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Cardiac complications in patients hospitalised with COVID-19

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Abstract

Aims: To determine the frequency and pattern of cardiac complications in patients hospitalised with coronavirus disease (COVID-19).

Methods and results: CAPACITY-COVID is an international patient registry established to determine the role of cardiovascular disease in the COVID-19 pandemic. In this registry, data generated during routine clinical practice are collected in a standardised manner for patients with a (highly suspected) severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection requiring hospitalisation. For the current analysis, consecutive patients with laboratory confirmed COVID-19 registered between 28 March and 3 July 2020 were included. Patients were followed for the occurrence of cardiac complications and pulmonary embolism from admission to discharge. In total, 3011 patients were included, of which 1890 (62.8%) were men. The median age was 67 years (interquartile range 56–76); 937 (31.0%) patients had a history of cardiac disease, with pre-existent coronary artery disease being most common (*n*=463, 15.4%). During hospitalisation, 595 (19.8%) patients died, including 16 patients (2.7%) with cardiac causes. Cardiac complications were diagnosed in 349 (11.6%) patients, with atrial fibrillation (*n*=142, 4.7%) being most common. The incidence of other cardiac complications was 1.8% for heart failure (*n*=55), 0.5% for acute coronary syndrome (*n*=15), 0.5% for ventricular arrhythmia (*n*=14), 0.1% for bacterial endocarditis (*n*=4) and myocarditis (*n*=3), respectively, and 0.03% for pericarditis (*n*=1). Pulmonary embolism was diagnosed in 198 (6.6%) patients.

Conclusion: This large study among 3011 hospitalised patients with COVID-19 shows that the incidence of cardiac complications during hospital admission is low, despite a frequent history of cardiovascular disease. Long-term cardiac outcomes and the role of pre-existing cardiovascular disease in COVID-19 outcome warrants further investigation.

Keywords

COVID-19/coronavirus, cohorts, patient registry, cardiac complications, pulmonary embolism

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Introduction

Coronavirus disease 19 (COVID-19) is a global pandemic with more than 50 million confirmed cases across 191 countries as of the 15th of November 2020.[1] While respiratory symptoms are the dominant feature of this disease, the occurrence of acute cardiac injury and cardiovascular complications has generated considerable concern and the number of such reports is rapidly accumulating.[2–8] A study of 41 patients in Wuhan, China reported that 12% of patients with COVID-19 had virus-related acute cardiac injury.[2] Subsequent larger studies from China, with sample sizes ranging from 138 to 416 patients, reported acute cardiac injury in 7.2% to 27.8% among hospitalised patients.[3–5] For all these studies, cardiac injury has been defined as serum levels of cardiac biomarkers above the 99th percentile reference limit, regardless of abnormalities on electro and/or echocardiography. In addition to these studies, case reports of patients with myocarditis have been published both in the context of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[6–8] and Middle East respiratory syndrome coronavirus (MERS-CoV).[9] A systematic recording of the incidence of myocarditis and other cardiac complications in larger cohorts has been lacking thus far.[10] In this study, we evaluated the incidence and pattern of clinically diagnosed cardiac complications and the occurrence of pulmonary embolism within the CAPACITY-COVID collaborative consortium (www.capacity-covid.eu) (NCT04325412).

Methods

CAPACITY-COVID is an international patient registry that has specifically been established to determine the role of cardiovascular disease in the COVID-19 pandemic.[11] Currently, 79 centres across 13 countries (Belgium, Egypt, France, Iran, Israel, Italy, The Netherlands, Portugal, Russia, Saudi Arabia, Spain, Switzerland and the United Kingdom) have joined the consortium. A list of all participating hospitals can be found on our website (www.capacity-covid.eu).

Within CAPACITY-COVID, the case report form (CRF) of the International Severe Acute Respiratory and emerging Infection Consortium (ISARIC)[12] and the World Health Organization (WHO) has been extended by the addition of approximately 400 variables for the collection of in-depth information regarding cardiovascular history, the use of cardiovascular medications, ECG, cardiac biomarkers, echocardiography and cardiac outcomes. Data are collected in a standardised manner from electronic medical records. All adult patients (⩾18 years) with (highly suspected) COVID-19 that have been admitted to a hospital are eligible for inclusion. In The Netherlands, 45 hospitals contribute to the registry and together these sites have included 48.3% of all hospitalised patients during the first wave of the pandemic between the 27 March and 24 August 2020.

Local ethics approval was obtained in all participating hospitals. For hospitals asking for informed consent, the procedure varied among sites, with some centres handling an opt-in approach and others opt-out following local and national rules and regulations. In some centres, informed consent was not required for the retrospective collection of (pseudo)anonymised data generated during routine clinical care.

In the current study, data from centres that had initiated data collection before 3 July were used. The occurrence of cardiac complications during hospitalisation was determined according to the diagnostic criteria of the European Society of Cardiology (ESC) guidelines for myocarditis,[13] pericarditis,[14] endocarditis,[15] heart failure[16] and acute coronary syndrome.[17] For arrhythmias, the American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Rhythm Society (HRS) 2006 key data elements and definitions for electrophysiological studies and procedures were used.[18]

Missing data were not imputed due to the descriptive nature of this study. Continuous variables are summarised as median (interquartile ranges (IQR)) or mean (standard deviation (SD)) and categorical data with frequency (percentages). For univariate comparisons, the independent sample *t*-test or Mann–Whitney U test were used as appropriate. Categorical data were compared using the chi-square test. A P value less than 0.05 was considered statistically significant. Statistical analyses were performed by using R Studio (version 1.3.959; Vienna, Austria).

Results

For this analysis, outcome data of 3011 patients were available (Supplementary Figure 1). The median age was 67 years (IQR 56–76 years) and 62.8% were men. Nearly one-third of patients (31.0%) had a history of cardiac disease, most commonly coronary artery disease (n=463, 15.4%) and arrhythmia/conduction disorders (n=453, 15.1%) (Table 1). The median duration of hospital admission was 7 days (IQR 4–14 days). During hospitalisation, 837 (27.8%) patients required admission to a critical care unit (high dependency unit (HDU) or intensive care unit (ICU)) of which 731 (87.3%) received mechanical ventilation. The median duration of stay at a critical care unit was 13 days (IQR 7–23 days). Compared to patients admitted to the general ward, patients admitted to a critical care unit tended to be younger and have fewer comorbidities (Supplementary Table 1). At discharge, 595 patients (19.8%) had died (median age 76 years (IQR 69–82 years) and 68.4% were men), with a high proportion of these patients having pre-existing comorbidities (Supplementary Table 1).

In total, 349 (11.6%) patients were diagnosed with a cardiac complication during hospitalisation (Table 2). When compared with patients that did not develop cardiac complications, patients that did develop these complications were older, more

Table 1. Baseline characteristics.

	All (%) *n*=3011	No cardiac complications (%) *n*=2662	Cardiac complications (%) *n*=349	*P* value
Demographics				
Age, median (IQR), years	67 (56–76)	66 (55–76)	72 (64–77)	<**0.001**
Men	1890 (62.8)	1641 (61.7)	249 (71.3)	**0.001**
Cardiovascular risk factors				
BMI, mean (SD), kg/m^2	28.1 (5.4)	28.1 (5.4)	28.0 (5.0)	0.80
Diabetes mellitus	690 (23.1)	606 (22.9)	84 (24.4)	0.58
Dyslipidemia	996 (35.2)	861 (34.5)	135 (40.7)	**0.030**
Hypertension	1317 (44.6)	1137 (43.6)	180 (52.6)	**0.002**
Other comorbidities				
Auto-immune/inflammatory disease	297 (9.9)	259 (9.7)	38 (11.0)	0.54
CKD	313 (10.4)	253 (9.5)	60 (17.3)	<**0.001**
COPD	373 (12.4)	316 (11.9)	57 (16.5)	**0.019**
Pre-existing cardiac disease				
Any	937 (31.0)	790 (29.8)	147 (42.2)	<**0.001**
Arrhythmia/conduction disorder	453 (15.1)	371 (14.0)	82 (23.5)	<**0.001**
Heart failure	160 (5.3)	125 (4.7)	35 (10.3)	<**0.001**
Coronary artery disease	463 (15.4)	390 (14.7)	73 (20.9)	**0.003**
Valvular disease	128 (4.3)	103 (3.9)	25 (7.2)	**0.006**
Congenital heart disease	11 (0.4)	10 (0.4)	1 (0.3)	–
Other[a]	32 (1.1)	28 (1.1)	4 (1.1)	–

[a]Left ventricular hypertrophy *n*=14; pericarditis *n*=4; pulmonary hypertension *n*=4; diastolic dysfunction *n*=2; endocarditis *n*=2; acute myocardial infarction without coronary artery disease *n*=2; coronary spasms *n*=2; microvascular cardiac disease *n*=2; Takotsubo cardiomyopathy *n*=2; myocarditis *n*=1.
IQR: interquartile range; BMI: body mass index; SD: standard deviation; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease.

often men and frequently had a history of dyslipidemia, hypertension, chronic obstructive pulmonary disease (COPD) and chronic kidney disease (CKD) (Table 1). Cardiac complications occurred more frequently in patients admitted to a critical care unit (Supplementary Table 2). Arrhythmias and conduction disorders were the most common cardiac complications, occurring in 258 patients (8.6%) and most often concerned atrial fibrillation (*n*=142, 4.7%). Malignant ventricular rhythm disturbances were observed in 14 patients (0.5%). Other cardiac complications, including acute coronary syndrome, heart failure, endocarditis and pericarditis were diagnosed in 2% or fewer patients (Table 2). Endocarditis was of bacterial origin in all patients. All three patients diagnosed with COVID-19-related myocarditis had repolarisation abnormalities on ECG. One patient had severe left ventricular dysfunction (left ventricular ejection fraction (LVEF) 30%) with local wall motion abnormalities and raised levels of troponin, without chest pain. One patient underwent a magnetic resonance imaging (MRI) scan in an outpatient setting, confirming myocarditis with anteroseptal epicardial delayed enhancement. Next to these three patients, myocarditis was suspected in four additional patients but none fulfilled the diagnostic criteria.

Patients with pre-existing cardiac disease were overall more likely to develop cardiac complications during admission (Table 1), with 27.5% (*n*=11/40) and 30.9% (*n*=17/55) of patients diagnosed with cardiac ischaemia and heart failure, respectively, having a history of coronary artery disease or heart failure, suggestive of exacerbation of underlying disease.

Pulmonary embolism was reported in 198 cases (6.6%), with an incidence of 18.9% (*n*=158) in patients admitted to a critical care unit compared to 1.8% (*n*=40) in patients admitted to the general ward (Supplementary Table 2).

Among the 595 patients that died in hospital, the cause of death was of primary cardiac origin in 2.7% (*n*=16), with eight patients dying of heart failure, two of acute coronary syndrome, three of arrhythmia, two of endocarditis and one patient of COVID-19-related myocarditis. Twelve out of 16 patients in which the primary cause of death was deemed to be cardiac had an underlying pneumonia.

Discussion

To our knowledge, this is the largest cohort of patients with COVID-19 to date in which the occurrence of cardiac complications has been systematically recorded. The overall incidence of cardiac complications in this population is 11.6%, with atrial fibrillation being the most frequent complication.

Interestingly, only three patients were diagnosed with myocarditis during hospitalisation in this large study. Our

Table 2. Frequency of cardiac and other complications and cause of death.

	No.	% of total cohort (95% CI)[a] *n*=3011	% of patients with cardiac complications (95% CI)[a] *n*=349
Cardiac complications			
No cardiac complication	2662	88.4 (87.3–89.6)	–
Arrhythmia/conduction disorder	258	8.6 (7.6–9.6)	73.9 (69.3–78.5)
Supraventricular tachycardia	189	6.3 (5.4–7.1)	54.2 (48.9–59.4)
Atrial fibrillation	142	4.7 (4.0–5.5)	40.7 (35.5–45.8)
Atrial flutter	33	1.1 (0.7–1.5)	9.5 (6.4–12.5)
Ventricular arrhythmia	14	0.5 (0.2–0.7)	4.0 (2.0–6.1)
Conduction disorders[b]	37	1.2 (0.8–1.6)	10.6 (7.4–13.8)
AV-block grade 1	4	0.1 (0.0–0.3)	1.1 (0.03–2.3)
AV-block grade 2	1	0.03 (0.0–0.09)	0.3 (0.0–0.8)
AV-block grade 3	1	0.03 (0.0–0.09)	0.3 (0.0–0.8)
Left bundle branch block	4	0.1 (0.0–0.3)	1.1 (0.03–2.3)
Right bundle branch block	11	0.4 (0.1–0.6)	3.2 (1.3–5.0)
QTc prolongation	15	0.5 (0.2–0.7)	4.3 (2.2–6.4)
Sinus node dysfunction	10	0.3 (0.1–0.5)	2.9 (1.1–4.6)
Cardiac ischaemia[c]	40	1.3 (0.9–1.7)	11.5 (8.1–14.8)
Acute coronary syndrome	15	0.5 (0.2–0.7)	4.3 (2.2–6.4)
Type II ischemia	24	0.8 (0.5–1.1)	6.9 (4.2–9.5)
Bacterial endocarditis	4	0.1 (0.0–0.3)	1.1 (0.03–2.3)
Heart failure	55	1.8 (1.3–2.3)	15.8 (11.9–19.6)
De novo	38	1.3 (0.9–1.7)	10.9 (7.6–14.2)
Myocarditis	3	0.1 (0.0–0.2)	0.9 (0.0–1.8)
Pericarditis	1	0.03 (0.0–0.09)	0.3 (0.0–0.8)
Other[d]	21	0.7 (0.4–1.0)	6.0 (3.5–8.5)
Other complications			
Acute kidney injury	410	13.7 (12.4–14.8)	–
ARDS	751	25.1 (23.4–26.5)	–
Pulmonary embolism	198	6.6 (5.7–7.5)	–
Shock	128	4.3 (3.5–5.0)	–
Outcome			
Death	595	19.8 (18.3–21.2)	–
Cardiac[e]	16	0.5 (0.3–0.8)	–
Other	513	17.0 (15.7–18.4)	–
Unknown	66	2.2 (1.7–2.7)	–

AV: Atrioventricular; ARDS: Acute respiratory distress syndrome.
[a]Wald 95% confidence intervals (CIs) for proportions.
[b]For one patient conduction disorder not specified.
[c]For one patient, unknown whether acute coronary syndrome or type II ischaemia.
[d]In-hospital cardiac arrest *n*=5; repolarisation abnormalities *n*=5; Takotsubo cardiomyopathy *n*=3; cardiogenic shock *n*=2; pericardial effusion *n*=2; sudden death *n*=1; pacemaker implantation *n*=1, perforation of mitral valve leaflet *n*=1; pneumopericardium *n*=1.
[e]Heart failure *n*=8; acute coronary syndrome *n*=2; primary arrhythmia *n*=3; endocarditis *n*=2; myocarditis *n*=1.

findings suggest that the high frequency of raised troponin levels in previous studies[2–5] may predominantly reflect the occurrence of demand ischaemia and non-cardiac causes rather than acute myocardial infarction and myocarditis. In a meta-analysis of critically ill patients admitted to the ICU, involving trauma, surgical and sepsis patients among others, elevated troponin levels were found in a median of 43% of patients demonstrating the non-specific nature of this biomarker in severely ill patients.[19] An analysis of the frequency of raised troponin levels in our cohort on the subset of patients that did not develop cardiac complications was not possible, because troponins were only measured on clinical grounds. However, in the absence of corroborating evidence from electro and/or echocardiography caution should be exercised when interpreting troponin release as 'viral-related cardiac injury'. Intriguingly, one recent study by Puntmann et al. performing MRI in 100 recovered COVID-19 patients, found that 60% had signs of

myocardial inflammation 2–3 months after the diagnosis compared to a group of age and sex-matched healthy controls and risk-factor matched controls.[20] At the time of the MRI, 37 patients experienced atypical chest pain and/or palpitations. Only one-third of patients in this study had been hospitalised. Another study among 26 recovered patients that had all been hospitalised for COVID-19 showed myocardial oedema on MRI in 57% of patients.[21] The clinical implications of these findings remain to be explored in larger studies with longitudinal follow-up. Furthermore, it would be of value to compare patients with COVID-19 to patients that have experienced other viral infections to determine whether the high proportion of cardiac abnormalities on MRI is unique to SARS-CoV-2 or a more general feature of certain viral infections. For example, in a small study in 32 patients with H1N1 influenza and cardiac symptoms, 10 (31%) patients were positive for myocarditis on MRI.[22]

Pulmonary embolism appears to occur frequently in patients infected with SARS-CoV-2, diagnosed in 6.6% of patients and in 18.9% among the critically ill. An incidence of pulmonary embolism of 20.6% and 31.0% has also been described in two cohorts of COVID-19 patients admitted to the ICU.[23,24] One of these studies compared the incidence of pulmonary embolism during the same time interval in 2019 and found an absolute increased risk of 14.4% (20.6% vs. 6.1%).[23] Also, when compared to 40 patients with influenza, the incidence was significantly higher (20.6% vs. 7.5%). The authors of these studies hypothesise that the high prevalence of obesity and an inflammatory triggered hypercoagulability state may contribute to this increased incidence. To decrease the incidence of pulmonary embolism in patients with COVID-19, there is a clear need for randomised clinical trials assessing the optimal prophylactic antithrombotic treatment in these patients.

The most important limitation of our study is the absence of central adjudication of events. Although we tried to limit heterogeneity between sites by incorporating diagnostic criteria as outlined by the ESC for the various cardiac adverse events, it is still possible that not all patients fulfilled these criteria. As the diagnosis of myocarditis in particular can be challenging, centres reporting the occurrence of this complication were contacted to confirm these patients indeed fulfilled the diagnostic criteria as outlined by the ESC.[13] Another limitation of this study is that at the time of this analysis, all data collection had not yet been completed, including information on symptomatology, laboratory values and vitals at admission and data on cardiac biomarkers and echocardiography. CAPACITY-COVID is an ongoing registry and more detailed studies will be reported in due course.

In conclusion, this large study in 3011 hospitalised patients with confirmed COVID-19 shows that the overall incidence of serious cardiac complications is low, despite a frequent history of cardiovascular disease. Long-term cardiac outcomes and the role of different pre-existing cardiovascular diseases in COVID-19 outcome warrants further investigation.

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Conflict of interest

The author(s) declare that there is no conflict of interest.

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Supplementary material

Supplementary material for this article is available online.

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