





Outcomes of COVID-19 infection in pediatric pulmonary hypertension: A single-center experience

Raysa Morales-Demori MD¹  | George B. Mallory MD²  | Corey Chartan DO^{1,2} |
Ryan Coleman MD^{1,2} | Fadel Ruiz MD² | Natalie Villafranco MD² |
Elise Whalen MSN, APRN, FNP-C, CPN²  | Nidhy Varghese MD² 

¹Division of Critical Care, Department of Pediatrics, Baylor College of Medicine, Texas Children's Hospital, Houston, Texas, USA

²Division of Pulmonary Medicine, Department of Pediatrics, Baylor College of Medicine, Texas Children's Hospital, Houston, Texas, USA

Correspondence

Raysa Morales-Demori, MD, Division of Critical Care, Department of Pediatrics, Baylor College of Medicine, Texas Children's Hospital, 6651 Main St, MC E1420, Houston, TX 77030, USA.
Email: demori@bcm.edu

Abstract

Background: The global COVID-19 pandemic was particularly concerning for the pediatric pulmonary hypertension (PH) population due to immature immune systems and developmental comorbidities. This study aims to describe a single-center experience of pediatric PH patients diagnosed with COVID-19 disease.

Methods: A retrospective cohort study of all pediatric patients followed by the PH Center at Texas Children's Hospital diagnosed with COVID-19 infection from April 2020 to February 2021.

Results: We identified 23 patients with a median age of 58 months (interquartile range [IQR]: 25–75th, 21–132 months), 48% being Hispanics. Eight patients (35%) required hospitalization; median length of stay was 6 days (IQR: 25–75th, 5–8 days). Only three of these eight patients required increased respiratory support. Targeted PH therapy was escalated in four patients (two in dual and two in triple therapy). There was one mortality in a patient with failing Fontan physiology. Ninety-one percent of patients have had post-COVID outpatient follow-up, median of 101 days (IQR: 25–75th, 50–159 days) from diagnosis. Of the five patients with 6 min walk test (6MWT) data, three (60%) children walked less distance, median of -12 m (IQR: 25–75th, -12 to +49 m) compared to pre-COVID testing. Postinfection pulmonary function testing (PFT) was notable for decrease in predicted forced vital capacity (FVC; median -6%, range -11% to +6%) and forced expiratory volume in one second (FEV₁; median -14%, range -12% to -18%) in 75% of the patients with PFT data.

Conclusion: In our institution, COVID-19 was found more frequently in Hispanics and associated with low mortality.

KEYWORDS

COVID-19, outcomes, pediatrics, pulmonary hypertension

1 | INTRODUCTION

At the onset of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-Coronavirus 2, COVID-19) global pandemic, there was concern that patients of all ages with comorbidities, cardiovascular and pulmonary, would be at high risk for adverse outcomes from COVID disease.¹ Pulmonary hypertension (PH) is a severe disease marked by progressive pulmonary vascular disease and like other cardiorespiratory diseases, patients with PH are at particularly increased risk for clinical deterioration associated with respiratory infections. Acute respiratory failure in PH poses unique challenges due to negative hemodynamic effects due to mechanical ventilation and acidotic conditions affecting the efficacy of targeted pulmonary vasodilator therapy.¹ Unfortunately, underlying chronic respiratory disease has been reported to increase COVID mortality by 6%.¹ Additionally, COVID-19 has been associated with acute respiratory distress syndrome, a serious complication that could cause right ventricular (RV) systolic dysfunction, which, in patients with PH and chronic RV dysfunction, could be detrimental.¹

A few months into the pandemic, clinical reports suggested that PH patients were not as vulnerable as initially feared.² In one such early report, Horn et al.² described the collective experience of 32 PH centers in the United States and it was notable for 13 adult PH patients who required hospitalization due to COVID-19, 6 (55%) required mechanical ventilation and 1 died (8%). Authors hypothesized that the dysfunctional pulmonary endothelium³ and inhibition of the angiotensin-2 receptors by endothelin receptor antagonist therapy offer a synergistic "protection" for the PH patient from COVID-19 infection.² "Protection" provided by PH disease may derive from the altered responses of the pulmonary endothelium.

The long-term outcomes of COVID-19 disease remain unknown in the pediatric population. This is true in the pediatric PH population as well, compounded by a dearth of clinical information on short-term outcomes as well. We, therefore, aim to describe a single-center experience of pediatric PH patients diagnosed with COVID-19 disease and short-term outcomes.

2 | METHODS

This is a retrospective cohort study of all pediatric patients followed by the PH Center at Texas Children's Hospital who were diagnosed with COVID-19 infection from April 2020 through February 2021. Patients were diagnosed with PH by cardiac catheterization findings of mean pulmonary artery pressure (mPAP) >20 mmHg and indexed pulmonary vascular resistance (PVRi) ≥ 3 WU m² (cardiac catheterization data available for 15 [65%]), or based on expert interpretation of echocardiogram findings that suggested elevated pulmonary pressures. COVID-19 was diagnosed by positive polymerase chain reaction (PCR) test, either by direct review of result or report of positive testing that resulted outside of our institution.

Baseline (pre-infection) data collected for each patient included age, race/ethnicity, sex, World Symposium on Pulmonary Hypertension

(WSPH) group classification⁴ per primary PH provider type(s) (with some patients assigned to more than one group), number of PH targeted therapies, respiratory support, comorbidities (history of prematurity, congenital heart disease or congenital diaphragmatic hernia), echocardiogram (tricuspid regurgitation severity/velocity and RV systolic function in patients with biventricular physiology), 6-min walk test (6MWT) parameters (lowest and highest heart rate and SpO₂, distance walked in meters and % predicted), and pulmonary function test (PFT) parameters (FCV, FEV1, FEV1/FVC, FEF 25–75) if age-appropriate. Similar data was collected throughout the COVID-19 infection period but was expanded to include illness descriptors of symptoms, need for hospitalization, respiratory support, and length of stay. Post-infectious data obtained was based on inpatient or telemedicine outpatient encounters, and it included: illness resolution, type(s) and number of PH targeted therapies, respiratory support, echocardiogram (tricuspid regurgitation severity/velocity and RV systolic function in patients with biventricular physiology), 6MWT parameters (lowest and highest heart rate and SpO₂, distance walked in meters and % predicted), and pulmonary function test (PFT) parameters (FCV, FEV1, FEV1/FVC, FEF 25–75) if age-appropriate. This study was approved by the Baylor College of Medicine Institutional Review Board with consent waiver.

2.1 | Statistical analyses

Data were not normally distributed. Continuous variables were expressed as median (25–75th interquartile range [IQR]). Dichotomous variables were reported as numbers (percentages). Pearson Chi-square or Fischer's exact test were used to analyze dichotomous correlations in nominal data when appropriate. A $p < .05$ was considered statistically significant. All statistical analyses were performed with SPSS Statistics version 27 (IBM, Inc.).

3 | RESULTS

3.1 | Baseline

We identified 23 pediatric PH patients who were diagnosed with COVID-19 infection, with a median age of 58 months (IQR: 25–75th, 21–132 months). WSPH class Group 1 ($n:17$ or 74%), Group 2 ($n:2$ or 9%), Group 3 ($n:12$ or 52%), and Group 5 ($n:1$ or 4%). Race/ethnicity distribution were Hispanic ($n:11$ or 48%), Caucasian ($n:5$ or 22%), African American ($n:4$ or 17%), and Asian ($n:3$ or 13%). Main comorbidities were congenital heart disease ($n:17$ or 74%), premature birth ($n:5$ or 39%), and congenital diaphragmatic hernia ($n:3$ or 13%). Congenital heart disease consisted of atrioventricular septal defect ($n:5$), secundum atrial septal defect ($n:4$), single ventricular physiology ($n:3$), pulmonary vein stenosis ($n:2$), Shone's complex ($n:1$), Tetralogy of Fallot ($n:1$), pulmonary artery stenosis ($n:1$), and congenitally corrected transposition of the great arteries ($n:1$).

At baseline, 11 patients (47%) were on respiratory support: continuous nasal cannula ($n:5$ or 45%) with flow range of 1/8 to 2 L per min,

nocturnal noninvasive positive pressure ventilation (NIPPV; $n:2$ or 18%) or tracheostomy ($n:4$ or 36%), targeted PH medications use ranged from no therapy ($n:4$ or 17%), mono- ($n:7$ or 30%), dual- ($n:8$ or 35%), or triple therapy ($n:4$ or 17%). Catheterization data were available for 16 patients (74%). Cardiac catheterization was performed at a median of 290 days (IQR: 25–75th, 145–635 days) before COVID-19 infection. Median mean pulmonary arterial pressure of 31 mmHg (IQR: 25–75th 25–44 mmHg), median PVRi of 4.4 WU m^2 (IQR: 25–75th, 3.2–8.5 WU m^2),

and median transpulmonary gradient (TPG) of 19 mmHg (IQR: 25–75th, 9–35 mmHg; Table 1).

3.2 | Hospitalization

Eight of the 23 COVID-19 positive patients (35%) required hospitalization due to perceived clinical worsening or acute

TABLE 1 Characteristics of PH patients diagnosed with COVID-19

N	Age	Sex	Race/ethnicity	Baseline resp support	PH targeted therapy	Premie	WSPH Group	CDH	CHD	PVRi	TPG
1	1 m	M	Caucasian	RA	None	Yes	3	Yes			
2 ^a	8 m	F	Hispanic	NC	None	Yes	3	Yes			
3 ^a	17 m	M	Caucasian	NC	PDEi + ERA		2		Yes	7.2	21
4	2 y	M	Caucasian	RA	PDEi	Yes	1,3		Yes	11.4	38
5	2 y	F	Hispanic	RA	ERA		1		Yes	4.5	12
6	2 y	F	AA	NC	PDEi + ERA		1,3		Yes	5.3	16
7	2 y	F	Hispanic	Trach	PDEi	Yes	3		Yes	3.6	13
8	2 y	F	Asian	RA	None		1		Yes	1.1	7
9	3 y	F	AA	Trach	None	Yes	3		Yes		
10	4 y	M	AA	RA	PDEi		1,3		Yes		
11 ^a	4 y	F	Caucasian	Trach	PDEi + ERA		1,3		Yes	3.8	7
12 ^a	5 y	F	Hispanic	RA	PDEi	Yes	1		Yes	4.7	19
13	5 y	M	Hispanic	RA	PDEi + ERA	Yes	1,3		Yes	4.2	31
14	6 y	F	Hispanic	RA	PDEi + ERA + Prostacylin	Yes	1			8.9	39
15	7 y	M	Hispanic	NC	PDEi		1,3		Yes	10	32
16	7 y	F	Hispanic	RA	PDEi + ERA		1		Yes	2.3	7
17 ^a	8 y	M	Caucasian	Trach	PDEi + ERA	Yes	1,3	Yes	Yes	6	26
18	11 y	F	Hispanic	CPAP	PDEi + ERA + Prostacylin		1			8.9	37
19 ^{a,b}	12 y	M	Asian	NC	PDEi		1		Yes	3.5	7
20 ^a	12 y	M	Hispanic	BiPAP	PDEi + ERA + Selexipag		1,3		Yes	10.8	40
21	15 y	F	AA	RA	PDEi + ERA		5				
22 ^a	18 y	M	Asian	RA	PDEi + ERA		1,2		Yes	3.5	12
23	18 y	F	Hispanic	RA	PDEi + ERA + Prostacylin		1				

Note: N: Assigned case number for this study. Baseline respiratory (resp) support: Room air (RA), Nasal cannula (NC), tracheostomy (Trach). PH targeted therapy: Phosphodiesterase 5 inhibitors (PDEi), Endothelin receptor antagonist (ERA). History of prematurity (Premie). World Symposium of Pulmonary Hypertension (WSPH) Group. Congenital Diaphragmatic Hernia (CDH). Congenital Heart Disease (CHD). Hemodynamic catheterization data before COVID-19 infection: Pulmonary vascular resistance index (PVRi) in WU m^2 . Transpulmonary gradient (TPG).

^aRequired hospitalization.

^bMortality.

respiratory failure ($n=4$, 50%). The median age of these eight patients was 58 months (IQR: 25–75th, 17–148 months) and median length of stay was 6 days (IQR: 25–75th, 5–8 days). Six of the eight patients (75%) had congenital heart disease, three (38%) had a history of prematurity, and two (25%) had a history of congenital diaphragmatic hernia. Six patients (75%) had baseline respiratory support (two with tracheostomies, one on NIPPV at night, and four on nasal cannula oxygen supplementation). PH targeted therapy use in the hospitalized patients was two (25%) on single therapy, four (50%) on dual therapy, one (13%) on triple therapy, and one (13%) on no therapy. None of the patients required intubation; however, two (25%) required continuous NIPPV. One tracheostomy patient whose baseline was no support during the day was escalated to full ventilatory support, and one patient received an increase in oxygen flow via nasal cannula.

With respect to viral therapy, three patients (38%) received remdesivir, two (25%) received intravenous corticosteroids, and one (13%) got convalescent plasma. Death occurred in a patient with failing Fontan physiology. None of the hospitalized patients required extracorporeal membrane oxygenator support nor were diagnosed with multisystem inflammatory syndrome in children (MIS-C). By univariate analysis, none of the following variables were found to be associated with the increased need for hospitalization: ethnicity, history of prematurity, congenital heart disease, congenital diaphragmatic hernia, or the number of PH targeted therapies at the time of COVID-19 diagnosis (none vs. single vs. double vs. triple; all $p > .05$).

3.3 | Outpatient follow-up

Twenty-one of the identified 23 patients (91%) have had an outpatient follow-up encounter, median of 101 days (IQR: 25–75th, 50–159 days) after COVID-19 infection. Five patients underwent 6MWT, median 64 days after COVID-19 infection (range 42–133 days), and three of them walked a lesser distance than baseline, median of -12 m (IQR: 25–75th, -18 to $+49$ m). Four patients underwent pulmonary function testing and predicted forced vital capacity (FVC)% (median -10% , range -11% to $+6\%$) and predicted forced expiratory volume in the first second (FEV1%) (median -14% , range -12% to -18%) were decreased from baseline in three of the patients. PH therapy was escalated in four (20%) of the patients (two on dual therapy and two on triple therapy), and one patient required a transient increase of nasal cannula respiratory support with higher oxygen flow for 5 months post-COVID-19. Eleven patients with biventricular physiology/anatomy underwent post-COVID-19 echocardiogram. Of these 11 patients, 2 had worsening tricuspid regurgitation (TR) severity from mild to moderate, 1 had an increase in TR velocity from 4 to 5.1 m per s, and 2 had worsening RV systolic function. The remaining patients had stable post-COVID-19 echocardiograms compared to baseline.

3.4 | Specific population

3.4.1 | Trisomy 21

Five of our 23 patients had Trisomy 21, with 3 (60%) on dual therapy and 2 (40%) on single-agent therapy. All patients had history of complete atrioventricular septal defect, one of them was unrepaired at the time of infection. Respiratory support consisted of continuous oxygen therapy via nasal cannula ($n=1$), NIPPV at night ($n=1$), and tracheostomy ($n=1$); these latter two patients required hospitalization. The child who was only on nocturnal support was escalated to continuous NIPPV and the patient with tracheostomy required escalation from heat and moisture exchanger to continuous mechanical ventilation. Two Trisomy 21 patients required dose escalation of baseline PH targeted therapy but no new therapy classes at the time of outpatient follow-up. The five Trisomy 21 patients identified in our cohort survived COVID-19 disease.

4 | DISCUSSION

The Texas Children's Hospital Pulmonary Hypertension Center actively manages a total of 299 patients, ranging from 4 months of age to 21 years old, and the majority are females ($n=154$ or 52%). The race/ethnicity distribution is Caucasians ($n=107$ or 36%), Hispanics ($n=106$ or 35%) and African Americans ($n=64$ or 21%). One-hundred thirty-seven patients (46%) have had tracheostomies. PH targeted therapies consist of none ($n=91$ or 30%), single ($n=117$ or 40%), dual ($n=42$ or 14%), and triple agents ($n=49$ or 16%).

As vulnerable as the PH population was initially feared to be,¹ to date, these patients have been less affected than patients with other comorbidities.^{2,5} Our program is a large pediatric center, of which 8% have had diagnosed COVID-19 disease, 3% have required hospitalization, and 0.3% have died due to this illness. This study supports that COVID-19 disease does not typically or seriously affect pediatric patients with PH, and mortality due to this illness is rare. Consistent with what has been previously reported locally,⁶ we found that there is an ethnicity disparity characterized by Hispanics getting COVID-19 disease.

PH patients have had a lower incidence than expected of COVID-19 with respect both to diagnosis and complications.¹ None of our patients required intubation, or extracorporeal mechanical oxygenator use. One potential explanation for the low infectious rate is that our patients are young and accustomed to being in home isolation due to their medical complexity, history of complications due to infectious diseases, and/or need for technological support.^{2,7} Additionally, it has been proposed that a unique modulation of inflammatory response, either primary and developmental or secondary to the use of endothelin receptor antagonists and phosphodiesterase 5 inhibitors, have played a significant role in decreasing the severity of illness to COVID-19.^{2,3,5}

Our study found a slight female predominance (56%) in patients who got COVID-19 disease, as previously reported,⁸ and consistent

with the sex distribution in our PH population and with the national data from the Centers for Disease Control and Prevention.⁹ Despite Caucasians being the predominant race in our institution and consistent with our local data,⁶ Hispanics represented the primary race/ethnicity in our PH patients diagnosed and hospitalized with COVID-19. This finding is most likely due to our local demographics; however, SARS-CoV-2 has been reported more frequently in racial minorities,^{8,10} Hispanics being the race/ethnic group most affected by this disease nationally.⁹ Leeb et al. reported that Hispanics and African Americans required more hospitalizations and intensive care unit admissions.¹⁰ The race/ethnicity disparity has been previously explained due to socioeconomic factors such as exposure from adult family members whose occupations require being front-line providers with difficulties in social distancing¹⁰ and/or being part of multi-generational or multi-family households.¹¹ Additionally, there has been an association between obesity and COVID-19 disease, a comorbidity frequently present in Hispanics and African Americans.¹²

Our institution follows 37 patients with diagnosis of Down Syndrome and PH, comprising 13% of our population. In contrast to what has been reported in the adult literature,¹³ outcomes in pediatric PH patients with Trisomy 21 did not differ from the rest of our patients, characterized by two hospitalizations and no mortality, albeit that our numbers are small. The two patients who were hospitalized had similar hospital length of stay compared to the rest of our population.

The long-term outcomes of COVID-19 disease remain unknown, especially in patients with chronic lung disease like many of our PH patients. Adult literature reports that post-COVID PFTs were characterized by lower total lung capacity likely due to deconditioning; however, baseline PFT status is unclear in this cohort.¹⁴ Additionally, some adult patients had hypoxemia with exertion, did not reach their target distance, or walked less on their post-COVID 6MWT. In our identified cohort, three of five patients had decreased 6MWT distance and three of four patients had decreased percent predicted of FVC and FEV1 from baseline. An inherent limitation in the pediatric PH population is that patients may be too young or developmentally immature to perform 6MWT and PFT, and some outpatient encounters have been through telemedicine preventing objective testing.

Concerns have been expressed about the consequences of elevated PVR due to COVID-19 disease in the RV systolic function.¹ We have found that all, but two, of our patients with biventricular anatomy/physiology who underwent post-COVID echocardiogram as an outpatient had unchanged RV systolic function, although two had worsening TR severity, with one having worsening TR velocity compared to pre-COVID study. However, cardiac catheterization has not been performed in any of the 21 COVID-19 diagnosed patients to measure PVR postinfection.

5 | CONCLUSIONS

In our institution, COVID-19 infection in pediatric PH patients was overall rare and well-tolerated. Very few required hospitalizations and of these, none required intubation or extracorporeal membrane

oxygenation. While no risk factors were identified for COVID-19 diagnosis, infection was seen more frequently in Hispanics. Trisomy 21 patients with PH had a similar clinical course to non-Trisomy 21 PH children. Short-term follow-up has shown a negative impact on PFT and 6MWD; however, these functional tests will need to be followed long-term to determine the trajectory.

Although most of our pediatric PH patients have had favorable short-term outcomes of COVID-19 infection, the long-term consequences of this disease remain unknown and will need careful attention as a potential modifier of disease for the PH clinical landscape.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Raysa Morales-Demori: Conceptualization (lead); data curation (lead); formal analysis (lead); methodology (lead); writing – original draft (lead); writing – review & editing (lead). **George B. Mallory:** Writing – review and editing (equal). **Corey Chartan:** Writing – review and editing (equal). **Ryan Coleman:** Writing – review and editing (equal). **Fadel Ruiz:** Writing – review and editing (equal). **Natalie Villafranco:** Writing – review and editing (equal). **Elise Whalen:** Writing – review and editing (equal). All authors contributed to the study conception and design.

ORCID

Raysa Morales-Demori  <https://orcid.org/0000-0002-7602-7512>

George B. Mallory  <https://orcid.org/0000-0001-8099-4567>

Elise Whalen  <https://orcid.org/0000-0002-6191-8881>

Nidhy Varghese  <https://orcid.org/0000-0003-4422-3065>

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