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Impact of Noncardiac Comorbidities on Morbidity and Mortality in a Predominantly Male Population With Heart Failure and Preserved Versus Reduced Ejection Fraction

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Objectives The aim of this study was to evaluate the prevalence and prognostic impacts of noncardiac comorbidities in patients with heart failure (HF) with preserved ejection fraction (HFpEF) compared with those with HF with reduced ejection fraction (HFrEF).

Background There is a paucity of information on the comparative prognostic significance of comorbidities between patients with HFpEF and those with HFrEF.

Methods In a national ambulatory cohort of veterans with HF, the comorbidity burden of 15 noncardiac comorbidities and the impacts of these comorbidities on hospitalization and mortality were compared between patients with HFpEF and those with HFrEF.

Results The cohort consisted of 2,843 patients with HFpEF and 6,599 with HFrEF with 2-year follow-up. Compared with patients with HFrEF, those with HFpEF were older and had higher prevalence of chronic obstructive pulmonary disease, diabetes, hypertension, psychiatric disorders, anemia, obesity, peptic ulcer disease, and cancer but a lower prevalence of chronic kidney disease. Patients with HFpEF had lower HF hospitalization, higher non-HF hospitalization, and similar overall hospitalization compared with those with HFrEF ($p < 0.001$, $p < 0.001$, and $p = 0.19$, respectively). An Increasing number of noncardiac comorbidities was associated with a higher risk for all-cause admissions ($p < 0.001$). Comorbidities had similar impacts on mortality in patients with HFpEF compared with those with HFrEF, except for chronic obstructive pulmonary disease, which was associated with a higher hazard (1.62 [95% confidence interval: 1.36 to 1.92] vs. 1.23 [95% confidence interval: 1.11 to 1.37], respectively, $p = 0.01$ for interaction) in patients with HFpEF.

Conclusions There is a higher noncardiac comorbidity burden associated with higher non-HF hospitalizations in patients with HFpEF compared with those with HFrEF. However, individually, most comorbidities have similar impacts on mortality in both groups. Aggressive management of comorbidities may have an overall greater prognostic impact in HFpEF compared to HFrEF. (J Am Coll Cardiol 2012;59:998–1005) © 2012 by the American College of Cardiology Foundation

Many patients with heart failure (HF) have normal or nearly normal left ventricular ejection fractions (EFs), a condition referred to as diastolic HF or HF with preserved EF (HFpEF). Studies have reported a prevalence of HFpEF ranging from 30% to 70% (averaging about 50%) among patients with HF (1–3). Furthermore, the prevalence of HFpEF among patients with discharge diagnoses of HF has increased significantly over the past few decades (4). The prevalence of this condition is anticipated to keep increasing as the prevalence of elderly patients with comorbid conditions such as hypertension, diabetes mellitus (DM), and obesity increases. Although the morbidity and mortality of patients with HFpEF in comparison with those with heart failure with

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reduced ejection fraction (HFrEF) has varied, there is consensus that HFpEF is associated with substantial morbidity and mortality (3–6).

Previously, the few analyses that examined the causes of death in patients with HF suggested that a higher proportion of deaths are due to noncardiovascular causes in patients with HFpEF compared with those with HFrEF (7–9). This is consistent with the belief that comorbidities may play a more significant role in outcomes in HFpEF compared with HFrEF. However, the relative impacts of comorbidities on morbidity and mortality in HFpEF compared with HFrEF have not been well studied. Therefore, in a large, national cohort of ambulatory patients with HF, we examined the prevalence and relative impacts of a wide range of noncardiac comorbidities on morbidity and mortality in patients with HFpEF compared with those with HFrEF.

Abbreviations and Acronyms

COPD = chronic obstructive pulmonary disease

CVA = cerebrovascular accident

DM = diabetes mellitus

EF = ejection fraction

EPRP = External Peer Review Program

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

Methods

Patient cohort and comorbidities. We performed a retrospective study of a national cohort of veterans with HF treated in ambulatory clinics of U.S. Department of Veterans Affairs (VA) medical centers between October 1, 2000, and September 30, 2002. We used the VA External Peer Review Program (EPRP) data. As described previously (10), the sampling pool of outpatients for EPRP included ambulatory patients with chronic diseases including HF, DM, prior myocardial infarction, and chronic obstructive pulmonary disease (COPD), identified by International Classification of Disease-Ninth Revision (ICD-9), codes. Abstractors reviewed electronic medical records for validation of inclusion criteria, including documentation by clinicians of the diagnosis of HF and other chronic diseases listed previously (10). Patient-level data from the EPRP HF cohort were linked with 5 existing national VA databases to obtain demographic, comorbidity, laboratory, pharmacy, and outcome data. The EF and date of its ascertainment were obtained from the EPRP database. Of patients with known EFs (n = 17,456), only those with EF determinations within 1 year before to 3 months after the clinic visit (n = 9,451) were included in the present analyses. Patients were classified as having HFpEF when their EFs were ≥50% and as having HFrEF when their EFs were <50%.

Blood pressure, weight, height, and comorbidities of prior myocardial infarction, DM, hypertension, and COPD were obtained from the EPRP database. Other comorbidities were ascertained using ICD-9 codes from VA outpatient clinic files (containing demographics, diagnoses, and outpatient services) and patient treatment files (containing abstracts for patients discharged from VA hospitals) over a time period of 2 years before and at the index clinic visit (ICD-9 codes used to identify the comorbidities are listed in the Online Appendix). On the basis of the Charlson comorbidity index (11), we included the following noncardiac comorbidities: peripheral artery disease, cerebrovascular accident (CVA), dementia, chronic pulmonary disease, rheumatological disorders, acquired immunodeficiency syndrome, peptic ulcer disease, DM, liver disease, malignancy, and renal disease. Although they are not included in the Charlson comorbidity index, we included anemia, hypertension, psychiatric disorders, and obesity because previous studies have identified them as significant prognostic variables in patients with HF (12–14). For each patient, we calculated the total number of noncardiac comorbidities from these 15 comorbidities.

The most recent laboratory data within 1 year before to 2 weeks after the index visit were used. Renal insufficiency was defined as an estimated glomerular filtration rate < 60 ml/min/1.73 m^2, calculated using the 4-variable Modification of Diet in Renal Disease formula (15). Anemia was present if hemoglobin was <13 g/dl in men and <12 g/dl in women. Obesity was present if body mass index was ≥30 kg/m^2. Four patients were excluded because of missing systolic blood pressure, and 5 patients were excluded because of missing outcomes. For variables with <20% missing values, imputation procedures were performed. Variables with ≥20% missing values were excluded. Missing values for serum sodium (6.1%), hemoglobin (15.9%), and creatinine (11.7%) were imputed. Missing values were imputed using linear regression with baseline variables as predictors and constraints applied on the basis of observed minimal and maximal values. Analyses were repeated by excluding observations with imputed values, and the results were found to be concordant. Thus, models using imputed data are shown.

Statistical analyses. Univariate differences in baseline variables between HFpEF and HFrEF were evaluated using chi-square tests for categorical variables and 2-sample *t* tests for continuous variables. Covariates for multivariate models of mortality were selected on the basis of backward stepwise Cox proportional hazards models with removal set at a probability of 0.2. On the basis of these results, 19 variables were selected for the multivariate models. Additionally, history of hypertension, psychiatric disorder, peptic ulcer disease and rheumatological disorders were forced into the model to evaluate the effects of all noncardiac comorbidities in this population. Multivariate Cox proportional hazards models were run separately for the HFpEF and HFrEF groups to calculate the hazard ratios for mortality in each EF group. Finally, 23 variables were used for the multivariate analyses: age; serum sodium; sex; systolic blood pressure; past hospitalization for HF; use of beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and statins; and the 15 comorbidities. In models of HFrEF, we also used a categorical variable for the

severity of depressed EF: mild (40% ≤ EF <50%), moderate (30% ≤ EF <40%), and severe (EF <30%). To evaluate whether the prognostic impact of each comorbidity was different in the HFpEF versus HFrEF groups, we performed an interaction analysis. A backward elimination for the Cox proportional hazards analysis on the entire dataset was performed to examine the interaction of each of the 23 variables and the group variable representing HFpEF or HFrEF. In this analysis, we kept all 23 variables and the group in the model, allowing the interaction terms to be removed one by one for p values >0.05.

Kaplan-Meier survival curves were generated, and the log-rank test was used to compare time to first HF and first non-HF hospitalization between patients with HFpEF and those with HFrEF. Follow-up data were available for the first all-cause admission and HF admission. For survival analysis of non-HF admissions, only the first all-cause admission that was not documented as an admission for HF was considered an event. In addition, occurrence of an admission for HF was considered a censor for the observation of non-HF admission. All analyses were performed using SPSS version 18 (SPSS, Inc., Chicago, Illinois). Data are presented as mean ± SD unless otherwise specified, and p values <0.05 were considered significant.

Results

The cohort consisted of 9,442 veterans with HF, of whom 2,843 (30%) had HFpEF and 6,599 (70%) had HFrEF. All patients had 2-year follow-up. Patients had a mean age of 70 years, and 95% were men. Of patients with HFrEF, 25% had mildly reduced EFs, 31% had moderately reduced EFs, and 44% had severely reduced EFs.

As shown in Table 1, patients with HFpEF were older, with higher proportions of women and Caucasians. Compared with patients with HFrEF, patients with HFpEF had higher systolic blood pressure and serum sodium; higher prevalence rates of DM, hypertension, anemia, COPD, obesity, cancer, peptic ulcer disease, and psychiatric disorders; but a lower prevalence of past myocardial infarction

Table 1 Baseline Characteristics of Patients With HFpEF and Those With HFrEF

Variable	HFpEF (n = 2,843)	HFrEF (n = 6,599)	p Value	Age-Adjusted p Value
Age (yrs)	70.7 ± 10.1	69.5 ± 10.3	<0.001	NA
Men	91.1	96.4	<0.001	<0.001
Race			<0.001	<0.001
Caucasian	78.7	74.8		
African American	10.1	13.2		
Other/unknown	11.2	11.9		
DM	44.9	40.0	<0.001	<0.001
Hypertension	70.5	62.2	<0.001	<0.001
Peripheral artery disease	27.5	27.8	0.76	0.42
CVA	21.0	21.3	0.76	0.48
Atrial fibrillation	35.0	35.4	0.73	0.22
Past MI	27.1	40.4	<0.001	<0.001
Renal insufficiency	48.8	51.9	0.005	<0.001
Anemia	33.2	28.4	<0.001	<0.001
COPD	33.9	26.6	<0.001	<0.001
Obesity	51.0	34.7	<0.001	<0.001
Liver disease	1.7	1.7	1.00	0.81
Cancer	21.6	18.6	0.001	0.01
AIDS	0.3	0.3	1.00	0.84
Dementia	3.0	2.6	0.31	0.56
Psychiatric disorders	27.8	22.8	<0.001	<0.001
Rheumatological disorders	4.4	3.8	0.20	0.22
Peptic ulcer disease	8.1	6.0	<0.001	<0.001
Systolic blood pressure (mm Hg)	132.2 ± 21.0	124.5 ± 20.9	<0.001	<0.001
Serum sodium (mEq/l)	139.1 ± 3.4	139.0 ± 3.5	0.04	0.08
HF hospitalizations within previous 2 yrs	17.2	22.9	<0.001	<0.001
Medication use				
Beta-blockers	55.7	64.9	<0.001	<0.001
ACE inhibitors/ARBs	72.8	85.5	<0.001	<0.001
Statins	45.0	51.3	<0.001	<0.001

Values are mean ± SD or %.

ACE = angiotensin-converting enzyme; AIDS = acquired immunodeficiency syndrome; ARB = angiotensin receptor blocker; COPD = chronic obstructive pulmonary disease; CVA = cerebrovascular accident; DM = diabetes mellitus; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; MI = myocardial infarction.

and a mildly lower prevalence of renal insufficiency. In addition, patients with HFpEF had a lower frequency of HF hospitalization over the previous 2 years and were less frequently prescribed beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and statins. Patients with HFpEF had a higher number of noncardiac comorbidities per patient (mean 4.0 ± 1.7) compared with patients with HFrEF (mean 3.5 ± 1.7) ($p < 0.001$), ranging from a minimum of 0 to a maximum of 11 comorbidities per patient. There was a significant increase in the proportion of patients with HFpEF with an increasing number of noncardiac comorbidities ($p < 0.001$ by trend analysis) (Fig. 1).

We then examined whether the higher prevalence of comorbidities in patients with HFpEF was associated with more non-HF hospitalizations compared with patients with HFrEF. Compared with patients with HFrEF, a higher proportion of those with HFpEF had at least 1 non-HF-related admission ($p < 0.001$) but a similar proportion of at least 1 any-cause admission ($p = 0.19$) and a lower proportion of at least 1 HF admission ($p < 0.0001$) (Fig. 2). Similar results were noted in time-to-event analysis, demonstrated by a shorter time to first non-HF admission and a longer time to first HF admission in patients with HFpEF compared with those with HFrEF (Fig. 3). There was no significant difference in time to any-cause hospitalization ($p = 0.60$). Next, we examined whether the higher prevalence of noncardiac comorbidities in patients with HFpEF was a contributor to increased hospitalizations. On multivariate survival analysis, number of comorbidities (as a continuous variable) was significantly associated with time to all-cause admission (1.19; 95% confidence interval: 1.17 to 1.22; $p < 0.001$). When examined as a categorical variable, the increasing number of comorbidities also demonstrated an increasing hazard of hospitalization ($p < 0.001$) (Fig. 4).

During the 2-year follow-up period, there were 1,680 deaths among 6,599 patients with HFrEF (25.5%), whereas there were 563 deaths among 2,843 with HFpEF (19.8%) ($p < 0.001$) (Fig. 2). In patients with HFpEF, CVA, renal insufficiency, anemia, COPD, liver disease, cancer, dementia, rheumatological disorders, and absence of obesity were independent predictors of all-cause mortality. In patients with HFrEF, the association of baseline variables with mortality was found to be similar except for DM and peripheral artery disease, which were significantly associated with mortality in addition to previously mentioned comorbidities, and history of cancer and rheumatological disorders, which were not (Table 2). However, the interaction analyses revealed a significant interaction only between COPD and EF group ($p = 0.01$). COPD contributed a higher hazard for mortality in patients with HFpEF (1.61; 95% confidence interval: 1.36 to 1.92) compared with those with HFrEF (1.23; 95% confidence interval: 1.11 to 1.37). No other variables had significant interactions with EF group, indicating no significant differences in the prognostic impact of other comorbidities between the 2 EF groups.

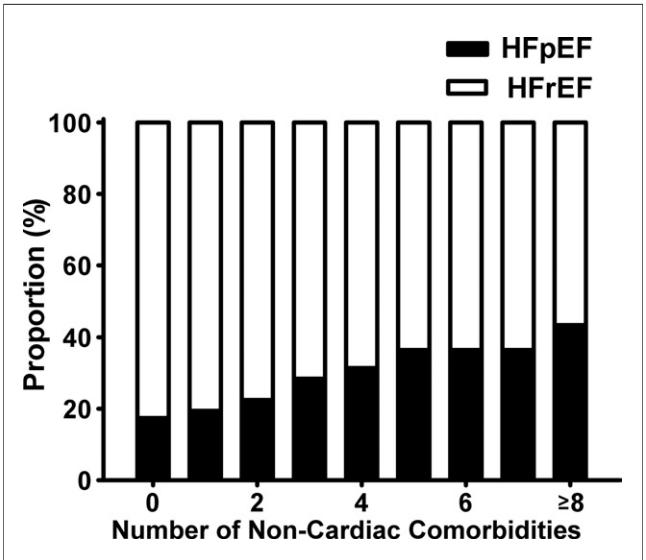

Figure 1 **Stacked Bar Chart Showing Relative Composition of the HF Population (HFpEF vs. HFrEF) Stratified by the Total Number of Noncardiac Comorbidities**

The x-axis represents the total number of prevalent comorbidities, and the y-axis demonstrates the relative proportion of patients with heart failure (HF) with preserved ejection fraction (HFpEF) and HF with reduced ejection fraction (HFrEF) for each category. As the number of prevalent comorbidities increases, there is a greater proportion of patients with HFpEF compared to patients with HFrEF ($p < 0.001$ by trend analysis).

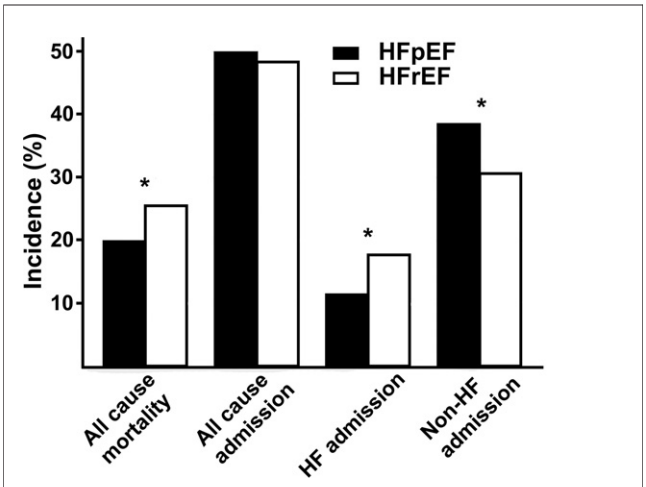

Figure 2 **Incidence of Death and at Least 1 All-Cause Admission, HF Admission, and Non–HF-Related Admission in Patients With HFpEF and Those With HFrEF**

The medians (interquartile ranges) follow-up for these end-points were 730 days (730 to 730 days), 518 days (138 to 730 days), 730 days (474 to 730 days), and 518 days (138 to 730 days), respectively. HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction. *$p < 0.001$.

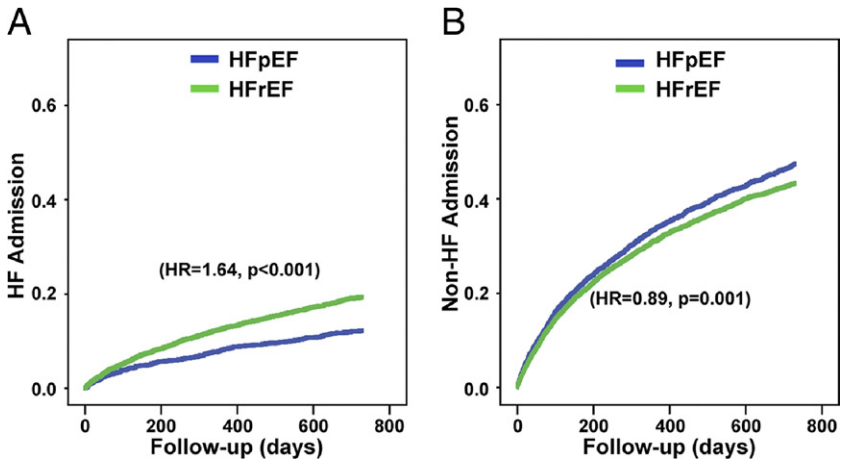

Figure 3 Kaplan-Meier Curves for Hospitalization in Patients With HFpEF and Those With HFrEF

(A) Heart failure (HF) admissions and **(B)** non-HF admissions. Hazard ratios (HRs) shown were calculated using univariate Cox proportional hazards models. HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction.

Discussion

In a large national ambulatory HF cohort, we demonstrate that patients with HFpEF have a significantly higher burden of noncardiac comorbidities compared with those with HFrEF. Patients with HFpEF experienced significantly more non-HF hospitalizations compared with those with HFrEF, although overall hospitalizations were similar in both groups. The increasing number of comorbidities was associated with an increase in all-cause hospitalizations. Furthermore, individually, most of the noncardiac comorbidities had similar prognostic impacts on mortality in HFpEF and HFrEF.

Our study adds to previous studies by demonstrating a higher burden of noncardiac comorbidities in ambulatory patients with HFpEF compared with those with HFrEF. Most of the large published studies evaluating comorbidities in patients with HFpEF were based on hospitalized HF cohorts (1,2,4). In contrast, our study evaluated a large nationally representative cohort of 9,442 ambulatory pa-

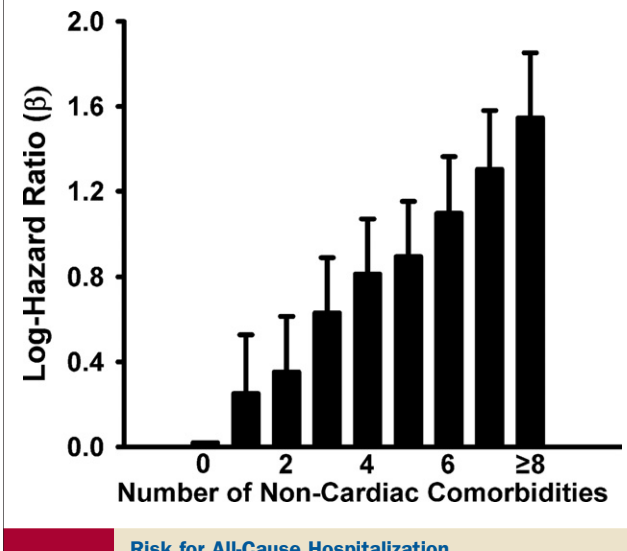

Figure 4 Risk for All-Cause Hospitalization Versus Number of Noncardiac Comorbidities

Log hazard ratios are based on Cox proportional hazards model ($p < 0.001$). Number of noncardiac comorbidities was used as a categorical variable. **Error bars** represent the upper limit of the 95% confidence interval.

Table 2 Hazard Ratios (95% Confidence Intervals) of Noncardiac Comorbidities for Mortality in Patients With HFpEF and Those With HFrEF

Variable	HFpEF	HFrEF	p Value for Interaction Analyses
DM	1.03 (0.86–1.24)	1.25‡ (1.13–1.38)	0.20
Hypertension	1.03 (0.85–1.24)	1.03 (0.93–1.15)	0.66
Peripheral artery disease	1.17 (0.97–1.40)	1.38‡ (1.25–1.53)	0.11
CVA	1.25* (1.02–1.52)	1.18† (1.05–1.32)	0.53
Renal insufficiency	1.28† (1.07–1.53)	1.25‡ (1.12–1.38)	0.86
Anemia	1.35† (1.13–1.61)	1.42‡ (1.28–1.57)	0.84
COPD	1.61‡ (1.36–1.91)	1.23‡ (1.11–1.37)	0.01
Obesity	0.67‡ (0.56–0.81)	0.83† (0.74–0.93)	0.09
Liver disease	2.31‡ (1.48–3.62)	1.41* (1.05–1.89)	0.06
Cancer	1.24* (1.03–1.49)	1.10 (0.98–1.24)	0.33
AIDS	2.38 (0.76–7.48)	1.52 (0.72–3.22)	0.53
Dementia	1.75† (1.21–2.51)	1.48† (1.16–1.90)	0.70
Psychiatric disorder	1.05 (0.87–1.27)	1.02 (0.91–1.15)	0.57
Rheumatological disorder	1.52* (1.06–2.17)	0.96 (0.75–1.23)	0.054
Peptic ulcer disease	0.81 (0.60–1.10)	1.07 (0.89–1.29)	0.21

Other baseline covariates used in the model were age, sex, systolic blood pressure, serum sodium, past heart failure hospitalization, and use of beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and statins. In the HFrEF group, reduced ejection fraction was used in the model as a categorical variable of mildly, moderately, or severely reduced ejection fraction. *$p < 0.05$; †$p < 0.01$; ‡$p < 0.001$.

Abbreviations as in Table 1.

tients with HF, a setting wherein patients are more representative of the overall HF population rather than the sickest subgroup of hospitalized patients. In addition, most of the previous investigations examined only a limited number of comorbidities in each study, and the specific comorbidities assessed varied across studies. In the present study, we included a comprehensive set of noncardiac comorbidities. Our study confirmed findings from previous studies demonstrating that patients with HFpEF are typically older and have comorbidities including hypertension (55% to 86%), DM (26% to 45%), CVA (15% to 17%), obesity (41% to 62%), COPD (7% to 31%), and anemia (21% to 53%), which were usually more prevalent than in patients with HFrEF (1–4,6,16). Although the prevalence of DM has varied across studies, the majority of studies have found a higher prevalence of DM in patients with HFpEF, consistent with the findings in our study. In the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure) registry, lower serum creatinine was noted in patients with HFpEF compared with those with HFrEF, while other studies demonstrated no significant difference in serum creatinine between the 2 groups (1,2,6). In our cohort, patients with HFpEF had a slightly lower prevalence of renal insufficiency in comparison with those with HFrEF. For our analysis, renal insufficiency was defined by estimated glomerular filtration rate, which may be a more accurate measure of renal function than serum creatinine.

Although overall hospitalizations were similar between HFpEF and HFrEF, non-HF hospitalizations were significantly higher in the HFPEF group. These findings are supported by a previous study of 1,077 patients with HF from Olmstead County, Minnesota, which suggested a higher frequency of admissions for patients with HFpEF compared with those with HFrEF (40% vs. 34%, respectively) although in that study, the difference was not statistically significant ($p = 0.069$) (17). These findings are consistent with the greater burden of noncardiac comorbidities we found in patients with HFpEF and underline the importance of comorbidity management in reducing the overall morbidity in patients with HFpEF. Focusing predominantly on the reduction of HF admissions in these patients may result in a lower impact on their overall frequency of hospitalization. This has also been evident in recent large trials of in HFpEF targeting the renin-angiotensin system, some of which showed modest reductions in HF hospitalizations (18,19) but failed to reduce all-cause mortality and/or non-HF hospitalizations (18–20). In the I-PRESERVE (Irbesartan in Heart Failure With Preserved Ejection Fraction) trial, more than 50% of patient hospitalizations were for noncardiovascular causes. This higher rate of noncardiovascular hospitalization occurred despite the trial's having multiple exclusion criteria for significant comorbidities (20). Patients in clinical practice, such as our study cohort, would be expected to have an even greater contribution of comorbidities to outcomes. Thus, it is possible that HF-specific treatment in patients with HFpEF may not be able to reduce total hospitalization or total mortality that is largely driven by competing noncardiac comorbidities.

The greater burden of comorbidities in HFpEF is also consistent with the prior finding of a higher proportion of noncardiovascular deaths in patients with HFpEF compared with those with HFrEF (7–9). However, on examination of the relative prognostic impacts of individual comorbidities on mortality in the HFpEF and HFrEF groups, we found that most comorbidities, including renal disease, anemia, prior CVA, liver disease, cancer, dementia, and obesity, had similar prognostic impacts on mortality in the 2 EF groups. Although these comorbidities have been shown, in various combinations, to be associated with intermediate-term or long-term mortality in HFpEF or in HFrEF (4,6,21), most previous studies did not examine the differential prognostic impacts of a comprehensive set of noncardiac comorbidities in both these EF groups. We found that only COPD was associated with a significantly higher hazard of death in patients with HFpEF compared with those with HFrEF, although COPD was an independent predictor of mortality in both groups. Although previous studies have found a higher prevalence of COPD in patients with HFpEF compared with those with HFrEF (2,6) and have demonstrated that COPD is associated with higher mortality in patients with HF, few studies have addressed its comparative prognostic role in preserved-EF and reduced-EF groups (21,22). One small study of 528 hospitalized patients with HF demonstrated results similar to ours in that the investigators found an increased risk for death associated with COPD in patients with HFpEF compared with those with HFrEF (23). The complex relationship between COPD and HF, including overlapping symptoms, contributes to difficulties in making the diagnosis of one in the presence of the other, and the role of each of the conditions in the progression and exacerbation of the other requires further study (22).

On the basis of our findings, a greater focus on the recognition and treatment of comorbidities in HFpEF appears warranted. Patients with HFpEF, who are often older and have multiple chronic health conditions with complex health care needs, may benefit from newer models of primary care to improve the fragmented and often ineffective care that such patients may receive in the current health care system (24). In addition, studies have also shown that although the clinical signs and symptoms of HF are similar between HFpEF and HFrEF, patients with HFpEF are less likely to receive diuretic agents for congestion, anticoagulation therapy for atrial fibrillation, smoking cessation counseling, complete discharge instructions, to have a cardiologist as a primary physician, or to undergo consultation with a cardiologist (1,6). Attempts to pursue case management strategies for patients with HFpEF, as done for those with HFrEF, may help reduce the morbidity

associated with this condition. Both conventional and novel strategies may be warranted to treat comorbidities. For example, as demonstrated by large randomized clinical trials, 1 of the most beneficial effects of better blood pressure control is the reduction of HF events (25,26). Smaller studies demonstrating benefits of treatment of anemia and sleep-disoreded breathing in patients with HFpEF need further evaluation in larger clinical trials (27,28). To increase the applicability of clinical trial results to the general population, our findings support changes in clinical trial strategy, as suggested recently by Kitzman and Rich (29). These include efforts to enroll a greater proportion of elderly patients in trials of HFpEF, to discourage the exclusion of patients with multiple comorbidities as they are the driving force of outcomes in HFpEF, and to include the primary evaluation of outcomes of functional ability rather than just mortality and HF hospitalizations.

Study limitations. This study had limitations inherent to retrospective observational studies. Also, our database had missing data for some variables, ranging from 6% to 16%. This had the potential to bias the study if the missing data were not completely random. To address this issue, we conducted the analyses both with imputed data and by excluding patients with missing data and found concordant results. In addition, the study cohort was predominantly male (91%), representative of the VA population, and the results may not be generalizable to women, who form a large proportion of patients with HFpEF. The male dominance may also explain the lower prevalence of HFpEF (30%) in our study cohort compared to other U.S. databases. Furthermore, patients were initially identified by ICD-9 codes for HF. Thereafter, the data abstractors for EPRP confirmed physician documentation of HF in the electronic medical records. Relying on physician diagnosis of HF lends itself to the possibility of some misclassification, especially in patients with HFpEF, in whom coexistent obesity and/or COPD may confound the diagnosis of HF.

Conclusions

Although there is a higher prevalence of noncardiac comorbidities in patients with HFpEF compared with those with HFrEF, most individual comorbidities have comparable prognostic impact on mortality in both EF groups. The higher overall burden of comorbidities in HFpEF is associated with higher non-HF morbidity in patients with HFpEF compared with those with HFrEF. This underlines the importance of therapeutic approaches with greater emphasis on management of comorbidities in patients with HFpEF. Treatment strategies aimed mainly at reducing HF morbidity and mortality may have less overall impact on morbidity and mortality in patients with HFpEF.

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Key Words: comorbidities ■ diastolic heart function ■ heart failure with preserved ejection fraction ■ heart failure with reduced ejection fraction ■ prognosis.

APPENDIX

For a list of ICD-9 codes used to identify comorbidities, please see the online version of this article.