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Clinical research

Systolic dysfunction is a predictor of long term mortality in men but not in women with heart failure

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KEYWORDS
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Aims To evaluate possible gender differences in clinical profile and outcome of patients hospitalised with heart failure.
Methods and results During 1996 a total of 1065 hospital in-patients had confirmed heart failure, with follow-up data through 2002. Women (58%) were significantly older, had higher prevalence of hypertension and diabetes, and lower prevalence of ischaemic heart disease, chronic pulmonary disease and alcoholism. The proportion of patients with normal left ventricular ejection fraction (LVEF) increased with age, but in all age groups women had normal LVEF more frequently than men. Echocardiography was performed less frequently in females: 62% vs. 71% in men, $P<0.01$, and this finding was consistent in all age groups. During follow-up (median 19 months) 507 patients died (216 men [48.8%] and 291 women [46.8%]). Gender was not a predictor of survival when LVEF was included in the model (RH Male Gender 0.8, 95% CI 0.6 to 1.1, $P=0.2$). There was a significant interaction gender-LVEF ($P=0.048$): survival was similar in both genders with LVEF >0.3 but women with LVEF ≤0.3 had a better prognosis than their male counterparts.
Conclusions Survival is similar in women irrespective of LVEF and in men with LVEF >0.3 while men with severely depressed LVEF have a worse prognosis.

Introduction

Heart failure is a rapidly expanding syndrome and has become the most important public health problem in cardiovascular medicine.[1] Heart failure in women probably accounts for more than half of all heart failure cases and admissions.[2–8] However, females are underrepresented in most heart failure trials, in part due to exclusion of older patients, as heart failure predominates in older women.[9] In recent trials only 20% of patients are women (range 0 to 32%).[3,10] On the other hand epidemiological and clinical data have shown clear differences in several aspects of cardiovascular disease, mainly ischaemic heart disease, between men and women, including risk factors, response to therapy, quality of care, and natural history.[11] In addition male gender is an established risk factor for coronary heart disease, the current main etiology of heart failure in the western world.[12]

Epidemiological studies, although relatively sparse, have suggested that female gender is an independent predictor of survival in patients with heart failure.[13,14] However, it is not clear whether differences in outcome

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Table 1 Heart failure or related diagnosis (International Classification of Diseases 9—Clinical Modification)

402.9	Hypertensive heart failure
428.0	Congestive heart failure
428.1	Left heart failure
428.9	Heart failure, unspecified
425.4	Primary cardiomyopathy
425.5	Alcoholic cardiomyopathy
425.9	Secondary cardiomyopathy, unspecified

reflect differences in clinical profile, patient's referral, stage of disease, management, and investigations approaches or a specific and independent biological factor. Moreover, results of studies in selected patients with left ventricular dysfunction are inconsistent. The origin of these inconsistencies remains controversial.

The aim of this study was to evaluate possible gender differences in the clinical profile and the outcome of non-selected patients admitted with heart failure. In order to achieve this purpose we compared the clinical profile, risk factors, co-morbidity, management and mortality rate between men and women in a large sample of patients with heart failure admitted to our Hospital.

Methods

Data are from the HOLA project (*H*eart failure: *O*bservation of *L*ocal *A*dmissions). This registry has been previously described elsewhere[8,15] and involved all medical departments of the Gregorio Marañón University Hospital. In summary, the study includes all admissions to our center from 1 January 1996 to 31 December 1996 that received, at least one of the International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM) codes in Table 1 as a diagnosis (1953 admissions), with follow-up data through 2002. The hospital records were collected and retrospectively reviewed. All available demographic and medical data, including LVEF if measured during admission or in the six previous months, were recorded for each patient.

Case definition

Because the evaluation was retrospective, it was decided to use criteria most likely to be found in a majority of the records. Patients were included if they were 16 years of age or older and had:

(a) Cardiac dysfunction fitting the European Society of Cardiology guidelines for the diagnosis heart failure:[16] presence of symptoms of heart failure plus objective evidence of cardiac dysfunction (left ventricular systolic dysfunction or moderate/severe valvular heart disease) and, in cases where the diagnosis is in doubt, response to treatment directed towards heart failure.

(b) Neither left ventricular systolic dysfunction nor moderate/severe valvular heart disease but, at least, one symptom (dyspnoea or oliguria) plus one sign (high jugular venous pressure, rales or pedal oedema) of heart failure and Chest Roentgenogram with evidence of heart failure (cardiomegaly, pulmonary oedema or vascular redistribution).

(c) No echocardiographic study during admission or in the previous year but at least one symptom of heart failure and one sign or Chest Roentgenogram evidence of heart failure.

Patients were excluded if:

(1) The presence of heart failure could not be objectively determined using the above criteria (454 admissions [23.3%]). In most cases these patients had presented previously heart failure but the present admission was due to another illness and there were no symptoms of heart failure at the time of admission.

(2) They had an acute myocardial infarction as primary reason for admission (69 admissions [3.5%]).

(3) Their hospital records were incomplete, or parts were not available for investigation (76 admissions [3.9%]).

After this process 1065 patients with 1354 admissions (1.27 admissions per patient) were included in the study.

Review

All data collected were reviewed by two cardiologists (MMS and JAGR—the case definition panel). Cases were included only if both cardiologists agreed that the case met the defining criteria. The reproducibility of the panel decisions for case definition, evaluated by random re-submission of 9% of the cases, was good, Cohen's k=0.89 (95% CI 0.77–0.99).

Statistical analysis

To assess the relationship between baseline characteristics and gender bivariate analysis were performed initially. The Chi-square statistic was used for categorical variables and the Student t test for continuous variables. Survival curves for all-cause mortality during follow-up were estimated according to the Kaplan–Meier method and compared by log-rank tests, in the case of age two groups above and below 75 years were considered. Each predictor, with a significance level <0.05, identified through this analysis was tested in a backward stepwise multivariate Cox proportional hazards model for time to death. Significance levels used for inclusion in/exclusion from the model were 0.05 and 0.10, respectively. Other baseline characteristics considered likely to have an important prognostic value or with a *P* value <0.15 (except data from the echocardiogram) were also forced into the model. Finally a second model was tested including data from the echocardiogram. The presence of an interaction between gender and each of the variables, selected as an independent factor with the multivariate Cox model, was tested using the Wald test.

For the first analysis, adjustment was performed with the following variables: age (included as a continuous variable), risk factors, previous myocardial infarction, previous stroke, atrial fibrillation, presence of left and right bundle-branch block, and co-morbidity. The second analysis also included left ventricular dysfunction and valvular disease, these variables were codified from no=0 to severe=3. We decided to include LVEF as a dichotomized variable in the final model, using a clinically relevant cutpoint of 0.3, although the interaction between gender and LVEF was also significant when a cutpoint of 0.4 or the original codification were used (results not shown). Results are expressed as relative hazard (RH) and 95% CI.

A commercially available microcomputer statistics program (SPSS 10.0 for Windows, Chicago, Illinois, U.S.A.) was used to perform all statistical analysis.

Results

Baseline patient data and discharge treatment

A total of 1065 patients, 443 men (42%) and 622 women (58%), met the inclusion criteria for the study. Patients

Table 2 Differences in age and sex of patients according to the inclusion criteria: (a), (b), and (c)

	Criterion a	Criterion b	Criterion c
Number of Patients (%)	536 (50.3)	166 (15.6)	363 (34.1)
Age (years)	71.4±10.4	75.4±10.4	79.4±9.8
% Female	51.1	68.7	64.5

included in the study according to criterion (a) were younger and less frequently female than patients included in the study according to criteria (b) and (c) (Table 2).

There were some noteworthy gender-related differences in the clinical profiles of men and women (Table 3). Women were significantly older (77.3±10.5 years vs 71.4±12.0, *P*<0.0001) and had more risk factors except tobacco consumption (women smoked less) and hypercholesterolaemia (no differences). In spite of the higher prevalence of most risk factors, women had a better vascular profile with less frequent ischaemic heart disease and were admitted less frequently in the cardiology department. However, women had a higher prevalence of atrial fibrillation. Men, on the other hand, more often had a history of chronic pulmonary disease, alcohol consumption, and renal disease.

In general terms, there were no clinically relevant differences in symptoms, physical signs, chest roentgenogram data and discharge treatment between women and men.

Echocardiography

An echocardiogram was performed in 706 patients (66%). Echocardiogram was performed less frequently in females: 62% vs 71% in men, *P*<0.01, and this finding was also consistent in all age groups: 86% vs 87% in patients <65 years old, 68% vs 72% in patients aged 65 to 79 years and 50% vs 56% in patients 80 years of age or older. A total of 325 patients (46%) had a normal LVEF (0.5 or over) and this proportion was higher in females: 60% vs 29% in men, *P*<0.01. The rate normal LVEF/depressed LVEF increased with age, but in all age groups women had a normal systolic function more frequently than men (Fig. 1).

Predictors of outcome

Follow-up data (range 0.5 days to 6 years) were available in 95% of patients and 91% had complete follow-up data at 1 year. The median length of follow-up was 19 months, similar in men and women. A total of 507 patients (216 men and 291 women) died during follow-up.

The independent predictors of death from all causes according to demographic and clinical characteristics are listed in Table 4. The risk of all-cause mortality during follow-up was significantly lower in women after adjustment for all other significant or known predictors (RH Male Gender: 1.3, 95% CI 1.1 to 1.5, *P*=0.008). However, gender was not one of the predictors of mortality during

Table 3 Characteristics of the patients according to gender, data in percentage except age in years

Risk Factors	Men	Women	*P*
Age (years)	71.4±12.0	77.3±10.5	<0.0001
Diabetes	24	34	0.00043
Hypertension	36	47	0.0007
Severe obesity	4	8	0.008
Current smoker	35	3	<0.0001
Hypercholesterolemia	11	12	0.50
Vascular Profile			
Previous MI	22	10	<0.0001
CAD in Angiography	12	5	0.00014
CABG	7	3	0.004
Peripheral artery disease	11	2	<0.0001
Stroke	13	11	0.28
Cardiac Profile			
Admission in Cardiology	27	16	<0.0001
Atrial fibrillation	44	53	0.0027
Previous valve surgery	5	5	0.80
Previous pacemaker	10	7	0.11
LBBB	11	10	0.54
RBBB	9	8	0.46
Comorbidity			
COPD	40	23	<0.0001
Alcoholism	17	1	<0.0001
Renal disease	17	12	0.015
Peptic Ulcer	8	5	0.12
Liver disease	5	4	0.42
Cancer	5	4	0.57
Dementia	5	6	0.79
Symptoms, signs and chest roentgenogram			
Dispnea	96	96	0.92
Oliguria	17	20	0.19
Oedemas	62	68	0.054
Rales	79	75	0.22
Elevated Jugular VP	35	34	0.76
Pleural effusions or interstitial oedema	83	82	0.74
Cardiomegaly	84	85	0.61
Echocardiography			
Performed	71	62	0.0042
LVEF <0.5	71	40	<0.0001
LVEF <0.3	48	22	<0.0001
Mitral Stenosis[a]	4	11	0.00048
Mitral Regurgitation[a]	23	27	0.26
Aortic Stenosis[a]	9	9	0.84
Aortic Regurgitation[a]	14	23	0.02
Treatment			
Diuretics	81	86	0.04
ACE inhibitors	55	51	0.27
Nitrates	52	47	0.138
Digoxin	43	50	0.032
Aspirin	32	24	0.016
Anticoagulants	29	24	0.076
Calcium channel blockers	11	11	0.85
Betablockers	4	5	0.76
Vasodilators	6	4	0.31

ACE=Angiotensin converting enzyme. CABG=Coronary arterial bypass graft. CAD=Coronary artery disease. COPD=Chronic obstructive pulmonary disease. MI=Myocardial infarction. LB=Left bundle branch block. RBBB=Right bundle branch block. LVEF=Left ventricular ejection fraction.

[a]Moderate or severe degree.

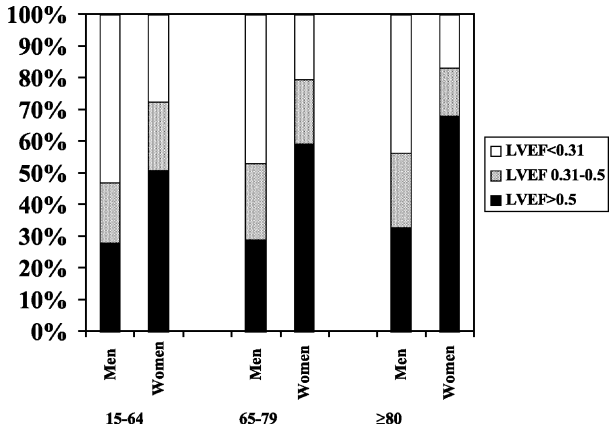

Fig. 1 Percentage of patients with: a) Normal LVEF b) LVEF: 0.31 – 0.5, and c) LVEF≤ 0.3 in different age (in years) and gender groups. LVEF: Left ventricular ejection fraction.

Table 4 Predictors of mortality during follow-up, Cox Regression in all patients, without data from echocardiography

	RH	CI 95%	*P*
Age	1.04	1.03–1.05	<0.0001
Male Gender	1.3	1.1–1.5	0.008
Stroke	1.6	1.3–2.0	0.0002
Renal disease	1.7	1.3–2.2	<0.0001
No Echocardiogram	1.4	1.2–1.7	0.0005
Increased jugular VP[a]	1.3	1.1–1.6	0.003
Cancer	1.6	1.1–2.3	0.026

[a]VP=venous pressure

Table 5 Predictors of mortality during follow-up, Cox Regression in patients with echocardiography

	RH	CI 95%	*P*
Age	1.03	1.02–1.04	<0.0001
COPD	1.6	1.2–2.0	0.001
Stroke	2.1	1.6–2.8	<0.0001
Renal disease	2.1	1.6–2.8	<0.0001
Aortic Stenosis[a]	1.3	1.1–1.4	0.003
LVEF ≦0.3	1.0	0.7–1.6	0.715
Male Gender	0.9	0.6–1.2	0.21
Gender-LVEF Interaction	1.7	1.0–2.9	0.048

COPD=Chronic pulmonary disease. LVEF=Left ventricular ejection fraction.

[a]Codified from no=0 to severe=3.

follow-up in patients with echocardiography when LVEF and gender-LVEF interaction were included in the model (RH Male gender [for patients with LVEF>0.3]: 0.9, 95% CI 0.6 to 1.2, *P*=0.21) (Table 5).

The presence of an interaction of gender with ischaemic etiology (previous MI or coronary disease) and with each one of the predictors of mortality depicted in Table 5 was tested. The only significant interaction found was gender-LVEF: Survival was similar in women with or without severely depressed LVEF (RH for LVEF≤0.3: 1.0, 95% CI 0.7–1.6, *P*=0.72) while men with severely depressed LVEF had a worse prognosis than men with LVEF>0.3 (gender-LVEF Interaction=1.7, 95% CI: 1.0–2.9, *P*=0.048), (Fig. 2). The trend to a gender-related difference in the prognostic value of LVEF was common to older patients (over 75 years) (Fig. 3) and to patients younger than 75 years of age (Fig. 4), with a non-significant 3-way interaction, *P*=0.48.

Re-admission rates

Re-admissions were frequent, 64% of patients had at least one re-admission, and 25% were re-admitted four or more times during follow-up. These figures were similar in men and women.

Discussion

Clinical profile

Using a large unselected sample of patients with heart failure, we found important differences in clinical profile between men and women hospitalized with heart failure. In agreement with previous findings,[2,17–19] women were older and more often had history of hypertension, diabetes and obesity and more preserved LVEF than men. In contrast, men more often had previous coronary heart disease. These differences could reflect a higher prevalence of hypertensive and diabetic heart disease in women in contrast to a higher prevalence of heart failure from ischemic heart disease in men.[3]

Men presented a higher prevalence of chronic pulmonary disease (40% vs 23% in women) and alcohol consumption (17% as compared with 1% in women). These important differences are probably related to cultural perception of tobacco and alcohol consumption in Spanish society, specially by older people.

Left ventricular ejection fraction

One key finding of our study was the very high percentage of heart failure with normal LVEF found in women, double than in men (60% vs 29%). Part of this difference is probably due to the higher age of women. However, in all age groups women had a normal systolic function more frequently than men, suggesting an independent gender-related biological factor. Moreover, real differences could be even higher because echocardiogram was less frequently performed in females. The lower frequency of echocardiographic studies found by us in women had not been previously reported and is in contrast with the similar rates of ejection fraction assessment found by Vaccarino[20] and the similar rate of echocardiography performance found by Philbin and DiSalvo.[21] However, these last authors found a less frequent use of other diagnostic procedures (coronary angiography, exercise testing, and holter monitoring) in women.

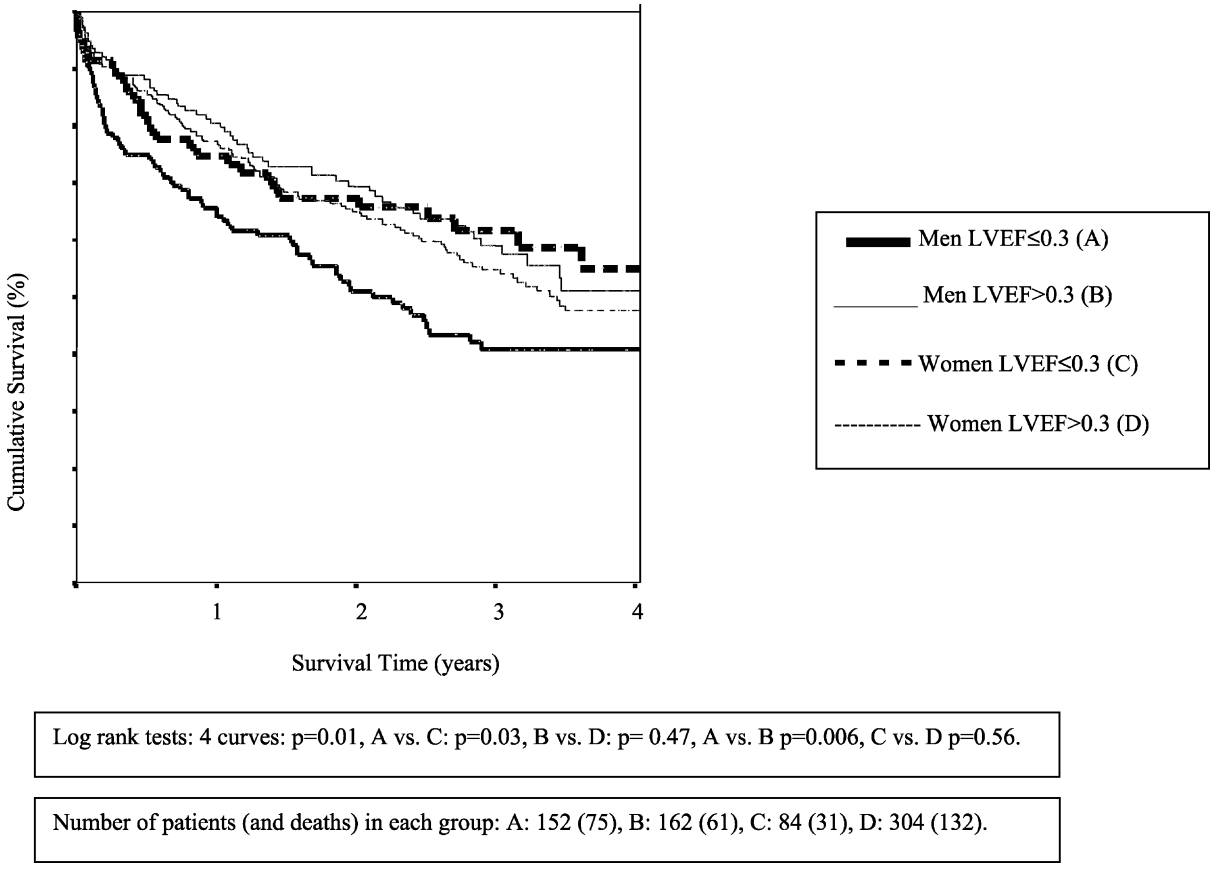

Fig. 2 Kaplan-Meier curves of survival in consecutively hospitalized patients with heart failure according to left ventricular ejection fraction (LVEF) and gender.

Differences in long term mortality

Two important epidemiological studies, both without LVEF measurement, found that survival rate was significantly greater in women with heart failure than in men.[13,14] Clinical studies in selected patients that included mainly younger patients (mean age <65 years), with depressed LVEF have also found lower mortality rates among women.[22–26] Our study is consistent with these findings. Results of previous studies are more conflicting in subgroups analysis according to etiology. In two of them[22,23] women survived longer than men only when heart failure was due to non-ischemic causes, while the CIBIS II trial[24] found the opposite. Finally in the MERIT-HF[25] and in the ATLAS[26] trials the survival advantage of women was significant even after adjustment for ischaemic aetiology. In our study of non-selected patients, ischemic aetiology was not a predictor of outcome and we found no significant interaction between ischaemic aetiology and gender. On the other hand, data from the SOLVD Registry, that included patients with and without systolic dysfunction, showed that men survived longer than women, and female gender was independently related to mortality in patients with ischaemic heart disease.[27] The inclusion of patients with normal LVEF in which, according to our findings, there are no gender-related differences in prognosis could explain, at least in part, this divergent result.

There is a paucity of data from non-selected patients, including elderly patients (mean age >72 years) with and without systolic dysfunction. Two small studies[2,28] found that female gender was an independent predictor of survival (RH=0.5). In the study by Burns et al.[28] LVEF data were not available in any patient and in the study by McDermott et al.[2] only 224 (54%) had undergone LVEF assessment. However, Vaccarino et al.[20] studying a larger sample of 2445 patients older than 65 years, 76% with LVEF assessment, found that gender was not an independent predictor of mortality.

According with our results, women's better survival in the presence of severe systolic dysfunction could be the main explanation for their better prognosis compared with men, since gender differences disappeared when LVEF was included in the model. In fact, we found a similar survival in women with or without severely depressed LVEF and in men with LVEF>0.3 whereas men with severely depressed LVEF had a worse prognosis, suggesting that systolic dysfunction is a predictor of long-term mortality in men but not in women with heart failure. It has been suggested that a higher rate of systolic dysfunction accounted for the higher rate of mortality among men.[10,20] However, prognostic value of

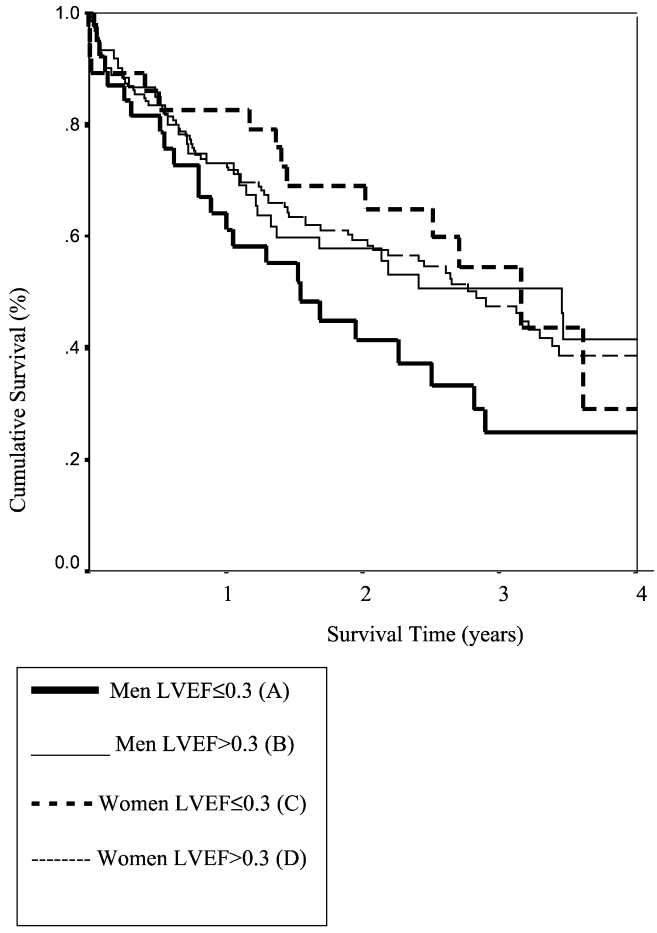

Fig. 3 Kaplan-Meier survival curves in consecutively hospitalized patients older than 75 years of age with heart failure according to left ventricular ejection fraction (LVEF) and gender.

systolic dysfunction has been questioned by others.[2] On the other hand, longer women's life expectancy found in general population–82.7 years vs 75.3 years for males in 1996 in Madrid[29]—clouds the interpretation of gender-related difference in mortality.

This gender-dependence influence of LVEF in heart failure prognosis had never been previously described and biological reasons that explain a different prognostic value of systolic dysfunction according to gender are unknown. However, an increasing number of female-related advantages in human heart failure and systolic dysfunction pathology and pathophysiology have been recently described, both in clinical and experimental settings. These differences affect left ventricular remodeling,[30] myocardium ion-channel activity,[31] skeletal muscle,[32] ventricular arrhythmias[33] and sympathetic activation.[34] Also in murine models of dilated cardiomyopathy female-related advantages were found in myocardial expression of TNF-receptor mRNAs[35] and in adaptive hypertrophic reserve.[36]

Limitations and strengths

Our study has several limitations. First, the obvious drawbacks of using hospital records for research could not be totally avoided in this study. To minimize the impact of varying diagnostic criteria among different doctors, and services, the cases had to fulfill well-defined inclusion criteria which were strict, highly reproducible and clinically recognizable. However, it is conceivable that these criteria while increasing the specificity could reduce the sensitivity by excluding milder forms of heart failure, thus, underestimating the true prevalence of heart failure admissions. Second, we did not have information on factors potentially important in the survival of heart failure patients such as catecholamine and atrial peptide

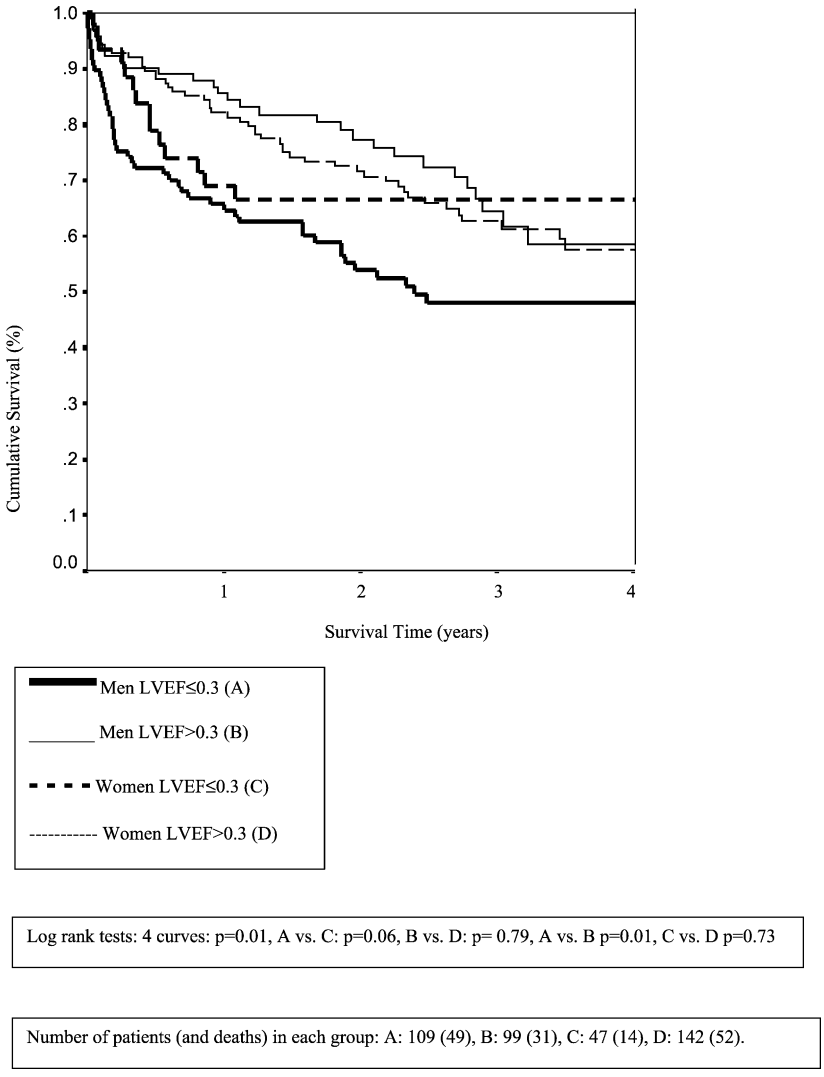

Fig. 4 Kaplan-Meier survival curves in consecutively hospitalized patients younger than 76 years of age with heart failure according to left ventricular ejection fraction (LVEF) and gender.

levels.[1] Finally, left ventricular function assessment was unavailable in approximately 34% of the patients and, thus, were excluded from the survival analysis in the model that included echocardiography data. Missing data on LVEF are unavoidable in a retrospective observational design study such as this. It has already been reported that a large portion of patients hospitalized for heart failure does not have LVEF assessed during hospitalization.[37] The lack of left ventricular function studies in patients admitted for heart failure points out a clear deficiency in the current clinical care of these patients.

Nevertheless, our study has several important strengths. First, it is based on a large sample of patients with heart failure without age restriction, and is free of selection biases unavoidable in studies based on patients enrolled in clinical trials. Second, the diagnosis of heart failure was validated by two cardiologists and included patients with heart failure and diastolic dysfunction, a common cause of heart failure in the elderly and in women.[17–19] Therefore our sample reflects typical patients admitted with clinical diagnosis of heart failure better than previous investigations. Finally, we had extensive information on medical history, clinical characteristics, and treatment of the patients included in the study. Such a level of clinical detail has hardly been matched by previous studies. Therefore we were able to examine the role of a large number of potential explanatory factors in the observed gender differences in mortality rate.

Conclusions

In conclusion, our findings indicate that women and men hospitalized with heart failure differ in clinical profile and left ventricular systolic function. Echocardiography was performed less frequently in women, specially in older women. Despite these differences, men and women have similar hospital course, treatment, and readmission rates. However during long-term follow-up a significant and previously unknown gender-LVEF interaction was

found: survival was similar in women irrespective of LVEF and in men with LVEF >0.3, while men with severely depressed LVEF had a worse prognosis.

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