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RESEARCH ARTICLE

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Associations of heart failure with susceptibility and severe complications of COVID-19: A nationwide cohort study

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Abstract

Infection is associated with occurrence and worsening of heart failure (HF). However, studies on the association of susceptibility and severe complications of coronavirus disease 2019 (COVID-19) with HF history are limited. From the Korean nationwide COVID-19 data set, 212,678 participants with at least one severe acute respiratory syndrome coronavirus 2 real-time reverse transcription polymerase chain reaction (RT-PCR) test were included between January 1 and June 4, 2020. To investigate the association of HF with susceptibility and severe complications of COVID-19, 1:4 ratio propensity score matching (PSM) and logistic regression analysis were performed. The primary outcome was a composite outcome of mechanical ventilation, intensive care unit (ICU) admission, and death. After PSM, COVID-19 PCR positivity did not show a significant difference according to HF history in multivariable analysis (odds ratio [OR]: 0.91, 95% confidence interval (CI) (0.79–1.04), $p = 0.146$). Of 7630 individuals with confirmed COVID-19 infection, 310 (4.1%) had HF history. The overall primary outcome occurred in 426 (5.6%) individuals, including 159 (2.1%) cases of mechanical ventilation, 254 (3.3%) cases of ICU admission, and 215 (2.8%) cases of death. In multivariate logistic analysis, presence of HF history was associated independently with primary outcome (OR: 1.99, 95% CI: 1.42–2.79, $p < 0.001$), particularly mortality (OR: 2.02, 95% CI: 1.36–3.00, $p < 0.001$). Our study demonstrated that HF history is associated poor prognosis, particularly mortality, in COVID-19. Patients with HF can have severe complication if infected with COVID-19; therefore, careful management are necessary.

KEYWORDS

COVID-19, heart failure, intensive care unit, mechanical ventilation, mortality

Hyung J. Kim, Moo-Suk Park, and Jae Il Shin contributed equally to this study as first authors.

1 | INTRODUCTION

The coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is the greatest health and economic threat in the 21st century.[1] The prognosis of most patients infected with COVID-19 is good, but a significant proportion of patients experience critical complications. COVID-19 patients with complications can require mechanical ventilation or hospitalization in an intensive care unit (ICU), and some complications can be fatal.[2] As of July 30, 2021, there were more than 196 million global cases of COVID-19 infection and more than 4 million deaths related to COVID-19.[3] Recently, there have been several studies on who is at risk for COVID-19 infection and who is at risk for severe complications of COVID-19. Older age, hypertension, diabetes mellitus, insulin resistance, cancer, lung disease, chronic kidney disease, and cardiovascular disease are known to be related to severe complications of COVID-19.[2,4] Furthermore, the risk of severe COVID-19 increases with number of underlying health conditions.[5]

Heart failure (HF) is a cardiovascular disease that is one of the major causes of morbidity and mortality worldwide. Infection is related closely to occurrence and aggravation of HF. Recently, research on the association between COVID-19 infection and HF has been proposed. A previous hospital-based study demonstrated that patients with HF history are prone to develop acute decompensation after COVID-19 infection.[6] Furthermore, meta-analysis of hospital-based case-control study demonstrated that patients with HF history was associated with mortality.[7]

Meanwhile, because these previous studies were hospital-based cohort studies, selection bias may exist. Moreover, in COVID-19 patients, studies on the association of susceptibility and severe complications of COVID-19, such as mechanical ventilation, admission to ICU, and mortality, with history of HF are limited, particularly in large sample size general population. We hypothesized that the risk of susceptibility and severe complications from COVID-19 infection would increase in patients with HF history. The purpose of this study was to investigate the association of HF history with susceptibility and severe complications of COVID-19 in a nationwide population-based cohort.

2 | METHODS

2.1 | Study design and participants

We performed a retrospective observational study using a nationwide COVID-19 data set in South Korea. South Korea has a public and single-payer health insurance system, National Health Insurance Service (NHIS). The health insurance data set includes health care information on demographics, hospital visit, diagnoses (via International Statistical Classification of Diseases and Related Health Problems 10 (ICD-10) codes), medical procedures, prescriptions, and mortality of the whole Korean population.[8,9] In the face of the COVID-19 pandemic, the Korea Centers for Disease Control and Prevention and NHIS released a nationwide data set from patients infected with COVID-19 from January 1 to June 4, 2020, for academic research.[10] The nationwide COVID-19 data set included patients living in South Korea who were diagnosed based on real-time reverse transcription polymerase chain reaction (RT-PCR) assays of nasal and pharyngeal swabs. The real-time RT-PCR assay kit followed the World Health Organization (WHO) guideline and was validated by the Korea Centers for Disease Control and Prevention.[11]

We included patients who visited an outpatient facility more than twice or were hospitalized more than once with HF (ICD code I110.0, hypertensive heart disease with HF; I13.0, hypertensive heart disease with hypertensive kidney disease with HF; I13.2, hypertensive heart disease with hypertensive kidney disease with HF and kidney failure; I25.5, ischemic cardiomyopathy; I42.0, dilated cardiomyopathy; I42.9, cardiomyopathy, unspecified; I43, cardiomyopathy in diseases classified elsewhere; I50/I50.0/I50.1/I50.9, HF/congestive HF/left ventricular failure/HF, unspecified) before COVID-19 RT-PCR.[12] Due to the retrospective analysis based on a fully anonymized data set, this study was approved by the Institutional Review Board of Seoul Hospital Ewha Womans University College of Medicine (2020-10-021), and the requirement for informed consent was waived.

2.2 | Study outcome

The primary outcome was defined as a composite of mechanical ventilation, admission to the ICU, and mortality during the 2 months after COVID-19 diagnosis. Mortality was defined as the occurrence of death within 2 months after COVID-19 diagnosis. Mechanical ventilation was identified by claim codes, including intubation or mechanical ventilation (M5850, M5857, M5858, and M5860). Admission to the ICU was defined as the presence of procedure codes for intensive care (AH110, AH150, AH180-95 AH190-5, AH210, AH250, AH280-9, AH28A, AH290-9, AH380-9, AH38A, AH390-9, AH501, AJ001–AJ011, AJ020-1, AJ031, AJ100-390, AJ2A0, AJ3A0, AJ500-590, V5100, V5200, V5210-20, V5500-5520). Mortality and time of death were provided by NHIS and have been validated.[8,13]

2.3 | Covariates

We acquired information regarding sex, age at COVID-19 diagnosis, and household income level (tertiles). In our COVID-19 data set, age is presented as an interval (10 years) due to privacy. Therefore, the age was divided by the median value and dichotomized based on the age of 60 years.[14] Comorbidities were defined using health claims according to ICD-10 codes and medication prescription in the NHIS data before COVID-19 RT-PCR test. Hypertension (I10-15), diabetes mellitus (E11–E14), and stroke (I60-63, I69) were ascertained by the diagnostic code of ICD-10.[15,16] Hypertension and diabetes mellitus were determined relevant only if participants had received antihypertensive or antidiabetic medications at the time of diagnosis.[17]

Atrial fibrillation was determined if participants had received at least two outpatient department or at least one admission with the diagnostic code "I48."[18] Asthma was determined if participants had the related code (J45, J46) as the primary diagnosis 2 times or more.[19] Chronic kidney disease was defined by the presence of diagnostic codes (N03, N05, N165, N18-9, N250, I12-3, Z490-2, Z940, Z992, E102, E112, E132, E142, or T861).[20] Malignancy was defined as the presence of diagnostic codes (C00–C97) with cancer specific deductible code (V027, V193-4) from the Health Insurance Review and Assessment Service.[21] The accuracy of the diagnosis algorithm with ICD-10 codes for comorbidities is 85.0%–94.1%.[10,22,23]

2.4 | Statistical analysis

In our study, comparative analysis of COVID-19 test susceptibility and severe complications of COVID-19 was performed in an unmatched cohort using propensity score matching (PSM). PSM was performed using a greedy nearest-neighbour algorithm to compare the population with and without HF, to balance the baselines of both groups, and to reduce potential confounding. To investigate association of HF with COVID-19 test positivity and severe complications of COVID-19, a 1:4 ratio PSM was performed among all individuals who received a COVID-19 PCR test and COVID-19–positive patients, respectively. For PSM, standardized mean differences <0.1 indicated suitability.

Logistic regression analysis was performed to investigate susceptibility and severe complications of COVID-19 according to history of HF by adjusting for sex, age, household income, hypertension, diabetes mellitus, stroke, atrial fibrillation, asthma, chronic kidney disease, and malignancy in unmatched cohorts and cohorts that were balanced after PSM. The results were demonstrated with odds ratio (OR) and 95% confidence interval (CI). For subanalysis, further analysis was performed for each severe complication of COVID-19, that is, mechanical ventilation, ICU admission, and death. Statistical analyses were executed using R software, version 3.3.3 (R Foundation for Statistical Computing), and SAS 9.4 version (SAS Inc.). Two-sided p <0.05 were considered significant.

3 | RESULTS

In our data set, 212,678 participants aged older than 20 years from the Korean nationwide COVID-19 cohort with at least one SARS-CoV-2 test were included between January 1 and June 4, 2020. To not include patients without history of HF but who developed acute cardiac dysfunction caused by COVID infection, we excluded 1944 individuals with newly diagnosed HF (1 month or less before the COVID-19 PCR test). After the exclusion, 195,811 individuals without HF and 14,923 (7.08%) individuals with HF were identified in the unmatched cohort. Then, we applied PSM for 41,150 individuals without HF and 14,080 individuals with HF, which were appropriately matched (Figure 1 and Table 1). In the unadjusted cohort and, the adjusted sex and age model, COVID-19 PCR positivity were less frequent in patients with HF history (unadjusted, OR: 0.85, 95% CI (0.70–0.97), $p = 0.013$) (sex and age adjusted, OR: 0.85, 95% CI (0.70–0.96), $p = 0.011$). However, COVID-19 PCR positivity did not show a significant difference according to HF history in the fully adjusted model (OR: 0.91, 95% CI (0.79–1.04), $p = 0.146$) (Table 1).

After excluding 1944 individuals with HF diagnosed 1 month or less before the COVID-19 PCR test as described above, from the overall 212,678 individuals, 7630 were positive on COVID-19 RT-PCR test. Of these 7630 patients, 310 (4.06%) had HF history in the unmatched cohort. Then, we applied PSM for 991 individuals without HF and 288 individuals with HF and showed that they were matched appropriately (Figure 1 and Table 2).

Among the 7630 COVID-19 infected patients in the unmatched cohort, the overall primary outcome occurred in 426 (5.58%), including 159 (2.08%) cases of mechanical ventilation, 254 (3.3%) cases of ICU admission, and 215 (2.82%) cases of death. In the unmatched cohort, severe complications of COVID-19 were more frequent in individuals with HF (Table 3, overall $p < 0.001$).

In the PSM matched cohort with 1279 COVID-19 infected patients, overall primary outcome (26.39% vs. 14.83%, $p < 0.001$) and mortality (17.71% vs. 9.28%, $p < 0.001$) were more frequent in individuals with HF; in contrast, frequency of mechanical ventilation and ICU admission did not differ by HF history (Table 3).

Adjustments for sex, age, household income, and comorbidities in the PSM matched cohort did not change the independent association between presence of HF history and primary outcome (adjusted OR: 1.99, 95% CI: 1.42–2.79, $p < 0.001$). In the secondary analyses for individual outcomes after PSM, presence of HF history was associated with mortality (adjusted OR: 2.02, 95% CI: 1.36–3.00, $p < 0.001$) but not with mechanical ventilation (adjusted OR: 1.58, 95% CI: 0.96–2.60, $p = 0.071$) or ICU admission (adjusted OR: 1.33, 95% CI: 0.84–2.08, $p = 0.221$).

4 | DISCUSSION

The key findings of this study are that history of HF is not related to susceptibility to COVID-19; in contrast, a history of HF is associated with severe complications, particularly mortality, from COVID-19 in large sample size general population.

Previous studies have shown that systemic infection causes acute HF and increases the all-cause mortality rate in patients with a history of HF. Various pathogens cause acute HF,[24] including parasites,[25,26] and viruses.[27] A recent study found that the incidence of acute HF increases in COVID-19 infection.[6] Meta-analysis of hospital based case-control study demonstrated that HF was associated with a poor outcome (OR: 2.86, 95% CI: 2.07–3.95) and mortality (OR: 3.46, 95% CI: 2.52–4.75).[7] Systemic infection caused by certain pathogens not only causes acute HF, but also increases the all-cause mortality in patients with a history of HF.[28] It has long been known that patients with a history of HF have an increased mortality rate from seasonal influenza.[28] In addition, patients with a history of HF who have been vaccinated for influenza, have reduced all-cause

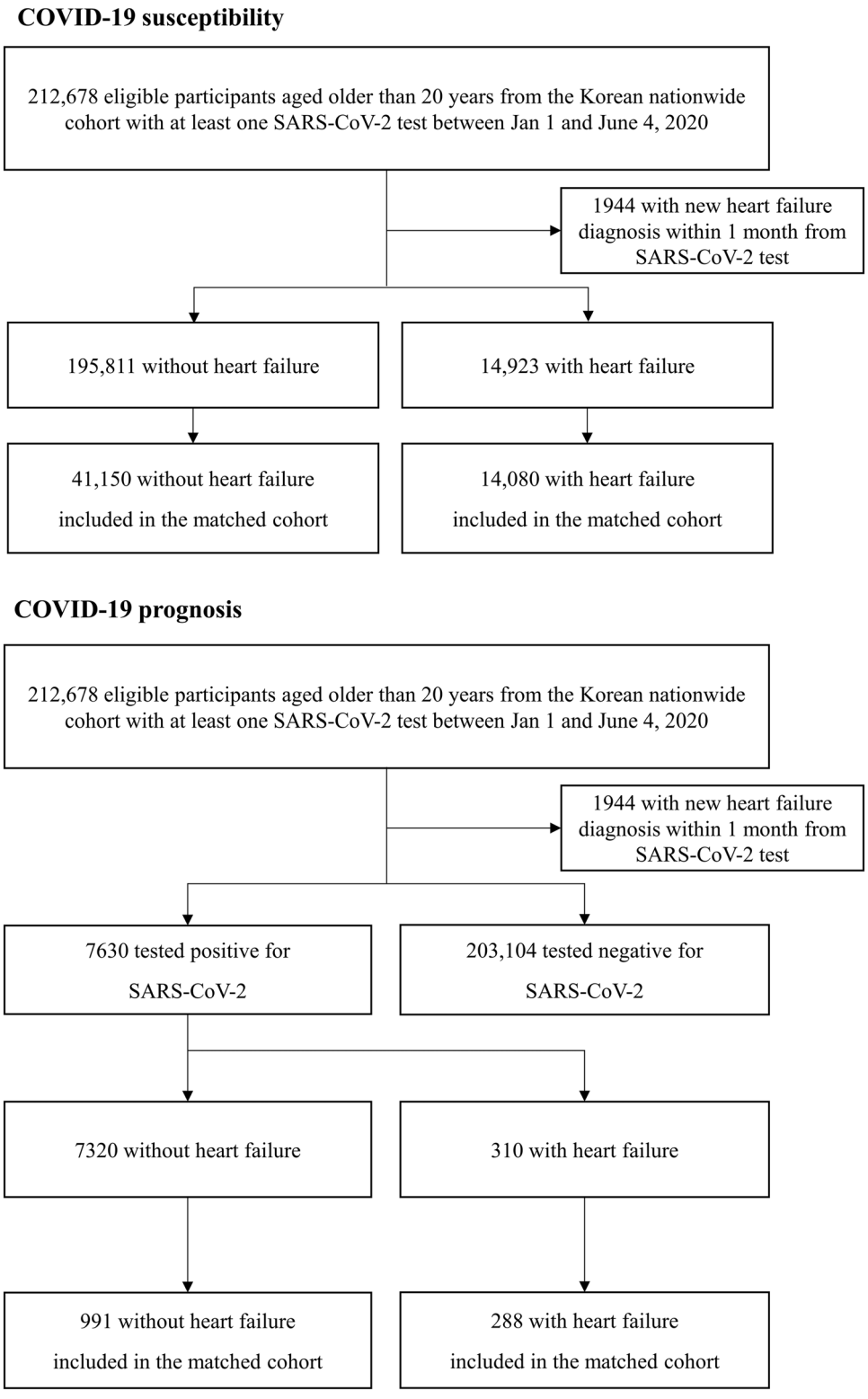

FIGURE 1 Flow chart depicting patient selection. COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

morbidity and mortality.[29] Furthermore, COVID-19 infection has been reported to increase all-cause mortality in patients with a history of HF.[6] Our research was meaningful in that results of our study reconfirmed the results of previous research and might give an additional information regarding association of HF with COVID-19 in the general population with PSM to minimize selection bias.

In our study, severe complications were observed in patients with a history of HF. However, when analyzed using PSM, only mortality

TABLE 1 Baseline characteristics of participants underwent COVID-19 test with and without heart failure before and after propensity score matching

Variable	Before propensity score matching		After propensity score matching		SMD*
	Without HF	With HF	Without HF	With HF	
N	195,811	14,923	41,150	14,080	
Sex, male	91,338 (46.65)	7606 (50.97)	20,788 (50.52)	7179 (50.99)	0.0041
Age (years)					0.0138
<60	138,336 (70.65)	2424 (16.24)	8279 (20.12)	2421 (17.19)	
≥60	57,475 (29.35)	12,499 (83.76)	32,871 (79.88)	11,659 (82.81)	
Household income					−0.0312
T1, lowest	65,558 (33.48)	5931 (39.74)	16,178 (39.31)	5777 (41.03)	
T2	66,665 (34.05)	3742 (25.08)	10,780 (26.20)	3606 (25.61)	
T3, highest	63,588 (32.47)	5250 (35.18)	14,192 (34.49)	4697 (33.36)	
Comorbidities					
Hypertension	50,628 (25.86)	13,846 (92.78)	37,068 (90.08)	13,003 (92.35)	0.0038
Diabetes mellitus	22,448 (11.46)	6074 (40.70)	15,173 (36.87)	5761 (40.92)	0.0022
Stroke	8673 (4.43)	2765 (18.53)	6404 (15.56)	2621 (18.62)	−0.0042
Atrial fibrillation	3266 (1.67)	3985 (26.70)	3007 (7.31)	3157 (22.42)	−0.0450
Asthma	11,869 (6.06)	2590 (17.36)	5342 (12.98)	2433 (17.28)	−0.0034
Chronic kidney disease	13,698 (7.00)	5485 (36.76)	10,323 (25.09)	4962 (35.24)	−0.0068
Malignancy	29,210 (14.92)	4379 (29.34)	12,044 (29.27)	4177 (29.67)	0.0082
COVID-19					
Unadjusted	Ref	0.55 [0.49-0.61]	Ref	0.85 [0.70-0.97]	0.013**
Sex and age adjusted	Ref	0.60 [0.54-0.68]	Ref	0.85 [0.70-0.96]	0.011**
Fully adjusted	Ref	0.82 [0.72-0.93]	Ref	0.91 [0.79-1.04]	0.146**

Note: Data are presented as number with percentage.

Abbreviations: HF, heart failure; SMD, standard mean difference; T, tertile.

*All standardized mean difference values were <0.1 in the propensity score matched cohort.

***p* value for odds ratio.

was increased in patients with a history of HF, and no difference was noted in terms of mechanical ventilation or ICU admission between the two groups. In contrast, a study from a tertiary hospital in Madrid, Spain, paradoxically reported that fewer patients with HF history received mechanical ventilation and ICU admission.[6] The COVID-19 pandemic caused an acute shortage of ventilators and ICU beds. Physicians provided mechanical ventilation and ICU beds to patients with a higher chance of survival with a reasonable life expectancy.[6] Although Korea also suffered the COVID-19 outbreak, the shortage of ventilators and ICU beds was not as severe as in Spain because of the much lower incidence of COVID-19 in Korea (COVID-19 cases-cumulative, Spain: 4,677,883, Republic of Korea: 220,182; WHO data as of August 16, 2021).[3] Nevertheless, the reason for these results was that most patients with a history of HF had old age and comorbidities and often were receiving care in long-term care hospitals in Korea. It is possible that many of these patients and guardians agreed to withdrawal of life-sustaining treatment. Therefore, there were many patients with a history of HF who did not receive mechanical ventilation or were admitted to the ICU despite clinical deterioration; as a result, after PSM, there were no differences in mechanical ventilation and ICU admission but only in mortality.

The association of increased risk of severe complication, particularity mortality, with COVID-19 infection can be explained by multifactorial pathophysiological mechanisms. Studies have shown that HF is an independent risk factor for a thromboembolic event.[30] In particular, COVID-19 infection promotes thromboembolic risk through mechanisms related to a hypercoagulable state due to thrombin activation by dysregulation of angiotensin signaling.[31] All of these mechanisms can increase the risk of thromboembolic events and subsequent increase in mortality. This hypercoagulable state is associated with acute coronary disease, which itself also increases mortality and exacerbates HF.[32] At the same time, COVID-19 infection can prompt and upregulate proinflammatory cytokines. These cytokines can cause immune activation and systemic inflammation,

TABLE 2 Baseline characteristics of COVID-19 patients with and without heart failure before and after propensity score matching

Variable	Before propensity score matching		After propensity score matching		SMD*
	Without HF	With HF	Without HF	With HF	
N	7320	310	991	288	
Sex, male	2886 (39.43)	124 (40.00)	387 (39.05)	111 (38.54)	0.0217
Age (years)					−0.0015
<60	5409 (73.89)	53 (17.10)	199 (20.08)	53 (18.40)	
≥60	1911 (26.11)	357 (82.90)	792 (79.92)	235 (81.60)	
Household income					0.0295
T1, lowest	3175 (43.47)	130 (41.94)	425 (42.89)	120 (41.67)	
T2	2101 (28.70)	78 (25.16)	255 (25.73)	71 (24.65)	
T3, highest	2044 (27.92)	102 (32.90)	311 (31.38)	97 (33.68)	
Comorbidities					
Hypertension	1399 (19.11)	281 (90.65)	892 (90.01)	259 (89.93)	0.0148
Diabetes mellitus	649 (8.87)	105 (33.87)	336 (33.91)	96 (33.33)	0.0061
Stroke	233 (3.18)	57 (18.39)	154 (15.54)	51 (17.71)	−0.0090
Atrial fibrillation	57 (0.78)	66 (21.29)	45 (4.54)	44 (15.28)	−0.0255
Asthma	295 (4.03)	42 (13.55)	96 (9.69)	38 (13.19)	−0.0168
Chronic kidney disease	345 (4.86)	73 (23.55)	195 (19.68)	69 (23.96)	−0.0116
Malignancy	480 (6.56)	59 (19.03)	157 (15.84)	59 (20.49)	−0.0232

Note: Data are presented as number with percentage.

Abbreviations: HF, heart failure; SMD, standard mean difference; T, tertile.

*All standardized mean difference values were <0.1 in the propensity score matched cohort.

TABLE 3 Severe complication in COVID-19 patients

Outcomes	Before propensity score matching				After propensity score matching			
	Without HF (*N* = 7320)	With HF (*N* = 310)	OR [95% CI]	*p value	Without HF1 (*N* = 991)	With HF (*N* = 288)	OR [95% CI]	*p value
Severe complication in COVID-19 patients								
Mechanical ventilation	132 (1.80)	27 (8.71)	5.20 [3.38–7.99]	<.001	61 (6.16)	27 (9.38)	1.58 [0.98–2.53]	0.059
Intensive care unit admission	220 (3.01)	34 (10.97)	3.98 [2.72–5.82]	<.001	83 (8.28)	33 (11.46)	1.42 [0.92–2.17]	0.110
Death	157 (2.14)	58 (18.71)	10.50 [7.58–14.55]	<.001	92 (9.28)	51 (17.71)	2.10 [1.45–3.05]	<0.001
Primary outcome[a]	343 (4.69)	83 (26.77)	7.44 [5.66–9.78]	<.001	147 (14.83)	76 (26.39)	2.06 [1.50–2.82]	<0.001

Note: Data are presented as number with percentage and OR [95% CI].

Abbreviations: CI, confidence interval; HF, heart failure; OR, odds ratio.

**p* value is derived from logistic regression analysis for severe complication in COVID-19.

[a]Composite of mechanical ventilation, admission to the intensive care unit, and mortality during the 2 months after COVID-19 diagnosis.

which lead to direct myocardial damage and inflammation and possibly contribute to worsening of HF.[33,34] In addition, these systemic cytokines and inflammation can stimulate leukocyte adhesion molecule expression on endothelial cells overlying atheroma and increase vascular shear stress at the level of the coronary arteries, resulting in plaque rupture and myocardial infarction.[32] Up to 30% of hospitalized COVID-19 patients, including those without HF, reveal elevated troponin levels as a marker of myocardial injury. Therefore, more patients with a history of HF experience myocardial injury.[35] Moreover, pulmonary hypertension, volume overload due to renal impairment, and medication for COVID-19 have been suggested to cause or exacerbate HF, which may increase mortality[36] (Figure 2).

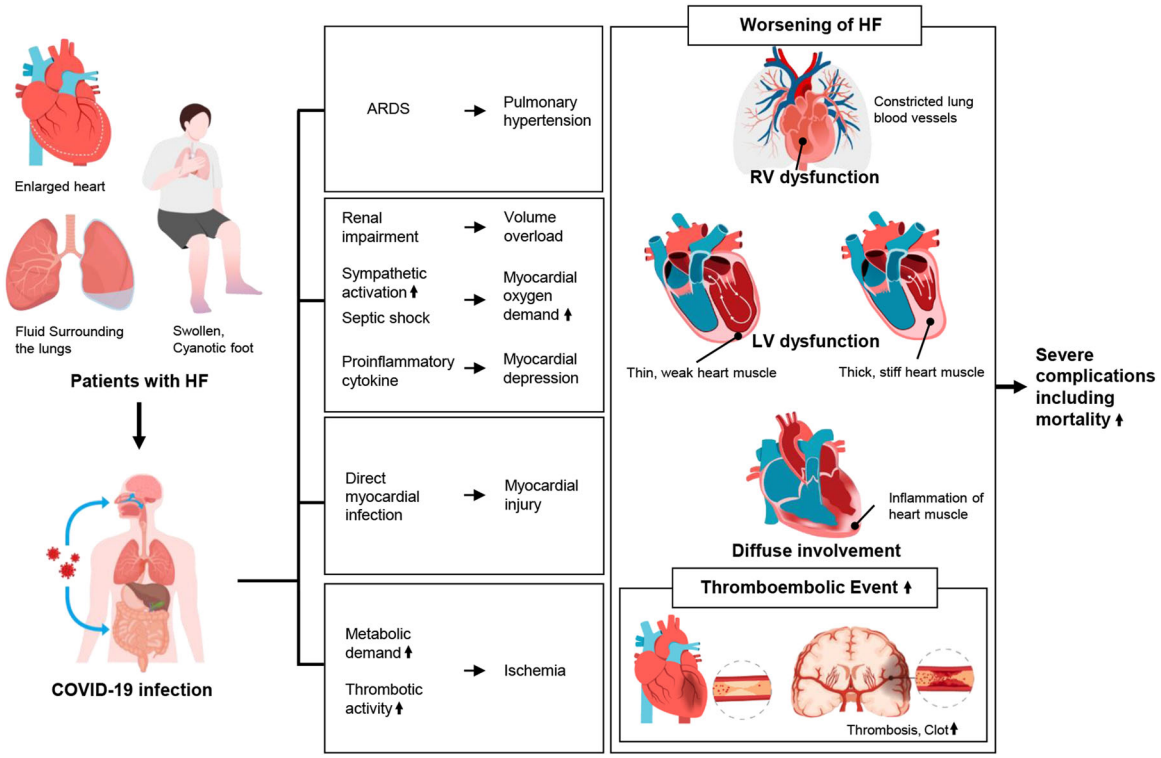

FIGURE 2 Possible mechanism regarding the association of COVID-19 infection and increase of mortality in HF. ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; HF, heart failure; LV, left ventricle; RV, right ventricle

Previous studies show that HF is a risk factor for systemic infection.[37] However, in our study, there was no increase in the susceptibility to COVID-19 in patients with a history of HF. The COVID-19 pandemic has changed the social and economic environment. As a result, people's socioeconomic behavior has changed. Self-protection through telecommuting and self-isolation has increased, and the government has made it mandatory to use masks for indoor activities. As a result, unlike the COVID-19 infection, infections by other pathogens are decreasing.[38] In Korea, relatively healthy people in their 20s to 40s who are active in social and economic activities were more likely to be infected with COVID-19. As many HF patients are elderly with poor social and economic activity and follow the self-protection guidelines, their susceptibility to COVID-19 did not increase.

Our study has limitations. First, because our study had a retrospective cohort design, a causal relationship could not be proven. Second, it is difficult to generalize our results for overall ethnicity because our data set consisted of only Koreans. Third, detailed information of severity or characteristics of HF could not be acquired because our data set did not deal with detailed estimates of cardiac echocardiography. Fourth, in our study, only patients who had a SARS-CoV-2 test were included, and the patients who took this test were not assigned randomly, which might have caused a selection bias.

In conclusion, our study demonstrates that history of HF is associated with increased risk of severe complications, particularly mortality, of COVID-19. Patients with HF might have poor prognosis if infected with COVID-19, indicating the need for careful management and monitoring.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Tae-Jin Song and Jinkwon Kim contributed to the conception and design of this study. Hyung Jun Kim, Moo-Suk Park, Jimin Jeon, Jae Il Shin, and Jin Park performed the acquisition, analysis or interpretation of data. Hyung Jun Kim, Jae Il Shin, Dong-Hyeok Kim, Tae-Jin Song, and Jinkwon Kim contributed to the drafting the work. All authors reviewed and approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in National Health Insurance Sharing System at https://nhiss.nhis.or.kr/bd/ab/bdaba021eng/do.

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