Anatomical complexity does not predict outcomes after COVID-19 in adults with congenital heart disease

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Few could have guessed the global devastation of COVID-19 when it was first reported more than a year ago. Community spread has been a major route of transmission as COVID-19 has a lower case fatality rate (2.3%) but much greater infectivity compared with previous outbreaks (severe acute respiratory syndrome, 2002–2003; Middle Eastern respiratory syndrome, 2012–ongoing).[1] Most patients experienced mild infection (81%), while 5% developed critical illness.[1] Risk factors for death that have been identified include age, disease severity and comorbidities such as cardiovascular disease, diabetes, hypertension, chronic respiratory disease and cancer.[1] Patients with congenital heart disease (CHD) were perceived to be especially vulnerable to infection due to their fragile physiology, particularly those with moderate to severe complex anatomy such as repaired tetralogy of Fallot, status post atrial or arterial switch procedure or Fontan circulation.[2 3] Data to quantify this risk have been limited—until now.

In this issue of *Heart*, Schwerzmann *et al*[4] describe the clinical course of 105 patients with CHD with COVID-19 infection, based on either a positive biochemical test (by PCR or ELISA) or strong clinical suspicion (based on symptoms and chest CT findings). This was a collaboration between 25 centres in nine countries, as part of the European Collaboration for Prospective Outcome research in Congenital Heart Disease. It is the largest multicentre cohort study thus far and the first publication of its kind.

The authors aimed to identify patient characteristics associated with 'complicated' infection, which they defined as either death or hospitalisation requiring non-invasive/invasive ventilation and/or inotropic support after COVID-19 infection. In total, 73/105 patients (70%) had mild disease, while 13 patients (12%) experienced a complicated infection (online supplemental table S1). At study conclusion, 91 patients (87%) had recovered; 9 cases (9%) were ongoing; and 5 patients (5%) had died. Two patients with Eisenmenger syndrome chose palliative care after diagnosis, which is an important reminder of the importance of advance care planning for patients with CHD. Cyanotic CHD (highest risk), Body Mass Index (BMI) of >25 kg/m^2 and ≥2 non-CHD-related comorbidities (see online supplemental table S1 and figure 1B for a full list) were identified as independent risk factors for complicated infection. Age was significant in univariate analysis but was omitted from multivariate analysis by study design because its OR was less than 5. Interestingly, other CHD-related features were not associated with complicated infection: underlying anatomical disease complexity (simple, moderate or complex) and main defect-related problems (valvular problem, heart failure, arrhythmia or pulmonary arterial hypertension) were not statistically significant in univariate analysis, though the study may have been underpowered for these analyses. Also, rather than using a unifying definition for comorbidities such as heart failure or renal failure, study authors relied on the discretion of individual clinicians at each study centre. Finally, it is unclear how many patients had a genetic syndrome in the entire cohort as only one patient with a complicated infection had this reported as a comorbidity in the authors' table 4.

WHAT DID WE ALREADY KNOW?

Radke *et al*[2] were the first to describe an institutional approach to disease prevention, management and risk stratification in adult congenital heart disease (ACHD), based on data from non-congenital patients and anecdotal experience. Subsequently, the European Society of Cardiology Working Group of Adult Congenital Heart Disease and the International Society for Adult Congenital Heart Disease recommended risk stratifying patients using a combination of anatomy and physiology.[3] This was based on our understanding of the likely interactions between the physiology of CHD and its end organ sequelae, and the pathophysiology of COVID-19 infection and its treatment (figure 1A).

Few studies examining COVID-19 infection in patients with CHD were published prior to Schwerzmann *et al*. Table S1 in the online supplemental material summarizes the 4 available cohorts/case series with more than 50 patients with CHD. Importantly, these additional studies also found that most patients with CHD experienced mild COVID-19 infection:

92% of adults in Sabatino *et al*[5] and 84% of adults in Lewis *et al*[6] compared with 70% of patients in Schwerzmann *et al*[4] did not require hospitalisation. However, these numbers include varying proportions of suspected COVID-19 cases. Lewis *et al*[6] also assessed the determinants of moderate/severe illness, which they defined as death, hospitalisation or need for new or increased supplemental oxygen. Their multivariate analysis (which included 10 children) found that moderate/severe infection was associated with a genetic syndrome (five patients had Down syndrome, and one had DiGeorge syndrome) and ACHD physiological stage C or D.[6] This is congruent with previous studies in which Down syndrome was associated with death or hospitalisation after COVID-19 infection and overlaps with variables identified by Schwerzmann *et al*.[4 7] Relatedly, both single-ventricle/Fontan physiology and complex congenital anatomy were not significant in univariate analysis, while pulmonary hypertension and obesity (BMI≥30 kg/m^2) were not significant after adjustment for multiple comparison.[6] Lastly, at least mild systolic dysfunction of the subaortic or subpulmonary ventricle was associated with longer hospitalisation (median of 18 days compared with 9 days, p=0.0004).[6]

ANATOMY DOES NOT PREDICT COVID-19 INFECTION SEVERITY

Taken together, the aforementioned data suggest that though patients with CHD with COVID-19 infection are decades younger as a cohort than those infected in the general population, their trajectories share important similarities. First, most patients with CHD experienced mild infection, which ranged from 70%–92% in the studies discussed.[4–6] Similarly, 81% of patients in the general cohort had experienced mild infection.[1] Second, the main predictors of moderate/severe infection in CHD remain patient characteristics,

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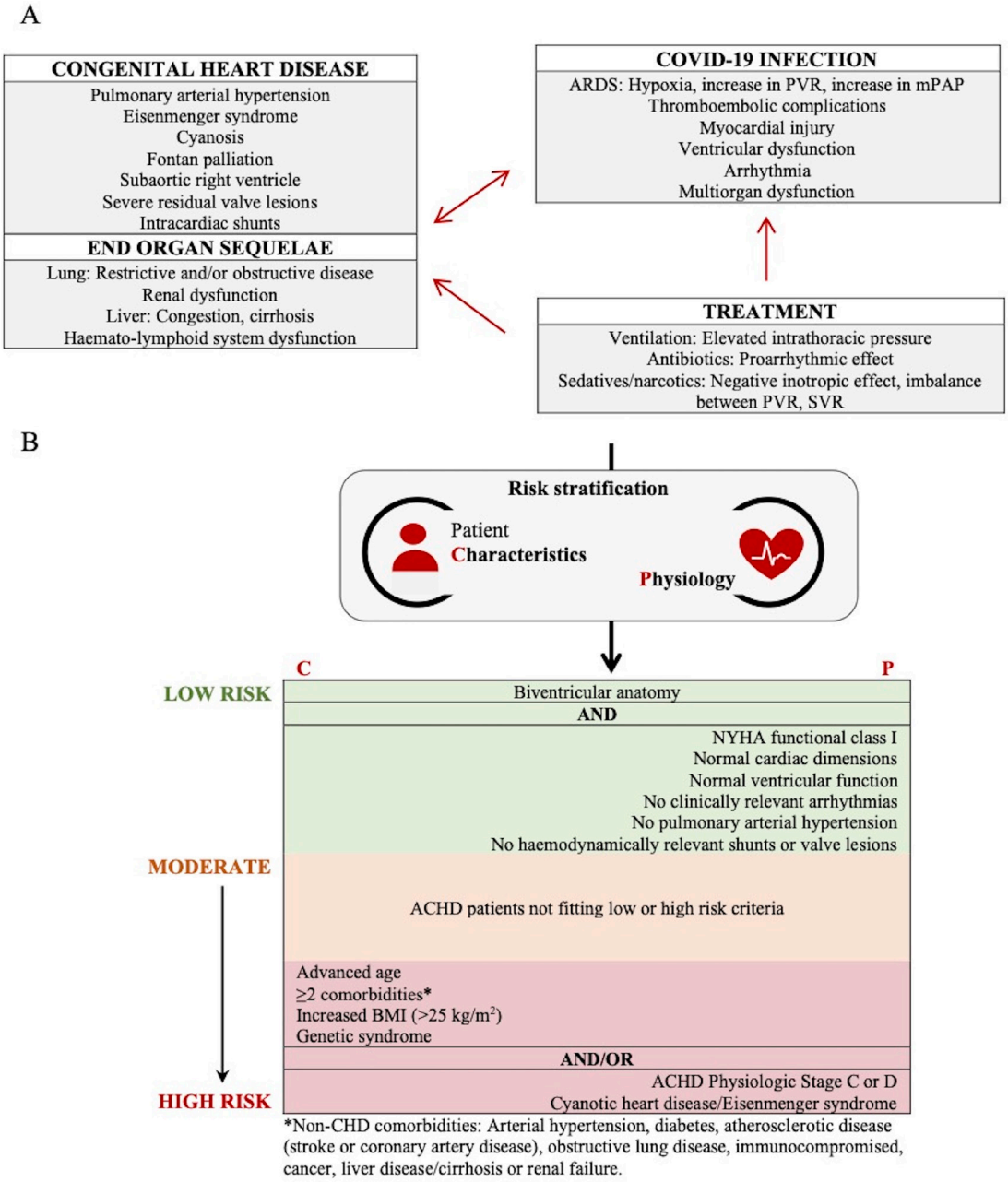

Figure 1 Conceptualisation of risk in patients with ACHD after COVID-19 infection. (A) Proposed interactions between the physiology of CHD and its end organ sequelae, and the pathophysiology of COVID-19 infection and its treatment. (B) Proposed risk stratification strategy based on current literature, adapted from Diller *et al* with permission.[3 4 6] ACHD, adult congenital heart disease; ARDS, acute respiratory distress syndrome; BMI, Body Mass Index; CHD, congenital heart disease; mPAP, mean pulmonary artery pressure; NYHA, New York Heart Association; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance.

such as advanced age, increased BMI and multiple comorbidities including a genetic syndrome.[4 6] This contrasts with our previous perception of increased risk in patients with CHD, particularly those with CHD of moderate or great complexity, regardless of relevant sequelae.[2 3]

These studies also identified two CHD-specific risk factors for severe COVID-19 infection: cyanotic heart disease and ACHD physiological stage C or D.[4 6] Unfortunately, the overlap between these variables makes it difficult to determine the relative importance of features such as cyanosis, pulmonary arterial hypertension, Eisenmenger syndrome, heart failure and ventricular dysfunction. Relatedly, Schwerzmann *et al*'s assessment of heart failure as a determinant of patient outcome after COVID-19 infection may be limited by small numbers, as they found 10 patients with heart failure as their main defect-related residual problem, of which only one patient experienced a complicated infection.[4] Furthermore, the number of patients with pre-existing clinical heart failure in the authors' table 4 highlights the fact that their analysis of heart failure as a main defect-related residual problem may not capture the full contribution of clinical heart failure or ventricular dysfunction to patient outcomes after COVID-19 infection.[4] Similarly, Lewis *et al*[6] found that more than mild ventricular dysfunction was associated with duration of hospitalisation but not moderate/severe infection, yet ACHD physiological stage C or D, which was associated with moderate/severe infection, includes characteristics such as NYHA class III/IV, moderate/severe

ventricular dysfunction, pulmonary arterial hypertension and Eisenmenger syndrome. One has the impression that some combination of these variables may be predictive of outcome after COVID-19 infection but not yet clearly how. More consistently, these studies seem to agree that anatomical classification of CHD complexity is not a major determinant of outcome after COVID-19 infection. Figure 1 shows a proposed, modified framework for risk stratification based on these results.

This synthesis is limited by several considerations. First, these studies examined hospital-based cohorts of patients who presented to care. There may be an uncaptured cohort of minimally symptomatic patients who did not seek assessment, or patients who were treated or died elsewhere. Second, the authors' definition of COVID-19 infection included suspected cases, which may overestimate the proportion of patients who did not require hospitalisation. Third, though Schwerzmann *et al*[4] describe the largest prospective cohort of patients with CHD with COVID-19 infection, the event rate of complicated infection was still low (13/105 patients). Comparatively, Lewis *et al*[6] and Sabatino *et al*[5] reported even fewer patients with an outcome of interest in their studies. Finally, that the study authors all used different definitions of COVID-19 infection, moderate/severe infection, as well as their independent variables limits comparison across studies. It is difficult to conclude with certainty the independent predictors of severe infection. Many risk factors need further examination and questions remain, such as the possible role of ACE inhibitor/angiotensin receptor blockers or the immune response of patients with a genetic syndrome or immunocompromise.

LESSONS LEARNED AND TO LEARN

The studies discussed here offer some reassurance that most patients with CHD experienced mild illness after COVID-19 infection. Contrary to our previous conceptualisation of risk, anatomical complexity does not appear to predict severe infection or death. Rather, patient-specific risk factors similar to those in the non-CHD cohort remain important, while strong CHD-specific risk factors for severe illness or death after COVID-19 infection were cyanotic heart disease and physiological stage. These results help us to tailor patient recommendations but require further confirmation in large international, multicentre studies that are sufficiently powered to answer our remaining questions. Newly published results from the very large worldwide COVID-19 study provide additional support for the aforementioned risk factors discussed.[8]

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Table S1. Articles on COVID-19 infection with more than 50 CHD patients

Authors, Country	Study design	N	N adults age ≥18 years	Suspected COVID	Confirmed COVID+	Age (years) Sex	Definition of moderate/severe infection	Moderate/severe infection	Death	Mild disease (Not hospitalized)	Hospitalized	Hospitalized with ventilation, inotropic support	CV complication	Current medications	Comorbidities associated with severe infection (OR; p value)
Mohammadzadeh et al, Iran(1)	Single centre telephone survey All CHD patients age ≥14 years with ≥1 visit during last year at private office or study hospital	309	Unknown	Confirmed COVID+ defined as: PCR+ and/or CT findings Confirmed COVID+: 18 (6%) Unknown status: 291 (94%) ≥1 symptom: 37 (12%) Asymptomatic: 272 (88%) COVID+ or ≥1 symptom: 38 (12%) 1 patient was asymptomatic but diagnosed COVID+ due to COVID+ household contact		Age: 14-72 Mean: 29 Sex: M=45%	Death or hospitalization	3/38 (8%)	1/18 COVID+ Decompensated after TVR for Ebstein anomaly. ICU roommate subsequently tested COVID+.	35/37 (95%) symptomatic 17/18 COVID+	2/37 symptomatic patients were hospitalized. No further details.		Unknown	Yes including ACE inhibitors	**Univariate analysis independent variables**: Status post Fontan, PH, Eisenmenger syndrome, reduced EF, diuretic use, age ≥30 **COVID+ (N=18) versus unknown status (N=291)**: Diuretic use (6/18) (p=0.023) Age ≥30 years (15/18) (p<0.001) **Symptomatic (N=37) versus asymptomatic (N=272):** Diuretic use (14/37) (p<0.001) Age ≥30 (24/37) (p=0.003)
Sabatino et al, Italy(2)	Cross-sectional survey of 8 high volume centres	76	72	66 adults (92%) 1 child (25%) Defined as symptoms and history of exposure	6 adults (8%) 3 children (75%) Defined as ≥2 PCR+ tests	72 adults: Age: 21-76 Mean: 36 Sex: M=53% 4 children: Age: 2 months to 2 years Sex: M=50%	Any CV complication*	7/76 (10%) 4/72 adults (6%) 3/4 children (75%)	0/76 (0%)	67/67 suspected COVID (88% of 76) 66/72 adults (92%) 1/4 children (25%)	9/9 COVID+ (12% of 76) Presumably all COVID+ patients were monitored in hospital for potential CV complications 6/72 adults (8%) 3/4 children (75%)	^1 adult: HF requiring ECMO support Adults or children: 1/9: Inotropic support 1/9: CPAP	Adults: 2/6: None 1/6: Chest pain ^1/6: HF, stroke, arrhythmia 1/6: HF 1/6: Stroke, arrhythmia Children: 1/3: HF, myocardial injury, pericardial effusion 2/3: HF, PH	Not assessed	Not assessed
Lewis et al, USA(3)	Retrospective single centre chart review	53	43	43 adults (100%) 10 children (100%) Unclear how many were confirmed versus suspected COVID-19 infection. 1 patient was asymptomatic. Suspected infection: Symptoms consistent with COVID-19 infection with a positive household or roommate contact. Confirmed COVID+: PCR+		Cohort: Median: 34 (IQR 16) Sex: M=58% Adults: Median: 37 (IQR 21) Sex: M=56% Children: Median: 3 (IQR 9) Sex: M=70%	Any of: Death, Hospitalization, or Need for new or increased respiratory support	9/53 (17%) 7/43 adults (16%) 2/10 children (2%)	3/53 (6%) 3/43 adults (7%) 1/3 at long term care facility 2/3 in ICU 0/10 children (0%)	44/53 (83%) 36/43 adults (84%) 8/10 children (80%)	7/53 (13%) 5/43 adults (12%) 2/10 children (20%) 2/43 (22%) remained at home or long-term care facility with increased supplemental oxygen 1/2 recovered 1/2 died	2/5 adults required supplemental oxygen 3/5 intubated 2/3 died 1/3 recovered 1/2 children required inotropic support, supplemental oxygens	Troponin: Adults: 4/7: No data 2/7: Normal 1/7: Elevated Children: 2/2: Normal	Yes, including ACE inhibitors	**Not significant:** Single ventricle/Fontan (OR 0.49; p=0.91) **Complex congenital anatomy (OR 2.86, p=0.36) Decreased ventricular function (OR 1.51, p=0.81) **Unadjusted univariate analysis:** PH (mPAP≥25 mmHg) (OR 15.25, p=0.011) Obesity (BMI≥30 kg/m^2) (OR 7.34, p=0.046) **Adjusted for multiple testing:** Genetic syndrome (OR 35.82; p=0.0002) ACHD physiologic stage C or D (OR 19.38; p=0.0020)
Schwerzmann et al, Europe(4)	Prospective cohort 25 centres, 9 countries	105	Unknown	27 (26%) Defined as symptoms and characteristic findings on CT chest	78 (74%) Defined as positive test by PCR or ELISA	Age: 16-75 Mean: 38 Sex: M=42%	Any of: Death, or Hospitalization requiring invasive/non-invasive ventilation or inotropic support (including ECMO)	13/105 (12%) 9/105 (9%) ongoing cases	5/105 (5%) 1/5 died after surgery for BAV with severe stenosis with decompensated HF 2/5 died in hospital 2/5 chose palliative care #1/2 discharged from ED 1/2 to palliative care	73/105 (70%)	31/105 (30%) #1 patient was discharged home from ED for palliative care	11/31 (10%) 3/11 died 3/11 ongoing 5/11 recovered	Not assessed	Not assessed	**Univariate analysis:** Age, per 5 years (OR 1.3; p=0.018) Residual cardiac defect (p=0.089) Cardiac complexity (p=0.423) **Multivariate analysis:** Cyanotic heart disease (OR 60.0; p>0.001) BMI >25 kg/m^2 (OR 16.4; 0=0.001) ***≥2 comorbidities (OR 6.7; 0.027)

Articles with fewer than 50 patients, or only pediatric patients or Down syndrome patients were included.
*CV (cardiovascular) complication: Any of: palpitation/arrhythmia, chest pain, myocardial injury (troponin T above 99th percentile upper reference limit, heart failure, stroke/transient ischaemic attack (TIA), pulmonary hypertension, pericardial effusion, or respiratory failure.
**Complex congenital anatomy: Any of: Unrepaired or palliated cyanotic heart defect; status post Fontan procedure; single ventricle physiology; pulmonary atresia; transposition of the great arteries; truncus arteriosus; or abnormalities of the atrioventricular or ventriculoarterial connection.
***Comorbidities: Arterial hypertension, diabetes, atherosclerotic disease (stroke or coronary artery disease), obstructive lung disease, immunocompromised, cancer, liver disease/cirrhosis or renal failure.
#Same patient. ^Same patient.
Abbreviations:
IQR interquartile range. OR odds ratio. N number of patients.
Suspected COVID-19-infection: Infection diagnosis based on symptoms consistent with COVID-19 infection and other clinical feature(s).
COVID+: Confirmed infection by polymerase chain reaction (PCR) test and/or other test (see table).
ACHD adult congenital heart disease. BAV bicuspid aortic valve. BMI body mass index. CHD congenital heart disease. CPAP continue positive airway pressure. CT chest thoracic computed tomographic imaging. ED Emergency department.
ECMO extracorporeal membrane oxygenation. ICU intensive care unit. ELISA enzyme-linked immunosorbent assay. HF heart failure. mPAP mean pulmonary artery pressure in mmHg. PH pulmonary hypertension. TIA transient ischaemic attack. TVR tricuspid valve replacement. USA United States of America.

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