

# Outcome of COVID-19-positive children with heart disease and grown-ups with congenital heart disease: A multicentric study from India

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## ABSTRACT

- Background** : Outcome data of children with heart disease who acquired COVID-19 infection are limited.
- Aims** : We sought to analyze outcome data and identify risk factors associated with mortality in children with heart disease and grown-ups with congenital heart disease (GUCH) who had a laboratory-confirmed COVID-19 infection.
- Settings and Design** : This is a retrospective, multicentric, observational study.
- Materials and Methods** : The study included children with heart disease and GUCH population, who presented with either symptomatic or asymptomatic COVID-19 infection to any of the participating centers. COVID-19-negative patients admitted to these centers constituted the control group.

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- Results** : From 24 pediatric cardiac centers across India, we included 94 patients with a median age of 12.5 (interquartile range 3–96) months and 49 (52.1%) patients were males. Majority (83 patients, 88.3%) were children. One-third of the patients (n = 31, 33.0%) had acyanotic congenital heart disease, and 41.5% (n = 39) were cyanotic, with > 80% of the patients being unoperated. Only 30 (31.9%) patients were symptomatic for COVID-19 infection, while the rest were incidentally detected positive on screening. A total of 13 patients died (case fatality rate: 13.8%). The in-hospital mortality rate among hospitalized patients was significantly higher among COVID-19-positive cases (13 of 48; 27.1%) as compared to COVID-negative admissions (9.2%) during the study period (P < 0.001). On multivariate analysis, the independent predictors of mortality among COVID-19-positive cases were severity of illness at admission (odds ratio [OR]: 535.7, 95% confidence interval [CI]: 6.9–41,605, P = 0.005) and lower socioeconomic class (OR: 29.5, 95% CI: 1.1–814.7, P = 0.046).
- Conclusions** : Children with heart disease are at a higher risk of death when they acquire COVID-19 infection. Systematic preventive measures and management strategies are needed for improving the outcomes.
- Keywords** : Congenital heart disease, grown-ups with congenital heart disease, low- and middle-income countries and SARS-CoV-2 infection, outcome, surgery

## INTRODUCTION

Children constitute between 2% and 14% of all COVID-19 cases worldwide.<sup>[1,2]</sup> Children in general are at a lower risk of serious illness and mortality due to COVID-19 as compared to adults.<sup>[3,4]</sup> However, children with comorbidities may be at a higher risk of serious illness and death.<sup>[5]</sup> Children with heart disease are perceived to be at a higher risk of serious complications from SARS-CoV-2 infection due to various reasons.<sup>[6]</sup> However, data about the outcomes of children with preexisting heart disease acquiring a COVID-19 infection are limited. The published large series either focused entirely<sup>[7,8]</sup> or mostly<sup>[9,10]</sup> on grown-ups with congenital heart disease (GUCH) population. The reports in children are limited to less than ten patients.<sup>[11]</sup> All these series, mostly from the developed nations, reported complication and mortality rates comparable to the general population.<sup>[8]</sup> Majority of the patients in these reports were already operated for congenital heart disease (CHD). On the other hand, majority of the patients with an CHD contracting a COVID-19 infection in low-and middle-income countries (LMICs) are unoperated for heart disease.<sup>[11,12]</sup>

Like most other countries in the world, India faced the raging pandemic from March 2020. Anticipating high number of COVID-19 cases, India adopted a strict nationwide lockdown in the beginning of the first wave of the COVID-19 pandemic. While the lockdown helped in slowing down the pandemic, it posed unforeseen challenges in access to limited pediatric cardiac centers, which are mostly concentrated in the metros. Late presentation and out-of-pocket expenses<sup>[13,14]</sup> are unique problems encountered in Indian health care, and these

challenges were exaggerated during the pandemic times. In addition, unfavorable demographics and socioeconomic status of most of these children in LMICs made timely detection and management of heart disease challenging in the pandemic times. These factors might impact the outcomes of children with heart disease. Therefore, the Pediatric Cardiac Society of India (PCSI) conducted this multicentric retrospective study to evaluate the outcomes of children with heart disease and GUCH population, who acquired COVID-19 during the first wave of the COVID-19 pandemic in India.

## MATERIALS AND METHODS

In this multicentric, retrospective, observational study, data from 24 Indian pediatric cardiac centers between April 1, 2020, and August 31, 2020, were collected. The detailed methodology is published elsewhere.<sup>[15]</sup> We included all consecutive children (<18 years) or GUCH patients seen in the outpatient departments or hospitalized in the participating pediatric cardiac facilities across India. Children with any form of heart disease including CHD, acquired heart diseases such as rheumatic heart disease, and previously diagnosed myocardial diseases were included in the study. Children presenting with multisystem inflammatory syndrome associated with COVID-19 in the absence of preexisting heart disease were excluded from the study. All the included patients had a positive naso- and oro-pharyngeal swab for SARS-CoV-2 nucleic acid using reverse-transcriptase quantitative-polymerase chain reaction (RT-PCR) assay or cartridge-based nucleic acid amplification test (CBNAAT) in the preceding 28 days. Tests may have been performed either due to symptoms suggestive of COVID-19 infection or for screening

prior to admission or intervention. COVID-19-negative patients with CHDs seen in the outpatient department or admitted to the participating centers during the same period constituted the control group. Ethical approval or a no-objection certificate was obtained at each of the participating institutions. The study was registered in the Clinical Trials Registry-India (CTRI) database (CTRI registration number CTRI/2020/10/028251).

We invited all the major pediatric cardiac centers of the country for participation in the study. Out of the 24 centers participating in the primary study,<sup>[15]</sup> only 13 centers reported encountering COVID-19 patients fulfilling the inclusion and exclusion criteria of the study. The site investigator was responsible for data collection using the study pro forma [Supplementary Appendix 1].

Demographic and clinical details and laboratory parameters of COVID-19-positive patients were collected [Supplementary Appendix 1]. COVID-19 status and approximate socioeconomic class (modified Kuppaswamy scale)<sup>[16]</sup> of the family were recorded. Presence or absence, and duration of symptoms suggestive of COVID-19, and presenting symptoms were noted. The severity of illness at presentation was classified into severe and nonsevere illness based on the presence of cyanotic spells, refractory heart failure, persistent shock, or requirement for ventilatory support. Due to the retrospective nature of the study, we could not discern the relative contribution of cardiac illness and respiratory involvement due to COVID-19 in causing a severe illness at presentation. However, the treating physician was required to identify the contribution of COVID-19 in the causation of death as definite, possible, or incidental. We classified the types of heart diseases into obstructive, acyanotic, and cyanotic CHD and acquired heart disease in children. Data regarding need for surgery, whether surgery was done in the index hospitalization, postoperative mortality, and in-hospital mortality were noted. The outcome data were recorded as death or hospital discharge.

We collected the hospital statistics including the number of outpatient visits, hospitalizations, surgeries performed, and mortality in COVID-19-negative patients from all these 13 centers over the same time period in 2020. The Risk Adjustment for Congenital Heart Surgery (RACHS-1) scoring<sup>[17]</sup> was used to stratify the complexity of all the surgeries performed in both COVID-19-positive and COVID-19-negative patients.

### Statistical analysis

Categorical variables were presented as frequency and percentages, and continuous variables were presented as mean  $\pm$  standard deviation, or median ( $Q_{25}$ - $Q_{75}$ ) as appropriate. Comparisons of various characteristics between COVID-positive and COVID-negative patients were done using the Chi-square test. All the categorical

and continuous predictors were compared with in-hospital mortality using the Chi-square test/Fisher's exact test and Wilcoxon rank sum test, respectively. A univariate followed by a step-wise logistic regression analysis was used to find out the independent predictors of mortality with entry and removal probability of 0.05 and 0.25, respectively. The results were presented as odds ratio (OR) and 95% confidence interval (CI). Stata 16.0 (StataCorp LLC, TX, USA) was used for all statistical analyses.  $P < 0.05$  was considered significant.

## RESULTS

Data of 94 patients (49 males; 52.1%) with COVID-19 infection seen at the 13 participating pediatric cardiac centers across India were analyzed. The study population included 10 neonates (10.6%), 37 infants (39.4%), 36 children aged between 1 and 18 years (38.3%), and 11 GUCH (11.7%) patients (range 18-62 years), and the median age was 13 months (range 3 days to 62 years). Two large centers contributed more than 15 COVID-19-positive cases each. Ninety-two patients had RT-PCR positivity, and two patients had CBNAAT positivity. The demographic characteristics at presentation are summarized in Table 1. One-third ( $n = 31$ , 33%) of the patients had acyanotic CHD, and 41.5% ( $n = 39$ ) were cyanotic. The details of cardiac lesions are summarized in Supplementary Table 1. Out of the 94 patients, only 18 (19.1%) patients had undergone

**Table 1: Baseline characteristics of coronavirus disease-2019-positive patients in the study**

Characteristics	Observed values ( $n=94$ ) Mean $\pm$ SD or $n$ (%)
Median age (IQR) (months)	12.5 (3-96)
Mean age - children* (months) ( $n=83$ )	40.0 $\pm$ 59.1
Mean age - GUCH (years) ( $n=11$ )	33.5 $\pm$ 14.3
Males	49 (52.1)
Details of heart disease	
CHD	
Cyanotic	39 (41.4)
Acyanotic	31 (33.0)
Obstructive	12 (12.8)
Acquired heart disease in children	12 (12.8)
Socioeconomic status	
Lower	22 (23.4)
Lower-middle	23 (24.5)
Middle	40 (42.5)
Upper	9 (9.6)
Malnourished on initial assessment	27 (28.7)
Duration of symptoms prior to admission (days)	4.0 $\pm$ 6.2
Severity of illness at admission	
Severe	12 (12.8)
Not severe	82 (87.2)
Mean SpO <sub>2</sub> (%)	89.1 $\pm$ 9.4
Prior ACE inhibitors/ARB	11 (11.7)

\* $<18$ -years-old including neonates and infants. SD: Standard deviation, IQR: Interquartile range, GUCH: Grown-ups with congenital heart disease, ACE: Angiotensin-converting enzyme, ARB: Angiotensin receptor blocker, SpO<sub>2</sub>: Oxygen saturation, CHD: Congenital heart disease

a previous percutaneous or surgical intervention. Syndromes associated with CHD were identified in seven children (7.4%).

Out of the 11 GUCH patients (6 females) included in the study, 5 were symptomatic for COVID-19 with fever. Two patients had serious illness due to acute respiratory distress syndrome (ARDS) related to COVID-19, and both the patients required noninvasive ventilation. Rest of the GUCH patients had mild illness. No deaths were observed in the GUCH population with COVID-19 infection. Two unoperated adult patients with atrial septal defect underwent surgery 1–3 months after recovery from COVID-19 infection.

Only 30 patients (31.9%) were symptomatic for COVID-19 at the time of testing, and the remaining patients had incidental positive reports, performed as part of preprocedural screening. Symptoms suggestive of COVID-19 included fever in 25 patients, tachypnea unexplained by heart disease in 14 children, and new-onset cyanosis in 5 patients, who did not have a cyanotic CHD. Nearly half of the patients ( $n = 48$ ; 51.1%) needed hospitalization following a positive COVID test and the rest were managed at home, a decision based on clinical assessment by the treating team, and prevailing hospital policies. The hospital course and major in-hospital complications are summarized in Table 2. Thrombotic complications were noted in three patients and included a left ventricular clot in a child with dilated cardiomyopathy, prosthetic heart valve thrombosis of mitral valve in a child with rheumatic heart disease, and ischemic stroke in an infant following closure of ventricular septal defect. One patient received dialysis and one patient required tracheostomy. Of the 13 patients requiring intubation and ventilation at admission, 9 died. Patients who survived invasive ventilation included one patient each requiring emergency aortic valve balloon dilatation, surgery for coarctation of aorta, management of atrial tachyarrhythmia, and surgical closure of ventricular septal defect.

Two neonates (one each underwent patenting ductus arteriosus [PDA] ligation; coarctation of aorta repair) underwent emergency surgery, and 3 children (one each underwent emergency balloon dilation of coarctation; pulmonary valve balloon dilation [PVBD]; aortic valve balloon dilation) underwent an emergent interventional procedure using strict personal protective equipment protocols. The patient who underwent PDA ligation already had ARDS and systemic inflammatory response syndrome, which did not improve even after PDA ligation. The patient who underwent PVBD expired a few days after the procedure due to ARDS and shock. Three children were detected to be COVID-19 positive upon retesting following a COVID-19-like respiratory illness in the postoperative period. In rest of the children who underwent a cardiac surgery during the index

**Table 2: Characteristics of hospitalized coronavirus disease-2019-positive patients in the study**

Characteristics	Observed values ( $n=48$ ) Mean $\pm$ SD or $n$ (%)
Complications during hospital stay*	
ARDS	7 (14.5)
Pneumothorax	1 (2.1)
Arrhythmia	2 (4.2)
Myopericarditis	1 (2.1)
Superadded infections	7 (14.5)
Elevated liver enzymes	4 (8.3)
Hypoglycemia	3 (6.2)
Acute kidney injury	3 (6.2)
Seizure	2 (4.2)
Investigations**	
Hemoglobin (g/dL)	13.0 $\pm$ 3.2
Neutrophil: lymphocyte ratio	1.5 $\pm$ 1.3
Platelet count (lakh/mm <sup>3</sup> )	2.6 $\pm$ 1.1
C-reactive protein (mg/dL)	6.0 $\pm$ 3.5
Serum creatinine (mg/dL)	0.5 $\pm$ 0.5
Need for medications related to COVID-19*	
Corticosteroids	12 (25)
Remdesivir	6 (12.5)
Heparin	14 (29.2)
Inotrope/ventilation requirement*	
Need for invasive ventilation	13 (27.1)
Need for noninvasive ventilation	6 (12.5)
Shock	11 (22.9)
Heart failure	12 (25)
Procedures during index hospitalization*	
Emergency interventions	3 (6.2)
Emergency surgery	2 (4.2)
Surgery after recovery from COVID-19	17 (35.4)
Death*	13 (27.1)

\*Percentage of number of hospitalized patients, \*\*Performed in limited number of patients. ARDS: Acute respiratory distress syndrome, COVID-19: Coronavirus disease-2019, SD: Standard deviation

hospitalization, the surgery was done after 10–28 days of recovery from COVID-19 infection. Apart from this, surgical or interventional management was required in another 51 patients but had to be deferred as most hospitals followed an “emergency cases-only” policy during the pandemic.

As compared to the COVID-19-negative group, COVID-19-positive patients had lesser proportion of neonates and GUCH patients [Table 2]. A higher proportion of COVID-19-positive patients required hospitalization and preoperative ventilation. However, the proportion of patients undergoing a cardiac surgery or emergency procedures was lower among hospitalized COVID-19-positive patients. RACHS-1 score distribution suggested increased complexity of surgeries performed in COVID-19-positive patients, but the difference was statistically insignificant, possibly due to small numbers.

A total of 13 deaths (13.8%) occurred in the COVID-19-positive cases including 3 among 19 patients operated for heart disease during index hospitalization. The overall mortality of the cohort as well as the in-hospital mortality was significantly higher in the COVID-19 positive-group as compared to all COVID-19-negative



patients in the corresponding study period [Table 3]. Majority of the excess deaths occurred in unoperated patients, and the postoperative mortality among the groups was comparable [Table 3]. The individual details of the deceased patients are presented in Table 4. In nine deaths (69.2%), the treating physician attributed COVID-19 infection as a definite causative factor for mortality.

On univariate analysis, lower socioeconomic class, presence of cyanosis, tachypnea, shock, ARDS, need for intubation, and severe illness at admission predicted mortality among COVID-19-positive patients with CHD [Table 5]. The type of CHD and surgery during index hospitalization, however, did not predict mortality. On multivariate analysis, the independent predictors of mortality were severity of illness at admission (OR: 535.7, 95% CI: 6.9–41,605,  $P = 0.005$ ), and lower socioeconomic class (OR: 29.5, 95% CI: 1.1–814.7,  $P = 0.046$ ).

## DISCUSSION

This multicentric retrospective study conducted under the aegis of the PCSI is one of the largest series of children with heart disease who acquired COVID-19 infection. Children with CHD represent a high-risk vulnerable group for any viral infection including COVID-19 infection. However, outcome studies are limited in children with heart disease and COVID-19 infection. The significant finding of our study is the higher case fatality rate observed among a predominantly young unoperated children with serious CHD and COVID-19 infection. The study represents real-time, cross-sectional practice across India.

A recently published large primary care data base study involving more than 200,000 children and adolescents estimated a hospitalization rate of 0.3%–1.3% with negligible fatality rate when they acquired a COVID-19 infection.<sup>[4]</sup> Even among children admitted to the pediatric intensive care units, the mortality is reported as low as 4%.<sup>[18]</sup> However, children with heart disease are a high-risk group and could have adverse outcomes following a COVID-19 disease. Early case series of children with COVID-19 hospitalized in general pediatric wards, and a few small case series consisting of children with CHD, suggested a high mortality rate when they had a COVID-19 infection.<sup>[19]</sup> In the initial phase of illness, the CDC in the USA reported that CHD was one of the frequent underlying medical conditions (18%) among patients <21 years, who died due to COVID-19.<sup>[20]</sup>

A few focused studies reported the outcomes of patients with CHD who acquired a SARS-CoV-2 infection, but all of them included predominantly operated GUCH population. The case fatality rate in a nationwide survey from Italy ( $n = 76$ ; only 4 children) and a single-center series from New York ( $n = 53$ ; only 10 children) was 0% and 6%, respectively.<sup>[9,10]</sup> A multicentric registry of 105 GUCH patients from 25 European centers, reported a case fatality rate of 4.8%.<sup>[7]</sup> However, a large worldwide multicentric study involving 1044 GUCH patients reported a case fatality rate of 2.8% only.<sup>[8]</sup> The authors suggested that structural CHD did not portend an increased risk of mortality due to COVID-19 infection as compared to the general population. However, these studies did not include patients who were operated during COVID-19 infection.<sup>[8-10]</sup>

**Table 3: Comparison of coronavirus disease-2019-positive versus coronavirus disease-2019-negative patients hospitalized during the study period**

	COVID-19 positive, n (%)	COVID-19 negative, n (%)	P
Total number of outpatient visits	94	9182	-
Age distribution among outpatient patients			
Neonate	10 (10.6)	1991 (21.7)	0.03
Infants/children	73 (77.7)	6390 (69.6)	
GUCH	11 (11.7)	801 (8.7)	
Number of children admitted	48 (51.1)	1187 (12.9)	<0.001
Overall mortality	13 (13.8)	109 (1.2)	<0.001
Among hospitalized patients	$n=48$	$n=1187$	
Total number			
Need for preoperative ventilation	13 (27.1)	123 (10.4)	<0.001
Proportion of admitted children undergoing surgery	19 (39.6)	686 (57.8)	0.01
Need for emergency surgery	2 (4.2)	245 (20.6)	0.003
RACHS category of surgeries performed	$n=19$	$n=686$	
Category 1	4 (21.1)	134 (19.5)	0.05
Category 2	5 (26.3)	344 (50.1)	
Category 3	9 (47.4)	147 (21.4)	
Category 4	0	5 (0.7)	
Others	1 (5.2)	56 (8.2)	
In-hospital mortality	13 (27.1)	109 (9.2)	<0.001
Preprocedural mortality	9 (18.8)	24 (2.0)	<0.001
Postoperative mortality	3/19 (15.8)	85/686 (12.4)	0.72

GUCH: Grown-ups with congenital heart disease, RACHS: Risk Adjustment for Congenital Heart Surgery

**Table 4: Individual details of the deceased patients with coronavirus disease-2019**

Age (months)	Gender	Diagnosis	SpO <sub>2</sub> (%)	Details	COVID as a cause of mortality
0.3	Male	Transposition of great arteries, intact ventricular septum, patent ductus arteriosus	80	COVID-19 negativity at admission. Postarterial switch operation - deterioration of respiratory status 2 days after extubation, reintubated and died due to pulmonary hemorrhage	Definite
1	Female	Large patent ductus arteriosus	88	Surgical ligation done for failed medical therapy	Definite
2	Male	Obstructed total anomalous pulmonary venous connection	74	COVID-19 negativity at admission. Following an emergency surgery, acute respiratory distress syndrome-like picture; COVID-19-positive on retest	Definite
3	Male	S/P infracardiac total anomalous pulmonary venous return repair, Restenosis of pulmonary vein confluence to left atrium	90	Had severe pulmonary hypertension and right ventricular dysfunction. Was planned for early surgery after recovery from COVID-19	No
6	Male	Tricuspid atresia, pulmonary atresia, generous patent ductus arteriosus	72	Patient died prior to scheduled surgery	Definite
9	Male	Severe pulmonary stenosis, moderate right ventricle dysfunction	82	Underwent emergency pulmonary valve balloon dilation in cath lab	Definite
20	Male	Tetralogy of Fallot, cyanotic spell	50	Died due to severe cyanotic spell, awaiting an emergency surgery	Possible
63	Male	Dilated cardiomyopathy in acute decompensated heart failure, left ventricle clot	85	Patient expired soon after visiting hospital emergency	Definite
86	Male	S/P mitral valve replacement, severe respiratory distress	80	Acute diarrhea for 2 days, severe dehydration, prosthetic heart valve thrombosis	Definite
2	Female	Large perimembranous ventricular septal defect	90	Patient was on mechanical ventilator in view of respiratory tract infection	Definite
12	Male	Tetralogy of Fallot	80	Patient was treated in a local hospital for COVID-19, and died early after transfer	Definite
1	Male	Situs inversus, dextrocardia, atrioventricular canal defect, and pulmonary hypertension	84	Patient died immediately after discharge against medical advice	No
144	Female	Bicuspid aortic valve, Aortic valve replacement for infective endocarditis	97	Patient died due to sequelae of infective endocarditis	No

COVID-19: Coronavirus disease-2019, SpO<sub>2</sub>: Oxygen saturation

The case fatality rate in our study population consisting of unoperated young children with serious heart disease was high (13.8%) as compared to the previously quoted studies involving a predominant GUCH population.<sup>[7-10]</sup> Most of the excess mortality was preprocedural. Severity of illness at admission was an independent predictor of mortality. Eventhough the postoperative mortality was comparable between the COVID-19-positive and COVID-19-negative patients, all the 13 hospitals reported a higher postoperative mortality in 2020 as compared to that of 2019.<sup>[15]</sup> A small study from Iran ( $n = 9$ ), which had a comparable patient population, reported a mortality of 22.2%.<sup>[11]</sup> Another interesting question was to ascertain the proportion of patients who died due to COVID-19 rather than with COVID-19, and this was difficult to assess in a retrospective study. Treating doctors opined that in 9 out of 13 deaths, COVID-19 could have been a definite causative factor.

The spectrum of SARS-CoV-2 infection in children is similar to that of the adult population and varies from an asymptomatic to a severe illness needing mechanical ventilation. COVID-19 risk estimation in patients with CHD is limited to GUCH population. The risk markers of death/severe disease varied between studies, and included male sex,<sup>[8]</sup> cyanosis,<sup>[7,8]</sup> pulmonary hypertension,<sup>[8]</sup>

hospitalization for heart failure,<sup>[8]</sup> obesity,<sup>[8]</sup> presence of comorbidities,<sup>[7,8]</sup> and advanced physiological state.<sup>[10]</sup> Expectedly, physiological factors were more predictive than anatomical factors in these studies. In our study, the mean SpO<sub>2</sub> was predictive of mortality on univariate analysis; however, the presence of pulmonary hypertension was not predictive. This could be related to the higher proportion of neonates and infants in our cohort with a treatable cause of pulmonary hypertension, unlike a GUCH population with residual pulmonary hypertension in other studies. Lower socioeconomic class is associated with a higher mortality in our study. Such a gradient in outcomes with socioeconomic class has been reported in COVID-19 and many conditions already, and the reasons are multifactorial.<sup>[21,22]</sup>

Pneumonia is the most common noncardiac cause of death in children with CHD, who are known to have poorer outcomes with influenza and other common respiratory viral and bacterial infections.<sup>[23,24]</sup> In addition, COVID-19 pneumonia in a child with CHD may lead to progressive hypoxia, worsening V/Q mismatch, embolic events, worsening pulmonary hypertension, and hypercapnic vasoconstriction. The combined effect is likely to be more pronounced in children with cyanotic CHD, leading to worsening of tissue oxygenation and perfusion. Endothelial dysfunction is widely prevalent in various

**Table 5: Univariate differences between dead and survivors among patients hospitalized with coronavirus disease-2019 and congenital heart disease**

Characteristics	Mean±SD or n (%)		P
	Death (n=13)	Survived (n=81)	
Mean age (months)	26.8±44.2	90.9±149.5	0.07
Gender			
Male	10 (20.4)	39 (79.6)	0.07
Female	3 (6.7)	42 (93.3)	
Socioeconomic class			
Upper and middle	3 (6.1)	46 (93.9)	0.04
Lower middle and lower	10 (22.2)	35 (77.8)	
Type of CHD			
Obstructive lesions	1 (8.3)	11 (91.7)	0.30
Acyanotic CHD	2 (6.5)	29 (93.6)	
Cyanotic CHD	7 (17.9)	32 (82.1)	
Acquired heart disease	3 (25.0)	9 (75.0)	
Pulmonary hypertension	8 (15.4)	44 (84.6)	0.77
Fever	5 (20.0)	20 (80.0)	0.32
Cyanosis	10 (25.0)	30 (75.0)	0.01
Tachypnea	10 (38.5)	16 (61.5)	<0.001
Shock at presentation	7 (63.6)	4 (36.4)	<0.001
Need for intubation	9 (69.2)	4 (30.8)	<0.001
ARDS	6 (85.7)	1 (14.3)	<0.001
SpO <sub>2</sub> (%)	80.9±11.5	90.4±8.4	<0.001
Severity of illness			
Not severe	4 (5.1)	78 (94.9)	<0.001
Severe	9 (72.7)	3 (27.3)	
Hemoglobin (g/dL)	12.5±2.2	13.2±3.4	0.65
Neutrophil/lymphocyte ratio	2.8±1.4	1.1±1.0	0.001
Platelets (lakhs/mm <sup>3</sup> )	2.5±1.4	2.6±1.0	0.41
Serum creatinine	1.1±1.0	0.4±0.3	0.10
Surgery during index hospitalization	3 (15.8)	16 (84.2)	0.72

CHD: Congenital heart disease, ARDS: Acute respiratory distress syndrome, SD: Standard deviation, SpO<sub>2</sub>: Oxygen saturation

forms of CHD, and endothelitis associated with COVID-19 could further aggravate it.<sup>[25-27]</sup> Vascular inflammation in the lung parenchyma and pulmonary vascular bed may contribute to adverse outcomes, especially if these children need to undergo early cardiac surgery using cardiopulmonary bypass. Extensive lung damage following cardiac surgery without an obvious cardiac cause was observed in four children who had undergone a cardiac surgery. Thus, the optimal timing of open-heart surgery following recovery from COVID-19 infection is a matter of debate, and it may be prudent to postpone it for 2 months if the clinical condition allows.<sup>[28-31]</sup>

COVID-19 could also lead to direct cardiac injury and dysfunction, and manifest as elevated troponins, myocarditis, heart failure, and arrhythmias.<sup>[19,32]</sup> In our series, only two children had arrhythmia and one patient had myo-pericarditis. However, troponin was not serially measured in most of these children. Coagulopathy and thrombotic manifestations are commonly reported in COVID-19 infection,<sup>[33]</sup> which was observed in three of our patients. In fact, coagulopathy could have played a causal role in death among two of them.

### Limitations

This retrospective multicentric study has inherent limitations. Further, selection bias due to inclusion of more serious patients presenting to the hospital during

the epidemic might influence the results. Hence, the case fatality rate in the population might be lower than reported. Because we collected data about the GUCH population in patients and control as per protocol, we cannot separate the effects in children alone, but we believe, this would not influence the implications or theme of our results.

The study has important implications. Most of the guidelines, risk classification, and consensus statements for COVID-19-positive children with CHD are not based on data.<sup>[34-38]</sup> This is the first report of sizable unoperated children with CHD and COVID-19. This study and similar data from LMICs are important as they have a higher burden of unoperated CHD and exposure to COVID-19. Children with CHD in developing countries, especially those with unoperated serious CHD, should be prioritized for vaccine allocation once approved for use in this age group. Efforts must focus on effective screening, early diagnosis, and timely management of serious CHD during the successive waves of the pandemic.

## CONCLUSIONS

Children with heart disease presenting to tertiary care pediatric centers are at a higher risk of mortality related to COVID-19 infection. Mortality is higher in children belonging to lower socioeconomic class and those with severe illness at presentation. Systematic preventive

measures and management strategies are needed for improving the outcomes in children with heart disease and grown-ups with congenital heart disease.

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### Conflicts of interest

There are no conflicts of interest.

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## SUPPLEMENTARY APPENDIX

### Supplementary Appendix 1

Study Pro forma: PCSI COVID study

Part 2: Details of CHD cases confirmed/suspected to have COVID

(Separate part 2 to be filled for each patient)

Site ID Participant ID

#### A. Presentation/admission

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Clinical inclusion criteria

Age :

Gender: M F

COVID 19 status : Suspect Confirm

If Confirm, Method of diagnosis: PCR Ag assay

Ab Rapid

First COVID detection date

Indication for testing : Screen before planned admission/Screened before consultation/symptomatic

Caregiver's relation

Caregiver's status

---

#### A. Other Demographics

Family member COVID positive: Father/Mothers/sibling/Others

Approximate social status Upper/Middle/Lower middle/Lower

- B. Preexisting cardiac diagnosis:
- C. Age at first cardiac diagnosis
- D. Any other co-morbidities (If Syndromic, Indicate here)
- E. Malnutrition: Yes/No
- F. Onset and admission

Date of admission

First symptom onset (days before admission)

How many days after symptom COVID was tested?

Presenting symptoms

#### G. Clinical features on admission

Fever Yes/No

SPO2

Tachypnea yes/No

Requirement of respiratory support Yes/No

BP

CFT

Height Weight

Clinically in shock Yes/No

#### H. Pre admission medications: (Tick whichever applicable)

- a. Diuretics
- b. Digoxin
- c. ACE Inhibitors/ARBs
- d. Beta-blockers
- e. Ibuprofen
- f. Other NSAIDs
- g. Antiarrhythmics

#### I. Hospital course

- a. Initially admitted in: Daycare/Ward/ICU
- b. Patient's most severe state: Mild symptoms/Severe symptoms/Critical

- c. Broad categories of treatment used
- i. Non-invasive ventilation? (Any) YES NO Unknown  
If YES, total duration: \_\_\_\_\_days Unknown
  - ii. Invasive ventilation? (Any) YES NO Unknown If YES, total duration: \_\_\_\_\_days Unknown
  - iii. Prone Positioning? YES NO Unknown If YES, total duration: \_\_\_\_\_days Unknown
  - iv. Inhaled Nitric Oxide? YES NO Unknown
  - v. Tracheostomy inserted? YES NO Unknown
  - vi. Extracorporeal support (ECMO)? YES NO Unknown If YES, total duration: \_\_\_\_\_days Unknown
  - vii. Renal replacement therapy (RRT) or dialysis? YES NO Unknown
  - viii. Inotropes/vasopressors? YES NO Unknown If YES, total duration: \_\_\_\_\_days Unknown
  - ix. ICU or High Dependency Unit admission? YES NO Unknown If YES, total duration: \_\_\_\_\_days Unknown

J. Medications while in the hospital

- a. Antivirals YES NO Unk
  - i. If yes Which drug Duration
- b. Chloroquine/hydroxychloroquine YES NO Unk
  - i. If yes, Duration
- c. Antibiotics YES NO Unk
  - i. If yes, which drug Duration
- d. Corticosteroids YES NO Unk
  - i. If yes, Which drug Oral/IV Duration
- e. Heparin YES NO Unk
  - Duration

K. Complications

<b>Viral pneumonia/pneumonitis</b>	<b>YES NO Unk</b>	<b>Stroke/Cerebrovascular accident</b>	<b>YES NO Unk</b>
Bacterial pneumonia	YES NO Unk	Meningitis/Encephalitis	YES NO Unk
Acute Respiratory Distress Syndrome	YES NO Unk	Bacteremia	YES NO Unk
If Yes : Severity Mild/Moderate/Severe			
Pneumothorax	YES NO Unk	Pulmonary embolism	YES NO Unk
Pleural effusion	YES NO Unk	Anemia	YES NO Unk
Cryptogenic organizing pneumonia (COP)	YES NO Unk	Rhabdomyolysis/Myositis	YES NO Unk
Bronchiolitis	YES NO Unk	Acute renal injury/Acute renal failure	YES NO Unk
Cardiac arrest	YES NO Unk	Gastrointestinal haemorrhage	YES NO Unk
Myocardial infarction	YES NO Unk	Pancreatitis	YES NO Unk
Cardiac ischaemia	YES NO Unk	Liver dysfunction	YES NO Unk
Cardiac arrhythmia	YES NO Unk	Hyperglycemia	YES NO Unk
Myocarditis/Pericarditis	YES NO Unk	Hypoglycemia	YES NO Unk
Endocarditis	YES NO Unk	Other	
Cardiomyopathy	YES NO Unk	If YES specify:	
Congestive heart failure		YES NO Unk	
Seizure			

A. Laboratory details

<b>Parameter</b>	<b>Value</b>	<b>Not done</b>	<b>Parameter</b>	<b>Value</b>	<b>Not done</b>
Hemoglobin			Urea		
WBC count (x10 <sup>9</sup> /L)			Create		
DLC	P L M E		Lactate		
Platelets			Na/K		
PT (seconds)			PCT		
APTT (S)			CRP		
INR			LDH		
AST/ALT			CKMB		
Bil Total			Trop I		
Blood Sugar Mg/dl			D Dimer		
S ferritin			IL- <sup>^</sup> levels		

N. In-Hospital outcome

- a. Death/survived

- b. Date of death/discharge
- c. Whether cardiac surgery done during index hospitalization? Yes/No
- d. Condition needed an elective surgery Yes/No
  - i. Surgery done later
  - ii. Awaiting surgery
- e. Remarks



**Supplementary Table 1: Diagnosis of individual lesions among coronavirus disease-2019-positive patients (n=94)**

Type of heart disease	n (%)
CHD	
Cyanotic CHD	39 (41.5)
Tetralogy of Fallot	16
Transposition of great arteries	5
VSD pulmonary atresia	5
TAPVC	3
Others	10
Acyanotic CHD	31 (33.0)
VSD	13
Atrial septal defect	8
Patent ductus arteriosus	6
Others	4
Obstructive CHD	12 (12.8)
Coarctation of aorta	5
Aortic stenosis	3
Pulmonary stenosis	3
Congenital mitral stenosis	1
Acquired heart disease in children	12 (12.8)
Infective endocarditis*	3
Idiopathic pulmonary hypertension	2
Dilated cardiomyopathy	2
Rheumatic heart disease	2
Others	3

\*All three had underlying heart disease but were primarily admitted for infective endocarditis. CHD: Congenital heart disease, VSD: Ventricular septal defect, TAPVC: Total anomalous pulmonary venous connection