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"For COVID" or "With COVID": Classification of SARS-CoV-2 hospitalizations in children

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Dr. Kim reviewed the charts, critically reviewed the manuscript and approved the final manuscript as submitted.

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Abstract

Objective: 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.

Patients and 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 under 18 years of age. Subjects had positive SARS-CoV-2 nasopharyngeal testing or were diagnosed with multisystem inflammatory syndrome in children (MIS-C), 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). Fourteen (12%) patients had MIS-C. Fifty-three (45%) admissions were categorized as unlikely to be caused by SARS-CoV-2 (kappa 0.78).

Conclusion: Although COVID-19 has considerable associated morbidity and mortality in children, reported hospitalization rates likely overestimate the true disease burden.

Introduction:

Hospitalization rates are often used as a marker for disease burden in adults with coronavirus disease 2019 (COVID-19) as they are less affected by testing patterns when compared to case rates. Over the course of the pandemic, hospitalization rates in children increased, signaling that perhaps pediatric disease severity is worse than initially described.[1,2] 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 in order to direct infection control precautions.[3,4] 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 overestimate the true burden of disease.

Although several prior investigations have documented severity of illness in hospitalized children with COVID-19,[5,6] we are unaware of any investigations that have reported interrater reliability of severity categories. Similarly, we are unaware of any investigations that have attempted to determine whether 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 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 less than 18 years of age with SARS-CoV-2 infection hospitalized between May 10, 2020 (when universal screening of all admissions began) through 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 (IPCD), which reports all MIS-C cases and all patients who test positive on admission to the children's hospital to the county DPH.

Infection was established by detection of SARS-CoV-2 ribonucleic acid via real-time reverse transcriptase polymerase chain reaction (PCR). Patients who tested positive in the emergency department or at an outside hospital prior to admission/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, as this is within the known persistent viral shedding period.[7] If patients tested positive greater than 90 days from their original positive at the time of admission, they were reported as a new positive.

Variables

We used two approaches for classification of SARS-CoV-2 hospitalizations. The first utilized previously published categorization system and classified patients as either asymptomatic,

mild/moderate, severe, critical, or the Centers for Disease Control and Prevention (CDC) definition of MIS-C.[8,9] Patients were considered asymptomatic if they did not have symptoms described by the CDC to be consistent with COVID-19.[10] "Mild/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 baseline but not new positive pressure ventilation were classified as "severe". Patients who received invasive or non-invasive mechanical ventilation or with sepsis or multiorgan failure were classified as "critical".[9] Initiation or uptitration of high-flow nasal cannula (HFNC) requires intensive care admission at our institution and was considered non-invasive 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 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). 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 [e.g. brief resolved unexplained events (BRUEs), increased seizure frequency], we erred towards an attribution of "likely", especially if no alternative explanation existed. For patients whose hospitalizations were "unlikely" to be caused by SARS-CoV-2, 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 history of 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 four 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 two investigators. We used a kappa statistic and a weighted kappa to calculate interrater agreement for the reason for admission ("likely" vs "unlikely" categorization) and for severity of illness, respectively. Disagreements were resolved by consensus after discussion among all four investigators. Descriptive statistics were calculated and reported as medians with interquartile ranges (IQR) 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 Hispanic/Latinx. Nineteen (16.2%) were immunocompromised, and 31 (26.5%) required intensive care unit admission attributable to COVID-19 or MIS-C. None died during the study period, though one immunocompromised patient died shortly after study conclusion from respiratory complications of COVID-19.

For classification of severity of illness, there was 100% agreement between reviewers for MIS-C designation (yes/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 PCR positive for Salmonella.

The tabulation of illness severity and likelihood of SARS-CoV-2 causing the hospitalization is depicted in **Table 2**; 46 (39.3%) were asymptomatic, 33 (28.2%) had mild/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. Fourteen (12%) patients had MIS-C; one 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% CI 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 demonstrate that most children hospitalized with SARS-CoV-2 have asymptomatic or mild/moderate disease, and nearly 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 non-specific 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.[11,12]

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 (e.g. other documented respiratory viral infections, worsening seizures, BRUEs), which may overestimate 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 very small proportion of reported infections.[13] As time has elapsed, we are learning that infection and transmission rates in children, though lower than adults, are non-negligble.[14] Rates of infection in children have increased in parallel with community prevalence.[15,16] The pediatric inpatient COVID-19 experience has been very different than 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 re-opening[2,17] and may influence policy decisions. Our findings demonstrate that such decisions should account for the fact that reported hospitalization rates overestimate the COVID-19 disease burden in children considerably.

Our study is limited by the single-center, retrospective design, which impacts generalizability. However, our proportion of asymptomatic patients is similar to other investigations[1,18,19], suggesting that our proportion of "unlikely" might align similarly. We had to make subjective assessments about disease severity and cause of hospitalization from documentation in the electronic medical record. While our interrater reliability was adequate, there were challenges inherent to this approach.

Table 1: *Demographic characteristics of patients hospitalized with SARS-CoV-2 infection*

Demographic characteristic	**Total (n=117)**
Median age, years (IQR)	**8 (1.5 – 14)**
Female sex, n (%)	**58 (49.6)**
Race/Ethnicity, n (%):	
Hispanic/LatinX	83 (70.9)
White Non-Hispanic	13 (11.1)
Asian	11 (9.4)
Native Hawaiian/Pacific Islander	3 (2.6)
Black/African American	2 (1.7)
Other/unknown	5 (4.3)
Immunocompromised, n (%)	**19 (16.2)**
ICU (attributable to SARS-CoV-2), n (%)	**31 (26.5)**
COVID-19 Treatments Provided, n (%)	
	79 (67.5)
None	26 (22.2)
Supplemental Oxygen	15 (12.8)
Remdesivir	28 (23.9)
Steroids	12 (10.3)
Immune Globulin	

Abbreviations: Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), interquartile range (IQR), Intensive care unit (ICU), Coronavirus disease 2019 (COVID-19).

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[+]	44	46 (39.3%)
Mild/moderate	28	5	33 (28.2%)
Severe	6	3	9 (7.7%)
Critical	14	1*	15 (12.8%)
MIS-C	14	0	14 (12.0%)
Total, n (%)	64 (54.7%)	53 (45.3%)	117 (100%)

Abbreviations: Coronavirus disease 2019 (COVID-19), multisystem inflammatory syndrome in children (MIS-C). *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. [+]The two asymptomatic patients that were designated as being admitted *likely* due to COVID-19 were i) solid organ transplant recipient who was admitted due to inability to isolate from infected family members and eventually tested positive after admission but remained asymptomatic ii) patient with baseline seizure disorder admitted for increased seizures with none of the CDC-described COVID-19 symptoms.[10]

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 E. coli (n=1) - Septic joint (n=1) - Tubo-ovarian abscess & urinary tract infection (n=1) - Salmonella enterica 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, cancelled due to SARS-CoV-2 infection (n=1) - Nephrectomy & 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+ mother (n=1) - Lupus, new diagnosis (n=1) - Inflammatory bowel disease, new diagnosis (n=1) - Palpitations with underlying arrythmia (n=1) - Lymphangioma (n=1) - Arteriovenous malformation (n=1) - Manic episode (n=1)	7 (13.2)

Abbreviations: Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)

References

1. Kim L, Whitaker M, O'Halloran A, et al. Hospitalization Rates and Characteristics of Children Aged <18 Years Hospitalized with Laboratory-Confirmed COVID-19 - COVID-NET, 14 States, March 1-July 25, 2020. *MMWR Morb Mortal Wkly Rep.* 2020;69(32):1081-1088.
2. Levin Z, Choyke K, Georgiou A, Sen S, Karaca-Mandic P. Trends in Pediatric Hospitalizations for Coronavirus Disease 2019. *JAMA pediatrics.* 2021.
3. Hanson KE, Caliendo AM, Arias CA, et al. The Infectious Diseases Society of America Guidelines on the Diagnosis of COVID-19: Molecular Diagnostic Testing. *Clin Infect Dis.* 2021.
4. Poline J, Gaschignard J, Leblanc C, et al. Systematic SARS-CoV-2 screening at hospital admission in children:a French prospective multicenter study. *Clin Infect Dis.* 2020.
5. Dong Y, Mo X, Hu Y, et al. Epidemiology of COVID-19 Among Children in China. *Pediatrics.* 2020;145(6).
6. Shekerdemian LS, Mahmood NR, Wolfe KK, et al. Characteristics and Outcomes of Children With Coronavirus Disease 2019 (COVID-19) Infection Admitted to US and Canadian Pediatric Intensive Care Units. *JAMA pediatrics.* 2020;174(9):868-873.
7. Centers for Disease Control and Prevention. Interim Guidance on Duration of Isolation and Precautions for Adults with COVID-19. https://www.cdc.gov/coronavirus/2019-ncov/hcp/duration-isolation.html. Published 2021. Updated February 13, 2021. Accessed March 30, 2021.
8. Centers for Disease Control and Prevention. Information for Healthcare Providers about Multisystem Inflammatory Syndrome in Children (MIS-C). https://www.cdc.gov/mis-c/hcp/. Published 2020. Updated February 17, 2021. Accessed March 30, 2021.
9. Chiotos K, Hayes M, Kimberlin DW, et al. Multicenter Initial Guidance on Use of Antivirals for Children With Coronavirus Disease 2019/Severe Acute Respiratory Syndrome Coronavirus 2. *Journal of the Pediatric Infectious Diseases Society.* 2020;9(6):701-715.
10. Centers for Disease Control and Prevention. Symptoms of COVID-19. https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html. Published 2020. Updated February 22, 2021. Accessed May 5, 2021.
11. Pasquel FJ, Messler J, Booth R, et al. Characteristics of and Mortality Associated With Diabetic Ketoacidosis Among US Patients Hospitalized With or Without COVID-19. *JAMA Netw Open.* 2021;4(3):e211091.
12. Taquet M, Luciano S, Geddes JR, Harrison PJ. Bidirectional associations between COVID-19 and psychiatric disorder: retrospective cohort studies of 62 354 COVID-19 cases in the USA. *Lancet Psychiatry.* 2021;8(2):130-140.
13. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA.* 2020;323(13):1239-1242.
14. Leidman E, Duca LM, Omura JD, Proia K, Stephens JW, Sauber-Schatz EK. COVID-19 Trends Among Persons Aged 0-24 Years - United States, March 1-December 12, 2020. *MMWR Morb Mortal Wkly Rep.* 2021;70(3):88-94.
15. American Academy of Pediatrics. Children and COVID-19: State-Level Data Report. https://services.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/children-

and-covid-19-state-level-data-report/. Published 2021. Updated March 25, 2021. Accessed March 30, 2021.
16. Leeb RT, Price S, Sliwa S, et al. COVID-19 Trends Among School-Aged Children - United States, March 1-September 19, 2020. *MMWR Morb Mortal Wkly Rep.* 2020;69(39):1410-1415.
17. U.S. News & World Report. Study: In School Talks, Pay Attention to Pediatric Hospitalizations for COVID-19. https://www.usnews.com/news/health-news/articles/2021-01-12/more-than-5-300-pediatric-hospitalizations-for-covid-in-22-states-study-shows. Published 2021. Accessed March 30, 2021.
18. Brookman S, Cook J, Zucherman M, Broughton S, Harman K, Gupta A. Effect of the new SARS-CoV-2 variant B.1.1.7 on children and young people. *The Lancet Child & adolescent health.* 2021;5(4):e9-e10.
19. Han MS, Choi EH, Chang SH, et al. Clinical Characteristics and Viral RNA Detection in Children With Coronavirus Disease 2019 in the Republic of Korea. *JAMA pediatrics.* 2021;175(1):73-80.

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