Cardiology in the Young

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Cardiovascular sequelae from COVID-19: perspectives from a paediatric cardiac ICU

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Abstract

Objective: Paediatric ICUs have shared the burden of the COVID-19 pandemic, including subspecialty cardiac ICUs. We sought to address knowledge gaps regarding patient characteristics, acuity, and sequelae of COVID-19 in the paediatric cardiac ICU setting. *Design:* Retrospective review of paediatric cardiac ICU admissions with COVID-19-related disease. *Setting:* Single centre tertiary care paediatric cardiac ICU. *Patients:* All patients with PCR/antibody evidence of primary COVID-19 infection, and/or Multisystem Inflammatory Syndrome in Children, were admitted between 26 March, 2020 and 31 March, 2021. *Interventions:* None. *Main outcomes measures:* Patient-level demographics, pre-existing conditions, clinical symptoms, and outcomes related to ICU admission were captured from medical records. *Results:* Among 1064 patients hospitalised with COVID-19/Multisystem Inflammatory Syndrome in Children, 102 patients (9.5%) were admitted to cardiac ICU, 76 of which were symptomatic (median age 12.5 years [IQR 7.5–16.0]). The primary system involved at presentation was cardiovascular in 48 (63%). Vasoactive infusions were required in 62% (n = 47), with eight patients (11%) requiring VA ECMO. Severity of disease was categorised as mild/moderate in 16 (21%) and severe/critical in 60 patients (79%). On univariate analysis, African-American race, presentation with gastrointestinal symptoms or elevated inflammatory markers were associated with risk for severe disease. All-cause death was observed in five patients (7%, n = 5/72) with four patients remaining hospitalised at the time of data query. *Conclusion:* COVID-19 and its cardiovascular sequelae were associated with important morbidity and significant mortality in a notable minority of paediatric patients admitted to a paediatric cardiac ICU. Further study is required to quantify the risk of morbidity and mortality for COVID-19 and sequelae.

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pathogen responsible for COVID-19 infection and its sequelae continues to impact global and local health care systems indiscriminately. The paediatric population are overall affected to a lesser extent than adults[1] but high-risk subpopulations with underlying chronic illnesses and other risk factors remain at increased risk for hospitalisation and admission to paediatric ICU.[2,3] Mild respiratory symptoms, fever, and vomiting/gastrointestinal symptoms are the most common presenting symptoms in the early disease course[2,4] yet severe respiratory disease can occur in a minority of cases. In the pre-Delta variant eras, less than 1% of children progressed to acute respiratory failure or multiple organ dysfunction although infants <1-year-old may be at higher risk of severe disease.[5,6] In addition, the post-infectious Multisystem Inflammatory Syndrome in Children emerged as a common cause of hospitalisation for children during the COVID-19 pandemic and is associated with more severe disease with as many as 70% of patients requiring admission to ICU[7] for cardiac and respiratory support for respiratory failure, circulatory failure, or cardiogenic shock.[8–12]

The impact and outcomes of children COVID-19 disease or its sequelae admitted to subspecialty cardiac ICUs may differ from the general paediatric ICU population but has not yet been described. In this study, we describe the demographics, clinical course, and outcomes for children admitted with COVID-19 disease or its sequelae to a dedicated subspecialty paediatric cardiac ICU.

Materials and methods

We performed a retrospective analysis of all patients admitted to the Texas Children's Hospital cardiac ICU between 26 March, 2020 (which marks the date of the first COVID-19 admission to Texas Children"s Hospital) and 31st March, 2021 with diagnosis of COVID-19 disease (PCR positive or SARS-CoV-2 antibody positive) or Multisystem Inflammatory Syndrome in

Children associated with COVID-19. The Baylor College of Medicine IRB approved the study with a waiver of informed consent without the need for ethics committee review.

The electronic health records were electronically and manually queried. Demographics and pre-existing comorbidities were reported for all patients with COVID-19 or COVID-19-related disease. We excluded otherwise asymptomatic patients with an incidental finding of SARS-CoV-2 infection on surveillance PCR or serology testing. For those with associated symptoms of COVID-19-related disease (ie. "true" disease), we examined primary presentation/chief complaint, duration of symptoms prior to admission, primary diagnosis and echocardiographic measures of ventricular function and coronary dilatation assessment at admission, as well as respiratory, cardiovascular, gastrointestinal, neurologic symptoms, and support or advanced therapies. Multisystem Inflammatory Syndrome in Children was diagnosed utilising CDC criteria.[13] Respiratory, gastrointestinal, neurologic, and cardiovascular symptoms were abstracted from medical records. Laboratory values were described numerically but also expressed as normal/abnormal depending on age-specific thresholds.

Clinical outcomes described include severity of disease, survival, duration of mechanical ventilation, residual symptoms at discharge and ICU, and hospital lengths of stay. We categorised each cardiac ICU admission's severity of illness as follows: mild disease – fever, sore throat, cough, and/or myalgia without dyspnoea; moderate disease – fever, dyspnoea, and/or chest imaging consistent with SARS-CoV-2 pneumonia and no change from baseline requirements if receiving long-term respiratory support; severe disease – fever, dyspnoea, and/or chest imaging consistent with SARS-CoV-2 pneumonia, with new or increased supplemental oxygen requirement and/or ventilatory support requirement; and critical disease – respiratory failure requiring mechanical ventilation, acute respiratory distress syndrome, cardiogenic shock, or organ dysfunction related to systemic inflammatory response syndrome. Cardiogenic shock included echocardiographic findings of left ventricular systolic dysfunction and need to initiate inotropic support. Systolic function on echocardiography was categorised as mild (40–48%), moderate (30–40%), and severe (<30%) systolic dysfunction. Electrocardiographic findings are limited to electrocardiographic's performed within the first 24 hours of admission. Clinical outcomes were only presented for those who completed hospitalisation at the time of study closure.

Descriptive statistics are provided with either total counts/frequencies with percentages (%) or median and 25–75% interquartile range describe the data. We also sought to determine if demographics and variables present at admission lead to the development of critical/severe disease versus mild/moderate disease. Chi-square analysis or Fisher's exact test, when appropriate, with relative risk for statistical significance at a p value ≤ 0.05 was used to look for associations between categorical variables, whereas Wilcoxon–Mann–Whitney test was used to compare non-parametric continuous variables. Statistical analyses were performed using JMP® (version 16, SAS, Cary, North Carolina, USA).

Results

During the study period, out of a total of 1064 patients admitted to acute care and ICU across the hospital system with the diagnosis of COVID-19-related conditions, 102 patients (9.5%) were cared for in the cardiac ICU (Supplementary Table 1). These 102 patients were amongst 896 unique patients (1194 unique admissions) admitted to the Texas Children"s Hospital cardiac ICU during the same time period (8.5%). Admission COVID-19 infection was confirmed by PCR from nasal swabs (67%) and/or COVID-19 IgM positive (41%). Twenty-six asymptomatic patients in whom SARS-CoV-2 infection were identified on routine surveillance screening were excluded from further analysis.

Demographics and pre-existing conditions

COVID-19-related symptoms were present at the time of cardiac ICU admission in 76 patients (75%). Of those, 39 (51%) were male, and the median age was 12.4 years [IQR 7.5–16.0]. The age range of patients admitted was between 29 days and 46 years with 68 patients (89%) aged 21 years or younger. Patients were admitted to cardiac ICU from the emergency department (n = 30, 39%); from an outside facility (n = 20, 26%); from our paediartic ICU (n = 18, 24%); or from an acute care floor (n = 8, 11%). Comorbidities occurred in 46 patients (61%) having at least one comorbidity, 24 (32%) with two, and 12 (16%) with three or more significant comorbidities (See Table 1). Only eight patients (11%) of symptomatic COVID-19 admissions were found to have underlying CHD. Of these, three patients had single ventricle physiology, and the five patients remaining had biventricular anatomy.

Primary presentation

The presenting symptoms included cardiovascular in 48 (63%), gastrointestinal in 47 (62%), and respiratory in 41 (54%; see Table 2). Patients presented to the cardiac ICU at a median time of 3 days [1–5] from the onset of symptoms. Primary diagnoses were not mutually exclusive and included Multisystem Inflammatory Syndrome in Children in 43 (57%), cardiogenic shock in 32 (42%), and COVID-19 pneumonia in 20 (26%). Laboratory values were abnormal in nearly all patients and included elevated D-Dimer levels (94%), C-reactive protein (91%), fibrinogen (78%), lactate dehydrogenase (69%), and ferritin (63%). Abnormal LV systolic function on echocardiogram was present in 25 (41%) patients on admission. Four (5%) patients had an arrhythmia on presentation: three with supraventricular tachycardia and one with ventricular tachycardia. Additional ECG abnormalities were present at the time of admission in 66 out of 76 symptomatic admissions (87%, see Table 2).

Supportive therapies

Vasoactive infusions were required in 38 patients (50%) within 2 hours of presentation (Table 2), and a total of 47 (62%) required vasoactive infusions during their hospital stay. Respiratory support was needed in 60 (79%): either via nasal cannula (n = 10, 13%), high-flow nasal cannula (n = 6, 8%), non-invasive positive pressure ventilation (n = 13, 17%), or invasive ventilation via endotracheal or pre-existing tracheostomy (n = 31, 41%). The median time from admission to invasive ventilation was 1.5 days [IQR 0–4.0], with a median duration of 5.5 days [2.0–10.0].

Adjunctive organ support therapy (Table 3) uses occurred in 56 (79%) patients. Prophylactic or therapeutic anticoagulation use occurred in 55 (72%) and 17 (22%) patients, respectively. Inhaled nitric oxide and prone positioning were utilised in eight patients (11%), mechanical circulatory support with venoarterial and venovenous extracorporeal membrane oxygenation in eight children (11%) (VA five patients, VV three patients) and continuous renal replacement therapy in four (5%) patients.

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Table 1. Demographic characteristics of patients with COVID-19 or COVID-19 related disease (n = 76).

Characteristic	n (%) or median [IQR]
Age, median (IQR), y	12.5 [7.5–16.0]
Age group (years)	
<1 (Newborn and Infant)	5 (7)
1–3 (Toddler)	7 (9)
3–6 (Preschool)	5 (7)
6–12 (School age)	20 (26)
12–21 (Adolescent)	31 (41)
>21 years (Adult)	8 (11)
Weight at admission (kg)	44.2 [24.1–81.6]
Height at admission (cm)	142.6 [116.6–162.9]
BSA at admission (m^2)	1.30 [0.88–1.82]
BMI at admission (kg/m^2)	21.9 [18.3–30.3]
Male	39 (51)
Race	
Caucasian	53 (70)
African-American	18 (24)
Asian	1 (1)
Other	2 (3)
Unknown	2 (3)
Hispanic/Latino	54 (71)
Unknown	1 (3)
Prior location to Cardiac ICU admission	
Outside hospital transfer	20 (26)
Emergency department	30 (39)
Hospital/Subspecialty floor	7 (9)
Operating room	1 (1)
Pediatric ICU	18 (24)
COVID-19 positive contact on past medical history	19 (25)
COVID-19 PCR + on admission	51 (67)
Not tested	3 (4)
COVID-19 PCR + at any time during hospital stay	59 (78)
Not tested	2 (3)
COVID-19 IgM + on admission	31 (41)
Not tested	10 (13)
COVID-19 IgM + at any time during hospital stay	36 (47)
Not tested	9 (12)
COVID-19 IgG + at any time during hospital stay	47 (62)
Not tested	17 (22)
Preexisting comorbidities (# not mutually exclusive)	
Any heart disease	13 (17)
Any CHD	8 (11)
Any acquired heart disease	8 (11)
None	30 (40)
Medically complex[a]	14 (18)
Immune suppression/malignancy	11 (14)
Obesity	20 (26)
Malignancy	4 (5)
Diabetes	3 (4)
Seizures	12 (16)
Sickle cell disease	2 (3)
Chronic lung disease	3 (4)
Other congenital malformations	7 (9)

[a]Defined as children who had a long-term dependence on technological support (including tracheostomy) associated with developmental delay and/or genetic anomalies

Targeted therapies

Clinicians targeted the viral infection with a variety of specific anti-viral or immunomodulatory therapies in 64 patients (84.2%). Ten (13%) received one therapy, 16 (21%) dual therapy and 38 (50%) >2 therapies. Given the variability in COVID-19 presentation, therapies were different for those diagnosed with Multisystem Inflammatory Syndrome in Children versus primary COVID-19 disease. Thirty-one (72%) of Multisystem Inflammatory Syndrome in Children patients received ≥3 therapies while 5 (17%) primary-related COVID-19 patient received <3 therapies. The most common pharmacotherapies for Multisystem Inflammatory Syndrome in Children was steroids (N = 42, 98%), then Anakinra (N = 35, 81%) and intravenous immunoglobulin (IVIG, N = 34, 79%). Although less commonly utilised, steroids were also the most commonly administered pharmacotherapy for primary COVID-19 (N = 11, 33%). Anti-viral therapy (remdesivir) was most frequently utilised for primary COVID-19 (N = 8, 24%) versus three patients with Multisystem Inflammatory Syndrome in Children (7%). Prophylactic anticoagulation therapies included either heparin, lovenox, or aspirin and were different between primary COVID-19 and Multisystem Inflammatory Syndrome in Children (45% vs. 93%, respectively).

Clinical outcomes

Severity of disease during the admission was mild/moderate in 16 (21%) and critical/severe in 60 (79%; Table 4). At the time of this report, of the 4 (5%) critically ill patients requiring ongoing intensive care, one required ongoing VV ECMO support at the time of data query and analysis. Median (IQR) cardiac ICU and hospital length of stays were 4 days [2–7] and 8 days [5–16], respectively, for the overall cohort. Symptoms persisted in 26 (33%) of the 67 patients discharged from hospital. Upon discharge, residual

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Table 2. Initial presentation of patients with COVID-19 or COVID-19 related disease (n = 76).

Primary presentation(# not mutual exclusive)/Chief Complaint	n (%) or median [IQR]
Asymptomatic	2 (3)
Respiratory	41 (54)
Gastrointestinal	47 (62)
Neurological	20 (26)
Cardiovascular	48 (63)
Cardiovascular with shock[a]	38 (50)
Other	24 (32)
Onset of symptoms prior admission (days)	3 [1–5]
Primary diagnosis (# not mutual exclusive)	
MIS-C	43 (57)
Cardiogenic shock[b]	32 (42)
Arrhythmia	8 (11)
COVID-19 pneumonia	20 (26)
Other	15 (20)
Laboratory values	
WBC (10^3/μL), (n = 72)	11.2 [7.7–15.0]
Platelet (10^3/μL), (n = 73)	175 [137–266]
LDH (U/L), (n = 58)	462 [322–844]
CRP (mg/dL), (n = 67)	17.3 [5.5–23.8]
Procalcitonin (ng/mL), (n = 62)	2.8 [0.4–11.4]
Ferritin (ng/mL), (n = 64)	334 [160–857]
Troponin I (ng/mL), (n = 58)	0.05 [0.01–0.60]
BNP (pg/mL), (n = 56)	120 [30–773]
PT (sec), (n = 61)	15.6 [14.7–17.1]
PTT (sec), (n = 62)	31.6 [27.7–37.3]
Fibrinogen (mg/dL), (n = 67)	536 [419–717]
D-Dimer (ug/mL), (n = 65)	3.2 [1.5–4.9]
Creatinine (mg/dL), (n = 73)	0.53 [0.34–0.97]
Abnormality of	
WBC (10^3/μL)	16 (22)
Platelet count (10^3/μL)	11 (15)
LDH (U/L), (age specific)	40 (69)
CRP (mg/dL)	61 (91)
Procalcitonin (ng/mL)	33 (53)
Ferritin (ng/mL), (age specific)	40 (63)
Troponin (ng/mL)	35 (60)
BNP (pg/mL)	30 (54)
PT (sec)	29 (48)
PTT (sec)	27 (44)
Fibrinogen (mg/dL)	52 (78)
D-Dimer (ug/mL)	61 (94)
Creatinine (mg/dL)	11 (15)
EKG on admission (n = 66)	
PR interval (msec)	132 [120–151]
QRS duration (msec)	80 [72–88]
QTc interval (msec)	428 [411–449]
AV block	0
Interventricular conduction delay	8 (12)
Ventricular hypertrophy	6 (9)
ST elevation	9 (14)
T wave inversion	5 (8)
Prolonged QTc	3 (5)
Low voltage	4 (6)
Echo on admission done	62 (82)
Echo (EF)[c]	
Normal	36 (59)
Mildly depressed	15 (25)
Moderately depressed	6 (10)
Severely depressed	4 (7)
ECHO (TR) velocity (if measured, m/sec, n = 20)	2.4 (2.2–2.6)
ECHO – coronary artery dilatation present in patients with coronary assessment (n = 35)	10 (29)

[a]Defined as requiring inotropic support (epinephrine or milrinone) within 2 hours of admission
[b]Cardiogenic shock was defined as the need for inotropic support and depressed LV systolic function on echocardiogram
[c]EF < 30% severely depressed, 30% – 40% moderately depressed, 40% – 48% mildly depressed, > 48% normal

symptoms were present in 16 (24%) including respiratory, gastrointestinal, neurologic, and cardiovascular systems. Of the 76 children with a completed hospital encounter, 5 died, with an overall hospital mortality of 6.6%. All of the non-survivors had primary COVID-19 infections, and none had MIS-C. The median age of non-survivors was 13.9 years [IQR 12–17 years] of which the majority were white (n = 4), Hispanic (n = 3), and female (n = 3). All patients were found to have comorbidities at the time of admission including end-stage single ventricle CHD (Fontan; n = 1), malignancy (n = 2), obesity (n = 2), rheumatological condition requiring immune suppression (systemic lupus erythematosus; n = 1). None of the five deaths presented with signs or symptoms of Multisystem Inflammatory Syndrome in Children. Progressive refractory hypoxemic respiratory failure was the most common cause of death for four patients of which two patients undergoing withdrawal of life-sustaining therapies with a do not resuscitate order in place (end-stage failing Fontan; obese adult male with ARDS, refractory GI bleed on VV-ECMO). The remaining patient passed suddenly from cardiovascular collapse with pulmonary haemorrhage in setting of pulmonary hypertension.

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Table 3. Clinical course and therapeutics of patients with COVID-19 or COVID-19 related disease (n = 76).

Organ support and COVID-19 related therapies	n (%) or median [IQR]
Vasoactive support required	47 (62)
Highest vasoactive inotrope score during admission	8 [5–14]
Maximum respiratory support	
None	16 (21)
Oxygen	10 (13)
HFNC	6 (8)
CPAP/BIPAP	13 (17)
Invasive ventilation (intubation/ tracheostomy/home ventilator)	31 (41)
Time from admission to invasive ventilation (days) excluding home ventilator (n = 28)	1.5 [0–4.0]
Duration of invasive ventilation (days)	5.5 [2.0–10.0)]
Advanced organ support related therapies(# not mutual exclusive)	
None	16 (21)
Inhaled NO	8 (11)
Prone positioning	8 (11)
Prophylactic anticoagulation used	55 (72)
Therapeutic anticoagulation used	17 (22)
Renal replacement therapy	4 (5)
Plasma exchange	2 (3)
Mechanical circulatory support	8 (11)
VV ECMO	3 (4)
VA ECMO	5 (7)
Duration of mechanical Support (n = 8)	12 [4.0–23.5]
COVID-19 related Pharmacotherapy (# not mutual exclusive)	
Steroids	53 (70)
Anakinra	43 (57)
IVIG	39 (51)
Azithromycin	13 (17)
Remdisivir	11 (14)
Convalescent plasma	6 (8)
Hydroxychloroquine	2 (3)
Tocilizumab	0

Table 4. Outcomes of patients with COVID-19 or COVID-19 related disease (n = 76).

Outcomes	n (%) or median [IQR]
Length of stay (days)	
CICU	4.0 [2.0–7.0]
Mixed ICU (PICU/CICU combined admissions)	5.0 [3.0–10.5]
Hospital	8.0 [5.3–16.0]
Discharged alive	67 (88)
Discharged alive, invasive ventilation patients (n = 24)	20 (83)
Discharged alive, ECMO Support patients (n = 8)	5 (56)
Currently admitted	4 (5)
Deceased	5 (7)
Residual symptoms at discharge (n = 67)(# not mutual exclusive)	
Asymptomatic	51 (76)
Respiratory	2 (3)
Gastrointestinal	1 (1)
Neurological	1 (1)
Cardiovascular	7 (10)
Other	9 (13)
Severity of Illness[a]	
Mild	9 (12)
Moderate	7 (9)
Severe	11 (14)
Critical	49 (64)

[a]Severity of illness categories: MILD disease including fever, sore throat, cough, and/or myalgia with no dyspnea; MODERATE disease including fever, dyspnea, and/or chest imaging consistent with SARS-CoV-2 pneumonia and no change from baseline requirements if receiving long-term respiratory support; SEVERE disease including fever, dyspnea, and/or chest imaging consistent with SARS-CoV-2 pneumonia, with new or increased supplemental oxygen requirement and/or ventilatory support requirement; and CRITICAL disease including respiratory failure requiring mechanical ventilation, acute respiratory distress syndrome, shock or systemic inflammatory response

Associations with severity of disease

Table 5 and Supplementary Table 2 display differences between severe/critical and mild/moderate forms of disease across demographic and clinical variables. Severe or critical disease occurred in 60 patients (79%), while 16 (21%) suffered only mild or moderate disease. Comparing preselected demographic variables, African-Americans relative risk 1.32 [interquartile 1.08–1.61] compared to white race for severe/critical disease. Hispanic ethnicity was less likely to develop severe disease (RR 0.76 [0.63–0.92]). Primary presentation with gastrointestinal symptoms (RR 1.33 [1.00–1.77]), cardiogenic shock (RR 1.50 [1.16–1.93]), primary diagnosis of Multisystem Inflammatory Syndrome in Children (RR 1.53 [1.15–2.05]), and cardiogenic shock (RR 1.47 [1.18–1.83]) increased the risk for more critical or severe disease. Significant elevation of C-reactive protein (RR 2.7 [0.85–8.26]) or procalcitonin (RR 1.3 [1.02–1.65]), and fibrinogen levels (RR 1.35 [0.94–1.96]) showed increased risk ratios for the severity of disease.

Discussion

This focused report of the clinical experience with COVID-19 shows significant morbidity and low but important mortality in a critically ill cohort of children presenting to a dedicated CICU with symptoms related to COVID-19 infection and its

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Table 5. Analysis of severe/critical disease versus mild/moderate disease characteristics.

Characteristic	Mild/moderate disease n = 16 (%)	Severe/critical disease n = 60 (%)	p-value (RR [CI])
Age, median [IQR], y	13.3 [7.6–19.9]	11.2 [4.1–16.4]	0.60
Age group (years)			0.42
<1 (Newborn and Infant)	2 (13)	3 (5)	0.19
1–3 (Toddler)	1 (6)	6 (10)	1.00
3–6 (Preschool)	2 (13)	3 (5)	0.19
6–12 (School age)	4 (25)	16 (27)	0.70
12–21 (Adolescent)	4 (25)	27 (45)	Reference
>21 years (Adult)	3 (19)	5 (8)	0.14
BSA at admission (m^2) median [IQR]	1.24 [0.67–1.61]	1.34 [0.99–1.86]	0.21
BMI at admission (kg/m^2) median [IQR]	19.7 [17.8–22.7]	23.5 [18.3–32.9]	0.09
Male	9 (56)	30 (50)	0.78
Female	7 (44)	30 (50)	
Race			0.23
Caucasian	15 (94)	38 (63)	Reference
African-American	1 (6)	17 (28)	0.05 (1.32 [1.08–1.61)]
Asian	0	1 (2)	1.00
Other	0	2 (3)	1.00
Unknown	0	2 (3)	1.00
Hispanic			0.05 (0.76 [0.63–0.92])
Yes	15 (94)	39 (67)	
No	1 (6)	19 (33)	
Prior location to cardiac ICU			0.22
Outside hospital transfer	2 (13)	18 (30)	
Emergency department	10 (63)	20 (33)	
Hospital/subspecialty floor	2 (13)	5 (8)	
Operating room	0	1 (2)	
Pediatric ICU	2 (13)	16 (27)	
COVID + contact on PMHx			0.75
Yes	3 (19)	16 (27)	
No	13 (81)	44 (73)	
Preexisting comorbidities(# not mutually exclusive)			
None	4 (25)	26 (43)	0.25
Medically complex[a]	4 (25)	10 (17)	0.48
Immune suppression	2 (13)	9 (15)	1.00
Obesity	2 (13)	18 (30)	0.21
Malignancy	0	4 (7)	0.57
Diabetes	0	3 (5)	1.00
Seizures	2 (13)	10 (17)	1.00
Any heart disease	8 (50)	5 (8)	<0.01 (0.44 [0.22–0.88])
Any CHD	4 (25)	4 (7)	0.05 (0.61 [0.30–1.22])
Acquired heart disease	5 (31)	3 (5)	0.01 (0.45 [0.18–1.10])

(*Continued*)

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Table 5. (*Continued*)

Characteristic	Mild/moderate disease n = 16 (%)	Severe/critical disease n = 60 (%)	p-value (RR [CI])
Sickle cell disease	1 (6)	1 (2)	0.38
Chronic lung disease	1 (6)	2 (3)	0.51
Congenital malformations	2 (13)	5 (8)	0.63

[a]Defined as children who had a long-term dependence on technological support (including tracheostomy) associated with developmental delay and/or genetic anomalies

sequelae. Much of the morbidity and mortality associated with the COVID-19 remains in the form of respiratory failure in the paediatric population. However, cardiovascular complications have emerged in the form of Multisystem Inflammatory Syndrome in Children,[14] and these appear to be significantly contributing to the burden of critical illness in children. Similar to published reports, a spectrum of cardiac disease observed in the paediatric population ranges from arrhythmias, myocarditis with cardiogenic and mixed shock states, pericardial effusions, valvular disease, and even coronary involvement in from of aneurysms.[7,15] In our institution, the cardiac ICU was identified as the optimal location for children with cardiovascular complications of COVID-19. In order to operationalise this, we adapted our system in a way similar to our adult counterparts[16] allowing us to accommodate this demand with a safe care model. Modifications included workforce and staffing reorganisations, hospital-level adaptations of new care pathways, new methods for education and training leveraging virtual communication platforms, and a close collaboration with both our paediatric ICU and our adult partner institutions. The floor design of our cardiac ICU conveniently included a "pod" design with single patient rooms that allowed us to accommodate all COVID-19 patients into a geographically separate row of rooms/"pod" where they could be cared for by multidisciplinary teams of critical care providers, nurses, and support staff.

Subspecialty ICUs focused on the care of patients with cardiovascular derangements are ideally suited for the management of COVID-19 disease given the impact of the virus on the cardiovascular system, evidenced by the high number of admissions presenting with cardiovascular symptoms and the evolving nature of Multisystem Inflammatory Syndrome in Children in the paediatric population.[12] Contemporary reports from the general paediatric ICU describe hypoxemic respiratory failure/pneumonia as the most common reason for admission,[2,17] yet varying degrees of cardiovascular dysfunction exist with respiratory system dysfunction. Although focused primarily on the medical and surgical management of CHD, our cardiac ICU observed a minority of COVID-19 admissions with coexisting CHD. Although unable to make generalisations regarding the susceptibility of COVID-19 in the CHD population from this analysis, the low proportion of CHD amongst all hospital admissions suggests an incidence equal to the general paediatric population.

The overlap that exists between active primary COVID-19 respiratory disease and the presence of cardiovascular dysfunction at presentation is challenging to delineate in our cohort given the confounding of triage decision making prior to disposition. We report a spectrum of illness severity that includes “mild” disease and may seem counterintuitive to admission criteria for an ICU. The evolving understanding of the natural history of primary COVID-19 and Multisystem Inflammatory Syndrome in Children would eventually inform triage decisions although some patients were admitted out of an abundance of caution depending on initial symptomatology. Most commonly, the presence of documented systolic dysfunction on presentation with/without troponin I elevation, electrocardiographic changes, or documented arrhythmias led to cardiacICU admission. Yet in light of this bias in sampling, our report highlights the significant morbidity experienced by the subset of paediatric patients experiencing active COVID-19 disease with associated cardiovascular dysfunction and/or Multisystem Inflammatory Syndrome in Children. In comparison to the prior reports of COVID-19 in the general paediatric ICU, multiorgan involvement and mortality rates reported in this study are higher and residual symptoms specific to the cardiovascular system also suggest a significant burden of disease for these patients.[2,18] Severe disease and mortality in primary COVID-19 infections were often observed in children with underlying co-morbidities such as diabetes, obesity, and chronic illnesses. Yet, except for obesity children with Multisystem Inflammatory Syndrome in Children were previously healthy prior to developing an exaggerated immune response. Additionally, at presentation children with Multisystem Inflammatory Syndrome in Children were found to have much more pronounced lab markers of inflammation, innate immune activation, and coagulopathy. Their cardiac dysfunction and myocarditis often progressed over an acute period. Resolution of laboratory and cardiac markers occurs more rapidly in patients with Multisystem Inflammatory Syndrome in Children.

As our study looks specifically at a cardiac ICU population, we are cognizant of the selection bias leading to triage decisions and cohort selection. Additionally, primary COVID-19 and/or Multisystem Inflammatory Syndrome in Children is a highly variable and dynamic disease processes leading to a heterogeneous spectrum of acuity and symptomatology at presentation. Finally, our presentation here of the therapies provided in this series of critically ill children is purely descriptive and associations with the outcome are outside the scope of this study.

In conclusion, this report confirms the significant burden of cardiovascular disease associated with COVID-19 in children through the lens of a large tertiary care cardiac ICU. While our ability to identify patient-level risk factors for hospitalisation and mortality related to COVID-19 in children continues to evolve, each hospital and ICU’s ability to modify these factors remains limited and often reactive. The need to understand the spectrum of cardiovascular pathology and sequelae related to COVID-19 is essential for paediatric hospitals with dedicated cardiac-specific subspecialty units in order to provide the

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highest quality of care. Additional cardiac ICU cohorts and predictive modelling may allow units to implement proactive risk assessment and treatment protocols.

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