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Original Research

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Effectiveness and Safety of COVID-19 Vaccination in Patients With Heart Failure: A Nationwide Retrospective Cohort Study

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AUTHOR'S SUMMARY

Heart failure (HF) is a complex cardiovascular disease with multiple comorbidities and possesses a high risk of mortality, and is often exacerbated by infectious diseases. Our large retrospective study using the national health insurance service data showed that the vaccination against coronavirus disease 2019 (COVID-19) in patients with HF was associated with reduced risk of COVID-19-related events and hospitalization for HF, all-cause mortality, and other various cardiovascular events. The findings of this study underscore the importance of timely vaccination against pandemic diseases such as COVID-19 in patients with HF.

ABSTRACT

Background and Objectives: We aimed to evaluate the efficacy and safety of coronavirus disease 2019 (COVID-19) vaccination in patients with heart failure (HF) using national databases.
Methods: We retrospectively analyzed the data from the Korean nationwide COVID-19 cohort, including patients with HF from February 2021 to June 2022. The study population was divided into the vaccinated (≥2 doses) and unvaccinated (≤1 dose) groups. Clinical outcomes assessed included hospitalization for HF, COVID-19-related events, and cardiovascular complications. Patients were matched by age, sex, and comorbidities, and were followed up for up to 15 months to assess vaccination-associated risks.
Results: We included 651,127 patients with HF (mean age 69.5 years; 50.2% male), of whom 112,693 (17.3%) were unvaccinated, and 538,434 (82.7%) were vaccinated. After propensity score matching, 73,559 patients in each group were compared. Over a median follow-up of 6 months, vaccination was associated with a significantly reduced risk of COVID-19 (hazard

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Conflict of Interest
The authors have no financial conflicts of interest.

Data Sharing Statement
The data that support the findings of this study are available from the National Health Insurance Service of Korea, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of the National Health Insurance Service of Korea.

Author Contributions
Conceptualization: Chun KH, Lee CJ; Data curation: Chun KH, Park H; Formal analysis: Park H; Investigation: Chun KH, Jeong W, Seo KD, Seo J, Kim H, Jang JY, Lee H, Park JK, Oh S, Yoon SJ; Methodology: Chun KH; Resources: Chun KH, Jeong W, Seo KD; Supervision: Oh J, Oh S, Kang SM; Writing - original draft: Chun KH, Lee CJ, Park H; Writing - review & editing: Chun KH, Lee CJ, Jeong W, Seo KD, Seo J, Oh J, Kang SM.

ratio [HR], 0.27; 95% confidence interval [CI], 0.22–0.33) and critical COVID-19 infection (HR, 0.47; 95% CI, 0.31–0.71). The vaccinated group also had a significantly lower risk of hospitalization for HF (HR, 0.53; 95% CI, 0.52–0.55) and all-cause mortality (HR, 0.18; 95% CI, 0.17–0.18) compared with the unvaccinated group. Additionally, vaccination was associated with a significantly lower risk of stroke, myocardial infarction, myocarditis/pericarditis, and venous thromboembolism compared with the unvaccinated patients (all, p<0.0001).
Conclusions: COVID-19 vaccination in patients with HF was associated with a reduced risk of hospitalization for HF, all-cause mortality, and other cardiovascular events.

Keywords: COVID-19; Vaccination; Heart failure; Mortality

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a respiratory infectious disease caused by a novel coronavirus that has become a global pandemic due to its high infectivity and the initial lack of effective therapeutic agents. As of November 30, 2023, the World Health Organization has reported 772,052,752 confirmed cases of COVID-19 worldwide, including 6,985,278 deaths.[1] Systemic inflammatory diseases, including upper respiratory infections, can exacerbate underlying conditions in patients with cardiovascular disease (CVD). Notably, mortality and serious complications are higher in patients with chronic CVDs during influenza epidemics.[2]

Several studies have shown that the mortality rate associated with severe COVID-19 infection is significantly higher than that of conventional influenza, with early COVID-19 mortality ranging from 1.40% to 3.67%.[3] Specifically, COVID-19 infection is closely linked to the risk of cardiovascular complications and death, as demonstrated by a recent systematic review of data on patients hospitalized with COVID-19 across several different countries.[4] The risk of COVID-19 infection is particularly elevated in patients with CVD, especially those with heart failure (HF), who are more vulnerable due to advanced age, multiple chronic conditions, poor health status, and weakened immune systems. The in-hospital mortality rate from COVID-19 in patients with chronic HF is higher than in the general population.[5]

COVID-19 vaccines were rapidly developed to mitigate the complications associated with COVID-19 infection. They not only reduced the risk of COVID-19 infection in the general population but also the progression to severe COVID-19, including the occurrence of cardiovascular complications.[6] These findings highlight the importance of vaccination as a preventive measure against COVID-19.

However, various acute and chronic cardiovascular adverse effects following COVID-19 vaccination have been reported, including rare cases of myocardial damage and subsequent HF, which contribute to vaccine hesitancy among HF patients. While the efficacy of vaccination has been extensively studied in the general population, there is limited research specifically focusing on patients with HF.

Therefore, this study aimed to investigate the efficacy and safety of COVID-19 vaccination in HF patients using data from the Korea Health Insurance Corporation database, which covers most of the Korean population, and the nationwide COVID-19 vaccination database. This research provides important evidence supporting the need for COVID-19 vaccination in this vulnerable population.

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METHODS

Ethical statement

The study protocol was approved by the Institutional Review Board of NHIS Ilsan Hospital (NHIMC 2023-01-032) and was conducted in accordance with the principles of the Declaration of Helsinki (2013). The requirement for written informed consent was waived, as the NHIS database consists of strictly anonymized clinical data and complies with the guidelines of the Personal Data Protection Act.

Material and data availability

The data of this study are available from the National Health Insurance Service (NHIS) of Korea, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. However, data are available from the authors upon reasonable request and with permission of the NHIS of Korea.

Data source

The study population was identified using claims data from the Korean NHIS, which serves as a single-payer for universal healthcare coverage to approximately 97% of the Korean population. As the COVID-19 vaccination began in Korea on February 26, 2021, we selected individuals from the NHIS database who had a treatment record for HF in the year preceding the vaccination start date (January 2020 to February 2021). Diagnoses in the NHIS database are coded according to the International Classification of Diseases, 10th revision (ICD-10). A treatment record for HF was defined as at least one hospitalization or two or more outpatient visits with a diagnosis code for HF (I50 and its subcodes) (**Supplementary Table 1**). Data on COVID-19 diagnosis and vaccination status were obtained from the Korea Disease Control and Prevention Agency (KDCA)-COVID-19-NHIS cohort (**Supplementary Table 2**). The KDCA maintains a registry of all individuals diagnosed with COVID-19, as it is classified as a notifiable infectious disease by law.

Study population

Initially, 717,237 patients with HF were screened. Exclusion criteria included age <18 years, any cardiovascular event within the 3 months preceding the start date, vaccination with Ad26.COV2.S (Janssen) vaccine, and recipients of a national medical aid program. The Janssen vaccination was excluded from the analysis due to its different dosage requirements compared to other vaccines.

The final cohort included 651,127 patients with HF (**Figure 1**). The following baseline characteristics were collected: age, sex, income level, region of residence, type of health insurance, and comorbidities such as hypertension, diabetes, dyslipidemia, chronic kidney disease (CKD), end-stage renal disease (ESRD), chronic obstructive pulmonary disease (COPD), liver disease, atrial fibrillation (AF), cancer, and ischemic heart disease (IHD). Comorbidities were defined as the presence of at least 1 inpatient diagnosis or 1 or 2 outpatient diagnoses (classified as principal or secondary) based on claims data in the 3 years preceding inclusion in the study cohort, as detailed in **Supplementary Table 3**. The Charlson comorbidity index (CCI) was calculated using this comorbidity data.[7]

To evaluate the clinical effectiveness of the vaccine, patients were categorized based on their vaccination status. The vaccinated group included individuals who received 2 or more doses of a COVID-19 vaccine, regardless of vaccine type, while the unvaccinated group included

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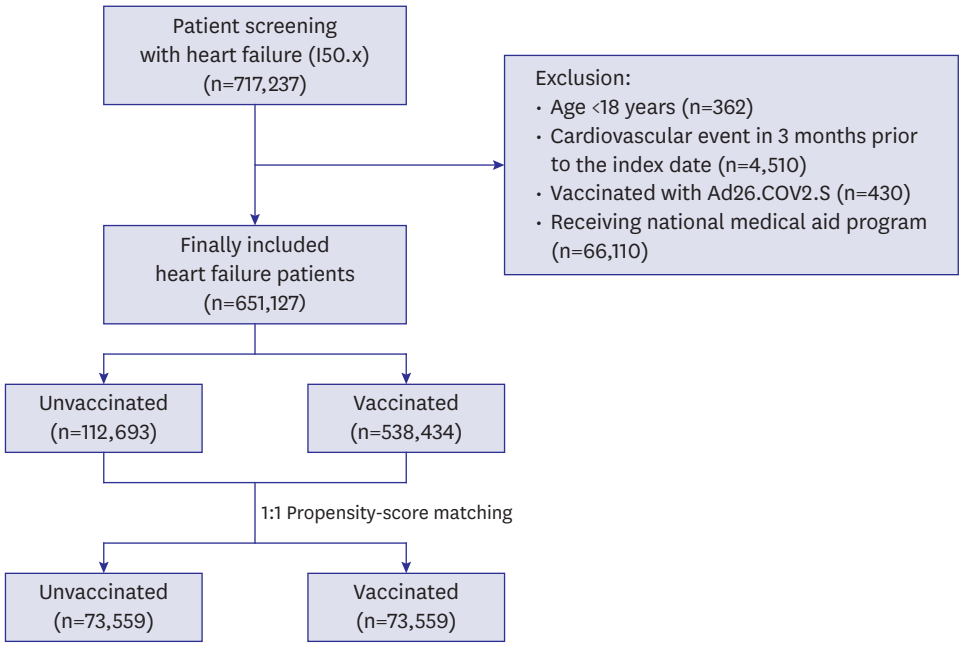

Figure 1. Flow chart of cohort construction.

those who either remained unvaccinated or received only one dose. The study cohort commenced on 26 February 2021, with the index date for the vaccinated group defined as the date of the second vaccination dose (**Supplementary Figure 1**). To minimize time-related bias for the comparative analysis of vaccine effectiveness, the index date of the unvaccinated group was matched to the corresponding second-dose date of the vaccinated group.

Outcomes

The primary outcomes were hospitalization for HF and all-cause mortality. Hospitalization for HF was defined as hospital admission with the principal diagnosis of HF-related diagnosis (ICD-10 codes I11.0, I13.0, I13.2, or I50.x). All-cause mortality data were retrieved from the NHIS eligibility database. Secondary outcomes encompassed COVID-19-related events (COVID-19 infection, critical COVID-19 infection, or COVID-19-related death), stroke (ischemic and hemorrhagic), myocarditis/pericarditis, venous thromboembolism (VTE), and acute myocardial infarction. Critical COVID-19 infection was defined as hospitalization for COVID-19 requiring at least one of the following treatments: high-flow nasal oxygen therapy, mechanical ventilation, tracheostomy, or extracorporeal membrane oxygenation.[8] COVID-19-related death was defined as death within 28 days of COVID-19 diagnosis.

To validate our findings, we also assessed negative control outcomes, including urinary tract infections, gastrointestinal bleeding, and acute cholecystitis, none of which were expected to be associated with vaccination status or cardiovascular events. The occurrence date for these events was defined as the first day on which they met the criteria for the corresponding outcome, with operational definitions described in **Supplementary Table 4**. These definitions were primarily based on a previously reported protocol using the same database,[9] with some modifications or new definitions.

Given that we hypothesized that COVID-19 vaccination would lead to improved clinical

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outcomes in HF patients compared to unvaccinated individuals, these clinical outcomes were tracked until the end of June 2022, which corresponds to 6 months after the last recorded COVID-19 infection case in December 2021. This follow-up period was chosen based on reports indicating that the effectiveness of COVID-19 vaccines can persist for up to 6 months.[10]

Statistical analyses

Continuous variables with normal distributions are presented as mean ± standard deviation and were compared using the Student's t-test. The differences between the compared groups were expressed as the standardized mean difference (SMD). The SMD, which represents effect size, is calculated by dividing the mean difference by the standard deviation, providing a measure of the magnitude of differences between groups. An SMD absolute value ≥0.1 was considered indicative of a significant difference between the 2 groups. The χ^2 test was used to assess the descriptive statistics and frequency of various factors, as well as to test for differences in proportions between groups.

To adjust for confounding variables between the 2 groups, propensity scores were generated based on age, sex, comorbidities (including hypertension, diabetes, dyslipidemia, CKD, COPD, liver disease, AF, cancer, ESRD, history of HF for >1 year, IHD, and CCI score), and date of COVID-19 vaccination. A 1:1 propensity score matching with a caliper of 0.25 was performed to optimize the probability of matching and maintain sample size (**Figure 1**). The logit of the propensity score was used as the distance measure for matching to ensure the stability of the distribution and minimize the impact of extreme values (**Supplementary Figure 2**). For survival analysis, a univariate Cox proportional hazards regression model was employed, and the hazard ratios (HRs) and 95% confidence intervals (CIs) of the outcomes were calculated to estimate the association between the outcomes and vaccination status in the matched cohort. Additionally, the cumulative probability of events was analyzed using the Kaplan–Meier method, and the log-rank test was used to compare the probability of event curves between the groups.

All statistical analyses were performed using SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA), and R, version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline characteristics

Between January 2020 and February 2021, a total of 651,127 patients with HF were identified from the NHIS database (**Table 1**) and followed up until June 30, 2022. The mean age of the cohort was 69.5 years, and 50.2% were male. The prevalence of key comorbidities was as follows: hypertension (84.7%), diabetes (55.2%), CKD (20.0%), AF (23.1%), and IHD (52.1%). Additionally, 70.1% of the patients had a history of HF for more than one year. The CCI, which quantifies comorbidity burden, indicated that 99.6% of patients had a score of ≥1, and 33.2% had a score of ≥2.

Coronavirus disease 2019 vaccination status

During the study period, the most commonly administered first dose of the COVID-19 vaccine was BNT162b2 (a messenger ribonucleic acid [mRNA] vaccine, hereafter referred to as the Pfizer vaccine), received by 53% of patients. This was followed by ChAdOx1 nCoV-19 (an adenovirus vector-based vaccine, hereafter referred to as the AstraZeneca vaccine)

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Table 1. Basic characteristics of the patients with heart failure (n=651,127)

Variables	Values
Demographics	
Age (years)	69.5±14.1
Age group	
18–39 years	20,840 (3.2%)
40–64 years	195,566 (30.0%)
≥65 years	434,721 (66.8%)
Sex	
Male	326,755 (50.2%)
Female	324,372 (49.8%)
Underlying comorbidities	
Hypertension	551,328 (84.7%)
Diabetes mellitus	359,393 (55.2%)
Dyslipidemia	544,368 (83.6%)
Chronic kidney disease	130,437 (20.0%)
Atrial fibrillation	150,296 (23.1%)
Chronic obstructive pulmonary disease	167,485 (25.7%)
Liver disease	375,719 (57.7%)
Cancer	111,244 (17.1%)
End-stage renal disease	12,709 (2.0%)
Ischemic heart disease	339,264 (52.1%)
Charlson comorbidity index	
0	2,653 (0.4%)
1	432,566 (66.4%)
2	188,614 (29.0%)
≥3	27,294 (4.2%)

Values are presented as mean ± standard deviation or number (%).

administered to 40% of patients, and mRNA-1273 (an mRNA vaccine, hereafter referred to as the Moderna vaccine) administered to 6.6% of patients. The most common vaccination regimen was 3 doses of the Pfizer vaccine (40.6%), followed by two doses of the AstraZeneca vaccine with a subsequent Moderna vaccine (25.6%), and 2 doses of the AstraZeneca vaccine with a subsequent Pfizer vaccine (11.8%) (**Supplementary Table 5**, **Supplementary Figure 3**).

Additionally, we examined how vaccination patterns varied based on residential area and income level. These factors could serve as indirect indicators of healthcare accessibility. Our analysis revealed that the proportion of rural residents was slightly higher in the vaccinated group compared to the unvaccinated group, while the proportion of residents in metropolitan and non-metropolitan cities was relatively lower (**Supplementary Tables 6** and **7**). This finding suggests that a higher level of healthcare accessibility in urban areas does not necessarily correlate with a higher vaccination rate, nor does residing in rural areas inherently imply lower healthcare accessibility. Given the overall high vaccination intent and accessibility in Korea, it can be inferred that regional disparities in vaccination rates may not be as pronounced.[11] Moreover, when stratifying economic status into tertiles based on health insurance contribution levels, we observed that the lowest income tertile was more prevalent in the unvaccinated group (**Supplementary Tables 6** and **7**).

Comparison after propensity score matching

Among the total study population, 104,341 (16.0%) patients had not been vaccinated, 8,352 (1.3%) received only one dose, 63,223 (9.7%) received two doses, and the majority (73%) received 3 or more doses of vaccines (**Supplementary Table 6**). Consequently, 112,693 (17.3%) were classified as unvaccinated, and 538,434 patients (82.7%) were classified as vaccinated

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Table 2. Differences between the COVID-19 vaccinated and unvaccinated groups before and after propensity score matching (n=651,127)

Variables	Before matching				After matching			
	Unvaccinated (n=112,693)	Vaccinated (n=538,434)	SMD	p value	Unvaccinated (n=73,559)	Vaccinated (n=73,559)	SMD	p value
Demographics								
Age (years)	75.0±15.4	68.4±13.6	0.463	<0.0001	72±16.3	71.9±15.4	0.009	0.1113
Age group								
18–39 years	4,149 (3.7%)	16,691 (3.1%)			3,830 (5.2%)	3,189 (4.3%)		
40–64 years	20,432 (18.1%)	175,134 (32.5%)			17,148 (23.3%)	17,339 (23.6%)		
≥65 years	88,112 (78.2%)	346,609 (64.4%)			52,581 (71.5%)	53,031 (72.1%)		
Male sex	51,713 (45.9%)	275,042 (51.1%)	−0.106	<0.0001	33,050 (44.9%)	32,978 (44.8%)	0.001	0.7059
Underlying comorbidities								
Hypertension	95,905 (85.1%)	455,423 (84.6%)	0.017	<0.0001	62,160 (84.5%)	62,551 (85.0%)	−0.003	0.1673
Diabetes mellitus	62,799 (55.7%)	296,594 (55.1%)	0.014	<0.0001	40,031 (54.4%)	40,155 (54.6%)	−0.002	0.5162
Dyslipidemia	88,344 (78.4%)	456,024 (84.7%)	−0.062	<0.0001	58,589 (79.6%)	58,503 (79.5%)	0.001	0.578
Chronic kidney disease	30,484 (27.1%)	99,953 (18.6%)	0.205	<0.0001	18,119 (24.6%)	18,350 (24.9%)	−0.003	0.163
Chronic obstructive pulmonary disease	34,494 (30.6%)	132,991 (24.7%)	0.134	<0.0001	20,530 (27.9%)	20,378 (27.7%)	0.002	0.3761
Liver disease	60,984 (54.1%)	314,735 (58.5%)	−0.087	<0.0001	39,692 (54.0%)	39,437 (53.6%)	0.003	0.1824
Atrial fibrillation	29,822 (26.5%)	120,474 (22.4%)	0.097	<0.0001	19,421 (26.4%)	19,691 (26.8%)	−0.004	0.1111
Cancer	22,838 (20.3%)	88,406 (16.4%)	0.1	<0.0001	13,022 (17.7%)	12,580 (17.1%)	0.006	0.0024
End-stage renal disease	4,089 (3.6%)	8,620 (1.6%)	0.128	<0.0001	2,211 (3.0%)	2,380 (3.2%)	−0.002	0.0113
Ischemic heart disease	57,159 (50.7%)	282,105 (52.4%)	−0.0163	<0.0001	38,077 (51.8%)	38,113 (51.8%)	−0.0005	0.851
Charlson comorbidity index								
0–1	60,618 (53.8%)	371,948 (69.1%)	0.356	<0.0001	43,351 (58.9%)	43,174 (58.7%)	−0.0004	0.1034
2	41,229 (36.6%)	147,385 (27.4%)			25,082 (34.1%)	25,405 (34.5%)		
≥3	10,321 (9.2%)	16,973 (3.2%)			5,126 (7.0%)	4,980 (6.8%)		

Values are presented as mean ± standard deviation or number (%).
COVID-19 = coronavirus disease 2019; SMD = standardized mean difference.

(**Table 2**). Compared with the vaccinated group, the unvaccinated group was older, more likely to be female, and had a higher prevalence of comorbidities, except for dyslipidemia, liver disease, and IHD.

Following propensity score matching, 73,559 patients from each group were included in the final analysis. Post-matching, the absolute value of the SMD was adjusted to <0.1 for all variables, indicating that the differences in each variable in the 2 groups were adequately balanced, and the propensity scores were well matched (**Table 2**, **Supplementary Figure 2**).

Clinical outcomes

In the propensity score-matched cohort, clinical outcomes were evaluated over a follow-up period of up to 15 months, with a median of 6 months (**Table 3**). Kaplan–Meier survival curves demonstrated that all clinical events, including COVID-19-related events, cardiovascular events, and all-cause mortality, were significantly more frequent in the unvaccinated group compared to the vaccinated group (all log-rank p<0.0001; **Figure 2**).

Cox proportional hazards regression analysis revealed that vaccination was associated with an approximately 73% reduction in the risk of COVID-19 infection (HR, 0.272; 95% CI, 0.223–0.332; p<0.0001) and a 53% reduction in the risk of critical COVID-19 infection (HR, 0.47; 95% CI, 0.311–0.711; p=0.0003). Additionally, the risk of COVID-19-related death was significantly lower in the vaccinated group (HR, 0.473; 95% CI, 0.274–0.817; p=0.0072) (**Figure 2A**).

Regarding primary outcomes, the vaccinated group had a 47% lower risk of hospitalization for HF than the unvaccinated group (HR, 0.531; 95% CI, 0.518–0.545; p<0.0001). For other cardiovascular outcomes, the vaccination group exhibited a 71% lower risk of stroke, a 61% lower risk of myocardial infarction, a 47% lower risk of myocarditis/pericarditis, and

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Table 3. Clinical outcomes according to COVID-19 vaccination in patients with heart failure

Clinical events	After matching			
	Unvaccinated (n=73,559)	Vaccinated (n=73,559)	HR (95% CI) (vs. unvaccinated)	p value
COVID-19 related events*				
COVID-19 infection	468 (0.6%)	172 (0.2%)	0.272 (0.223–0.332)	<0.0001
Critical COVID-19 infection	80 (0.11%)	52 (0.07%)	0.47 (0.311–0.711)	0.0003
COVID-19 related death	40 (0.05%)	22 (0.03%)	0.473 (0.274–0.817)	0.0072
Cardiovascular events				
Hospitalization for heart failure	16,961 (23.1%)	9,411 (12.8%)	0.531 (0.518–0.545)	<0.0001
Stroke (ischemic, hemorrhagic)	3,977 (5.4%)	1,200 (1.6%)	0.305 (0.285–0.325)	<0.0001
Acute myocardial infarction	165 (0.2%)	65 (0.1%)	0.394 (0.296–0.525)	<0.0001
Myocarditis/pericarditis	435 (0.6%)	231 (0.3%)	0.53 (0.452–0.622)	<0.0001
Venous thromboembolism	3,142 (4.3%)	1,601 (2.2%)	0.504 (0.475–0.536)	<0.0001
All-cause death	25,273 (34.4%)	5,328 (7.2%)	0.178 (0.173–0.183)	<0.0001
Negative control events				
Urinary tract infections	5,331 (7.3%)	7,361 (10.1%)	1.025 (0.975–1.055)	0.178
Gastrointestinal bleeding	895 (1.2%)	1,475 (2.0%)	1.065 (0.965–1.155)	0.108
Acute cholecystitis	401 (0.6%)	602 (0.8%)	1.085 (0.945–1.015)	0.101

CI = confidence interval; COVID-19 = coronavirus disease 2019; HR = hazard ratio.
*Follow-up duration for COVID-19 related events was different from other clinical outcome events. The last follow-up date of COVID-19 related events was 2021 December 21, and that of clinical outcome events was 2022 June 30.

a 50% lower risk of VTE compared to the unvaccinated group (all, p<0.0001). Additionally, we found that the all-cause mortality rate in the vaccinated group was 82% lower than in the unvaccinated group (HR, 0.178; 95% CI, 0.173–0.183; p<0.0001) (**Figure 2B**).

The unvaccinated group had a particularly higher mortality rate than the vaccinated group. When we explored which baseline characteristics differed by vaccination status, we found that unvaccinated group had a higher proportion of patients with a CCI score ≥2 (46% vs. 30%, **Table 2**), and lower economic level when tertiles were stratified (35.2% vs. 32.5%) even after propensity matching (**Supplementary Tables 6** and **7**). Therefore, to further adjust for these relevant factors, we performed additional multivariate Cox proportional hazards regression models. As shown in **Supplementary Table 8**, adjusting for these variables did not significantly change the HR. Through this analysis, we confirmed that differences in economic status (income level) did not significantly impact the association between vaccination and mortality. Additionally, to determine if the higher mortality in the unvaccinated group was attributable to its higher risk, we assessed deaths within the first 2 months of follow-up (**Supplementary Table 9**). During the first month of follow-up, 5.4% of total deaths occurred in the unvaccinated group and 4.4% in the vaccinated group. In the first two months, these percentages were 6.6% and 5.1%, respectively. Although the unvaccinated group had a higher initial mortality, the difference was not significant enough to conclude that early deaths were substantially higher compared to the vaccinated group.

To address possible bias in the operational definition of events, we also examined negative control events that were not expected to be associated with the COVID-19 vaccine or cardiovascular risk. No statistical differences were observed between the 2 groups in the risk of urinary tract infection, gastrointestinal bleeding, and acute cholecystitis (**Table 3**).

Subgroup analyses revealed interactions between vaccination and mortality risk reduction in certain subgroups, including age, sex, CKD, and AF (**Figure 3**). In particular, the HR for mortality was significantly lower in subgroups of patients under 65 years of age, men, and those without CKD, AF, or cancer history, and those with a CCI score <2 (all p-for-interaction <0.0001), indicating that vaccination was associated with a greater reduction in mortality risk

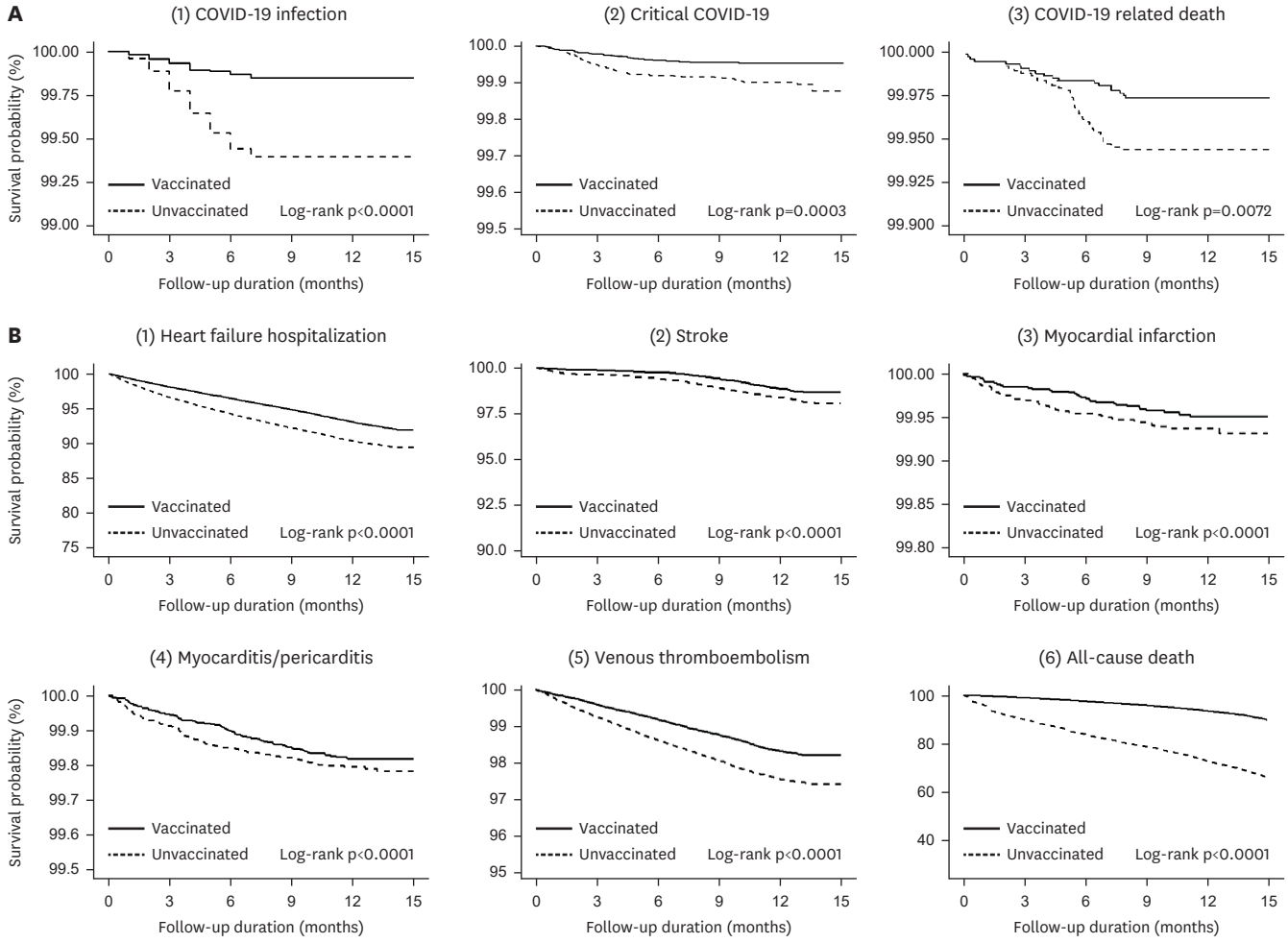

Figure 2. Kaplan-Meier curves for clinical events according to COVID-19 vaccination in the study patients. (A) COVID-19 related events and (B) cardiovascular events and mortality.
COVID-19 = coronavirus disease 2019.

in these groups.

DISCUSSION

In this nationwide analysis, we evaluated the efficacy and safety of COVID-19 vaccination in a cohort of Korean patients with HF. Our findings demonstrate that COVID-19 vaccination was significantly associated with a reduced risk of COVID-19-related events, cardiovascular events, and all-cause mortality in patients with HF. Importantly, we also demonstrated that COVID-19 vaccination is not associated with an increased risk of cardiovascular complications, addressing concerns regarding vaccine safety in this vulnerable population.

The clinical efficacy of COVID-19 vaccines in the general population has been well established in several studies. For example, a retrospective analysis demonstrated that COVID-19 vaccination is associated with a reduced risk of cardiovascular events, such as coronary heart disease, stroke, and HF, as well as a decrease in overall mortality in the general population.[12] Similarly, an Australian study involving older adults aged >65 years found that vaccinated

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Subgroup	Vaccinated	Unvaccinated	HR (95% CI)	p value for interaction
	Total N (events)			
Age				
≥65 years	53,031 (5,140)	52,581 (22,877)	0.175 (0.169–0.180)	<0.0001
<65 years	20,528 (188)	20,978 (2,396)	0.077 (0.067–0.090)	
Sex				
Male	32,978 (2,151)	33,050 (11,929)	0.143 (0.137–0.150)	<0.0001
Female	40,581 (3,177)	40,509 (13,344)	0.200 (0.193–0.208)	
HTN				
Yes	62,351 (4,937)	62,160 (22,603)	0.177 (0.172–0.183)	<0.0001
No	11,208 (391)	11,399 (2,670)	0.127 (0.114–0.141)	
DM				
Yes	40,155 (3,243)	40,031 (15,252)	0.170 (0.164–0.177)	0.2091
No	33,404 (2,085)	33,528 (10,021)	0.177 (0.168–0.185)	
Dyslipidemia				
Yes	58,503 (4,085)	58,589 (20,271)	0.166 (0.160–0.172)	<0.0001
No	15,056 (1,243)	14,970 (5,002)	0.203 (0.190–0.216)	
CKD				
Yes	18,350 (1,988)	18,119 (7,965)	0.192 (0.182–0.201)	<0.0001
No	55,209 (3,340)	55,440 (17,308)	0.162 (0.156–0.168)	
AF				
Yes	19,691 (1,854)	19,421 (7,496)	0.197 (0.187–0.207)	<0.0001
No	53,868 (3,474)	54,138 (17,777)	0.162 (0.157–0.168)	
COPD				
Yes	20,378 (2,043)	20,530 (9,095)	0.175 (0.167–0.183)	0.4191
No	53,181 (3,285)	53,029 (16,178)	0.170 (0.164–0.177)	
CCI score				
≥2	30,385 (2,998)	30,208 (12,436)	0.179 (0.172–0.186)	<0.0001
<2	43,174 (2,330)	43,351 (12,947)	0.155 (0.149–0.162)	
Cancer				
Yes	12,580 (396)	13,022 (1,198)	0.223 (0.199–0.249)	<0.0001
No	60,979 (4,932)	60,537 (24,075)	0.169 (0.164–0.175)	
HHF event				
Yes	9,411 (2,218)	16,961 (9,908)	0.290 (0.277–0.304)	<0.0001
No	64,148 (3,110)	56,598 (15,365)	0.153 (0.147–0.159)	

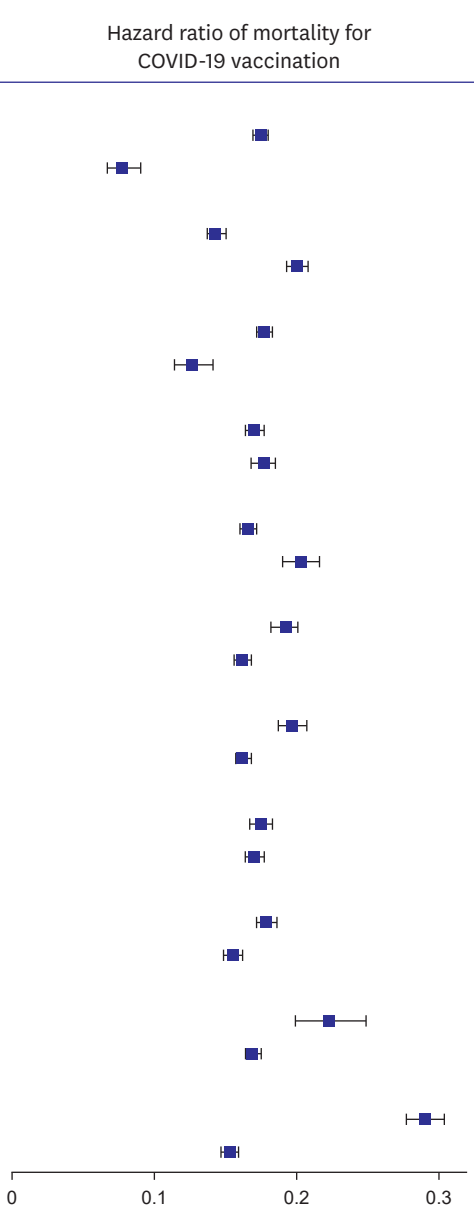

Figure 3. Forest plot of subgroup analyses for the all-cause mortality according to COVID-19 vaccination.
AF = atrial fibrillation; CCI = Charlson comorbidity index; CI = confidence interval; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; COVID-19 = coronavirus disease 2019; DM = diabetes mellitus; HHF = hospitalisation for heart failure; HTN = hypertension.

individuals had a lower risk of both overall mortality and COVID-19-related death compared to their unvaccinated counterparts.[6] However, to date, no prior research has systematically evaluated the impact of COVID-19 vaccination specifically in patients with HF.

Despite advances in pharmacotherapy and the availability of numerous drugs in both clinical research and practice, a significant proportion of patients still require re-hospitalization, some of whom are exacerbated by respiratory infections.[13][14] For example, influenza can trigger severe events in patients with HF, and there has been considerable interest in the potential of vaccination to prevent HF exacerbations and improve outcomes.[14] The Prospective Comparison of ARNI with ACEI to Determine Global in HF (PARADIGM-HF) study investigated the association between influenza vaccination and prognosis in patients

with HF, finding that influenza vaccination was associated with a lower risk of all-cause mortality.[15] Similarly, a study involving over 100,000 U.S. veterans with HF demonstrated that influenza vaccination was linked to a reduced risk of 1-year mortality.[16] More recently, research on over 130,000 Danish patients with HF revealed that earlier and more frequent influenza vaccination was associated with a greater reduction in mortality.[17] Based on these findings, both the American College of Cardiology/American Heart Association and the European Society of Cardiology have recently issued a class IIa recommendation for influenza vaccination in patients with HF.[18][19]

Broader population-based studies have shown that influenza vaccination is associated with a significant reduction in mortality among patients with IHD[20] and older patients with CVD.[21] Based on these findings, we hypothesized that COVID-19 vaccination would similarly improve outcomes in patients with HF. Notably, Mohseni et al.[22] found that while influenza vaccination does not impact exacerbations of COPD, it is associated with a 35% reduction in serious cardiovascular events in patients with HF. These findings suggest that reducing infection plays a critical role in preventing HF exacerbations.

We also examined other cardiovascular events during the follow-up period according to vaccination status. Regarding stroke events, a global study of hospitalized patients with COVID-19 reported that 0.7% experienced incident acute ischemic stroke, with a higher prevalence observed in those with underlying HF.[23] In our study, stroke incidence was significantly lower in the vaccinated compared to the unvaccinated group. Additionally, given the significant associations of myocarditis/pericarditis[24] and VTE[25][26] with COVID-19 infection, these events in patients with HF require particular attention. Early in the vaccination rollout, there were reports linking COVID-19 vaccines to VTE, even as a rare manifestation,[27] and subsequent reports of vaccine-related myocarditis raised ongoing health policy concerns.[28] However, the significantly lower incidence of events in the vaccinated group in our study suggests that the benefits of vaccination against COVID-19 outweigh the risks of adverse effects.

Whether the prevention of COVID-19 infection through vaccination directly contributed to the reduction in exacerbated HF or mortality remains unclear. Although we could not establish a definitive cause–and–effect relationship, our findings suggest that national vaccination efforts may positively impact the prognosis of patients with HF. Previous studies indicate that 30–50% of COVID-19 infections are asymptomatic.[29] If COVID-19 vaccination can prevent these subclinical infections, which may exacerbate HF, it should be actively recommended for these patients, similar to influenza vaccination. There are many factors that contribute to the high mortality rate among HF patients. As seen in the characteristics of this cohort, they have old age and many comorbidities, and these can lead to higher mortality. In our cohort, a higher CCI score (≥2) independently indicated an increased risk of mortality (HR, 1.555; 95% CI, 1.530–1.580, data not shown), regardless of vaccination status. In general, the lower vaccination rate among older adults with multiple comorbidities may be attributed to several factors. First, vaccine hesitancy in this population could have played a role, as individuals with multiple comorbidities may have been more concerned about potential vaccine-related adverse effects. Second, limited access to healthcare and mobility issues could have hindered vaccination uptake, particularly in frail elderly individuals. Third, income level may have influenced vaccination status, and it is also possible that income level contributed to mortality regardless of vaccination status. We additionally adjusted for income level, and the association with vaccination remained statistically consistent without significant differences. While the unvaccinated group showed a relatively high 15-month

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mortality rate of 34%, the overall mortality across the entire matched cohort was 20.8%. When converted to a 12-month follow-up period using an exponential survival model, this corresponds to an estimated 1-year mortality rate of 17.1%. This rate is comparable to the 1-year mortality rate of 16% in hospitalized HF patients, which was reported in previous Korean Heart Failure Statistics.[30] That report applied a broad definition of HF, including cases with either a primary or secondary ICD-10 code for HF. In contrast, our study population was more selectively defined, consisting of patients with either a history of HF admission or at least 2 outpatient HF diagnoses, and included only cases with HF recorded as a primary diagnosis. This suggests that our cohort likely included patients with more definitive and clinically relevant HF, thereby justifying a somewhat higher observed mortality. Moreover, a Korean registry of acute HF reported a 1-year mortality rate of 18.2%.[31] Therefore, although the mortality rate in the unvaccinated subgroup may appear high in isolation, the overall cohort-level mortality is clinically acceptable and reflects the vulnerability of high-risk HF patients represented in real-world data.

Regarding the generalizability of our findings, this lower vaccination rate in high-risk populations could potentially lead to an overestimation of vaccine-associated improvements in outcomes, particularly among older adults with multiple comorbidities. However, we addressed this concern through propensity score matching and additional multivariate regression analysis, ensuring a balanced comparison between vaccinated and unvaccinated groups. In this context, a prospective study focusing on the nationwide HF population is warranted.

Our study has several limitations. First, given the retrospective nature of the analysis, there may be potential biases due to unobserved or unmeasured variables between the vaccinated and unvaccinated groups. For example, we could not control for factors such as patients' level of frailty, their ability to perform activities of daily living, or whether they resided in a nursing facility. To address these biases, we employed propensity matching to minimize the underlying differences between the 2 groups as much as possible. However, the administration of vaccination is closely linked to healthcare accessibility, attitudes toward health, and adherence to medications. While propensity matching was used in this study, these factors likely acted as unmeasured confounders. Since they were not analyzed, this remains a limitation of our study. Second, this study utilized NHIS claims data, where the definition of HF, comorbidities, and clinical events was primarily based on ICD-10 codes and medical practice codes. As a result, discrepancies may exist between actual clinical diagnoses and those reported in the database. A known limitation of studies using claims data is the lack of imaging information, which prevented us from distinguishing between types of HF. Third, the study did not analyze the effects of vaccination or dose-dependent effects by vaccine subtype. As shown in the supplemental data, vaccine profiles were highly heterogeneous, making it impractical to compare the effects of each vaccine type. Fourth, we acknowledge that the follow-up period for COVID-19 infection was shorter compared to that for other clinical events. We utilized data directly from the KDCA, which is responsible for the centralized management of COVID-19 reporting. As mentioned in the methods section, the follow-up for COVID-19 infection was limited to December 21, 2021. Therefore, the analysis did not fully capture COVID-19-related events after this point, including the emergence of the omicron variant, due to the limitations in the follow-up period. This limitation may have affected the assessment of clinical events related to COVID-19 infection. Lastly, we did not analyze HF-specific drug treatments due to the absence of this information. Since medical therapies are crucial in the treatment of HF, future studies should investigate whether the effects of COVID-19 vaccination observed in this study are

independent of these treatments.

In conclusion, our results showed that COVID-19 vaccination during the pandemic was significantly associated with a lower risk of COVID-19 infection, severe illness from COVID-19, hospitalization for HF, all-cause mortality, and various cardiovascular events in HF patients compared to those unvaccinated. From a healthcare perspective, generating evidence to support infection prevention policies, particularly for high-risk populations, is crucial. Given the reduced risk in both COVID-19 infection and mortality observed in vaccinated HF patients, our findings suggest that vaccination should be prioritized in this vulnerable population, especially considering their higher risk of severe outcomes. We believe our results could help support clinical guidance that emphasizes vaccination as a key preventive strategy in managing HF patients, particularly those with comorbidities.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1
ICD-10 codes for diagnosis of heart failure

Supplementary Table 2
COVID-19-related information provided the Korea Centers for Disease Control and Prevention

Supplementary Table 3
List of ICD-10 and payment codes for the operational definition of underlying comorbidities

Supplementary Table 4
Operational definitions for clinical outcomes

Supplementary Table 5
Vaccination status by COVID-19 vaccine type and combinations

Supplementary Table 6
Baseline characteristics of heart failure patients by number of COVID-19 vaccinations (n=651,127)

Supplementary Table 7
Baseline residential area and income distribution of patients according to COVID-19 vaccination status

Supplementary Table 8
Adjusted risk for all-cause death according to COVID-19 vaccination

Supplementary Table 9
Number of deaths within the first 2 months of cohort follow-up

Supplementary Figure 1
Definitions of COVID-19 vaccinated and unvaccinated group in the study patients.

Supplementary Figure 2
Standardized mean differences before and after propensity score matching.

Supplementary Figure 3
Vaccination status by COVID-19 vaccine type and combinations.

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