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Original Article

Markers for severe disease and long-term sequelae in pediatric patients with severe acute respiratory syndrome coronavirus 2 infection

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Abstract ***Background*:** Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has resulted in substantial global morbidity and mortality since late 2019. Children can be infected but the disease predominantly affects adults, and research into the acute and chronic sequelae mostly pertains to this population. This study determines the clinical and demographic parameters associated with severe acute disease and chronic complications from COVID-19 in the pediatric population.

***Methods*:** A retrospective chart review was undertaken of all patients between birth and 21 years of age who were positive for SARS-CoV-2 by polymerase chain reaction (PCR) and were admitted to two tertiary care hospitals between March 1, 2020, and January 21, 2021. Markers for severe disease were defined as supplemental oxygen requirement, positive pressure ventilation, and acute chest radiograph abnormality at presentation. Chronic disease was defined as symptoms persisting >4 weeks.

***Results*:** Review of 101 patients with positive SARS-CoV2 testing found 67 presentations consistent with acute symptomatic infection. Age distribution was bimodal, with predominance in infancy and adolescence. Most (75%) had an extrapulmonary comorbidity, and fewer patients (33%) had pre-existing lung disease. A history of pulmonary comorbidity and obesity was significantly associated with markers for severe disease. Long-term chronic complications were associated with history of underlying lung disease and acute severe COVID-19.

***Conclusions*:** Demographic and clinical markers were associated with severe COVID-19 in children. Moreover, both the presence of pulmonary comorbidity and severe acute COVID-19 are associated with long-term sequelae.

Key words pediatric COVID-19.

Coronavirus disease 2019 (COVID-19) is caused by a novel coronavirus (SARS-CoV-2) that has infected more than four million children since the onset of the pandemic in late 2019.[1] Of the reported COVID-19 hospital admissions in the USA, hospitalizations of children ranged from 1.7%–4.1% of the total cumulated hospitalizations, and 0.1%–1.6% of all the child COVID-19 cases resulted in hospitalization, with higher hospitalization rates in children from racial minorities and under 2 years of age.[2]

Severe disease occurs in 10%–20% of the adults with acute COVID-19, which correlates with age, male gender, and multiple comorbidities.[1,3,4] Several case reports in adults have shown long-term clinical functional sequelae following COVID-19 and prolonged radiologic abnormalities.[5] Clinical manifestations in pediatrics are known to be milder than in adults and only a small fraction of the hospitalized patients for COVID-19 are children.

Limited data exist regarding the acute and chronic manifestations of COVID-19 in the pediatric population. The aim of this study is to identify markers for severe acute disease and chronic long-term complications of COVID-19 in a hospitalized pediatric population.

Methods

A retrospective chart review study was conducted of the pediatric population between birth and 21 years of age, admitted to either St. Louis Children's or Barnes Jewish Hospitals for management of acute COVID-19 respiratory infection. The Washington University Institutional Review Board determined

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that this project was exempt from patient consent requirements based on the study design (IRB ID #: 202101041).

A search of the medical record database between March 1, 2020, and January 31, 2021, identified appropriate charts for review. Inclusion criteria were defined as patients between birth and 21 years of age with positive SARS-CoV-2 nasopharyngeal polymerase chain reaction (PCR) swabs who were admitted to one of the participating hospitals for at least one night. Exclusion criteria were defined as the detection of pathogens in addition to SARS-CoV-2 on the nasopharyngeal swab, or diagnosis of secondary bacterial pneumonia or bloodstream infection following identification of SARS-CoV-2. Exclusion of these patients was necessary to eliminate other potential confounding infections as explanations for the patients' symptoms. Long-term symptoms were defined as those persisting for least 4 weeks from initial symptom onset.

Based on previous definitions,[6,7] severe disease presentation was defined as a patient having at least one of the following: (i) requirement for supplemental oxygen; (ii) requirement for non-invasive or invasive positive pressure ventilation; (iii) acute chest radiograph abnormalities on presentation.

Data analysis was conducted using SPSS version 27. For descriptive analysis, single variable distribution, central tendency, and dispersion were calculated. Univariate comparisons were made using the χ^2 test. Student's *t*-test was used for comparison between parametric variables, and Mann-Whitney *U*-test was used for comparison between non-parametric variables. A P value of <0.05 was considered significant. Variables were tested for confounders and collinearity. We conducted multivariable logistic models for variables associated with a P value <0.2 in the univariate analysis. We conducted standard backward elimination by stepwise logistic regression analysis method. For the multivariable analysis, P value of <0.05 was considered significant.

Results

Patients younger than 21 years with positive SARS-CoV-2 PCR nasal swabs ($n = 102$) were admitted to the participating hospitals between March 1, 2020, and January 31, 2021. One patient was excluded from the analysis due to co-infection with SARS-CoV-2 and adenovirus, so 101 patients were included in the data analysis (Fig. 1). Demographic and clinical characteristics are listed in Table 1. Median age at presentation was 16 years, inter-quartile range (IQR): 9.46–18.25. The age distribution was bimodal, with the two most common age groups being patients younger than 1 year of age (14.9%) and older than 16-years of age (53.3%). The majority of the cohort were non-Caucasian (57.4%) and female (62.3%). Average body mass index (BMI) was 26.1 ± 11.7, and more than a quarter of the cohort fulfilled the criteria for obesity (BMI >30). Asthma (14.8%) and sleep-related breathing disorders (4.9%) were the most common pulmonary comorbidities (Table 1). Most patients (75.5%) had a history of extrapulmonary comorbidity, most commonly neurologic diseases (12.9%), diabetes mellitus (9.9%), or genetic syndromes (6.9%) (Table 1).

Of the 101 patients reviewed for the study, 67 (66.3%) had symptoms consistent with SARS-CoV-2 infection while the remainder were asymptomatic and received SARS-CoV-2 PCR testing for other reasons, such as elective surgery or pediatric intensive care unit (PICU) admission for trauma (Fig. 1). Nearly half of the 67 patients ($n = 31$, 44.9%) were admitted initially to the pediatric intensive care unit (PICU), and nearly one quarter ($n = 22$, 22.9%) required oxygen to maintain appropriate oxyhemoglobin saturation. Smaller numbers of patients required non-invasive ($n = 9$, 9.4%) or invasive positive pressure ventilation ($n = 11$, 11.5%). Of the patients who had chest imaging, 23 (41.1%) had acute radiographic abnormality. Among that group, 17 required either supplemental oxygen or positive pressure ventilation support.

Figure 2 represents univariate comparisons for clinical and epidemiological parameters associated with markers of severe acute COVID-19. A history of pulmonary comorbidity was significantly associated with supplemental oxygen support (OR = 3.5, $P = 0.01$) and necessity for positive pressure support (OR = 4.2, $P = 0.01$). Obesity (BMI >30) was associated with positive pressure support and abnormal chest radiograph at the presentation (OR = 3.4, $P = 0.04$; OR = 3.5, $P = 0.04$, respectively) and trended towards statistical significance in association with supplemental oxygen support (OR = 2.6, $P = 0.07$). Of note, the distribution of obese patients was not statistically different between patients with and without pulmonary comorbidity, therefore these parameters could not be considered as confounders. Mean BMI was higher among patients who required oxygen than among patients maintained on room air (29.49 ± 15.3 vs 25.37 ± 10.26) and was higher among patients supported by positive pressure (29.6 ± 11.6) *vs* patients that were not supported by positive pressure (25.8 ± 11.9). Female gender was associated with increased odds of acute chest radiograph abnormalities (OR = 3.6, $P = 0.03$). Age at presentation and patients' ethnicities were not associated with disease severity. Table 2 represents multivariate logistic regression for severe acute COVID-19, defined by requirement for oxygen support during acute phase. The presence of pulmonary comorbidity increased the odds for severe acute COVID-19 in 3.5 times ($P = 0.03$), adjusted to the patient's age and the presence of obesity. Patients with obesity (BMI >30) were found to have 3.3 times increased odds ($P = 0.06$) of severe disease compared with non-obese patients, adjusted for the patient's age and presence of pulmonary comorbidity.

Of the cohort of 67 patients, 24 returned for follow up chest radiographs >4 weeks after discharge (Fig. 1). Chronic abnormalities were noted in four patients, three of them had chronic atelectasis and one of them had chronic opacities that were consistent with lung scarring. The remainder had normal chest radiographs. Of the same cohort of acute disease patients, six developed chronic respiratory complications such as persistent tachypnea, persistent hypoxemia, and/or chronic ground glass opacities in chest CT. Ten patients developed chronic non-respiratory complications, such as recurrent leg pain with

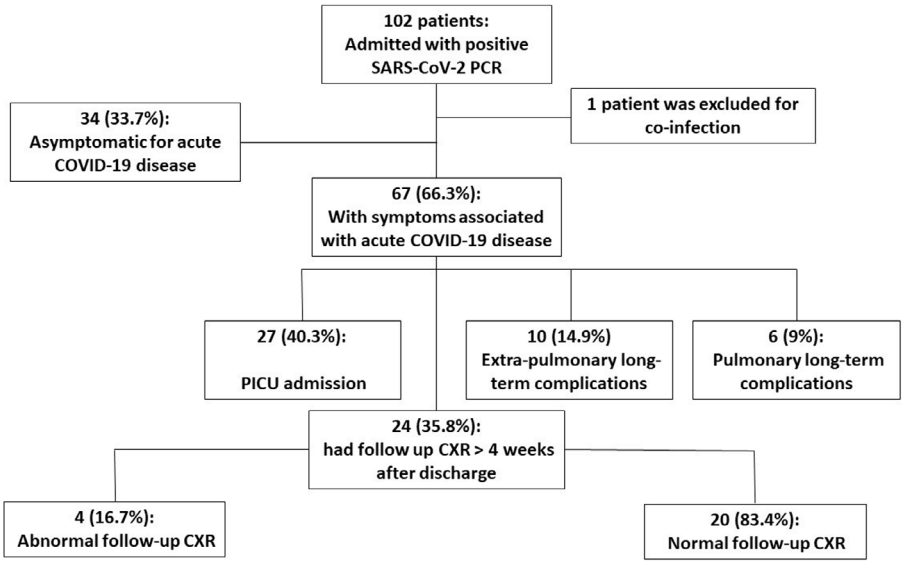

Fig. 1 Flow chart of charts reviewed.

Table 1 Demographic and clinical characteristics of 101 pediatric hospitalized patients with acute SARS-CoV-2 infection

Variable	Values
Age in years (median, min-max)	16 (IQR 9.46–18.25)
0–1 year	10 (14.9%)
2–5 years	5 (7.5%)
6–10 years	8 (11.9%)
11–15 years	8 (11.9%)
16–21 years	36 (53.7%)
Non-Caucasian (*N*, %)	66 (57.4%)
Females (*N*, %)	63 (62.3%)
Average body mass index (±STD)	26.1 ± 11.7
Median (min-max)	24.5 (9.6–78)
Obesity, defined as body mass index >30	24 (26.7%)
Patients with extrapulmonary comorbidity (*N*, %)	71 (75.5%)
Neurologic disease (epilepsy, global developmental delay, cerebral palsy)	13 (12.9%)
Diabetes mellitus	10 (9.9%)
Genetic syndromes (DiGeorge, Holt-Oram syndrome, Angelman, Prader–Willi, trisomy 21)	7 (6.9%)
Morbid obesity (body mass index >40)	6 (5.9%)
Hematologic disorders	5 (5%)
Psychiatric disorders	5 (5%)
Immunodeficiency	4 (4%)
Cardiac/vascular abnormalities	4 (4%)
Non-diabetes endocrine disorders	3 (3%)
Pregnancy	2 (2%)
Other	12 (11.9%)
Patients with pulmonary comorbidity (*N*, %)	25 (31.3%)
Asthma	15 (14.8%)
Sleep-related breathing disorder	6 (7.5%)
Pulmonary vasculitis with diffuse alveolar hemorrhage	3 (3%)
Other	1 (1%)

erythema ($n = 1$), Guillain–Barré syndrome ($n = 1$), adrenal insufficiency ($n = 1$), or multisystem inflammatory syndrome in children (MIS-C) ($n = 1$). History of pulmonary comorbidity and markers for acute severe disease, such as supplemental oxygen or positive pressure supports, showed statistically significant association with chronic pulmonary and non-pulmonary complications (Table 3). Chronic chest radiography findings were also associated with a history of acute severe disease and the necessity for oxygen or positive pressure supports.

Discussion

This study reviews the presentation and outcomes of a pediatric cohort of hospitalized patients with acute COVID-19. We focused on symptomatic children who were admitted to the hospital with acute infection in order to better identify markers associated with severe acute COVID-19 and markers associated with long-term sequelae and chronic complications. Two-thirds of our patients presented with symptoms associated with acute COVID-19, which is a rate similar to that found in previous studies of pediatric populations.[8] This study demonstrates that a history of pulmonary comorbidity and obesity is associated with more severe COVID-19. A history of pulmonary comorbidity and severe COVID-19, are also risk factors for further long-term morbidity.

Previous studies of clinical manifestations and disease severity in pediatric populations with COVID-19 demonstrated that 11.7% of the patients with positive SARS-CoV-2 PCR were admitted to hospital.[9] Among those, about 31% presented with severe disease and 7% required mechanical ventilation.[9] In this study the cohort showed a lower proportion requiring oxygen (22.9%), but a higher proportion needing invasive mechanical ventilation (11.5%). Higher rates of PICU

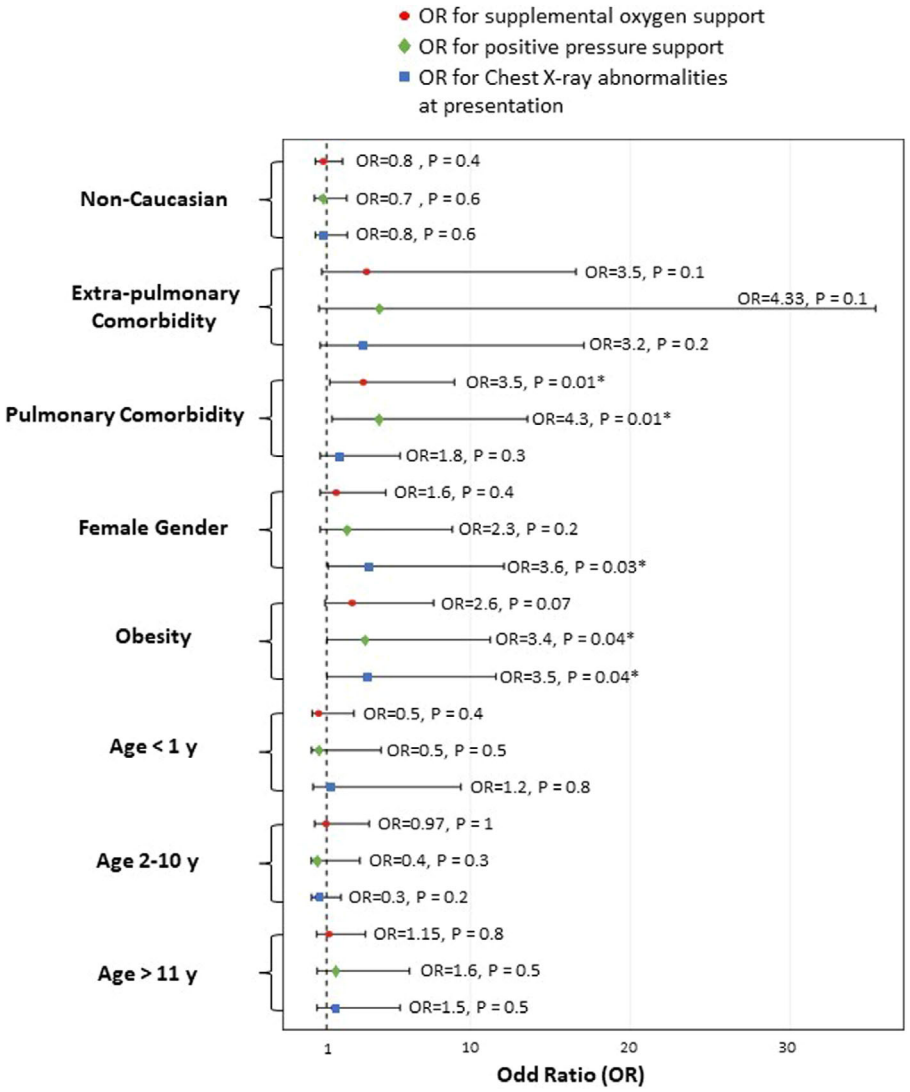

Fig. 2 Univariate comparison of clinical and demographic parameters associated with markers for severe COVID-19.

Table 2 Multivariate logistic regression for severe acute COVID-19

Variable	Pv	Odds ratio	Confidence interval for odd ratios
Age at presentation	0.26	0.99	0.99–1.004
Presence of pulmonary comorbidity	0.03	3.47	1.14–10.54
Obesity (body mass index >30)	0.06	3.33	0.95–11.23

Abbreviation: Pv - P value.

admissions were found in our cohort compared to previous reports.[9,10] One likely reason for this finding is that, in the first months of the pandemic, the threshold for admission to the PICU was lower compared with later months, as much was initially unknown about the novel coronavirus. Admission patterns to the PICU changed as the pandemic progressed.

This study demonstrates that a history of pulmonary comorbidity is associated with severe acute disease, similar to results demonstrated in another large retrospective study.[9] There is growing evidence that children with history of comorbidities are at risk for severe COVID-19.[11,12] Similar to previous studies[8] we also showed absence of gender disparities as risk factors for severe disease. Due to lack of large sample size, subanalysis regarding each severe disease risk factor was not performed.

Obesity is reported to be a risk factor for acute severe COVID 19 in adults, with increasing evidence of similar trend in children.[1,3,4,8,10] In this study, obesity was associated with all four markers for severe disease, supporting previous evidence that obesity in pediatric patients is an important risk factor for severe COVID-19. Obesity was also found to be associated with increased oxygen requirements, adjusted to patient age and presence of pulmonary comorbidity. Possible mechanisms for obesity increasing the risk of severe COVID-19 in children

Table 3 Clinical and demographic parameters associated with chronic COVID-19 complications

Clinical/Demographic feature	*P*	OR (95% confidence interval)
Chronic non-respiratory complications (*N* = 10, 14.9%)		
Ethnicity (non-Caucasian)	0.4	0.4 (0.08–2.8)
History of comorbidities	0.1	0.8 (0.7–1)
History of pulmonary comorbidities	0.003*	7.7 (1.7–33.6)
Gender (female)	0.2	4.1 (0.5–34.5)
History of symptomatic COVID-19	0.05*	0.7 (0.6–0.8)
History of PICU admission for acute COVID-19	0.08	4.2 (0.8–22.5)
History of oxygen requirements	0.001*	11.9 (2.6–54)
History of positive pressure support	0.002*	9.2 (2–42.8)
Obesity (body mass index >30)	0.25	2.26 (0.55–9.27)
Chronic respiratory complications (*N* = 6, 9%)		
Ethnicity (non-Caucasian)	0.4	0.4 (0.08–2.8)
History of comorbidities	0.3	0.8 (0.7–1)
History of pulmonary comorbidities	0.008*	12.9 (1.4–122.3)
Gender (female)	0.7	1.6 (0.2–15.9)
History of symptomatic COVID-19	0.3	0.8 (0.7–1)
History of PICU admission for acute COVID-19	0.5	2 (0.3–13.5)
History of oxygen requirements	0.02*	6.8 (1.1–42.7)
History of positive pressure support	0.06	5 (0.81–31)
Obesity (body mass index >30)	0.19	3.1 (0.54–17.87)
Chronic abnormalities in chest X-Ray (*N* = 4, 16.7%)		
Ethnicity (non-Caucasian)	0.7	0.6 (0.05–7.1)
History of comorbidities	0.5	0.9 (0.8–1)
History of pulmonary comorbidities	0.3	3.6 (0.3–41.6)
Gender (female)	0.3	0.7 (0.6–1)
History of symptomatic COVID-19	0.5	0.9 (0.8–1)
History of PICU admission for acute COVID-19	0.2	4.4 (0.4–50.2)
History of oxygen requirements	0.03*	12 (1–148.3)
History of positive pressure support	0.02*	15 (1.1–198)
Obesity (body mass index >30)	0.3	3 (0.33–27.32)

* statistically significant P value (defined as 0.05 or lower).

include alteration of respiratory mechanics during illness due to larger body habitus or baseline increased risk for vasculopathy, which is then exacerbated with SARS-CoV-2 infection.[13]

Female gender was associated with increased odds of acute CXR abnormalities (OR = 3.6, $P = 0.03$) in our cohort. However, gender differences were not associated with other clinical parameters for acute disease severity. In previous studies both in children and adults, male gender was found to be independently associated with severe COVID-19.[9,14] Of note, radiologic findings in chest X-rays do not always correlate with clinical status and this might explain this gender discrepancies.

In our study, age was not found to be correlated with severe COVID-19. A systematic review of the clinical manifestations of COVID-19 in young infants found that patients younger than 3 months with SARS-CoV-2 infection tended to have mild to moderate disease severity with a relatively high hospitalization rate (92%) and pediatric intensive care unit admission rate (21%).[15] Age <1 year was associated with increased risk for severe disease,[16,17] but this finding is inconsistent.[11,18,19] In general, data in the literature regarding the correlation between age and disease severity in the pediatric population is still lacking.

There is increasing evidence for chronic sequelae and complications secondary to COVID-19. Several case reports in adults showed increased long term sequala for COVID-19 including interstitial lung disease, pulmonary fibrosis, and pulmonary hypertensions.[5,20] In our cohort, 12% of the symptomatic patients had chronic respiratory complications. In symptomatic patients who had radiologic follow up, 16.7% were found to have chronic chest radiograph abnormalities and 13.3% of symptomatic patients had chronic non-respiratory complications. Factors found to be associated with long-term complications were a history of pulmonary comorbidity and markers for severe acute disease. These results support the idea that severe acute COVID-19 potentially places children at increased risk for long-term sequelae. The etiology is unclear but it could be related to iatrogenic interventions, such as prolonged mechanical ventilation,[21] injury related to the virus, or inflammatory injury secondary to exaggerated host response to SARS-CoV-2 infection.[22]

The main limitation of this study is the selection bias inherent in reviewing only children who were hospitalized. The results of this study may not be generalizable to the pediatric population at large, who do not become ill enough to require medical care. A second limitation of this study is that the small sample size limits the ability to draw broader conclusions or create statistically meaningful sub-group analysis or multivariate models. Finally, there was limited follow up for many of the study subjects, which potentially introduces selection bias into some of the results. Furthermore, only half of the patients had a clinical status that justified obtaining chest radiographs on admission and only a small fraction of them had follow-up chest radiographs. Future multicenter studies are required to increase the power of these results.

In conclusion, we identified several risk factors for severe acute COVID-19, such as the presence of pulmonary and extra pulmonary comorbidities and pediatric obesity. We also identified a subset of pediatric patients who demonstrated long-term sequelae from acute COVID-19. The presence of pulmonary comorbidity and severe acute COVID-19 are both strong markers for long-term morbidity in the pediatric population.

Disclosure

The authors declare no conflict of interest.

Author contributions

Dr. Guy Hazan and Dr. Steven Brennan conceptualized and designed the study, designed the data-collection instruments, collected data, carried out the initial analyses drafted the initial manuscript, and reviewed and revised the manuscript. Dr. Mehr Zahra Shah designed the data-collection instruments, collected data, and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of it.

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