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Gender differences in clinical features and outcomes of patients over 75 years presenting with acute heart failure. Results of a nationwide study (2016–2019)

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Abstract

Background: *Heart failure (HF) is a major health problem in Western countries, and a leading cause of hospitalizations and death. There is a scarcity of data on the influence of sex on HF outcomes in elderly patients. The aim of the present study was to analyze differences between men and women in clinical characteristics, in-hospital mortality, 30-day HF readmission rates, cardiovascular mortality and HF readmission rates at 1 year after discharge in patients older than 75 years hospitalized for HF in Spain.*

Methods: *Retrospective analysis of patients discharged with a main diagnosis of HF from all Spanish public hospitals between 2016 and 2019. Patients aged 75 years or older were selected, and a comparison was made between male and female patients.*

Results: *From 2016 to 2019, a total of 354,786 episodes of HF in this age subgroup were identified, 59.2% being women. The overall mean age was 85.2 ± 5.4 years, being higher in women (85.9 ± 5.5 vs. 84.2 ± 5.3 years, $p < 0.001$). Risk-adjusted in-hospital mortality was lower in women (odds ratio [OR]: 0.96, 95% confidence interval [CI]: 0.92–0.97; $p < 0.001$). Female sex also showed a protective effect for 30-day readmissions, with an OR of 1.06 (95% CI: 1.04–1.09; $p < 0.001$). One-year cardiovascular mortality (24.1% vs. 25.0%; $p < 0.001$) and one-year HF readmission rates (30.8% vs. 31.6%; $p = 0.001$) were lower in women.*

Conclusions: *Almost 60% of hospital admissions for HF in people aged 75 years or older between 2016 and 2019 in Spain were female patients. Female sex seems to play a protective role on in-hospital mortality and the rate of admissions and mortality at 1 year after discharge.* (Cardiol J)

Keywords: acute heart failure, gender, prognosis, readmissions, elderly

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Introduction

Heart failure (HF) has been considered the great cardiovascular "epidemic" of the 21st century, due to its high and increasing prevalence and incidence and high mortality [1–3]. One of the main reasons for this large epidemiological magnitude is the increasing age of the population, as the prevalence and severity of HF increases significantly with age. Several studies show that the prevalence of HF is more than 10–15% in people over 80 years of age [3–5], and that age is a risk factor for increased mortality [6, 7]. In addition, admissions for acute HF are more frequent in older people [5], and this carries a significant economic cost to the system [8]. The increase in life expectancy in Western countries means that an increasingly larger segment of the population aged over 75 years is becoming common, which translates into an increase in the incidence of admissions for acute HF in this age group [5].

The role of sex in HF is controversial. Recent reviews have highlighted the differences between men and women in the pathophysiology of HF and the important gaps in knowledge about the management and prognosis of chronic HF in women [9–11]. These gaps are even greater in acute HF and its short-term prognosis (mortality and readmissions) after discharge for decompensated HF. With this aim, the analyses, herein, show the differences between male and female patients in clinical characteristics, in-hospital mortality, 30-day HF readmission rates, and cardiovascular mortality and HF readmission rates at 1 year after discharge in patients aged 75 years or more, hospitalized for HF in all of the Spanish National Health System hospitals between 2016 and 2019.

Methods

A retrospective observational study of all episodes of patients admitted for acute HF to all hospitals of the National Health System in Spain was conducted. The source of the data was the Minimum Basic Data Set (MBDS) of the Spanish National Health System, which includes information on the demographic characteristics of discharged patients and administrative variables related to the diagnoses and procedures performed on patients during hospitalization episodes, coded according to the International Classification of Diseases in its tenth revision (ICD-10). All episodes of patients aged 75 years or older registered with the principal diagnosis of HF, admitted between 1 January, 2016 and 31 December, 2019 were selected. To improve data quality and consistency, inpatient episodes that were transferred to another acute hospital were concatenated with data from the concatenated episode attributed to the index episode, and the following episodes were excluded: (a) discharges to home with 1 day or less of hospital stay, (b) discharges due to transfer to another hospital that could not be concatenated, (c) voluntary discharges, (d) discharges with other destinations or unknown discharge destination, and (e) episodes of patients with ventricular assist device implantation or cardiac transplantation procedures in the index episode or during the 12 months before the index episode. For the purpose of this analysis, the total group was divided into two subgroups: men and women 75 years of age or older. Patients were anonymized and assigned a random number to preserve their privacy. The study was conducted under the Declaration of Helsinki and was exempt from review by the Research Ethics Committee because de-identified data were used. Clinical characteristics and comorbidities of both groups, crude and risk-adjusted in-hospital mortality, the rate of readmissions for HF at 30 days and 1 year after discharge from the index episode, and cardiovascular mortality at 1 year after discharge were analyzed.

Statistical analysis

Continuous variables were expressed as mean and standard deviation and categorical variables as numbers and percentages. Comparisons between continuous variables were performed using the Student t-test for two factors and analysis of variance (ANOVA) with the Bonferroni correction for 3 or more, and categorical variables using the χ^2 test or the Fisher exact test. The probability of death and cardiovascular readmissions at 1 year after discharge from the index episode was assessed in the two age subgroups using Kaplan-Meier curves and compared using Mantel's log-rank test. The risk-standardized in-hospital mortality ratio was calculated, defined as the quotient between the expected outcome (which individually considers the performance of the hospital where the patient is treated) and the expected outcome (which considers a standard performance according to the mean of all hospitals) multiplied by the crude mortality rate of the study population [12, 13]. The variables included in the mortality models were considered independent variables, adapting the models to the MBDS data structure after grouping the secondary diagnoses according

to the clinical condition categories developed by Pope et al. [14]. A backward elimination technique was used to select the variables included in the adjustment models, and only comorbidities with statistical significance and odds ratio (OR) > 1.0 were considered. The calibration of the models was assessed by calculating the risk deciles of observed and expected in-hospital mortality obtained by the multilevel logistic model. A significant decrease in the likelihood ratio statistical test was found compared to the null model to assess goodness-of-fit. Discrimination was assessed by calculating receiver operating characteristic curves and their corresponding area under the curve (AUROC).

The predictive model for 30 and 365-day readmissions was a mixed Poisson or negative binomial model, according to need, considered as the dependent variable the number of readmissions in that period and, as the exposure variable, the sum of days at risk for each patient, counting the effective days of follow-up, unless the patient had died, in which case only the date of death was counted. The model specification considered age and sex strata, as well as comorbidity risk factors, using the grouping of secondary diagnoses according to the categories of clinical conditions developed by Pope et al. [14]. For the analysis of 1-year mortality, a Cox proportional hazards model was fitted and the assumption of proportionality of the model was assessed. Hazard ratios and their 95% confidence intervals (CI) were obtained for the risk factors. The discrimination of the model was analyzed using the C statistic. All statistical tests were bilateral, and differences found were considered significant for $p < 0.05$. Statistical analyses were performed with STATA 17 and SPSS 21.0.

Results

From 2016 to 2019, a total of 354,786 episodes of persons older than 74 years and with a principal diagnosis of HF were included, 59.2% of them being women. The mean age of the overall population was 85.2 ± 5.4 years, the crude in-hospital mortality was 12.6%, and the crude 30-day cardiovascular readmission rate was 11.8%. The proportion of HF with preserved left ventricular ejection fraction was 57.6%, being more common in women (59.4% vs. 54.6%, $p < 0.001$), although mortality and readmission rates were similar in patients with preserved and reduced HF. Table 1 shows the differences in clinical characteristics according to sex. Women had a higher mean age than men (85.9 ± ± 5.5 vs. 84.2 ± 5.3 years, $p < 0.001$), and a higher proportion over 90 years of age (20.5% vs. 12.8%, $p < 0.001$). The prevalence of coronary heart disease, cancer, diabetes, stroke, renal failure and chronic respiratory diseases was higher in men, while that of hypertension, psychiatric disorders and valvular heart disease was higher in women (Table 1).

Mortality

Crude in-hospital mortality was slightly higher in women (12.8% vs. 12.5%; $p = 0.004$). The multilevel adjustment model showed acceptable discrimination (AUROC = 0.69) and calibration (Fig. 1). Female sex had an OR of 0.95, 95% CI 0.93–0.97; $p < 0.001$, behaving as a protective variable. Other relevant determinants of in-hospital mortality were the presence on admission of cardiogenic shock, stroke, cancer, pneumonia or acute myocardial infarction (Table 2). One-year mortality due to cardiovascular causes from the start of the index episode to 1 year after discharge was 24.43%, being lower in women than in men (24.1% and 25.0%, respectively, $p < 0.001$). Figure 2 shows the survival curves for the two groups.

Heart failure readmissions

The crude 30-day cardiovascular readmission rate was the same in both subgroups (11.8%). The multilevel adjustment model for readmissions showed low discrimination (AUROC = 0.60) and acceptable calibration (Fig. 3). Female sex showed a protective effect for 30-day readmissions, with an OR of 0.94 (95% CI: 0.92–0.98; $p < 0.001$; Table 3). The existence of competing risks of readmission rate with mortality in women was not observed (hazard ratio [HR]: 0.92; 95% CI: 0.90–0.95; $p < 0.001$ for competing risks, and HR: 0.92; 95% CI: 0.89–0.94; $p < 0.001$, for proportional risks). Readmissions due to HF at 1 year after discharge were 31.1%, being lower in women than in men (30.8% and 31.6%, respectively, $p = 0.001$). Figure 4 shows the readmission-free curves for the two groups.

Discussion

The results of this nation-wide study, which included 354,786 episodes of acute HF in patients older than 74 years between 2916 and 2019 in Spain, show that almost 60% of hospital admissions for HF in this age group were women. Differences in characteristics were observed between both sexes, being the prevalence of coronary heart disease, cancer, diabetes, stroke, renal failure and chronic respiratory diseases higher in men, while that of

Table 1. Comparison of clinical features and comorbidities between male and female patients aged 75 or more years with acute heart failure in Spain (2016–2019)

	Male (n = 144,865)	Female (n = 209,921)	P
Age [years] (mean ± standard deviation)	84.22 ± 5.29	85.86 ± 5.46	< 0.001
History of coronary artery bypass graft surgery	4.71%	1.20%	< 0.001
History of percutaneous transluminal coronary angioplasty	11.79%	5.12%	< 0.001
History of cancer	3.18%	1.47%	< 0.001
Diabetes mellitus	36.10%	35.09%	< 0.001
Protein-caloric malnutrition	2.12%	2.02%	0.047
Chronic liver disease	2.53%	1.72%	< 0.001
Dementia/cognitive impairment	10.08%	15.42%	< 0.001
Major psychiatric disorders	0.43%	0.77%	< 0.001
Hemiplegia/functional disability	0.33%	0.30%	0.120
Cardiogenic shock	0.34%	0.28%	0.003
Acute pulmonary edema	25.54%	32.70%	< 0.001
Acute myocardial infarction	0.64%	0.53%	< 0.001
Unstable angina	0.88%	0.76%	< 0.001
Chronic coronary syndrome	31.11%	15.94%	< 0.001
Valvular heart disease	30.96%	35.99%	< 0.001
Systemic hypertension	24.45%	28.60%	< 0.001
Stroke	0.27%	0.23%	0.016
Peripheral arteriopathy	10.64%	4.73%	< 0.001
Chronic obstructive pulmonary disease	28.41%	6.26%	< 0.001
Pneumonia	4.90%	3.91%	< 0.001
Renal failure	50.70%	42.90%	< 0.001
Trauma or other injuries	2.11%	2.75%	< 0.001

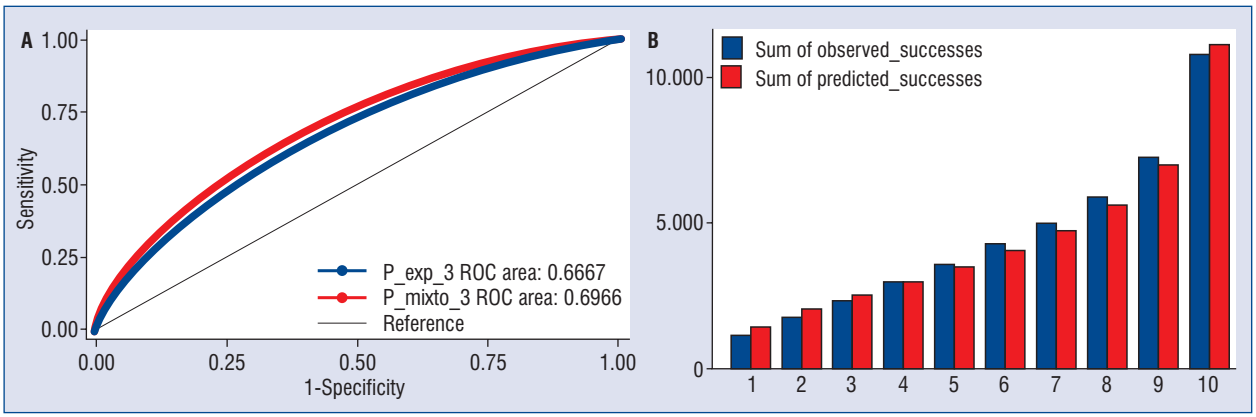

Figure 1. A, B. Discrimination and calibration of the multilevel logistic model for in-hospital mortality; ROC — receiver operating characteristic curve.

hypertension, psychiatric disorders and valvular heart disease was higher in women. In-hospital and 1-year mortality rates, as well as 30-day and 1-year readmission rates for HF, were significantly lower in women. Female sex seems to have a protective effect on mortality and readmissions.

Table 2. Independent predictors of in-hospital mortality in the studied population (multilevel logistic regression model of risk).

	OR	95% CI		P
Sex (female)	0.95	0.93	0.97	< 0.001
Age	1.07	1.07	1.07	< 0.001
Metastatic cancer, acute leukemia and other severe cancers	2.60	2.46	2.75	< 0.001
Protein-calorie malnutrition	1.56	1.47	1.66	< 0.001
Chronic liver disease	1.52	1.42	1.62	< 0.001
Dementia or other specified brain disorders	1.41	1.37	1.45	< 0.001
Major psychiatric disorders	1.15	1.02	1.31	0.026
Hemiplegia, paraplegia, paralysis, functional disability	1.63	1.39	1.91	< 0.001
Cardiogenic shock	19.61	16.88	22.77	< 0.001
Cardio-respiratory failure and shock	1.61	1.57	1.64	< 0.001
Acute myocardial infarction	2.03	1.82	2.17	< 0.001
Unstable angina and other acute ischemic heart disease	1.71	1.56	1.88	< 0.001
Stroke	3.40	2.93	3.95	< 0.001
Vascular disease and complications	1.13	1.09	1.18	< 0.001
Pneumonia	2.04	1.96	2.13	< 0.001
Renal failure	1.64	1.61	1.68	< 0.001

CI — confidence intervals; OR —odds ratio

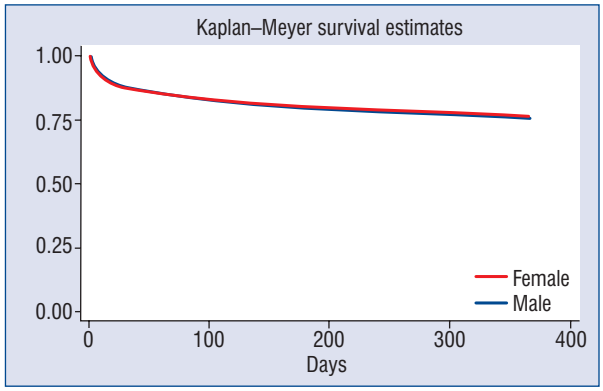

Figure 2. One-year mortality due to cardiovascular causes after discharge for the index episode of heart failure in men and women.

There are some studies in the literature that have compared the characteristics and prognosis of HF in relation to sex [3, 9–11, 15]. A recent large review has highlighted that there are pathophysiological differences between women and men, with a predominance of the HF phenotype with preserved ventricular ejection fraction in women and reduced ventricular ejection fraction in men [9]. Likewise, there are gaps in different aspects of knowledge about HF in women (lack of representation in clinical trials, effect of cardiac resynchronization therapy, influence of pharmacokinetic characteristics on the dosing of drugs, quality of life and prognosis) [9]. Overall, the prevalence of HF in the Spanish adult population is similar in men and women [3]. In people aged 75 or more years, the prevalence in Spain was 15.6% in men and 16.4% in women [3]. Some studies have suggested that women with chronic HF have a worse quality of life than men [10], although they may have a better prognosis, with lower mortality rates [11, 15]. Older studies showed that women received a lower proportion of favorable prognostic treatments than men [9], but more recent studies report that the use of pharmacological treatment has improved in women [15], although the use of nonpharmacological treatments (cardiac resynchronization therapy, implantable defibrillators, and heart transplantation) remains lower in women [15].

Most of the aforementioned studies refer to patients with chronic HF [9–11, 15], with few data to date on the short- and medium-term prognosis of acute HF, and there are no studies in the literature that have specifically analyzed clinical and prognostic differences in relation to sex in the 75 years or higher age group. The results of our study show that the clinical characteristics of women with acute HF are similar to those found in other studies [9, 10, 15], with a higher proportion of HF with preserved left ventricular ejection fraction

Table 3. Independent predictors of 30-day heart failure readmissions in the studied population (multilevel logistic regression model of risk).

	OR	95% CI		P
Sex (female)	0.94	0.92	0.98	< 0.001
Age	1.02	1.01	1.03	0.003
History of coronary artery bypass graft surgery	1.09	1.01	1.17	0.022
Diabetes mellitus	1.13	1.10	1.16	< 0.001
Other significant endocrine and metabolic disorders; disorders of fluid/electrolyte/acid-base balance	1.07	1.03	1,11	< 0,001
Other psychiatric disorders	1.08	1.01	1.15	0.016
Hemiplegia, paraplegia, paralysis, functional disability	1.19	0.96	1.47	0.105
Cardio-respiratory failure and shock	1.08	1.05	1.11	< 0.001
Acute coronary syndrome	1.22	1.09	1.36	< 0.001
Coronary atherosclerosis or angina	1.17	1.14	1,.21	< 0,001
Valvular and rheumatic heart disease	1.19	1.16	1.22	< 0.001
Specified arrhythmias and other heart rhythm disorders	1.10	1.07	1.13	< 0.001
Vascular or circulatory disease	1.04	1.01	1.08	0.023
Chronic obstructive pulmonary disease	1.14	1.11	1.18	< 0.001
Fibrosis of lung or other chronic lung disorders	1.15	1.08	1.23	< 0.001
Asthma	1.11	1.05	1.17	< 0.001
Renal failure	1.40	1.36	1.43	< 0.001

CI — confidence intervals; OR —odds ratio

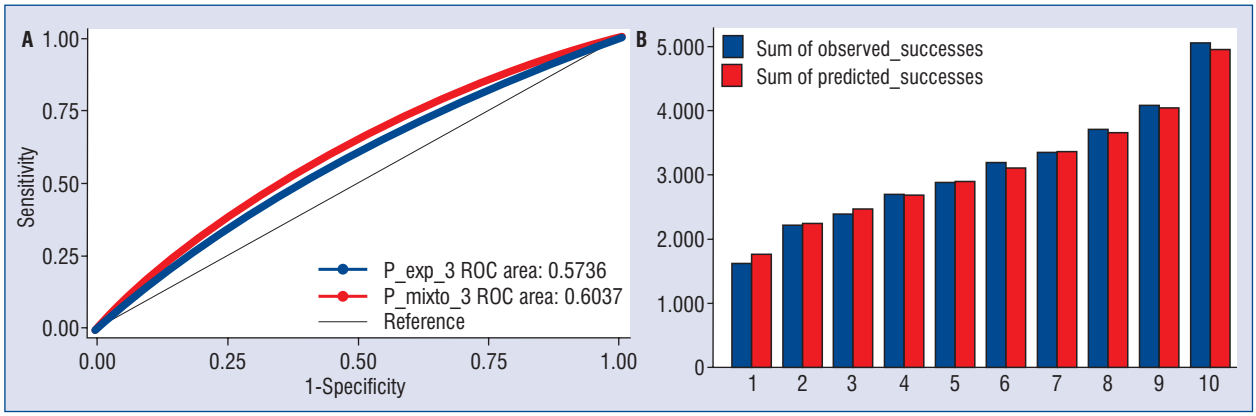

Figure 3. A, B. Discrimination and calibration of the multilevel logistic model for 30-day heart failure readmissions after the index episode; ROC — receiver operating characteristic curve.

and a higher age than men, a lower prevalence of coronary heart disease, cancer, diabetes, stroke, renal failure and chronic respiratory diseases, and a higher prevalence of hypertension, psychiatric disorders and valvular heart disease. In-hospital and 1-year mortality were significantly, although slightly, lower in women, which coincides with the results of the studies in chronic HF [9–11, 15]. Likewise, the rate of readmissions for HF at 30 days and 1 year was also lower in the present series, in contrast to that reported by older studies [11]. This may be due to the improved treatment experienced in recent years in the female group [15]

Limitations of the study

The current study has several strengths. It is a recent study, with a very large number of patients, that analyses all cases of acute HF admissions in

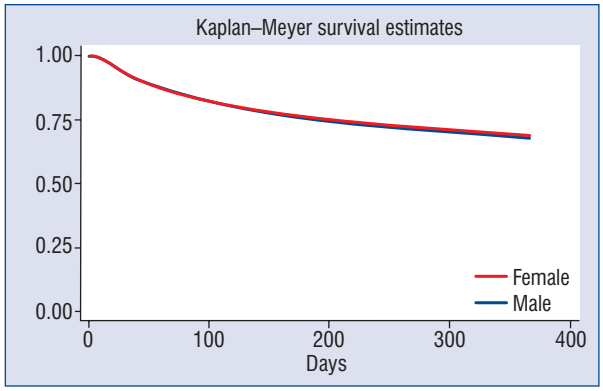

Figure 4. One-year heart failure readmission-free curves after discharge for the index episode of heart failure in men and women.

a whole country, including the various subtypes of HF according to left ventricular ejection fraction, and one that compares the characteristics and outcomes of male and female patients aged over 75 years. It also has some limitations, related to its retrospective nature and the lack of some variables of interest in the database analyzed, such as, for example, the absence of data on the pharmacological treatment received by the patients. However, the large number of cases and their nation-wide nature allow us to provide reliable data on the characteristics and prognosis of these patients with acute HF and the sex-related differences, who have been scarcely studied to date.

Conclusions

From the results of this study, it can be concluded that almost 60% of hospital admissions for HF in people aged 75 years or older between 2016 and 2019 in Spain were female patients, and that female sex seems to play a protective role on in-hospital mortality and the rate of admissions and mortality at 1 year after discharge.

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Conflict of interest: None declared

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