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ORIGINAL RESEARCH ARTICLE

Heart failure in COVID-19: the multicentre, multinational PCHF-COVICAV registry

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Abstract

Aims We assessed the outcome of hospitalized coronavirus disease 2019 (COVID-19) patients with heart failure (HF) compared with patients with other cardiovascular disease and/or risk factors (arterial hypertension, diabetes, or dyslipidaemia). We further wanted to determine the incidence of HF events and its consequences in these patient populations.

Methods and results International retrospective Postgraduate Course in Heart Failure registry for patients hospitalized with COVID-19 and CArdioVascular disease and/or risk factors (arterial hypertension, diabetes, or dyslipidaemia) was performed in 28 centres from 15 countries (PCHF-COVICAV). The primary endpoint was in-hospital mortality. Of 1974 patients hospitalized with COVID-19, 1282 had cardiovascular disease and/or risk factors (median age: 72 [interquartile range: 62–81] years, 58% male), with HF being present in 256 [20%] patients. Overall in-hospital mortality was 25% (n = 323/1282 deaths). In-hospital

mortality was higher in patients with a history of HF (36%, *n* = 92) compared with non-HF patients (23%, *n* = 231, odds ratio [OR] 1.93 [95% confidence interval: 1.44–2.59], $P < 0.001$). After adjusting, HF remained associated with in-hospital mortality (OR 1.45 [95% confidence interval: 1.01–2.06], $P = 0.041$). Importantly, 186 of 1282 [15%] patients had an acute HF event during hospitalization (76 [40%] with de novo HF), which was associated with higher in-hospital mortality (89 [48%] vs. 220 [23%]) than in patients without HF event (OR 3.10 [2.24–4.29], $P < 0.001$).

Conclusions Hospitalized COVID-19 patients with HF are at increased risk for in-hospital death. In-hospital worsening of HF or acute HF de novo are common and associated with a further increase in in-hospital mortality.

Keywords COVID-19; SARS-CoV2; Heart failure; Cardiovascular disease; Risk factors

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Introduction

Coronavirus disease 2019 (COVID-19) became an unprecedented global challenge affecting all fields of medicine. Although initially seen as a viral disease affecting primarily the lungs, it has been hypothesized that other organ systems are affected as well.[1] Systemic hyperinflammation after initial viral pneumonia and/or direct viral infection play an important role in the development of the systemic manifestations of COVID-19.[2] Because the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) infects its host through angiotensin-converting enzyme (ACE) 2 receptors, which are also localized on the endothelium, subsequent endothelial dysfunction and generalized endotheliitis may lead to further pathophysiological cascade.[2] Patients with a history of cardiovascular (CV) disease, heart failure (HF), and/or CV risk factors seem to be at higher risk for COVID-19 and an unfavourable clinical course once infected.[3–6] A possible explanation might be the pre-existing endothelial dysfunction.[5] Various cardiac manifestations during COVID-19 have been reported, and biomarkers of cardiac damage are increased in 5–25% of hospitalized COVID-19 patients.[7] Studies have demonstrated an increased mortality in patients with concomitant CV disease. A large retrospective cohort study in US veterans tested positive for SARS-CoV-2 in the ambulatory setting reported that patients with COVID-19 and previously diagnosed HF had a higher risk of hospital admissions and 30 day mortality.[8] An impaired prognosis can be expected in patients requiring hospitalization with COVID-19 diagnosis. Single-centre and nationwide cohort studies showed that COVID-19 affected referral and hospitalizations of patients with acute HF and that HF was associated with high mortality.[9–18] Yet, the impact of COVID-19 on HF patients and vice versa the relevance of HF events during COVID-19 in a multicentre international cohort is unknown.[19,20] Therefore, the Postgraduate Course in Heart Failure (PCHF) group built an international multicentre registry for hospitalized COVID-19 patients with CV diseases and/or risk factors (CVDRF). The aim of the study was to assess the outcome of patients with a history of HF compared with patients without a history of HF in this CVDRF population. The second aim was to study the incidence of HF events and its consequences.

Methods

Ethics

The study was approved by the Ethics Committee of Zurich, Switzerland (BASEC-Nr. 2020-00853) and registered in the ClinicalTrials.gov database as The Global PCHF-COVICAV Registry (PCHF-COVICAV), Identifier NCT04390555. For the leading investigating centre in Switzerland, informed consent was given by all patients but waived for patients who died before consent could be retrieved. Further details on ethics/informed consent per contributing country are listed in the supplements.

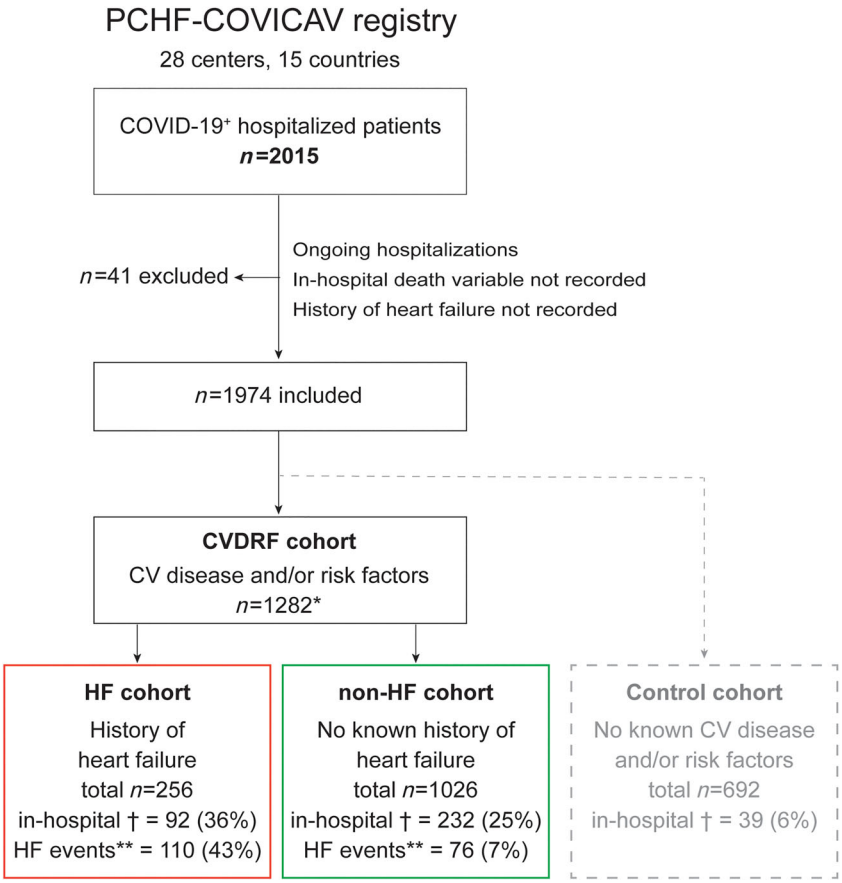
Study population

This multicentre, international retrospective cohort study included adult hospitalized patients (≥18 years old) with laboratory confirmed COVID-19 defined as positive result by polymerase chain reaction testing of a nasopharyngeal sample or a positive blood antigen test. Exclusion criteria for the registry were (i) age less than 18 years at hospitalization and (ii) outpatients. The following cohorts were defined (*Figure 1*).

Cardiovascular disease and/or risk factor cohort

Subjects with pre-existing CV disease and/or cardiac manifestations of COVID-19 (HF, acute coronary syndrome, myocarditis, arrhythmias, pulmonary embolism, and sudden cardiac arrest) and/or one of the following CV risk factors: arterial hypertension, diabetes, or dyslipidaemia, were extensively

Figure 1 Flow chart with inclusion and exclusion of patients in the multicentre registry. *Patients with a history of cardiovascular disease, cardiovascular manifestation during hospitalization for COVID-19, arterial hypertension, diabetes, or dyslipidaemia. **Patients with an HF event at admission or during hospitalization for COVID-19. CV, cardiovascular; CVDRF, cardiovascular disease and/or risk factors; HF, heart failure; PCHF-COVICAV, Postgraduate Course for Heart Failure registry for COronaVirus-19 patients with CArdioVascular disease and/or risk factors.



characterized as the main population for the study. We defined two subgroups:

i HF subgroup: patients with a history of HF according to the European Society of Cardiology guidelines, including HF with preserved ejection fraction (HFpEF), HF with mid-range ejection fraction (HFmrEF), or HF with reduced ejection fraction (HFrEF).[21]
ii Non-HF subgroup: patients with CVDRF, but without a history of HF.

Inpatients with COVID-19, not meeting CVDRF criteria, served as a separate control cohort. For these patients, only the following variables were recorded: age, sex, intensive care unit (ICU) hospitalization (binary yes/no), and in-hospital death.

Dataset

Patients were included from the beginning of the COVID-19 pandemic (early 2020) until data transfer deadline (20th of May 2020, = first wave). Patients that were still hospitalized after the data transfer deadline (20th of May 2020) or without available information on the primary endpoint or on HF status (history of HF) (study primary focus) were excluded from the data analysis (Supporting Information, *Table S1*).

Study procedures

The demographic (age, gender, and race), clinical (medical history, current medication at admission, cardiac manifestations of COVID-19 at admission, signs and symptoms at admission, and physical examination at admission), laboratory, chest X-ray and/or computed tomography, electrocardiography, echocardiography, in-hospital clinical course, and complications of COVID-19 data were extracted from electronic medical records using a standardized data collection form. Definitions of measured variables, calculated variables, and causes of death categories are shown in Supporting

Information, Methods and Supporting Information, *Table S2*. More than one cause of death could be entered by the researchers.

Data pooling and standardization

Data were collected from 28 university or large regional centres in 15 countries. All investigators were affiliated with the PCHF, an international advanced HF training programme initiated by the Heart Failure Association of the European Society of Cardiology, the European Heart Academy, and the University of Zurich. Patient inclusion was limited by COVID-19 rate and local regulations to COVID-19 triage. Whenever centres provided a selection of eligible patients, we tried to obtain consecutive patients.

Data cleaning, quality check, and validation

Definitions of clinical manifestations may vary between countries and centres. We developed a standardized data collection form, accompanied by a dictionary, which were used by all participating centres to reduce heterogeneity (Supporting Information, *Table S2*). The pseudonymized forms (secured keys are stored by the local centres) were collected by the core working group, merged into one general database, and a general identifier per patient was created.

Data quality of all variables was checked. For categorical variables, numbers not identifying any of the predefined categories were excluded. For continuous variables, time variables (expressed in number of days): negative values (<0 days) and values >365 days, were excluded. For laboratory data, units were recalculated to the units presented in the manuscript for centres where other lab units are used.

Data quality for continuous values was further checked by systematic evaluation of mean, median, minimum, maximum, and range of values for every centre and compared with the overall values. We identified outliers and implausible values, and if necessary, we queried contributors to resolve any issues encountered.

Laboratory measurements

The following laboratory parameters were collected: haemoglobin, leukocytes (lymphocytes and neutrophils), platelets, plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP), high-sensitivity cardiac troponin T or I, C-reactive protein (CRP), procalcitonin, arterial blood gases (pCO_2, lactate), aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, creatinine for calculation of eGFR, serum sodium and potassium, D-dimers, and international normalized ratio (INR).

Endpoints

The primary endpoint was in-hospital death. Because the mortality rates due to COVID-19 are known to vary across countries,[22] the individual data points per country are shown in Supporting Information, *Table S3*. The secondary endpoints were intensive care hospitalization and length of stay, the duration of hospitalization, and the need for and duration of non-invasive mechanical ventilation.

Statistical analysis

Categorical variables are presented as *n* (%). Continuous variables are described by medians with lower and upper quartiles. Available data are shown in *Tables 1* and *2* as *n* (%) for all variables. The intergroup differences were tested using Student's *t*-test for normally distributed data and the Mann–Whitney *U* test for non-normally distributed data. Proportions were compared using χ^2 test or Fisher's exact test, where appropriate. The associations between clinical variables and an HF event and between clinical and laboratory variables and in-hospital mortality were tested using logistic regression models.

To estimate the effect of HF and HF events on in-hospital mortality, Kaplan–Meier curves with time to in-hospital death were constructed (*Figure 2A,B*). Time to event was calculated from date of hospital admission to in-hospital all-cause death. Patients were censored at time of hospital discharge and end of follow-up time (30 days after initial hospital admission).

Confounders for multivariable regression were identified based on clinical knowledge and published literature. For the logistic regression analysis in *Figure 2C,D*, multivariable analysis was sequentially adjusted for age, sex, risk factors (arterial hypertension, diabetes, dyslipidaemia, and history of smoking), and co-morbidities [malignancy and chronic kidney disease (CKD) with eGFR <60 mL/min/1.73 m^2] to test which variables most strongly represent the increased risk associated with HF. We tested for interaction between history of HF with sex and age. For *Table 3* and Supporting Information, *Table S9*, the multivariable model included variables that were statistically significant in the univariable models (all represented in the tables). The following sensitivity analyses were performed: (i) the baseline characteristics and outcomes for the analysed cohort in the multivariable model of *Table 3* and the cohort with missing data are shown in Supporting Information, *Table S4*, (ii) exclusion of Italy as the largest contributing country to the registry (Supporting Information, Results), and (iii) comparison of baseline characteristics and in-hospital course of the five largest contributing countries to the registry (Supporting Information, *Table S5*). All analyses were performed using SPSS (IBM, Version 26) and STATISTICA 13.3 (StatSoft, Inc), and *P* values <0.05 were considered statistically significant.

Table 1 Baseline clinical characteristics

Variables, units	CVDRF, overall *n* = 1282	HF subgroup *n* = 256	Non-HF subgroup *n* = 1026
Demographic parameters			
Age, years	72 [62–81] (1281)	76 [68–84]** (256)	71 [61–80] (1025)
Sex, male	746/1282 (58)	145/256 (57)	601 (59) (1026)
Race, Caucasian	962/1101 (84)	219/234 (94)*	743/867 (86)
Body mass index, kg/m^2	27 [24–31] (907)	28 [24–32] (213)	27 [24–31] (694)
Cardiovascular risk factors			
Arterial hypertension	986/1277 (77)	214/254 (84)*	772/1023 (75)
Dyslipidaemia	563/1275 (44)	153/255 (60)**	410/1020 (40)
Diabetes mellitus	434/1279 (34)	112/256 (44)**	316/1023 (31)
Previous/current smoker	375/1218 (31)	96/244 (39)*	279/974 (29)
Family history of heart disease	123/1024 (12)	63/225 (28)**	60/799 (8)
Cardiovascular diseases			
Ischaemic heart disease	306/1226 (24)	154/249 (62)**	152/977 (16)
Prior ACS	163/1100 (15)	89/232 (38)**	74/868 (9)
Atrial fibrillation	233/1242 (19)	100/255 (39)**	133/987 (13)
Significant valvular heart disease	115/1231 (9)	63/250 (25)**	52/981 (5)
Stroke/transient ischaemic attack	132/1113 (12)	50/238 (21)**	82/875 (9)
Peripheral artery disease	125/1242 (10)	45/254 (18)**	80/988 (8)
Other co-morbidities			
Chronic kidney disease[a]	185/1233 (15)	73/250 (29)**	112/983 (11)
COPD or asthma	185/1110 (15)	63/238 (26)**	124/872 (14)
Malignancy	143/1111 (13)	33/238 (14)	110/873 (13)
Treatment before admission			
Loop diuretics	307/1227 (25)	160/252 (63)**	147/975 (15)
ACE inhibitors	331/1101 (30)	105/235 (45)**	226/866 (26)
ARB	251/1103 (23)	50/236 (21)	201/867 (23)
Beta-blockers	457/1234 (37)	171/253 (68)**	286/981 (29)
Calcium channel blockers	335/1230 (27)	67/253 (26)	268/977 (27)
MRA	97/1231 (8)	66/253 (26)**	31/978 (3)
Oral antidiabetics incl. SGLT2i	260/1236 (21)	60/237 (24)	200/981 (20)
Insulin	154/1236 (12)	46/254 (18)	108/982 (11)
Statin	466/1234 (38)	130/253 (51)**	336/981 (34)
Antiplatelet treatment	392/1233 (32)	133/252 (53)**	259/980 (26)
Oral anticoagulants	186/1236 (15)	80/252 (32)**	106/983 (11)
NSAIDS	47/1234 (4)	11/253 (4)	36/981 (4)
Pacemaker	62/1241 (5)	27/255 (11)**	35/986 (4)
ICD/CRT	15/1111 (1)	14/238 (6)**	1/873 (0)
Signs and symptoms at admission			
Fever	783/1077 (73)	160/238 (67)*	623/839 (74)
Cough	655/1069 (61)	151/235 (64)	504/834 (60)
Dyspnoea	692/1073 (64)	193/238 (81)**	499/835 (60)
Orthopnoea	100/1072 (9)	57/236 (24)**	43/836 (5)
Chest pain	100/1078 (9)	29/239 (12)	71/839 (8)
Tiredness/fatigue	361/1073 (34)	102/238 (43)**	259/835 (31)
Runny nose	58/1076 (5)	18/237 (8)	40/839 (5)
Sore throat	74/1076 (7)	27/237 (11)*	47/839 (6)
Gastrointestinal symptoms	193/1077 (18)	33/238 (14)	160/839 (19)
Myalgia	177/1075 (16)	54/237 (23)*	123/838 (15)
Altered smell or taste	79/1064 (7)	25/231 (11)*	54/833 (6)
Body temperature, °C	37.5 [36.7–38.1] (1125)	37.8 [37.0–38.2]* (228)*	37.4 [36.6–38.1] (897)
Respiratory rate, /min	20 [17–25] (794)	21 [18–24] (178)	20 [16–25] (616)
Heart rate, b.p.m.	85 [75–99] (1156)	85 [75–100] (96)	85 [76–98] (910)
Systolic blood pressure, mmHg	130 [120–144] (1166)	130 [111–140]** (248)	130 [120–145] (918)
Diastolic blood pressure, mmHg	76 [67–84] (1163)	75 [62–82]* (247)	77 [68–84] (916)
Oxygen saturation	94 [90–96] (1118)	93 [89–96]** (233)	94 [90–96] (885)
Peripheral oedema	106/1052 (10)	70/231 (30)**	36/821 (4)
Chest X-ray			
Inflammatory changes	731/894 (82)	173/204 (85)	558/690 (81)
Signs of congestion	250/885 (28)	98/199 (49)**	152/686 (22)
Pleural effusion	159/888 (18)	56/203 (28)**	103/685 (15)
Computed tomography			
Subpleural ground glass	305/425 (72)	75/109 (69)	230/316 (73)
Consolidations	157/425 (37)	36/109 (33)	121/316 (38)

(*Continues*)

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Table 1 (continued)

Variables, units	CVDRF, overall *n* = 1282	HF subgroup *n* = 256	Non-HF subgroup *n* = 1026
Laboratory parameters			
Haemoglobin, g/L	128 [114–141] (1138)	120 [106–135]** (246)	130 [117–142] (892)
White blood cells, × 10^9/L	6.8 [5.0–9.7] (1201)	7.5 [5.3–10.6]* (253)	6.5 [4.9–9.5] (948)
Lymphocytes, %	15 [10–22] (1132)	13 [7–20]** (231)	15 [10–23] (901)
Neutrophils, %	76 [67–83] (1129)	79 [71–85]* (229)	76 [67–83] (900)
Blood platelets, 10^9/L	196 [154–262] (1019)	177 [141–256]* (207)	199 [157–262] (812)
NT-proBNP, ng/L	733 [226–2352] (408)	2352 [885–6630]** (100)	506 [149–1572] (308)
hs-troponin T or I, × ULN	0.9 [0.3–3.5] (500)	1.1 [0.4–5.7] (113)	0.9 [0.3–2.9] (387)
C-reactive protein, mg/L	63 [26–130] (1155)	58 [31–130] (236)	64 [25–130] (919)
Procalcitonine, ng/mL	0.2 [0.1–0.4] (589)	0.2 [0.1–0.6]** (93)	0.1 [0.1–0.3] (496)
pCO_2, kPa (arterial blood gas)	4.6 [4.1–5.1] (754)	4.6 [4.0–5.3] (151)	4.5 [4.1–5.1] (603)
Lactate, mmol/L	1.2 [0.9–1.9] (667)	1.6 [1.0–2.0]** (138)	1.2 [0.9–1.8] (529)
Albumin, g/L	34 [30–38] (613)	33 [28–37]* (133)	35 [30–38] (480)
ALT, U/L	28 [18–44] (1133)	24 [16–42]* (236)	29 [19–45] (897)
AST, U/L	35 [24–56] (828)	33 [21–63] (203)	36 [24–54] (625)
Creatinine, mg/dL	1.0 [0.8–1.4] (1075)	1.3 [1.0–1.9]** (233)	1.0 [0.8–1.3] (842)
GFR, mL/min/1.73 m^2	64 [43–86] (1074)	49 [34–71] (233)	67 [47–89] (841)
Potassium, mmol/L	4.0 [3.7–4.4] (1173)	4.2 [3.7–4.6]** (254)	4.0 [3.7–4.4] (919)
Sodium, mmol/L	138 [135–141] (1194)	139 [136–141]* (256)	138 [135–140] (938)
INR	1.1 [1.0–1.2] (824)	1.2 [1.1–1.5]** (275)	1.1 [1.0–1.2] (649)
D-dimers, μg/mL	1.0 [0.6–1.9] (568)	1.1 [0.5–1.9] (125)	1.0 [0.6–1.9] (443)

ACE, angiotensin-converting enzyme; ACS, acute coronary syndrome; ALT, alanine transaminase; ARB, angiotensin receptor blocker; AST, aspartate transaminase; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; CVDRF, patient cohort with cardiovascular disease and/or risk factors; HF, heart failure; ICD, internal cardiac defibrillator; INR, international normalized ratio; MRA, mineralocorticoid receptor antagonists; NSAID, non-steroidal inflammatory drugs; NT-proBNP, N-terminal pro-type brain natriuretic peptide; SGLT2i, sodium-glucose transporter inhibitors.
Results are presented as an *n* patients/available *n* (with percentage) or as a median [lower and upper quantile] (available *n*).
*$P < 0.05$.
**$P < 0.001$.
[a]Chronic kidney disease: eGFR < 60 mL/min/1.73 m^2.

Table 2 In-hospital events

Variables	CVDRF, overall *n* = 1282	HF subgroup *n* = 256	Non-HF subgroup *n* = 1026
Cardiac manifestations during hospitalization			
Heart failure event	186/1150 (16)	110/240 (46)**	76/910 (8)
Acute coronary syndrome	39/1150 (3)	13/240 (5)	26/910 (3)
Myocarditis	12/1149 (1)	5/240 (2)	7/909 (1)
Ventricular arrhythmias	18/1137 (2)	8/238 (3)*	10/899 (1)
Pulmonary embolism	33/1122 (3)	9/229 (4)	24/893 (3)
Other thromboembolic events	25/1135 (2)	8/237 (3)	17/898 (2)
In-hospital course and outcome			
Mechanical ventilation	211/1202 (18)	54/253 (21)	157/949 (17)
Non-invasive ventilation	358/1066 (34)	111/233 (48)**	247/833 (30)
Respiratory failure	650/1267 (51)	160/254 (63)**	490/1013 (48)
Sepsis	191/1133 (17)	43/236 (18)	148/897 (16)
Septic shock	109/1132 (10)	23/235 (10)	86/897 (10)
Multi-organ failure	199/1137 (18)	60/237 (25)**	139/900 (15)
Renal replacement therapy	60/1074 (6)	15/235 (6)	45/839 (5)
ICU	301/1275 (24)	85/254 (33)**	216/1021 (21)
ICU, length of stay, days	4 [0–11] (457)	4 [0–8] (129)	4 [0–14] (32)
Length of hospital stay, days	11 [5–19] (834)	12 [6–19] (143)	11 [5–19] (706)
In-hospital death	323/1282 (25)	92/256 (36)**	231/1026 (23)

CVDRF, patient cohort with cardiovascular disease and/or risk factors; HF, heart failure; ICU, intensive care unit hospitalization.
Results are presented as a number of patients (with percentage) or as a median [with lower and upper quartile].
*$P < 0.05$.
**$P < 0.001$.

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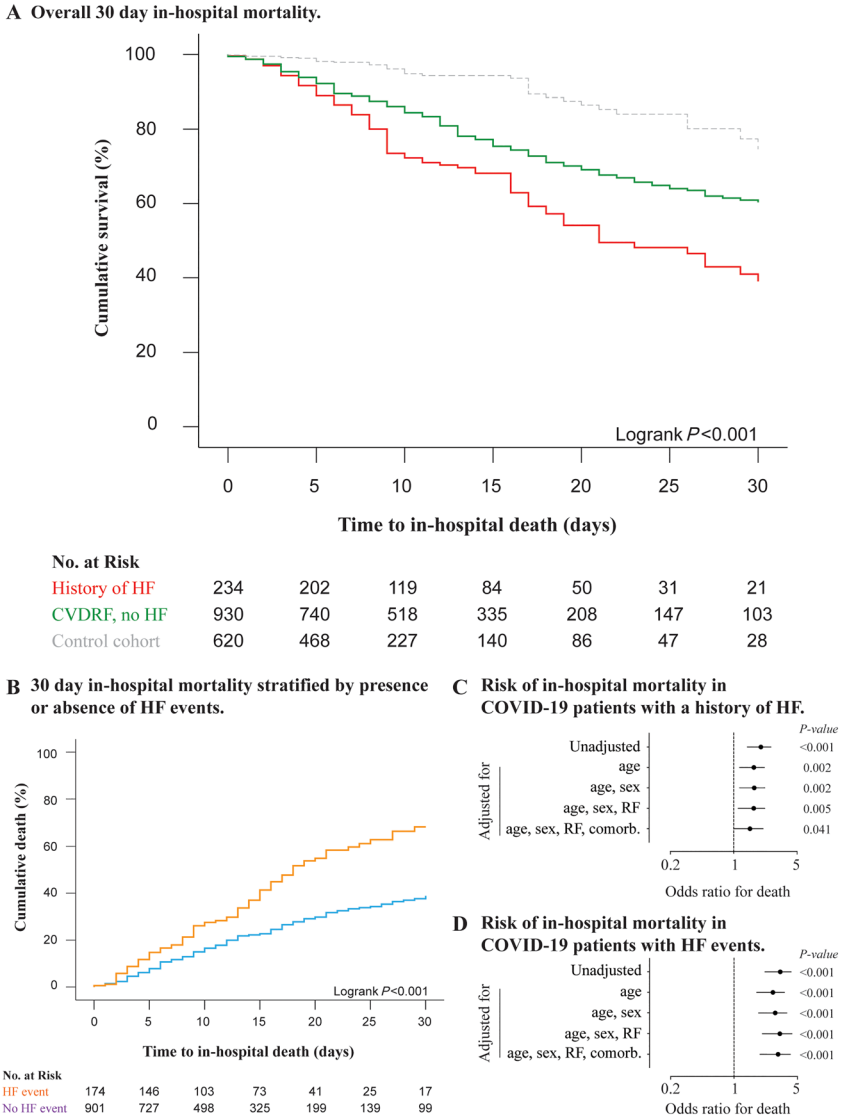
Figure 2 (A) Kaplan–Meier curve showing overall 30 day in-hospital mortality, stratified for patients with a history of heart failure (HF), patients with cardiovascular disease and/or risk factors without HF (CVDRF, no HF), and patients without CVDRF (control cohort). (B) Thirty-day in-hospital mortality for patients with CVDRF, stratified for the occurrence of an HF event at admission or during hospitalization for COVID-19. (C, D) Step-wise modelling of risk of in-hospital mortality in COVID-19 patients with a history of HF (C) or HF events (D), adjusted for age, sex, risk factors (arterial hypertension, diabetes, hypercholesterolaemia, and smoking), and co-morbidities (malignancy and chronic kidney disease with eGFR $<$ 60 mL/min/1.73m^2) (data available in Supporting Information, *Tables* S8 and S10). comorb., co-morbidities; HF, heart failure; RF, risk factors.



Results

Description of the study population

The registry included 2015 hospitalized patients with laboratory confirmed COVID-19; 28 patients were excluded due to ongoing hospitalization or unknown survival status at discharge and 13 due to unknown HF status (see flow chart *Figure 1* and Supporting Information, *Table S2*). Patients with CVDRF (*n* = 1282, 58% male, median age 72 [interquartile range 62–81] years) were classified into patients with a history of HF (HF subgroup, *n* = 256, 20% of CVDRF, 57% male, 32% HFpEF) and patients without a history of HF (non-HF subgroup, *n* = 1026, 80% of CVDRF, 59% male) (*Table 1*). HF patients were older (76 [68–84] vs. 71 [61–80] years, $P < 0.001$) and had more risk factors and co-morbidities than non-HF patients (*Table 1*). Patients with HF showed a higher NT-proBNP than non-HF patients and were further characterized by a lower haemoglobin and blood platelets, but higher white blood cell counts, lactate, liver tests, and creatinine at the emergency blood sampling. However, high-sensitivity troponin levels and CRP were not significantly different between

Table 3 Predictors of heart failure events in patients with COVID-19 and cardiovascular risk factors/disease

	Univariable models		Multivariable model	
Variables, units	OR (95% CI)	*P*	OR (95% CI)	*P*
Demographic parameters				
Age, per 5 years	**1.20 (1.12–1.28)**	**<0.001**	1.08 (0.99–1.17)	0.09
Sex, men	1.29 (0.94–1.77)	0.12	—	—
Body mass index, kg/m^2	0.99 (0.96–1.03)	0.46	—	—
Cardiovascular risk factors				
Arterial hypertension	**1.79 (1.16–2.76)**	**0.008**	1.29 (0.78–2.13)	0.32
Dyslipidaemia	**1.76 (1.28–2.42)**	**<0.001**	1.15 (0.77–1.70)	0.49
Diabetes	**1.59 (1.16–2.19)**	**0.004**	1.27 (0.87–1.86)	0.22
Smoking	1.06 (0.74–1.51)	0.77	—	—
Cardiovascular diseases				
History of heart failure	**9.29 (6.57–13.12)**	**<0.001**	**6.21 (3.99–9.68)**	**<0.001**
Ischaemic heart disease	**2.82 (2.03–3.92)**	**<0.001**	1.01 (0.61–1.67)	0.98
Atrial fibrillation	**3.79 (2.67–5.39)**	**<0.001**	**2.10 (1.38–3.20)**	**<0.001**
Valvular heart disease	**3.41 (2.17–5.36)**	**<0.001**	1.15 (0.66–2.01)	0.62
Stroke/TIA	**1.67 (1.08–2.58)**	**0.022**	1.08 (0.63–1.85)	0.77
Peripheral artery disease	**1.70 (1.07–2.68)**	**0.024**	0.78 (0.44–1.41)	0.41
Other co-morbidities				
CKD (eGFR < 60 mL/min/1.73 m^2)	**2.99 (2.11–4.23)**	**<0.001**	**1.71 (1.10–2.68)**	**0.017**
COPD or asthma	**1.53 (1.03–2.25)**	**0.034**	0.91 (0.56–1.45)	0.68
Malignancy	1.33 (0.85–2.07)	0.21	—	—

CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive lung disease; eGFR, estimated glomerular filtration rate; OR, odds ratio; TIA, transient ischaemic attack.
The multivariable model included variables with a *P* value < 0.10 in the univariable models. $\chi^2 = 180.5$, $P < 0.001$, included $n = 1064/1282$.
The statistically significant OR (95% CI) in the univariable and multivariable models were presented with bold.

HF and non-HF patients (*Table 1*). A total of 95/1282 (7%) patients were hospitalized with symptoms of acute HF; the other patients had mainly COVID-19 symptoms without overt decompensation at hospitalization. Of the 220 patients where ACE inhibitor was discontinued, the date of withdrawal was recorded in 190 patients. In 97% (185 out of 190), ACE inhibitor was withdrawn directly after admission.

Data of COVID-19 hospitalized patients without CV disease, cardiac manifestation of COVID-19 and/or CV risk factors (n = 692, age 54 [44–63] years, 55% male), were briefly summarized for survival status at discharge (n = 39/692 in-hospital deaths, 6%) and intensive care hospitalization (n = 86/692; 12%) (Supporting Information, *Table S7*).

In-hospital mortality

The CVDRF cohort had high overall in-hospital mortality (25%, n = 323/1282 deaths). In-hospital mortality was higher in patients with HF (36%, n = 92) compared with non-HF patients (23%, n = 231, $P < 0.001$) with an odds ratio (OR) of 1.93 [95% confidence interval, CI: 1.44–2.59] (*Figure 2A,C*). After adjusting for age, sex, risk factors, and co-morbidities, HF remained associated with in-hospital mortality (OR 1.45 [95% CI: 1.01–2.06], P = 0.041) (*Figure 2C* and Supporting Information, *Figure S1* and *Table S8*). Interaction for history of HF and age was significant (P = 0.029), with an OR for history of HF and in-hospital death of 2.02 ([95% CI: 1.17–3.49], P = 0.012) in the <75 years age group and 1.26 [95% CI: 0.80–1.99], P = 0.32) in the ≥75 years age group. There was no significant interaction between history of HF and sex (P = 0.42).

Main causes of in-hospital death (available in 250/323 deaths) were respiratory failure/acute respiratory distress syndrome (n = 127, 51%), multiple organ failure (n = 84, 34%), CV death (n = 34, 14%), and septic shock (n = 35, 14%). CV death was more reported in the HF subgroup (n = 16/76 (21%) vs. n = 18/174 (10%), P = 0.023) (Supporting Information, *Figure S2A*).

Patients with HF more often required intensive care hospitalization and non-invasive ventilation (33% vs. 21%, and 48% vs. 30%, respectively, both $P < 0.001$); however, length of stay on intensive care or total hospitalization duration were not significantly different (*Table 2*). In a subgroup analysis, patients with HFrEF more often required ICU hospitalization; however, we did not see a difference in in-hospital death, compared with patients with HFpEF (Supporting Information, *Table S11*).

In patients with HF, age, valvular heart disease, malignancy, previous treatment with loop diuretics, the absence of ACE inhibitor treatment, higher creatinine, higher CRP, and low lymphocyte count were associated with higher in-hospital mortality. After multivariable adjustment, higher age (OR 1.18 [95% CI: 1.06–1.34], per 5 years), absence of ACE inhibition (OR 3.75 [95% CI: 1.89–7.44]), and a higher CRP level at admission (OR 1.73 [95% CI: 1.25–2.37], per 1 Ln mg/L)

remained significantly associated with in-hospital mortality in patients with HF (Supporting Information, *Table S9*).

In-hospital heart failure events

Of all patients in the CVDRF cohort, 186 (15%) patients experienced HF events at admission or during hospitalization, of which 110/240 (46%) patients in the HF subgroup and 76/910 (8%) in the non-HF subgroup, the latter accounting for 40% of all observed HF events (*Table 2*). In the CVDRF cohort, patients with an HF event were at a two-fold increased risk for in-hospital mortality compared with those without HF events (n = 89 [48%] vs. n = 220 [23%], $P < 0.001$, OR 3.10 [2.24–4.29]), even after adjustment for age, sex, risk factors, and co-morbidities (*Figure 2B,D* and Supporting Information, *Table S10*). Interaction for HF events and age was significant (P = 0.023), with an OR for HF events and in-hospital death of 3.41 (95% CI [1.96–5.93], $P \leq 0.001$) in the <75 years age group and 2.82 (95% CI [1.71–4.65], $P < 0.001$) in the ≥75 years age group. There was no significant interaction between HF events and sex (P = 0.58). Age, CV diseases, CV risk factors, history of HF, atrial fibrillation, and CKD were significantly associated with HF events. After multivariable adjustment, CKD (eGFR < 60 mL/min/1.73 m^2) (OR 1.71 [1.10–2.68], P = 0.017), atrial fibrillation (2.10 [1.38–3.20], $P < 0.001$), and history of HF (OR 6.21 [3.99–9.68], $P < 0.001$) remained independently associated with HF events in patients hospitalized for COVID-19 (*Table 3*).

Discussion

In this registry of 1282 patients with CV disease and/or risk factors hospitalized for COVID-19, we assessed a population with a high overall in-hospital mortality (25%). Particularly, patients with a history of HF (256 patients) experienced a 1.5-fold increased likelihood for in-hospital death after adjustment for known confounders. Those experiencing an in-hospital HF event, which occurred in 186 patients (40% without history of HF), had a three-fold increased adjusted likelihood for in-hospital death.

Cardiovascular disease and CV risk factors have been increasingly recognized as predisposing determinants of worse outcomes in COVID-19 since the beginning of the pandemic. However, the role of HF remains elusive. In this multicentre registry, we observed a high in-hospital mortality that was particularly high in patients with pre-existing HF. Although HF patients in the CVDRF cohort were older and presented with more CV risk factors and co-morbidities than non-HF patients, HF remained independently associated with in-hospital mortality, after adjustment for potential confounders. HF prevalence in the present registry was 20%, thus corroborating findings of registries that primarily focused on CV risk factors, such as diabetes and hypertension, or ischaemic heart disease, reporting an HF prevalence between 4.1% and 23%.[20,23–25] These observations also apply to ambulatory patients with COVID-19. Among 31 051 patients with COVID-19, 6148 (20%) had pre-existing HF and those have a 30 day mortality and 30 day admission rate of 5.4% and 18.5%, respectively.[8] In contrast, in our study, we only observed patients already hospitalized. There, HF was present in 29% of all patients who died while hospitalized compared with 17% in survivors, suggesting HF as a potential contributor to COVID-19 in-hospital mortality. Findings from other studies reinforce this hypothesis, by showing that non-survivors were more likely to have a history of HF (52%) than survivors (12%).[20] Yet another study reported a very high prevalence of HF (49%) in deceased patients (n = 113).[26] Further, a recent single-centre registry included 152 (4.9%) HF patients with a similarly high mortality among patients with chronic HF (48.7%). In contrast to our study, HF was not independently associated with mortality.[11] The HF patients of this study were older (82 ± 12 years old) compared with the HF population in our registry. In our registry, a subgroup analysis for a younger or older age than 75 years showed heterogeneity for the primary outcome. However, there was a consistent association of HF and in-hospital death in the overall CVDRF cohort. In contrast to the multicentre French registry, we did not observe a difference in in-hospital mortality between HFpEF and HFrEF patients—however, the latter more often required ICU hospitalization (Supporting Information, *Table S11*).[27]

Interestingly, not only patients with pre-existing HF seem to be at risk for developing an HF event when infected with COVID-19, but also a substantial number of patients with CV risk factors without previously known HF. Further, not only a history of HF but particularly HF *events* when hospitalized for COVID-19 were associated with an excess mortality, thus supporting and extending findings from a single-centre registry from Madrid demonstrating that HF events were associated with a high mortality.[11] Several risk factors could potentially contribute to these HF events, triggered by COVID-19.

Nevertheless, the pathophysiology of COVID-19 and risk of HF still remains incompletely understood. Imaging studies have shown myocardial inflammation, frequently persisting after recovery from COVID-19.[28,29] In addition, in a systematic echocardiographic evaluation in 100 COVID-19 patients, both right ventricular and left ventricular diastolic and systolic dysfunction were found in 39% and 26% of patients.[30] Of note, 40% of the HF events were de novo. One mechanism might be direct infection with SARS-CoV-2 of myocardial tissue, through the ACE 2 receptor.[7] However, careful analysis of pathology specimens of deceased COVID-19 patients revealed viral inclusion structures in endothelial cells, and in addition, an accumulation of inflammatory cells associated with the endothelium in other organs than the lung, such as heart and kidney, suggestive of an overwhelming

inflammatory response.[2] The findings in our HF cohort strengthen this hypothesis, as patients with high CRP as a surrogate for a more severe inflammatory response had a worse outcome. Further, HF is characterized by profound endothelial dysfunction, particularly in advanced ischaemic heart disease.[5,31,32] Ischaemic heart disease was prevalent in 64% of the HF group.

We recognized a high number of ACE inhibitor and angiotensin receptor blocker withdrawal in our cohort. This may have been influenced by the discussion on these medications at the beginning of the pandemic. Subsequent studies clearly demonstrate that renin–angiotensin–aldosterone system inhibitors should be continued in hospitalized COVID-19 patients if there is an indication for treatment.[33,34] Thromboembolic events are of major concern in COVID-19 patients. We observed pulmonary embolism and other thrombotic events in 33 out of 1122 (3%) and in 25 out of 1135 patients (2%), respectively. As other studies reported higher prevalence of such events, we suppose that in our study thromboembolic events are underestimated.[35,36] However, due to the high risk profile of our study population, anticoagulation or platelet antiaggregation treatment was used in most of the study patients prior to and/or during hospitalization (1046/1214 [82%]).

Taken together, HF may be recognized as the end of a spectrum of CV risk factors, with more advanced pre-existing endothelial dysfunction and thereby associated with a higher risk for an overwhelming inflammatory response to COVID-19. Our results thereby reinforce the importance of HF as a significant risk factor for death in hospitalized patients. As important questions about the pathophysiology, treatment and prognosis of HF patients with COVID-19 remain unanswered; prospective outcome studies in COVID-19 patients with HF are needed.

Limitations

This registry was established within the PCHF network with investigators dedicated to HF care. Although all patients who were consecutively admitted to the hospitals are included into the registry, a certain selection bias cannot be excluded. We are further aware that our study may have the limitations of multicentre registries, both having limited opportunities for data verification of each patient and the disadvantages of the retrospective observational nature of our analysis, with its inherent potential selection bias and missing data. Lastly, mortality rates due to COVID-19 are known to vary across countries; we added a Supporting Information, *Table S3* showing the detailed in-hospital death per country. Our findings should therefore be confirmed in prospective outcome trials.

Conclusions

In this multinational multicentre registry, we demonstrate a higher mortality for hospitalized COVID-19 patients with HF compared with patients without HF, even after adjustment for other conditions and co-morbidities. Particularly, patients experiencing an HF event during hospitalization for COVID-19 are at high risk for death, an important proportion of whom did not have a history of HF. The cause of death in most cases was not related to respiratory failure alone but rather to multi-organ failure.

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Conflict of interest

Sander Trenson: travel grants from Abbott, Daiichi Sankyo, and Boston Scientific; speaker fees from Novartis and Boehringer Ingelheim. Nana K. Poku: travel grants from Servier, Vifor Pharma, and Boehringer Ingelheim; speaker fees from Servier. Tor Biering-Sørensen: steering committee member of the Amgen financed GALACTIC-HF trial; advisory board: Sanofi Pasteur and Amgen; speaker honorarium: Novartis and Sanofi Pasteur; research grant: GE Healthcare and Sanofi Pasteur. Tor Biering-Sørensen, Mats C. Højbjerg

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Author contributions

Sokolski, Trenson, Sokolska, Ruschitzka, and Flammer had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Sokolski, Trenson, Sokolska, Ponikowski, Ruschitzka, and Flammer. Acquisition, analysis, interpretation of data; administrative, technical, or material support; revision of the manuscript: all authors. Drafting of the manuscript: Sokolski, Trenson, Sokolska, Mullens, Lund, Ruschitzka, and Flammer. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: Trenson and Sokolski. Statistical advice: Held and Schindler. Supervision: Ruschitzka and Flammer.

Data availability statement

The registry procedures, data acquisition, and statistics were provided reliably according to the rules of Good Clinical Practice. The anonymized datasets of the current study might be available from the corresponding author on reasonable request.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Univariable regression models for demographical parameters, cardiovascular risk factors, cardiovascular diseases and comorbidities and their association with in-hospital mortality in patients with CVDRF. BMI = body mass index, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, eGFR = estimated glomerular filtration rate, PAD = peripheral artery disease.

Figure S2. Reported causes of death in patients with cardiovascular disease and/or risk factors during hospitalization for COVID-19 (available in 253/323 deceased patients) in several subgroups: (A): total CVDRF group (cardiovascular disease and/or risk factors), further subdivided in patients with or without history of heart failure and (B) patients from the CVDRF group with a heart failure event at admission/during COVID-19 hospitalization (more than 1 cause of death could be reported per patient). CVDRF = cardiovascular disease and/or risk factors; HF = heart failure.

Figure S3. Age distribution in patients with cardiovascular disease/and or risk factors (CVDRF cohort).
Table S1. Excluded patients (*n*) from the registry for the primary endpoint: regression analysis for in-hospital death in patients with CVDRF with HF *versus* patients with CVDRF without HF. CVDRF: cardiovascular disease and/or risk factors.
Table S2. Data collection sheet.
Table S3. In-hospital death per country.
Table S4. Sensitivity analysis.
Table S5. Baseline characteristics, in-hospital course and outcome for the 5 largest contributing countries to the registry (CVDRF group: cardiovascular disease and/or risk factors).
Table S6. Distribution of patients per country (alphabetical order).
Table S7. Demographics and endpoints in the total group and the sugbroups with or without Cardiovascular Disease/Risk Factors.
Table S8. Risk of in-hospital death in COVID-19 patients with a history of heart failure.
Table S9. Predictors of in-hospital death in patients with history of HF and COVID-19.
Table S10. Risk of in-hospital death in COVID-19 patients experiencing heart failure events.
Table S11. The comparison of patients with HFpEF vs HFrEF.
Table S12. The comparison of patients with ADHF vs AHF de novo.
Table S13. Treatment of acute heart failure in hospitalized COVID-19 patients.
Table S14. Number and percentage of patients with multi-organ failure (MOF) and these requiring vasopressors or inotropic support.
Table S15. Total number of admission mortality in relation to the magnitude of COVID-19 cases per country.

References

1. Gupta A, Madhavan MV, Sehgal K, Nair N, Mahajan S, Sehrawat TS, Bikdeli B, Ahluwalia N, Ausiello JC, Wan EY, Freedberg DE, Kirtane AJ, Parikh SA, Maurer MS, Nordvig AS, Accili D, Bathon JM, Mohan S, Bauer KA, Leon MB, Krumholz HM, Uriel N, Mehra MR, Elkind MSV, Stone GW, Schwartz A, Ho DD, Bilezikian JP, Landry DW. Extrapulmonary manifestations of COVID-19. *Nat Med* 2020; **26**: 1017–1032.
2. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, Mehra MR, Schuepbach RA, Ruschitzka F, Moch H. Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 2020; **395**: 1417–1418.
3. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, Wang H, Wan J, Wang X, Lu Z. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiol* 2020; **5**: 811–818.
4. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan. *China Intensive Care Med* 2020; **46**: 846–848.
5. Nägele MP, Barthelmes J, Ludovici V, Cantatore S, von Eckardstein A, Enseleit F, Lüscher TF, Ruschitzka F, Sudano I, Flammer AJ. Retinal microvascular dysfunction in heart failure. *Eur Heart J* 2018; **39**: 47–56.
6. Alvarez-Garcia J, Lee S, Gupta A, Cagliostro M, Joshi AA, Rivas-Lasarte M, Contreras J, Mitter SS, LaRocca G, Tlachi P, Brunjes D, Glicksberg BS, Levin MA, Nadkarni G, Fayad Z, Fuster V, Mancini D, Lala A. Prognostic impact of prior heart failure in patients hospitalized with COVID-19. *J Am Coll Cardiol* 2020; **76**: 2334–2348.
7. Sokolski M, Sokolska JM, Zymliński R, Biegus J, Banasiak W, Reczuch K, Ponikowski P. Cardiac emergencies during the coronavirus disease 2019 pandemic in the light of the current evidence. *Kardiol Pol* 2020; **78**: 818–824.
8. Rumery K, Seo A, Jiang L, Choudhary G, Shah NR, Rudolph JL, Wu WC, Erqou S. Outcomes of coronavirus disease-2019 among veterans with pre-existing diagnosis of heart failure. *ESC Heart Fail.* 2021; **8**: 2338–2344.
9. Doolub G, Wong C, Hewitson L, Mohamed A, Todd F, Gogola L, Skyrme-Jones A, Aziz S, Sammut E, Dastidar A. Impact of COVID-19 on inpatient referral of acute heart failure: a single-centre experience from the south-west of the UK. *ESC Heart Fail.* 2021; **8**: 1691–1695.
10. Andersson C, Gerds T, Fosbøl E, Phelps M, Andersen J, Lamberts M, Holt A, Butt JH, Madelaire C, Gislason G, Torp-Pedersen C, Køber L, Schou M. Incidence of new-onset and worsening heart failure before and after the COVID-19 epidemic lockdown in Denmark: a nationwide cohort study. *Circ Heart Fail* 2020; **13**: e007274.
11. Rey JR, Caro-Codón J, Rosillo SO, Iniesta ÁM, Castrejón-Castrejón S, Marco-Clement I, Martín-Polo L, Merino-Argos C, Rodríguez-Sotelo L, García-Veas JM, Martínez-Marín LA, Martínez-Cossiani M, Buño A, Gonzalez-Valle L, Herrero A, López-Sendón JL, Merino JL, CARD-COVID Investigators. Heart failure in COVID-19 patients: prevalence, incidence and prognostic implications. *Eur J Heart Fail* 2020; **22**: 2205–2215.
12. Cannatà A, Bromage DI, Rind IA, Gregorio C, Bannister C, Albarjas M, Piper S, Shah AM, McDonagh TA. Temporal trends in decompensated heart failure and outcomes during COVID-19: a multisite report from heart failure referral centres in London. *Eur J Heart Fail* 2020; **22**: 2219–2224.
13. König S, Hohenstein S, Meier-Hellmann A, Kuhlen R, Hindricks G, Bollmann A. In-hospital care in acute heart failure during the COVID-19 pandemic: insights from the German-wide Helios hospital network. *Eur J Heart Fail* 2020; **22**: 2190–2201.
14. Bollmann A, Hohenstein S, König S, Meier-Hellmann A, Kuhlen R, Hindricks G. In-hospital mortality in heart failure in Germany during the Covid-19 pandemic. *ESC Heart Fail.* 2020; **7**: 4416–4419.
15. Pareek M, Singh A, Vadlamani L, Eder M, Pacor J, Park J, Ghazizadeh Z, Heard A, Cruz-Solbes AS, Nikooie R, Gier C, Ahmed ZV, Freeman JV, Meadows J, Smolderen KGE, Lampert R, Velazquez EJ, Ahmad T, Desai NR. Relation of cardiovascular risk factors to mortality and cardiovascular events in hospitalized patients with coronavirus disease 2019 (from the Yale COVID-19 Cardiovascular Registry). *Am J Cardiol* 2021; **146**: 99–106.

16. Bocchi EA, Lima IGCV, Biselli B, Salemi VMC, Ferreira SMA, Chizzola PR, Munhoz RT, Pessoa RS, Cardoso FAM, Bello MVDO, Hajjar LA, Gomes BR. Worsening of heart failure by coronavirus disease 2019 is associated with high mortality. *ESC Heart Fail* 2021; **8**: 943–952.
17. König S, Ueberham L, Pellissier V, Hohenstein S, Meier-Hellmann A, Thiele H, Ahmadli V, Borger MA, Kuhlen R, Hindricks G, Bollmann A. Hospitalization deficit of in- and outpatient cases with cardiovascular diseases and utilization of cardiological interventions during the COVID-19 pandemic: insights from the German-wide Helios hospital network. *Clin Cardiol* 2021; **44**: 392–400.
18. Sokolski M, Gajewski P, Zymliński R, Biegus J, Berg JMT, Bor W, Braunschweig F, Caldeira D, Cuculi F, D'Elia E, Edes IF, Garus M, Greenwood JP, Halfwerk FR, Hindricks G, Knuuti J, Kristensen SD, Landmesser U, Lund LH, Lyon A, Mebazaa A, Merkely B, Nawrocka-Millward S, Pinto FJ, Ruschitzka F, Semedo E, Senni M, Sepehri Shamloo A, Sorensen J, Stengaard C, Thiele H, Toggweiler S, Tukiendorf A, Verhorst PM, Wright DJ, Zamorano P, Zuber M, Narula J, Bax JJ, Ponikowski P. Impact of coronavirus disease 2019 (COVID-19) outbreak on acute admissions at the emergency and cardiology departments across Europe. *Am J Med* 2020; **134**: 482–489.
19. Inciardi RM, Adamo M, Lupi L, Cani DS, Di Pasquale M, Tomasoni D, Italia L, Zaccone G, Tedino C, Fabbricatore D, Curnis A, Faggiano P, Gorga E, Lombardi CM, Milesi G, Vizzardi E, Volpini M, Nodari S, Specchia C, Maroldi R, Bezzi M, Metra M. Characteristics and outcomes of patients hospitalized for COVID-19 and cardiac disease in Northern Italy. *Eur Heart J* 2020; **41**: 1821–1829.
20. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; **395**: 1054–1062.
21. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola V-P, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of. *Eur Heart J* 2016; **37**: 2129–2200.
22. Nkhata SG, Ngoma TN, Chilenga PM. SARS-CoV 2 (Covid-19) heterogeneous mortality rates across countries may be partly explained by life expectancy, calorie intake, and prevalence of diabetes. *Hum Ecol Interdiscip J* 2020; **21**: 1–6.
23. Tomasoni D, Italia L, Adamo M, Inciardi RM, Lombardi CM, Solomon SD, Metra M. COVID-19 and heart failure: from infection to inflammation and angiotensin II stimulation. Searching for evidence from a new disease. *Eur J Heart Fail* 2020; **22**: 957–966.
24. Mancia G, Rea F, Ludergnani M, Apolone G, Corrao G. Renin–angiotensin–aldosterone system blockers and the risk of COVID-19. *N Engl J Med Massachussetts Medical Society* 2020; **382**: 2431–2440.
25. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, Gong W, Liu X, Liang J, Zhao Q, Huang H, Yang B, Huang C. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiol* 2020; **5**: 802–810.
26. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, Ma K, Xu D, Yu H, Wang H, Wang T, Guo W, Chen J, Ding C, Zhang X, Huang J, Han M, Li S, Luo X, Zhao J, Ning Q. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ* 2020; **368**: 1091.
27. Panagides V, Vincent F, Weizman O, Jonveaux M, Trimaille A, Pommier T, Cellier J, Geneste L, Marsou W, Deney A, Attou S, Delmotte T, Fauvel C, Ezzouhairi N, Perin B, Zakine C, Levasseur T, Ma I, Chavignier D, Noirclerc N, Darmon A, Mevelec M, Karsenty C, Duceau B, Sutter W, Mika D, Pezel T, Waldmann V, Ternacle J, Cohen A, Bonnet G, Critical COVID-19 France Investigators. History of heart failure in patients with coronavirus disease 2019: insights from a French registry. *Arch Cardiovasc Dis* 2021; **24** S1875-2136(21)000875.
28. Manka R, Karolyi M, Polacin M, Holy EW, Nemeth J, Steiger P, Schuepbach RA, Zinkernagel AS, Alkadhi H, Mehra MR, Ruschitzka F. Myocardial edema in COVID-19 on cardiac MRI. *J Heart Lung Transplant* 2020; **39**: 730–732.
29. Puntmann VO, Carerj ML, Wieters I, Fahim M, Arendt C, Hoffmann J, Shchendrygina A, Escher F, Vasa-Nicotera M, Zeiher AM, Vehreschild M, Nagel E. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). *JAMA Cardiol* 2020; **5**: 1265–1273.
30. Szekely Y, Lichter Y, Taieb P, Banai A, Hochstadt A, Merdler I, Gal Oz A, Rothschild E, Baruch G, Peri Y, Arbel Y, Topilsky Y. Spectrum of cardiac manifestations in COVID-19: a systematic echocardiographic study. *Circulation* 2020; **142**: 342–353.
31. Barthelmes J, Nägele MP, Ludovici V, Ruschitzka F, Sudano I, Flammer AJ. Endothelial dysfunction in cardiovascular disease and Flammer syndrome—similarities and differences. *EPMA J BioMed Central Ltd* 2017: 99–109.
32. Shah SJ, Lam CSP, Svedlund S, Saraste A, Hage C, Tan RS, Beussink-Nelson L, Faxén UL, Fermer ML, Broberg MA, Gan LM, Lund LH. Prevalence and correlates of coronary microvascular dysfunction in heart failure with preserved ejection fraction: PROMIS-HFpEF. *Eur Heart J* 2018; **39**: 3439–3450.
33. Lopes RD, Macedo AVS, de Barros E, Silva PGM, Moll-Bernardes RJ, Dos Santos TM, Mazza L, Feldman A, D'andréa Saba Arruda G, de Albuquerque DC, Camiletti AS, de Sousa AS, de Paula TC, Giusti KGD, Domiciano RAM, Noya-Rabelo MM, Hamilton AM, Loures VA, Dionísio RM, Furquim TAB, de Luca FA, Dos Santos Sousa ÍB, Bandeira BS, Zukowski CN, de Oliveira RGG, Ribeiro NB, de Moraes JL, Petriz JLF, Pimentel AM, Miranda JS, de Jesus Abufaiad BE, Gibson CM, Granger CB, Alexander JH, de Souza OF, BRACE CORONA Investigators. Effect of discontinuing vs continuing angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on days alive and out of the hospital in patients admitted with COVID-19: a randomized clinical trial. *JAMA* 2021 Jan 19; **325**: 254–264.
34. Volpe M, Battistoni A. Systematic review of the role of renin-angiotensin system inhibitors in late studies on Covid-19: a new challenge overcome? *Int J Cardiol* 2020; **321**: 150–154.
35. Poissy J, Goutay J, Caplan M, Parmentier E, Duburcq T, Lassalle F, Jeanpierre E, Rauch A, Labreuche J, Susen S, Lille ICU Haemostasis COVID-19 Group. Pulmonary embolism in patients with COVID-19: awareness of an increased prevalence. *Circulation* 2020; **142**: 184–186.
36. Ameri P, Inciardi RM, di Pasquale M, Agostoni P, Bellasi A, Camporotondo R, Canale C, Carubelli V, Carugo S, Catagnano F, Danzi G, Dalla Vecchia L, Giovinazzo S, Gnecchi M, Guazzi M, Iorio A, La Rovere MT, Leonardi S, Maccagni G, Mapelli M, Margonato D, Merlo M, Monzo L, Mortara A, Nuzzi V, Piepoli M, Porto I, Pozzi A, Provenzale G, Sarullo F, Sinagra G, Tedino C, Tomasoni D, Volterrani M, Zaccone G, Lombardi CM, Senni M, Metra M. Pulmonary embolism in patients with COVID-19: characteristics and outcomes in the cardio-COVID Italy multicenter study. *Clin Res Cardiol* 2021; **110**: 1020–1028.