Outcome of Heart Failure with Preserved Ejection Fraction in a Population-Based Study

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ABSTRACT

BACKGROUND

The importance of heart failure with preserved ejection fraction is increasingly recognized. We conducted a study to evaluate the epidemiologic features and outcomes of patients with heart failure with preserved ejection fraction and to compare the findings with those from patients who had heart failure with reduced ejection fraction.

METHODS

From April 1, 1999, through March 31, 2001, we studied 2802 patients admitted to 103 hospitals in the province of Ontario, Canada, with a discharge diagnosis of heart failure whose ejection fraction had also been assessed. The patients were categorized in three groups: those with an ejection fraction of less than 40 percent (heart failure with reduced ejection fraction), those with an ejection fraction of 40 to 50 percent (heart failure with borderline ejection fraction), and those with an ejection fraction of more than 50 percent (heart failure with preserved ejection fraction). Two groups were studied in detail: those with an ejection fraction of less than 40 percent and those with an ejection fraction of more than 50 percent. The main outcome measures were death within one year and readmission to the hospital for heart failure.

RESULTS

Thirty-one percent of the patients had an ejection fraction of more than 50 percent. Patients with heart failure with preserved ejection fraction were more likely to be older and female and to have a history of hypertension and atrial fibrillation. The presenting history and clinical examination findings were similar for the two groups. The unadjusted mortality rates for patients with an ejection fraction of more than 50 percent were not significantly different from those for patients with an ejection fraction of less than 40 percent at 30 days (5 percent vs. 7 percent, P=0.08) and at 1 year (22 percent vs. 26 percent, P=0.07); the adjusted one-year mortality rates were also not significantly different in the two groups (hazard ratio, 1.13; 95 percent confidence interval, 0.94 to 1.36; P=0.18). The rates of readmission for heart failure and of in-hospital complications did not differ between the two groups.

CONCLUSIONS

Among patients presenting with new-onset heart failure, a substantial proportion had an ejection fraction of more than 50 percent. The survival of patients with heart failure with preserved ejection fraction was similar to that of patients with reduced ejection fraction.

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HEART FAILURE HAS CLASSICALLY BEEN considered to be a clinical syndrome associated with cardiac dilatation and impaired cardiac contractility.[1] However, studies have found that increasing numbers of patients presenting with clinical heart failure have an ejection fraction of more than 50 percent.[1-3] This entity, which has been termed "heart failure with preserved ejection fraction," is attributed to abnormalities of diastolic function, although the exact mechanism is debated.[4,5]

Prior data suggest that patients who have heart failure with preserved ejection fraction tend to be older, to be female, and to have a history of hypertension.[1,3,6,7] The prognosis for such patients has been reported to be better than that for patients who have heart failure with reduced ejection fraction.[3,6,8-10] However, most available data are based on ambulatory populations, with less information on patients admitted to the hospital with heart failure.[3,6,8-12] The results of these studies have been inconsistent or conflicting, and the estimates of rates of mortality and rehospitalization vary widely, since they are derived from heterogeneous populations with different inclusion criteria.[2,6,13,14]

We conducted a large, population-based cohort study to evaluate the epidemiologic features and outcomes of patients with heart failure with preserved ejection fraction and to compare the findings with those from patients who had heart failure with reduced ejection fraction.

METHODS

PATIENTS

Between April 1, 1999, and March 31, 2001, we identified all newly admitted patients with a primary discharge diagnosis of heart failure from 103 hospitals in Ontario, Canada, as part of the Enhanced Feedback for Effective Cardiac Treatment (EFFECT) study. The criteria for the selection of the sample population have been described previously.[15] The hospitals included teaching hospitals and community-based institutions from both rural and urban settings. All had admitted more than 30 patients with heart failure during the two years of sampling.

At each hospital, patients with heart failure (*International Classification of Diseases, Ninth Revision, Clinical Modification* code 428) were identified by using the Canadian Institute for Health Information hospital discharge abstracts.[16,17] On the basis of chart review, we included only patients presenting to the hospital for the first time with heart failure who met the Framingham Study criteria for heart failure.[18]

We excluded patients who had a previous recorded admission for heart failure, those in whom heart failure developed after admission (i.e., as an in-hospital complication), those who were transferred from another acute care facility, those 105 years of age or older, nonresidents of the province of Ontario, and those with an invalid Ontario health-insurance-card number. We also excluded all patients whose left ventricular ejection fraction had not been evaluated by echocardiography, left ventricular angiography, or radionuclide angiography and all patients who had any severe primary left-sided valvular abnormality on echocardiography.

The records of patients who met the inclusion and exclusion criteria were reviewed for abstraction of clinical data. For hospitals treating at least 125 suitable candidates during the study period, a random sample of 125 charts was reviewed. For hospitals that treated fewer than 125 suitable candidates during the study period, all charts were reviewed.

Patients with documented left ventricular function were divided into three groups: those with an ejection fraction of less than 40 percent (heart failure with reduced ejection fraction), those with an ejection fraction of 40 to 50 percent (heart failure with a borderline ejection fraction), and those with an ejection fraction of more than 50 percent (heart failure with preserved ejection fraction). Those with an ejection fraction of 40 to 50 percent were excluded from most of the analyses, because we wanted to have two distinct groups for comparison. Approval of the institutional ethics review board was obtained from each participating institution before the study. Because the study involved only the review of records obtained as a part of routine medical care, no patient consent was required.

DATA COLLECTION AND VARIABLE DEFINITIONS

We defined a set of clinical and demographic factors that may potentially be associated with death from heart failure and that were available from chart review. For each patient, the time to death was calculated by linking the hospital discharge data to the Registered Persons Database (RPDB)

with the use of each patient's encrypted health care number. The RPDB provides data on the vital status of residents of Ontario and records deaths both in and out of the hospital. Data for each patient were censored one year after admission, so that there was one year of follow-up for each patient.

The primary end point of the study was death from any cause after the index hospitalization for heart failure. Secondary outcomes included rates of 30-day and 1-year readmission to the hospital for heart failure. Other secondary outcomes were in-hospital complication rates, including myocardial infarction, admission to a coronary care unit or intensive care unit (ICU), renal failure, hypotension, shock, and the need for mechanical ventilation.

STATISTICAL ANALYSIS

The demographic and clinical characteristics of patients with heart failure with preserved ejection fraction and of those with reduced ejection fraction were compared. Dichotomous variables were compared by the chi-square test and continuous variables by Student's t-test.

We used Cox proportional-hazards analysis to identify factors associated with an increased risk of death after hospitalization for heart failure. Candidate variables were included in the initial Cox regression model if they were associated with death in a univariate analysis (P<0.20). Backward variable elimination, with an elimination criterion of a P value of more than 0.05, was then used to create a parsimonious model for predicting death. By forcing an indicator variable denoting ejection-fraction group into the model at each stage of the variable selection process, we determined the adjusted hazard ratio for death among patients with reduced ejection fraction as compared with those with preserved ejection fraction. We determined that the assumption of proportional hazards was met in all Cox regression models. Survival curves were constructed for the two ejection-fraction groups after adjustment for all covariates in the final model. In a separate analysis, the independent predictors of death for patients with reduced ejection fraction and for patients with preserved ejection fraction were determined with the use of Cox proportional-hazards regression and methods similar to those described above. The results are shown as means ±SD unless otherwise indicated. Statistical analysis was performed with SAS software, version 8.2; a P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

A total of 9945 patients were admitted and met the predefined criteria for heart failure at the 103 participating hospitals during the study period. Of these, 5775 patients were excluded because echocardiography, angiography, or nuclear scintigraphy was not performed at admission. Another 717 patients who had undergone echocardiography were excluded because their ejection fraction had not been documented, and 649 were excluded because they had severe aortic or mitral valve disease. Two patients were excluded because they did not have a valid health-card number.

Among the remaining hospitalized patients with heart failure whose ejection fraction had been measured, 880 (31 percent) had a preserved ejection fraction (more than 50 percent) and 1570 (56 percent) had a reduced ejection fraction (less than 40 percent). The remaining 352 (13 percent) had a borderline ejection fraction (40 to 50 percent); to provide more distinct comparison groups, the data from the group with borderline ejection fraction were excluded from most of the presented data analysis.

CLINICAL CHARACTERISTICS

The clinical characteristics of the study patients are shown in Table 1. Patients with preserved ejection fraction were older (75 vs. 72 years, P<0.001), were more likely to be female (66 percent vs. 37 percent, P<0.001), and had a significantly higher incidence of hypertension (55 percent vs. 49 percent, P=0.005) than those with reduced ejection fraction. Patients with preserved ejection fraction had significantly lower rates of other modifiable cardiac risk factors, including smoking, diabetes, and hyperlipidemia. Patients with preserved ejection fraction also had lower rates of peripheral vascular disease, angina, prior myocardial infarction, and prior coronary-artery bypass surgery. However, patients with preserved ejection fraction had significantly higher rates of atrial fibrillation (31.8 percent vs. 23.6 percent, P<0.001) and chronic obstructive pulmonary disease (17.7 percent vs. 13.2 percent, P=0.002).

Table 2 summarizes the symptoms and clin-

Table 1. Characteristics of Patients.*

Characteristic	Reduced Ejection Fraction (<40%) (N=1570)	Preserved Ejection Fraction (>50%) (N=880)	P Value
Mean LVEF — %	25.9	62.4	<0.001
Age — yr	71.8 ± 12	75.4 ± 11.51	<0.001
Male sex — no. (%)	983 (62.6)	302 (34.3)	<0.001
Coronary artery disease or ischemia — no. (%)	764 (48.7)	312 (35.5)	<0.001
Hypertension — no. (%)	772 (49.2)	485 (55.1)	0.005
Hyperlipidemia — no. (%)	350 (22.3)	136 (15.5)	<0.001
Diabetes — no. (%)	611 (38.9)	279 (31.7)	<0.001
Cerebrovascular accident or transient ischemic attack — no. (%)	229 (14.6)	133 (15.1)	0.72
Angina — no. (%)	440 (28.0)	201 (22.8)	0.005
Ever smoked — no. (%)	754 (48.0)	322 (36.6)	<0.001
Currently smoking — no. (%)	271 (17.3)	106 (12.0)	<0.001
Peripheral vascular disease — no. (%)	236 (15.0)	92 (10.5)	<0.001
Atrial fibrillation — no. (%)	370 (23.6)	280 (31.8)	<0.001
Cancer — no. (%)	182 (11.6)	105 (11.9)	0.80
COPD — no. (%)	207 (13.2)	156 (17.7)	0.002
Prior myocardial infarction — no. (%)	612 (39.0)	146 (16.6)	<0.001
Prior CABG — no. (%)	203 (12.9)	51 (5.8)	<0.001
Prior PCI — no. (%)	48 (3.1)	16 (1.8)	0.07
Peptic ulcer disease — no. (%)	94 (6.0)	74 (8.4)	0.02
Hepatitis or cirrhosis — no. (%)	20 (1.3)	16 (1.8)	0.28
Dementia — no. (%)	76 (4.8)	49 (5.6)	0.43
Hemoglobin <10 g/dl — no. (%)	155 (9.9)	186 (21.1)	<0.001
Mean systolic blood pressure — mm Hg	146	156	<0.001
Mean respiratory rate — breaths/min	26	26	0.17
Serum sodium <136 mmol/liter — no. (%)	362 (23.1)	209 (23.8)	0.70
Serum creatinine >150 mmol/liter — no. (%)	296 (18.9)	195 (22.2)	0.95
Dialysis — no. (%)	18 (1.1)	9 (1.0)	0.78

* Plus–minus values are means ±SD. LVEF denotes left ventricular ejection fraction, COPD chronic obstructive pulmonary disease, CABG coronary-artery bypass grafting, and PCI percutaneous coronary intervention.

ical findings of the two groups. The presenting symptoms in patients with preserved ejection fraction were largely similar to those in patients with reduced ejection fraction. The main differences were that patients with preserved ejection fraction had lower rates of acute pulmonary edema, paroxysmal nocturnal dyspnea, and S_3 and a higher rate of bilateral ankle edema.

HOSPITAL COURSE

Table 3 shows in-hospital treatment and complications. A cardiologist was the primary physician for 33.6 percent of patients with reduced ejection fraction but for only 24.7 percent of patients with preserved ejection fraction (P<0.001). Cardiology consultations were obtained for 43.8 percent of patients with reduced ejection fraction but for only 37.3 percent of patients with preserved ejection fraction (P=0.002). Although the rates of hypotension and cardiogenic shock were significantly higher among patients with reduced ejection fraction than among those with preserved ejection fraction, the rates of renal failure, cardiac arrest, acute coronary syndrome, and admission to a coronary care unit or ICU did not differ significantly between the two groups.

Table 2. Presenting Symptoms and Signs of Heart Failure.

Variable	Reduced Ejection Fraction (<40%) (N=1570)	Preserved Ejection Fraction (>50%) (N=880)	P Value
	no. (%)		
Symptoms			
Acute pulmonary edema	332 (21.1)	152 (17.3)	0.02
Dyspnea or shortness of breath	1511 (96.2)	835 (94.9)	0.11
Chest pain	399 (25.4)	212 (24.1)	0.47
Orthopnea	729 (46.4)	374 (42.5)	0.06
Syncope	27 (1.7)	10 (1.1)	0.26
Paroxysmal nocturnal dyspnea	473 (30.1)	220 (25.0)	0.007
Signs			
Bilateral ankle edema	888 (56.6)	581 (66.0)	<.001
Wheezing	302 (19.2)	173 (19.7)	0.80
Neck-vein distention	962 (61.3)	506 (57.5)	0.07
Crackles or rales on lung examination	1324 (84.3)	743 (84.4)	0.95
Hepatojugular reflux	119 (7.6)	69 (7.8)	0.82
Hepatomegaly	81 (5.2)	38 (4.3)	0.35
Presence of S3	196 (12.5)	74 (8.4)	0.002
Presence of S4	80 (5.1)	33 (3.8)	0.13
Chest radiographic signs			
Pulmonary edema	814 (51.8)	414 (47.0)	0.02
Pleural effusion	716 (45.6)	360 (40.9)	0.03

OUTCOMES

The unadjusted mortality and readmission rates for the two groups are summarized in Table 3. At 30 days, the mortality rate among patients with reduced ejection fraction was 7.1 percent, as compared with 5.3 percent among those with preserved ejection fraction, but this difference was not significant (P=0.08). The mortality rates at one year were 25.5 percent and 22.2 percent, respectively (P=0.07). Even after adjustment for other significant predictors, the risk of death was not significantly higher among patients with reduced ejection fraction than among those with preserved ejection fraction at one year (hazard ratio, 1.13; 95 percent confidence interval, 0.94 to 1.36; P=0.18). The adjusted survival curves are shown in Figure 1. The one-year rate of readmission for heart failure was 16.1 percent among patients with reduced ejection fraction and 13.5 percent among those with preserved ejection fraction (P=0.09). The unadjusted combined one-year end point of death and readmission for heart failure was 36.1 percent for patients with re-duced ejection fraction and 31.1 percent for those with preserved ejection fraction (P=0.01). Patients with borderline ejection fraction (40 to 50 percent) had unadjusted mortality rates of 5.1 percent at 30 days and 21.3 percent at 1 year. Although these mortality rates were not significantly different from those among either patients with reduced ejection fraction or patients with preserved ejection fraction, they were more similar to the mortality rates among patients with preserved ejection fraction.

The predictors of death among patients with preserved ejection fraction included age, systolic blood pressure, the presence of peripheral vascular disease, hyponatremia, a history of cancer, dementia, renal dysfunction, dialysis, anemia, and respiratory rate. The predictors of the risk of death among patients with a reduced ejection fraction were similar but also included the presence of cirrhosis and did not include the presence of cancer, dialysis, or anemia or the respiratory rate. The results of these multivariate analyses are reported in Table 4.

**Table 3. In-Hospital Care, Complications, and Outcomes.**

Variable	Reduced Ejection Fraction (<40%) (N=1570)	Preserved Ejection Fraction (>50%) (N=880)	P Value
	no. (%)		
In-hospital care			
Cardiologist as primary physician	527 (33.6)	217 (24.7)	<0.001
Consultation with a cardiologist	687 (43.8)	328 (37.3)	0.002
Sodium restricted	1069 (68.1)	539 (61.2)	<0.001
Fluid restricted	216 (13.8)	113 (12.8)	0.52
Weight recorded on >50% of hospital days	301 (19.2)	154 (17.5)	0.31
Complications			
Atrial fibrillation or flutter	116 (7.4)	64 (7.3)	0.92
Hypotension	94 (6.0)	30 (3.4)	0.005
Cardiac arrest	36 (2.3)	11 (1.2)	0.07
Cardiogenic shock	16 (1.0)	2 (0.2)	0.03
Acute coronary syndrome (myocardial infarction or unstable angina)	81 (5.2)	38 (4.3)	0.35
Renal failure	437 (27.8)	235 (26.7)	0.55
Bilevel positive airway pressure or continuous positive airway pressure	124 (7.9)	57 (6.5)	0.20
Mechanical ventilation	94 (6.0)	28 (3.2)	0.002
Readmission to coronary care unit or intensive care unit	77 (4.9)	29 (3.3)	0.06
Assessment for heart transplantation at admission	7 (0.4)	4 (0.5)	0.98
Outcomes			
30-Day mortality	112 (7.1)	47 (5.3)	0.08
1-Yr mortality	400 (25.5)	195 (22.2)	0.07
30-Day readmission for heart failure*	73 (4.9)	38 (4.5)	0.66
1-Yr readmission for heart failure*	240 (16.1)	114 (13.5)	0.09
30-Day mortality or readmission for heart failure	182 (11.6)	83 (9.4)	0.10
1-Yr mortality or readmission for heart failure	566 (36.0)	274 (31.1)	0.01

* Readmission rates were calculated for the 2339 patients who survived the index admission: 1493 with reduced ejection fraction and 846 with preserved ejection fraction.

DISCUSSION

We performed a large, population-based cohort study examining the clinical features and outcomes of patients admitted to the hospital for the first time with heart failure. We found that about one third of the patients admitted with heart failure in whom left ventricular function was measured had an ejection fraction of more than 50 percent. These patients were more likely to be women, were older, and were more likely to have a history of hypertension than those with an ejection fraction of less than 40 percent. These observations are consistent with those of some previous reports.[7,9,19] In contrast to previous studies, however, our study found that patients with a reduced ejection fraction had higher rates of diabetes, coronary artery disease, and hyperlipidemia; this finding is in keeping with the concept that myocardial infarction or ischemia constitutes a major cause of heart failure associated with a low ejection fraction. Patients with a preserved ejection fraction had a significantly higher rate of atrial fibrillation, which may be both a conse-

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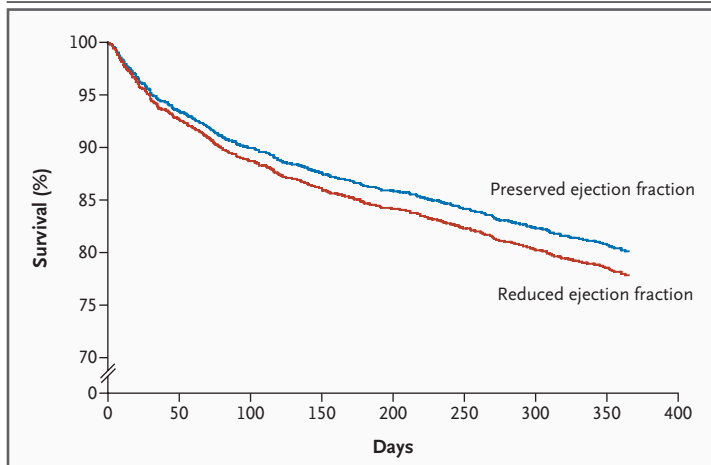
Figure 1. Adjusted Survival Curves for Patients with Heart Failure with Reduced or Preserved Ejection Fraction over the Year after the First Hospital Admission.

The data were adjusted for differences in baseline variables, including age, sex, and coexisting conditions. The adjusted mortality rate was not significantly higher for patients with reduced ejection fraction than for patients with preserved ejection fraction at one year (hazard ratio, 1.13; 95 percent confidence interval, 0.94 to 1.36; P=0.18).

quence and a precipitant of clinical deterioration in this setting.[20] The rates of most other noncardiac associated conditions did not differ significantly between the groups, except for chronic obstructive lung disease, which was more frequent in the group with preserved ejection fraction.

Although subtle differences between groups were observed on physical examination and review of presenting symptoms, these were largely unhelpful in distinguishing between the two types of heart failure defined on the basis of ejection fraction. This finding is also consistent with those of other studies[7] that failed to discriminate between the two conditions on clinical grounds. Imaging methods such as echocardiography are the current mainstay for distinguishing between these two entities. Although the diagnosis of heart failure itself is determined clinically, biomarkers such as B-type natriuretic peptide and other emerging candidates may help confirm the diagnosis in patients who do not have a reduced ejection fraction.[7,21]

Our principal findings are related to morbidity and mortality. Patients with heart failure with a preserved ejection fraction had complication rates that were similar to those of patients with a reduced ejection fraction, including similar rates of cardiac arrest, acute coronary syndrome, renal failure, and admission to the ICU or coronary care unit. Despite similar rates of in-hospital complications in the two groups, patients with a preserved ejection fraction were less likely to receive primary care from a cardiologist and were less likely to have had a cardiology consultation than patients with a reduced ejection fraction. It is not clear whether this difference had an effect on the outcomes of our cohort.

Our study showed that patients with a preserved ejection fraction had high 30-day and 1-year mortality rates that were not significantly lower than those of patients with a reduced ejection fraction, with or without adjustment for clinical differences between the two groups. Multivariate analysis showed that many of the predictors of death among patients with a preserved ejection fraction were similar to those for patients with a reduced ejection fraction, as described in previous studies.[22]

The data from other studies of patients with heart failure with a preserved ejection fraction have been inconsistent with respect to mortality and readmission rates.[6,19,23,24] Some reports have estimated the annual mortality rate among patients with heart failure with a preserved ejection fraction to be in the range of 5 to 8 percent and have concluded that this entity is not as ominous as heart failure with a reduced ejection fraction.[23] In contrast, Senni and Redfield reviewed 13 smaller studies examining the outcomes of patients with heart failure and found that 6 of the 13 studies did not show a significant difference in mortality between the two conditions.[19] Another, larger single-center study by Varadarajan and Pai[12] actually found a higher mortality rate among patients with heart failure with a preserved ejection fraction, although there were limitations to this analysis.[23] More recent large clinical studies, such as the Danish Investigators of Arrhythmia and Mortality on Dofetilide–Congestive Heart Failure (DIAMOND–CHF) registry, the Euro Heart Failure survey, and the Management to Improve Survival in Congestive Heart Failure (MISCHF) study, all found lower relative mortality rates among those with heart failure with a preserved ejection fraction, but a high absolute mortality rate in this group, ranging from 10 percent at 12 weeks to 17 percent at 1 year.[21,25,26]

All these previous studies had several limitations. The majority of the subjects were clinic-based or referral patients. Among hospitalized

Table 4. Multivariate Models of One-Year Mortality in the Entire Cohort of Patients with Heart Failure, in Patients with Heart Failure and Reduced Ejection Fraction, and in Patients with Heart Failure and Preserved Ejection Fraction.*

Model	Hazard Ratio (95% CI)	P Value
Entire heart-failure cohort		
Reduced vs. preserved ejection fraction	1.13 (0.94–1.36)	0.18
Age	1.03 (1.02–1.04)	<0.001
Peripheral vascular disease	1.58 (1.27–1.96)	<0.001
Cancer	1.41 (1.13–1.76)	0.003
Dementia	1.98 (1.49–2.63)	<0.001
Systolic blood pressure (per 10 mm Hg increase)	0.90 (0.89–0.91)	<0.001
Hemoglobin <10 g/dl	1.38 (1.08–1.66)	0.003
Serum sodium <136 mmol/liter	1.52 (1.11–1.71)	<0.001
Serum creatinine >150 μmol/liter	1.63 (1.34–1.97)	<0.001
Respiratory rate (per 5-breath/min increase)	1.08 (1.02–1.14)	0.008
Cirrhosis	2.59 (1.57–4.28)	0.002
Heart failure with reduced ejection fraction		
Age	1.03 (1.02–1.04)	<0.001
Peripheral vascular disease	1.50 (1.12–1.95)	0.002
Dementia	1.83 (1.26–2.65)	0.002
Serum sodium <136 mmol/liter	1.52 (1.21–1.90)	<0.001
Serum creatinine >150 μmol/liter	1.77 (1.41–2.23)	<0.001
Systolic blood pressure (per 10 mm Hg increase)	0.91 (0.89–0.92)	<0.001
Cirrhosis	3.07 (1.71–5.51)	<0.001
Heart failure with preserved ejection fraction		
Age	1.05 (1.03–1.06)	<0.001
Peripheral vascular disease	2.00 (1.31–3.08)	0.002
Cancer	1.97 (1.36–2.85)	<0.001
Dementia	2.37 (1.50–3.74)	0.001
Dialysis	3.59 (1.07–12.07)	0.04
Respiratory rate (per 5-breath/min increase)	1.18 (1.07–1.29)	0.001
Hemoglobin <10 g/dl	1.60 (1.15–2.24)	0.006
Serum sodium <136 mmol/liter	1.61 (1.16–2.25)	0.005
Serum creatinine >150 μmol/liter	1.49 (1.04–2.12)	0.03
Systolic blood pressure (per 10 mm Hg increase)	0.92 (0.90–0.94)	<0.001

* CI denotes confidence interval.

patients, some were not admitted for heart failure, but heart failure developed after admission. In addition, these reports typically did not use an objective system for the classification of heart failure. In contrast, our study included only patients who were admitted with their first episode of heart failure, and we required all subjects to meet the Framingham criteria for heart failure. Thus, our study can be seen as an assessment of the clinical course of heart failure with a preserved ejection fraction as compared with that of heart failure with a reduced ejection fraction from the same point in the evolution of the disease.

The prognosis of heart failure with a preserved ejection fraction has also been evaluated in a few clinical trials, the largest of which were the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) trials.

These studies also found a large difference in mortality between patients with preserved ejection fraction and those with reduced ejection fraction, but the patients enrolled in the CHARM-Preserved trial were significantly younger than those in our study (average age, 67 vs. 75 years), were predominantly male, and were more heterogeneous.[27,28] They were thus enrolled at different points in their disease and represented a different study population than those traditionally thought to have heart failure with a preserved ejection fraction.

Our study had several limitations. Of the potentially eligible patients, only 42 percent had a documented assessment of left ventricular function at the time of admission to the hospital. Other studies have shown variation in the rates of assessment of ejection fraction in patients with heart failure.[29-31] This may have resulted in a selection bias; several other studies have shown that physicians paradoxically tend to refer patients who are younger and less sick for investigations such as assessment of left ventricular function or angiography.[29,32] Thus, we may have underestimated the actual risk of complications and death among patients with heart failure with a preserved ejection fraction, who tend to be older women with coexisting conditions.

In addition, the assessment of ejection fraction could not be standardized, and therefore, there may have been variations among different operators and different techniques that resulted in the misclassification of some patients. We excluded the group with a borderline ejection fraction (40 to 50 percent) in order to minimize the effects of misclassification. We included only patients whose ejection fraction had been assessed on admission, and although there has been concern that left ventricular function may become transiently impaired in patients presenting with pulmonary edema, this concern has not been substantiated in longitudinal follow-up studies.[33]

Restricting our analysis to patients hospitalized with a primary discharge diagnosis of heart failure presumably resulted in a more homogeneous study population than those in previous reports. However, we could not control for the decision-making process that led to the admission of a patient, and it is conceivable that for a given symptom severity, physicians are less likely to admit a patient who has a normal ejection fraction. Our data regarding symptom frequency are reassuring in this respect, but they do not entirely exclude the possibility that our group of patients with a preserved ejection fraction had to meet a higher admission standard. Finally, some patients may not have received a discharge diagnosis of heart failure once their ejection fraction was known to be normal, even though their symptoms and signs were consistent with the presence of heart failure; such an ascertainment bias could also have reduced the number of patients with "mild" heart failure with a preserved ejection fraction included in the cohort.

In summary, we determined the clinical features and outcomes of a large, population-based cohort of patients with heart failure with a preserved ejection fraction. Our study differs from others by including only patients admitted with confirmed heart failure and by including patients from small and large community hospitals as well as academic teaching institutions. In our analysis, approximately one third of patients admitted with heart failure had an ejection fraction of more than 50 percent, and such patients could not be reliably distinguished from those with an ejection fraction of less than 40 percent on clinical grounds. The in-hospital complication rates of the two groups were similar. The adjusted one-year mortality rate among patients with heart failure with a reduced ejection fraction was similar to that of patients with a preserved ejection fraction; the morbidity rates in the two groups were similar; and the absolute mortality rate among patients with heart failure with a preserved ejection fraction was higher than previously reported values.

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