

SARS-CoV-2 With Concurrent Respiratory Viral Infection as a Risk Factor for a Higher Level of Care in Hospitalized Pediatric Patients

Lea Dikranian, MD,* Suzanne Barry, DO,† Ashar Ata, MBBS, MPH, PhD,‡ Katie Chiotos, MD,§
 Katja Gist, DO,|| Utpal Bhalala, MD,¶ Valerie Danesh, PhD,# Smitty Heavner, MS,** Varsha Gharpure, MD,††
 Erica C. Bjornstad, MD, PhD, MPH,‡‡ Olivia Irby, MD,§§ Julia A. Heneghan, MD, MS,|||| Vicki Montgomery, MD,¶¶
 Neha Gupta, MD,### Aaron Miller, MD,*** Allan Walkey, MD,††† Sandeep Tripathi, MD, MS,‡‡‡
 Karen Boman, BS,§§§ Vikas Bansal, MBBS, MPH,||||| Vishakha Kumar, MD, MBA,§§§§ Rahul Kashyap, MBBS,||||||
 Imran Sayed, MD,¶¶¶ and Christopher Woll, MD,###

From the Society of Critical Care Medicine Discovery Viral Infection and Respiratory Illness Universal Study:
 COVID-19 Registry Investigator Group

Objective: As of early 2021, there have been over 3.5 million pediatric cases of SARS-CoV-2, including 292 pediatric deaths in the United States. Although most pediatric patients present with mild disease, they are still at risk for developing significant morbidity requiring hospitalization and intensive care unit (ICU) level of care. This study was performed to evaluate if the presence of concurrent respiratory viral infections in pediatric patients admitted to the hospital with SARS-CoV-2 was associated with an increased rate of ICU level of care.

Design: A multicenter, international, noninterventive, cross-sectional study using data provided through The Society of Critical Care Medicine Discovery Network Viral Infection and Respiratory Illness Universal Study database.

Setting: The medical ward and ICU of 67 participating hospitals.

Patients: Pediatric patients younger than 18 years hospitalized with SARS-CoV-2.

Interventions: None.

Measurements and Main Results: A total of 922 patients were included. Among these patients, 391 required ICU level care and 31 had concurrent non-SARS-CoV-2 viral coinfection. In a multivariate analysis, after accounting for age, positive blood culture, positive sputum culture, preexisting chronic medical conditions, the presence of a viral respiratory coinfection was associated with need for ICU care (odds ratio, 3.6; 95% confidence interval, 1.6–9.4; $P < 0.01$).

Conclusions: This study demonstrates an association between concurrent SARS-CoV-2 infection with viral respiratory coinfection and the need for ICU care. Further research is needed to identify other risk factors that can be used to derive and validate a risk-stratification tool for disease severity in pediatric patients with SARS-CoV-2.

Key Words: COVID-19, SARS-CoV-2, severe disease, coinfection

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Over the last year, there have been over 30 million cases of SARS-CoV-2 in the United States resulting in more than 500,000 deaths.¹ Data provided by the American Academy of Pediatrics and the Children's Hospital Association, indicate that 3.5 million children have tested positive for SARS-CoV-2 representing 11.7% of total US cases.² As of early 2021, there have been 292 pediatric deaths in the United States alone due to SARS-CoV-2.² Although our knowledge of SARS-CoV-2 is evolving, there continues to be a paucity of information pertaining to pediatric patients. Most initial clinical presentations appear to be mild or asymptomatic. However, children are still at risk of developing severe illness necessitating hospitalization.^{3–6}

One in three children hospitalized with SARS-CoV-2 in the United States are admitted to the intensive care unit (ICU). The ICU admission rate for hospitalized children is similar to the ICU admission rate for hospitalized adults in the United States.⁶ In pediatric patients infected with SARS-CoV-2, viral coinfection is common.^{7–15} In a study from Wuhan, China, 33% of children with SARS-CoV-2 had coinfection with other respiratory pathogens.¹⁶ Prior studies evaluating pediatric patients infected with non-SARS-CoV-2 respiratory viruses showed that viral coinfection can adversely impact the length of stay, mortality, need for mechanical ventilation as well as admission to the ICU.^{17–20}

From the *Pediatric Emergency Medicine, Division of Emergency Medicine, Childrens Hospital of Michigan, Detroit, MI; †Section of Critical Care Medicine, Department of Pediatrics, ‡Departments of Surgery and Emergency Medicine, Albany Medical Center, Albany, NY; §Division of Critical Care Medicine, Department of Anesthesia and Critical Care Medicine, Children's Hospital of Philadelphia, Philadelphia PA; ||Department of Pediatrics, University of Colorado Anschutz Medical Campus, Aurora, CO; ¶University of Texas Medical Branch, Driscoll Health System, Corpus Christi, TX; #Baylor Scott & White Health, Dallas, TX; **Department of Medicine, Prisma Health, Greenville, SC; ††Department of Pediatrics, Advocate Children's Hospital, Park Ridge, IL; ‡‡Division of Nephrology, Department of Pediatrics, University of Alabama Birmingham, Birmingham, AL; §§Division of Critical Care Medicine, Department of Pediatrics, Arkansas Childrens Hospital, Little Rock, AK; |||Division of Pediatric Critical Care, Department of Pediatrics, University of Minnesota Masonic Children's Hospital, Minneapolis, MN; ¶¶Division of Critical Care Medicine, Department of Pediatrics, University of Louisville and Norton Childrens Hospital, Louisville, KY; ###Department of Pediatrics, Section of Critical Care Medicine, University of Oklahoma College of Medicine, Oklahoma City, OK; ***St. Louis University School of Medicine, St. Louis, MO; †††The Pulmonary Center, Division of Pulmonary, Allergy, Sleep and Critical Care; Department of Medicine; Boston University School of Medicine, Boston, MA; ‡‡‡Department of Pediatrics OSF Saint Francis Medical Center/University of Illinois College of Medicine at Peoria, Peoria, IL; §§§Division of Nephrology and Hypertension, Department of Medicine;

Mayo Clinic, Rochester, MN; |||||Division of Research, Hospital Corporation of America Healthcare, Nashville, TN; ¶¶¶Division of Pediatric Critical Care Medicine, Department of Pediatrics, University of Colorado Anschutz Medical Campus, Childrens Hospital Colorado, Aurora, CO; and ###Section of Pediatric Emergency Medicine, Departments of Pediatrics and Emergency Medicine, Albany Medical Center, Albany, NY.

Reprints: Christopher Woll, MD, Albany Medical Center Albany, MC-139, 43

New Scotland Ave, Albany, NY 12208 (e-mail: wollc@amc.edu).

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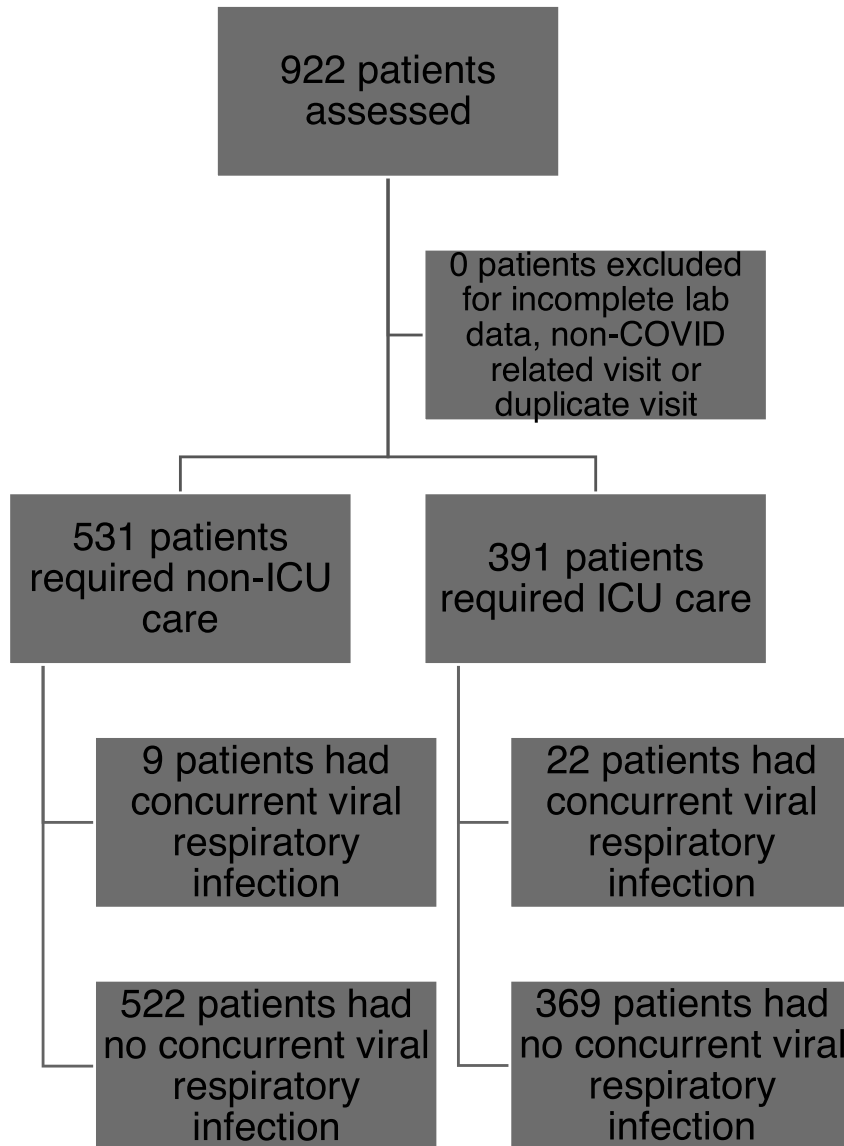


FIGURE 1. Patient flowchart.

The aim of this study was to evaluate if the presence of concurrent respiratory viral infections in pediatric patients hospitalized with SARS-CoV-2 is associated with an increased rate of ICU care.

METHODS

This study was an international multicenter, noninterventional, cross-sectional study of pediatric patients younger than 18 years hospitalized with SARS-CoV-2. The data were provided through the Society of Critical Care Medicine Discovery Network Viral Infection and Respiratory Illness Universal Study database²¹ and collected from March 1 to November 16, 2020. The study was approved by the Albany Medical Center IRB, study number 5854. The study was also approved by each participating sites IRB. Data use agreements were executed between all participating sites. Cases were defined as patients younger than 18 years admitted to a participating site's hospital with acute SARS-CoV-2. Multi-system inflammatory syndrome in children cases were included. Non-SARS-CoV-2-related admissions and repeated admissions

were excluded from the study. There were 26 categories of signs and symptoms, 41 pediatric comorbidities, and 36 categories of COVID-19-related complications in the Viral Infection and Respiratory Illness Universal Study registry report.²² Preexisting chronic medical conditions were defined a priori and included categories of cardiac, pulmonary, renal, neurologic, gastrointestinal, rheumatologic, immunologic, endocrinologic, oncologic, hematologic and transplant related disease. Children with documented non-SARS-CoV-2 respiratory viral infections were defined as “concurrent respiratory viral infection.” Children with positive bacterial blood, sputum or urine cultures were defined as “concurrent bacterial infections.” Positive cultures were defined as a specimen growing any bacterial pathogen. Severe disease was defined as need for ICU care. Two sample *t* test was used to compare means in patients with and without coinfection. χ^2 or Fisher exact tests were used to determine differences in demographics between the ICU and non-ICU-admitted patients. Logistic regression was used to determine an association of dichotomous variables between the ICU group compared with the non-ICU group. Those variables identified as statistically

TABLE 1. Demographics

Variable	Intensive Care Unit-N (%)	Nonintensive Care Unit-N (%)	P
Age group	N = 368	N = 452	
<=6 months	35 (9.5)	101 (22.3)	<0.001
>6 months to 1 year	19 (5.2)	24 (5.3)	
>1 to 5 years	64 (17.4)	80 (17.7)	
>5 to 10 years	67 (18.2)	60 (13.3)	
>10 to 15 years	91 (24.7)	91 (20.1)	
>15 to 18 years	92 (25.0)	97 (21.4)	
Sex	N = 386	N = 490	
Female	171 (44.3)	243 (49.6)	0.119
Ethnicity	n = 391	n = 531	
Non-Hispanic/White	169 (43.2)	232 (43.7)	<0.001
Non-Hispanic/Black or AA	103 (26.3)	113 (21.3)	
Hispanic or Latino	26 (6.7)	29 (5.5)	
Other	87 (22.3)	109 (20.5)	

significant in univariate analysis were included in a multivariate analysis. All statistical analyses were performed using STATA 15.1 (STATA Corp., College Station, TX).

RESULTS

A total of 922 hospitalized children were included, of which 391 required ICU level care. Thirty-one children had concurrent respiratory viral infections, 9 of which did not require ICU level care. No patients were excluded because of repeat admissions, incomplete data entry, or non-SARS-CoV-2-related hospitalization (Figure 1 (Supplemental digital content, <http://links.lww.com/PEC/B13>). Demographic information is presented in Table 1.

In a univariate analysis, the odds of requiring ICU care were 3.5 times higher if a concurrent respiratory viral infection was present compared with those without a viral coinfection (odds ratio [OR], 3.5; 95% confidence interval [CI], 1.6–7.6; *P* < 0.01) (Table 2). The presence of a preexisting chronic medical condition increased the odds of requiring ICU care by 1.8 (95% CI, 1.4–2.4; *P* < 0.001), having a positive blood culture increased the odds of requiring ICU care by 4.0 (95% CI, 1.7–9.6; *P* < 0.01) and a positive sputum culture increased the odds of requiring ICU care by 7.5 (OR, 7.5; 95% CI, 2.2–26.0; *P* < 0.01) (Table 2 and Supplemental Table 1, <http://links.lww.com/PEC/B13>). In a multivariate analysis accounting for age, positive blood culture, positive sputum culture, and preexisting chronic medical conditions, the pres-

TABLE 3. Adjusted Multivariate Analysis. Odds of Requiring ICU Level of Care

Variable	aOR (95% CI)	P
Concurrent respiratory viral infection (31)	3.6 (1.6–8.1)	<0.01
Positive blood culture (27)	3.9 (1.6–9.4)	<0.01
Positive sputum culture (19)	6.3 (1.8–22.1)	<0.01
Preexisting chronic conditions* (343)	1.8 (1.3–2.3)	<0.01

*Corrected congenital heart disease, uncorrected congenital heart disease, arrhythmia, cardiomyopathy, acquired cardiac disease, chronic invasive positive pressure ventilation, chronic noninvasive positive pressure ventilation, chronic lung disease, cystic fibrosis, congenital anomalies of the kidney and urinary tract, static encephalopathy, epilepsy, developmental delay, chronic liver disease, chronic cholestasis, inflammatory bowel disease, malnutrition, immunodeficiency, systemic lupus erythematosus.
aOR indicates adjusted odds ratio.

ence of a respiratory viral coinfection increased the odds of requiring ICU care by 3.6-fold (OR, 3.6; 95% CI, 1.6–9.4; *P* < 0.01) (Table 3). The most commonly identified respiratory viruses were rhinovirus/enterovirus (32.3%), RSV (16.1%), and adenovirus (6.5%). The remainder of identified concurrent respiratory infections included coronavirus NL63, parainfluenza-2, parainfluenza-3, parainfluenza-4, and human metapneumovirus (3.2% each). There were 8 unspecified viruses, which all came from the same institution, and three patients had multiple respiratory viral coinfections. The mean age was lower in children with concurrent respiratory infections (3.6 years; 95% CI, 2.1–5.1; *P* < 0.001) compared to those without coinfection (8.8 years; 95% CI, 8.4–9.3; *P* < 0.001). Hospital and ICU length of stay were not statistically different in patients with and without coinfection (Table 4).

DISCUSSION

In this study, we identified 922 hospitalized pediatric patients with SARS-CoV-2 related illnesses with validated data pooled by 67 health care systems. To our knowledge, this is the largest study evaluating viral coinfections as a risk factor for severe SARS-CoV-2 infection in pediatric patients. Previous studies have evaluated the presence of viral coinfections in pediatric patients with SARS-CoV-2, but these studies have been limited small sample size.^{16,23–25} This study demonstrates a statistically significant increase in the need for ICU care in pediatric patients admitted to the hospital with SARS-CoV-2 who also have a concurrent respiratory viral infection.

Because our knowledge of how SARS-CoV-2 infections affect the pediatric population is evolving, providers have relied on real-time physiologic status to help guide intervention and

TABLE 2. Unadjusted Univariate Analysis. Odds of Requiring ICU Level of Care

Variables	Patients Without Condition Who Required ICU, n (%)	Patients With Condition Who Required ICU, n (%)	OR (95% CI)	P
Concurrent respiratory illness (31)	369 (41.5)	22 (68.8)	3.5 (1.6–7.6)	<0.01
Positive blood culture (27)	371 (41.5)	20 (74.1)	4.0 (1.7–9.6)	<0.01
Positive sputum culture (19)	375 (41.5)	16 (84.2)	7.5 (2.2–26.0)	<0.01
Preexisting chronic conditions* (343)	214 (37.0)	177 (51.6)	1.8 (1.4–2.4)	<0.001

*Corrected congenital heart disease, uncorrected congenital heart disease, arrhythmia, cardiomyopathy, acquired cardiac disease, chronic invasive positive pressure ventilation, chronic noninvasive positive pressure ventilation, chronic lung disease, cystic fibrosis, congenital anomalies of the kidney and urinary tract, static encephalopathy, epilepsy, developmental delay, chronic liver disease, chronic cholestasis, inflammatory bowel disease, malnutrition, immunodeficiency, systemic lupus erythematosus.

TABLE 4. Two Sample *t* Tests

Variables	Mean (95% CI)	<i>P</i>
Age (y)		<0.001
Patients without viral coinfection	8.8 (8.4–9.3)	
Patients with viral coinfection	3.6 (2.1–5.1)	
Hospital length of stay (d)		0.86
Patients without viral coinfection	6.3 (3.8–8.8)	
Patients with viral coinfection	5.2 (2.6–7.7)	
ICU length of stay (d)		0.31
Patients without viral coinfection	7.9 (6.5–9.4)	
Patients with viral coinfection	4.7 (1.6–7.8)	

Comparison of those patients with and without viral coinfection.

disposition decisions.^{26–28} This study provides information that may be used in conjunction with other clinical criteria to anticipate severe illness requiring ICU level of care. Currently, there are no risk stratification tools to help predict those at risk of severe disease in pediatric patients infected with SARS-CoV-2. The development of such a tool could identify pediatric patients infected with SARS-CoV-2 who are at high risk of developing severe disease and could therefore minimize unnecessary admissions, and appropriately identify patients who are more likely to warrant an escalation of therapy or monitoring. Minimizing unnecessary admissions in this population could help mitigate health care worker exposure to SARS-CoV-2, health care system surge, and financial burden for the patients' families. Identification of patients who are at high risk for severe disease could also aid in facilitating the appropriate utilization of emerging therapeutics which may be of benefit to this population.²⁹

There are several limitations to this study. First, this is a cross-sectional, multicenter study that relies on provider documentation and charting to extract data, leading to the missing demographic information. Intensive care unit admission was at the treating physician's discretion but not always clearly documented as to the physiologic criteria that warranted ICU level of care. Second, this is an international population with many regional variations in testing capabilities. Different hospitals use different SARS-CoV-2 and respiratory viral tests which have varying sensitivities and specificities resulting in differing rates of false positives and false negatives at different sites. Also, the hospitals used different testing patterns to identify concurrent viral coinfections which raises the possibility of missed viral coinfections. It is also possible that the threshold for testing for viral coinfection differed between the general wards and the ICU, again potentially missing concurrent viral infections as viral coinfection was assumed not present if viral testing was not performed. Third, the design of this study did not account for the timing of coinfections. It is unclear if coinfections developed before the need for ICU care or if the coinfection was identified while the child was already admitted to the ICU. Lastly, a selection bias exists as the database focuses only on patients who required hospital admission rather than all pediatric cases in the community.

CONCLUSIONS

In conclusion, the presence of SARS-CoV-2 infection and concurrent respiratory viral infection in pediatric patients is independently associated with a higher rate of ICU care. In addition, we also found that positive blood cultures, positive sputum cultures as well as preexisting chronic pediatric conditions also increased the odds of requiring admission to the ICU. As best practices for

diagnosis and treatment are evolving, further research is needed to identify other risk factors that can be used to derive and validate a risk-stratification tool for disease severity in pediatric patients with SARS-CoV-2. Early identification of patients at high risk for severe disease is crucial as it may help with health care resource allocation and may help inform treatment decisions as some therapies (antiviral therapy, steroids, convalescent plasma) may be most effective while patients are less critically ill.²³

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Unusual Presentations of Childhood Systemic Lupus Erythematosus to the Emergency Department: Erratum

In the October 2017 online issue, the name of the first author was presented incorrectly. The correct name of the first author is Ayse Gultekingil.

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Keser AG, Ertugrul İ, Teksam O, et al. Unusual Presentations of Childhood Systemic Lupus Erythematosus to the Emergency Department. *Pediatr Emerg Care*. 2017;33:e100–e102.