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COVID-19 in congenital heart disease (COaCHeD) study

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ABSTRACT

Background COVID-19 has caused significant worldwide morbidity and mortality. Congenital heart disease (CHD) is likely to increase vulnerability and understanding the predictors of adverse outcomes is key to optimising care.

Objective Ascertain the impact of COVID-19 on people with CHD and define risk factors for adverse outcomes.

Methods Multicentre UK study undertaken 1 March 2020–30 June 2021 during the COVID-19 pandemic. Data were collected on CHD diagnoses, clinical presentation and outcomes. Multivariable logistic regression with multiple imputation was performed to explore predictors of death and hospitalisation.

Results There were 405 reported cases (127 paediatric/278 adult). In children (age <16 years), there were 5 (3.9%) deaths. Adjusted ORs (AORs) for hospitalisation in children were significantly lower with each ascending year of age (OR 0.85, 95% CI 0.75 to 0.96 (p<0.01)). In adults, there were 24 (8.6%) deaths (19 with comorbidities) and 74 (26.6%) hospital admissions. AORs for death in adults were significantly increased with each year of age (OR 1.05, 95% CI 1.01 to 1.10 (p<0.01)) and with pulmonary arterial hypertension (PAH; OR 5.99, 95% CI 1.34 to 26.91 (p=0.02)). AORs for hospitalisation in adults were significantly higher with each additional year of age (OR 1.03, 95% CI 1.00 to 1.05 (p=0.04)), additional comorbidities (OR 3.23, 95% CI 1.31 to 7.97 (p=0.01)) and genetic disease (OR 2.87, 95% CI 1.04 to 7.94 (p=0.04)).

Conclusions Children were at low risk of death and hospitalisation secondary to COVID-19 even with severe CHD, but hospital admission rates were higher in younger children, independent of comorbidity. In adults, higher likelihood of death was associated with increasing age and PAH, and of hospitalisation with age, comorbidities and genetic disease. An individualised approach, based on age and comorbidities, should be taken to COVID-19 management in patients with CHD.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Infection with respiratory viruses can have serious consequences in people with congenital heart disease, however, understanding of the impact of COVID-19 in this population is limited.

WHAT THIS STUDY ADDS

⇒ New data pertaining to the impact of the first two waves of the COVID-19 pandemic in the UK on people with congenital heart disease, and identification of key risk factors for worse outcomes.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Identification of medical and non-medical factors associated with increased rates of death in children and adults with congenital heart disease could help inform future decision-making regarding shielding when rates of COVID-19 infection are high or there are new variants.

INTRODUCTION

The COVID-19 pandemic commenced in theUK in 2020 and by 23 March 2020 groups in the population considered high risk of severe disease were advised to 'shield' or severely limit social contacts. The British Congenital Cardiac Association (BCCA) was asked to help define which subgroups of patients with congenital heart disease (CHD) should receive tailored clinical advice based on professional consensus due to limited evidence beyond experience with other viruses. The BCCA commissioned the UK-wide COVID-19 in CHD (COaCHeD) study to address the knowledge vacuum for patients

with CHD in the UK and to document the experience of COVID-19 illness in patients with CHD.

Knowledge of the effects of COVID-19 infection on people with CHD has been informed by studies within the adult population.[1 2] Data from the paediatric population remain limited, although severe disease, hospitalisation and death are less frequently reported than for adults.[3–5] We published data on early reported cases of COVID-19 from a review of the literature in 2020 to help guide this study.[6] Paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV2 (COVID-19) (PIMS-TS/MIS-C) has a clear cardiac phenotype but is not specifically associated with CHD.[7 8]

This study aimed to investigate the impact of COVID-19 infection on children and adults with CHD over the first and second waves of the pandemic in the UK, during which management evolved due to research, shielding and seasonal variation. We specifically investigated the risk factors predictive of survival or a medical decision to admit to hospital.

METHODS

This multicentre study involved 23 congenital cardiac services in 18 UK centres (12 paediatric, 11 adult).It had ethical approval from the Health Research Authority, HRA/HRCW:20/HRA/2958 and the Royal Brompton and Harefield NHS Foundation Trust was the co-ordinating centre.

Participants were children (aged under 16 years) and adults (16 years and older) with CHD who were infected with COVID-19, defined as SARS-COV-2 confirmed by PCR testing or lateral flow testing (LFT), between 1 March 2020 and 30 June 2021.

Children were eligible for inclusion if they had a diagnosis of CHD, arrhythmic disease (confirmed electrophysiological diagnosis), inherited cardiac disease (such as hypertrophic cardiomyopathy) and/or previous cardiac transplantation. Children with PIMS-TS/MIS-C but without CHD were excluded. Adults were eligible for inclusion if they had a diagnosis of CHD. Adults with arrhythmia, inherited cardiac disease and previous cardiac transplantation were excluded.

Congenital cardiologists who were members of the BCCA were prompted to report cases by monthly updates in the BCCA newsletter and emails from the central study team. To improve ascertainment, adult patients, or parents of children, could self-refer to the study team. Several patient support charities disseminated information about the study including Little Hearts Matter, the Brompton Fountain, the Somerville Foundation, ECHO (Evelina Children's Heart Organisation) and Leeds Congenital Hearts.

Clinicians completed standardised questionnaires using clinical case notes. As data were anonymised, individual consent was waived. Information was collected on demographics (age, area deprivation and ethnicity), cardiac diagnosis/interventions, oxygen saturations, comorbidities (defined as a confirmed diagnosis of an additional medical or psychological condition above that of the diagnosis of CHD), genetic disease (defined as a specific disease-causing mutation or syndrome) and outcomes following COVID-19 infection. For self-referred/parent-referred participants, standardised questionnaires were self-completed, and consent was sought to contact the local cardiologist to validate data. Duplicate reports were merged with the primary report.

Data analysis

Only the patient's first episode of COVID-19 infection was included in analyses. 'Severe disease' was defined as an episode requiring hospital admission, including emergency department assessment and 'hospice at home' management. Analysis of hospital admissions in this study include cases who were admitted to hospital for other reasons and were subsequently found to have COVID-19. Death with COVID-19 was defined according to UK government criteria as death within 28 days of a positive COVID-19 test.[9] Ethnicity was grouped using the Office for National Statistics Census 2011 framework into white, Asian, black, mixed and other. Participants were assigned to quintiles of deprivation according to area deprivation score reported by clinicians using English and Welsh indices of deprivation.[10 11] Children's weights were converted to z-scores for age and sex. Adult body mass index (BMI) was included as a binary variable (<30 kg/m^2 or ≥30 kg/m^2). Baseline oxygen saturations at diagnosis were categorised as <90% or ≥90%.

Factors related to mortality in COVID-19 (age, sex, obesity, deprivation and ethnicity) or to CHD outcomes (type of circulation, pulmonary arterial hypertension (PAH), comorbid conditions, genetic diagnosis and oxygen saturations) were investigated as potential predictors of hospital admission in both adults and children, and mortality in adults. Due to the low number of deaths, predictors of mortality in children were not explored. We explored individual predictors in univariable analyses then constructed a multivariable model using stepwise addition and evaluation of model fit. No interaction terms were significant. In a sensitivity analysis, multivariable models were adjusted for COVID-19 wave (wave 1 before 1 September 2020; wave 2 on and after 1 September 2020) to take account of potential changes in the approach to management. We initially used a complete-case approach then applied multiple imputation using chained equations to address missing data and minimise bias. The imputation model generated 25 imputed datasets and included all variables in the analysis model, as well as the outcome and one auxiliary variable (CHD diagnosis).

Analyses were performed using Stata V.17 (StataCorp. 2021). Data are presented as median and IQR or n (%) for continuous and categorical data, respectively. A $p<0.05$ was considered statistically significant.

Table 1 Demographic and characteristic data of participants in the study presented as all cases and as paediatric and adult subgroups

	All patients (n=405)	Children (<16) (n=127)	Adults (≥16) (n=278)
Age in years at COVID-19 diagnosis Median (IQR)	26 (11–38)	5 (1–10) (52 (11–122) months)	32 (25–46)
Age≤1 year, n (%)		32 (25.2)	
Age>50 years, n (%)			41 (14.7)
Sex, n (%)			
Female	189 (46.7)	52 (40.9)	137 (49.3)
Male	194 (47.9)	75 (59.1)	119 (42.8)
Missing	22 (5.4)	0 (0.0)	22 (7.9)
Ethnicity, n (%)			
White	174 (43.0)	59 (46.5)	115 (41.4)
Asian/Asian British (including Chinese)	41 (10.1)	23 (18.1)	18 (6.5)
Black/black British	11 (2.7)	6 (4.7)	5 (1.8)
Mixed	4 (1.0)	3 (2.4)	1 (0.4)
Other (including Arab)	7 (1.7)	6 (4.7)	1 (0.4)
Missing	168 (41.5)	30 (23.6)	138 (49.6)
Deprivation quintile, n (%)			
1	99 (24.4)	28 (22.0)	71 (25.5)
2	75 (18.5)	29 (22.8)	46 (16.5)
3	73 (18.0)	17 (13.4)	56 (20.1)
4	61 (15.1)	17 (13.4)	44 (15.8)
5	55 (13.6)	15 (11.8)	40 (14.4)
Missing	42 (10.4)	21 (16.5)	21 (7.6)
No in household (excluding patient), n(%)			
0–3	52 (12.8)	20 (15.7)	32 (11.5)
4–6	48 (11.8)	32 (25.2)	16 (5.7)
>11 (includes care homes, hospital, etc)	2 (0.4)	0 (0.0)	2 (0.7)
Missing	303 (74.8)	75 (59.0)	228 (82.0)
Anthropometry			
Adult BMI Median (IQR)	22.9 (18.3–27.1)	16.7 (15.2–19.5)	24.4 (22–29)
Adult BMI>30, n (%)			37 (9.14)
Weight z-scores (children) Median (IQR		–0.72 (–2.2 to 0.89)	
IOTF category (children) n (%)			
Grade 3 Thin		30 (23.6)	
Grade 2 Thin		9 (7.1)	
Grade 1 Thin		12 (9.5)	
Normal		18 (14.2)	
Overweight		4 (3.2)	
Obese		1 (0.8)	
Missing		53 (41.7)	
Circulation, n (%)			
Biventricular	334 (82.5)	106 (83.5)	228 (82.0)
Mixed	6 (1.5)	2 (1.6)	4 (1.4)
Univentricular	63 (15.6)	17 (13.4)	46 (16.6)

Continued

Table 1 Continued

	All patients (n=405)	Children (<16) (n=127)	Adults (≥16) (n=278)
Missing	2 (0.5)	2 (1.6)	0 (0.0)
Genetic diagnosis, n (%)†			
Yes	57 (14.1)	29 (22.8)	28 (10.1)
No	279 (68.9)	70 (55.1)	209 (75.2)
Missing	69 (17.0)	28 (22.1)	41 (14.8)
At least one comorbidity, n (%)*			
Yes	170 (42.0)	54 (42.5)	116 (41.7)
No	164 (40.5)	47 (37.0)	117 (42.1)
Missing	71 (17.5)	26 (20.5)	45 (16.2)

*Comorbidities across multiple organ systems, including neurodisability, chronic lung disease, immune deficiency (myelodysplastic syndrome, asplenia), chronic kidney disease, diabetes and previous malignancy (online supplemental table 6 for complete list).
†Genetic diagnosis—16 different diagnoses including Trisomy 21, 22q11 microdeletion syndrome, Noonan syndrome, William syndrome, Ehlers Danlos syndrome, Nemaline Myopathy and Hurler syndrome (online supplemental table 5 for complete list).
BMI, body mass index; IOTF, International Obesity Task Force.

RESULTS

There were 405 eligible participants; median (IQR) age of participants was 26(11–38) years and 189 (46.7%) were female (table 1).

A broad spectrum of CHD was represented (table 2; online supplemental table 1). Of these, 128 (31.6%) had an associated genetic diagnosis (online supplemental table 2) and 170 (42.0%) at least one comorbidity (online supplemental table 3). Seventy-four (18.3%) were asymptomatic and identified through hospital screening or the UK test and trace system.[12] The case/hospitalisation ratio was 29.1% (118/405) and case fatality ratio was 7.2% (29/405).

Paediatric cases

There were 127 paediatric cases, of whom 32 (25.2%) were ≤1 year and 52 (40.9%) were female. Median (IQR) age at COVID-19 diagnosis was 52 (11–122) months. Twenty-nine (22.8%) had an underlying genetic diagnosis, of whom 12 had T21, and 54 at least one comorbidity. The most common presenting symptoms were fever (n=31 (24.4%)), coryza (n=26 (20.5%)) and respiratory distress (n=24 (18.9%)); 50 (39.4%) were asymptomatic.

Deaths

Five children died (four aged ≤12 months); in one case, death was due to COVID-19 pneumonitis. All children who died had significant CHD-related comorbidity which was stated as the primary cause of death on the death certificate, including sepsis, multiorgan failure and acute renal failure, and prolonged hospital admission before death (range 12–90 days). These children met UK criteria for a death involving COVID-19,[9] however, in the view of their clinical team COVID-19 was not the primary cause of death.

Hospital admissions

There were 44 (34.6%) children admitted to hospital (34 in a cardiac specialist centre; 10 in a local district hospital); 24 were female, and median (IQR) age at diagnosis was 13.5 (2.8–72) months. Twenty-six hospitalised paediatric cases had at least one comorbidity, most often respiratory disease, preterm birth and neurological disease, 11 had a genetic diagnosis and 6 had univentricular circulations.

Approximately half of paediatric cases managed in hospital had respiratory distress prior to admission (n=21) and 27 were treated with antibiotic therapy. Ten children required oxygen therapy and 11 were intubated and ventilated (clinicians reported ventilating 5 children due to COVID-19 and 6 due to CHD). Eight were treated with inotropes (two prior to COVID-19 infection), of which seven were also ventilated. Ten cases were asymptomatic and identified as having COVID-19 while admitted to hospital for another non-related reason. Median (IQR) length of stay was 7 (4–30) days (table 3).

Predictors of hospitalisation

In univariable analyses (table 4), the OR of hospitalisation decreased significantly with each additional year of age (OR 0.83, 95% CI 0.75 to 0.91 (p<0.001)), and was significantly increased for females (OR 2.32, 95% CI 1.10 to 4.88 (p=0.03)) and those presenting with respiratory distress (OR 24.04, 95% CI 6.58 to 87.85 (p<0.001)). Asymptomatic cases were at reduced risk of hospitalisation (OR 0.28, 95% CI 0.18 to 0.63 (p=0.002)).

In a multivariable logistic regression analysis using imputed data, the OR for hospitalisation decreased significantly with each additional year of age (OR 0.85, 95% CI 0.75 to 0.96 (p<0.01)), after adjustment for ethnicity, sex, deprivation, number of comorbidities, circulation type, baseline oxygen saturations and weight z-score (table 5). No other independent predictors of hospitalisation were identified. In sensitivity analyses including COVID-19

Table 2 Primary cardiac diagnosis of participants

Congenital heart disease category	All (n=405) n (%)	Children (n=127) n (%)	Adults (n=278) n (%)
Hypoplastic left heart syndrome	11 (2.7)	9 (7.1)	2 (0.7)
Functionally univentricular heart	34 (8.4)	7 (5.5)	27 (9.7)
Common arterial trunk	6 (1.5)	5 (3.9)	1 (0.4)
Transposition of the great arteries and VSD/double outlet right ventricle transposition type	20 (4.9)	11 (8.7)	9 (3.2)
Interrupted aortic arch	1 (0.3)	0 (0.0)	1 (0.4)
Transposition of the great arteries	13 (3.2)	3 (2.4)	10 (3.6)
Pulmonary atresia with intact ventricular septum	12 (3.0)	2 (1.6)	10 (3.6)
Pulmonary atresia with VSD	23 (5.7)	5 (3.9)	18 (6.5)
Miscellaneous congenital heart disease*	11 (2.7)	1 (0.8)	10 (3.6)
Atrioventricular septal defect	33 (8.2)	12 (9.5)	21 (7.6)
Tetralogy of Fallot/double outlet right ventricle tetralogy type	52 (12.8)	17 (13.4)	35 (12.6)
Aortic stenosis	31 (7.7)	6 (4.7)	25 (9.0)
Tricuspid valve abnormality/Ebstein abnormality	11 (2.7)	2 (1.6)	9 (3.2)
Mitral valve abnormality	15 (3.7)	5 (3.9)	10 (3.6)
Total anomalous pulmonary venous connection	3 (0.7)	2 (1.6)	1 (0.4)
Aortic arch obstruction	30 (7.4)	4 (3.2)	26 (9.4)
Pulmonary stenosis	15 (3.7)	6 (4.7)	9 (3.2)
Subaortic stenosis	1 (0.3)	0 (0.0)	1 (0.4)
VSD±atrial septal defect±patent ductus arteriosus	41 (10.1)	11 (8.7)	30 (10.8)
Atrial septal defect	21 (5.2)	4 (3.2)	17 (6.1)
Patent ductus arteriosus	1 (0.3)	1 (0.8)	0 (0.0)
Arrhythmia	1 (0.3)	1 (0.8)	0 (0.0)
Miscellaneous terms†	10 (2.7)	5 (3.9)	5 (1.8)
Cardiomyopathy (including post-transplant)	8 (2.2)	8 (1.3)	NA
Aortic regurgitation	1 (0.3)	0 (0.0)	1 (0.3)

Note: A single primary cardiac diagnosis was assigned to each case using a hierarchical system.[18]
*Miscellaneous congenital heart disease includes: congenitally corrected transposition of the great arteries±other morphological changes.
†Miscellaneous terms include: postcardiac transplant and aortic root dilatation/dissection.
VSD, ventricular septal defect.

wave, hospitalisation risk was significantly higher in the first wave, while younger age remained an independent predictor (online supplemental table 4).

Adult cases

There were 278 adult cases; 137 (49.3%) were female, 28 (10.1%) had a genetic diagnosis and 116 (41.7%) at least one comorbidity. Median (IQR) age at diagnosis of COVID-19 was 32 (25–46) years. The most common presenting symptoms were fever (31 (11.2%)), coryza (26 (9.4%)) and respiratory distress (24 (8.6%)); 25 (9.0%) were asymptomatic.

Deaths

Death occurred in 24 (8.6%), all adult congenital heart disease (ACHD) cases met the UK criteria for death involving COVID-19.[9] Of these, 19 had comorbidities, 8 had associated genetic disease (T21 was most common), 2 had univentricular circulation and 9 had PAH.

Predictors of death

Univariable analysis showed a significant increased risk of death in adults with PAH (OR 5.89, 95% CI 2.30 to 15.07 (p<0.001)), genetic disease (OR 4.89, 95% CI 1.76 to 13.64 (p=0.0020) and lower baseline oxygen saturations (OR 1.97, 95% CI 1.29 to 2.99 (p=0.002)) while the likelihood of hospitalisation was significantly greater with each increased year of age (OR 1.05, 95% CI 1.02 to 1.08 (p<0.001)).

In multivariable logistic regression analyses using imputed data, the OR for death increased significantly with each year of age (OR 1.05, 95% CI 1.01 to 1.10 (p<0.01)) and with the presence of PAH (OR 5.99, 95% CI 1.34 to 26.91 (p=0.02)) after adjustment for ethnicity, sex, quintile of deprivation, number of comorbidities, type of circulation, genetic disease, baseline oxygen saturations and BMI (table 6). In sensitivity analyses, COVID-19 wave was not an

Table 3 Clinical features and management of COVID-19 infection for all cases and hospitalised cases

Variable	All cases (n=405)	Hospitalised patients	
		Children (n=44)	Adults (n=74)
Symptoms prior to hospital admission, n (%)			
Shortness of breath	88 (21.7)	21 (47.7)	22 (29.7)
Coryza	97 (24.0)	15 (34.1)	15 (20.3)
Anosmia	46 (11.4)	0 (0.0)	3 (4.1)
Chest Pain	16 (4.0)	0 (0.0)	3 (4.1)
Asymptomatic	75 (18.5)	10 (22.7)	5 (6.8)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Medications administered, n (%)			
Intravenous antibiotics	43 (10.6)	27 (61.4)	14 (18.9)
Antivirals	9 (2.2)	9 (20.5)	0 (0.0)
Steroids	19 (4.7)	8 (18.2)	10 (13.5)
Immunoglobulin	2 (0.5)	2 (4.5)	0 (0.0)
Missing	308 (76.0)	2 (4.5)	50 (6.8)
Respiratory support in hospital, n (%)			
Oxygen	28 (6.9)	10 (22.7)	8 (10.8)
High flow oxygen	6 (1.5)	5 (11.4)	1 (1.4)
Non-invasive ventilation	3 (0.7)	3 (6.8)	0 (0.0)
Intubation and ventilation	12 (3.0)	11 (25.0)	1 (1.4)
Nitric oxide	2 (0.5)	2 (4.6)	0 (0.0)
Missing	276 (68.1)	1 (2.3)	50 (67.6)
Circulatory support in hospital, n (%)			
Inotropes	9 (2.2)	8 (18.2)	1 (1.4)
Extra-corporeal membrane oxygenation	1 (0.3)	1 (2.3)	0 (0.0)
Missing	312 (77.0)	1 (2.3)	55 (74.3)
Death within 28 days of COVID-19, n (%)			
Yes	29 (7.1)	5 (11.4)	17 (23.0)
No	361 (88.9)	39 (88.6)	48 (64.9)
Missing	16 (3.9)	0 (0.0)	9 (12.2)
Length of hospital stay (days), median (IQR)			
		7 (4-30)	8 (4-18)
Missing n (%)		9 (20.5)	41 (55.4)

independent predictor of mortality (online supplemental table 5).

Hospital admissions

There were 74 (26.6%) cases admitted to hospital; 38 were female and their median (IQR) age was 38 (28–52) years. Comorbidity was present in 50, univentricular circulation in 9, genetic disease in 18 and PAH in 19 patients. There was a wide range of cardiac diagnoses (table 2). Five cases were asymptomatic and admitted to hospital for another non-related reason. Median (IQR) length of hospital admission was 8 (4–18) days (table 3).

Predictors of hospitalisation

Univariable analysis showed that severe disease (defined as an episode requiring hospital admission, including emergency department assessment and 'hospice at home' management) was significantly associated with PAH (OR 3.74, 95% CI 1.80 to 7.79 (p<0.001)), greater BMI (OR 1.07, 95% CI 1.02 to 1.13 (p=0.01)), additional comorbidities (OR 6.85, 95% CI 3.39 to 13.87 (p<0.001)), genetic disease (OR 7.78, 95% CI 3.18 to 19.04 (p<0.001) and lower baseline oxygen saturation (OR 1.51, 95% CI 1.11 to 2.05 (p=0.008)). The OR for hospitalisation was significantly greater with each increased year of age in adults (OR 1.04, 95% CI 1.02 to 1.06 (p<0.001)).

Multivariable logistic regression analysis using imputed data demonstrated that the OR for hospitalisation increased significantly with each year of age (OR 1.03, 95% CI 1.00 to 1.05 (p=0.04)), greater number of comorbidities (OR 3.23, 95% CI 1.31 to 7.97 (p=0.01)) and

Table 4 Predictors of hospitalisation and death (in the adult population) in univariable logistic regression models

	Children	Adults	
	Severe disease	Death	Hospitalisation
Outcome	OR (95% CI)	OR (95% CI)	OR (95% CI)
Pulmonary arterial hypertension		5.89 (2.30 to 15.07) p<0.001	3.74 (1.80 to 7.79) p<0.001
Body mass index >30 kg/m^2		0.48 (0.11 to 2.21) p=0.35	1.93 (0.95 to 3.94) p=0.07
Body mass index	0.94 (0.83 to 1.06) p=0.29	1.05 (0.98 to 1.12) p=0.17	1.07 (1.02 to 1.13) p=0.01
z-score weight	0.91 (0.77 to 1.09) p=0.31		
Univentricular circulation	1.03 (0.35 to 3.01) p=0.95	0.41 (0.09 to 1.79) p=0.23	0.57 (0.26 to 1.25) p=0.16
Prior use of anticoagulation	0.99 (0.41 to 2.40) p=0.99	1.22 (0.40 to 3.72) p=0.73	1.46 (0.72 to2.98) p=0.30
At least one comorbidity	1.54 (0.70 to 3.39) p=0.28	2.13 (0.86 to 5.25) p=0.10	6.85 (3.39 to13.87) p<0.001
Genetic disease	0.72 (0.30 to 1.74) p=0.47	4.89 (1.76 to 13.64) p=0.002	7.78 (3.18 to 19.04) p<0.001
Baseline oxygen saturations <90%	1.62 (0.61 to 4.25) p=0.33	2.51 (0.98 to 6.46) p=0.06	2.24 (1.15 to 4.39) p<0.001
Baseline oxygen saturations	1.19 (0.72 to 1.72) p=0.61	1.97 (1.29 to 2.99) p=0.002	1.51 (1.11 to 2.05) p=0.008
Female sex	2.32 (1.10 to 4.88) p=0.03	0.75 (0.32 to 1.76) p=0.50	1.07 (0.62 to 1.87) p=0.81
Age (years)	0.83 (0.75 to 0.91) p<0.001	1.05 (1.02 to 1.08) p<0.001	1.04 (1.02 to 1.06) p<0.001
Age >50 years		3.79 (1.48 to 9.72) p=0.006	3.56 (1.73 to 7.33) p=0.001
Age≤1 year	6.00 (2.56 to 14.04) p<0.001		
Ethnicity (reference: white)			
Asian	1.79 (0.67 to 4.76) p=0.25	0.98 (0.20 to 4.76) p=0.98	1.01 (0.35 to 2.91) p=0.98
Black	3.90 (0.66 to 23.15) p=0.13	1.96 (0.20 to 18.91) p=0.56	1.35 (0.22 to 8.43) p=0.75
Mixed or other	0.61 (0.24 to 1.52) p=0.29	0.54 (0.22 to 1.36) p=0.19	0.56 (0.33 to 0.73) p=0.05
Asymptomatic	0.28 (0.18 to 0.63) p=0.002	0.63 (0.08 to 5.08) p=0.665	0.84 (0.30 to 2.39) p=0.745
Respiratory distress	24.04 (6.58 to 87.85) p<0.001	1.31 (0.52 to 3.31) p=0.57	1.57 (0.86 to 2.88) p=0.15

'Severe disease' defined as an episode requiring hospital admission, including emergency department assessment and 'hospice at home' management).

genetic disease (OR 2.87, 95% CI 1.04 to 7.94 (p=0.04)) after adjustment for ethnicity, sex, quintile of deprivation, baseline oxygen saturations, PAH and BMI (table 7). The OR for hospitalisation was significantly lower in those with univentricular or mixed circulation compared with biventricular (OR 0.27, 95% CI 0.09 to 0.81 (p=0.02)). In sensitivity analyses including COVID-19 wave, hospitalisation risk was significantly higher in the first wave; older age remained an independent predictor while the influence of comorbidities and genetic disease were attenuated (online supplemental table 6).

DISCUSSION

This large UK-wide study describes paediatric and adult CHD populations in the UK diagnosed with COVID-19 during the first two waves of the pandemic, a period of changing infection rates attributable to seasonal variation, shielding and evolution of disease variants. Key findings are that 7% of patients died (fulfilling the UK criteria for death involving COVID-19[9]) and 29% were admitted to hospital with COVID-19 (who were either symptomatic with the disease or asymptomatic and admitted for another reason). Independent predictors of hospitalisation with COVID-19 infection were younger age in children, and older age, comorbidities and genetic disease in adults. Older age and PAH (Eisenmenger syndrome) were independent predictors of death for adults with CHD and COVID-19.

Case-fatality rate in the paediatric population was low with only one death directly attributed to COVID-19 pneumonitis. Low fatalities secondary to COVID-19 ranging from 0% to 6% were also seen in other paediatric cardiology studies.[3–5 13] One Indian study reported 13 (27%) deaths in children with CHD, however, most were young and unoperated.[14] Within the paediatric CHD population, hospital admission rates with COVID-19 were also low.[3–5]

Previous reports are consistent with our finding of greater risk of severe disease in younger patients[13 14] and highlights the potential vulnerabilities of neonates/infants who are unoperated[14] or undergoing cardiac surgery. Given these vulnerabilities, consideration of limiting social contacts in these groups prior to a planned hospital admission for intervention may help protect against disease transmission at this critical time.

Table 5 Predictors of hospitalisation in children using multivariable logistic regression with the multiple imputation model (n=127)

Outcome	OR	P value	95% CI
Ethnicity (Reference: white)			
Asian	1.12	0.87	0.30 to 4.13
Black	2.46	0.38	0.33 to 18.40
Mixed/other	0.54	0.28	0.17 to 1.66
Univentricular circulation	0.32	0.23	0.05 to 2.05
Age (years)	0.85	<0.01	0.75 to 0.96
Female sex	2.57	0.05	0.98 to 6.73
Deprivation quintile (Reference: 1=most deprived)			
2	0.55	0.35	0.15 to 1.96
3	2.12	0.33	0.47 to 9.52
4	0.73	0.70	0.14 to 3.71
5	0.88	0.89	0.15 to 5.21
No of comorbidities	1.64	0.32	0.62 to 4.33
Genetic disease	0.56	0.34	0.18 to 1.83
Oxygen saturations <90%	2.29	0.31	0.46 to 11.44
Z-score weight	0.91	0.38	0.74 to 1.12

Hospitalised patients with CHD in this study represent a fraction of all UK reported COVID-19 admissions (n=113/474 304; 0.02%)[15] and deaths (n=21/128 297; 0.02%)[9] between 19 March 2020 and 30 June 2021. The BCCA published online guidelines for vulnerable groups with CHD on its website related to UK government advice.[16] Given the lack of published evidence of risk within the CHD population, stricter social distancing measures were advised for patients with PAH and infants under 1 year with unrepaired CHD, both of which are groups confirmed to have higher OR for adverse outcomes within our study, as well as for patients with univentricular circulation and cardiomyopathies, who we have not found to be at higher risk. In contrast, we found that adults with univentricular circulation were less likely to be admitted to hospital than those with biventricular circulation, one hypothesis for this could be that those with univentricular circulation may have adopted a more cautious approach in terms of preventative measures against COVID-19. Consistent with previous reports from the general adult population, we identified an increased risk of hospitalisation in older patients. However, the median age of patients with ACHD admitted to hospital was lower than for the UK adult population with COVID-19; this has also been demonstrated in similar studies of the ACHD population.[1 2 12]

Table 6 Predictors of mortality in adults using multivariable logistic regression with the multiple imputation model (n=278)

Outcome	OR	P value	95% CI
Ethnicity (Reference: white)			
Asian	1.19	0.47	0.31 to 12.63
Black	1.19	0.91	0.05 to 28.66
Mixed/other	0.73	0.57	0.25 to 2.15
Univentricular circulation	0.70	0.67	0.13 to 3.79
Age (years)	1.05	<0.01	1.01 to 1.10
Female sex	0.47	0.18	0.16 to 1.41
Deprivation quintile (Reference: 1=most deprived)			
2	0.26	0.14	0.04 to 1.54
3	0.32	0.19	0.06 to 1.76
4	0.32	0.21	0.05 to 1.92
5	1.54	0.53	0.39 to 6.07
No of comorbidities	0.30	0.11	0.07 to 1.31
Genetic disease	4.63	0.05	0.99 to 21.61
Pulmonary arterial hypertension	5.99	0.02	1.34 to 26.91
Oxygen saturations <90%	2.41	0.25	0.54 to 10.82
BMI ≥30	2.02	0.40	0.39 to 10.50

Table 7 Predictors of hospitalisation in adults using multivariable logistic regression with the multiple imputation model (n=278)

Outcome	OR	P value	95% CI
Ethnicity (Reference: white)			
Asian	1.52	0.50	0.45 to 5.14
Black	0.42	0.43	0.05 to 3.66
Mixed/other	0.49	0.05	0.24 to 1.01
Univentricular circulation	0.27	0.02	0.09 to 0.81
Age (years)	1.03	0.04	1.00 to 1.05
Female sex	0.90	0.78	0.45 to 1.82
Deprivation quintile (Reference: 1=most deprived)			
2	0.79	0.63	0.29 to 2.10
3	0.61	0.33	0.23 to 1.65
4	0.44	0.13	0.15 to 1.28
5	0.42	0.13	0.13 to 1.29
No of comorbidities	3.23	0.01	1.31 to 7.97
Genetic disease	2.87	0.04	1.04 to 7.94
Pulmonary arterial hypertension	1.14	0.80	0.41 to 3.19
Oxygen saturations <90%	2.73	0.06	0.94 to 7.90
BMI ≥30	1.58	0.36	0.59 to 4.27

BMI, body mass index.

Of deaths within the ACHD population, 10 (3.6%) were directly attributed to COVID-19, which is consistent with a large international study of patients with ACHD where 24 (2.3%) deaths were directly attributed to COVID-19.[1] Other studies reported higher rates, including a US study with 41 (10.5%) deaths, however, this study was unable to differentiate cases that had COVID-19 as a primary or secondary cause.[13] Risk of death in patients with ACHD with PAH was elevated in this study in keeping with the published literature.[1 2] Such patients represent a high-risk

population in terms of complications and mortality due to reduced cardiorespiratory reserve and chronic cyanosis. Acute COVID-19 exacerbates hypoxaemia and thrombotic risk associated with PAH. The higher complication risk within this group supports the principle that each patient with CHD should receive individualised care.

People with T21 may have comorbidities in different organ systems impacting on their ability to cope with infection; these include CHD, increased risk of PAH, obesity and respiratory disease. Some studies have shown more severe outcomes for those with T21 and COVID-19, but importantly also for those with additional comorbidities.[17] Although we observed higher likelihood of hospitalisation and mortality for people with genetic disease, particularly T21, in our complete case models, this was attenuated after imputation of missing data. Nevertheless, the data suggest that people with T21 are a high-risk group and should have priority for vaccine roll-out regardless of CHD involvement.

Many paediatric cases (50/127 (39.4%)) were asymptomatic, including ten managed in hospital who were admitted for another medical reason. Our findings highlight the importance of testing asymptomatic children with CHD who may act as a pool for transmission, especially if unvaccinated against COVID-19.

Although inequalities have been highlighted as important to COVID-19 infection risk, we did not find that demographic factors such as sex, deprivation and ethnicity, were associated with increased risk of hospitalisation or death. However, it may be that our study was underpowered to detect such differences as, for example, data on ethnicity was missing in 42%.

This study was representative of adult and paediatric patients with CHD admitted to specialist cardiac centres with COVID-19 throughout the first and second waves of the pandemic, and our findings are generalisable to this population. However, some adult centres did not participate so case ascertainment was incomplete. As all paediatric specialist cardiac centres in Great Britain took part, there was potential to ascertain all cases admitted to paediatric intensive care with COVID-19, however children with asymptomatic, mild and self-limiting illness or those managed at home, in emergency departments or district hospitals were less likely to have been reported to the study. In contrast, clinical thresholds to admit patients may have been lower, particularly during the first pandemic wave, reflecting medical caution at a time when understanding of disease COVID-19 progression in patients with CHD was lacking. Overall, disease burden is likely to have been higher than we ascertained and case-hospitalisation and case-fatality ratios lower.

Reliance on data collection from medical records also presented some limitations, such as missing data, and we were unable to ascertain longer-term outcomes, therefore, late complications and deaths may not have been captured. Although we recorded ventilation in the paediatric population, we were unable to use this as a measure of COVID-19 severity as clinicians reported that this was precipitated by COVID-19 in only half of cases, and by underlying CHD or other comorbidity in the remainder.

Future research

The evolution of vaccination, new variants and release from lockdown have had an impact on COVID-19 distribution, with subsequent waves affecting larger numbers of young patients. Further studies are required to explore the impact of these changes on populations affected by CHD.

CONCLUSIONS

Overall, in the paediatric population there was a low risk of death or severe disease secondary to COVID-19, but neonates and infants experienced higher rates of hospitalisation. In adults with CHD, risk of COVID-19 death and severe disease was related to older age, particularly in those with associated PAH, multiple comorbidities and genetic disease. Individual clinical management plans should be formulated based on these risk factors.

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Supplementary Data

Supplementary Table 1

Congenital heart disease category	**Children in hospital [n=44] n(%)**	**Adults in hospital [n=74] n(%)**
Hypoplastic left heart syndrome	3 (6.8)	0 (0.0)
Functionally univentricular heart	3 (6.8)	5 (6.8)
Common arterial trunk	1 (2.3)	0 (0.0)
Transposition of the great arteries and VSD/ Double outlet right ventricle transposition type	5 (11.4)	2 (2.7)
Interrupted aortic arch	0 (0.0)	0 (0.0)
Transposition of the great arteries	1 (2.3)	1 (1.4)
Pulmonary atresia with intact ventricular septum	0 (0.0)	2 (2.7)
Pulmonary atresia with VSD	1 (2.3)	7 (9.5)
Miscellaneous congenital heart disease	0 (0.0)	3 (4.1)
Atrioventricular septal defect	6 (13.6)	10 (13.5)
Tetralogy of Fallot/ Double outlet right ventricle tetralogy type	3 (6.8)	10 (13.5)
Aortic stenosis	3 (6.8)	5 (6.8)
Tricuspid valve abnormality/ Ebstein abnormality	1 (2.3)	1 (1.4)
Mitral valve abnormality	2 (4.5)	5 (6.8)
Total anomalous pulmonary venous connection	1 (2.3)	0 (0.0)
Aortic arch obstruction	2 (4.5)	3 (4.1)
Pulmonary stenosis	2 (4.5)	1 (1.4)
Subaortic stenosis	0 (0.0)	0 (0.0)
VSD +/- atrial septal defect +/- patent ductus arteriosus	0 (0.0)	0 (0.0)
Atrial septal defect	6 (13.6)	11 (14.9)
Patent ductus arteriosus	2 (4.5)	8 (10.8)
Arrhythmia	0 (0.0)	0 (0.0)
Miscellaneous terms	0 (0.0)	0 (0.0)
Cardiomyopathy (including post-transplant)	1 (2.3)	0 (0.0)
Aortic regurgitation	1 (2.3)	0 (0.0)

Supplementary Table 1:
Primary cardiac diagnosis of participants in the study who were admitted to hospital

Note: A single primary cardiac diagnosis was assigned to each case using a hierarchical system[19]; VSD: ventricular septal defect

**Miscellaneous congenital heart disease includes: congenitally corrected transposition of the great arteries +/- other morphological changes. #Miscellaneous terms include: post cardiac transplant and aortic root dilatation/ dissection.*

Supplementary Table 2

Genetic diagnoses and syndromes
22q11 microdeletion syndrome
Bardet Biedl syndrome type 2
Beaulieu-Boycott-Innes syndrome
CHARGE syndrome
Ehlers Danlos syndrome
Hurler Syndrome
Marfan syndrome
Nemaline Myopathy - ACTA gene exon
Noonan syndrome
Oculofaciocardiodental syndrome
POLR2A mutation
Trisomy 21
Tuberous Sclerosis
Turner syndrome
VACTERL syndrome
William syndrome

Supplementary Table 2: List of genetic diagnoses and syndromes that participants in the study were known to live with.

Supplementary Table 3

Comorbidities
Acquired brain injury
Anorectal malformation
Asthma
Bilateral hearing loss
Bulbar palsy
Chronic kidney disease
Chronic lung disease
Colonic stricture
COPD
Developmental delay
Diabetes
Endocarditis
Epilepsy
Extra dural haematoma
Gastroesophageal reflux disease
Haematological disease
Hydronephrosis
Hypercholesterolaemia
Hypothyroidism
Immune deficiency (Myelodysplastic Syndrome, Asplenia)
Left hemidiaphragm palsy
Medullary nephrocalcinosis
Mental health disease
Migraine
Necrotising enterocolitis (previous)
Neurodisability
Osteoporosis
Prematurity
Previous malignancy
Recurrent lower respiratory tract infection / aspiration
Renal dysplasia
Scoliosis
Single kidney
Unsafe swallow – Nasogastric / Gastrostomy feeding
Vitamin / Iron deficiencies

Supplementary Table 3: List of associated co-morbidities that participants in the study lived with.

Supplementary Table 4

Outcome	**Odds Ratio**	**P-value**	**95% Confidence Interval**
Ethnicity *(Reference: White)*			
- Asian	0.94	0.93	0.22-4.03
- Black	5.01	0.15	0.57-44.09
- Mixed/Other	0.48	0.29	0.12-1.85
Univentricular circulation	0.17	0.08	0.02-1.23
Age (years)	**0.88**	**<0.05**	**0.77-1.00**
Female sex	2.58	0.07	0.91-7.29
Deprivation quintile *(Reference: 1=most deprived)*			
- 2	0.89	0.88	0.19-4.08
- 3	2.87	0.22	0.53-15.58
- 4	0.97	0.97	0.15-6.26
- 5	1.12	0.91	0.14-8.96
Number of comorbidities	1.52	0.46	0.51-4.54
Genetic disease	0.52	0.31	0.15-1.83
Oxygen saturations <90%	5.45	0.06	0.93-31.97
Z-score weight	0.92	0.49	0.72-1.17
Second wave of COVID-19 *(Reference: first COVID-19 wave)*	**0.04**	**<0.01**	**0.01-0.23**

Supplementary table 4: Predictors of hospitalisation in children (n=127) – sensitivity analysis adjusted for COVID-19 wave

Supplementary Table 5

Outcome	**Odds Ratio**	**P-value**	**95% Confidence Interval**
Ethnicity *(Reference: White)*			
- Asian	2.08	0.44	0.33-13.16
- Black	1.42	0.84	0.05-39.56
- Mixed/Other	0.72	0.57	0.23-2.21
Univentricular circulation	0.79	0.79	0.14-4.33
Age (years)	**1.05**	**<0.01**	**1.01-1.09**
Female sex	0.50	0.21	0.17-1.49
Deprivation quintile *(Reference: 1=most deprived)*			
- 2	0.27	0.16	0.04-1.66
- 3	0.25	0.12	0.04-1.41
- 4	0.37	0.26	0.07-2.06
- 5	1.71	0.43	0.45-6.60
Number of comorbidities	0.34	0.14	0.08-1.46
Genetic disease	4.64	0.07	0.86-24.94
Pulmonary arterial hypertension	**6.34**	**0.02**	**1.39-28.84**
Oxygen saturations <90%	2.05	0.36	0.43-9.81
BMI ≥30	2.16	0.34	0.43-10.76
Second wave of COVID-19 *(Reference: first COVID-19 wave)*	0.47	0.24	0.14-1.66

Supplementary Table 5: Predictors of mortality in adults (n=278) – sensitivity analysis adjusted for COVID-19 wave.

Supplementary Table 6

Outcome	**Odds Ratio**	**P-value**	**95% Confidence Interval**
Ethnicity *(Reference: White)*			
- Asian	1.45	0.55	0.43-4.95
- Black	0.46	0.48	0.05-3.93
- Mixed/Other	0.45	0.04	0.21-0.96
Univentricular circulation	**0.26**	**0.02**	**0.09-0.78**
Age (years)	1.02	0.06	1.00-1.05
Female sex	0.96	0.91	0.48-1.91
Deprivation quintile *(Reference: 1=most deprived)*			
- 2	0.77	0.60	0.29-2.07
- 3	0.49	0.19	0.17-1.42
- 4	0.43	0.13	0.15-1.28
- 5	0.37	0.08	0.12-1.14
Number of comorbidities	**3.52**	**0.01**	**1.30-9.50**
Genetic disease	2.93	0.05	0.99-8.65
Pulmonary arterial hypertension	1.01	0.98	0.36-2.80
Oxygen saturations <90%	2.85	0.05	0.97-8.40
BMI ≥30	1.60	0.37	0.57-4.49
Second wave of COVID-19 *(Reference: first COVID-19 wave)*	**0.36**	**0.03**	**0.15-0.90**

Supplementary Table 6: Predictors of hospitalisation in adults (n=278) – sensitivity analysis adjusted for COVID-19 wave