LONG-TERM PROGNOSIS AND MODES OF DEATH IN HEART FAILURE PATIENTS WITH REDUCED VERSUS PRESERVED LEFT VENTRICULAR SYSTOLIC FUNCTION

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Abstract

Background: There are conflicting reports regarding the prognosis of heart failure patients with preserved (HFPSF) comparative to reduced systolic left ventricular function (HFRSF). We evaluated the clinical characteristics, mortality rates and modes of death in 309 consecutive symptomatic heart failure patients. In 133(56%) patients LVEF was <50% (HFRSF), and in 133 (44%), LVEF was ≥50% (HFPSF).

Methods: Three hundred nine consecutive patients hospitalized between January 1, 2009 and January 1, 2010 (176 men and 133 women, mean age 64.3 years) were followed up for a mean period of 23±14 months. The severity of symptoms at admission was assessed by NYHA classification. 196 patients were in NYHA class I-II, and 113 in III–IV. All patients underwent chest X-ray, echocardiogram, and a 6-minute walking test. We compared the clinical profiles, mortality rates and modes of death.

Results: More than a third (44%) of the patients had preserved systolic LVEF based on echocardiography. Compared to the HFPSF group, HFRSF patients were predominantly younger males with ischemic aetiology and less cardiovascular comorbidities such as obesity, hypertension, diabetes mellitus and atrial fibrillation. During a mean follow-up period of 1.9 years, 22 (7.1%) patients died: 14 of cardiac causes and 8 of non-cardiac causes (4 of respiratory causes, 2 of stroke, 1 of major bleeding and 1 of cancer). Overall mortality was similar between the two groups: 8 (6%) in HFPSF patients and 14 (7.9%) in HFRSF patients (p=0.67). HFRSF patients had higher death rates due to pump failure compared to the HFPSF group [5/14(36%) vs. 1/8(12%) patients, p=0.5]. Non-cardiac deaths were more frequent in HFPSF group [4/8 (50%) patients vs. 4/14(28%) patients, respectively, p=0.5]. The prevalence of arrhythmic death was similar in the two groups [5/14(36%) vs.3/8(37%) patients, p=0.6]. With Cox stepwise regression analysis for survival, the independent predictors for mortality were age, gender, ischemic etiology of heart failure and renal impairment.

Conclusions: Although the characteristics of HFPSF and SHF patients are different, the mortality rates were similar in our study. The mode of death was different among the two groups of patients, as pump failure death rate was higher in patients with LVEF <50%, while non-cardiac death was higher in heart failure patients with preserved systolic function. The differences were not statistically significant. A high NYHA class at admission, age over 65, male gender and renal impairment were related to a worse prognosis.

Keywords: Heart failure reduced LV systolic function, preserved LV systolic function, outcome, and mode of death

Background

Heart failure (HF) represents a significant health problem /1/. Heart failure with preserved systolic left ventricular function (HFPSVF) is a common condition in heart failure patients and represents as a serious clinical problem. The literature indicates that over the last years the number of patients hospitalized with heart failure and preserved LVF is increasing /2/. The prognosis in these patients was considered to be better than in patients with low LVF. However, some studies suggest that the outcome in these patients is not so good /3/. Regarding these conflicting data, we aimed to evaluate the mortality and morbidity in patients with heart failure and preserved LVF compared to those in patients with reduced LVF.

Methods

Our HF centre is a secondary teaching centre, assembling most HF patients in the south-west counties of Romania. We included in the study HF patients who were hospitalized in our department for symptomatic HF. We reviewed patients' records for clinical, laboratory, echocardiographic and electrocardiographic parameters. 309 consecutive patients hospitalized between January 1, 2009 and January 1, 2010 (176 men and 133 women, mean age 64.3 years). The patients were followed up for a mean period of 23±14 months. The severity of symptoms at admission was assessed by NYHA classification. 65 (21%) patients were in NYHA class I, 131 (42%) in II, and 113 (37%) in III–IV. All patients underwent chest X-ray, echocardiogram, and a 6-minute walking test. We compared the clinical profiles, mortality rates and modes of death. We categorized HFPSF as symptomatic HF patients with left ventricular ejection fraction (LVEF) $\geq$ 50% and HFRSF as symptomatic HF patients with LVEF < 50% per echocardiogram. We analyzed in- hospital mortality rates. 22 patients (7%) died during the follow-up period. The mode of death was categorized as hemodynamic cardiac death (pump failure), arrhythmic (sudden) cardiac death or non-cardiac. Hemodynamic cardiac death mode was defined as worsening heart failure (cardiogenic shock, pulmonary edema or increase in heart failure symptoms and drug therapy) prior to death. Arrhythmic death mode was defined as instantaneous or acute in clinical setting (within 24 h), in the absence of pre-existing circulatory failure. A non-cardiac death included a variety of etiologies of mortality (stroke, respiratory infection, cancer, major bleeding).

Data analysis

Continuous data are presented as numbers or means ± standard deviation, and categorical variables as numbers and percentages. The independent samples t-test was used to compare continuous variables, and the chi-square test was used to compare categorical variables. Fisher's exact test was used in cases of small sample sizes. Survival curves were plotted by the Kaplan–Meier method, using the log-rank test for comparison between the two ejection fraction groups. In order to determine the adjusted hazard ratio for death among patients with HFRHF and HFPSF, we used Cox proportional-hazards multivariate analysis. The results were considered statistically significant when the p-value was <0.05. The MedCalc 12.3.0.0 statistical software for Windows was used to perform statistical analysis. Parameters included in the multivariate stepwise Cox regression analysis included all significant clinical and laboratory parameters, as well as drug treatment, on univariate analysis. Parameters included in the multivariate analysis were gender, age, body mass index, NYHA class at admission, ischemic heart disease, hypertension, diabetes, atrial fibrillation, serum urea, glomerular filtration rate (GFR) for serum creatinine (derived from the MDRD Study equation), NT-proBNP, sodium, hemoglobin, distance at 6-min walk test, ED-5D-5L quality of life score /3/, Hamilton depression score /4/ and LVEF.

Results

The study analysis included 309 patients who were followed at our HF centre for a mean period of 23±14 months. This cohort of patients included 176 (56%) patients with HFRSF and 133 (44%) patients with HFPSF. Patients' mean age was 64.3 years, 133 (43%) patients were females. Patients' characteristics according to their HF profile (HFRSF/HFPSF) are presented elaborated in table 1. Their baseline laboratory data are detailed in table 2.

Table 1. Characteristics of HFRSF and HFPSF patients.

Variable	**EF<50% (n=176)**	**EF≥50% (n=133)**	**p-value**
Age (years)	66 ±7.5	61± 8.9	<0.0001
Female gender	60 (34%)	73 (55%)	0.0003
Body mass index (kg/m^2)	31± 6.2	33±2.5	0.0005
Ischemic etiology n (%)	110 (63%)	46 (35%)	<0.03
History of hypertension n (%)	93 (53%)	101 (76%)	0.0001
Diabetes mellitus n (%)	51 (29%)	65 (48%)	0.001
Atrial fibrillation n (%)	56 (32%)	66 (50%)	0.002
Six-minute walk (m)	181± 38	261±64	<0.0001
New York Heart Association Class (1–4)	2.5 ± 0.4	2.1 ± 0.8	< 0.0001
EQ-5D-5L Euro QOL score/4/	50± 15	31.2±12.7	< 0.0001
Hamilton Depression Scale score/5/	8.7±3.1	7.2±2.8	< 0.0001
Beta blockers therapy n (%)	151 (86%)	110 (84%)	NS
ACEI/ARB[b] therapy n (%)	110 (63%)	87 (66%)	NS
Spironolactone therapy n (%)	142 (81%)	47 (36%)	<0.0001
Diuretics therapy n (%)	163 (93%)	119 (90%)	NS

Continuous variables are presented as mean ± 1 standard deviation

EF= ejection fraction; ACEI=angiotensin-converting enzyme inhibitors; ARB=angiotensin receptor blockers.

EQ-5D-5L: measurement of health-related quality of life scale, EuroQOL Group.

Table 2. Laboratory tests of HFRSF and HFPSF patients.

Variable	EF<50% (n=176)	EF≥50% (n=133)	p-value
Hemoglobin (g/dl)	13.8±1.7	14.5±1.8	0.0005
Ht (%)	43.4±5.1	43.6±4.3	NS
Creatinine (mg/dl)	1.18±0.29	0.99±0.28	<0.0001
Urea (mg/dl)	30±19.8	24±11.5	0.002
GFR (ml/min/1.73 m^2)	57.58±19	74.28±19	<0.0001
Sodium (mEq/l)	136.5 ± 3.2	137.4 ± 3.4	0.01
Uric acid (mg/dl)	6.0±1.6	7.0±3.3	0.0005
Total cholesterol (mg/dl)	157.0 ± 34	163.0 ± 42	NS
NT-proBNP (pg/ml)	821.4±720	520.8±360	< 0.0001

Data are presented as mean± 1 standard deviation

74.28±19 <0.0001

As we see, the clinical profile of the HFPSF patient is different from the HFRSF patient. HFPSF patients are more likely to be younger, have female gender and a higher prevalence of cardiovascular comorbidities, such as obesity, diabetes mellitus, hypertension, renal impairment and atrial fibrillation. Patients with HFRSF are more frequently older men, with ischemic heart disease; they have a higher NYHA class, a higher depression scale score, a lower distance at six-minute walk test, a poorer quality of life and higher levels of NT-proBNP. The treatment in both heart failure group patients was similar, excepting a higher rate of Spironolactone receiving patients among those having LVEF< 50% (p<0.0001).

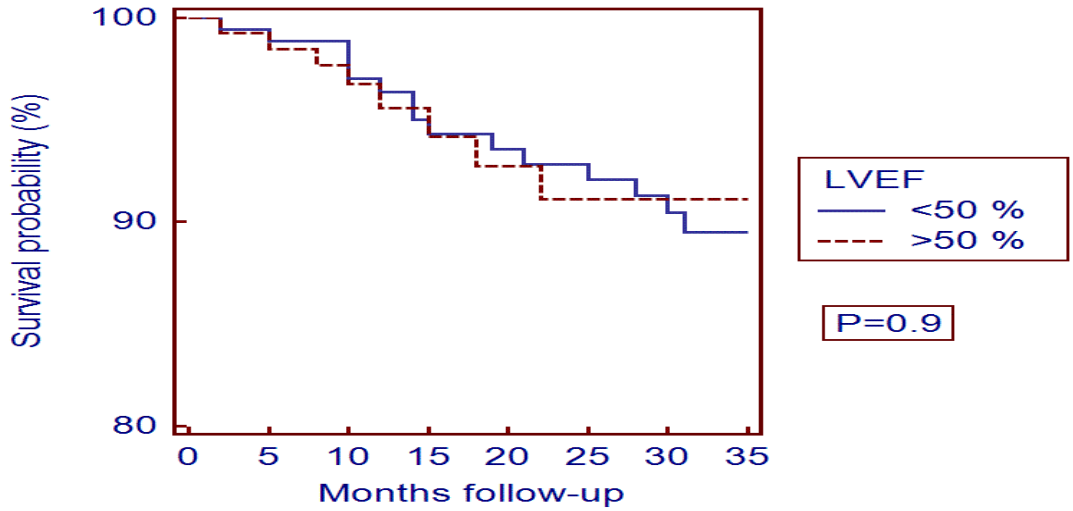


Fig.1. Kaplan–Meier survival curves in HFRSF and HFPSF patients (p-value 0.9, Log-rank test).

During mean follow-up period of 23±14 months, 22 (7%) patients died. The mortality rates of both SHF and the HFPSF patients groups were similar: 14 (7.9%) in HFRSF and 8 (6%) in HFPSF; p=0.67. At log-rank test for Kaplan-Meyer survival curves: p=0.9 (fig.1).

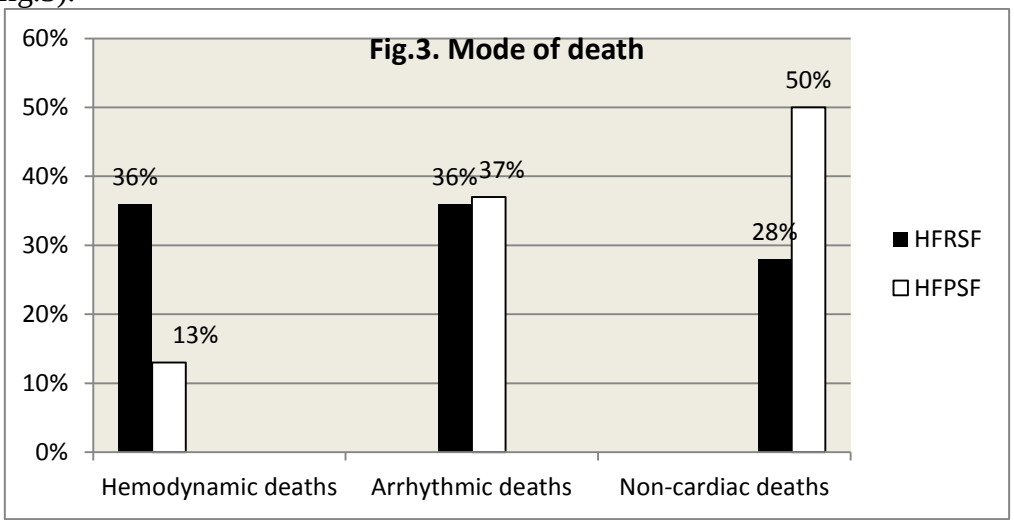
We analyzed the possible association of the following parameters with mortality: LVEF, age, gender, atrial fibrillation, diabetes mellitus, hypertension, ischemic etiology and body mass index (table 3). Using Cox stepwise multivariate analysis, we found that age, gender,

ischemic etiology of heart failure and increased serum urea were independent variables associated with mortality.

Table 3. Cox logistic regression multivariate analysis for mortality.

Variable	HR (95% CI)[a]	p-value
Age	1.04 (1.00–1.08)	0.02
Gender	1.05 (1.05–2.45)	0.006
Ischemic heart disease	1.50 (1.05–2.63)	0.005
Urea	1.03 (1.01–1.06)	0.02
NYHA class	1.42 (1.04– 2.18)	0.03

As demonstrated in fig.3, the HFRSF patients had a higher prevalence of mortality due to pump failure comparing with the HFPSF patients, but the difference was not statistically significant [5/14 (36%) patients vs. 1/8 (13%), p=0.5]. The prevalence of sudden cardiac death was similar [5/14 (36%) vs. 3/8 (37%), p=0.6]. Non-cardiac deaths were more frequent in heart failure patients with preserved systolic function [4/8 (50%) vs. 4/14 (28%), p=0.6](fig.3).



Discussion

The main finding of this study is that, although there are large differences in the clinical profiles of heart failure patients with reduced or preserved systolic function, mortality is similar.

However, we observe that the prevalence of various modes of death is different. In patients with reduced systolic function, death rate due to aggravated heart failure was 2.7 times more common than in patients with preserved systolic function, while non-cardiac death rate was 1.7 times more common in HFPSF. Arrhythmic (sudden) cardiac death rate was similar in both groups.

There are many controversies regarding HFPSF. In definition, cut-off value of normal LVEF varies between 35% and 50%. Although many studies and guidelines for diagnosing heart failure with preserved systolic function were published in the last years, there is no consent regarding the definition. We chose as cut-off value for HF with preserved systolic function a LVEF ≥ 50% /8/.

Probably due to definition variations, the prevalence of HFPSF is controversial, between 24% and 60% of the total HF population, usually higher in older HF patients /9,10/.

In our study, HFPSF patients were younger, were more frequent females and had a higher prevalence of cardiovascular comorbidities, such as obesity, diabetes mellitus, hypertension, renal impairment and atrial fibrillation. Similar results were observed in other studies/11, 12/. In contrast, heart failure patients with reduced LVEF were more frequent males and older. Reduced systolic function heart failure was associated more frequent with ischemic etiology, higher levels of NT-proBNP, depression and a poorer quality of life. /13, 14, 15, 16, 17/ Heart failure treatment with beta-blockers, ACE inhibitors, angiotensin receptor antagonists and diuretics was similar in both groups. Spironolactone had a significant statistical higher usage in patients with reduced LVEF, probably due to more severe signs and symptoms of heart failure. /18, 20/.

The mortality rate in our study was 7.1% (7, 9% in HFRSF and 6% in HFPSF patients, p=0.67). 0ver the follow-up period of 23±14 months, the total mortality rate was similar in the two groups. The mechanisms of death were different, but no statistically significant. In patients with LVEF < 50%, the major cause of death was the aggravation of heart failure. Among patients with preserved systolic function, non-cardiac causes of death (stroke, cancer, major bleeding) were predominant . Sudden cardiac deaths had similar rates in the two study groups.

Our data are concordant to those reported, as several studies demonstrate similar mortality rates among heart failure patients with reduced and preserved systolic function /8,19,22,23,24/.

As regarding medical treatment, excepting Spironolactone, that was used more frequent in patients with LVEF< 50%, there were not significant differences among the two groups. The beneficial effect of aldosterone receptor antagonism was demonstrated in systolic heart failure (*Ephesus study*/20/), while its effect in preserved LV heart failure is now being tested (*Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist -TOPCAT study)/21/.*

The similar rate of arrhythmic (sudden) cardiac death in the two patient groups leads to the question of a potential benefit of implantable cardioverter-defibrillator devices in patients with heart failure having a preserved systolic function /24/.

Conclusions

The arbitrary cut-off levels of LVEF in different HFPSF studies lead to controversies regarding the patient cohort.

The prognosis of heart failure patients is poor, indifferent of the LVEF.

Heart failure patients with reduced and preserved systolic function have different clinical characteristics, but similar total mortality rates. Death due to pump failure is higher among patients with reduced LVEF, while non-cardiac death occurs at higher rates in those with preserved LV systolic function.

As arrhythmic cardiac death has similar rates in both types of heart failure, more efforts have to be done to prevent it.

The treatment protocol of HF with preserved LVEF has to be improved.

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