Original Research

COVID-19 Disease Characterization and Outcomes Comparison in Pediatrics

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Abstract

Background
It has been reported that children experience less severe COVID-19 symptoms than adults; however, the literature that supports this idea is evolving. The purpose of this study was to retrospectively characterize hospitalized COVID-19-positive pediatric patients with a focus on the assessment of risk factors for poorer outcomes, mortality, and evaluation of interventions utilized and associated clinical outcomes.

Methods
We conducted a multi-center retrospective chart review of patients 18 years old or younger who were COVID-19 positive and admitted to any US HCA Healthcare Pediatric service line between January 1, 2020, and November 30, 2020. We identified 6081 children across 4 states and included them in our data analysis. Negative Binomial Regression was used to measure the associations between characteristics abstracted from medical records and length of hospital stay.

Results
Of the total cohort, 2.7% had at least one comorbidity. The majority of patients were discharged shortly after admission with 93.6% of patients spending less than 48 hours as an inpatient. The mortality rate during the study period was 0.1%. Factors found to be significantly associated with an increased length of stay were time in the intensive care unit (ICU), surgeries, developmental disorders, diabetes, post-traumatic stress disorder (PTSD), suicidal ideation, and type of admission.

Conclusion
The results of this cohort show there was a low disease burden at baseline and during hospitalization in pediatric patients positive for COVID-19. However, as the pandemic continues, future studies that further describe COVID-19 in children will be crucial to fully understand the disease course.

Keywords
COVID-19; SARS-CoV-2; coronavirus; pandemic; pediatrics; child; adolescent; disease characterization; treatment outcomes; comorbidity; retrospective studies; binomial regression analysis; critical care; hospitalization; pharmacotherapy

Introduction
The novel coronavirus disease 2019 (SARS-CoV-2) pandemic has resulted in nearly 769 million cases and over 6.9 million deaths worldwide to date. It produced an exponential spike in critically ill patients presenting with severe upper respiratory symptoms and placed a substantial strain on healthcare systems across the world.[1] SARS-CoV-2, also named COVID-19, causes severe acute respiratory syndrome by entering cells through angiotensin-converting enzyme 2 (ACE-2) cell receptors.[2] Severity of symptoms among those infected can range from mild to severe with significant morbidity

and mortality depending on patient-specific characteristics. There is emerging data that support the view that the majority of children infected with COVID-19 are asymptomatic or experience mild disease,[4-6] with a small percentage of children progressing to severe respiratory symptoms and/or multisystem inflammatory syndrome (MIS-C).[7-10] The reason for severe presentations in these pediatric patients is not yet fully understood. More recent studies support the age-dependent expression of ACE-2 receptors in pediatric patients, and it was hypothesized that a lower expression of ACE-2 receptors led to a lower disease impact and a milder course of infection.[2,3] The Centers for Disease Control and Prevention (CDC) *Morbidity and Mortality Weekly Report* published in April 2020, reported that of 149 082 cases in the United States (U.S.), 2572 (1.7%) occurred in patients under 18 years of age.[11] Of these cases, 15 were admitted to the ICU and 3 died from respiratory complications.[11] This was the first report to describe the disease in the U.S. pediatric population. In September 2021, the American Academy of Pediatrics reported that children were 28.9% of newly reported COVID-19 cases in the US.[12]

Treatment in pediatric patients remains variable across the U.S. due to the delayed release of evidence-based guidelines to support successful treatment options. As of this writing (February 2021), remdesivir is the only US Food and Drug Administration (FDA)-approved pharmacologic agent for the treatment of COVID-19 in patients 12 years and older, and the current standard of care remains primarily supportive.[13] Though information is accumulating, there is a general lack of comprehensive studies in which detailed outcomes and clinical characterization of COVID-19 in pediatric patients are provided.

HCA Healthcare is the largest system of providers of pediatric services in the US, operating 85 neonatal intensive care units (NICUs) and 20 pediatric intensive care units (PICUs) across 21 states.[14] The purpose of this study was to retrospectively characterize COVID-19-positive patients admitted to pediatric service lines across the country with a focus on the assessment of risk factors for poorer outcomes, mortality, and evaluation of interventions utilized and associated clinical outcomes. We hypothesized that pediatric patients with pre-existing comorbidities would have a higher risk of mortality, meaning that the mortality rates would be similar to the national mortality rates, and there would be a negligible difference in outcomes regardless of the treatment course.

Methods

Our data analyst extracted data from 156 medical facilities across 34 states and included all patients admitted to a pediatric service line with a COVID-19 infection confirmed by polymerase chain reaction (PCR) or antigen methods between January 1 and November 30, 2020. Patients were excluded from data collection if they were over 18 years old or tested negative for COVID-19 upon admission. This study was determined to be Institutional Review Board (IRB) exempt, and all patient-sensitive data were deidentified.

The cohort was grouped by age, and the age characterizations were categorized as follows: 0 to 1 year (infants), greater than 1 year to 12 years (children), and 13 to 18 years (adolescents). Patient demographic data included age, sex, race, and preexisting comorbidities. Patients' hospital course is described in terms of admission type (ie, emergency, observation, surgery, inpatient, or ICU); supplemental oxygen used; type of oxygen delivery (ie, oxygen mask, nasal cannula, bilevel positive airway pressure [BiPAP], continuous positive airway pressure [CPAP], tracheal collar, or ventilator); and utilization of medications targeting COVID-19 symptoms (ie, anakinra, azithromycin, dexamethasone, hydroxychloroquine, methylprednisolone, prednisolone, prednisone, remdesivir, or tocilizumab). Descriptive results are presented as absolute numbers and percentages or as medians and interquartile ranges (IQR), as appropriate. Factors impacting length of stay were measured using negative binomial regression. Data were secondarily sourced retrospectively after patient discharge or expiration.

Length of stay was analyzed statistically via negative binomial regression, as hospital stay is best analyzed as count data over scalar data. Due to overdispersion, a negative binomial was chosen over Poisson. The covariates utilized in the regression were chosen by one of two

methods: either it was deemed significant via lasso regression from all available data within the attached tables or it was clinically relevant and intentionally included.

Results

Patient Characteristics

Between January 1 and November 30, 2020, a total of 6081 pediatric patients tested positive for COVID-19 on admission at an included medical facility and were captured in our data set. The median (IQR) age was 11 years (3-15) with 3089 (50.8%) females and 2992 (49.2%) males (**Table 1**). Of the races reported, White was the most common with 2300 patients (37.8%), followed by Multiracial/Other with 2109 patients (34.7%), Black non-Hispanic (1577; 25.9%), Asian (80; 1.3%), Native American (14; 0.2%), and Hispanic (1; 0.0%). There was an overall low prevalence of comorbidities in this pediatric cohort with 166 (2.7%) patients having at least one comorbidity and 135 (2.2%) having one comorbidity only. The most prevalent comorbidity present at baseline was diabetes (49 patients; 0.8%), developmental disorders (85 patients; 1.4%), and pregnancy (89 patients; 1.5%) (**Table 2**). When categorized by age group, adolescents had the highest prevalence of comorbidities with 39 having diabetes, 53 having developmental disorders, and 89 patients being pregnant. A large percentage of patients included in this study were admitted to facilities located in Texas (36.6%) and Florida (29.6%), these states having a combined 81 HCA Healthcare hospitals.

Hospital Stay and Interventions

Most patients were discharged shortly after admission with 5690 (93.6%) spending less than 48 hours inpatient (1 died). The remaining 391 (6.4%) patients in the cohort spent more than 48 hours inpatient (2 died). Among the patients who presented to the hospital, the emergency department was the most common area of admission with 5505 patients (90.5%), followed by inpatient admission with 502 patients (8.3%), and ICU admission with 241 patients (4.0%). There were 37 patients (0.6%) who were classified as observation status on admission and 37 patients (0.6%) who were either admitted for surgery or required surgery on the same day of admission.

Supplemental oxygen was required in 197 patients (3.2%) and used in 71 (2.8%) adolescents, 78 (3.2%) children, and 48 (4.2%) infants (**Table 3**). Of those who required oxygen support that exceeded baseline, non-invasive delivery was most common with a nasal cannula and oxygen mask being utilized most often, 118 (1.9%) and 77 (1.3%), respectively. Invasive ventilation was used in 18 patients (0.3%) overall and half of those patients were categorized as infants. Out of the entire infant cohort that received oxygen support, 9 (18.8%) required mechanical ventilation.

Among the targeted pharmacologic therapies to treat COVID-19 symptoms, the most frequently prescribed medication was dexamethasone, where 205 patients (3.4%) received at least one dose while admitted for a median

Table 1. Demographic Characteristics of Pediatric Patients Treated in Hospital With a Positive COVID-19 Test

	Adolescents (n = 2511)	Children (n = 2415)	Infants (n = 1155)	Total (N = 6081)
Sex				
Female	1400 (55.8%)	1148 (47.5%)	541 (46.8%)	3089 (50.8%)
Male	1111 (44.2%)	1267 (52.5%)	614 (53.2%)	2992 (49.2%)
Race				
Asian	32 (1.3%)	37 (1.5%)	11 (1.0%)	80 (1.3%)
Black	659 (26.2%)	694 (28.7%)	224 (19.4%)	1577 (25.9%)
Hispanic	0 (0%)	1 (0.0%)	0 (0%)	1 (0.0%)
Multiracial/Other	816 (32.5%)	838 (34.7%)	455 (39.4%)	2109 (34.7%)
Native Americans	6 (0.2%)	4 (0.2%)	4 (0.3%)	14 (0.2%)
White	998 (39.7%)	841 (34.8%)	461 (39.9%)	2300 (37.8%)

Table 2. Baseline Characteristics of Pediatric Patients Treated in Hospital With a Positive COVID-19 Test

	Adolescents (n = 2511)	Children (n = 2415)	Infants (n = 1155)	Total (N = 6081)
Anxiety Disorders	37 (1.5%)	7 (0.3%)	0 (0%)	44 (0.7%)
Bipolar Disorders	16 (0.6%)	1 (0.0%)	0 (0%)	17 (0.3%)
Depression	47 (1.9%)	6 (0.2%)	0 (0%)	53 (0.9%)
Developmental Disorders	53 (2.1%)	30 (1.2%)	2 (0.2%)	85 (1.4%)
Eating Disorders	1 (0.0%)	0 (0%)	0 (0%)	1 (0.0%)
Impulse Disorders	7 (0.3%)	2 (0.1%)	0 (0%)	9 (0.1%)
Other Mood Disorders	4 (0.2%)	2 (0.1%)	0 (0%)	6 (0.1%)
Personality Disorders	2 (0.1%)	0 (0%)	0 (0%)	2 (0.0%)
Psychoses	26 (1.0%)	3 (0.1%)	0 (0%)	29 (0.5%)
Schizophrenia	11 (0.4%)	0 (0%)	0 (0%)	11 (0.2%)
Uncategorized Other Mental Disorders	2 (0.1%)	0 (0%)	0 (0%)	2 (0.0%)
Bleeding Disorder	1 (0.0%)	0 (0%)	0 (0%)	1 (0.0%)
Cerebrovascular Disease	1 (0.0%)	0 (0%)	1 (0.1%)	2 (0.0%)
Chronic Kidney Disease	2 (0.1%)	1 (0.0%)	4 (0.3%)	7 (0.1%)
Clotting Disorder	7 (0.3%)	3 (0.1%)	0 (0%)	10 (0.2%)
Coronary Artery Disease	0 (0%)	0 (0%)	1 (0.1%)	1 (0.0%)
Diabetes	39 (1.6%)	10 (0.4%)	0 (0%)	49 (0.8%)
Heart Failure	1 (0.0%)	3 (0.1%)	2 (0.2%)	6 (0.1%)
Pregnancy	89 (3.5%)	0 (0%)	0 (0%)	89 (1.5%)
Prior VTE	1 (0.0%)	0 (0%)	0 (0%)	1 (0.0%)
Peripheral Vascular Disease	0 (0%)	1 (0.0%)	1 (0.1%)	2 (0.0%)
Anemia	2 (0.1%)	0 (0%)	0 (0%)	2 (0.0%)
Chronic Blood Loss	13 (0.5%)	0 (0%)	0 (0%)	13 (0.2%)
Congestive Heart Failure	0 (0%)	2 (0.1%)	1 (0.1%)	3 (0.0%)
Coagulopathy	7 (0.3%)	1 (0.0%)	0 (0%)	8 (0.1%)
Complicated Hypertension	2 (0.1%)	0 (0%)	1 (0.1%)	3 (0.0%)
Obesity	2 (0.1%)	0 (0%)	0 (0%)	2 (0.0%)
Moderate Renal Failure	1 (0.0%)	1 (0.0%)	2 (0.2%)	4 (0.1%)
Severe Renal Failure	1 (0.0%)	0 (0%)	2 (0.2%)	3 (0.0%)

Abbreviation: VTE = venous thromboembolism

duration of 1 day. Following a similar trend, steroids as a pharmacologic class were most commonly prescribed, where 353 patients (5.8%) received either dexamethasone, methylprednisolone, prednisolone, or prednisone. Remdesivir, a more targeted therapy against COVID-19, was prescribed to 17 patients (0.3%) in this cohort and the median length of use was 5 days. Anakinra, an interleukin-1 receptor antagonist, was utilized in 2 children for a median of 9 days of therapy, whereas tocilizumab, a similar agent that modulates the inflammatory pathway via inhibition of interleukin-6, was used in 1 adolescent for 2 days. As a whole, the adolescent patient subgroup was prescribed the most medications to treat COVID-19 symptoms, which ranged from 0 to 2 different pharmacologic agents during inpatient stay.

Clinical Outcomes

The median length of ICU stay was 0 hours and the median (range) was 0 hours (0-70). This highly skewed median and large range indicates that few patients had any ICU time, while a

Table 3. Clinical Course and Interventions of Pediatric Patients Treated in Hospital With a Positive COVID-19 Test

	Adolescents (n = 2511)	Children (n = 2415)	Infants (n = 1155)	Total (N = 6081)
Any Supplemental Oxygen Used	71 (2.8%)	78 (3.2%)	48 (4.2%)	197 (3.2%)
BiPAP Used	2 (0.1%)	7 (0.3%)	0 (0%)	9 (0.1%)
Nasal Cannula Used	45 (1.8%)	42 (1.7%)	31 (2.7%)	118 (1.9%)
Oxygen Mask Used	24 (1.0%)	34 (1.4%)	19 (1.6%)	77 (1.3%)
Tracheal Collar Used	0 (0%)	1 (0.0%)	0 (0%)	1 (0.0%)
IV Based Oxygen	2 (0.1%)	3 (0.1%)	3 (0.3%)	8 (0.1%)
CPAP Used	2 (0.1%)	4 (0.2%)	0 (0%)	6 (0.1%)
Invasive Ventilation Used	3 (0.1%)	6 (0.2%)	9 (0.8%)	18 (0.3%)
Noninvasive Ventilation Used	2 (0.1%)	8 (0.3%)	4 (0.3%)	14 (0.2%)
Length of Invasive Ventilation – In Days				
Median (IQR)	0 (0-10)	0 (0-1)	3 (1-12)	1 (0-6)
Range	(0-34)	(0-6)	(0-70)	(0-70)
Length of Noninvasive Ventilation – In Days				
Median (IQR)	0 (0-0)	0.50 (0-2)	0 (0-3)	0 (0-2)
Range	(0-4)	(0-6)	(0-71)	(0-71)
Intensive Care Unit Visited	66 (2.6%)	73 (3.0%)	102 (8.8%)	241 (4.0%)
Length of ICU Stay – In Hours				
Median (IQR)	51.64 (26.26–88.77)	58.52 (31.2–149.25)	43.7 (20.1–73.2)	46.03 (23.08–102.38)
Range	(2.95-61.93)	(0.13-116.97)	(0.3-199.65)	(0.13-199.65)

Abbreviations: BiPAP = bilevel positive airway pressure; IV = intravenous; CPAP = continuous positive airway pressure; IQR = interquartile range; ICU = intensive care unit

small minority spent significant time there. The median (IQR) duration of invasive mechanical ventilation was 1 day (0-6) and ranged from 0-70 days. Of the total patients who required ICU admission, 102 patients (42.3%) were infants. Among those who were admitted to the ICU during hospitalization, the data revealed that within age groups, infants spent the most time on invasive ventilation with a median (IQR) of 3 days (1-12).

Factors found to be statistically significantly associated with either increasing or decreasing length of stay are summarized in **Table 4**. Among the laboratory values found to be clinically significant (eg, supplemental O_2 level, pulse, SpO_2), we believe clinical significance was low because these values are discrete and only summarized the lowest or highest lab values charted during the entirety of the admission. A clinically significant factor that was associated with a decreased length of stay is the length of time under invasive ventilation. While this may seem counterintuitive, given that invasive ventilation was rarely used, the few patients with time under invasive ventilation had a disproportionate effect on the overall magnitude of the effect on length of stay. Only 18 patients total (0.3%) required invasive ventilation in our cohort, and given both the contrary effect of their lengths of stay and the small number of patients requiring this intervention, belies their atypical nature in comparison to the other patients in our cohort. It is likely that invasive ventilator use is not the actual characteristic decreasing their lengths of stay, but rather, it is confounded by the actual reason, though, admittedly of all the data collected for this study, no other variable could be identified by variable selection to fit these criteria. Clinically significant factors that were associated with an increased length of stay were total time spent in ICU, number of surgeries, developmental disorders, diabetes, post-traumatic stress disorder (PTSD), suicidal ideation, and inpatient versus emergency and observation versus emergency. Of note, the majority of the cases included in this study, 4031 (66.3%) were from

Table 4. Factors Associated With Length of Hospital Stay Derived From Negative Binomial Regression (Items >1 Increase Length of Stay)

Parameter	Incident rate ratio	Lower confidence bound	Upper confidence bound	*P* value
Lowest supplemental O_2 level	0.83	0.73	0.95	.005
Length of time under invasive ventilation	0.94	0.92	0.97	<.001
Minimum pulse	0.98	0.98	0.98	<.001
Minimum SpO_2	0.99	0.99	1	.013
Maximum SpO_2	1.00	1.00	1.00	.022
Total length of time In ICU	1.00	1.00	1.00	<.001
Maximum pulse	1.02	1.02	1.02	<.001
Emergency vs same day	1.22	0.44	3.33	.698
Final supplement O_2 level	1.21	1.07	1.36	.003
Number of surgeries	1.38	1.14	1.67	.001
Developmental disorders	1.57	1.19	2.07	.002
Diabetes	1.82	1.29	2.58	.001
Post-traumatic stress disorder	2.17	1.44	3.27	<.001
Suicidal	3.05	2.21	4.22	<.001
Inpatient vs emergency	7.07	5.93	8.43	<.001
Observation vs emergency	30.18	23.32	39.06	<.001

Abbreviations: O_2 = oxygen; SpO_2 = oxygen saturation; ICU = intensive care unit

Florida and Texas combined, contributing to 40 and 41 of the medical centers included in this study respectively.

Discussion

Patient Characteristics

Our study summarizes the clinical course and outcomes of 6081 pediatric patients from 156 different medical facilities across 34 states between January 1 and November 30, 2020. All children tested positive for COVID-19 infection on admission; however, it is important to note that patients may not have been admitted exclusively for management of COVID-19 symptoms, as inclusion in this study was based on having a positive COVID-19 test regardless of symptom presentation. Of the children admitted during this time frame, only 18 patients (0.3%) required invasive ventilation, with 205 patients (3.1%) requiring any type of supplemental oxygen, and a total of 3 patients (0.1%) expiring overall. These findings suggest that COVID-19 infection is less severe in children compared to adults with a possibility of less respiratory system involvement than in hospitalized adult patients. A majority of the cases were from Florida and Texas, which aligns with the high prevalence of COVID-19 cases in those demographic areas during the study time frame. This leads us to suggest that in areas with higher rates of COVID-19 infection, children are at higher risk for hospitalization, though, it is important to note that the medical centers included in this study were not equally distributed. Therefore, it would be difficult to ascertain COVID-19-associated demographic trends in the US during this study period since there was not an equal number of facilities in each state.

Similar to previous reports of COVID-19 in children, clinical outcomes appeared to be better overall, as evidenced by the low mortality rate in this study. It is important to identify that our study did not specifically identify or capture patients who might have met the criteria for MIS-C, as our study's protocol was created prior to the case definition for MIS-C by the CDC.

Comorbidities and Clinical Outcomes

We hypothesized that patients with pre-existing comorbidities would have poorer clinical outcomes if hospitalized with COVID-19;

however, the overall prevalence of comorbidities was low at baseline. The most commonly reported comorbidity was pregnancy in 89 patients (1.5%), which attests to the low prevalence of pre-existing physical and mental disorders in this cohort. Only 2 patients were clinically obese which might align with the findings of overall less severe disease found in this study, considering obesity is a risk factor for severe COVID-19 disease in adults. However, with the rise in childhood obesity, this is still an unexpected finding at baseline considering Texas and Florida have nearly 25% of children and adolescents classified as overweight or obese.[15] With only 3 deaths being reported, we are unable to confidently comment on whether comorbidities increase the risk of mortality due to COVID-19. However, our data would suggest that children with pre-existing illnesses do not appear to have a higher risk for death if hospitalized with COVID-19 since so few deaths were observed, though this was not analyzed statistically and is merely an observation for further research. However, the regression analysis was indicative that pediatric patients with developmental disorders, diabetes, PTSD, and suicidal ideation have a longer length of stay when hospitalized. We identified an overall mortality rate of 0.1% in the cohort, which is similar to the current national rate between 0.0% and 0.2% reported in the literature.[11]

Pharmacologic Therapies

The final aim was to compare the targeted pharmacologic treatments used during the hospital stay and to determine if differences in clinical outcomes were observed. Medications included in this study were considered potential treatment options for COVID-19 symptoms at the time, including anakinra, azithromycin, hydroxychloroquine, remdesivir, steroids (dexamethasone, methylprednisolone, prednisolone, and prednisone), and tocilizumab. At the time of the study, the only FDA-approved agent to treat COVID-19 was remdesivir. Dexamethasone remains a first-line treatment option for patients who have increased oxygen requirements at baseline. Overall pharmacologic utilization in this cohort to treat COVID-19 in children was low, with patients receiving a range of 0 to 2 medications while hospitalized. Considering the current CDC and National Institute of Health (NIH) treatment guidance, it is not surprising that the most commonly prescribed medication was dexamethasone, with steroids being the most commonly prescribed class of medications overall. Only 3 patients received an interleukin inhibitor such as anakinra or tocilizumab, which is now considered a treatment option for patients who meet the criteria for immunomodulatory agents to treat severe MIS-C per American College of Rheumatology guidelines. Low prescribing rates for these agents could be attributed either to the lack of evidence to support their use in COVID-19 during this study's timeline or potentially, these patients were not severely ill and did not meet the case definition for severe MIS-C.

Limitations

There were several limitations in our study, the first being that this study did not have the statistical power necessary to analyze mortality, despite the study containing one of the largest cohorts of COVID-19-positive pediatric patients to date. In order to statistically analyze an outcome, enough outcome events (in this case, mortality) must occur in the study cohort. This study only had 3 deaths. If this were analyzed via regression, it would be difficult to draw any conclusions from such a small number of outcomes. While underpowered studies are useful for setting a framework for further study, we are unlikely to add anything of substance in this area given much better-powered studies exist. It was for this reason no attempt was made to analyze mortality. However, hospital length of stay had adequate data for a sufficiently powered analysis. Second, the EMR data obtained for this study is primarily a billing database, thus specific aspects of care were not recorded if unnecessary for later billing purposes, which could bias the results by missing some amount of unrecorded care. Third, as with all secondary-source retrospectively obtained data research, we cannot determine causality as we only assessed associations between statistically tested aspects of care and outcomes.

Conclusion

In this cohort of children and adolescents hospitalized with a positive COVID-19 test on admission, there was a generally low disease burden, with the vast majority being hospitalized for less than 48 hours. A very high proportion of these patients survived hospitalization with only 3 deaths in a fairly large cohort. Our

data supports the existing literature that suggests COVID-19 disease is less severe in pediatric patients. Providers and parents may find these collective findings useful in guiding their decisions in regard to reintegrating children into school and extracurricular settings during the later stages of the pandemic.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Drs Rowland and Schauble are employees of Presbyterian St. Luke's Medical Center, a hospital affiliated with the journal's publisher.

Mr Cornett is an employee of HCA Healthcare Graduate Medical Education, an organization affiliated with the journal's publisher.

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