ORIGINAL RESEARCH

Sex- and Race-Related Differences in Characteristics and Outcomes of Hospitalizations for Heart Failure With Preserved Ejection Fraction

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***Background*—**Sex and race have emerged as important contributors to the phenotypic heterogeneity of heart failure with preserved ejection fraction (HFpEF). However, there remains a need to identify important sex- and race-related differences in characteristics and outcomes using a nationally representative cohort.

***Methods and Results*—**Data were obtained from the Agency for Healthcare Research and Quality Healthcare Cost and Utilization Project—Nationwide Inpatient Sample files between 2008 and 2012. Hospitalizations with a diagnosis of HFpEF were included for analysis. Demographics, hospital characteristics, and age-adjusted comorbidity prevalence rates were compared between men and women and whites and blacks. In-hospital mortality was determined and compared for each subgroup. Multivariable regression analyses were used to identify and compare correlates of in-hospital mortality for each subgroup. A sample of 1 889 608 hospitalizations was analyzed. Men with HFpEF were slightly younger than women with HFpEF and had a higher Elixhauser comorbidity score. Men experienced higher in-hospital mortality compared with women, a finding that was attenuated after adjusting for comorbidity. Blacks with HFpEF were younger than whites with HFpEF, with lower rates of most comorbidities. Hypertension, diabetes, anemia, and chronic renal failure were more common among blacks. Blacks experienced lower in-hospital mortality compared with whites, even after adjusting for age and comorbidity. Important correlates of mortality among all 4 subgroups included pulmonary circulation disorders, liver disease, and chronic renal failure. Atrial fibrillation was an important correlate of mortality only among women and blacks.

***Conclusions*—**Differences in patient characteristics and outcomes reinforce the notion that sex and race contribute to the phenotypic heterogeneity of HFpEF. **(*J Am Heart Assoc*. 2017;6:e003330. DOI: 10.1161/JAHA.116.003330.)**

Key Words: epidemiology • heart failure • mortality

Heart failure (HF) with preserved ejection fraction (HFpEF) comprises more than half of all HF hospitalizations in the United States.[1] Unfortunately, there are limited treatment options for this subtype of HF, as pharmacologic therapies to date have largely failed to improve clinical outcomes.[2] Heterogeneity has been cited as a cause of failed clinical trials in HF,[3] and is of particular relevance in HFpEF,[4] which represents a syndrome with a diverse set of pathophysiologies, etiologies, and manifestations.

Sex and race are likely important contributors to the phenotypic heterogeneity of HFpEF, an observation stemming from subgroup analyses of registries such as Irbesartain in Patients With Heart Failure and Preserved Ejection Fraction (I-PRESERVE),[5] Acute Decompensated Heart Failure National

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Registry (ADHERE),[6] Atherosclerosis Risk in Communities Study (ARIC),[7] and the Cardiovascular Research Network.[8] While these results have revealed important differences in baseline features and outcomes between men and women and whites and blacks, the generalizability of these findings have been limited by a modest number of analyzed patients, selection bias inherent to these registries, and/or geographic homogeneity.

Consequently, there is a need to identify important sex- and race-related differences in characteristics and outcomes of HFpEF using a nationally representative cohort. Given its central role in the pathophysiology of HFpEF,[9,10] characterizing comorbidity and its impact on outcomes classified by sex and race have the potential to inform the development of future therapeutic strategies. Accordingly, this study aimed to compare and contrast clinical characteristics and outcomes of men and women and whites and blacks with HFpEF using the Nationwide Inpatient Sample (NIS), an all-payer national administrative database.

Methods

Data Source and Study Population

Data originated from the Agency for Healthcare Research and Quality Healthcare Cost and Utilization Project—NIS files from 2008 to 2012.[11] The NIS is a 20% stratified sample of all nonfederal US hospitals. Each record in the NIS includes all reported diagnosis codes based on the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*). Hospitalizations are weighted based on a sampling scheme that permits inferences for a nationally representative population. Accordingly, cases included for analyses were weighted based on the NIS sampling scheme, and all analyses were performed on weighted data in order to provide nationally representative estimates, as studies using the NIS have previously done.[12–14]

Hospitalizations from 2008 to 2012 for acute HFpEF among adults aged 18 years and older were included for analysis. Hospitalizations for HFpEF were identified based on the presence of acute diastolic HF without concurrent systolic HF, which included *ICD-9-CM* codes 428.31 (acute diastolic HF) and 428.33 (acute on chronic diastolic HF), a strategy that has previously been demonstrated to identify a cohort of HFpEF whose characteristics correlate well with clinical trials and community-based studies that define HFpEF based on clinical criteria.[15] Subgroups for analysis were determined a priori, and were stratified by sex (men/women) and race (white/black). Other individual races represented a small proportion of this cohort, and were therefore not analyzed separately. Cases with missing data on age, sex, and/or race were excluded.

Baseline Characteristics and Outcome Variables

Patient-level characteristics were obtained from the NIS and included demographics (age, sex, race, and primary payer status) and Agency for Healthcare Research and Quality comorbidity measures, which were based on the Elixhauser method.[16] The Elixhauser score, a summary index score based on a validated weighted calculation of the Elixhauser comorbidities,[17] was also determined. Coronary artery disease (CAD; *ICD-9-CM* codes 414.0x, 414, 414.2, 414.3, 414.4, 414.8, and 414.9), atrial fibrillation or flutter (AF; *ICD-9-CM* codes 427.3x), history of coronary artery bypass grafting (CABG; *ICD-9-CM* code V4581), and prior percutaneous coronary intervention (PCI; *ICD-9-CM* code V4582) were determined based on *ICD-9-CM* codes. Hospital-level characteristics were also collected from the NIS, derived from the American Hospital Association Annual Survey Database. Outcome measures included in-hospital all-cause mortality, as recorded in the NIS.

Statistical Analysis

All analyses were performed and presented as weighted data using the NIS discharge weighting variable.[18] Baseline characteristics of sex and race subgroups were compared using Student *t* tests for continuous variables and Pearson chi-square tests for categorical variables. Comorbidity prevalence rates were compared between subgroups using logistic regression. To account for the impact of advanced age, which is associated with changes in cardiovascular morphology and function, comorbidity burden, and outcomes,[19] results were stratified by an age cutoff of 75 years. Interactions between age and sex and age and race were assessed based on the Wald test.

Unadjusted rates of in-hospital mortality were calculated for each subgroup. Rates were compared between subgroups, stratified by an age cutoff of 75 years. Model 1 represented adjusted rates of in-hospital mortality accounting for demographics (sex, race, and primary payer status) and hospital characteristics (region, urban setting, teaching status, and size). Model 2 added the Elixhauser score to model 1 covariates. To determine whether results would differ if an alternative age cutoff were chosen, a sensitivity analysis was performed for comparisons of in-hospital mortality of sex and race subgroups stratified by an age cutoff of 65 years.

Multivariable regression analysis was performed to identify correlates of in-hospital mortality within each subgroup. Variables incorporated into each model included demographics (age ≥75 years, sex, race, primary payer status), hospital characteristics (region, urban setting, teaching status, and size), and comorbidities including anemia, chronic pulmonary disease, diabetes mellitus, hypertension, hypothyroidism, liver disease, neurodegenerative disease, obesity, peripheral vascular disorders, pulmonary circulation disorders, chronic renal

failure (CRF), AF, CAD, valvular disease, and history of revascularization (prior CABG and/or prior PCI). Each variable was tested for an interaction with sex and race. Noncollinearity between variables was confirmed using the variance inflation factor, with a threshold of 2.5.

The Taylor linearization approach, based on a first-order Taylor series linear approximation of the derivative of the log weighted likelihood function, was used to compute the standard errors of the regression coefficients for all regression analyses.[20] All statistical tests were 2-sided, and a *P* value <0.01 was set to be statistically significant. All statistical analyses were conducted using SPSS version 20 (IBM Corporation, Armonk, NY).

Results

There were 1 889 608 hospitalizations for HFpEF. Patients with HFpEF were predominantly 75 years and older, women, white, and recipients of Medicare (Table 1). Most hospitalizations occurred in the Southern region of the United States and in urban areas and large hospitals. The most common comorbidities included hypertension (69%), AF (43%), diabetes (43%), and CAD (42%). The mean Elixhauser score was 8.0±7.2. The total number of cases excluded because of missing data was 213 248 (age missing=0, sex missing=113, and race missing=213 135). For excluded cases, mean age, sex and race, primary payer status, and mean Elixhauser

Table 1. Characteristics of Hospitalizations for HFpEF, Stratified by Sex and Race

Variable	All (N=1 889 608)	Men (n=680 845)	Women (n=1 208 763)	White (n=1 421 065)	Black (n=275 120)
Mean age, (±SD), y	75.8±12.9	73.3±13.2	77.2±12.5	77.8±11.6	67.4±14.7
Age, %					
18–74 y	39.3	47.6	34.6	33.3	64.9
≥75 y	60.7	52.4	65.4	66.7	35.1
Sex, %					
Women	64.0	…	…	63.9	65.2
Race, %					
White	75.2	75.3	75.1	…	…
Black	14.6	14.1	14.8	…	…
Other	10.2	10.6	10.1	…	…
Primary payer, %					
Medicare	81.8	77.4	84.3	85.7	68.2
Medicaid	5.2	5.3	5.1	2.7	13.1
Private including HMO	9.8	12.7	8.2	9.2	12.7
Self-pay	1.8	2.5	1.4	1.1	4.0
Hospital region, %					
Northeast	26.6	26.3	26.7	28.0	21.4
Midwest	20.6	20.3	20.8	22.2	20.2
South	37.4	37.0	37.6	35.6	50.3
West	15.5	16.4	14.9	14.2	8.1
Hospital setting, %					
Academic	45.1	45.8	44.7	41.7	61.0
Urban	89.5	89.8	89.3	88.0	93.7
Hospital size, %					
Small	12.7	12.4	12.9	13.5	8.8
Medium	26.5	26.2	26.7	26.8	25.8
Large	60.8	61.4	60.5	59.7	65.4
Discharge to home, %	63.5	68.1	61.0	60.3	74.3
Length of stay (mean±SD), d	7.0±7.3	7.1±7.7	7.0±7.1	7.0±7.0	7.0±8.2

HFpEF indicates heart failure with preserved ejection fraction; HMO, health maintenance organization. All *P* values <0.001.

score were similar to those of cases included for primary analysis (Table S1).

Men and Women With HFpEF

Men with HFpEF were slightly younger than women with HFpEF (Table 1). Both men and women were predominantly white and Medicare recipients. Hospital characteristics were similar between sexes. With regard to discharge disposition, men were more commonly discharged to home compared with women.

Prevalence of comorbidity

Men had a higher mean Elixhauser score compared with women (Figure 1A). This difference was more prominent among patients 75 years and older, and less so among those younger than 75 years. CAD, AF, CRF, and history of PCI and CABG were more common among men compared with women (Figure 2A). Sex differences were more prominent in patients 75 years and older for CAD, CABG, and CRF, and less prominent for AF.

Some comorbidities were more common in men irrespective of age, including liver disease and peripheral vascular disorders, while others were more common in women irrespective of age, including obesity, hypothyroidism, and pulmonary circulation disorders (Figure 2A). Valvular disease and anemia were more common in women, an observation driven by differences in age younger than 75 years. Hypertension was also slightly more common in women, driven by an increased prevalence among age 75 years and older. Some comorbidities exhibited unique age-dependent prevalence patterns with respect to sex; chronic pulmonary disease and diabetes were more common in women younger than 75 years and more common in men 75 years and older.

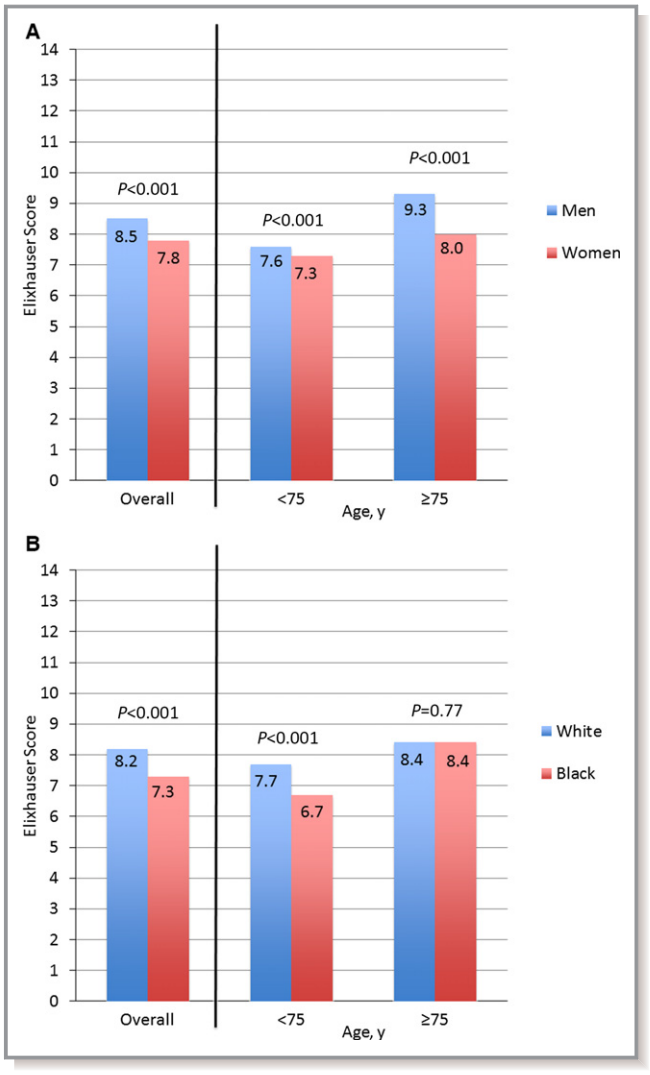

Figure 1. Age-stratified mean Elixhauser comorbidity summary score by sex (A) and race (B).

In-hospital mortality

Women experienced lower in-hospital mortality compared with men (4.2% versus 4.6%, $P<0.001$). When stratified by age alone, women in both age strata (<75 and ≥75 years) were less likely to die in the hospital compared with men (Table 2). In a logistic regression model including race, primary payer status, and hospital characteristics (model 1), women 75 years and older were less likely to die in the hospital, a difference that was attenuated after adjusting for the Elixhauser score in model 2. Women younger than 75 years were nearly as likely to die in the hospital as men according to both models, albeit with a statistically significant difference in model 1. A sensitivity analysis using an age cutoff of 65 years revealed similar findings (Table S2).

In multivariable regression analysis, the risk of in-hospital mortality was increased by over 50% among those older than 75 years in both men and women (Table 3). With regard to comorbidities, pulmonary circulation disorders, liver disease, and CRF were the strongest correlates of in-hospital mortality in both subgroups. Anemia, diabetes, hypertension, CAD, and a history of revascularization were inversely associated with in-hospital mortality in both subgroups. Of note, AF was a correlate of in-hospital mortality among women, but not men (P for interaction <0.001).

Whites and Blacks With HFpEF

Whites with HFpEF were on average 10 years older than blacks with HFpEF (Table 1). Whereas 67% of whites were 75 years and older, only 35% of blacks were 75 years and older; 86% of whites were 65 years and older and 58% of blacks were 65 years and older. Blacks were more commonly hospitalized in the South and at academic institutions compared with whites. Blacks were also more commonly

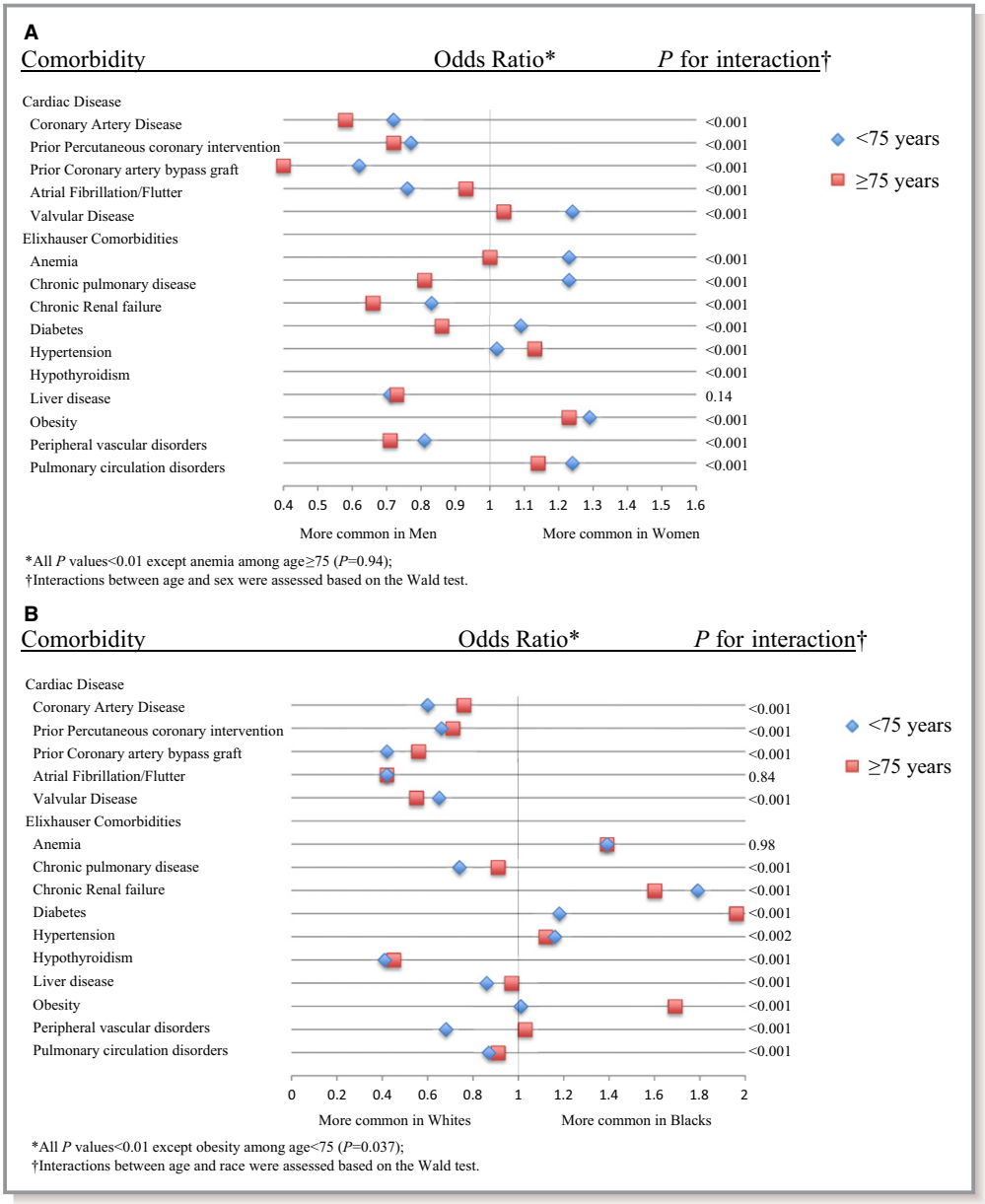

Figure 2. Age-stratified prevalence of comorbidity by sex (A) and race (B).

discharged to home and had a similar length of stay compared with whites.

Prevalence of comorbidity

Whites had a higher mean Elixhauser score compared with blacks (Figure 1B), a finding driven by differences among age younger than 75 years. Scores were similar between whites and blacks among those aged 75 years and older. Accordingly, there was a higher prevalence of most comorbidities in whites compared with blacks (Figure 2B). These included CAD, a history of PCI and CABG, and chronic pulmonary disease, which exhibited more prominent differences among those younger than 75 years; and valvular disease, AF, hypothyroidism, and pulmonary circulation disorders, which exhibited similar differences in patients in both age strata. On the other hand, hypertension, CRF, anemia, and diabetes were more common among blacks. Race differences in hypertension and CRF were more prominent among those younger than 75 years, and the difference in diabetes was more prominent among those 75 years and older. Some comorbidities exhibited unique age-dependent prevalence patterns with respect to race: liver disease and peripheral vascular disorders were more common in whites younger than 75 years, and obesity was more common in blacks 75 years and older.

Table 2. Adjusted In-Hospital Mortality By Sex (Women Versus Men; Men as Reference)

Age Strata	Age-Stratified ModelOdds Ratio (95% CI)	Model 1*Odds Ratio (95% CI)	Model 2†Odds Ratio (95% CI)
18–74 y	0.94 (0.91–0.96)‡	0.94 (0.92–0.97)‡	0.99 (0.96–1.02)
≥75 y	0.81 (0.80–0.83)‡	0.83 (0.81–0.84)‡	0.93 (0.91–0.95)‡
	P for interaction <0.001	*P* for interaction <0.001	*P* for interaction=0.015

*Adjusted for demographics and hospital characteristics.
†Adjusted for model 1 covariates plus the Elixhauser comorbidity summary score.
‡*P*<0.01.

In-hospital mortality

Blacks experienced lower in-hospital mortality compared with whites (3.0% versus 4.6%, *P*<0.001). When stratified by age alone, blacks had lower in-hospital mortality among those younger than 75 years as well as those 75 years and older (Table 4). In a logistic regression model that included demographics and hospital characteristics (model 1), blacks in both age strata remained less likely to die. Additional adjustment for the Elixhauser score (model 2) revealed similar results. A sensitivity analysis using an age cutoff of 65 years revealed similar findings (Table S3).

In multivariable regression analysis, the risk of in-hospital mortality was increased by over 50% among both whites and blacks older than 75 years (Table 5). With regard to comorbidities, pulmonary circulation disorders, liver disease, and CRF were the strongest predictors of in-hospital mortality in both race subgroups. Anemia, diabetes mellitus, hypertension, CAD, and a history of revascularization were inversely associated with in-hospital mortality in both subgroups. Notably, the presence of AF was associated with a 20% increase in mortality among blacks but a minimal albeit statistically significant increase in mortality among whites (*P* for interaction <0.001).

Discussion

There are several important findings in this study, which represents the largest sex- and race-related subgroup analysis of HFpEF to date. First, compared with women, men with HFpEF were younger with a higher burden of comorbidities. Second, men experienced comparable rates of risk-adjusted in-hospital mortality compared with women. Third, blacks with HFpEF were younger than whites, with more prevalent hypertension, CRF, anemia, and diabetes mellitus. Fourth, blacks had lower in-hospital mortality compared with whites, even after adjusting for age and comorbidity. Finally, atrial fibrillation was an important correlate for in-hospital mortality among women and blacks, but not men or whites.

This cohort strongly paralleled the demographic and clinical characteristics of HFpEF observed in more modestly

Table 3. Correlates of In-Hospital Mortality Among Men and Women

Variable	Men Odds Ratio (95% CI)	Women Odds Ratio (95% CI)	*P* for Interaction
Age ≥75 y	1.68 (1.63–1.72)	1.54 (1.50–1.58)	<0.001
White race	1.31 (1.27–1.35)	1.22 (1.19–1.25)	<0.001
Pulmonary circulation disorders	2.04 (1.96–2.12)	1.86 (1.80–1.91)	<0.001
Liver disease	1.59 (1.50–1.68)	1.56 (1.47–1.65)	0.46
Chronic renal failure	1.24 (1.21–1.27)	1.39 (1.36–1.41)	<0.001
Chronic pulmonary disease	1.06 (1.03–1.08)	1.06 (1.04–1.08)	0.76
Atrial fibrillation/flutter	1.00 (0.98–1.03)*	1.09 (1.07–1.11)	<0.001
Anemia	0.91 (0.89–0.94)	0.86 (0.84–0.88)	0.007
Diabetes mellitus	0.75 (0.74–0.77)	0.80 (0.78–0.81)	<0.001
Hypertension	0.67 (0.66–0.69)	0.65 (0.64–0.66)	0.43
Coronary artery disease	0.83 (0.81–0.85)	0.83 (0.81–0.85)	0.82
History of revascularization	0.67 (0.64–0.69)	0.68 (0.65–0.70)	0.73

*All *P* values <0.005 except atrial fibrillation/flutter in men (*P*=0.72).

Table 4. Adjusted In-Hospital Mortality By Race (Blacks Versus Whites; Whites as Reference)

Age Strata	Age-Stratified ModelOdds Ratio (95% CI)	Model 1*Odds Ratio (95% CI)	Model 2†Odds Ratio (95% CI)
18–74 y	0.69 (0.66–0.71)‡	0.68 (0.65–0.70)‡	0.69 (0.67–0.72)‡
≥75 y	0.79 (0.76–0.81)‡	0.77 (0.75–0.80)‡	0.76 (0.73–0.78)‡
	P for interaction <0.001	*P* for interaction=0.001	*P* for interaction=0.001

*Adjusted for demographics and hospital characteristics.
†Adjusted for model 1 covariates plus the Elixhauser comorbidity summary score.
‡*P*<0.01.

sized cohorts of HFpEF[21–26]—patients were predominantly elderly, women, and white, with a high burden of comorbidity, which most commonly included hypertension, CAD, atrial fibrillation, diabetes mellitus, and chronic lung disease.

Men and Women With HFpEF

Despite younger age, men with HFpEF had a higher mean Elixhauser score, a weighted score associated with hospital mortality.[17] This finding was more prominent among patients 75 years and older compared with those in the younger strata, paralleling differences of age-adjusted in-hospital mortality rates where men aged 75 years and older died almost 25% more often than women in the same age group. After adjusting for the Elixhauser score, sex-related differences in mortality were attenuated, extending observations from smaller studies derived from the Get With the Guidelines—Heart Failure[27] and Acute Decompensated Heart Failure National Registry Emergency Module (ADHERE-EM) databases,[6] that in-hospital mortality is comparable between sexes. Given its observed influence on in-hospital mortality, our study builds on prior data by demonstrating the potential utility of the Elixhauser score in risk-stratifying hospitalized patients with HFpEF, further highlighting the importance of comorbidity on outcomes within the HFpEF population.[28–30]

To our knowledge, our study is the first to report on age-stratified sex differences of noncardiac comorbidity patterns in HFpEF. These findings reveal differences in comorbidity profile that may offer insight into differing pathophysiologic mechanisms of HFpEF that exist between men and women. The observation that chronic pulmonary disease and diabetes mellitus were more common in women among younger patients and more common in men among older patients suggests that the influence of comorbidity is complicated and is likely modulated by several other factors including age. Future studies should therefore build on the characterization of sex-based comorbidity profiles provided here, and further examine their potential impact on the incidence, natural history, and outcomes of HFpEF.

Table 5. Correlates of In-Hospital Mortality Among Whites and Blacks

Variable	White Odds Ratio (95% CI)	Black Odds Ratio (95% CI)	*P* for Interaction
Age ≥75 y	1.53 (1.50–1.57)	1.61 (1.53–1.69)	<0.001
Women	0.85 (0.84–0.86)	0.91 (0.87–0.96)	<0.001
Pulmonary circulation disorders	1.82 (1.77–1.87)	2.83 (2.65–3.03)	<0.001
Liver disease	1.42 (1.35–1.49)	1.94 (1.75–2.16)	<0.001
Chronic renal failure	1.35 (1.32–1.37)	1.37 (1.31–1.44)	0.26
Chronic pulmonary disease	1.06 (1.04–1.08)	0.97 (0.93–1.02)*	<0.001
Atrial fibrillation/flutter	1.03 (1.01–1.04)	1.21 (1.15–1.27)	<0.001
Anemia	0.90 (0.89–0.92)	0.76 (0.72–0.80)	<0.001
Diabetes mellitus	0.79 (0.78–0.80)	0.72 (0.68–0.75)	<0.001
Hypertension	0.64 (0.63–0.65)	0.66 (0.63–0.69)	0.14
Coronary artery disease	0.83 (0.82–0.85)	0.81 (0.76–0.85)	0.05
History of revascularization	0.68 (0.66–0.70)	0.59 (0.54–0.66)	<0.001

*All *P* values <0.005 except chronic pulmonary disease in blacks (*P*=0.28).

Whites and Blacks With HFpEF

Our study revealed that blacks with HFpEF were on average about 10 years younger than whites with HFpEF, consistent with the observation that blacks with HFpEF present at younger ages.[7] Indeed, 65% of blacks in our study were younger than 75 years, including about 40% who were younger than 65 years. Although blacks had a lower Elixhauser score and lower prevalence of most comorbidities compared with whites, hypertension, diabetes mellitus, anemia, and CRF were more frequent among blacks in our study. This is congruent with prior literature[7,31–33] and may offer an explanation for the age discrepancy observed between races. Higher rates of hypertension at younger ages implicate hypertensive remodeling as one potential reason that blacks with HFpEF present at a younger age.[32] Given the relationship between inflammation and the pathophysiology of HFpEF, higher rates of diabetes mellitus, anemia, and CRF[10,34] may also explain this increased vulnerability to developing HFpEF at a younger age, as these diseases expose blacks to higher cumulative levels of systemic inflammation compared with whites of a similar age.

Consistent with recently published data from the Cardiovascular Research Network,[8] blacks experienced lower in-hospital mortality compared with whites in our national cohort. Although it has been suggested that this finding may be related to the observation that blacks with HFpEF present at younger ages, blacks continued to demonstrate lower in-hospital mortality compared with whites even after controlling for age. Higher rates of chronic diseases at a younger age have also been proposed as an explanation for lower in-hospital mortality among blacks. It has been posited that by virtue of having chronic diseases such as hypertension and CRF at younger ages, blacks experience more frequent contact with healthcare providers who might then recognize decompensated HF earlier and/or initiate disease-modifying therapies, leading to less severe HF upon presentation to the hospital.[35] Our study does not support this notion, as in-hospital mortality remained lower for blacks even after adjusting for comorbidity. While this study reinforces an important race-related difference, an explanation for this finding remains unclear and requires further investigation.

Correlates of In-Hospital Mortality

Multivariable regression analysis performed within each sex and race subgroup revealed similar correlates of in-hospital mortality. Pulmonary circulation disorders, liver disease, and CRF were the strongest correlates of in-hospital mortality for each subgroup, highlighting their importance in HFpEF regardless of sex or race. Some comorbidities emerged as particularly impactful on in-hospital mortality among certain subgroups. For example, pulmonary circulation disorders, which include pulmonary hypertension, was associated with an almost 3-fold increase in mortality among blacks. Whether this relates to recognized deficiencies in nitric oxide synthase among blacks[36] is unknown and underscores the importance of linking population-based study findings such as these to genotypic and phenotypic variations in sex and race subgroups.

Several studies to date have demonstrated an association between atrial fibrillation and mortality in HFpEF.[37–39] By examining sex and race subgroups, our study builds on this prior literature by demonstrating prevalent AF to be a correlate of in-hospital mortality only among women and blacks. This confirms sex differences previously observed in the I-PRESERVE registry,[5] and for the first time identifies race-related differences with regard to outcomes in patients with concurrent HFpEF and atrial fibrillation. Sex- and race-related differences in left ventricular adaptation to stressors have previously been demonstrated, as women[40–42] and blacks[43–45] have a predilection for developing concentric left ventricular hypertrophy and greater diastolic dysfunction compared with men and whites. Whether these differences contribute to an increased vulnerability to atrial fibrillation among women and blacks is not well understood and warrants investigation.

Conversely, these data demonstrate that CAD and a history of revascularization are associated with improved survival. Although data regarding the prognostic implications of CAD in HFpEF are conflicting,[26,46–48] contemporary data suggest that revascularization in patients with HFpEF and CAD is associated with improved outcomes,[48] an observation noted in all subgroups analyzed in our study. Thus, this study further supports the need to rigorously investigate the potential benefit of aggressive CAD screening with the intent of revascularization to improve outcomes.

Study Limitations

There are important limitations to our study. First, this was a retrospective cohort derived from a database that approximated the national distribution of key hospital characteristics. Cases analyzed represented deidentified hospitalizations, which may have yielded overrepresentation of certain factors in the cases of repeat hospitalizations. Despite this limitation, the NIS sampling design has been validated[12,13] and is commonly used to examine patterns in national healthcare in a range of subpopulations including those with HFpEF.[15] Second, echocardiographic data were not available to confirm the diagnosis of HFpEF. Moreover, the proportion of HFpEF that comprised important subtypes of HFpEF such as recovered ejection fraction and borderline ejection fraction could not be identified. Prior work on HFpEF from the NIS[15] demonstrated patient characteristics and outcomes to be similar to registries and community-based studies, supporting

its validity for examining this population. With that said, this does not eliminate the potential uncertainty regarding the diagnosis of HFpEF, as identifying patients with HFpEF, especially in the setting of comorbidities, which can mimic HF symptoms, has been notoriously challenging even in clinical trials.[49] Third, about 10% of the cohort were excluded from analysis because of missing data, predominantly related to race. While an analysis of these excluded cases demonstrated similar findings with regard to age, sex, primary payer status, and mean Elixhauser score to the remainder of the cohort, the potential for a systematic bias related to missing data from hospitals with particular characteristics (geographic location, size) cannot be excluded. Finally, unmeasured variables including coronary anatomy and medications may have had an impact on outcomes. Despite lacking this granularity, large administrative databases have been cited as useful resources with potential to identify sources of heterogeneity in common diseases,[50] which was the primary aim of this study.

Conclusions

This contemporary nationally representative cohort of HFpEF revealed important sex- and race-related differences in demographics, comorbidity profile, and in-hospital mortality. These findings reinforce the notion that sex and race contribute to the phenotypic heterogeneity of HFpEF. Tailoring therapeutic interventions based on these sex- and race-related differences may offer a viable strategy to improve outcomes in HFpEF.

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SUPPLEMENTAL MATERIAL

Table S1. Baseline Characteristics of Excluded Cases Due to Missing Data

Variable	Included Cases (n=1,889,608)	Excluded Cases (n=213,248)	p-value
Mean Age (± SD, years)	75.8 ± 12.9	75.8 ± 12.8	0.27
Age (%)			
18-74	39.3	39.5	0.04
≥ 75	60.7	60.5	
Sex (%)			
Female	64.0	65.2	<0.001
Race (%)			
White	75.2	84.3	0.127
Black	14.6	7.8	
Other	10.2	8.0	
Primary Payer (%)			
Medicare	81.8	80.1	<0.001
Medicaid	5.2	5.2	
Private including HMO	9.8	11.9	
Self pay	1.8	1.4	
Elixhauser Summary Score	8.0 ± 7.2	7.8 ± 7.0	<0.001

Table S2. Sensitivity Analysis of Adjusted In-Hospital Mortality By Sex (Women vs. Men; Men as reference)

Age Strata	Age-Stratified Model Odds Ratio (95% CI)	Model 1† Odds Ratio (95% CI)	Model 2‡ Odds Ratio (95% CI)
18-64 years	0.98 (0.94-1.02)	0.99 (0.95-1.03)	1.02 (0.97-1.06)
≥65 years	0.86 (0.84-0.87)*	0.87 (0.85-0.88)*	0.96 (0.92-0.99)
	p-for-interaction<0.001	p-for-interaction< 0.001	p-for-interaction= 0.001

*p-value<0.01

† Adjusted for demographics and hospital characteristics

‡ Adjusted for Model 1 covariates plus the Elixhauser comorbidity summary score

Table S3. Sensitivity Analysis of Adjusted In-Hospital Mortality By Race (Blacks vs. Whites; Whites as reference)

Age Strata	Age-Stratified Model Odds Ratio (95% CI)	Model 1† Odds Ratio (95% CI)	Model 2‡ Odds Ratio (95% CI)
18-64 years	0.72 (0.68-0.75)*	0.69 (0.65-0.72)*	0.71 (0.68-0.75)*
≥65 years	0.73 (0.71-0.75)*	0.72 (0.70-0.74)*	0.70 (0.69-0.72)*
	p-for-interaction=0.53	p-for-interaction=0.63	p-for-interaction=0.22

*p-value<0.01

† Adjusted for demographics and hospital characteristics

‡ Adjusted for Model 1 covariates plus the Elixhauser comorbidity summary score