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ORIGINAL RESEARCH

CONGENITAL HEART DISEASE

COVID-19–Related Thrombotic and Bleeding Events in Adults With Congenital Heart Disease

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ABBREVIATIONS AND ACRONYMS

ACHD = adult congenital heart disease

ARDS = acute respiratory distress syndrome

DVT = deep venous thrombosis

ECMO = extracorporeal membrane oxygenation

ICU = intensive care unit

MI = myocardial infarction

PE = pulmonary embolism

TE = thromboembolic events

ABSTRACT

BACKGROUND Altered coagulation is a striking feature of COVID-19. Adult patients with congenital heart disease (ACHD) are prone to thromboembolic (TE) and bleeding complications.

OBJECTIVES The purpose of this study was to investigate the prevalence and risk factors for COVID-19 TE/bleeding complications in ACHD patients.

METHODS COVID-19-positive ACHD patients were included between May 2020 and November 2021. TE events included ischemic cerebrovascular accident, systemic and pulmonary embolism, deep venous thrombosis, myocardial infarction, and intracardiac thrombosis. Major bleeding included cases with hemoglobin drop >2 g/dl, involvement of critical sites, or fatal bleeding. Severe infection was defined as need for intensive care unit, endotracheal intubation, renal replacement therapy, extracorporeal membrane oxygenation, or death. Patients with TE/bleeding were compared to those without events. Factors associated with TE/bleeding were determined using logistic regression.

RESULTS Of 1,988 patients (age 32 [IQR: 25-42] years, 47% male, 59 ACHD centers), 30 (1.5%) had significant TE/bleeding: 12 TE events, 12 major bleeds, and 6 with both TE and bleeding. Patients with TE/bleeding had higher in-hospital mortality compared to the remainder cohort (33% vs 1.7%; $P < 0.0001$) and were in more advanced physiological stage ($P = 0.032$) and NYHA functional class ($P = 0.01$), had lower baseline oxygen saturation ($P = 0.0001$), and more frequently had a history of atrial arrhythmia ($P < 0.0001$), previous hospitalization for heart failure ($P < 0.0007$), and were more likely hospitalized for COVID-19 ($P < 0.0001$). By multivariable logistic regression, prior anticoagulation (OR: 4.92; 95% CI: 2-11.76; $P = 0.0003$), cardiac injury (OR: 5.34; 95% CI: 1.98-14.76; $P = 0.0009$), and severe COVID-19 (OR: 17.39; 95% CI: 6.67-45.32; $P < 0.0001$) were independently associated with increased risk of TE/bleeding complications.

CONCLUSIONS ACHD patients with TE/bleeding during COVID-19 infection have a higher in-hospital mortality from the illness. Risk of coagulation disorders is related to severe COVID-19, cardiac injury during infection, and use of anticoagulants. (JACC Adv 2023;2:100701)

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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.

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Initial experience with novel COVID-19 demonstrated an association with thrombotic and hemorrhagic complications, with an adverse impact on the disease course.[1] Adults with congenital heart disease (ACHD) are a potentially vulnerable group inherently prone to thrombosis and/or bleeding. We previously demonstrated that ACHD patients who do poorly with COVID-19 have a higher physiological stage severity,[2] a metric that reflects heart failure, valve dysfunction, arrhythmias, or symptoms. Given the ongoing persistence of global COVID-19, there is an opportunity to describe the impact of COVID-19-related coagulation disorders in the complex ACHD population in order to provide the best treatment. Therefore, we aimed to describe the prevalence of thromboembolic and bleeding complications associated with COVID-19 infection in ACHD patients and identify factors associated with these complications.

METHODS

STUDY DESIGN AND INCLUSION CRITERIA. The current study was conducted as part of an international, multicenter, retrospective cohort study on acute outcomes from COVID-19 infection among ACHD patients.[2] Collaborators from ACHD centers globally participated after approval by local ethics oversight. Informed consent was waived given the nature of the study design. Oregon Health and Science University served as the online data coordinating center, using a secure data collection tool (REDCap). Data analysis for the present substudy was performed at Monaldi Hospital, Naples, Italy.

Eligible patients met the following inclusion criteria for enrollment: known diagnosis of congenital heart disease (CHD), age 18 years or older at enrollment, and COVID-19 diagnosis. Patients with a presumptive diagnosis were also included from areas with high disease incidence, where local guidelines at the beginning of the pandemic recommended considering positive those with highly suggestive symptoms during the early phases of the pandemic due to the lack of testing availability. Patients with no diagnosis of CHD were excluded.

DATA COLLECTION. All consecutive patients meeting the inclusion criteria were recruited at local ACHD center from the beginning of COVID-19 pandemic until November 2021, when enrollment was closed. For each patient, comprehensive clinical data were retrospectively obtained from existing medical records by researchers at each center. Data included cardiac diagnoses, comorbidities, previous interventions and most recent outpatient vital signs, laboratory and echocardiographic findings. Specific information regarding previous indications for anticoagulation or antiplatelet therapy and current medications were collected. Details of the COVID-19 infection diagnosis and disease course were also recorded. Severe viral infection was defined as need for intensive care unit (ICU) admission, endotracheal intubation for mechanical ventilation, acute respiratory distress syndrome, renal replacement therapy, need for extracorporeal membrane oxygenation, or death. No protected patient identifiers were collected, including dates. Additional details on study design and data collection have been previously published.[2] Data were reviewed at the data coordinating center for internal consistency. All inconsistencies and outliers were flagged, and queries were sent to local investigators for confirmation or correction. Anatomic classification and physiological stage were designated according to the 2018 American College of Cardiology/American Heart Association on ACHD.[3]

ENDPOINT. The study endpoints were COVID-19 coagulation disorders, defined as occurrence of a thromboembolic (TE) or bleeding event either clinically evident or subclinical events detected with appropriate tests during disease course or within 4 weeks from diagnosis, which is the recognized cutoff to define "long COVID".[4] TE events included ischemic cerebrovascular accident/transient ischemic attack, systemic embolism, pulmonary embolism (PE), deep venous thrombosis (DVT), myocardial infarction (MI), or intracardiac thrombosis. Ischemic cerebrovascular accidents, PE, DVT, and intracardiac thrombosis were diagnosed with appropriate imaging tests, and MI was defined according to the fourth universal definition of MI.[5] Bleeding episodes were considered major if they fulfilled the International Society on Thrombosis and Haemostasis criteria, specifically a hemoglobin drop >1.24 mmol/L (2 g/dl), bleeding necessitating hospitalization or interventions, requirement of ≥2 units of packed red blood cell transfusion, bleeding in critical sites (intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome), or fatal bleeding.

STATISTICAL ANALYSIS. Patients identified as having TE/bleeding were compared to those without either event. Statistical analysis was carried out using R version 4.0.5. Data normality was assessed by Shapiro-Wilk testing. Continuous variables were reported as mean ± SD or median (IQR) according to data distribution. Comparisons between groups were assessed with Student *t*-test or Wilcoxon rank-sum test. Categorical variables were presented as

frequencies (percentage of total). Differences in proportions were evaluated with chi-square testing. ORs with 95% CIs were determined using binary logistic regression to examine the association between risk factor exposure and coagulation disorder. Variables with >20% missing values were excluded. All predictors with a univariate P value <0.10, as well as the clinically relevant variables, were included in a multivariable model, after which stepwise backward selection based on Bayesian Information Criteria was allowed to determine the best-fit model. To test collinearity between variables included in the same model, variance inflation factors were calculated; values close to 1 were considered as absence of collinearity. A value of $P < 0.05$ was considered statistically significant for all tests.

RESULTS

STUDY POPULATION. A total of 59 CHD centers contributed to the study. Of 2,135 submitted patients, 1,988 (median age 32 [IQR: 25-42] years, 47% male) met full inclusion criteria and were used in the analysis. Of these, 1,686 (84%) had a positive polymerase chain reaction for SARS-CoV-2. The cohort included a broad representation of the spectrum of CHD anatomic complexity and physiological stage. A breakdown by anatomic classification is shown (Supplemental Table 1). Of the total, 235 (12%) had Fontan circulation and 48 (2%) had Eisenmenger physiology. From the total cohort, 281 (14%) were on antiplatelet therapy, and 197 (10%) were prescribed anticoagulation. Indications for anticoagulation/antiplatelet therapy before COVID-19 and type of medications prescribed during infection are summarized in Supplemental Table 2.

THROMBOEMBOLISM/BLEEDING EVENTS. Overall, 30 (1.5%) patients (median age 35.5 [IQR: 24.7-50] years, 50% male) had an event meeting criteria for TE/bleeding. This included 12 patients with a TE event, 12 with major bleeding, and 6 patients who experienced both. Patients with TE/bleeding included 8 with repaired tetralogy of Fallot, 4 with a repaired ventricular septal defect, 4 Fontan patients, 3 with a systemic right ventricle, and 2 with partial anomalous venous return, as well as single patients with pulmonary atresia, Eisenmenger, Ebstein's, bicuspid aortic valve, subaortic stenosis, atrial septal defect, atrioventricular septal defect, Shone's, and heterotaxy. Nineteen (63%) had a history of atrial arrhythmia, and 13 (43%) were on anticoagulants before infection.

As expected, coagulation disorders were almost always detected in hospitalized patients. Of those with TE/bleeding, 24 (80%) were hospitalized, and 19 (63%) were admitted in the ICU. Among all hospitalized patients, combined TE/bleeding incidence was 8.1%, and 18.6% among those were admitted to ICU. In particular, 4.7% of hospitalized patients and 10.7% of ICU patients had a TE event, and similarly, 3.7% and 9.8% had major bleeding in hospital and in ICU, respectively.

TE events included 6 patients with DVT, 5 with PE, 3 with systemic emboli, 4 with cerebral ischemia, and 1 with mechanical prosthesis thrombosis. Major bleeding complications reported were brain hemorrhages in 4, massive hemoptysis in 1, retroperitoneal bleeding in 1, vaginal bleeding in 1, and gastrointestinal bleeding requiring transfusion in 2. In addition, 9 patients experienced minor bleeding episodes. Ten out of the 30 patients (33%) died from COVID-19, and in 4 of these cases, the ultimate cause of death was either a TE or bleeding complications.

Main baseline demographic and clinical data in those with and without TE/bleeding are shown in **Table 1**. Patients with coagulation disorders had similar age, sex, and body mass index compared to the group without these events. Anatomic complexity was not associated with TE/bleeding, whereas advanced physiological stage was associated (NYHA functional class 3-4; $P = 0.032$). Patients with events had high NYHA functional class and lower oxygen saturation prior to infection. A higher proportion of patients with TE/bleeding had a history of atrial arrhythmia, previous hospitalization for heart failure, known coronary artery disease, and need for anticoagulation or antiplatelet therapy. There was no difference in hemoglobin, liver, or renal function between the groups.

CLINICAL COURSE OF INFECTION WITH OR WITHOUT COAGULATION DISORDERS. Clinical events and laboratory findings during COVID-19 infection were compared between those with or without TE/bleeding (**Table 2**). Overall, 44 patients (2.2%) died due to COVID-19-related complications. Those with TE/bleeding were more likely to be hospitalized, more likely to be placed in intensive care, had a longer hospital stay, more frequent arrhythmias, and more often required antiviral therapy, among all other indicators of severe disease. Liver and renal function laboratory tests were worse. Cardiac injury, defined in agreement with the fourth universal definition of MI,[5] was demonstrated by increased troponin values and was reported in only 55 patients (2.7% among all hospitalized patients), but was more common among those with TE/bleeding. Patients

TABLE 1 Baseline Demographic and Clinical Data in the Study Population and Stratified According to the Occurrence of Thromboembolism or Bleeding Events

	All (N = 1,988)	Thromboembolism or Bleeding Events (n = 30)	No Events (n = 1,958)	*P* Value
Age (y)	32 (25-42)	35.5 (24.7-50)	32 (25-42)	0.36
Male	929 (47%)	15 (50%)	914 (47%)	0.46
Weight (Kg)	73.5 (63-89)	66 (50-81.8)	73.8 (63-89)	0.12
Height (cm)	167 (160-175)	162 (160-169.2)	167 (160-175)	0.052
Body mass index (kg/m^2)	25.9 (23-30.8)	25.0 (22.1-27.6)	26.0 (22.9-30.8)	0.41
Smoking/vaping	231 (12%)	4 (20%)	227 (12%)	0.64
Anatomic complexity				
I	319 (16%)	7 (23%)	312 (16%)	0.83
II	1,050 (53%)	13 (43%)	1,037 (53%)	
III	619 (31%)	10 (33%)	609 (32%)	
Physiopathological stage				**0.032**
A	490 (25%)	10 (33%)	480 (25%)	
B	707 (35%)	7 (23%)	700 (36%)	
C	658 (33%)	10 (33%)	648 (33%)	
D	116 (6%)	3 (10%)	113 (6%)	
Unknown	17 (0.03%)		17 (0.8%)	
Systemicrightventricle	265 (13%)	3 (10%)	259 (13%)	0.21
Eisenmenger syndrome	48 (2%)	1 (5%)	47 (2%)	0.36
Fontan palliation	235 (12%)	4 (13%)	231 (12%)	1.00
Cyanosis	158 (8%)	4 (13%)	154 (8%)	0.75
Oxygen saturation (%)	97 (96-99)	94 (94-96.5)	97 (96-99)	**0.0001**
NYHA functional class				
I	1,052 (53%)	3 (10%)	1,049 (54%)	**0.001**
II	569 (29%)	1 (3%)	568 (29%)	
III	170 (8%)	12 (40%)	158 (8%)	
IV	22 (1.1%)	9 (30%)	13 (0.7%)	
Unknown	175 (9%)	5 (16%)	170 (9%)	
History of atrial arrhythmia	461 (23%)	19 (63%)	442 (22.5%)	**<0.0001**
Indication for anticoagulation	197 (10%)	13 (43%)	184 (9%)	**<0.0001**
Previous antiplatelet therapy	281 (14%)	13 (43%)	268 (14%)	**<0.0001**
History of ventricular tachycardia	204 (10%)	6 (20%)	198 (10%)	0.07
PMK/ICD	277 (13%)	4 (13%)	273 (14%)	0.85
Mechanical prosthetic valve	198 (10%)	6 (20%)	192 (10%)	0.06
Previous endocarditis	99 (5%)	2 (6%)	97 (5%)	0.82
Pulmonary arterial hypertension	135 (7%)	3 (10%)	134 (7%)	0.38
Previous hospitalization for HF	169 (8.5%)	9 (30%)	160 (8%)	**0.0007**
Diabetes	110 (5%)	1 (3%)	109 (6%)	0.47
Previous coronary artery disease	36 (1.8%)	3 (15%)	33 (1.6%)	**<0.0001**
Systemic ventricle systolic function				
Normal	1,635 (82%)	20 (66%)	1,615 (83%)	0.36
Mildly reduced	179 (9%)	5 (17%)	174 (16%)	
Moderately reduced	77 (4%)	3 (10%)	74 (4%)	
Severely reduced	7 (0.4%)	2 (7%)	5 (0.2%)	
Unknown	90 (4.5%)		90 (4.5%)	
Baseline subpulmonary ventricle systolic function				
Normal	998 (50%)	15 (50%)	983 (50%)	0.53
Mildly reduced	221 (11%)	10 (33%)	211 (11%)	
Moderately reduced	102 (5%)	5 (17%)	97 (5%)	
Severely reduced	19 (0.9%)	0	19 (0.9%)	
Unknown	648 (33%)		648 (33%)	
At least moderate valvular disease	645 (32%)	4 (20%)	641 (32%)	0.25

Values are median (IQR) or n (%). **Bold** indicate statistically significant values.
HF = heart failure; ICD = implantable defibrillator cardioverter; PMK = pacemaker.

TABLE 2 COVID-19 Infection Data in the Study Population and Stratified According to the Occurrence Thromboembolism or Bleeding Events

	All (N = 1,988)	Thromboembolism or Bleeding Events (n = 30)	No Events (n = 1,958)	*P* Value
Pregnancy	58 (3%)	1 (3%)	57 (3%)	1.00
Hospital admission	293 (15%)	24 (80%)	269 (14%)	**<0.0001**
Length of in-hospital stay (d)	7 (3-13)	13 (10-18)	6 (3-12)	**0.0008**
Cardiac injury	55 (2.7%)	11 (55%)	44 (2.2%)	**<0.0001**
New arrhythmia	SVT→39 (1.9%)	5 (16%)	34 (1.7%)	**<0.0001**
	VT→18 (0.9%)	6 (20%)	12 (0.6%)	**<0.0001**
ICU	102 (5%)	19 (63%)	83 (4.2%)	**<0.0001**
Mechanical ventilation	58 (2.9%)	15 (50%)	43 (2.1%)	**<0.0001**
ARDS	50 (2.5%)	13 (43%)	37 (1.8%)	**<0.0001**
ECMO	9 (0.4%)	7 (23%)	2 (0.1%)	**<0.0001**
CRRT	18 (0.9%)	8 (26%)	10 (0.5%)	**<0.0001**
Death	44 (2.2%)	10 (30%)	34 (1.7%)	**<0.0001**
Severe disease	121 (6%)	19 (63%)	102 (5.2%)	**<0.0001**
COVID-19 treatment	238 (12%)	14 (47%)	224 (11%)	**<0.0001**
Antibiotic	166 (8%)	10 (33%)	156 (8%)	**<0.0001**
Anti-inflammatory drugs	79 (4%)	5 (16%)	74 (4%)	**0.001**
Antiviral/anti-SARS-CoV-2 spike IgG	86 (4%)	4 (13%)	82 (4%)	**0.012**
Convalescent/hyperimmune plasma	7 (0.3%)	2 (6%)	5 (0.2%)	**<0.0001**
Anticoagulation	243 (12%)	22 (73%)	221 (5.2%)	**<0.0001**
Peak creatinine (mg/dl)	1 (0.8-1.3)	1.6 (0.83-1.9)	1 (0.8-1.2)	**0.033**
GFR (ml/min)	49.8 (43.5-63.2)	30.4 (22.9-39.2)	55.7 (41.2-70.7)	**0.0006**
ALT (U/L)	31 (22-47)	33 (20-48.5)	29 (19-50)	1.00
AST (U/L)	29 (19-50)	39 (26-58.5)	30 (22-46)	1.00
Total bilirubin (mg/dl)	0.9 (0.5-1.3)	1.5 (1-2.2)	0.8 (0.5-1.2)	**0.002**
BNP (upper level of normal)	1.5 (0.8-6)	2.56 (1.76-8.22)	1.34 (0.86-5.8)	**0.011**
WBC (*1,000 u/L)	7.4 (5.1-11)	13.6 (8-18.3)	7.2 (5.09-10.5)	**0.0001**
CRP (mg/L)	14.5 (3.646)	66 (11.3-119.5)	13.3 (2.75-43.1)	**0.002**
Platelets (*1,000 u/L)	194 (133-260)	110 (79-216)	200 (139-262)	**0.004**

Values are n (%) or median (IQR). **Bold** indicate statistically significant values.

ALT = alanine transaminase; ARDS = acute respiratory distress syndrome; AST = aspartate transaminase; BNP = brain natriuretic peptide; CRP = C-reactive protein; CRRT = continuous renal replacement therapy; ECMO = extracorporeal membrane oxygenation; GFR = glomerular filtration rate; ICU = intensive care unit; IgG = immunoglobulin G; WBC = white blood cells.

with TE/bleeding had higher in-hospital mortality compared to the remainder of the cohort (33% vs 1.7%, $P < 0.0001$). Further details on history, antithrombotic treatment, and clinical course during COVID-19 for those with coagulopathic events are presented in the Supplemental Table 3.

Factors related to the course of COVID-19 disease that were significant univariate predictors of TE/bleeding included hospital admission, development of new supraventricular (defined as new onset of sustained atrial fibrillation/flutter/tachycardia) and ventricular tachycardia (defined as new onset of sustained ventricular tachycardia), and all the indices of severe disease such as need for intubation or mechanical support (**Table 3**).

FACTORS ASSOCIATED WITH THROMBOEMBOLISM OR BLEEDING. By univariate logistic regression, factors significantly associated with TE/bleeding included advanced physiological stage, NYHA functional class, previous atrial arrhythmia, previous antiplatelet therapy, previous indication for anticoagulant therapy, anticoagulant use during COVID-19, presence of a mechanical valve prosthesis, history of coronary artery disease, and previous hospital admission for heart failure (**Table 3**). Results of univariate analysis for thrombotic and bleeding events alone are shown in Supplemental Tables 4 and 5.

On multivariable analysis, previous indication to anticoagulation (OR: 4.92; 95% CI: 2-11.76; $P = 0.0003$), cardiac injury (OR: 5.34; 95% CI: 1.98-14.76; $P = 0.0009$), and severe COVID-19 (OR: 17.39; 95% CI: 6.67-45.32; $P < 0.0001$) were independently associated with increased risk of bleeding and/or thrombosis (**Table 3**, **Central Illustration**). When repeating the multivariable analysis with the exclusion of 302 with presumptive COVID-19 diagnosis, the results were confirmed.

DISCUSSION

To our knowledge, this is the first study addressing the risks for and impact of COVID-19-related coagulation disorders in ACHD. In our population of 1,988 patients, TE, or bleeding occurred in 1.5% of the total cases and was associated with higher morbidity and in-hospital mortality. Risks for coagulation disorders identified herein are of interest. Disease complexity was not associated with TE/bleeding, but NYHA functional class and more advanced physiological stage were univariate predictors of the outcome. Those with events had more often been hospitalized for heart failure prior to infection, yet did not differ by echocardiographic report of ventricular function. Cyanosis was not a discriminator, but baseline oxygen saturation was lower in those with coagulopathy. Noticeably, 20% of patients with endpoint events showed both thrombotic and bleeding complications, suggesting that those events have overlapping pathogenesis. Importantly, coagulation disorders were more prevalent in patients taking anticoagulants or antiplatelet therapy prior to infection, as well as in conditions related to these therapies such as prior atrial arrhythmia, mechanical valves, and coronary artery disease. Interestingly, previous use of anticoagulant agents, cardiac injury, and severe COVID-19 were all independently associated with increased risk of bleeding and/or thrombosis. When analyzing risk factors for TE or bleeding events alone, prior indication to anticoagulation remained associated to both outcome events.

TABLE 3 Risk Factors for the Occurrence of Thromboembolism/Bleeding Events in the ACHD Population

	OR (95% CI)	*P* Value
Age	1.01 (0.99-1.04)	0.12
Male	1.12 (0.54-2.30)	0.74
Oxygen saturation	0.98 (0.96-1.00)	0.26
Physiological class	2.59 (1.09-2.59)	**0.001**
NYHA functional class III-IV	3.49 (1.62-7.20)	**0.009**
Baseline atrial fibrillation	5.92 (2.48-12.96)	**<0.0001**
History of ventricular tachycardia	2.16 (0.79-5.04)	0.094
Previous indication to anticoagulation	5.5 (2.50-11.58)	**<0.0001**
Anticoagulation during COVID-19	18.25 (7.89-49.56)	**<0.0001**
Previous antiplatelet therapy	2.3 (1.11-4.80)	**0.025**
Mechanical valve	2.77 (1.08-6.20)	**0.016**
Congestive heart failure admission	4.96 (2.12-10.70)	**<0.0001**
Coronary artery disease	6.48 (1.49-19.50)	**0.003**
New supraventricular arrhythmia	11.6 (3.7-30.0)	**<0.0001**
New ventricular tachycardia	37.4 (12.2-103.5)	**<0.0001**
Hospitalization	24.1 (10.4-65.6)	**<0.0001**
Duration of hospitalization	1.03 (1.00-1.06)	**0.029**
Cardiac injury	31.1 (13.8-69.6)	**<0.0001**
ICU	36.3 (17.0-81.2)	**<0.0001**
Mechanical ventilation	51.86 (23.1-118.2)	**<0.0001**
ARDS	46.7 (20.6-106.1)	**<0.0001**
ECMO	165.1 (40.8-825.1)	**<0.0001**
CRRT	84.7 (28.6-253.2)	**<0.0001**
Severe COVID-19	36.7 (17.1-83.8)	**<0.0001**
Multivariable analysis		
Previous indication to anticoagulation	4.92 (2.00-11.76)	**0.0003**
Cardiac injury	5.34 (1.98-14.76)	**0.0009**
Severe COVID-19	17.39 (6.67-45.32)	**<0.0001**

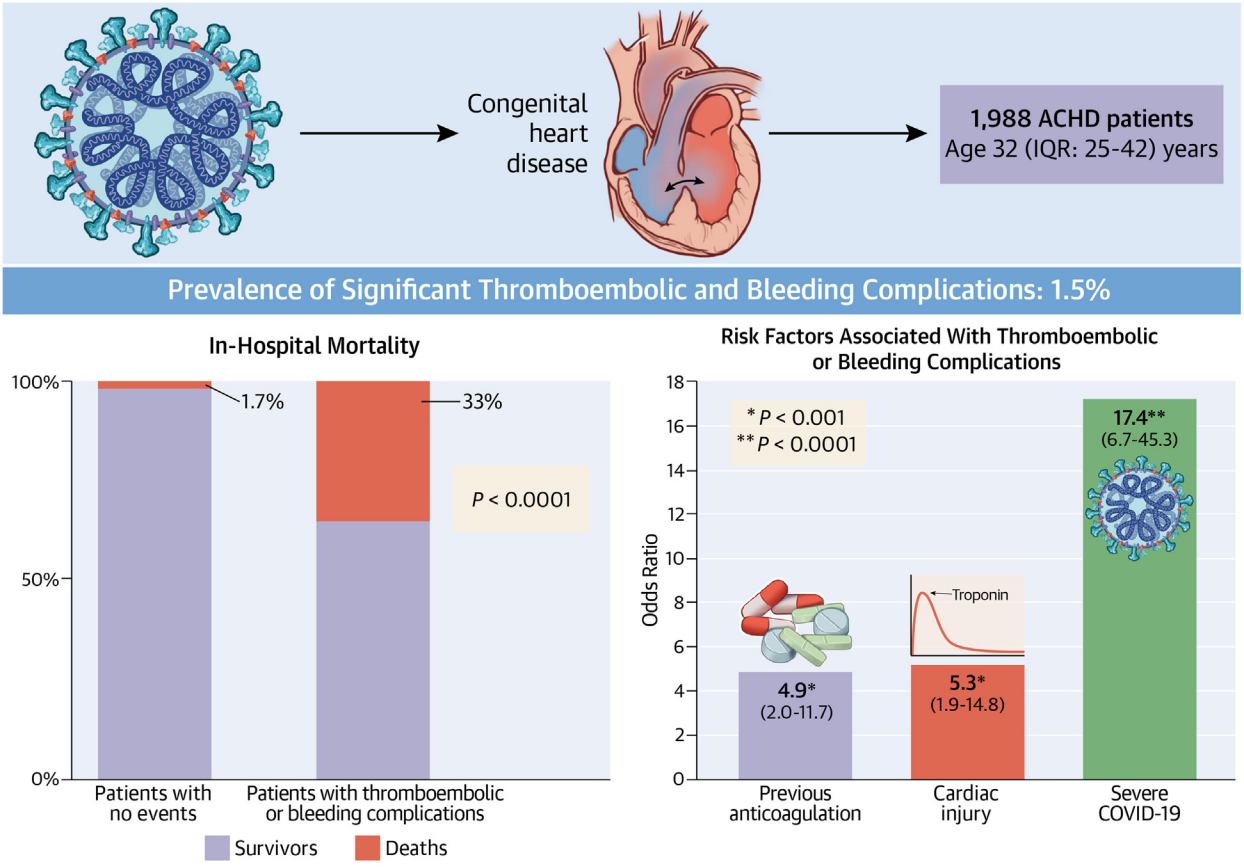
Bold indicate statistically significant values.

ARDS = acute respiratory distress syndrome; CRRT = continuous renal replacement therapy; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit.

Concern for coagulopathic events was raised early on in the COVID-19 pandemic. TE complications as well as gastrointestinal bleeding were both associated with increased in-hospital mortality in COVID-19 patients.[6,7] Altered coagulation has been plausibly related to multiple mechanisms. A pronounced inflammatory response causing a cytokine storm seemed to play a role, which, coupled with direct endothelial injury by viral invasion and blood stasis evoked Virchow's triad triggering a systemic prothrombotic state and facilitating bleeding.[8] A systematic review of 42 studies enrolling 8,271 COVID-19 patients during the first pandemic wave found a 5% incidence of TE events and 31% among ICU patients.[7] In an international multicenter study involving roughly 1 million individuals with COVID-19, the 90-day cumulative incidence of venous thromboembolism was approximately 1% overall and 4.5% for hospitalized patients, with higher incidence in patients >65 years of age.[9] Bleeding rates were reported to be 4.8% overall and 7.6% in critically ill patients.[10] The findings stimulated the implementation of numerous ongoing clinical trials to establish the optimal thromboprophylactic management of COVID-19 patients. Waiting for additional trial data, the American Society of Hematology guideline panel suggested the routine administration of heparin in critically ill COVID-19 patients,[11] while the International Society on Thrombosis and Haemostasis recommended therapeutic anticoagulation even in selected hospitalized noncritical ill patients.[12] Nevertheless, despite these measures and improved treatment regimens overall, the burden of TE remained unaltered between the first and second waves of the pandemic.[13]

Many ACHD patients, such as those with Fontan palliation or cyanosis, are generally considered at risk for coagulopathic disorders. Certain conditions may present a unique interplay of multiple risk factors that impact coagulation. These include atypical flow patterns causing stasis of blood, the presence of prosthetic materials that may be prothrombotic, chronic hepatic congestion that may impact clotting factor production, a higher incidence

CENTRAL ILLUSTRATION **COVID-19 Related Coagulation Disorders in ACHD Patients**



Fusco F, et al. JACC Adv. 2023;2(10):100701.

Among 1,988 COVID-19 positive ACHD patients with median age of 32 (IQR: 25-42) years the incidence of coagulopathy was 1.5% and was associated with significantly higher risk of death (bottom left panel). Previous indication to anticoagulation, cardiac injury during infection and COVID-19 severity were independently associated to the risk of coagulation disorders (bottom right panel, OR and 95% CI are reported inside the bars of the bar graph). ACHD = adult patients with congenital heart disease.

of supraventricular arrhythmias,[14] or cyanosis with compensatory erythrocytosis. Persistent shunts may also predispose to paradoxical systemic embolic events such as stroke.[15] Furthermore, patients with univentricular physiology and Fontan palliation, or with Eisenmenger syndrome are known to have paradoxical vulnerability to both thrombotic and hemorrhagic diathesis, likely due to altered platelet function, endothelial dysfunction, and deranged coagulation factor production.[16-18] In turn, coagulopathies themselves may have devastating detrimental effects on the global hemodynamics of ACHD patients. Therefore, COVID-19-related coagulation disorders seem particularly concerning in this vulnerable population.

Our data found the incidence of TE/bleeding events during COVID-19 among ACHD patients to be harmonious with previous reports in the general population.[1,6,7,10,11] Yet, despite the overall low prevalence in our large cohort, the absolute burden of COVID-19 coagulation disorders may be high when considering the large number of ACHD patients worldwide, many of whom have the risk factors we identified. Alteration of coagulation is a strong marker of poor outcome in COVID-19; in our ACHD cohort, in-hospital mortality was significantly higher among those who experienced coagulation disorders compared to those with no coagulopathy. While it is impossible to know whether coagulation disorders were more prevalent simply due to being more

detectable in hospitalized patients rather than a direct cause of poor outcome, in 4/10 patients dying with coagulopathic changes, the cause of death was the TE/bleeding event, highlighting its potential devastating effects. Moreover, our data may potentially be helpful for early identification of ACHD patients at higher risk to develop TE/bleeding events during the course of infection. Although severe COVID-19 was the strongest predictor of coagulopathy in our ACHD cohort, multivariable logistic regression showed that baseline indication for anticoagulation was associated with increased risk of coagulation disorders independently from COVID-19 severity, suggesting that particular attention should be paid to the management of COVID-19-positive ACHD patients under this medication.

It could be argued that a switch in anticoagulation therapy during infection could represent a confounding factor in our analysis. Nevertheless, it should be noted that, for most patients with TE, previous oral anticoagulant therapy was upgraded to heparin infusion with possibility of a closer follow-up of coagulation parameters (ie, activated partial thromboplastin time measurement). While multiple confounders are likely to play a role in these associations, the data show patients on anticoagulation had a higher risk of events, though this is purely observational. Anticoagulation is extensively used in the ACHD population to prevent TE events, independently from risk scores commonly used in the population with acquired heart disease.[19] Use of these medications is likely an indirect indicator of disease severity and preexisting vulnerability to coagulation issues.

The most consistent hemostatic abnormalities described in COVID-19 in the general population include thrombocytopenia[20] and increased D-dimer levels.[21] C-Reactive protein, among others, has been found to be associated with death or thrombosis in COVID-19 patients[22] and has been proposed as a useful biomarker to follow disease course.[23] Unfortunately, despite significant differences of platelets and C-reactive protein values between groups, the role of biomarkers could not be assessed in the logistic regression analysis due to the amount of missing laboratory data in our cohort, reflecting the fact that many patients with mild infections did not receive laboratory testing.

Ideally, global vaccination campaigns could lead to significant improvements in overall risk by both preventing infection and reducing severity of the subsequent disease course. Early data have shown COVID-19 vaccine safety in the ACHD population.[24,25] However, further data are required to ascertain whether routine COVID-19 vaccination may reduce the risk of TE/bleeding in the ACHD population. In addition, it is interesting to point out that current data suggest that only partial protection may be achieved through vaccination against newer variants,[26] which have also been involved in increased thrombotic risk.[27] Incomplete immunization may also lead to potentially persistent intermittent outbreaks.[28] Moreover, early administration of antiviral therapy in susceptible individuals may also have an impact on TE/bleeding events. In our population, the higher proportion of patients treated with antiviral therapy in the group with events may be influenced by the more severe infection course in these patients. Further, occult TE has been suspected even in patients with only mild disease, which is a substantial proportion of cases.[29,30] Therefore, the cases we identified may be only the most severe, meaning that the real burden of coagulopathy in the ACHD population is likely much greater than realized.

STUDY LIMITATIONS. Our study is limited by its retrospective design, including a highly heterogeneous population. Furthermore, all patients in our study were followed by ACHD-specialized tertiary centers. Consequently, the study was susceptible to referral bias and could include more complicated ACHD patients and/or worse COVID-19 infections. Yet our cohort represents a wide sample of the ACHD spectrum. The impact of COVID-19 coagulopathy in patients who were infected but did not seek care through participating ACHD clinics could not be determined. Asymptomatic individuals represented only a fraction of cases in our cohort, whereas they are said to be much higher in the general population (up to one-third or more). Due to the retrospective nature of the study, routine laboratory or imaging tests were not performed in all patients leading to a potential underestimation of event rate. Our risk factor analysis was limited by our relatively low number of cases and missing data; therefore, potential effects of confounding were more difficult to explore. Our population was skewed towards younger ages, and the potential effects of age could not be determined. Hospitalization greatly enhances detection and reporting of events, and thus the associations we found during disease course are expected to be influenced by significant confounding. For example, endotracheal intubation could trigger significant inflammatory mediators and alter coagulation independently of viral effects. Thus, it is difficult to fully ascertain the cause-and-effect relationship between coagulation events and outcomes. In addition, our study focused on short-term effects and did not explore potential medium- and long-term

complications from COVID-19 coagulopathy. COVID-19 vaccination has been rarely implicated in the development of an immune-mediated prothrombotic case.[31] Despite early data suggesting a moderate safety of COVID-19 vaccination in ACHD patients,[24,25] an increased thrombotic risk from the vaccination could not be excluded in our study due to absence of data on the vaccination status in our population. Nevertheless, most cases occurred before availability of vaccines, and 21 out of 30 (70%) patients with COVID-19 coagulopathy were infected before COVID-19 vaccination, while 4 (13%) were infected early after vaccine approval and were most likely unvaccinated. For the remaining 16% of patients who had a thrombotic/bleeding complication, date of infection was not available. Moreover, the effects of different viral variants on the risk of coagulopathy could not be determined in our study. Considering current worldwide infection and vaccination numbers, a probable transition to a new phase of COVID-19 from pandemic to endemic disease, with more and less virulent variants, has been postulated.[32] Thus, the clinical features of the disease will likely be constantly changing. Despite all these limits, to the best of our knowledge, this is the first study to investigate the impact of COVID-19 coagulation disorders in a large ACHD population with an international multicenter study.

CONCLUSIONS

ACHD patients are prone to COVID-19-related coagulation disorders, which are associated with higher in-hospital mortality. Our data may allow identification of an ACHD population at higher risk of events requiring strict monitoring: patients with previous indications for anticoagulation, cardiac injury, and severe COVID-19 displayed the highest risk. Anticoagulation therapies were not protective in this observational study. Our results suggest value in maintaining vigilance for coagulation disorders due to COVID-19 in ACHD patients and supporting the implementation of preventive measures in this population including aggressive vaccination efforts.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Coagulation disorders in ACHD patients are associated to raise in-hospital mortality and morbidity risk.

COMPETENCY IN PATIENT CARE: Particular attention should be paid for prevention and timely recognition of coagulation disorders in ACHD patients with risk factors. Use of anticoagulation during COVID-19 does not seem to reduce the risk, although our findings are purely observational. Our data may allow identification of ACHD patients at higher risk of developing coagulation disorders during COVID-19 infection.

TRANSLATIONAL OUTLOOK 1: Long-term effects from COVID-19 thrombosis in survivors of ACHD patients should be explored with a prospective study.

TRANSLATIONAL OUTLOOK 2: Randomized controlled trial, despite significant difficulties, may provide definite data on the role of anticoagulation during COVID-19 infection in ACHD patients.

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APPENDIX For supplemental tables, please see the online version of this paper.