Impact of atrial fibrillation on patients hospitalized for acute myocarditis: Insights from a nationally-representative United States cohort

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Background: Atrial fibrillation (AF) is associated with increased all-cause mortality in the general population. However, the impact of AF on the in-hospital outcomes of acute myocarditis (AM) patients is not well characterized.

Methods: Patients (age ≥ 18 years) with a primary diagnosis of AM in the National Inpatient Sample from 2007 to 2014 were included, using the ICD-9-CM diagnostic codes. We compared the in-hospital outcomes between the AF group and propensity score-matched control group without AF.

Results: AF was reported in 602 (9%) of the AM patients. Compared to those without AF, AM patients with AF experienced higher in-hospital mortality (odds ratio [OR] 1.7, 95% confidence interval [CI] 1.1-2.7, \( P = 0.02 \)). AF was associated with higher risk of cardiogenic shock (OR 1.9, 95% CI 1.3-2.8, \( P < 0.001 \)), cardiac tamponade (OR 5.6, 95% CI 1.2-25.3, \( P = 0.002 \)) and acute kidney injury (OR 1.6, 95% CI 1.1-2.1, \( P = 0.02 \)). Furthermore, patients with AF were more likely to have non-routine hospital discharge (31.6% vs 38.4% \( P = 0.02 \)), longer length of stay and higher cost of hospitalization.

Conclusions: AF was associated with increased risk of in-hospital mortality and complications in patients admitted to the hospital with acute myocarditis.

KEYWORDS
atrial fibrillation, myocarditis, outcomes

1 | INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac rhythm disorder in clinical practice affecting 2.3% to 3.4% of the adult population worldwide.\(^1,2\) Furthermore, the prevalence and incidence of AF are expected to increase exponentially in the future.\(^1,2\) While several studies have concluded that AF is associated with increased all-cause mortality in the general population,\(^3,4\) very little is known regarding the impact of AF on the prognosis of the patients hospitalized with acute myocarditis (AM). Since AF prevalence is increasing,\(^1,2\) a negative prognostic impact of AF on the natural course of AM has imperative clinical implications. The aim of this study was to describe the outcomes of patients with myocarditis complicated by AF in a large nationally-representative database.

2 | METHODS

2.1 | Data source

Our study was conducted using the National Inpatient Sample (NIS) database, which is part of the Healthcare Cost and Utilization Project sponsored by Agency for Healthcare Research and Quality (AHRQ).\(^5\) NIS is the largest all-payer inpatient stays database in the United States. It represents a 20% stratified sample of all discharges from
community hospitals in the United States with approximately 8 million discharges per year. Each patient discharge record in the NIS database includes a single primary diagnosis, and up to 24 secondary diagnoses along with the demographic characteristics, length of stay (LOS), procedures performed, comorbidities, and complications identified during the index admission. Discharge weights provided in the database allows for calculating national estimates of all discharges in the United States.

2.2 Study population and outcome variables

NIS data were queried by using the International Classification of Diseases, ninth Revision, Clinical Modification (ICD-9-CM) codes to identify the study variables. All patients (age ≥ 18 years) with a primary diagnosis of AM (code 422.0, 422.90-422.93, 422.99, and 429.0) from 2007 to 2014 were included. The primary diagnosis is the condition chiefly responsible for hospitalization (after clinical evaluation and diagnostic investigation) and is usually derived after reviewing the patient admission record according to the AHRQ. The approach of identifying AM hospitalizations according to ICD-9-CM codes have been used in prior work examining the NIS. The included myocarditis patients were then stratified into two major groups. The first group was myocarditis patients with AF. The second group constituted the control (no-AF) group. The presence of AF was based on ICD-9-CM code 427.31, which has been previously validated. The primary outcome was the impact of AF on inpatient mortality. Secondary outcomes were the impact of AF on inpatient complications like cardiogenic shock, cardiac tamponade, respiratory complications, ischemic strokes, deep venous thrombosis/pulmonary embolism, sepsis, acute kidney injury, and the requirement for a new pacemaker. We also evaluated the length of hospital stay, discharge pattern, and hospitalization costs. The ICD codes used to identify these complications are available in Table S1, Supporting Information.

2.3 Statistical analysis

We used the hospital trend/discharge weight provided by AHRQ to generate national estimates including sum, rates, and averages. \( \chi^2 \) test for categorical variable or t test for continuous variable were used to compare baseline characteristics between patient with and without AF. To compare clinical outcomes between patients with and without AF, we created 1:1 matched groups based on propensity score analysis using nearest neighbor matching with a caliper of 0.1 (Table 2). The propensity score was estimated using a multivariable logistic regression model with 25 patient- and hospital-level variables as independent variables and indicator for AF as the dependent variables. This model demonstrated very good discrimination (C-statistic = 0.79) and calibration (P-value for Hosmer-Lemeshow goodness of fit test = 0.09). Success of matching was assessed based on the standardized differences in patient- and hospital-level covariates between the two groups. Finally, hierarchical model with unique hospital identification number as a random effect in the model was used to compare clinical outcomes between the two groups: mixed effect logistic model to estimate odds ratio (OR) for binary outcomes while linear mixed model to evaluate difference in cost and LOS. All the analyses were performed using STATA 14 (StataCorp, College Station, Texas) with level of significance set at 0.05.

3 RESULTS

3.1 Patient population

The study population included 6642 patients from the national inpatient sample registry; all admitted with AM from 2007 to 2014. Of these (38.7% women and 43.8% ≥ 17.8 years old), AF was reported in 602 patients (9%) (Figure 1). The mean age for the AM group with AF was 59.2 ± 16.1 years vs 42.3 ± 17.1 years for the group without AF (\( P < 0.001 \)). AM patients with AF were more commonly white (83.6% vs 69.8%, \( P < 0.001 \)) and more likely to have an Elixhauser score ≥ 4 (33.5% vs 17.5%, \( P < 0.001 \)). Concerning comorbidity, AM patients with AF were more likely to have peripheral vascular disease, hypertension, diabetes, anemia, congestive heart failure, chronic obstructive pulmonary disease, renal failure, and coagulation disorder compared to those without AF; and less likely to have obesity, liver failure, and malignancy. Baseline clinical characteristics between the two groups before propensity matching are depicted in Table 1.

3.2 Myocarditis patients with and without AF

After adjusting for patient-level and hospital-level characteristics, AM patients with AF experienced higher in-hospital mortality compared to those without AF (odds ratio [OR] 1.7, 95% confidence interval [CI] 1.1-2.7, \( P = 0.02 \)). The AF group had a higher risk of cardiogenic shock (OR 1.9, 95% CI 1.3-2.8, \( P < 0.001 \)), cardiac tamponade (OR 5.6, 95% CI 1.2-25.3, \( P = 0.002 \)) and acute kidney injury (OR 1.6, 95% CI 1.1-2.1, \( P = 0.02 \)). Furthermore, AM patients with AF were more likely to have non-routine hospital discharge (38.4% vs 31.6%, \( P = 0.02 \)), longer LOS (6 days vs 4 days, \( P = 0.002 \)) and higher mean cost of hospital stay (37 063$ vs 26 900$, \( P = 0.002 \)) (Table 2). However, there was no statistical difference regarding other complications including stroke, respiratory complications, venous thromboembolism, sepsis, or pacemaker requirement (Table 3).

4 DISCUSSION

Our study revealed two important findings. First, there was a higher risk of in-hospital mortality in hospitalized AM patients with AF. Second, when they concurrently occur, AM and AF synergistically confer a poor prognosis and higher risk of in-hospital complications compared to AM patients without AF. Prevalent AF among AM patients was associated with advanced age, white race, and a high burden of comorbidity (as quantified by Elixhauser score). The previous observation parallels the AF distribution in the general population. Although AF-AM cohort had a high burden of comorbidity, it appears that AF had a major influence on the in-hospital outcomes given the worse outcome among AF-AM group even after rigorous control of confounding factors through propensity matching. Our findings among AM patients with AF are in contrast with findings from
previous studies that showed no increased mortality in AM patients with new-onset AF.\textsuperscript{12–15} In the study by Magnani et al. which included 112 patients with biopsy-confirmed myocarditis, presentation with new-onset atrial arrhythmias (AF or flutter) did not predict mortality or the need for cardiac transplantation.\textsuperscript{12} However, previous studies lacked national representation and/or sufficient power limiting inferences that could be drawn about the influence of AF on in-hospital outcomes.\textsuperscript{12–15} Higher mortality among patients with AF underscores the burden of this complication in patients with AM. AF can induce several neurohormonal, biochemical, and electrophysiological changes at the cellular and extracellular matrix level with subsequent worsening of the myocardial dysfunction.\textsuperscript{16,17} Thus, it is expected to find higher rates of mortality and morbidity including cardiogenic shock and acute kidney injury in patients with AF than in patients without AF.

In our study, patients with AF were more likely to develop cardiac tamponade. The reason for a higher proportion of cardiac tamponade among AF-AM patients, however, is unclear and needs to be studied further. AF was associated with longer LOS. Factors like hemodynamic instability (eg, due to rapid ventricular response), higher complications rate (cardiogenic shock, cardiac tamponade, and acute kidney injury) and the use of Vitamin K antagonists impelling international normalized ratio monitoring before discharge may account for the previous findings. However, our study lacks information on rate control and the pattern of anticoagulant agent use. Therefore, the precise reason underlying this association is not entirely apparent. Given the observed increased LOS, the association of AF with an increased cost of hospitalization was expected. We found that AF was associated with an increased median cost of approximately $10,163 per hospitalization after adjustment of confounders. Our study also showed an increased risk of nonroutine discharge, including home with home health care, short- and long-term care facilities in the AF cohort, further adding to the overall cost.

### TABLE 1  Baseline characteristics of patients admitted for myocarditis in the United States according to presence of atrial fibrillation before propensity score matching

| Total | Without AF | With AF | P-value |
|-------|------------|---------|---------|
| No. of observation (unweighted) | 6642 | 6040 | 602 | — |
| No. of observation (weighted) | 32,202 | 29,293 | 2909 | — |
| Age mean (SD) | 43.8 (17.8) | 42.3 (17.1) | 59.2 (16.1) | <0.001 |
| Female | 38.7% | 38.6% | 39.5% | 0.66 |
| Race/ethnicity | — | — | — | <0.001 |
| White | 71.0% | 69.8% | 83.6% | — |
| Black | 16.0% | 16.5% | 11.0% | — |
| Hispanic | 10.4% | 11.0% | 3.9% | — |
| Asia | 2.4% | 2.5% | 1.3% | — |
| Peripheral vascular disease | 2.4% | 2.2% | 4.9% | <0.001 |
| Hypertension | 31.7% | 30.1% | 47.5% | <0.001 |
| Diabetes | 11.8% | 11.3% | 17.6% | <0.001 |
| Obese | 11.6% | 11.5% | 12.6% | 0.45 |
| Anemia | 13.6% | 13.1% | 17.7% | 0.002 |
| CHF | 15.6% | 14.8% | 24.2% | <0.001 |
| COPD | 14.3% | 13.7% | 19.9% | <0.001 |
| Renal failure | 7.1% | 6.3% | 15.2% | <0.001 |
| Liver disease | 2.3% | 2.3% | 2.4% | 0.82 |
| Coagulation disorder | 8.6% | 7.9% | 14.7% | <0.001 |
| Malignancy | 0.63% | 0.61% | 0.83% | 0.52 |
| Elixhauser score | — | — | — | <0.001 |
| 0-1 | 48.3% | 50.3% | 28.5% | — |
| 2-3 | 32.6% | 32.1% | 37.8% | — |
| ≥4 | 18.9% | 17.5% | 33.5% | — |
| Hospital bed size | — | — | — | 0.12 |
| Small | 11.0% | 11.1% | 10.5% | — |
| Medium | 22.3% | 22.6% | 19.3% | — |
| Large | 66.5% | 66.2% | 70.1% | — |
| Hospital location | — | — | — | 0.29 |
| Rural | — | 7.5% | 9.3% | — |
| Urban non-teaching | — | 34.4% | 33.5% | — |
| Urban teaching | — | 57.9% | 57.1% | — |

Abbreviations: AF, atrial fibrillation; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease.
### TABLE 2  
Baseline characteristics of patients admitted for myocarditis in the United States according to presence of atrial fibrillation after propensity score matching

|                          | Without AF | With AF | P-value |
|--------------------------|------------|---------|---------|
| No. of observation (unweighted) | 582        | 582     | –       |
| No. of observation (weighted)  | 2828       | 2813    | –       |
| Age mean (SD)             | 60.3 (16.1) | 59.4 (16.0) | 0.26    |
| Female                    | 45.8%      | 39.3%   | 0.24    |
| Race/ethnicity            | –          | –       | 0.97    |
| White                     | 76.8%      | 83.1%   | –       |
| Black                     | 15.2%      | 11.4%   | –       |
| Hispanic                  | 6.2%       | 4.0%    | –       |
| Asia                      | 1.8%       | 1.4%    | –       |
| Peripheral vascular disease| 4.8%       | 4.9%    | 0.89    |
| Hypertension              | 51.3%      | 47.9%   | 0.24    |
| Diabetes                  | 21.1%      | 17.8%   | 0.16    |
| Obese                     | 14.2%      | 12.5%   | 0.39    |
| Anemia                    | 17.8%      | 18.0%   | 0.93    |
| CHF                       | 23.0%      | 24.2%   | 0.63    |
| COPD                      | 20.9%      | 19.7%   | 0.61    |
| Renal failure             | 13.4%      | 15.2%   | 0.35    |
| Liver disease             | 1.7%       | 2.5%    | 0.31    |
| Coagulation disorder      | 13.2%      | 14.7%   | 0.45    |
| Malignancy                | 1.20%      | 0.86%   | 0.56    |
| Elixhauser score          | –          | –       | 0.25    |
| 0-1                       | 31.6%      | 28.1%   | –       |
| 2-3                       | 35.9%      | 38.1%   | –       |
| ≥4                        | 32.4%      | 33.6%   | –       |
| Hospital bed size         | –          | –       | 0.66    |
| Small                     | 11.0%      | 10.6%   | –       |
| Medium                    | 20.2%      | 19.2%   | –       |
| Large                     | 68.7%      | 70.1%   | –       |
| Hospital location         | –          | –       | 0.43    |
| Rural                     | 10.1%      | 9.4%    | –       |
| Urban nonteaching         | 34.8%      | 33.1%   | –       |
| Urban teaching            | 54.9%      | 57.3%   | –       |

Abbreviations: AF, atrial fibrillation; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease.

### TABLE 3  
Clinical outcomes of patients presenting with myocarditis according to presence of atrial fibrillation

|                          | Without AF | With AF | OR (95% CI)a | P-value |
|--------------------------|------------|---------|--------------|---------|
| In-patient mortality     | 5.4%       | 8.8%    | 1.7 (1.1, 2.7) | 0.02    |
| Cardiogenic shock        | 10.8%      | 18.2%   | 1.9 (1.3, 2.8) | <0.001  |
| Cardiac tamponade        | 0.34%      | 1.9%    | 5.6 (1.2, 25.3) | 0.02    |
| Respiratory complications| 0.69%      | 0.52%   | 0.75 (0.16, 3.3) | 0.71    |
| DVT/PE                   | 2.2%       | 2.4%    | 1.1 (0.50, 2.3) | 0.84    |
| Sepsis                   | 12.8%      | 13.1%   | 1.1 (0.72, 1.42) | 0.93    |
| Requirement for pacemaker| 0.86%      | 1.6%    | 1.8 (0.60, 5.4) | 0.28    |
| Acute kidney injury      | 22.1%      | 30.2%   | 1.6 (1.1, 2.1)  | 0.002   |
| Nonroutine home dischargeb | 31.6%   | 38.4%   | 1.4 (1.1, 1.9)  | 0.02    |
| Cost, mean (SD)          | 26 900 (49 081) | 37 063 (61 480) | –        | 0.002   |
| Length of stay, median (Q1, Q3) | 4 (2, 8) | 6 (3, 11) | –        | 0.002   |

Abbreviations: AF, atrial fibrillation; CI, confidence interval; DVT, deep vein thrombosis; OR, odds ratio; Q1, first quartile; Q3, third quartile; PE: pulmonary embolism.

a Represents odds ratio (with 95% CI) of AF vs no-AF based on propensity matched analysis.

b Nonroutine home discharge include home with health care, transfer to short term hospital or other intermediate or long term care facility.
5 | LIMITATIONS

Our study has some limitations that deserve to be emphasized. First, in the NIS database variables are identified using a coding system that is subject to coding errors and documentation disparities. However, the use of ICD-9-CM codes to identify AM or AF has been implemented and validated in previous studies with a reasonable diagnostic performance. Second, our database lacked information on AF subtypes (paroxysmal or permanent), rate control, the pattern of anticoagulation, antiarrhythmic drugs, steroids, and echocardiographic parameters (e.g., ejection fraction). Therefore, the impact of the antecedent variables on outcomes cannot be determined, and our ability to precisely identify opportunities to reduce adverse outcomes are limited. Despite lacking this granularity, analysis of large administrative databases is a useful resource for hypothesis-generation which was the primary goal of our study.

Third, despite the rigorously adjusted baseline characteristics using propensity score analysis, there is the risk of unmeasured residual confounding in the registry-based retrospective data analysis, for example, AF can be a marker of AM that is complicated at the time of hospitalization. Similarly, in the multicenter Lombardy registry on myocarditis, the patients with severe myocarditis were more likely to present with arrhythmias and more likely to have adverse outcomes. Lastly, our study is limited to the in-hospital outcomes; follow-up data were not reported. However, strengths of this study included the nationally-representative large sample size which involves multiple centers and populations across the United States. The NIS database design has been validated and is commonly used to examine patterns in the US health system among a range of subpopulations including AM. Furthermore, we matched the study patients using propensity score to control for the discrepancies in baseline characteristics.

6 | CONCLUSION

AF is a frequently encountered arrhythmia in patients admitted to the hospital with acute myocarditis, and it confers an increased risk of inhospital mortality and complications. Rigorous studies to identify strategies to improve outcomes for this vulnerable subpopulation are warranted.

CONFLICTS OF INTEREST

The authors declare no potential conflict of interests.

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**SUPPORTING INFORMATION**

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

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