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## CLINICAL RESEARCH

# History of heart failure in patients with coronavirus disease 2019: Insights from a French registry<sup>☆</sup>



*Antécédents d'insuffisance cardiaque cardiaque chez les patients atteints de la COVID-19 : données d'un registre français*

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**Abbreviations:** ACE2, angiotensin-converting enzyme 2; COVID-19, coronavirus disease 2019; CHF, chronic heart failure; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; qSOFA, quick sequential organ failure assessment; RAAS, renin-angiotensin-aldosterone system; RT-PCR, real-time reverse transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

<sup>☆</sup> Tweet: History of heart failure in patients with COVID-19 was associated with a higher risk of in-hospital death or orotracheal intubation. @CCF\_cardio @SFCardio.

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## KEYWORDS

Heart failure;  
COVID-19;  
HFpEF;  
HFrEF;  
RAAS inhibitors

## Summary

**Background.** – Although cardiovascular comorbidities seem to be strongly associated with worse outcomes in patients with coronavirus disease 2019 (COVID-19), data regarding patients with preexisting heart failure are limited.

**Aims.** – To investigate the incidence, characteristics and clinical outcomes of patients with COVID-19 with a history of heart failure with preserved or reduced ejection fraction.

**Methods.** – We performed an observational multicentre study including all patients hospitalized for COVID-19 across 24 centres in France from 26 February to 20 April 2020. The primary endpoint was a composite of in-hospital death or need for orotracheal intubation.

**Results.** – Overall, 2809 patients (mean age  $66.4 \pm 16.9$  years) were included. Three hundred and seventeen patients (11.2%) had a history of heart failure; among them, 49.2% had heart failure with reduced ejection fraction and 50.8% had heart failure with preserved ejection fraction. COVID-19 severity at admission, defined by a quick sequential organ failure assessment score  $> 1$ , was similar in patients with versus without a history of heart failure. Before and after adjustment for age, male sex, cardiovascular comorbidities and quick sequential organ failure assessment score, history of heart failure was associated with the primary endpoint (hazard ratio [HR]: 1.41, 95% confidence interval [CI]: 1.06–1.90;  $P=0.02$ ). This result seemed to be mainly driven by a history of heart failure with preserved ejection fraction (HR: 1.61, 95% CI: 1.13–2.27;  $P=0.01$ ) rather than heart failure with reduced ejection fraction (HR: 1.19, 95% CI: 0.79–1.81;  $P=0.41$ ).

**Conclusions.** – History of heart failure in patients with COVID-19 was associated with a higher risk of in-hospital death or orotracheal intubation. These findings suggest that patients with a

history of heart failure, particularly heart failure with preserved ejection fraction, should be considered at high risk of clinical deterioration.

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## MOTS CLÉS

COVID-19 ;  
SARS-COV 2 ;  
Femme ;  
Résultats ;  
Facteurs de risque

## Résumé

**Contexte.** — Les antécédents cardiovasculaires semblent associés à un risque de complications accru chez les patients atteints de la COVID-19. Cependant, peu de données sont actuellement disponibles concernant les patients ayant une insuffisance cardiaque connue.

**Objectifs.** — Définir l'incidence, les caractéristiques et le pronostic clinique des patients atteints de la COVID-19 avec un antécédent d'insuffisance cardiaque à fraction d'éjection préservée ou réduite.

**Méthodes.** — Via une étude observationnelle rétrospective et multicentrique, tous les patients hospitalisés du 26 février au 20 avril 2020 pour une infection à SARS-CoV-2 parmi 24 centres français ont été inclus. Le critère de jugement principal était un critère composite comprenant la mortalité intra-hospitalière ou la nécessité d'une intubation orotrachéale.

**Résultats.** — Au total, 2809 patients ( $66,4 \pm 16,9$  ans) ont été inclus. Trois cent dix-sept patients (11,2 %) avaient un antécédent d'insuffisance cardiaque. Parmi ces derniers, 49,2 % avait une fraction d'éjection réduite et 50,8 % une fraction d'éjection préservée. La sévérité de l'infection à l'admission, définie par un score qSOFA > 1, était similaire entre les patients avec ou sans antécédent d'insuffisance cardiaque. Avec ou sans ajustement sur l'âge, le genre masculin, les comorbidités cardiaques et le score qSOFA, l'existence préalable d'une insuffisance cardiaque était associée de manière significative au critère de jugement principal (HR : 1,41, IC95 % : 1,06–1,90 ;  $p=0,02$ ). Ce résultat est principalement imputable aux patients ayant un antécédent d'insuffisance cardiaque à fraction d'éjection préservée (HR : 1,61, IC95 % : 1,13–2,27 ;  $p=0,01$ ) par rapport à ceux ayant une fraction d'éjection réduite (HR : 1,19, IC95 % : 0,79–1,81 ;  $p=0,41$ ).

**Conclusions.** — L'existence d'une insuffisance cardiaque préalable chez les patients présentant une infection COVID-19 est associée à un risque accru de mortalité ou d'intubation orotrachéale. Ces résultats suggèrent que ces patients, particulièrement ceux à fraction d'éjection préservée, doivent être considérés comme à haut risque de dégradation clinique et surveillés de manière rapprochée.

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## Background

Since its emergence in December 2019 in China, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread rapidly around the world, causing the coronavirus disease 2019 (COVID-19). This respiratory infection exhibits varied clinical features and severity forms, ranging from asymptomatic to severe respiratory failure and death [1]. The association between COVID-19 and cardiovascular risk factors, such as male sex, hypertension, diabetes, obesity, chronic kidney disease and cardiovascular diseases, was highlighted rapidly [2]. These cardiovascular comorbidities are also associated with a more severe clinical presentation and a higher risk of death [3]. This greater vulnerability may be directly related to the pathogenesis of COVID-19. The infection is caused by binding of the viral surface spike protein to the human angiotensin-converting enzyme 2 (ACE2) receptor, which is highly expressed on the surface of pulmonary endothelial cells and cardiomyocytes [4]. As ACE2 is a negative regulator of the activation of the renin-angiotensin-aldosterone system (RAAS), patients with underlying chronic heart failure (CHF) could be especially vulnerable to COVID-19 [5–7]. Whereas acute heart

failure (HF) is frequently reported in patients with COVID-19, and may account for up to one third of deaths [8], the impact of preexisting HF seems negative [9]. However, most of the registries or cohorts used generic terminology, such as “cardiac diseases”, with little granularity. A recent Spanish study did not observe any association between preexisting CHF and mortality, but reported a limited sample size of patients ( $n=154$ ) and did not distinguish between HF subtypes [10] — namely, HF with reduced ejection fraction (HFrEF) or preserved ejection fraction (HFpEF).

The aim of this study was to examine the incidence, characteristics and clinical outcomes of patients with a history of HFrEF or HFpEF hospitalized for COVID-19.

## Methods

### Study design

The Critical COVID-19 France registry is a multicentre observational study initiated by the French Society of Cardiology (ClinicalTrials.gov identifier: NCT04344327). From 26 February to 20 April 2020, all consecutive patients hospitalized

in COVID-19 units for a diagnosis of SARS-CoV-2 infection defined by the World Health Organization criteria [11] were included in 24 French centres [12]. A complete list of the Critical Covid-19 France Investigators is provided in the Appendix. "COVID-19 units" were created in France to cope with the surge of patients during the outbreak. These units were located in medical wards of each hospital, and were managed by a large pool of physicians, regardless of their specialty. A cardiologist participated in the management of patients in these COVID-19 units, as well as physicians from other specialties. The patients admitted to these units were all-comer stable patients with COVID-19 requiring hospitalization, regardless of preexisting cardiac or non-cardiac comorbidities. Patients were eligible to be included in the registry if they presented with a positive laboratory finding for SARS-CoV-2 on real-time reverse transcriptase polymerase chain reaction (RT-PCR) of nasal and pharyngeal swabs or lower respiratory tract aspirate (confirmed case) or if they presented with a typical disease pattern on computed tomography, including ground glass opacity, crazy paving, consolidation and reticular pattern, and did not require immediate admission to an intensive care unit. The Critical COVID-19 France study was declared to and authorized by the French data protection committee (Commission Nationale Informatique et Liberté; authorisation No. 2207326v0), and was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Informed consent was obtained from each patient. The authors had full access to and take full responsibility for the integrity of the data.

## Data collection

All data were collected by local investigators on an electronic case-report form via REDCap software (Research Electronic Data Capture, Vanderbilt University, Nashville, TN, USA) hosted by a secured server from the French Institute of Health and Medical Research at the Paris Cardiovascular Research Centre. Patient demographics, including age, body mass index and sex, were obtained. Underlying comorbidities present in the patients' electronic health records were collected: cardiovascular risk factors (current or history of smoking, hypertension, diabetes, dyslipidaemia, chronic kidney disease) and preexisting cardiovascular diseases, including coronary artery disease, history of HF, known left ventricular ejection fraction (LVEF) value, atrial fibrillation or stroke.

## Study definitions

CHF was defined according to the European Society of Cardiology guidelines [13]. History of HF was synonymous with preexisting CHF, and was defined as any previous episode of HF documented by a cardiologist, whether or not it required hospitalization. Patients with a history of HF had to have a report of an echocardiographic evaluation on their record. The terminology of HFrEF referred to patients with CHF and an LVEF < 50%, and HFpEF to those with CHF and an LVEF  $\geq$  50%, based on the LVEF as assessed by echocardiography before admission. The LVEF value was collected as a binary variable ( $\geq$  or < 50%). In a subset of patients with HFrEF ( $n=156$ ), a more granular

LVEF range (< 35%, 35–49%, > 50%) could be reported in the case-report form by the local investigator. Cardiac medications at admission were also collected (RAAS inhibitors, diuretics, beta-blockers and anticoagulation). Additional data included clinical variables, blood test results at admission and chest computed tomography characteristics. The New York Heart Association class was defined at patient admission. The severity at admission was assessed using the quick sequential organ failure assessment (qSOFA) score [14] (qSOFA score > 1 for severe illness) and the percentage of pulmonary parenchymal infiltrate on chest computed tomography (severe if > 50% of the total parenchyma) [15]. All medical interventions (including pharmacological agents to treat SARS-CoV-2) were left to the discretion of the referring medical team. Acute HF refers to rapid onset or worsening of symptoms and/or signs of HF during the study period, associated with symptoms of volume overload and/or improvement after initiation of diuretic therapy, as defined by the European Society of Cardiology guidelines [13]. Diagnosis of acute HF was made by the physician in charge of the patient, with a multivariable approach, including clinical examination, biomarkers (B-type natriuretic peptide [BNP] or N-terminal prohormone of BNP [NT-proBNP]), chest radiography, computed tomography and echocardiographic evaluation when available and indicated, as recommended and defined by the international guidelines [13]. Most of the investigating centres measured either BNP or NT-proBNP. To analyse the largest number of patients, we have therefore reported BNP or NT-proBNP value as a single semiquantitative value (elevated or not), according to each local laboratory threshold. The reported biomarker concentrations were measured at patient admission.

## Study endpoint

The primary composite endpoint was in-hospital death or need for orotracheal intubation. The date of final follow-up for patients still hospitalized was 21 April 2020.

## Statistical analysis

Categorical data are reported as counts and percentages. Continuous data are reported as means  $\pm$  standard deviations for normally distributed data and as medians (interquartile ranges) for non-normally distributed data. Comparisons used the  $\chi^2$  test or Fisher's exact test for categorical variables, and Student's *t*-test or the Mann–Whitney–Wilcoxon test, as appropriate, for continuous variables. Survival probability was assessed with Kaplan–Meier curves, and compared using a log-rank test. A Cox proportional hazard model was used to estimate the association of HF with the primary endpoint. The multivariable analysis included all variables known to be clinically relevant or associated with the primary endpoint by univariate analysis. Age, body mass index and qSOFA were entered as continuous variables in the multivariable analysis. A Cox model was also used to assess interactions in subgroups of patients: age (< 65 years or  $\geq$  65 years), sex (male versus female), body mass index (< 30 kg/m<sup>2</sup> or  $\geq$  30 kg/m<sup>2</sup>), hypertension, diabetes, coronary artery disease, stroke, chronic kidney disease, RAAS inhibitors and qSOFA score ( $\leq$  1 or > 1).



A two-tailed  $P$ -value  $<0.05$  was considered statistically significant. All data were analysed using R software, version 3.6.3 (R Project for Statistical Computing, Vienna, Austria).

## Results

### Study population

Overall, 2809 consecutive patients (mean age  $66.4 \pm 16.9$  years; 57.6% male) hospitalized for a SARS-CoV-2 infection from 26 February to 20 April 2020 were analysed (Table 1, Fig. 1). The median time from onset of symptoms to hospitalization was 7.0 (3–10) days. Among patients with minimal ( $n=930$ ), moderate ( $n=844$ ) and severe ( $n=422$ ) parenchymal involvement, 112 (12.2%), 57 (6.9%) and 23 patients (5.6%) had a negative RT-PCR, respectively. Patients had a high cardiovascular disease burden, including history of obesity (30.3%), hypertension (50.6%), diabetes (23.7%), dyslipidaemia (27.9%), stroke (8.98%), atrial fibrillation (14.3%), coronary artery disease (12.4%) and HF (11.3%). Targeted cardiovascular therapies included beta-blockers (25.6%), RAAS inhibitors (33.6%) and anticoagulant treatments (14.3%). Regarding patients with a history of HF at admission, 51.4% of patients were in New York Heart Association class III or IV, 61.6% of patients had a qSOFA score  $>1$  and 80.8% had a minimal or moderate COVID-19-related pulmonary infiltrate. Overall, 179 patients (6.49%) presented with signs of HF, of whom 38 (25.3%) had a previous diagnosis of HFrEF and 38 (23.8%) had a previous diagnosis of HFpEF. One hundred and three patients (4.21%) with no previous history of HF also had signs of HF. Details of treatments administered before and during hospitalization in the different groups are reported in Table A.1.

### Association of HF with endpoints

In-hospital death or need for orotracheal intubation occurred in 789 patients (28.1%). Patients with a history of HF were older and had more comorbidities compared with patients without previous HF (Table 1). At admission, acute HF decompensation was more frequent in patients with versus without a history of HF (24.0% vs. 4.21%;  $P < 0.001$ ), but the qSOFA score was similar in these two groups. The primary composite endpoint occurred in 35.6% of patients with a history of HF versus 26.5% of those without a history of HF ( $P < 0.001$ ; Table 2). The association of baseline characteristics with the primary endpoint is detailed in Table A.2. Advanced age and male sex were associated with the primary endpoint. In addition, elevated body mass index, hypertension, use of RAAS inhibitors, diabetes, stroke, coronary artery disease, chronic kidney disease and HF were also associated with the primary endpoint, as was the qSOFA score at admission. After adjustment for confounding factors, including age, male sex, cardiovascular comorbidities and qSOFA score at admission, history of HF remained independently associated with the primary endpoint (hazard ratio [HR]: 1.37, 95% confidence interval [CI]: 1.03–1.82;  $P = 0.03$ ; Table 3, Fig. 2A). Neither hypertension nor RAAS inhibitors remained independently associated with the primary endpoint.

### Outcomes in patients with HFrEF versus HFpEF

Baseline characteristics of the study population according to history and subtype of HF are detailed in Table 1. Among the 317 patients with history of HF, 156 had a reduced ejection fraction (49.2% HFrEF, 5.6% overall) and 161 had a preserved ejection fraction (50.8% HFpEF, 5.7% overall). Compared with the HFrEF group, patients with HFpEF were similar in terms of age and sex, but had a higher cardiovascular disease burden, including history of hypertension, stroke, valvular heart disease and coronary artery disease, and less frequently received beta-blockers and RAAS inhibitors (Table 1). Severity at admission was similar in the two groups as assessed by the qSOFA score or/and chest computed tomography. Echocardiographic data during hospitalization were available for 148 patients (46.7%) in the HF population, and are reported in Table A.3. The primary endpoint occurrence was similar in patients with HFrEF versus HFpEF (respectively, 33.3% vs. 37.9%;  $P = 0.47$ ). Among patients with CHF who reached the primary endpoint ( $n = 113$ , 35.6%), in-hospital death or need for orotracheal intubation was observed in 10.3% and 26.9% of those with HFrEF, and in 19.3% and 23.0% of those with HFpEF, respectively (Table 2). In the univariate analysis, both types of HF were associated with the primary endpoint (Table A.2). HFpEF (HR: 1.61, 95% CI: 1.13–2.27;  $P = 0.01$ ), but not HFrEF (HR: 1.19, 95% CI: 0.79–1.81;  $P = 0.41$ ), remained associated with the primary endpoint after adjustment for confounding factors, including age, male sex, body mass index, stroke, coronary artery disease, chronic kidney disease, hypertension, RAAS inhibitors and qSOFA score (Table 3, Fig. 2B). After further adjustment for biomarkers, when available, HFpEF remained independently associated with the primary endpoint (HR: 1.72, 95% CI: 1.12–2.66;  $P = 0.01$ ; Table A.4). The sensitivity analysis including only the patients with positive RT-PCR demonstrated similar results (Table A.5). The subgroup analysis suggested that patients with HFpEF aged  $<65$  years seemed to be associated with worse outcomes (Fig. A.1), whereas absence of coronary artery disease or previous anticoagulation therapy was associated with worse outcomes in patients with HFrEF (Fig. A.2).

## Discussion

The main findings of this multicentre observational study are as follows:

- history of HF was observed in 11.3% of patients hospitalized for COVID-19;
- patients with COVID-19 with a history of CHF had a high cardiovascular disease burden, but severity at admission was similar in patients with versus without a history of CHF;
- CHF was associated with a 37% increased risk of occurrence of the primary endpoint of in-hospital death or need for orotracheal intubation;
- this higher risk seemed to be driven by history of HFpEF.

Our study parallels previous observations that cardiovascular diseases are frequent among patients hospitalized for COVID-19 [16]. More than half of the patients had hypertension, 30.3% were obese, 12.4% had a history of coronary

**Table 1** Baseline characteristics of the overall population (n=2809), and according to heart failure subtypes.

	n	Overall (n=2809)	No HF (n=2492)	HF		Overall P-value	HFrEF versus HFpEF P-value
				HFrEF (n=156)	HFpEF (n=161)		
<b>Demographics</b>							
Age (years)	2806	66.4 ± 16.9	65.4 ± 16.9	74.1 ± 13.5	75.6 ± 16.1	<0.001	0.36
Male sex	2809	1619 (57.6)	1420 (57.0)	99 (63.5)	100 (62.1)	0.14	0.90
Body mass index (kg/m <sup>2</sup> )	2439	27.8 ± 6.03	27.8 ± 5.95	27.1 ± 6.29	28.3 ± 6.94	0.22	0.12
Obesity	2439	740 (30.3)	658 (30.5)	38 (27.7)	44 (30.3)	0.79	0.73
<b>Cardiovascular risk factor</b>							
Smoking	2747	369 (13.4)	304 (12.5)	36 (23.7)	29 (18.5)	<0.001	0.33
Hypertension	2793	1413 (50.6)	1174 (47.4)	107 (68.6)	132 (82.0)	<0.001	0.008
Diabetes	2794	661 (23.7)	545 (22.0)	52 (33.5)	64 (40.3)	<0.001	0.27
Dyslipidaemia	2793	778 (27.9)	637 (25.7)	73 (47.1)	68 (42.5)	<0.001	0.48
<b>Co-existing conditions</b>							
COPD	2809	158 (5.62)	125 (5.02)	14 (8.97)	19 (11.8)	<0.001	0.47
Chronic kidney disease	2774	386 (13.9)	281 (11.4)	50 (33.1)	55 (34.6)	<0.001	0.88
Stroke	2772	249 (8.98)	185 (7.52)	24 (15.6)	40 (25.3)	<0.001	0.047
Peripheral artery disease	2772	139 (5.01)	97 (3.94)	17 (11.1)	25 (15.7)	<0.001	0.30
Atrial fibrillation	2791	399 (14.3)	278 (11.2)	54 (35.3)	67 (41.6)	<0.001	0.30
Coronary artery disease	2809	347 (12.4)	230 (9.23)	74 (47.4)	43 (26.7)	<0.001	<0.001
Valvular heart disease	2790	111 (3.98)	70 (2.82)	17 (11.1)	24 (15.2)	<0.001	<0.001
History of HFrEF	2809	156 (5.55)	0 (0.0)	156 (100)	0 (0.0)	<0.001	<0.001
History of HFpEF	2809	161 (5.73)	0 (0.0)	0 (0.0)	161 (100)	<0.001	<0.001
Active malignancy	2809	184 (6.55)	161 (6.46)	16 (10.3)	7 (4.35)	0.08	0.17
Venous thromboembolic disease	2809	210 (7.48)	174 (6.98)	15 (9.62)	21 (13.0)	0.010	0.43
<b>Chronic medications</b>							
Anticoagulation	2809	403 (14.3)	278 (11.2)	59 (37.8)	66 (41.0)	<0.001	0.64
Beta-blocker	2809	718 (25.6)	531 (21.3)	107 (68.6)	80 (49.7)	<0.001	0.001
RAAS inhibitor	2809	945 (33.6)	768 (30.8)	100 (64.1)	77 (47.8)	<0.001	0.001
Diuretic	2809	547 (19.5)	381 (15.3)	87 (55.8)	79 (49.1)	<0.001	0.28
<b>Clinical characteristics</b>							
NYHA functional class I or II	2445			54 (39.4)	62 (45.3)		0.39
NYHA functional class III or IV				83 (60.6)	75 (54.7)		
Heart rate (beats/min)	2564	86.6 ± 17.9	86.8 ± 17.7	86.9 ± 19.1	83.1 ± 19.4	0.044	0.09
Systolic blood pressure (mmHg)	2762	131 ± 21.9	131 ± 21.2	124 ± 25.5	137 ± 25.8	<0.001	<0.001
Diastolic blood pressure (mmHg)	2762	74.3 ± 13.4	74.5 ± 13.1	72.0 ± 15.8	73.7 ± 15.8	0.07	0.35
Respiratory frequency (cpm)	2054	23.4 ± 6.57	23.3 ± 6.52	24.3 ± 7.36	23.0 ± 6.52	0.26	0.17
Glasgow score < 15	2772	192 (6.93)	156 (6.34)	15 (9.80)	21 (13.3)	0.001	0.43
Heart failure signs	2756	179 (6.49)	103 (4.21)	38 (25.3)	38 (23.8)	<0.001	0.85
qSOFA > 1	2051	1264 (61.6)	1124 (61.5)	67 (60.9)	73 (64.6)	0.79	0.67

Table 1 (Continued)

	n	Overall (n = 2809)	No HF (n = 2492)	HF		Overall P-value	HFrEF versus HFpEF P-value
				HFrEF (n = 156)	HFpEF (n = 161)		
Laboratory tests							
Leukocytes (G/L)	2758	7.29 ± 4.77	7.22 ± 4.83	8.11 ± 4.52	7.54 ± 3.95	0.06	0.24
Lymphocytes (G/L)	2718	1.31 ± 3.49	1.34 ± 3.70	1.11 ± 0.71	0.97 ± 0.63	0.33	0.08
Haemoglobin (g/dL)	2766	13.1 ± 1.98	13.2 ± 1.94	12.6 ± 2.16	12.3 ± 2.28	< 0.001	0.30
Platelets (G/L)	2739	221 ± 99.4	221 ± 99.3	220 ± 106	208 ± 93.6	0.29	0.30
D-dimer (µg/L)	1124	1646 ± 3679	1444 ± 2265	4349 ± 12229	2571 ± 4350	< 0.001	0.30
GFR (mL/min/m <sup>2</sup> )	2765	81.8 ± 29.4	83.9 ± 28.5	65.7 ± 31.8	65.5 ± 31.5	< 0.001	0.97
Elevated BNP or NT-proBNP <sup>a</sup>	1737	916 (52.7)	685 (46.4)	125 (91.9)	106 (84.1)	< 0.001	0.08
Troponin elevation <sup>b</sup>	1725	556 (32.2)	415 (27.8)	84 (70.6)	57 (49.6)	< 0.001	0.002
Diagnostic method							
Parenchymal involvement	2196					0.07	0.53
Minimal or moderate < 50%		1774 (80.8)	1608 (81.4)	81 (77.9)	85 (73.3)		
Severe > 50%		422 (19.2)	368 (18.6)	23 (22.1)	31 (26.7)		
Positive SARS-CoV-2 RT-PCR	2759	2530 (91.7)	2252 (91.9)	137 (90.7)	141 (89.8)		

Data are expressed as mean ± standard deviation or number (%). BNP: B-type natriuretic peptide; COPD: chronic obstructive pulmonary disease; GFR: glomerular filtration rate; HF: heart failure; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; NT-proBNP: N-terminal prohormone of B-type natriuretic peptide; NYHA: New York Heart Association; qSOFA: quick sequential organ failure assessment; RAAS: renin-angiotensin-aldosterone system; RT-PCR: real-time reverse transcriptase polymerase chain reaction; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

<sup>a</sup> BNP > 100 pg/mL or NT-proBNP > 300 pg/mL.

<sup>b</sup> Above each centre's threshold.

Table 2 Occurrence of the primary endpoint according to heart failure subtypes.

Endpoints	Overall	No HF	HF	HFrEF	HFpEF	Overall P-value	HFrEF versus HFpEF P-value
Primary endpoint	789 (28.1)	660 (26.5)	113 (35.6)	52 (33.3)	61 (37.9)	< 0.001	0.47
Orotracheal intubation	363 (12.9)	316 (12.7)	47 (14.8)	16 (10.3)	31 (19.3)	0.033	0.022
In-hospital death	349 (12.4)	270 (10.8)	79 (24.9)	42 (26.9)	37 (23.0)	< 0.001	0.50

Data are expressed as number (%). HF: heart failure; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction.

artery disease and 11.3% had preexisting CHF. Previous studies reported that patients with cardiovascular comorbidities were at high risk of respiratory failure [1], and accounted for 30–35% of COVID-19-related deaths [17]. However, most of the studies used generic terminology (e.g. ‘‘cardiovascular diseases’’), encompassing various conditions such as HF, coronary artery disease and hypertension [18]. To our knowledge, the present study is the first to specifically focus on CHF in patients with COVID-19.

Acute myocardial injury defined by elevated biomarkers has been reported in approximately 25% of hospitalized patients with COVID-19 [19]. This cardiac tropism may be related to the pathogenesis of COVID-19. The SARS-CoV-2

surface spike protein binds to the human ACE2 receptor, which is highly expressed on pulmonary alveolar cells [20] and cardiomyocytes [4]. This portal of entry could induce direct viral cardiomyocyte toxicity [20]. In addition, microvascular dysfunction (vasculitis), oxygen demand mismatch (hypoxia) and exacerbated inflammatory state could indirectly induce myocardial injury, leading to myocardial function impairment and HF [21]. The development of congestive HF is relatively frequent in COVID-19, and was reported in 23% of patients in Wuhan (52% of non-survivors) [22]. Studies have reported rates of HF-related death ranging from 19.4% to 49.0% in patients infected with SARS-CoV-2 [8,23]. Furthermore, a healthcare database study showed



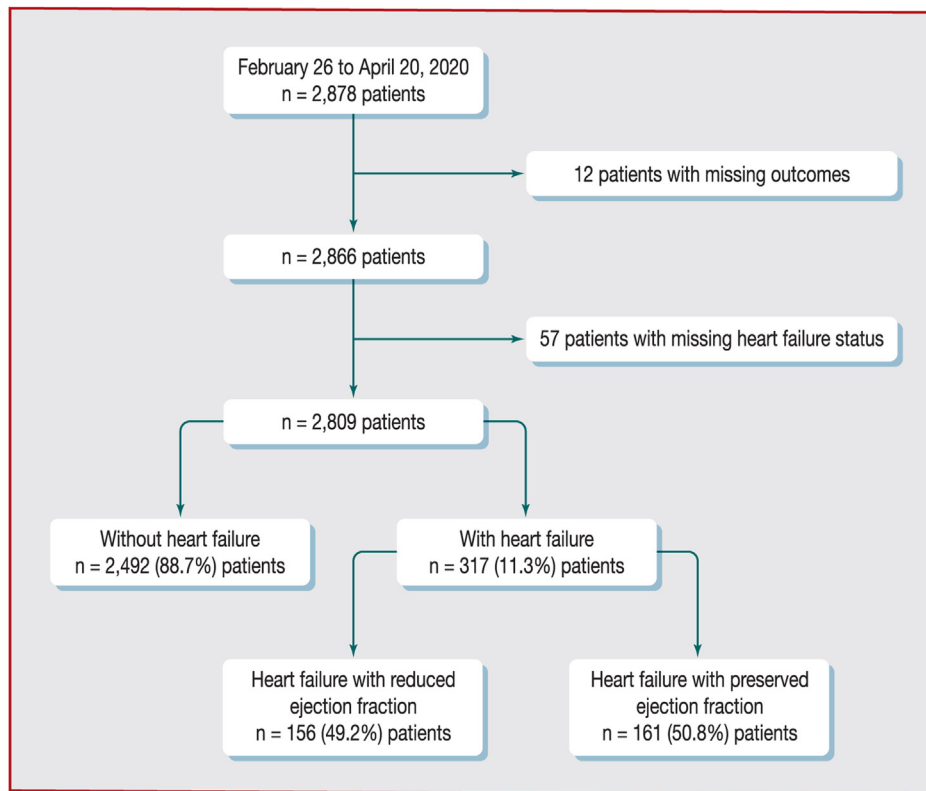


Figure 1. Study flowchart of the included population.

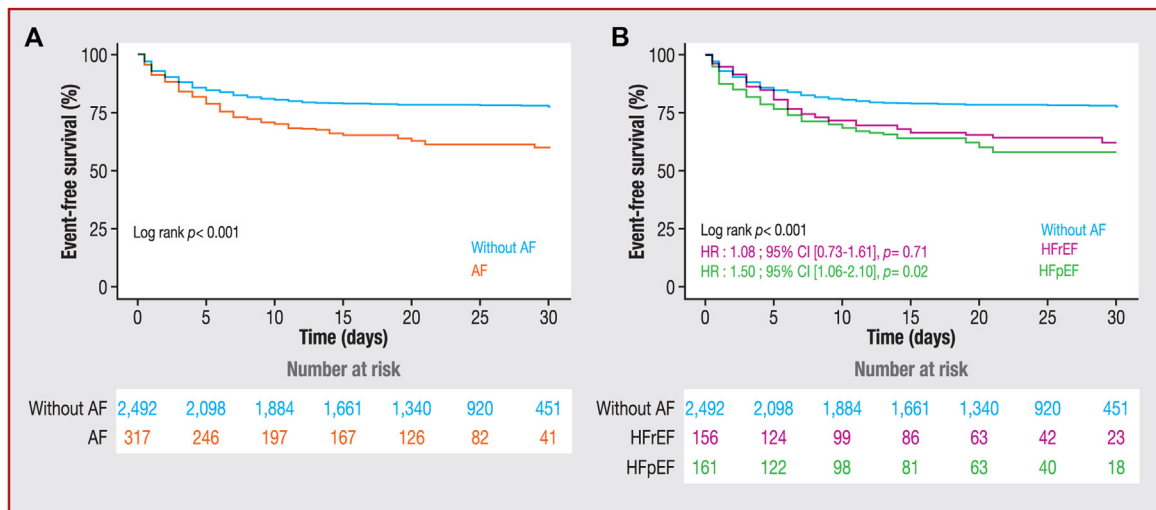


Figure 2. A. Kaplan–Meier survival curves divided according to heart failure status. B. Kaplan–Meier survival curves divided according to heart failure subtypes. CI: confidence interval; HF: heart failure; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; HR: hazard ratio.

that patients with a history of HF carried a worse prognosis when hospitalized for COVID-19 [24].

This vulnerability in patients with preexisting CHF has previously been described with other viral infections, such as Middle East respiratory syndrome-related coronavirus [25].

The unexpected finding of our study was that the poor prognosis observed in patients with CHF seemed to be driven by patients with HFpEF. Indeed, HFpEF was associated with a 1.57-fold increased risk of in-hospital death

or need for orotracheal intubation, whereas no association was observed in patients with HFrEF. This result contradicts another study that did not find any discrepancies between HFpEF and HFrEF [26]. However, a recent review considered patients with HFpEF to be at high risk of adverse events [27]. Our finding regarding HFpEF seemed to be mainly related to the risk of orotracheal intubation rather than in-hospital death. Still, the exact physiopathology of HFpEF at its beginning is unclear. These patients may have

**Table 3** Parameters associated with the primary endpoint by multivariable analysis.

	Hazard ratio (95% CI)	P-value
<b>Global HF model (referent)</b>		
Age (per 1-year increase)	1.01 (1.01–1.02)	< 0.001
Male sex (female sex)	1.58 (1.28–1.95)	< 0.001
Body mass index (per 1-kg/m <sup>2</sup> increase)	1.02 (1.00–1.03)	0.06
Hypertension (vs. no hypertension)	1.08 (0.82–1.43)	0.57
Diabetes (vs. no diabetes)	1.34 (1.07–1.68)	0.01
Coronary artery disease (vs. no coronary artery disease)	0.84 (0.62–1.15)	0.28
Stroke (vs. no stroke)	0.92 (0.67–1.26)	0.60
Chronic kidney disease (vs. no chronic kidney disease)	1.51 (1.17–1.95)	< 0.001
Heart failure (any, HFrEF or HFpEF) (vs. no heart failure)	1.41 (1.06–1.90)	0.02
RAAS inhibitor treatment (vs. no RAAS treatment)	0.96 (0.75–1.22)	0.72
Beta-blocker treatment (vs. no beta-blocker)	0.90 (0.70–1.16)	0.40
qSOFA score > 1 (vs. 0 or 1)	2.10 (1.68–2.64)	< 0.001
<b>HFrEF/HFpEF model (referent)</b>		
Age (per 1-year increase)	1.01 (1.01–1.02)	< 0.001
Male sex (female sex)	1.58 (1.28–1.95)	< 0.001
Body mass index (per 1-kg/m <sup>2</sup> increase)	1.02 (1.00–1.03)	0.06
Hypertension (vs. no hypertension)	1.07 (0.81–1.41)	0.62
Diabetes (vs. no diabetes)	1.34 (1.07–1.68)	0.01
Coronary artery disease (vs. no coronary artery disease)	0.87 (0.64–1.18)	0.36
Stroke (vs. no stroke)	0.91 (0.66–1.24)	0.55
Chronic kidney disease (vs. no chronic kidney disease)	1.52 (1.18–1.96)	0.001
HFrEF (vs. no heart failure)	1.19 (0.79–1.81)	0.41
HFpEF (vs. no heart failure)	1.61 (1.13–2.27)	0.01
RAAS inhibitor (vs. no RAAS treatment)	0.96 (0.75–1.23)	0.75
Beta-blocker (vs. no beta-blocker)	0.91 (0.70–1.16)	0.44
qSOFA score > 1 (vs. 0 or 1)	2.10 (1.67–2.64)	< 0.001

CI: confidence interval; HF: heart failure; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; qSOFA: quick sepsis-related organ failure assessment; RAAS: renin-angiotensin-aldosterone system inhibitors.

more severe systemic inflammation, endothelial and mitochondrial dysfunction, oxidative stress and RAAS activation than patients with HFrEF [28]. These dysregulations may be responsible for myocardial ischaemia and diffuse fibrosis, leading to impaired left ventricular relaxation, decreased left ventricular compliance and longitudinal contractile dysfunction. Szekely et al. reported echocardiographic features in 100 patients hospitalized for non-severe COVID-19 [29]. Among them, left ventricular diastolic and systolic dysfunctions were observed in 16% and 10% of patients, respectively. Therefore, patients with HFpEF and SARS-CoV-2 infection may be more sensitive to haemodynamic changes induced by the sepsis or the fluid administered to maintain blood pressure, which could worsen respiratory function. These assumptions seem to be confirmed by a previous report suggesting that diuretic therapy plays a role in suspected HFpEF episodes [30]. Diagnosis of HF is therefore essential for close monitoring of patients, but is challenging, because HF shares several clinical features with COVID-19, such as dyspnoea and pulmonary infiltrate. Given the difficulty associated with performing echocardiography under strict isolation [31], biomarkers (e.g., troponin and natriuretic peptides) may help to identify these patients.

ACE2 plays a protective counter-regulatory role in the deleterious activation of RAAS [32]. Circulating ACE2 activity seems to be associated with more advanced HF, and

higher levels of ACE2 have been described in HFrEF than in HFpEF [33]. As circulating ACE2 promotes lung homeostasis [20], and is probably reflective of myocardium ACE2 receptor shedding [34], we could speculate that it may participate differently in the vulnerability observed in our cohort according to HF subtype. The role of pharmacological agents modulating the RAAS pathway has also been studied with scrutiny in COVID-19. It has been suggested that ACE2 inhibitors and angiotensin-receptor blockers, mainly administered for hypertension and/or HF, could upregulate ACE2 receptors and thus predispose patients to this infection [35]. However, a recent meta-analysis reported that RAAS inhibitors may reduce COVID-19 mortality in patients with hypertension [36]. These results are consistent with the present study, where hypertension and RAAS inhibitors were not associated with outcomes after adjustment for HF and hypertension, suggesting a role of confounding by indication.

### Study limitations

Our study has some limitations. First, because of its retrospective observational design, some data were not available. We did not gather information about previous intake of mineralocorticoid receptor antagonists or sacubitril/valsartan in patients with HF, which may impact the

prognosis. Second, only a trend of association between HFrEF and the primary endpoint was observed. The lack of statistical power related to the small sample of patients with HFrEF may explain this result. Third, we were unable to investigate the impact on outcomes of the dedicated COVID-19 treatment, and its potential cardiac toxicity (antiviral therapies and hydroxychloroquine). Fourth, the distinction between HFrEF and HFpEF was based on the previously reported LVEF using the cut-off of 50%, and did not include the mid-range LVEF (40–49%) [13]. Fifth, it would have been interesting to evaluate the clinical impact of BNP and NT-proBNP in all patients, but unfortunately this information was available in only 38% of the population. Sixth, the pathophysiological process explaining the difference in outcomes between HFrEF and HFpEF is unknown, and requires further investigation. Lastly, the study population represents a limited number of the patients admitted for COVID-19. Present results cannot be generalized to all patients with SARS-CoV-2 infection, because ambulatory and critically ill patients were not included; furthermore, most of the patients were included in university hospitals, with possible selection bias.

## Perspectives

Given the surge of patients with COVID-19 presenting with mild or moderate symptoms, there is a clinical need to better stratify the risk of developing a severe form of the disease, using both symptoms and preexisting conditions [37]. This study highlights the importance of the history of HF, and particularly the history of HFpEF. Although the results are only generalizable to symptomatic and hospitalized patients, the present study suggests that they may potentially benefit from closer monitoring to identify any clinical worsening. Further studies will be needed to evaluate the incremental value of this finding to the currently existing stratifying tool.

## Conclusions

History of HF was common in patients hospitalized for COVID-19. The primary endpoint of in-hospital death or need for orotracheal intubation was more frequently observed in patients with HF. The association of HF with outcomes seemed to be driven by the history of HFpEF. These findings suggest that, among patients with COVID-19, those with a history of HF should be considered to be at high risk of clinical worsening, and should be closely monitored.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.acvd.2021.04.003>.

## Disclosure of interest

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The other authors declare that they have no competing interest.

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