Received: 8 March 2024 | Revised: 14 April 2024 | Accepted: 6 May 2024

DOI: 10.1002/joa3.13071

Journal of Arrhythmia Open Access WILEY

ORIGINAL ARTICLE

Impact of COVID-19 infection on the in-hospital outcome of patients hospitalized for heart failure with comorbid atrial fibrillation: Insight from the National Inpatient Sample (NIS) database 2020

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Abstract

Introduction: Atrial fibrillation (AF) and heart failure (HF) commonly coexist, resulting in adverse health and economic consequences such as declining ventricular function, heightened mortality, and reduced quality of life. However, limited information exists on the impact of COVID-19 on AF patients that hospitalized for HF.

Methods: We analyzed the 2020 U.S. National Inpatient Sample to investigate the effects of COVID-19 on AF patients that primarily hospitalized for HF. Participants aged 18 and above were identified using relevant ICD-10 CM codes. Adjusted odds ratios for outcomes were calculated through multivariable logistic regression. The primary outcome was inpatient mortality, with secondary outcomes including system-based complications.

Results: We identified 322,090 patients with primary discharge diagnosis of HF with comorbid AF. Among them, 0.73% (2355/322,090) also had a concurrent diagnosis of COVID-19. In a survey multivariable logistic and linear regression model adjusting for patient and hospital factors, COVID-19 infection was associated with higher in-hospital mortality (aOR 3.17; 95% CI 2.25, 4.47, $p < 0.001$), prolonged length of stay (β_{LOS} 2.82; 95% CI 1.71, 3.93, $p < 0.001$), acute myocarditis (aOR 6.64; 95% CI 1.45, 30.45, p 0.015), acute kidney injury (AKI) (aOR 1.48; 95% CI 1.21, 1.82, $p < 0.001$), acute respiratory failure (aOR 1.24; 95% CI 1.01, 1.52, p 0.045), and mechanical ventilation (aOR 2.00; 95% CI 1.28, 3.13, p 0.002).

Conclusion: Our study revealed that COVID-19 is linked to higher in-hospital mortality and increased adverse outcomes in AF patients hospitalized for HF.

KEYWORDS
atrial fibrillation, COVID-19 infection, epidemiology, heart failure, National Inpatient Sample

1 | INTRODUCTION

Atrial fibrillation (AF) and heart failure (HF) commonly coexist, sharing a complex pathophysiological interplay involving neurohormonal hyperactivation, fibrosis, and electrophysiologic remodeling. The causative relationship between the two conditions remains incompletely understood, with each exacerbating the other in a vicious circle.[1] In chronic HF, AF prevalence is 25%–39%, rising to 40% in HF with preserved ejection fraction (HFpEF).[2] Numerous data showed that baseline AF in HF is associated with adverse outcomes, including higher mortality, increased HF hospitalization, and diminished quality of life.[3,4] Considering the projected increase in HF cases to 8 million Americans by 2030, with associated treatment costs exceeding $160 billion, and estimates indicating that AF will affect 12 million individuals by the same year, various guidelines have been introduced to address this issue comprehensively.[5,6]

The emergence of COVID-19 has raised concerns about significant cardiovascular implications, including an increased risk of incident AF, worsening HF resulting in more complicated hospitalization courses, and overall higher all-cause mortality, particularly in individuals with preexisting cardiac conditions.[7,8] Data also revealed complex pathological mechanisms of cardiac injury, involving both cellular-level electrical and mechanical dysfunction, as well as multiorgan interplay, resulting in adverse short and long-term cardiac outcomes.[9]

While recent research has exhibited the association between COVID-19 infection and patients with either HF or AF, the information on patients hospitalized for HF with the coexistence of AF is limited. Therefore, our study aims to investigate in-hospital outcomes among HF patients with comorbid AF and concurrent COVID-19 infection using a comprehensive nationwide database.

2 | METHODS

2.1 | Data source and the research type

We employed the Health Care Utilization Project National Inpatient Sample (HCUP-NIS) database for the year 2020. Briefly, the HCUP-NIS is sponsored by the Agency for Healthcare Research and Quality (AHRQ) and is the largest publicly available all-payer inpatient database in the United States that utilizes a survey design database of discharge data for inpatient hospital care from nonfederal, nonrehabilitation, acute care, and short-term hospitals. In addition, it approximates about 20% of hospital admissions and discharges, providing national estimates of the characteristics of the patients, diagnoses, and hospital-based procedures performed in US acute-care hospitals. All hospital discharges from the sample are recorded and weighed to ensure they are nationally representative.

2.2 | Study population

Our study examined all patients aged 18 and older hospitalized with the primary discharge diagnosis of HF and comorbid AF between January and December 2020. We used the ICD-10-CM to identify eligible discharge records, stratifying patients into those with and without COVID-19 infection. Supplementary Table S1 shows the ICD-10 CM codes used, while Supplementary Figure S1 presents the study population flow diagram.

2.3 | Outcome measurements

Our primary outcome was to compare inpatient mortality among patients primarily hospitalized for HF with comorbid AF, considering the presence or absence of COVID-19 infection. We also evaluated various in-hospital outcomes, including acute myocarditis, Takotsubo cardiomyopathy (TTC), cardiogenic shock, acute kidney injury (AKI), acute respiratory failure (ARF), acute pulmonary embolism (PE), deep venous thrombosis (DVT), percutaneous left ventricular assist device (LVAD) therapy, intra-aortic balloon pump (IABP) therapy, renal replacement therapy (RRT), utilization of mechanical ventilation, ischemic stroke, length of hospital stay (LOS) and total hospital charges (THC) for both COVID-19 and non-COVID-19 patients.

2.4 | Statistical analyses

Data analyses were performed using StataBE 17.0 (StataCorp, College Station, Texas). All analyses were conducted using weighted samples for national estimates in adjunct with HCUP regulations for use of the NIS database. Continuous variables were presented as mean and standard deviation (SD) while categorical variables were presented as percentages. Proportions were compared using Fisher's exact test and continuous variables were compared using the student *t*-test.

Multivariable survey logistic and linear regression analyses were employed to calculate adjusted odds ratios (ORs) for primary and secondary outcomes. Outcomes were adjusted for potential patients and hospital-level confounders, including age, gender, race, Charlson Comorbidity Index, median income, hospital bed size, hospital location, teaching status, insurance type, and a range of comorbidities including hypertension, hyperlipidemia, diabetes mellitus, obesity, smoking history, COPD, CKD stages 1–4, ESRD, CAD, history of PCI, history of CABG, and history of cardiac device implantation. A *p*-value of <0.05 was considered statistically significant.

2.5 | Ethical considerations

The NIS database lacks patient and hospital-specific identifiers, making this study exempt from the Institutional Review

Board (IRB) approval. The study adhered to ethical standards for human subjects set by the responsible institution and the Helsinki Declaration.

2.6 | Data availability statement

NIS is a large, publicly available all-payer inpatient database that contains hospitalization data on more than 7 million hospital stays. The large sample size is ideal for assessing national and regional estimates while also enabling analysis of rare conditions, uncommon treatments, and special populations. The NIS database is available at: https://www.hcup-us.ahrq.gov.

3 | RESULTS

3.1 | Patient and hospital characteristics

A total of 320,090 patients were identified with a primary discharge diagnosis of HF with comorbid AF. Among them, 0.73% (2355/320,090) had concurrent COVID-19 infection. Patients with COVID-19 were significantly younger on average (73.3 vs. 74.6, $p=0.021$). The proportion of females was comparable between the two groups (44.16 vs. 46.62, $p=0.306$). In the COVID-19 group, 62.28% were Caucasian, 20.47% were African American, 12.72% were Hispanic, and 4.53% were others. Similarly, in the non-COVID-19 group, 72.86% were Caucasian, 15.95% were African American, 6.58% were Hispanic, and 4.61% were others. Patients with COVID-19 exhibited significantly lower percentages of certain comorbidities compared to those without COVID-19, including smoking history (31.21% vs. 39.70%, $p<0.001$), chronic obstructive pulmonary disease (COPD) (16.35% vs. 23.19%, $p<0.001$), and chronic kidney disease (CKD) stage 1–4 (30.79% vs. 42.16%, $p<0.001$). Both cohorts showed no significant differences in terms of the Charlson Comorbidity Index as well as the majority of comorbidities, including hypertension, hyperlipidemia, diabetes mellitus, obesity, end-stage renal disease (ESRD), coronary artery disease (CAD), CHA_2DS_2-VASc score, history of percutaneous intervention (PCI), history of coronary bypass graft (CABG), and history of cardiac device implantation.

The highest proportion of the cohort with COVID-19 was observed in the South (33.33%), followed by the Northeast (26.96%), Midwest (23.14%), and West (16.56%). Most of these hospitalizations occurred in teaching hospitals (77.92%). Similarly, for cohort without COVID-19, the highest proportion was in the South (39.61%), but surprisingly, followed by the Midwest (23.15%), Northeast (19.67%), and West (17.57%). Most of these were also admitted to teaching hospitals (71.02%). Regardless of COVID-19 status, the study population showed a comparability proportion in terms of hospital bed size. Table 1 displays the baseline characteristics of our study population.

3.2 | Primary outcome

The inpatient crude mortality rate in the cohort with COVID-19 infection was significantly higher compared to those without COVID-19 infection (9.98% vs. 3.13%, $p<0.001$). After adjusting for confounders in the multivariable model, the mortality-adjusted odds ratio (aOR) was 3.17 (95% CI: 2.25–4.47, $p<0.001$). Table 2 shows clinical outcomes for HF hospitalizations with comorbid AF, comparing those with and without COVID-19.

3.3 | Secondary outcome

3.3.1 | Resource utilization

Resource utilization was evaluated through LOS and procedures such as mechanical ventilation, RRT, IABP, and LVAD placement. The mean LOS in the COVID-19 cohort was significantly higher compared to the non-COVID-19 cohort (8.7 days vs. 5.7 days). After adjusting for confounders, the COVID-19 cohort had 2.82 more days of hospitalization (95% CI: 1.71–3.93, $p<0.001$). Additionally, mechanical ventilation was significantly more common among those with COVID-19 (51.0% vs. 2.11%) with an adjusted odds ratio (aOR) of 2.00 (95% CI: 1.28–3.13, $p=0.002$). The use of other mentioned procedures was more frequent in the COVID-19 cohort, although not statistically significant.

3.3.2 | Total hospitalization charges (THC)

THC reflected the total amount of financial resources billed to the payer. In the group with COVID-19, the mean THC was $82,279, whereas for those without COVID-19, the mean THC was $62,476. After adjusting for confounders, the cohort with COVID-19 incurred an additional mean THC of $13,774 compared to the cohort without COVID-19 (95% CI: $3790 to $23,758, $p=0.007$).

3.3.3 | In-patient complication

We observed a significantly higher risk of acute myocarditis (0.42% vs. 0.08%, aOR 6.64, 95% CI 1.45–30.45, $p=0.015$), along with an increased risk of AKI (43.95% vs. 37.32%, aOR 1.48, 95% CI 1.21–1.82, $p<0.001$) and acute respiratory failure (28.03% vs. 23.44%, aOR 1.24, 95% CI 1.01–1.52, $p=0.045$) in the cohort with COVID-19 infection compared to those without. However, there was a heightened risk of TTC, PE, DVT, and ischemic stroke, although it did not reach statistical significance.

4 | DISCUSSION

To the best of our knowledge, this study is the first to utilize the NIS sample database to investigate the impact of COVID-19 on

TABLE 1 Baseline characteristics of hospitalized HF with comorbid AF patients with and without COVID-19 infection.

Patient characteristics	With COVID-19 infection (%)	Without COVID-19 infection (%)	*p*-value
Number of patients	2355 (0.73%)	319,735 (99.27%)	
Age at index admission, years	73.3	74.6	0.021
Women (%)	44.16	46.62	0.306
Racial distribution			<0.001
Caucasian	62.28	72.86	
African American	20.47	15.95	
Hispanic	12.72	6.58	
Others	4.53	4.61	
Charlson Comorbidity Index score			0.092
1	9.55	7.99	
2	10.62	13.62	
3	79.83	78.39	
Insurance type			0.003
Medicaid	73.92	80.7	
Medicare	10.78	7.55	
Private	13.15	10.17	
Uninsured	2.16	1.57	
Median annual income in patient's zip code (USD)			0.002
1–43,999	34.55	30.67	
44,000–55,999	25.32	28.24	
56,000–73,999	26.82	22.40	
≥74,000	13.30	18.69	
Hospital characteristics			
Hospital region			0.001
Northeast	26.96	19.67	
Midwest	23.14	23.15	
South	33.33	39.61	
West	16.56	17.57	
Hospital bed size			0.722
Small	22.72	24.12	
Medium	30.36	29.02	
Large	46.92	46.87	
Location and teaching status of the hospital			0.001
Rural	9.98	10.30	
Urban nonteaching	12.10	18.68	
Urban teaching	77.92	71.02	
Comorbidities			
Hypertension	8.07	7.84	0.863
Hyperlipidemia	58.39	59.55	0.612
Diabetes mellitus	9.13	9.78	0.634
Obesity	25.05	26.49	0.484
Smoking history	31.21	39.70	<0.001
COPD	16.35	23.19	<0.001
CKD, stage 1–4	30.79	42.16	<0.001
ESRD	0.64	0.85	0.614

TABLE 1 (Continued)

Patient characteristics	With COVID-19 infection (%)	Without COVID-19 infection (%)	*p*-value
CAD	47.98	51.98	0.096
Hx of PCI	0.85	0.66	0.618
Hx of CABG	0.42	0.26	0.472
History of cardiac device implantation (ICD, pacemaker, CRT-D, CRT-P)	11.04	10.12	0.500
Percentage of Paroxysmal Atrial fibrillation	59.24	59.17	0.509
CHA_2DS_2-VASc score (%)			0.162
≤1	9.98	7.70	
2	16.35	16.16	
3	30.79	29.27	
≥4	42.89	46.87	

Abbreviations: CABG, coronary artery bypass grafting; CAD, coronary artery disease; CHA2DS2-VASc, score for atrial fibrillation stroke risk; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CRT-D, cardiac resynchronization Therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; ESRD, end-stage renal disease; ICD, implantable cardioverter-defibrillator; PCI, percutaneous coronary intervention.

TABLE 2 Clinical outcomes for patients hospitalized primarily for HF with comorbid atrial fibrillation with and without COVID-19 infection.

Outcome	With COVID-19 infection (%)	Without COVID-19 infection (%)	aOR (95% CI)	*p*-value
Number of patients	2355 (0.73%)	319,735 (99.27%)		
Inpatient mortality	9.98%	3.13%	3.17 (2.25, 4.47)	<0.001
Mean length of stay (days)	8.7	5.7	2.82[a] (1.71, 3.93)	<0.001
Mean total hospital charge	$82,279	$62,476	$13,774[a] (3790, 23,758)	0.007
Acute myocarditis	0.42%	0.08%	6.64 (1.45, 30.45)	0.015
Takotsubo cardiomyopathy	0.21%	0.12%	1.90 (0.26, 13.96)	0.530
Acute myocardial infarction	21.66%	22.41%	0.91 (0.72, 1.16)	0.460
Acute kidney injury	43.95%	37.32%	1.48 (1.21, 1.82)	<0.001
Acute respiratory failure	28.03%	23.44%	1.24 (1.01, 1.52)	0.045
Acute pulmonary embolism	1.27%	0.66%	1.96 (0.86, 4.45)	0.107
Deep venous thrombosis	1.27%	0.75%	1.71 (0.77, 3.83)	0.190
Percutaneous left ventricular assist device	0.42%	0.34%	1.28 (0.34, 4.76)	0.713
IABP	1.06%	0.33%	2.51 (0.84, 7.51)	0.100
RRT	9.55%	5.96%	1.10 (0.77, 1.57)	0.603
Mechanical ventilation	5.10%	2.11%	2.00 (1.28, 3.13)	0.002
Ischemic Stroke	1.06%	0.45%	1.54 (0.56, 4.18)	0.400

Abbreviations: IABP, intra-aortic balloon pump; RRT, renal replacement therapy.

[a]Beta-coefficient from a multivariable linear regression model.

individuals hospitalized for HF and concurrent AF. The data mainly involves an elderly population, averaging age over 70 years, with a high Charlson Comorbidity Index (CCI) indicating multiple comorbidities. The COVID-19 cohort, with an average age of 73.3 years, is slightly younger than the non-COVID-19 cohort (74.6 years), possibly due to increased disease awareness prompting hospitalization in a population with numerous comorbidities. Racial differences were noted, with Caucasians predominant in both cohorts. Unexpectedly, the COVID-19 cohort included more African American (20.47%) and Hispanic (12.72%) populations than the non-COVID-19 cohort. These findings align with other studies, such as the recent meta-analysis by Mude et al., revealing disproportionately higher prevalence, hospitalization, and mortality ratios among African American and Hispanic populations compared to White populations.[10] The

recognized racial disparities highlight the importance of expanding focus beyond medical treatment to address socioeconomic and structural determinants of health disadvantages for minority populations or those at risk.[11]

Our study reveals a significant 3.17-fold increase in in-patient mortality in the COVID-19 cohort, focusing only on patients hospitalized for HF with comorbid AF, compared to those without COVID-19. This correlates with global data trends. Early in the pandemic, numerous studies highlighted the impact of COVID-19 on patients with pre-existing cardiovascular disease, exemplified by Zuin et al.'s CDC-WONDER 2020 database analysis, showing a 13.2% and 25.9% increase in HF-related mortality during the pandemic compared to 2019 and 2018, respectively.[12] Additionally, Bhatt et al.'s data focusing on patients with a history of HF hospitalized primarily for COVID-19 demonstrated increased mortality risk (up to 24.2% among total COVID-19 hospitalizations), greater in-hospital resource utilization, higher ICU admission rates, increased mechanical ventilation use, and more central venous catheter insertions.[13]

The complex association resulting in elevated mortality rates in our COVID-19 cohort can be explained by a multidirectional interaction. Firstly, HF hospitalization in COVID-19-infected patients may stem from acute viral illness or the development of various cardiac complications, including myocarditis, hypoxic cellular injury, and a systemic cytokine storm.[14] Furthermore, recent data also indicates a potential link between COVID-19 and heightened Renin-Angiotensin-Aldosterone system overactivation, resulting in worsened fluid retention and leading to HF hospitalization.[15] Secondly, COVID-19 can induce conduction system diseases, leading to new-onset AF during index hospitalization. In addition, it is linked to adverse clinical outcomes among individuals with pre-existing AF, such as exacerbated AF with a rapid ventricular rate, the use of antiarrhythmic therapy, and a higher risk of death.[16,17] For example, data from Bernstein et al. demonstrates that pre-existing AF is associated with a fatal COVID-19 clinical course, including ICU admission and higher mortality.[18] The arrhythmogenicity in COVID-19 patients results from direct myocardial damage and is aggravated by multiple organ dysfunction, leading to hypoxia, a catecholamine surge, and an uncontrolled cytokine storm.[19] This, in turn, triggers various cellular changes, including cellular hypertrophy, vascular endothelial dysfunction, and fibrosis.[20] Additionally, COVID-19-induced myocardial inflammation represents a shared pathophysiological feature between AF and COVID-19, both influenced by an uncontrolled immune response.[21] Markers of inflammation, such as procalcitonin, C-reactive protein, and interleukin-6, correlate with disease severity and mortality in both conditions. These combined factors contribute to an increased overall mortality rate compared to those without COVID-19.[22]

Additionally, hospitalization costs, resource utilization, and the duration of hospital stay for the COVID-19-infected cohort remained high even after adjusting for confounders. This is potentially attributed to the observed higher percentage of in-hospital complications, including AKI, ARF, and the need for mechanical ventilation, compared to the cohort without COVID-19 infection. Therefore, preventive measures for COVID-19, especially in this vulnerable subset of populations, including universal standard precautions, vaccination, and early identification and isolation of patients with suspected disease, are crucial to reduce inpatient admissions and mitigate the burden on the healthcare system.[23]

In our analysis of in-patient complications, we observed 6.64-fold higher odds of acute myocarditis in the COVID-19 cohort. This is concurrent with existing literature highlighting the virus's infectious potential for myopericarditis and its association with the aggravation of HF.[24,25] For example, using the US Premier Healthcare Database from March 2020 to January 2021, Boehmer et al. demonstrated a substantial 16-fold higher risk of acute myocarditis in COVID-19 patients than those without.[26] This underscores the value of a thorough evaluation of HF etiology to guide treatment strategies together with stabilizing hemodynamic status. In contrast to previous reports establishing an association between COVID-19 infection and the higher risk of venous thromboembolism (VTE) in individuals with pre-existing cardiac conditions,[27,28] our current study did not find such an association for deep vein thrombosis (DVT) or PE. This discrepancy is likely due to our study's focus on AF patients, with the majority of the cohort having a CHA2DS2-VASc score of ≥4 (Up to 40%), reflecting a high thromboembolic risk and possibly being on anticoagulants at baseline. Consequently, the observed risk of DVT/PE in this cohort is present but not statistically significant.

The major strength of this study is its extensive population for analysis, avoiding referral bias, which is common in single-center cohort studies. The included patients represent a diverse sample admitted for HF with comorbid AF across the US, reflecting in-patient disease burden and characteristics. The large dataset enhances the study's power to detect even minor differences between groups. Furthermore, robust adjustments for demographics, hospital characteristics, and the Charlson comorbidity index minimize the impact of potential confounders.

Notable limitations in our study should be noted. First, the administrative and cross-sectional nature of the NIS database restricted the capture of patient-level data, including radiographic, echocardiographic, and laboratory results, crucial for stratifying patient severity. Furthermore, the inaccuracies in ICD-10 coding further hindered the identification of HF subtypes, preventing the analysis of COVID-19 impact based on HF subclassification. In addition, the release of the COVID-19 ICD-10 code on April 1, 2020, may have led to underreporting of the actual case. Furthermore, the database's emphasis on in-hospital events raises the possibility of overlooking post-hospitalization outcomes, such as out-of-hospital sudden cardiac death, long-term mortality, and complications. Finally, the analysis of in-hospital complications between groups cannot establish causation due to the inability to establish a temporal relationship between the outcome and COVID-19.

5 | CONCLUSION

Our study revealed a significant association between COVID-19 and adverse outcomes in hospitalized HF patients with comorbid AF, including heightened in-patient mortality rate, prolonged hospital stays, increased charges, and elevated risks of in-hospital complications, such as acute myocarditis, AKI, ARF, and the utilization of mechanical ventilation. Future prospective and longitudinal cohort studies are imperative to better delineate these associations.

AUTHOR CONTRIBUTIONS

All authors had access to the data and a role in writing the manuscript.

FUNDING INFORMATION

None.

CONFLICT OF INTEREST STATEMENT

All the authors declare that there are no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data from the findings of this study were inferred can be obtained from the corresponding author upon reasonable request. All data and materials support the published claims and comply with field standards.

ETHICS STATEMENT

For this type of study, Ethics approval is not required.

PATIENT CONSENT STATEMENT

For this type of study, formal consent is not required.

CLINICAL TRIAL REGISTRATION

Not applicable.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

Not applicable.

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SUPPORTING INFORMATION

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

How to cite this article: Wattanachayakul P, Suenghataiphorn T, Srikulmontri T, Rujirachun P, Malin J, Danpanichkul P, et al. Impact of COVID-19 infection on the in-hospital outcome of patients hospitalized for heart failure with comorbid atrial fibrillation: Insight from the National Inpatient Sample (NIS) database 2020. J Arrhythmia. 2024;40:895–902. https://doi.org/10.1002/joa3.13071