ORIGINAL ARTICLE

Severity of Illness Caused by Severe Acute Respiratory Syndrome Coronavirus 2 Variants of Concern in Children: A Single-Center Retrospective Cohort Study

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Background. Recent COVID-19 surges are attributed to emergence of more transmissible SARS-CoV-2 variants of concern (VOCs). The relative severity of VOCs in children is unknown.

Methods. We performed a single-center retrospective cohort study of children ≤18 years old diagnosed with COVID-19 from October 2020–February 2022 and whose SARS-CoV-2 isolate underwent Illumina sequencing. We measured the frequency of five markers of COVID-19 severity. Logistic regression models were fitted to estimate the odds of each severity marker with each VOC.

Results. Among 714 children, 471 (66.0%) were infected with a VOC: 96 (13.4%) alpha, 38 (5.3%) gamma, 119 (16.7%) delta, and 215 (30.1%) omicron. High-risk medical conditions and increasing age were independently associated with COVID-19 severity. After adjusting for age, race, ethnicity, high-risk medical conditions, and COVID-19 community incidence, neither alpha, delta, nor omicron was associated with severe COVID-19. Gamma was independently associated with hospitalization (OR 6.7, 95% CI 2.0–22.1); pharmacologic treatment (OR 5.7, 95% CI 1.2–26.8); respiratory support (OR 11.9, 95% CI 2.7–62.4); and severe disease per the WHO Clinical Progression Scale (OR 11.7, 95% CI 2.1–90.5). Upon subgroup analyses, omicron was independently associated with ICU admission and severe disease per the WHO Clinical Progression Scale in children without SARS-CoV-2 immunization or prior COVID-19 infection.

Conclusions. Compared to non-VOC COVID-19, the gamma VOC was independently associated with increased COVID-19 severity, as was omicron in children without SARS-CoV-2 immunization or prior COVID-19 infection. SARS-CoV-2 vaccination and prior COVID-19 prevented severe outcomes during the omicron surge.

Keywords. children; COVID-19; outcomes; SARS-CoV-2; severity.

Coronavirus disease 2019 (COVID-19) is generally associated with less severe outcomes in children than in adults [1]. However, COVID-19 morbidity and mortality in children are nontrivial and may escalate because the authorization of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine and vaccine uptake for younger pediatric age groups occurred much later than in adolescents and adults; return to in-person learning in schools and daycare, which may promote respiratory viral transmission; and the emergence of variants of concern (VOCs) that may be associated with increased transmissibility, immune evasion, and/or worse clinical outcomes [2, 3]. Very little is known about VOC-specific clinical outcomes in children [4].

SARS-CoV-2 genomic surveillance data reported by the Centers for Disease Control and Prevention (CDC) [5] indicated that the alpha and gamma VOCs emerged and expanded in the midwestern United States in early 2021. The delta VOC emerged in the summer of 2021 and was predominant until the rapid emergence and expansion of the omicron VOC in December 2021. Concomitant with surges of the more transmissible delta and omicron VOCs, increasing pediatric COVID-19 incidence and hospitalizations were observed [6–10]. However, it is unclear if increases in hospitalizations were solely related to increased COVID-19 incidence or if certain VOCs are associated with more severe disease. The objective of this single-center retrospective cohort study was to compare COVID-19 severity in children with prevalent VOCs compared to those infected with other SARS-CoV-2 lineages. These data provide a framework for comparing outcomes among newly emerging variants. Improved understanding of the association between VOCs and clinical outcomes is essential to guide public health response and prepare children's hospitals for expected healthcare resource needs based on observed SARS-CoV-2 molecular epidemiology.

METHODS

Setting and Participants

This retrospective cohort study was conducted at the Ann & Robert H. Lurie Children's Hospital of Chicago, a tertiary care academic free-standing urban children's hospital associated with multiple urban and suburban ambulatory care facilities. The Lurie Children's Institutional Review Board approved this study (IRB 2020-3792). Using residual diagnostic samples from pediatric inpatients and outpatients who tested positive by SARS-CoV-2 polymerase chain reaction (PCR) in our clinical microbiology laboratory, we perform surveillance for SARS-CoV-2 variants using whole-genome sequencing (WGS) with the Center for Pathogen Genomics and Microbial Evolution at Northwestern University. A small subset of samples was also sequenced at the Regional Innovative Public Health Laboratory (RIPHL) at the Chicago Department of Public Health and Rush University Medical Center through their COVID-19 surveillance program. Samples from SARS-CoV-2 PCR-positive patients were saved by the clinical microbiology laboratory and considered eligible for WGS as part of ongoing WGS surveillance if they had enough residual viral transport media remaining after clinical COVID-19 testing and a sufficiently low cycle threshold value for the SARS-CoV-2 N open reading frame by quantitative PCR (i.e., sufficiently high viral load, defined as cycle threshold < 30). Each week, the clinical microbiology laboratory randomly selected ~10–50 eligible samples for WGS depending on positive test volume each week; the microbiology laboratory was blinded to patient outcome data. For the present study, all patients ≤18 years old at our children's hospital with sequenced SARS-CoV-2 isolates between October 15, 2020, and February 20, 2022, were included. If patients had more than one positive sample, only the clinical encounter associated with the first sample was included.

SARS-CoV-2 Whole Genome Sequencing

Laboratory methods for viral RNA extraction, cDNA synthesis, viral genome amplification, sequencing library preparation, Illumina sequencing, genome assembly, and bioinformatics analyses are described in Supplemental Material. Consensus genome sequences were deposited in the GISAID public database (Supplementary Table 1).

Study Data and Definitions

A manual chart review was performed for all subjects. The following demographic and clinical information were collected: age, sex, race, ethnicity, presence of COVID-19 symptoms, respiratory viral co-infections, SARS-CoV-2 vaccine status, receipt of SARS-CoV-2 monoclonal antibodies for mild early infection in high-risk patients, and comorbidities (Supplementary Table 2). Specific definitions for these data are described in the Supplemental Materials. Charts were reviewed for several markers of COVID-19 severity, including hospitalization for COVID-19; pharmacologic treatment for COVID-19 (i.e., including remdesivir, corticosteroids, or tocilizumab, but excluding monoclonal antibodies because these are given to high-risk outpatients early in infection to prevent subsequent morbidity); respiratory support; intensive care unit (ICU) admission for COVID-19; severe disease as classified by the COVID-19 World Health Organization (WHO) Clinical Progression Scale [11] (score ≥6; Supplementary Table 3); and death caused by COVID-19. Charts were reviewed by a study team infectious diseases clinician to determine if hospitalization was for observation and/or management of COVID-19 symptoms; patients who were incidentally found to be SARS-CoV-2-positive during hospitalization were not classified as experiencing the outcome of hospitalization for COVID-19. Based on the lineage of SARS-CoV-2 identified by WGS, children were grouped based on whether their COVID-19 infection was caused by a VOC (i.e., alpha, beta, gamma, delta, or omicron), as well as the specific VOC lineage, using CDC classification as of February 20th, 2021 [12]. Of note, after completion of this study, the alpha, beta, gamma, and delta VOCs were reclassified as "variants being monitored" by the CDC because US incidence subsequently declined in a significant and sustained manner.

Statistical Analyses

Demographic, clinical, and outcome categorical variables for the entire cohort, as well as for patient subgroups infected with either a non-VOC, alpha, gamma, delta, or omicron were summarized and reported as frequencies and percentages. Frequencies of these variables among subgroups were compared using Pearson's chi-squared test, and continuous variables were compared using Kruskal–Wallis test. Next, to assess the clinical severity associated with each VOC, a series of logistic regression models were fitted to estimate odds of each severity marker of interest with each VOC in comparison to non-VOCs, adjusting for COVID-19 incidence and relevant demographic and clinical co-variates associated with COVID-19 outcomes, including Black race [13], Hispanic ethnicity [13], age [1], and high-risk medical conditions [14]. We also adjusted for trends in pediatric COVID-19 community incidence using publicly available data from the Chicago Department of Public Health. Odds ratios (OR) and 95% confidence intervals (CI) were estimated and tested for statistical significance for each VOC included in the model compared to the non-VOC group. Two-sided P values < 0.05 were considered statistically significant. Statistical analyses were performed using Stata/IC 16.0 (StataCorp, College Station, TX) and R version 4.1.0.

RESULTS

During the 16-month study period (October 15th, 2020–February 20th, 2022), 4337 pediatric patients younger than 18 years old were diagnosed with COVID-19 by SARS-CoV-2

through our medical center laboratory; 1729 were diagnosed October 15th, 2020–December 11th, 2021 (the pre-omicron study period), and 2498 were diagnosed December 12th, 2021–February 20th, 2022 (the omicron study period). SARS-CoV-2 PCR-positive samples from 714 patients with COVID-19 (16.5% of our patients diagnosed with COVID-19) underwent whole genome sequencing; 499/1729 (28.9%) and 215/2498 (8.9%) were sequenced during the pre-omicron and omicron study periods, respectively. Among these, 471 (66.0%) were infected with a VOC: 96 (13.4%) alpha, 3 (0.4%) beta, 38 (5.3%) gamma, 119 (16.7%) delta, and 215 (30.1%) omicron. The proportion, frequency, and chronology of VOC emergence are illustrated in Figure 1. Because of the very low prevalence of beta infections, these three patients were excluded from further analyses. Clinical, demographic, and outcome data for the entire cohort, and for subgroups of patients infected with a non-VOC, or with the alpha, gamma, delta, or omicron VOC, are listed in Table 1. The median (IQR) age of patients included in this study was 5 (1,11) years (range <1 month–18 years old) and significantly younger during the delta and omicron periods. Statistically significant differences between these subgroups were also observed among race, ethnicity, and medical conditions associated with a high risk of COVID-19 complications. Greater than 90% of patients had COVID-19 symptoms, which did not differ among subgroups. Respiratory viral co-infections were rare, occurring in 3 (0.4%) patients (rhinovirus/enterovirus, influenza A, and coronavirus 229E).

In bivariate analyses (Table 1), statistically significant differences between subgroups were observed for three markers of severity—hospitalization for COVID-19, respiratory support, and severe disease as classified by the WHO Clinical Progression Scale (score ≥6; Supplementary Table 3). In each case, the frequency of these outcomes was highest in those children infected with gamma. There was one COVID-19-associated death, and this was associated with a non-VOC infection.

To determine the association between each VOC (in comparison to non-VOC infections) and clinical severity, we fitted a series of logistic regression models for five markers of disease severity, adjusting for temporal changes in COVID-19 incidence and relevant clinical and demographic characteristics (Table 2). For COVID-19 pharmacologic treatment, respiratory support, ICU admission, and severe disease as classified by the WHO Clinical Progression Scale, increasing age was associated with increased severity, with odds increasing by ~20% for each year increase. Having a high-risk medical condition was independently associated with hospitalization (OR 6.1, 95% CI 2.6–15.9, P < .001); odds of the other severity markers could not be calculated because zero children without a high-risk condition experienced the severity marker. Compared to non-VOCs, infection with either alpha, delta, or omicron was not associated with any markers of COVID-19 severity. However, infection with gamma was independently associated with hospitalization

(OR 6.7, 95% CI 2.0–22.1, P = .002), COVID-19 pharmacologic treatment (OR 5.7, 95% CI 1.2–26.8; P = .02), respiratory support (OR 11.9, 95% CI 2.7–62.4, P = .001), and severe disease as classified by the WHO Clinical Progression Scale (OR 11.7, 95% CI 2.1–90.5, P = .007). The relative adjusted probabilities of the COVID-19 severity markers among VOC types are illustrated in Figure 2.

To account for the possible protective effect from severe outcomes related to immunologic protection against COVID-19, we performed a sensitivity analysis whereby we repeated the multivariable analyses described above but excluded 37 children who were either fully vaccinated against SARS-CoV-2 (n = 20), received a monoclonal antibody for early mild infection (n = 5), and/or reported prior COVID-19 (n = 16); three fully vaccinated children and one unvaccinated child who received a monoclonal antibody had a prior COVID-19 infection (Supplementary Table 4). There were no significant changes in the association between VOCs and clinical outcomes following this sensitivity analysis for alpha, gamma, and delta. However, omicron was independently associated with ICU admission (OR 7.4, 95% CI 1.1–63.3; P = .04) and severe disease as classified by the WHO Clinical Progression Scale (OR 15.9, 95% CI 1.8–354; P = .03), and there was a trend toward an association with COVID-19 pharmacologic treatment (OR 5.7, 95% CI 0.97–35.7; P = .05). To assess the individual impact of SARS-CoV-2 vaccination or prior COVID-19 infection, these models were repeated; first we excluded 20 children who were fully vaccinated (Supplementary Table 5), and then we excluded 16 children with prior COVID-19 infection (Supplementary Table 6). In these models, omicron remained independently associated with severe disease as classified by the WHO Clinical Progression Scale in both models (Supplementary Tables 5 and 6), and independently associated with ICU admission in the model excluding fully vaccinated children (Supplementary Table 5).

DISCUSSION

In this single-center retrospective cohort study of children with COVID-19 in the Chicago area, severe COVID-19 outcomes were relatively rare, confirming previous findings of COVID-19 in children [1]. In our cohort of children with COVID-19 irrespective of prior SARS-CoV-2 vaccination or prior COVID-19 infection, SARS-CoV-2 infection with the gamma VOC was independently associated with increased COVID-19 severity. This is evidenced by its association with hospitalization for COVID-19, receipt of COVID-19 pharmacologic treatment, respiratory support, and WHO Clinical Progression Scale score ≥6. These data may suggest that recent increases in pediatric COVID-19 hospitalizations during the delta [7] and omicron [10, 15] surges are primarily related to profoundly increased COVID-19 incidence rather than increased delta or omicron virulence in children.
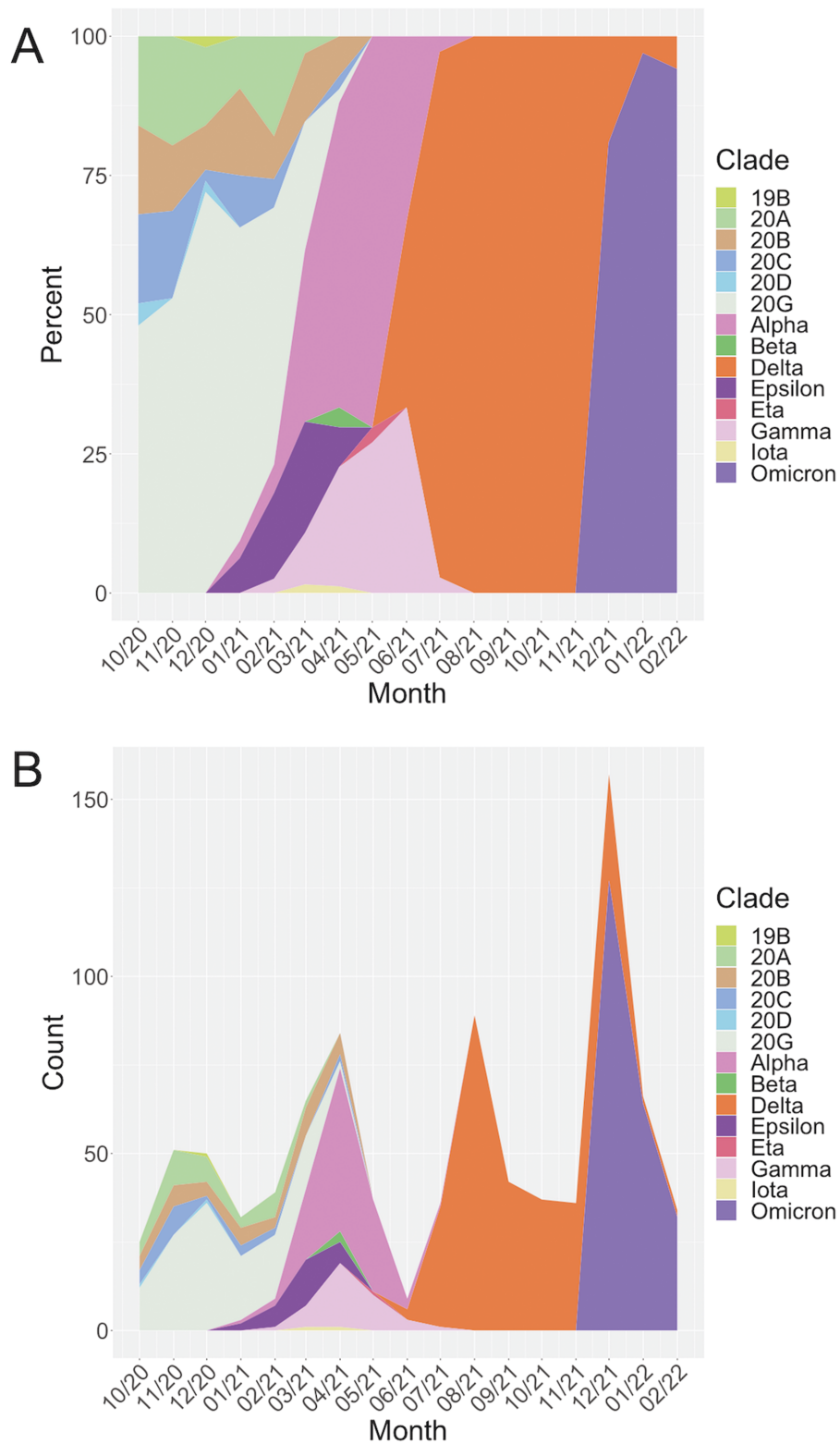
Figure 1. SARS-CoV-2 molecular epidemiology. proportions (A) and frequencies (B) of lineages of SARS-CoV-2 identified in pediatric patients during 16-month study period (October 2020–February 2022). Lineages are listed in the legend in chronological order of their emergence/classification.

However, when excluding children who likely had protection from severe COVID-19 afforded by SARS-CoV-2 vaccination, monoclonal antibodies for an early mild infection, and/ or reported prior COVID-19, omicron was independently associated with ICU admission and WHO Clinical Progression Scale score ≥6. An independent association between omicron

Table 1. Demographics, Clinical Characteristics, and Markers of COVID-19 Severity of 714 Children with COVID-19 Stratified by SARS-CoV-2 Variant

	Entire Cohort, n (%) (n = 714)	Non-VOC, n (%) (n = 243)	Alpha, n (%) (n = 96)	Gamma, n (%) (n = 38)	Delta, n (%) (n = 119)	Omicron, n (%) (n = 215)	P value
Age (years; median [IQR])	5 (1, 11)	7 (1, 12)	9 (2, 14)	7 (1, 14)	4 (1, 11)	3 (1, 7)	**.0001***
12–18	169 (23.6%)	75 (30.8%)	38 (39.5%)	13 (34.2%)	21 (17.6%)	22 (10.2%)	
6–11	162 (22.6%)	54 (22.2%)	21 (21.8%)	9 (23.6%)	33 (27.7%)	42 (19.5%)	
1–5	249 (34.8%)	71 (29.2%)	22 (22.9%)	8 (21.0%)	43 (36.1%)	105 (48.8%)	
0–<1	134 (18.7%)	43 (17.6%)	15 (15.6%)	8 (21.0%)	22 (18.4%)	46 (21.3%)	
Sex (male)	365 (51.1%)	124 (51.0%)	47 (48.9%)	21 (55.2%)	53 (44.5%)	119 (55.3%)	.4
Race (Black)	111 (15.5%)	22 (9.0%)	24 (25%)	8 (21.0%)	25 (21.0%)	32 (14.8%)	**.001***
Ethnicity (Hispanic)	283 (39.6%)	117 (48.1%)	37 (38.5%)	16 (42.1%)	42 (35.2%)	71 (33.0%)	**.015***
High-risk condition for COVID-19 complications	154 (21.5%)	37 (15.2%)	25 (26.0%)	9 (23.6%)	21 (17.6%)	62 (28.8%)	**.005***
Respiratory viral co-infection[ab]	3 (0.4%)[ab]	0 (0%)	0 (0%)	0 (0%)	1 (0.8%)[a]	2 (0.9%)[b]	.46
Prior COVID-19 infection	16 (2.2%)	2 (0.8%)	0 (0%)	0 (0%)	1 (0.8%)	13 (6.1%)	**.002***
Fully vaccinated against SARS-CoV-2	20 (2.8%)	0 (0%)	0 (0%)	1 (2.6%)	1 (0.8%)	18 (8.4%)	**<.001***
Outpatient treatment with monoclonal antibody[cd]	5 (0.7%)[cd]	0 (0%)	3 (3.1%)[c]	0 (0%)	0 (0%)	2 (0.9%)[d]	**<.001***
Symptoms of COVID-19	653 (91.4%)	223 (91.7%)	88 (91.6%)	34 (89.4%)	107 (89.9%)	198 (92.0%)	.92
Hospitalized for COVID-19	36 (5.0%)	8 (3.2%)	7 (7.2%)	6 (15.7%)	8 (6.7%)	7 (3.3%)	**.014***
COVID-19 pharmacologic treatment	17 (2.3%)	4 (1.6%)	2 (2.0%)	3 (7.8%)	4 (3.3%)	4 (1.9%)	.2
remdesivir	16 (2.2%)	4 (1.6%)	1 (1.0%)	3 (7.8%)	4 (3.3%)	4 (1.9%)	
dexamethasone	13 (1.8%)	3 (1.2%)	1 (1.0%)	3 (7.8%)	2 (1.6%)	4 (1.9%)	
tocilizumab	1 (0.1%)	1 (0.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Respiratory support	15 (2.1%)	3 (1.2%)	0 (0%)	4 (10.5%)	3 (2.5%)	5 (2.3%)	**.014***
Nasal cannula	4 (0.5%)	1 (0.4%)	0 (0%)	1 (2.6%)	1 (0.8%)	1 (0.5%)	
High-flow nasal cannula	1 (0.1%)	0 (0%)	0 (0%)	1 (2.6%)	0 (0%)	0 (0%)	
Continuous positive airway pressure	1 (0.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)	
Bilevel positive airway pressure	5 (0.7%)	1 (0.4%)	0 (0%)	2 (5.2%)	1 (0.8%)	1 (0.5%)	
Mechanical ventilation	4 (0.5%)	1 (0.4%)	0 (0%)	0 (0%)	1 (0.8%)	2 (0.9%)	
Intensive care unit admission	14 (1.9%)	3 (1.2%)	1 (1.0%)	2 (5.2%)	3 (2.5%)	5 (2.3%)	.45
WHO Clinical Progression Scale ≥6	11 (1.5%)	2 (0.8%)	0 (0%)	3 (7.8%)	2 (1.6%)	4 (1.9%)	**.041***
0-2 (mild)	655 (91.7%)	230 (94.6%)	85 (88.5%)	32 (84.2%)	111 (93.2%)	194 (90.2%)	
3-5 (moderate)	48 (6.7%)	11 (4.5%)	11 (11.4%)	3 (7.8%)	6 (5.0%)	17 (7.9%)	
6-9 (severe)	10 (1.4%)	1 (0.4%)	0 (0%)	3 (7.8%)	2 (1.6%)	4 (1.9%)	
10 (morbid)	1 (0.1%)	1 (0.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
COVID-19-related death	1 (0.1%)	1 (0.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1

IQR, interquartile range; y, years; m, month.

*Bolded values indicate statistical significance (P < .05).

[ab]Co-infection with rhinovirus/enterovirus

[a], influenza A

[b], and coronavirus 229E

[b];

[cd]monoclonal antibody treatments included casirivimab-imdevimab

[c]and bamlanivimab/eteseivmab

[d]

and WHO Clinical Progression Scale score ≥6 persisted when excluding vaccinated and previously infected children separately. Thus, our findings suggest that immunity against SARS-CoV-2, which may now be as high as 75% of US children based on national seroprevalence of anti-nucleocapsid antibodies (i.e., seroprevalence from prior COVID-19 infection, excluding vaccination) [16], prevented many severe outcomes during the omicron surge. National pediatric seroprevalence of anti-spike antibodies (i.e., combined seroprevalence from prior COVID-19 infection and/or vaccination) is not reported by the CDC but certainly even higher than anti-nucleocapsid seroprevalence. These findings are supported by a shift in age to younger populations during the delta and omicron periods which occurred after vaccine became available to adolescents. These additional findings suggest that in children without SARS-CoV-2 immunity from prior infection or vaccination, omicron remains an important public health threat that is associated with more severe disease compared to earlier SARS-CoV-2 lineages. Our findings underscore the ongoing importance of COVID-19 prevention in children through vaccination and nonpharmacologic interventions, as well as early treatment with antiviral medications and/or monoclonal antibodies in high-risk children, particularly those with an anticipated suboptimal immune response to vaccination. Additionally, our study also highlights

Table 2. Association Between COVID-19 Severity and SARS-CoV-2 Variants of Concern (*n* = 711)

	Marker of COVID-19 severity: odds ratio (95% confidence interval; *P* value)				
	Hospitalized for COVID-19	COVID-19 Pharmacologic Treatment	Respiratory Support	Intensive Care Unit Admission	WHO Clinical Progression Scale Score ≥6
Age	1.01 (0.94–1.1; 0.9)	**1.2 (1.1–1.3; <0.001)***	**1.2 (1.1–1.3; 0.002)***	**1.2 (1.1–1.3; 0.002)***	**1.2 (1.1–1.3; <0.001)***
Race (Black)	1.01 (0.36–2.6; >0.9)	0.83 (0.24–2.5; 0.8)	0.67 (0.17–2.2; 0.5)	0.96 (0.24–3.2; >0.9)	1.0 (0.24–3.6;>0.9)
Ethnicity (Hispanic)	1.23 (0.57–2.67; 0.6)	0.68 (0.24–1.8; 0.4)	0.60 (0.2–1.7; 0.3)	0.92 (0.32–2.57; 0.9)	0.73 (0.21–2.3; 0.6)
High-risk condition for COVID-19 complications	**6.1 (2.8–13.9, <0.001)***	–	–	–	–
Pediatric COVID-19 community incidence	1.0 (1.0–1.0; 0.2)	1.0 (1.0–1.0; 0.4)	1.0 (1.0–1.0; 0.6)	1.0 (1.0–1.0; 0.3)	1.0 (1.0–1.0; 0.5)
SARS-CoV-2 lineage					
Non-VOC	ref	ref	ref	ref	ref
Alpha VOC	2.2 (0.73–6.6; 0.15)	2.4 (0.6–10.5; 0.2)	2.3 (0.41–12.9; 03)	2.5 (0.53–13.6; 0.2)	2.8 (0.44–22.6; 0.3)
Gamma VOC	**6.7 (2.0–22.1; 0.002)***	**5.7 (1.2–26.8; 0.02)***	**11.9 (2.7–62.4; 0.001)***	5.4 (0.92–31.4; 0.05)	**11.7 (2.1–90.5; 0.007)***
Delta VOC	2.8 (0.95–8.0; 0.06)	2.8 (0.68–12.2; 0.15)	3.4 (0.7–17.9; 0.13)	2.7 (0.56–14.8; 0.2)	3.3 (0.51–26.3; 0.2)
Omicron VOC	0.79 (0.20–2.7; 0.7)	2.7 (0.53–13.0; 0.2)	2.3 (0.43–13.4; 0.3)	4.5 (0.94–24.1; 0.06)	4.9 (0.79–39.7; 0.09)

VOC, variant of concern; ref, reference group for VOC odds ratio calculations; N/A, not applicable. ORs for high-risk conditions could not calculated for some outcomes because having a high-risk condition was mutually inclusive with the outcome of interest.
*Bolded values indicate statistical significance (*P* < .05).

the importance of genomic surveillance in children to monitor for emergence of variants with increased virulence and/or immune escape.

Our findings support previous observations in Brazil [6] whereby younger adult patients without comorbidities were hospitalized with severe COVID-19 infections during a surge in gamma SARS-CoV-2 infections between December 2020 and January 2021. However, the reasons for the observed association between gamma and COVID-19 severity in children in this study remain hypothetical. Gamma shares several mutations with other VOCs in the spike protein receptor-binding domain, including several that have been previously linked with humoral immune evasion in adults (i.e., K417T, E484K, and N501Y) [17]. There are similarly several mutations unique to the gamma VOC in the N-terminal domain of the spike (L18F, T20N, P26S, D138Y, R190S). While many of these mutations map to regions of neutralizing antibody binding [18], the impact of these mutations on neutralization remains unclear. More research on the neutralizing antibody responses to SARS-CoV-2 in children and their relationship to these mutations is needed. While differential susceptibility to antibody neutralization may be one explanation, several VOCs besides gamma would be expected to confer this phenotype [18]. An alternative explanation is a difference in cellular tropism unique to gamma in children. Gamma carries a unique mutation in the membrane-proximal heptad repeat region (HR2) of Spike responsible for fusion activity and tropism, V1176F [19]. However, because the gamma variant seems to be no longer circulating in any country

since being replaced by the delta and/or omicron VOCs, the public health impact of identifying the virologic mechanism for increased gamma VOC has diminished.

A notable strength of this study includes classification of patients based on confirmed SARS-CoV-2 lineage, which limited misclassification bias; prior studies [6, 7] compared patient outcomes during different time periods, which was used as a proxy of SARS-CoV-2 lineage. This study has several limitations. As a single-center study, our findings may not be generalizable to other geographic locations and patient populations. Furthermore, it is possible as a tertiary care children's hospital, our patient population may not be representative of the broader community pediatric population, which could introduce bias. However, the referral area for our hospital in Chicago extends throughout the city and suburban areas and includes a diverse patient base in terms of demographics and medical complexity. Also, COVID-19 testing volumes remained very high at our Chicago and suburban testing facilities throughout the pandemic. These patient referral characteristics likely expand generalizability. This study was limited to those infections for which SARS-CoV-2 was able to be sequenced, biasing the study to the inclusion of infections associated with relatively low cycle threshold values (i.e., high viral loads). Although we limited our definition of high risk for COVID-19 complications to those for which there are high-quality and reproducible data per CDC classification (i.e., meta-analysis, systematic review, or observational study; not small studies, case reports/series, or conflicting evidence; Supplementary Table 2) [14], these data are
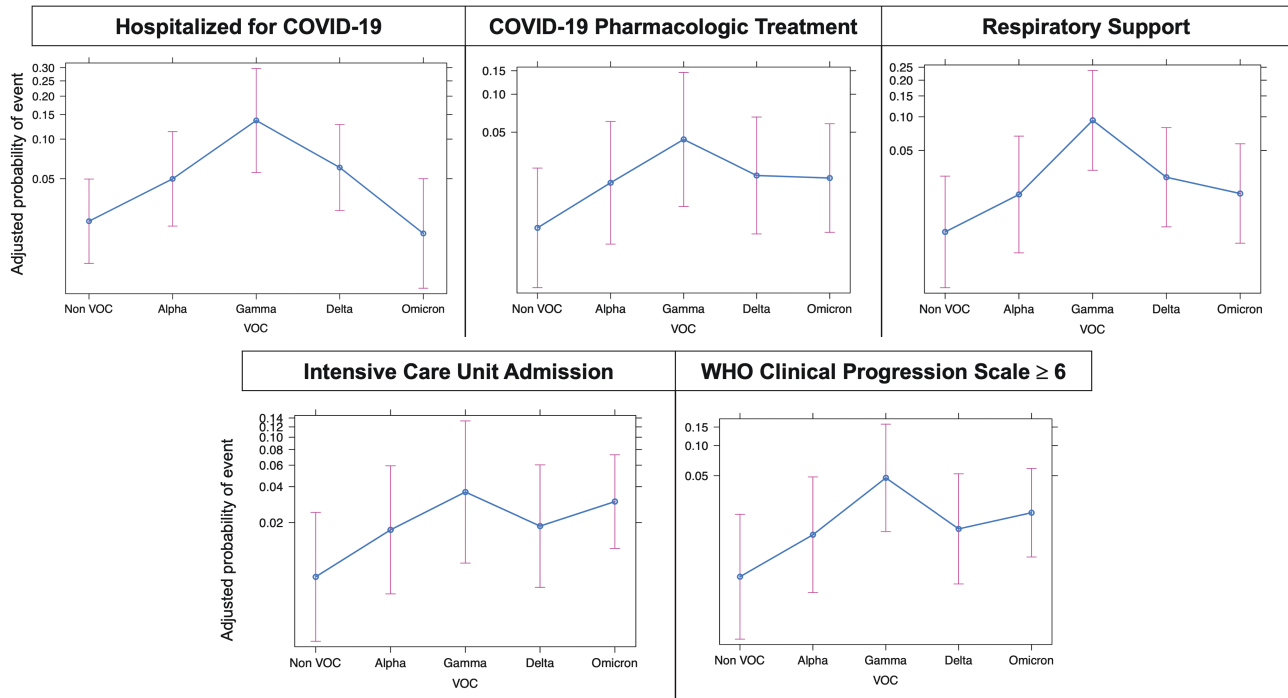
Figure 2. Predictor effect displays for the multivariable logistic regressions fitted for various COVID-19 severity markers in a pediatric cohort. The effect plots illustrate the adjusted probabilities of each marker for the VOC variable. Compared with Non-VOC COVID-19 infections, infections caused by the gamma VOC were significantly more likely to be associated with hospitalization for COVID-19, COVID-19 pharmacologic treatment, respiratory support, and WHO Clinical Progression Scale score ≥6 (Odds ratios listed in Table 2). Alpha, delta, and omicron infections did not significantly differ from non-VOC infections for any severity marker.

predominantly from adult populations and may not all apply to children. Nonetheless, based on our observations of COVID-19 severity being strongly associated with having a high-risk condition, those adult data likely translate well to children.

In summary, compared to non-VOC COVID-19 infections, the gamma VOC was independently associated with increased COVID-19 severity, as were older age and high-risk medical conditions. Omicron was independently associated with increased COVID-19 severity in children without SARS-CoV-2 immunization or prior COVID-19 infection. Thus, immunity against SARS-CoV-2 from vaccination, monoclonal antibodies, and/or prior COVID-19 prevented many severe outcomes during the omicron surge. These findings highlight that COVID-19 prevention in children through vaccination and nonpharmacologic interventions remains a public health priority. Ongoing genomic surveillance should prioritize identifying emergence and clinical outcomes associated with future variants. Although children generally have mild COVID-19 infection, the emergence of more virulent VOCs could dramatically change our clinical and public health response to COVID-19 in children through our iterative risk-benefit analyses of public health and pharmacologic interventions.

Supplementary Data

Supplementary materials are available at *Journal of the Pediatric Infectious Diseases Society* online (http://jpids.oxfordjournals.org).

Notes

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