Clinical outcome of COVID-19 in patients with adult congenital heart disease

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ABSTRACT

Aims Patients with adult congenital heart disease (ACHD) are a potentially vulnerable patient cohort in case of COVID-19. Some cardiac defects may be associated with a poor COVID-19 outcome. Risk estimation in ACHD is currently based on expert opinion. The aim of this study was to collect clinical outcome data and to identify risk factors for a complicated course of COVID-19 in patients with ACHD.

Methods Twenty-five ACHD centres in nine European countries participated in the study. Consecutive patients with ACHD diagnosed with COVID-19 presenting to one of the participating centres between 27 March and 6 June 2020 were included. A complicated disease course was defined as hospitalisation for COVID-19 requiring non-invasive or invasive ventilation and/or inotropic support, or a fatal outcome.

Results Of 105 patients with a mean age of 38±13 years (58% women), 13 had a complicated disease course, of whom 5 died. In univariable analysis, age (OR 1.3, 95% CI 1.1 to 1.7, per 5 years), ≥2 comorbidities (OR 7.1, 95% CI 2.1 to 24.5), body mass index of ≥25 kg/m² (OR 7.2, 95% CI 1.9 to 28.3) and cyanotic heart disease (OR 13.2, 95% CI 2.5 to 68.4) were associated with a complicated disease course. In a multivariable logistic regression model, cyanotic heart disease was the most important predictor (OR 60.0, 95% CI 7.6 to 474.0).

Conclusions Among patients with ACHD, general risk factors (age, obesity and multiple comorbidities) are associated with an increased risk of complicated COVID-19 course. Congenital cardiac defects at particular high risk were cyanotic lesions, including unrepaired cyanotic defects or Eisenmenger syndrome.

INTRODUCTION

The first wave of COVID-19 caused by SARS-CoV-2 hit Europe in March 2020. As of the end of September, more than 3.3 million cases with >190,000 deaths have been counted by the European Centre for Disease Prevention and Control.7 As a response to the pandemic, European countries have developed strategies for minimizing transmission of the virus, spread of the infection and disease-related morbidity and mortality. This includes the identification of vulnerable patients with underlying medical conditions associated with poor COVID-19 outcome, requiring particular protection.

Patients with adult congenital heart disease (ACHD) represent such a potentially vulnerable patient cohort. With an estimated ACHD prevalence of 3000 per million adults, more than 2.5 million adults with congenital cardiac defects are currently living in Europe.2 A cure of the congenital cardiac defect by surgery or other interventions is still exceptional and many patients with ACHD face a lifelong increased risk of cardiovascular complications, such as heart failure, arrhythmias, pulmonary hypertension and premature death.3 4 Respiratory diseases—in particular, pneumonia—are the most common non-cardiac cause of death in patients with ACHD, especially among patients with genetic disorders.5 Therefore, yearly influenza vaccination is recommended for most patients with ACHD.6

Patients with ACHD with simple lesions and no genetic disorder may not be at higher COVID-19 risk than the general population, whereas patients with more complex disease (eg, Fontan physiology, cyanotic heart disease, defects with impaired subpulmonary or subaortic ventricular function) may be at risk of haemodynamic compromise, hypoxia or paradoxical embolism if COVID-19-related complications occur. These uncertainties have led to substantial concerns among patients, relatives and treating physicians. In the absence of reported data, risk estimation is currently based on expert opinion. The aims of this study were to collect clinical outcome data and to identify risk factors for a complicated course of COVID-19 in patients with ACHD in European reference centres.

METHODS

As part of a research initiative within the European Collaboration for Prospective Outcome Research in Congenital Heart Disease (EPOCH, https://

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www.sacher-registry.com/epoch/), this collaborative study was launched among different ACHD centres across Europe.

A total of 25 ACHD centres in nine European countries participated in the study. All patients with ACHD diagnosed with COVID-19 (positive test for SARS-CoV-2 by means of PCR test, antibody and SARS-CoV-2 antigen-based ELISA) or strong clinical suspicion (based on symptoms and thoracic CT findings) presenting to or contacting one of the participating centres were included. The study started on March 27 and data reported until 6 June 2020 were analysed. Only patients actively reporting to their centres or hospitalised for COVID-19 at the participating centres were included.

The following data were collected: type of cardiac defect, complexity of cardiac defect according to the most recent European ACHD guidelines, defect-related residual cardiac problems, gender, age (in years), weight category, most clinically relevant comorbidity according to the treating cardiologist’s perception, number of comorbidities, clinical course and outcome. Definitions for categories within these different study characteristics are provided as online supplemental material 1. A complicated disease course was defined as hospitalisation for COVID-19 requiring non-invasive or invasive ventilation and/or inotropic support, extracorporeal membrane oxygenation or a fatal outcome. In patients with a complicated disease course, further detailed information on patient characteristics and disease course was obtained from the treating physicians of the pertinent centre. The presumed causal relationship between the congenital heart defect and the COVID-19 outcome was adjudicated after discussion with the treating physician and within the steering committee of the study (MS, JR, DT and MG). The following categories were discriminated: death or complicated disease course due to SARS-CoV-2 infection (COVID-19 was the main reason for outcome), death or complicated disease course with coincidental SARS-CoV-2 infection (pre-existing disease was the main reason for outcome).

Table 1 Characteristics of patients with ACHD and COVID-19 disease course

| Characteristic                                      | Overall (N=105) | Uncomplicated course (n=92) | Complicated course (n=13) | P value* |
|----------------------------------------------------|----------------|-----------------------------|---------------------------|----------|
| Age (years)                                        | 38±13          | 37±12                       | 47±13                     | 0.009    |
| Age range (years)                                  | 16–75          | 16–75                       | 21–64                     |          |
| Female gender, n (%)                               | 61 (58)        | 56 (61)                     | 5 (38)                    | 0.125    |
| BMI (kg/m²), n (%)                                 |                |                             |                           | 0.001    |
| BMI<25                                             | 66 (63)        | 63 (68)                     | 3 (23)                    |          |
| BMI 25–30                                          | 26 (25)        | 21 (23)                     | 5 (38)                    |          |
| BMI>30                                             | 13 (12)        | 8 (9)                       | 5 (38)                    |          |
| Comorbidities, n (%)                               |                |                             |                           | 0.003    |
| None                                               | 62 (59)        | 58 (63)                     | 4 (31)                    |          |
| One                                                | 23 (22)        | 21 (23)                     | 2 (15)                    |          |
| Two or three                                       | 20 (19)        | 13 (14)                     | 7 (54)                    |          |
| Cardiac defect                                      |                |                             |                           |          |
| Cyanotic heart disease or ES                        | 7              | 3                           | 4 (2 deaths)              |          |
| Fontan circulation                                  | 5              | 4                           | 1                         |          |
| TGA                                                 | 9              | 8                           | 1                         |          |
| Other complex defect                                | 4              | 4                           | 0                         |          |
| Tetralogy of Fallot                                 | 18             | 17                          | 1 (1 death)               |          |
| Ebstein anomaly                                     | 4              | 4                           | 0                         |          |
| Aortic coarctation                                  | 10             | 9                           | 1                         |          |
| Other moderately complex defect                     | 8              | 7                           | 1                         |          |
| Repaired shunt lesion                               | 17             | 17                          | 0                         |          |
| Residual shunt lesion                               | 5              | 3                           | 2                         |          |
| Repaired valve lesion                               | 12             | 9                           | 3 (2 deaths)              |          |
| Unrepaired valve lesion                             | 3              | 3                           | 0                         |          |
| Other simple defect                                 | 3              | 3                           | 0                         |          |
| Cardiac defect complexity, n (%)                   |                |                             |                           | 0.423    |
| Complex                                            | 25 (24)        | 20 (22)                     | 5 (38)                    |          |
| Moderately complex                                 | 39 (37)        | 36 (39)                     | 3 (23)                    |          |
| Simple                                             | 41 (39)        | 36 (39)                     | 5 (38)                    |          |
| Main defect related residual problems               |                |                             |                           | 0.089    |
| No residual problems                                | 39 (37)        | 34 (37)                     | 5 (38)                    |          |
| Valvular problems                                   | 38 (36)        | 36 (39)                     | 2 (15)                    |          |
| Heart failure                                       | 10 (10)        | 9 (10)                      | 1 (8)                     |          |
| Arrhythmia                                         | 11 (10)        | 9 (10)                      | 2 (15)                    |          |
| Pulmonary hypertension                             | 7 (7)          | 4 (4)                       | 3 (23)                    |          |

TGA includes patients with TGA after atrial switch, arterial switch and Rastelli-type procedure, as well as patients with congenitally corrected TGA; residual shunt lesion includes patients with a residual shunt after defect repair and patients with small, unrepaired shunts; other simple/moderately complex/complex defects include patients with corresponding lesions not included in any of the other categories.

*P value for the comparison of patients with and without complicated course.

ACHD, adult congenital heart disease; BMI, Body Mass Index; ES, Eisenmenger syndrome; TGA, transposition of the great arteries.
Data were analysed using STATA 15.1 statistical software. Distribution of continuous variables was assessed using visual inspection of the histogram and expressed as mean and SD for symmetrically distributed variables and as median and IQR for other data. Between-group comparisons in table 1 were performed using an unpaired Student’s t-test or a $\chi^2$ test for continuous and nominal variables. Predictors of the main variable of interest (complicated clinical course, table 2) were analysed by univariable logistic regression. Due to the low number of events, multivariable analysis was restricted to variables with univariable OR of $>5$ (and a 95% CI with the lower margin $>1$) and was calculated with cluster-robust SEs. Due to the sparsity of the outcome data, the ORs were recalculated in a second model with an exact logistic regression fit (see table 2).

In univariable analysis, age, overweight and multiple comorbidities were predictive of a complicated disease course (see table 2). When using a Body Mass Index (BMI) of $>25$ kg/m$^2$ as cut-off, the corresponding OR was 7.2 (95% CI 1.9 to 28.3, $p=0.004$). Among specific heart defects, highest risk for a complicated disease course was observed in un repaired cyanotic heart defects or patients with Eisenmenger syndrome (figure 1). In a multivariable analysis of these three variables, all were independently associated with complications, and cyanotic heart disease was by far the most important predictor of a complicated disease course.

### Results

By 6 June, a total of 105 patients with ACHD were included in this study. Table 3 summarises the number of patients with ACHD per country reported to have COVID-19 and the number of yearly patient visits at the corresponding centres. Overall, 78 (74%) patients had a confirmed diagnosis of COVID-19 by testing, while in 27 patients (26%) the diagnosis was based on clinical grounds.

### Discussion

This is the first report on the outcome of COVID-19 in a sizeable cohort of European patients with ACHD with different types of congenital cardiac defects. The main findings of our study are the observation that risk factors derived from the general population, in particular, age, overweight and multiple comorbidities, are equally important for determining outcome in the ACHD population, in addition to the congenital cardiac defect. Congenital cardiac defects with very high risk for a complicated disease course in case of COVID-19 were un repaired cyanotic heart disease or severe pulmonary hypertension with Eisenmenger syndrome. Such defects were present in 4 of 13 patients with a complicated course but represent only ca. 2% of all patients under follow-up at the participating centres. For other complex lesions, that is, univentricular physiology after Fontan palliation or defects with subaortic right ventricles, no such strong association was observed.

SARS-CoV-2 infection can cause both pulmonary and systemic inflammation, leading to acute respiratory distress syndrome and respiratory failure, sepsis, cardiac injury and thromboembolic complications, both in the venous and arterial circulations. Patients with cyanotic heart disease, including patients with Eisenmenger syndrome, exhibit chronic hypoxaemia with often markedly decreased resting oxygen saturations as a result of both a right-to-left shunt and severe abnormal pathobiology of the pulmonary tissue and pulmonary vascular bed. Such patients are at risk of rapid deterioration in case of respiratory tract infections with impaired oxygenation. In case of severe
### Table 4 Patients with complicated COVID-19 course

| Age (years) | Sex   | Main diagnosis | Clinical background and disease course | Main cause of fatal outcome/ relation to congenital heart defect |
|-------------|-------|---------------|----------------------------------------|---------------------------------------------------------------|
| 40–50       | Male  | Repaired tetralogy of Fallot | Pre-existing severe biventricular dysfunction and progressive heart failure (had implanted CRT-D), cardiac-related liver cirrhosis and right lung hypoplasia due to an occluded right pulmonary artery; decision regarding cardiac and liver transplant was pending. Admitted with ARDS; due to comorbidities, the patient was not considered a candidate for extensive cardiorespiratory support; patient died at day 3 after hospital admission. | Death due to SARS-CoV-2 infection (ARDS related to COVID-19); Comorbidities: three (heart failure, liver and lung disease) |
| >60         | Male  | Repaired pulmonary valve stenosis | Mild pulmonary regurgitation, acquired cardiovascular disease (coronary artery disease, previous ischaemic stroke, abdominal aneurysm, atrial fibrillation) and COPD; NYHA class II prior to COVID-19. Admitted with bilateral pneumonia leading to ARDS requiring intubation on the day of admission; renal failure occurred 3 days after presentation; patient died on day 11 after admission with multigorgan failure. | Death due to SARS-CoV-2 infection (ARDS related to COVID-19); Comorbidities: three (previous stroke, coronary artery disease and lung disease) |
| 40–50       | Female| Bicuspid aortic valve with severe aortic stenosis | Presentation with decompensated heart failure due to severe aortic stenosis, requiring urgent surgical aortic valve replacement; at admission, COVID-19 was not suspected; complicated postoperative course with cardiogenic shock requiring vena-venous ECMO. Developed ARDS on first postoperative day and tested positive for SARS-CoV-2; patient died 7 days after surgery. | Death with SARS-CoV-2 infection (postoperative death due to heart failure); Comorbidities: one (heart failure) |
| 50–60       | Female| Eisenmenger syndrome with unrepaired complete AVID | Severe pulmonary hypertension, heart failure and moderate leucopenia; presentation at the emergency department with bilateral pneumonia and ARDS. Due to the patient’s functional status (NYHA class III) prior to COVID-19 and personal preferences, she was transferred to a palliative care centre; she died on day 32 after initial hospital admission. | Death due to SARS-CoV-2 infection (ARDS related to COVID-19); Comorbidities: two (heart failure and pulmonary hypertension) |
| 40–50       | Female| Eisenmenger syndrome with unrepaired complete AVSD | Severe pulmonary hypertension, heart failure and severely reduced renal function; presentation at the emergency department with ARDS. Due to the patient’s functional status (NYHA class IV) prior to COVID-19 and personal preferences, she was discharged home; patient died at home 22 days after initial hospital presentation. | Death due to SARS-CoV-2 infection (ARDS related to COVID-19); Comorbidities: three (heart failure, pulmonary hypertension and kidney failure) |
| 20–30       | Male  | Unrepaired atrial secundum septal defect Down syndrome | History of bronchial asthma, NYHA class I prior to COVID-19. Admitted with bilateral pneumonia and ARDS, requiring non-invasive ventilation; pulmonary thromboembolism occurred on day 4 after hospital admission; case still ongoing. | Admission due to SARS-CoV-2 infection; Comorbidities: two (respiratory disease and genetic syndrome) |
| 50–60       | Male  | Partial anomalous pulmonary venous connection, PFO with severe right-to-left shunt | History of type 2 diabetes mellitus and oesophageal cancer; incidental diagnosis of partial anomalous partial anomalous pulmonary venous connection during the diagnostic cancer workup; normal right ventricular dimensions, no evidence of pulmonary hypertension. Hospital admission for elective oesophagectomy; at admission, COVID-19 was not suspected; recurrent postoperative hypoxemia requiring reintubation. Diagnosed with COVID-19 on postoperative day 4; subsequently severe ARDS with haemodynamic instability, severe pulmonary hypertension and multiple secondary infectious complications; diagnosis of a PFO with severe right-to-left shunting on postoperative day 23; emergent vena-venous ECMO on postoperative day 26 and percutaneous PFO closure on postoperative day 27; weaning from ECMO 7 days after PFO closure; case is still ongoing, slow recovery. | Admission for non-cardiac surgery. PFO was a contributor to complicated disease course; partial anomalous pulmonary venous return likely not substantially contributing to disease course. Comorbidities: two (diabetes and cancer) |
| 30–40       | Female| Eisenmenger syndrome with persistent ductus arteriosus and atrial septal defect | Obesity grade I (BMI 33 kg/m2). NYHA class III prior to COVID-19. ARDS secondary to bilateral pneumonia and bacterial superinfection; vena-venous ECMO since day 1 of hospitalisation; a thromboembolic event occurred during hospitalisation; case still ongoing. | Admission due to SARS-CoV-2 infection; Comorbidities: one (pulmonary hypertension) |
| 30–40       | Female| Fontan palliation for tricuspid atresia | NYHA class II prior to COVID-19. Admitted with bilateral pneumonia leading to ARDS, requiring intubation the day after admission. The patient fully recovered 28 days after hospital admission. | Admission due to SARS-CoV-2 infection; Comorbidities: zero |
| >60         | Male  | Unrepaired CCTGA with VSD and residual severe pulmonary stenosis Persistent right-to-left shunt through VSD with baseline oxygen saturation at 85% | History of atrial flutter; NYHA class II prior to COVID-19. Admitted with bilateral pulmonary hypertension requiring transfer to the ICU for non-invasive ventilation at day 2 of hospitalisation; the patient experienced recurrent flutter during his hospitalisation and remained short of breath at last follow-up (NYHA III). | Admission due to SARS-CoV-2 infection; Comorbidities: zero |
| 50–60       | Male  | Repaird aortic coarctation Mechanical aortic valve replacement for severe aortic stenosis | History of diabetes, stroke, heart failure with preserved ejection fraction and atrial fibrillation; NYHA class II prior to COVID-19. Admitted to the hospital with bilateral pneumonia requiring ICU transfer for non-invasive ventilation 2 days after admission; patient recovered 22 days after hospital admission, but impaired renal function persisted after hospital discharge. | Admission due to SARS-CoV-2 infection; Comorbidities: three (diabetes, stroke and heart failure) |
| 50–60       | Male  | Bentall procedure for bicuspid valvulopathy and aortopathy | History of diabetes and hypertension; NYHA class II previous to COVID-19. Admitted with bilateral pneumonia requiring non-invasive ventilation; patient fully recovered 16 days after hospital admission. | Admission due to SARS-CoV-2 infection; Comorbidities: two (diabetes and arterial hypertension) |

ALCAPA, This footnote is not necessary - no such abbreviation is used in table 4; ARDS, acute respiratory distress syndrome; AVSD, atrioventricular septal defect; BMI, Body Mass Index; CCTGA, congenitally corrected transposition of the great arteries; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronisation therapy defibrillator; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; NYHA, New York Heart Association; PFO, persistent foramen ovale; VSD, ventricular septal defect.
COVID-19, pre-existing hypoxaemia can be exacerbated by an increase in right-to-left shunting due to the rise in pulmonary vascular resistance and an inflammation-related decrease in systemic vascular resistance.17 These patients are furthermore at increased risk of paradoxical embolism. The potentially increased prothrombotic risk due to pre-existing haemostatic abnormalities, venous stasis, endothelial injury and inflammatory response may also contribute to a worse outcome in these patients.

Our study underscores the importance of a comprehensive risk assessment, not only taking into account the underlying congenital defect but also, more importantly, considering general risk factors and comorbidities for risk estimation in case of COVID-19. The most important general risk factor for COVID-19-related mortality is age.12 13 In line with previous studies, we observed an increasing risk of complications with advancing age. At present, the median age of patients with ACHD followed up at specialised centres is 35 years, and the prevalence of adults with CHD older than 60 years is estimated at 5%–10% of the entire ACHD population only.14 15 This young age may make them less susceptible for virus invasion, and hence patients with ACHD tend to have a milder COVID-19 course.16 This may explain why patients with univentricular physiology after Fontan palliation—mostly young adults—were at lower risk of a complicated disease course as intuitively anticipated by the anatomical absence of a subpulmonary ventricle.

Overweight emerged as a risk factor in our study, independent of other comorbidities and defect complexity. This was not the case in a large cohort study from New York, with a median patient age of 62 years, and 46% of them being obese,17 nor in the first reports from China12 or Italy.18 In line with our findings, Kass et al described an inverse correlation between age and BMI among patients admitted with COVID-19 to the Johns Hopkins Hospital, in which younger individuals with severe disease were more likely obese.19 Our study supports their hypothesis that, among younger patients with less comorbidities, obesity may play a more important role than among elderly patients with multiple comorbidities for predicting COVID-19 outcomes.

Acquired cardiovascular and other comorbidities associated with fatal COVID-19 outcomes are infrequently found in the ACHD population. In the Spanish ACHD cohort, 75% of patients were younger than 45 years, and the prevalence of hypertension, diabetes and ischaemic heart disease was only 14%, 2.7% and 1.5%, respectively. Still, even in young patients with ACHD with fewer comorbidities than encountered in an elderly population, the presence of multiple comorbidities confers a markedly increased risk of a complicated disease course. The observed OR of two or more comorbidities for a complicated disease course in this study was 7.1 (95% CI 2.1 to 24.5) in the univariable regression model and 6.7 (95% CI 1.2 to 35.8) in the multivariable regression model. Hence, patients with ACHD with multiple comorbidities should be considered as vulnerable patients, independent of the underlying defect complexity.

There are limitations inherent to this study. First, we did not systematically test all patients with ACHD under follow-up at participating centres for COVID-19. Hence, we may have missed cases, with most likely mild disease course. As a consequence, we are not able to provide data regarding the prevalence and disease course of COVID-19 among the ACHD population. Currently, the paper describes outcome data of only 0.2% of the ACHD population followed by the centres in the past year, a number certainly lower than the prevalence of COVID-19 among the general population. Second, despite data collection in 25 European ACHD centres with more than 46 000 yearly patient visits, the absolute number of COVID-19 cases among patients with ACHD was still small, limiting statistical analysis. The small sample size may also explain the non-significant p value for gender differences related to a complicated COVID-19 course, despite different proportions observed between the groups. Due to the lack of observational data at the beginning of the pandemic, many patients with ACHD were routinely advised to adhere to the concept of physical distancing and personal protection with strict hygiene measures. These recommendations, backed up by a self-perception of being at risk, may have effectively prevented COVID-19 cases and contributed to the overall low number of infected patients with ACHD. The small sample size resulted in large CIs. Further confirmation of our results by other study groups is necessary. In this respect, the results of another cohort study supported by...
the International Society for Adult Congenital Heart Disease are eagerly awaited.

In conclusion, our study provides first evidence that, among patients with ACHD advanced age, obesity and multiple comorbidities are associated with an increased risk of a complicated COVID-19 course, independent of the underlying cardiac defect. Congenital cardiac defects at particular high risk of a complicated disease course in case of COVID-19 were cyanotic lesions, including unrepaired cyanotic defects or severe pulmonary hypertension with Eisenmenger syndrome. These data can be used to identify patients with ACHD more vulnerable for a complicated COVID-19 course. Given the paucity of data so far, further confirmation of our findings is needed.

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