RESEARCH ARTICLE

Factors Associated With Severe Illness in Patients Aged <21 Years Hospitalized for COVID-19

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ABSTRACT

OBJECTIVES: To describe coronavirus disease 2019 (COVID-19)–related pediatric hospitalizations during a period of B.1.617.2 (Δ) variant predominance and to determine age-specific factors associated with severe illness.

METHODS: We abstracted data from medical charts to conduct a cross-sectional study of patients aged <21 years hospitalized at 6 United States children's hospitals from July to August 2021 for COVID-19 or with an incidental positive severe acute respiratory syndrome coronavirus 2 test. Among patients with COVID-19, we assessed factors associated with severe illness by calculating age-stratified prevalence ratios (PR). We defined severe illness as receiving high-flow nasal cannula, positive airway pressure, or invasive mechanical ventilation.

RESULTS: Of 947 hospitalized patients, 759 (80.1%) had COVID-19, of whom 287 (37.8%) had severe illness. Factors associated with severe illness included coinfection with respiratory syncytial virus (RSV) (PR 3.64) and bacteria (PR 1.88) in infants; RSV coinfection in patients aged 1 to 4 years (PR 1.96); and obesity in patients aged 5 to 11 (PR 2.20) and 12 to 17 years (PR 2.48). Having ≥2 underlying medical conditions was associated with severe illness in patients aged <1 (PR 1.82), 5 to 11 (PR 3.72), and 12 to 17 years (PR 3.19).

CONCLUSIONS: Among patients hospitalized for COVID-19, factors associated with severe illness included RSV coinfection in those aged <5 years, obesity in those aged 5 to 17 years, and other underlying conditions for all age groups <18 years. These findings can inform pediatric practice, risk communication, and prevention strategies, including vaccination against COVID-19.

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Coronavirus disease 2019 (COVID-19)–related hospitalizations among patients aged <18 years increased nearly fivefold after the B.1.617.2 (Δ) variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) became the predominant variant in the United States in June 2021.[1,2] This coincided with the unseasonal circulation of other respiratory viruses, such as respiratory syncytial virus (RSV) starting in June 2021.[3–5] Although persons aged <21 years generally experience mild illness when infected with SARS-CoV-2,[6–8] some experience severe outcomes from COVID-19, such as requirement of critical care services[6,9–11] and death.[10,12–15] Risks of hospitalization and severe illness in the pre-Δ period were higher in children and adolescents who were Black or Hispanic, were born prematurely, or had diabetes, asthma, obesity, congenital cardiac anomalies, or immunocompromising conditions.[7,9,14,16–20] We performed a chart abstraction study to obtain granular clinical data not available in surveillance-based studies on hospitalized pediatric patients during the Δ variant case surge.[2,21] We previously published a descriptive report on patients aged <18 years who were hospitalized for COVID-19 or with an incidental positive SARS-CoV-2 test at 6 children's hospitals.[22]

In this analysis, we provide age-specific factors associated with severe illness in our cohort, and we describe presenting signs and symptoms, laboratory data, coinfection status, treatments, and discharge conditions by age group and reason for hospitalization. Age-stratified findings are particularly beneficial for clinical decision-making in pediatric populations. Finally, this paper expands the previous cohort of hospitalized patients to those aged <21 years.

METHODS

Study Design and Case Definition

We conducted a cross-sectional study with 6 children's hospitals in the United States (in Arkansas, the District of Columbia, Florida, Illinois, Louisiana, and Texas). We abstracted charts of patients aged <21 years who were hospitalized with a positive SARS-CoV-2 nucleic acid amplification or antigen test or a provider diagnosis of COVID-19 at any point from July 1 to August 31, 2021, a period of high community transmission of SARS-CoV-2 in each hospital catchment area.[23]

Data Collection and Entry

For each patient we abstracted demographic characteristics, medical history, presentation, hospital course, and outcomes. Using the provider documentation, abstractors determined hospitalization reason as either for COVID-19 or with an incidental positive SARS-CoV-2 test. Among those hospitalized for COVID-19, abstractors assigned COVID-19 as the primary reason for hospitalization or as a contributing reason (if provider documentation indicated that COVID-19 was partly responsible for the hospitalization, but not the clear primary reason). A patient with an incidental positive test was defined as having asymptomatic or mild infection and being hospitalized for a reason apparently unrelated to COVID-19. To audit the abstractors' determinations and to minimize abstraction errors, 5% of all charts were reviewed by a second abstractor. When medical documentation was unclear, project leaders adjudicated hospital reason determination. Patients with multisystem inflammatory syndrome in children (n = 25) were excluded from this analysis and are described in Supplemental Table 5.

Variable Definitions

Among patients aged 2 to 20 years, patients were classified as having obesity if their BMI calculation or reported BMI was ≥95th percentile, or if they had a clinical diagnosis of obesity. Other underlying medical conditions were abstracted based on provider documentation. Depending on number of organ systems affected, patients were categorized as having 0, 1, or ≥2 underlying medical conditions, restricting to 1 condition per organ system group.[22] Patients were considered fully vaccinated if they had received 2 doses of a messenger RNA–based COVID-19 vaccine ≥14 days before hospital admission date, consistent with completion of the primary series, as documented in the medical chart. During the study period, COVID-19 vaccination was recommended for persons aged 12 years and older, and the Pfizer-BioNTech was the only vaccine authorized for persons aged 12 to 17 years.[24] Prevalence of tachycardia and tachypnea was calculated using age-normalized cutoffs, as described elsewhere.[12,25] Chest radiographs were defined as either normal or abnormal, and abnormal radiographs were further classified as having an infiltrate or consolidation on the basis of interpretations provided in radiologist reports.

Viral coinfection was defined as having a positive viral test. Bacterial coinfection was defined as having a positive blood culture (not considered to be a contaminant), respiratory bacterial culture, or a provider-assigned diagnosis of bacterial infection, including bacterial pneumonia.

Highest level of respiratory support was defined preferentially as invasive mechanical ventilation (IMV) including extracorporeal membrane oxygenation, bilevel or continuous positive airway pressure (BiPAP or CPAP), high-flow nasal cannula (HFNC), or nasal cannula.

Severe Illness Definition

We defined "severe illness" as receiving HFNC, BiPAP, CPAP, or IMV at any point during the hospitalization to identify patients with significant respiratory illness. We did not include ICU admission or medication requirements in the definition of severe illness given possible interhospital differences in ICU admission parameters and critical care requirements for other disease processes, such as diabetic ketoacidosis.

Statistical Analysis

We provided descriptive statistics for the full cohort, stratified by hospitalization

reason. Among those hospitalized for COVID-19 (as either the primary or contributing reason for hospitalization), we further described clinical presentation and hospital course stratified by age groups (<1, 1 to 4, 5 to 11, 12 to 17, and 18 to 20 years).[26] We selected these age groups a priori based on COVID-19 vaccine eligibility cohorts, age-specific applicability of certain underlying medical conditions (eg, preterm birth, RSV infection, and obesity), and the goal of filling a literature gap in granular clinical information about infants and young children. Admission, peak, and/or nadir laboratory values were summarized. We conducted subgroup analyses among neonates (aged <1 month) and nonneonate infants (aged 1 to 12 months) and among patients aged ≥2 years with and without obesity, using 2-sided Mann–Whitney U and χ^2 tests, with significance established at α of .05.

We assessed factors associated with severe illness among patients hospitalized for COVID-19 using log-binomial mixed-effects regression models with hospital-specific random intercepts to account for correlations of observations from the same hospital. We used log-binomial rather than logistic or probit regression because the prevalence of severe illness was not rare, and prevalence risk ratios would provide more reasonable estimates of association than prevalence odds ratios. For each of the age groups (<1, 1 to 4, 5 to 11, 12 to 17, and 18 to 20 years), we selected exposure variables that are relevant to that group to determine the independent effect of each exposure on the prevalence of severe illness. We calculated the prevalence ratios (PR) with 95% confidence interval (CI). Because our goal was to help pediatric hospital providers recognize potential factors associated with severe illness in admitted patients, rather than to develop a composite risk incorporating other factors, we ran a distinct model for each exposure variable. Given the objective of this study, to raise awareness of potential factors for severe illness in children hospitalized with COVID-19, we did not correct for multiple comparisons. Although this raises the type I error risk, it lowers the greater risk of missing statistical associations that could prove valuable in clinical practice. All analyses were conducted in SAS (version 9.4; SAS Institute).

Regulatory Approval

This activity was reviewed by the Centers for Disease Control and Prevention and the participating institutions and determined to be public health surveillance. It was conducted according to federal law and CDC policy (45 C.F.R. part 46.102(l)(2), 21 C.F.R. part 56, 42 U.S.C. Sect. 241(d), 5 U.S.C. Sect. 552a, and 44 U.S.C. Sect. 3501 et seq.).

RESULTS

Of 947 patients, 759 (80.1%) were hospitalized for COVID-19 and 188 (19.9%) had an incidental positive SARS-CoV-2 test. COVID-19 was the primary reason for hospitalization for 494 (52.2%) patients and a contributing reason for 265 (28.0%) patients. Two patients received a provider diagnosis of COVID-19 without documentation of a positive SARS-CoV-2 nucleic acid amplification or antigen test. In the full cohort, 491 (51.8%) were male, 205 (21.6%) were aged <1 year, 337 (35.6%) were aged 12 to 17 years, 266 (28.1%) were non-Hispanic Black, 282 (29.8%) were Hispanic, and 518 (54.7%) were insured through Medicaid. Of 394 vaccine-eligible patients in the full cohort (aged 12 to 20 years), 4 (1.0%) were fully vaccinated at admission. Of 318 vaccine-eligible patients hospitalized for COVID-19, 2 (0.6%) were fully vaccinated. Among those hospitalized for COVID-19 as the primary reason, 344 (69.6%) had at least 1 underlying medical condition and none were fully vaccinated (Table 1).

Findings at Presentation

Presenting signs and symptoms among the 759 patients hospitalized for COVID-19 included objective fever (*n* = 503, 66.3%), shortness of breath (*n* = 389, 51.3%), and nausea or vomiting (*n* = 316, 41.6%). Tachypnea was present at admission in 176 patients aged 12 to 17 years (64.7%), and tachycardia was present in 28 patients aged 18 to 20 years (60.9%). "COVID-19" and "pneumonia" were the most common admitting diagnoses (Table 2). Median C-reactive protein values at admission exceeded normal values in all age groups (Table 3).

Hospital Course and Outcomes

Among the 759 patients hospitalized for COVID-19, 287 (37.8%) had severe illness. Of all patients, 62 (8.2%) received IMV as the highest level of respiratory support (including 10 who received extracorporeal membrane oxygenation), for a median duration of 7 days; 9.6% (*n* = 26) of patients aged 12 to 17 years, and 13% (*n* = 6) of patients aged 18 to 20 years received IMV, for respective median durations of 9.5 and 17 days.

Of 573 patients hospitalized for COVID-19 with at least 1 chest radiograph, 79.8% had an abnormality, including 52.2% with an infiltrate or consolidation. Viral coinfection was identified in 101 patients aged <5 years (33.9%), compared to 12 patients aged 5 to 20 years (2.6%). Bacterial coinfection was identified in 50 patients aged <5 years (16.8%) and 87 patients aged 5 to 20 years (18.9%) (Table 2). Coinfection testing was common in patients with and without severe illness. Of those with severe illness, 62.4% had a viral coinfection test and 49.2% had a bacterial culture; respective findings among patients without severe illness were 49.1% and 40.0%.

A total of 227 (29.9%) patients were admitted to the ICU, for a median duration of 4 days. ICU admission prevalence ranged from 19.3% (*n* = 34) for patients aged <1 year to 39.7% (*n* = 108) for patients aged 12 to 17 years. Remdesivir use ranged from 12.5% (*n* = 22) for patients aged <1 year to 63.0% (*n* = 29) for patients aged 18 to 20 years. Baricitinib, Tocilizumab, and other monoclonal antibodies were used rarely and mostly among patients aged ≥12 years. Thirty-three (4.3%) patients were discharged on oxygen, of whom 9 had underlying chronic respiratory failure. Eleven (1.4%) died, 72.7% of whom were aged 12 to 17 years (Table 4).

TABLE 1 Characteristics of Patients with SARS-CoV-2-Related Hospitalization by Admission Reason, 6 Hospitals, United States, July to August 2021, *N* = 947

	COVID-19 as Primary Reason (*n* = 494)	COVID-19 as Contributing Reason (*n* = 265)	Incidental SARS-CoV-2 Positive Test (*n* = 188)	All (*N* = 947)
Male sex, *n* (%)	249 (50.4)	147 (55.5)	95 (50.5)	491 (51.8)
Age, years, *n* (%)				
<1	106 (21.5)	70 (26.4)	29 (15.4)	205 (21.6)
1–4	69 (14.0)	53 (20.0)	36 (19.1)	158 (16.7)
5–11	84 (17.0)	59 (22.3)	47 (25.0)	190 (20.1)
12–17	202 (40.9)	70 (26.4)	65 (34.6)	337 (35.6)
18–20	33 (6.7)	13 (4.9)	11 (5.9)	57 (6.0)
Race and ethnicity, *n* (%)				
White, non-Hispanic	153 (31.0)	68 (25.7)	66 (35.1)	287 (30.3)
Black, non-Hispanic	123 (24.9)	93 (35.1)	50 (26.6)	266 (28.1)
Hispanic	155 (31.4)	75 (28.3)	52 (27.7)	282 (29.8)
Other or unknown	63 (12.8)	29 (10.9)	20 (10.6)	112 (11.8)
Insurance, *n* (%)				
Medicaid	274 (55.5)	152 (57.4)	92 (48.9)	518 (54.7)
Private	132 (26.7)	61 (23.0)	57 (30.3)	250 (26.4)
Uninsured	28 (5.7)	12 (4.5)	7 (3.7)	47 (5.0)
Other or unknown	60 (12.1)	40 (15.1)	32 (17.0)	132 (13.9)
Underlying medical conditions,[a] *n* (%)				
0	150 (30.4)	84 (31.7)	82 (43.6)	316 (33.4)
1	141 (28.5)	95 (35.8)	59 (31.4)	295 (31.2)
2 or more	203 (41.1)	86 (32.5)	47 (25.0)	336 (35.5)
Condition,[b] *n* (%)				
Obesity	211 (42.7)	50 (18.9)	29 (15.4)	290 (30.6)
Asthma	94 (19.0)	32 (12.1)	15 (8.0)	141 (14.9)
Neurologic or neurodevelopmental disorder	42 (8.5)	22 (8.3)	12 (6.4)	75 (7.9)
Feeding tube dependent	48 (9.7)	14 (5.3)	6 (3.2)	68 (7.2)
Seizure disorder	40 (8.1)	20 (7.5)	7 (3.7)	67 (7.1)
Other gastrointestinal disorder	31 (6.3)	14 (5.3)	11 (5.9)	56 (5.9)
Preterm birth	26 (5.3)	21 (7.9)	7 (3.7)	54 (5.7)
Depression	17 (3.4)	9 (3.4)	20 (10.6)	46 4.9)
Congenital heart disease	18(3.6)	13 (4.9)	10 (5.3)	41 (4.3)
Diabetes type 1	1 (0.2)	20 (7.5)	5 (2.7)	26 (2.7)
Vaccination status,[c] *n* (%)				
Fully vaccinated	0 (0)	2 (0.8)	2 (1.1)	4 (0.4)
Partially vaccinated	8 (1.6)	7 (2.6)	5 (2.7)	20 (2.1)
Not vaccinated	227 (46.0)	74 (27.9)	69 (36.7)	370 (39.1)
Ineligible	259 (52.4)	182 (68.7)	112 (59.6)	553 (58.4)

[a] Defined by the following groups: neurologic and developmental conditions (attention deficit hyperactivity disorder, autism spectrum disorder, cerebral palsy, cognitive dysfunction, muscular dystrophy, neural tube defect or spina bifida, neurologic or neurodevelopmental disorder, neuropathy, plegias or paralysis, preterm birth [for children aged <2 y only], seizure disorder, and wheelchair or walker-dependence or bed-bound status); respiratory conditions (active tuberculosis, asthma or reactive airway disease, chronic hypoxemic respiratory failure with oxygen or ventilator dependence, cystic fibrosis, current smoking or e-cigarette use, tracheostomy dependence, and other chronic lung diseases); cardiovascular conditions (congenital heart disease, valvular heart disease, hypertension, and other cardiovascular disease); metabolic and endocrine conditions (dyslipidemia, obesity, thyroid disorder, type 1 diabetes, type 2 diabetes, and other endocrine disorders); gastrointestinal or hepatic conditions (Crohn's disease, feeding tube dependence, liver disease, malnutrition, ulcerative colitis, and other gastrointestinal disorders); and psychiatric conditions (anxiety, borderline personality disorder, depression, substance use disorder, and other psychiatric diagnoses).

[b] List is not exhaustive but includes the top 3 diagnoses for each age category.

[c] Fully vaccinated was defined as having received 2 doses of a messenger RNA–based COVID-19 vaccine at least 14 d before hospital admission date. Partially vaccinated was defined as having received only 1 dose of a messenger RNA–based COVID-19 vaccine at least 14 d before hospitalization. All vaccinated patients in this study received the Pfizer-BioNTech (BNT162b2) vaccine.

TABLE 2 Presentation of Patients Hospitalized for COVID-19, by Age Group, 6 Hospitals, United States, July to August 2021, *N* = 759

	<1 Years (*n* = 176)	1–4 Years (*n* = 122)	5–11 Years (*n* = 143)	12–17 Years (*n* = 272)	18–20 Years (*n* = 46)
Presenting sign or symptom,[a] *n* (%)					
Constitutional	176 (100)	122 (100)	143 (100)	270 (99.3)	46 (100)
Objective fever	120 (68.2)	88 (72.1)	101 (70.6)	165 (60.7)	29 (63.0)
Poor appetite	77 (43.8)	63 (51.6)	68 (47.6)	118 (43.4)	19 (41.3)
Lower respiratory	119 (67.6)	91 (74.6)	100 (69.9)	237 (87.1)	38 (82.6)
Cough	103 (58.5)	86 (70.5)	91 (63.6)	196 (72.1)	31 (67.4)
SOB or dyspnea	70 (39.8)	49 (40.2)	54 (37.8)	188 (69.1)	28 (60.9)
Upper respiratory	123 (69.9)	79 (64.8)	84 (58.7)	137 (50.4)	21 (45.7)
Sore throat	2 (1.1)	7 (5.7)	36 (25.2)	59 (21.7)	10 (21.7)
Rhinorrhea or nasal congestion	120 (68.2)	77 (63.1)	69 (48.3)	114 (41.9)	16 (34.8)
Neurologic	8 (4.5)	19 (15.6)	49 (34.3)	122 (44.9)	15 (32.6)
Headache	0 (0)	3 (2.5)	40 (28.0)	89 (32.7)	13 (28.3)
Gastrointestinal	57 (32.4)	62 (50.8)	88 (61.5)	166 (61.0)	26 (56.5)
Nausea or vomiting	47 (26.7)	44 (36.1)	69 (48.3)	136 (50.0)	20 (43.5)
Diarrhea	29 (16.5)	37 (30.3)	36 (25.2)	72 (26.5)	15 (32.6)
Rash	11 (6.3)	7 (5.7)	8 (5.6)	4 (1.5)	1 (2.2)
Admission diagnosis,[b] *n* (%)					
COVID-19	131 (74.4)	86 (70.5)	103 (72.0)	216 (79.4)	38 (82.6)
Pneumonia	12 (6.8)	32 (26.2)	40 (28.0)	97 (35.7)	16 (34.8)
COVID-19 pneumonia	8 (4.5)	27 (22.1)	35 (24.5)	90 (33.1)	16 (34.8)
Bronchiolitis	37 (21.0)	16 (13.1)	1 (0.7)	0 (0)	0 (0)
RSV	26 (14.8)	14 (11.5)	3 (2.1)	1 (0.4)	0 (0)
Initial vitals,[c] *n* (%)					
Febrile temperature	58 (33.0)	37 (30.3)	25 (17.5)	70 (25.7)	15 (32.6)
Tachycardic	29 (16.5)	42 (34.4)	55 (38.5)	128 (47.1)	28 (60.9)
Tachypneic	36 (20.5)	31 (25.4)	92 (64.3)	176 (64.7)	25 (54.3)
Chest radiograph performed, *n* (%)	103 (58.5)	90 (73.8)	106 (74.1)	232 (85.3)	42 (91.3)
Any abnormality	78 (75.7)	66 (73.3)	84 (79.2)	196 (84.5)	33 (78.6)
Infiltrate or consolidation	36 (35.0)	38 (42.2)	52 (49.1)	147 (63.4)	26 (61.9)
Coinfections, *n* (%)					
Viral	57 (32.4)	44 (36.1)	6 (4.2)	6 (2.2)	0 (0)
RSV	42 (23.9)	26 (21.3)	4 (2.8)	3 (1.1)	0 (0)
Other[d]	22 (12.5)	23 (18.9)	3 (2.1)	3 (1.1)	0 (0)
Bacterial[e]	23 (13.1)	27 (22.1)	30 (21.0)	43 (15.8)	14 (30.4)
Fungal	0 (0)	1 (0.8)	1 (0.7)	5 (1.8)	1 (2.2)

SOB, shortness of breath.

[a] As documented in the history of present illness. Constitutional: objective fever (body temperature ≥38°C), poor appetite, dehydration, chills, fatigue, lethargy, arthralgia or myalgia, and subjective fever; lower respiratory: cough and SOB or dyspnea; upper respiratory: sore throat, rhinorrhea or nasal congestion, and conjunctivitis; neurologic: headache, altered mental status, and seizures; gastrointestinal: nausea or vomiting, abdominal pain, and diarrhea.

[b] List is not exhaustive but includes the top 3 diagnoses for each age category.

[c] Febrile temperature is defined as body temperature ≥38°C for all ages. Tachycardia and tachypnea abnormal ranges are age-normalized.

[d] Included adenovirus, human coronavirus 229E, human coronavirus HKU1, human coronavirus NL63, human coronavirus OC43, human metapneumovirus, influenza virus, parainfluenza virus, and rhinovirus or enterovirus.

[e] Out of 137 patients, 23 (16.8%) had a positive bacterial culture. Bacteria isolated included *Enterococcus sp*, *Escherichia coli*, *Facklamia hominis*, *Micrococcus sp*, *Propionibacterium acnes, Pseudomonas aeruginosa*, *Salmonella enterica*, *Staphylococcus aureus*, *Staphylococcus capitis*, *Staphylococcus epidermidis, Streptococcus* (group B), *Streptococcus intermedius,* and *Streptococcus pneumoniae.*

TABLE 3 Admission and Hospital Course Laboratory Values[a] of Patients Hospitalized for COVID-19, by Age Group, 5 Hospitals,[b] United States, July to August 2021, *N* = 759

	<1 Years (*n* = 176)	1–4 Years (*n* = 122)	5–11 Years (*n* = 143)	12–17 Years (*n* = 272)	18–20 Years (*n* = 46)
WBC, 10^9/L					
Admission, *n*	54	54	73	145	31
Median (IQR)	9.8 (6.3–13.0)	8.1 (5.5–13.9)	5.8 (4.3–8.5)	5.3 (3.9–7.5)	5.6 (4.5–8.1)
Peak, *n*	62	54	72	147	33
Median (IQR)	10.7 (6.6–13.4)	9.8 (6.0–13.9)	6.8 (4.9–9.8)	7.1 (4.8–10.5)	7.2 (4.8–11.3)
Nadir, *n*	62	54	73	147	33
Median (IQR)	8.1 (5.7–12.1)	6.9 (4.7–12.0)	4.9 (3.5–7.4)	4.8 (3.6–6.8)	4.6 (4.3–7.0)
Hemoglobin, g/dL					
Admission, *n*	36	31	39	96	27
Median (IQR)	11.0 (9.8–12.8)	11.4 (9.7–12.5)	12.4 (11.3–13.6)	13.2 (11.8–14.8)	13.3 (12.2–15.0)
Nadir, *n*	29	24	35	91	27
Median (IQR)	10.8 (8.8–11.9)	10.8 (9.4–12.3)	12.3 (10.9–13.9)	12.6 (10.3–14.1)	12.2 (10.9–13.8)
Platelets, cells/mm^3					
Admission, *n*	65	54	74	149	32
Median (IQR)	362 (263–451)	273 (183–355)	231 (146–306)	211 (157–275)	189 (161–260)
Peak, *n*	64	53	73	151	34
Median (IQR)	370 (280–470)	296 (234–367)	270 (191–359)	264 (197–350)	258 (191–331)
Nadir, *n*	63	53	74	151	34
Median (IQR)	333 (249–412)	239 (149–314)	208 (144–270)	195 (143–242)	177 (132–227)
D-dimer, mg FEU/L					
Admission, *n*	12	19	49	166	18
Median (IQR)	0.9 (0.7–1.3)	0.7 (0.5–1.3)	0.9 (0.5–1.7)	1.0 (0.6–1.6)	0.9 (0.6–1.6)
Peak, *n*	13	22	58	173	23
Median (IQR)	0.9 (0.9–1.1)	0.7 (0.5–1.5)	1.0 (0.5–2.0)	1.0 (0.6–1.9)	1.0 (0.6–2.8)
Creatinine, mg/dL					
Admission, *n*	73	68	99	209	32
Median (IQR)	0.3 (0.2–0.3)	0.3 (0.2–0.4)	0.5 (0.3–0.5)	0.7 (0.5–0.8)	0.7 (0.5–0.9)
Peak, *n*	75	67	99	213	36
Median (IQR)	0.3 (0.2–0.3)	0.3 (0.2–0.4)	0.5 (0.4–0.6)	0.7 (0.6–0.9)	0.8 (0.5–1.0)
AST, U/L					
Peak, *n*	66	51	90	187	34
Median (IQR)	47 (31–70)	57 (41–89)	62 (34–92)	59 (35–107)	77 (43–121)
ALT, U/L					
Peak, *n*	66	51	90	187	34
Median (IQR)	23 (17–34)	27 (17–40)	31 (16–71)	40 (22–100)	57 (29–141)
CRP, mg/L					
Admission, *n*	40	39	69	162	23
Median (IQR)	11.0 (5.0–41.0)	26.0 (6.0–88.0)	15.0 (7.0–45.0)	36.5 (14.0–72.0)	54.0 (24.0–70.0)
Peak, *n*	43	39	74	172	28
Median (IQR)	14.0 (5.0–45.0)	30.0 (8.0–88.0)	20.5 (9.0–56.0)	42.5 (14.0–82.5)	61.0 (39.5–102)
Procalcitonin, ng/mL					
Admission, *n*	48	33	55	131	17
Median (IQR)	0.2 (0.1–0.4)	1.1 (0.2–7.1)	0.1 (0.1–0.4)	0.2 (0.1–0.4)	0.1 (0.1–0.2)
Peak, *n*	49	32	62	141	19
Median (IQR)	0.2 (0.1–0.3)	1.1 (0.2–6.5)	0.1 (0.1–0.4)	0.2 (0.1–0.4)	0.1 (0.1–0.2)

TABLE 3 Continued

	<1 Years (*n* = 176)	1–4 Years (*n* = 122)	5–11 Years (*n* = 143)	12–17 Years (*n* = 272)	18–20 Years (*n* = 46)
Ferritin, ng/mL					
Admission, *n*	13	22	45	122	13
Median (IQR)	140 (75–253)	94 (62–201)	156 (92–300)	243 (126–447)	305 (205–580)
Peak, *n*	16	25	52	132	17
Median (IQR)	175 (83–486)	99 (67–207)	192 (101, 377)	243 (128–559)	305 (109–629)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; WBC, white blood cells.
[a] Normal age- and sex-specific values were referenced from the Harriet Lane Handbook.[25] Laboratory measurements > or < than a value of detection were designated as equal to those values.
[b] Laboratory data were not available from Children's National Hospital, Washington, DC.

Factors Associated With Severe Illness among Patients Hospitalized for COVID-19

Factors associated with severe illness in infants included RSV coinfection (PR = 3.64; 95% CI, 2.50–5.30), bacterial coinfection (PR = 1.88; 95% CI, 1.21–2.94), and presence of ≥2 underlying medical conditions versus none (PR = 1.82; 95% CI, 1.04–3.18). Preterm birth was not significantly associated with severe illness (PR = 1.45; 95% CI, 0.93–2.25) (Fig 1, Panel A).

Among patients aged 1 to 4 years, severe illness was associated with RSV coinfection (PR = 1.96; 95% CI, 1.31–2.93) (Fig 1, Panel B). Among 298 patients aged <5 years hospitalized for COVID-19, respiratory support was required among 71.3% of patients who had a viral coinfection and 38.1% of patients who did not have a viral coinfection (Supplemental Table 6).

Among patients aged 5 to 11 years, severe illness was associated with feeding tube dependence (PR = 2.77; 95% CI, 1.54–4.96), bacterial coinfection (PR = 2.34; 95% CI, 1.36–4.02), gastrointestinal condition (PR = 2.32; 95% CI, 1.26–4.27), and obesity (PR = 2.20; 95% CI, 1.25 –3.87) (Fig 1, Panel C).

Among patients aged 12 to 17 years, severe illness was associated with presence of 1 (PR = 2.95; 95% CI, 1.29–6.75) or ≥2 (PR = 3.19; 95% CI, 1.41–7.20) underlying medical conditions versus none, obesity (PR = 2.48; 95% CI, 1.74–3.55), feeding tube dependence (PR = 1.55; 95% CI, 1.08–2.23), and neurologic or neurodevelopmental disorder (PR = 1.40; 95% CI, 1.05–1.88) (Fig 1, Panel D).

Subgroup Analyses

Detailed findings are provided on patients hospitalized for COVID-19 as the primary reason (Supplemental Table 7) or as a contributing reason (Supplemental Table 8), or hospitalized with an incidental positive SARS-CoV-2 test (Supplemental Table 9).

Of 58 neonates hospitalized for COVID-19, 5 (9%) had a RSV coinfection, 6 (10%) were born prematurely, 8 (14%) required ICU admission, 7 (12%) had severe illness, and 1 (2%) died. The most common discharge diagnoses for neonates were "COVID-19" (*n* = 53, 91%), "neonatal fever" (*n* = 24, 41%), and "bronchiolitis" (*n* = 4, 7%). Of 118 nonneonate infants hospitalized for COVID-19, 37 (31%) had RSV, 31 (26%) were born prematurely, 26 (22%) required ICU admission, 53 (45%) had severe illness, and 1 (1%) died (Supplemental Table 10).

Among 260 patients aged 2 to 20 years with obesity hospitalized for COVID-19, 41.5% required ICU admission, 10.8% required IMV, and 1.5% died. Patients with obesity were more likely to present with tachypnea, tachycardia, and infiltrate or consolidation on chest radiograph ($P <$ .001 for all), and they had higher admission C-reactive protein and ferritin ($P <$ .001 for both) compared to patients without obesity (Supplemental Table 11).

DISCUSSION

In this multicenter retrospective study of pediatric patients hospitalized for COVID-19 during the Δ surge, we provide robust clinical details and age-stratified factors associated with severe illness related to COVID-19. Over one-third of patients in this cohort had severe illness requiring ventilatory support (HFNC, BiPAP, CPAP, or IMV). RSV coinfection in children aged <5 years and obesity in those aged 5 to 17 years were significantly associated with severe illness. Additional age-specific factors included neurologic or neurodevelopmental disorders, gastrointestinal conditions, feeding tube dependence, and bacterial coinfection. Overall, patients incidentally positive for SARS-CoV-2 comprised only one-fifth of admissions. Of the 394 (41.6%) vaccine-eligible patients, only 4 (1.0%) were fully vaccinated. These data illustrate the extent of clinical illness in a primarily unvaccinated pediatric population during the initial Δ variant surge in the United States.

Our findings approximate those from previous studies. Among patients aged <18 years hospitalized for COVID-19 in our cohort, 29.5% required ICU admission, 7.9% received IMV, and 1.5% died. These figures slightly exceed those in a pre-Δ study of patients aged <18 years with COVID-19–associated hospitalization in 14 states from March 2020 to May 2021, in which 24.8% were admitted to the ICU, 5.3% received IMV, and 0.5% died.[14] In a Δ-era study from the same surveillance network from July 1 to December 18, 2021, 27.8% were admitted to the ICU, 6.3% received IMV, and 0.6% died.[21] Discrepancies may be because of differences in the study populations, such as prevalence of underlying medical conditions, and because patients incidentally positive for SARS-CoV-2 (ie, admitted with a positive SARS-CoV-2 result

TABLE 4 Hospital Course and Outcomes of Patients Hospitalized for COVID-19, by Age Group, 6 Hospitals, United States, July to August 2021, *N* = 759

	<1 Years (*n* = 176)	1–4 Years (*n* = 122)	5–11 Years (*n* = 143)	12–17 Years (*n* = 272)	18–20 Years (*n* = 46)
Hospital duration, days, median (IQR)	2 (1–4)	3 (2–5)	2 (1–5)	4 (2–7)	6 (2–11)
IMV duration, days, median (IQR)	6 (4.5–12.5)	6 (1–16)	5.5 (1–11)	9.5 (5–23)	17 (7–29)
ICU requirement					
Any admission, *n* (%)	34 (19.3)	31 (25.4)	37 (25.9)	108 (39.7)	17 (37.0)
Duration, d, median (IQR)	3 (1–7)	3 (2–5)	3 (1–7)	4 (2–8)	6 (4–11)
Treatments, *n* (%)					
Remdesivir	22 (12.5)	30 (24.6)	36 (25.2)	139 (51.1)	29 (63.0)
Baricitinib	0 (0)	0 (0)	1 (0.7)	8 (2.9)	1 (2.2)
Tocilizumab	2 (1.1)	1 (0.8)	4 (2.8)	21 (7.7)	4 (8.7)
Other monoclonal antibody	0 (0)	0 (0)	1 (0.7)	11 (4.0)	5 (10.9)
Glucocorticoid	41 (23.3)	64 (52.5)	70 (49.0)	186 (68.4)	33 (71.7)
Dexamethasone	36 (20.5)	54 (44.3)	50 (35.0)	142 (52.2)	30 (65.2)
Antibiotic	97 (55.1)	69 (56.6)	91 (63.6)	154 (56.6)	32 (69.6)
Anticoagulation	9 (5.1)	11 (9.0)	27 (18.9)	161 (59.2)	30 (65.2)
Vasoactive support	6 (3.4)	2 (1.6)	5 (3.5)	21 (7.7)	5 (10.9)
Highest respiratory support, *n* (%)					
Nasal cannula	22 (12.5)	14 (11.5)	24 (16.8)	51 (18.8)	15 (32.6)
HFNC	43 (24.4)	32 (26.2)	14 (9.8)	53 (19.5)	7 (15.2)
BiPAP or CPAP	5 (2.8)	10 (8.2)	11 (7.7)	43 (15.8)	7 (15.2)
IMV	12 (6.8)	7 (5.7)	11 (7.7)	26 (9.6)	6 (13.0)
ECMO[a]	1 (0.6)	1 (0.8)	1 (0.7)	5 (1.8)	2 (4.3)
Complications,[b] *n* (%)					
Viral pneumonia	31 (17.6)	42 (34.4)	48 (33.6)	149 (54.8)	28 (60.9)
Bacterial pneumonia	11 (6.3)	10 (8.2)	15 (10.5)	24 (8.8)	7 (15.2)
Bronchiolitis	38 (21.6)	18 (14.8)	0 (0)	0 (0)	0 (0)
Pleural effusion	2 (1.1)	4 (3.3)	5 (3.5)	26 (9.6)	4 (8.7)
Discharge diagnosis,[b] *n* (%)					
COVID-19	159 (90.3)	108 (88.5)	121 (84.6)	244 (89.7)	42 (91.3)
Pneumonia	16 (9.1)	36 (29.5)	44 (30.8)	112 (41.2)	13 (28.3)
COVID-19 pneumonia	13 (7.4)	35 (28.7)	38 (26.6)	108 (39.7)	13 (28.3)
Acute respiratory failure	33 (18.8)	29 (23.8)	23 (16.1)	71 (26.1)	15 (32.6)
Bronchiolitis	40 (22.7)	18 (14.8)	0 (0)	0 (0)	0 (0)
RSV	39 (22.2)	20 (16.4)	1 (0.7)	2 (0.7)	0 (0)
Outcome, *n* (%)					
Discharged on oxygen[c]	4 (2.3)	8 (6.6)	7 (4.9)	12 (4.4)	2 (4.3)
New mobility restriction	0 (0)	0 (0)	3 (2.1)	6 (2.2)	2 (4.3)
Died	2 (1.1)	0 (0)	1 (0.7)	8 (2.9)	0 (0)

ECMO, extracorporeal membrane oxygenation.
[a] Patients receiving IMV include those receiving ECMO.
[b] List is not exhaustive but includes the top 3 responses in each age category.
[c] Includes 9 patients noted to have chronic respiratory failure before hospitalization.

but not for COVID-19) were included in the previous studies. Presenting signs and symptoms in our cohort were similar to those in pre-Δ studies, with a predominance of fever, cough, dyspnea, and nausea or vomiting.[10,29]

Consistent with previous studies of hospitalized patients,[17,30] we found elevations in inflammatory markers. Previous studies have found that inflammatory markers appear to be associated with intensive care admission[15,19] and organ dysfunction due to COVID-19.[31] Remdesivir and glucocorticoids were frequently used in our cohort, which is consistent with recommendations from the National Institutes of Health and treatment

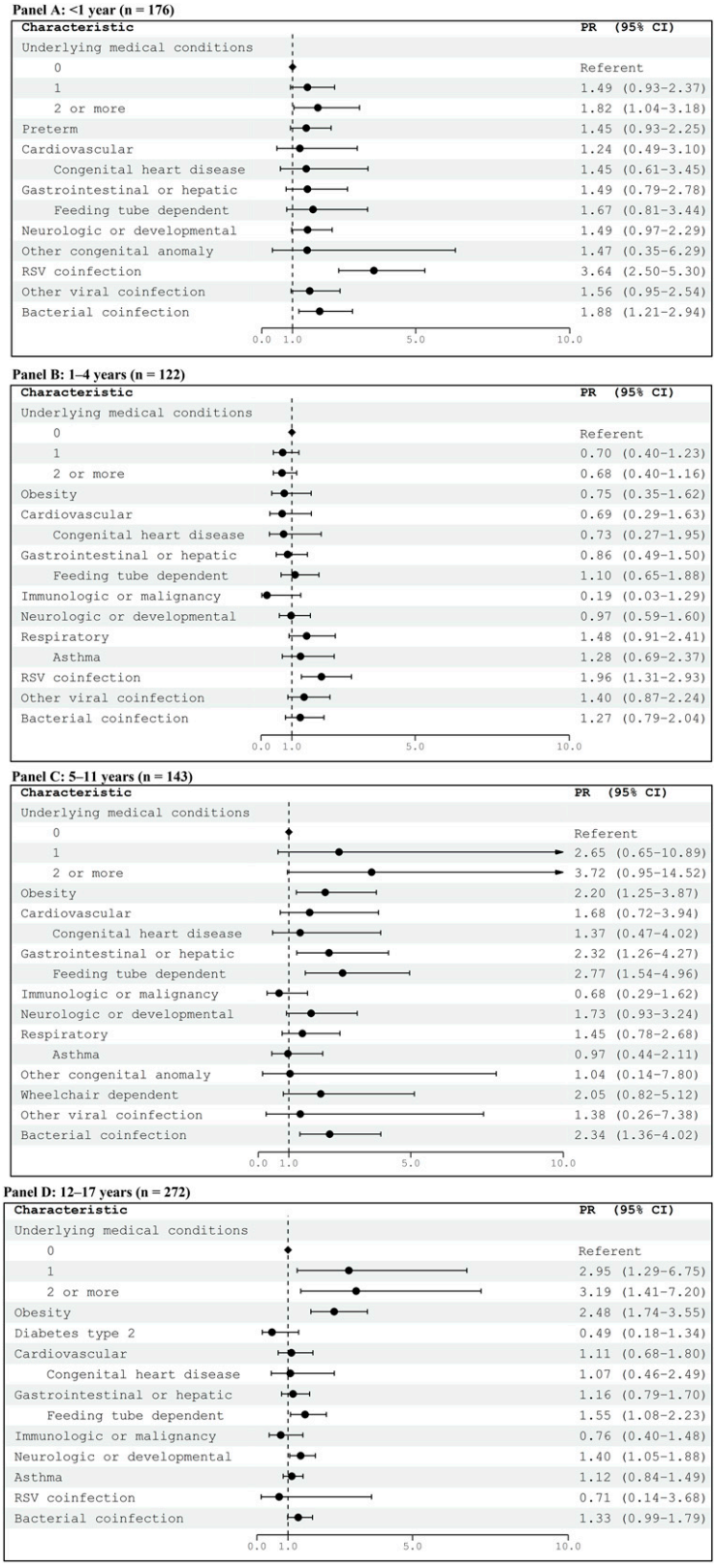

FIGURE 1 Forest plots of prevalence ratios of factors associated with severe disease, defined as requiring ventilatory support. Unless otherwise specified, the referent group is absence of the characteristic of interest.

authorizations during the study period by the United States Food and Drug Administration, and may indicate illness severity in this cohort.[32,33]

Few neonates hospitalized for COVID-19 in our cohort experienced severe illness, compared to nearly one-half of nonneonate infants and two-fifths of patients aged 1 to 4 years. This may be because of provider practice of hospitalizing neonates with relatively mild illness. It may also reflect the high prevalence of viral and bacterial coinfections among nonneonate infants and young children. Importantly, although these coinfections were associated with severe illness in our cohort, the causal pathologic relationship cannot be determined given the study design. Longitudinal studies are needed to understand the morbidity implications of concomitant COVID-19 and other illnesses. In light of our findings, this is especially important for coinfection with RSV and SARS-CoV-2 in young children.

Obesity had a strong association with severe illness in our cohort. Patients aged 5 to 11 and 12 to 17 years with obesity were over twice as likely to have severe illness compared to their peers who did not have obesity. This mirrors pre-Δ studies, which reported an association between obesity and requirements for IMV and critical care,[17,34] and between obesity and hypoxia.[35] Given this consistent association between obesity and COVID-19 severity, and the rising prevalence of childhood obesity in the United States,[36] pediatricians should follow national recommendations for obesity screening and referral[37] and promote COVID-19 vaccination for children and adolescents with obesity.

Strengths of this analysis are that we distinguished patients hospitalized with an incidentally positive SARS-CoV-2 test from those hospitalized for COVID-19, and we provided robust, age-stratified clinical data and regression analyses, which may assist health care providers with management decisions. The limitations of the study should also be considered. First, completeness and accuracy of data capture could not be guaranteed. We minimized abstraction errors and

discrepancies through universal quality checks and random audits. Missing data may have contributed to underreporting of certain variables, resulting in sample sizes that were insufficient for age-specific prevalence ratio calculations. This limitation is especially relevant for vaccination, which may not be fully captured in inpatient records.[38] Second, our severe illness definition differs from previous studies, affecting comparisons.[2,14] We excluded ICU admission from our severity definition to control for differences in critical care requirement thresholds and to focus on severe respiratory illness as a more specific outcome measure. For some patients with respiratory coinfections, such as RSV, this definition may not exclusively reflect illness due to COVID-19. Third, because illness severity could influence coinfection testing and provider diagnoses, prevalence ratios for coinfections may be overestimated. However, since viral coinfection testing and bacterial cultures were conducted on patients with and without severe illness, confounding by indication should not dramatically alter findings. Fourth, distinguishing between an incidental positive test and COVID-19 as the reason for hospitalization was based on clinical judgement, which could introduce misclassification bias. Finally, given Omicron variant emergence,[39] the limited geographic range of our cohort, the fact that these data are derived from children's hospitals, and increased pediatric COVID-19 vaccination eligibility and coverage since our study period closed, generalization of these findings may be limited.

CONCLUSION

During the July to August 2021 Δ variant surge, over one-third of patients aged <21 years hospitalized for COVID-19 in our cohort had severe illness. RSV was associated with increased prevalence of severe illness for patients aged <5 years. In those aged 5 to 17 years, obesity and the presence of ≥2 underlying medical conditions were associated with severe illness. The majority of vaccine-eligible patients were unvaccinated. These findings may help health care providers identify patients more susceptible to severe illness and determine appropriate management, support public health efforts to increase COVID-19 vaccination of persons aged ≥5 years, and inform discussions around vaccination for children aged <5 years. The findings also reveal a need for research on the severity and pathogenicity of respiratory viral coinfections with COVID-19. Finally, this analysis may offer a baseline against which the pathogenicity of Omicron and future variants could be compared.

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