

Original Research

Trends and sex differences in atrial fibrillation among patients hospitalized due to asthma: Insights from a nationwide population-based discharge database in Spain, 2016–2021



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ABSTRACT

Aims: To analyze changes in the prevalence of atrial fibrillation (AF) in patients hospitalized due to asthma; to compare hospital outcomes in asthma patients with and without AF, assessing sex differences; to identify variables associated with the presence of AF; and to analyze the factors associated with in-hospital mortality (IHM) among asthma patients with AF.

Methods: We used data from the Registry of Specialized Care Activity-Basic Minimum Data Set to select all patients aged ≥ 40 years with an asthma diagnosis in Spain, from 2016 to 2021. We stratified the study population according to the presence of AF and sex.

Results: We identified 65,233 hospitalizations that met the inclusion criteria (14.85 % with AF). The prevalence of AF significantly increased over time, with the male sex being a protective factor for its presentation. IHM were significantly higher in patients with AF. Older age, being a woman, congestive heart failure, renal disease, obstructive sleep apnea, hypertension, and hyperthyroidism were associated with the presence of AF. Advanced age and the presence of cancer and COVID-19 were factors associated with a higher IHM, as well as admission to an intensive care unit and the use of invasive mechanical ventilation. There were no association of sex with the IHM.

Conclusions: AF is highly prevalent among subjects hospitalized due to asthma, with this prevalence having increased significantly in Spain over time. The presence of AF in patients with asthma was associated significantly with a higher LOHS and IHM. Sex was not associated with IHM in these patients.

1. Introduction

Asthma is a common chronic airway inflammatory disease, characterized by reversible airway obstruction [1]. It often starts in childhood and is a major cause of morbidity in adulthood [2]. Its prevalence is increasing in many countries [3], leading to a major global medical and economic burden [4].

Atrial fibrillation (AF) is the most common sustained arrhythmia worldwide and the most common arrhythmia for which the patients are hospitalized [5]. It is emerging as a growing epidemic [6] and is associated with marked morbidity, mortality and medical burden [7].

There is epidemiological evidence that supports the existence of an association between asthma and AF [8]. A study in Taiwan found that people with asthma treated with controller medications were 1.2 times more likely to develop AF [9]. On the other hand, a Norwegian study

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Abbreviations

AF	Atrial fibrillation
CCI	Charlson Comorbidity Index
ICD-10	International Classification of Diseases, Tenth Revision
IHM	in-hospital mortality
LOHS	length of the hospital stay
PSM	Propensity score matching
RAE-CMBD	Registry of Specialized Care Activity-Basic Minimum Data Set

also detected an association between a history of asthma diagnosed by a doctor and incident AF, as well as an increased risk of incident AF in patients with uncontrolled asthma [10]. On the contrary, administrative data from National Health Services hospitals in England found no association of asthma with AF [11]. Finally, in the Multi-Ethnic Study of Atherosclerosis, an association was found between persistent asthma and incident AF in models adjusted for risk factors [12].

Underlying mechanism driving increased AF risk among individuals with asthma has not yet been defined. Elevated levels of biomarkers of systemic inflammation have been reported in adults with uncontrolled asthma and in patients with AF [13,14]. In addition, short-acting and long-acting β 2-agonists, the most common prescribed medications to relieve asthma symptom, have been shown to influence heart rate and increase the risk of arrhythmias [15]. Current use of corticosteroids, either oral or inhaled, has also independently associated with a higher risk of AF, in patients with asthma [7,16]. Other plausible mechanisms include dysfunction of the airway autonomic nervous system, that may be involved in the airway hyperresponsiveness observed in patients with asthma [17].

However, there is a paucity of research investigating the association between asthma and AF [18]. Our study aimed to investigate changes in the prevalence of AF in patients hospitalized due to asthma in Spain over the period from 2016 to 2021. We described and compared clinical characteristics and hospital outcomes in asthma patients, with and without AF, assessing sex differences. We also identified variables independently associated with the presence of AF in men and women hospitalized due to asthma. Lastly, we analyzed the factors associated with in-hospital mortality (IHM) among those asthma patients admitted with AF.

2. Methods

2.1. Study design, study population, and data assessment

An observational, retrospective, population-based study was conducted, using data gathered from the hospital discharge reports of the Registry of Specialized Care Activity-Basic Minimum Data Set (RAE-CMBD, its acronym in Spanish) in Spain. The RAE-CMBD assembles information regarding age, sex, admission and discharge dates, the discharge destination (home, death, social institution, or voluntary discharge), as well as up to 20 diagnoses and 20 procedures performed during hospitalization in both public and private Spanish hospitals. The RAE-CMBD collects data of patients who are hospitalized in a medical or surgical services, including intensive care units, for at least 24 h. Those patients that are treated only at the emergency departments and not moved to a hospital room are not included in the database. Further details about the RAE-CMBD can be found online [19].

This study period was from January 1, 2016, to December 31, 2021. Discharge reports were coded according to the International Classification of Diseases, Tenth Revision (ICD-10).

The study population included patients aged ≥ 40 years who had an asthma code in the primary position of the diagnostic fields, either with

or without exacerbation. In line with the RAE-CMBD methodology, the primary diagnosis is that which, at the time of discharge, is considered by the attending physician as the principal cause that occasioned the patient's hospitalization. Subjects with asthma for whom the variables sex, age, admission and/or discharge dates, and discharge destination were not recorded, were excluded.

We stratified the study population according to the presence of AF and sex. Patients were considered to suffer AF if a ICD10 code for this condition was recorded in any of the diagnostic fields (2-20). We excluded 361 patients who had a code for AF with a present on admission indicator (POA) of "No" or "Unknown".

Comorbidity was assessed using the Charlson Comorbidity Index (CCI) modified for use with the ICD10, as previously described by other authors [20,21].

Study covariables included the presence of COVID-19 (only for the years 2020 and 2021), pneumonia, influenza, obesity, obstructive sleep apnea, gastroesophageal reflux disease, anxiety, depression, hypertension, hypothyroidism, hyperthyroidism, bronchiectasis, and smoking. We also described the use of invasive and non-invasive mechanical ventilation. All ICD10 codes to identify these diagnoses and procedures are detailed in [Supplementary Table 1](#).

Regarding hospitalization outcomes, we analyzed admission to the intensive care unit, the length of the hospital stays (LOHS), and IHM.

2.2. Propensity score matching

Propensity score matching (PSM) was utilized to generate comparable populations based on age, year of admission, and comorbidities present at hospital admission. The two PSM analyses performed were as follows: women with and without AF, and men with and without AF. Multivariable logistic regression was employed for the PSM as previously described by Austin [22].

2.3. Statistical analysis

The prevalence of AF in patients with asthma was calculated, and further broken down by year and sex.

A descriptive analysis was carried out, in which categorical variables were expressed as absolute frequencies and percentages, and continuous variables as means with standard deviations or as medians and interquartile ranges, depending on whether or not the variable conformed to normality.

Temporal trends were analyzed using the Cochran-Mantel-Haenszel, Cochran-Armitage, linear regression *t*-test, or Jonckheere-Terpstra tests, depending on the type of variable.

Categorical variables were compared using Fisher's exact test, and continuous variables were compared using the *t*-test or the Mann-Whitney test, as required.

To analyze the factors associated with the presence of AF among patients hospitalized due to asthma, multivariable logistic regression was used, considering the effect of sex and the rest of the study covariables.

Likewise, using this same statistical technique, we identified the factors associated with IHM in women and men with asthma and AF and the effect of AF on IHM.

2.4. Ethics

In Spain, the Ministry of Health is responsible for the maintenance and management of the RAE-CMBD. The researchers must submit a request explaining the objectives of the research and the data needed, and then Ministry evaluates it and, if considered ethically acceptable and clinically relevant, supplies the database [23]. According to Spanish legislation, it is not necessary for patients to provide written consent as this registry is mandatory, and anonymity is always guaranteed.

3. Results

Between 2016 and 2021 in Spain, there were 65,233 hospitalizations of patients aged ≥ 40 years who had an asthma code in the first diagnosis position. Of these, 14.85 % (n = 9688) had an AF code.

3.1. Time trends in the prevalence of atrial fibrillation in patients hospitalized due to asthma

The overall prevalence of AF among subjects hospitalized due to asthma in Spain significantly increased between 2016 and 2021 (13.91 % vs. 14.09 %), as reflected in Fig. 1. It is observed that the prevalence of AF increased in women throughout the study period (16.74 % vs. 18.55 %; $p < 0.001$), while it decreased in men (13.57 % vs. 9.55 %; $p < 0.001$). As can be seen in Fig. 1, the prevalence of AF showed higher values in women than in men in all study years.

Characteristics, clinical variables, and hospital outcomes in patients due to asthma according to the presence of atrial fibrillation.

As indicated in Table 1, women make up a higher percentage among those suffering from AF than among those who do not suffer from this arrhythmia (84.93 % vs. 79.72 %; $p < 0.001$), with the opposite effect being observed among men (15.07 % vs. 20.38 %; $p < 0.001$).

Patients with AF had a higher mean age (80.47 years vs. 67.9 years; $p < 0.001$) and more comorbidity according to the CCI (2.42 vs. 1.7; $p < 0.001$) than those without AF. Similarly, patients with AF had significantly higher frequency of codes for the following diseases: pneumonia, obesity, obstructive sleep apnea, hypertension, hypothyroidism, and hyperthyroidism. However, they had significantly lower frequency of COVID-19, influenza, gastroesophageal reflux disease, anxiety, depression, bronchiectasis, and smoking.

The frequency of non-invasive mechanical ventilation was higher in patients with AF than in those without AF (2.69 % vs. 2.22 %; $p = 0.004$), while the frequency of invasive mechanical ventilation was lower in those with AF (0.6 % vs. 1.11 %; $p < 0.001$).

The highest frequency of admission to the intensive care unit corresponded to patients without AF (2.58 % vs. 1.8 %; $p < 0.001$). The median LOHS was significantly longer in patients with AF (7 days vs. 6 days; $p < 0.001$). The crude IHM was three times higher in patients with AF than those who do not have this pathology (4.13 % vs. 1.36 %; $p < 0.001$).

Comparison of characteristics, clinical variables, and hospital outcomes in women and men hospitalized due to asthma according to atrial fibrillation status.

The total number of asthma admissions among women showed a very significant decrease, practically by half, in 2020 and 2021 compared to the previous four years, as seen in Table 2.

Among women with asthma, those with AF have a mean age, eleven

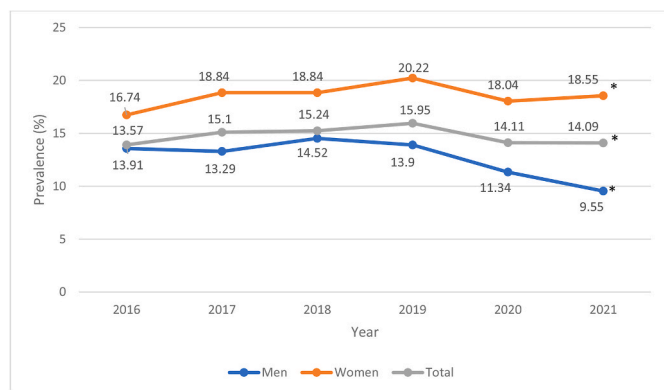


Fig. 1. Time trend in the prevalence of atrial fibrillation among patients hospitalized with a primary diagnosis of asthma in Spain (2016–2021) * $P < 0.001$ for time trend from 2016 to 2021.

Table 1

Distribution of study covariates and hospital outcomes for people hospitalized with asthma in Spain (2016–2021), according to the presence of atrial fibrillation.

	Atrial fibrillation		p-value
	YES	NO	
Women, n (%)	8228 (84.93)	44278 (79.72)	<0.001
Age, mean (SD)	80.47(8.65)	67.9(15.01)	<0.001
40–54 years old, n (%)	114(1.18)	13317 (23.98)	<0.001
55–69 years old, n (%)	914(9.43)	14267 (25.69)	
70–84 years old, n (%)	5256 (54.25)	19589 (35.27)	
≥ 85 years old, n (%)	3404 (35.14)	8372(15.07)	
CCI, mean (SD)	2.42(1.41)	1.7(1.17)	<0.001
Myocardial infarction, n (%)	300(3.1)	920(1.66)	<0.001
Congestive heart failure, n (%)	3879 (40.04)	5512(9.92)	<0.001
Peripheral vascular disease, n (%)	248(2.56)	797(1.43)	<0.001
Cerebrovascular disease, n (%)	351(3.62)	1045(1.88)	<0.001
Dementia, n (%)	382(3.94)	1396(2.51)	<0.001
Diabetes mellitus, n (%)	3023(31.2)	11627 (20.93)	<0.001
Rheumatoid disease, n (%)	302(3.12)	1369(2.46)	<0.001
Mild/moderate/severe liver disease, n (%)	332(3.43)	2199(3.96)	0.012
Renal disease, n (%)	1888 (19.49)	4140(7.45)	<0.001
Cancer and metastatic cancer, n (%)	291(3)	1225(2.21)	<0.001
COVID-19, n (%)	21(0.22)	286(0.51)	<0.001
Pneumonia, n (%)	442(4.56)	1856(3.34)	<0.001
Influenza, n (%)	143(1.48)	1113(2)	<0.001
Tobacco use, n (%)	1017(10.5)	15094 (27.17)	<0.001
Obesity, n (%)	2140 (22.09)	11510 (20.72)	0.002
Obstructive sleep apnea, n (%)	1256 (12.96)	6211(11.18)	<0.001
Gastroesophageal reflux disease, n (%)	332(3.43)	3128(5.63)	<0.001
Anxiety, n (%)	474(4.89)	4010(7.22)	<0.001
Depression, n (%)	579(5.98)	3793(6.83)	<0.001
Hypertension, n (%)	3921 (40.47)	20994(37.8)	<0.001
Hypothyroidism, n (%)	993(10.25)	4722(8.5)	<0.001
Hyperthyroidism, n (%)	261(2.69)	680(1.22)	<0.001
Bronchiectasis, n (%)	489(5.05)	3108(5.6)	0.029
Invasive lung ventilation, n (%)	58(0.6)	615(1.11)	<0.001
Non-invasive lung ventilation, n (%)	261(2.69)	1233(2.22)	0.004
Admission to Intensive Care Unit, n (%)	174(1.8)	1435(2.58)	<0.001
LOHS, median (IQR)	7(6)	6(5)	<0.001
IHM, n (%)	400(4.13)	758(1.36)	<0.001

SD Standard deviation; CCI: Charlson comorbidity index; LOHS: Length of hospital stay; IQR Inter quartile range; IHM: In-hospital mortality.

years higher, than those who do not have AF. Also, the prevalence of most concomitant conditions is higher, being remarkable the differences for congestive heart failure (41.35 % vs. 10.91 %), diabetes mellitus (32.04 % vs. 21.92 %), and renal disease (19.54%vs. 8.06 %) (all $p < 0.001$). The crude IHM found was 4.16 % and 1.44 % for women with and without AF, respectively.

After performing the PSM, the IHM remained above among women with AF (4.16 % vs. 3.06 %; $p < 0.001$), as indicated in Table 2.

Like it was found among women, the number of asthma admissions dropped dramatically in the years of the COVID19 pandemic among men.

The mean age of men with AF was sixteen years higher than that of men without AF ($p < 0.001$). Also, the prevalence of almost all studied comorbidities is much higher. The raw IHM was 3.97 % among those with AF and 1.08 % among those without ($p < 0.001$).

After matching using the PSM, the IHM remained significantly higher

Table 2

Distribution of study covariates and hospital outcomes for women with asthma in Spain (2016–2021), according to the presence of atrial fibrillation before and after propensity score matching (PSM).

	Atrial fibrillation before PSM			Atrial fibrillation after PSM		
	YES	NO	p-value	YES	NO	p-value
Year 2016, n(%)	1432(17.4)	8556(19.32)	<0.001	1432(17.4)	1447(17.59)	0.974
Year 2017, n(%)	1661(20.19)	8816(19.91)		1661(20.19)	1644(19.98)	
Year 2018, n(%)	1702(20.69)	9036(20.41)		1702(20.69)	1719(20.89)	
Year 2019, n(%)	1724(20.95)	8525(19.25)		1724(20.95)	1701(20.67)	
Year 2020, n(%)	871(10.59)	4828(10.9)		871(10.59)	895(10.88)	
Year 2021, n(%)	838(10.18)	4517(10.2)		838(10.18)	822(9.99)	
Age, mean (SD)	80.79(8.46)	69.4(14.67)	<0.001	80.79(8.46)	80.68(9)	0.418
40–54 years old, n (%)	81(0.98)	8920(20.15)	<0.001	81(0.98)	79(0.96)	0.008
55–69 years old, n (%)	732(8.9)	11345(25.62)		732(8.9)	709(8.62)	
70–84 years old, n (%)	4405(53.54)	16520(37.31)		4405(53.54)	4216(51.24)	
≥85 years old, n (%)	3010(36.58)	7493(16.92)		3010(36.58)	3224(39.18)	
CCI, mean (SD)	2.43(1.4)	1.73(1.17)	<0.001	2.43(1.4)	2.41(1.41)	0.457
Myocardial infarction, n (%)	220(2.67)	649(1.47)	<0.001	220(2.67)	195(2.37)	0.214
Congestive heart failure, n (%)	3402(41.35)	4832(10.91)	<0.001	3402(41.35)	3245(39.44)	0.013
Peripheral vascular disease, n (%)	168(2.04)	585(1.32)	<0.001	168(2.04)	158(1.92)	0.576
Cerebrovascular disease, n (%)	287(3.49)	867(1.96)	<0.001	287(3.49)	277(3.37)	0.668
Dementia, n (%)	343(4.17)	1263(2.85)	<0.001	343(4.17)	377(4.58)	0.195
Diabetes mellitus, n (%)	2636(32.04)	9704(21.92)	<0.001	2636(32.04)	2672(32.47)	0.548
Rheumatoid disease, n (%)	276(3.35)	1236(2.79)	0.005	276(3.35)	246(2.99)	0.182
Mild/moderate/severe liver disease, n (%)	276(3.35)	1703(3.85)	0.031	276(3.35)	266(3.23)	0.662
Renal disease, n (%)	1608(19.54)	3568(8.06)	<0.001	1608(19.54)	1617(19.65)	0.860
Cancer and metastatic cancer, n (%)	210(2.55)	913(2.06)	0.005	210(2.55)	195(2.37)	0.450
COVID 19, n (%)	18(0.22)	200(0.45)	0.003	18(0.22)	33(0.4)	0.035
Pneumonia, n (%)	355(4.31)	1397(3.16)	<0.001	355(4.31)	329(4)	0.310
Influenza, n (%)	113(1.37)	876(1.98)	<0.001	113(1.37)	114(1.39)	0.947
Tobacco use, n (%)	541(6.58)	9894(22.35)	<0.001	541(6.58)	445(5.41)	0.002
Obesity, n (%)	1921(23.35)	9991(22.56)	0.119	1921(23.35)	1963(23.86)	0.441
Obstructive sleep apnea, n (%)	996(12.11)	4735(10.69)	<0.001	996(12.11)	999(12.14)	0.943
Gastroesophageal reflux disease, n (%)	279(3.39)	2644(5.97)	<0.001	279(3.39)	255(3.1)	0.291
Anxiety, n (%)	434(5.27)	3614(8.16)	<0.001	434(5.27)	434(5.27)	1.000
Depression, n (%)	548(6.66)	3528(7.97)	<0.001	548(6.66)	572(6.95)	0.458
Hypertension, n (%)	3362(40.86)	17736(40.06)	0.172	3362(40.86)	3402(41.36)	0.526
Hypothyroidism, n (%)	943(11.46)	4499(10.16)	<0.001	943(11.46)	879(10.68)	0.112
Hyperthyroidism, n (%)	238(2.89)	606(1.37)	<0.001	238(2.89)	220(2.67)	0.394
Bronchiectasis, n (%)	386(4.69)	2457(5.55)	0.002	386(4.69)	372(4.52)	0.603
Invasive lung ventilation, n (%)	41(0.5)	423(0.96)	<0.001	41(0.5)	47(0.57)	0.521
Non-invasive lung ventilation, n (%)	232(2.82)	978(2.21)	0.001	232(2.82)	209(2.54)	0.267
Admission to Intensive Care Unit, n (%)	141(1.71)	1032(2.33)	0.001	141(1.71)	127(1.54)	0.389
LOHS, median (IQR)	7(7)	6(6)	<0.001	7(6)	6(5)	<0.001
IHM, n (%)	342(4.16)	636(1.44)	<0.001	342(4.16)	252(3.06)	<0.001

SD Standard deviation; CCI: Charlson comorbidity index; LOHS: Length of hospital stay; IQR Inter quartile range; IHM: In-hospital mortality.

among men who had AF (3.97 % vs. 2.26 %; $p = 0.008$), as seen in [Table 3](#).

Variables associated with presenting atrial fibrillation in women and men hospitalized due to asthma.

As shown in [Table 4](#), after multivariable adjustment, older age, congestive heart failure, renal disease, obstructive sleep apnea, hypertension, and hyperthyroidism were associated with the presence of AF in men and women hospitalized due to asthma.

Peripheral vascular disease was associated with the presence of AF (OR 1.48, 95%CI 1.11–1.97) only among in men. However, in women, the variables that were also associated with the presence of AF included cerebrovascular disease (OR 1.17; 95%CI 1.02–1.36), diabetes (OR 1.22; 95%CI 1.151–1.29), pneumonia (OR 1.19; 95%CI 1.05–1.36), and hypothyroidism (OR 1.12; 95%CI 1.03–1.21).

When the entire database was analyzed, and after controlling the effect to age and other covariates, being a woman was associated with a 15 % higher probability of presenting an AF diagnosis than being a man (OR 1.15; 95 % CI 1.08 1.23).

Variables associated with in-hospital mortality in patients hospitalized due to asthma who also suffer atrial fibrillation.

As seen in [Table 5](#), for men and women with asthma and AF, advanced age and the presence of cancer and COVID-19 were factors associated with a higher IHM. Likewise, having received invasive lung ventilation and having been admitted to the intensive care unit were

associated with the risk of death.

In women with asthma and AF, the presence of congestive heart failure, dementia, pneumonia, and bronchiectasis showed a significant association with the IHM.

When analyzing both sexes together, it is observed that there is no association of this variable with the IHM in subjects admitted due to asthma who also suffer from AF.

4. Discussion

In this nationwide population study, we found that the prevalence of AF among subjects hospitalized due to asthma was 14.85 %, a higher figure than that reported in the studies by Warnier et al. [24], Cepelis et al. [10] and Tattersall et al. [12] (0.6 %, 4.5%–6%, and 1.3 % respectively). The difference may be because these studies followed asthma patients in the clinic, who generally had mild disease compared to our hospitalized asthma patients. Furthermore, they found that arrhythmias were associated with disease severity [10]. However, the prevalence found in our study was also higher than that observed by Carter et al. [11] and Taha et al. [25] in hospitalized patients with asthma (4.1 % and 8.95 % respectively). The reason for this discrepancy is not clear, but it may be due to differences in associated comorbidities. Another possibility is that our study may overestimate the prevalence of AF by not recognizing patients with recurrent admissions, that was

Table 3

Distribution of study covariates and hospital outcomes for men with asthma in Spain (2016–2021), according to the presence of atrial fibrillation before and after propensity score matching (PSM).

	Atrial fibrillation before PSM			Atrial fibrillation after PSM		
	YES	NO	p-value	YES	NO	p-value
Year 2016, n(%)	264(18.08)	1945(17.26)	<0.001	264(18.08)	283(19.38)	0.75
Year 2017, n(%)	274(18.77)	2061(18.29)		274(18.77)	279(19.11)	
Year 2018, n(%)	323(22.12)	2225(19.75)		323(22.12)	325(22.26)	
Year 2019, n(%)	290(19.86)	2087(18.52)		290(19.86)	291(19.93)	
Year 2020, n(%)	174(11.92)	1535(13.62)		174(11.92)	149(10.21)	
Year 2021, n(%)	135(9.25)	1414(12.55)		135(9.25)	133(9.11)	
Age, mean (SD)	78.62(9.41)	62.03(14.85)	<0.001	78.62(9.41)	78.23(9.97)	0.278
40–54 years old, n (%)	33(2.26)	4397(39.03)	<0.001	33(2.26)	32(2.19)	0.011
55–69 years old, n (%)	182(12.47)	2922(25.93)		182(12.47)	178(12.19)	
70–84 years old, n (%)	851(58.29)	3069(27.24)		851(58.29)	775(53.08)	
≥85 years old, n (%)	394(26.99)	879(7.8)		394(26.99)	475(32.53)	
CCI, mean (SD)	2.4(1.48)	1.6(1.15)	<0.001	2.4(1.48)	2.37(1.47)	0.615
Myocardial infarction, n (%)	80(5.48)	271(2.41)	<0.001	80(5.48)	82(5.62)	0.872
Congestive heart failure, n (%)	477(32.67)	680(6.04)	<0.001	477(32.67)	414(28.36)	0.011
Peripheral vascular disease, n (%)	80(5.48)	212(1.88)	<0.001	80(5.48)	89(6.1)	0.476
Cerebrovascular disease, n (%)	64(4.38)	178(1.58)	<0.001	64(4.38)	62(4.25)	0.855
Dementia, n (%)	39(2.67)	133(1.18)	<0.001	39(2.67)	29(1.99)	0.220
Diabetes mellitus, n (%)	387(26.51)	1923(17.07)	<0.001	387(26.51)	409(28.01)	0.361
Rheumatoid disease, n (%)	26(1.78)	133(1.18)	0.052	26(1.78)	31(2.12)	0.504
Mild/moderate/severe liver disease, n (%)	56(3.84)	496(4.4)	0.317	56(3.84)	44(3.01)	0.222
Renal disease, n (%)	280(19.18)	572(5.08)	<0.001	280(19.18)	267(18.29)	0.538
Cancer and metastatic cancer, n (%)	81(5.55)	312(2.77)	<0.001	81(5.55)	92(6.3)	0.389
COVID 19, n (%)	3(0.21)	86(0.76)	0.016	3(0.21)	8(0.55)	0.131
Pneumonia, n (%)	87(5.96)	459(4.07)	0.001	87(5.96)	86(5.89)	0.938
Influenza, n (%)	30(2.05)	237(2.1)	0.903	30(2.05)	36(2.47)	0.455
Tobacco use, n (%)	476(32.6)	5200(46.15)	<0.001	476(32.6)	479(32.81)	0.906
Obesity, n (%)	219(15)	1519(13.48)	0.112	219(15)	188(12.88)	0.098
Obstructive sleep apnea, n (%)	260(17.81)	1476(13.1)	<0.001	260(17.81)	245(16.78)	0.463
Gastroesophageal reflux disease, n (%)	53(3.63)	484(4.3)	0.234	53(3.63)	54(3.7)	0.922
Anxiety, n (%)	40(2.74)	396(3.51)	0.126	40(2.74)	34(2.33)	0.480
Depression, n (%)	31(2.12)	265(2.35)	0.585	31(2.12)	27(1.85)	0.596
Hypertension, n (%)	559(38.29)	3258(28.92)	<0.001	559(38.29)	581(39.79)	0.404
Hypothyroidism, n (%)	50(3.42)	223(1.98)	<0.001	50(3.42)	42(2.88)	0.397
Hyperthyroidism, n (%)	23(1.58)	74(0.66)	<0.001	23(1.58)	17(1.16)	0.339
Bronchiectasis, n (%)	103(7.05)	651(5.78)	0.052	103(7.05)	99(6.78)	0.771
Invasive lung ventilation, n (%)	17(1.16)	192(1.7)	0.127	17(1.16)	10(0.68)	0.176
Non-invasive lung ventilation, n (%)	29(1.99)	255(2.26)	0.500	29(1.99)	39(2.67)	0.220
Admission to Intensive Care Unit, n (%)	33(2.26)	403(3.58)	0.009	33(2.26)	27(1.85)	0.434
LOHS, median (IQR)	6(6)	5(4)	<0.001	6(5)	6(5)	0.441
IHM, n (%)	58(3.97)	122(1.08)	<0.001	58(3.97)	33(2.26)	0.008

SD Standard deviation; CCI: Charlson comorbidity index; LOHS: Length of hospital stay; IQR Inter quartile range; IHM: In-hospital mortality.

described in the study by Taha et al. [25]. In any case, the association between asthma and AF might be explained by several mechanisms, including respiratory failure associated with asthma exacerbation [25], chronic systemic inflammation [26], whose level is higher in patients with persistent or uncontrolled asthma [27], and asthma therapy [7,28]. Unfortunately, our database does not contain information about medications used during hospitalization.

We also observed that the prevalence of AF among subjects hospitalized due to asthma in Spain significantly increased between 2016 and 2021, but only in women, while it decreased in men, expanding upon the data from previous studies in regard to the relationship between asthma and AF. Although previous studies have not assessed sex differences in hospitalization trends for patients with asthma and atrial fibrillation, there is epidemiological evidence of increasing prevalence of AF over time both on an age-adjusted and absolute basis, with slightly more hospitalizations in women than men, though this difference has been declining [5].

Furthermore, we demonstrated that being a man was a protective factor for presenting AF, suggesting a sex difference in the risk of AF among asthmatic patients. Other studies have also identified an effect modification by sex, where women with asthma have a higher risk of AF compared to those without asthma [12,25]. However, the precise mechanism of this association is not completely clear. In the same way, there is a significant sex disparity in asthma. During childhood, boys

have an increased prevalence of asthma, while in adulthood, women have a higher prevalence and severity of asthma, which is closely related to sex hormone differences [29].

After multivariable adjustment, older age, congestive heart failure, renal disease, obstructive sleep apnea, hypertension, and hyperthyroidism were associated with the presence of AF in men and women hospitalized due to asthma. Furthermore, peripheral vascular disease was associated with the presence of AF only among in men. However, in women, the variables that also were associated with the presence of AF were cerebrovascular disease, diabetes, pneumonia, and hypothyroidism. Other authors have also described that asthma patients with AF are also older and have a higher frequency of comorbidities as compared with those without AF [25]. Comorbidities that have been associated with a higher risk of arrhythmia include cardiac comorbidities and renal failure [25,30].

As previously described [25], hospitalized asthmatic patients with AF in our study were associated with higher LOHS and IHM. In fact, the crude IHM was three times higher in patients with AF than in those without this disease. For men and women with asthma and AF, advanced age and the presence of cancer and COVID-19 were factors associated with a higher IHM. In the study by Toha et al. [25], patients older than 65 years, male sex, and multiple comorbidities, such as acute respiratory failure, pneumonia, sepsis, acute myocardial infarction, chronic heart failure and renal failure, were also independent predictors of IHM in the

Table 4
Multivariable analysis of factors associated with presenting atrial fibrillation diagnosed among patients hospitalized with asthma in Spain (2016–2021), according to sex.

	Women OR(95%CI)	Men OR(95%CI)	Both OR(95%CI)
40–54 years old	1	1	1
55–69 years old	2.98(2.36–3.76)	3.55(2.43–5.17)	3.24(2.66–3.95)
70–84 years old	9.09(7.25–11.4)	13.06 (9.12–18.7)	10.38 (8.58–12.56)
≥85 years old	10.92 (8.68–13.74)	18.72 (12.84–27.3)	12.75 (10.49–15.49)
Congestive heart failure	3.46(3.26–3.66)	3.61(3.11–4.19)	3.47(3.29–3.66)
Peripheral vascular disease	NS	1.48(1.11–1.97)	NS
Cerebrovascular disease	1.17(1.02–1.36)	NS	1.2(1.05–1.36)
Diabetes mellitus	1.22(1.15–1.29)	NS	1.18(1.12–1.24)
Renal disease	1.29(1.19–1.39)	1.65(1.37–1.97)	1.34(1.25–1.44)
Pneumonia	1.19(1.05–1.36)	NS	1.19(1.06–1.33)
Obstructive sleep apnea	1.17(1.07–1.27)	1.57(1.33–1.87)	1.23(1.14–1.33)
Hypertension	1.06(1–1.12)	1.18(1.03–1.35)	1.08(1.02–1.13)
Hypothyroidism	1.12(1.03–1.21)	NS	1.12(1.04–1.22)
Hyperthyroidism	1.81(1.53–2.13)	1.7(1–2.9)	1.8(1.53–2.11)
Year 2016	1	1	1
Year 2017	NS	NS	1.1(1.02–1.18)
Year 2018	NS	NS	1.16(1.07–1.25)
Year 2019	NS	NS	1.18(1.09–1.27)
Year 2020	NS	NS	1.12(1.02–1.23)
Year 2021	NS	NS	NS
Men	NA	NA	1
Women			1.15 (1.08–1.23)

NA not applicable; NS: Not significant.

Table 5
Multivariable analysis of factors associated with in-hospital mortality during admission for patients with asthma in Spain (2016–2021), according to the presence of atrial fibrillation.

	Women OR(95%CI)	Men OR(95%CI)	Both Sex OR(95%CI)
40–69 years old	1	1	1
70–84 years old	4.95 (1.77–13.87)	NS	NS
≥85 years old	12.97 (4.6–36.58)	NS	10.13 (1.36–75.6)
Congestive heart failure	1.3(1.03–1.64)	NS	1.35 (1.09–1.68)
Dementia	1.78 (1.17–2.71)	NS	1.89 (1.29–2.79)
Cancer and metastatic cancer	1.92(1.1–3.34)	3.6(1.5–8.66)	2.22 (1.41–3.51)
COVID 19	7.01 (2.01–24.45)	NS	5.94 (1.87–18.84)
Pneumonia	2.1(1.41–3.13)	NS	1.91 (1.32–2.78)
Bronchiectasis	1.59(1–2.53)	NS	1.63 (1.08–2.46)
Invasive lung ventilation	4,33(2,85-6,57)	5.92 (1.23–28.59)	4,86(3,4–5,59)
Admission to Intensive Care Unit	3.11 (1.69–5.76)	10.82 (2.89–40.59)	3.66 (2.11–6.32)
Men	NA	NA	0.85 (0.62–1.16)

NA not applicable; NS: Not significant.

subgroup of asthmatic patients with arrhythmias. Likewise, as previously reported [25], having received invasive mechanical ventilation and having been admitted to the intensive care unit were also associated with the risk of death. By sexes, in women with asthma and AF, the presence of congestive heart failure, dementia, pneumonia, and

bronchiectasis showed a significant association with the IHM in our study. However, we found no association between IHM in subjects admitted due to asthma who also suffered from AF.

There are several limitations worth noting in this study. First, the RAE-CMBD has the possibility of coding errors as it is an administrative dataset. Misclassification in the diagnosis of asthma could have occurred. Second, data were extracted after only hospital admissions but not emergency department visits, so possibly, those patients with less severe asthma are not analyzed in our study. Third, information about the severity of asthma, the type of atrial fibrillation and the drugs used for treatment, like bronchodilators and corticosteroids, which might confound the association between arrhythmia and asthma, was not available in our database. Fourth, this study was limited to inpatient outcomes, not having follow-up data after discharge. Fifth, As commented in the methods section our study population only included patients with a primary diagnosis of asthma in their discharge report. In our opinion this means that possibly most of these patients had an asthma exacerbation when admitted to the hospital, but due to the limitations of RAE-CMBD this cannot be confirmed. However, previous epidemiological investigations have defined a primary diagnosis of asthma in hospital discharge data as an asthma exacerbation [31–33]. Sixth, in our investigation only patients with an AF prior to hospital admission were analyzed. Therefore, we did not analyze the very small proportion (0.6 %) of patients who developed AF during their hospital stay. Due to the very small number of these patients is unlikely that, if these patients were included, the results of the study would significantly change. Seventh, in our study we found an association between asthma and AF, but we could not determine if AF was caused by asthma, pneumonia or any other concomitant condition or infection. Finally, as the RAE-CMBD is anonymized, we cannot identify readmissions, and this could affect our results by overestimating the prevalence of AF.

In conclusion, by using a large database discharge, we demonstrated that AF is highly prevalent among subjects hospitalized due to asthma, with this prevalence having increased significantly in Spain between 2016 and 2021. The presence of AF in patients with asthma was associated significantly with a higher LOHS and IHM. Sex was not associated with IHM in these patients. Clinicians should improve the control of patients with asthma, as excessive use of medications prescribed to relieve asthma symptom can influence heart rate and increase the risk of arrhythmias. In addition, they should advise their patients with asthma to avoid risk factors for AF, such as not smoking, following a heart-healthy Mediterranean-style diet, being physically active and keeping to a normal weight. Finally, they should be aware of the association of asthma and AF, to diagnose it early and intervene on it, in order to improve the outcomes of patients with this association.

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Leon: Writing – original draft, Writing – review & editing. **David Carabantes-Alarcon:** Software, Writing – review & editing. **Ricardo Omaña-Palanco:** Validation, Writing – review & editing. **Valentín Hernández-Barrera:** Validation, Writing – review & editing. **Natividad Cuadrado-Corrales:** Conceptualization, Validation, Writing – original draft, Writing – review & editing.

Declaration of competing interest

All authors declare that they have none Conflict of Interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.rmed.2023.107508>.

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