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Characteristics and outcomes of acute COVID-19 infection in paediatric and young adult patients with underlying cardiac disease

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Abstract

Objective To describe outcomes of acute coronavirus disease 2019 in paediatric and young adult patients with underlying cardiac disease and evaluate the association between cardiac risk factors and hospitalisation. *Study design* We conducted a retrospective single-institution review of patients with known cardiac disease and positive severe acute respiratory syndrome coronavirus 2 RT-PCR from 1 March, 2020 to 30 November, 2020. Extracardiac comorbidities and cardiac risk factors were compared between those admitted for coronavirus disease 2019 illness and the rest of the cohort using univariate analysis. *Results* Forty-two patients with a mean age of 7.7 ± 6.7 years were identified. Six were 18 years of age or more with the oldest being 22 years of age. Seventy-six percent were Hispanic. The most common cardiac diagnoses were repaired cyanotic (n = 7, 16.6%) and palliated single ventricle (n = 7, 16.6%) congenital heart disease. Fourteen patients (33.3%) had underlying syndromes or chromosomal anomalies, nine (21%) had chronic pulmonary disease and eight (19%) were immunosuppressed. Nineteen patients (47.6%) reported no symptoms. Sixteen (38.1%) reported only mild symptoms. Six patients (14.3%) were admitted to the hospital for acute coronavirus disease 2019 illness. Noncardiac comorbidities were associated with an increased risk of hospitalisation ($p = 0.02$), particularly chronic pulmonary disease ($p = 0.01$) and baseline supplemental oxygen requirement ($p = 0.007$). None of the single ventricle patients who tested positive required admission. *Conclusions* Hospitalisations for coronavirus disease 2019 were rare among children and young adults with underlying cardiac disease. Extracardiac comorbidities like pulmonary disease were associated with increased risk of hospitalisation while cardiac risk factors were not.

Introduction

In March 2020, the World Health Organization declared the spread of the novel severe acute respiratory syndrome coronavirus 2 a global pandemic.[1] Based on the initial data from pandemic epicentres over the ensuing months, the burden of the resulting coronavirus disease 2019 in paediatric populations appeared low compared to the disease burden in adults and particularly the elderly. Paediatric patients comprise only 2% of reported cases and the majority of infections reported in children were asymptomatic or resulted in only mild illness.[2–7] Deaths among patients under 21 years of age have been rare.[8]

Even though most paediatric and young adult cases of coronavirus disease 2019 have been asymptomatic or mild, more severe cases and hospitalisations have been reported.[7] The risk factors for more severe illness in this group are not well understood.[6,9–11] Previous reports suggest age, obesity, type 1 diabetes, genetic disorders, immunosuppression, chronic pulmonary disease, and Latino, Hispanic, or Black racial or ethnic identification may place paediatric and young adult patients at higher risk for more severe illness and hospitalisation.[7,10–15]

While clinical evidence suggests that underlying cardiovascular disease increases the risk for severe coronavirus disease 2019 illness, hospitalisation, and death in adult patients,[16–18] clarity on the role of underlying congenital heart disease and other paediatric-onset chronic cardiovascular conditions has been slower to emerge. While several studies of mostly adult patients with underlying congenital heart disease showed very rare hospitalisations and deaths due to coronavirus disease 2019 infection,[19,20] more recent data from a large database of over 800 hospitals in the United States found an association between diagnostic codes for congenital cardiac and circulatory anomalies and increased risk of severe disease and hospitalisation in patients under 18 years of age.[21] Given that children with heart disease tend to be at increased risk of morbidity from other viral respiratory infections[22] and are more likely to have conditions associated with immune dysregulation, such as DiGeorge syndrome, trisomy 21, and heterotaxy syndrome, it is important to continue to clarify their risk during this evolving pandemic.

Here, we report the characteristics and outcomes of paediatric and young adult patients with known underlying cardiovascular disease and confirmed severe acute respiratory syndrome coronavirus 2 infection cared for at a large free-standing children's hospital in a part of the United States heavily affected by the coronavirus disease 2019 pandemic.

Methods

Study setting and cohort

This study was conducted at Children's Hospital Los Angeles, a large University-affiliated free-standing children's hospital in Los Angeles, CA. The hospital and the Heart Institute generally care for patients under 23 years of age, with 11,963 reported outpatient visits across the greater Los Angeles area in FY 2020. During the coronavirus disease 2019 pandemic, severe acute respiratory syndrome coronavirus 2 RT PCR testing was performed not only on patients with symptoms suggestive of infection, but also on all patients admitted to the hospital for any reason, and on those with any planned outpatient procedures, including those under anaesthesia (such as cardiac catheterisation), sedation (such as MRI) or prolonged interactive testing (such as exercise stress test).

Our Cerner electronic medical records system was queried for all patients between 1 march, 2020 and 30 November, 2020 who tested positive for severe acute respiratory syndrome coronavirus 2 by RT-PCR and also had an order placed for a transthoracic echocardiogram at any time at our institution. These patients' charts were reviewed, and only patients with a history of structural, functional, or electrophysiological heart disease were included in the study cohort. Patients were excluded if they had no significant cardiac disease, including those with isolated patent foramen ovale, non-cardiac chest pain, innocent heart murmur, or normal screening echocardiogram related to chemotherapy or scoliosis surgery. Additional patients may have been included in this study if they or their families had contacted our office and reported positive testing at another site or medical facility. In these cases, the documented telephone notes regarding symptoms and clinical status were reviewed and, since it was not clinically indicated for the office to collect documented confirmation of the positive tests, these patients were only included if they reported symptoms consistent with coronavirus disease 2019 infection or confirmed symptomatic or hospitalised close contacts. This study was reviewed and approved by the Institutional Review Board.

Study variables and outcomes

Each patient's chart was reviewed retrospectively. Demographic, anthropomorphic, and geographic data were recorded, including primary language, ethnicity, race, age, weight, and body mass index (measured only in patients 2 years of age or older). All underlying non-cardiac diagnoses and co-morbidities were recorded. Cardiac diagnoses and procedures were recorded in detail, and the echocardiogram most closely temporally related to the positive severe acute respiratory syndrome coronavirus 2 test was assessed for significant residual lesions and ventricular function. Congenital heart disease was categorised into the following groups: Left to Right shunt (repaired and un-repaired), cyanotic (repaired and un-repaired), obstructive lesions (left and right, repaired and un-repaired), single ventricle palliation (systemic to pulmonary artery shunt and cavo-pulmonary shunt). Acquired heart disease was categorised as valve disease, cardiomyopathy or cardiac tumor, history of heart transplantation, pulmonary hypertension (defined by mean pulmonary artery pressure >25 mmHg), vasculopathy/arteriopathy/venous anomaly, and primary arrhythmia.

The primary outcome of interest was moderate or severe illness, defined as death or hospitalisation for symptoms attributable to the severe acute respiratory syndrome coronavirus 2 infection where there was no alternative explanation, including respiratory distress, gastrointestinal symptoms or haemodynamic instability. Patient illness was classified as mild if they reported symptoms by telephone and stayed at home, or were evaluated in the emergency department and deemed not ill enough to be admitted to the hospital. Asymptomatic was defined as those with no symptoms who tested positive when screened because of an exposure or an anticipated procedure. In those with moderate to severe illness, the length of hospitalisation, level of care, days in intensive care unit and use of severe acute respiratory syndrome coronavirus 2 specific therapies were recorded. In addition to potential cardiac risk factors (Table 2), pulmonary risk factors were assessed, including the use of supplemental oxygen therapy, chronic lung disease as diagnosed by a pulmonologist using standard clinical definitions, obstructive sleep apnoea diagnosed by sleep study, asthma, and restrictive lung disease diagnosed by pulmonary function testing. Other co-morbidities that were recorded included obesity (body mass index ≥ 95th percentile for age and sex in patients ≥ 2 years of age), immunosuppression (by concurrent immunologic disease or medications), or an underlying syndrome or genetic or chromosomal anomaly.

Statistical analysis

Baseline characteristics of the cohort were described using means and standard deviations for normally distributed numerical data, medians and ranges for skewed numerical data, and proportions for categorical data. Fisher's exact testing was used to compare the prevalence of underlying risk factors in patients admitted to the hospital versus patients with mild or asymptomatic disease. Stata version 14.2 was used for all analysis.

Results

Baseline cohort characteristics and non-cardiac risk factors

A total of 42 patients with established structural, functional, or electrophysiological cardiovascular disease were identified who tested positive for acute novel coronavirus infection by severe acute respiratory syndrome coronavirus 2 PCR testing between 1 March, 2020 and 30 November, 2020. Three patients who reported positive testing outside of our facility who had close household contacts ill or hospitalised with confirmed coronavirus disease 2019 were included. The cohort's baseline characteristics are presented in Table 1. Average age and weight were 7.7 years and 31.6 kg, respectively. Six patients were 18 years of age or greater and the oldest patient was 22 years of age. Body mass index percentiles were ≥85th in 31.3% and ≥95th in 15.6%. 76.2% of the cohort identified as Hispanic. Fourteen patients (33.3%) had an underlying syndrome or known genetic or chromosomal anomaly, the most common of which were trisomy 21 (n = 2) and heterotaxy syndrome (n = 2).

Nine patients (21%) carried diagnoses of chronic pulmonary disease, including a history of chronic lung disease (n = 3), obstructive sleep apnoea (n = 2), a combination of chronic lung

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Table 1. Baseline characteristics of patient cohort.

N	42
Age, mean ± SD	7.7 ± 6.7 years
Age by category, n (%)	
<1 year	5 (11.9)
1–10 years	21 (50)
10–18 years	10 (23.8)
≥18 years	6 (14.3)
Male, n (%)	24 (57.1)
Weight, mean ± SD	31.6 ± 26.9 kg
BMI*, mean ± SD (n = 32 patients ≥2 years of age)	20.0 ± 5.9 kg/m^2
BMI greater than 85th percentile, n (%)	10 (31.3)
BMI greater than 95th percentile, n (%)	5 (15.6)
Primary language, n (%)	
English	25 (59.5)
Spanish	16 (38.1)
Chinese	1 (2.4)
Race/ethnicity, n (%)	
Hispanic	32 (76.2)
Caucasian/White, non-Hispanic	3 (7.1)
Unknown	3 (7.1)
Black	2 (4.8)
Asian	2 (4.8)
On supplemental oxygen at baseline, n (%)	3 (7.1)
Syndromic diagnosis or chromosomal/genetic anomaly**, n (%)	14 (33.3)
Immunosuppressed status, n (%)	8 (19)
Chronic pulmonary disease***, n (%)	9 (21.4)

*BMI was analysed only in patients 2 years of age or greater based on current guidelines from the Centers for Disease Control and Prevention
**Syndromic diagnoses and known chromosomal/genetic anomalies included heterotaxy syndrome (n = 2), trisomy 21 (n = 2), tuberous sclerosis (n = 1), *BMPR2* mutation (n = 1), chromosome 4q deletion (n = 1), Lowry–MacLean syndrome (n = 1), VACTERL association (n = 1), *ABCC6* mutation (n = 1), 8p23.1 chromosomal deletion (n = 1), Duchenne muscular dystrophy (n = 1), Li Fraumeni syndrome (n = 1), and CHARGE association (n = 1)
***Chronic pulmonary diseases include chronic lung disease or dependence on supplemental oxygen therapy for pulmonary insufficiency, obstructive sleep apnoea, asthma, and restrictive lung disease

disease, obstructive sleep apnoea, and lung hypoplasia (n = 1), moderate persistent asthma that was poorly controlled on multiple medications (n = 1), and restrictive lung disease related to musculoskeletal abnormalities (n = 2). Three patients were on home supplemental oxygen therapy at the time of their positive severe acute respiratory syndrome coronavirus 2 test – one for obstructive sleep apnoea, one for chronic lung disease, and one for primary pulmonary arterial hypertension. One of the obstructive sleep apnoea patients was treated with continuous positive airway pressure at home. Eight patients (19%) were immunosuppressed with either concurrent chemotherapy for an underlying oncologic process (n = 3), a solid organ transplantation medical immunosuppression regimen (n = 3), or chronic oral corticosteroid therapy (n = 2).

Table 2. Cardiovascular diagnoses and cardiac therapy histories.

N	42
Cardiac diagnosis category, n (%)	
Repaired cyanotic CHD	7 (16.7)
Single ventricle with cavopulmonary anastomosis	7 (16.7)
Unrepaired left-to-right shunt lesion	6 (14.3)
Cardiomyopathy or cardiac tumour	4 (9.5)
Vasculopathy or vascular anomaly	4 (9.5)
Repaired obstructive CHD	3 (7.1)
Unrepaired obstructive CHD	2 (4.8)
Unrepaired cyanotic CHD	2 (4.8)
Repaired left-to-right shunt lesion	2 (4.8)
History of heart transplantation	2 (4.8)
Primary pulmonary hypertension	1 (2.4)
Supraventricular tachycardia	1 (2.4)
Rheumatic mitral valve disease	1 (2.4)
History of cardiac surgery or intervention, n (%)	25 (59.5)
Presence of residual or unrepaired haemodynamically significant lesion (n = 34 with congenital or structural lesion or history of cardiac intervention), n (%)	17 (50)
Systemic ventricular function at baseline prior to test, n (%)	
Normal	35 (83.3)
Mildly reduced	4 (9.5)
Moderately reduced	3 (7.1)
Baseline cardiac cyanosis, n (%)	5 (11.9)
On cardiac medications, n (%)	20 (47.6)
Angiotensin converting enzyme inhibitor	8 (19.1)
Diuretic	6 (14.6)
Beta blocker	4 (9.5)
Pulmonary vasodilator	4 (9.5)
Digoxin	1 (2.4)
Baseline anticoagulation therapy, n (%)	16 (38.1)

Underlying cardiovascular disease and cardiac treatment histories

The most common underlying cardiac diagnoses were repaired cyanotic congenital heart disease (n = 7, 16.6%), single ventricle congenital heart disease palliated with cavo-pulmonary anastomosis (n = 7, 16.6%), and un-repaired left-to-right shunt lesions (n = 6, 14.3%), accounting for nearly half of the cohort (see Table 2). There were nine additional patients with other forms of repaired or unrepaired congenital heart disease. Four had cardiomyopathy or cardiac tumour: anthracycline induced cardiomyopathy with mild left ventricular systolic dysfunction (n = 1), cardiomyopathy associated with muscular dystrophy (n = 1), persistently mild left ventricular systolic dysfunction of unknown aetiology in the setting of end stage renal disease and chronic dialysis therapy (n = 1), and rhabdomyoma associated with underlying tuberous sclerosis (n = 1). Two patients had a history of orthotopic heart transplantation. Four patients had vasculopathy or vascular

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anomalies: history of Kawasaki disease with coronary artery aneurysms (n = 1), generalised arterial calcification of infancy type 2 involving the aorta and pulmonary arteries requiring multiple interventions (n = 1), atresia of the inferior vena cava to right atrial junction requiring recanalisation and stent implantation (n = 1), and Takayasu arteritis (n = 1). There was one patient with primary pulmonary arterial hypertension on triple pulmonary vasodilator medications, one patient being treated with a beta blocker for a history of supraventricular tachycardia, and one with rheumatic mitral valve disease that had been surgically repaired.

Twenty-five (59.5%) patients had undergone a cardiac operation or catheterisation procedure for their underlying cardiovascular disease, and seventeen (50%) of the 34 patients with congenital or structural lesions or history of surgical or transcatheter intervention had evidence of residual or unrepaired haemodynamically significant cardiac lesions. The residual lesions included severe pulmonary valve insufficiency after complete repair of tetralogy of Fallot using a transannular patch augmentation of the pulmonary outflow tract (n = 3), palliated single ventricle congenital heart disease without Fontan completion (n = 3), residual outflow tract obstruction after repair (n = 2), and residual insufficiency after valve repair (n = 2). Unrepaired lesions included tetralogy of Fallot (n = 1), pulmonary valve stenosis n = 2), patent ductus arteriosus (n = 2) and atrial septal defect (n = 1).

Five patients had baseline cyanosis secondary to unrepaired cyanotic congenital heart disease or single ventricle congenital heart disease without Fontan completion. Seven patients had reduced systolic function of the systemic ventricle on echocardiogram prior to diagnosis with severe acute respiratory syndrome coronavirus 2 infection. Twenty (47.6%) patients were taking cardiac medications and 16 (38.1%) were on baseline anticoagulation therapy.

Outcomes of acute severe acute respiratory syndrome coronavirus 2 infection

Nineteen patients (47.6%) reported no symptoms and tested positive for severe acute respiratory syndrome coronavirus 2 infection on pre-procedural screening (n = 17) or screening due to infected contacts (n = 2). Sixteen (38.1%) reported only mild symptoms, including transient fever, anosmia and ageusia, upper respiratory congestion, cough, headache, and diarrhoea. Three of the mildly symptomatic patients required inpatient admission for reasons that were ultimately deemed to be unrelated to their severe acute respiratory syndrome coronavirus 2 infection. For example, one patient with history of supraventricular tachycardia underwent an exploratory laparotomy for bilious emesis and abdominal pain that identified intussusception secondary to Burkitt's lymphoma. Another patient was readmitted after Fontan completion for shortness of breath secondary to a large post-operative chylous effusion; the patient's symptoms resolved with chest tube placement and evacuation of the fluid. The third, a teenager with a history of transcatheter atrial septal defect closure and known medulloblastoma, was admitted with an exacerbation of chronic nausea, vomiting, and headache that was attributed to a recent wean in his chronic steroid therapy.

Six patients (14.3%) were admitted to the hospital for moderate or severe acute coronavirus disease 2019 illness. Details regarding the underlying characteristics of these patients, their presenting symptoms, and their hospital courses are presented in Table 3. All six of the admitted patients were of Hispanic ethnicity. Two patients had repaired congenital heart disease without significant residual lesions, one had a small atrial septal defect, two had moderate pulmonic valve stenosis that had not yet met threshold for intervention, and one had mild left ventricular dysfunction secondary to anthracycline chemotherapy. Three of the admitted patients had echocardiography during admission and no changes were noted compared to the most recent pre-admission echocardiograms. Only one of the admitted patients was taking a chronic cardiac medication. All of these patients had at least one underlying non-cardiac comorbidity. One patient required intubation and mechanical ventilation and three required intensive care unit level care for respiratory failure. None required inotropic support. One patient on chemotherapy for treatment of acute lymphoblastic leukaemia had multiple readmissions following this admission for fever in the setting of neutropenia and had persistently positive severe acute respiratory syndrome coronavirus 2 PCR tests. All were alive at the conclusion of the study period. One patient who was not in the admitted cohort died during the study period due to complications of medulloblastoma unrelated to severe acute respiratory syndrome coronavirus 2 infection.

Patients who were hospitalised for coronavirus disease 2019 were more likely to have at least one underlying non-cardiac comorbidity ($p = 0.02$, Table 4), to have chronic pulmonary disease ($p = 0.01$) and to be on supplemental oxygen therapy at baseline ($p = 0.007$). The frequency of underlying syndromes or chromosomal/genetic anomalies and cardiac risk factors, including ventricular dysfunction, prevalence of residual or unrepaired lesions, baseline cardiac cyanosis, and use of cardiac medications were generally similar between those who were admitted to the hospital for coronavirus disease 2019 and those with mild or asymptomatic disease. None of the single ventricle patients who tested positive required admission. Although all admitted patients reported Hispanic ethnicity, this did not achieve statistical significance as a univariate risk factor for hospital admission ($p = 0.7$).

Discussion

In this report, we describe the characteristics and outcomes of our centre's patients with established underlying cardiac disease who were known to be acutely infected with severe acute respiratory syndrome coronavirus 2. A wide variety of cardiac diseases and a spectrum of severity were represented in our cohort, from a small atrial septal defect and controlled supraventricular tachycardia to cardiomyopathy, primary pulmonary hypertension, palliated single ventricle congenital heart disease, and cyanotic congenital heart disease. Our sampling methodology selected for children presenting to our institution for admissions, operations, catheterisations, and advanced imaging or testing. Sampling therefore likely skews the sample towards children with a higher degree of medical complexity who interact more frequently with the medical system. As such, other significant comorbidities, including chronic respiratory disease and underlying syndromes and chromosomal anomalies were relatively common in our cohort.

Based on our sampling methods, it is impossible to estimate the incidence of hospital admission among paediatric patients with underlying cardiac disease infected with severe acute respiratory syndrome coronavirus 2 or to compare this population to the general paediatric population. The study is also limited by the small number of patients with severe acute respiratory syndrome coronavirus 2 infection at our single institution. However, it is notable that a large cardiac referral centre that cares for many of the thousands of children with established cardiac disease across a large

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Table 3. Characteristics of patients with underlying cardiac disease presenting with moderate or severe acute COVID-19.

	Patient					
	1	2	3	4	5	6
Age (years) Race/ethnicity	1.2 Hispanic	2.5 Hispanic	3.0 Hispanic	6.5 Hispanic	18.7 Hispanic	21.1 Hispanic
Acute illness presentation	Acute on chronic resp. failure	Fever/neutropenia, O2 requirement	Fever, vomiting, increased O2	Fever, cough, vomiting/dehydration	Fever, cough, respiratory failure	Fever, respiratory failure
Cardiac history	Moderate pulmonic valve stenosis, no intervention	Anthracycline induced cardiomyopathy	Moderate pulmonic valve stenosis, no intervention	Small atrial septal defect without right heart dilation	Repaired coarctation of aorta, hypertrophic cardiomyopathy	Repaired atrioventricular canal defect
Residual cardiac lesions	Pulmonic valve stenosis	No	Pulmonic valve stenosis	No	No	No
Cardiac medications	Chlorothiazide diuretic	None	None	None	None	None
Ventricular dysfunction	No	Yes, mild	No	No	No	No
Non-cardiac comorbidities	CLD of prematurity on supplemental home oxygen	High risk B-cell ALL on chemotherapy	CHARGE syndrome; CLD, OSA on supplemental home oxygen	ESRD status-post renal transplant on immunosuppressive medication regimen	Lowry–Mclean syndrome, CLD	Trisomy 21, obesity, ALL on chemotherapy, OSA on nighttime oxygen therapy
Respiratory support during admission	Intubation for 4 days	Simple mask oxygen	Increased nasal cannula oxygen	None	BiPAP, supplemental oxygen	CPAP, supplemental oxygen
ICU level care required	Yes	No	No	No	Yes	Yes
SARS-CoV-2 therapies administered	Remdesivir and Dexamethasone	Remdesivir	None	None	Remdesivir, Dexamethasone, Lovenox	Remdesivir and Dexamethasone
Length of admission (days)	15	4	6	3	6	41
Readmission for SARS-CoV-2 symptoms	No	Yes, multiple admissions for fever with persistently positive PCR	No	No	No	No
Alive at end of study period	Yes	Yes	Yes	Yes	Yes	Yes

ALL=acute lymphoblastic leukaemia; BiPAP=bilevel positive airway pressure; CLD=chronic lung disease; CPAP=continuous positive airway pressure; ESRD=end stage renal disease; OSA=obstructive sleep apnoea; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2

area heavily affected by the coronavirus disease 2019 pandemic only saw six hospital admissions and no deaths attributable to severe acute respiratory syndrome coronavirus 2 infection among its patients during the study period.

In contrast to these rare admissions among our centre's patients, in Los Angeles County there were approximately 3000 hospital admissions for novel coronavirus-related illnesses among the general population on the final day of our study period alone, and more than one million cases and 15,000 deaths at the time of writing this manuscript.[23] There is no compelling reason to believe that infection rates in our centre's cardiac patients were meaningfully different from the surrounding community. We also believe it would be unlikely for a patient followed by our centre for underlying cardiac disease to be admitted at another hospital in the area without our knowledge and documentation in the chart, or without transfer to our hospital for specialised paediatric care.

Traditional cardiac risk factors for more severe acute respiratory infections in children did not appear to apply to acute severe acute respiratory syndrome coronavirus 2 infection in our cohort. For example, the great majority of patients who required cardiac medications or who had ventricular dysfunction or residual haemodynamically significant cardiac lesions reported asymptomatic or mild infections. None of the five patients with residual cyanotic congenital heart disease or the seven with palliated single ventricle congenital heart disease, those we consider among the most at risk for severe respiratory infections, required hospital admission for acute severe acute respiratory syndrome coronavirus 2 infection during this study period.

Patients in this cohort with an extracardiac comorbidity, however, were at increased risk of hospital admission for more severe illness. All six cardiac patients admitted for acute severe acute respiratory syndrome coronavirus 2 infection during the study period had at least one extracardiac co-morbid condition and half of the admitted patients had multiple extracardiac comorbid conditions. Three patients had immune suppression due to oncological processes and concurrent chemotherapy in two and recent solid organ

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Table 4. Prevalence of comorbid and underlying cardiac risk factors among patients admitted for acute COVID-19 versus those who were mildly ill or asymptomatic.

Variable	Patients admitted for acute SARS-CoV-2 illness (N = 6), N (%)	Patients with mild or asymptomatic SARS-CoV-2 infection (N = 36), N (%)	p-value***
≥1 comorbiditiy*	6 (100)	17 (47)	**0.02**
≥2 comorbidities*	3 (50)	6 (17)	0.1
Syndrome or chromosomal/genetic anomaly	3 (50)	11 (31)	0.4
Immunosuppression	3 (50)	5 (14)	0.07
Chronic pulmonary disease**	4 (67)	5 (12)	**0.01**
Home supplemental oxygen therapy	3 (50)	1 (3)	**0.007**
Obesity	1 (17)	4 (11)	0.7
Overweight or obese	2 (33)	8 (22)	0.6
Systemic ventricular dysfunction	1 (17)	5 (14)	0.7
Residual/Unrepaired cardiac lesions	2 (33)	15 (42)	0.5
Baseline cardiac cyanosis	0 (0)	5 (14)	0.4
Cardiac medications	1 (17)	19 (53)	0.2
Single ventricle physiology	0 (0)	7 (19)	0.6

*Comorbidities include obesity, immunosuppression by concurrent immunologic disease or medications, an underlying syndrome or genetic or chromosomal anomaly, and a history of chronic pulmonary disease (including chronic lung disease or dependence on supplemental oxygen therapy for pulmonary insufficiency, obstructive sleep apnoea, asthma, or restrictive lung disease)
**Chronic pulmonary diseases include chronic lung disease or dependence on supplemental oxygen therapy for pulmonary insufficiency, obstructive sleep apnoea, asthma, and restrictive lung disease
***p-values were derived using univariate analysis by Fisher's exact testing. A p-value under 0.05 was considered statistically significant and these p-values are bolded

transplantation requiring medical immune suppression in one. Four of the admitted patients had chronic pulmonary diseases, and two of these patients required supplemental oxygen at home. Three had a known syndromic diagnosis or chromosomal anomaly, and one was obese. When comorbidities were analysed individually as risk factors, only chronic pulmonary disease was associated with hospitalisation to a statistically significant degree, and immune suppression approached statistical significance. While obesity has been identified as a strong risk factor for more severe coronavirus disease 2019 and hospitalisation in large groups of paediatric patients,[7,21] it was not associated with more severe disease in our patients. This finding could be due in part to the small number of patients used in our analysis, which limits our sensitivity to detect potential risk factors in cardiac patients. Additionally, with only six patients in the hospitalised group it was not appropriate to attempt to fit a multivariable regression model. Data from a large multicentre study could potentially allow for regression analysis to better characterise the contribution of each risk factor.

It is important to note that a large majority of our cohort was of Hispanic ethnicity, which itself has been associated with more severe coronavirus disease 2019 in children and young adults.[7] Although all six admitted patients in our cohort were Hispanic, our results did not identify this as a statistically significant risk factor due to our small number of patients and the predominance of Hispanic patients in both comparison groups. The results may be reflective of the disproportionately high rates of severe acute respiratory syndrome coronavirus 2 infection in Hispanic communities in our region, but they are not conclusive regarding ethnicity as a risk factor for more severe disease.

There were concerns early in the pandemic that paediatric patients with underlying cardiac disease would be at elevated risk for moderate to severe illness from severe acute respiratory syndrome coronavirus 2 infection given their risk of illness and hospitalisation with other respiratory viruses and elevated prevalence of immune dysfunction. Additionally, many paediatric cardiac patients are prescribed angiotensin-converting enzyme inhibitors that may upregulate the angiotensin converting enzyme 2 receptors that are used by the novel coronavirus to infect cells. This interaction between severe acute respiratory syndrome coronavirus 2 and the renin-angiotensin-aldosterone system provided a potential reason that hypertensive adult patients tended to have more severe illness.[24]

However, the limited evidence that has emerged has not been entirely clear on the role of underlying cardiac disease and the risk of severe coronavirus disease 2019 in children and young adults. A national survey from Italy described only rare admissions and no deaths in a cohort of 76 patients with congenital heart disease and severe acute respiratory syndrome coronavirus 2 infection between February and April 2020. Only four patients in this cohort were under 18 years of age and all four were asymptomatic.[19] Similarly, a large congenital heart disease centre in New York City reported only nine cases of moderate or severe coronavirus disease 2019 and three deaths among their congenital heart disease patients between March and July 2020. Only two patients under 21 years of age required hospitalisation and none died. In their cohort, most of whom were adults, cardiac risk factors like anatomical complexity, decreased ventricular function, and single ventricle physiology were not associated with severe disease.[20] In contrast, a recent large cross-sectional database study of over 40,000 patients from over 800 hospitals in the United States found that diagnostic codes for cardiac and circulatory anomalies were associated with increased risk of severe disease and hospitalisation in patients under 18 years of age.[21] However, while large clinical databases are able to include more patients and may be more representative of the population, they are limited by the use of diagnostic codes, which can have low specificity and introduce significant misclassification of both risk factors and outcomes. These problems are magnified in

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the study of congenital heart diseases, which are highly variable and not clinically described well by current diagnostic codes.

As noted above, this study is limited by including a small number of patients from a single institution and by sampling only patients who presented to the hospital for admissions, procedures and other tests in accordance with hospital protocol as opposed to a more population-based research protocol. However, the results show that our centre's large population of paediatric and young adult patients with a wide variety of cardiac diseases did not experience a heavy burden of coronavirus disease 2019 illness during the first 9 months of the global pandemic. Our findings further support previous reports that paediatric cardiac diseases do not appear to significantly increase the risk of severe coronavirus disease 2019 or hospitalisation. The findings would be strengthened by further reports from other paediatric heart centres.

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Ethics Approval. This study was reviewed and approved by the Institutional Review Board at Children's Hospital Los Angeles and was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

Consent to Participate. The Institutional Review Board waived the requirement for consent to participate.

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