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The significance of heart failure in hospitalised patients with pulmonary embolism. A gender-specific analysis

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Abstract

Background: Heart failure (HF) is a risk factor for the development of pulmonary embolism (PE). Few studies have examined sex differences in risk of PE among HF patients.

Aims: (a) To examine the incidence, characteristics and in-hospital outcomes among patients hospitalised with PE according to HF status; (b) to compare the in-hospital mortality (IHM) after PE between HF and non-HF patients and (c) to identify variables associated with IHM. All analyses were stratified by sex.

Methods: We included all adult patients hospitalised for PE from 1 January 2016 to 31 December 2018. Data were collected from the Spanish National Hospital Discharge Database. Poisson regression models were constructed to quantify the difference in the incidences between HF and non-HF populations. Propensity score matching (PSM) was used to obtain comparable subgroups by sex and HF status.

Results: We identified 46,835 PE hospitalisations, 11.4% with HF. Adjusted incidence of PE was higher in HF patients than in those without HF (Incidence Rate Ratio 1.11; 95% CI 1.08-1.13). Crude and PSM adjusted IHM were significantly higher in men and women hospitalised with PE suffering HF than in men and women without HF ($P < .001$). Women with HF who suffered a PE had lower IHM than men with this condition ($P < .001$) after adjusting.

Conclusions: Adjusted incidence of PE was higher in HF patients than in those without HF. After PSM suffering, HF was associated to higher IHM in men and women. Women with PE and HF had lower IHM than men with these conditions.

1 | INTRODUCTION

Heart failure (HF) is a common, costly and potentially fatal cause of hospitalisation,[1] which has seen a steady and significant increase in recent years.[2] It is a risk factor for the development of pulmonary embolism (PE) in hospitalised patients, as consequence of vascular anomalies, hypercoagulability, an impaired blood flow,[3,4] although large differences exist in the reported frequency of venous thromboembolic events in individuals with HF.[5] On the other hand, this disease seems to be an independent predictor of mortality in patients presenting with acute PE.[6,7] Moreover, PE could be an independent predictor of rehospitalisation or death among patients with HF.[8,9]

Despite that, previous studies have shown low rates of prophylaxis for venous thromboembolism (VTE) in HF hospitalised patients.[10] Further understanding of the association between PE and HF could help guide more tailored prophylaxis strategies in this population.[11]

In spite of the demonstrated relationship between both conditions, few studies have examined the difference in risk of VTE between men and women with HF. In some studies this relationship has been evaluated, not specifically in HF patients, with inconsistent findings, although most studies found an excess risk among men.[12-14] Conversely, Melgaard et al found a higher risk of VTE in women compared with men among incident HF patients, mainly driven by an excess risk of PE.[15] On the other hand, they did not study sex-related differences in mortality in these patients.

The aims of this study were: (a) to examine the incidence, clinical characteristics and in-hospital outcomes (length of hospital stay [LOHS] and in-hospital mortality [IHM]) among patients hospitalised with PE according to the presence or not of concomitant HF in Spain in the period from 2016 to 2018; (b) to compare the in-hospital outcomes after PE between patients with HF and propensity score-matched non-HF patients and (c) to identify variables independently associated with in-hospital-mortality after PE among patients with and without HF. All analyses were stratified by sex.

What's known?

Heart failure is a risk factor for the development of pulmonary embolism, as consequence of vascular anomalies, hypercoagulability and impaired blood flow. Few studies have examined the difference in risk of venous thromboembolism between men and women with heart failure. In some studies this relationship has been evaluated, with inconsistent findings, although most studies found an excess risk among men.

What's new?

Our findings revealed that incidence of pulmonary embolism in Spain from 2016 to 2018 was higher in heart failure patients than in those without heart failure. Furthermore, heart failure was a risk factor for in-hospital mortality after pulmonary embolism. Women with pulmonary embolism and heart failure had lower in-hospital mortality than men with these conditions. Variables associated with in-hospital mortality included older age, increased comorbidity and atrial fibrillation while obesity had a protective effect.

2 | METHODS

2.1 | Design, setting and participants

This is a retrospective epidemiological investigation conducted using the hospital discharge reports collected by the Spanish National Hospital Discharge Database (SNHDD) for the period from 2016 to 2018.

The SNHDD is an administrative database that collects de-identified data from all patients discharged from public or private Spanish hospitals. Patient information includes a primary diagnosis, up to 19 secondary diagnoses and a maximum of 20 diagnostic or therapeutic procedures conducted during the hospital admission coded using the 10th Revision of the International Classification of Diseases (ICD-10). Over 4 million registries are included in the SNHDD each year. More details regarding the SNHDD can be found elsewhere.[16]

2.2 | Study population

Our study population includes all adult patients (aged ≥18 years), from 1 January 2016 to 31 December 2018, who were admitted to any Spanish hospital with a primary diagnosis of PE.

According to the SNHDD, the primary diagnosis is the clinical condition that, after all appropriate diagnosis procedures are conducted, is considered the main reason to hospitalise the patient. We defied as PE patients those who in their discharge report had as primary diagnosis the ICD 10 codes I26.92 (Saddle embolus of pulmonary artery without acute cor pulmonale) or I26.99 (Other pulmonary embolism without acute cor pulmonale). Following the recommendation of Smith et al,[17] patients with PE secondary to obstetrical complications, septic or iatrogenic PE and acute cor-pulmonale, in any diagnosis position, were excluded (ICD10 codes are shown in Table S1).

Once the study population was identified, it was stratified according to the presence of HF. We considered that a patient suffered HF if in any of the secondary diagnosis fields (2-20) we found any of the following ICD 10 codes "I50.xx (Heart failure)," "I11.x (Hypertensive heart disease with heart failure)," "I13.0 (Hypertensive heart and chronic kidney disease with heart failure and stage 1 through stage 4 chronic kidney disease, or unspecified chronic kidney disease)", or "I13.2 (Hypertensive heart and chronic kidney disease with heart failure and with stage 5 chronic kidney disease, or end-stage renal disease)". Those patients without any of these codes were classified as "non-HF patients".

2.2.1 | Study variables

The main study outcome variables are the incidence of EP according to the presence of HF and in hospital outcomes such as LOHS and IHM.

Patients' characteristics analysed include age and sex. Age was categorised in three groups (18-64 years, 65-79 years and 80 years or over).

The Charlson Comorbidity Index (CCI) was used to assess the comorbidity of each patient as proposed by Quan et al.[18] The calculation of the CCI was performed excluding HF as a disease. The CCI is

categorised according to the number of conditions (CCI = 0, CCI 1-2 and CCI >2). We also independently described and analysed those conditions included in the CCI with a prevalence over 1%.

Shown in Table S2 are the codes used to identify patients suffering from obesity, coagulopathy, atrial fibrillation and valvular heart disease, and those who underwent inferior vena cava filter and thrombolytic therapy as therapeutic procedures.

To assess the severity of PE, we used the definition for "massive PE" proposed by Smith et al.[17] A patient was classified as affected by a *"Massive PE"* if the discharge report included codes for any of the following procedures or diagnosis; mechanical ventilation, vasopressors medication or non-septic shock, in any of the procedures (1-20) or diagnosis fields (2-20), as described by Smith et al.[17] We had to use this algorithm because the ICD 10 does not include a specific code for severe PE (see Table S2 for ICD 10 codes).

Patients who had received any surgical procedure during their hospitalisation were identified using a specific variable included in the SNHDD.[16]

2.2.2 | Propensity score matching method

As can be seen in Table 1, patient's characteristics (age, CCI and sex) are very different between patients with and without HF who have suffered a PE. Therefore, to make these populations comparable, we used propensity score matching (PSM). PSM was conducted with multivariable logistic regression including as matching variables year of hospitalisation, age, CCI conditions and if a surgery was conducted. We matched men and women with HF with non-HF men and women separately. To assess the effect of sex in the association of PE concomitantly with HF, we also matched men suffering PE and HF with women suffering these two same conditions. These methods have been described before.[19,20]

2.2.3 | Statistical methods

To calculate the incidence rates of admission for PE per 100 000 inhabitants according to the presence of HF, we estimated the Spanish populations suffering HF using prevalence data from the Base de Datos Clínicos de Atención Primaria (BDCAP).[21] This prevalence was multiplied by the adult Spanish population in 2016, 2017 and 2018 obtained from the Spanish National Statistics Institute to obtain the total populations with and without HF.[22] Poisson regression models adjusted by sex and age were constructed to quantify the difference in the incidences between HF and non-HF populations providing Incidence Rate Ratios (IRR) with their 95% Confidence Intervals (CI) as measure of association.

We show counts and proportions for categorical variables and means with standard deviations (SD) or medians with interquartile ranges (IQR) for continuous variables.

TABLE 1 Incidence rates, sex and age distribution, clinical characteristics and hospital outcomes of patients hospitalised with pulmonary embolism (PE) according to heart failure (HF) status in Spain from 2016 to 2018

	HF	No HF	*P*-value
Total, n (incidence rate * 100,000)	5341 (125)	41494 (98)	<.001
Men, n (%)	1984 (37.15)	19820 (47.77)	<.001
Women, n (%)	3357 (62.85)	21674 (52.23)	<.001
Age, mean (SD)	79.17 (11.54)	69.53 (15.81)	<.001
18-64 years, n (%)	549 (10.28)	13396 (32.28)	<.001
65-79 years, n (%)	1623 (30.39)	14856 (35.8)	<.001
80 years or over, n (%)	3169 (59.33)	13242 (31.91)	<.001
CCI, mean (SD)	0.92 (0.83)	0.70 (0.63)	<.001
CCI = 0, n (%)	2092 (39.17)	20299 (48.92)	<.001
CCI 1-2, n (%)	2933 (54.91)	19824 (47.78)	<.001
CCI >2, n (%)	316 (5.92)	1371 (3.3)	<.001
Massive PE, n (%)	286 (5.35)	1142 (2.75)	<.001
LOHS days, median (IQR)	9 (7)	7 (5)	<.001
IHM, n (%)	647 (12.11)	2349 (5.66)	<.001

CCI, Charlson Comorbidity Index; HF, heart failure; IHM, in-hospital mortality; IQR, inter quartile range; LOHS, length on hospital stay; SD, standard deviation. Incidence rate per 100,000 inhabitants with and without HF. *P* value for comparison of HF versus non-HF subjects.
*Significant difference estimated using Poisson regression models adjusted by year, age and sex.

The statistical test to compare the un-matched study populations included Fisher Exact test (proportions), *T* test (means) or Mann-Whitney tests (medians). Once the populations were matched, we used McNemar's test (proportions), Paired *t*-test (means) or Wilcoxon signed-rank test (medians).

To identify variables independently associated with IHM among patients with PE suffering or not HF, for men and women separately and for the entire HF populations, we constructed seven multivariable logistic regression models.

These multivariable models were constructed including variables statistically significant in the bivariate analysis and those that even if not statistically significant were considered relevant from an epidemiological or clinical viewpoint. We included all variables in the initial model and one at each step, we decided to eliminate or not variables according to their significance in the model evaluated (Wald statistic) and comparing the model's goodness of fit (Hosmer-Lemenshow statistic) with the previous step using the likelihood Ratio test. Once we obtained a final model, we examined the effects of interactions. Results are shown as Odds Ratio (OR) with their 95% CI.

Stata version 14 (Stata, College Station, Texas, USA) was used for PSM and all data analysis.

2.2.4 | Ethical aspects

The SNHDD is provided free of charge by the Spanish Ministry of Health (SMH) to any investigator who sends a justified request.[23] The SMH is responsible for assessing the ethical aspects of the request and if the proposal is admitted, it provides a de-identified database with the requested information. All patients have given their informed consent to be included in the SNHDD. Because of the previous and, according to the Spanish legislation, it is not necessary to obtain the approval by an ethics committee. The study was conducted in accordance with the Helsinki Declaration.

3 | RESULTS

From 2016 to 2018 in Spain, 46 835 adult patients were admitted to Spanish hospitals with a primary diagnosis of PE. The proportion of these patients with a code for HF in their discharge report was 11.40% (5341). As can be seen in Table 1, the crude incidence per 100.000 adults was 125 and 98 for those suffering and not suffering concomitant HF, respectively ($P < .001$). After adjusting by age and sex, using Poisson regression, the IRR obtained was 1.11 (95% CI 1.08-1.13). Therefore, after adjustment, subjects suffering HF had an 11% higher risk of being hospitalised with PE in Spain in the period from year 2016 to year 2018 than subjects not suffering HF.

According to sex, women represent 62.85% among those with PE and HF and 52.23% among those with PE not suffering HF ($P < .001$). Patients with concomitant HF are 10 years older (mean ages 79.17 years vs 69.53 years; $P < .001$), have higher mean CCI (0.92 vs 0.71; $P < .001$) and more frequently suffered a "massive PE" (5.35% vs 2.75%; $P < .001$). The crude IHM was more than twice higher ($P < .001$) among HF sufferers.

When we compare the frequency of comorbid conditions, procedures and hospital outcomes in men hospitalised with PE according to the presence of HF, we obtain the results found in Table 2.

Before matching men suffering HF admitted with PE have a much higher mean age (75.42 vs 66.7 years; $P < .001$) than men without HF. Men suffering HF had significantly higher prevalence all the conditions analysed exception made of cancer and coagulopathy,

TABLE 2 Prevalence of specific comorbid conditions, diagnostic and therapeutic procedures and hospital outcomes in men hospitalised with pulmonary embolism (PE) according to heart failure (HF) status in Spain from 2016 to 2018 before and after propensity score matching

	Before propensity score matching			After propensity score matching		
	HF	No HF	*P*-value	HF	No HF	*P*-value
Age mean (SD)	75.42 (12.82)	66.7 (15.02)	<.001	75.42 (12.82)	75.98 (12.08)	.153
CCI, mean (SD)	1.09 (1.02)	0.77 (0.70)	<.001	1.09 (1.02)	1.11 (1.04)	.516
AMI, n (%)	144 (7.26)	655 (3.3)	<.001	144 (7.26)	153 (7.71)	.587
PVD, n (%)	179 (9.02)	917 (4.63)	<.001	179 (9.02)	188 (9.48)	.622
CVD, n (%)	114 (5.75)	641 (3.23)	<.001	114 (5.75)	127 (6.4)	.388
Dementia, n (%)	91 (4.59)	599 (3.02)	<.001	91 (4.59)	83 (4.18)	.535
Rheumatoid disease, n (%)	44 (2.22)	295 (1.49)	.012	44 (2.22)	45 (2.27)	.915
Liver disease, n (%)	122 (6.15)	1145 (5.78)	.499	122 (6.15)	119 (6)	.842
Diabetes, n (%)	423 (21.32)	2850 (14.38)	<.001	423 (21.32)	427 (21.52)	.877
COPD, n (%)	333 (16.78)	1822 (9.19)	<.001	333 (16.78)	323 (16.28)	.669
Renal disease, n (%)	358 (18.04)	1701 (8.58)	<.001	358 (18.04)	363 (18.3)	.837
Cancer, n (%)	173 (8.72)	2083 (10.51)	.013	173 (8.72)	162 (8.17)	.530
Atrial fibrillation, n (%)	462 (23.29)	1308 (6.6)	<.001	462 (23.29)	451 (22.73)	.678
Valvular heart disease, n (%)	315 (15.88)	783 (3.95)	<.001	315 (15.88)	296 (14.92)	.403
Obesity, n (%)	235 (11.84)	1920 (9.69)	.002	235 (11.84)	220 (11.09)	.455
Coagulopathy, n (%)	26 (1.31)	404 (2.04)	.026	26 (1.31)	14 (0.71)	.057
Inferior vena cava filter	15 (0.76)	207 (1.04)	.223	15 (0.76)	15 (0.76)	1.000
Undergone surgery, n (%)	36 (1.81)	367 (1.85)	.907	36 (1.81)	28 (1.41)	.313
Thrombolytic therapy, n (%)	108 (5.44)	1249 (6.3)	.131	108 (5.44)	98 (4.94)	.474
Massive PE, n (%)	121 (6.10)	578 (2.92)	<.001	121 (6.10)	67 (3.38)	<.001
LOHS, median (IQR)	9 (7)	7 (5)	<.001	9 (7)	7 (6)	<.001
IHM, n (%)	250 (12.6)	1110 (5.6)	<.001	250 (12.6)	146 (7.36)	<.001

AMI, acute myocardial infarction; CCI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; IHM, in-hospital mortality; IQR, inter quartile range; LOHS, length on hospital stay; PVD, peripheral vascular disease; SD, standard deviation. *P* value for comparison of men with heart failure (HF) vs non-HF men.

TABLE 3 Prevalence of specific comorbid conditions, diagnostic and therapeutic procedures and hospital outcomes in women hospitalised with pulmonary embolism (PE) according to heart failure (HF) status in Spain from year 2016 to year 2018 before and after propensity score matching

	Before propensity score matching			After propensity score matching		
	HF	No HF	*P*-value	HF	No HF	*P*-value
Age mean (SD)	81.38 (10.08)	72.13 (16.06)	<.001	81.38 (10.08)	81.69 (9.87)	.199
CCI, mean (SD)	0.82 (0.77)	0.65 (0.60)	<.001	0.82 (0.87)	0.84 (0.86)	.414
AMI, n (%)	100 (2.98)	262 (1.21)	<.001	100 (2.98)	83 (2.47)	.203
PVD, n (%)	124 (3.69)	409 (1.89)	<.001	124 (3.69)	113 (3.37)	.467
CVD, n (%)	168 (5)	801 (3.7)	<.001	168 (5)	183 (5.45)	.411
Dementia, n (%)	340 (10.13)	1639 (7.56)	<.001	340 (10.13)	373 (11.11)	.191
Rheumatoid disease, n (%)	134 (3.99)	704 (3.25)	.026	134 (3.99)	127 (3.78)	.659
Liver disease, n (%)	130 (3.87)	853 (3.94)	.861	130 (3.87)	112 (3.34)	.239
Diabetes, n (%)	697 (20.76)	3250 (14.99)	<.001	697 (20.76)	707 (21.06)	.764
COPD, n (%)	151 (4.5)	559 (2.58)	<.001	151 (4.5)	142 (4.23)	.591
Renal disease, n (%)	553 (16.47)	1775 (8.19)	<.001	553 (16.47)	590 (17.58)	.230
Cancer, n (%)	185 (5.51)	1541 (7.11)	.001	185 (5.51)	173 (5.15)	.515
Atrial fibrillation, n (%)	787 (23.44)	1469 (6.78)	<.001	787 (23.44)	790 (23.53)	.931
Valvular heart disease, n (%)	560 (16.68)	1165 (5.38)	<.001	560 (16.68)	530 (15.79)	.321
Obesity, n (%)	598 (17.81)	3157 (14.57)	<.001	598 (17.81)	578 (17.22)	.521
Coagulopathy, n (%)	42 (1.25)	355 (1.64)	.095	42 (1.25)	33 (0.98)	.296
Inferior vena cava filter	30 (0.89)	178 (0.82)	.667	30 (0.89)	29 (0.86)	.896
Undergone surgery, n (%)	62 (1.85)	320 (1.48)	.103	62 (1.85)	69 (2.06)	.537
Thrombolytic therapy, n (%)	177 (5.27)	1255 (5.79)	.229	177 (5.27)	149 (4.44)	.112
Massive PE, n (%)	165 (4.92)	564 (2.60)	<.001	165 (4.92)	93 (2.77)	<.001
LOHS, median (IQR)	9 (7)	7 (6)	<.001	9 (7)	8 (6)	<.001
IHM, n (%)	397 (11.83)	1239 (5.72)	<.001	397 (11.83)	262 (7.8)	<.001

AMI, acute myocardial infarction; CCI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; IHM, in-hospital mortality; IQR, inter quartile range; LOHS, length on hospital stay; PVD, peripheral vascular disease; SD, standard deviation. *P* value for comparison of women with heart failure (HF) vs non-HF women.

more frequently coded in non-HF men, and liver disease with no difference between groups. Regarding procedures and surgery, no differences were found.

Massive PE (6.10% vs 2.92%; $P < .001$), LOHS (9 days vs 7; $P < .001$) and IHM (12.6% vs 5.6%; $P < .001$) showed significantly higher figures among men with HF than among men without concomitant HF.

After PSM, men with HF suffering PE and matched non-HF men had no differences in any of the conditions or procedures analysed. However, even if the differences decrease, HF men still showed more massive PE (6.10% vs 3.38%; $P < .001$), higher median LOHS (9 vs 7 days: $P < .001$) and higher IHM (12.6% vs 7.36%; $P < .001$).

The prevalence of comorbid conditions, procedures and hospital outcomes in women hospitalised suffering PE with and without HF before and after PSM is shown in Table 3.

As reported among men, women with concomitant HF had significantly higher prevalence of almost all conditions studied. Only cancer was more frequent among non-HF women and no differences were found for liver disease, coagulopathy, inferior vena cava filter, undergone surgery and thrombolytic therapy. After PSM, women suffering HF had higher prevalence of massive PE (4.92% vs 2.77%; $P < .001$), longer LOHS (9 days vs 8 days; $P < .001$) and higher IHM (11.83% vs 7.8%; $P < .001$).

To assess the effect of sex in the association of PE concomitantly with HF shown in Table 4 are the results of men suffering PE and HF and women suffering PE and HF before and after PSM.

Prior to matching, women are significantly older (81.38 years vs 75.42 years; $P < .001$) and had more frequently coded dementia, rheumatoid disease and obesity. Men had a higher mean CCI (1.02 vs 0.87; $P < .001$) and higher prevalence of acute myocardial infarction, peripheral vascular disease, liver disease chronic obstructive pulmonary disease and cancer. No significant differences were found for any of the procedures or hospital outcome variables analysed.

After PSM women with HF who suffered a PE had lower IHM than men with these conditions (9.48% vs 12.60%; $P < .001$).

The variables associated with IHM for the study populations are shown in Table 5. For all groups analysed besides the presence of HF

TABLE 4 Prevalence of specific comorbid conditions, diagnostic and therapeutic procedures and hospital outcomes in men and women suffering HF and hospitalised with pulmonary embolism (PE) in Spain from 2016 to 2018 before and after propensity score matched

	Before propensity score matching			After propensity score matching		
	HF men	HF Women	*P*-value	HF men	HF Women	*P*-value
Age mean (SD)	75.42 (12.82)	81.38 (10.08)	<.001	75.42 (12.82)	77.62 (10.55)	<.001
CCI, mean (SD)	1.09 (1.02)	0.82 (0.87)	<.001	1.09 (1.02)	0.9 (0.9)	<.001
AMI, n (%)	144 (7.26)	100 (2.98)	<.001	144 (7.26)	97 (4.89)	.002
PVD, n (%)	179 (9.02)	124 (3.69)	<.001	179 (9.02)	120 (6.05)	<.001
CVD, n (%)	114 (5.75)	168 (5)	.242	114 (5.75)	118 (5.95)	.787
Dementia, n (%)	91 (4.59)	340 (10.13)	<.001	91 (4.59)	104 (5.44)	.112
Rheumatoid disease, n (%)	44 (2.22)	134 (3.99)	<.001	44 (2.22)	35 (1.76)	.306
Liver disease, n (%)	122 (6.15)	130 (3.87)	<.001	122 (6.15)	104 (5.24)	.218
Diabetes, n (%)	423 (21.32)	697 (20.76)	.628	423 (21.32)	430 (21.67)	.787
COPD, n (%)	333 (16.78)	151 (4.5)	<.001	333 (16.78)	150 (7.56)	<.001
Renal disease, n (%)	358 (18.04)	553 (16.47)	.140	358 (18.04)	373 (18.8)	.539
Cancer, n (%)	173 (8.72)	185 (5.51)	<.001	173 (8.72)	167 (8.42)	.734
Atrial fibrillation, n (%)	462 (23.29)	787 (23.44)	.896	462 (23.29)	485 (24.45)	.392
Valvular heart disease, n (%)	315 (15.88)	560 (16.68)	.443	315 (15.88)	351 (17.69)	.126
Obesity, n (%)	235 (11.84)	598 (17.81)	<.001	235 (11.84)	245 (12.36)	.345
Coagulopathy, n (%)	26 (1.31)	42 (1.25)	.852	26 (1.31)	26 (1.31)	.999
Inferior vena cava filter	15 (0.76)	30 (0.89)	.595	15 (0.76)	24 (1.21)	.148
Undergone surgery, n (%)	36 (1.81)	62 (1.85)	.932	36 (1.81)	34 (1.71)	.809
Thrombolytic therapy, n (%)	108 (5.44)	177 (5.27)	.788	108 (5.44)	110 (5.54)	.889
Massive PE, n (%)	121 (6.10)	165 (4.92)	.063	121 (6.10)	109 (5.49)	.415
LOHS, median (IQR)	9 (7)	9 (7)	.073	9 (7)	9 (7)	.120
IHM, n (%)	250 (12.60)	397 (11.83)	.402	250 (12.60)	187 (9.48)	<.001

AMI, acute myocardial infarction; CCI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; IHM, in-hospital mortality; IQR, inter quartile range; LOHS, length on hospital stay; PVD, peripheral vascular disease; SD, standard deviation. *P* value for comparison of men with heart failure (HF) vs women with HF.

and sex, the risk of dying in the hospital was significantly associated with higher age and with a higher number of CCI conditions.

Atrial fibrillation and massive PE were positively associated with a higher IHM. However, obesity was associated with lower IHM.

Among women with HF, those who had a surgery coded in their discharge report had a higher risk of dying in the hospital (OR 2.43; 95% CI 1.31-4.53).

Finally, when we analysed the effect of HF for men and women, we found that this condition increased the IHM by 78% (OR 1.78; 95% CI 1.42-2.22) among men and by 58% (OR 1.58; 95% CI 1.33-1.87) among women.

The results of the multivariable logistic regression confirmed that, among patients suffering PE and HF, men had a higher IHM than women (OR1.23; 95% CI 1.03-1.63).

4 | DISCUSSION

Using administrative data from SNHDD, we demonstrated a higher incidence of PE among the HF population than among non-HF subjects. During PE admission, we identify that 11.4% had a history of HF. In this way, Ne et al detected not only a high prevalence of congestive HF in patients admitted with PE but also a high incidence for subsequent HF hospitalisation after an acute episode of PE.[24] The mechanisms responsible for this association are thought to be associated with decreased left ventricular function and reduced ejection fraction, increased venous stasis and chronic inflammation in the cardiovascular system.[25]

Our results are consistent with previous studies that indicate that the risk of VTE is higher in HF hospitalised patients than in those matched without HF. So, Beemath et al[26] found that HF diagnosis was associated with an increased relative risk of VTE from 1979 to 2003, with the greatest excess risk in younger patients, individual of black race and women with HF.

Women were overrepresented among patients with PE and HF. In fact, HF is more frequent in this sex in patients with preserved ejection fraction.[27] Melgaard et al[15] also demonstrated, among incident heart failure patients, that women had a higher risk of PE compared with men. Furthermore, women with HF had a higher mean age, but a lower prevalence of vascular disease and diabetes. We

TABLE 5 Multivariable analysis using logistic regression to identify variables associated with in-hospital mortality for patients hospitalised for pulmonary embolism (PE) according to sex and heart failure (HF) status in Spain from 2016 to 2018

	Men			Women			
	HF	Non-HF	Both	HF	Non-HF	Both	Both sex with HF
Variable	OR (CI 95%)	OR (CI 95%)	OR (CI 95%)	OR (CI 95%)	OR (CI 95%)	OR (CI 95%)	OR (CI 95%)
18-64 years	1	1	1	1	1	1	1
65-79 years	1.67 (1.07-3.21)	1.73 (1.19-5.61)	1.66 (1.15-2.85)	3.12 (1.69-6.08)	1.49 (1.02-4.14)	1.97 (1.22-3.79)	2.22 (1.01-4.92)
80 years or over	3.22 (1.29-6.04)	2.68 (1.61-7.7)	3.1 (1.43-6.73)	6.02 (1.35-10.91)	2.24 (1.15-8.02)	4.17 (2.44-9.11)	3.83 (1.73-8.46)
CCI 0	1	1	1	1	1	1	1
CCI 1-2	1.86 (1.32-2.62)	1.5 (0.97-2.3)	1.71 (1.31-2.23)	1.57 (1.24-1.98)	1.81 (1.35-2.42)	1.66 (1.39-1.99)	1.88 (1.48-2.39)
CCI >2	2.38 (1.44-3.92)	2.43 (1.37-4.3)	2.46 (1.69-3.58)	2.31 (1.44-3.7)	2.43 (1.35-4.37)	2.36 (1.63-3.4)	2.6 (1.78-3.79)
Atrial fibrillation	1.44 (1.06-1.96)	1.46 (1-2.14)	1.44 (1.13-1.82)	1.37 (1.08-1.74)	1.56 (1.18-2.07)	1.46 (1.22-1.75)	1.35 (1.08-1.68)
Obesity	0.4 (0.22-0.73)	0.64 (0.33-1.25)	0.49 (0.31-0.77)	0.56 (0.4-0.79)	0.53 (0.34-0.82)	0.54 (0.42-0.71)	0.42 (0.27-0.66)
Undergone surgery	NS	NS	NS	2.43 (1.31-4.53)	NS	1.66 (1.02-2.71)	1.86 (1.01-3.47)
Heart failure	NA	NA	1.78 (1.42-2.22)	NA	NA	1.58 (1.33-1.87)	NA
Men	NA	NA	NA	NA	NA	NA	1.23 (1.03-1.63)

CCI, Charlson Comorbidity Index; CI, confidence interval; HF, heart failure; NA, not applicable; NS, not significant; OR, odds ratio.

also found that women with heart failure had an older mean age than men with this disease, as well as a lower ICC, with an inferior prevalence of peripheral vascular disease, acute myocardial infarction and chronic obstructive pulmonary disease.

Not surprisingly, after PSM and logistic regression analysis, the IHM was higher among patients with PE and HF than in those without HF in our study. HF patients have poor reserve and are less likely to tolerate thromboembolic events.[8] So, these patients could be unable to tolerate the hemodynamic and ventilatory demands of PE because of baseline pulmonary hypertension and right ventricular dysfunction.[28] In fact, PE may be the primary cause of death in 3% to 10% of patients with HF.[29] In this way, Darze et al[9] also demonstrated that PE complicates the hospital outcomes of patients with severe HF, increasing the LOHS and the chance of death or readmissions at 3 months. In any case, in a large US inpatient database sample over 14 years, Basnet et al[30] identified a decrease in the trend of mortality among HF hospitalisations associated with PE.

HF men and women had higher massive PE, LOHS and IHM than non-HF men and women. As we have previously commented, patients with HF have an increased risk of developing PE and they have an underlying compromised cardiopulmonary reserve. In addition, massive PE occurs more likely among inpatients with underlying cardiopulmonary disease and it can lead to impaired right ventricular function, dilatation of the right ventricle and myocardial ischemia, which could lead to an additional worsening of left ventricular function and cardiac output. As consequence of their higher mortality rate, these patients may require more aggressive strategies of PE prevention.[31]

Women with HF who suffered a PE had lower IHM than men with this same condition. Based on health insurance claims databases of more than 25.000 patients with congestive HF, Gürgöze et al[32] also showed that overall men had a worse prognosis compared with women. Just as women are more likely to develop HF with a preserved ejection fraction, men are more likely to have HF with a reduced ejection fraction and thus poorer outcomes.[33]

Variables associated with IHM for both sexes were older age, higher CCI, atrial fibrillation and surgery (only in women with HF) while obesity had a protective effect. Previous researches have shown that factors such as higher age and the presence of comorbidities increase the risk of mortality in HF patients.[34] On the other hand, our findings confirm the existence of an "obesity paradox" among patients with HF. Previously, it has been also demonstrated that higher body mass index (BMI) is associated with lower in-hospital mortality risk.[35] The underlying mechanisms of this phenomenon are not known. A potential explanation is that the increased cardiac output and myocardial demands, besides the higher prevalence of endothelial dysfunction, may cause obese patients to be diagnosed with HF at an earlier stage than patients with lower BMI. Another possibility can be the presence of cardiac cachexia, which would appear in patients with advanced HF and it is characterised by significant weight loss in the absence of peripheral oedema.[36]

The main strength of this study is that we used a large nationwide database, representing an enormous number of hospitalisations in

Spain. Thus, it is a more real-world representation of hospitalised patients than population included in other types of studies. However, our study also has limitations that must be acknowledged. First, the diagnosis of PE was based on administrative data, which depends on the quality of medical coding and may be subject to coding errors and loss of medical nuance. According to the SNHDD methodology additional diagnoses, including risk factors such as tobacco or alcohol use are coded only if they affect the patient's treatments received, investigations required and/or resources used during the hospital stay. Thus, the utility of the SNHDD for these risk factors is low and therefore we decided not to analyse them. Secondly, measures of HF severity were not available from this database. Nor did we have data on baseline medications and the concurrent use of anticoagulants and/or antiplatelet therapy. Finally, we cannot exclude the possibility of unmeasured confounders that might not have been included in the multivariable models performed in this analysis.

In conclusion, the current study demonstrates that incidence and mortality of PE are higher in HF patients than in those without HF. Women are overrepresented among patients with PE and HF but they have lower IHM than men with these conditions. Variables associated with IHM in both sexes include older age, increased comorbidity and atrial fibrillation while obesity has a protective effect. These data highlight the need to improve strategies to prevent the development of PE in patients with HF and reduce the mortality of this population, taking into account the existing differences by sex.

DISCLOSURES

None.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are derived from the Hospital Discharge Database of the Spanish National Health System, as stated in the Methods section. The analysis that supports the findings of this study is available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.

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