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# Heart failure with mid-range ejection fraction in patients admitted to internal medicine departments: Findings from the RICA Registry

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ABSTRACT

*Aim:* To improve the knowledge on characteristics, treatment and prognosis in patients with heart failure (HF) and mid-range ejection fraction discharged after an acute HF episode.
*Methods:* We prospectively included and followed 2753 patients admitted with HF to Internal Medicine units. Patients were classified according to ejection fraction (EF) into three strata: reduced, EF <40% (HFrEF); mid-range EF 40–49% (HFmrEF); and preserved EF ≥50% (HFpEF). Clinical, echocardiographic, laboratory data and treatment at discharge were recorded and the groups were compared. A multivariable analysis was performed to evaluate the association of EF with outcomes in these three groups.
*Results:* A total of 10.2% of patients had HFmrEF. They were more likely to be men and to have a history of chronic kidney disease and higher levels of NT-proBNP than those with HFpEF. Compared to patients with HFrEF, these patients had less frequently ischaemic aetiology and chronic obstructive pulmonary disease, and a higher proportion of atrial fibrillation and hypertension. In HFmrEF, the use of beta-blockers, aldosterone antagonists and antiplatelet drugs was lower than in HFrEF, but the use of calcium channel blockers and anticoagulants was higher. There were no differences between groups in 30-day and 1-year readmission rates. However, patients with HFrEF had significantly higher 1-year mortality (28%) than patients with HFmrEF and HFpEF (20% and 22%, $p < 0.001$).
*Conclusions:* Clinical characteristics and treatment among patients with HF differ depending on EF strata. Prognosis of patients with HFmrEF is closer to that of HFpEF, being medium term survival better than in HFrEF.
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## 1. Introduction

Heart failure (HF) is a major health problem due to its high morbidity and mortality. Traditionally, this condition has been classified according to left ventricular ejection fraction (EF) values into two different groups: HF with reduced EF (HFrEF) and HF with preserved EF (HFpEF). The first entity, also known as HF with systolic dysfunction, is defined by impaired myocardial contractility with an EF usually <40%. In the case of HFpEF, characterized by diastolic function abnormalities, the most commonly used cut-off point is EF ≥50%. HFrEF and HFpEF have different clinical characteristics, aetiologies and treatments, although therapies improving HFpEF patients have yet to be demonstrated.

The *2013 ACCF/AHA Guideline for the management of heart failure* describes an intermediate group of patients with EF in the range of 40% to 50% [1]. In the recently published *European Society of Cardiology (ESC)*

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[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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*guidelines*, a new term is defined for patients with HF and EF between 40 and 49%: HF with mid-range or borderline EF (HFmrEF) [2]. It is unclear whether these patients have similar clinical characteristics, prognosis and treatment to HFpEF or HFrEF. The guideline authors recognize this separate category as a 'grey area' and suggest investigation to increase the knowledge on them.

Limited data exist on the epidemiology, treatment and short or long-term prognosis of patients with HFmrEF. In addition, patients with HF treated by internists have different characteristics to those treated by cardiologists [3]. The objective of our study was to describe the clinical characteristics, treatment and prognosis of a group of patients with HFmrEF discharged after admission to Internal Medicine departments for acute HF.

## 2. Methods

### 2.1. Patients

Patient data were collected from the Spanish National Registry on Heart Failure (RICA) that began in February 2008. This registry is a multicenter, prospective, cohort study. It includes patients from 52 Spanish public and private hospitals over 50 years of age admitted to Internal Medicine departments for a first episode of HF or for decompensation of chronic HF, according to the criteria of European Society of Cardiology. For this study, patients were followed for at least one year. Exclusion criteria were HF due to pulmonary hypertension, refusal to participate in the study, or death during the index admission. The study protocol was approved by the Ethical Committee of the University Hospital 'Reina Sofía', Cordoba (Spain) according to 1975 Declaration of Helsinki and all patients provided informed consent.

### 2.2. Variables and blood sampling

Data were collected at the time of enrolment, using a web-based form (www.registrorica.org) [4]. Age, sex, comorbidities, body mass index (BMI), HF aetiology, length of stay, and laboratory data were collected. Drugs prescribed at discharge and New York Heart Association (NYHA) functional class in the month before admission were also included.

Within the first 48 h of admission, blood samples were obtained to measure laboratory variables, including N-terminal pro-B-type natriuretic peptide (NT-proBNP). The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease equation (MDRD-4). Renal failure was defined as eGFR < 60 ml/min/1.73 $m^2$. EF was determined by 2D echocardiography. According to 2016 ESC Guidelines, the pooled population was divided into three groups: HFrEF (EF < 40%), HFmrEF (EF 40–49%) and HFpEF (EF ≥ 50%) [2].

### 2.3. Endpoints

Primary end-point was all-cause mortality at 30 days and 1 year after discharge, and secondary end-point was readmission due to worsening HF in the same follow-up period.

### 2.4. Statistical analysis

Continuous variables were expressed as mean (95% confidence interval) or median (with 25th to 75th interquartile range), and categorical variables as frequencies and percentages. Continuous variables were compared using ANOVA or non-parametric Kruskal-Wallis test. Categorical variables were compared using the Chi-square test. Analysis comparing survival times of patients according to EF strata were evaluated by Kaplan-Meier curves and the log-rank test. To explore the association of EF with mortality or readmission, Cox proportional hazards models were used. A multivariable analysis was then conducted using the stepwise Cox regression model to avoid multicollinearity.

**Table 1**
Characteristics of patients categorized by left ventricular ejection fraction (EF) groups: reduced (EF < 40%), mid-range (EF 40–49%) and preserved (EF ≥ 50%).

| | Overall (n = 2753) | HFrEF (n = 808) | HFmrEF (n = 281) | HFpEF (n = 1664) | p |
|---|---|---|---|---|---|
| Age (years) | 81 (75–85) | 79 (72–84) | 80 (74–84) | 81 (76–86) | <0.001[a,c] |
| Women | 1462 (53) | 303 (38) | 118 (42) | 1041 (63) | <0.001[b,c] |
| BMI (kg/$m^2$) | 28.2 (24.9–32.0) | 27.0 (24.1–30.1) | 27.7 (24.4–31.5) | 28.9 (25.6–32.9) | <0.001[a,b,c] |
| NYHA III-IV | 1035 (38) | 343 (43) | 104 (37) | 588 (35) | 0.003[c] |
| Previous HF | 1696 (62) | 548 (68) | 169 (60) | 979 (59) | <0.001[a,c] |
| Systolic blood pressure | 136 (120–155) | 130 (115–150) | 140 (120–155) | 139 (120–158) | <0.001[a,c] |
| Heart rate | 84 (71–100) | 84 (73–100) | 85 (70–104) | 83 (71–100) | 0.110 |
| LVEF | 54 (40–62) | 32 (25–37) | 45 (44–46) | 60 (55–66) | 0.001[a,b,c] |
| Length of stay | 7 (5–12) | 7 (5–13) | 8 (5–11) | 7 (5–11) | 0.231 |
| *Aetiology of HF* | | | | | |
| Hypertension | 1027(37) | 132 (16) | 85 (30) | 810 (49) | <0.001[a,b,c] |
| Ischaemic | 767(28) | 397 (49) | 107 (38) | 263 (16) | <0.001[a,b,c] |
| Valvular | 494(18) | 90 (11) | 54 (19) | 350 (21) | <0.001[a,c] |
| Others | 460 (17) | 187 (23) | 35 (13) | 238 (14) | <0.001[a,c] |
| *Comorbidities* | | | | | |
| Chronic kidney disease | 1319 (41) | 364 (45) | 126 (45) | 643 (39) | 0.004[b,c] |
| Diabetes | 1319 (48) | 392 (49) | 151 (54) | 776 (47) | 0.081 |
| Hypertension | 2363 (86) | 657 (81) | 232 (83) | 1474 (89) | <0.001[b,c] |
| Atrial fibrillation | 1536 (56) | 366 (45) | 156 (56) | 1014 (61) | <0.001[a,c] |
| COPD | 706 (26) | 231 (29) | 60 (21) | 415 (25) | 0.033[a] |
| *Precipitating factor* | | | | | |
| Respiratory infection | 804 (29) | 200 (25) | 78 (28) | 526 (32) | 0.002[c] |
| Atrial fibrillation | 541 (20) | 124 (15) | 57 (20) | 360 (22) | 0.001[c] |
| Non-adherence to treatment | 181 (7) | 72 (9) | 15 (5) | 94 (6) | 0.006[c] |
| Uncontrolled hypertension | 169 (6) | 39 (5) | 16 (6) | 114 (7) | 0.137 |
| Myocardial ischemia | 179 (7) | 89 (11) | 20 (7) | 70 (4) | <0.001[b,c] |
| Anaemia | 35 (1) | 6 (1) | 2 (1) | 27 (2) | 0.126 |
| Others | 941 (34) | 299 (37) | 99 (35) | 543 (34) | 0.092 |
| *Laboratory* | | | | | |
| Haemoglobin (g/dL) | 12.0 (10.7–13.4) | 12.4 (11.0–13.8) | 12.1 (10.7–13.4) | 11.9 (10.5–13.2) | <0.001[c] |
| Creatinine (mg/dL) | 1.2 (0.9–1.6) | 1.2 (1.0–1.6) | 1.2 (0.9–1.6) | 1.1 (0.9–1.5) | <0.001[c] |
| NT-proBNP(pg/mL) | 3461 (1569–7851) | 5758 (3029–11,718) | 3816 (1641–8000) | 2740 (1294–6331) | <0.001[a,b,c] |

Data are expressed as mean (95% confidence interval) or median with 25th to 75th interquartile range for continuous variables and as frequencies (percentages) for categorical variables. BMI: body mass index; COPD: chronic obstructive pulmonary disease; EF: left ventricular ejection fraction; HFmrEF: heart failure with mid-range EF; HFpEF: heart failure with preserved EF; HFrEF: heart failure with reduced EF; NT-proBNP: N-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association class.

[a] $p < 0.05$ for comparison between HFrEF and HFmrEF.
[b] $p < 0.05$ for comparison between HFmrEF and HFpEF.
[c] $p < 0.05$ for comparison between HFrEF and HFpEF.

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