

## BRIEF REPORT

# “For COVID or “With COVID: Classification of SARS-CoV-2 Hospitalizations in Children

Lauren E. Kushner, MD,<sup>a</sup> Alan R. Schroeder, MD,<sup>b,c</sup> Joseph Kim, MD,<sup>c</sup> Roshni Mathew, MD<sup>a</sup>

## ABSTRACT

**OBJECTIVES:** Pediatric hospitalization rates are used as a marker of coronavirus disease 2019 (COVID-19) disease severity in children but may be inflated by the detection of mild or asymptomatic infection via universal screening. We aimed to classify COVID-19 hospitalizations using an existing and novel approach and to assess the interrater reliability of both approaches.

**METHODS:** This retrospective cohort study characterized severity of illness and likelihood of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection as the cause of hospitalization in pediatric patients <18 years of age. Subjects had positive SARS-CoV-2 nasopharyngeal testing or were diagnosed with multisystem inflammatory syndrome in children and were hospitalized between May 10, 2020 (when universal screening of all admissions began) and February 10, 2021, at a university-based, quaternary care children’s hospital in Northern California. Hospitalizations were categorized as either likely or unlikely to be caused by SARS-CoV-2 (novel approach), and disease severity was categorized according to previously published classification of disease severity.

**RESULTS:** Of 117 hospitalizations, 46 (39.3%) were asymptomatic, 33 (28.2%) had mild to moderate disease, 9 (7.7%) had severe illness, and 15 (12.8%) had critical illness (weighted  $\kappa$ : 0.82). A total of 14 (12%) patients had multisystem inflammatory syndrome in children. A total of 53 (45%) admissions were categorized as unlikely to be caused by SARS-CoV-2 ( $\kappa$ : 0.78).

**CONCLUSIONS:** Although COVID-19 has considerable associated morbidity and mortality in children, reported hospitalization rates likely lead to overestimation of the true disease burden.

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DOI:<https://doi.org/10.1542/hpeds.2021-006001>

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Address correspondence to Dr Roshni Mathew, Center for Academic Medicine, Pediatric Infectious Diseases, Stanford University, 453 Quarry Rd, Stanford, CA 94304. E-mail: [roshnim@stanford.edu](mailto:roshnim@stanford.edu)

HOSPITAL PEDIATRICS (ISSN Numbers: Print, 2154-1663; Online, 2154-1671).

Dr Kushner submitted the human subjects research proposal, designed the data collection tool, reviewed the charts, and critically reviewed the manuscript; Dr Schroeder conceptualized and designed the study, drafted the initial manuscript, and reviewed the charts; Dr Kim reviewed the charts and critically reviewed the manuscript; Dr Mathew drafted the initial manuscript and reviewed the charts; and all authors approved the final manuscript as submitted.

**FINANCIAL DISCLOSURE:** The authors have indicated they have no financial relationships relevant to this article to disclose.

**FUNDING:** No external funding.

**POTENTIAL CONFLICTS OF INTEREST:** Dr Schroeder is an Associate Editor at *Hospital Pediatrics*.

**COMPANION PAPER:** Companions to this article can be found online at [www.hospeds.org/cgi/doi/10.1542/hpeds.2021-005919](http://www.hospeds.org/cgi/doi/10.1542/hpeds.2021-005919) and [www.hospeds.org/cgi/doi/10.1542/hpeds.2021-006084](http://www.hospeds.org/cgi/doi/10.1542/hpeds.2021-006084)



<sup>a</sup>Divisions of Infectious Diseases, <sup>b</sup>Pediatric Critical Care, and <sup>c</sup>Hospital Medicine, Department of Pediatrics, Stanford University School of Medicine, Stanford, California

Hospitalization rates are often used as a marker for disease burden in adults with coronavirus disease 2019 (COVID-19) because they are less affected by testing patterns, when compared with case rates. Over the course of the pandemic, hospitalization rates in children increased, signaling that perhaps pediatric disease severity is worse than initially described.<sup>1,2</sup> However, most public reporting of COVID-19 hospitalizations is based simply on detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in hospitalized patients rather than the presence of a clinical syndrome. Hospitals have increasingly transitioned to universal screening for all hospitalizations to direct infection control precautions.<sup>3,4</sup> Given the high proportion of asymptomatic or mild disease in children, pediatric SARS-CoV-2 hospitalization rates may be more reflective of community prevalence and lead to overestimation of the true burden of disease.

Although, in several previous investigations, researchers have documented the severity of illness in hospitalized children with COVID-19,<sup>5,6</sup> we are unaware of any investigations in which researchers have reported interrater reliability of severity categories. Similarly, we are unaware of any investigations in which researchers have attempted to determine if hospitalizations were likely to have been caused directly by SARS-CoV-2 infection. The aims of this investigation were to (1) classify pediatric SARS-CoV-2 hospitalizations by using an existing and novel framework and (2) determine the interrater reliability of these classification schemes. A better understanding of the extent to which SARS-CoV-2 infection is causing pediatric hospitalization may assist with public health and county policy decisions.

## METHODS

### Subjects and Setting

This retrospective cohort study included patients <18 years of age with SARS-CoV-2 infection hospitalized between May 10, 2020, (when universal screening of all admissions began) and February 10, 2021,

at a university-based, quaternary care children's hospital in Northern California. Our aim was to define a cohort that most represented reporting of COVID-19 hospitalizations to the Santa Clara County Department of Public Health (DPH). The patients in our cohort were obtained from an organizational dashboard that captured hospitalized patients placed in isolation for SARS-CoV-2. Patients with multisystem inflammatory syndrome in children (MIS-C) that would not have been placed in isolation were obtained from the infection prevention and control department, which reports all MIS-C cases and all patients who test positive for SARS-CoV-2 on admission to the children's hospital to the county DPH.

Infection was established by detection of SARS-CoV-2 RNA via real-time reverse transcriptase polymerase chain reaction. Patients who tested positive in the emergency department or at an outside hospital previous to admission or transfer were reported to the DPH by the testing facility per mandatory reporting requirements. Readmissions within 90 days were not reported, even if tested positive because this is within the known persistent viral shedding period.<sup>7</sup> If patients tested positive >90 days from their original positive result at the time of admission, they were reported as having a new positive result.

### Variables

We used 2 approaches for classification of SARS-CoV-2 hospitalizations. In the first, we used a previously published categorization system and classified patients as either asymptomatic, mild or moderate, severe, critical, or the Centers for Disease Control and Prevention (CDC) definition of MIS-C.<sup>8,9</sup> Patients were considered asymptomatic if they did not have symptoms described by the CDC to be consistent with COVID-19.<sup>10</sup> Mild or moderate severity applied to patients who had symptoms attributable to COVID-19 but did not require supplemental oxygen. Patients requiring new or increased oxygen support from the baseline but not new positive-pressure ventilation were classified as severe.

Patients who received invasive or noninvasive mechanical ventilation or with sepsis or multiorgan failure were classified as critical.<sup>9</sup> Initiation or uptitration of high-flow nasal cannula (HFNC) requires intensive care admission at our institution and was considered noninvasive positive-pressure ventilation, so patients requiring HFNC were classified as having critical illness. We also recorded COVID-19 specific treatments received, as an additional way to capture the severity of illness.

Because the above severity classification approach does not indicate whether SARS-CoV-2 infection caused the hospitalization, we also categorized the hospitalization as likely or unlikely to have been caused by SARS-CoV-2. For this categorization, we reviewed admission and discharge medical documentation and attempted to discern whether the hospitalization would have occurred in the absence of SARS-CoV-2 infection (Supplemental Figure 1). Patients initially admitted for non-COVID-19 reasons who developed new or worsening COVID-19 symptoms that would have ultimately driven hospital admission were labeled as likely. If there was an uncertain link between SARS-CoV-2 and cause of admission (eg, brief resolved unexplained events (BRUEs), increased seizure frequency), we erred toward an attribution of likely, especially if no alternative explanation existed. For patients whose hospitalizations were unlikely to be caused by SARS-CoV-2, the severity of illness was determined by symptoms attributable to COVID-19, not to an alternative illness. For example, a patient with a severe traumatic brain injury who underwent mechanical ventilation for airway protection would not be labeled as critical unless there was also lung disease consistent with COVID-19. Given multiple reports of disparities in COVID-19, we opted to collect information on race and ethnicity, as documented in the electronic medical record. Immunocompromised was defined as currently receiving chemotherapy, having an oncologic diagnosis, or having a history of a solid organ or hematopoietic stem

cell transplant. Other causes for immune compromise were not included.

## Statistical Analysis

The first 25 charts were first reviewed independently by all 4 investigators, then as a group to solidify our methodology for the likely versus unlikely designation for cause of admission. These 25 subjects were excluded from the  $\kappa$  calculation. The remainder of the charts were then reviewed independently by 2 investigators. We used a  $\kappa$  statistic and a weighted  $\kappa$  to calculate interrater agreement for the reason for admission (likely versus unlikely categorization) and severity of illness, respectively. Disagreements were resolved by consensus after discussion among all 4 investigators. Descriptive statistics were calculated and reported as medians with interquartile ranges and proportions, as appropriate. The investigation was approved by the institutional review board.

## RESULTS

The characteristics of our 117-patient cohort are depicted in Table 1. Most (83; 70.9%) identified as Latino. A total of 19 (16.2%) were immunocompromised, and 31 (26.5%) required ICU admission attributable to COVID-19 or MIS-C. None died during the study period, although 1 immunocompromised patient died shortly after study conclusion from respiratory complications of COVID-19.

For classification of the severity of illness, there was 100% agreement between reviewers for MIS-C designation (yes or no). For the remaining 4 categories, there was 93.3% agreement between reviewers ( $\kappa$  0.82). For determination of COVID-19 as the likely cause of admission, there was 89% agreement between reviewers ( $\kappa$  = 0.78). Examples of disagreements included patients with new or worsening seizures, patients with BRUEs, and a patient who had fever and diarrhea with a stool polymerase chain reaction positive for *Salmonella*.

The tabulation of illness severity and likelihood of SARS-CoV-2 causing the hospitalization is depicted in Table 2; 46

**TABLE 1** Demographic Characteristics of Patients Hospitalized With a SARS-CoV-2 Infection

Demographic Characteristic	Total (n = 117)
Median age, y (IQR)	8 (1.5–14)
Female sex, n (%)	58 (49.6)
Race and/or ethnicity, n (%)	
Latino	83 (70.9)
White Non-Hispanic	13 (11.1)
Asian American	11 (9.4)
Native Hawaiian or Pacific Islander	3 (2.6)
Black and/or African American	2 (1.7)
Other or unknown	5 (4.3)
Immunocompromised, n (%)	19 (16.2)
ICU (attributable to SARS-CoV-2), n (%)	31 (26.5)
COVID-19 treatments provided, n (%)	
None	79 (67.5)
Supplemental oxygen	26 (22.2)
Remdesivir	15 (12.8)
Steroids	28 (23.9)
Immunoglobulin	12 (10.3)

IQR, interquartile range.

(39.3%) were asymptomatic, 33 (28.2%) had mild or moderate disease, 9 (7.7%) had severe illness, and 15 (12.8%) had critical illness. Of the 15 with critical illness, the maximum respiratory support was invasive ventilation for 5, positive-pressure ventilation for 4, and HFNC for 3. None received vasopressor support. A total of 14 (12%) patients had MIS-C; 1 underwent invasive ventilation, and 5 received vasopressor support. Three of the patients recovered with no specific treatments for MIS-C. Most patients received intravenous immunoglobulin alone or with methylprednisolone or aspirin. One patient received anakinra.

SARS-CoV-2 was likely to be the cause of admission in 64 (54.7%; 95% confidence interval 45.2%–63.9%) patients and unlikely in 53 (45.3%; 95% CI 36.1%–54.8%) patients. Common alternative diagnoses in hospitalizations deemed unlikely to be caused by SARS-CoV-2 are summarized in Table 3.

## DISCUSSION

Our findings reveal that most children hospitalized with SARS-CoV-2 have asymptomatic or mild or moderate disease, and nearly one-half of these hospitalizations were not caused by

infection from the virus itself. Additionally, we demonstrate that interrater reliability for an existing and novel pediatric COVID-19 hospitalization classification system is adequate but not perfect. Part of the challenge in attributing patient symptoms to SARS-CoV-2 is that most symptoms are

**TABLE 2** Tabulation of COVID-19 Severity and Likelihood That SARS-CoV-2 Infection Was the Cause of Hospitalization

COVID-19 Severity	Likely	Unlikely	Total, n (%)
Asymptomatic	2 <sup>a</sup>	44	46 (39.3)
Mild or moderate	28	5	33 (28.2)
Severe	6	3	9 (7.7)
Critical	14	1 <sup>b</sup>	15 (12.8)
MIS-C	14	0	14 (12.0)
Total, n (%)	64 (54.7)	53 (45.3)	117 (100)

<sup>a</sup>The 2 asymptomatic patients who were designated as being admitted likely because of COVID-19 were (1) a solid organ transplant recipient who was admitted because of an inability to isolate from infected family members and eventually tested positive after admission but remained asymptomatic and (2) a patient with baseline seizure disorder admitted for increased seizures with none of the CDC-described COVID-19 symptoms.<sup>10</sup>

<sup>b</sup>Patient admitted for complex congenital heart disease surgery who was asymptomatic on admission but tested positive several days after admission. Recovery was complicated by prolonged respiratory failure, which may have been exacerbated by COVID-19.

**TABLE 3** Alternative Diagnoses in the 53 Hospitalizations Deemed Unlikely to be Caused by SARS-CoV-2

Category	Examples	n (%)
Other documented infection	Odontogenic infection (n = 2); pyelonephritis (n = 1); cellulitis (n = 1); central line infection (n = 1); neonatal sepsis with <i>E coli</i> (n = 1); septic joint (n = 1); tubo-ovarian abscess and urinary tract infection (n = 1); <i>Salmonella enterica</i> gastroenteritis (n = 1); bacterial lymphadenitis (n = 1).	10 (18.9)
Procedures or surgeries	Cardiac surgery or catheterization (n = 3); enteric tube placement or replacement (n = 2); central line placement (n = 1); transplant surgery, canceled because of SARS-CoV-2 infection (n = 1); nephrectomy and dialysis catheter placement (n = 1).	8 (15.1)
Hematologic-oncologic issue	Chemotherapy admission (n = 3); spinal cord mass (n = 2); pancytopenia in liver transplant patient on myelosuppressive medications (n = 1); severe acute on chronic anemia (n = 1).	7 (13.2)
Acute appendicitis	With appendicolith (n = 4).	7 (13.2)
Metabolic issue or ingestion	Diabetic ketoacidosis (n = 2); intentional ingestion (n = 2); acute on chronic liver failure (n = 1); anaphylaxis from ingestion of food allergen (n = 1).	6 (11.3)
Neurologic or neurosurgical issue	Moya Moya (n = 2); seizure with underlying neurologic abnormality and predisposition to seizures (n = 2); scoliosis surgery complication (n = 1).	5 (9.4)
Gynecologic or urologic issue	Nephrolithiasis and urinary retention (n = 1); pelvic mass (n = 1); abnormal uterine bleeding (n = 1).	3 (5.7)
Other	Newborn delivered to SARS-CoV-2–positive mother (n = 1); lupus, new diagnosis (n = 1); inflammatory bowel disease, new diagnosis (n = 1); palpitations with underlying arrhythmia (n = 1); lymphangioma (n = 1); arteriovenous malformation (n = 1); manic episode (n = 1).	7 (13.2)

nonspecific and common features of other disease processes. Additionally, we are still learning about clinical manifestations of infection. We may ultimately learn, for example, that SARS-CoV-2 could play a role in common conditions such as appendicitis, diabetic ketoacidosis, and some manifestations of mental illness, in which case we may have underestimated the proportion of likely SARS-CoV-2–related hospitalizations.<sup>11,12</sup>

Alternatively, several of the hospitalizations categorized as likely to be caused by SARS-CoV-2 had additional diagnoses that made the role of COVID-19 unclear (eg, other documented respiratory viral infections, worsening seizures, and BRUEs), which may lead to overestimation of the proportion of likely COVID-19

hospitalizations. Nonetheless, despite the imperfect precision, our findings illustrate how reliance on reported hospitalization rates in children may lead to an inflated sense of disease burden in this population.

At the start of the pandemic, children were considered to be minimally impacted and represented a small proportion of reported infections.<sup>13</sup> As time has elapsed, we are learning that infection and transmission rates in children, although lower than that of adults, are non-negligible.<sup>14</sup> Rates of infection in children have increased in parallel with community prevalence.<sup>15,16</sup> The pediatric inpatient COVID-19 experience has been different from adults with regards to severity and volume; however, reports of increased

COVID-19 hospitalizations in children have captured news headlines, leading to concerns over school reopening<sup>2,17</sup> and may influence policy decisions. Our findings reveal that such decisions should account for the fact that reported hospitalization rates lead to overestimation of the COVID-19 disease burden in children considerably.

Our study is limited by the single-center, retrospective design, which has an impact on generalizability. However, our proportion of asymptomatic patients is similar to other investigations,<sup>1,18,19</sup> suggesting that our proportion of “unlikely” might align similarly. We had to make subjective assessments about the disease severity and cause of hospitalization from documentation in the electronic medical record. Although our interrater reliability was adequate, there were challenges inherent to this approach.

### Acknowledgments

We acknowledge the departments of Infection Prevention and Control and the Enterprise Analytics at Lucile Packard Children’s Hospital for information on reporting to the DPH and development of the dashboard, respectively. We thank Monika Roy, MD, from the Santa Clara County Department of Public Health, for providing our team with further insight into the COVID-19 hospitalization reporting process.

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