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Clinical profile and causes of death according to ejection fraction in patients with heart failure cared for in a specialized Cardiology unit

Perfil clínico y causas de muerte de los pacientes con insuficiencia cardíaca atendidos en una unidad especializada de Cardiología según su fracción de eyección

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Abstract

Background and objective

Patients with heart failure are classified into three phenotypes based on left ventricular ejection fraction. This work aimed to compare the clinical profile, treatment, prognosis, and causes of death of patients with heart failure and reduced (<40%, HF-rEF), preserved (≥50%, HF-pEF), or mid-range (40–49%, HF-mrEF) left ventricular ejection fraction.

Methods

An analysis was conducted on the clinical data included in a prospective registry of patients with heart failure who were referred to a specific Cardiology unit from 2010 to 2019.

Results

A total of 1404 patients with HF-rEF, 239 patients with HF-mrEF, and 266 patients with HF-pEF were analyzed. Significant differences were observed among the groups in regard to several clinical characteristics and the frequency of prescription of neurohormonal blocking drugs. A multivariate Cox regression revealed an increased risk of all-cause mortality in patients with HF-pEF (hazard ratio 1.36; 95% confidence interval 1.03–1.80; p = .028) and patients with HF-mrEF (hazard ratio 1.36; 95% confidence interval 1.03–1.78; p= .029) as compared to patients with HF-rEF. Heart failure was the most frequent cause of death in the three subgroups. A higher relative weight of sudden death as a cause of death was observed among patients with HF-rEF while the relative weight of non-cardiovascular causes of death was higher among patients with HF-pEF and HF-mrEF.

Conclusions

This study confirms the existence of significant differences among patients with HF-rEF, HF-mrEF, and HF-pEF with regard to their clinical profile, therapeutic management, prognosis, and causes of death.

Resumen

Antecedentes y objetivos

Los pacientes con insuficiencia cardíaca se caracterizan en 3 fenotipos en función de su fracción de eyección ventricular izquierda. El propósito de este estudio fue comparar el perfil clínico, el tratamiento, el pronóstico y las causas de muerte de los pacientes con insuficiencia cardíaca y fracción de eyección ventricular izquierda reducida (<40%, IC-FEr), preservada (≥50%, IC-FEp) o en rango medio (40–49%, IC-FErm).

Metodología

Análisis de la información clínica recogida en un registro prospectivo de pacientes con insuficiencia cardíaca remitidos a una consulta monográfica de Cardiología entre 2010 y 2019.

Resultados

Se estudiaron 1.404 pacientes con IC-FEr, 239 pacientes con IC-FErm y 266 pacientes con IC-FEp. Se observaron diferencias significativas entre los 3 grupos en relación con diversas características clínicas, y en cuanto a la tasa de prescripción de fármacos moduladores de la respuesta neurohormonal. La regresión de Cox multivariante reveló un incremento del riesgo de muerte por cualquier causa en los pacientes con IC-FEp (hazard-ratio 1,36; intervalo de confianza al 95% 1,03–1,80; p = 0,028) e IC-FErm (hazard-ratio 1,36; intervalo de confianza al 95% 1,03–1,78; p = 0,029) en comparación con los pacientes con IC-FEr. La insuficiencia cardíaca fue la causa más frecuente de muerte en los 3 grupos; se observó un mayor peso relativo de la muerte súbita en los pacientes con IC-FEr, mientras que las causas no cardiovasculares de muerte tuvieron un peso relativo mayor en los pacientes con IC-FEp e IC-FErm.

Conclusiones

El estudio confirma la existencia de diferencias significativas en el perfil clínico, manejo terapéutico, pronóstico y causas de muerte de los pacientes con IC-FEr, IC-FErm e IC-FEp.

Keywords

Heart failure; Ejection fraction; Causes of death; Prognosis

Palabras clave

Insuficiencia cardíaca; Fracción de eyección; Causas de muerte; Pronóstico

Introduction

Historically, left ventricular ejection fraction (LVEF) has been considered the functional parameter of choice for evaluating cardiac contractility.

For patients with heart failure, the presence of a reduced LVEF (<40%) (HFrEF) identifies a phenotype characterised by impaired systolic function as a result of various causal agents—ischaemia, genetic and toxic alterations, and viral damage—. In these patients, treatment with neurohormonal response modifying drugs is associated with a significant prognostic benefit.1

On the other end of the spectrum, patients with HF and preserved LVEF (>50%) (HFpEF) present a phenotype characterised by the presence of microvascular dysfunction, myocyte hypertrophy, and interstitial fibrosis due to pathological ventricular remodelling attributable to the impact of comorbidities, and cardiovascular risk factors.2 For these patients, the prognostic benefit from neurohormonal blockade has not been consistently demonstrated.

Recently, the concept of HF with mid-range LVEF (HFmrEF) has been coined to describe patients with an LVEF between 40% and 49%.1 This subgroup has been under-represented in clinical trials, meaning we have little scientific evidence to guide therapeutic management.

The aim of our study was to describe the clinical profile, prognosis, and causes of death in HF patients treated in a specialised cardiology unit in a Spanish university hospital, paying attention to the possible differences in these aspects between the three subgroups defined according to the LVEF.

Methodology

Study description

We performed an observational study based on a clinical registry of patients treated in the specialized cardiology consultation unit for HF at the A Coruña University Hospital Complex between 2010 and 2019.

The registry has a prospective design and includes consecutive patients evaluated in the unit at the time of their first visit to the clinic, although some of the collected information is retrospective and sourced from medical and nursing notes present in the electronic medical history.

Maintenance of the Cardiology HF unit clinical registry was performed by specific research support staff using the smart heart failure monitoring system IT tool (SIMon-IC®), a medical history management tool developed by the centre's own IT Services department. This application allows for data collected on each patient to be recorded in a case report form and includes baseline information related to their clinical situation prior to their first consultation in our unit, as well as information related to their subsequent follow-up visits and their clinical evolution, vital status, and hospitalisation episodes.

During the study period, the only necessary criteria for a patient to be referred to the Cardiology HF unit was the existence of a confirmed diagnosis of previous HF, including an echocardiographic assessment.

The patients gave their informed consent for their clinical data to be used for research purposes. The study protocol was approved by the Clinical Research Ethics Committee of Galicia.

Endpoint variables

The patient's vital status was monitored from the moment of their first visit in the HF unit until their time of death or, alternatively, until 15 May 2020. For patients who received a heart transplant, follow-up ended on the date of that intervention.

The endpoint variables analysed in this study were the composite of death or hospitalisation due to HF and all-cause mortality. For the purposes of the survival analysis, a heart transplant was considered an event equivalent to hospitalisation for HF but was not counted as a mortality event.

The following were considered cardiovascular causes of death: sudden death or due to arrhythmia, death due to refractory HF, cerebrovascular accident, ischaemia or arterial thromboembolism, venous thromboembolism, and death attributable to complications from a cardiovascular procedure.

Statistical analysis

Categorical variables were defined using proportions while continuous variables were defined using a mean ± standard deviation. The Chi-squared test was used to compare categorical variables between groups and the ANOVA or Kruskal–Wallis tests for comparing the quantitative variables. Adaption of the quantitative variables to the normal distribution was evaluated using the Kolmogorov–Smirnov test and Qsingle bondQ plots.

We used the Kaplan–Meier method to construct the curves for overall survival and hospitalisation free survival due to HF in the three patient groups defined according to their LVEF function. The comparison of time until each of the endpoints of interest was carried out using the log rank test.

With the aim of controlling the effect of a potential confounding bias over the statistical association observed in the univariate analysis between LVEF groups and clinical endpoints, we designed a simple multivariate adjustment using the Cox regression model.

Added to the model as adjustment covariates were the baseline clinical characteristics and analytical parameters that showed an uneven distribution between the three groups (univariate $p < 0.10$) and which, at the same time, could be associated with the prognosis based on clinical reasoning and review of the prior literature. These were: age, sex, history of hospitalisation for HF, coronary artery disease, heart valve disease, infiltrative cardiomyopathy, active or past smoking, peripheral artery disease, neoplasia, atrial fibrillation or flutter, presence of signs of congestion, systolic blood pressure, heart rate, haemoglobin, glomerular filtration rate, and NTproBNP.

Excluded from this analysis were variables with ≥5% missing data (left ventricular end-diastolic diameter, left ventricular end-systolic diameter, bilirubin, and pulmonary artery blood pressure). In total, 53 (2.8%) patients with missing data for one of the covariates selected for the adjustment were excluded from the final multivariate model.

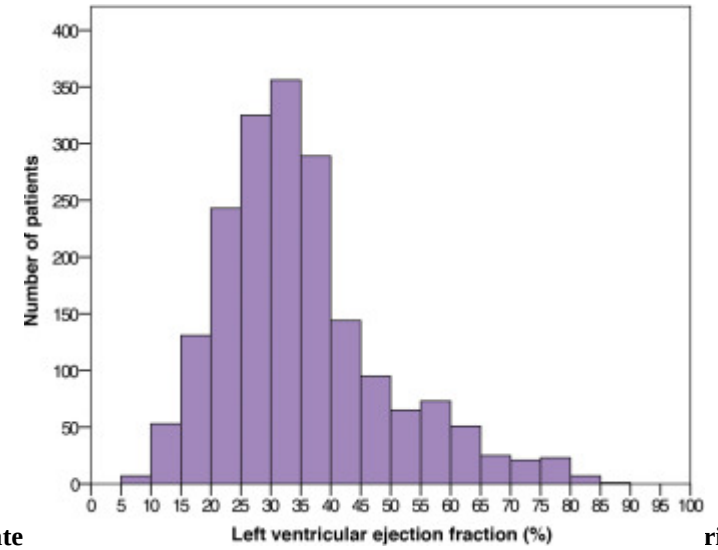
A significance level of $p < 0.05$ was considered for all the hypothesis testing. The statistical analysis was performed with SPSS 20.

Results

Baseline clinical characteristics

The study included 1909 consecutive patients who attended for Cardiology HF unit for the first time between 2010 and 2019. Of those, 1346 (70.5%) were patients belonging to the centre's own health district of reference and 563 (29.5%) patients were referred from other hospitals in the autonomous community.

The mean age of the patients was 63.3 (12.3%) years; 537 (28.1%) were women and 1372 (71.9%) were men. A history of HF was present in 908 (47.6%) of the patients. In total, 1404 (73.5%) patients presented reduced LVEF (<40%), 239 (12.5%) presented mid-range LVEF (40−49%), and 266 (13.9%) presented preserved LVEF (>50%). Fig. 1 shows the distribution of LVEF in the 1909 patients included in the study.



Mate rial and Methods

Figure 1. Distribution of the left ventricular ejection fraction values in 1909 patients with heart failure at the time of follow-up.

Table 1 shows a comparison of the baseline clinical characteristics of the patients with HFrEF, HF-mrEF, and HF-pEF. The three groups differed significantly in terms of mean age, male/female ratio, associated comorbidities, and prevalence of cardiovascular risk factors.

Patients with HFpEF presented a clinical profile suggestive of greater severity, with a higher prevalence of congestive signs, lower haemoglobin plasma levels, lower glomerular filtration rate, and higher pulmonary artery blood pressure.

The patients with HFrEF had larger ventricular diameters.

Table 1. Clinical characteristics of 1909 patients with heart failure according to their left ventricular ejection fraction (LVEF).

Variables	LVEF < 40% (n = 1404)	LVEF 40–49% (n = 239)	LVEF ≥ 50% (n = 266)	p
Medical history				
Age (years), mean (standard deviation)	62.6 (11.4)	63 (14.7)	67.3 (13.4)	<0.001
Female, n (%)	364 (26)	65 (27)	108 (41)	<0.001
Prior hospital admission due to heart failure	703 (50%)	93 (39%)	112 (42%)	0.001
Obesity	483 (34%)	77 (32%)	95 (36%)	0.704
Arterial hypertension	742 (53%)	127 (53%)	153 (58%)	0.372
Diabetes mellitus	444 (32%)	64 (27%)	75 (28%)	0.216
Smoker or ex-smoker	881 (63%)	115 (48%)	102 (38%)	<0.001
Dyslipidaemia	764 (54%)	119 (50%)	140 (53%)	0.393
Coronary artery disease	618 (44%)	105 (44%)	68 (26%)	<0.001
Myocardial infarction	455 (32%)	73 (31%)	54 (20%)	<0.001
Valvular heart disease	143 (10%)	35 (15%)	68 (26%)	<0.001
Infiltrative cardiomyopathy	17 (1.2%)	18 (7.5%)	44 (17%)	<0.001
Chronic obstructive pulmonary disease	153 (11%)	19 (8%)	30 (11%)	0.362
Cerebrovascular disease	125 (9%)	26 (11%)	28 (11%)	0.492
Peripheral artery disease	110 (8%)	19 (8%)	10 (4%)	0.036
Neoplasia	184 (13%)	34 (14%)	50 (19%)	0.019
Atrial fibrillation or flutter	309 (22%)	69 (29%)	103 (39%)	<0.001
Clinical situation				
New York Heart Association functional classification				0.845
Class I	157 (11%)	26 (11%)	25 (9%)	
Class II	773 (55%)	136 (57%)	140 (53%)	
Class III	424 (30%)	70 (29%)	91 (34%)	
Class IV	50 (4%)	7 (2%)	10 (4%)	
Signs of pulmonary oedema[a]	164 (12%)	21 (9%)	43 (16%)	0.032
Signs of systemic congestion[b]	201 (14%)	46 (19%)	67 (25%)	<0.001
Systolic blood pressure (mm Hg)	117 (20)	120 (22)	126 (22)	<0.001
Heart rate (beats per minute)	72 (15)	69 (13)	70 (14)	0.006
Laboratory				
Haemoglobin (g/dL)	13.7 (1.8)	13.7 (2.5)	13.1 (1.9)	<0.001
Creatinine (mg/dL)	1.21 (0.71)	1.36 (1.25)	1.32 (1)	0.611
Bilirubin (mg/dL)	0.73 (0.44)	0.75 (0.37)	0.89 (0.62)	<0.001
Glomerular filtration rate (mL/min/m^2)	77 (34)	76 (38)	66 (29)	<0.001
NTproBNP (pg/mL)	3200 (4890)	3266 (5920)	3099 (4935)	0.091
Echocardiogram				
LVEF (%)	28 (7)	44 (3)	61 (9)	<0.001
Left ventricular end-diastolic diameter (mm)	61 (20)	54 (9)	47 (7)	<0.001
Left ventricular end-systolic diameter (mm)	52 (16)	42 (8)	31 (6)	<0.001
Pulmonary artery systolic pressure (mmHg)	39 (13)	40 (14)	47 (19)	<0.001

Variables with missing data (n): heart rate (n = 6), systolic blood pressure (n = 26), bilirubin (n = 122), glomerular filtration rate (n = 27), NTproBNP (n = 5), left ventricular end-diastolic diameter (n = 348), left ventricular end-systolic diameter (n = 532), pulmonary artery systolic pressure (n = 1052).

[a] Presence of lung crackles, clinical physical diagnosis of pleural effusion or radiological signs indicative of pleural effusion, interstitial oedema or alveolar oedema.

[b] Presence of peripheral oedema, ascites, congestive hepatomegaly, or hepatojugular reflux.

Treatment

Table 2 shows the prescribing frequencies for the main drug groups in the three patient subpopulations defined according to their LVEF during the monitoring period in the specialised HF unit.Patients

Table 2. Prescribing of main drug groups during the follow-up period in the specialised heart failure clinic in the three patient groups defined according to their left ventricular ejection fraction (LVEF).

Variables	LVEF < 40% (n = 1404)	LVEF 40–49% (n = 239)	LVEF ≥ 50% (n = 266)	p
Beta blockers	1371 (98%)	205 (86%)	186 (70%)	<0.001
Angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers and/or sacubitril/valsartan	1307 (93%)	191 (80%)	137 (52%)	<0.001
Angiotensin-converting enzyme inhibitors	917 (65%)	142 (59%)	88 (33%)	<0.001
Angiotensin II receptor blockers	262 (19%)	38 (16%)	53 (20%)	0.483
Sacubitril- valsartan	478 (34%)	37 (16%)	8 (3%)	<0.001
Mineralocorticoid receptor antagonists	1164 (83%)	157 (66%)	146 (55%)	<0.001
Loop diuretics	1225 (87%)	192 (80%)	230 (87%)	0.016
Other diuretics	80 (6%)	21 (9%)	22 (8%)	0.084
Digoxin	170 (12%)	27 (11%)	33 (12%)	0.921
Ivabradine	271 (19%)	22 (9%)	6 (2%)	<0.001
Sodium-glucose cotransporter-2 inhibitors	99 (7%)	8 (3%)	1 (0.4%)	<0.001

Beta blockers were prescribed to 1371 (97.6%) patients with HFrEF, 205 (85.8%) patients with HFmrEF, and 186 (69.9%) patients with HFpEF ($p < 0.001$); angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and/or sacubitril-valsartan were prescribed to 1307 (93.1%) patients with HFrEF, 191 (79.9%) patients with HFmrEF, and 137 (51.5%) patients with HFpEF ($p < 0.001$), and mineralocorticoid receptor antagonists were prescribed to 1164 (82.9%) patients with HFrEF, 157 (65.7%) patients with HFmrEF and 146 (54.9%) patients with HFpEF ($p < 0.001$).

In total, 484 (34.5%) patients with HFrEF, 45 (18.8%) patients with HFmrEF, and 24 (9%) patients with HFpEF were bearers of an implantable defibrillator ($p < 0.001$) during clinical monitoring in the HF unit.

Prognosis

Mean monitoring of the vital status of the study patients was 1387 (standard deviation 1003) days. During this period, 283 (20.2%) patients with HFrEF, 68 (28.4%) patients with HFmrEF and 82 (30.5%) patients with HFpEF died. A heart transplant was performed on 95 (6.8%) patients with HFrEF, 11 (4.6%) patients with HFmrEF and 7 (2.6%) patients with HFpEF. In total, 572 (30%) patients presented some type of hospitalisation for HF during monitoring.

Fig. 2 shows the curves for overall survival (2a) and survival free from admission for HF (2b) in the study patients according to their LVEF status, estimated using the Kaplan–Meier method. The log rank test showed a statistically significant difference between the groups in terms of both events (overall survival, $p < 0.001$; survival free from admission for HF, $p = 0.026$).

Following the multivariate adjustment for possible confounding factors defined in the Methodology section and taking the HFrEF category as a reference, a hazard ratio of 1.36 was estimated for risk of all-cause death (95% confidence interval [CI] 1.03–1.80; $p = 0.028$) for patients with HFpEF and 1.36 (95% CI 1.03–1.78; $p = 0.029$) for patients with HFmrEF. This analysis did not detect significant differences between the groups with regard to the risk of the composite endpoint of all-cause death or hospitalisation for HF, with a hazard ratio for patients with HFpEF of 1.24 (95% CI: 1–1.54; $p = 0.053$) and a hazard ratio for patients with HFmrEF of 1.07 (95% CI: 0.85–1.34; $p = 0.556$).

Causes of death

Information was obtained about the primary cause of death in 422 (97.5%) of the 433 deaths recorded throughout follow-up; of the 11 patients who died due to unknown causes, 3 belonged to the HFmrEF group and 8 to the HFrEF group. Fig. 3 represents the relative weight of the different causes of death in the three HF patient groups according to their LVEF.

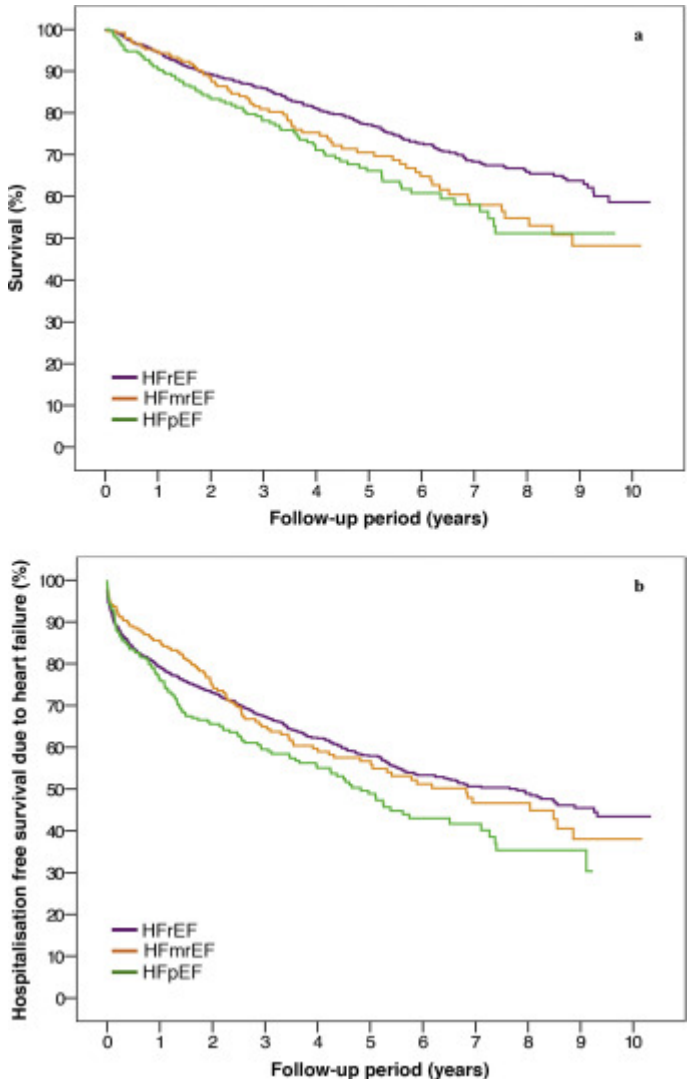


Figure 2. Curves for overall survival (2a) and hospitalisation free survival due to heart failure (2b) in 1909 patients with heart failure, according to their left ventricular ejection fraction.
HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; HFmrEF: heart failure with mid-range ejection fraction.

Refractory HF was the most common individual cause of death in the 3 groups, affecting 94 (33.2%) patients with HFrEF, 24 (35.3%) patients with HFmrEF, and 28 (34.1%) patients with HFpEF.

Sudden death was the form of death in 83 (29.3%) patients with HFrEF, 12 (17.6%) patients with HFmrEF, and 9 (11%) patients with HFpEF.

Non-cardiovascular causes explained 83 (29%) deaths in patients with HFrEF, 29 (42.6%) patients with HFmrEF and 35 (42.7%) patients with HFpEF. Neoplasia (n = 62, 14.3%) and infections (n = 48, 11.1%) were the most common non-cardiovascular causes of death.

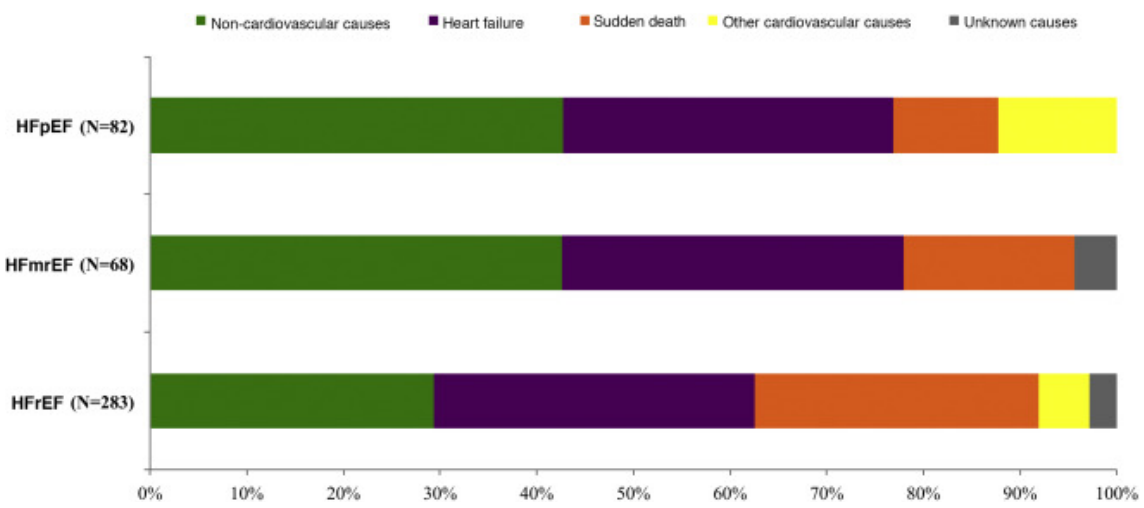


Figure 3. Main cause of death in 433 patients with heart failure, classified according to their left ventricular ejection fraction status at the time of starting follow-up.
HFrEF: heart failure with reduced ejection fraction; HFmrEF: heart failure with mid-range ejection fraction; HFpEF: heart failure with preserved ejection fraction.

Discussion

In this manuscript we present a comparison of the clinical characteristics, therapeutic management, prognosis, and causes of death in 1909 patients with HF who were treated consecutively in a specialized Cardiology consultation unit over a 10-year period, according to the three categories of LVEF defined by scientific societies1 —HFrEF, HFmrEF, and HFpEF—.

The general clinical profile of the subjects included in our study reveals a certain selection bias, typical of the types of patients who are preferably referred to specialised Cardiology HF units.[3]

The study cohort presents a relatively low mean age and a high prevalence of coronary artery disease as an underlying cause of HF. There also exists a clear predominance of the HFrEF phenotype, to which almost 3/4 of the cohort correspond. This figure represents a highly relevant difference compared to the profile of HF patients treated in other care contexts. A recent analysis of the RICA registry, which included 4752 patients hospitalised for HF in Spanish Internal Medicine departments between 2008 and 2018 showed a prevalence of HFpEF of 62.2%.[4]

The HF patient profile represented in our study is that in which, a priori, we could expect greater prognostic benefit from a specialised therapeutic approach that includes aggressive dose titration of disease-modifying drugs, implantation of intracardiac devices and, in the case of refractory disease, advanced measures like heart transplant and mechanical ventricular assistance.[5] Nevertheless, it is worth noting that the selection of patients seen in our specialized consultation unit is a reflection of the clinical criteria of the doctors of reference, as the sole requirement that had to be met for their referral was the presence of a prior confirmed diagnosis of HF.

Our analysis reveals significant differences in terms of the clinical characteristics of patients with HF according to their LVEF. Patients with HFrEF were frequently male and presented a higher prevalence of coronary artery disease, prior myocardial infarction, and peripheral artery disease; on the other hand, we observed in the group of patients with HFpEF a higher representation of the female sex, older age, higher blood pressure levels, and a higher prevalence of atrial fibrillation, valve disease, infiltrative cardiomyopathy, and prior neoplastic disease.

Broadly speaking, the clinical characteristics of the HFmrEF phenotype proved intermediate between the other 2 subgroups, with an emphasis on a high prevalence of coronary artery disease and prior myocardial infarction, similar to that observed in patients with HFrEF.

The differences observed in terms of the clinical characteristics of patients with HFrEF, HFmrEF, and HFpEF are consistent, in global terms, with previous literature.[6] While it has been suggested that the HFmrEF phenotype might represent a transition stage between HFpEF and HFrEF,[7] the description of a clinical profile and of added "intermediate" comorbidities between both phenotypes invites us to think of HFmrEF as an independent clinical entity.[6] However, other authors have suggested that the high prevalence of ischaemic heart disease observed in patients with HFmrEF means these individuals should be classified in the HFrEF subgroup.[8]

Nevertheless, the published studies show significant heterogeneity among their results. It should be noted that the use of LVEF as the only variable for classifying the phenotype of HF patients is of limited value[9]; when determining this parameter, there is a significant intra- and interoperator variability which, despite its undeniable clinical utility, hinders standardisation of the measure and, therefore, calls into question its use as the primary inclusion criteria in research study and as a therapeutic guideline in individual subjects. What's more, the LVEF is a dynamic parameter that can undergo various evolutionary trajectories throughout the HF patient follow-up process.[10]

In our series, patients with HFpEF presented the most advanced clinical situation of the three subgroups studied at the time of their first visit to the HF clinic, and a higher prevalence of congestive signs, worse parameters for liver and renal function, lower serum haemoglobin levels, and higher pulmonary blood pressure.

However, we did not observe statistically significant differences between the three phenotypes with regard to the subjective functional class or the natriuretic peptide plasma levels. This last finding reinforces the impression the severe clinical involvement of patients with HFpEF; a priori, a higher elevation of natriuretic peptides would be expected in patients with HFrEF given the higher degree of parietal stress in these cases as a consequence of the adaptive process of spherical remodelling and ventricular dilation.[11] The unusual level of severity of patients with HFpEF included in our cohort seems to be the result of a referral bias typical to the specific context in which the study was carried out.

One notable finding is the high number of patients with HFmrEF and, to a lesser degree, with HFpEF, who received treatment with recommended drugs with a class I indication due to evidence of prognostic improvement in patients with HFrEF,[1] as is the case with beta blockers or renin-angiotensin-aldosterone system inhibitors. While we may not have consistent evidence of their clinical benefit for patients with HF and LVEF that is closer to normal limits, this situation has also been described in previous studies.[12] The high prevalence of comorbidities such as arterial hypertension, coronary artery disease, and atrial fibrillation, likely to be treated with these kinds of drugs, is the most likely explanation for this result.

Our cohort of patients with HFpEF and HFmrEF presented lower long-term survival than the patients with HFrEF. This statistical effect maintained its significance following the multivariate adjustment for potential confounding factors, including demographic characteristics, underlying aetiology, associated comorbidity and variables representative of the degree of HF progression, such as the presence of signs of congestion, haemoglobin, and liver and renal function parameters.

In the review of previous literature, it is worth noting that there is significant heterogeneity among the results, attributable to the different characteristics of the populations studied. Nevertheless, a meta-analysis of 12 observational studies, including 109,257 patients, suggests that patients with HFmrEF would comprise a subgroup with better prognosis than that of patients with HFrEF or HFpEF.[6] In the RICA registry[4] patients with HFrEF presented significantly higher one-year mortality than the patients with HFpEF or HFmrEF.

The elevated mortality observed in our study in patients with HFpEF and HFmrEF once again seems to be conditioned by a referral bias that has resulted in a selection of patients with a significant level of severity and with specific cardiopathies associated with poor prognosis, such as valve disease or infiltrative cardiomyopathy.

On the other hand, in some studies it is possible that the classification of patients with HF and recovered LVEF into the HFpEF or HFmrEF phenotypes may have conditioned an improvement in the overall prognosis of these subgroups.[13] It is known that patients whose LVEF increases in response to therapeutic interventions comprise a subpopulation of HFrEF with a significantly lower risk of adverse clinical events during follow-up.[14]

Given the design of our study, we cannot know with certainty how many patients assigned to the HFpEF and HFmrEF groups could correspond to patients with a history of HFrEF and LVEF recovery. However, it is our opinion that it is likely a number of cases of little relevance, as they are patients who have already started treatment and who have already experienced a positive response. Therefore, these patients are less likely to be referred to a specialised clinic.

Lastly, it is worth mentioning that, for the moment, we do not have truly effective therapeutic measures for modifying the progress of the disease and improving prognosis of HF patients who do not have reduced LVEF, which contributes to explaining the poor prognosis observed in our series in the HFpEF and HFmrEF subgroups.

In our study, cardiovascular causes, and more specifically HG progression, were the most common cause of death in the three patient subgroups with HF defined according to LVEF. This finding is also consistent with that described by other authors.[12, 15] However, it must be noted that the relative weight of the cardiovascular causes of death was greater in the HFrEF group as a result of the greater frequency of sudden death. The relationship between more depressed LVEF and an increased arrhythmic risk is well-established, particularly in patients with coronary artery disease.

The clinical practice guidelines1 recommend implanting an automated defibrillator to prevent against sudden death in patients with LVEF < 35% and symptomatic HF and/or previous myocardial infarction. However, it is important to remember the limited predictive value of LVEF use as the sole risk marker of sudden death in clinical practice, particularly in patients with HF of non-ischaemic etiology.[16] Lastly, we observed a greater relative weight of non-cardiovascular causes of death in patients with HF-pEF and HF-mrEF, which seems attributable to a higher degree of associated comorbidity.[17]

This study presents some limitations. Firstly, its observational and retrospective nature condition the possibility of selection bias, information bias, and confounding factors. The use of LVEF as a primary parameter for characterising patients with HF into three subgroups, following the definition from the clinical practice guidelines,[1] constitutes in itself another limitation, given the significant inter- and intraoperator variability, which could give rise to a classification bias.

In addition, in the study we only analysed the initial LVEF measurement without considering potential changes to this parameter over the course of the patients' evolution.

Lastly, as has been widely discussed before, the study is based on a historical cohort of patients with HF treated in a specialised Cardiology unit at a single centre, which causes a referral bias. This situation has conditioned an under-representation of the HFmrEF and HFpEF phenotypes, and the selection, within these subgroups, of patients with particularly severe HF symptoms.

Therefore, our results should be considered with caution, and it may not be possible to extrapolate them to other different healthcare contexts.

Conclusions

The analysis of the historical cohort of patients treated in our specialised Cardiology HF unit over the 2010–2019 period confirms the existence of relevant differences in terms of clinical profile, treatment, prognosis, and causes of mortality among patients with HFpEF, HFmrEF, and HFrEF. Looking to the future, it would be important to perform new studies that offer the option to delve deeper into the phenotype characterisation of each of these clinical entities, beyond simple differentiation in terms of LVEF, with the goal of defining the most appropriate therapeutic approach in each case.

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Conflicts of interest

Eduardo Barge-Caballero declares having received professional fees for consulting with Boehringer Ingelheim, Vifor, and AstraZeneca and professional fees for presentations for Novartis, Rovi, Boehringer Ingelheim, AstraZeneca and Servier. The other authors declare that they do not have any conflicts of interest.

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