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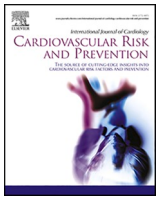

Rehospitalization, mortality and associated variables in primary care patients with heart failure and preserved ejection fraction after first hospitalization

Victoria Cendrós [a,b], Mar Domingo [c], Elena Navas [a], Miguel Ángel Muñoz [a,f], Antoni Bayés-Genís [c,d,e], José María Verdú-Rotellar [a,e,*]

[a] Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol), Barcelona, Spain
[b] Department of Medicine, Universitat de Barcelona, Barcelona, Spain
[c] Heart Failure Unit and Cardiology Department, Hospital Universitari Germans Trias i Pujol, Badalona, Spain
[d] Department of Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain
[e] Network Center for Biomedical Research into Cardiovascular Diseases (CIBERCV), Spain
[f] Department of Medicine and Life Sciences, Pompeu Fabra University, Barcelona, Spain

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ABSTRACT

Introduction: There is a paucity of studies providing insights into the progression of primary care patients with heart failure and preserved ejection fraction (HFpEF).
Objetive: To investigate the characteristics associated with mortality and rehospitalizations in primary care patients with heart failure and preserved ejection fraction (HFpEF), previously hospitalized.
Methods: Retrospective cohort study that included primary care patients with previous heart failure (HF) hospitalization and ejection fraction ≥50 of 328 primary care centers of Catalonia. Demographic, comorbidities, clinical, and treatment variables were collected. Outocomes: Mortality and HF rehospitalization. Adjusted Cox regression models were performed.
Results: Study included 2895 patients. Mean age was 77(SD 9.7) years, 57 % were female. Mean follow up was 2.0[1.0–9.0] years. A total of 864(29.8 %) patients died, 831(28.7 %) were hospitalized. Mortality was associated with male sex(HR 1.26, 95 % CI 1.06–1.49), age >75 years(HR 2.76, 95 % CI 2.24–3.39), Charlson Index (HR 2.03, 95 % CI 1.21–3.42), body mass index(BMI) ≤30 kg/m^2(HR 1.44, 95 % CI 1.22–1.69) and loop diuretics (HR 1.36, 95 % CI 1.11–1.65); hemoglobin levels(HR 0.87, 95 % CI 95 % 0.82–0.91) were protective. HF rehospitalization was associated with male sex(HR 1.14, 95 % CI 1.03–1.33), age >75 years(HR 1.37, 95 % CI 1.17–1.61), atrial fibrillation(HR 1.44, 95 % CI 1.25–1.67), and loop diuretics(HR 1.37, 95 % CI 1.15–1.63). Hemoglobin(HR 0.91, 95 % CI 0.87–0.95) were protective.
Conclusion: High proportion of HFpEF patients were hospitalized or died at 5 years follow up. Comorbidities, demographic, analytical and treatment variables played a relevant role as prognostic factors.

1. Introduction

Heart failure (HF), which affects more than 64 million people worldwide [1], is a public health problem associated with a significant burden on patients and healthcare systems' [2]. In Spain, 2 % of the population had HF in 2019, but approached 9 % in those older than 80 years, and 2.78 new cases per 1000 person-year were diagnosed [3]. While the incidence seems to be declining, the prevalence is increasing due to population ageing, especially in HF and preserved ejection fraction (HFpEF) phenotype [1]. These patients are normally managed in primary care setting. Patients with chronic HFpEF remain at high risk of death, despite mortality rates from HF having slightly fallen in recent years [2].

Although the main costs are due to hospital admissions (39 %), primary care represents 20 % of the health care resource utilization [4].

The HFpEF phenotype differs from the HF and reduced ejection (HFrEF) phenotype in terms of demographics, comorbidities, responses

* Corresponding author. Atenció Primària Barcelona Ciutat. Institut Català de la Salut-IDIAP Jordi Gol Departament de Salut, Generalitat de Catalunya Numància, 23, 4a planta, 08029, Barcelona, Spain.
E-mail address: verdujm@gmail.com (J.M. Verdú-Rotellar).

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Abbreviations

BMI	Body mass index
eGFR	Estimated glomerular filtration rate
HF	Heart failure
HFpEF	Heart failure and preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
LVEF	Left ventricular ejection fraction
SIDIAP	Information System for the Development of Research in Primary Care

to therapies, and outcomes. HFpEF is more common in elderly, female, and obese patients, and is usually associated with other comorbidities. In addition, low socioeconomic status has been found to be associated with greater risk of incident heart failure, including HFpEF [5].

HF is the leading cause of hospitalization in persons aged 65 years or older [5].

One year mortality in HFpEF ranges from 20 % to 29 %, depending on whether the diagnosis was made in the community or after a hospitalization, respectively [6–8]. A systematic review [9] revealed significant differences in outcomes depending on methodology: mortality in patients with HFpEF tends to be higher when it comes from registries focused in HF than in data obtained from community-based registries. The variables associated with higher mortality and hospitalizations also depend on the type of registry [9].

To our knowledge, there is limited data from population-based cohort studies focused on HFpEF with a previous hospital admission in primary care patients. Most of these studies have been conducted using records from Northern Europe [10,11] and there is scarce information on mortality, rehospitalizations and associated variables in the Mediterranean region.

Characterizing this population in our area, would help to identify patients at highest risk who require more intensive treatment and follow-up, and to design future clinical trials.

The objective of our study is to investigate the characteristics associated with the mortality and rehospitalizations in a real-world Mediterranean cohort of HFpEF primary care patients previously hospitalized by HF.

2. Methods

2.1. Study design and data source

This was a retrospective study including information about primary care HFpEF patients. Data source was the Information System for the Development of Research in Primary Care (SIDIAP) in Catalunya (Spain). This anonymized database contains information from the clinical records of eight million people attended in 328 primary healthcare care centers managed by the Institut Català de la Salut [12] (approximately 80 % of the Catalan population and 10 % of the Spanish population). The high quality of SIDIAP and its representativeness has been previously documented, specifically for cardiovascular diseases and risk factors [13].

The information recorded in the SIDIAP includes demographic and clinical data (coded by International Classification of Diseases, 10th revision), laboratory tests, socio-economic indicators, vaccinations, treatments (drugs invoiced at any community pharmacy), and all-cause mortality. SIDIAP can be linked to other data sources such as hospital discharge information. This register includes diagnoses and hospital procedures.The registry has a validation system which checks the consistency of the data and identifies potential errors.

2.2. Patients

The study included all patients >18 years old with a left ventricular ejection fraction (LVEF) ≥ 50 % registered in the SIDIAP database who had been hospital discharged with a HF diagnosis (Fig. 1).

LVEF ≥50 % was selected as a cut off because it is the recommended by the European Guidelines [14] In the absence of echocardiographic data and NT-proBNP a well-documented previous hospital admission may validate diagnosis of HF [15].

2.3. Clinical variables

All clinical data were collected through SIDIAP. Non-smokers were defined as patients who had never smoked or had quit smoking for more than one year. Obesity was defined as a body mass index (BMI) ≥30 kg/m^2. Chronic kidney disease was defined when the estimated glomerular filtration rate (eGFR) was <60 mL/min per 1.73 m^2. Anaemia was diagnosed according to the WHO definition as <13 g/dl (males) and <12 g/dL (females). The Charlson comorbidity index measures the aggregate prognostic burden of comorbidity disease to predict mortality, based on age.

2.4. Follow-up and events

Patients were selected between 2009 and 2017 and followed-up until December 2018.

The outcomes were the HF rehospitalization and all-cause mortality.

2.5. Statistical analysis

Continuous variables were summarized using means ± standard deviations (SD) or medians and interquartile range (IQR), while categorical variables were summarized using frequencies and percentages. Missing data were not imputed or treated. To evaluate associations and relationships between variables, the Chi-square test was applied for categorical variables, while the Student's *t*-test was used for continuous variables. Survival curves for the endpoints were plotted. The association between different variables and the defined clinical endpoints was examined using univariable and multivariable Cox regression analyses (backward stepwise method). The proportionality and linearity assumptions were tested. In the analyses not involving all-cause death, i.e. first HF hospitalization, the competing risk strategy method by Fine & Gray was adopted, considering death as the competing event for HF-related hospitalization. A predictive models were developed including those variables with a p-value <0.05 in the multivariable regression Cox analyses, and others relevant predictors (i.e. sex). Performance of the model was assessed by Harrell's C-statistic (discrimination) and calibration plots (calibration). Statistical analysis was performed using R software for Windows, version 3.6.1, Vienna, Austria.

3. Results

3.1. Demographics and clinical data of study patients

Of the 37, 822 patients with a HF SIDIAP-H discharge report, 32,263 (85.3 %) did not have a LVEF registered in the SIDIAP database. Among the 5559 patients with ejection fraction registered in their clinical records, 2895 (52.1 %) had LVEF ≥50 % and were included in the analysis (Fig. 1).

Table 1 shows the characteristics of the cohort of all patients and by sex. In summary: patients mean age was 77.1 (SD 9.7) years, were predominantly women (57.4 %) and more than 50 % had a Charlson comorbidity index ≥3. Obesity, hypertension, atrial fibrillation, and chronic kidney disease were more frequently present in women. Percentage of diabetes, coronary heart disease and obstructive pulmonary disease were higher in men.

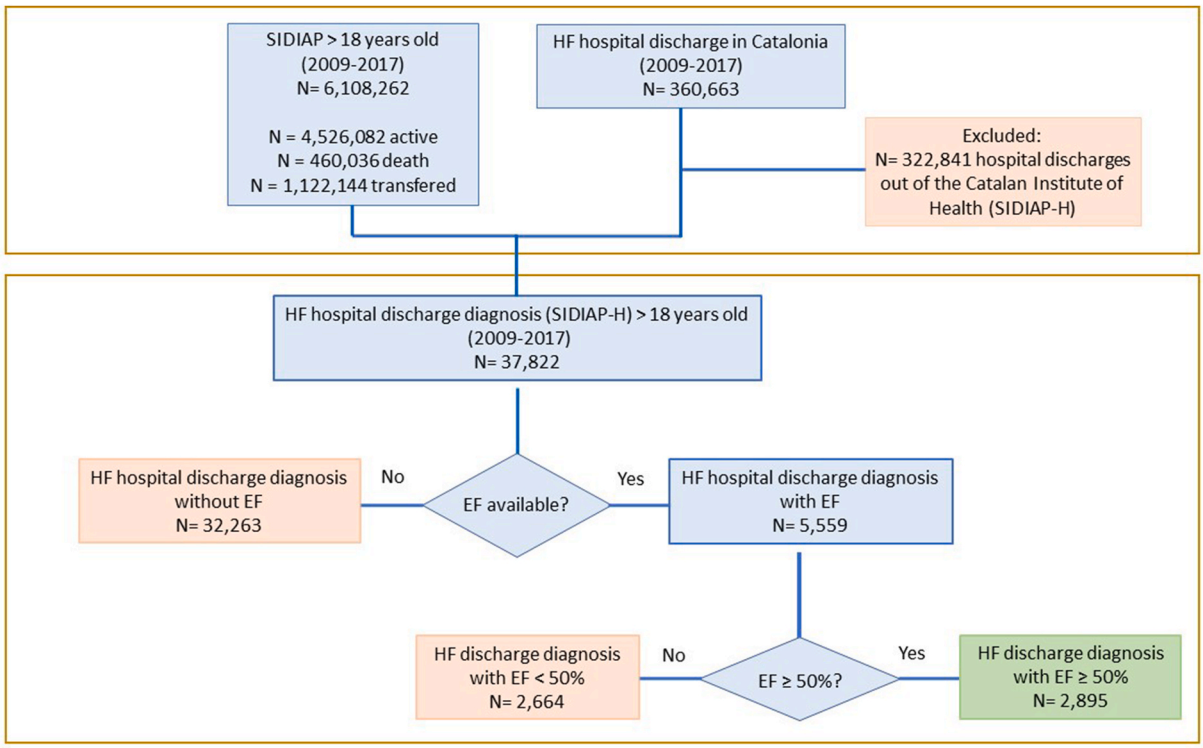

Fig. 1. Flow chart of study population.
EF: ejection fraction; SIDIAP: Information System for the Development of Research in Primary Care.

4. Events

4.1. Mortality

Over the median follow-up of 2.0 [1.0–9.0] years, 864 (29.8 %) patients died. During the first year, death occurred in 9 %, and in 23.6 % of patients during the 5-years of follow-up. Mortality was 10.29 (CI 95 % 9.6–10.9) 1000 patient-years.

The univariate analysis for mortality is shown in Table 2.

Multivariate analysis (Table 3) showed that variables directly related to mortality were: Male sex, age, BMI $\leq$30 kg/m^2, Charlson Index >4 and treatment with loop diuretic. Hemoglobin levels were inversely related to mortality.

4.2. Heart failure rehospitalization

Over a median follow-up of 2.0 [1.0–9.0] years, 831 (28.7 %) patients were hospitalized. Heart failure readmission occurred in 7 % during the first year, and 25,3 % of patients during the five years of follow-up. HF rehospitalization was 17.21 (CI 95 % 16.24–18.18) 1000 patient-years.

The univariate analysis for Heart failure rehospitalization is shown in Table 2.

Multivariate analysis (Table 3) showed that variables directly related to HF hospital readmission were: male sex, age, the presence of atrial fibrillation, and a treatment with loop diuretic. Hemoglobin levels were also inversely related to hospital readmission.

Fig. 2 shows the Kaplan–Meier curves of the HF rehospitalization and all-cause mortality.

5. Discussion

In this retrospective population-based cohort study, we found that a high proportion of the HFpEF patients were either hospitalized or died within 5 years of follow-up. We also found demographic variables, comorbidities, and analytical and treatment variables played a relevant role as prognostic factor: age, male sex, and loop diuretics was related to higher risk of mortality and rehospitalization. Charlson >4 and BMI $\leq$30 kg/m^2 were associated only with mortality and atrial fibrillation only with rehospitalization. Hemoglobin levels were inversely related in both.

5.1. Characteristics of the patients

Compared with other similar studies [6,10,11,16], our cohort showed a greater percentage of patients >75 years and a greater proportion of women, as well as higher prevalence of obesity, type-2 diabetes and chronic obstructive pulmonary disease and a lower prevalence of chronic kidney disease and coronary heart disease. Charlson comorbidity index was $\geq$3 in 55 % of the patients, which is comparable to other community HF studies [6,9].

Cardiovascular and non-cardiovascular morbidities showed sex differences, In accordance with the prevailing literature [5], we found that coronary artery disease was more prevalent in men while obesity, atrial fibrillation and chronic kidney disease were more commmon in women. However, type-2 diabetes did not follow this trend; nonetheless, there are controversies regarding the effect of sex on diabetes, with contradictory results reported in the literature [5].

5.2. Mortality

In our study, the percentage of death at 5-year of follow-up were 25 %. These results are aligned with those published by Vaduganathan et al. [9] who in their review reported mortality ranges from 13 % to 23 %, over a mean follow-up period of 26–50 months.Our results are also similar to the community-based cohort study by Iorio et al. [6], who found 20 % of deaths during a median follow-up of 31 months. The ESC Heart Failure Long-Term Registry [7] described 9.7 % of deaths at 1-year of follow-up, a percentage comparable to that found in our cohort.

Table 1
Baseline characteristics of the study population by sex.

	ALL (N = 2895)	Female (N = 1663)	Male (N = 1232)	p-value
Demographic variables				
Age (years), mean (SD)	77.1 (9.7)	78.7 (8.7)	74.8 (10.0)	<0.001
Clinical variables				
Body mass index (kg/m2), mean (SD)	31.1 (6.1)	31.8 (6.5)	30.1 (5.3)	<0.001
Tobacco, N (%)				<0.001
Non-smoker	2644 (92.8)	1590 (97.2)	1054 (86.8)	
Smoker	205 (7.1)	45 (2.7)	160 (13.2)	
[a]Obesity, N (%)	1195 (51.7)	739 (56.3)	456 (45.6)	<0.001
Hypertension, N (%)	2354 (81.3)	1400 (84.2)	954 (77.4)	<0.001
Diabetes Mellitus, N (%)	1302 (45.0)	713 (42.9)	589 (47.8)	0.009
Microalbuminuria, N (%)	589 (20.3)	299 (18.0)	290 (23.5)	<0.001
Dyslipidemia, N (%)	1498 (51.7)	887 (53.3)	611 (49.6)	0.051
Coronary artery disease, N (%)	473 (16.3)	207 (12.4)	266 (21.6)	<0.001
Valvular heart disease, N (%)	866 (29.9)	537 (32.3)	329 (26.7)	0.001
Atrial fibrillation, N (%)	1454 (50.2)	879 (52.9)	575 (46.7)	0.001
Stroke, N (%)	312 (10.8)	179 (10.8)	133 (10.8)	1.000
Peripheral artery disease, N (%)	260 (8.9)	81 (4.8)	179 (14.5)	<0.001
[b]Anemia, N (%)	587 (21.9)	299 (19.2)	288 (25.5)	<0.001
[c]Chronic kidney disease, N (%)	906 (33.7)	560 (35.7)	346 (30.8)	0.009
COPD, N (%)	943 (32.6)	445 (26.8)	498 (40.4)	<0.001
Charlson index, N (%)				<0.001
0	169 (5.8)	114 (6.8)	55 (4.4)	
1–2	1121 (38.7)	690 (41.5)	431 (35.0)	
3–4	1038 (35.9)	586 (35.2)	452 (36.7)	
>4	567 (19.6)	273 (16.4)	294 (23.9)	
LVFE, mean (SD)	61.5 (7.2)	62.2 (7.2)	60.5 (7.2)	<0.001
LVFE, N (%)				<0.001
≥55 %	2434 (84.1)	1452 (87.3)	982 (79.7)	
<55 %	461 (15.9)	211 (12.7)	250 (20.3)	
LVFE, N (%)				<0.001
>65 %	761 (26.3 %)	480 (28.9 %)	281 (22.8 %)	
≤65 %	2134 (73.7 %)	1183 (71.1 %)	951 (77.2 %)	
Treatment variables				
ACEi/ARB, N (%)	2007 (69.3)	1179 (70.9)	828 (67.2)	0.037
Beta-blockers, N (%)	1425 (49.2)	829 (49.8)	596 (48.4)	0.456
MRA, N (%)	277 (9.5)	156 (9.3)	121 (9.8)	0.738
Loop diuretic, N (%)	2065 (71.3)	1243 (74.7)	822 (66.7)	<0.001
Tiazide, N (%)	270 (9.3)	166 (9.9)	104 (6.4)	0.179
Digoxin, N (%)	406 (14.0)	280 (16.8)	126 (10.2)	<0.001
Calcium channel blockers, N (%)	889 (30.7)	507 (30.5)	382 (31.0)	0.796
Anti-platelet drugs, N (%)	1080 (37.3)	556 (33.4)	524 (42.5)	<0.001
Anticoagulants, N (%)	1157 (40.0)	680 (40.9)	477 (38.7)	0.254
Statins, N (%)	1459 (50.4)	804 (48.3)	655 (53.2)	0.012
Analytical variables				
Hemoglobin (g/dl), mean (SD)	13.5 (1.6)	13.1 (1.4)	14.1 (1.8)	<0.001
Estimated GFR (ml/min per 1.73m2), mean (SD)	68.0 (19.7)	67.0 (19.2)	69.3 (20.2)	0.003
Serum potassium, mean (SD)	4.7 (0.5)	4.7 (0.5)	4.7 (0.5)	1.000
Others				
Coronary artery disease AND statins, N(%)	345 (11.9)	143 (8.6)	202 (16.4)	<0.001

ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; MRA, mineral corticoid receptor antagonist. (a) Body mass index >30 kg/m2. (b) According to WHO criteria: <13 g/dL in men and <12 g/dL in women. (C) Estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration equation) < 60 mL/min per 1.73m2.

However, our outcomes were lower than those reported in other studies carried out in Scandinavia [10,11] who analyzed mortality in HFpE primary care patients, such as that of Lindberg [10] in which mortality/100 patients-year was 22.7, or in the study of Huusko [11] that at 5 years follow up, found more than 50 % of the patients died; figures of both studies double that of our cohort.

5.3. HF rehospitalization

Regarding rehospitalizations, our cohort has a slightly higher proportion than the rest of the studies, except for that of Huusko [11], which presents 39 % after 5 years of follow-up.

The higher number of rehospitalizations observed in our study may be attributable to the older age of the patients and the greater burden of comorbidities.

5.4. Characteristics associated with the mortality and rehospitalizations

As in most studies [5–7,9–11], age is an independent risk factor for both death and hospitalization in our study.

In our HFpEF cohort, male sex was an independent predictor of mortality and HF hospitalization, as it has been reported previously [6], [17–19]. These results a contrast with those observed in the large prospective cohort study from the "Get With The Guidelines-Heart Failure" registry [20] where females had a higher adjusted risk of HF readmission over a 5-year follow-up. Iorio [6] et al. do not find significant differences in mortality at one year.

In our cohort, the Charlson index greater than 4, the use of diuretics and low hemoglobin levels and a body mass index less than 30 were associated with an increase in mortality.

At Charlson index greater than 3 has been shown to be directly associated with mortality in studies similar to ours, such as that of Iorio et al. [6]. The use of loop diuretics has been associated with excess of mortality in several population studies; the recommendation is to prescribe the minimum dose possible in order to keep the patient asymptomatic[14]. Nevertheless, it is not possible to ascertain if patients needing loop diuretics are in a more severe clinical situation or the use of diuretics is the direct cause of worse outcomes. Low hemoglobin levels are a risk factor described both in HF registries, clinical trials, and in community studies [9,11].

Regarding obesity, our study goes supports the concept of obesity paradox. A BMI ≤30 kg/m^2 was directly related to mortality, although recent studies showing a neutral effect with mortality and even being related to an increase in hospitalizations [5], an issue that is not we

Table 2
Univariate analysis for heart failure rehospitalization and all-causes of mortality.

	[ALL] (N = 2895)	Heart Failure rehospitalization			Death		
		No (N = 2064)	Yes (N = 831)	P-Value	No (N = 2031)	Yes (N = 864)	P-Value
Age (years), mean (SD)	77.1 (9.7)	76.7 (10.1)	77.9 (8.7)	0.001	75.4 (9.9)	80.9 (8.1)	<0.001
Smoking habit (%)	205 (7.1)	162 (7.9)	43 (5.2)		163 (8.1)	42 (4.9)	
Body mass index(kg/m2), mean (SD)	31.1 (6.1)	30.9 (6.1)	31.5 (6.0)	0.064	31.6 (6.0)	29.9 (6.0)	<0.001
Obesity,[a] N (%)	1195 (51.7)	834 (50.7)	361 (54.0)	0.158	906 (54.8)	289 (43.7)	<0.001
Hypertension, N (%)	2354 (81.3)	1671 (81.0)	683 (82.2)	0.474	1648 (81.1)	706 (81.7)	0.758
Diabetes Mellitus, N (%)	1302 (45.0)	858 (41.6)	444 (53.4)	<0.001	905 (44.6)	397 (45.9)	0.518
Microalbuminuria, N (%)	589 (20.3)	390 (18.9)	199 (23.9)	0.003	406 (20.0)	183 (21.2)	0.498
Dyslipidemia, N (%)	1498 (51.7)	1056 (51.2)	442 (53.2)	0.344	1067 (52.5)	431 (49.9)	0.206
Coronary artery disease, N (%)	473 (16.3)	323 (15.6)	150 (18.1)	0.127	314 (15.5)	159 (18.4)	0.057
Valvular heart disease, N (%)	866 (29.9)	613 (29.7)	253 (30.4)	0.725	587 (28.9)	279 (32.3)	0.075
Atrial fibrillation, N (%)	1454 (50.2)	974 (47.2)	480 (57.8)	<0.001	974 (48.0)	480 (55.6)	<0.001
Stroke, N (%)	312 (10.8)	225 (10.9)	87 (10.5)	0.785	210 (10.3)	102 (11.8)	0.272
Peripheral artery disease, N (%)	260 (8.9)	186 (9.0)	74 (8.9)	0.985	165 (8.1)	95 (11.0)	0.016
Anemia,[b] N (%)	587 (21.9)	379 (19.8)	208 (27.0)	<0.001	326 (17.2)	261 (32.8)	<0.001
[c]Chronic kidney disease, N (%)	906 (33.7)	623 (30.2)	283 (34.1)	0.047	548 (27.0)	358 (41.4)	<0.001
COPD, N (%)	943 (32.6)	661 (32.0)	282 (33.9)	0.343	626 (30.8)	317 (36.7)	0.002
Charlson index, N (%)				0.077			<0.001
3–4	1038 (35.9)	388 (18.8)	179 (21.5)		688 (33.9)	350 (40.5)	
>4	567 (19.6)	130 (6.3)	39 (4.6)		344 (16.9)	223 (25.8)	
LVFE, mean (SD)	61.5 (7.2)	61.6 (7.2)	61.2 (7.3)	0.193	61.7 (7.3)	61.0 (7.2)	0.033
ACEi/ARB, N (%)	2007 (69.3)	1412 (668.4)	595 (71.6)	0.101	1431 (70.5)	576 (66.7)	0.048
Beta-blockers, N (%)	1425 (49.2)	1006 (48.7)	419 (50.4)	0.437	1042 (51.3)	383 (44.3)	0.001
MRA, N (%)	277 (9.5)	189 (9.1 (	88 (10.6)	0.265	198 (9.7)	79 (9.1)	0.662
Loop diuretic, N (%)	2065 (71.3)	1414 (68.5)	651 (78.3)	0.001	1395 (68.7)	670 (77.5)	<0.001
Hemoglobin (g/dl), mean (SD)	13.5 (1.6)	13.6 (1.6)	13.3 (1.7)	<0.001	13.7 (1.6)	13.1 (1.6)	<0.001
Estimated GFR (mL/min per 1.73m^2, mean (SD)	68.0 (19.7)	68.4 (19.9)	66.9 (19.1)	0.072	70.2 (19.0)	62.6 (20.2)	<0.001
Serum potassium (meq/l), mean (SD)	4.7 (0.5)	4.7 (0.5)	4.7 (0.5)	1.000	4.7 (0.5)	4.7 (0.5)	1.000

ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; MRA, mineral corticoid receptor antagonist. (a) Body mass index >30 kg/m2. (b) According to WHO criteria: <13 g/dL in men and <12 g/dL in women. (C) Estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration equation) < 60 mL/min per 1.73m2.

Table 3
Multivariate analysis: Cox regression analysis for all-causes of mortality and for rehospitalization.

Predictors	All-causes of mortality		
	Hazard Ratio	95%CI	P Value
Sex (Male)	1.26	1.06–1.49	0.008
Age (years) > 75	2.76	2.24–3.39	<0.001
Body mass index ≤30	1.44	1.22–1.69	<0.001
Charlson index			
0	Ref		
1–2	1.17	0.70–1.95	0.556
3–4	1.72	1.03–2.87	0.036
>4	2.03	1.21–3.42	0.008
Loop diuretic	1.36	1.11–1.65	0.003
Hemoglobin (g/dl)	0.87	0.82–0.91	<0.001
Rehospitalizacion Predictors	**Hazard Ratio**	**95%CI**	**P Value**
Sex (Male)	1.14	1.03–1.33	0.04
Age (years) > 75	1.37	1.17–1.61	**<0.001**
Atrial fibrillation	1.44	1.25–1.67	**<0.001**
Loop diuretic	1.37	1.15–1.63	**<0.001**
Hemoglobin (g/dl)	0.91	0.87–0.95	**<0.001**

observed in our cohort.

Regarding diabetes, information from literature is controversial. In our cohort we did not find a direct relationship between diabetes and mortality, as was reported by the ESC HF registry [7], and in contrast to a Iorio and Lindberg studies [6,10].

As Anker shows in his recent review [21], atrial fibrillation was related to a higher probability of hospitalization in patients with HFpEF. Nevertheless, regarding mortality, the data are contradictory.

6. Study limitations

Retrospective studies are prone to various biases, such as selection bias and information bias. We minimized selection bias by limiting the population to patients with HFpEF who had a previous admission.

Data were retrospectively obtained from public primary care centers and hospitals. Although SIDIAP includes 80 % of the population attended in Catalonia, there may be an underrepresentation of populations that do not regularly use public primary healthcare, such as those with a higher socioeconomic status who rely on private healthcare services. Episodes attended in private health centers could not be included. Nevertheless, the use of private hospitals is scarce for HF patients, and the majority of HF hospitalizations (98 %) are managed in public hospitals.

Since we did not have access to the mortality causes we could not analyze competing risk regarding hospitalization for comorbidities.

Additionally, since natriuretic peptides were not available in the standardized clinical information of our database during the evaluated period, we did not have access to levels of this prognostic biomarker. In the absence of NT-proBNP, a previous hospitalization was used as an inclusion criterion.

No data on cause of death - in HFpEF patients the competing risk of death and hospitalization for comorbidities is not at all negligible.

7. Implications and future lines of research

Recent studies have shown that the prognosis of HFpEF depends more on the patient's phenotype than on ejection fraction. More than 25 % of patients visited their primary care physician in the month prior to hospital admission, which may influence the management of comorbidities most related to admissions and mortality. Prospective studies in primary care are necessary to identify these phenotypes, including the measurement of biomarkers such as natriuretic peptides, and to evaluate the impact of new treatments that have been shown to reduce morbidity

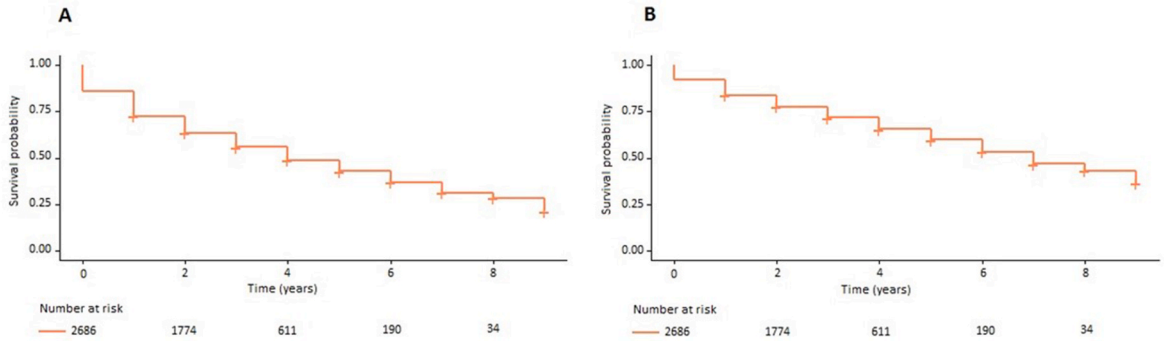

Fig. 2. Kaplan–Meier curves for the total mortality and Heart failure rehospitalization.
A: all-cause mortality B: Heart failure rehospitalization.

and mortality, such as SGLT2 inhibitors.

8. Conclusion

In this retrospective population-based cohort study, we found that a high proportion of the HFpEF patients were hospitalized or died within 5 years of follow-up. Mortality in our study was lower than in other studies from Northern Europe.

Demographic variables, comorbidities, and analytical and treatment variables played a relevant role as prognostic factors. Age, male sex, and loop diuretics was related to higher risk of mortality and rehospitalization. A Charlson Index$>$ 4 and BMI $\leq$30 kg/m^2 were associated only with mortality, while atrial fibrillation was associated only with rehospitalization. Hemoglobin levels were inversely related to both outcomes.

CRediT authorship contribution statement

Victoria Cendrós: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Mar Domingo:** Writing – review & editing, Writing – original draft, Validation, Supervision, Investigation, Data curation, Conceptualization. **Elena Navas:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Miguel Ángel Muñoz:** Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Conceptualization. **Antoni Bayés-Genís:** Writing – review & editing, Writing – original draft, Resources, Investigation, Funding acquisition, Conceptualization. **José María Verdú-Rotellar:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Methodology, Investigation, Formal analysis, Conceptualization.

Ethics

This study followed the Guidelines of the Helsinki Declaration and was approved by the Clinical Research Ethics Committee (P18/010).

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Declaration of competing interest

None to declare.

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