD,† Larisa Strom, MPH,‡ Sandeep Tripathi, MD, MS,§ John S. Kim, MD,* Kristina Michaud, DO,† Kathleen Chiotos, MD, MSCE,¶ Heda R. Dapul, MD,¶ Varsha P. Gharpure, MD,** Erica C. Bjornstad, MD, PhD, MPH,†† Julia A. Heneghan, MD,‡‡ Katherine Irby, MD,§§ Vicki Montgomery, MD,¶¶ Neha Gupta, MD,¶¶ Manoj Gupta, MD,*** Karen Boman, BS,††† Vikas Bansal, MBBS, MPH,¶¶¶ Rahul Kashyap, MBBS, MBA,†††† and Katja M. Gist‡‡‡, DO, MSc,* on behalf of the VIRUS Investigators

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From the *Division of Pediatric Critical Care Medicine, Department of Pediatrics, University of Colorado Anschutz Medical Campus, Children’s Hospital Colorado, Aurora, Colorado; †The Children’s Hospital of San Antonio, San Antonio and Baylor Scott & White Health, Houston, Texas; ‡Department of Biostatistics and Informatics, Colorado School of Public Health, University of Colorado, Aurora, Colorado; §Department of Pediatrics, OSF Saint Francis Medical Centre; University of Illinois College of Medicine at Peoria, Peoria, Illinois; §§Division of Critical Care Medicine and Department of Pediatrics, Children’s Hospital of Philadelphia, Philadelphia, Pennsylvania; ¶Division of Critical Care Medicine, Department of Pediatrics, NYU Langone Medical Center, New York, New York; **Division of Critical Care Medicine, Department of Pediatrics, University of Oklahoma, Park Ridge, Illinois; ††Division of Nephrology, Department of Pediatrics, University of Alabama at Birmingham, Birmingham, Alabama; †††Division of Pediatric Critical Care Medicine, Department of Pediatrics, University of Minnesota Masonic Children’s Hospital, Minneapolis, Minnesota; §§§Division of Pediatric Critical Care Medicine, Department of Pediatrics, Arkansas Children’s Hospital, Little Rock, Arkansas; †Division of Critical Care Medicine, Department of Pediatrics, University of Louisville and Norton Children’s Hospital, Louisville, Kentucky; ¶¶Division of Critical Care Medicine, Department of Pediatrics, University of Oklahoma College of Medicine, Oklahoma City, Oklahoma; ††Division of Pediatric Cardiology, Department of Pediatrics, Lincoln Hospital, Bronx, New York; ††††Division of Pulmonary and Critical Care Medicine, Department of Medicine, Society of Critical Care Medicine, Mount Prospect, Illinois; ‡‡‡Division of Pulmonary and Critical Care Medicine, Department of Medicine, Mayo Clinic, Rochester, Minnesota; and §§§§Division of Pulmonary and Critical Care Medicine, Department of Medicine, Boston University School of Medicine, Boston, Massachusetts.

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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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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 2019 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 χ2 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.
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 1.

| 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 (%)                              |                        |                                          |                                        | 0.18 |
| Hispanic                                      | 261 (33.1)             | 87 (30.1)                                | 174 (34.8)                             |      |
| 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) | <0.0001 |
| Any GI/liver comorbidity                      | 112 (14.2)             | 21 (7.3)                                 | 91 (18.2)                              |      |
| 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)                              | 0.55 |
| 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.
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 |
| Measenteric 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)                                | 64 (21.1)                                            | 86 (44.6)                                   | <0.0001|
| Total bilirubin           | 67 (13.4)                                 | 42 (13.7)                                            | 25 (13.0)                                   | 0.82   |

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 = 0.003). 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 COVID-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 = 0.001). 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.

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 presence of GI symptoms has been reported with variable incidence in other pediatric COVID-19 studies. In one study, the incidence of GI symptoms in COVID-19 parallels the incidence in this report. This study is in agreement with the incidence in other pediatric COVID-19 studies. 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. This study is in agreement with the systematic review and meta-analysis from Mao et al20 and Dong et al9 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 al12 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 was 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.

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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. 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. This study is in agreement with the systematic review and meta-analysis from Mao et al20 and Dong et al9 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 al12 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 was 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.
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.\(^1\) 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 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 (%)                              | 99 (32.2)                                            | 26 (13.5)                                    | <0.0001|
| White                                         | 80 (26.1)                                            | 96 (49.7)                                    | 0.09   |
| Black                                         | 128 (41.7)                                           | 71 (36.8)                                    |        |
| Male                                          | 164 (53.4)                                           | 113 (58.6)                                   | 0.26   |
| Race                                          | 146 (47.5)                                           | 84 (43.5)                                    |        |
| Hispanic                                      | 64 (20.9)                                            | 57 (29.5)                                    |        |
| Other                                         | 21 (6.8)                                             | 16 (8.3)                                     |        |
| Missing/not specified                         | 76 (24.8)                                            | 36 (18.7)                                    |        |
| Ethnicity, n (%)                              | 8 (2.6)                                              | 55 (28.5)                                    | 0.02   |
| 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)                                    | 0.04   |
| 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   |
| 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   |
| Hospital length of stay                       | 3.0 (1,7,6)                                          | 6.6 (4,10)                                   | <0.0001|
| ICU length of stay                            | 2 (0.7)                                              | 0 (0)                                        |        |
| N missing (%)                                  | 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 (0.1)                                              | 6 (16.2)                                     |        |
| Invasive ventilation                          | 6.0 (3.5,13)                                         | 4.9 (2.6,7)                                  | 0.26   |
| N missing (%)                                  | 1 (0.7)                                              | 3 (10.3)                                     |        |
| Non-invasive ventilation                      | 2.6 (1,5.6)                                          | 1.9 (3.2)                                    | 0.45   |
| N missing (%)                                  | 1 (0.7)                                              | 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 (%)                               | 122 (39.7)                                           | 149 (77.2)                                   | <0.0001|
| Critical illness                              | 59 (19.5)                                            | 77 (41.2)                                    | <0.0001|
| Prolonged hospital length of stay             | 5 (1.6)                                              | 6 (3.1)                                      | 0.35   |

N indicates number of patients.
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.

Our study findings are similar to Miller et al\textsuperscript{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.\textsuperscript{23–26} All these reviews consistently adds to our understanding of the impact of GI involvement toward outcomes, specifically HLOS.

A recent study published by Sahn et al\textsuperscript{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\textsuperscript{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.\textsuperscript{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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Collaborative coauthors list: Bolivia (Clinica Los Olivos: Rolando Claire-del Granado, Jose A. Mercado, Esdenka Vega-Terrazas, Maria F. Iturriaga-Caceres); Columbia (Clinica Medical SAS: Oscar Y. Gavidia, Felipe Pachon, Yeymi A. Sanchez); Croa-
tia (University Hospital of Split: Tanja Kovacevic, Josko Markic, Tatjana Cipovic Ardalic, Branka Polic, Ivo Ivic, Dominc Care, Robert Glavicin); India (BSES MG Hospital, Mumbai: Girish Vdagaoekar, Rekha Ediga, Shilpa Basety, Shwetha Dammroddey); Phani Sreeharsha Kasumalla; Gandhi Medical College and Hospi-
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pital/Bayero University, Kano: Fatimah Hassan-Hanga, Hadiza Galadanci, Abubukar Shehu Gezawa, Halima M. S. Kabara, Taiwo Gboluwawo Amole, Halima Kabir, Dalha Gwario Harlili, Abdul-
lahi S Ibrahim); Pakistan (Dow University Hospital: Muhammad Sohaib Asghar, Mashaal Syed, Syed Anosh Ali Naqvi; The Aga Khan University Hospital: The Aga Khan University Hospital: Sirda Ishaque, Ali Faisal Saleem, Naveed Ur Rehman Siddiqui, Salma Sherali, Yasmin Hashwani, Shafia Ishaque); Saudi Arabia (King Saud University: Mohammed A. Almazayd, Mohammed I. Alarifi, Jara M. Macrambon, Ahmad Abdullah Bukhari, Hus-
sain A. Albakri, Kazi N. Asfina, Khalith M. Aldossary); USA [Advocate Children's Hospital, IL: Varsha P. Ghpurare, Usman Raheemi]; Albany Medical Center: Suzanne Barry, Christopher Woll, Gregory Wu, Erin Carrole, Kathryn Burke, Mustafa Mohamed; Allina Health (Abbott Northwestern Hospital, United Hospi-
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ers Jr., Glenda Hefley; Baylor Scott & White Health: Valerie C. Danesh, Gueorgui Dubroqem, Amber L. Davis, Marissa J. Hammers, Jill M. McGayhe, Amanda C. Farris, Elisa Priest, Roslyn Korsmo, Lorie Fares, Kathy Skiles, Susan M. Shor, Kenya Burns, Corrie A. Dowell, Gabriela “Hope” Gonzales, Melody Flores, Lindsay New-
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ell, Gabriela Hope Gonzales, Melody Flores, Lindsay Newman, Debra A. Wilk, Jason Ettlinger, Himani Darji, Jacceline Bomar; Beaumont Children's Hospital: Paras B. Khandhar, Elizabeth Kring; Boston Children's Hospital: Catherine Ross, Jennifer Blu-
menthal; Cardinal Glennon Children's Hospital: Aaron S. Miller, Lavindan A. Davis, Rosemary Naqvi, Rauli R. Inja; Cedars Sinai Medical Center: Pooja A. Nawathe, Isabel Pedrazza, Jennifer Tsing, Karen Carr, Anila Chaudhary, Kathleen Guglielmi; Children's Center, Mayo Clinic Rochester: Grace Arteaga, Emily Levy, Aysun Tekin, Rahul Kashyap, Mayank Sharma, Vikas Bansal, Neha Deo, Shahzad Qamar, Romil Singh, Marija Bogoevicij; Children's Hospi-
tal of Philadelphia: Kathleen Chiotos, Allison M. Blatz, Giyoyung Lee, Ryan H. Burnett, Guy I. Syndey, Danielle M. Traylor; Cle-
ments University Hospital at UT Southwestern Medical Center: Sreekanth Cheruku, Farzin Ahmed, Christopher Deonarine, Ash-
ley Jones, Mohammad-Ali Shaikh, David Preston, Jeannette Chin; Detar Family Medicine residency: Sidney Ontai, Brian Contreras, MD, Uzoma Obinwanko, Nneka Amamasi, Amir Sharafi; Hassen-
feld Children's Hospital at NYU Langone: Heda R. Dapul, Sourabh Verma, Alan Salas, Ariel Daube, Michelle Korn, Michelle Ramirez, Logi Rajagopalan, Laura Santos; Jacoby Medical Center: Asher G. Bercow, Mark Shlovomovich; Johns Hopkins School of Medicine: J. H. Streetmagne; Lincoln Medical and Mental Health Center: Manoj K. Gupta, Franscere E. Ould, Akshay Nandavara; Lucile Packard Children's Hospital Stanford: Andy Y. Wem, Atie DeCar; Univer-
sity of Minnesota Masonic Children's Hospital: Juliana A. Henehghen, Ronald A. Reikoff, Sarah Eichen, Lexi Goertzen, Scott Rajala, Ghiulane Feusson, Ben Tang; Medical Center Navicent Health: Amy B. Christie, Dennis W. Ashley, Rajani Adiga; Mercy Hospital and Medical Center, Chicago: Travis Yamanaka, Nicholas A. Bar-
eras, Michael Markos, Anita Fareeduddin, Rohan Mehta; Nicklaus Children's Hospital: Prithvi Senth, Meghna Nadiger, Balagangad-
ar Hotapally; OSF Saint Francis Medical Center: Bhagat S. Aul-
ak, Sandeep Tripathi, Jennifer A. Bandy, Lisa M. Kreps, Dawn R. Bolliger, Jennifer A. Bandy; Sarasota Memorial Hospital: Antonia L. Vilella, Sara B. Kutner, Kacie Clark, Danielle Moore; Seattle Children's Hospital: Shina Menon, John K. McGuire, Deana Rich; St. Joseph Mercy Ann Arbor, Ann Arbor: Harry L. Anderson, III, Dixy Rajkumar, Ali Abunayla, Jerrihly Heiter; St. Joseph's Cand-
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