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Prognostic Impact of Prior Heart Failure in Patients Hospitalized With COVID-19

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ABSTRACT

BACKGROUND Patients with pre-existing heart failure (HF) are likely at higher risk for adverse outcomes in coronavirus disease-2019 (COVID-19), but data on this population are sparse.

OBJECTIVES This study described the clinical profile and associated outcomes among patients with HF hospitalized with COVID-19.

METHODS This study conducted a retrospective analysis of 6,439 patients admitted for COVID-19 at 1 of 5 Mount Sinai Health System hospitals in New York City between February 27 and June 26, 2020. Clinical characteristics and outcomes (length of stay, need for intensive care unit, mechanical ventilation, and in-hospital mortality) were captured from electronic health records. For patients identified as having a history of HF by International Classification of Diseases-9th and/or 10th Revisions codes, manual chart abstraction informed etiology, functional class, and left ventricular ejection fraction (LVEF).

RESULTS Mean age was 63.5 years, and 45% were women. Compared with patients without HF, those with previous HF experienced longer length of stay (8 days vs. 6 days; $p < 0.001$), increased risk of mechanical ventilation (22.8% vs. 11.9%; adjusted odds ratio: 3.64; 95% confidence interval: 2.56 to 5.16; $p < 0.001$), and mortality (40.0% vs. 24.9%; adjusted odds ratio: 1.88; 95% confidence interval: 1.27 to 2.78; $p = 0.002$). Outcomes among patients with HF were similar, regardless of LVEF or renin-angiotensin-aldosterone inhibitor use.

CONCLUSIONS History of HF was associated with higher risk of mechanical ventilation and mortality among patients hospitalized for COVID-19, regardless of LVEF. (J Am Coll Cardiol 2020;76:2334–48) © 2020 by the American College of Cardiology Foundation.

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Coronavirus disease-2019 (COVID-19), caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), is a rapidly expanding pandemic associated with overwhelming morbidity and mortality across the globe (1). History of cardiovascular disease has repeatedly been associated with worse prognosis (2,3), whereas de novo cardiovascular involvement in its various forms, from myocardial injury to myocarditis and shock, has also been amply described (4–7). Among patients hospitalized with COVID-19, patients with heart failure (HF) represent a population at the highest potential risk for complications due to a high prevalence of underlying frailty or renal dysfunction among other comorbidities (8). Yet data as to the clinical course and outcomes of COVID-19 among patients with a history of HF are scarce (9–12). Furthermore, it is unknown as to whether the clinical course of COVID-19 differs according to left ventricular ejection fraction (LVEF) or background medications, including renin-angiotensin-aldosterone system inhibitors (RAASi) (13).

The Mount Sinai Healthcare System is a large academic health care institution that serves a racially and ethnically diverse patient population in New York City, once the global epicenter of the disease. Here, we present the clinical characteristics, hospital course, and outcomes of the largest cohort to date of patients with a history of HF hospitalized with laboratory-confirmed COVID-19.

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METHODS

STUDY POPULATION AND DESIGN. We conducted a retrospective cohort study of consecutive patients at least 18 years or older hospitalized with confirmed COVID-19 infection by positive reverse transcription polymerase chain reaction at 1 of 5 Mount Sinai Healthcare System hospitals (Mount Sinai Hospital, Mount Sinai Morningside, and Mount Sinai West located in Manhattan; Mount Sinai Brooklyn located in Brooklyn; and Mount Sinai Queens located in Queens). Patients were admitted from February 27, 2020 to June 26, 2020, and they were followed-up until July 18, 2020. The Mount Sinai Institutional Review Board approved this research under a broad regulatory protocol that allowed for analysis of limited patient-level data.

DATA COLLECTION AND OUTCOMES. Demographics, laboratory measurements, disease diagnoses, comorbidities, procedures, and outcomes (death, need for intensive care unit [ICU], intubation and mechanical ventilation, length of stay [LOS], and hospital discharge) were collected from electronic health records. Patients were considered right-censored if they were discharged from the hospital alive or remained admitted at the time of data freeze (July 18th). Comorbidities were extracted using the International Classification of Disease-9th and/or 10th (ICD-9/10) Revision codes for atrial fibrillation, asthma, obesity, coronary artery disease, cancer, chronic kidney disease, chronic obstructive pulmonary disease, diabetes, HF, and hypertension (Supplemental Appendix).

Manual chart review was performed for patients identified as having a history of HF by ICD-9/10 codes, to collect historic variables of interest, including etiology of HF, date of HF diagnosis, baseline New York Heart Association functional class, and LVEF before index COVID-19 admission. Laboratory values and cardiovascular procedures performed during admission, as well as specific outcomes (need for vasopressors or vasodilators, acute kidney injury, shock, thromboembolic events, arrhythmias, causes of death, and 30-day readmission rate) were also abstracted. Patients with a history of HF were classified into 3 groups according to LVEF category: HF with reduced EF (HFrEF) (≤40%); HF with mid-range EF (HFmrEF) (41% to 49%); and HF with preserved EF (HFpEF) (≥50%) (14).

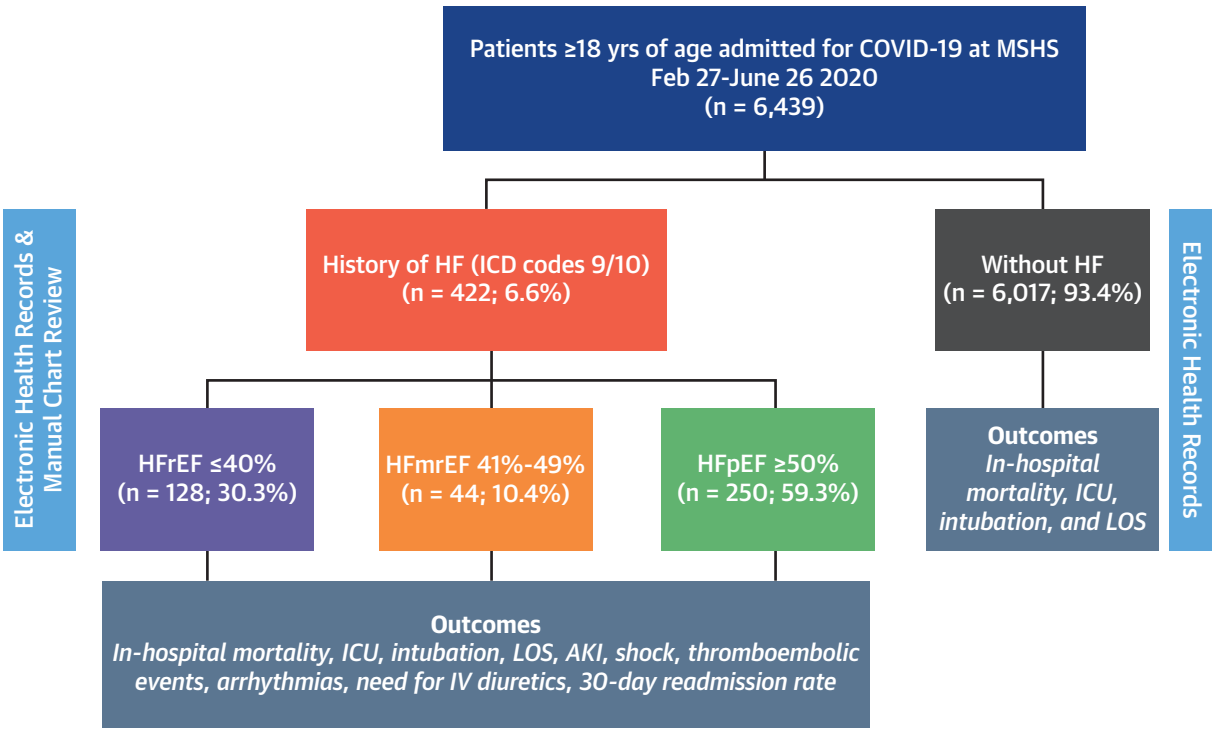
STATISTICAL ANALYSIS. Continuous variables are presented as mean ± SD or median (interquartile range [IQR]) when they did not show a normal distribution. Categorical variables are expressed as absolute number of patients (percentage). Variables were compared between patients with and without a history of HF as well as between LVEF categories and survivors and nonsurvivors using the Fisher exact test or chi-square test for categorical variables, and the Student's *t*-test, analysis of variance, Wilcoxon, or Kruskal-Wallis, as appropriate, for continuous variables. Multiple imputation by chained equation (m = 20) was applied whenever necessary, and variables with >20% of missing data were not included in the models (Supplemental Appendix) (15).

To determine the impact of HF history on outcomes, a multivariable logistic regression analysis was performed, adjusted by age, sex, race, obesity, hypertension, diabetes, coronary artery disease, atrial fibrillation, chronic kidney disease, chronic obstructive pulmonary disease, previous treatment with RAASi, systolic blood pressure, heart rate, oxygen saturation, white blood count, lymphocytes, creatinine, and albumin. In addition, we calculated the adjusted odds ratio (adjOR) in the subgroup of

ABBREVIATIONS AND ACRONYMS

AdjOR = adjusted odds ratio
CI = confidence interval
COVID-19 = coronavirus disease-2019
HF = heart failure
HFpEF = heart failure with preserved ejection fraction
HFmrEF = heart failure with mid-range ejection fraction
HFrEF = heart failure with reduced ejection fraction
ICD = International Classification of Disease
ICU = intensive care unit
IQR = interquartile range
LOS = length of stay
LVEF = left ventricular ejection fraction
RAASi = renin-angiotensin-aldosterone inhibitor
SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2

FIGURE 1 **Consort Diagram of the Study Population**



A total of 6,439 patients were admitted for coronavirus disease-2019 (COVID-19) during the study period and 422 (6.6%) patients had a history of heart failure (HF). AKI = acute kidney injury; HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; ICD = International Classification of Diseases; ICU = intensive care unit; IV = intravenous; LOS = length of stay; MSHS = Mount Sinai Health System.

patients with available values of D-dimer and troponin (n = 1,777).

To evaluate the impact of LVEF category and previous treatment with RAASi on in-hospital mortality, a multivariable Cox regression analysis was performed, adjusted by age, sex, race, body mass index, hypertension, diabetes, atrial fibrillation, chronic kidney disease, chronic obstructive pulmonary disease, baseline New York Heart Association functional class, previous mitral regurgitation, systolic blood pressure, heart rate, oxygen saturation, lymphocytes, creatinine, brain natriuretic peptide, and troponin.

All statistical tests were 2-tailed, and statistical significance was defined as a p value <0.05. Analyses were performed using Stata version 14 (StataCorp, College Station, Texas).

RESULTS

CLINICAL CHARACTERISTICS. A total of 6,439 patients were admitted for COVID-19 during the study period, and 422 (6.6%) had a history of HF (Figure 1). Overall, the mean age was 63.5 ± 18 years, 45% were women, and the mean body mass index was 29.0 ± 7.5 kg/m^2. Hypertension (34.5%), obesity (27.9%), and diabetes mellitus (22.8%) were the most frequent comorbidities, and one-third of patients were treated with RAASi before COVID-19 admission. Table 1 summarizes the clinical characteristics of the study population stratified by history of HF. Compared with patients without HF, those with a history of HF were older, had a higher prevalence of comorbidities, and were receiving a greater number of medications for cardiovascular disease. Patients with a history of HF presented with higher systolic blood pressure (126 mm Hg vs. 119 mm Hg; p < 0.001) and lower oxygen saturation (91% vs. 94%; p < 0.001); however, respiratory rate and temperature were similar to those without HF. Patients with a history of HF had lower lymphocyte count, hemoglobin, platelet count, sodium, and alanine aminotransferase, but had higher median values of creatinine, total bilirubin, lactate, D-dimer, troponin, natriuretic peptides, and inflammatory

markers (e.g., C-reactive protein or interleukin-6). In terms of in-hospital management, patients with HF received supplemental oxygen by nasal cannula (72.0% vs. 51.8%; $p < 0.001$) and anticoagulation (82.2% vs. 55.0%; $p < 0.001$) more frequently compared with patients without a history of HF, with no major differences in the administration of antiviral or steroid therapy.

OUTCOMES IN PATIENTS WITH HF COMPARED WITH PATIENTS WITHOUT HF. Median LOS for the overall cohort was 6 days (IQR: 3 to 12 days), whereas median LOS among patients with a history of HF was longer (8 days; IQR: 4 to 13 days). A requirement for ICU care was observed in nearly one-fifth (17.1%) of patients, whereas intubation with mechanical ventilation was observed in 12.6% in the study population. Both outcomes were more likely among patients with a history of HF compared with those without HF (odds ratio [OR]: 1.52; 95% confidence interval [CI]: 1.20 to 1.92; $p = 0.001$, and OR: 2.18; 95% CI: 1.71 to 2.77; $p < 0.001$; respectively). Overall mortality was 25.8%; however, the risk of mortality among patients with HF was twice that of patients without HF (40.0% vs. 24.9%; OR: 2.02; 95% CI: 1.65 to 2.48; $p < 0.001$) (**Figure 2A**).

After a multivariable logistic regression that adjusted for relevant demographic variables, comorbidities, previous treatment with RAASi, and markers of clinical severity on admission, history of HF persisted as an independent risk factor for the need for ICU care (adjOR: 1.71; 95% CI: 1.25 to 2.34; $p = 0.001$), intubation and mechanical ventilation (adjOR: 3.64; 95% CI: 2.56 to 5.16; $p < 0.001$), and in-hospital mortality (adjOR: 1.88; 95% CI: 1.27 to 2.78; $p = 0.002$) (**Figure 3**). In the subgroup of patients who had both D-dimer and troponin assessed on admission ($n = 1,777$), the increased risk was sustained despite adjustment for these markers (Supplemental Figure 1).

CLINICAL PROFILE, MANAGEMENT, AND ECHOCARDIOGRAPHY IN PATIENTS WITH HF STRATIFIED BY LVEF. Of 422 patients with a history of HF, 250 (59.3%), 128 (30.3%), and 44 (10.4%) had HFpEF, HFrEF, and HFmrEF, respectively. **Table 2** summarizes the clinical characteristics and outcomes of the study population according to the LVEF. Overall, patients with HFpEF were older, more frequently women, with a higher body mass index and prevalence of previous lung disease than patients with HFrEF, whereas those with HFmrEF fell in between (Supplemental Figure 2). Patients with HFpEF had less frequent ischemic heart disease, smaller left ventricular diameters, less mitral regurgitation, lower previous 1-year HF admission rate, less frequent left bundle branch block, or presence of defibrillators and cardiac resynchronization devices. Expectedly, neurohormonal therapy was also less frequently prescribed in patients with HFpEF compared with those with HFrEF or HFmrEF. On hospital presentation, there were no significant differences in symptoms among groups. Patients with HFpEF presented with lower oxygen saturation and lower median values of hemoglobin, D-dimer, alanine aminotransferase, bilirubin, and natriuretic peptides compared with those with HFrEF. They were also treated with hydroxychloroquine or macrolides and noninvasive ventilation more frequently than the other 2 groups, whereas antiplatelet and neurohormonal therapies were more common among patients with HFrEF.

Echocardiography was performed in 80 of 422 (19.0%) patients with history of HF during the COVID-19 hospitalization (Supplemental Table 1). Interestingly, 14 (17.5%) presented with worsening LVEF of ≥10 points. De novo severe tricuspid and mitral regurgitation was encountered in 9 (11.3%), and 6 (7.5%) patients, respectively, in comparison with the study before admission. Other cardiovascular tests such as cardiac computed tomography and left or right heart catheterization were performed rarely on a case-by-case basis during the COVID-19 hospitalization (**Table 2**).

OUTCOMES AMONG PATIENTS WITH HF STRATIFIED BY LVEF. Among the 422 patients with a history of HF hospitalized for COVID-19, there were no significant differences in LOS, need for ICU care, intubation and mechanical ventilation, acute kidney injury, shock, thromboembolic events, arrhythmias, or 30-day readmission rates across LVEF strata. However, cardiogenic shock (7.8% vs. 2.3% vs. 2%; $p = 0.019$) and HF-related causes for 30-day readmission (47.1% vs. 0% vs. 8.6%) were significantly higher in patients with HFrEF than in those with HFmrEF or HFpEF. Finally, although this was a smaller group of patients, mortality was observed to be lower among patients with HFmrEF (22.7%) compared with the 2 other HF categories (38.3% in HFrEF and 44% in HFpEF). **Figure 2B** shows the Kaplan-Meier survival curves of the HF population according to LVEF category.

Risk factors for in-hospital mortality among patients with HF by multivariable Cox regression included older age, more severe HF (baseline New York Heart Association functional classes III and IV), previous mitral regurgitation, lower systolic blood pressure, lower oxygen saturation, lower lymphocyte count, and increased troponin concentrations. Again, neither LVEF category nor previous treatment with RAASi were independently associated with worse

TABLE 1 Clinical Characteristics, Management, and Outcomes of the Study Population According to HF History

	Total (N = 6,439)	HF (n = 422; 6.6%)	Non-HF (n = 6,017; 93.4%)	p Value
Age, yrs	63.5 ± 17.6	72.5 ± 13.3	62.9 ± 17.7	<0.001
Female	2,892 (44.9)	186 (44.1)	2,706 (45.0)	0.720
BMI, kg/m^2	29.0 ± 7.5	29.5 ± 8.4	28.9 ± 7.3	0.207
Race				<0.001
Black	1,614 (25.1)	134 (31.8)	1,480 (24.6)	
Hispanic/Latino	1,738 (27.0)	120 (28.4)	1,618 (26.9)	
White	1,481 (23.0)	105 (24.9)	1,376 (22.9)	
Asian	321 (5.0)	21 (5.0)	300 (5.0)	
Other	963 (15.0)	34 (8.1)	929 (15.4)	
Unknown	322 (5.0)	8 (1.9)	314 (5.2)	
Comorbidities				
Obesity	1,796 (27.9)	169 (40.0)	1,627 (27.0)	<0.001
Hypertension	2,222 (34.5)	382 (90.5)	1,840 (30.6)	<0.001
Diabetes mellitus	1,470 (22.8)	269 (63.7)	1,201 (20.0)	<0.001
Dyslipidemia	1,139 (17.7)	228 (54.0)	911 (15.1)	<0.001
CAD	901 (14.0)	235 (55.7)	666 (11.1)	<0.001
Stroke	379 (5.9)	114 (27.0)	265 (4.4)	<0.001
Atrial fibrillation	464 (7.2)	160 (37.9)	304 (5.1)	<0.001
CKD	436 (6.8)	177 (41.9)	259 (4.3)	<0.001
COPD	292 (4.5)	94 (22.3)	198 (3.3)	<0.001
Asthma	378 (5.9)	58 (13.7)	320 (5.3)	<0.001
OSA	193 (3.0)	57 (13.5)	136 (2.3)	<0.001
Background treatment				
RAAS inhibitors	1,927 (29.9)	260 (61.6)	1,667 (27.7)	<0.001
Beta-blockers	1,781 (27.7)	354 (83.9)	1,427 (23.7)	<0.001
MRA	175 (2.7)	60 (14.2)	115 (1.9)	<0.001
Loop diuretics	993 (15.4)	318 (75.4)	675 (11.2)	<0.001
Thiazides	635 (9.9)	64 (15.2)	571 (9.5)	<0.001
Antiplatelet	1,793 (27.9)	327 (77.5)	1,466 (24.5)	<0.001
Anticoagulant	613 (9.5)	175 (41.5)	438 (7.3)	<0.001
Statins	1,848 (28.7)	351 (83.2)	1,497 (24.9)	<0.001
Clinical presentation				
Systolic BP, mm Hg	120 ± 25	126 ± 30	119 ± 24	<0.001
Diastolic BP, mm Hg	69 ± 15	68 ± 17	69 ± 15	0.408
Heart rate, beats/min	86 ± 18	87 ± 20	86 ± 18	0.181
Respiratory rate, rpm	20 ± 5	21 ± 5	20 ± 5	<0.001
Saturation O_2, %	94 ± 10	91 ± 9	94 ± 10	<0.001
Temperature, °F	98.2 ± 1.5	98.5 ± 1.7	98.2 ± 1.5	<0.001
Laboratory data				
WBC, k/μl	7.9 (5.8–11.5)	7.0 (5.2–10.3)	8.0 (5.8–11.6)	<0.001
Neutrophils, %	72 (61–83)	76 (66–84)	72 (61–83)	<0.001
Lymphocytes, %	16 (9–25)	14 (8–20)	17 (9–25)	<0.001
Hemoglobin, g/dl	11.6 (9.7–13.2)	10.9 (9.3–13.0)	11.7 (9.7–13.2)	<0.001
Platelets, k/μl	254 (183–359)	199 (144–281)	260 (187–364)	<0.001
INR	1.2 (1.1–1.4)	1.2 (1.1–1.5)	1.2 (1.1–1.4)	<0.001
Fibrinogen, mg/dl	581 (450–718)	524 (429–645)	589 (454–725)	<0.001
D-dimer, Ug/ml	1.70 (0.83–3.44)	1.97 (0.97–3.42)	1.68 (0.82–3.44)	0.049
Glucose, mg/dl	106 (88–154)	118 (90–185)	106 (88–151)	<0.001
Sodium, mmol/l	140 (137–142)	139 (135–141)	140 (137–142)	<0.001
Potassium, mmol/l	4.4 (4.0–4.8)	4.5 (4.1–5.0)	4.4 (4.0–4.8)	0.004
Creatinine, mg/dl	0.9 (0.7–1.8)	2.1 (1.2–4.9)	0.9 (0.7–1.6)	<0.001
BUN, mg/dl	19 (12–42)	36 (20–60)	18 (12–38)	<0.001
ALT, U/l	34 (20–66)	23 (14–41)	36 (20–68)	<0.001
Bilirubin, mg/dl	0.6 (0.4–0.8)	0.6 (0.4–0.9)	0.5 (0.4–0.8)	<0.001
Albumin, g/dl	2.7 (2.3–3.2)	2.9 (2.5–3.3)	2.7 (2.3–3.2)	<0.001
Troponin I*, ng/ml	0.06 (0.02–0.19)	0.07 (0.03–0.19)	0.05 (0.02–0.18)	0.022

Continued on the next page

TABLE 1 Continued

	Total (N = 6,439)	HF (n = 422; 6.6%)	Non-HF (n = 6,017; 93.4%)	p Value
BNP, pg/ml	123 (42–456)	514 (154–1383)	86 (32–262)	<0.001
Lactate, mmol/l	1.5 (1.1–2.2)	1.6 (1.1–2.4)	1.5 (1.1–2.2)	0.373
CRP, mg/l	58.9 (19.1–137.6)	75.2 (32.2–148.5)	57.8 (18.4–136.9)	<0.001
Ferritin, ng/ml	746 (348–1593)	759 (330–2107)	745 (350–1570)	0.535
Procalcitonin, ng/ml	0.17 (0.06–0.79)	0.38 (0.10–1.44)	0.16 (0.06–0.72)	<0.001
Interleukin-6, pg/ml	54.4 (22.0–126.0)	66.1 (30.3–131.0)	53.7 (21.8–125.0)	0.051
ECG at admission				
QT interval	379 (53)	401 (60)	377 (53)	<0.001
QT corrected interval	453 (43)	474 (46)	452 (42)	<0.001
Treatment				
Hydroxychloroquine	3,758 (58.4)	249 (59.0)	3,509 (58.3)	0.782
Azithromycin	3,305 (51.3)	227 (53.8)	3,078 (51.2)	0.295
Hydroxy+azithrom	2,850 (44.3)	182 (43.1)	2,668 (44.3)	0.628
Remdesivir	166 (2.6)	6 (1.4)	160 (2.7)	0.121
Tocilizumab	291 (4.5)	13 (3.1)	278 (4.6)	0.141
Steroids	1,869 (29.0)	140 (33.2)	1,729 (28.7)	0.052
Anticoagulant†	3,655 (56.8)	347 (82.2)	3,308 (55.0)	<0.001
Nasal cannula	2,755 (53.5)	304 (72.0)	2451 (51.8)	<0.001
Outcomes				
ICU	1,098 (17.1)	98 (23.2)	1,000 (16.6)	<0.001
LOS ICU, days	7 (3–15)	5 (2–11)	7 (3–15)	0.057
ICU mortality	636 (57.9)	72 (73.5)	564 (56.4)	0.001
LOS, days	6 (3–12)	8 (4–13)	6 (3–12)	<0.001
Intubation	813 (12.6)	96 (22.8)	717 (11.9)	<0.001
Still admitted	228 (3.5)	0 (0.0)	228 (3.8)	<0.001
In-hospital mortality	1,664 (25.8)	169 (40.0)	1,495 (24.9)	<0.001

Values are mean ± SD, n (%), or median (interquartile range). *N = 2,264. †In those patients without previous anticoagulation.

ALT = alanine transaminase; BMI = body mass index; BNP = brain natriuretic peptide; BP = blood pressure; BUN = blood urea nitrogen; CAD = coronary artery disease; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein; ECG = electrocardiogram; HF = heart failure; ICU = intensive care unit; INR = international normalized ratio; LOS = length of stay; MRA = mineraloid receptor antagonist; OSA = obstructive sleep apnea; RAAS = renin-angiotensin-aldosterone system; rpm = respirations per minute; WBC = white blood cells.

prognosis (Table 3). Remarkably, race was not associated with worse outcomes.

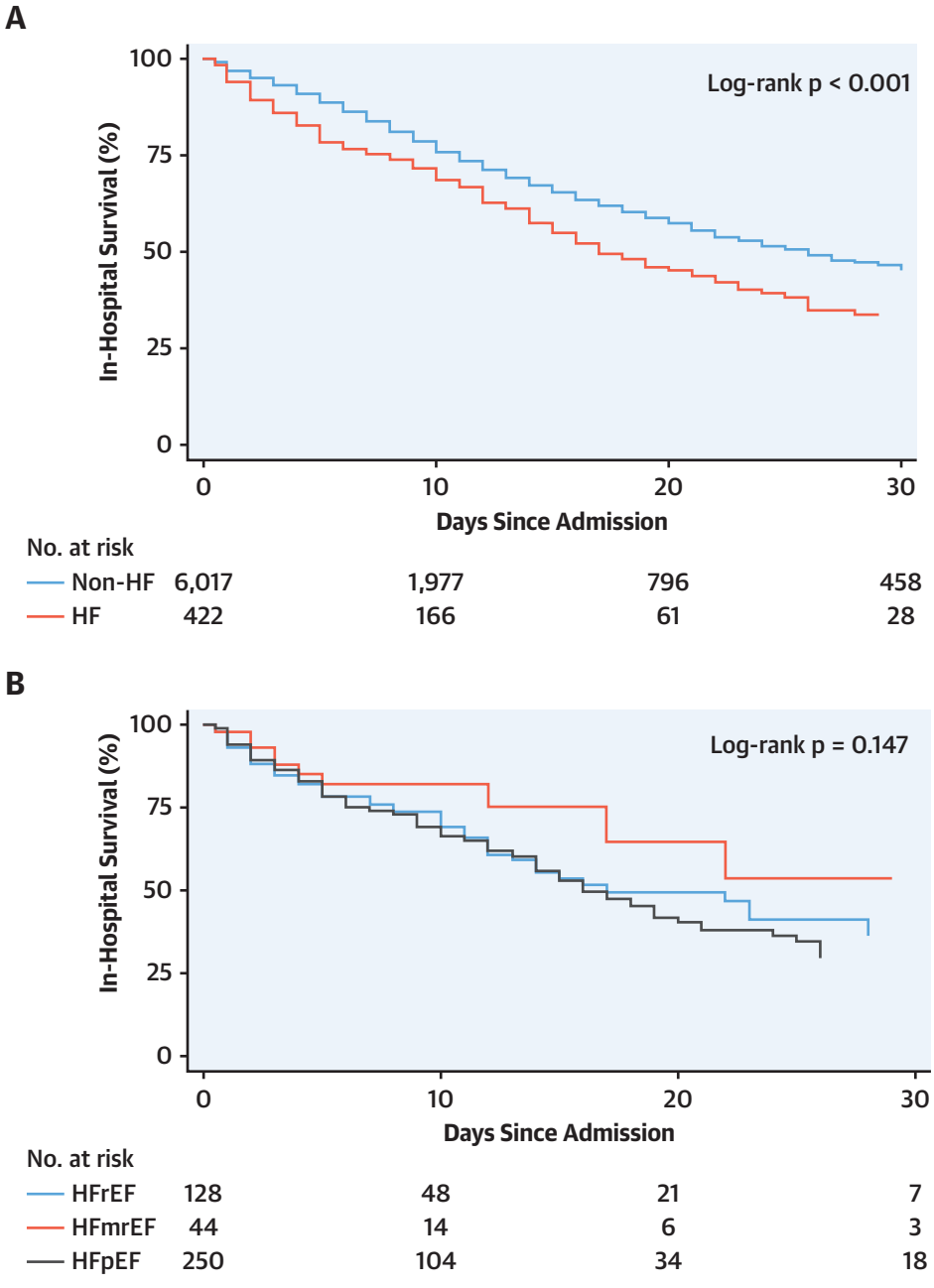
DISCUSSION

Patients with HF represent a population at particularly high risk for worse outcomes with COVID-19. In this multihospital retrospective cohort study from New York City, which was once the global epicenter of COVID-19, we showed that approximately 7% of patients had a history of HF. Compared with patients without HF, history of HF was associated with a nearly 2-fold higher risk of death, >3 times higher risk of mechanical ventilation, and longer LOS despite adjustment for relevant clinical factors. Interestingly, no major differences were noted in the clinical course and outcomes among patients with HFpEF, HFmrEF, or HFrEF (Central Illustration). Finally, previous RAASi use was not associated with a worse prognosis among patients with a history of HF. These simple yet powerful findings revealed the substantially increased risk patients with HF face once hospitalized with COVID-19, regardless of EF, and also pointed to the importance of maintaining RAASi in patients in whom these medications are strongly indicated.

PROGNOSTIC IMPACT OF HISTORY OF HF. Although cardiovascular disease, including HF, has been identified as a risk factor for worse outcomes in COVID-19 (16–19), specific data on the clinical profile, hospital course, and prognosis of patients with a history of HF, particularly in the United States, have been limited (10,11). Specifically, 2 smaller studies (<100 patients each) from Italy and Denmark showed mortality rates of 36% to 37% among patients with cardiovascular disease (wherein HF was well represented) compared with 26% in the overall cohorts. The present analysis included a diverse cohort of >400 patients with HF and included detailed information on comorbid conditions, severity of HF, medications, LVEFs, and specific outcomes.

Patients with HF frequently have a high number of comorbid conditions that contribute to the increased

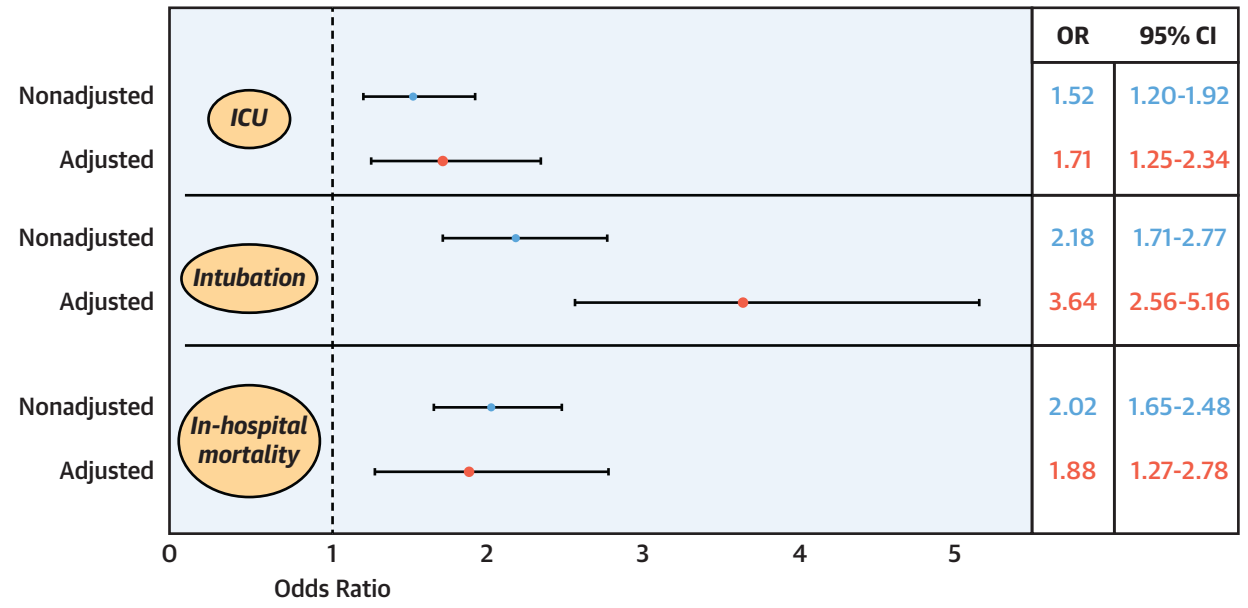
FIGURE 2 Kaplan-Meier Survival Curves



(A) Kaplan-Meier survival curves in patients hospitalized with COVID-19 according to HF history. **(B)** Kaplan-Meier survival curves in patients with HF hospitalized with COVID-19 according to left ventricular ejection fraction (LVEF) category. Abbreviations as in Figure 1.

risk of adverse outcomes encountered in the face of acute illness. However, our results revealed that a history of HF itself was associated with a near doubling risk of mortality despite adjustment for co-morbid conditions. The systemic effects of COVID-19, particularly on the cardiovascular system, have been increasingly recognized (20). In particular, SARS-CoV-2 has been found within macrophages, endothelial cells, and pericytes (21,22), with a recent study demonstrating evidence of active viral replication in the myocardium on autopsy (23). Widespread inflammation, as well as increased micro- and

FIGURE 3 Forest Plot of the Effect of a History of HF on Outcomes in Patients Admitted for COVID-19



After a multivariable logistic regression adjusting for age, sex, race, obesity, hypertension, diabetes, coronary artery disease, atrial fibrillation, chronic kidney disease, chronic obstructive pulmonary disease, previous treatment with renin-angiotensin-aldosterone inhibitors, systolic blood pressure, heart rate, oxygen saturation, white blood count, lymphocytes, creatinine, and albumin on admission, history of HF persisted as an independent risk factor for the need for intensive care unit (ICU) care, intubation and mechanical ventilation, and in-hospital mortality. CI = confidence interval; OR = odds ratio; other abbreviations as in Figure 1.

macrovascular thrombosis, may underlie the cardiac manifestations of arrhythmias, myocarditis, and de novo LV dysfunction that have been reported (20,22). Our group previously showed that the degree of myocardial injury, reflected by increased troponin concentrations, correlated with increasing risk of mortality in the setting of COVID-19 (4). In the present analysis, we saw higher mean troponin concentrations among patients with HF compared with those without HF. Specific mechanisms by which patients with pre-existing HF are more susceptible to deleterious cardiac manifestations and subsequent increased mortality related to infection with SARS-CoV-2 remains to be further elucidated.

IMPACT OF LVEF AND RAASi AMONG PATIENTS WITH HF HOSPITALIZED WITH COVID-19. It was particularly interesting to note the lack of difference in LOS, ICU requirement, intubation and mechanical ventilation, acute renal failure, intravenous diuretic requirement, and mortality among patients with HF based on LVEF. Despite substantial evidence pointing to equivalent outcomes in other settings, patients with HFpEF are often considered at lower risk for mortality compared with their HFrEF counterparts. The present analysis added to this mounting body of literature (24,25), which demonstrated similar outcomes among patients with HFpEF and HFrEF, even in the setting of acute COVID-19. In contrast, our results suggested that patients with HFmrEF could have a better prognosis, because they can represent a distinct and more favorable HF phenotype (26,27).

Similarly, in the early stages of the pandemic, RAASi were thought to confer increased risk due to increased angiotensin-converting enzyme 2 expression, hence facilitating increased viral entry into host cells (13,21,28). Among patients with HF, particularly those with reduced EFs, RAASi form the essential cornerstone of management, and as such, discontinuation of these medications could lead to deleterious effects in the long term. In accordance with subsequent papers that disproved the postulated adverse effects of angiotensin-converting enzyme/angiotensin receptor blockers in the setting of COVID-19 (29,30), our analysis also showed no association between RAASi and adverse events but specifically in the patient population who benefitted from them the most. As such, we offer additional support for continuation of these life-saving medications in patients with HF amidst the COVID-19 pandemic.

CLINICAL IMPLICATIONS. The present analysis of patients with HF with COVID-19 can entail several clinical implications. First, the strong association

TABLE 2 Clinical Characteristics of the Patients With HF Admitted for COVID-19 According to the LVEF Category

	HFrEF (n = 128; 30.3%)	HFmrEF (n = 44; 10.4%)	HFpEF (n = 250; 59.3%)	p Value
Age, yrs	69.9 ± 13.7	71.2 ± 15.3	74.1 ± 12.5	0.013
Female	37 (28.9)	18 (40.9)	131 (52.4)	<0.001
BMI, kg/m^2	27.4 ± 6.7	31.3 ± 12.0	30.2 ± 8.2	0.002
Race				0.207
Black	46 (35.9)	12 (27.3)	76 (30.4)	
Hispanic/Latino	41 (32.0)	16 (36.4)	63 (25.2)	
White	28 (21.9)	12 (27.3)	65 (26.0)	
Asian	2 (1.6)	1 (2.3)	18 (7.2)	
Other	10 (7.8)	3 (6.8)	21 (8.4)	
Unknown	1 (0.8)	0 (0.0)	7 (2.8)	
Comorbidities				
Obesity	41 (32.0)	23 (52.3)	105 (42.0)	0.038
Hypertension	114 (89.1)	39 (88.6)	229 (91.6)	0.657
Diabetes mellitus	74 (57.8)	28 (63.4)	167 (66.8)	0.228
Dyslipidemia	73 (57.0)	25 (56.8)	130 (52.0)	0.601
CAD	86 (67.2)	26 (59.1)	123 (49.2)	0.003
Stroke	35 (27.3)	10 (22.7)	69 (27.6)	0.794
AF/flutter	48 (37.5)	23 (52.3)	89 (35.6)	0.109
CKD	49 (38.3)	18 (40.9)	110 (44.0)	0.560
COPD	19 (14.8)	10 (22.7)	65 (26.0)	0.048
Asthma	12 (9.4)	8 (18.2)	38 (15.2)	0.198
OSA	8 (6.3)	7 (15.9)	42 (16.8)	0.016
HF history				
Ischemic HF	70 (54.7)	21 (47.7)	67 (26.8)	<0.001
HF duration, yrs	3.9 ± 3.9	4.5 ± 2.7	4.2 ± 3.4	0.036
LVEF, %	30 ± 9	45 ± 2	61 ± 6	<0.001
LVEDD, mm	55 ± 9	50 ± 7	46 ± 8	<0.001
Septum, mm	11 (3)	12 (3)	12 (3)	0.014
Mod/severe MR	37 (32.5)	10 (23.8)	21 (9.0)	<0.001
Baseline NYHA functional class				0.942
I	9 (7.2)	3 (7.1)	21 (8.7)	
II	65 (52.0)	26 (61.9)	128 (53.1)	
III	46 (36.8)	12 (28.6)	83 (34.4)	
IV	5 (4.0)	1 (2.4)	9 (3.7)	
Past 1-yr HF admission	58 (45.3)	18 (40.9)	90 (36.1)	0.221
No. of 1-yr HF admissions	1.2 (2.7)	0.6 (0.8)	0.7 (1.5)	0.025
LBBB	22 (17.2)	3 (6.8)	9 (3.6)	<0.001
ICD	44 (34.4)	3 (6.8)	6 (82.4)	<0.001
CRT	15 (11.7)	1 (2.3)	1 (0.4)	<0.001
Background treatment				
RAAS inhibitors	96 (75.0)	32 (72.7)	132 (52.8)	<0.001
Beta-blockers	116 (90.6)	38 (86.4)	200 (80.0)	0.026
MRA	26 (20.3)	8 (18.2)	26 (10.4)	0.024
SGLT2i	5 (3.9)	1 (2.3)	6 (2.4)	0.819
Loop diuretics	96 (75.0)	33 (75.0)	189 (75.5)	0.990
Thiazides	13 (10.2)	6 (13.6)	45 (18.0)	0.126
Antiplatelet	104 (81.3)	36 (81.8)	187 (74.8)	0.280
Anticoagulant	55 (43.0)	19 (43.2)	101 (40.4)	0.865
Statins	115 (89.8)	37 (84.1)	199 (79.6)	0.041
Clinical presentation				
Fever	41 (32.0)	21 (47.7)	100 (40.0)	0.130
Cough	50 (39.1)	25 (56.8)	108 (43.2)	0.122
Shortness of breath	76 (59.4)	27 (61.4)	151 (60.4)	0.968
Weakness/fatigue	38 (29.7)	15 (34.1)	61 (24.4)	0.294
Systolic BP, mm Hg	122 ± 27	128 ± 27	127 ± 32	0.313
Diastolic BP, mm Hg	70 ± 15	71 ± 17	67 ± 17	0.140

Continued on the next page

TABLE 2 Continued

	HFrEF (n = 128; 30.3%)	HFmrEF (n = 44; 10.4%)	HFpEF (n = 250; 59.3%)	p Value
Heart rate, beats/min	86 ± 20	87 ± 23	88 ± 20	0.657
Respiratory rate, rpm	20 ± 5	21 ± 5	21 ± 5	0.818
Saturation O_2, %	92 ± 9	94 ± 6	91 ± 10	0.045
Temperature, °F	98.5 ± 1.8	98.2 ± 1.2	98.6 ± 1.8	0.403
Any sign of congestion	61 (47.7)	16 (36.4)	101 (40.4)	0.285
Laboratory data				
WBC, k/μl	6.7 (4.6–9.8)	6.4 (4.8–11.6)	7.3 (5.3–10.6)	0.164
Neutrophils, %	77 (65–85)	70 (62–84)	76 (68–84)	0.379
Lymphocytes, %	13 (8–20)	16 (9–24)	13 (8–20)	0.232
Hemoglobin, g/dl	11.6 (9.9–13.6)	10.5 (9.4–13.3)	10.7 (8.9–12.7)	0.005
Platelets, k/μl	192 (137–258)	213 (142–318)	203 (145–284)	0.450
INR	1.2 (1.1–1.6)	1.3 (1.1–1.4)	1.2 (1.1–1.5)	0.377
Fibrinogen, mg/dl	520 (410–633)	565 (457–651)	519 (432–650)	0.578
D-dimer, UG/ml	2.15 (1.22–3.59)	1.14 (0.77–2.18)	1.97 (1.01–3.67)	0.014
Glucose, mg/dl	120 (93–189)	109 (87–170)	119 (90–186)	0.572
Sodium, mmol/l	139 (136–142)	139 (136–141)	138 (135–141)	0.864
Potassium, mmol/l	4.5 (4.1–5.1)	4.5 (4.2–4.8)	4.5 (4.0–4.9)	0.508
Creatinine, mg/dl	1.7 (1.2–3.4)	1.8 (1.1–3.3)	2.2 (1.2–5.5)	0.162
BUN, mg/dl	38 (21–59)	29 (16–49)	37 (21–64)	0.131
ALT, U/l	28 (18–52)	18 (12–28)	22 (14–34)	0.001
Bilirubin, mg/dl	0.7 (0.5–1.1)	0.6 (0.4–0.8)	0.6 (0.4–0.8)	0.045
Albumin, g/dl	2.9 (2.4–3.3)	3.2 (2.5–3.5)	2.9 (2.5–3.3)	0.361
Troponin I, ng/ml	0.07 (0.03–0.22)	0.07 (0.02–0.16)	0.08 (0.03–0.19)	0.627
Peak troponin, ng/ml	0.10 (0.03–0.25)	0.09 (0.03–0.42)	0.13 (0.04–0.39)	0.183
BNP, pg/ml	678 (235–1862)	585 (177–1121)	378 (125–1271)	0.018
Lactate, mmol/l	1.6 (1.1–2.7)	1.6 (1.1–2.2)	1.6 (1.1–2.3)	0.590
CRP, mg/l	93.4 (41.0–160.7)	67.6 (27.3–131.7)	73.7 (32.2–131.7)	0.363
Ferritin, ng/ml	960 (319–2811)	508 (183–861)	760 (348–2017)	0.126
Procalcitonin, ng/ml	0.33 (0.08–1.23)	0.19 (0.11–0.56)	0.46 (0.10–1.77)	0.109
Interleukin-6, pg/ml	71.4 (36.6–144.2)	66.8 (31.3–126.3)	60.4 (26.2–124.0)	0.943
CV tests during admission				
ECG	126 (98.4)	43 (97.7)	235 (94.0)	0.102
Sinusal	83 (65.9)	25 (58.1)	174 (74.0)	0.005
AF/flutter	20 (15.9)	13 (30.2)	45 (19.2)	
Other	23 (18.3)	5 (11.6)	16 (6.8)	
LBBB	15 (12.5)	3 (7.3)	10 (4.5)	0.020
QT interval	412 (62)	398 (55)	395 (59)	0.030
QTc interval	487 (45)	475 (53)	466 (43)	<0.001
Echocardiography	30 (23.4)	9 (20.5)	41 (16.5)	0.254
LVEF, %	34 ± 14	41 ± 18	58 ± 11	<0.001
Mod/severe MR	10 (33.3)	1 (11.1)	10 (25.6)	0.481
Mod/severe TR	10 (33.3)	2 (22.2)	8 (20.5)	0.464
Cardiac CT	6 (4.7)	0 (0.0)	2 (0.8)	0.031
RHC	3 (2.3)	0 (0.0)	0 (0.0)	0.057
LHC	3 (2.3)	0 (0.0)	1 (0.4)	0.141
Treatment				
Hydroxychloroquine	65 (50.8)	21 (47.7)	163 (65.2)	0.007
Azithromycin	59 (46.1)	20 (45.5)	148 (59.2)	0.027
Hydroxy+azithrom	46 (35.9)	15 (34.1)	121 (48.4)	0.030
Remdesivir	1 (0.8)	1 (2.3)	4 (1.6)	0.576
Tocilizumab	4 (3.1)	2 (4.6)	7 (2.8)	0.763
Steroids	37 (28.9)	13 (29.6)	90 (36.0)	0.331
Anticoagulant*	59 (80.8)	20 (80.0)	126 (84.6)	0.718
Antiplatelet	72 (56.3)	19 (43.2)	105 (42.0)	0.028

Continued on the next page

TABLE 2 Continued

	HFrEF (n = 128; 30.3%)	HFmrEF (n = 44; 10.4%)	HFpEF (n = 250; 59.3%)	p Value
RAAS inhibitor (only if present at baseline)				
Continued	25 (26.0)	11 (34.4)	20 (15.4)	0.028
Stopped	71 (74.0)	21 (65.6)	110 (84.6)	
Beta-blockers	74 (57.8)	23 (52.3)	105 (42.0)	0.012
MRA	10 (7.8)	2 (4.6)	6 (2.4)	0.044
IV diuretics	50 (39.1)	14 (31.8)	92 (36.8)	0.689
Statins	67 (52.3)	25 (56.8)	120 (48.0)	0.475
Nasal cannula	93 (72.7)	30 (68.2)	181 (72.4)	0.833
CPAP/BIPAP	34 (26.6)	10 (22.7)	93 (37.2)	0.039
Inotropes	10 (7.9)	1 (2.3)	7 (2.8)	0.078
Vasopressors	25 (19.5)	6 (13.6)	41 (16.4)	0.608
MCS	2 (1.6)	0 (0.0)	0 (0.0)	0.166
RRT (excluding pts with long-term dialysis)	5 (3.9)	1 (2.3)	16 (6.4)	0.382
Outcomes				
ICU	27 (21.1)	11 (25.0)	60 (24.0)	0.783
LOS ICU, days	7 (3–13)	3 (1–5)	5 (2–13)	0.117
LOS, days	8 (3–14)	7 (3–12)	8 (4–13)	0.682
Intubation	28 (21.9)	8 (18.2)	60 (24.0)	0.670
AKI	57 (44.5)	15 (34.1)	102 (40.8)	0.468
Shock	34 (26.6)	5 (11.4)	52 (20.8)	0.096
Cardiogenic	10 (7.8)	1 (2.3)	5 (2.0)	0.019
Septic	24 (18.8)	3 (6.8)	47 (18.8)	0.134
Hypovolemic	5 (3.9)	1 (2.3)	6 (2.4)	0.819
Thromboembolic events	8 (6.3)	1 (2.3)	10 (4.0)	0.207
ACS	5 (3.9)	0 (0.0)	5 (2.0)	0.383
Stroke	1 (0.8)	0 (0.0)	1 (0.4)	1.000
PE	0 (0.0)	0 (0.0)	3 (1.2)	0.680
Others	2 (1.6)	1 (2.3)	1 (0.4)	0.210
Arrhythmias	23 (18.0)	9 (20.5)	32 (12.8)	0.243
AF/SVT	17 (13.3)	9 (20.5)	31 (12.4)	0.352
NSVT	2 (1.6)	1 (2.3)	0 (0.0)	0.086
VT	3 (2.3)	0 (0.0)	0 (0.0)	0.057
VF	2 (1.6)	0 (0.0)	0 (0.4)	0.473
30-day readmission rate	17 (17.7)	3 (8.3)	35 (18.6)	0.347
Non-CV	6 (35.3)	2 (66.7)	23 (65.7)	0.019
CV non-HF	3 (17.7)	1 (33.3)	9 (25.7)	
CV HF related	8 (47.1)	0 (0.0)	3 (8.6)	
Death	49 (38.3)	10 (22.7)	110 (44.0)	0.026
Non-CV	40 (81.6)	9 (90.0)	102 (92.7)	0.157
CV non-HF	5 (10.2)	0 (0.0)	5 (4.6)	
CV HF related	4 (8.2)	1 (10.0)	3 (2.7)	

Values are mean ± SD, n (%), or median (interquartile range). *In those patients without previous anticoagulation.

ACS = acute coronary syndrome; AF = atrial fibrillation; AKI = acute kidney injury; BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; CRP = C-reactive protein; CRT = cardiac resynchronization therapy; CT = computed tomography; CV = cardiovascular; ICD = implantable cardioverter defibrillator; LBBB = left bundle branch block; LHC = left heart catheterization; LVEDD = left ventricular end-diastolic diameter; MCS = mechanical circulatory support; MR = mitral regurgitation; NSVT = non-supraventricular tachycardia; NYHA = New York Heart Association; PE = pulmonary embolism; RHC = right heart catheterization; RRT = renal replacement therapy; SGLT2i = sodium-glucose co-transporter-2 inhibitors; SVT = supraventricular tachycardia; TR = tricuspid regurgitation; VF = ventricular fibrillation; VT = ventricular tachycardia; other abbreviations as Table 1.

with increased risk of mechanical ventilation and mortality may help triage patients upon presentation to the hospital. Furthermore, because of this increased risk, the utmost caution must also be taken to prevent exposure for patients with HF. Several centers have reported a reduction of HF hospitalization during the pandemic (31–34), and as such, the reliance on telemonitoring and telemedicine may increase for patients where COVID-19 is rampant (35–38). Future studies are needed to understand the impact of telemonitoring on long-term care and outcomes for this population. Among patients with severe HF, weighing the risk of exposure to COVID-19 against the benefit of life-saving therapies, such as

TABLE 3 Risk Factors for In-Hospital Mortality in Patients With HF Admitted for COVID After Cox Proportional Hazards Regression Analysis

	HR	95% CI	p Value	aHR	95% CI	p Value
Age (for each increase of 5 yrs)	1.18	1.10–1.26	<0.001	**1.15**	**1.05–1.25**	**0.002**
Female	1.08	0.79–1.47	0.642	1.13	0.77–1.64	0.538
Race						
White (ref)	–	–	–	–	–	–
Black	0.62	0.41–0.94	0.025	0.84	0.51–1.36	0.467
Hispanic/Latino	0.76	0.50–1.14	0.179	1.10	0.69–1.75	0.679
Asian	0.87	0.43–1.77	0.698	1.25	0.58–2.71	0.575
Other	0.87	0.47–1.60	0.649	1.15	0.59–2.23	0.684
Unknown	2.18	0.78–6.07	0.137	1.67	0.55–5.04	0.365
BMI (for each increase of 1 kg/m^2)	1.00	0.98–1.02	0.822	1.01	0.99–1.03	0.274
Hypertension	0.82	0.50–1.34	0.432	1.05	0.61–1.82	0.860
Diabetes mellitus	0.75	0.55–1.03	0.071	1.02	0.70–1.50	0.915
AF/flutter	1.28	0.94–1.75	0.113	0.91	0.63–1.31	0.597
Chronic kidney disease	0.70	0.51–0.97	0.032	0.75	049–1.14	0.175
COPD	1.28	0.90–1.81	0.164	1.09	0.74–1.60	0.676
LVEF category						
HFmrEF (ref)	–	–	–	–	–	–
HFrEF	1.68	0.82–3.43	0.157	1.44	0.67–3.11	0.347
HFpEF	1.98	1.00–3.92	0.049	1.54	0.74–3.22	0.250
NYHA functional class III/IV	1.53	1.11–2.11	0.009	**1.61**	**1.13–2.30**	**0.009**
Past moderate/severe MR	1.65	1.13–2.40	0.009	**1.62**	**1.04–2.51**	**0.033**
Previous RAAS inhibitors	0.80	0.59–1.09	0.152	0.84	0.59–1.19	0.319
Systolic BP (for each increase of 10 mm Hg)	0.90	0.85–0.95	<0.001	**0.93**	**0.88–0.99**	**0.015**
Heart rate, beats/min (for each increase of 1 beats/min)	1.01	1.00–1.01	0.070	1.01	0.99–1.01	0.114
Saturation O_2, % (for each increase of 1%)	0.96	0.95–0.97	<0.001	**0.97**	**0.96–0.99**	**0.001**
Lymphocytes, % (for each increase of 1%)	0.95	0.93–0.97	<0.001	**0.97**	**0.95–0.99**	**0.005**
Creatinine, mg/dl (for each increase of 1 mg/dl)	1.00	0.95–1.04	0.946	1.04	0.98–1.11	0.191
BNP (for each increase of 100 pg/ml)	1.00	0.99–1.01	0.427	1.00	0.99–1.01	0.356
Troponin, ng/ml (for each increase of 1 ng/ml)	1.07	1.01–1.13	<0.001	**1.08**	**1.01–1.16**	**0.017**

Bold indicates risk factors for in-hospital mortality among patients with HF by multivariable Cox regression.
aHR = adjusted hazard ratio; CI = confidence interval; HR = hazard ratio; other abbreviations as in Tables 1 and 2.

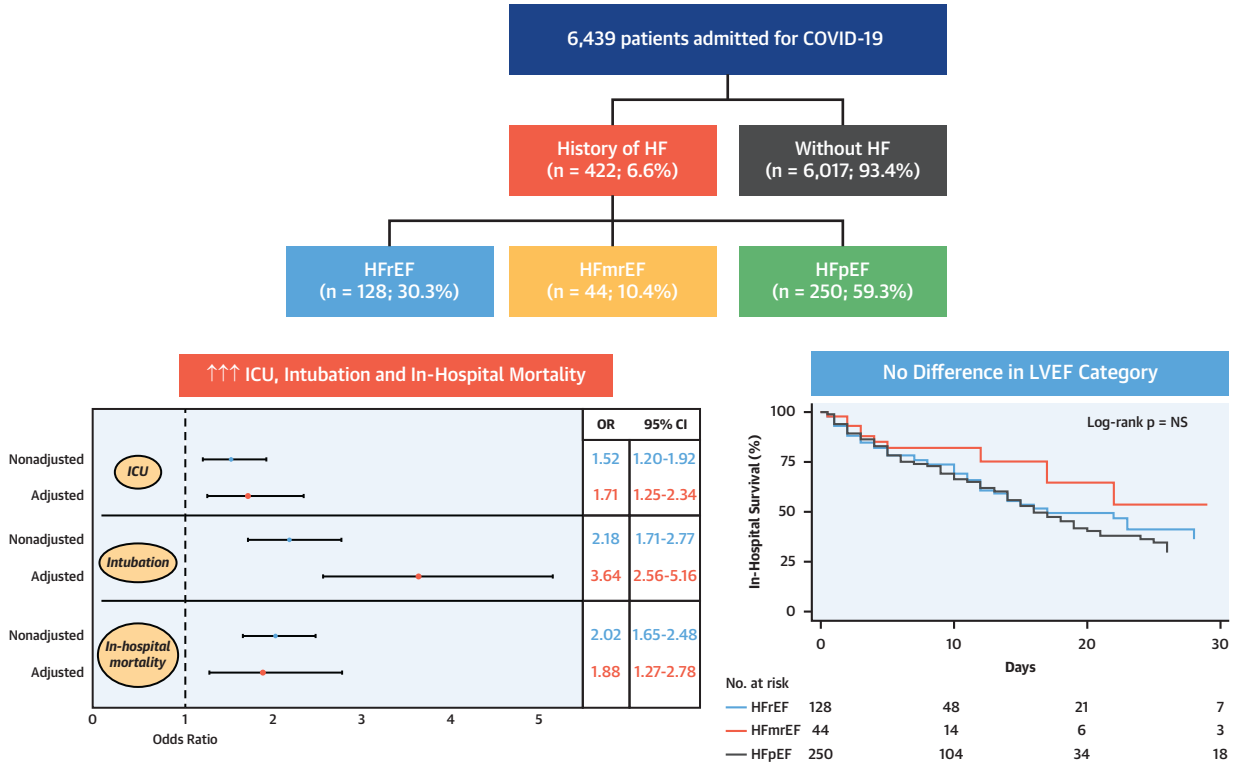
mechanical circulatory support and heart transplantation, is particularly relevant and must be carefully considered on a case-by-case basis (39). Finally, understanding the mechanisms that underlie the high risk of complications and mortality among patients with HF begs the question of whether specific therapies to combat acute infection in COVID-19 should be used based on the history of HF. Recent studies have pointed to the potential benefits of corticosteroids and anticoagulation, as well as antiviral therapies in the treatment of more severe COVID-19 cases (40–42). Because inflammation underlies both chronic HF (43) and acute COVID-19, it may be that anti-inflammatory drugs are particularly effective in mitigating adverse events in this population. This hypothesis and others will warrant further longitudinal follow-up studies.

STUDY LIMITATIONS. First, the use of electronic health records for patient-level data in such a large sample size was subject to error. Because history of HF was identified using ICD-9/10 codes, it was possible that some patients with history of HF were not appropriately classified. However, for those patients identified as having a history of HF, we manually verified history, clinical data, and outcomes to ensure accuracy. Second, it was not possible to ascertain causes of death nor 30-day readmission rate in the overall cohort. In addition, we did not capture readmissions to other hospitals; however, the Mount Sinai Health system is large and far-reaching within New York City, and as such, it was more likely that most rehospitalizations were reflected. Finally, because of the small number of patients with echocardiographic studies performed during the hospitalization for COVID-19, related imaging findings should be interpreted with caution.

CONCLUSIONS

History of HF is associated with an almost 2-fold increased risk of death among patients hospitalized

CENTRAL ILLUSTRATION History of Heart Failure and Coronavirus Disease-2019



Alvarez-Garcia, J. et al. J Am Coll Cardiol. 2020;76(20):2334–48.

Patients with pre-existing heart failure (HF) are at nearly twice the risk of mortality and 3 times the risk of mechanical ventilation compared with patients without HF when hospitalized for coronavirus disease-2019 (COVID-19), yet outcomes among patients with HF were similar regardless of left ventricular ejection fraction (LVEF). **(Top panel)** Consort diagram of the study population. **(Bottom right panel)** Kaplan-Meier survival curves in patients hospitalized with COVID-19 according to LVEF category. **(Bottom left panel)** Forest plot of the effect of history of HF on outcomes in patients admitted for COVID-19. CI = confidence interval; HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HR = hazard ratio; ICU = intensive care unit.

with COVID-19, despite adjustment for other prognostic and clinically relevant factors. Importantly, neither LVEF category nor previous treatment with RAASi were associated with worse prognosis among patients with HF and COVID-19. If these findings are confirmed in other populations, history of HF may help guide triage upon hospital presentation and potentially dictate aggressive therapies in the treatment of COVID-19.

AUTHOR RELATIONSHIP WITH INDUSTRY

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Patients with a history of HF hospitalized for COVID-19 face nearly 3 times the risk of mechanical ventilation and twice the risk of mortality compared with patients without HF. Outcomes of patients with HF are independent of LVEF or use of RAASi medications.

TRANSLATIONAL OUTLOOK: Prospective studies are warranted to elucidate the mechanisms responsible for the association of HF and adverse outcomes in patients with COVID-19 and to identify management strategies that improve survival.

REFERENCES

1. John Hopkins University. COVID-19 Map. Johns Hopkins Coronavirus Resource Center. Available at: https://coronavirus.jhu.edu/map.html. Accessed July 29, 2020.

2. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497–506.

3. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020;323:1061–9.

4. Lala A, Johnson KW, Januzzi JL, et al. Prevalence and impact of myocardial injury in patients hospitalized with COVID-19 infection. J Am Coll Cardiol 2020;76:533–46.

5. Giustino G, Croft LB, Oates CP, et al. Takotsubo cardiomyopathy in COVID-19. J Am Coll Cardiol 2020;76:628–9.

6. Bhatla A, Mayer MM, Adusumalli S, et al. COVID-19 and cardiac arrhythmias. Heart Rhythm 2020;17:1439–44.

7. Fried JA, Ramasubbu K, Bhatt R, et al. The variety of cardiovascular presentations of COVID-19. Circulation 2020;141:1930–6.

8. DeFilippis EM, Reza N, Donald E, Givertz MM, Lindenfeld JA, Jessup M. Considerations for heart failure care during the COVID-19 pandemic. J Am Coll Cardiol HF 2020;8:681–91.

9. Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ 2020;368:m1091.

10. Inciardi RM, Adamo M, Lupi L, et al. Characteristics and outcomes of patients hospitalized for COVID-19 and cardiac disease in Northern Italy. Eur. Heart J 2020;41:1821–9.

11. Andersson C, Andersson C, Gerds T, et al. Incidence of new-onset and worsening heart failure before and after the COVID-19 epidemic lockdown in Denmark: a nationwide cohort study. Circ Hear Fail 2020;13:e007274.

12. Jiménez-Blanco Bravo M, Cordero Pereda D, Sánchez Vega D, et al. Heart failure in the time of COVID-19. Cardiology 2020;145:481–4.

13. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin-angiotensin-aldosterone system inhibitors in patients with Covid-19. N Engl J Med 2020;382:1653–9.

14. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. J Am Coll Cardiol 2013;62:e147–239.

15. Little RJA, Rubin DB. Statistical Analysis with Missing Data. 3rd Edition. New York: Wiley, 1991.

16. Guo T, Fan Y, Chen M, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). JAMA Cardiol 2020;5:811–8.

17. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City Area. JAMA 2020;323:2052–9.

18. Shi S, Qin M, Cai Y, et al. Characteristics and clinical significance of myocardial injury in patients with severe coronavirus disease 2019. Eur Heart J 2020;41:2070–9.

19. Petrilli CM, Jones SA, Yang J, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. BMJ 2020;369:m1966.

20. Atri D, Siddiqi HK, Lang JP, Nauffal V, Morrow DA, Bohula EA. COVID-19 for the cardiologist: basic virology, epidemiology, cardiac manifestations, and potential therapeutic strategies. J Am Coll Cardiol Basic Trans Science 2020;5:518–36.

21. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020;181:271–80.e8.

22. Chen L, Li X, Chen M, Feng Y, Xiong C. The ACE2 expression in human heart indicates new potential mechanism of heart injury among patients infected with SARS-CoV-2. Cardiovasc Res 2020;116:1097–100.

23. Lindner D, Fitzek A, Bräuninger H, et al. Association of cardiac infection with SARS-CoV-2 in confirmed COVID-19 autopsy cases. JAMA Cardiol 2020 July 27 [Epub ahead of print].

24. Lam CSP, Gamble GD, Ling LH, et al. Mortality associated with heart failure with preserved vs. reduced ejection fraction in a prospective international multi-ethnic cohort study. Eur Heart J 2018;39:1770–80.

25. Shiga T, Suzuki A, Haruta S, et al. Clinical characteristics of hospitalized heart failure patients with preserved, mid-range, and reduced ejection fractions in Japan. ESC Heart Fail 2019;6:475–86.

26. Kalogeropoulos AP, Fonarow GC, Georgiopoulou V, et al. Characteristics and outcomes of adult outpatients with heart failure and improved or recovered ejection fraction. JAMA Cardiol 2016;1:510–8.

27. Nadruz W, West E, Santos M, et al. Heart failure and midrange ejection fraction: implications of recovered ejection fraction for exercise tolerance and outcomes. Circ Heart Fail 2016;9:e002826.

28. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med 2020;8:e21.

29. Bozkurt B, Kovacs R, Harrington B. Joint HFSA/ACC/AHA Statement Addresses Concerns Re: Using RAAS Antagonists in COVID-19. J Card Fail 2020;26:370.

30. Zhang Y, Coats AJS, Zheng Z, et al. Management of heart failure patients with COVID-19: a joint position paper of the Chinese Heart Failure Association & National Heart Failure Committee and the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2020;22:941–56.

31. Cox ZL, Lai P, Lindenfeld JA. Decreases in acute heart failure hospitalizations during COVID-19. Eur J Heart Fail 2020;22:1045–6.

32. Hall ME, Vaduganathan M, Khan MS, et al. Reductions in heart failure hospitalizations during the COVID-19 pandemic. J Card Fail 2020;26:462–3.

33. McIlvennan CK, Allen LA, DeVore AD, Granger CB, Kaltenbach LA, Granger BB. Changes in care delivery for patients with heart failure during the COVID-19 pandemic: results of a multicenter survey. J Card Fail 2020;26:635–6.

34. Bromage DI, Cannatà A, Rind IA, et al. The impact of COVID-19 on heart failure hospitalization and management: report from a heart failure unit in London during the peak of the pandemic. Eur J Heart Fail 2020;22:978–84.

35. Gorodeski EZ, Goyal P, Cox ZL, et al. Virtual visits for care of patients with heart failure in the era of COVID-19: a statement from the Heart Failure Society of America. J Card Fail 2020;26:448–56.

36. Abraham WT, Fiuzat M, Psotka MA, O'Connor CM. Heart failure collaboratory statement on heart failure remote monitoring in the landscape of COVID-19 and social distancing. J Am Coll Cardiol HF 2020;8:692–4.

37. Food and Drug Administration. Enforcement policy for non-invasive remote monitoring devices used to support patient monitoring during the coronavirus disease 2019 (COVID-19) public health emergency (Revised). Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/enforcement-policy-non-invasive-remote-monitoring-devices-used-support-patient-monitoring-during. Accessed October 20, 2020.

38. Virani SA, Clarke B, Ducharme A, et al. Optimizing access to heart failure care in Canada during the COVID-19 pandemic. Can J Cardiol 2020;36:1148–51.

39. Singhvi A, Barghash M, Lala A, et al. Challenges in heart transplantation during COVID-19: a single center experience. J Heart Lung Transplant 2020;39:894–903.

40. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with Covid-19 - preliminary report. N Engl J Med 2020 July 17 [E-pub ahead of print].

41. Paranjpe I, Fuster V, Lala A, et al. Association of treatment dose anticoagulation with in-hospital survival among hospitalized patients with COVID-19. J Am Coll Cardiol 2020;76:122–4.

42. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19 — preliminary report. N Engl J Med 2020 May 20 [E-pub ahead of print].

43. Murphy SP, Kakkar R, McCarthy CP, Januzzi JL. Inflammation in heart failure: JACC state-of-the-art review. J Am Coll Cardiol 2020;75:1324–40.

KEY WORDS coronavirus, COVID-19, heart failure, left ventricular ejection fraction, outcome, renin-angiotensin-aldosterone system inhibitor

APPENDIX For an expanded Methods section as well as supplemental figures and a table, please see the online version of this paper.