Late Mortality and Determinants in Patients with Heart Failure and Preserved Systolic Left Ventricular Function: The Israel Nationwide Heart Failure Survey*

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Key words: heart failure, diastolic dysfunction, pharmacotherapy, mortality

Abstract

Background: Heart failure with preserved systolic left ventricular function is a major cause of cardiac disability.

Objectives: To examine the prevalence, characteristics and late clinical outcome of patients hospitalized with HF-PSF on a nationwide basis in Israel.

Methods: The Israel nationwide HF survey examined prospectively 4102 consecutive HF patients admitted to 93 internal medicine and 24 cardiology departments in all 25 public hospitals in the country. Echocardiographic LV function measurements were available in 2845 patients (69%). The present report relates to the 1364 patients who had HF-PSF (LV ejection fraction ≥ 40%).

Results: Mortality of HF-PSF patients was high (in-hospital 3.5%, 6 months 14.2%, 12 months 22.0%), but lower than in patients with reduced systolic function (all $P < 0.01$). Mortality was higher in patients with HF as the primary hospitalization diagnosis (16.0% vs. 12.5% at 6 months, $P = 0.07$ and 26.2% vs. 18.0% at 12 months, $P = 0.0002$). Patients with HF-PSF who died were older (78 ± 10 vs. 71 ± 12 years, $P < 0.001$), more often female ($P = 0.05$) and had atrial fibrillation more frequently (44% vs. 33%, $P < 0.01$). There was also a relationship between mortality and pharmacotherapy: after adjustment for age and co-morbid conditions, mortality was lower in patients treated with angiotensin-converting enzyme inhibitors ($P = 0.0003$) and angiotensin receptor blockers ($P = 0.002$) and higher in those receiving digoxin ($P = 0.003$) and diuretic therapy ($P = 0.009$).

Conclusions: This nationwide survey highlights the very high late mortality rates in patients hospitalized for HF without a decrease in systolic function. The findings mandate a focus on better evidence-based treatment strategies to improve outcome in HF-PSF patients.

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It is now well established that clinical heart failure, severe enough to necessitate hospitalization, may occur in patients in whom systolic left ventricular function, by conventional criteria, is relatively preserved (heart failure with preserved systolic function) [1-3]. Patients with HF-PSF have reduced exercise capacity and impaired quality of life [4]. The ADHERE registry reported in-hospital data [3] and the European Heart Survey involved 12 weeks follow-up [5], while information from randomized clinical trials [6,7] necessarily related to a selected trial population only. At a community level, the risk of death due to HF-PSF is high because of the high prevalence of HF and especially HF-PSF in older patients [8], a prevalence that may be increasing [9].

The Israel heart failure survey (Heart Failure Survey in ISrael, HFSIS) was designed to examine at nationwide level the demographics, management and outcome in consecutive patients hospitalized with HF. The present study reports the clinical characteristics, pharmacotherapeutic management, and also late (6 and 12 months) outcome in patients with HF-PSF.

Patients and Methods

Patient population

The survey was conducted during a consecutive 2 month period in 93 of the 98 internal medicine and 24 of the 25 cardiology departments in Israel, thus encompassing 117 of 123 departments and including all 25 public hospitals in the country. Since almost all hospital medicine in Israel is conducted in the national public health system, the survey is estimated to include more than 90% of the hospitalized HF population in the country during the survey period.

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HF-PSF = heart failure with preserved systolic left ventricular function

Data collection

The survey included all patients with HF, as determined by the local survey team in each center according to a heart failure diagnosis category (DRG), be this the primary or secondary diagnosis. HF was diagnosed according to clinical presentation (symptoms, physical examination), radiography, echocardiography; radionuclide studies and cardiac catheterization findings. Detailed data regarding patient characteristics, in-hospital course, management during hospitalization, pre-hospital and discharge medications and diagnoses were collected and recorded on pre-specified structured forms. Mortality during the first year after the index hospitalization was assessed for 99% of patients by matching their identification numbers with the National Population Registry. The protocol was approved by the ethics committee at each of the participating hospitals.

Echocardiographic measurements and diagnosis of HF-PSF

Echocardiographic LV function measurements were taken and analyzed locally on site in each of the participating hospitals and were available for 2845 patients. Preserved LV systolic function was arbitrarily defined as an LVEF ≥ 40%, which allows comparison of the findings with those collected in other surveys and clinical trials of HF-PSF [5,7,10]. We also examined late mortality in the subset of patients with normal or near normal (≥ 50%) echocardiographic systolic LV function.

Statistical analysis

Data were analyzed using the SAS software package. The comparison of proportions was done using the chi-square test. Student's *t*-test was used to compare means for continuous variables. A multivariate logistic regression model was used to identify predictors of 12 month mortality among hospital survivors. These analyses included patient characteristics (age, gender, diabetes mellitus, systemic hypertension, atrial fibrillation) and drug treatment at discharge (digoxin, diuretic, beta-blocker, ACE inhibitor, angiotensin receptor blocker, aspirin, coumadin, calcium antagonist, statin). A stepwise selection method was used with a significance level of 0.05 for entering/removing an exploratory variable. Late mortality was analyzed using the Kaplan-Meier method with log-rank test to examine for differences between groups.

Results

Patient population

HFSIS enrolled 4102 consecutive patients admitted with a primary or secondary diagnosis of HF (2004 and 2098 patients respectively). LV systolic function was determined from echocardiography, which was available in 2845 (69.4%) of the 4102 patients. LVEF was ≥ 50% in 763 (26.8%), 40–49% in 600 (21.1%), 30–39% in 736 (25.9%) and < 30% in the remainder (743, 26.1%). The 1364/2845 patients with LVEF ≥ 40% (48.9%) were defined as having HF-PSF and form the basis of the present report.

LVEF = left ventricular ejection fraction
ACE = angiotensin-converting enzyme

LV function measurements were not available in 1257 patients. These patients were older (77 ± 12 vs. 72 ± 12 years, $P < 0.0001$), more often women (49.5% vs. 40.1%, $P < 0.0001$), hypertensive (78.4% vs. 73.9%, $P = 0.002$), in atrial fibrillation (36.6% vs. 31.6%, $P = 0.001$) and less often had an ischemic etiology (78.3% vs. 83.9%, $P = 0.0001$). Patients not studied by echo and hence excluded from the present report had higher 12 month mortality (34.3% vs. 25.4%, $P < 0.0001$).

Clinical characteristics of patients with HF-PSF

The demographic and clinical characteristics of patients with HF-PSF are shown in Table 1. Compared with the reduced LV function group, HF-PSF patients were older (73 ± 12 vs. 71 ± 12 years, $P < 0.002$) and more often female (52% vs. 29%, $P < 0.0001$), had a higher prevalence of systemic hypertension (79% vs. 69%, $P < 0.0001$) and less frequently ischemic heart disease (75% vs. 92%, $P < 0.0001$). Diabetes mellitus was less frequent (48% vs. 53%, $P = 0.01$), but almost 30% were obese (vs. 19%, $P < 0.0001$). Paroxysmal or chronic atrial fibrillation was more frequent in HF-PSF patients (36% vs. 28%, $P < 0.0001$). Echocardiographic LV dimensions were smaller in the HF-PSF group (LV end dystolic 44 ± 16 vs. 49 ± 20 mm, $P < 0.0001$) and by definition EF was higher (50 ± 19 vs. 27 ± 7%).

Pharmacotherapy in patients with HF-PSF

In patients with HF-PSF, in contrast to the reduced LV systolic function group, drug therapy at discharge included half the usage of digoxin (9% vs. 18%, $P < 0.0001$), lesser use of diuretics (70% vs. 78%, $P < 0.0001$), ACE inhibitors (57% vs. 66%, $P < 0.0001$), beta-blockers (58% vs. 66%, $P < 0.0001$), statins (40% vs. 46%, $P = 0.001$) and aspirin (66% vs. 73%, $P < 0.0001$), and a greater use of calcium antagonists (33% vs. 14%, $P < 0.0001$). Angiotensin receptor blockers were used slightly less frequently in patients with HF-PSF (8% vs. 10%, $P = 0.14$). Oral anticoagulants were administered similarly to 20% of patients with HF-PSF and 19% of those with reduced systolic function ($P = 0.63$).

Mortality rates in patients with HF-PSF

Hospital mortality was 3.5% (47/1363) in patients with HF-PSF; at 6 months 193/1360 (14.2%) had died and at 12 months 299/1360 (22.0%). During the same time frame mortality for patients with reduced systolic function was higher (4.5% in-hospital, 19.3% at

Table 1. Demographic and clinical data in patients with preserved vs. reduced LV systolic function

	Preserved LV function (EF ≥ 40%) (n=1364)	Reduced LV function (EF < 40%) (n=1481)	*P*
Age (yrs)	73 ± 12	71 ± 12	< 0.002
Female gender	706 (52%)	436 (29%)	< 0.0001
Ischemic heart disease	1023 (75%)	1365 (92%)	< 0.0001
Systemic hypertension	1075 (79%)	1028 (69%)	< 0.0001
Diabetes mellitus	656 (48%)	782 (53%)	0.01
Obesity	397 (29%)	279 (19%)	< 0.0001
Atrial fibrillation	484 (35%)	416 (28%)	< 0.0001

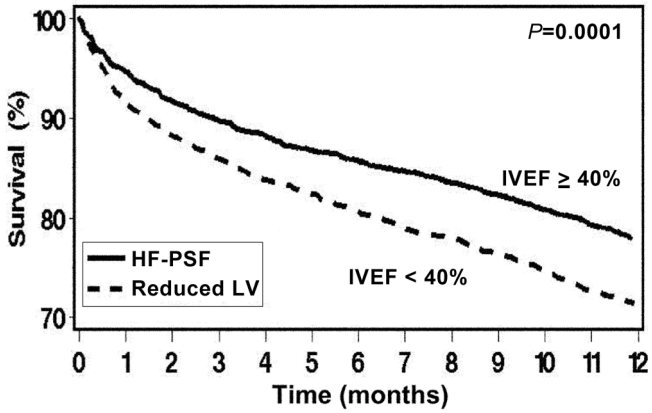

Figure 1. Twelve month survival curves (Kaplan-Meier analysis) for patients hospitalized with heart failure and preserved (HF-PSF) vs. reduced systolic LV function. Mortality for HF-PSF patients was greater than 20% by one year, but lower than in the reduced LV function group ($P < 0.001$).

6 months and 28.6% at 12 months) ($P < 0.01$ for all). Survival curves for patients with HF-PSF in comparison to those with reduced LV function are shown in Figure 1.

Outcome data in patients with HF as primary vs. secondary diagnosis

HF was the primary diagnosis in 666 patients with HF-PSF; in 698 it was a secondary or past diagnosis. Mortality was higher in patients with HF as their primary diagnosis. Death occurred during the index admission in 23 (3.5%) primary HF-PSF patients (NS vs. secondary group), at 6 months in 106/664 (16.0%) primary vs. 87/696 (12.5%) secondary ($P = 0.07$), and by 12 months in 174/664 (26.2%) primary vs. 125/696 (18.0%) in the secondary group ($P = 0.0002$).

Outcome data in patients with near-normal systolic function (LVEF ≥ 50%)

To examine whether late outcome was more favorable in patients with lesser degrees of systolic LV dysfunction, we examined mortality in the subset of patients with LVEF ≥ 50%. Late (12 month) mortality was not lower or different in this EF ≥ 50% subset (190/761, 24.9%). Further analyses regarding late mortality were therefore performed for the HF-PSF group as a whole.

Determinants of late mortality in HF-PSF patients

Determinants of late mortality in patients with HF-PSF are presented in Table 2. Patients who died were older and more often female. By univariate analysis there was no difference in the prevalence of associated diseases such as ischemic heart disease, diabetes mellitus or systemic hypertension. In patients who died, atrial fibrillation was more common, admission heart rate was not different but blood pressure was lower. There was no difference in echocardiographic LV dimension or ejection fraction, which were normal or near normal in patients who died and in the survivors.

The relation between drug therapy at discharge and late mortality is shown in Table 3. At 12 months, mortality was higher in patients treated with digoxin and diuretic and lower in patients receiving beta-blocker, ACE inhibitor, angiotensin receptor blocker, aspirin and statin. There was no relation between mortality and use of calcium antagonists or coumadin. It is noteworthy that prior use of a diuretic ($P = 0.02$) and digoxin ($P = 0.06$) predicted increased and beta-blocker ($P = 0.01$) decreased late mortality, but there was no relation between mortality and other pre-hospital drug treatment. A stepwise logistic model, including clinical variables (associated disease) and discharge medications (see methods), was used to define independent predictors of late mortality in hospital survivors with HF-PSF [Table 3]. Increasing age (odds ratio 1.04), diabetes mellitus (OR = 1.41) and drug treatment with digoxin (OR = 1.90), diuretics (OR = 1.63), ACE

Table 2. Determinants of 12 month mortality in patients with HF-PSF

	Alive (n=1061)	Dead (n=299)	*P*
Age (yrs)	71 ± 12	78 ± 10	< 0.001
Females	534 (50%)	170 (57%)	0.05
Ischemic heart disease	805 (76%)	216 (72%)	0.20
Systemic hypertension	842 (79%)	230 (77%)	0.36
Diabetes mellitus	499 (47%)	155 (52%)	0.14
Atrial fibrillation	352 (33%)	131 (44%)	< 0.001
Systolic BP (mmHg) (admission)	150 ± 32	141 ± 33	< 0.001
Diastolic BP (mmHg) (admission)	80 ± 17	75 ± 16	< 0.001
Heart rate (beats/min) (admission)	84 ± 22	84 ± 19	0.73
LV end-diastolic dimension (mm)	44 ± 17	43 ± 16	0.51
LVEF (%)	50 ± 10	50 ± 9	0.98

Table 3. Relation between demographics, drug treatment (at discharge) and 12 month mortality in patients with HF-PSF

Unadjusted data	No.	Dead	Odds ratio (treatment vs. no treatment)	95% confidence interval	*P*
Total group	1314	250 (19.2%)	–	–	–
Digoxin	123	39 (31.7%)	2.15	1.43–3.23	< 0.001
Diuretic	916	204 (22.3%)	2.17	1.54–3.06	< 0.001
Beta-blocker	756	123 (16.3%)	0.65	0.50–0.86	0.002
ACE inhibitor	750	124 (16.5%)	0.68	0.52–0.90	0.006
Angiotensin receptor blocker	111	14 (12.6%)	0.59	0.33–1.05	0.07
Ca antagonist	429	93 (21.7%)	1.28	0.96–1.70	0.10
Aspirin	866	145 (16.7%)	0.65	0.49–0.86	0.003
Coumadin	257	46 (17.9%)	0.91	0.64–1.29	0.59
Statin	529	74 (14.0%)	0.56	0.42–0.75	< 0.001
Multivariate stepwise (adjusted) model					
Age (yrs)			1.04	1.03–1.06	0.0001
Diabetes mellitus			1.41	1.05–1.89	0.02
Digoxin			1.90	1.24–2.89	0.003
Diuretic			1.63	1.14–2.36	0.009
ACE inhibitor			0.58	0.43–0.78	0.0003
Angiotensin receptor blocker			0.38	0.20–0.69	0.002

OR = odds ratio

inhibitors (OR = 0.58) and angiotensin receptor blockers (OR = 0.38) were significant independent determinants of 1 year mortality. Treatment with beta-blockers did not predict outcome after correction for age and other variables.

Discussion

This nationwide survey showed that in patients hospitalized with HF and preserved systolic ventricular function (HF-PSF), both in-hospital (> 3%) and late mortality were high – almost 15% at 6 months and more than 20% at one year. The need for hospitalization in a heart failure patient carries an adverse prognosis even when LV ejection fraction is not reduced [11,12]. Prognosis was not better in the subset with near normal function (LVEF ≥ 50%), as noted recently in a study in hospitals in Ontario, Canada [13].

HF-PSF was reported with a similar 50% prevalence in hospitalized patients in the European [14] and North American ADHERE databases [10]. The ADHERE database reported a 2.8% in-hospital mortality (lower than the 3.9% in patients with systolic dysfunction) [3]. The European Heart Survey reported 10% mortality at 12 weeks for HF-PSF patients [5], and a Danish study a 19% mortality at one year [12]. In France, a registry involving 120 cardiology, general medicine and geriatrics departments (1058 patients) found that 53% had an LVEF > 40%, but did not report outcome [15]. At a community level (including clinically unrecognized HF), diastolic dysfunction alone was associated with an eight to tenfold increase in all-cause mortality [16]. The latter surveys may have been selective, since hospitals likely to be included were those with a particular interest in heart failure or with a strong academic affiliation.

Pathophysiologic considerations

It is likely that most patients with HF-PSF have diastolic dysfunction as a major pathophysiologic abnormality. Causes of diastolic dysfunction include ventricular hypertrophy (increased chamber stiffness), myocardial ischemia (increased muscle stiffness) and ventricular fibrosis (increased muscle stiffness) [17]. Abbreviated diastolic time periods accentuate filling abnormalities. Older patients have increased myocardial collagen content and decreased LV compliance (increased chamber stiffness) [18]. These mechanisms explain the high prevalence of HF-PSF in older patients, hypertensives and patients with ischemic heart disease and atrial fibrillation. While pathophysiology may vary on an individual basis, clinical management of patients with HF-PSF aims at reversing the consequences of diastolic dysfunction (i.e., systemic and pulmonary venous congestion) with, in addition, a treatment strategy aimed at reducing responsible factors such as myocardial hypertrophy, fibrosis and ischemia [19].

Determinants of late outcome

Mortality was lower in younger patients, in men without comorbidity (diabetes mellitus) and in those with sinus rhythm. Mortality was also lower in HF-PSF patients treated with ACE inhibitors and angiotensin receptor blockers. The magnitude of the effect was in keeping with that in randomized trials of HF with reduced systolic LV function [20,21] and similar to a registry of HF-PSF patients reported by Philbin et al. [22]. The effect of angiotensin receptor blockers in the Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM)-preserved study was modest, but the CHARM-preserved population was less ill and at lower risk of death [7]. The Irbesartan in chronic HF Patients with Preserved LV Function (I-PRESERVE) and other new studies will provide further information regarding effects of angiotensin receptor blockers on outcome in HF-PSF patients [23].

Only a small number (< 10%) of HF-PSF patients received digoxin, but late mortality in these patients was high. It is possible that these findings reflected selection bias. An analysis of 988 patients with LVEF > 45% from the randomized Digitalis Investigation Group study showed that predictors of death included renal dysfunction, reduced functional class, older age and male gender, but there was no relation to treatment with digoxin [24].

Potential limitations of the study

While registry data are valuable for generating or supporting a clinical hypothesis, randomized controlled trials are needed to confirm trends or findings. A particular strength of the present report is the nationwide design of the survey, avoiding selection bias introduced by research interests of physicians, and the availability of specialized structured heart failure programs. It should be noted that we could not include patients in whom measurements of LV function were not available, and this created a bias against inclusion of a group of older patients with adverse clinical outcome. We cannot speculate regarding a possible differing prevalence of reduced versus preserved LV systolic function in this patient group. Since the survey was based on data reported from each medical center, some peripheral, we are dependent on physician interpretation and on local recording and analysis of echocardiographic LV function. Systematic echo assessment of diastolic dysfunction was not included since it was not available in all patients and its interpretation is less standardized outside a core laboratory.

Clinical implications

Hospitalization for heart failure may account for up to a third of all hospitalizations in internal medicine and cardiology departments [25], and HF-PSF for almost a half of these. One may speculate that HF-PSF could be prevented by early and aggressive management of systemic hypertension, its major associated disease, particularly in women. Randomized trials will determine the clinical efficacy of newer drugs and treatment modalities as they become available.

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Capsule

Tuberculosis pili

Tuberculosis kills approximately 3 million people each year. The pathogenic agent M*ycobacterium tuberculosis* invades and replicates within macrophages, constructing for itself an intracellular vacuole that shelters it from immune surveillance and attack. Alteri et al. have investigated how M. *tuberculosis* binds to and invades potential host cells. On the surface of the microbe, they discovered fine fibers, referred to as pili, that are 2 to 3 nm wide and are likely to be important in enabling the microbe to adhere to target cells. They isolated the pili and characterized their composition using mass spectrometry and immunochemistry. The pili are assembled from low molecular weight protein subunits; these bind to the protein laminin, which is an abundant component of the extracellular matrix within human tissues. Furthermore, the sera of tuberculosis patients contained antibodies that recognized the pilin subunit. The unanticipated identification of what may represent a key protein in the early stages of host colonization by M. *tuberculosis* may lead to the development of new therapies and vaccines.

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