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Significant and constant increase in hospitalization due to heart failure in Spain over 15 year period

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ABSTRACT

Background: To examine trends in the incidence, characteristics, and in-hospital outcomes of heart failure (HF) hospitalizations from 2001 to 2015 in Spain.
Methods: Using the Spanish National Hospital Discharge Database (SNHDD) we selected admissions with a primary or secondary diagnosis of HF. The primary end points were trends in the incidence of hospitalizations and in-hospital mortality (IHM). Trends with primary and secondary diagnosis of HF were evaluated separately.
Results: The incidence of HF coding increased significantly from 466.16 cases per 100,000 inhabitants in 2001–03 to 780.4 in 2013–15 ($p < .001$). Age increased over time (76.33 ± 10.92 years in 2001–03 vs. 79.4 ± 10.78 years in 2013–15; $p < .001$). We found a decrease in the percentage of women over the study period (53.07% vs. 52%; $p < .001$). We detected a significant increase in comorbidity according to the Charlson Comorbidity Index over time (mean 2.17 ± 0.98 in 2001–03 vs. 2.46 ± 1.04 in 2013–15). The most common associated comorbidities were atrial fibrillation (42.23%), hypertension (38.87%) and type 2 diabetes (34.3%). For the total time period, IHM was 12.79%. IHM decreased significantly over time from 13.47% in 2001–03 to 12.30% in 2013–15. Patients with HF coded as a secondary diagnosis have 66% higher risk of dying in the hospital that those with HF coded as a primary diagnosis.
Conclusions: This research shows an increase of hospitalizations due to HF in Spain, particularly in patients with HF as a secondary diagnosis. Advance age and comorbidity in acute HF has increased in the recent years. However, IHM is decreasing while readmissions remain stable.

1. Introduction

Nowadays, heart failure (HF) could be considered a global pandemic. It affects more many millions of people worldwide and causes more than one million hospitalizations in the United States and Europe [1]. Even though recent studies have reported a decreasing incidence of HF in some European countries like the United Kingdom, the burden of the disease continues to rise [2,3]. The incidence of HF varies by age,

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; APC, annual percentage of change; CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; ER, emergency room; HF, heart failure; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; IHM, in-hospital mortality; LOHS, length of hospital stay; OR, Odds Ratio; SNHDD, Spanish National Hospital Discharge Database; TD2M, type 2 diabetes mellitus

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and particularly in individuals older than 85 years, it seems be increasing rapidly [3].

On the other hand, comorbidities associated with HF have also changed over the last years. Recently, HF has been considered a complex syndrome. It is frequently related to other chronic diseases such as hypertension, type 2 diabetes (T2DM), coronary heart disease, atrial fibrillation, renal failure, dementia, anemia, and chronic obstructive pulmonary disease (COPD) [4,5]. Therefore, HF affects more elderly individuals with multiple comorbidities leading to an increase risk of hospitalizations [2,6]. Hospitalizations due to HF vary according to the country and the period evaluated. For example, in the United States, hospital admissions due to HF tripled from 1,274,000 in 1979 to 3,860,000 in 2004 [7]. In Spain, in the period 2003–2013, the rate of hospitalization due to HF raised 76% [8]. However, some recent reports suggest that hospitalization rates due to HF have been trending downward in last years [9].

Studies assessing HF hospital admissions in Spain, have been carried out in specific regions, but there are no broad epidemiological studies evaluating this situation in the entire country over the last 15 years. Most studies have analysed HF when it is coded as the principal diagnosis in the Spanish National Hospital Discharge Database (SNHDD). No studies have analysed outcomes when HF is a secondary diagnosis [10]. For these reasons, we decided to conduct this research.

Using the SNHDD, the purposes of this study were to i) examine trends in the incidence, characteristics, and in-hospital outcomes of HF hospitalizations from 2001 to 2015; ii) compare clinical variables among patients according to the diagnosis position (primary or secondary) of HF in the discharge report; and iii) identify factors associated with in-hospital mortality (IHM) among patients according to the diagnosis position of HF.

2. Methods

2.1. Data source

This retrospective observational study was performed using the SNHDD. Details of the design and description of the SNHDD are available online [11]. Briefly, this nationally representative database, which compiles all public hospital data, covers > 95% of hospital admissions in Spain. The SNHDD includes patient variables (sex, date of birth), admission and discharge dates, up to 14 discharge diagnoses, and up to 20 procedures performed during the hospital stay [11].

2.2. Patient population

We selected admissions of patients (aged ≥18 years) with a primary or secondary diagnosis of HF in the SNHDD database. These were identified using the following International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes, as recommended by the American College of Cardiology (ACC)/American Heart Association (AHA) task force on performance measures: 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, and 428.12 [12]. We collected data from between January 1, 2001 and December 31, 2015. HF was classified as a primary diagnosis if any of the codes appear as the first diagnosis in the SNHDD database. Otherwise, it was classified as secondary if it occurs at any other diagnosis position (positions 2–14).

2.3. Covariates

Clinical characteristics included information on overall comorbidity at the time of discharge, which was assessed by calculating the Charlson comorbidity index (CCI) [13]. Regardless of the position in the diagnoses coding list, we retrieved data about comorbidities for patients with a primary or secondary diagnosis of HF as described by Quan et al. using the enhanced ICD-9-CM [14].

Other diagnoses included in the CCI for analysis were ischemic coronary disease (codes 410.x, 412.x, 413.x, 414.0, 414, 414.00, 414.01, 414.2–9), atrial fibrillation (code 427.31), anemia (codes 285.2, 285.2x, 285.9), pneumonia (480–488, 507.0–507.8), pulmonary embolism (codes 415.11 and 415.19), hypertension (codes 401; 401.0; 401.1; 401.9), acute renal failure (codes 584.x), TD2M (codes 250.x0 and 250.x2), and COPD (codes 490, 491, 491.0, 491.1, 491.2x, 491.8, 491.9, 492, 492.0, 492.8, 496).

Regardless the position in the procedures coding list, we retrieved data about the following in-hospital procedures: echocardiogram (code 88.72), non-invasive mechanical ventilation (code 93.90), invasive mechanical ventilation (codes 96.7, 96.70, 96.71, 96.72), heart catheterization (code 37.21–37.23), red cell transfusion (codes 99.00, 99.01–99.08), and pacemaker (codes 37.70–37.74; 37.80–37.83).

We estimated the proportion of admissions through the emergency room (ER), the readmissions rate (patients that had been discharged from the same hospital within the previous 30 days), and the median of length of hospital stay (LOHS).

2.4. End points

The main end points in our investigation were trends in the incidence of hospitalizations and IHM in patients admitted with a diagnosis of HF in any diagnosis position. In addition, we evaluated trends in patients admitted with primary and secondary diagnosis of HF separately. IHM was defined as the proportion of patients who died during admission for each year of study.

2.5. Statistical analysis

We considered five time periods that included three consecutive years each (2001–03; 2004–06; 2007–09; 2010–12; 2013–15). We estimated incidence rates of admission for HF calculated per 100,000 inhabitants, in order to assess time trends, by dividing the number of cases per year, sex, and age group by the corresponding number of people in that population group, according to the data from the Spanish National Institute of Statistics, as reported on 31 December of each year [15]. Trends in the incidences were assessed using Poisson regression models adjusted by sex and age when appropriate.

In our study, we used log linear joinpoint regression to identify the period in which trend changes in annual HF incidence rates occurred, stratified by sex and diagnosis position. The incidence rates included in the joinpoint regression were adjusted by age and sex, when appropriate, using the direct standardization method and the 2015 Spanish population as the reference.

We also estimated the annual percentage of change (APC) in each of the periods delimited by the points of change. The analysis started with the minimum number of joinpoints and tested whether the inclusion of one or more joinpoints was statistically significant [16]. In the final model, each joinpoint indicated a significant trend change, and the APC was obtained in each of the segments delimited by the joinpoints, using the weighted least squares technique. The Joinpoint Regression Program, version 4.0.4, was used for the analysis [17].

A descriptive statistical analysis was performed for all continuous variables and categories. Variables are expressed as proportions, as means with standard deviations, or as medians with interquartile ranges (LOHS). A bivariable analysis according to year was performed using the χ^2 test for linear trend (proportions), ANOVA (means), and Kruskall-Wallis (medians), as appropriate.

To identify variables associated with IHM as a binary outcome among patients with HF, we performed three multivariable logistic regression analyses, one for each diagnosis position of HF (primary, secondary, both). The variables included in the models were those with significant results in the bivariable analysis and those considered relevant in other investigations. Estimates were Odds Ratio (OR) with their 95%CI.

All statistical analysis was performed with Stata version 10.1 (Stata, College Station, Texas, USA). Statistical significance was set at $p < .05$ (2-tailed).

2.6. Ethical aspects

The study maintains data confidentiality at all times. Given the anonymous and mandatory nature of the database, it was not necessary to obtain informed consent or approval by an ethics committee in accordance with Spanish legislation.

3. Results

The number of hospitalizations in Spain with HF diagnosis was over 3.4 million between 2001 and 2015. Patients with a primary diagnosis of HF accounted for 44.09% of the total.

3.1. Trends in HF hospitalizations

We found that the incidence of HF coding increased significantly from 466.16 cases per 100,000 inhabitants in 2001–03 to 780.4 in 2013–15 ($p < .001$). Age increased significantly over time (76.33 ± 10.92 years in 2001–03 vs. 79.4 ± 10.78 years in 2013–15; $p < .001$). Analysis of sex distribution showed a decrease in the percentage of women over the study period (53.07% vs. 52%; $p < .001$) (Table 1).

The results of the joinpoint analysis showed that sex and age-adjusted admissions in patients with HF in any diagnosis position increased by 4.28% per year from 2001 to 2007 and by 2.49% per year from 2007 to 2015 (Fig. 1A). In men, admissions increased from 2001 to 2007 by 4.29% per year and from 2007 to 2015 by 2.63% per year (Fig. 1B). In women, admissions increased by 3.08% per year over the study period (Fig. 1C).

We detected a significant increase in comorbidity according to the CCI over time (2.17 ± 0.98 in 2001–03 vs. 2.46 ± 1.04 in 2013–15; $p < .001$). The most common associated comorbidities for patients hospitalized for HF were atrial fibrillation (42.23%), hypertension (38.87%), and T2DM (34.3%). As can be seen in Table 1, the frequency of all conditions analysed increased over time ($p < .001$) except COPD, which showed no change over the study period, and Ischemic Coronary disease that significantly decreased (29.94% to 26.63%; $p < .001$) (Table 1).

There was a significant increase in the frequency of use of echocardiography (from 24.14% in 2001–03 to 27.3% in 2013–15; $p < .001$), heart catheterization (from 3.67% in 2001–03 to 5.43% in 2013–15; $p < .001$), pacemaker implantation (from 1.11% in 2001–03 to 1.13% in 2013–15; $p < .001$), and red cell transfusion (from 6.02% in 2001–03 to 8.32% in 2013–15; $p < .001$). The frequency of use of non-invasive mechanical ventilation increased over time and that of invasive mechanical ventilation decreased in parallel ($p < .001$) (Table 1).

Median LOHS for admissions for HF was 8 days in the period 2001–03, decreasing to 7 days in 2013–15 ($p < .001$). The proportion of ER admissions and the readmissions also increased during the study period in the bivariable analysis, from 91.48% to 14.78% respectively in the period 2001–03 to 92.41% and 17.42% respectively in 2013–15 ($p < .001$ in both cases).

For the total time period, crude IHM was 12.79%. IHM decreased significantly ($p < .001$) over time from 13.47% in 2001–03 to 12.3% in 2013–15.

3.2. Trends in HF as primary diagnosis

As can be seen in Table 2, although the proportion of hospital admissions with HF coded as primary diagnosis decreased from 47.83% in the period 2001–03 to 41.74% in the period 2013–15 ($p < .001$), their incidence rates also increased. The joinpoint analysis shown in Fig. 1D–F yielded lines very similar to those observed for the total HF hospitalizations, with significant and constant increase of hospitalization rates overtime. The mean age increased from 76.36 years in the first time period to 79.7 years in the last one ($p < .001$). Remarkably, the proportion of patients aged 85 years or over also increased from 22.27% to 35.95% ($p < .001$).

Comorbidity according to the CCI rose over the study period from

Table 1
Characteristics of hospital admissions with primary or secondary diagnosis of heart failure in Spain (2001–2015).

Variable	2001–03	2004–06	2007–09	2010–12	2013–15	Total
Number of hospital admissions	470.637	573.072	693.591	793.806	890.831	3.421.937
Incidence per 100,000 population*	466.16	540.82	631.92	701.86	780.40	629.11
Female sex, N (%)*	249,771 (53.07)	302,067 (52.71)	365,756 (52.73)	417,270 (52.57)	463,219 (52)	1,798,083 (52.55)
Age, years, Mean (SD)*	76.33 (10.92)	77.04 (10.9)	77.89 (10.84)	78.77 (10.75)	79.40 (10.78)	78.13 (10.88)
CCI, Mean (SD)*	2.17 (0.98)	2.29 (1.01)	2.34 (1.01)	2.4 (1.03)	2.46 (1.04)	2.35 (1.02)
Ischemic coronary, N (%)*	140,931 (29.94)	174,267 (30.41)	201,269 (29.02)	216,893 (27.32)	237,197 (26.63)	970,557 (28.36)
Atrial fibrillation, N (%)*	171,740 (36.49)	229,163 (39.99)	292,036 (42.1)	347,864 (43.82)	404,351 (45.39)	1,445,154 (42.23)
Anemia, N (%)*	1039 (0.22)	1400 (0.24)	1855 (0.27)	2380 (0.3)	2686 (0.3)	9360 (0.27)
Pneumonia, N (%)*	35,486 (7.54)	46,279 (8.08)	63,740 (9.19)	80,013 (10.08)	97,887 (10.99)	323,405 (9.45)
Pulmonary embolism, N (%)*	3999 (0.85)	4652 (0.81)	6048 (0.87)	7918 (1)	8403 (0.94)	31,020 (0.91)
Hypertension, N (%)*	152,845 (32.48)	225,298 (39.31)	280,669 (40.47)	322,254 (40.6)	349,035 (39.18)	1,330,101 (38.87)
Acute renal failure, N (%)*	37,949 (8.06)	49,956 (8.72)	114,120 (16.45)	193,872 (24.42)	257,229 (28.88)	653,126 (19.09)
TD2M, N (%)*	134,448 (28.57)	189,263 (33.03)	242,159 (34.91)	285,023 (35.91)	322,988 (36.26)	1,173,881 (34.3)
COPD, N (%)	91,789 (19.5)	112,369 (19.61)	135,865 (19.59)	155,677 (19.61)	174,806 (19.62)	670,506 (19.59)
Echocardiogram, N (%)*	113,622 (24.14)	146,379 (25.54)	186,072 (26.83)	212,372 (26.75)	243,156 (27.3)	901,601 (26.35)
Non invasive mechanical ventilation, N (%)*	3397 (0.72)	6893 (1.2)	15,863 (2.29)	34,738 (4.38)	49,443 (5.55)	110,334 (3.22)
Invasive mechanical ventilation, N (%)*	13,231 (2.81)	15,969 (2.79)	17,937 (2.59)	18,004 (2.27)	19,042 (2.14)	84,183 (2.46)
Heart catheterization, N (%)*	17,262 (3.67)	25,496 (4.45)	34,491 (4.97)	40,129 (5.06)	48,396 (5.43)	165,774 (4.84)
Pacemaker, N (%)*	5230 (1.11)	6210 (1.08)	7267 (1.05)	8723 (1.1)	10,040 (1.13)	37,470 (1.09)
Red cell transfusion, N (%)*	28,352 (6.02)	38,657 (6.75)	52,618 (7.59)	66,195 (8.34)	74,125 (8.32)	259,947 (7.6)
ER admission, N (%)*	430,548 (91.48)	525,092 (91.63)	631,823 (91.09)	728,632 (91.79)	823,220 (92.41)	3,139,315 (91.74)
Readmission, N (%)*	69,581 (14.78)	90,381 (15.77)	113,472 (16.36)	134,210 (16.91)	155,157 (17.42)	562,801 (16.45)
LOHS, Median (IQR)*	8 (9)	8 (8)	8 (8)	7 (8)	7 (8)	8 (8)
IHM, N (%)*	63,410 (13.47)	75,163 (13.12)	89,188 (12.86)	100,172 (12.62)	109,592 (12.3)	437,525 (12.79)

CCI Charlson Comorbidity Index. ER Emergency room. T2DM Type 2 diabetes mellitus. COPD Chronic obstructive pulmonary disease. LOHS Length of hospital stay. IHM In hospital mortality.

* $P < .001$ to assess time trend from 2001 to 2015.

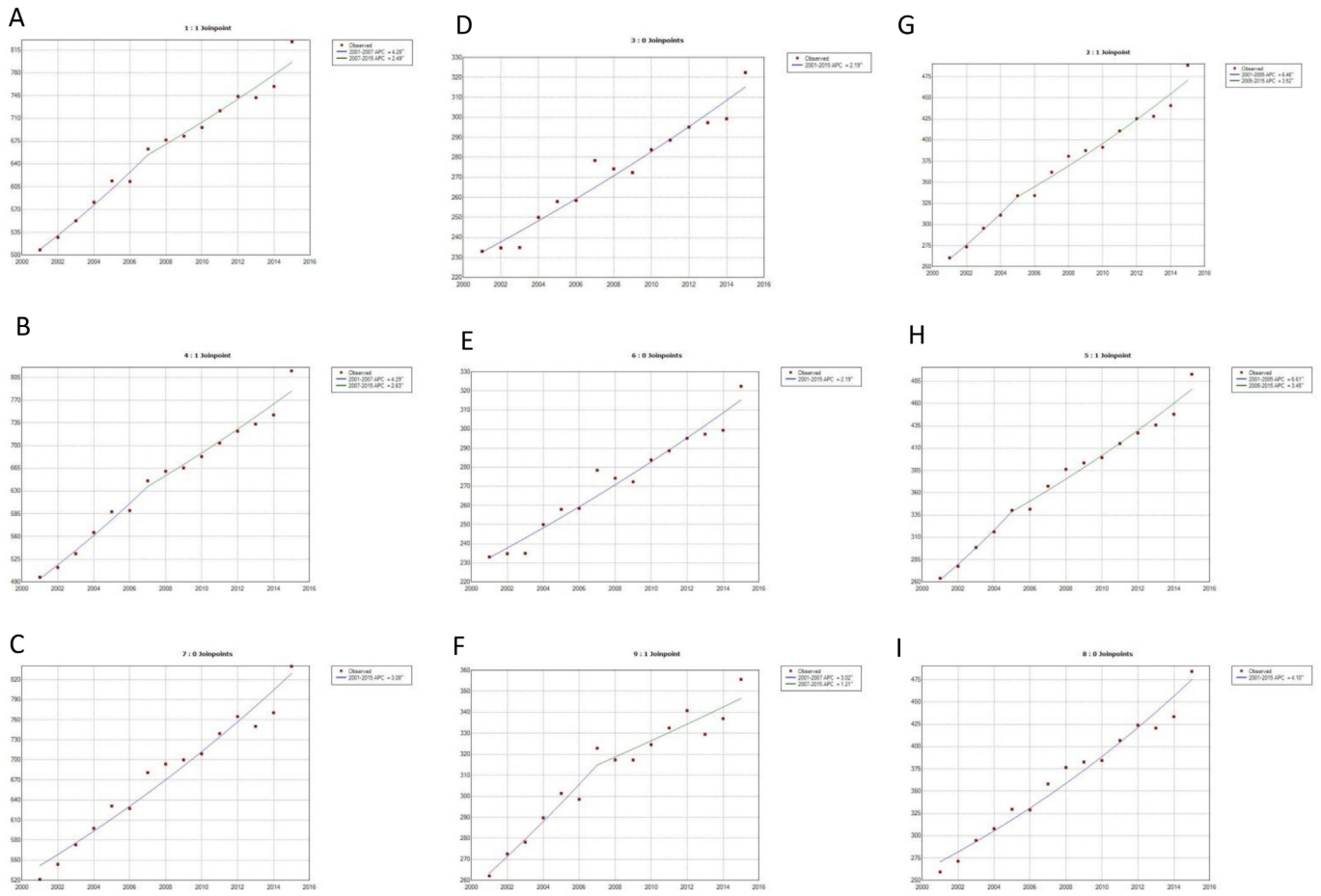

Fig. 1. Joinpoint analysis in annual admissions in patients with primary and/or secondary diagnosis of HF in Spain from 2001 to 2015 according to gender.
Footnote: APC: Annual percent change (based on rates that were sex and aged-adjusted using the Spanish National Statistics Institute Census projections) calculated by using joinpoint regression analysis. ˆAPC is significantly different from zero (two-side $P < .05$).
A. Joinpoint analysis in annual admissions in patients with primary and secondary diagnosis of HF.B. Joinpoint analysis in annual admissions in men with primary and secondary diagnosis of HF.C. Joinpoint analysis in annual admissions in women with primary and secondary diagnosis of HF.D. Joinpoint analysis in annual admissions in patients with a primary diagnosis of HF.E. Joinpoint analysis in annual admissions in men with a primary diagnosis of HF.F. Joinpoint analysis in annual admissions in women with a primary diagnosis of HF.G. Joinpoint analysis in annual admissions in patients with a secondary diagnosis of HF.H. Joinpoint analysis in annual admissions in men with a secondary diagnosis of HF.I. Joinpoint analysis in annual admissions in women with a secondary diagnosis of HF.

29.54% of patients with 3 or more conditions in 2001–03 to 44.66% in 2013–15 ($p < .001$). The prevalence of chronic conditions and use of procedures, among patients with HF as primary diagnosis, followed the results found in the total sample. The crude IHM decreased slightly but significantly from 9.96% to 9.58% over the study period.

3.3. Trends in HF as secondary diagnosis

Shown in Table 3 are the characteristics of hospital admissions with Secondary diagnosis of HF in Spain from 2001 to 2015. The proportion of HF admissions with this disease coded as a secondary diagnosis rose from 52.17% in the first period to 58.26% in the last period ($p < .001$). As can be seen in Fig. 1G–I, over the last years the hospitalization rates of HF as a secondary diagnosis have risen significantly. APC seemed to be higher among men than women (6.61% vs. 4.10%).

The evolution over time of the clinical variables analysed was similar to those described for the total sample. The IHM decreased significantly from 16.69% to 14.25% ($p < .001$).

3.4. Differences in admissions for HF coded as primary or secondary diagnosis

The results of the joinpoint regression show higher APC for HF as secondary diagnosis than primary diagnosis. Over the entire time period, the patients admitted with HF as the primary diagnosis were female in a significantly higher proportion (54.81% vs. 50.76; $p < .001$) and had a lower CCI (≥3, 38.63% vs. 41.96%; $p < .001$).

Regarding specific clinical conditions, patients with a primary diagnosis of HF also had more atrial fibrillation, acute renal failure, and T2DM. However, the prevalence of ischemic coronary disease, pneumonia, pulmonary embolism, and hypertension was lower. The proportion of patients with HF as the primary diagnosis who were admitted through the ER or readmitted after a discharge in the previous 30 days was higher than in those with HF as a secondary diagnosis. LOHS (median 7 days vs. 8 days) and IHM (9.73% vs. 15.2%) was lower among patients with a primary diagnosis of HF.

Shown in Table 4 are the IHM among patients with HF coded in the primary or secondary diagnostic position according to study variables. As can be seen, the IHM, stratified by any of the study variables, is significantly higher for those with a secondary diagnosis HF.

3.5. Factors associated with in-hospital mortality

The factors independently associated with IHM according to diagnosis position of HF are shown in Table 5. Regardless of the diagnosis position of HF, IHM decreased significantly over the study period.

Table 2
Characteristics of hospital admissions with primary diagnosis of heart failure in Spain (2001–2015).

Variable		2001–03	2004–06	2007–09	2010–12	2013–15	Total
HF as primary diagnosis*	N (%)	225,116 (47.83)	262,738 (45.85)	306,032 (44.12)	343,125 (43.23)	371,848 (41.74)	1,508,859 (44.09)
Female sex*	N (%)	124,287 (55.21)	144,994 (55.19)	168,872 (55.18)	188,193 (54.85)	200,620 (53.95)	826,966 (54.81)
Age, years*	Mean (SD)	76.36 (10.67)	77.23 (10.59)	78.18 (10.44)	79.06 (10.39)	79.7 (10.37)	78.32 (10.54)
Age groups,years N (%)	18–44	2570 (1.14)	2855 (1.09)	2888 (0.94)	2917 (0.85)	2603 (0.7)	13,833 (0.92)
	45–54*	6590 (2.93)	6881 (2.62)	7431 (2.43)	7357 (2.14)	7802 (2.1)	36,061 (2.39)
	55–64*	17,773 (7.9)	19,345 (7.36)	20,551 (6.72)	21,622 (6.3)	22,251 (5.98)	101,542 (6.73)
	65–74*	56,948 (25.3)	58,184 (22.15)	57,538 (18.8)	55,252 (16.1)	56,988 (15.33)	284,910 (18.88)
	75–84*	91,096 (40.47)	111,134 (42.3)	131,294 (42.9)	144,553 (42.13)	148,527 (39.94)	626,604 (41.53)
	≥85*	50,139 (22.27)	64,339 (24.49)	86,330 (28.21)	111,424 (32.47)	133,677 (35.95)	445,909 (29.55)
CCI *	Mean (SD)	2.08 (0.97)	2.21 (1)	2.29 (1.01)	2.36 (1.02)	2.44 (1.03)	2.3 (1.02)
CCI. N (%)*	1	69,642 (30.94)	69,130 (26.31)	72,605 (23.72)	72,835 (21.23)	71,500 (19.23)	355,712 (23.57)
	2	88,964 (39.52)	101,955 (38.8)	117,113 (38.27)	127,987 (37.3)	134,281 (36.11)	570,300 (37.8)
	≥3	66,510 (29.54)	91,653 (34.88)	116,314 (38.01)	142,303 (41.47)	166,067 (44.66)	582,847 (38.63)
Ischemic coronary*	N (%)	62,463 (27.75)	74,546 (28.37)	84,642 (27.66)	91,336 (26.62)	98,016 (26.36)	411,003 (27.24)
Atrial fibrillation*	N (%)	91,150 (40.49)	116,801 (44.46)	144,598 (47.25)	168,599 (49.14)	190,800 (51.31)	711,948 (47.18)
Anemia*	N (%)	555 (0.25)	740 (0.28)	912 (0.3)	1108 (0.32)	1199 (0.32)	4514 (0.3)
Pneumonia*	N (%)	5592 (2.48)	7106 (2.7)	9596 (3.14)	12,161 (3.54)	13,832 (3.72)	48,287 (3.2)
Pulmonary embolism*	N (%)	807 (0.36)	907 (0.35)	1033 (0.34)	1253 (0.37)	1263 (0.34)	5263 (0.35)
Hypertension*	N (%)	72,209 (32.08)	102,018 (38.83)	121,656 (39.75)	137,798 (40.16)	142,435 (38.3)	576,116 (38.18)
Acute renal failure*	N (%)	20,929 (9.3)	25,466 (9.69)	56,633 (18.51)	95,357 (27.79)	123,060 (33.09)	321,445 (21.3)
TD2M	N (%)	68,528 (30.44)	92,426 (35.18)	114,481 (37.41)	132,743 (38.69)	146,061 (39.28)	554,239 (36.73)
COPD	N (%)	43,703 (19.41)	51,492 (19.6)	60,216 (19.68)	67,048 (19.54)	72,499 (19.5)	294,958 (19.55)
Echocardiogram*	N (%)	62,381 (27.71)	76,527 (29.13)	94,902 (31.01)	107,635 (31.37)	119,236 (32.07)	460,681 (30.53)
Non invasive mechanical ventilation*	N (%)	1166 (0.52)	2250 (0.86)	5275 (1.72)	12,875 (3.75)	18,527 (4.98)	40,093 (2.66)
Invasive mechanical ventilation*	N (%)	2963 (1.32)	3341 (1.27)	3276 (1.07)	3078 (0.9)	3003 (0.81)	15,661 (1.04)
Heart catheterization *	N (%)	4853 (2.16)	7403 (2.82)	10,294 (3.36)	13,025 (3.8)	16,403 (4.41)	51,978 (3.44)
Pacemaker*	N (%)	1094 (0.49)	1297 (0.49)	1353 (0.44)	1639 (0.48)	1656 (0.45)	7039 (0.47)
Red cell transfusion *	N (%)	8484 (3.77)	11,877 (4.52)	16,358 (5.35)	20,149 (5.87)	21,942 (5.9)	78,810 (5.22)
ER admission*	N (%)	212,977 (94.61)	248,840 (94.71)	288,114 (94.15)	326,563 (95.17)	355,537 (95.61)	1,432,031 (94.91)
Readmission*	N (%)	34,391 (15.28)	42,969 (16.35)	52,073 (17.02)	60,707 (17.69)	67,557 (18.17)	257,697 (17.08)
LOHS*	MediaN (IQR)	8 (7)	7 (7)	7 (8)	7 (7)	7 (6)	7 (7)
IHM*	N (%)	22,432 (9.96)	25,802 (9.82)	29,765 (9.73)	33,163 (9.66)	35,612 (9.58)	146,774 (9.73)

CCI Charlson Comorbidity Index. ER Emergency room. T2DM Type 2 diabetes mellitus. COPD Chronic obstructive pulmonary disease. LOHS Length of hospital stay. IHM In hospital mortality.

* $P < .001$ to assess time trend from 2001 to 2015.

Females had a higher risk of dying during their hospitalization than males after multivariable adjustment. Those patients with higher age and CCI have significantly higher ORs for IHM than those patients with lower age and CCI.

Being admitted to the hospital through the ER or being a readmission are statistically associated with IHM among patients hospitalized with HF coded in primary or secondary diagnosis position. When we adjusted for possible confounders, we obtained an OR for secondary diagnosis position of 1.66 (95%CI 1.64–1.68). This means that those patients with HF coded as a secondary diagnosis have 66% higher risk of dying in the hospital that those with HF coded as a primary diagnosis.

4. Discussion

Our results demonstrated that hospitalizations due to HF have been increasing during recent years in Spain. These findings have also been recently reported by some other authors [3,18,20]. In the Atherosclerosis Risk in Communities (ARIC) Study Community Surveillance, an increase of HF hospital admissions in some states of the United States has also been reported [18]. In this investigation HF was identified using ICD 9 codes in any diagnostic position [18]. However, when we compare the incidence of hospitalizations due to HF coded as primary and secondary diagnosis, we observed differences between Spain and the United States [9]. In our country, the increase of hospitalizations is seen in both principal and secondary diagnosis; but, in the United States, it has only increased as a secondary diagnosis from 2001 to a peak in 2006 but decreased afterwards to a somewhat plateau until 2014. For primary diagnosis a significant and constant decrement for HF was found from 2001 to 2014 [9]. According to Akintoye et al., this decrease of hospitalizations due to HF in the United States has been attributed to a higher degree of adherence to clinical practice guidelines published since 2005 by the AHA/ACC [9].

Several studies have analysed the trend in hospitalization in European countries showing contradictory results [19–25]. The heterogeneity of findings across studies likely reflects differences in population demographics and definitions of HF.

In Italy, Frigerio et al. have observed that HF as secondary diagnosis has increased and those as a principal diagnosis remain relatively stable. According to the authors, these results might reflect better prevention measures and disease treatment [19].

In Germany from 2000 to 2013 the rate of HF cases identified by the primary diagnosis increased by 28.4% after age-standardization, from 261 to 335 cases per 100,000 population [20].

Schmidt et al. identified HF in Denmark using primary and secondary diagnoses from all inpatient admissions from 1983 to 2012. The standardized hospitalization rate per 100,000 person-years decreased overall from 210 in 1983 to 164 in 2012. The overall decrease reflected an initial average increase of 1.1% per year until 2000, followed by a subsequent decline of 3.5% per year [21].

In Poland the total number of first-time hospitalizations for HF as the primary diagnosis showed a downward trend from 2010 to 2016 (reduction by 12%, $p = .07$) [22].

In Slovenia between 2004 and 2012 it was found that the overall crude annual main and any position HF hospitalization rates increased from 249 to 298 (19.8%, $P < .001$) and from 711 to 862 (21.2%, $P < .001$), respectively, whereas overall standardized main and any HF hospitalization rates decreased from 249 to 232 (7.1%, $P = .002$) and from 711 to 671 (5.7%, $P = .014$), respectively [23].

In France, the age-standardized rate of patients hospitalized for HF remained steady between 2002 and 2012 using HF as either primary or secondary diagnosis [24].

Table 3
Characteristics of hospital admissions with secondary diagnosis of heart failure in Spain (2001–2015).

Variable		2001–03	2004–06	2007–09	2010–12	2013–15	Total
HF as secondary diagnosis*	N (%)	245.521 (52.17)	310.334 (54.15)	387.559 (55.82)	450.681 (56.77)	518.983 (58.26)	1.913.078 (55.91)
Female sex*	N (%)	125,484 (51.11)	157,073 (50.61)	196,884 (50.8)	229,077 (50.83)	262,599 (50.6)	971,117 (50.76)
Age, years*	Mean (SD)	76.31 (11.14)	76.87 (11.14)	77.65 (11.14)	78.54 (11.02)	79.19 (11.05)	77.98 (11.14)
Age groups,years N (%)*	18–44	3790 (1.54)	4649 (1.5)	5244 (1.35)	5255 (1.17)	5340 (1.03)	24,278 (1.27)
	45–54	7629 (3.11)	9101 (2.93)	11,266 (2.91)	11,800 (2.62)	13,007 (2.51)	52,803 (2.76)
	55–64	19,058 (7.76)	24,127 (7.77)	29,066 (7.5)	31,367 (6.96)	34,955 (6.74)	138,573 (7.24)
	65–74	60,680 (24.71)	68,859 (22.19)	74,116 (19.12)	75,151 (16.67)	82,889 (15.97)	361,695 (18.91)
	75–84	97,211 (39.59)	127,439 (41.07)	159,000 (41.03)	183,743 (40.77)	199,801 (38.5)	767,194 (40.1)
	≥85	57,153 (23.28)	76,159 (24.54)	108,867 (28.09)	143,365 (31.81)	182,991 (35.26)	568,535 (29.72)
CCI *	Mean (SD)	2.25 (0.98)	2.35 (1.01)	2.38 (1.02)	2.43 (1.03)	2.47 (1.04)	2.39 (1.02)
CCI. N (%)*	1	57,257 (23.32)	64,592 (20.81)	77,295 (19.94)	84,237 (18.69)	93,241 (17.97)	376,622 (19.69)
	2	101,645 (41.4)	122,289 (39.41)	149,282 (38.52)	169,893 (37.7)	190,657 (36.74)	733,766 (38.36)
	≥3	86,619 (35.28)	123,453 (39.78)	160,982 (41.54)	196,551 (43.61)	235,085 (45.3)	802,690 (41.96)
Ischemic coronary*	N (%)	78,468 (31.96)	99,721 (32.13)	116,627 (30.09)	125,557 (27.86)	139,181 (26.82)	559,554 (29.25)
Atrial fibrillation*	N (%)	80,590 (32.82)	112,362 (36.21)	147,438 (38.04)	179,265 (39.78)	213,551 (41.15)	733,206 (38.33)
Anemia*	N (%)	484 (0.2)	660 (0.21)	943 (0.24)	1272 (0.28)	1487 (0.29)	4846 (0.25)
Pneumonia*	N (%)	29,894 (12.18)	39,173 (12.62)	54,144 (13.97)	67,852 (15.06)	84,055 (16.2)	275,118 (14.38)
Pulmonary embolism*	N (%)	3192 (1.3)	3745 (1.21)	5015 (1.29)	6665 (1.48)	7140 (1.38)	25,757 (1.35)
Hypertension*	N (%)	80,636 (32.84)	123,280 (39.72)	159,013 (41.03)	184,456 (40.93)	206,600 (39.81)	753,985 (39.41)
Acute renal failure*	N (%)	17,020 (6.93)	24,490 (7.89)	57,487 (14.83)	98,515 (21.86)	134,169 (25.85)	331,681 (17.34)
TD2M*	N (%)	65,920 (26.85)	96,837 (31.2)	127,678 (32.94)	152,280 (33.79)	176,927 (34.09)	619,642 (32.39)
COPD	N (%)	48,086 (19.59)	60,877 (19.62)	75,649 (19.52)	88,629 (19.67)	102,307 (19.71)	375,548 (19.63)
Echocardiogram*	N (%)	51,241 (20.87)	69,852 (22.51)	91,170 (23.52)	104,737 (23.24)	123,920 (23.88)	440,920 (23.05)
Non invasive mechanical ventilation*	N (%)	2231 (0.91)	4643 (1.5)	10,588 (2.73)	21,863 (4.85)	30,916 (5.96)	70,241 (3.67)
Invasive mechanical ventilation*	N (%)	10,268 (4.18)	12,628 (4.07)	14,661 (3.78)	14,926 (3.31)	16,039 (3.09)	68,522 (3.58)
Heart catheterization *	N (%)	12,409 (5.05)	18,093 (5.83)	24,197 (6.24)	27,104 (6.01)	31,993 (6.16)	113,796 (5.95)
Pacemaker*	N (%)	4136 (1.68)	4913 (1.58)	5914 (1.53)	7084 (1.57)	8384 (1.62)	30,431 (1.59)
Red cell transfusion *	N (%)	19,868 (8.09)	26,780 (8.63)	36,260 (9.36)	46,046 (10.22)	52,183 (10.05)	181,137 (9.47)
ER admission*	N (%)	217,571 (88.62)	276,252 (89.02)	343,709 (88.69)	402,069 (89.21)	467,683 (90.12)	1,707,284 (89.24)
Readmission*	N (%)	35,190 (14.33)	47,412 (15.28)	61,399 (15.84)	73,503 (16.31)	87,600 (16.88)	305,104 (15.95)
LOHS*	MediaN (IQR)	9 (10)	9 (10)	8 (9)	8 (9)	8 (9)	8 (9)
IHM*	N (%)	40,978 (16.69)	49,361 (15.91)	59,423 (15.33)	67,009 (14.87)	73,980 (14.25)	290,751 (15.2)

CCI Charlson Comorbidity Index. ER Emergency room. T2DM Type 2 diabetes mellitus. COPD Chronic obstructive pulmonary disease. LOHS Length of hospital stay. IHM In hospital mortality.

* $P < .001$ to assess time trend from 2001 to 2015.

In the United Kingdom, an investigation conducted in > 4 million inhabitants shows that although the incidence of heart failure is decreasing, hospitalizations are increasing and affect mainly elderly patients with comorbidity and depressed socioeconomic situation. [3]. However other study conducted in England using ICD-10 codes for HF as a primary diagnosis found that the average HF admissions per 100,000 patient population fell significantly by 27.3% ($P < .001$), from 6.96/100000 in 2004 to 5.06/100000 in 2010 [25].

The increase of HF hospital admissions in Spain could be due to many factors. First, positive trends in hospitalizations rates regardless

Table 4
In hospital mortality among patients with a heart failure hospitalization codified in the primary or secondary diagnostic position. Spain, 2001–2015.

		Primary	Secondary	Both
Deaths*	N (%)	146,774 (9.73)	290,751 (15.20)	437,525 (12.79)
Year, N (%)*	2001–03	22,432 (9.96)	40,978 (16.69)	63,410 (13.47)
	2004–06	25,802 (9.82)	49,361 (15.91)	75,163 (13.12)
	2007–10	29,765 (9.73)	59,423 (15.33)	89,188 (12.86)
	2010–12	33,163 (9.66)	67,009 (14.87)	100,172 (12.62)
	2013–15	35,612 (9.58)	73,980 (14.25)	109,592 (12.3)
Gender, N (%)*	Male	62,658 (9.19)	142,341 (15.11)	204,999 (12.62)
	Female	84,116 (10.17)	148,410 (15.28)	232,526 (12.93)
Age groups in years, N (%)*	18–44	585 (4.23)	2575 (10.61)	3160 (8.29)
	45–54	1273 (3.53)	5151 (9.76)	6424 (7.23)
	55–64	4503 (4.43)	14,354 (10.36)	18,857 (7.85)
	65–74	17,417 (6.11)	42,011 (11.62)	59,428 (9.19)
	75–84	56,982 (9.09)	112,576 (14.67)	169,558 (12.17)
	≥85	66,014 (14.8)	114,084 (20.07)	180,098 (17.75)
CCI. N (%)*	1	30,621 (8.61)	44,161 (11.73)	74,782 (10.21)
	2	53,018 (9.3)	107,507 (14.65)	160,525 (12.31)
	≥3	63,135 (10.83)	139,083 (17.33)	202,218 (14.59)
ER admission, N (%)*	No	6897 (8.98)	23,322 (11.33)	30,219 (10.69)
	Yes	139,877 (9.77)	267,429 (15.66)	407,306 (12.97)
Readmission, N (%)*	No	111,479 (8.91)	232,439 (14.46)	343,918 (12.03)
	Yes	35,295 (13.7)	58,312 (19.11)	93,607 (16.63)
LOHS*	Median (IQR)	6 (10)	8 (13)	7 (12)

* $P < .001$ comparing those hospitalized with HF as primary diagnosis with those as a secondary diagnosis. CCI Charlson Comorbidity Indez.ER Emergency room. LOHS Length of hospital stay.

Table 5
Factors independently associated with in-hospital mortality among heart failure hospitalized patients according to diagnostic position. Spain 2001–2015.

		Primary	Secondary	Both
		OR (IC95%)	OR (IC95%)	OR (IC95%)
Year	2001–3	1	1	1
	2004–6	0.93 (0.92–0.95)	0.91 (0.9–0.93)	0.92 (0.91–0.93)
	2007–10	0.87 (0.86–0.89)	0.85 (0.83–0.86)	0.86 (0.85–0.87)
	2010–2	0.82 (0.81–0.84)	0.79 (0.78–0.8)	0.8 (0.79–0.81)
	2013–15	0.79 (0.77–0.8)	0.73 (0.72–0.74)	0.75 (0.74–0.76)
Gender	Male	1	1	1
	Female	1.03 (1.02–1.05)	1.06 (1.05–1.07)	1.05 (1.04–1.06)
Age groups in years. N (%)	18–44	1	1	1
	45–54	0.82 (0.74–0.9)	0.86 (0.82–0.91)	0.84 (0.81–0.88)
	55–64	1 (0.91–1.09)	0.89 (0.85–0.93)	0.9 (0.86–0.93)
	65–74	1.37 (1.26–1.5)	0.98 (0.93–1.02)	1.04 (1–1.08)
	75–84	2.2 (2.02–2.39)	1.31 (1.26–1.37)	1.49 (1.43–1.54)
	≥85	4.07 (3.75–4.43)	2.05 (1.97–2.14)	2.48 (2.39–2.57)
CCI	1	1	1	1
	2	1.1 (1.08–1.12)	1.31 (1.29–1.32)	1.23 (1.22–1.24)
	≥3	1.33 (1.31–1.35)	1.62 (1.6–1.64)	1.51 (1.5–1.52)
ER admission		1.03 (1.01–1.05)	1.29 (1.28–1.31)	1.22 (1.2–1.23)
Readmission		1.61 (1.59–1.64)	1.39 (1.37–1.4)	1.47 (1.46–1.48)
LOHS		1.01 (1.01–1.01)	1.01 (1.01–1.01)	1.01 (1.01–1.01)
HF codified as secondary diagnosis		NA	NA	1.66 (1.64–1.68)

CCI Charlson Comorbidity Index. ER Emergency room. LOHS Length of hospital stay. HF Heart failure.

code position are mainly due to the ≥85 years old group while remaining groups did not change or remained stabilized. Previous regional studies for the period 2003–2013 already showed that this increasing trend mostly concern to this age group [8]. Aging of the HF patients could also explain the increase in CCI but differences in trends with other countries, like United States, cannot be explained by the slight differences in relative weight of this age group in the population or minor changes in life expectancy in the last 10 years, supporting the role of factors related to differences in the management of these more complex patients [9,18]. In Spain, acute HF are mainly seen in elderly individuals with several chronic conditions. These findings contrast with the concept of acute HF considered as a syndrome associated with comorbidities [26].

Beside the aging of population and the increase in comorbidities other possible reason for the higher incidence and prevalence of HF in our country include the high prevalence of smoking, obesity, sedentary lifestyle, and blood pressure and a decrease in the threshold for admission of heart failure patients that would likely increase the rate of hospitalizations [27]. The increase in hospital admissions of HF causes higher healthcare costs in our country with a worsening of the quality of life of patients with HF who often suffer from the phenomenon of post-hospitalization syndrome [8,10].

The rise observed in codification of heart failure as a secondary diagnosis has also been reported in other studies [28]. Thus, Agarwal et al. [28] stated that the code 428 ICD-9 code in a secondary position has been increasing in the United States in recent years. This might result from the fact that patients with HF are admitted for another reason as will be commented in the limitations section.

Mean values of the CCI have been increasing over the study period. These results are congruent with the multi-morbidity HF concept as the leading cause of hospitalization in developed countries [29]. Among comorbidities observed in the study, the increased frequency in the diagnosis of T2DM, hypertension, and renal failure was prominent. T2DM has been reported to be an independent risk factor for hospitalization due to heart failure [30]. The increasing proportion of acute renal failure observed throughout the period might be related to aging, heart failure itself or other associated cardiovascular risk factors such as hypertension and diabetes [31].

A surprising result of our investigation is that during the study period, hospital readmissions remained stable. Several studies have analysed readmission after HF hospitalizations finding inconclusive results [22–24,27,32]. A local study conducted in Spain found in the 2003–2013 period, 30-day readmission rates had a relative mean annual growth of +1.36%, increasing from 17.6% to 22.1%, with similar trends for cardiovascular and non-cardiovascular causes [32].This trend agrees with data from Medicare patients in USA [27]. However these studies were conducted using HF only as a primary diagnosis. Bueno et al. considered that the shortened hospital stay may have caused these higher readmission rates, suggesting that it is certainly plausible that the effort to discharge patients quickly has led to transfers to non-acute institutional settings and occasionally sent patients out of the hospital before they are fully treated [27].

Niedziela et al., in Poland, from 2010 to 2016, found stable all-cause hospital readmission rates in 12-month follow-up related to principal diagnosis of HF [22].

In Slovenia, using the same method we used, the 30 day readmission rate remained stable from 2008 to 2011 for HF as a primary diagnosis and increased significantly for HF in any diagnosis position [23].

In France, from 2002 to 2012 using HF as primary or secondary diagnosis readmission rates increased significantly in both women and men [24].

Previous investigations suggest that readmissions mainly seem to be related with aging and comorbidity [22–24,27,32]. Therefore, health policies should address the burden of early readmissions following HF hospitalization, with emphasis on a population strategy including early and well-coordinated multidisciplinary interventions [32].

Access to community HF teams and rapid follow-up have been shown to reduce the risk of readmission significantly, and may well have a much larger effect on reducing admission risk than access to GPs alone [33–35].

Using specialized HF units certainly allows appropriate implementation and up titration of evidenced-based pharmacologic care, device recommendation and focused patient education. Furthermore, teams are pro-active in identifying early symptoms and reinforcing patient and caregiver education, maintaining communication with the most vulnerable HF patients [33–35]. Adequate social support and multidisciplinary management utilizing nursing care in coordination with a cardiologist and general doctors have shown to be beneficial in preventing hospitalizations for heart failure [34].

In Spain the Comín-Colet J et al. evaluated the feasibility and efficacy of an integrated hospital-primary care program for the management of patients with heart failure in an integrated health area covering

a population of 309,345 finding that patients included in the program had lower risk of clinically-related readmission (hazard ratio = 0.71: 95%CI 0.66–0.76), and a lower risk of readmission for heart failure (hazard ratio = 0.86 95%CI, 0.80–0.94; $P < .001$) [35].

We believe that heart failure units have possible contributed to reduce the readmission rate in Spain and based on our results; it would be advisable in our country to develop programs and multidisciplinary units for the management of HF as has been suggested by other authors [36]. Furthermore, interventions to limit cardiovascular risk factors, and to continue the monitoring of HF hospitalizations and mortality are needed [19,21].

IHM rates are similar or slightly higher than previously published studies with similar methodology for a former timespan [20–25]. We also observed an overall decrease over the period for both, primary and secondary diagnosis, but mortality was higher for those patients with HF coded as secondary, probably because the condition leading to hospitalization mostly determine in-hospital prognosis [28]. This decrease in IHM has also been observed in the United States [9] and authors attributed them to improvements in adherence to clinical guidelines [37]. Nevertheless, IHM is not homogeneous in our study. We found an expected age positive trend with higher IHM rate in groups over 65 years. This association was independent of comorbidity, also a known predictor of IHM in patients with HF [38]. Unlike United States series where males had 17% increased risk of death, after adjusting for age, comorbidities, readmission and year of admission, we found a higher IHM rate among women [39]. Gender related differences on clinical and epidemiological characteristics of HF has been previously described [40]. Since our estimates are adjusted for some of these gender related differences (age, comorbidities, readmission) we think excess of risk for women might be due to a differential management according medical services responsible of the patient, whether related or not with other clinical variables at admission that eventually determine this assignation but also prognosis variables not included in the model or a residual confounding effect [41].

In this investigation we tried to assess the real magnitude of HF on hospital admission for the entire Spanish population from 2001 to 2015 and that is the reason why we include HF as a primary or secondary diagnosis. According to the SNHDD methodology the first or primary diagnosis is the condition established after study to be chiefly responsible for occasioning the admission of the patient to the hospital for care. [11].Secondary diagnosis include all those conditions, that according to the discharging physician, have appeared during the hospitalization or were present at the time of admission and have affected in any way the hospitalization of the patient. Affecting the hospitalization means that resulted in a longer duration; that more diagnostic or therapeutic procedures were needed as a consequence of these conditions; or that were associated with the in-hospital mortality. In our opinion, if we include only HF as a primary diagnosis, we could miss admission with primary diagnosis such as infectious diseases (e.g. pneumonia, influenza, gastroenteritis) or atrial fibrillation among others, were patients were really admitted to the hospital because these conditions trigger HF, making hospitalization necessary, rather than the primary diagnosis itself [42]. Another reason to include HF as primary and secondary diagnosis is that coding practices in administrative databases change overtime, as has been demonstrated in other investigations, and this may underestimate the real burden of HF [43,44]. Finally several studies conducted in other countries have also included either primary or secondary diagnosis to assess the temporal trends in HF hospitalizations. [9,18,19,21,23,24]. For all the previous, we consider that the same strategies to improve the clinical management and prevention of HF would be applicable to patients admitted with a primary or secondary diagnosis of HF. Our study has some limitations as our national database only encodes diagnosis. The 428 code has shown to have a good diagnostic sensitivity to establish acute HF, but some important biological variables such as NT-proBNP or left ejection fraction to imply the diagnosis of HF are missing [28]. Pharmacologic treatment received during hospitalization was not available in the database. We could only evaluate IHM, and therefore we were not able to determine the impact of out-hospital mortality on readmissions. The social and functional situation of the patients was not available, both factors which may influence the prognosis and medical needs in patients with acute HF [45].

Despite these limitations, our estimates are based on a large sample size covering data from an entire country with a 15-year follow-up period and using a standardized methodology.

In conclusion, this study shows an increase of hospitalizations due to heart failure in Spain, particularly in patients with heart failure as a secondary diagnosis. Advance age and comorbidity in acute heart failure has increased in the recent years. However, in-hospital mortality is decreasing while readmissions remain stable.

Competing interests

The authors declare that they have no competing interests.

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