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Sex Differences in long-term outcomes following acute heart failure hospitalization: Findings from the Get with The Guidelines - Heart Failure Registry

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Abstract

Background and Aims: Sex differences in long-term outcomes following hospitalization for heart failure (HF) across ejection fraction (EF) subtypes are not well described. In this study, we evaluated the risk of mortality and re-hospitalization among males and females across the spectrum of EF over 5 years of follow-up following an index HF hospitalization event.

Methods: Patients hospitalized with HF between 1/1/2006 – 12/31/2014 from the AHA's GWTG-HF registry with available 5-year follow-up using Medicare Part A claims data were included. The association between sex and risk of mortality and readmission over a 5-year follow-up period for each HF subtype (HFrEF [EF≤ 40%], HFmrEF [EF 41 to 49%], and HFpEF[EF > 50%]) was assessed using adjusted Cox models. The effect modification by the HF subtype for the association between sex and outcomes was assessed by including multiplicative interaction terms in the models.

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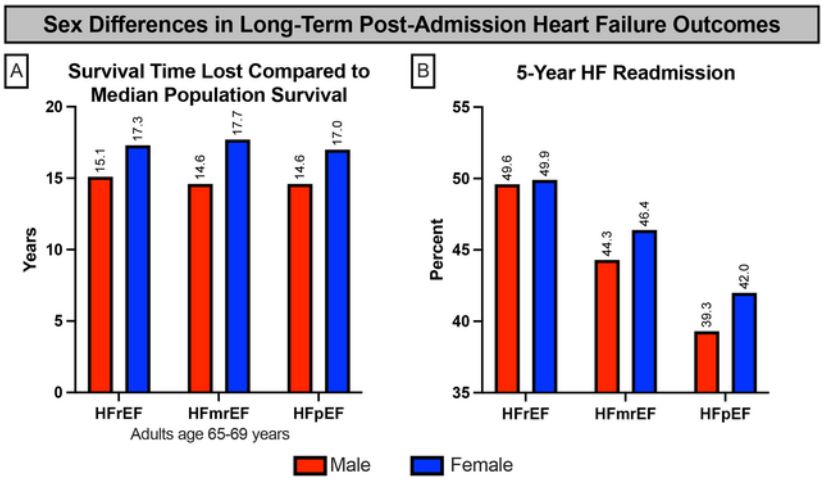
Results: 155,670 patients (81y, 53.4% females) were included. Over 5-years follow-up, males and females had comparably poor survival post-discharge; however, females (vs. males) had greater years of survival lost to HF compared with the median age- and sex-matched U.S. population (HFpEF: 17.0y vs. 14.6y; HFmrEF: 17.3y vs. 15.1y; HFrEF: 17.7y vs. 14.6y). In adjusted analysis, females (vs. males) had a lower risk of 5-year mortality (aHR 0.89, 95% CI 0.87–0.90, p<0.001), and the risk difference was most pronounced among patients with HFrEF (aHR 0.87, 95% CI 0.85–0.90; $P_{interaction}$[sex*HF subtype]=0.04). Females (vs. males) had a higher adjusted risk of HF readmission over 5-year follow-up (aHR 1.06, 95% CI 1.04–1.08, p<0.001, with the risk difference most pronounced among patients with HFpEF (aHR 1.11, 95% CI 1.07–1.14; $P_{interaction}$[sex*HF subtype]<0.01).

Conclusion: While females (vs. males) had lower adjusted mortality, females experienced a significantly greater loss in survival time than the median age- and sex-matched U.S. population and had a greater risk of rehospitalization over 5 years following HF hospitalization.

Graphical Abstract



(A)Females with Heart Failure have excess life years lost after index heart failure hospitalization than males when compared with the median sex- and age-specific United States life expectancy and (B) females have higher risk for rehospitalization for heart failure compared to males.

Survival time (Panel A) following HF hospitalization for adults aged 65–69 years.

Abbreviations: HF – heart failure, HFrEF – heart failure with reduced ejection fraction, HFmrEF – heart failure with mildly reduced ejection fraction, HFpEF – heart failure with preserved ejection fraction.

Keywords

Heart Failure; Outcomes; Sex Differences; Ejection Fraction

Introduction

Sex differences in heart failure (HF) characteristics, risk factors, and phenotypes have been well described.[1] Female patients with HF tend to be older and are more likely to have HF with preserved ejection fraction (HFpEF), while male patients are more likely to have reduced ejection fraction and HF of ischemic etiology.[2] Several traditional cardiovascular risk factors are more strongly associated with the risk of HF in females than males.[3,4] Specifically, obesity is associated with HFpEF versus HF with reduced ejection fraction (HFrEF), and this association is more prominent among females vs males.[5] Females (vs males), on average, have lower cardiorespiratory fitness levels and lower lean body mass and may be more predisposed to lower cardiovascular exercise reserve and accelerated declines in exercise capacity with the development of HFpEF at older ages.[6,7] Moreover, risk factors related to disorders of pregnancy, hormonal changes, and autoimmune conditions have also been identified to play an important role in the sex differences in HF epidemiology.[8,9] In addition to the sex differences in the epidemiology of HF, females (vs. males) with prevalent HF have greater symptom burden and worse quality of life and are less likely to receive evidence-based therapies for HF.[10]

Despite the potential impact of sex on HF, investigations into sex differences in long-term outcomes following hospitalization for acute decompensated HF in contemporary cohorts are limited. Most existing evidence on sex differences in HF outcomes comes from secondary analysis of RCTs and has been limited by the under-representation of women, lack of long-term follow-up, and lack of data across the ejection fraction spectrum.[11–14] Accordingly, we aim to assess the risk of long-term mortality and re-hospitalization among hospitalized male and female patients age 65 years of age or older with HF across the spectrum of ejection fraction in the Get With The Guidelines-HF registry.

Methods

Study Cohort

The current study utilized the American Heart Association's Get With The Guidelines®-Heart Failure registry (GWTG-HF), which has been described previously.[15] GWTG-HF is a performance improvement-based registry consisting of patients hospitalized for HF across participating centers. Trained study personnel at each center collect and document individual patient data, including demographics, vital signs and laboratory results, clinical comorbidities, HF treatment information, and imaging findings. Limited data is stored and aggregated centrally, and the Duke Clinical Research Institute serves as the data analysis center. IQVIA (Parsippany, NJ) serves as the data collection and coordination center. Patients from the GWTG-HF registry were linked to CMS Medicare Part A inpatient claims files as described previously.[16] All adults in the United States with age 65 years or older or with certain chronic illnesses or disability such as end-stage kidney disease are eligible for Medicare. Briefly, Medicare data consisted of inpatient files containing institutional claims for facility services covered under Medicare Part A, and the Medicare denominator files include date of birth, sex, date of death, and program eligibility, and patients were linked to their Medicare claims without using direct identifiers.[16]

The present study included 183,404 patients with non-missing sex and age ≥ 65 years admitted with a primary diagnosis of HF across 444 GWTG-HF participating centers between January 1, 2006, and December 31, 2014 (Supplemental Figure 1). Patients were excluded at centers with >25% missing data on the medical history panel, missing quantitative ejection fraction (n = 17,371), and discharge to hospice care/palliative care (n = 7,326). Patients who were transferred from another hospital were excluded (n = 3,037). Finally, among patients with multiple hospitalizations, only the index hospitalization was included.

Exposure variables of interest: Sex and HF Subtypes

The primary exposure variable was patient sex (male vs. female). The patient population was stratified by subtype of HF by EF: HF with reduced EF (HFrEF) with EF ≤ 40%, HF with mildly reduced EF (HFmrEF) with EF 41–49%, and HF with preserved EF (HFpEF) with EF ≥ 50%. EF was ascertained during the index admission or, if not available, using the most recent EF recorded.

Outcomes of interest: 5-year mortality and readmission

Long-term outcomes of interest for the present study included 5-year all-cause readmission, 5-year HF readmission, and 5-year all-cause mortality. These outcomes were assessed via linkage of the GWTG-HF registry to CMS Medicare fee-for-service Part A administrative claims data, with follow-up data through December 31, 2019. All-cause mortality was assessed via death dates within the Medicare beneficiary denominator files, and readmissions were assessed via Medicare inpatient claims. HF hospitalization was categorized as any hospitalization where HF was listed as the primary diagnosis via the International Classification of Diseases (ICD) 9th Revision-Clinical Modification (428.x, 402.x1, 404.x1, and 404.x3) and ICD-10 (I11.0, I13.x, I50.x) codes. All time-to-event outcomes were defined as the time from index admission to the time of event, where the event is readmission/mortality through 5 years after the index admission date. Follow-up for readmission was censored early if Medicare eligibility ended before 5 years.

Statistical Analysis

Baseline patient characteristics across sex and HF subtypes were reported as proportions for categorical variables and medians with 25th and 75th percentile for continuous variables. The absolute standardized difference (absolute difference between group means or proportions divided by a pooled estimate of the population standard deviation) was used to assess the magnitude of imbalance between groups, with a standardized difference >10% considered clinically meaningful.

Differences in the risk of clinical outcomes (5-year readmission and mortality) between male and female subgroups within each HF subtype strata were assessed using unadjusted cumulative incidence rates. Cumulative incidence function curves for readmission outcomes were created and tested for significant differences across sex with Gray's test. Kaplan-Meier (K-M) cumulative incidence curves were created for mortality, and differences were tested using the log-rank test. Median survival in years for patients with HF stratified by their age at the time of the index HF hospitalization was calculated using the Kaplan-

Meier estimate of the survival distribution for the GWTG cohort. The median survival for different sex and HF subtype groups were compared with the age and sex-specific population survival estimates based on the National Vital Statistics Report 2010 for the United States population. Locally estimated scatterplot smoothing (LOESS) curves for the 5-year unadjusted mortality rates were created for continuous EF for the overall population and by sex. Temporal trends of admission year vs 5-year mortality by sex and the binomial proportion for patients with HFrEF, HFmrEF, and HFpEF were assessed using Cochran-Armitage trend tests.

Associations between sex and risk of clinical outcomes over 5-year follow-up were assessed using multivariable Cox proportional hazards models. Unadjusted and adjusted hazard ratios were reported for the risk of each outcome for female vs. male sex, with adjustment for demographics, medical history, Social Deprivation Index,[17] continuous EF, and hospital characteristics. Cause-specific Cox models were used for readmission models to account for death as a competing event. Time-to-event outcomes were defined as the time from index hospitalization to time of the event through the 5-year post-admission date. Multiplicative interaction testing was performed to assess if the associations between 5-year clinical outcomes and sex were modified by the HF subtype based on EF, and $p_{interaction} < 0.1$ was considered statistically significant. During the 5-year follow-up period, the assumption of proportional hazards was not met. To address this, sensitivity analyses were conducted separately for 1-year follow-up and landmarking at 1-year post-admission.

Missing data were not imputed in univariate tables. For model covariates, missing Race was imputed to “White”, missing medical history values and active smoking were imputed to “No”, and missing rural location and academic hospital were imputed to “No”. Statistical analyses were conducted in SAS version 9.4 (SAS Institute, Cary, NC).

Results

Of 155,670 patients included in this study (median age 81 years, 53.4% female), 70,022 (45%) had HFrEF, 14,582 (9%) had HFmrEF, and 71,066 (46%) had HFpEF. Patients with HFrEF were more commonly male (59.3%), while patients with HFpEF were more commonly female (66.6%). Female (vs. male) patients with HF were older and had a lower prevalence of atherosclerotic vascular disease, tobacco use, and chronic kidney disease (Table 1). On admission, female (vs. male) patients with HF had higher EF, higher blood pressure, lower serum creatinine, and comparable cardiac biomarker levels. There were no clinically relevant differences across hospital characteristics, in-hospital mortality, or length of stay between the two sex groups. These patterns of sex differences in clinical characteristics were largely consistent across each HF subtype (Supplemental Tables 1–3). Among patients with HFrEF, females (vs. males) had a lower burden of comorbid coronary artery disease, kidney disease, and atrial fibrillation with higher LVEF but no meaningful differences in GDMT (Supplemental Table 1). Among patients with HFpEF, females (vs. males) had a greater burden of depression and higher EF (Supplemental Table 3).

Sex differences in the survival time lost following HF hospitalization

The median survival time following HF hospitalization was mostly comparable for males and females across the EF spectrum (difference in median survival in male vs. female patients <6 months for each HF subtype and age group) (Figure 1). However, compared to the estimated age- and sex-matched population median survival, the loss in survival time following HF hospitalization was greater in female (vs.) male patients across all HF subtypes and age groups. For the index event age of 65–69 years, the median life years lost to HF for female vs. male patients was 17.0 vs. 14.6 for HFpEF, 17.3 vs. 15.1 for HFrEF, and 17.7 vs. 14.6 for HFmrEF. A similar pattern of sex difference in life years lost to HF was observed for other age groups.

Temporal Trends in All-Cause Mortality After HF Hospitalization

In unadjusted analysis, the 5-year risk of mortality increased slightly over the study period (from 2006 to 2014) for both male and female patients with HF across the EF spectrum (Supplemental Figure 2A–C).

Sex differences in all-cause mortality across HF subtypes

Across HF subtypes, the 5-year mortality risk was high following the index HF hospitalization episode with modest differences between female and male patients (Table 2). Across continuous distribution of the EF, the mortality rates were lower with higher EF among patients with HFrEF, with a plateau in this trend among patients with HFmrEF and HFpEF (Supplemental Figure 3). In adjusted analysis, female (vs. male) patients hospitalized with HF had a lower risk of 5-year mortality (adjusted HR 0.89, 95% CI 0.87 – 0.90 p<0.001). However, the magnitude of this association was modified by the HF subtype ($P_{interaction}$ HF subtype*Sex = 0.04, Figure 3), with a stronger association noted among patients with HFrEF (adjusted HR 0.87, 95% CI 0.85 – 0.89) than those with HFmrEF (adjusted HR 0.92, 95% CI 0.88 – 0.96) and HFpEF (adjusted HR 0.90, 95% CI 0.88 – 0.82). A divergent separation in mortality rates among female and male patients was noted at a very high EF range. However, the proportion of HF patients with supranormal EF who were male is very low (Supplemental Figure 3).

In sensitivity analysis landmarking at 1-year follow-up, a similar pattern of association was observed between sex and mortality risk in the first year and between 1–5 years following the index hospitalization across HF subtype strata (Supplemental Tables 4–7). (Supplemental Table 4–7).

Sex differences in readmission across HF subtypes

The risk of readmission over a 5-year follow-up was high following the index HF hospitalization episode across each HF subtype strata with modest differences between female and male patients (Table 2). In adjusted analysis, female (vs male) patients had a significantly higher risk of all-cause (HR 1.03, 95% CI 1.02 – 1.04, p<0.001) and HF readmission (HR 1.06, 95% CI 1.04 – 1.08, p<0.001) (Table 3). The magnitude of the association between sex and 5-year HF readmission differed by HF subtype ($P_{interaction}$ HF Subtype*Sex <0.001, Figure 3), with higher risk noted among female (vs. male) patients with HFpEF (aHR 1.11, 95% CI 1.07–1.14) and HFmrEF (aHR 1.08, 95% CI 1.03 – 1.14)

than those HFrEF (aHR 1.03, 95% CI 1.00 – 1.05). In sensitivity analysis landmarking at 1-year follow-up, a similar pattern of association was observed between sex and readmission risk in the first year and between 1–5 years following the index hospitalization across HF subtype strata (Supplemental Tables 4–7).

Discussion

In this cohort study of GWTG-HF participants hospitalized for HF with available long-term follow-up using Medicare claims data, we observed meaningful sex differences in long-term outcomes. First, the risk of mortality over 5-year follow-up is lower among female (vs. male) patients following HF hospitalization, with a more exaggerated difference noted among patients with HFrEF. Second, despite the lower risk of mortality, females (vs. male) patients experience a significantly greater loss in survival time following HF hospitalization (**Graphical Abstract**). Third, the risk of readmission is significantly higher among female (vs. male) patients following a HF hospitalization, with a more pronounced sex difference noted among patients with HFpEF and HFmrEF. Finally, the risk of mortality following HF hospitalization has increased steadily over time for both male and female patients.

We observed a significantly lower 5-year risk of mortality following HF hospitalization in female (vs. male) patients. Consistent with our observations, prior studies have reported an increased risk of mortality in male (vs. female) patients with HF. In a meta-analysis of multiple RCTs, the risk of mortality at 3 years was reported to be 23% greater in male vs. female patients with chronic stable HFrEF.[13] However, the proportional representation of female patients was small in included studies, and the average follow-up period was relatively short. In the Swedish HF registry, female patients (37% of the cohort) with HF have an 18–20% lower risk of mortality over a median 2.1-year follow-up than male patients.[2] The present study adds to the existing data by evaluating the sex differences in mortality risk over a 5-year follow-up in a large, nationally representative cohort (>50% female) of patients hospitalized with HF.

A key observation from the present study is the excess survival time lost following HF hospitalization among female (vs. male) patients. Despite a lower risk of mortality, female patients, on average, lose 2–3 extra years of survival following HF hospitalization. This was largely driven by a higher median survival among females (vs. males) without HF in the general population. Thus, once an HF event occurred, the patient is on a fixed and accelerated trajectory toward death, attenuating the sex differences in survival noted in the absence of HF. We also observed an increased risk of all-cause and HF hospitalization among female (vs. male) patients with HF. Thus, HF hospitalization has a disproportionately exaggerated impact on survival and hospitalization among female (vs. male) patients. These observations support the need for more aggressive care of female patients post-discharge.

The sex differences in risk of mortality and readmission following HF hospitalization were modified by the baseline EF. Specifically, the lower risk of mortality among female (vs. male) patients, while observed within each EF strata, was most pronounced at lower EF thresholds. The excess risk of readmission among female (vs. male) patients was most pronounced among patients with HFpEF. In contrast, in the Swedish HF registry, female

(vs. male) patients with HF had a comparable and consistently lower risk of mortality across the EF strata with no significant interaction between EF and sex.[2] Similarly, female patients in the Swedish registry with HFpEF or HFmrEF had a comparable risk of HF hospitalization to males. These differences in findings between the GWTG-HF and Swedish registry may be related to several factors. First, the population characteristics, treatment patterns, and prevalence of prognostic factors differ substantially in the GWTG-HF vs. the Swedish HF registry. The Swedish registry included 43% chronic stable outpatients with HF and had younger patients with lower prevalence of BMI, diabetes, hypertension, ischemic heart disease, kidney disease, and other non-cardiovascular comorbidities. Furthermore, the use of evidence-based therapies such as ICDs was much lower in the Swedish registry than GWTG-HF.[18]

Several factors may explain the observed differences in 5-year outcomes among male vs. female patients with HF across the EF strata. Among patients with HFrEF, females had a lower burden of adverse prognostic factors such as ischemic heart disease, atrial fibrillation, kidney disease, and higher mean LV EF, which may contribute to a lower risk of mortality.[19,20] Among patients with HFpEF, female patients had a higher burden of non-cardiac comorbidities such as depression and more supranormal EF, which have been associated with a higher risk of hospitalization.[21,22] Furthermore, prior studies have reported that the burden of HF symptoms,[12] exercise intolerance,[23] frailty,[24] and sarcopenia[25] is higher in female vs male patients with HFpEF, which may also contribute to increased hospitalization rates. Finally, during the study period, no effective therapies were available to improve outcomes for HFpEF, limiting the opportunities to mitigate the risk of adverse outcomes and exaggerating the sex differences in readmission risk. It is noteworthy that the utilization of GDMT and length of stay did not differ between the male and female patients in the GWTG-HF, and thus, differences in care pattern assessed in the GWTG-HF registry did not contribute to the observed sex differences in outcomes. This is in contrast with findings from the Swedish registry, whereby female patients were less likely to receive optimal GDMT than male patients.[2] It is plausible that differences in post-discharge care patterns, such as access to transition of care programs, outpatient follow-up, cardiac rehabilitation use, utilization of optimal GDMT over time, and use of home health and other care facilities, may have contributed to the observed sex disparities in readmission burden.

Implications regarding contemporary management of HF

Our study findings have important implications regarding the management of patients following HF hospitalization. First, our study findings highlight the substantial adverse impact of HF hospitalization on female patients. Despite comparable care patterns during the hospitalization and largely favorable prognostic factors, we observed a greater loss in the median survival as compared with population mean survival among female (vs. male) patients with HF. The readmission risk was also higher among female vs. male HF patients following discharge. These findings suggest that female patients may need more aggressive post-discharge care to mitigate these disparities in HF outcomes. This is particularly relevant as recent studies have demonstrated that female patients with HF are more likely to benefit from the transition of care programs.[26] Specifically, a pre-specified secondary analysis of the PACT-HF trial demonstrated that a transitional care model was associated with a significant reduction in all-cause emergency department visits among females but not males following

hospitalization for HF.[26] Similarly, prior studies have demonstrated that female patients with HF are less likely to participate in and benefit from traditional CR programs.[27] In contrast, tailored cardiac rehabilitation programs designed specifically for female patients are more effective than traditional CR programs in improving adherence, symptom burden, and quality of life.[28] In addition to these non-pharmacologic management strategies, female patients with HFpEF are more likely to benefit from pharmacotherapies such as sacubitril-valsartan.[29] Future studies are needed to determine if aggressive implementation of these therapies among female patients following HF hospitalization may mitigate the observed sex disparities.

Strengths and Limitations

The GWTG-HF registry was linked to Medicare administrative claims data in the present study, and this allowed for a broad, generalizable investigation into sex differences in long-term outcomes among patients with HF. We were able to accurately categorize patients into HF subgroups from LVEF data collected as part of the GWTG-HF clinical registry, as opposed to relying on ICD administrative claims codes for HF subgroup classification. Finally, our cohort was roughly 50% women with a wide distribution of ages over 65, which contrasts with previous evaluations of sex differences from post-hoc analyses of RCTs that had a lower proportion of females and patients of advanced age. Nevertheless, this study is not without limitations. As participation in the GWTG-HF registry is voluntary, there is potential selection bias. However, GWTG-HF is nationally representative and is composed of both rural and urban hospitals and academic and non-academic hospitals. Second, this analysis was limited to U.S adults with available Medicare, thus, study findings may not be generalizable to younger patients or patients not residing in the United States. Third, patients may have had substantive EF change and may have transitioned from reduced EF to preserved EF during the follow-up period, and we did not have access to follow-up EF data. Fourth, we do not have data on angiographic coronary artery anatomy among the study participants and could not compare the burden of obstructive and non-obstructive coronary artery disease among male and female patients with HF. Fifth, the study may not be as generalizable in the current era of recommending ARNi and SGLT2i medical therapy across the spectrum of LVEF given the benefit on post-discharge outcomes, however, the relative differences by sex are not likely to vary. Sixth, we do not have data on quality of life and functional status among participants of the GWTG-HF registry and thus could not compare sex differences in these meaningful outcomes. Finally, outcome analyses were adjusted for clinical covariates, however, there may be residual confounding which may have impacted the study findings.

Conclusions

Among GWTG-HF participants with Medicare hospitalized for HF, the long-term prognosis is poor, with substantial sex differences in outcomes. Female (vs. male) patients have a modestly lower risk of mortality but experience a greater loss in survival time following HF hospitalization compared to the median U.S. life expectancy. Furthermore, the adjusted risk of readmission risk is also higher in females, and this is particularly pronounced among patients with HFpEF and HFmrEF.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

IQVIA (Parsippany, New Jersey) serves as the data collection and coordination center, and the Duke Clinical Research Institute (Durham, NC) serves as the data analysis center.

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Disclosures:

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Abbreviations

HF	heart failure
EF	ejection fraction
HFrEF	heart failure with reduced ejection fraction
GWTG	Get With The Guidelines
HFmrEF	heart failure with mildly reduced ejection fraction
HFpEF	heart failure with preserved ejection fraction
ACEi	angiotensin-converting enzyme inhibitors
ARB	angiotensin receptor blocker
RAS	renin-angiotensin system
MRA	mineralocorticoid receptor antagonist
ARNi	angiotensin receptor neprilysin-inhibitor
ICD	Implantable Cardioverter-Defibrillator

BNP	brain natriuretic peptide
eGFR	estimated glomerular filtration rate
IQR	interquartile range

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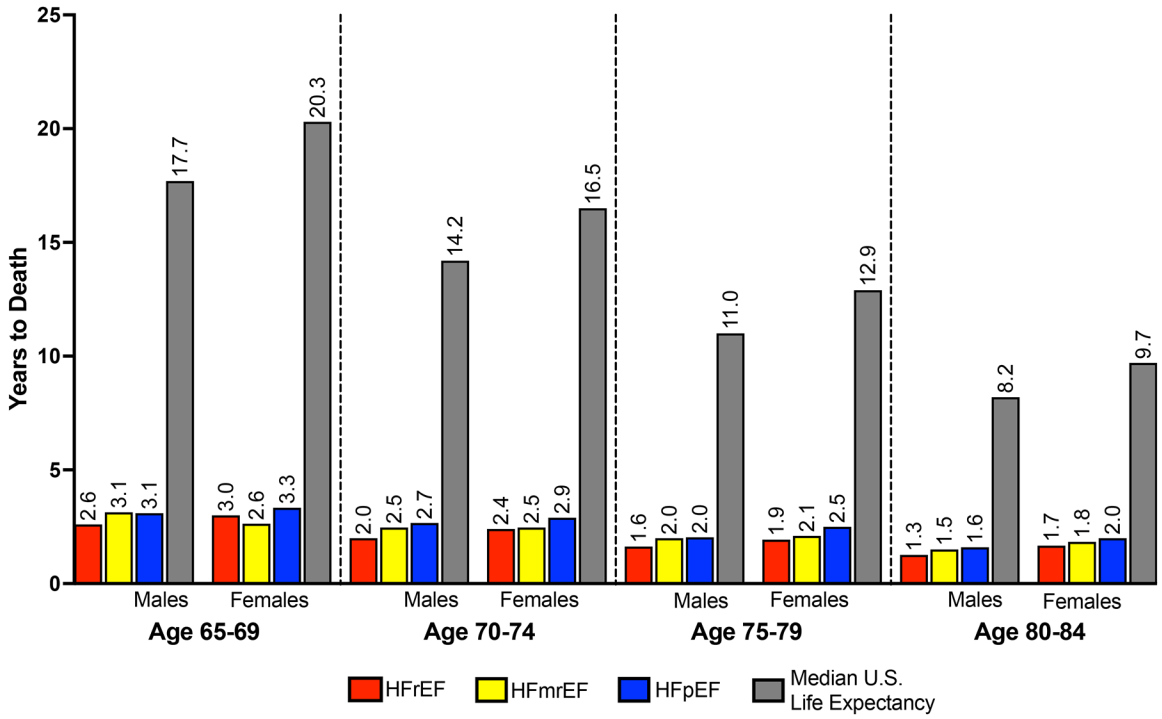

Figure 1: Median survival after HF hospitalization for males and females across all HF subtypes based on EF compared with the median sex- and age-specific United States life expectancy.

This figure highlights the differences in median survival between males and females across the spectrum of EF, which is substantially lower than the median sex- and age-specific U.S. life expectancy.

Sex- and age-specific median U.S. survival in years were assessed based on the National Vital Statistics Report for the United States population (year 2010).

Abbreviations: HFrEF – heart failure with reduced ejection fraction, HFmrEF – heart failure with mildly reduced ejection fraction, HFpEF – heart failure with preserved ejection fraction.

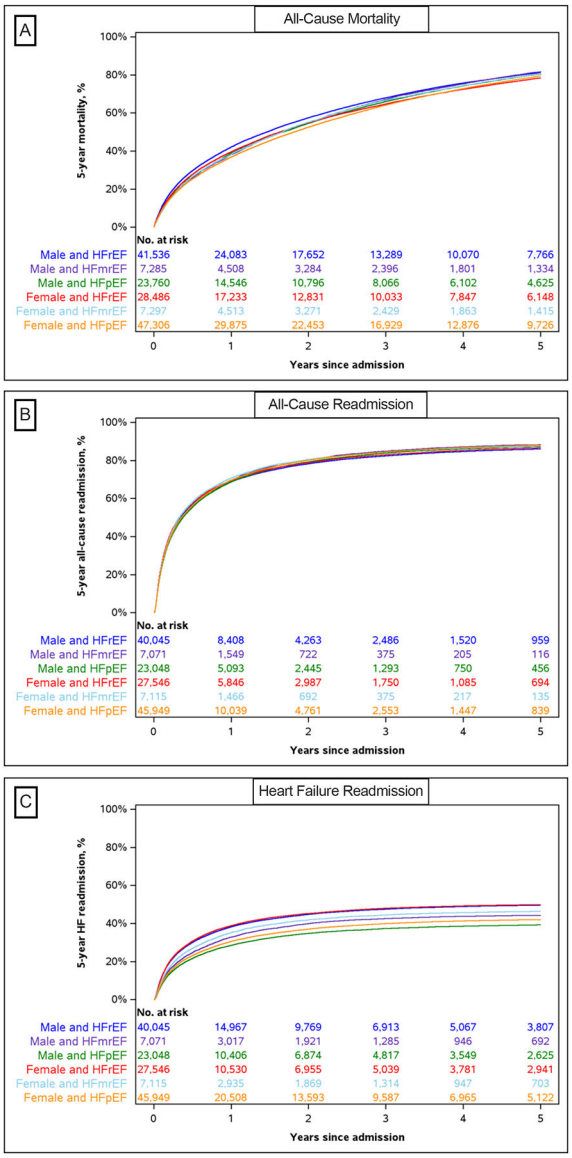

Figure 2: Cumulative incidence curves of (A) 5-year all-cause mortality, (B) 5-year all-cause readmission, and (C) 5-year heart failure readmission by sex and EF group.

This figure highlights the differences in all-cause mortality, all-cause readmission, and heart failure readmission between males and females and across the HF subtypes based on EF. Abbreviations: HF – heart failure, HFrEF – heart failure with reduced ejection fraction, HFmrEF – heart failure with mildly reduced ejection fraction, HFpEF – heart failure with preserved ejection fraction.

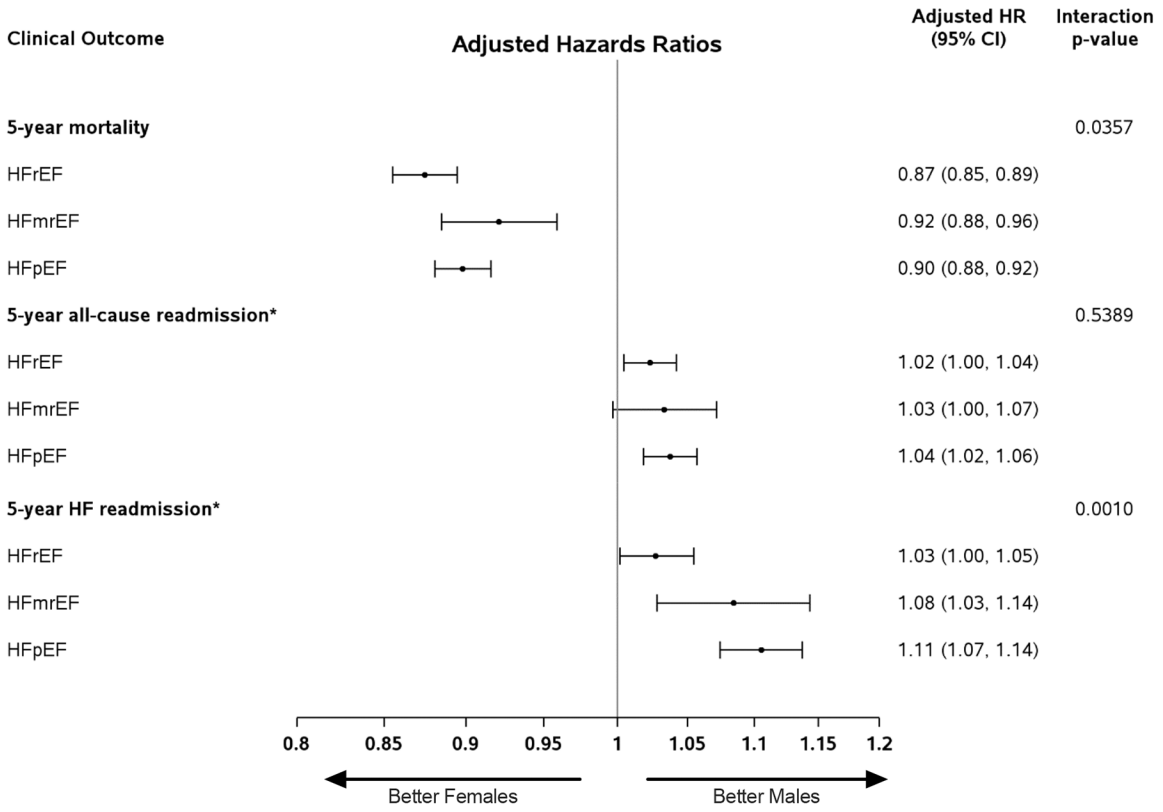

Figure 3: Adjusted association between sex and risk of adverse outcomes (mortality, all-cause readmission, and HF readmission) over 5 years follow up following index HF hospitalization stratified by HF subtypes based on EF.

Female (vs. male, referent group) patients had a significantly lower 5-year mortality risk and a slightly higher 5-year readmission risk, and HF subtype modified the association between sex and 5-year outcomes.

* Assessed among subset of patients discharged alive

Cause-specific Cox models were used for readmission models to account for death as a competing event. Adjustment factors: age, race, insurance status, anemia, atrial fibrillation/flutter, COPD/asthma, hypertension, hyperlipidemia, peripheral vascular disease, coronary artery disease, prior MI, stroke, history of HF, diabetes, active smoking, renal insufficiency, continuous EF

Table 1:

Baseline characteristics of study participants stratified by sex.

	Overall (N=155,670)	Male (N=72,581)	Female (N=83,089)	Absolute Std. Diff (%)
Demographics				
Age, years	81.0 (74.0–87.0)	79.0 (72.0–85.0)	82.0 (75.0–88.0)	30.33
Race/Ethnicity				6.17
White	120,617 (79.6%)	56,926 (80.6%)	63,691 (78.7%)	
Black	17,521 (11.6%)	7,427 (10.5%)	10,094 (12.5%)	
Hispanic	7,347 (4.8%)	3,418 (4.8%)	3,929 (4.9%)	
Asian	2,208 (1.5%)	1,021 (1.4%)	1,187 (1.5%)	
Other/Not Documented	3,832 (2.5%)	1,807 (2.6%)	2,025 (2.5%)	
Social Deprivation Index score	47.0 (23.0–72.0)	46.0 (23.0–70.0)	48.0 (24.0–74.0)	6.76
Insurance status				13.83
Other	22,580 (18.2%)	11,222 (19.5%)	11,358 (17.1%)	
Medicaid	7,650 (6.2%)	2,601 (4.5%)	5,049 (7.6%)	
Medicare	93,247 (75.3%)	43,613 (75.7%)	49,634 (74.9%)	
No Insurance/Not Documented	381 (0.3%)	192 (0.3%)	189 (0.3%)	
Medical History				
Hypertension	111,589 (78.4%)	50,560 (76.1%)	61,029 (80.3%)	10.20
Prior MI	29,612 (20.8%)	16,277 (24.5%)	13,335 (17.6%)	17.13
Prior PCI	22,285 (15.6%)	12,467 (18.8%)	9,818 (12.9%)	16.06
Prior CABG	29,698 (20.9%)	18,904 (28.5%)	10,794 (14.2%)	35.33
Peripheral vascular disease	20,133 (14.1%)	10,896 (16.4%)	9,237 (12.2%)	12.16
Smoking in the prior year	12,386 (8.7%)	7,185 (10.8%)	5,201 (6.8%)	14.09
COPD/Asthma	45,225 (31.8%)	21,329 (32.1%)	23,896 (31.4%)	1.42
Atrial fibrillation/flutter	63,871 (44.9%)	30,858 (46.5%)	33,013 (43.4%)	6.05
Coronary artery disease	77,458 (54.4%)	41,617 (62.7%)	35,841 (47.2%)	31.50
Anemia	31,438 (22.1%)	13,423 (20.2%)	18,015 (23.7%)	8.47
Ischemic etiology	86,015 (60.4%)	46,092 (69.4%)	39,923 (52.5%)	35.06
Depression	16,147 (11.3%)	5,867 (8.8%)	10,280 (13.5%)	14.95
ICD (ICD only or CRT-D)	18,902 (13.3%)	13,240 (19.9%)	5,662 (7.5%)	36.92
CVA/TIA	24,350 (17.1%)	10,881 (16.4%)	13,469 (17.7%)	3.58
Diabetes	58,786 (41.3%)	28,349 (42.7%)	30,437 (40.1%)	5.32
CRT-D or CRT-P	8,324 (5.8%)	5,660 (8.5%)	2,664 (3.5%)	21.21
Chronic dialysis	4,952 (3.5%)	2,348 (3.5%)	2,604 (3.4%)	0.59
Hyperlipidemia	74,499 (52.3%)	36,552 (55.0%)	37,947 (49.9%)	10.20
Renal insufficiency	34,540 (24.3%)	18,291 (27.5%)	16,249 (21.4%)	14.35
Admission Results (or closest to admission)				
Ejection fraction, (median)	45 (30–58)	38 (25–53)	52 (35–60)	55.37

	Overall (N=155,670)	Male (N=72,581)	Female (N=83,089)	Absolute Std. Diff (%)
Ejection fraction obtained:				3.83
Index admission	75,274 (64.2%)	34,395 (63.2%)	40,879 (65.1%)	
Within the last year	37,537 (32.0%)	17,916 (32.9%)	19,621 (31.2%)	
> 1 year ago	4,414 (3.8%)	2,081 (3.8%)	2,333 (3.7%)	
Heart rate, bpm	80 (70–94)	80 (69–93)	81 (70–95)	8.85
SBP, mmHg	138 (119–158)	133 (116–153)	141 (122–162)	27.47
DBP, mmHg	72 (62–84)	73 (63–84)	72 (62–84)	1.94
BMI, kg/m^2	27.3 (23.5–32.3)	27.3 (24.0–31.7)	27.3 (23.0–33.0)	5.31
Serum Creatinine, mg/dL	1.3 (1.0–1.9)	1.5 (1.1–2.0)	1.2 (0.9–1.7)	23.83
eGFR, ml/min/1.73m2 *	46.0 (31.0–63.9)	47.7 (32.5–65.8)	44.4 (29.8–62.2)	12.45
Serum sodium, mEq/L	138 (135–141)	138 (136–141)	138 (135–141)	4.31
Hemoglobin, g/dL	11.6 (10.3–13.0)	11.9 (10.5–13.3)	11.4 (10.2–12.7)	4.44
BUN, mg/dL	27 (19–39)	28 (20–42)	25 (18–37)	19.76
HbA1c, %	6.6 (5.9–7.5)	6.6 (6.0–7.5)	6.5 (5.9–7.5)	4.51
Potassium, mEq/L	4.2 (3.8–4.6)	4.2 (3.8–4.6)	4.2 (3.8–4.6)	4.84
Troponin, mg/mL	0.1 (0.0–0.1)	0.1 (0.0–0.1)	0.0 (0.0–0.1)	3.01
BNP, pg/mL	815 (408–1612)	868 (423–1710)	777 (395–1530)	6.51
Discharge vitals and labs (or closest to discharge)				
Heart rate, bpm	75 (66–86)	74 (66–85)	75 (66–86)	4.36
SBP, mmHg	120 (107–136)	118 (104–133)	122 (109–139)	19.91
DBP, mmHg	64 (57–72)	65 (58–73)	63 (56–71)	13.05
BMI, kg/m^2	26.6 (22.8–31.6)	26.5 (23.2–30.8)	26.7 (22.4–32.4)	8.64
Serum Creatinine, mg/dL	1.4 (1.0–1.9)	1.5 (1.1–2.0)	1.2 (0.9–1.7)	23.49
eGFR(CKD-EPI), ml/min/1.73m2	45.3 (30.5–63.1)	47.7 (32.4–65.8)	43.3 (29.1–61.2)	16.13
Serum sodium, mEq/L	138 (135–140)	138 (135–140)	138 (135–140)	1.58
BUN, mg/dL	29 (20–43)	31 (22–45)	28 (19–41)	18.06
Potassium, mEq/L	4.1 (3.8–4.4)	4.1 (3.8–4.4)	4.1 (3.8–4.4)	1.11
Medications at discharge				
ACEI/ARB (% prescribed)	81,678 (52.5%)	38,052 (52.4%)	43,626 (52.5%)	17.33
Beta-blocker (% prescribed)	120,168 (77.2%)	56,885 (78.4%)	63,283 (76.2%)	10.60
Mineralocorticoid receptor antagonist (% prescribed)	22,931 (14.7%)	12,177 (16.8%)	10,754 (12.9%)	17.27
Hospital Characteristics				
Region				2.87
Northeast	50,723 (32.6%)	23,443 (32.3%)	27,280 (32.8%)	
Midwest	37,757 (24.3%)	17,500 (24.1%)	20,257 (24.4%)	
South	50,756 (32.6%)	23,641 (32.6%)	27,115 (32.6%)	
West	16,434 (10.6%)	7,997 (11.0%)	8,437 (10.2%)	
Academic/Teaching Hospital	116985 (75.9%)	54,800 (76.2%)	62,185 (75.7%)	1.11

	Overall (N=155,670)	Male (N=72,581)	Female (N=83,089)	Absolute Std. Diff (%)
Number of beds	376.0 (226.0–570.0)	383.0 (228.0–581.0)	368.0 (221.0–539.0)	5.23
Location				1.16
Rural	7,093 (4.7%)	3,213 (4.5%)	3,880 (4.8%)	
Urban	145282 (95.3%)	67,797 (95.5%)	77,485 (95.2%)	
In-Hospital Outcomes				
In-hospital Mortality	4,896 (3.1%)	2,417 (3.3%)	2,479 (3.0%)	1.98
Length of stay (Median)	4.0 (3.0–6.0)	4.0 (3.0–6.0)	4.0 (3.0–6.0)	1.36

Values shown are n (%) unless otherwise stated.

Standardized difference represents the absolute difference in rank-based means or proportions divided by the standard deviation and multiplied by 100.

* eGFR calculated using the CKD-EPI equation

Abbreviations: MI – myocardial infarction, PCI – percutaneous coronary intervention; CABG – coronary artery COPD – chronic obstructive pulmonary disease; ICD – implantable cardioverter-defibrillator; CRT – cardiac resynchronization therapy, CVA – cerebrovascular accident, TIA – transient ischemic attack, SBP – systolic blood pressure, DBP – diastolic blood pressure, BMI – body mass index, eGFR – estimated glomerular filtration rate, BUN – blood urea nitrogen, ACEi – angiotensin converting enzyme inhibitor, ARB – angiotensin receptor blockade

Table 2.

Unadjusted cumulative incidence (95% CI) of 5-year clinical outcomes by sex, stratified by heart failure subgroups

Outcome	Male	Female	P-value
HFrEF			
5-year mortality	81.3 (80.9, 81.7)	78.4 (78.0, 78.9)	<0.001
5-year all-cause readmission *	86.1 (85.7, 86.4)	86.7 (86.2, 87.1)	0.043
5-year HF readmission *	49.6 (49.1, 50.1)	49.9 (49.3, 50.5)	0.302
HFmrEF			
5-year mortality	81.7 (80.8, 82.6)	80.6 (79.7, 81.5)	0.295
5-year all-cause readmission *	88.3 (87.5, 89.1)	87.7 (86.9, 88.4)	0.710
5-year HF readmission *	44.3 (43.1, 45.5)	46.4 (45.2, 47.6)	0.006
HFpEF			
5-year mortality	80.5 (80.0, 81.0)	79.5 (79.1, 79.8)	<0.001
5-year all-cause readmission *	87.4 (86.9, 87.8)	88.1 (87.8, 88.4)	0.004
5-year HF readmission *	39.3 (38.7, 40.0)	42.0 (41.6, 42.5)	<0.001

* Assessed among subset of patients discharged alive

Abbreviations: HF – heart failure, HFrEF – heart failure with reduced ejection fraction, HFmrEF – heart failure with mildly reduced ejection fraction, HFpEF – heart failure with preserved ejection fraction

Table 3.

Hazard ratios for 5-year clinical outcomes in female versus male patients.

Outcome	Unadjusted hazard ratio (95% CI)	P-Value	Adjusted hazard ratio (95% CI)	P-Value
5-year mortality	0.93 (0.92, 0.95)	<.0001	0.89 (0.87, 0.90)	<.0001
5-year all-cause readmission *	1.01 (0.99, 1.02)	0.2431	1.03 (1.02, 1.04)	<.0001
5-year HF readmission *	0.96 (0.94, 0.98)	<.0001	1.06 (1.04, 1.08)	<.0001

Referent group = males

* Assessed among subset of patients discharged alive

Adjustment factors: age, race, insurance status, anemia, atrial fibrillation/flutter, COPD/asthma, hypertension, hyperlipidemia, peripheral vascular disease, coronary artery disease, prior MI, stroke, history of HF, diabetes, active smoking, renal insufficieny, continuous EF, region, academic hospital, number of beds, rural location, Social Deprivation Index.