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Atrial fibrillation and heart failure with preserved ejection fraction: Insights on a unique clinical phenotype from a nationally-representative United States cohort

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ABSTRACT

Background: Atrial fibrillation (AF) and heart failure often occur concomitantly, representing a clinical phenotype at high-risk for poor outcomes. Differences in the characteristics, management, and in-hospital outcomes of AF among those with heart failure with preserved ejection fraction (HFpEF) and those with heart failure with reduced ejection fraction (HFrEF) are not well characterized.

Methods and results: Using the National Inpatient Sample, we identified hospitalizations in 2008–2012 for HFpEF and for HFrEF, with and without AF based on ICD-9-CM codes. We examined patient characteristics, procedural rates, and in-hospital outcomes. AF was common among both HFpEF and HFrEF, and increased in prevalence over the study period. A very low proportion of the cohort underwent either direct-current cardioversion or catheter-ablation. Compared to those without AF, those with AF experienced higher in-hospital mortality regardless of heart failure subtype. In multivariable regression analysis, AF was associated with in-hospital mortality in HFpEF (OR 1.10, CI [1.08–1.11]), but not in HFrEF (OR 0.93 [0.92–0.94], p-for-interaction < 0.001).

Conclusions: Our study revealed that the prevalence and adverse impact of AF on those with HFpEF is substantial, providing a rationale to rigorously investigate strategies, such as rhythm-control, to improve outcomes for this particularly vulnerable subpopulation.

1. Introduction

Heart failure [1] and atrial fibrillation (AF) [2] each affect over 5 million people across the United States, and represent conditions independently associated with poor outcomes [3,4]. Frequently occurring together, heart failure can beget AF, and AF can beget heart failure [5,6]. When they concurrently occur, heart failure and AF synergistically confer a poor prognosis compared to those without these conditions or with either condition alone [7].

Characterizing this vulnerable patient population and identifying factors associated with poor outcomes are critical to improving the outcomes of those with concurrent heart failure and AF. Although there are a myriad of studies that have characterized patients with heart failure with reduced ejection fraction (HFrEF) and AF, much less is known about patients with HFpEF and AF. A recent meta-analysis performed on about 54,000 patients comparing outcomes among HFpEF with concurrent AF (HFpEF-AF) and HFrEF with concurrent AF (HFrEF-AF) revealed some insight [8], but incorporated studies comprised of a very select subgroup of patients, limiting inferences that could be drawn. Moreover, this study specifically focused on long-term outcomes, and did not describe the independent association of AF on mortality. Consequently, despite recognition that HFpEF-AF is a potentially important phenotype of HFpEF [9], the relative impact of AF on in-hospital mortality within HFpEF remains poorly characterized.

Our study sought to use a nationally-representative cohort to examine HFpEF with AF in relation to HFrEF with AF, and quantify the relative impact of AF on mortality.

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2. Methods

2.1. Data source and study population

We used data from the Agency for Healthcare Research and Quality Healthcare Cost and Utilization Project—National Inpatient Sample (NIS) files from 2008 to 2012 [10]. The National Inpatient Sample is a 20% stratified sample of all nonfederal US hospitals. Hospitalizations are weighted based on a sampling scheme to permit inferences for a nationally representative population. Accordingly, we weighted hospitalizations based on the NIS sampling scheme, and performed all analyses on weighted data in order to provide nationally-representative estimates, as studies using the NIS have previously done [11,12]. Each record in the NIS represents a patient hospitalization, and includes all procedure and diagnosis International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM) codes recorded for each discharge.

We included all hospitalizations with a diagnosis of acute heart failure among adults aged ≥18 years in 2008–2012 for analysis. We identified acute heart failure hospitalizations based on ICD-9-CM codes—acute heart failure with preserved ejection fraction: 428.31 and 428.33; acute heart failure with reduced ejection fraction: 428.21 and 428.23. The approach of identifying heart failure hospitalizations according to ICD-9-CM codes has extensively been used in several prior studies examining both Medicare [13–15] and the NIS [16,17]. Although codes specifically for HFrEF and HFpEF have not been formally validated, they have been used in prior work and have identified cohorts of HFpEF and HFrEF whose characteristics correlate well with those observed in clinical trials and community-based studies [18]. To avoid systematic bias of including an emerging phenotype of heart failure known as "heart failure with mid-range ejection fraction," [19] those with combined acute systolic and diastolic heart failure were excluded from analysis. The presence of AF was based on ICD-9-CM code 427.31, which has previously demonstrated good diagnostic performance [20].

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee. Given the retrospective nature of this study, the Weill Cornell Institutional Review Board did not require informed consent for this study.

2.2. Baseline characteristic and outcome variables

We collected all baseline characteristic and outcome variables from the NIS. We collected patient-level variables including socio-demographics and comorbid conditions based on previously validated Elixhauser methods. We also collected hospital characteristics derived from the American Hospital Association Annual Survey Database, and all-cause mortality. Based on patient characteristics, we calculated CHADS2 and CHA2DS2-VASc [21] scores for each hospitalization. We also calculated an Elixhauser score, a summary index score based on a validated weighted-calculation of the Elixhauser comorbidities [22], for each hospitalization. Finally, we identified the performance of direct-current cardioversion (DCCV) and catheter-ablations based on the presence of ICD-9-CM procedure codes 99.61 (atrial cardioversion) and 37.34 (ablation of heart tissue via a peripherally inserted catheter) respectively. To ensure DCCV was performed for AF, we did not count cases of DCCV accompanied by diagnostic codes for other atrial arrhythmias such as atrial flutter, atrioventricular nodal tachycardia, and paroxysmal supraventricular tachycardia (Supplemental Table 1). To ensure catheter-ablation was performed for AF, we did not count cases of ablation accompanied by diagnostic codes for other arrhythmias, or those who likely underwent ablation of the atrioventricular junction, similar to prior studies [23,24] (Supplemental Table 2). The primary outcome measure was in-hospital all-cause mortality.

2.3. Statistical analysis

To compare baseline characteristics, we used Student's *t*-tests for continuous variables, and Pearson chi-squared tests for categorical variables. To compare in-hospital mortality, we used the Pearson chi-squared tests. To assess temporal trends for AF prevalence and use of procedures over the 5-year study period, we used the autoregressive integrated moving average model for time series.

We performed multivariable regression analyses to identify correlates of the use of DCCV and catheter-ablation. We also used multivariable regression analysis to determine the association of AF with in-hospital mortality. In these models, we included socio-demographic factors (age, sex, race, payer status), hospital characteristics (hospital size, geographic region, urban setting, and academic status), and comorbidity burden via the Elixhauser score. We used the Taylor linearization method "with replacement" design to compute the standard errors of the regression coefficients for all regression analyses; the Taylor linearization approach is based on a first-order Taylor series linear approximation of the derivative of the log weighted likelihood function [25]. All statistical tests were 2-sided, and a p-value of <0.01 was set to be statistically significant given the size of the cohort. All statistical analyses were conducted using SAS, version 9.2 (SAS Institute, Cary, NC) or SPSS, version 20 (IBM Corporation, Armonk, NY).

3. Results

There were 4,641,890 hospitalizations with acute heart failure that met inclusion criteria. Among them, 45.3% were for HFpEF and 54.7% were for HFrEF.

3.1. Baseline characteristics

Among those with HFpEF, 42.1% had concurrent atrial fibrillation (HFpEF-AF). This prevalence increased from 37.4% in 2008 to 44.7% in 2012 (Fig. 1). Those with HFpEF-AF were older, more commonly white, and more commonly recipients of Medicare compared to those with HFpEF without AF (Table 1). With regard to comorbidity, those with HFpEF-AF were more likely to have hypothyroidism and valvular heart disease compared to those with HFpEF without AF; and less likely to have anemia, chronic renal failure, diabetes, and obesity compared to

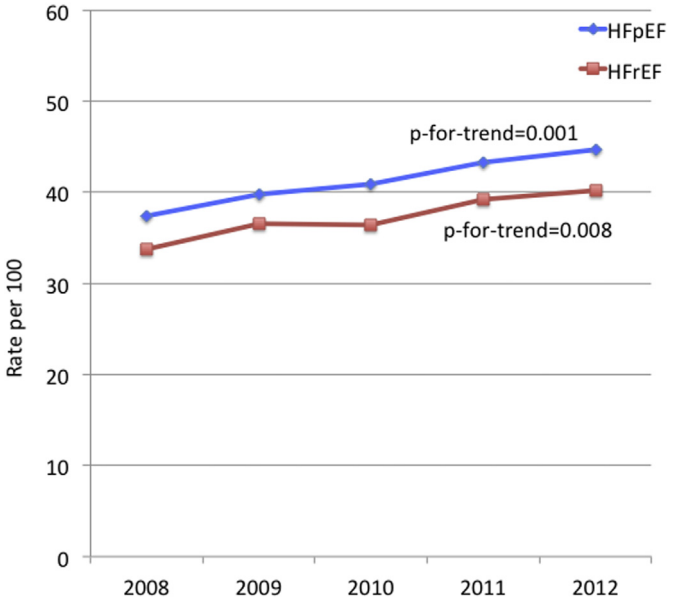

Fig. 1. Prevalence of concurrent AF with HF. Line graph demonstrating prevalence of atrial fibrillation with heart failure.