Predictors of COVID-19 outcomes in adult congenital heart disease patients: Anatomy versus function

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ABSTRACT

Background: It is unclear whether patients with adult congenital heart disease (ACHD) should be considered as an increased risk population with poor outcomes when suffering from COVID-19.

Aims: This study aimed to collect clinical outcome data and to identify risk factors of a complicated course of COVID-19 among ACHD patients.

Methods: Among all outpatients who came to medical attention via telemedicine or direct physician contact at our institution between September 1, 2020 and March 31, 2021, we included all with a COVID-19 diagnosis. The incidence of COVID-19, a clinical course of the disease, and outcome were determined.

Results: One hundred and four (8.7%) out of 1 197 patients who were seen at our outpatient clinic for ACHD patients met the definition of COVID-19. Most of them reported a mild course of COVID-19 (99 [95.5%]). Five patients (4.5%) experienced severe symptoms and needed hospitalization. Two patients (1.9% of all with a confirmed diagnosis, 40% with severe infection) died. In the multivariable analysis, decreased systemic ventricular systolic function and any significant valve stenosis were predictors of a complicated disease course.

Conclusions: Our study confirmed previous results showing that a physiology-based model, rather than an anatomy-based model, better predicted COVID-19 outcomes among ACHD patients, which is of importance for patients and healthcare providers during the COVID-19 pandemic.

Key words: COVID-19, adult congenital heart disease, outcome

INTRODUCTION

The novel SARS-CoV-2 responsible for COVID-19 is known to damage the cardiovascular system, leading to increased morbidity and mortality in patients with underlying cardiovascular diseases [1]. It is unclear whether patients with adult congenital heart disease (ACHD) should be considered as an increased risk population with poor outcomes when suffering from COVID-19 as they are typically younger than those with acquired cardiac disease and are less likely to have comorbidities [2]. On the other hand, the heterogeneity of this population makes the prediction of their response to COVID-19 very challenging. In a patient with ACHD, the severity of the disease is determined not only by defective anatomy or surgical repair but also by the current physiology, as physiological variables may have a prognostic value. According to the American Heart Association/American College of Cardiology Adult Congenital Heart Disease Guidelines, the more advanced physiological stage is characterized by the presence of moderate or greater valvular heart disease (stenosis or regurgitation), moderate/severe ventricular dysfunction, hypoxemia, hemodynamically significant shunt, arrhythmias,

WHAT'S NEW?

It is unclear whether patients with adult congenital heart disease (ACHD) should be considered as an increased risk population with poor outcomes when suffering from COVID-19 as they are typically younger than those with acquired cardiac disease and are less likely to have comorbidities. We confirmed that anatomical complexity does not predict an adverse outcome. Decreased systemic ventricular systolic function and any significant valve stenosis were predictors of death or hospitalization. Our study showed that a physiology-based model, instead of an anatomy-based model, better predicts COVID-19 outcomes among ACHD patients. This information is important both for patients and medical care providers facing the next wave of COVID-19.

pulmonary arterial hypertension, Eisenmenger syndrome, or evidence of end-organ dysfunction [3]. Those with cyanotic lesions, genetic lesions, or an advanced physiological stage have been considered at the highest risk for moderate/severe COVID-19 [4, 5]. However, the results were based on small studies and need to be validated in a larger ACHD population. This study aimed to collect clinical outcome data and to identify risk factors of a complicated course of COVID-19 among ACHD patients.

METHODS

The study was conducted in a tertiary referral center for an ACHD as a retrospective registry of patients diagnosed with COVID-19. From all outpatients who had routine clinic appointments via telemedicine or direct physician contact at our institution between September 1, 2020 and March 31, 2021, we included all with a COVID-19 diagnosis (positive test for SARS-CoV-2 infection using a PCR test, antibody, and SARS-CoV-2 antigen-based ELISA or if someone had contact with an infected person in their household and developed typical symptoms).

The following variables of interest were demographic and historical medical data: body mass index (BMI), history of surgery for defects, a type of cardiac defect, the complexity of cardiac defect according to the European ACHD guidelines [6], New York Heart Association (NYHA) functional class before COVID-19, clinically relevant comorbidity, a clinical course, and an outcome of the COVID-19 disease. A severe COVID-19 was defined as death or the need for hospitalization requiring oxygen supply, non-invasive or invasive ventilation, or circulatory support. No need for hospitalization was defined as a mild course. Symptoms and infection duration were quantified and confirmed with the patient. A minimum temperature of ≥38.0°C was used to define fever. Echocardiographic data were collected from each patient's most recent echocardiogram within 12 months before infection. The following variables were assessed from standard transthoracic echocardiograms: significant (at least moderate) valvular stenosis or regurgitation (definition according to the ESC valvular heart disease guidelines), at least moderate systemic ventricular dysfunction (ejection fraction of systemic ventricular function at least 40%), or any subpulmonic ventricular dysfunction. The diagnosis of pulmonary arterial hypertension had to be confirmed by cardiac catheterization.

The local research ethics board approved the study (IK-NPIA-0021-19/1901/2021). For this type of retrospective study, formal patient consent was not required.

Statistical analysis

Continuous variables were presented as the mean (standard deviation [SD]), and categorical variables were expressed as numbers and frequencies. A univariate logistic regression model was used to determine the odds ratios (ORs) and 95% confidence intervals (CIs) for risk factors associated with hospitalization and/or death related to COVID-19. All variables with a significance threshold

Table 1. Characteristics of ACHD patients diagnosed with COVID-19

Parameters	N = 104
Age, years, mean (SD)	38.5 (12)
Male, n (%)	48 (46)
BMI, kg/m^2, mean (SD)	25.5 (4.2)
Complex CHD, n (%)	28 (26.9)
Prior intervention, n (%)	60 (57.6)
Genetic syndrome, n (%)	7 (6.7)
Baseline oxygen saturation, %, mean (SD)	95.1 (5.7)
CHD-associated PAH, n (%)	10 (9.6)
Decreased systemic ventricular systolic function, n (%)	10 (9.6)
Decreased subpulmonary ventricular systolic function, n (%)	9 (8.6)
Significant valvular regurgitation (any), n (%)	26 (25)
Significant valvular stenosis (any), n (%)	10 (9.6)
Acquired comorbidities, n (%)	39 (37.5)
Medications	
β-blockers, n (%)	44 (42.3)
ACE-I/ARB, n (%)	31 (29.8)
Diuretics, n (%)	21 (20.2)
Oral anticoagulation, n (%)	18 (17.3)
Antiplatelet therapy, n (%)	2 (1.9)
COVID-19 symptoms	
Fever, n (%)	53 (51)
Cough, n (%)	49 (47)
Shortness of breath, n (%)	18 (17)
Fatigue, n (%)	71 (68)
Anosmia, n (%)	48 (46)
Ageusia, n (%)	46 (44)
Gastrointestinal symptoms, n (%)	14 (13.5)
Hospitalization, n (%)	5 (4.5)
Death, n (%)	2 (1.9)
None, n (%)	11 (10.6)

Abbreviations: ACEI, angiotensin-converting-enzyme inhibitors; ARB, angiotensin receptor blockers; BMI, body mass index; CHD, congenital heart disease; PAH, pulmonary arterial hypertension; SD, standard deviation

Table 2. Characteristics of patients with severe COVID-19 infections

Age	Sex	Main diagnosis	Clinical background	SARS-CoV-2 infection course
19	Male	Repaired tetralogy of Fallot, Down syndrome	NYHA class II, decreased RV function, significant pulmonary stenosis, oxygen saturation at rest 94%, BMI 21 kg/m^2	Hospitalization due to SARS-CoV-2 bilateral pneumonia requiring non-invasive ventilation, fully recovered after 21 days after hospital admission
51	Female	Repaired tetralogy of Fallot	NYHA class II, systemic hypertension, BMI 28.1 kg/m^2	Death due to SARS-CoV-2 infection 14 days after admission (ARDS related to COVID-19 requiring intubation), renal failure
36	Female	common arterial trunk type IV (unrepaired)	NYHA class II, permanent atrial flutter/atrial fibrillation, severely reduced biventricular function, oxygen saturation at rest 76%, BMI 32.4 kg/m^2	Hospitalization due to heart failure exacerbation, SARS-CoV-2 infection during hospital stay worsening the clinical course of the disease, died suddenly on day 10 after hospital admission
31	Female	unrepaired cyanotic CHD: single ventricle, transposition of the great arteries, significant pulmonary stenosis	NYHA class II, moderate mitral regurgitation, oxygen saturation at rest 94%, BMI 17.5 kg/m^2	Hospitalization due to bilateral pneumonia requiring oxygen-therapy with a face mask fully recovered 14 days after hospital admission
51	Female	congenitally corrected transposition of the great arteries, history of ASD and VSD closure, and TV replacement	NYHA class II/III, severe systemic RV dysfunction, permanent atrial fibrillation BMI 22.5 kg/m^2	Hospitalization due to severe gastrointestinal symptoms of COVID-19 infection (gastritis) with subsequent HF exacerbation (patient required inotropic agents), fully recovered after 28 days

Abbreviations: ASD, atrial septal defect; NYHA, New York Heart Association class; TV, tricuspid valve; VSD, ventricular septal defect; other — see Table 1

of P <0.01 in the univariate model were included in the multivariable logistic regression analysis to identify independent predictors of a complicated SARS-CoV-2 infection course in ACHD patients. A two-sided P-value of <0.05 was considered statistically significant. All data were analyzed with an R software package version 4.0.0 (R Foundation, Vienna, Austria).

RESULTS

During 6 months of observation, 1197 patients were seen by cardiologists (28% were consulted via telemedicine) at our outpatient clinic for ACHD. The mean age of the entire cohort was 38.5 ±14 years. In 243 (20.3%) patients, a complex congenital cardiac defect was diagnosed. We identified 104 (8.7%) patients who met our definition for a SARS-CoV-2 infection. Overall, 89 (86%) patients had a diagnosis confirmed with testing, while in 15 (14%) patients, the diagnosis was based on clinical grounds. Table 1 summarizes the baseline characteristics of ACHD patients diagnosed with COVID-19. Most patients reported a mild course of COVID-19 disease (99 [95.5%]). Five patients (4.5%) experienced severe symptoms and needed hospitalization. Two patients (1.9% of all with a confirmed diagnosis, 40% with severe infection) died.

Table 2 summarizes details on patient characteristics and clinical history of individuals with severe COVID-19.

In the univariable analysis, decreased systemic and subpulmonary ventricular systolic function, and any significant valvular stenosis were predictors of hospitalization and/or death. In the multivariable analysis, decreased systemic ventricular systolic function and any significant valve stenosis were predictors of a complicated disease course (Table 3).

Table 3. Uni- and multivariable analysis for COVID-19 — related hospitalization and/or death

Variable	OR (95% CI)	P-value
Univariable analysis		
Age, years	1.00 (0.93–1.08)	0.98
Male sex	0.26 (0.03–2.56)	0.26
History of intervention	1.11 (0.18–6.91)	0.96
Complex CHD (vs. moderate/mild)	4.44 (0.70–28.12)	0.11
Genetic disorder	3.88 (0.37–40.29)	0.26
Baseline oxygen saturation	0.95 (0.37–1.08)	0.41
BMI, kg/m^2	0.93 (0.74–1.16)	0.52
CHD-associated PAH	2.5 (0.25–24.83)	0.43
Acquired comorbidities	2.63 (0.42–16.45)	0.30
Decreased systemic ventricular systolic function	7.58 (1.10–52.23)	0.04
Decreased subpulmonary ventricular systolic function	8.76 (1.25–61.42)	0.03
Significant valvular regurgitation (any)	2.08 (0.33–13.21)	0.44
Significant valvular stenosis (any)	7.58 (1.10–52.23)	0.04
Multivariable analysis		
Decreased systemic ventricular systolic function	20.75 (1.69–254.74)	0.02
Significant valvular stenosis (any)	20.75 (1.69–254.74)	0.02

Abbreviations: OR, odds ratio; other — see Table 1

DISCUSSION

This is the first sizable single-center report on the outcome of COVID-19 among ACHD patients in Europe. The main finding of our study is that decreased systemic ventricular function and significant valvular stenosis identify patients with a severe course of COVID-19. Our results are in agreement with the real-world data, which has already been published and confirmed the thesis that anatomical complexity itself does not predict an adverse outcome. In the first publication by Lewis et al., the authors concluded that an ACHD Physiological Stage C or D was associated with a moderate/severe COVID-19. Moderate/severe ventricular dysfunction and at least moderate valvular stenosis were among the criteria that placed patients at Physiological Stage C or D. Similarly, Broberg et al. [7] found that reduced subaortic ventricular function was predictive of a severe course. In the work by Ruperti-Repilado et al. [8], more than 90% of ACHD experts pointed out that pulmonary arterial hypertension (PAH), cyanotic heart disease, and

Fontan palliation are the most important factors of an unfavorable outcome. In our analysis, neither baseline oxygen saturation, PAH, nor ACHD complexity were important as outcome predictors. These results provide important knowledge regarding our current perception of risks and shift us away from an anatomy- to a physiology-based model.

In the article by Schwerzmann et al. [4], the authors demonstrated that general risk factors (age, obesity, and multiple comorbidities) may predict a complicated course of COVID-19. Obesity is a well-known risk factor for a severe course of COVID-19, along with hospitalization, transferto the intensive care unit, being put on a ventilator, and, finally, dying [10]. This was not the case in our study as in our cohort the mean BMI was 25.5 kg/m^2 — much lower than reported by others [3, 7]. Acquired comorbidities (systemic hypertension, diabetes, atrial fibrillation, or ischemic heart disease) are infrequent in the ACHD population. We found them in 39 (37.5%) cases and did not demonstrate they influenced the COVID-19 outcome. Older age was a risk factor for COVID-related death in ACHD and the general population. In our population, it has not been shown to be an important prognostic factor. Although the mean age and the frequency of acquired cardiac risk factors were comparable with previously published reports, this phenomenon remains to be explained.

This is the first study in which an attempt was made to determine the rate of infection among the ACHD population. In a small series of patients with Fontan circulation from Italy, the authors estimated that the 1-year COVID-19 incidence was 11% [11]. During the autumn and winter of 2020/2021, our outpatient clinic treated 1 197 ACHD patients. Yet only 104 (8.7%) of them were COVID-19 positive. Of these, only 5 patients had a severe course and 2 died, resulting in an overall case/fatality ratio (in those tested) of 1.9%. Broberg et al. [7] reported a similar case/fatality ratio at the level of 2.3%. Our results concern the period before the common vaccination program and during the first year of the COVID-19 pandemic.

The ACHD patients are known to greatly benefit from prompt access to continuous expert care. Authors from Italy reported cancellation of all elective hospital procedures during the first year of the COVID-19 pandemic but stable the overall number of urgent hospital admission during that time [12]. Our center did not restrict access to medical care. In response to patients' requests, we implemented new alternative ways of communication. Twenty-eight percent of consultations were carried out using telemedicine.

The spectrum of COVID-19 symptoms in our population was like those described in other ACHD cohorts [13], with fatigue and fever being the most frequent (68% and 51%, respectively). Notably, 10.6% of patients were completely asymptomatic; diagnoses were made incidentally through COVID-19 PCR testing, after a known exposure, or through the SARS-CoV-2 antibody test. As the ACHD population is relatively young, the real proportion of patients who had COVID-19 may be higher.

Study limitations

The limitation of our study is its retrospective design. We did not test every patient treated at our outpatient clinic for SARS-CoV-2. As we know, some patients have asymptomatic infections; this implies that other asymptomatic carriers were likely to be among this population. The preceding limitations suggested that the true case/fatality ratio might be lower, and on the other hand, the rate of SARS-CoV-2 infections might be higher. Our study focused on short-term death and serious complications and did not address potential medium and long-term complications. Further studies on the longer-term consequences of COVID-19 in ACHD are needed. We are also aware that the logistic regression model performed for our dataset with few events involves some uncertainty, and the results should be interpreted with caution.

CONCLUSIONS

In conclusion, our study confirmed previous results showing that a physiology-based model, instead of an anatomy-based model, better predicts COVID-19 outcomes among ACHD patients. This information is important both for patients and medical care providers facing the next stage of the pandemic.

Article information

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Conflict of interest: None declared.

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