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# Increased susceptibility to SARS-CoV-2 infection in patients with reduced left ventricular ejection fraction

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## Abstract

**Aims** Cardiovascular disease has been recognized as a major determinant of coronavirus disease 2019 (COVID-19) vulnerability and severity. Angiotensin-converting enzyme (ACE) 2 is a functional receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and is up-regulated in patients with heart failure. We sought to examine the potential association between reduced left ventricular ejection fraction (LVEF) and the susceptibility to SARS-CoV-2 infection.

**Methods and results** Of the 1162 patients with acute coronary syndrome (ACS) who underwent percutaneous coronary intervention between February 2014 and October 2018, we enrolled 889 patients with available clinical follow-up data. Follow-up was conducted by telephone interviews 1 month after the start of the French lockdown which began on 17 March 2020. Patients were divided into two groups according to LVEF <40% (reduced LVEF) ( $n = 91$ ) or  $\geq 40\%$  (moderately reduced + preserved LVEF) ( $n = 798$ ). The incidence of COVID-19-related hospitalization or death was significantly higher in the reduced LVEF group as compared with the moderately reduced + preserved LVEF group (9% vs. 1%,  $P < 0.001$ ). No association was found between discontinuation of ACE-inhibitor or angiotensin-receptor blockers and COVID-19 test positivity. By multivariate logistic regression analysis, reduced LVEF was an independent predictor of COVID-19 hospitalization or death (odds ratio: 6.91, 95% confidence interval: 2.60 to 18.35,  $P < 0.001$ ).

**Conclusions** In a large cohort of patients with previous ACS, reduced LVEF was associated with increased susceptibility to COVID-19. Aggressive COVID-19 testing and therapeutic strategies may be considered for patient with impaired heart function.

**Keywords** Coronavirus disease 2019; Heart failure; Acute coronary syndrome

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## Introduction

Since December 2019, coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in considerable morbidity and mortality in more than 180 countries worldwide.<sup>1</sup> As early as mid-February, a large cluster of COVID-19 occurred in northeast France (Grand Est), and more specifically the Strasbourg healthcare system has faced high hospitalization and mortality rates. As of 12 June 2020, more than 15 000 patients in Grand Est have been tested positive for

COVID-19 with a reported death toll amounting to 3499 patients, and the numbers continue to rise.<sup>2</sup>

Previous investigations have shown that cardiovascular disease (CVD) was a common co-morbidity in patients with severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS).<sup>3,4</sup> In line with these findings, early studies reported from China demonstrated that the incidence of underlying CVD was 8.7–15% in patients with COVID-19.<sup>5–7</sup> Given the higher prevalence of cardiovascular (CV) risk factors among patients with COVID-19 in the USA,

the rate of CVD among those patients may even be higher in western countries.

In particular, the case fatality rate is likely to be higher in patients with underlying CVD, diabetes (DM), hypertension (HT), and cancer.<sup>8</sup> Recent studies have shown the prominent role of heart failure (HF) both as a risk factor of a more severe clinical condition and of increased mortality and as a possible consequence of COVID-19-related myocardial damage.<sup>9,10</sup> The incidence of new-onset HF during COVID-19 associated hospitalization was reported to be 23% and was more common in non-survivors compared with survivors (52% vs. 12%,  $P < 0.0001$ ).<sup>10</sup> More recently, a report from Northern Italy indicated a higher prevalence of pre-existing HF in non-survivors (63% vs. 27%,  $P = 0.009$ ).<sup>9</sup> Although the increased presence of HF holds true for severe patients with COVID-19, given the scarce availability of data regarding this topic, it remains unclear whether the severe condition following COVID-19 is mainly due to exacerbation of pre-existing cardiac dysfunction or new onset cardiomyopathy.

Angiotensin-converting enzyme 2 (ACE2) is a functional receptor on cell surfaces for both SARS-CoV and SARS-CoV-2 and is known to be increased in patients with HF.<sup>11,12</sup> Whether increased ACE2 expression due to HF may be responsible for host vulnerability and disease severity in the ongoing COVID-19 outbreak has not been explored. The present study was therefore performed to examine the potential association between reduced left ventricular ejection fraction (LVEF) following acute coronary syndrome (ACS) and the COVID-19 susceptibility.

## Methods

### Study participants

This retrospective, single centre study included patients from the Strasbourg Registry of Acute Coronary Syndrome and VASP (vasodilator-stimulated phosphoprotein) assessment. A total of 1162 patients with ACS were enrolled at our institution (Nouvel Hôpital Civil, Université de Strasbourg, Strasbourg, France) between February 2014 and October 2018. These patients with ACS were sub-classified as having ST elevation myocardial infarction (STEMI), non-STEMI, or unstable angina pectoris, and they were all treated by percutaneous coronary intervention (PCI). Demographic characteristics, medical history, biological, angiographic, and echocardiographic data were recorded.

### Echocardiographic assessments

Transthoracic echocardiography (TTE) was performed at the time of admission for the ACS events. Left ventricular ejection fraction was assessed using two-dimensional TTE and the

biplane Simpson method. Patients were considered to have a reduced ejection fraction if their LVEF was  $<40\%$ .<sup>13</sup>

### Data collection

All patients underwent telephone interviews by senior physicians (A. C., A. C. U., A. E., A. T., J. H., M. K., and T. C.) 1 month after the start of the French lockdown, which began on 17 March 2020. A standardized questionnaire was used to collect health status, symptoms, medications, adverse events, COVID-19 status, and cardiac medical care in line with the COVID-19 outbreak (Supporting Information, *Data S1*). Patient data were censored at the time of the interview, which occurred between 17 April and 22 April 2020. Data from each confirmed patient with COVID-19 were obtained from our institution's electronic medical records. Data were entered into a computerized database and cross-checked by two independent senior physicians (A. C. and O. M.). Information included clinical symptoms at presentation, laboratory examinations, treatments, and outcomes during hospital stay. The present study was approved by the Research Ethics Committee of Strasbourg Hospital (CE-2020-69), and the requirement for informed consent was waived by the Ethics Committee. The investigation conforms with the principles outlined in the Declaration of Helsinki.

### Clinical endpoints

The primary endpoint of this study was the composite of hospitalization or death related to COVID-19. The secondary endpoints included positive result of COVID-19 by a reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay of a specimen collected on a nasopharyngeal swab.

### Study definitions

Based on the World Health Organization (WHO) guidance, a 'confirmed case' of COVID-19 was defined by a positive test of a RT-PCR assay of a specimen collected on a nasopharyngeal swab. A 'suspect case' was defined by the adapted WHO definition of a patient with fever and respiratory illness (at least one sign/symptom of respiratory disease, e.g. cough and shortness of breath). The definition of COVID-19 hospitalization was any hospitalization due to severe SARS-CoV-2 infection, and ICU admission was defined as any severe acute respiratory failure related to COVID-19 requiring invasive mechanical ventilation. COVID-19 death was defined as any death related to severe SARS-CoV-2 infection.

## Statistical analysis

Categorical variables are expressed as numbers (%), and continuous variables are expressed as mean  $\pm$  SD or median and inter-quartile values. We compared categorical variables using  $\chi^2$  tests or Fisher's exact tests, as appropriate. Unpaired Student's *t*-test was used to analyse continuous variables that showed normal distributions, and the Wilcoxon test was used to analyse continuous variables with skewed distributions. Univariate and multivariate logistic regression analyses were performed to identify independent predictors of the primary and secondary endpoints. Variables with *P* values  $<0.05$  in univariate analyses were included in the multivariate analyses. Propensity score matching was used to limit the risk of error and the number of biases between the LVEF  $<40\%$  and LVEF  $\geq 40\%$  groups. The propensity score model was developed using logistic regression and the model included age, sex, smoking, hypertension, obesity, dyslipidaemia, diabetes, family history of coronary artery disease (CAD), previous myocardial infarction, previous PCI, pre-existing atrial fibrillation, peripheral artery disease, previous stroke, chronic kidney disease and medications at the time of telephone interview as covariates. A nearest neighbour algorithm was used to match patients in the two groups in a 1:1 ratio, with a calliper width equal to 0.2 of the standard deviation of the logit of the propensity score. *P* values of  $<0.05$  were considered to indicate statistical significance. All analyses were performed using JMP 13 software® (SAS Institute, Cary, NC).

## Results

### Patients characteristics

Of the 1162 patients with ACS, 170 patients (15%) died between the index event and 1 January 2020, and 101 patients (9%) were lost to follow-up at the time of the present telephone interview (Figure 1). Of 891 patients with available clinical follow-up data, we enrolled 889 patients who underwent echocardiographic assessments at the time of the index event. Those patients were divided into two groups according to  $<40\%$  (reduced LVEF) ( $n = 91$ ) or LVEF  $\geq 40\%$  (moderately reduced + preserved LVEF) ( $n = 798$ ). Higher incidence of previous stroke (11% vs. 4%,  $P = 0.006$ ), chronic kidney disease (18% vs. 9%,  $P = 0.01$ ), and a lower incidence of family history of CAD (12% vs. 22%,  $P = 0.03$ ) was observed in the reduced LVEF group (Table 1). The reduced LVEF subset was likely to be associated with the occurrence of STEMI (70% vs. 53%,  $P = 0.002$ ) and LAD lesion (79% vs. 57%,  $P < 0.001$ ).

### Medications during the COVID-19 pandemic

At a median follow-up of 1602 days (interquartile range: 1342 to 1941 days), patients in the reduced LVEF group had less aspirin (77% vs. 85%,  $P = 0.047$ ) and more anti-aldosterone drugs (29% vs. 6%,  $P < 0.001$ ) than those in the moderately reduced + preserved LVEF group (Supporting Information, Table S1).

### Clinical features during the COVID-19 pandemic

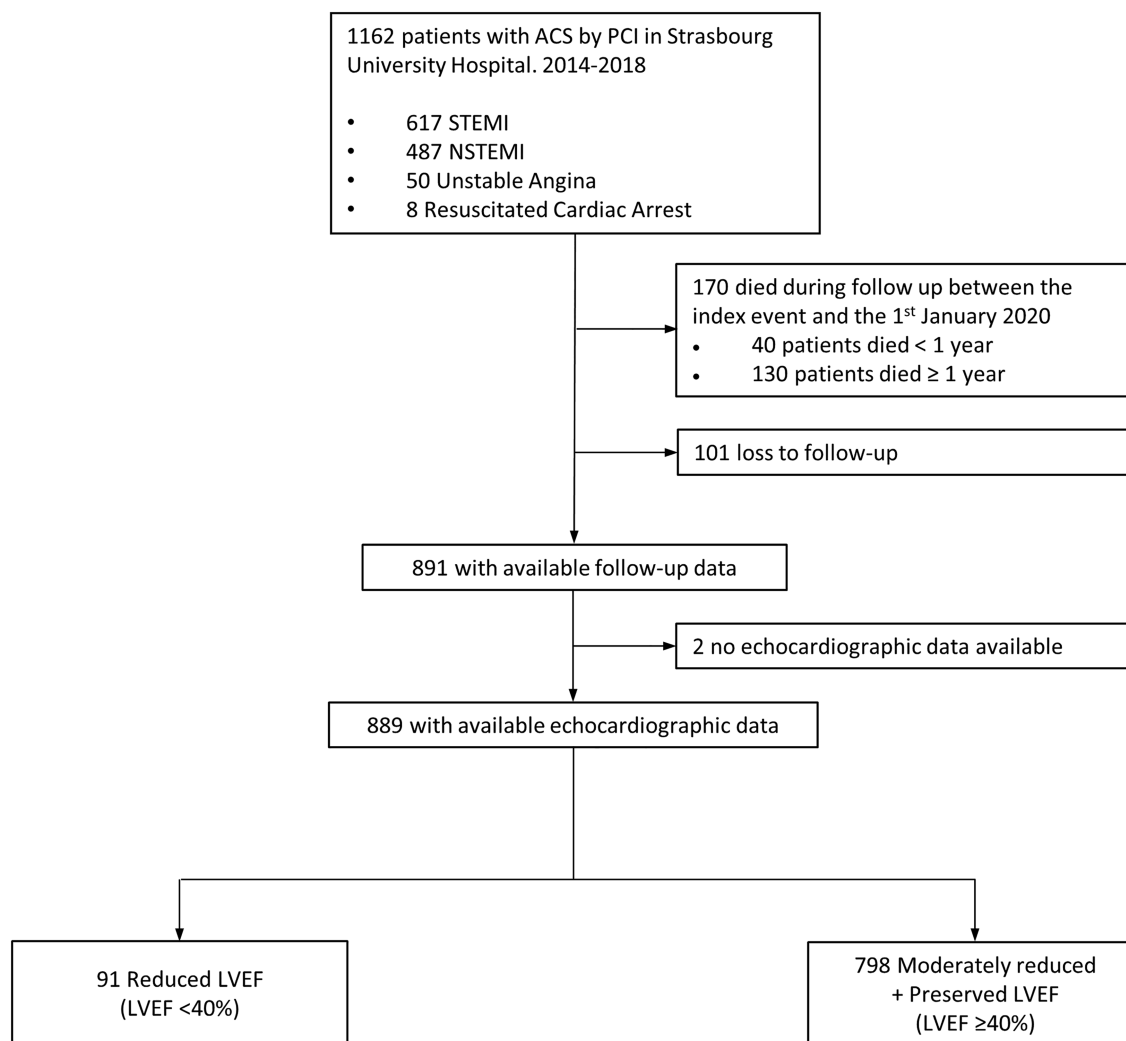
The COVID-19 diagnostic test was performed in 39 patients (4%). Among those, 20 patients (2%) had RT-PCR-confirmed COVID-19. The geographical distribution of the confirmed cases is shown in Supporting Information, Figure S1. More nasopharyngeal swabs were performed (10 [11%] vs. 29 [4%],  $P = 0.004$ ), and more COVID-19 confirmed cases were found (8 [9%] vs. 12 [2%],  $P < 0.001$ ) in the reduced LVEF group (Table 2 and Figure 2). Consistently, the positive rate was two-fold higher in the reduced LVEF group (80% vs. 41%,  $P = 0.04$ ).

The rate of the primary outcome (hospitalization or death related to COVID-19 infection) was significantly higher in patients with reduced LVEF (8 [9%] vs. 10 [1%],  $P < 0.001$ ) (Table 3 and Figure 2), which was mainly driven by the higher incidence of hospitalization in the patients with reduced LVEF (8 [9%] vs. 10 [1%],  $P < 0.001$ ). While the rates of all-cause death was similar in the two groups, the rates of all cause hospitalization since 1 January 2020 (9 [10%] vs. 26 [3%],  $P = 0.006$ ) was significantly higher in the reduced LVEF group (Table 3). Clinical characteristics and outcomes among three different LVEF groups consisting of reduced, moderately reduced, and preserved LVEF groups are shown in Supporting Information, Tables S2 and S3.

### Predictors of positive COVID-19 test

In univariate logistic regression analysis, smoking (odds ratio [OR]: 0.17, 95% confidence interval [CI]: 0.04 to 0.75,  $P = 0.02$ ), obesity (OR: 2.59, 95% CI: 1.06 to 6.33,  $P = 0.04$ ), reduced LVEF (OR: 6.31, 95% CI: 2.51 to 15.89,  $P < 0.001$ ), and statin administration (OR: 0.29, 95% CI: 0.11 to 0.73,  $P = 0.008$ ) were significant predictors of confirmed COVID-19 (Supporting Information, Table S4). Likewise, the multivariate logistic regression analysis identified smoking (OR: 0.17, 95% CI: 0.04 to 0.77,  $P = 0.02$ ), obesity (OR: 3.29, 95% CI: 1.28 to 8.49,  $P = 0.01$ ), reduced LVEF (OR: 6.66, 95% CI: 2.51 to 17.64,  $P < 0.001$ ), and statin administration (OR: 0.35, 95% CI: 0.14 to 0.91,  $P = 0.03$ ) as the sole independent predictors of confirmed COVID-19.

**Figure 1** Study flowchart. ACS, acute coronary syndrome; ICU, intensive care unit; LVEF, left ventricular ejection fraction; NSTEMI, non-ST-segment elevation acute coronary syndrome; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.



## Predictors of COVID-19-related hospitalization and death

In univariate logistic regression analysis, smoking (OR: 0.19, 95% CI: 0.04 to 0.85,  $P = 0.03$ ), reduced LVEF (OR: 7.60, 95% CI: 2.92 to 19.77,  $P < 0.001$ ), and statin administration (OR: 0.24, 95% CI: 0.09 to 0.63,  $P = 0.004$ ) were significant predictors of COVID-19-related hospitalization or death (Table 4). In contrast, the use of ACE-inhibitor (ACE-I) or angiotensin-receptor blockers (ARBs) was not related to the adverse outcomes (OR: 0.79, 95% CI: 0.28 to 2.24,  $P = 0.66$ ). By multivariate logistic regression analysis, smoking (OR: 0.22, 95% CI: 0.05 to 1.00,  $P = 0.049$ ), reduced LVEF (OR: 6.91, 95% CI: 2.60 to 18.35,  $P < 0.001$ ), and statin administration (OR: 0.29, 95% CI: 0.11 to 0.78,  $P = 0.01$ ) remained as

independent predictors of COVID-19-related hospitalization or death (Table 4).

## Propensity score matching

Results of propensity score matching are shown in Supporting Information Tables S5 and S6. A total of 88 patients with reduced LVEF were compared with 88 patients with moderately reduced or preserved LVEF. In the matched cohort, the rate of COVID-19 testing was similar between the two groups (10% vs. 7%,  $P = 0.42$ ). Consistent with the unmatched cohort, the prevalence of COVID-19 confirmed case was significantly higher in the reduced LVEF group (89% vs. 17%,  $P = 0.01$ ). The magnitude of reduced LVEF in predicting

**Table 1** Baseline characteristics

|   | Total (N = 889) | Reduced LVEF (N = 91) | Moderately reduced + preserved LVEF (N = 798) | P value |
|---|-----------------|-----------------------|---|---------|
| Age (years)                               | 63 ± 13         | 66 ± 14               | 63 ± 13                                       | 0.07    |
| Male sex                                  | 690 (78)        | 68 (75)               | 622 (78)                                      | 0.49    |
| Cardiovascular risk factors               |                 |                       |   |         |
| Smoking                                   | 343 (39)        | 31 (34)               | 312 (39)                                      | 0.35    |
| Hypertension                              | 507 (57)        | 51 (56)               | 456 (57)                                      | 0.84    |
| Obesity (BMI > 30 kg/m <sup>2</sup> )     | 214 (25)        | 18 (20)               | 196 (25)                                      | 0.27    |
| Dyslipidaemia                             | 434 (49)        | 52 (57)               | 382 (48)                                      | 0.09    |
| Diabetes                                  | 225 (25)        | 30 (33)               | 195 (24)                                      | 0.08    |
| Family history of coronary artery disease | 186 (21)        | 11 (12)               | 175 (22)                                      | 0.03    |
| Coexisting disorder                       |                 |                       |   |         |
| Previous MI                               | 145/888 (16)    | 21/91 (23)            | 124/797 (16)                                  | 0.07    |
| Previous PCI                              | 155 (17)        | 19 (21)               | 136 (17)                                      | 0.36    |
| History of AF                             | 55 (6)          | 9 (10)                | 46 (6)  | 0.12    |
| Peripheral artery disease                 | 71 (8)          | 11 (12)               | 60 (8)  | 0.13    |
| Previous stroke                           | 41/888 (5)      | 10/91 (11)            | 31/797 (4)                                    | 0.006   |
| CKD (Cr level >130 µmol/L)                | 90/888 (10)     | 16/91 (18)            | 74/797 (9)                                    | 0.01    |
| Types of ACS                              |                 |                       |   |         |
| STEMI                                     | 487 (55)        | 64 (70)               | 423 (53)                                      | 0.002   |
| NSTEMI-ACS                                | 402 (45)        | 27 (30)               | 375 (47)                                      | 0.002   |
| Killip classification                     |                 |                       |   | < 0.001 |
| Killip 1                                  | 751 (85)        | 41 (46)               | 710 (89)                                      |         |
| Killip 2                                  | 92 (10)         | 22 (25)               | 79 (9)  |         |
| Killip 3                                  | 28 (3)          | 19 (21)               | 9 (1)   |         |
| Killip 4                                  | 15 (2)          | 7 (8)                 | 8 (1)   |         |
| Culprit vessel                            |                 |                       |   | < 0.001 |
| LAD                                       | 525 (59)        | 72 (79)               | 453 (57)                                      |         |
| Non-LAD                                   | 364 (41)        | 19 (21)               | 345 (43)                                      |         |
| Multi-vessel disease                      | 501 (56)        | 57 (63)               | 444 (56)                                      | 0.20    |

ACS, acute coronary syndrome; AF, atrial fibrillation; BMI, body mass index; CKD, chronic kidney disease; Cr, creatinine; LAD, left anterior descending; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI-ACS, non-ST-segment elevation acute coronary syndrome; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

Values are n (%), n/N (%), or mean ± SD.

**Table 2** COVID-19 testing and symptoms

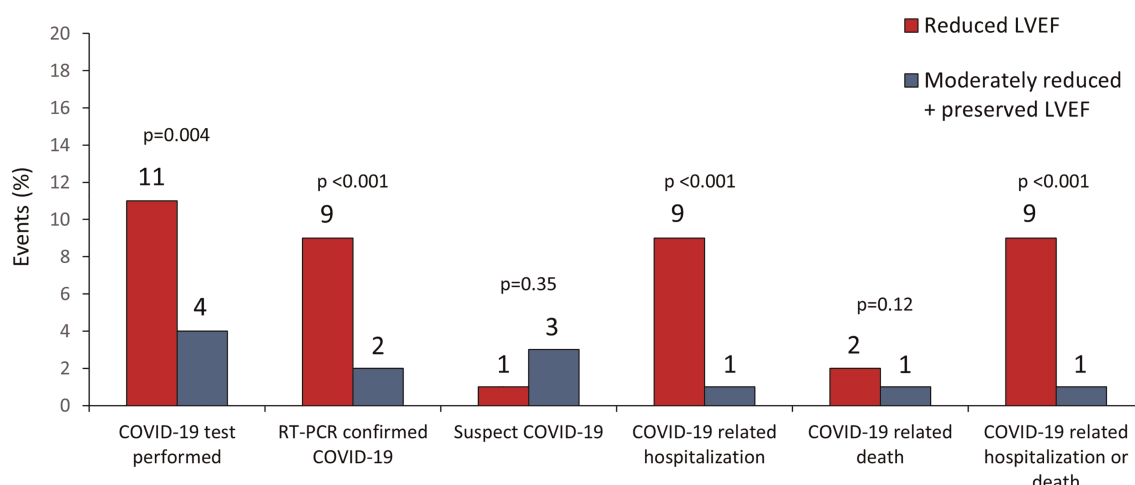
|   | Total (N = 889) | Reduced LVEF (N = 91) | Moderately reduced + preserved LVEF (N = 798) | P value |
|---|-----------------|-----------------------|---|---------|
| Diagnostic test                         |                 |                       |   |         |
| COVID-19 diagnostic testing performed   | 39 (4)          | 10 (11)               | 29 (4)  | 0.004   |
| RT-PCR confirmed COVID-19               | 20 (2)          | 8 (9)                 | 12 (2)  | < 0.001 |
| COVID-19 positive rate (n = 39)         | 20/39 (51)      | 8/10 (80)             | 12/29 (41)                                    | 0.04    |
| Suspect COVID-19                        | 28 (3)          | 1 (1)                 | 27 (3)  | 0.35    |
| Confirmed or suspected cases            | 48 (5)          | 9 (10)                | 39 (5)  | 0.08    |
| Symptoms among tested cases (n = 39)    |                 |                       |   |         |
| Fever                                   | 31/39 (79)      | 9/10 (90)             | 22/29 (76)                                    | 0.65    |
| Myalgia                                 | 16/39 (41)      | 2/10 (20)             | 14/29 (48)                                    | 0.15    |
| Dyspnoea                                | 28/39 (72)      | 9/10 (90)             | 19/29 (66)                                    | 0.23    |
| Cough                                   | 19/39 (49)      | 5/10 (50)             | 14/29 (48)                                    | 1.00    |
| Anosmia                                 | 8/39 (21)       | 2/10 (20)             | 6/29 (21)                                     | 1.00    |
| Ageusia                                 | 10/39 (26)      | 3/10 (30)             | 7/29 (24)                                     | 0.70    |
| Diarrhoea                               | 9/39 (23)       | 5/10 (50)             | 4/29 (14)                                     | 0.03    |
| Symptoms among confirmed cases (n = 20) |                 |                       |   |         |
| Fever                                   | 18/20 (90)      | 7/8 (88)              | 11/12 (92)                                    | 1.00    |
| Myalgia                                 | 9/20 (45)       | 1/8 (13)              | 8/12 (67)                                     | 0.03    |
| Dyspnoea                                | 20/20 (100)     | 8/8 (100)             | 12/12 (100)                                   | -       |
| Cough                                   | 11/20 (55)      | 5/8 (63)              | 6/12 (50)                                     | 0.67    |
| Anosmia                                 | 6/20 (30)       | 2/8 (25)              | 4/12 (33)                                     | 1.00    |
| Ageusia                                 | 7/20 (35)       | 3/8 (38)              | 4/12 (33)                                     | 1.00    |
| Diarrhoea                               | 8/20 (40)       | 5/8 (63)              | 3/12 (25)                                     | 0.17    |

COVID-19, coronavirus disease 2019; LVEF, left ventricular ejection fraction; RT-PCR, reverse-transcriptase-polymerase-chain-reaction.

Values are n (%) or n/N (%).



**Figure 2** Prevalence of COVID-19-related events in reduced and moderately reduced + preserved LVEF groups. COVID-19, coronavirus disease 2019; LVEF, left ventricular ejection fraction; RT-PCR, reverse-transcriptase–polymerase-chain-reaction.



COVID-19-related hospitalization or death was confirmed with the additional propensity score analysis adjusting for patient co-morbidities and current medications (OR: 8.70; 95% CI: 1.06 to 71.11;  $P = 0.04$ ).

discontinuation of ACE-I or ARBs and the COVID-19 susceptibility among patients with previous ACS.

## Discussions

The current study drawn from a cohort of 889 patients is the first study to specifically evaluate the impact of reduced LVEF on the susceptibility to COVID-19. The salient findings of the present study are the following: (i) reduced LVEF following ACS was associated with increased risk of SARS-CoV-2 infection, and (ii) no association was found between

## Heart failure and viral respiratory disease

Prior studies reported that influenza infection can be devastating for patients with CVD and leads to significant morbidity and mortality each year.<sup>14,15</sup> It is noteworthy that more patients died of CV causes than pneumonia/influenza causes during prior influenza epidemics.<sup>15</sup> Consistent with these findings, a number of studies in the available literature suggest an association between pre-existing CVD and severe COVID-19.<sup>8,10</sup> While CV risk factors including age, DM, and

**Table 3** Clinical outcomes

| Characteristic                                     | Total<br>(N = 889) | Reduced LVEF<br>(N = 91) | Moderately reduced + preserved LVEF<br>(N = 798) | P value |
|--|--------------------|--------------------------|--|---------|
| Primary end point                                  |                    |                          |  |         |
| COVID-19-related hospitalization or death          | 18 (2)             | 8 (9)                    | 10 (1)   | < 0.001 |
| Death  |                    |                          |  |         |
| COVID-19-related death                             | 6 (1)              | 2 (2)                    | 4 (1)  | 0.12    |
| All cause death since 1 January 2020               | 22 (2)             | 4 (4)                    | 18 (2)   | 0.27    |
| Cardiovascular death since 1 January 2020          | 3 (0.3)            | 0 (0)                    | 3 (0.4)  | 1.00    |
| Hospitalization                                    |                    |                          |  |         |
| COVID-19-related hospitalization                   | 18 (2)             | 8 (9)                    | 10 (1)   | < 0.001 |
| Hospitalization in ICU                             | 5 (1)              | 1 (1)                    | 4 (1)  | 0.42    |
| All cause hospitalization since 1 January 2020     | 35 (4)             | 9 (10)                   | 26 (3)   | 0.006   |
| Heart failure hospitalization since 1 January 2020 | 7 (1)              | 2 (2)                    | 5 (1)  | 0.16    |

COVID-19, coronavirus disease 2019; ICU, intensive care unit; LVEF, left ventricular ejection fraction. Values are n (%).

**Table 4** Univariate and multivariate logistic regression analyses for prediction of COVID-19-related hospitalization or death

|                                       | Univariate analysis |         | Multivariate analysis |         |
|---------------------------------------|---------------------|---------|-----------------------|---------|
|                                       | OR (95% CI)         | P value | OR (95% CI)           | P value |
| Age (years)                           | 1.02 (0.99–1.06)    | 0.20    |                       |         |
| Male sex                              | 0.75 (0.26–2.12)    | 0.58    |                       |         |
| Smoking                               | 0.19 (0.04–0.85)    | 0.03    | 0.22 (0.05–1.00)      | 0.049   |
| Hypertension                          | 2.68 (0.88–8.22)    | 0.08    |                       |         |
| Obesity (BMI > 30 kg/m <sup>2</sup> ) | 1.99 (0.76–5.21)    | 0.16    |                       |         |
| Dyslipidaemia                         | 2.13 (0.79–5.72)    | 0.13    |                       |         |
| Diabetes                              | 1.91 (0.73–4.98)    | 0.19    |                       |         |
| Family history                        | 0.75 (0.22–2.63)    | 0.65    |                       |         |
| Previous MI                           | 0.30 (0.04–2.25)    | 0.24    |                       |         |
| Previous PCI                          | 0.95 (0.27–3.31)    | 0.93    |                       |         |
| History of AF                         | 1.93 (0.43–8.61)    | 0.39    |                       |         |
| Peripheral artery disease             | 1.45 (0.33–6.45)    | 0.62    |                       |         |
| Previous stroke                       | 1.22 (0.16–9.40)    | 0.85    |                       |         |
| CKD (Cr level > 130 µmol/L)           | 1.11 (0.25–4.91)    | 0.89    |                       |         |
| STEMI                                 | 0.65 (0.26–1.67)    | 0.38    |                       |         |
| NSTE-ACS                              | 1.52 (0.60–3.91)    | 0.38    |                       |         |
| Multi-vessel disease                  | 2.76 (0.90–8.45)    | 0.08    |                       |         |
| LAD lesion                            | 1.82 (0.64–5.16)    | 0.26    |                       |         |
| Reduced LVEF                          | 7.60 (2.92–19.77)   | < 0.001 | 6.91 (2.60–18.35)     | < 0.001 |
| Treatment at the time of interview    |                     |         |                       |         |
| Aspirin                               | 1.52 (0.35–6.68)    | 0.58    |                       |         |
| P2Y12 inhibitors                      | 1.90 (0.61–5.86)    | 0.27    |                       |         |
| OAC                                   | 1.14 (0.33–3.99)    | 0.84    |                       |         |
| Beta-blockers                         | 1.19 (0.34–4.14)    | 0.79    |                       |         |
| ACE-I/ARBs                            | 0.79 (0.28–2.24)    | 0.66    |                       |         |
| Anti-aldosterone                      | 2.40 (0.69–8.50)    | 0.17    |                       |         |
| Statins                               | 0.24 (0.09–0.63)    | 0.004   | 0.29 (0.11–0.78)      | 0.01    |

ACE-I, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; CKD, chronic kidney disease; Cr, creatinine; LAD, left anterior descending; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; OAC, oral anticoagulant; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

HT have been increasingly recognized to overlap with pathways that regulate immune function and may confer increased susceptibility to disease complications, the relationship between impaired heart function and COVID-19 susceptibility has not been investigated.

## Angiotensin-converting enzyme 2 expression and COVID-19

A special attention was given to COVID-19 because SARS-CoV-2, as well as SARS-CoV, binds its viral spike proteins to ACE2 proteins for cell entry and induces subsequent down-regulation of ACE2 surface expression.<sup>16</sup> Dysregulated ACE2 may result in unopposed angiotensin II accumulation and local renin-angiotensin-aldosterone system (RAAS) activation, which can exacerbate tissular injury and promote inflammation and thrombosis. Expression of ACE2 throughout the gastrointestinal tract, and most prevalently in enterocytes, may serve as a secondary site for enteric SARS-CoV-2 infection. Common CVD disorders were described to alter the integrity of the gastrointestinal-blood barrier and induce gut dysbiosis, systemic inflammation, and bacteraemia. Development of gastrointestinal leakage and gut dysbiosis has been closely related to hyperactivation of the ACE/Ang

II/AT1R (angiotensin II type 1 receptor) axis from ACE2 loss.<sup>17</sup> Consistent with this paradigm, higher diarrhoea prevalence could be observed in patients with reduced LVEF (Table 2).

There has been a growing concern whether the increased incidence of mortality and complications in patients with COVID-19 with pre-existing CV disorders is due to the use of ACE-I and ARBs.<sup>16,18</sup> A question arose whether RAAS inhibition may increase risk of adverse events of COVID-19 through up-regulation of ACE2 and increase viral load. Lately, a retrospective study identified lower mortality rates in patients with COVID-19 with ACE-I and ARBs therapies.<sup>19</sup> In contrast, a largest observational study including 18 472 patients tested for COVID-19 was recently reported by Mehta *et al.*, indicating no association between ACEI or ARBs use and COVID-19 test positivity after adjustment by overlap propensity-score weighting.<sup>20</sup> Instead, a higher likelihood of hospital admission was found in patients under ACEI or ARBs. Given the strong relationship between RAAS inhibitors administration and underlying CVD, caution should be taken when interpreting results from observational studies particularly when statistical adjustments are not performed. Importantly, the present study was dedicated to patients with ACS who require ACE-I/ARBs, suggesting that the discontinuation of those medications was not associated with COVID-19 test positivity nor severity.



In line with our findings, Sama *et al.* recently described that ACE-I/ARBs were not associated with increased plasma concentration of ACE2 in patients with HF.<sup>12</sup> Nevertheless, given the current limited and conflicting evidences regarding this topic, further studies are warranted to confirm our findings.

## Heart failure and COVID-19

In the heart, ACE2 is localized on the surface of coronary endothelial cells, cardiomyocytes, and cardiac fibroblasts.<sup>21</sup> Up-regulation of ACE2 in CVD has been described in experimental studies, using myocardial tissues from patients with HF<sup>11</sup> and assays of ACE2 plasma levels.<sup>12</sup> A recent study including 2022 patients with HF has demonstrated that plasma levels of ACE2 were increased in patients with HF, and the strongest predictor was male sex, consistently with the increased prevalence and severity of COVID-19 in men.<sup>12</sup> ACE2 up-regulation may thus increase the susceptibility to COVID-19 and induce a more severe clinical course of the disease through a larger viral load. According to this hypothesis, concerns regarding reduced LVEF after ACS events as a cause of ACE2 up-regulation can be expected. Despite the limited number of events and the observational nature of the study, it is noteworthy that the positive rate of COVID-19 was two-fold higher in patients with reduced LVEF. We confirmed the magnitude of reduced LVEF by an additional propensity analysis adjusting for patient co-morbidities and current medications.

## Factors related to COVID-19 susceptibility

In the present study, statin use and smoking were found to be related to the COVID-19 susceptibility. While no clinical data yet exists for a protective role of statins on SARS-CoV-2 infection, there are some evidence that they may reduce the severity of viral infections. A retrospective study of 3043 patients reported that statin use is associated with reduced mortality during and after hospitalization for influenza virus infection (adjusted OR 0.59; 95% CI 0.38 to 0.92).<sup>22</sup> Another large matched cohort study found a significantly reduced risk of influenza-related/pneumonia-related death (OR 0.60; 95% CI 0.44 to 0.81) among moderate-dose statin users.<sup>23</sup> The identification of the mechanisms leading to the reduction in COVID-19 test positivity in statin-treated patients is beyond the scope of the present work. Nevertheless, recent reports suggested that its anti-inflammatory effects by preserving myeloid differentiation primary response 88 levels<sup>24</sup> and direct interaction with the main protease of SARS-CoV-2<sup>25</sup> may play an important role in COVID-19. Furthermore, endothelial cell activation/damage due to the virus infection induces acute inflammatory and hypercoagulable

response by the down-regulation of nitric oxide formation, increased oxidative stress, procoagulant microparticles shedding, tissue factor expression, and cytoadhesins cytokine release, which all can be targeted by statins. However, data with regard to clinical outcomes and measures of COVID-19 severity in patients taking statins must be interpreted with caution and be considered only hypothesis generating. Confounders of statin discontinuation may include frailty and various co-morbidities, which were not fully evaluated and adjusted in the present study.

Early studies from China suggested that smoking is most likely associated with negative progression and adverse outcomes of hospitalized patients with COVID-19.<sup>26</sup> Conversely, current smoker had a lower probability of developing COVID-19 in our study, which was in line with the early report from Paris, France.<sup>27</sup> In this study, the rate of smoker was 77% lower in the COVID-19 outpatients and inpatients compared with the French general population. Likewise, reports from China and the USA have also shown lower rate of current smoker in patients with COVID-19 than the general population.<sup>27</sup> Although the protective/noxious impacts of smoking on COVID-19 have not been fully investigated, there is evidence that nicotine modulates ACE2 expression, which may be responsible for the lower probability of SARS-CoV-2 infection.<sup>28</sup> However, this hypothesis requires further investigation and the role of smoking in patients with COVID-19 cannot be ruled out to date.

## Future perspective

In a randomized control trial, patients receiving influenza vaccine after myocardial infarction or PCI had a significant attenuation in CV mortality and morbidity compared with their non-vaccinated counterparts.<sup>29</sup> A study of elderly Spanish community-dwelling individuals with congestive HF found that influenza vaccination was associated with a reduction of 37% in the adjusted risk of mortality.<sup>30</sup> While no available vaccination exists for patients with COVID-19 to date, it may be reasonable to triage patients with COVID-19 according to the presence of underlying CVD including HF for more aggressive testing and treatment strategies. Patients with pre-existing heart dysfunction represents one of the highest priority group to receive vaccination.

## Limitations

We acknowledge the following limitations: first, the analyses were performed on the basis of a single centre data set with uncertain generalizability. Second, the incidence of diagnostic testing was higher in the reduced LVEF group, which may have increased the number of positivity. However, the positive rate remained significantly higher in the

reduced LVEF group than the moderately reduced + preserved LVEF group. Third, the echocardiographic data were collected in the acute phase of ACS, indicating that the LVEF may have improved over time. Certain patients may have been mis-classified due to the recovery of LVEF at the chronic phase. However, previous ACS studies have indicated that reduced LVEF in acute phase was persistent at follow-up period in a considerable number of patients.<sup>31,32</sup> Similar to our study, the reduced LVEF at baseline was associated with LAD lesion and STEMI, which were also the determinants of the reduced LVEF at chronic phase. Accordingly, although there might have been several mis-classifications by using the echocardiographic data at the acute phase, a lower LVEF at chronic phase would have been observed in the reduced LVEF group compared with the moderately reduced + preserved LVEF group. In order to confirm our findings, larger studies restricted to patients with ACS with regular echocardiographic follow-up are crucially needed. Forth, given the limited size of the cohort, multivariate analysis should be interpreted with caution. Of note, the present study was not powered to detect certain differences. The effect of the low event rates might have been more pronounced when analysing small subgroups. As with similar evaluation of registry data, there are inherent limitations in this type of study, mainly related to unknown confounding factors.

## Conclusions

In a large cohort of patients with previous ACS, patients with LVEF <40% were associated with increased susceptibility to

COVID-19. No association was found between ACE-I or ARBs discontinuation and COVID-19 test positivity.

## Conflict of interest

None declared.

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## Supporting information

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

### Data S1 Supporting Information

**Figure S1:** Geographical distribution of COVID-19 cases in Strasbourg region as of 21 April 2020 in the study cohort

**Table S1.** Medication therapy at discharge and at follow-up

**Table S2.** COVID-19 testing and symptoms among 3 difference LVEF groups.

**Table S3.** Clinical outcomes among 3 different LVEF groups.

**Table S4.** Univariate and multivariate logistic regression analyses for prediction of confirmed COVID-19 (RT-PCR +)

**Table S5.** Patient characteristics in the matched cohort

**Table S6.** Clinical outcomes in the matched cohort

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