

# COVID-19 in Adults With Congenital Heart Disease



Craig S. Broberg, MD, MCR,<sup>a</sup> Adrienne H. Kovacs, PhD,<sup>a</sup> Soraya Sadeghi, BS,<sup>b</sup> Marlon S. Rosenbaum, MD,<sup>c</sup> Matthew J. Lewis, MD, MPH,<sup>c</sup> Matthew R. Carazo, MD,<sup>d</sup> Fred H. Rodriguez III, MD,<sup>d</sup> Dan G. Halpern, MD,<sup>e</sup> Jodi Feinberg, NP,<sup>e</sup> Francisca Arancibia Galilea, MD,<sup>f</sup> Fernando Baraona, MD,<sup>f</sup> Ari M. Cedars, MD,<sup>g</sup> Jong M. Ko, BS,<sup>g</sup> Prashob Porayette, MD,<sup>h</sup> Jennifer Maldonado, BS,<sup>h</sup> Berardo Sarubbi, MD,<sup>i</sup> Flavia Fusco, MD,<sup>i</sup> Alexandra A. Frogoudaki, MD, PhD,<sup>j</sup> Amiram Nir, MD,<sup>k</sup> Anisa Chaudhry, MD,<sup>l</sup> Anitha S. John, MD, PhD,<sup>m</sup> Arsha Karbassi, MD,<sup>n</sup> Arvind K. Hoskoppal, MD, MHS,<sup>o</sup> Benjamin P. Frischhertz, MD,<sup>p</sup> Benjamin Hendrickson, MD,<sup>q</sup> Berto J. Bouma, MD, PhD,<sup>r</sup> Carla P. Rodriguez-Monserrate, MD,<sup>s</sup> Christopher R. Broda, MD,<sup>t</sup> Daniel Tobler, MD,<sup>u</sup> David Gregg, MD,<sup>v</sup> Efrén Martínez-Quintana, MD, PhD,<sup>w</sup> Elizabeth Yeung, MD,<sup>x</sup> Eric V. Krieger, MD,<sup>y</sup> Francisco J. Ruperti-Repilado, MD,<sup>z</sup> George Giannakoulas, MD,<sup>aa</sup> George K. Lui, MD,<sup>bb</sup> Georges Ephrem, MD, MSc,<sup>cc</sup> Harsimran S. Singh, MD, MSc,<sup>dd</sup> Hassan MK. Almeneisi, MD,<sup>ee</sup> Heather L. Bartlett, MD,<sup>ff</sup> Ian Lindsay, MD,<sup>gg</sup> Jasmine Grewal, MD,<sup>hh</sup> Jeremy Nicolarsen, MD,<sup>ii</sup> John J. Araujo, MD,<sup>jj</sup> Jonathan W. Cramer, MD,<sup>kk</sup> Judith Bouchardy, MD,<sup>ll</sup> Khalid Al Najashi, MD,<sup>mmm</sup> Kristi Ryan, NP,<sup>nn</sup> Laith Alshawabkeh, MD,<sup>oo</sup> Lauren Andrade, MD,<sup>pp</sup> Magalie Ladouceur, MD, PhD,<sup>qq</sup> Markus Schwerzmann, MD,<sup>rr</sup> Matthias Greutmann, MD,<sup>ss</sup> Pablo Meras, MD,<sup>tt</sup> Paolo Ferrero, MD,<sup>uu</sup> Payam Dehghani, MD,<sup>vv</sup> Poyee P. Tung, MD,<sup>ww</sup> Rocio Garcia-Orta, MD, PhD,<sup>xx</sup> Rose O. Tompkins, MD,<sup>yy</sup> Salwa M. Gendi, MD,<sup>zz</sup> Scott Cohen, MD, MPH,<sup>aaa</sup> Scott Klewer, MD,<sup>bbb</sup> Sebastien Hascoet, MD,<sup>ccc</sup> Shabnam Mohammadzadeh, MD,<sup>ddd</sup> Shailendra Upadhyay, MD,<sup>eee</sup> Stacy D. Fisher, MD,<sup>fff</sup> Stephen Cook, MD,<sup>ggg</sup> Timothy B. Cotts, MD,<sup>hhh</sup> Jamil A. Aboulhosn, MD<sup>b</sup>

## ABSTRACT

**BACKGROUND** Adults with congenital heart disease (CHD) have been considered potentially high risk for novel coronavirus disease-19 (COVID-19) mortality or other complications.

**OBJECTIVES** This study sought to define the impact of COVID-19 in adults with CHD and to identify risk factors associated with adverse outcomes.

**METHODS** Adults (age 18 years or older) with CHD and with confirmed or clinically suspected COVID-19 were included from CHD centers worldwide. Data collection included anatomic diagnosis and subsequent interventions, comorbidities, medications, echocardiographic findings, presenting symptoms, course of illness, and outcomes. Predictors of death or severe infection were determined.

**RESULTS** From 58 adult CHD centers, the study included 1,044 infected patients (age: 35.1 ± 13.0 years; range 18 to 86 years; 51% women), 87% of whom had laboratory-confirmed coronavirus infection. The cohort included 118 (11%) patients with single ventricle and/or Fontan physiology, 87 (8%) patients with cyanosis, and 73 (7%) patients with pulmonary hypertension. There were 24 COVID-related deaths (case/fatality: 2.3%; 95% confidence interval: 1.4% to 3.2%). Factors associated with death included male sex, diabetes, cyanosis, pulmonary hypertension, renal insufficiency, and previous hospital admission for heart failure. Worse physiological stage was associated with mortality ( $p = 0.001$ ), whereas anatomic complexity or defect group were not.

**CONCLUSIONS** COVID-19 mortality in adults with CHD is commensurate with the general population. The most vulnerable patients are those with worse physiological stage, such as cyanosis and pulmonary hypertension, whereas anatomic complexity does not appear to predict infection severity. (J Am Coll Cardiol 2021;77:1644–55) © 2021 by the American College of Cardiology Foundation.



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From the <sup>a</sup>Knight Cardiovascular Institute, Oregon Health & Science University, Portland, Oregon, USA; <sup>b</sup>Ahmanson/UCLA Adult Congenital Heart Center, Los Angeles, California, USA; <sup>c</sup>Division of Cardiology, Columbia University Medical Center, New York, New York, USA; <sup>d</sup>Division of Cardiology, Emory University School of Medicine, Atlanta, Georgia, USA; <sup>e</sup>Division of Cardiology, York University Langone Health, New York, New York, USA; <sup>f</sup>Instituto Nacional del Tórax - Pontificia Universidad Católica de

Early data on the coronavirus disease-2019 (COVID-19) pandemic identified heart disease as a risk factor for mortality (1,2), but there is also uncertainty about what conditions merit inclusion under this general term (3). Adults with congenital heart disease (CHD), numbering >1.5 million in the United States (4,5), are recognized as a population with significant morbidity (6) and as vulnerable to many types of cardiovascular deterioration and dysfunction. As such, they have largely been considered high risk and often adopt a highly restrictive lifestyle and employment choices accordingly. Early publications in CHD reported different risks (7,8) but suggested worse risk in higher physiological stages (9).

In the absence of data, consensus recommendations for COVID-19 and CHD have been made based on

sensible suppositions regarding at-risk subtypes, including a proposed risk stratification for COVID-19 complications (10). Another group outlined the potential viral impact of CHD (11). Others have based recommendations on anatomic and/or physiological stage (12).

To more accurately inform risk stratification and provide guidance for individual patients with CHD and their providers, we established this large international study. Our overarching objectives were to determine which adults with CHD are most vulnerable to the adverse consequences of COVID-19 and to quantify the magnitude of those consequences. Specifically, we aimed to determine risk factors associated with death (primary outcome) or

## ABBREVIATIONS AND ACRONYMS

<b>CHD</b>	= congenital heart disease
<b>CI</b>	= confidence interval
<b>COVID-19</b>	= coronavirus disease-2019
<b>eGFR</b>	= estimated glomerular filtration rate
<b>ICU</b>	= intensive care unit
<b>OR</b>	= odds ratio
<b>PAH</b>	= pulmonary arterial hypertension
<b>PCR</b>	= polymerase chain reaction

Chile, Santiago, Chile; <sup>8</sup>Division of Cardiology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; <sup>9</sup>Division of Cardiology, University of Iowa Stead Family Children's Hospital, Iowa City, Iowa, USA; <sup>10</sup>Monaldi Hospital, Adult Congenital Heart Disease Unit, Naples, Italy; <sup>11</sup>Second Cardiology Department, ATTIKON University Hospital, Athens, Greece; <sup>12</sup>Shaare Zedek Medical Center, Jerusalem, Israel; <sup>13</sup>Penn State Hershey Heart and Vascular Institute, State College, Pennsylvania, USA; <sup>14</sup>Division of Cardiology, Children's National Hospital, Washington, DC, USA; <sup>15</sup>McMaster University, Hamilton, Ontario, Canada; <sup>16</sup>UPMC Adult Congenital Heart Disease Program, Pittsburgh, Pennsylvania, USA; <sup>17</sup>Division of Cardiovascular Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, USA; <sup>18</sup>University of Tennessee Health Science Center, Le Bonheur Heart Institute, Memphis, Tennessee, USA; <sup>19</sup>Department of Cardiology, Amsterdam University Medical Center, Amsterdam, the Netherlands; <sup>20</sup>Department of Cardiology, Boston Children's Hospital, Boston, Massachusetts, USA; <sup>21</sup>Department of Pediatrics, Baylor College of Medicine, Houston, Texas, USA; <sup>22</sup>Division of Cardiology, University Hospital of Basel, Basel, Switzerland; <sup>23</sup>Division of Cardiology, Medical University of South Carolina, Charleston, South Carolina, USA; <sup>24</sup>Cardiology Service, Universitario Insular-Materno Infantil, Las Palmas de Gran Canaria, Spain; <sup>25</sup>Anschutz Medical Campus, Colorado's Adult and Teen Congenital Heart Program, Aurora, Colorado, USA; <sup>26</sup>Division of Cardiology, University of Washington School of Medicine, Seattle, Washington, USA; <sup>27</sup>Division of Cardiology, University Hospital Geneva, Geneva, Switzerland; <sup>28</sup>Cardiology Department, AHEPA University Hospital, Thessaloniki, Greece; <sup>29</sup>Division of Cardiovascular Medicine and Pediatric Cardiology, Stanford University School of Medicine, Stanford, California, USA; <sup>30</sup>Indiana University School of Medicine, Krannert Institute of Cardiology, Indianapolis, Indiana, USA; <sup>31</sup>Weill Cornell Medicine, New York Presbyterian Hospital, Department of Medicine and Pediatrics, New York, New York, USA; <sup>32</sup>Cincinnati Children's Hospital Medical Center, The Heart Institute, Cincinnati, Ohio, USA; <sup>33</sup>Department of Pediatrics and Medicine, University of Wisconsin, Madison, Wisconsin, USA; <sup>34</sup>Division of Pediatric Cardiology, University of Utah, Salt Lake City, Utah, USA; <sup>35</sup>University of British Columbia, St. Paul's Hospital, Vancouver, British Columbia, Canada; <sup>36</sup>Providence Adult and Teen Congenital Heart Program, Pediatric and Adult Cardiology, Spokane, Washington, USA; <sup>37</sup>Department of Pediatric and Adult Congenital Heart Disease, Somer Incare Cardiovascular Center, Rionegro, Colombia; <sup>38</sup>Division of Cardiovascular Medicine, University of Nebraska Medical Center, Omaha, Nebraska, USA; <sup>39</sup>Department of Cardiology and Cardiac Surgery, University Hospital Lausanne, Lausanne, Switzerland; <sup>40</sup>Pediatric Cardiology Department, Prince Sultan Cardiac Center, Riyadh, Saudi Arabia; <sup>41</sup>OSF Healthcare Children's Hospital of Illinois, Adult Congenital Heart Program, Peoria, Illinois, USA; <sup>42</sup>Department of Cardiovascular Medicine, University of California San Diego, La Jolla, California, USA; <sup>43</sup>Division of Cardiology, Hospital of University of Pennsylvania, Philadelphia, Pennsylvania, USA; <sup>44</sup>Hôpital Européen Georges Pompidou, Adult Congenital Heart Disease Unit, Paris, France; <sup>45</sup>University Hospital Inselspital, Center for Congenital Heart Disease, Bern, Switzerland; <sup>46</sup>Department of Cardiology, University of Zurich, Zurich, Switzerland; <sup>47</sup>University Hospital La Paz, Madrid, Spain; <sup>48</sup>ASST Papa Giovanni XXIII, Cardiovascular Department, University of Milano, Bergamo, Italy; <sup>49</sup>Prairie Vascular Research Network, University of Saskatchewan, Regina, Saskatchewan, Canada; <sup>50</sup>University of Texas at Houston, Adult Congenital Heart Disease, Houston, Texas, USA; <sup>51</sup>Cardiology Department, Hospital Universitario Virgen de las Nieves, Granada, Spain; <sup>52</sup>Cedars-Sinai Medical Center, The Geurin Family Congenital Heart Program, Los Angeles, California, USA; <sup>53</sup>West Virginia University, Adult Congenital Heart Disease Program, Morgantown, West Virginia, USA; <sup>54</sup>Medical College of Wisconsin, Adult Congenital Heart Disease Program, Milwaukee, Wisconsin, USA; <sup>55</sup>Division of Cardiology, University of Arizona, Tucson, Arizona, USA; <sup>56</sup>Hôpital Marie Lannelongue, Le Plessis Robinson, France; <sup>57</sup>Tehran University of Medical Sciences, Tehran, Iran; <sup>58</sup>Connecticut Children's Medical Center, Pediatric Cardiology Hartford, Connecticut, USA; <sup>59</sup>Department of Medicine and Pediatrics, University of Maryland School of Medicine, Baltimore, Maryland, USA; <sup>60</sup>Helen DeVos Children's Hospital, Adult Congenital Heart Center, Grand Rapids, Michigan, USA; and the <sup>61</sup>Department of Medicine and Pediatrics, University of Michigan Medical School, Ann Arbor, Michigan, USA.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

**FIGURE 1** Global Distribution of Contributing Centers

**Points** identify the location of the 58 congenital heart centers participating in the study.

severe infection, meaning need for intensive care unit (ICU) admission, endotracheal intubation, acute respiratory distress syndrome, or renal replacement therapy (secondary outcome).

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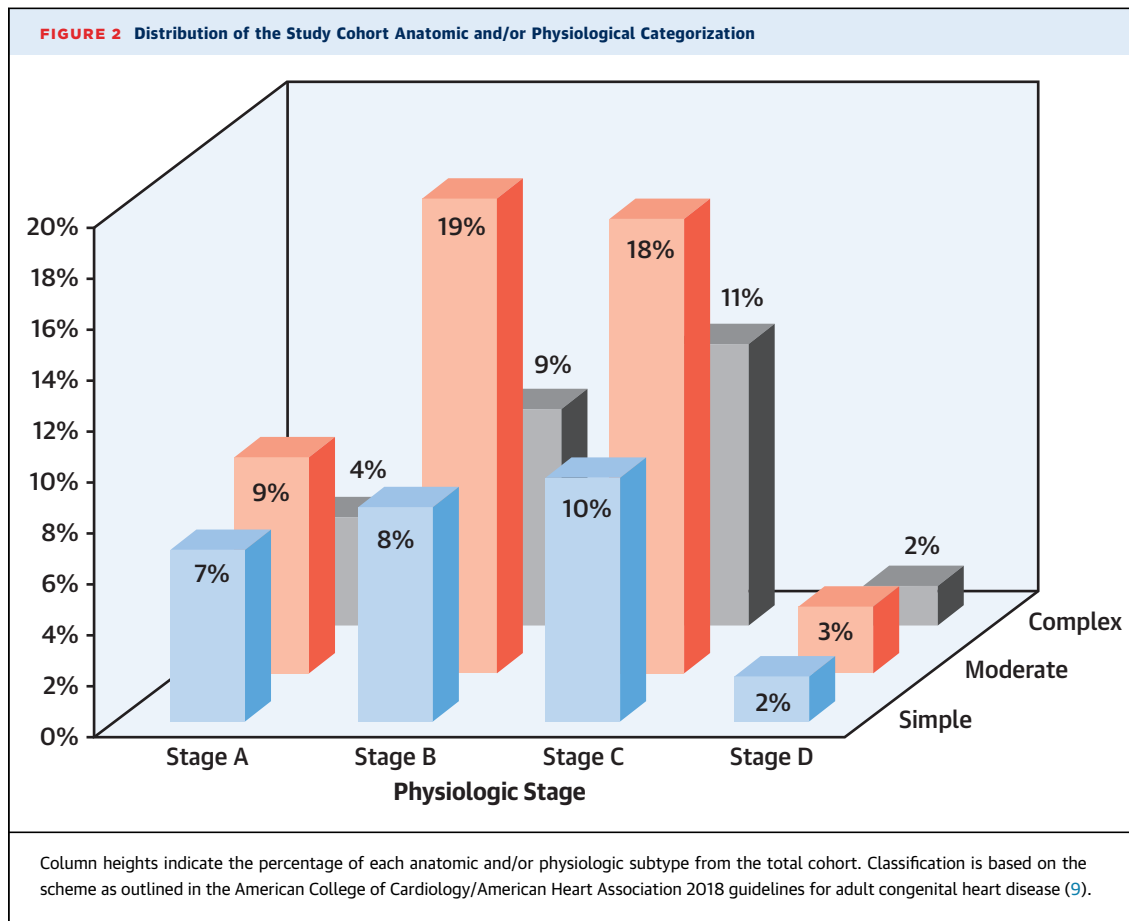
## METHODS

**STUDY DESIGN.** This was an international, multi-center, retrospective cohort study. Collaborators from adult CHD centers globally were recruited via the Adult Congenital Heart Association, the International Society for Adult Congenital Heart Disease, the Alliance for Adult Research in Congenital Cardiology, the Canadian Adult Congenital Heart Network, and by word of mouth to colleagues worldwide. Study administration and coordination was done by the University of California, Los Angeles, whereas Oregon Health and Science University served as the data coordinating center. The overall study was approved by both host institutions, and each participating center obtained local ethics approval.

**ELIGIBILITY CRITERIA.** Eligible patients met the following inclusion criteria for enrollment: known

diagnosis of CHD, age 18 years or older, and either positive polymerase chain reaction (PCR) for the novel coronavirus or positive antibody test following a clinical illness. Patients with a presumptive diagnosis of COVID-19 based upon clinical symptoms and circumstances were also included, because testing availability and sensitivity were known to vary by location and assay and over time. Patients with a known familial aortopathy were included as were those with syndromes if a congenital heart defect was present. We excluded patients with patent foramen ovale, mitral valve prolapse, hypertrophic cardiomyopathy, ventricular noncompaction, congenital arrhythmia, or those who had undergone heart transplantation.

**DATA COLLECTION.** For each patient, comprehensive clinical data were abstracted from existing medical records by collaborating investigators at each center. Data included anatomic diagnoses, subsequent interventions, general anatomic classification, and physiological stage based on the 2018 American College of Cardiology/American Heart Association joint guidelines on adult CHD (9), a history of major cardiac and noncardiac comorbidities, medications at



most recent outpatient visit, and most recent laboratory and echocardiographic findings obtained before but within 12 months of infection. Echo findings included semi-quantitative valve assessment (mild to moderate to severe). PCR testing results, clinical presentation, and laboratory and imaging results during infection and course of illness were also recorded, including details of any hospitalization. Race and ethnicity were requested for patients from collaborating centers within the United States.

Data were entered online using the Research Electronic Data Capture data management system, which enables multiuser data collection. Patients were given study-specific identifiers. No protected patient identifiers, including dates, were collected.

Quality control was performed by the data coordinating center. Data were reviewed for internal consistency. For example, designation of cyanosis was confirmed by a reported resting oxygen saturation of <90%, and patients with Fontan physiology were ensured to have an anatomic defect consistent with single ventricle palliation. All inconsistencies and outliers were flagged, and queries

were sent to local investigators for confirmation or correction.

We used a hierarchical classification to categorize patients by their single most complex defect type (13), such that each patient was included in only 1 defect category. Patients identified as having Eisenmenger physiology, with both cyanosis and pulmonary hypertension in the setting of a shunt, were designated as such, and removed from their respective anatomic defect category. Patients with a systemic right ventricle included those with transposed great arteries and an atrial switch operation, or congenitally corrected transposition (biventricular repairs only). Contributing site investigators were asked to designate anatomic severity (simple, moderate, or complex) based on the guideline classification scheme (9), and designations were reviewed for consistency with the given congenital defect. Discrepancies were clarified or corrected with site investigators as needed. Similarly, physiological stage designation was compared with other collected data, such as New York Heart Association functional class, arrhythmia history, end-organ dysfunction, valve disease, and so

on. Discrepancies were flagged for review by local investigators. In some instances when physiological stage was not provided by local investigators, who might not have been familiar with the classification scheme, physiological stage was imputed based on other provided data with agreement of 2 investigators blinded to outcomes.

**STATISTICAL ANALYSES.** From available data, body surface area, body mass index, and estimated glomerular filtration rate (eGFR; based on the Modification of Diet in Renal Disease equation) were calculated. Severe viral infections were defined as those that required ICU admission, endotracheal intubation for mechanical ventilation, acute respiratory distress syndrome, renal replacement therapy, need for extracorporeal membrane oxygenation, or death. Other cases were considered mild, including hospitalizations that did not include 1 of the aforementioned criteria, because some patients had other indications for admission. Patients with either moderate or severe valve regurgitation or stenosis of any valve, by recent echocardiography as reported by local investigators, were identified as having moderate to severe valve dysfunction.

Data analyses were performed using SPSS Statistics for Windows, version 25 (IBM Corp, Armonk, New York). Overall rates of the primary outcome (death) and the secondary outcome (severe infection) were quantified with 95% confidence intervals (CI). Similar rates were determined by decade of age, CHD defect group, and by anatomic and/or physiological classification scheme. Groups with or without primary and secondary outcomes were compared using the chi-square test, Fisher exact test, Student's *t*-test, or Mann-Whitney *U* test, as appropriate. Odds ratios (ORs) with 95% CIs were determined using binary logistic regression to report the strength of association between risk factor exposure and mortality. Because of limited mortality events, multivariable regression was limited to specific comparisons with no more than 2 independent predictors, and categorical variables were collapsed to dichotomous variables to avoid empty cells. Analysis including only PCR-positive patients was repeated to explore whether the method of diagnosis affected results. Statistical significance was defined as  $p < 0.05$ . Because of the exploratory nature of this study, no corrections were made for multiple tests.

## RESULTS

**STUDY COHORT.** A total of 58 CHD centers contributed to the study (Figure 1). Of 1,115 submitted patients, 1,044 met full inclusion and/or exclusion

**TABLE 1 Presenting Symptoms of COVID-19 Infection**

Fever	458 (44)
Dry cough	405 (39)
Malaise/fatigue	403 (39)
Myalgia	282 (27)
Dyspnea	235 (23)
Loss of smell	236 (23)
Headache	149 (14)
Chest pain	130 (12)
Diarrhea	108 (10)
Congestion	107 (10)
Productive cough	65 (6)
None*	60 (6)
Loss of taste	66 (6)
Abdominal pain, nausea, vomiting	57 (5)
Chills	39 (4)
Other/miscellaneous	48 (5)

Values are n (%). \*Asymptomatic subjects tested before an elective procedure or in response to a suspected exposure to the novel coronavirus.

criteria. Mean age was  $35.1 \pm 13.0$  years (range 18 to 86 years), and 51% were women. Most patients ( $n = 907$ ; 87%) had a positive PCR test or positive antibodies detected after a clinical illness. The remainder ( $n = 137$ ) were diagnosed based on clinical presentation alone. Most patients ( $n = 787$ ; 75%) were followed by U.S. centers, with race reported in 784 and ethnicity in 739.

The cohort included a broad representation of the spectrum of CHD complexity and comorbidity. The anatomic and/or physiological classification for the cohort is shown in Figure 2. Previous atrial arrhythmia occurred in 259 (25.9%) patients, and previous ventricular arrhythmia in 103 (9.7%) patients. There were 132 (12.6%) patients with implanted pacemakers or defibrillators, 161 (15.4%) patients with hypertension, 88 (8.4%) with known genetic syndromes, 65 (6.2%) with diabetes, and 19 (1.8%) patients with cirrhosis. In addition, 23 women were pregnant at the time of infection.

Fever, dry cough, and malaise were the most common presenting symptoms, occurring in approximately one-half of the cohort (Table 1). There were 60 (6%) patients who had no presenting symptoms but were tested based upon a known incidental exposure or need for clearance before a procedure. Of the total cohort, 179 patients (17%) required hospitalization, which included those who tested positive during admission for other indications. Serum troponin was reported in 30 patients, all but 1 of whom were hospitalized and was elevated in 22 patients.

**PRIMARY OUTCOME: FATALITIES.** Death occurred in 28 subjects, of whom 4 were deemed unrelated to acute COVID-19 infection. One patient died from

metastatic cancer, 1 from bacterial pneumonia, and 1 from cardiac arrest at home without previous positive COVID-19 testing. One additional death occurred in a patient with a systemic right ventricle who, 4 months after COVID-19 hospitalization, presented with ventricular arrhythmia and cardiogenic shock. The remaining 24 deaths (mean age: 40.8 ± 17.6 years; range 18 to 85 years; 75% male) were all adjudicated as COVID-19 related, resulting in a 2.3% COVID-19 related case/fatality rate (95% CI: 1.4% to 3.2%). All were PCR positive, except 1 young adult with an uncorrected atrioventricular septal defect and Eisenmenger syndrome who presented with fever, cough, anosmia, myalgia, and an elevated leukocyte count, and who died of hemoptysis. Treating providers deemed the clinical picture consistent with COVID-19, although testing could not be performed. When analysis was restricted to the 907 patients with positive PCR or antibodies, the COVID-19 case/fatality ratio was 2.5% (95% CI: 1.5% to 3.6%).

All COVID-19 deaths occurred in hospitalized subjects. Median hospital duration before death was 9 days (range 1 to 74 days). Of these, 19 patients were intubated, 10 had a significantly elevated troponin consistent with myocardial damage, 9 required renal replacement therapy, and 3 were placed on extracorporeal membrane oxygenation. One patient had been living in a nursing home before infection and had previously decided against resuscitation. In terms of CHD diagnoses, 10 patients were cyanotic, 5 of whom had Eisenmenger syndrome. Two additional patients had pulmonary arterial hypertension (PAH) without cyanosis. Three patients who died had Fontan physiology. One had asplenia, poor systolic function, and protein-losing enteropathy and presented in respiratory distress; the second had 'failing Fontan' physiology with multiple admissions prior to infection; the third had resting cyanosis, prior atrial and ventricular arrhythmia, and mitral valve dysfunction. Two patients had a systemic RV in the setting of transposition of the great arteries, both of whom had had multiple prior admissions for congestive heart failure. There were 7 deaths in patients with diabetes, all obese, age 42 to 85 years, and all with simple defects.

**RISK FACTORS FOR DEATH.** Factors associated with death (Table 2) included male sex, higher body mass index, previous atrial arrhythmia, diabetes, previous heart failure admission, cyanosis, lower resting oxygen saturation, PAH, increased subpulmonic ventricular systolic pressure as estimated by the most recent echocardiogram, and eGFR <60 ml/min/m<sup>2</sup> before infection. Age was skewed towards younger subjects

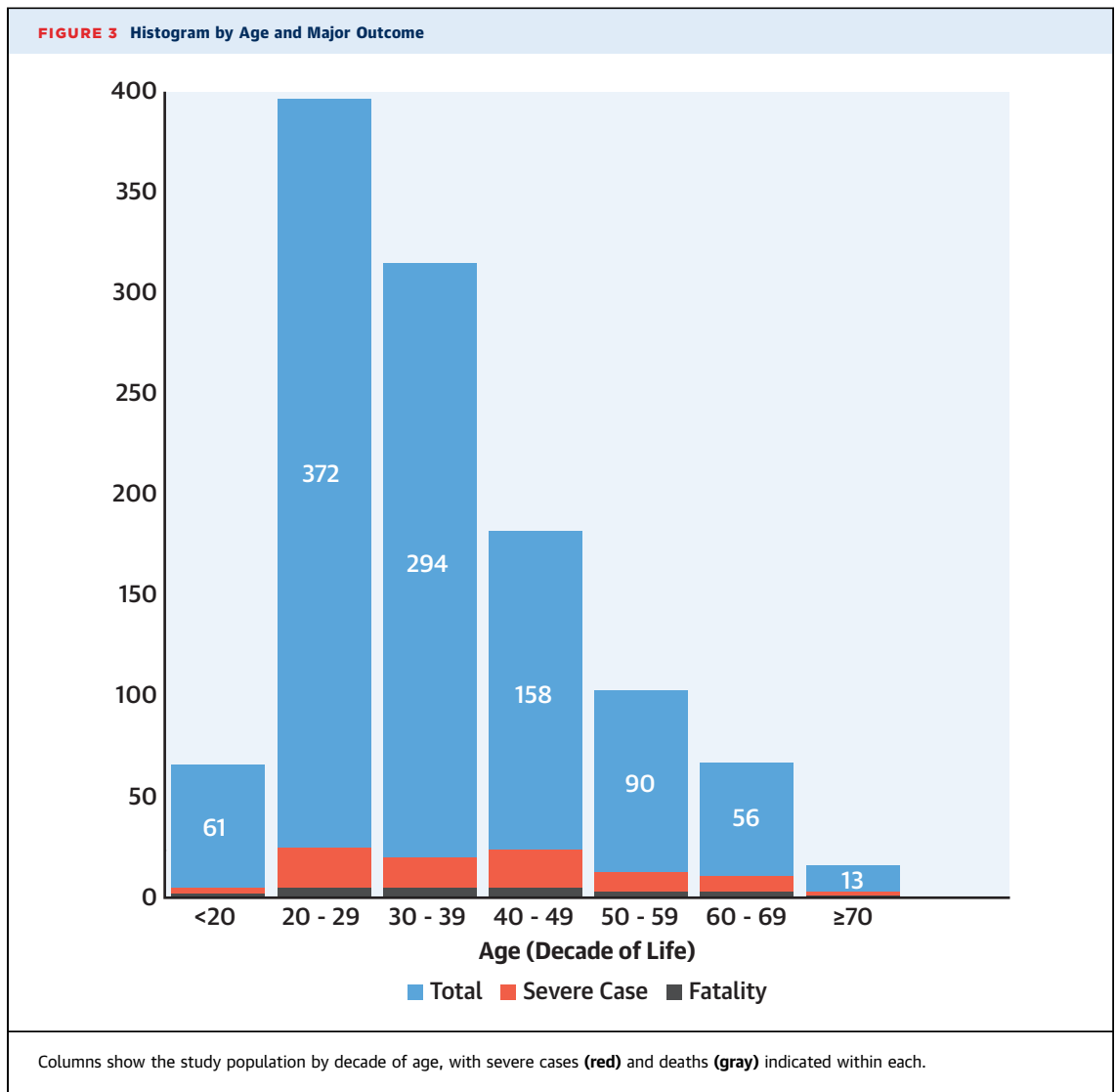
**TABLE 2 Baseline Characteristics**

	Survived	Died	p Value
<b>Demographics</b>			
Age, yrs	32 ± 17	39 ± 31	0.16
Male	486/1,015 (48)	20/24 (83)	0.001
Weight, kg	77.5 ± 21.4	91.0 ± 35.1	0.075
Height, cm	168 ± 11	164 ± 12	0.23
Body mass index	27.1 ± 6.6	32.3 ± 10.4	0.016
Black*	66/771 (8.6)	2/13 (15.4)	0.39
Hispanic*	99/726 (14)	3/13 (23)	0.33
Smoking/vaping	80/1,020 (7.8)	1/24 (4.2)	0.51
<b>Medications</b>			
ACE/ARB use	274/1,005 (27)	9/24 (38)	0.27
Beta-blocker use	348/1,007 (34)	12/24 (50)	0.65
<b>Medical/cardiac history</b>			
Previous atrial arrhythmia	248/1,002 (25)	11/24 (46)	0.019
Pacemaker or implanted defibrillator	103/1,009 (12.9)	2/24 (8.3)	0.66
Hypertension	156/1,003 (16)	5/24 (21)	0.48
Diabetes	58/1,014 (5.7)	7/24 (29.2)	<0.001
Known coronary artery disease	22/1,004 (2.2)	2/24 (8.3)	0.049
Previous heart failure admission	88/1,001 (8.8)	10/24 (42)	<0.001
Ejection fraction <40%	34/654 (5.2)	1/19 (5.3)	0.99
Systemic ventricular ejection fraction by echo	57 ± 10	54 ± 9	0.19
Systemic right ventricle (biventricular)	59/1,020 (5.8)	2/4 (50)	0.60
Moderate-severe valve dysfunction	333/807 (41)	13/20 (65)	0.058
Fontan palliation	115/1,017 (11.3)	3/24 (12.5)	0.86
Pulmonary hypertension	66/1,008 (6.5)	7/24 (29)	<0.001
Sub-pulmonic ventricular systolic pressure by echo, mm Hg	39 ± 22	54 ± 30	0.006
Previous resting oxygen saturation, %	96 ± 4	92 ± 5	<0.001
Cyanosis (oxygen saturation <90%)	74/998 (7.7)	10/24 (42)	<0.001
Supplemental oxygen use	28/1,002 (2.8)	4/24 (17)	<0.001
<b>Laboratory findings</b>			
Hemoglobin	14.2 ± 3.1	15.5 ± 3.4	0.09
Creatinine, mg/dl	0.87 ± 0.35	1.29 ± 1.19	0.086
eGFR <60 ml/min/1.73 m <sup>2</sup> †	38/1,015 (3.7)	4/24 (17)	0.001
Albumin, mg/dl	4.3 ± 0.6	4.0 ± 0.7	0.042

Values are mean ± SD or n/N (%). \*Data on race and ethnicity were requested from U.S. centers. †Estimated glomerular filtration rate (eGFR) is based on the Modification of Diet in Renal Disease equation.  
 ACE = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker medication.

(Figure 3) and was not significantly associated with death despite a higher proportion of deaths in older groups. Factors not associated with death were systemic ventricular systolic function (either by reported ejection fraction or semi-quantitative designation), Fontan palliation, systemic hypertension, at least moderate valve dysfunction, smoking and/or vaping history, use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers before infection, previous arrhythmias, presence of a pacemaker and/or defibrillator, or race/ethnicity. Troponin elevation was also not associated with death, because 3 of 6 patients with a normal troponin died, and 9 of 17 patients with a troponin >50 ng/ml survived. ORs for significant univariate predictors of COVID-19-related death are shown in Table 3.





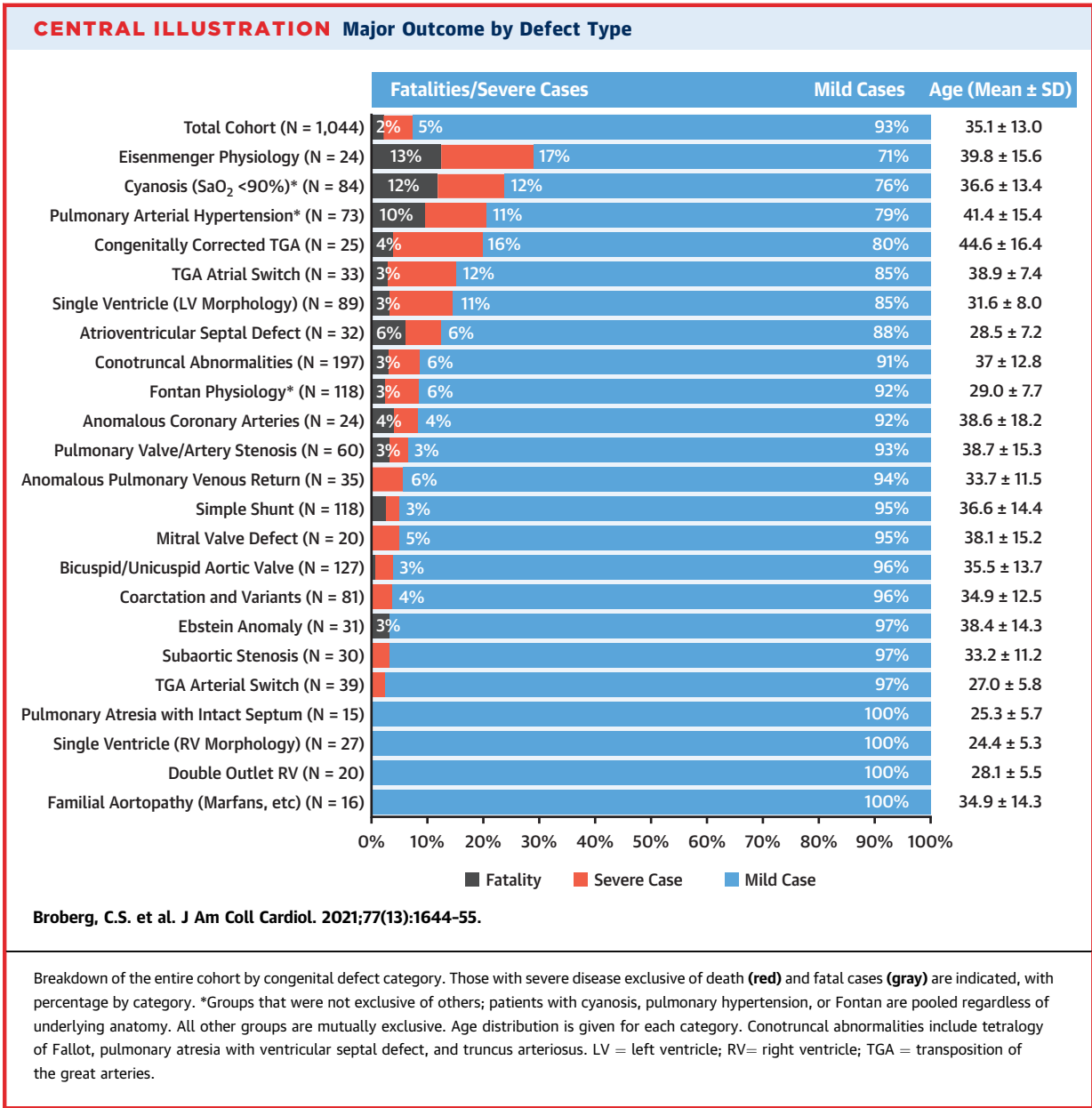
Previous heart failure admission, cyanosis, diabetes, and physiological stage were all strongly predictive.

Death and severe cases were distributed across the age spectrum (Figure 3), although as a percentage were proportionately greater in older age decades. Anatomic complexity was not associated with death, but physiological stage was, with a higher proportion of deaths in more severe stages ( $p = 0.002$  by chi-square test). Overall rates of death for stage A (healthiest) through stage D (least healthy) were 0%, 1.1%, 3.9%, and 7.9% respectively. Paradoxically, there were no deaths among the complex anatomy + physiological stage D group ( $n = 0$  of 16); rather, the highest rates of death were among those with simple anatomy + physiological stage D ( $n = 3$  of 19).

To further consider the possible effects of age on anatomic and physiological designations, we divided

the entire cohort into age tertiles, specifically 18 to 27 years, 28 to 39 years, and 40 years or older (Table 4). Deaths were more common in the oldest tertile (3.8%). In each tertile, deaths were generally more common in physiological stage C or D, regardless of anatomic complexity. To explore the potential for interaction between anatomy and physiology as predictors of death, we performed a multiple binary logistic regression analysis using physiological stages (AB vs. CD) and anatomic complexity (severe vs. simple and/or moderate) as independent variables. Physiological stage CD was predictive (OR: 6.6; 95% CI: 2.2 to 19.4;  $p = 0.001$ ), whereas complex anatomy was not predictive (OR: 0.7; 95% CI: 0.3 to 1.9;  $p = 0.47$ ).

Rates of mortality and/or severe course varied by CHD diagnosis (Central Illustration). The highest



mortality rates were observed in patients with Eisenmenger physiology, patients with cyanosis (with or without PAH), and those with PAH (with or without cyanosis). Of patients with cyanosis but without PAH, there were 5 deaths among 47 (10.6%). Conversely, of 35 patients with PAH but without cyanosis, only 2 died (5.7%). Generally, defect groups with higher mortality tended to have an older mean age (Central Illustration).

All analyses were repeated using only the cohort of 907 patients who tested positive by PCR or who had confirmed positive antibody testing after a clinical presentation. There were no changes in variable

significance; male sex, oxygen saturation, use of supplemental oxygen, cyanosis, PAH, previous heart failure admission, diabetes, physiological stage, creatinine, low eGFR, and estimated sub-pulmonic ventricular systolic pressure remained significant. However, beta-blocker use and lower left ventricular ejection fraction were significantly associated with COVID-19–related death. Other variables were not.

**SECONDARY OUTCOME: SEVERE CASES.** There were 67 (6.4%) patients who required ICU care, 36 of whom were intubated. Of those intubated, 18 (52%) died. Variables of significance for predicting severe disease course (Table 5) were identical to those predictive of



**TABLE 3 ORs for Variables Associated With Case/Fatality**

	OR	95% CI	p Value
Cyanosis (oxygen saturation <90%)	8.9	3.8–20.8	<0.001
Previous heart failure admission	7.4	3.2–17.2	<0.001
Diabetes	6.8	2.7–17.0	<0.001
Physiological stage C or D	6.4	2.2–19.0	0.001
Supplemental oxygen use	7.0	2.2–21.7	0.001
Pulmonary arterial hypertension	5.9	2.4–14.7	<0.001
Male	5.4	1.8–16.0	0.002
eGFR <60 ml/min/1.73 m <sup>2</sup>	5.1	1.7–15.8	0.004
Body mass index	1.08	1.04–1.13	0.001
Age (per yr)	1.03	1.002–1.06	0.033

CI = confidence interval; OR = odds ratio; other abbreviation as in Table 2.

death. Beta-blockers and having a systemic right ventricle were also significant. Additional complications from the entire cohort included new arrhythmias in 36 (3.4%) patients and bleeding or coagulopathic events (as judged by contributing providers) in 32 (3.1%) patients. Of the 23 pregnant women, all survived, but 2 were treated in the ICU late in pregnancy.

**DISCUSSION**

In adults with CHD, we found a case/fatality ratio from COVID-19 of 2.3% (95% CI: 1.4% to 3.2%) among mostly symptomatic infections. This figure was

harmonious with the reported cumulative world fatality rate of 2.2%, although mortality varied considerably by location (14). Early experience with the COVID-19 pandemic identified heart disease as a risk factor but likely implied heart failure, coronary atherosclerosis, cardiomyopathies, and PAH (15). Our data suggested that extrapolation to include adults with CHD could be problematic, because many did not have these acquired cardiovascular problems or other high-risk features. Yet, our findings confirmed noncardiac risk factors reported elsewhere, including obesity, diabetes, and pregnancy (16,17).

Older age was a risk factor for COVID-related death in the general population. Our population was skewed towards younger ages, which might have affected some comparisons. The case/fatality ratio tended to be higher in the older age tertile, and age was a univariate predictor by binary regression. Many patients with CHD were younger, particularly patients with a Fontan single ventricle, which might offer protection and explain some of the favorable outcomes in our study. In addition, the anatomic and/or physiological makeup of the population with CHD population was expected to differ by age, with more complex anatomy expected in younger groups but more complex physiology in older groups. Thus, it was plausible that elements defining stage C or D in younger individuals differed from older patients, regardless of physiological status as determined by factors such as PAH, heart failure, or cyanosis, which clearly affected outcome.

Anatomic complexity in the absence of advanced physiological status did not seem to increase risk, consistent with published experience (8,18). For example, a patient with noncyanotic Fontan physiology without heart failure or arrhythmia did not appear to be at higher risk for COVID-19 death or severe infection compared with someone without CHD with comparable comorbidities, although many CHD providers might have predicted otherwise. However, there was inherent heterogeneity within the CHD spectrum, which encompassed a range of anatomic and physiological states, and some patients did fall into high-risk categories.

Despite limited data, recommendations based on sensible assumptions from what is known about the CHD community of patients have been published (10,11). Only 2 previous publications addressed COVID-19 in the CHD population from areas with high early incidence. The first, from Italy, reported that clinical event rates were not high, and there were no deaths. However, most patients had clinically suspected virus rather than confirmed infection by PCR (7). In the second, a recent a study of 53 PCR-positive

**TABLE 4 Mortality Based on Anatomic Complexity or Physiological Stage (by Age Tertile)**

	Stage A	Stage B	Stage C	Stage D	Total
<b>Age 18–27 yrs</b>					
Simple	0/27 (0)	0/29 (0)	1/32 (3.1)	<b>1/6 (16.7)</b>	2/94 (2.1)
Moderate	0/36 (0)	1/73 (1.4)	1/38 (2.6)	<b>1/6 (16.7)</b>	3/153 (2)
Complex	0/24 (0)	0/34 (0)	<b>2/45 (4.4)</b>	0/6 (0)	2/109 (1.8)
Total	0/87 (0)	1/136 (0.7)	<b>4/115 (3.5)</b>	<b>2/18 (11.1)</b>	7/356 (2)
<b>Age 28–40 yrs</b>					
Simple	0/21 (0)	0/32 (0)	0/32 (0)	0/5 (0)	0/90 (0)
Moderate	0/26 (0)	1/57 (1.8)	2/74 (2.7)	0/11 (0)	3/168 (1.8)
Complex	0/17 (0)	0/33 (0)	<b>2/48 (4.2)</b>	0/4 (0)	2/102 (2)
Total	0/64 (0)	1/122 (0.8)	4/154 (2.6)	0/20 (0)	5/360 (1.4)
<b>Age ≥40 yrs</b>					
Simple	0/22 (0)	0/26 (0)	<b>2/35 (5.7)</b>	<b>2/8 (25)</b>	<b>4/91 (4.4)</b>
Moderate	0/26 (0)	1/62 (1.6)	<b>5/71 (7)</b>	<b>1/11 (9.1)</b>	<b>7/170 (4.1)</b>
Complex	0/3 (0)	<b>1/21 (4.8)</b>	0/21 (0)	0/6 (0)	1/51 (2)
Total	0/51 (0)	2/109 (1.8)	<b>7/127 (5.5)</b>	<b>3/25 (12)</b>	<b>12/312 (3.8)</b>
<b>Total cohort</b>					
Simple	0/70 (0)	0/87 (0)	<b>3/99 (3)</b>	<b>3/19 (15.8)</b>	6/275 (2.2)
Moderate	0/88 (0)	3/192 (1.6)	<b>8/183 (4.4)</b>	<b>2/28 (7.1)</b>	13/491 (2.6)
Complex	0/44 (0)	1/88 (1.1)	<b>4/114 (3.5)</b>	0/16 (0)	5/262 (1.9)
Total	0/202 (0)	4/367 (1.1)	<b>15/396 (3.8)</b>	<b>5/63 (7.9)</b>	<b>24/1028 (2.3)</b>

Values are n/N (%). Columns represent different physiological stages. Anatomic complexity is given by row. Groups with ≥3% fatality rate are indicated in bold.

subjects with CHD who received care in New York City, there were 3 (6%) deaths (8). Those at highest risk of death or severe infections were adults with advanced physiological stages (C and D) (9). The present study, which was approximately 20-fold higher than these previous publications, showed a case/fatality ratio similar to that of the general population (19).

Concern for myocardial damage from these and other viruses is inherently justifiable.

Historical data from previous viral epidemics confirmed adverse pulmonary and cardiovascular effects in the patient population with CHD (20-22). Cardiac injury from these challenges might have resulted from an overwhelming immune inflammatory cytokine response, direct viral invasion of cardiomyocytes, or poor myocardial oxygenation from severe hypoxia due to lung injury (23). These mechanisms might have plausibly complicated patients with CHD who were already prone to myocardial dysfunction, limited myocardial oxygenation, or pulmonary vascular disease. Yet, it could also be postulated that pre-conditioning in CHD paradoxically protects the myocardium to such stresses, and thus lessens the overall impact on the myocardium (12). We found little risk from systolic dysfunction or valve dysfunction, although our assessments of these were subjective and not uniformly assessed among centers. However, we did find significant risk in those with previous heart failure admission, which was consistent with other reports of CHD and PAH (24,25).

Our data confirmed that cyanosis and PAH, especially when combined (Eisenmenger syndrome), portends a high rate of adverse events. This was not surprising because of the reduced functional capacity, multiorgan consequences of chronic cyanosis and the limited reserve of these patients (26-29). Increased risk from COVID-19 in PAH was documented (30). It was less clear whether cyanosis or PAH conveyed the most vulnerability; our limited experience suggested that cyanosis might be the stronger risk factor. We found that 6% of patients with CHD required ICU admission, a lower rate than that observed in non-CHD hospitalized patients (31).

The spectrum of presenting symptoms of COVID-19 in our population was similar to those described in the general population, although fever was less frequent (44% vs. 90%) (32). Reasons for this discrepancy are not clear but likely reflect less vigorous reporting methods herein. Of note, 6% of patients were completely asymptomatic; diagnoses were made incidentally through COVID PCR testing before a procedure or after a known exposure. The increasing availability and access to PCR and

**TABLE 5 Factors Compared Based on Mild Versus Severe Cases**

	Mild Case	Severe Case*	p Value
<b>Demographics</b>			
Age, yrs	32 ± 16	40 ± 23	0.001
Male	454/963 (47)	52/76 (68)	<0.001
Weight, kg	77.5 ± 20.8	83.0 ± 33.0	0.16
Height, cm	168 ± 11	166 ± 12	0.063
Body mass index	27.2 ± 6.5	29.2 ± 9.9	0.091
Smoking/vaping history	76/967 (7.9)	5/77 (6.5)	0.66
Black	62/739 (8.4)	6/45 (13.3)	0.25
Hispanic	93/695 (14)	9/44 (21)	0.19
<b>Medications</b>			
ACE/ARB use	255/953 (27)	28/76 (37)	0.058
Beta-blocker use	325/956 (34)	35/75 (46)	0.027
<b>Medical/cardiac history</b>			
Previous atrial arrhythmia	233/950 (25)	26/76 (34)	0.061
Pacemaker or implantable defibrillator	119/956 (12)	13/77 (17)	0.26
Hypertension	147/951 (16)	14/76 (18)	0.49
Diabetes	50/961 (5.2)	15/77 (20)	<0.001
Known coronary artery disease	20/952 (2.1)	4/76 (5.3)	0.079
Previous heart failure admission	72/951 (7.6)	26/74 (35)	<0.001
Ejection fraction <40%	29/617 (4.7)	6/56 (11)	0.052
Systemic ventricular ejection fraction by echo	57 ± 10	53 ± 10	0.001
Systemic right ventricle (biventricular)	51/967 (5.3)	10/77 (13)	0.005
Moderate-severe valve dysfunction by echo	316/766 (41)	30/61 (49)	0.28
Fontan palliation	108/964 (11.2)	10/77 (13)	0.64
Pulmonary hypertension	58/955 (6.1)	15/77 (20)	<0.001
Sub-pulmonic ventricular systolic pressure by echo, mm Hg	38 ± 21	52 ± 28	0.006
Previous resting oxygen saturation, %	96 ± 4	93 ± 6	<0.001
Cyanosis (oxygen saturation <90%)	64/947 (6.8)	20/75 (27)	<0.001
Supplemental oxygen use	24/950 (2.5)	8/76 (10.5)	<0.001
<b>Laboratory findings</b>			
Hemoglobin	14.21 ± 3.1	14.8 ± 2.8	0.105
Creatinine, mg/dl	0.86 ± 0.34	1.12 ± 0.85	0.043
eGFR <60 ml/min/1.73 m <sup>2</sup>	35/962 (3.6)	7/77 (9.1)	0.019
Albumin, mg/dl	4.3 ± 0.6	4.0 ± 0.6	0.013

Values are mean ± SD or n/N (%). \*Severe case includes need for intensive care, endotracheal intubation, renal replacement therapy, extracorporeal membrane oxygenation, or death.  
 Abbreviations as in Table 2.

serological testing as the months of the pandemic unfolded allowed for inclusion of mostly confirmed positive COVID-19 cases in our study compared with previous publications (7). However, the denominator in any case/fatality ratio remains fluid because it is dependent on multiple physiological, institutional, psychosocial, and even geopolitical factors.

**STUDY LIMITATIONS.** Our study could not determine the rate of infection among adults with CHD, because it was impossible to accurately measure the size of the population from which to base our case load. All patients in our study were followed by CHD centers, meaning the study was susceptible to referral bias and could thus have included more complicated patients with CHD and/or worse COVID-19 infections.

The prevalence of death among adults with CHD who were infected but did not have access to specialized CHD care could not be determined. We included 60 asymptomatic patients; this implied there were likely other asymptomatic carriers among the population, although the prevalence of asymptomatic infections was unknown. The preceding limitations suggested that the true case/fatality ratio might actually be lower. It could be argued also that our sample included those with better access to care, and therefore, they had better outcomes than others not accounted for herein. In addition, we had predominantly American participation with lower participation from adult CHD centers with different socioeconomics and health care delivery models and could not confidently generalize our findings to patients globally.

Because we identified 24 COVID-19 related deaths, risk factor analysis was limited, and potential effects of confounding were more difficult to explore. Specifically, multivariate regression or risk score modeling was limited to study-only specific potential confounding. Due to referral bias, our sample might have had over-representation of sicker or more complex patients, including asymptomatic patients with who had PCR testing before procedures. This might partly explain our paradoxical finding of a slightly lower mortality among those with complex lesions (Table 4). A recent change in case complexity among inpatient CHD services during the pandemic was shown (33).

Our study focused on short-term death and serious complications and did not address potential medium- and long-term complications. Our identification of severe cases might facilitate future study of unfavorable physiological downstream effects. There were also known neuropsychiatric outcomes (33) and emerging information about longer-term consequences of patients hospitalized for COVID-19 (34,35).

Although we did not observe a relationship between our primary or secondary outcomes with race/ethnicity among the U.S. cohort, this should not be interpreted to suggest that Black and Hispanic adults with CHD were not disproportionately affected by COVID-19. Authors of a recent systematic review of 37 studies reported that African American/Black and Hispanic populations had higher rates of infection, hospitalization, and COVID-19-related deaths compared with non-Hispanic White populations, although case/fatality rates did not differ (36). It was likely that factors related to health care access, exposure (36), and racism (37) would also affect

outcomes of Black and Hispanic adults with CHD living in the United States.

## CONCLUSIONS

We found that the presence of a structural congenital heart defect did not necessarily portend an increased risk of mortality or morbidity from COVID-19 infection. This finding was important for both patients and providers worldwide who are now facing high numbers of cases throughout the population. Yet, recognizing the inherent heterogeneity across the CHD population, we identified several factors associated with mortality and severe infections. These showed that susceptibility might be based on physiological factors, not the complexity of the underlying anatomic defect. Our findings were harmonious with general population studies that showed risks associated with age, male sex, diabetes, and renal insufficiency.

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**ADDRESS FOR CORRESPONDENCE:** Dr. Jamil A. Aboulhosn, UCLA Adult Congenital Heart Center, 100 UCLA Medical Plaza, Suite 630, East Los Angeles, California 90095, USA. E-mail: [aboulhosn@mednet.ucla.edu](mailto:aboulhosn@mednet.ucla.edu). Twitter: [@jaboulho](https://twitter.com/aboulho).

## PERSPECTIVES

**COMPETENCY IN PATIENT CARE:** The case/fatality rate among adults with CHD who develop novel coronavirus infection is 2.3%. Mortality is more closely related to physiological factors such as cyanosis and pulmonary hypertension and to male sex, diabetes, and renal insufficiency, than to the complexity of cardiac defects.

**TRANSLATIONAL OUTLOOK:** Systematic efforts are needed to target preventive measures at patients with CHD who are at greatest risk of mortality and severe morbidity due to COVID-19.

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**KEY WORDS** adult congenital heart disease, coronavirus, COVID-19, hospitalization



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