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Clinical Presentation, Management, and In-Hospital Outcomes of Patients Admitted With Acute Decompensated Heart Failure With Preserved Systolic Function

A Report From the Acute Decompensated Heart Failure National Registry (ADHERE) Database

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OBJECTIVES The aims of this analysis were to describe the clinical characteristics, management, and outcomes of patients hospitalized for acute decompensated heart failure (HF) with preserved systolic function (PSF).

BACKGROUND Clinically meaningful characteristics of these patients have not been fully studied in a large database.

METHODS Data from >100,000 hospitalizations from the Acute Decompensated Heart Failure National Registry (ADHERE) database were analyzed.

RESULTS Heart failure with PSF was present in 50.4% of patients with in-hospital assessment of left ventricular function. When compared with patients with systolic dysfunction, patients with PSF were more likely to be older, women, and hypertensive and less likely to have had a prior myocardial infarction or be receiving an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker. In-hospital mortality was lower in patients with PSF compared with patients with systolic dysfunction (2.8% vs. 3.9%; adjusted odds ratio [OR]: 0.86; $p = 0.005$), but duration of intensive care unit stay and total hospital length of stay were similar. Serum creatinine >2 mg/dl was associated with increased in-hospital mortality in both systolic function groups (PSF: 4.8%; systolic dysfunction: 8.4%; $p < 0.0001$), and the most powerful predictors of in-hospital mortality in both groups were blood urea nitrogen >37 mg/dl (OR: 2.53; 95% confidence interval [CI]: 2.22 to 2.87) and systolic blood pressure ≤125 mm Hg (OR: 2.58; 95% CI: 2.33 to 2.86).

CONCLUSIONS Heart failure with PSF is common and is characterized by a unique patient profile. Event rates are worrisome and reflect a need for more effective management strategies. (J Am Coll Cardiol 2006;47:76–84) © 2006 by the American College of Cardiology Foundation

Patients living with heart failure (HF) experience approximately 1 million annual hospitalizations for HF (1). About one-half of these hospitalizations may occur in patients who have HF with preserved systolic function (PSF), typically defined as symptomatic HF occurring in the setting of a measured left ventricular (LV) ejection fraction ≥40% (2,3).

Heart failure with PSF has not been studied as extensively as HF with systolic dysfunction. The limited data that are available in patients hospitalized for HF with PSF suggest that demographic characteristics, comorbidities, HF etiology, and pathology differ from those of patients with systolic dysfunction (2–6). Patients with PSF are usually older, more often women, and more likely to be obese than those with systolic dysfunction (2–6). In addition, patients with PSF typically have a left ventricle that is normal in size but has abnormal relaxation properties; in contrast, patients with systolic dysfunction usually have a left ventricle that is dilated but relaxes normally (5,6). Despite these differences, however, the clinical features of HF with PSF are similar to those of HF with systolic dysfunction and typically include evidence of volume overload, reduced exercise capacity, and impaired quality of life (3,4).

Important data are lacking regarding management, clinical outcomes, and predictors of in-hospital mortality for patients with HF and PSF. As a separate issue, renal dysfunction is an emerging risk factor for increased mortality and worsening HF in patients with systolic dysfunction,

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
ADHERE = Acute Decompensated Heart Failure National Registry
ARB = angiotensin II receptor blocker
BP = blood pressure
BUN = blood urea nitrogen
CART = classification and regression tree
CI = confidence interval
HF = heart failure
LV = left ventricular
OR = odds ratio
PSF = preserved systolic function

but similar data for patients with PSF are not available (7–11). Expanding the database relating to HF with PSF is essential for designing truly relevant clinical investigations in the future.

The primary goals of the present analysis were to characterize the clinical features, management, and outcomes of patients hospitalized for HF with PSF and to identify clinically relevant differences in these parameters from the same measures in patients hospitalized for HF with systolic dysfunction. A large cohort of patients from the Acute Decompensated Heart Failure National Registry (ADHERE) database served as the source of clinical data.

METHODS

The ADHERE procedures and the patients' characteristics that the registry tracks have been previously described (12). Briefly, medical records are retrospectively reviewed at participating sites by the research coordinator, and data from consecutive eligible male and female patients ≥18 years of age at the time of hospital admission are entered into the registry electronically (12). These data include demographic information, medical history, baseline clinical characteristics, initial evaluation, treatment received, procedures performed, hospital course, and patient disposition. Importantly, registry participation does not require any alteration of treatment or hospital care, and entry of data into the registry is not contingent on the use of any particular therapeutic agent or treatment regimen. Institutional review board approval is required for all participating centers; however, informed consent of individuals is not required for registry entry (12). In order to preserve patient confidentiality, direct patient identifiers are not collected. Registry entries thus reflect individual hospitalization events or "patient episodes," not individual patients, and multiple hospitalizations of the same patient may be entered into the registry as separate records. Longitudinal outcomes for each patient are not available.

Statistical analyses. Data from the ADHERE database were used for retrospective analyses of clinical characteristics, treatments, and outcomes for patient episodes of HF with PSF (LV ejection fraction ≥40%) or systolic dysfunction (LV ejection fraction <40%), based on the availability of LV ejection fraction assessment during hospitalization. Univariate comparisons between different groups were performed using chi-square, analysis of variance, and Wilcoxon tests, as appropriate. Two-sided p values were reported. In addition, mortality in the two systolic function groups was compared using logistic regression adjusted for mortality risk factors (described in later text). The effect of renal insufficiency (defined as serum creatinine >2 mg/dl) on mortality was evaluated separately in the two systolic function groups using logistic regression. To address the confounding circumstance of multiple readmissions of the same patients, the mortality analysis was also performed in a subset of unique patients with a first admission for HF. The Hosmer-Lemeshow test and the area under the receiver-operator curve were used to assess the fit and the discrimination of the models, respectively. Unless otherwise noted, these analyses were performed using version 8.2 of SAS software (SAS Institute Inc., Cary, North Carolina).

Mortality risk factors. Owing to anticipated differences in medical history and clinical characteristics at presentation between the two systolic function groups, it was important to adjust the mortality comparison for relevant prognostic factors. Because the number of collected characteristics was large and because certain data for some patient episodes were missing, a classification and regression tree (CART) analysis was used as a primary tool to identify key mortality predictors for all patient episodes with in-hospital LV ejection fraction assessments (13). The CART analysis is a nonparametric statistical method based on recursive partitioning that creates a binary decision tree, with a split in each node identifying the optimal discrimination value for a specified outcome variable. Patient episodes with missing data for a given predictor variable were included in the analysis using surrogate variables with information similar to that contained in the primary splitter variable. The tree was constrained to have at least 1,000 patient episodes in the parent nodes and at least 500 patient episodes in the final nodes, and its predictive ability was assessed using 10-fold cross-validation. The analysis was implemented using version 5.0 of CART software developed by Salford Systems (San Diego, California).

Of almost 80 demographic, medical history, and initial evaluation variables collected in the ADHERE database, 51 variables satisfied predetermined criteria of no more than 5% missing and at least 2% event frequency (for dichotomous variables). The following variables were analyzed: 3 demographic (age, gender, race [African American vs. other]); 20 medical history (history of atrial fibrillation, active malignancy, coronary artery disease, coronary artery disease diagnosis by angiogram, cardiac valvular disease, chronic obstructive pulmonary disease/asthma, chronic renal insufficiency, chronic renal dialysis, diabetes, HF, hyperlipidemia/dyslipidemia, hypertension, implantable cardioverter-defibrillator, liver disease, myocardial infarction, pacemaker, peripheral vascular disease, revascularize-

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Table 1. Demographic Characteristics and Medical History

Characteristic	Systolic Function		p*	No LVEF Assessment (n = 45,607)
	Preserved (n = 26,322)	Reduced (n = 25,865)		
Age (yrs, mean ± SD)	73.9 ± 13.2	69.8 ± 14.4	<0.0001	72.8 ± 14.1
Women (%)	62	40	<0.0001	51
Admission at academic center (%)	30	35	<0.0001	33
Medicare/Medicaid insurance (%)	80	73	<0.0001	81
African American (%)	17	22	<0.0001	22
Hypertension, CAD, or diabetes (%)	91	88	<0.0001	92
Hypertension (%)	77	69	<0.0001	72
CAD (%)	50	59	<0.0001	61
Diabetes mellitus (%)	45	40	<0.0001	46
Chronic renal insufficiency (%)	26	26	0.98	35
History of heart failure (%)	63	72	<0.0001	86
Prior myocardial infarction (%)	24	36	<0.0001	33
COPD or asthma (%)	31	27	<0.0001	33
Cardiac valvular disease (%)	21	22	0.13	24
Peripheral vascular disease (%)	17	17	0.33	19
Ventricular tachycardia (%)	3	11	<0.0001	10

*Comparison between preserved and reduced systolic function groups.
CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; LVEF = left ventricular ejection fraction.

tion, stroke, ventricular tachycardia/fibrillation); 15 chronic medications (diuretics, angiotensin-converting enzyme [ACE] inhibitors, angiotensin II receptor blockers [ARBs], anti-arrhythmics, aspirin, beta-blockers, calcium channel blockers, clopidogrel, digoxin, glitazone, lipid-lowering agents, nitrate, nonsteroidal anti-inflammatory drugs, peripheral vasodilators, warfarin); 12 initial evaluation assessments (atrial fibrillation on electrocardiogram, blood urea nitrogen [BUN], creatinine, diastolic blood pressure [BP], systolic BP, heart rate, hemoglobin, sodium, dyspnea at rest, fatigue, peripheral edema, rales); and insurance type (Medicare/Medicaid vs. other). For most (41 of 51) variables, fewer than 0.09% of the values were missing, but for six variables, more than 1% of the values were missing in patient episodes with in-hospital LV ejection fraction assessments.

Findings from the CART analyses were supported by multiple logistic regression analysis based on complete cases.

RESULTS

As of January 2004, the ADHERE database included 105,388 patient admissions for HF at 274 centers. Left ventricular ejection fraction was quantitatively determined during hospitalization in 52,187 (49.52%) of these admissions. In this population, 26,322 admissions (50.4%) presented with PSF.

In the remaining patient hospitalizations (n = 53,201), qualitative assessment of in-hospital LV ejection fraction (normal, mild, moderate, or severe impairment) was available in 7,594 cases (14.3%), with no information about in-hospital LV ejection fraction in the remaining 45,607 patient admissions. The measurement of LV ejection fraction in the group with qualitative LV ejection fraction assessment demonstrated the presence of intact systolic function in 71% of patient episodes. Descriptive data on this group are very similar to the PSF group. The data regarding the group without an in-hospital assessment of LV ejection fraction are clinically distinct and reflect an apparent higher risk profile. These data are shown in the tables, but are not the focus of this manuscript.

Demographics and clinical characteristics. Demographics and characteristics of the past medical history for patient episodes of HF with PSF are shown in Table 1. These episodes were characterized by advanced age, predominance of female gender, and a lower proportion of African Americans. More than 90% of patient episodes with PSF had a history of hypertension, coronary artery disease, or diabetes. Additionally, a prior history of HF was present in almost two-thirds of patient episodes with PSF, and a history of a prior myocardial infarction was present in 24%.

Clinical presentation. Clinical characteristics of patient episodes of HF with PSF at presentation are shown in Table 2. Episodes of HF with PSF were associated with a generally higher systolic BP, resulting in a higher rate of systolic hypertension (systolic BP >140 mm Hg) and a lower rate of hypotension (systolic BP ≤90 mm Hg). In addition, heart rate was lower and atrial fibrillation and peripheral edema occurred more often. The frequency of dyspnea at rest and parameters of renal function were similar for both groups.

Management. Before hospitalization, approximately two-thirds of patient episodes of HF with PSF were treated with diuretics (Table 3). The use of an ACE inhibitor or an ARB, use of digoxin, and use of spironolactone occurred less often in patient episodes with PSF compared with those with systolic dysfunction. Conversely, beta-blocker use was slightly higher in patient episodes with PSF compared with those with systolic dysfunction.

During hospitalization, the use of oral therapies for HF increased relative to the before-hospitalization period in both groups, but more so for patient episodes with systolic

Table 2. Clinical Presentation

Characteristic	Systolic Function		p*	No LVEF Assessment
	Preserved (n = 26,322)	Reduced (n = 25,865)		(n = 45,607)
Admission to ED or observation unit (%)	79	75	<0.0001	79
Admission to intensive care unit (%)	14	18	<0.0001	12
Peripheral edema (%)	69	63	<0.0001	65
Rales (%)	69	67	0.0002	67
Systolic BP >140 mm Hg (%)	61	44	<0.0001	46
Systolic BP (mm Hg, mean ± SD)	152.5 ± 32.7	138.9 ± 30.9	<0.0001	140.9 ± 32.5
Systolic BP ≤90 mm Hg (%)	1	4	<0.0001	4
Diastolic BP (mm Hg, mean ± SD)	78.7 ± 20.6	80.0 ± 20.4	<0.0001	76.0 ± 19.7
Initial serum Cr (mg/dl, mean ± SD)	1.7 ± 1.5	1.6 ± 1.3	0.0281	1.9 ± 1.8
Serum Cr >2 mg/dl (%)	17	18	0.57	24
BUN (mg/dl, mean ± SD)	29.3 ± 19.3	30.2 ± 19.8	<0.0001	34.5 ± 22.5
Heart rate (beats/min, mean ± SD)	86.8 ± 22.0	92.9 ± 22.7	<0.0001	86.7 ± 20.7
Dyspnea at rest (%)	34	34	0.19	35
Atrial fibrillation on first ECG (%)	21	17	<0.0001	20

*Comparison between preserved and reduced systolic function groups.
BP = blood pressure; BUN = blood urea nitrogen; Cr = creatinine; ECG = electrocardiogram; ED = emergency department; LVEF = left ventricular ejection fraction.

dysfunction (Tables 3 and 4). With the exception of ARBs, all oral medications were used significantly less often during patient episodes with PSF (Table 4). Furthermore, the difference in the use of these agents became greater during hospitalization (Tables 3 and 4). For example, the use of an ACE inhibitor in patients without diabetes increased by 73% in patient episodes with PSF, compared with 82% in patient episodes with systolic dysfunction.

Whereas the use of intravenous diuretics during hospitalization was high in patient episodes with PSF, parenteral vasodilators, nesiritide, and inotropes were used infrequently and significantly less often than in patient episodes with systolic dysfunction (Table 4).

The pattern of use of oral therapy for HF at discharge (Table 5) was similar to that reported before (Table 3) and during hospitalization (Table 4). Diuretic use remained high in both groups, whereas the use of ACE inhibitors or ARBs, use of beta-blockers, use of digoxin, and use of spironolactone was lower for patient episodes of HF with PSF.

Outcomes during hospitalization. Clinical outcomes during hospitalization are shown in Table 6. In-hospital mortality was significantly lower for patient episodes of HF with PSF compared with episodes with systolic dysfunction. Length of stay in the two groups was similar, but the need for intensive care unit management was significantly lower in patient episodes of HF with PSF. The proportion of patients losing weight during hospitalization and the proportion discharged with persistent symptomatic HF of mild-to-moderate severity was similar in both groups.

Adjusted mortality analysis. On the basis of data from all patient episodes with quantitative in-hospital LV ejection fraction assessments, CART analysis identified elevated BUN, lower systolic BP, low sodium, older age, elevated creatinine, presence of dyspnea at rest, and absence of chronic beta-blocker use as mortality risk factors. Among these variables, the two main contributors to higher mortality (the top splits in the tree) were BUN >37 mg/dl and systolic BP ≤125 mm Hg. When the CART analysis was carried out in the PSF and

Table 3. Use of Non-Intravenous Medications Before Hospitalization

Medication	Systolic Function		p*	No LVEF Assessment
	Preserved (n = 26,322)	Reduced (n = 25,865)		(n = 45,607)
Diuretic (%)	64.8	65.5	0.14	76.6
ACE inhibitor (%)	36.1	42.5	<0.0001	43.4
Patients without history of diabetes, n/total (%)	4,468/14,501 (30.8)	5,898/15,376 (38.4)	<0.0001	10,290/24,814 (41.5)
Patients with history of diabetes, n/total (%)	5,026/11,800 (42.6)	5,076/10,465 (48.5)	<0.0001	9,489/20,753 (45.7)
ARB (%)	12.7	10.9	<0.0001	12.2
ACE inhibitor or ARB (%)	47.3	52.3	<0.0001	54.3
Beta-blocker (%)	45.5	44.2	0.0026	52.4
Patients without history of MI, n/total (%)	8,262/19,956 (41.4)	6,377/16,587 (38.4)	<0.0001	14,727/30,517 (48.3)
Patients with history of MI, n/total (%)	3,717/6,345 (58.6)	5,053/9,254 (54.6)	<0.0001	9,156/15,050 (60.8)
Digoxin (%)	18.7	30.4	<0.0001	32.5
Spironolactone (%)	5.4	11.4	<0.0001	13.0

*Comparison between preserved and reduced systolic function groups.
ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; LVEF = left ventricular ejection fraction; MI = myocardial infarction.

Table 4. Use of Non-Intravenous and Intravenous Medications During Hospitalization

Medication	Systolic Function		p*	No LVEF Assessment (n = 45,607)
	Preserved (n = 26,322)	Reduced (n = 25,865)		
Non-intravenous medications				
Diuretic (%)	73.9	79.5	<0.0001	72.0
ACE inhibitor (%)	55.2	68.8	<0.0001	51.5
Patients without history of diabetes, n/total (%)	7,727/14,513 (53.2)	10,765/15,393 (69.9)	<0.0001	12,675/24,834 (51.0)
Patients with history of diabetes, n/total (%)	6,790/11,809 (57.5)	7,040/10,471 (67.2)	<0.0001	10,820/20,770 (52.1)
ARB (%)	15.1	12.9	<0.0001	13.6
ACE inhibitor or ARB (%)	67.0	78.8	<0.0001	63.0
Beta-blocker (%)	58.4	68.6	<0.0001	56.9
Patients without history of MI, n/total (%)	11,087/19,972 (55.5)	11,257/16,603 (67.8)	<0.0001	16,324/30,543 (53.4)
Patients with history of MI, n/total (%)	4,279/6,350 (67.4)	6,492/9,261 (70.1)	0.0003	9,633/15,061 (64.0)
Digoxin (%)	25.7	48.6	<0.0001	36.5
Spironolactone (%)	12.5	27.4	<0.0001	18.9
Intravenous medications				
Diuretic (%)	91	89	<0.0001	85
Diuretic, no. of vasoactive agents (%)	69	56	<0.0001	62
Vasoactive therapy (%)	23	37	<0.0001	26
Inotropes, any (%)	8	19	<0.0001	12
Dobutamine (%)	3	11	<0.0001	6
Dopamine (%)	5	10	<0.0001	5
Milrinone (%)	1	5	<0.0001	3
Vasodilator, any (%)	18	24	<0.0001	17
Nesiritide (%)	8	14	<0.0001	10
Nitroglycerin (%)	11	12	0.0485	8
Nitroprusside (%)	1	1	0.0227	<1

*Comparison between preserved and reduced systolic function groups.
Abbreviations as in Table 3.

systolic dysfunction groups separately, elevated BUN and lower systolic BP were confirmed as the most important mortality predictors within each group. In addition, increased heart rate was identified as a mortality predictor in patient episodes of HF with PSF, but not in patient episodes of HF with systolic dysfunction. Multivariate odds ratios (ORs) and corresponding 95% confidence intervals (CIs) for in-hospital death are reported for each of the mortality risk factors previously identified by the CART model (Table 7). The CART analysis in patients with new-onset HF identified the same mortality risk factors (elevated BUN, low systolic BP, low serum sodium concentration, and advanced age) as in all patient episodes with quantitative in-hospital LV ejection fraction assessment. Moreover, these findings were supported by multiple logistic regression analyses (data not shown). Because heart rate was selected as a mortality risk factor in several CART and logistic regression models, it was added to the final list of adjustments, which included BUN, systolic BP, sodium, age, creatinine, heart rate, dyspnea at rest, and chronic beta-blocker use. Because adding second-order interaction terms increased the predictive power of the model (as determined by the area under the receiver-operator curve) by only 1%, these terms were not included in the final model.

Table 5. Use of Non-Intravenous Medications at Discharge

Medication	Systolic Function		p*	No LVEF Assessment (n = 45,607)
	Preserved (n = 26,322)	Reduced (n = 25,865)		
Diuretic (%)	79.5	83.7	<0.0001	79.6
ACE inhibitor (%)	47.1	61.5	<0.0001	46.2
Patients without history of diabetes, n/total (%)	6,606/14,508 (45.5)	9,683/15,387 (62.9)	<0.0001	11,379/24,823 (45.8)
Patients with history of diabetes, n/total (%)	5,798/11,804 (49.1)	6,204/10,466 (59.3)	<0.0001	9,689/20,763 (46.7)
ARB (%)	13.2	11.0	<0.0001	12.3
ACE inhibitor or ARB (%)	58.9	71.3	<0.0001	57.4
Beta-blocker (%)	52.2	62.6	<0.0001	52.2
Patients without history of MI, n/total (%)	9,904/19,964 (49.6)	10,326/16,598 (62.2)	<0.0001	14,918/30,531 (48.9)
Patients with history of MI, n/total (%)	3,841/6,348 (60.5)	5,866/9,255 (63.4)	0.0003	8,869/15,055 (58.9)
Digoxin (%)	21.1	44.1	<0.0001	33.1
Spironolactone (%)	10.6	24.7	<0.0001	17.0

*Comparison between preserved and reduced systolic function groups.
Abbreviations as in Table 3.

Table 6. Clinical Outcomes During Hospitalization

Outcome	Systolic Function			No LVEF Assessment (n = 45,607)
	Preserved (n = 26,322)	Reduced (n = 25,865)	p*	
Mortality (%)	2.8	3.9	<0.0001	4.8
Length of hospitalization (days, median [interquartile range])	4.9 [3.1–7.6]	5.0 [3.2–8.1]	<0.0001	3.8 [2.3–6.1]
Admitted to ICU (%)	18.9	24.7	<0.0001	15.3
Length of ICU/CCU stay (days, median [interquartile range])	2.7 [1.4–4.9]	3.0 [1.6–5.1]	<0.0001	2.0 [1.0–3.8]
Weight loss >10 lbs (%)	79.8	80.7	0.0298	75.8
	26.9	30.4	<0.0001	23.2
Asymptomatic at discharge (%)	55	55	0.21	51

*Comparison between preserved and reduced systolic function groups.
CCU = coronary care unit; ICU = intensive care unit; LVEF = left ventricular ejection fraction.

Whereas the adjustment for gender and race (percent African American) did not affect the mortality difference between the PSF and systolic dysfunction groups (unadjusted OR: 0.70; 95% CI: 0.64 to 0.77; $p < 0.0001$; and OR after adjustment for gender and race: 0.68; 95% CI: 0.61 to 0.75; $p < 0.0001$), the adjustment for gender, race, and eight mortality risk factors reduced the magnitude of mortality difference (adjusted OR: 0.86; 95% CI: 0.77 to 0.96; $p = 0.005$). However, it remained statistically significant. The Hosmer-Lemeshow test was not significant ($p = 0.16$), and the area under the receiver-operator curve was 0.76, indicating that the final adjusted model provides an adequate fit and a high degree of discrimination. Thus, the mortality differences between the two systolic function groups are real and are not accounted for by known risk factors. Similar results were obtained in the subset of patients with new-onset HF (9,758 patients with PSF vs. 7,204 patients with systolic dysfunction): after adjustment for gender, race, and eight risk factors, the mortality OR for PSF versus systolic dysfunction increased (unadjusted OR: 0.68; 95% CI: 0.56 to 0.83; $p = 0.0001$; and adjusted OR: 0.79; 95% CI: 0.63 to 0.98; $p = 0.03$), but remained statistically significant.

Patient episodes with renal insufficiency (serum creatinine >2 mg/dl) had significantly greater in-hospital mortality regardless of LV function both before and after adjusting for gender, race, and mortality risk factors (Table 8).

DISCUSSION

This analysis of the ADHERE database, which involved more than 25,000 patient episodes of HF with PSF, represents the largest clinical evaluation of this population to date. Data from the ADHERE database confirm findings of previous smaller studies and provide new insights into patient episodes of HF with PSF. The ADHERE database clearly indicates that PSF is associated with one-half of all hospitalizations for HF. As noted before, patients admitted with HF and PSF are typically older and more likely to be women. Our data now provide additional demographics and clinical characteristics and further describe the clinical presentation of this disorder. Observed differences in treatment between the PSF and systolic dysfunction groups reflect a lack of evidence-based strategies for management of HF with PSF. However, even when such strategies exist, as in HF with systolic dysfunction, they may be infrequently followed; only 71% of patients with systolic dysfunction in this evaluation were prescribed an ACE inhibitor or ARB at hospital discharge. We have demonstrated that the risk of in-hospital death is lower for patient episodes of HF with PSF, but all other clinically important outcomes are similar. Importantly, in-hospital mortality risk factors are virtually identical for both systolic function groups with elevated BUN and lower systolic BP, the two most important predictors of in-hospital mortality.

Table 7. Multivariate* Odds Ratios and 95% Confidence Intervals for Identified Mortality Risk Factors

Mortality Risk Factors	All Patient Episodes with Quantitative LVEF Assessment	Systolic Function		No LVEF Assessment
		Preserved	Reduced	
Systolic BP ≤125 mm Hg	2.58 (2.33–2.86)	2.66 (2.28–3.11)	2.33 (2.03–2.68)	2.23 (2.03–2.44)
BUN >37 mg/dl	2.53 (2.22–2.87)	2.57 (2.11–3.14)	2.51 (2.12–2.97)	2.03 (1.81–2.28)
Sodium ≤132 mmol/l	1.99 (1.76–2.26)	1.72 (1.40–2.12)	2.15 (1.83–2.52)	1.97 (1.76–2.21)
Age >73 yrs	1.76 (1.58–1.96)	2.08 (1.74–2.48)	1.62 (1.41–1.85)	2.13 (1.92–2.36)
Dyspnea at rest	1.55 (1.40–1.72)	1.56 (1.34–1.82)	1.55 (1.35–1.77)	1.56 (1.42–1.71)
Cr >1.5 mg/dl	1.39 (1.22–1.58)	1.24 (1.02–1.52)†	1.50 (1.27–1.77)	1.37 (1.22–1.54)
No chronic beta-blocker	1.37 (1.23–1.51)	1.51 (1.29–1.77)	1.28 (1.17–1.46)	1.60 (1.46–1.76)
Heart rate >78 beats/min	1.34 (1.20–1.49)	1.55 (1.32–1.84)	1.14 (0.98–1.32)‡	1.40 (1.27–1.54)

$p < 0.0001$ unless noted otherwise. *Adjusted for all variables shown in the table. †$p = 0.03$. ‡$p = 0.08$.
BP = blood pressure; BUN = blood urea nitrogen; Cr = creatinine; LVEF = left ventricular ejection fraction.

Table 8. Mortality According to Renal Function

Category	Systolic Function	
	Preserved (n = 26,002)*	Reduced (n = 25,447)*
Mortality (Cr >2 mg/dl vs. Cr ≤2 mg/dl)	4.8% vs. 2.3%	8.4% vs. 2.9%
Unadjusted OR (95% CI)	2.12 (1.80–2.49); p < 0.0001	3.11 (2.72–3.55); p < 0.0001
Adjusted† OR (95% CI)	2.45 (2.07–2.92); p < 0.0001‡	2.72 (2.36–3.14); p < 0.0001§

*Based on patients with available assessments of Cr at presentation. †Adjusted for gender, race, age, systolic blood pressure, sodium, pulse, dyspnea at rest, and chronic beta-blocker use. No adjustment for blood urea nitrogen or Cr was made owing to high correlation of these variables and renal insufficiency status. ‡Based on the data for 24,833 patients with preserved systolic function with complete covariate information. The Hosmer-Lemeshow test was not statistically significant (p = 0.59), and the area under the curve was 0.73. §Based on the data for 24,396 patients with reduced systolic function with complete covariate information. The Hosmer-Lemeshow test was not statistically significant (p = 0.14), and the area under the curve was 0.75.
CI = confidence interval; Cr = creatinine; OR = odds ratio.

Apart from age and gender, the other clinically relevant differences between patient episodes of HF with PSF and with systolic dysfunction were the lower rate of prior myocardial infarction and the higher rate of systolic hypertension in the PSF group. Rales, peripheral edema, and a history of HF were common in both groups. It is quite notable to observe the similarity of presentation characteristics for patients with HF and either PSF or systolic dysfunction. The use of bedside clinical assessment may not be adequate to determine underlying ventricular function in the setting of decompensated HF.

Consistent with the similarity in presentation and treatment, the hospital course of patient episodes of HF with either PSF or systolic dysfunction is also quite similar. The length of stay is almost identical, and a similar proportion of patient episodes are discharged with persistent symptoms. Approximately 70% of the patients in both systolic function groups were discharged with weight loss of <10 lbs, despite evidence of congestion at presentation. This high rate of seemingly ineffective therapy and persistent symptomatology is of concern and indicates an opportunity to improve the quality of care. Given the presence of volume overload (e.g., rales and peripheral edema are found in nearly 70% of patient episodes of HF with PSF), a reasonable target of acute therapy might be more effective volume reduction.

Although the use of oral neurohormonal blocking agents increased during hospitalization and at discharge, these therapies were used significantly less often in patient episodes of HF with PSF. Similar patterns of medication use were documented in previous studies of patients hospitalized for HF with PSF (2,3,6).

Among parenteral medications, diuretics were used in the vast majority of admissions in both systolic function groups. The use of intravenous vasoactive therapies was low, particularly in patient episodes with PSF. The use of vasodilators and nesiritide was significantly lower in the PSF group (vs. the systolic dysfunction group). The observed use of inotropes is inexplicable given the known mortality risks associated with these agents, the absence of a reasonable indication for use (i.e., cardiogenic shock or impending cardiogenic shock), and the extremely low rate of frank hypotension in patient episodes of HF with PSF (14–16).

It is apparent that evidence-based therapies for chronic HF with systolic dysfunction are frequently used in patients with PSF without data to substantiate the efficacy of this approach. In some cases, these medications may have been used to manage comorbidities such as hypertension, coronary artery disease, and diabetes (which are present with high frequency in this patient population). Nevertheless, clinical trials evaluating the impact of these therapies in patients with HF and PSF are clearly needed.

The data from the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM)-Preserved trial would suggest at least a modest morbidity benefit associated with chronic use of the ARB candesartan in patients with PSF (17). The ongoing Irbesartan in Heart Failure with Preserved Systolic Function trial is evaluating the ARB irbesartan in a similar patient population. In the ADHERE database, fewer than 16% of patient episodes with documented HF and PSF were treated with an ARB before, during, and after hospitalization, but this may change as the benefit of ARBs is more definitively established.

There may be reasonable arguments to support the use of beta-blockers in patients presenting with HF and PSF (e.g., clinical benefits in hypertension and ischemic heart disease, a reduction in heart rate with a corresponding increase in the diastolic filling period, the relief of ischemia with an improvement in compliance, the reduction in sympathetic activation, and regression of ventricular hypertrophy), but there have been no published clinical trials to date of beta-blockers in this setting (18,19). Interestingly, our dataset suggests an increased mortality risk associated with an absence of chronic beta-blocker use in HF with PSF.

Aldosterone antagonists have a protean cardiovascular profile. Among the many described benefits of aldosterone antagonism is selective targeting of the extracellular matrix, which may improve ventricular compliance by retarding collagen deposition and reducing fibrosis (20,21). Available data indicate that aldosterone antagonists promote regression of ventricular hypertrophy and reduce the incidence of sudden cardiac death in patients with LV dysfunction, but no data have yet been acquired specifically in the setting of HF with PSF (22–24).

Within the Digitalis Investigation Group trial, the use of digoxin was associated with an improvement in clinical outcomes in the subset of patients with HF and PSF. Explanations for this benefit are incompletely resolved (25).

Natriuretic peptides have been shown to exert positive lusitropic effects and are indicated in the management of patients with acute decompensated HF (26,27). Within the Vasodilatation in the Management of Acute CHF (VMAC) trial, nearly 15% of acutely symptomatic patients had HF with PSF (26). For each time point of data collection within the 3-h primary end point period, nesiritide led to a greater decrease in pulmonary capillary wedge pressure than either nitrates or placebo (26).

Previous studies have established that patients with HF and PSF are at risk for adverse clinical outcomes. In a population-based study, mortality risk of HF patients with PSF was four-fold greater than that of age- and gender-matched controls without HF (28). Similar findings were recently reported for subjects with diastolic dysfunction but without HF (29). In a recent study of 170 patients with HF, high rates of mortality and hospital readmission (during a mean follow-up of 2.4 years) were evident both in patients with LV ejection fraction <40% and in those with LV ejection fraction ≥40%, without significant differences between the groups (6). Consistent with the results of these earlier studies, the present analysis of the ADHERE database also demonstrates worrisome event rates for HF with PSF which, albeit lower than for HF with systolic dysfunction, do raise concerns and point out the lack of effective management strategies for HF with PSF.

Renal insufficiency contributes to increased mortality in patients with HF. The in-hospital mortality rates in the PSF and systolic dysfunction groups (2.8% and 3.9%, respectively) are further increased in patients with baseline serum creatinine >2.0 mg/dl (4.8% and 8.4%, respectively). Thus, renal insufficiency is a clear risk factor for in-hospital mortality, regardless of LV function.

A unique contribution of this study is identification of mortality predictors using the ADHERE database. Classification and regression tree analysis for all patients with a quantitative in-hospital assessment of LV ejection fraction identified seven variables that were predictive of in-hospital mortality. Among these variables, elevated BUN (>37 mg/dl) and lower systolic BP (<125 mm Hg) were determined to be the strongest multivariate predictors of mortality in the overall cohort of patient admissions for HF with quantitative in-hospital assessment of LV ejection fraction (including *both* PSF and systolic dysfunction). These findings are consistent with our previously reported mortality risk assessment for acute decompensated HF, but vary slightly because the analysis was restricted to those with quantitative in-hospital assessment of LV ejection fraction (30). Elevated BUN or reduced systolic BP were both associated with a >2-fold increase in in-hospital mortality. Other mortality predictors included elevated serum creatinine, low serum sodium, increasing age, dyspnea at rest, and an absence of chronic beta-blocker use in both systolic function groups. Increased heart rate, on the other hand, was a risk factor for mortality in patient episodes of HF with PSF, but not in admissions for HF with systolic dysfunction. The prognostic value of mortality predictors in patient episodes with HF and quantitative in-hospital LV ejection fraction assessment also is evident for primary admissions for HF, suggesting that the data are broadly applicable and are not confounded by multiple readmissions in high-risk patients.

Study limitations. The ADHERE database is not a clinical trial but a registry. As such, there are no treatment requirements, randomization, or longitudinal follow-up. Because no patient identifiers are collected, patients may be entered in the registry more than once, and after-discharge patient status cannot be assessed. The data are observational, and the analysis is retrospective. In addition, the results may be influenced by assessment and treatment regimens that are not standardized and vary by institution. The data presented apply to those patients with a recent measurement of LV function, as the patient cohort without an in-hospital assessment of LV ejection fraction differs from the primary cohort of patients with a measured LV ejection fraction. Therefore, these data should not be extrapolated to patients without a recent measurement of LV ejection fraction.

Conclusions. This analysis from the ADHERE database further describes HF with PSF, especially in the context of acute decompensation necessitating hospitalization. The profile of a patient presenting to the hospital with HF and PSF is now well characterized. Presentation and initial management for HF with either PSF or systolic dysfunction are quite similar. However, evidence-based treatment strategies for HF with PSF are much less well established. The ADHERE database demonstrates significant in-hospital mortality of patients with HF, regardless of LV function. Patient episodes of HF with PSF, however, are associated with lower in-hospital mortality than are episodes of HF with systolic dysfunction. Several variables appear to predict an increased risk of death, most notably BUN >37 mg/dl and systolic BP <125 mm Hg. The mortality rates in both the PSF and systolic dysfunction groups were increased in the presence of impaired renal function (serum Cr >2 mg/dl). It is apparent that the adverse outcomes are driven, at least in part, by the lack of evidence-based treatment algorithms. The role of parenteral therapies in the management of patients with HF and PSF clearly requires further investigation. Newer therapies that alleviate symptoms and improve outcomes are needed for acute decompensated HF, irrespective of LV function.

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APPENDIX

For a list of the ADHERE Scientific Advisory Committee, please see the online version of this article.