

Sex Differences in the Management and Outcomes of Heart Failure with Preserved Ejection Fraction in Patients Presenting to the Emergency Department with Acute Heart Failure

Short title: Zsilinszka et al.: Sex Differences in HFpEF

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Abstract

Heart failure (HF) with preserved ejection fraction (HFpEF) represents 50% of the HF population. Although more common in women than men, there are limited data characterizing sex differences in the management and outcomes of HFpEF patients that present acutely to the emergency department (ED). Using data from the ADHERE-EM registry linked to Medicare claims, we conducted a retrospective analysis of patients presenting to the ED with acute HF. We identified patients with HFpEF (EF \geq 40%) and stratified them by sex to compare baseline characteristics, ED therapies, hospital length of stay (LOS), in-hospital mortality, and post-discharge outcomes. We compared outcomes using Cox proportional hazards models and linear mixed models. Of 4161 patients with HFpEF, 2808 (67%) were women, and were typically older and more likely to have hypertension, but less likely to have diabetes or a smoking history (all $p < 0.01$). Women were more likely than men to present to the ED with a systolic blood pressure >140 mmHg (62.5% vs. 56.4%, $p=0.0001$), and also had a greater presenting EF. There were no sex differences in ED therapies, adjusted 30- and 180-day all-cause mortality, in-hospital mortality, or 30- and 180-day hospital readmissions. After adjusting for covariates, women had a longer hospital LOS (0.40 days; 95% CI 0.10, 0.70; $p=0.008$). Women with HFpEF presenting to the ED were more likely to have elevated systolic blood pressure, but overall ED management strategies were similar to men. We observed adjusted differences in hospital LOS, but no differences in 30- and 180-day outcomes.

Key words: heart failure with preserved ejection fraction; sex differences in management; sex differences in outcomes

Heart failure (HF) is a major and increasing public health problem worldwide. HF affects more than 5 million Americans, leads to more than 1 million hospitalizations, and accounts for more than \$30 billion in annual medical costs.¹ HF with preserved ejection fraction (HFpEF) represents approximately 50% of the HF population, and has adverse event rates similar to HF with reduced ejection fraction.² The emergency department (ED) is the primary setting where initial acute HF management takes place; more than 80% of acute HF patients who present to the ED are admitted.³ Recent studies highlight differences in baseline characteristics and initial management strategies for men versus women presenting to the ED with all types of HF, including HFpEF and HF with reduced ejection fraction,⁴⁻⁶ but it is unknown whether these differences hold true in the HFpEF population, and whether there are sex differences in short- and long-term outcomes in HFpEF patients following acute HF ED presentation.

To address these issues, we used data from the Acute Decompensated HF National Registry Emergency Module (ADHERE-EM) database linked to Medicare claims to evaluate sex differences in patients with HFpEF that presented to the ED with acute HF, with regard to presentation, treatments, and outcomes.

Methods

The ADHERE-EM registry enrolled patients that presented to the ED with acute HF and collected details about presenting ED symptoms, ED management, patient disposition, and inpatient course. Data for the ADHERE-EM registry were collected between January 2004 and September 2005 at 83 hospitals in the United States. Additional details about the ADHERE-EM registries have been described previously.^{4,7}

We linked Medicare claims with data from ADHERE-EM, using methods previously described.⁸ Medicare claims were obtained for each patient in the study in order to determine readmission and mortality rates. The Medicare inpatient file includes institutional claims submitted for facility costs covered under Medicare Part A, as well as beneficiary, physician, hospital identifiers, admission and discharge dates, and diagnosis and procedure codes. The denominator files include beneficiary identifiers, date of birth, sex, race/ethnicity, date of death, and information about program eligibility and enrollment. Claims for Medicare beneficiaries enrolled in a Medicare-managed care plan were not included.

From the linked data set, we identified patients who were ≥ 65 years with an ADHERE-EM record linked to Medicare inpatient claims; we included in our cohort patients enrolled in fee-for-service Medicare for at least 6 months prior to the index admission and at least 30 days following index admission or died during that period in order to ensure that patients had stable insurance coverage. The number of patients that lost insurance during this time period was negligible, typically $<1\%$. Further enrollment criteria included patients that had a principal ED admitting diagnosis of HF, and had preserved left ventricular ejection fraction (LVEF $\geq 40\%$). We excluded patients who had missing LVEF data, had a reduced ejection fraction (LVEF $<40\%$), were transferred to another acute care facility or hospice, or were not admitted to the inpatient unit (Figure 1).

HFpEF was defined as LVEF $\geq 40\%$ or qualitatively defined as normal or mildly impaired based on the ADHERE-EM case report form. The primary outcome was 30-day all-cause mortality, defined as 30 days from index presentation to the ED. Secondary outcomes were in-hospital mortality and index hospital length of stay (LOS). Post-discharge outcomes (defined as after the index presentation) included total days alive and out of the hospital at 30 days, 180-day

all-cause mortality, and total days alive and out of the hospital at 180 days. As a sensitivity analysis, we restricted the outcomes to LVEF $\geq 50\%$ for the primary and secondary outcomes.

Demographics, medical history, clinical presentation, laboratory measurements, and procedures are presented, and are stratified by sex. Continuous variables are presented as median (Q1–Q3) and categorical variables are presented as proportions. Differences between the groups were assessed using chi-square tests for categorical variables and Wilcoxon rank sum tests for continuous variables.

The association between all-cause mortality (30-day, 180-day, and in-hospital mortality) was assessed using Cox proportional hazards models, including a robust covariance estimate to account for correlation within sites. Continuous outcomes (days alive and out of hospital, length of stay) were assessed using linear mixed models, including the random effect of site. Multivariable models were adjusted for the covariates measured on presentation to the ED, and that have been shown in the main ADHERE registry to be associated with mortality, as well as those that have been used in previous ADHERE-EM analyses^{9,10}; these covariates are listed in Table 1 and 3.

We used a 2-sided $\alpha = 0.05$ to establish statistical significance and will report 95% confidence intervals. We used SAS version 9.3 (SAS Institute Inc., Cary, NC) for all analyses. The institutional review board of the Duke University Health System approved the study.

Results

A total of 17,614 patients were enrolled in the ADHERE-EM, and 4161 patients were included in the primary analysis cohort. Of these, 2808 (67.5%) were women and 1353 (32.5%) were men. The median age of the overall population was 81.5 years, and men were younger than

women (Table 1). In the overall HFpEF cohort, 70.9% had prior HF, 82.7% hypertension, 43.9% diabetes, and 42.1% had a smoking history. Women were more likely to have hypertension and less likely to have diabetes or a smoking history compared with men (Table 1). Women were also more likely to present with a greater EF than men, more likely to present with a systolic blood pressure >140mmHg, less likely to present with peripheral edema, and had lower median blood urea nitrogen/creatinine and troponin T values at baseline (Table 1). ED management strategies and procedures did not differ significantly by sex (Figures 2 and 3).

At 30 days, cumulative all-cause mortality was 7.1% (n=297). In women, 30-day mortality was 6.4% (n=181) compared to 8.6% (n=116) for men (Table 2). In the unadjusted Cox proportional hazard model, women had a lower 30-day all-cause mortality compared with men (hazard ratio [HR] 0.75; 95% confidence intervals [CI] 0.55–1.00, p=0.05). After adjustment for covariates, there was no difference between men and women (HR: 0.81; 95% CI 0.61–1.06; p=0.13) (Table 3). Total days alive and out of the hospital at 30 days was also similar between men and women (-0.25 days; 95% CI -0.69–0.18; p=0.25) in the adjusted analysis.

In-hospital mortality was 2.7% (n=77) for women and 3.1% (n=42) for men (Table 2). The unadjusted Cox proportional hazard model showed no significant in-hospital mortality differences between the sexes (HR 0.88; 95% CI 0.58–1.32, p=0.53), and there were no significant differences after adjustment for covariates (HR 0.88; 95% CI 0.55–1.40); p=0.59) (Table 3).

Median hospital LOS was 5 days (IQR 3–7) for women and 4 days (IQR 3–7) for men (Table 2). In the unadjusted analysis, hospital LOS was not longer in women compared with men (0.26 days; 95% CI -0.06–0.57; p=0.11). In the adjusted model, hospital LOS was longer in women (0.40 days; 95% CI 0.10–0.70; p=0.008) (Table 3).

All-cause mortality at 180 days was 23.7% (n=666) in women and 24.8% (n=336) in men (Table 2). There were no significant differences between the sexes in either the unadjusted or adjusted analyses for 180-day mortality (Figure 4). Median total days alive and out of the hospital at 180 days was 169 days for women and 170 days for men (Table 2), with no significant differences after adjusting for covariates (Table 3). After the LVEF cutoff was increased to $\geq 50\%$ for sensitivity analysis, there were no significant differences between men vs. women in primary or secondary outcomes.

Discussion

We performed a large, retrospective cohort analysis examining the clinical features and outcomes of HFpEF patients presenting to the ED with AHF. This is one of the largest studies to examine sex differences in ED AHF patients with HFpEF. The number of women with HFpEF outnumbered men 2:1; there were significant differences regarding baseline characteristics, including age and presence of hypertension. Women had a longer hospital LOS after adjustment for covariates. No other differences in post-discharge outcomes were observed.

Knowledge regarding sex-based differences and clinical outcomes in HFpEF patients who present with acute HF to the ED is limited. While post-discharge outcomes and in-hospital mortality was similar between men and women in our study, we did find differences in baseline characteristics, clinical presentation, and length of hospital stay. There are multiple theories as to the pathophysiology behind observed baseline gender differences in HFpEF, the leading of which suggest that

Our study develops the findings of prior chronic HFpEF studies of sex differences by extending these findings to the acute setting. In our study, women were more likely to be older

and have a history of hypertension. However, our study also found that women presented with a higher EF compared with men, suggesting that the higher presenting blood pressure is a function of women tending to have a higher EF, as corroborated by previous studies.¹¹ Women were also less likely to have a history of diabetes and smoking, as well as lower blood urea nitrogen, creatinine, and troponin values. These observations are consistent with those of previous reports.^{12-174,5} Women were less likely than men to present with edema, but were more likely to present with blood pressure >140mmHg. Previous studies have also shown that fewer women than men present with low systolic blood pressures.⁴ While hypertension causes increased chamber stiffness in both sexes, it is persistently higher in women of all ages; these data have both clinical and research implications, as they may inform future trial design.. For example, if a clinical trial excludes patients based on age or presenting blood pressure, then the trial may indirectly reduce the number of women eligible for the study.

Despite differences in presenting characteristics, the treatment patterns for women were largely comparable to men. When hospitalized for HF, women were equally likely to receive diuretics, but less likely to be treated with vasoactive medications and evidence-based therapy compared to men.^{5,18} ED approaches to the management of acute HF, including HFpEF, are important, as previous studies suggest targeted ED management strategies may influence outcomes.¹⁹ A recent study looking at time to early IV HF therapy in ED acute HF patients showed that delays in initiating IV HF therapy was associated with modestly higher risk for in-hospital mortality and longer LOS in older patients.²⁰ A sex-based analysis of the ADHERE registry revealed that women were less likely to receive vasoactive therapy and procedure-oriented therapy.^{5,6} However, in our analysis, we found no sex differences in the administration

of diuretics, vasoactive therapy, vasodilators, or ED procedures (such as dialysis, mechanical ventilation, coronary angiography, catheterization, or coronary bypass) in HFpEF patients.

With the exception of LOS, differential outcomes based on sex were not observed. One of our principal findings related to in-hospital mortality. Earlier studies suggest female sex is associated with a lower mortality risk, but more recent analyses suggest otherwise.²¹⁻²³ A prior study of the overall ADHERE registry showed no sex differences regarding in-hospital mortality rates or hospital length of stay.⁵ Another study investigating risk stratification in women enrolled in the ADHERE-EM registry found no in-hospital mortality differences between men and women.⁴ However, all of these previous studies were derived from populations that included either all types of HF or exclusively HFpEF. After adjusting for baseline differences, we found no mortality difference between groups for in-hospital, 30-day, or 180-day mortality. This suggests sex should not result in differential treatment. We also examined whether there were any sex differences in both 30- and 180-day total days alive and out of the hospital, and found no association with either short- or long-term readmissions. Past studies, such as the Epidemiology, Practice, Outcomes, and Cost of HF study, reported that overall HF readmission rates were high, but not associated with sex, even after adjusting for potential confounders.^{24,25} One previous study looking at sex-related differences in patients hospitalized for acute HF did find a lower all-cause readmission rate in women; however, this study analyzed 1-year readmission rates and included all types of HF.

In our cohort, women had a 1-day longer median hospital LOS than men. After adjustment for covariates, this LOS sex difference persisted. While prior analyses showed that sex was an important determinant of hospital LOS in the broad HF population, our study exclusively examined sex differences in hospital LOS in the HFpEF population.²⁶ Interestingly,

our findings show that women present with a higher systolic blood pressure and a higher EF than men. Given these baseline differences, LOS should have been shorter, as systolic blood pressure has been associated with a shorter LOS, lower hospital mortality, and lower 60- to 90-day mortality.^{2,10,27-30} Nevertheless, in our cohort we noted a longer hospital LOS in women, despite the higher presenting systolic blood pressure. The reason for the difference in LOS is uncertain: social determinants, biologic differences, and undertreatment of hypertension in women likely contribute to these findings. Future studies are needed to investigate the management of hypertension in the ED for this population, in order to determine sex differences in oral HF and oral blood pressure administration, and systolic blood pressure at hospital discharge.

Our analysis has some limitations. First, our analysis is limited by data included in the registry, as well as incomplete and missing data in some circumstances; additionally, the dataset did not include the timing of when the echocardiography was performed for EF assessment, and did not include information on inpatient medication strategies, both of which could affect the validity of our results. Second, our population was limited to patients enrolled in ADHERE-EM from 2000–2007 who were ≥ 65 years old and could be linked to Medicare claims data, which may limit the generalizability of the study. Third, patients presenting to the ED, but directly discharged from the ED, were not included in this study. Finally, although we adjusted for a number of covariates, there is the possibility that unmeasured confounders remain unaccounted for in our analysis.

In summary, women with AHF who present to the ED and have a preserved EF differ from men by both baseline characteristics and clinical presentation. However, no differences in ED treatment were observed. Women had similar adjusted mortality and readmission rates compared to men, but longer hospital LOS. The observed sex differences in hospital LOS and

ED presentation imply clinical and phenotypic differences between men and women with HFpEF. Future studies investigating differences in sex-specific management in the ED for AHF and a preserved EF may lead to differences in hospital LOS.

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Figure Legends

Figure 1. Study population derivation

This figure displays the study population, from the initial cohort, through exclusions, to the final study cohort.

ADHERE-EM = Acute Decompensated Heart Failure National Registry Emergency Module;

CMS = Centers for Medicare & Medicaid; LVEF = left ventricular ejection fraction

Figure 2. Procedures received during or following ED care, according to sex

This figure displays the procedures received during or post-ED care, according to sex.

*These procedures were performed following ED care

PTCA = percutaneous transluminal coronary angioplasty; PCA/LHC = primary coronary angioplasty/left heart catheterization; CABG = coronary artery bypass grafting

Figure 3. EMS and ED care received, according to sex

This figure displays the type of care that males and females received by EMS and in the ED (IV vasoactives include: dobutamine, dopamine; IV vasodilators include: nesiritide, milrinone, nitroglycerin, nitroprusside)

EMS = emergency medical services; IV = intravenous

Figure 4. Kaplan-Meier cumulative incidence curve of 180-day mortality, according to sex

This figure displays the Kaplan-Meier cumulative incidence of 180-day mortality of males and females.

Fig. 1

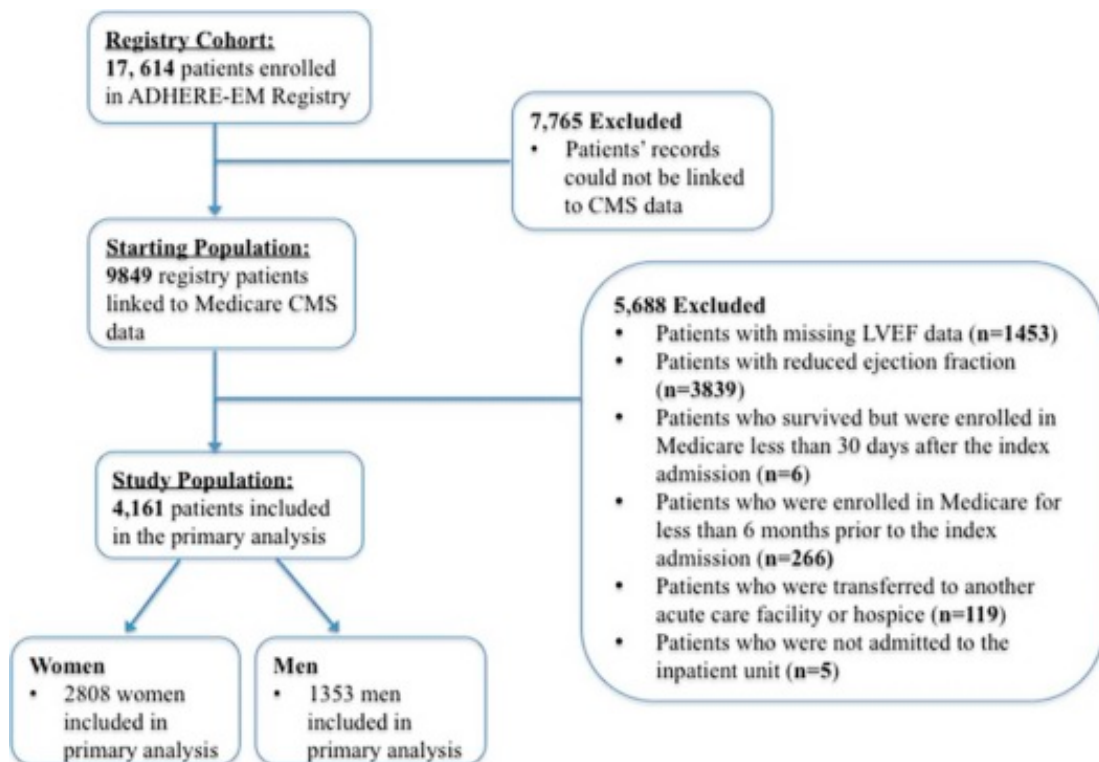


Fig. 2

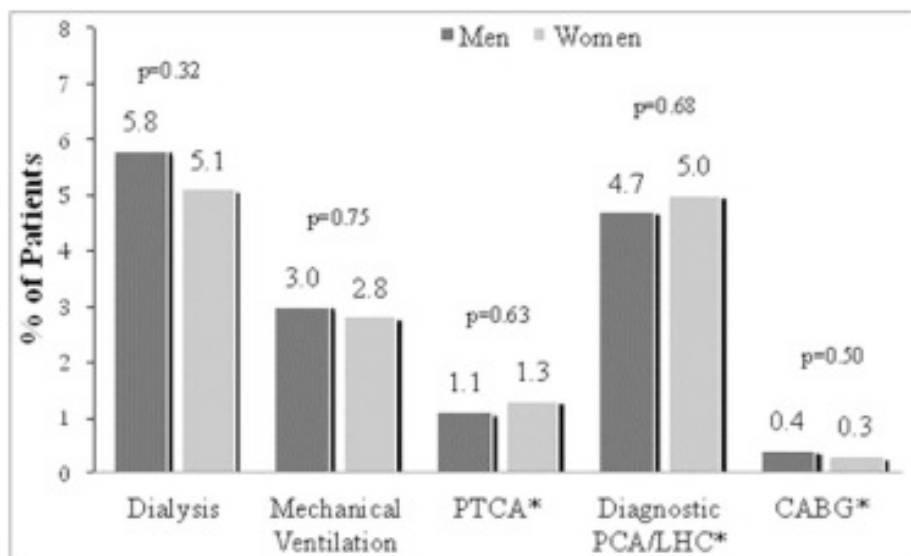


Fig. 3

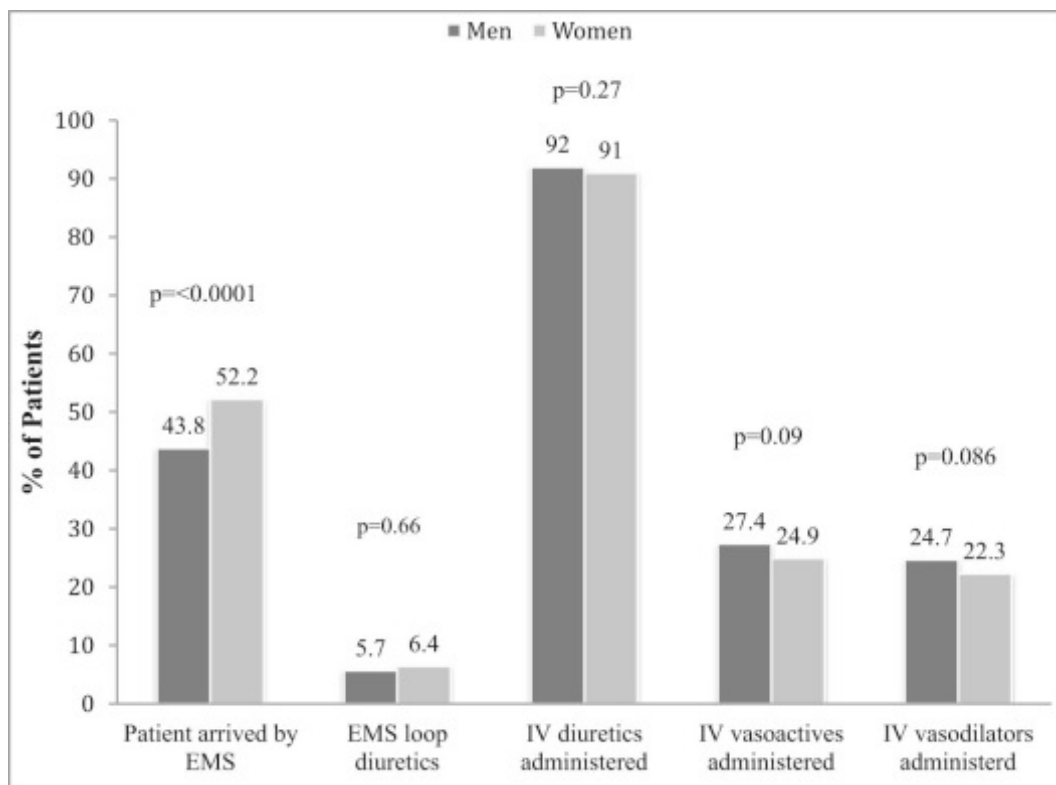


Fig. 4

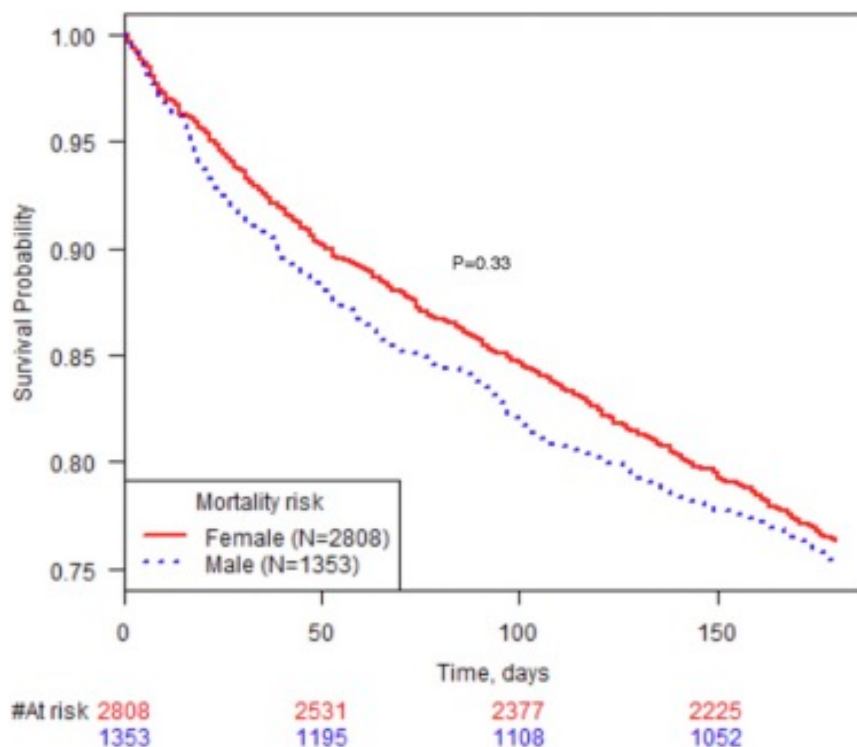


Table 1. Baseline characteristics

Demographics	Female (n=2808)	Men (n=1353)	p-value
Age, years*	82.4 (76.0-87.7)	79.9 (73.8-84.9)	<0.0001
Race			
White	2297 (81.8)	1113 (82.3)	0.58
African-American	311 (11.1)	137 (10.1)	
Other	200 (7.1)	103 (7.6)	
Comorbidities			
Prior HF	1989 (70.8)	961 (71.0)	0.90
LVEF % (N=3791)	55 (50.0-60.0)	50 (45.0-57.0)	<0.001
Atrial fibrillation	1157 (41.2)	555 (41.0)	0.91
Hypertension	2366 (84.3)	1074 (79.4)	<0.0001
Diabetes	1175 (41.8)	650 (48.0)	0.0002
COPD/asthma	943 (33.6)	491 (36.3)	0.09
Smoking (N=3858)	935 (36.1)	815 (64.2)	<0.0001
Clinical presentation			
Dyspnea	2578 (91.8)	1255 (92.8)	0.29
Edema	1804 (64.3)	932 (68.9)	0.003
Rales	1828 (65.1)	879 (65.0)	0.93
JVP	504 (18.0)	244 (18.0)	0.95
SBP, mmHg (N=4152)	150 (130-173)	145 (125-168)	<0.0001
SBP >140 mmHg	1751 (62.5)	762 (56.3)	0.0001
SBP <115 mmHg	329 (11.8)	195 (14.4)	0.02
Oxygen saturation, % (N=4072)	95 (91-98)	95 (91-97)	0.50
Laboratory values			
BNP, pg/mL (N=3011)	661 (372-1180)	632 (352-1130)	0.16
BUN, mg/dL (N=4147)	24 (17-35)	26 (19-39)	<0.0001
Creatinine, mg/dL (N=4148)	1.2 (0.9-1.6)	1.5 (1.1-2.0)	<0.0001
Troponin I, ug/L (N=2367)	0.05 (0.03-0.10)	0.05 (0.04-0.10)	0.04
Troponin T, ug/L (N=531)	0.02 (0.01-0.06)	0.04 (0.02-0.07)	0.0002

*Cells contain median (interquartile range [IQR]) or n (%).

BNP = blood natriuretic peptide; BUN = blood urea nitrogen; COPD = chronic obstructive pulmonary disease; HF = heart failure; JVP = jugular venous pressure; LVEF = left ventricular ejection fraction; SBP = systolic blood pressure

All variables adjusted for: age, dyspnea at rest, edema, rales, elevated jugular venous pressure, heart rate, systolic blood pressure, oxygen saturation, congestion on X-ray, blood urea nitrogen, troponin I or T, brain natriuretic peptide, creatinine, history of hypertension, history of smoking, history of diabetes, history of atrial fibrillation, history of chronic obstructive pulmonary disease, prior history of HF, IV diuretics given, time to earliest IV diuretics, IV vasoactives/vasodilators given, time to earliest IV vasoactives/vasodilators, invasive procedures performed (e.g., dialysis, mechanical ventilation, coronary artery bypass graft, catheterization, percutaneous transluminal coronary angioplasty), arrival by EMS, and loop diuretics, nitroglycerine, or morphine given in EMS.

Table 2. Observed outcomes according to sex

Outcome	Female (n=2808)	Male (n=1353)
30-day all-cause mortality	181 (6.4%)	116 (8.6%)
In-hospital mortality	77 (2.7%)	42 (3.1%)
Length of stay, days	5 (3-7)	4 (3-7)
Total days alive and out of hospital at 30 days	25 (21-27)	25 (21-27)
180-day all-cause mortality	666 (23.7%)	336 (24.8%)
Total days alive and out of hospital at 180 days	169 (148-175)	170 (143-175)

Cells contain n (%) or median (interquartile range)

Table 3. Association of outcomes with sex; unadjusted and adjusted

Outcome	Unadjusted Results		Adjusted [‡] Results	
	HR* (95% CI) or Beta [†] (95% CI)	p- value	HR* (95% CI) or Beta [†] (95% CI)	p- value
30-day all-cause mortality	0.75 (0.55, 1.00)	0.05	0.81 (0.61, 1.06)	0.13
In-hospital mortality	0.88 (0.58, 1.32)	0.53	0.88 (0.55, 1.40)	0.59
Length of stay, days	0.26 (-0.06, 0.57)	0.11	0.40 (0.10, 0.70)	0.008
Total days alive and out of the hospital at 30 days	0.03 (-0.41, 0.47)	0.90	-0.25 (-0.69, 0.18)	0.25
180-day all-cause mortality	0.94 (0.79, 1.12)	0.46	0.96 (0.77, 1.20)	0.74
Total days alive and out of the hospital at 180 days	3.11 (-1.45, 7.66)	0.18	0.53 (-3.05, 4.11)	0.77

*Hazard ratio is for females relative to males.

[†]Beta represents the difference in outcome among females relative to males.

[‡]All variables adjusted for: age, dyspnea at rest, edema, rales, elevated jugular venous pressure, heart rate, systolic blood pressure, oxygen saturation, congestion on X-ray, blood urea nitrogen, troponin I or T, brain natriuretic peptide, creatinine, history of hypertension, history of smoking, history of diabetes, history of atrial fibrillation, history of chronic obstructive pulmonary disease, prior history of HF, IV diuretics given, time to earliest IV diuretics, IV vasoactives/vasodilators given, time to earliest IV vasoactives/vasodilators, invasive procedures performed (e.g., dialysis, mechanical ventilation, coronary artery bypass graft, catheterization, percutaneous transluminal coronary angioplasty), arrival by EMS, and loop diuretics, nitroglycerine, or morphine given in EMS.

CI = confidence interval; EMS = emergency medical services; HR = hazard ratio; IV = intravenous; All other abbreviations can be found in Table 1.