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Clinical presentation, disease course, and outcome of COVID-19 in hospitalized patients with and without pre-existing cardiac disease: a cohort study across 18 countries

The CAPACITY-COVID Collaborative Consortium and LEOSS Study Group*

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See the editorial comment for this article 'Sharpening focus through wider collaboration: evolving heterogeneity in the bi-directional relationship between cardiovascular disease and COVID-19', by Amit Kaura *et al.*, https://doi.org/10.1093/eurheartj/ehab622.

Aims Patients with cardiac disease are considered high risk for poor outcomes following hospitalization with COVID-19. The primary aim of this study was to evaluate heterogeneity in associations between various heart disease subtypes and in-hospital mortality.

Methods and results We used data from the CAPACITY-COVID registry and LEOSS study. Multivariable Poisson regression models were fitted to assess the association between different types of pre-existing heart disease and in-hospital mortality. A total of 16 511 patients with COVID-19 were included (21.1% aged 66–75 years; 40.2% female) and 31.5% had a history of heart disease. Patients with heart disease were older, predominantly male, and often had other comorbid conditions when compared with those without. Mortality was higher in patients with cardiac disease (29.7%; $n = 1545$ vs. 15.9%; $n = 1797$). However, following multivariable adjustment, this difference was not significant [adjusted risk ratio (aRR) 1.08, 95% confidence interval (CI) 1.02–1.15; $P = 0.12$ (corrected for multiple testing)]. Associations with in-hospital mortality by heart disease subtypes differed considerably, with the strongest association for heart failure (aRR 1.19, 95% CI 1.10–1.30; $P < 0.018$) particularly for severe (New York Heart Association class III/IV) heart failure (aRR 1.41, 95% CI 1.20–1.64; $P < 0.018$). None of the other heart disease subtypes, including ischaemic heart disease, remained significant after multivariable adjustment. Serious cardiac complications were diagnosed in <1% of patients.

Conclusion Considerable heterogeneity exists in the strength of association between heart disease subtypes and in-hospital mortality. Of all patients with heart disease, those with heart failure are at greatest risk of death when hospitalized with COVID-19. Serious cardiac complications are rare during hospitalization.

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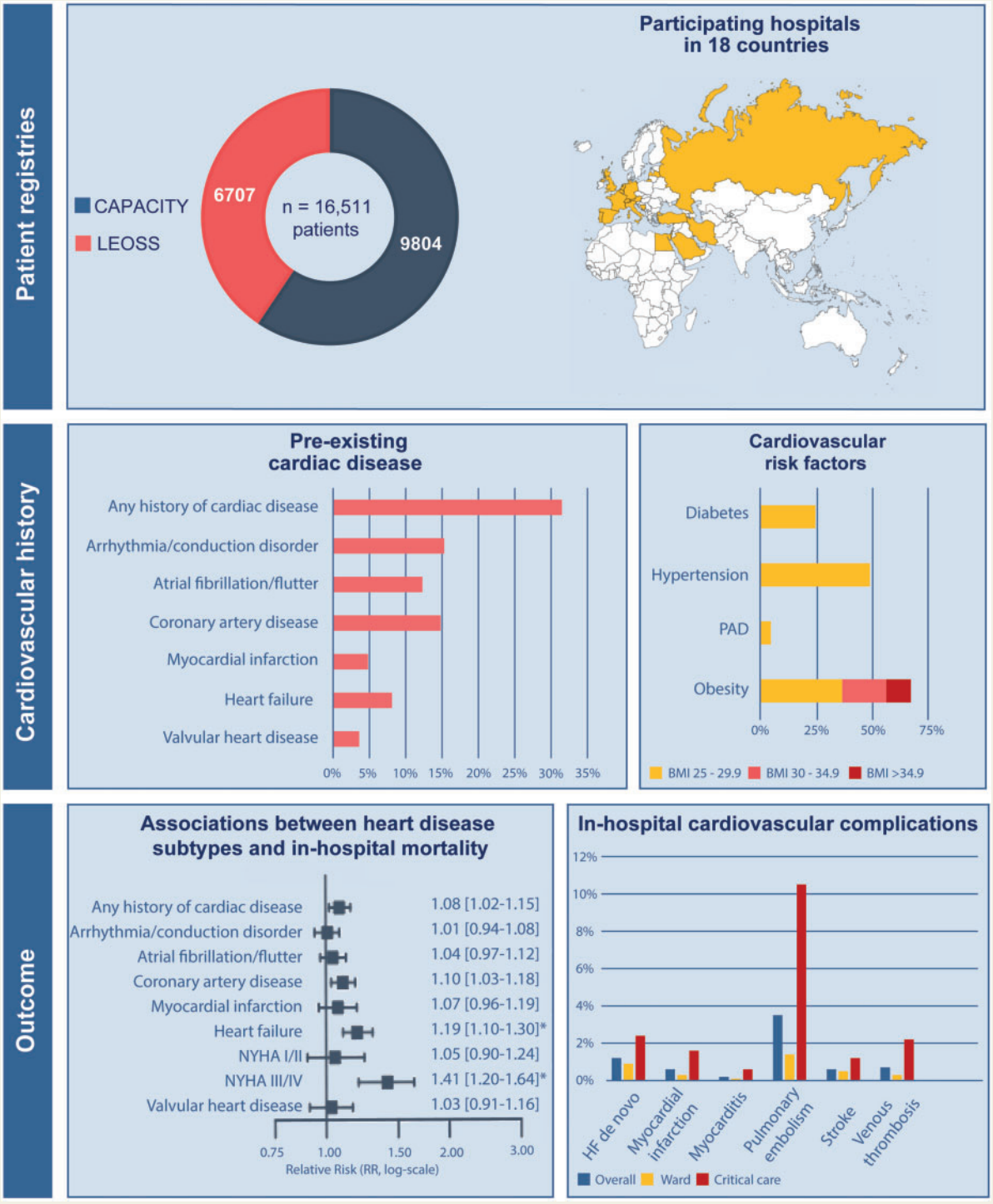
Graphical Abstract



After multivariable adjustment, the strongest association was found for heart failure and in-hospital mortality (aRR 1.19, 95% CI 1.10–1.30; $P < 0.018$ and in particular for severe (NYHA class III/IV) heart failure (aRR 1.41, 95% CI 1.20–1.64; $P < 0.018$). For the other heart disease subtypes, including ischaemic heart disease, no significant associations with in-hospital mortality were found after correction for multiple testing. BMI = body mass index; NYHA = New York Heart Association; PAD = peripheral arterial disease. *Significant after correcting for multiple testing.

Keywords COVID-19 • SARS-CoV-2 • Epidemiology • Patient registry • Comorbidity • Cardiovascular disease

Introduction

Coronavirus disease 2019 (COVID-19) has rapidly spread across the globe since December 2019, leading to >225 million confirmed cases and almost 4.7 million fatalities as of 19 September 2021.[1] Although the disease is not as lethal [case fatality ratio (CFR) ~0.3–1%][2,3] as the Middle-East respiratory syndrome (MERS; CFR ~35%)[4] and the severe acute respiratory syndrome (SARS; CFR 14–15%),[5] it has become clear that morbidity and mortality are much higher than in pandemic influenza (CFR 0.1%),[6,7] especially among the elderly[3].

Studies show that a significant number of patients who develop severe symptoms of COVID-19 have underlying comorbidities, of which cardiovascular disease (CVD) is reported in 10–30% of inpatients in Western European and American cohorts.[8–11] Patients with pre-existing cardiac disease have consistently been reported to be at increased risk of an unfavourable outcome both among the general population and in those requiring hospitalization when compared with patients without these conditions.[8,12] In one of the largest cohort studies of hospitalized patients thus far ($n = 20\,133$), chronic cardiac disease was significantly associated with mortality [adjusted hazard ratio (HR) 1.16, 95% confidence interval (CI) 1.08–1.24].[8] Another study by Fried *et al.* ($n = 11\,721$) across 38 states in the USA, found an adjusted odds ratio (aOR) of 1.22 (95% CI 1.06–1.41) and 1.44 (95% CI 1.27–1.63) for mechanical ventilation and death, respectively, related to cardiac disease.[11] The Chinese Center for Disease Control and Prevention reports a CFR five times higher among those with CVD compared with patients without any comorbidities.[13] These observations are in line with previous studies among patients with influenza and other respiratory tract infections.[14,15]

Previous studies have predominantly evaluated the association between having any chronic cardiac disease and COVID-19-related mortality, where all cardiac disease subtypes are analysed together.[8,11,12] However, from a clinical point of view, it is likely that not all cardiac diseases mediate a similar risk. Increasing our understanding of the clinical course of COVID-19 in patients across different heart disease subtypes is of pivotal importance. Firstly, it can provide guidance for healthcare professionals in the management of these patients and would better inform shielding guidelines. Secondly, it can bring some clarity for patients, concerned about how their own cardiac disease influences their risk from COVID-19.[16] Reducing these concerns might also have a positive impact on healthcare-seeking behaviour during the pandemic, diminishing the detrimental collateral damage the outbreak has provoked in patients with heart disease who are afraid of attending hospitals.[17]

The aim of the current study was to investigate whether there is heterogeneity in the strength of association per heart disease subtype and in-hospital mortality. Furthermore, we describe the disease trajectory of COVID-19 in hospitalized patients with and without pre-existing cardiac disease, from documentation at hospital admission to discharge or death, including the prevalence of cardiac complications.

Methods

Study design and setting

For this study we used data collected in the CAPACITY-COVID registry (www.capacity-covid.eu) and the Lean Open Survey on SARS-CoV-2-infected patients (LEOSS) study (www.LEOSS.net). Data collected within CAPACITY-COVID and LEOSS are available on request.

CAPACITY-COVID is a multinational patient registry specifically established to determine the role of CVD in the COVID-19 pandemic (NCT04325412).[18] All adult patients (≥18 years) hospitalized with confirmed or highly suspected COVID-19 are eligible for inclusion in the registry. The extent and scope of inclusion vary per site, depending on local resources and preference. The majority of participating centres ($n = 56$) use a non-selective inclusion, i.e. every adult patient with (highly suspected) COVID-19 or a random sample is included in the registry, and 18 centres apply a selective inclusion, including only patients for whom a cardiologist has been consulted, only patients with a history of CVD or cardiovascular risk factors, or a selection based on department of admission i.e. only patients admitted to the ward or intensive care unit (ICU). Since the launch of the registry in March 2020, 74 centres across 13 countries have joined the consortium.

Within CAPACITY-COVID, the ISARIC core case report form (CRF)[19] has been used as the core data set which was extended with ~400 additional variables to capture in-depth information regarding cardiovascular history, the use of cardiovascular medications, cardiac investigations such as ECG and echocardiography, and cardiovascular outcomes. The data dictionary is available online (www.capacity-covid.eu). Only data generated during routine clinical care are collected, and patients do not undergo any additional investigations for the purpose of this registry. Data are collected in a REDCap database after pseudonymization which is managed by the University Medical Center Utrecht, Utrecht, the Netherlands.

Variable definitions handled in CAPACITY-COVID are incorporated in the REDCap (CRF) and can be found online among the study documents at: https://capacity-covid.eu/for-professionals/. For the registration of cardiac complications, the diagnostic criteria of the European Society of Cardiology (ESC) guidelines for myocarditis,[20] pericarditis,[21] endocarditis,[22] and acute coronary syndrome[23] were incorporated to minimize heterogeneity in the adjudication of these events. 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.[24] In the absence of a definition, a clinical diagnosis as indicated in the electronic health record (EHR) was handled.

LEOSS is a European multicentre cohort study established in March 2020, collecting information on both hospitalized and ambulant patients with laboratory-confirmed COVID-19. A detailed description of the study design has been previously reported.[25] In short, patients of all ages can be included in LEOSS. Case collection is anonymized, realized by, among others, the absence of any variables containing directly identifying information in the CRF, only a small subset of variables associated with a high risk of re-identification, and the categorized collection of continuous variables (such as age).[26] The CRF of LEOSS can be provided upon request. Currently centres from Austria, Belgium, Bosnia and Herzegovina, Germany, Italy, Latvia Spain, Switzerland, Turkey, and the UK contribute data to the registry. The data collection is coordinated by the University Hospital of Cologne in Germany.

Study population

We excluded patients only treated in an ambulatory setting, children (age <18 years), and patients for which the region of inclusion, COVID-19 status, admission date, history of cardiac disease, age, or outcome were unconfirmed. All hospitalized patients aged ≥18 years with a laboratory-confirmed severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) infection registered between March 2020 and May 2021 were

included. A list of all participating sites that contributed with data to the current study is provided in Supplementary material online, *Table S1*. The informed consent procedure varied by study site, following local and national rules and regulations during the pandemic. Within CAPACITY-COVID, the majority of participating sites handled an opt-out approach, where patients received written information during or after hospital admission. For sites in the UK, informed consent was not required under emergency legislation during the pandemic. Inclusion in LEOSS did not require informed consent due to anonymous case collection. Medical ethics approval was obtained nationally or independently for each participating site complying with the Declaration of Helsinki.

Statistical analysis

Continuous variables in CAPACITY-COVID were categorized to align with LEOSS prior to merging the datasets from these two different sources. Multiple imputation (R package mice) was performed to deal with missing data across baseline variables required for the regression models through the generation of 10 imputed datasets. The following variables were included in the multiple imputation model: all variables indicated with an asterisk in *Tables* 1–3, together with the presence of pre-existing cardiac disease, arrhythmia/conduction disorder, heart failure, coronary artery disease (CAD), valvular heart disease, month and year of hospital admission, extent of inclusion (all/random sample vs. selected inclusion as described above), cohort (CAPACITY-COVID vs. LEOSS), and region of inclusion (Central Europe, Netherlands/Belgium, Middle East, Southern Europe, and the UK). Baseline variables with >40% missing values were excluded from further analysis.

For the main analyses, multivariable modified Poisson models with robust standard errors were used to estimate the association between a history of cardiac disease and in-hospital mortality across the 10 pooled imputed datasets. Heterogeneity in associations was also determined across various clinically relevant subgroups including age (≤65 and >65 years), sex, body mass index (BMI) (<30 and ≥30 kg/m^2), diabetes, hypertension, chronic kidney disease (CKD). and chronic obstructive pulmonary disease (COPD). In the secondary analyses, associations between pre-defined specific types of heart disease and in-hospital mortality were determined. The following heart disease subtypes were analysed: arrhythmias/conduction disorders, CAD, myocardial infarction (MI), heart failure, and valvular heart disease. To be able to determine differences in the association between the pre-defined cardiac disease subtypes and in-hospital mortality in adults vs. the elderly, analyses were also performed in patients ≤65 and >65 years. The cut-off was set at 65 since most COVID-19 vaccination strategies in Europe have defined the elderly as those >65 years of age.[27]

All analyses were adjusted for the following covariates: age, sex, BMI, diabetes, hypertension, CKD, COPD, and geographic region of inclusion (see above). For the sensitivity analyses, we excluded patients included by centres employing a selective inclusion strategy, as previously outlined. In addition, we assessed the direction and magnitude of the associations based on registry of inclusion (CAPACITY-COVID vs. LEOSS), next to fitting models in the dataset of the combined cohorts.

Logistic regression on the non-imputed dataset was used to determine associations between the most prevalent COVID-19 symptoms at presentation and eight different age categories in the total cohort, and after stratification on pre-existing cardiac disease. Due to low numbers of young patients with a history of cardiac disease, the four lowest age categories were merged in the stratified analyses (18–55 years).

Results of the modified Poisson regression models are reported as risk ratios (RRs) with 95% CIs and the logistic regression models as odds ratios (ORs) with 95% CIs. Statistical significance was set at an alpha of 5%, and all hypothesis tests were two-sided. The main regression analyses were corrected for multiple testing using the Holm–Bonferroni method. Continuous variables were summarized as means (SD) or medians [interquartile range (IQR)] and categorical variables as counts (%). All analyses were performed in R Studio (version 1.3.959, Vienna, Austria).

Results

Baseline characteristics

In total, 20 954 patients had been included in CAPACITY-COVID or LEOSS between March 2020 and May 2021. After applying exclusion criteria, 16 511 patients from 18 countries were retained for the final analysis (Supplementary material online, *Figure S1*). Baseline characteristics stratified by the presence of pre-existing cardiac disease and age (≤65 and >65 years) are summarized in *Table 1*.

Most patients were aged between 76 and 85 ($n = 3720$; 22.5%), and more than half the cohort was composed of individuals >65 years old ($n = 8861$; 53.6%). Most patients were white ($n = 12\ 20$; 84.5%), predominantly male ($n = 9864$; 59.8%), and 68.0% ($n = 7080$) had a BMI >25 kg/m^2. At baseline, almost a third of patients ($n = 5198$; 31.5%) had pre-existing heart disease, of which cardiac arrhythmias/conduction disorders ($n = 2503$; 15.3%) and CAD ($n = 2420$; 14.8%) were most common (Supplementary material online, *Table S2*). In total, 1314 patients (8.1%) had been previously diagnosed with heart failure. Other frequent major comorbidities were diabetes ($n = 4031$; 24.9%) and CKD ($n = 2196$; 13.5%).

Compared with patients without a history of cardiac disease, patients with pre-existing heart disease were generally older, more often male (63.6% vs. 58.1%), and had a higher burden of cardiovascular risk factors and other comorbid conditions at baseline (*Table 1*). Detailed phenotyping of underlying pre-existing cardiac diseases of patients registered in CAPACITY-COVID, including arrhythmias, conduction disorders, and type of ischaemic and valvular heart disease are outlined in Supplementary material online, *Table S3*. To evaluate heterogeneity across datasets, baseline characteristics were also stratified by the cohort of origin (CAPACITY-COVID vs. LEOSS; Supplementary material online, *Table S2*). Patients in LEOSS tended to be younger with an overall higher prevalence of heart disease.

Complaints at admission

The median duration from symptom onset to hospital admission was 6 days [IQR 2–9]. Fever, cough, and shortness of breath were the most common symptoms at presentation to the hospital, reported in 54.9, 51.8, and 49.8% of patients, respectively (*Table 2*). The odds of having these symptoms varied across age, with fever, cough, and dyspnoea being reported less frequently in the younger (<45 years) and older (>65 years) age groups (Supplementary material online, *Figure S2*). The probability of experiencing a sore throat, anosmia, and chest pain declined with age, while fatigue was reported more often with increasing age. Heterogeneity in complaints and vital signs at admission was also assessed by stratification by cohort of inclusion (CAPACITY-COVID vs. LEOSS; Supplementary material online, *Table S4*). Of symptoms overlapping with CVD, chest pain was most common, reported by 9.2% of patients. Fewer than 5% of patients experienced (pre-) syncope, palpitations, orthopnoea, or peripheral oedema (Supplementary material online, *Table S4*). After stratification by age, the pattern of complaints did not differ between patients

Table 1 Baseline characteristics of the total cohort, stratified by pre-existing cardiac disease and age

	Overall	No pre-existing cardiac disease		Pre-existing cardiac disease		*P*-value
		≤65 years	>65 years	≤65 years	>65 years	
Total	16 511	6651	4662	999	4199	
Age (years), *n* (%)*						<0.001
18–25	239 (1.4)	233 (3.5)	0 (0.0)	6 (0.6)	0 (0.0)	
26–35	704 (4.3)	682 (10.3)	0 (0.0)	22 (2.2)	0 (0.0)	
36–45	1128 (6.8)	1066 (16.0)	0 (0.0)	62 (6.2)	0 (0.0)	
46–55	2299 (13.9)	2054 (30.9)	0 (0.0)	245 (24.5)	0 (0.0)	
56–65	3280 (19.9)	2616 (39.3)	0 (0.0)	664 (66.5)	0 (0.0)	
66–75	3485 (21.1)	0 (0.0)	2175 (46.7)	0 (0.0)	1310 (31.2)	
76–85	3720 (22.5)	0 (0.0)	1816 (39.0)	0 (0.0)	1904 (45.3)	
>85	1656 (10.0)	0 (0.0)	671 (14.4)	0 (0.0)	985 (23.5)	
Female sex, *n* (%)*	6627 (40.2)	2587 (38.9)	2150 (46.2)	283 (28.4)	1607 (38.3)	<0.001
Ethnicity, *n* (%)*						<0.001
Arab	496 (3.5)	291 (5.3)	89 (2.2)	54 (6.2)	62 (1.6)	
Asian	898 (6.3)	544 (9.8)	165 (4.0)	82 (9.4)	107 (2.8)	
Black	384 (2.7)	266 (4.8)	67 (1.6)	27 (3.1)	24 (0.6)	
Latin-American	21 (0.1)	10 (0.2)	6 (0.1)	4 (0.5)	1 (0.0)	
White	12120 (84.5)	4154 (75.0)	3704 (90.1)	685 (78.5)	3577 (93.8)	
Other	416 (2.9)	272 (4.9)	79 (1.9)	21 (2.4)	44 (1.2)	
BMI (kg/m^2), *n* (%)*						<0.001
Underweight (<18.5)	239 (2.3)	42 (1.0)	118 (4.2)	16 (2.3)	63 (2.2)	
Normal weight (18.5–24.9)	3091 (29.7)	1024 (25.1)	1001 (35.6)	157 (22.2)	909 (32.5)	
Overweight (25.0–29.9)	3854 (37.0)	1518 (37.1)	991 (35.2)	262 (37.0)	1083 (38.7)	
Obese (30.0–34.9)	2069 (19.9)	915 (22.4)	470 (16.7)	154 (21.8)	530 (18.9)	
Morbidly obese (> 34.9)	1157 (11.1)	588 (14.4)	234 (8.3)	119 (16.8)	216 (7.7)	
Cardiovascular risk factors, *n* (%)						
Diabetes*	4031 (24.9)	1041 (15.9)	1210 (26.5)	339 (34.7)	1441 (34.9)	<0.001
Hypertension*	7975 (49.5)	1797 (27.6)	2567 (56.7)	602 (61.9)	3009 (73.1)	<0.001
Peripheral arterial disease*	654 (4.8)	54 (0.9)	165 (4.3)	48 (6.0)	387 (11.5)	<0.001
Comorbidities, *n* (%)						
Chronic kidney disease*	2196 (13.5)	260 (4.0)	626 (13.7)	152 (15.5)	1158 (28.0)	<0.001
COPD*	1563 (9.6)	226 (3.5)	541 (11.8)	117 (12.0)	679 (16.5)	<0.001
Use of cardiovascular drugs, *n* (%)						
ACE inhibitors*	3021 (18.8)	591 (9.2)	863 (19.1)	310 (31.9)	1257 (30.6)	<0.001
Aldosterone antagonist	563 (3.5)	44 (0.7)	86 (1.9)	72 (7.4)	361 (8.8)	<0.001
Antiplatelet	3044 (18.7)	274 (4.2)	859 (18.7)	417 (42.6)	1494 (36.2)	<0.001
Angiotensin receptor blocker*	2159 (13.5)	480 (7.5)	681 (15.1)	179 (18.5)	819 (20.1)	<0.001
Calcium channel blocker	2769 (17.0)	640 (9.7)	881 (19.2)	228 (23.3)	1020 (24.8)	<0.001
Diuretic	3338 (20.5)	425 (6.5)	860 (18.8)	261 (26.8)	1792 (43.5)	<0.001
Insulin	1204 (7.4)	286 (4.3)	334 (7.2)	138 (14.0)	446 (10.7)	<0.001
Lipid lowering*	4789 (30.5)	760 (12.1)	1372 (31.0)	514 (53.3)	2143 (53.0)	<0.001
Oral antidiabetic	2139 (13.0)	576 (8.7)	667 (14.3)	182 (18.2)	714 (17.0)	<0.001

*Variables included in the multiple imputation model.
ACE = angiotensin-converting enzyme; BMI = body mass index; COPD = chronic obstructive pulmonary disease.

with and without a history of cardiac disease (Supplementary material online, *Figure S3*).

Outcomes

The median duration of hospitalization was 9 [5–18] days (*Table 3*). More than one in four patients were admitted to a critical care unit (*n* = 3916; 27.6%) with a median length of stay of 12 [6–23] days. The proportion of patients admitted to a critical care unit increased with age until 75 years. Patients aged >75 years were predominantly treated on the ward (Supplementary material online, *Table S5*). Overall, the comorbidity burden among patients on a critical care unit was lower than for patients admitted to the ward only (Supplementary material online, *Table S5*). Patients that were

Table 2 Complaints, vitals, and laboratory values at admission stratified by pre-existing cardiac disease and age

	Overall	No pre-existing cardiac disease		Pre-existing cardiac disease		*P*-value
		≤65 years	>65 years	≤65 years	>65 years	
Total	16 511	6651	4662	999	4199	
Symptom onset to admission (days), median [IQR]	6 [2–9]	7 [3–10]	5 [1–9]	6 [3–9]	4 [1–8]	<0.001
Complaints at admission, *n* (%)						
Anosmia	723 (4.6)	463 (7.4)	129 (2.9)	51 (5.2)	80 (2.0)	<0.001
Cough	8158 (51.8)	3688 (58.6)	2095 (47.2)	535 (55.0)	1840 (45.6)	<0.001
Dyspnoea	7798 (49.8)	3238 (51.8)	2105 (47.7)	512 (52.8)	1943 (48.4)	<0.001
Fatigue	4214 (26.8)	1593 (25.3)	1275 (28.7)	277 (28.5)	1069 (26.5)	0.001
Fever	8638 (54.9)	3842 (61.0)	2327 (52.5)	563 (57.9)	1906 (47.2)	<0.001
Gastrointestinal symptoms	3030 (19.2)	1282 (20.4)	847 (19.1)	190 (19.5)	711 (17.6)	0.007
Palpitations	162 (1.0)	49 (0.8)	37 (0.8)	17 (1.7)	59 (1.5)	<0.001
Sore throat	1108 (7.0)	616 (9.8)	258 (5.8)	75 (7.7)	159 (3.9)	<0.001
Vitals at admission, *n* (%)						
Temperature (°C)*						<0.001
<35.1	72 (0.6)	13 (0.3)	27 (0.8)	4 (0.5)	28 (0.9)	
35.1–37.2	4898 (41.7)	1741 (37.5)	1427 (43.2)	307 (41.5)	1423 (46.6)	
37.3–37.9	2546 (21.7)	1028 (22.2)	686 (20.8)	162 (21.9)	670 (21.9)	
38.0–38.9	2920 (24.9)	1229 (26.5)	815 (24.7)	192 (26.0)	684 (22.4)	
39.0–39.9	1139 (9.7)	549 (11.8)	309 (9.4)	66 (8.9)	215 (7.0)	
>39.9	158 (1.3)	79 (1.7)	38 (1.2)	8 (1.1)	33 (1.1)	
Respiratory rate (breaths/min)						0.142
<16	1168 (10.8)	437 (10.4)	345 (11.3)	76 (11.1)	310 (10.9)	
16–21	4914 (45.4)	1919 (45.5)	1383 (45.3)	323 (47.2)	1289 (45.2)	
22–29	3219 (29.8)	1221 (28.9)	915 (30.0)	207 (30.2)	876 (30.7)	
>29	1512 (14.0)	644 (15.3)	410 (13.4)	79 (11.5)	379 (13.3)	
Heart rate (b.p.m.)						<0.001
<45	51 (0.4)	12 (0.3)	13 (0.4)	5 (0.7)	21 (0.7)	
45–59	293 (2.5)	64 (1.4)	87 (2.6)	14 (1.9)	128 (4.2)	
60–89	6037 (51.2)	2075 (44.6)	1836 (55.3)	384 (51.6)	1742 (56.8)	
90–119	4627 (39.3)	2177 (46.8)	1201 (36.2)	297 (39.9)	952 (31.0)	
>119	775 (6.6)	321 (6.9)	185 (5.6)	44 (5.9)	225 (7.3)	
Systolic blood pressure (mmHg)						<0.001
<80	79 (0.7)	15 (0.3)	30 (0.9)	7 (0.9)	27 (0.9)	
80–99	566 (4.8)	178 (3.8)	154 (4.6)	47 (6.3)	187 (6.1)	
100–119	2606 (22.1)	1094 (23.6)	644 (19.4)	183 (24.7)	685 (22.3)	
120–139	4291 (36.5)	1953 (42.1)	1092 (32.9)	264 (35.6)	982 (32.0)	
140–179	3827 (32.5)	1298 (28.0)	1246 (37.5)	229 (30.9)	1054 (34.3)	
>179	403 (3.4)	98 (2.1)	157 (4.7)	12 (1.6)	136 (4.4)	
Diastolic blood pressure (mmHg)						<0.001
<40	44 (0.4)	10 (0.2)	14 (0.4)	4 (0.5)	16 (0.5)	
40–59	1218 (10.4)	282 (6.1)	396 (11.9)	80 (10.8)	460 (15.0)	
60–89	8452 (71.9)	3421 (73.9)	2385 (71.9)	526 (70.9)	2120 (69.2)	
90–109	1823 (15.5)	843 (18.2)	455 (13.7)	119 (16.0)	406 (13.3)	
>109	216 (1.8)	73 (1.6)	69 (2.1)	13 (1.8)	61 (2.0)	
Oxygen saturation (%)*						<0.001
<60	67 (0.6)	28 (0.6)	18 (0.5)	5 (0.7)	16 (0.5)	
60–69	57 (0.5)	23 (0.5)	15 (0.5)	3 (0.4)	16 (0.5)	
70–79	206 (1.8)	70 (1.5)	67 (2.0)	15 (2.0)	54 (1.8)	
80–89	1313 (11.2)	409 (8.8)	444 (13.4)	79 (10.7)	381 (12.5)	
90–95	4768 (40.6)	1736 (37.5)	1429 (43.1)	296 (40.1)	1307 (42.8)	
96–100	5330 (45.4)	2362 (51.0)	1346 (40.6)	341 (46.1)	1281 (41.9)	

Continued

Table 2 *Continued*

	Overall	No pre-existing cardiac disease		Pre-existing cardiac disease		*P*-value
		≤65 years	>65 years	≤65 years	>65 years	
Laboratory values at admission, *n* (%)						
CRP (mg/L)*						<0.001
<3	540 (4.7)	296 (6.5)	114 (3.5)	36 (5.0)	94 (3.1)	
3–29	2664 (23.2)	1152 (25.5)	639 (19.8)	169 (23.5)	704 (23.5)	
30–69	2605 (22.7)	962 (21.3)	745 (23.1)	176 (24.5)	722 (24.1)	
70–119	2225 (19.4)	782 (17.3)	668 (20.7)	142 (19.7)	633 (21.1)	
120–179	1657 (14.4)	615 (13.6)	510 (15.8)	95 (13.2)	437 (14.6)	
180–249	965 (8.4)	371 (8.2)	301 (9.3)	54 (7.5)	239 (8.0)	
>249	812 (7.1)	346 (7.6)	250 (7.7)	47 (6.5)	169 (5.6)	
White blood cell count ($\times 10^9$/L)*						
<1.0	33 (0.3)	18 (0.4)	9 (0.3)	1 (0.1)	5 (0.2)	<0.001
1.0–3.9	1327 (11.5)	572 (12.5)	361 (11.2)	83 (11.3)	311 (10.5)	
4.0–7.9	6110 (53.0)	2478 (54.1)	1659 (51.4)	407 (55.2)	1566 (52.6)	
8.0–11.9	2773 (24.1)	1067 (23.3)	775 (24.0)	177 (24.0)	754 (25.3)	
12.0–15.9	935 (8.1)	333 (7.3)	315 (9.8)	52 (7.1)	235 (7.9)	
16.0–19.9	288 (2.5)	96 (2.1)	97 (3.0)	14 (1.9)	81 (2.7)	
>20	60 (0.5)	19 (0.4)	14 (0.4)	3 (0.4)	24 (0.8)	
Lymphocyte count ($\times 10^9$/L)*						<0.001
<0.1	70 (0.7)	24 (0.6)	22 (0.8)	7 (1.1)	17 (0.7)	
0.10–0.29	333 (3.5)	73 (2.0)	123 (4.4)	16 (2.6)	121 (4.8)	
0.30–0.49	931 (9.7)	241 (6.5)	324 (11.6)	31 (5.1)	335 (13.3)	
0.50–0.79	2447 (25.5)	794 (21.4)	786 (28.2)	153 (25.0)	714 (28.4)	
0.80–1.49	4175 (43.4)	1803 (48.7)	1119 (40.2)	273 (44.7)	980 (39.0)	
1.50–2.99	1480 (15.4)	688 (18.6)	366 (13.1)	126 (20.6)	300 (11.9)	
>3.0	176 (1.8)	80 (2.2)	47 (1.7)	5 (0.8)	44 (1.8)	
Haemoglobin (mmol/L)*						<0.001
<3.73	31 (0.3)	9 (0.2)	13 (0.4)	0 (0.0)	9 (0.3)	
3.73–4.90	180 (1.6)	64 (1.4)	44 (1.4)	11 (1.5)	61 (2.0)	
4.91–6.15	764 (6.6)	208 (4.5)	235 (7.3)	60 (8.1)	261 (8.7)	
6.16–7.39	2101 (18.2)	624 (13.6)	633 (19.6)	135 (18.3)	709 (23.6)	
7.4–9.25	6469 (56.0)	2656 (57.9)	1882 (58.3)	364 (49.4)	1567 (52.1)	
>9.25	2010 (17.4)	1025 (22.4)	419 (13.0)	167 (22.7)	399 (13.3)	
Platelets ($\times 10^9$/L)						<0.001
<10	25 (0.2)	10 (0.2)	10 (0.3)	0 (0.0)	5 (0.2)	
10–49	98 (0.9)	45 (1.0)	28 (0.9)	2 (0.3)	23 (0.8)	
50–119	931 (8.4)	273 (6.2)	269 (8.8)	51 (7.1)	338 (11.7)	
120–449	9681 (87.2)	3950 (89.2)	2649 (86.4)	638 (88.6)	2444 (84.9)	
450–799	350 (3.2)	146 (3.3)	110 (3.6)	29 (4.0)	65 (2.3)	
800–1199	11 (0.1)	5 (0.1)	1 (0.0)	0 (0.0)	5 (0.2)	

*Variables included in the multiple imputation model.
CRP = C-reactive protein; IQR = interquartile range.

admitted to a critical care unit tended to be more ill at admission based on vitals and laboratory values at hospital admission (Supplementary material online, *Table S6*). During hospital admission, 20.2% ($n = 3342$) of patients died. Mortality was strongly related to age, with a mortality of 0.8% ($n = 2$) in patients aged 18–25 years and 39.4% ($n = 652$) in patients aged >85 years (Supplementary material online, *Table S7*). Oxygen saturation levels were lower at admission in those who died, while the levels of inflammatory markers (C-reactive protein and total white blood cell count) were higher (Supplementary material online, *Table S8*). In patients with cardiac disease, 29.7% ($n = 1545$) died during admission vs. 15.9% ($n = 1797$) in patients without chronic heart disease (*Table 3*). In addition

Table 3 Outcome at discharge stratified by pre-existing cardiac disease and age

	Overall	No pre-existing cardiac disease		Pre-existing cardiac disease		*P*-value
		≤65 years	>65 years	≤65 years	>65 years	
Total	16 511	6651	4662	999	4199	
Admission						
Duration of hospitalization (days), median [IQR]	9 [5–18]	8 [4–17]	9 [5–18]	10 [5–19]	9 [5–17]	<0.001
Admission to a critical care unit, n (%)*	3916 (27.6)	1824 (32.6)	1056 (26.0)	300 (33.8)	736 (20.1)	<0.001
Duration of stay critical care unit (days), median [IQR]	12 [6–23]	13 [7–23]	12 [6–23]	11 [5–22]	12 [5–23]	0.248
Treatment, *n* (%)						
Invasive ventilation	2680 (16.2)	1262 (19.0)	729 (15.6)	211 (21.1)	478 (11.4)	<0.001
Non-invasive ventilation	1818 (11.1)	855 (13.0)	484 (10.4)	152 (15.4)	327 (7.8)	<0.001
ECMO	316 (1.9)	232 (3.5)	50 (1.1)	19 (1.9)	15 (0.4)	<0.001
Complications, *n* (%)						
Cardiac						
Myocarditis	37 (0.2)	19 (0.3)	9 (0.2)	2 (0.2)	7 (0.2)	0.575
Myocardial infarction	95 (0.6)	13 (0.2)	27 (0.6)	12 (1.2)	43 (1.0)	<0.001
Heart failure *de novo*	197 (1.2)	48 (0.7)	53 (1.1)	10 (1.0)	86 (2.0)	<0.001
Thrombo-embolic						
Pulmonary embolism	569 (3.5)	258 (3.9)	192 (4.1)	36 (3.6)	83 (2.0)	<0.001
Stroke	106 (0.6)	21 (0.3)	38 (0.8)	5 (0.5)	42 (1.0)	<0.001
Venous thrombosis	121 (0.7)	63 (1.0)	35 (0.8)	3 (0.3)	20 (0.5)	0.014
Outcome, *n* (%)						
Deceased*	3342 (20.2)	507 (7.6)	1290 (27.7)	133 (13.3)	1412 (33.6)	<0.001

*Variables included in the multiple imputation model.
ECMO = extracorporeal membrane oxygenation; IQR = interquartile range.

to heart disease, other comorbidities were also more prevalent in patients that died in hospital (Supplementary material online, *Table S7*).

Cardiac and thrombo-embolic complications

During hospitalization, serious cardiac complications including myocarditis, MI, and new-onset heart failure were diagnosed in 0.2% ($n = 37$), 0.6% ($n = 95$), and 1.2% ($n = 197$) of patients, respectively (*Table 3*). Other serious cardiac complications registered only in CAPACITY-COVID, including malignant ventricular arrhythmias, endocarditis, and pericarditis, were also uncommonly diagnosed (<1% of patients; Supplementary material online, *Table S9*). MI and new-onset heart failure were diagnosed more frequently in patients with pre-existing cardiac disease compared with those without (*Table 3*). Among thrombo-embolic complications, pulmonary embolism was most prevalent, being diagnosed in 3.5% ($n = 569$) of patients (*Table 3*). All complications occurred more often in patients admitted to a critical care unit and in patients that died in hospital (Supplementary material online, *Tables S10* and *S11*), with the difference being most pronounced for pulmonary embolism, which was diagnosed in 10.5% ($n = 405$) of the critically ill vs. 1.4% ($n = 144$) among patients only admitted to the ward. Venous thrombo-embolic complications were diagnosed less frequently among patients with a history of heart disease (*Table 3*).

Association between prior history of cardiac disease and in-hospital mortality

The multivariable modified Poisson regression model fitted in the total population yielded a non-statistically significant association between any pre-existing cardiac disease and in-hospital mortality (aRR 1.08, 95% CI 1.02–1.15, $P = 0.12$) (*Figure 1*). This association was further explored across different clinically relevant subgroups (Supplementary material online, *Table S12*). Apart from age and sex, displaying a trend towards an interaction with prior heart disease ($P = 0.10$ and $P = 0.09$, respectively), the subgroup analyses did not reveal any other interactions. Furthermore, sensitivity analyses by the exclusion of patients included from centres that handled a selective inclusion ($n = 707$) did not yield any different results (Supplementary material online, *Table S13*).

Association between different pre-existing cardiac comorbidities and in-hospital mortality

To assess heterogeneity in the associations between different types of heart disease and in-hospital mortality, modified Poisson regression models were fitted for all pre-specified cardiac disease subgroups. After multivariable adjustment, the strongest association was found for heart failure and in-hospital mortality (aRR 1.19, 95% CI 1.10–1.30; $P < 0.018$) and in particular for severe (NYHA class III/IV)

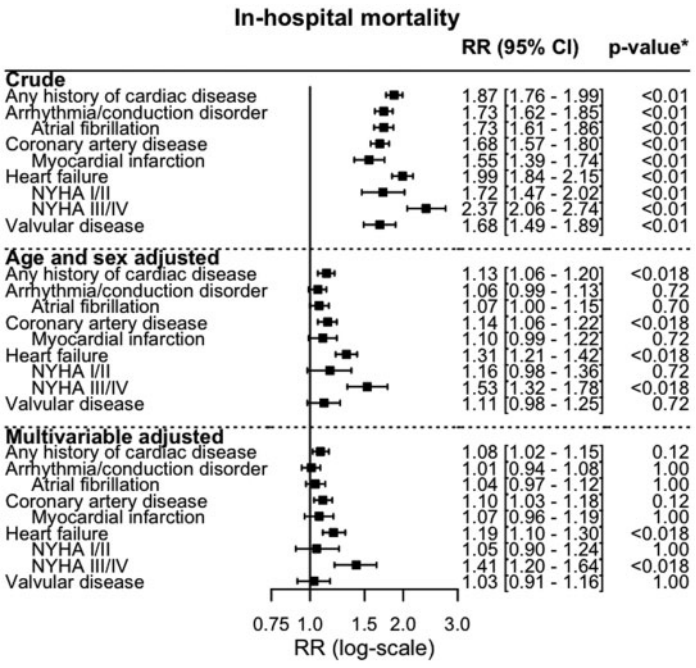


Figure 1 Associations (crude: top; age- and sex-adjusted: centre; multivariable adjusted: bottom) between any history of cardiac disease, heart disease subtypes, and in-hospital mortality. *P*-values are adjusted for multiple testing.

heart failure (aRR 1.41, 95% CI 1.20–1.64; $P < 0.018$) (*Figure 1*). For the other heart disease subtypes, including ischaemic heart disease, no significant associations with in-hospital mortality were found after correction for multiple testing (*Figure 1*; Supplementary material online, *Table S14*).

Since the elderly (>65 years) and adults with comorbidities are defined as two of the main risk groups being prioritized in ongoing vaccination campaigns and statistical interaction was established between pre-existing cardiac disease and age, associations between the various heart disease subtypes and in-hospital mortality were also determined in patients ≤65 years and >65 years old (*Figure 2*). However, for none of the heart disease subtypes was the interaction with age found to be significant. As heterogeneity in treatment intensity may impact the associations between pre-existing heart disease and in-hospital mortality, we also performed a separate analysis in patients admitted only to the wards vs. patients that had been admitted to a critical care unit. A strong interaction was found between having any history of cardiac disease, arrhythmia/conduction disorders, valvular heart disease, and admission to a critical care unit (Supplementary material online, *Table S15*). The adjusted RRs between these pre-existing heart conditions and in-hospital mortality overall were lower in patients that had been admitted to a critical care unit when compared with patients only admitted to the ward.

Discussion

A large proportion of patients developing severe COVID-19 requiring hospitalization have underlying CVD. The aim of this study was to describe and compare the disease course and outcomes in hospitalized COVID-19 patients with and without pre-existing cardiac disease. The most important findings of this work are: (i) the symptoms of COVID-19 at presentation are age dependent and do not differ in individuals with and without prior cardiac disease; (ii) serious cardiac complications are diagnosed infrequently during hospitalization and are seen more often in patients with known cardiac disease at baseline; and (iii) the association between prior heart disease and in-hospital mortality varies across heart disease subtypes, where (iv) heart failure associates most strongly with in-hospital mortality, and (v) there was no significant association with ischaemic heart disease (*Graphical Abstract*).

In line with others,[28] we found that COVID-19 symptoms at admission vary mainly with age, with no evidence that prior cardiac disease influences this relationship or the symptoms. Typical symptoms of COVID-19, including fever, cough, and shortness of breath, were reported less often in the elderly. Overall complaints mimicking cardiac disease, such as chest pain, palpitations, and orthopnoea, were reported by only a minority of patients (<10%). In this regard, it is interesting that cardiac-like symptoms such as chest pain and palpitations have been reported by 17–44% and 20–32% of patients in the 2–3 months after the active infection as part of the so-called 'long COVID' syndrome.[29–32] Whether these complaints are related to cardiovascular involvement in the convalescent phase of the disease or should predominantly be viewed as an epiphenomenon remains unclear.

According to our study, serious cardiac complications are rarely diagnosed during hospitalization with COVID-19, with a prevalence of <2% of patients. To aid the interpretation of these numbers, it is of

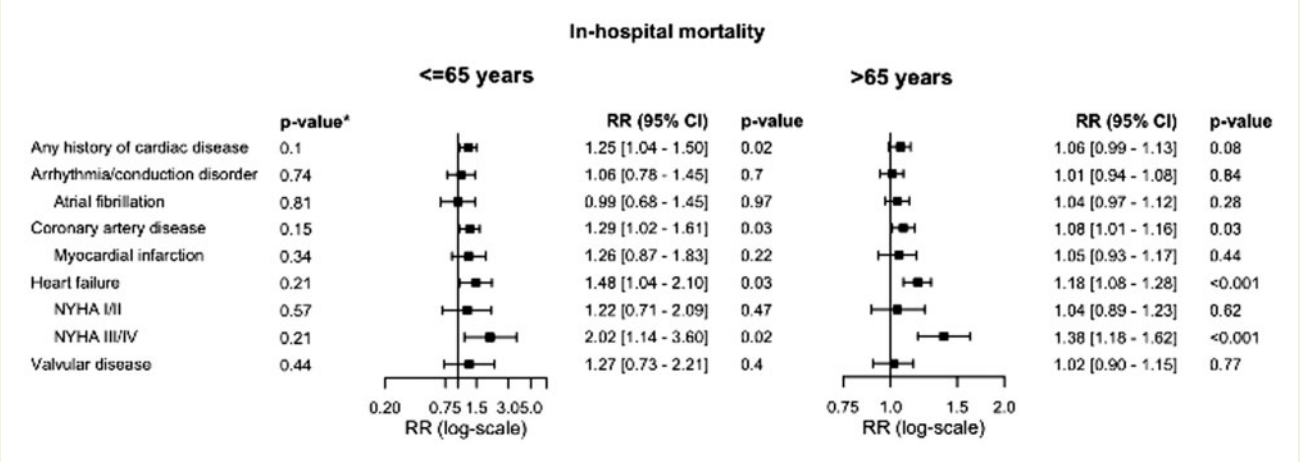


Figure 2 Multivariable adjusted associations between any history of cardiac disease, heart disease subtypes, and in-hospital mortality in patients aged ≤65 (left) and >65 years (right). **P*-value of the interaction of heart disease subtype and age. Patients with prior myocardial infarction are included in the coronary artery disease group. *P*-values are not adjusted for multiple testing.

interest to relate them to the occurrence of cardiac complications in patients hospitalized for other (viral) infectious diseases. A recent large French retrospective cohort study found that the prevalence of MI and atrial fibrillation was lower in patients with COVID-19 than in those with seasonal influenza, with a prevalence of 0.6% vs. 1.1% and 12.4% vs. 15.8%, respectively.[7] Unfortunately, this study did not report the prevalence of any other cardiac complications, including heart failure and myocarditis. As cardiomyocytes express angiotensin-converting enzyme 2 (ACE2),[33,34] the docking receptor of SARS-CoV-2, it has been speculated that SARS-CoV-2 may infect cardiomyocytes, replicate in cardiac tissue, and thereby induce direct myocardial damage. These concerns have also been triggered by the finding that raised levels of troponin above test-specific upper limits are found in up to a third of patients at hospital admission.[35,36] Histopathological studies of myocardial tissue in the setting of COVID-19 have been scarce up to this point. A literature review evaluating findings of 22 studies across 277 post-mortem examinations found evidence for myocarditis in <2%.[37] This finding contrasts with the results of a number of cardiac magnetic resonance (CMR) studies evaluating tissue characteristics and function 2–3 months after an established SARS-CoV-2 infection.[32,38–40] In the largest study by Kotecha *et al.*, among 148 patients that had a troponin elevation during hospitalization, non-ischaemic myocarditis-like late gadolinium enhancement was found in 26% of patients, with a third showing signs of active myocarditis.[39] These findings were not associated with left ventricular dysfunction. In CMR studies conducted predominantly among clinically recovered mildly symptomatic or asymptomatic cases, up to 60% were described to have raised native T2 times, which the authors suggested might be due to ongoing myocardial inflammation.[32,40] Whether these CMR findings are unique to patients that have been infected with SARS-CoV-2, or also are seen in other (viral) infectious diseases, has been poorly investigated. Evidence of a clear causal relationship between SARS-CoV-2 and myocarditis thereby remains elusive. It can be speculated that most patients may have troponin elevations secondary to profound hypoxia and a supply/demand imbalance rather than direct damage due to viral invasion in cardiac tissue.[36] However, the discrepancy in the limited number of patients diagnosed with cardiac complications during hospitalization and the significant proportion of patients with abnormal findings in imaging studies is a concern and warrants further investigation. Cardiac complications may have been missed, due to the overlapping symptomatology with COVID-19, and there might have been a limited access to and/or performance of cardiac diagnostic testing.

In contrast to cardiac complications, which in our study were rarely diagnosed during hospitalization, venous thrombosis and thromboembolism are common features of COVID-19, with a prevalence 3–4 times higher when compared with seasonal influenza.[7] Thrombo-embolic events are especially common in patients admitted to the ICU, with pulmonary embolism being diagnosed >5 times as often (10.5% vs. 1.4%) in our cohort compared with patients treated on the ward only. The prevalence of pulmonary embolism in the ICU population in our study is lower than in studies based on data originating from patients hospitalized in the first months of the pandemic, that reported a prevalence of up to 20.6%.[41,42] This discrepancy most probably reflects the implementation of enhanced antithrombotic prophylactic strategies in patients admitted with COVID-19 during 2020 and 2021.[43,44] Interestingly, we observed that thrombo-embolic complications were less common among patients with known cardiac disease. This observation is possibly related to pre-admission use of anticoagulants for the treatment of pre-existing cardiac conditions. This will be explored in ongoing analyses.

Among different heart disease subtypes, heart failure and in particular severe heart failure (NYHA class III/IV) was most strongly associated with in-hospital mortality in this study across the spectrum of different heart disease subtypes. Others have also identified patients with heart failure as one of the groups at particular risk.[45,46] Among 6439 hospitalized patients, in-hospital mortality was significantly higher among patients with a history of heart failure (aOR 1.88, 95% CI 1.27–2.78).[45] Similar findings were reported by Tomasoni

et al. ($n = 692$) with a crude HR of 2.43 (95% CI 1.69–3.50) for heart failure remaining significant after adjustment for age, sex, various comorbidities and vitals, and laboratory values at admission (adjusted HR 2.25, 95% CI 1.26–4.02).[46] Whether the absolute risk of being hospitalized in the presence of heart failure is also increased was recently investigated in a population-based study, which found an aOR of 4.43 (95% CI 2.59–8.04; $P < 0.001$).[47] Besides age and male sex, heart failure had the strongest association with in-hospital mortality among various different comorbidities in this study.

Importantly, besides heart failure, none of the other types of heart disease was associated with in-hospital mortality after adjustment for age, sex, BMI, diabetes, hypertension, CKD, and COPD. This heterogeneity was also evident in the population-based study by Petrilli et al. in which patients with CAD did not seem to be at increased risk of hospitalization due to COVID-19 (aOR 1.08, 95% CI 0.81–1.44; $P = 0.60$).[47] It could therefore be questioned whether all patients with heart disease should be defined as a group at risk, certainly when viewed in the context of other demographic factors such as age and sex, as these appear to contribute to COVID-19 outcome to a much larger extent than pre-existing cardiac disease.[12] This finding is of relevance for clinicians in countries with low vaccination rates and limited critical care capacity, that sometimes are forced to employ strict prioritization of the initiation and continuation of critical care treatment during this pandemic. Based on the results of this study, a history of cardiac disease, besides severe heart failure, should by itself presumably not be a reason to refrain from critical care treatment.

As heart failure is primarily a disease of the elderly, with a steep increase in the prevalence as well as severity beyond the age of 75 years,[48,49] a majority of heart failure patients are among the first to have been vaccinated according to current vaccine strategies across Europe.[27] Adults with comorbidities are identified as an additional priority group, but current advice lacks detail on which comorbidities should be considered high risk. Therefore, we also determined the strength per heart disease subtype and in-hospital mortality in patients <65 years. Due to the lower comorbidity burden in this group, we hypothesized that the associations for the different types of heart disease would be higher in this patient population. However, due to the limited prevalence of heart disease in those aged <65 years, we lacked sufficient power to draw any strong conclusions based on this analysis.

Limitations

Our study determines associations on a population level (e.g. all patients with heart failure) rather than individual risks, and is limited to patients with COVID-19 that were hospitalized. In some countries that provided data, hospitalization and potentially life-sustaining treatments, such as mechanical ventilation, might have been withheld in those with high frailty, including those with severe heart failure, which may have led to an overestimation of the associations found. Conversely, in younger patients treated more intensively, the associations of pre-existing cardiac disease with in-hospital mortality may be underestimated. This heterogeneity may have an impact on the associations found. Furthermore, we could not reliably investigate associations between heart disease subtypes and HDU/ICU admission since we observed that patients admitted to a critical care unit were overall younger with fewer comorbidities. Since age in particular is well known to be associated with a more severe COVID-19 disease course, this difference in baseline characteristics in those admitted to HDU/ICU is suggestive of an underlying selection of patients admitted to a critical care department. The mechanisms behind this selection are likely to be complex, influenced by, amongst others, the variability in critical care bed numbers across participating countries and available staff that may have led to demand for life-saving resources (nearly) exceeding supply, patient preference, as well as cultural differences in clinical decision-making. A further study limitation is that we only examined the impact of pre-existing cardiac disease on in-hospital mortality, which excludes the many deaths that have occurred in community settings and nursing homes. Moreover, there was no central adjudication of events in either of the two registries. Finally, echocardiographic data, providing more in-depth insight into heart failure aetiology at baseline as well as the degree of systolic and diastolic dysfunction prior to hospitalization, are lacking.

Future perspectives

With the availability of several effective vaccines for COVID-19, there is hope of starting the containment of COVID-19 during 2021. During the first year of the pandemic, the scientific community has improved the understanding of this new disease considerably, including its effects on the cardiovascular system. However, many aspects are still unknown. Evidence for a strong causal relationship between SARS-CoV-2 and myocarditis is still lacking. The discrepancy between the low prevalence of clinically diagnosed cardiac complications among the most ill requiring hospitalization and the large proportion of only mildly or even asymptomatic patients with abnormal findings on CMR after the acute phase of the disease has ceased warrant further investigation to understand their specificity and significance. In addition, studies on the long-term incidence of major adverse cardiac events are required. Future studies should also evaluate the added value of different pre-existing heart disease subtypes, especially heart failure, in prognostic models.

Conclusion

In this large retrospective cohort study across 18 countries, more than one in three patients hospitalized with COVID-19 had underlying chronic cardiac disease. Patients with a history of heart disease were older, more frequently male, and had a higher burden of other comorbid conditions at baseline. Inherently, patients with a history of heart disease have a poorer outcome once hospitalized with COVID-19. However, after multivariable adjustment and correction for multiple testing, we did not find a significant association between chronic heart disease and in-hospital mortality. When evaluating the associations between specific heart disease subtypes and in-hospital mortality, considerable heterogeneity was detected. Of all patients with heart disease, those with heart failure are at greatest risk of death when hospitalized with COVID-19. None of the other heart disease subtypes investigated was significantly associated with in-hospital mortality. Furthermore, besides pulmonary embolism, serious cardiovascular complications are rarely diagnosed during hospital admission.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Appendix

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