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Trend from 2001 to 2015 in the prevalence of bronchiectasis among patients hospitalized for asthma and effect of bronchiectasis on the in-hospital mortality

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ABSTRACT

Objective: We aimed to analyze the prevalence of bronchiectasis among patients hospitalized with asthma and to assess the effect of suffering bronchiectasis on in-hospital mortality (IHM).

Methods: We used the Spanish National Hospital Discharge Database from 2000 to 2015 to evaluate all admissions for asthma exacerbation as the main diagnosis, dividing them according to the presence or absence of associated bronchiectasis. We assessed time trends in the prevalence, clinical characteristics, length of hospital stay, costs, and IHM.

Results: Of 342,644 admissions for asthma, 10,377 (3.02%) had bronchiectasis. The prevalence of bronchiectasis increased from 2.16% in 2001 to 4.47% in 2015 ($p < 0.001$). Compared to patients without bronchiectasis, those with bronchiectasis were more frequently women (77.06% vs. 22.94%, $p < 0.001$), were older (68.87 ± 15.16 vs. 47.05 ± 30.66 years, $p < 0.001$) and had more comorbid conditions (Charlson comorbidity index ≥ 2 : 9.45% vs. 6.58%, $p < 0.001$). *Pseudomonas* (8% vs. 0.66%, $p < 0.001$), *Aspergillus* (0.93% vs. 0.15%, $p < 0.001$), eosinophilia (0.29% vs. 0.17%, $p = 0.005$) and IHM (2.07% vs. 1.2%, $p < 0.001$) were more frequent in patients with bronchiectasis. After multivariable adjustments, IHM was not associated with bronchiectasis. The presence of bronchiectasis was associated with a longer length of hospital stay and higher costs.

Conclusions: Admissions for asthma with bronchiectasis have increased over time in Spain. In our investigation, the presence of bronchiectasis was not associated with higher IHM, but it increased the length of hospital stay and costs.

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Introduction

Bronchiectasis is the third-most common chronic inflammatory disease of the airway, after asthma and chronic obstructive pulmonary disease (COPD) (1). An increasing body of literature has shown that the association between COPD and bronchiectasis is a frequent phenomenon leading to more exacerbations and worse prognosis (2,3). There is less evidence on the association between asthma and bronchiectasis. The pathophysiological mechanisms by which the two diseases are linked are still not well established (1). Furthermore, in investigations of the different

etiologies of bronchiectasis, bronchial asthma accounts for a small percentage of cases, ranging from 1.4% to 5.4% according to the series (4–6).

In previous studies that have evaluated this prevalence of bronchiectasis in asthmatic patients, highly variable percentages have been obtained, ranging from 2% to 80% of cases, due in part to the different methodologies used (7–13). On the other hand, although the presence of bronchiectasis seems to be related to a greater severity of asthma (14,15), the impact that its presence may have on the evolution of the disease is unknown (16).

Among the studies that have analyzed the association between asthma and bronchiectasis, few have

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been performed in hospitalized patients. In addition, great variability has been found in the results of these studies between different countries (10,17,18). Analyzing the trends and characteristics of hospitalizations for these diseases at a national level and comparing these results with those described in other countries could help improve their management. The National Hospital Discharge Database provides a large alternative information source to describe and analyze the trends and characteristics of hospitalization for asthma with and without bronchiectasis at the national level.

In this study, we aim to (1) analyze the prevalence of bronchiectasis among patients hospitalized with asthma and to assess the effect of suffering bronchiectasis on in-hospital mortality (IHM) and (2) identify factors associated with in-hospital mortality (IHM) among patients hospitalized with asthma with and without concomitant bronchiectasis.

Methods

When discharging a hospitalized patient in the Spanish health system, physicians must declare all diagnoses made and procedures performed using the codes of the International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM). This information is collected in the Spanish National Hospital Discharge Database (SNHDD), which compiles data from almost all (>95%) hospitals in Spain (19). The SNHDD includes patient variables (gender, date of birth), admission, and discharge dates, up to 14 diagnoses at discharge and up to 20 procedures performed during the hospital stay.

Study population

We selected all hospital admissions in Spain from January 1, 2001, to December 31, 2015, that were recorded in the SNHDD for patients whose primary diagnosis was asthma (ICD-9-CM codes 493.xx).

We confirmed that all cases included in our study sample did not have another subject in the database with a code for asthma with the same age, gender, year of admission and hospital, as this would be the same patient. In this case, only the first admission was analyzed, and the second or posterior admissions were discharged. Our study population included 342,644 patients.

We stratified the database according to the presence of bronchiectasis (ICD-9-CM code 494) as a secondary diagnosis.

Clinical characteristics included age, gender and information on overall comorbidity at the time of hospitalization, which was assessed using the Charlson comorbidity index (CCI) (20). Patients were divided into three categories: patients with no previously recorded comorbidity, patients with one comorbidity and patients with two or more comorbidities.

Risk factors considered in the data analysis included current smoking (ICD-9-CM codes: 305.1 and V15.82), obesity (ICD-9-CM code 278.xx) and eosinophilia (ICD-9-CM code 288.3), recorded during hospitalization for asthma.

We analyzed pathogens documented during hospitalizations using the following ICD-9-CM codes: 481 for *Streptococcus pneumoniae*, 482.2 for *Haemophilus influenza*, 482.1 for *Pseudomonas aeruginosa*, 482.41 and 482.42 for *Staphylococcus aureus*, 117.3 for *Aspergillus*, 482.84 for *Legionella*, and 480.9 for virus.

Regardless of the position in the procedures coding list, we retrieved data about the following in-hospital procedures: computerized axial tomography of the thorax (ICD-9-CM code 87.41), bronchoscopy (ICD-9-CM codes 33.21–33.24), noninvasive mechanical ventilation (ICD-9-CM code 93.90), invasive mechanical ventilation (ICD-9-CM codes 96.7, 96.70, 96.71, 96.72), aerosol therapy (ICD-9-CM code 93.94), and oxygen therapy (ICD-9-CM code 93.96).

We estimated the readmission rate (patients who had been discharged from the same hospital within the previous 30 days) and the mean length of hospital stay (LOHS). We also estimated costs. Costs were calculated using diagnosis-related groups (DRGs) (21). All costs are inflation adjusted. Finally, we analyzed the IHM, defined as the proportion of patients who died during their hospital admission for each time period studied.

Statistical analysis

A descriptive statistical analysis was performed. Quantitative variables were expressed as the mean with standard deviation (SD). The normal distribution was checked for continuous variables (age, length of hospital stay, and costs) using the Kolmogorov-Smirnov normality test, and for these three variables, the p values was >0.05, so we accepted that these variables follow a normal distribution in our population.

Qualitative variables were expressed as frequencies and percentages. Comparisons were performed using the chi-square test, chi-square test for trend tests, Fisher's exact test, *t*-test, or ANOVA, as appropriate.

To assess the time trends in the prevalence, we analyzed each single year, but in the tables, the period

prevalence in three five-year periods is shown to make the tables easier to read. More detailed year-by-year data are shown in Supplementary Tables 1–4.

We used a Poisson regression model to assess changes in the prevalence of bronchiectasis among patients hospitalized for asthma exacerbation and in the IHM from 2001 to 2015 according to gender. To control for confounding factors, these models were adjusted by age, gender and CCI as appropriate. The results of the Poisson regression are shown as incidence rate ratios (IRR) with 95% confidence intervals.

Poisson regression is useful for modeling counts or events that occur randomly over a fixed period of time or in a fixed space. Often, it is useful when the probability of any particular incidence occurring is very small while the population is very large. The more important assumptions for Poisson regression are as follows: (i) the response variable is a count per unit of time or space; (ii) independence: the observations must be independent of one another; and (iii) the mean must be equal to variance (overdispersion). These assumptions were fulfilled in our investigation. To check the possible overdispersion of the Poisson model, we also performed a negative binomial regression model that allows us to check the magnitude of overdispersion with the alpha parameter. If alpha is zero or close to zero, we do not have overdispersion, and it would be better to use Poisson; if it is greater than zero, we would have to use a negative binomial regression model. In our case, the alpha was near zero and not significant, so we could assume that overdispersion would not invalidate the Poisson model.

Predictors of IHM among patients hospitalized for asthma exacerbation with and without bronchiectasis were identified using unconditional logistic regression analyses.

The multivariable models were built using the “enter modeling” method. The process included the following steps:

1. Each independent variable was analyzed using bivariate analysis.
2. For the selection of variables for the multivariable analysis, in the initial model, we included independent variables that showed a significant association with the dependent variable ($p < 0.10$) and those found scientifically relevant by other authors.
3. To fit the multivariable model, we used the Wald statistic (WS) to assess the importance of each variable; variables that we considered (according to this test) to not improve the model were deleted, and a new model was reanalyzed (expert

opinion method for independent variable selection). The likelihood ratio test was used to compare successive models with previous models.

4. Once the final model was fitted, we checked for collinearity and interactions between the remaining variables. The measure of association provided is the odds ratio (OR) with a 95% confidence interval.

Estimates were made using STATA version 14 (StataCorp LP, College Station, Texas, USA). Statistical significance was set at a 2-tailed alpha of 0.05.

Ethical aspects

Full data confidentiality was observed according to Spanish legislation. The Spanish Ministry of Health evaluated our study protocol, considered it to fulfill the ethical requirements of Spanish legislation, and provided us with the anonymous database.

In Spain, the retrospective use of de-identified registry data do not require ethical approval by an Ethics Committee or informed consent according to Spanish legislation (second paragraph, point 5 Order 3470/2009, 16 December and the Spanish Biomedical Investigation Law (14/2007, 3 June, article 2.e). We enclose as [supplementary data](#) the “No necessity report” from the Alcorcon Ethics Committee for investigation with the Spanish National Hospital Discharge Database (Conjunto Minimo Basico de Datos).

Results

In our study, we identified a total of 342,644 admissions with asthma as the primary diagnosis in Spain between 2001 and 2015. Of these, 10,377 patients (3.02%) had bronchiectasis as a secondary diagnosis. Patients with asthma and bronchiectasis included 7,997 women (77.06%).

Table 1 shows the characteristics of patients admitted to the hospital with asthma according to the presence or absence of concomitant bronchiectasis.

Female gender was predominant in both groups. In our study, the mean age was higher in patients with concomitant bronchiectasis than in those without (68.87 ± 15.16 vs. 47.05 ± 30.86 years, respectively, $p < 0.001$) and was associated with more comorbidities according to the CCI (for ≥ 2 comorbid conditions, 9.45% vs. 6.58%, respectively, $p < 0.001$). In contrast, the percentage of obesity was lower in the first group of patients (9.15% vs. 9.80%, respectively, $p = 0.025$).

Table 1. Characteristics of patients admitted to the hospital with asthma according to the presence or absence of concomitant bronchiectasis in Spain from 2001 to 2015.

Factors		Bronchiectasis		<i>p</i> -value
		No (<i>n</i> = 332,267)	Yes (<i>n</i> = 10,377)	
Gender, <i>N</i> (%)	Male	113,087 (34.03)	2,380 (22.94)	<0.001
	Female	219,180 (65.97)	7,997 (77.06)	
Age groups, <i>N</i> (%)	<40 years	131,178 (39.48)	579 (5.58)	<0.001
	40–64 years	65,551 (19.73)	2,415 (23.27)	
	65–74 years	48,772 (14.68)	2,870 (27.66)	
	≥75 years	86,766 (26.11)	4,513 (43.49)	
Age (years), mean (SD) median [minimum-maximum]		47.05(30.86) 46 [1–93]	68.87 (15.16) 70 [26–87]	<0.001
Charlson comorbidity index, <i>N</i> (%)	0	248,756 (74.87)	6,422 (61.89)	<0.001
	1	61,653 (18.56)	2,974 (28.66)	
	≥ 2	21,858 (6.58)	981 (9.45)	
Tobacco use, <i>N</i> (%)	No	281,401 (84.69)	8,734 (84.17)	0.144
	Yes	50,866 (15.31)	1,643 (15.83)	
Obesity, <i>N</i> (%)	No	299,639 (90.18)	9,427 (90.85)	0.025
	Yes	32,628 (9.82)	950 (9.15)	
<i>Pseudomonas aeruginosa</i> infection, <i>N</i> (%)	No	330,067 (99.34)	9,547 (92)	<0.001
	Yes	2,200 (0.66)	830 (8)	
<i>S. Pneumoniae</i> infection, <i>N</i> (%)	No	331,854 (99.88)	10,365 (99.88)	0.805
	Yes	413 (0.12)	12 (0.12)	
Legionella infection, <i>N</i> (%)	No	332,263 (100)	10,377 (100)	0.724
	Yes	4 (0)	0 (0)	
<i>S. Aureus</i> infection, <i>N</i> (%)	No	332,207 (99.98)	10,376 (99.99)	0.527
	Yes	60 (0.02)	1 (0.01)	
<i>H. Influenzae</i> infection, <i>N</i> (%)	No	332,217 (99.98)	10,376 (99.99)	0.656
	Yes	50 (0.02)	1 (0.01)	
Virus infection, <i>N</i> (%)	No	331,826 (99.87)	10,374 (99.97)	0.004
	Yes	441 (0.13)	3 (0.03)	
Aspergilosis infection, <i>N</i> (%)	No	331,761 (99.85)	10,280 (99.07)	<0.001
	Yes	506 (0.15)	97 (0.93)	
Thoracic computed tomography, <i>N</i> (%)	No	319,783 (96.24)	9,031 (87.03)	<0.001
	Yes	12,484 (3.76)	1,346 (12.97)	
Bronchoscopy, <i>N</i> (%)	No	329,843 (99.27)	10,179 (98.09)	<0.001
	Yes	2,424 (0.73)	198 (1.91)	
Invasive mechanical ventilation, <i>N</i> (%)	No	328,858 (98.97)	10,293 (99.19)	0.031
	Yes	3,409 (1.03)	84 (0.81)	
Noninvasive mechanical ventilation, <i>N</i> (%)	No	327,074 (98.44)	10,125 (97.57)	<0.001
	Yes	5,193 (1.56)	252 (2.43)	
Eosinophilia, <i>N</i> (%)	No	331,697 (99.83)	10,347 (99.71)	0.005
	Yes	570 (0.17)	30 (0.29)	
Aerosol therapy, <i>N</i> (%)	No	259,419 (78.08)	8,634 (83.2)	<0.001
	Yes	72,848 (21.92)	1,743 (16.8)	
Oxygen therapy, <i>N</i> (%)	No	259,658 (78.15)	8,175 (78.78)	0.125
	Yes	72,609 (21.85)	2,202 (21.22)	
Readmission, <i>N</i> (%)	No	304,189 (91.55)	8,617 (83.04)	<0.001
	Yes	28,078 (8.45)	1,760 (16.96)	
In hospital mortality, <i>N</i> (%)	No	328,284 (98.8)	10,162 (97.93)	<0.001
	Yes	3,983 (1.2)	215 (2.07)	
Length of stay (days), mean (SD), median [minimum-maximum]		6.17 (5.16) 6 [1–24]	9.39 (8.84) 10 [3–126]	<0.001
Cost (euros), mean (SD), median [minimum-maximum]		2655.11 (2148.66) 2498 [485–11,562]	3094.24 (2124.07) 2916 [2498–51708]	<0.001

For microorganisms isolated, the proportion of patients infected by *Pseudomonas aeruginosa* was higher among those who had associated bronchiectasis than among those who did not (8% vs. 0.66%, respectively, $p < 0.001$). The results were similar for *Aspergillus* species (0.93% vs. 0.15%, respectively, $p < 0.001$).

For procedures, computerized axial tomography of the thorax and bronchoscopy were performed in more patients with bronchiectasis than in those without bronchiectasis (12.97% and 1.91% vs. 3.76% and 0.73%, respectively, $p < 0.001$). Furthermore, the percentage of

patients who required noninvasive mechanical ventilation was significantly higher among those with bronchiectasis (2.43% vs. 1.56%, respectively, $p < 0.001$). However, the use of invasive mechanical ventilation was lower (0.81% vs. 1.03%, $p = 0.031$). Eosinophilia was more frequent in patients with concomitant bronchiectasis (0.29% vs. 0.17%, $p = 0.005$), and nebulizers were less frequent in the bronchiectasis group (16.8% vs. 21.92%, respectively, $p < 0.001$).

The mean LOHS was higher in patients with bronchiectasis (9.39 vs. 6.17 days, respectively, $p < 0.001$).

Table 2. Prevalence, clinical characteristics, diagnosis procedures and outcomes of male patients admitted to the hospital with asthma and suffering concomitant bronchiectasis in Spain from 2001 to 2015.

Factors	2001–2005	2006–2010	2011–2015	p-value for trend
Prevalence, n (%)	621 (1.53)	755 (1.94)	1004 (2.79)	<0.001
Age (years), mean (SD)	63.55 (17.61)	64.54 (17.33)	67.64 (16.49)	<0.001
Age groups, n (%)				
<40 years	67 (10.79)	93 (12.32)	80 (7.97)	<0.001
40–64 years	160 (25.76)	181 (23.97)	247 (24.6)	
65–74 years	210 (33.82)	225 (29.8)	221 (22.01)	
≥75 years	184 (29.63)	256 (33.91)	456 (45.42)	<0.001
Charlson comorbidity index, n (%)				
0	448 (72.14)	490 (64.9)	571 (56.87)	
1	120 (19.32)	207 (27.42)	296 (29.48)	
≥2	53 (8.53)	58 (7.68)	137 (13.65)	0.01
Tobacco use, n (%)				
Obesity, n (%)	196 (31.56)	244 (32.32)	381 (37.95)	0.229
<i>Pseudomonas aeruginosa</i> infection, n (%)	34 (5.48)	37 (4.9)	68 (6.77)	0.024
<i>S. Pneumoniae</i> infection, n (%)	40 (6.44)	78 (10.33)	77 (7.67)	0.474
Legionella infection, n (%)	1 (0.16)	1 (0.13)	0 (0)	NA
<i>S. Aureus</i> infection, n (%)	0 (0)	0 (0)	0 (0)	NA
<i>H. Influenzae</i> infection, n (%)	0 (0)	0 (0)	0 (0)	0.341
Virus infection, n (%)	0 (0)	1 (0.13)	0 (0)	0.504
Aspergilosis infection, n (%)	0 (0)	0 (0)	1 (0.1)	0.48
Thoracic computed tomography, n (%)	84 (13.53)	119 (15.76)	152 (15.14)	0.494
Bronchoscopy, n (%)	8 (1.29)	22 (2.91)	27 (2.69)	0.106
Invasive mechanical ventilation, n (%)	10 (1.61)	7 (0.93)	8 (0.8)	0.272
Noninvasive mechanical ventilation, n (%)	6 (0.97)	10 (1.32)	29 (2.89)	0.008
Eosinophilia, n (%)	2 (0.32)	2 (0.26)	7 (0.7)	0.348
Aerosol therapy, n (%)	47 (7.57)	103 (13.64)	244 (24.3)	<0.001
Oxygen therapy, n (%)	102 (16.43)	149 (19.74)	247 (24.6)	<0.001
In-hospital mortality, n (%)	14 (2.25)	15 (1.99)	14 (1.39)	0.406
Readmission, n (%)	107 (17.23)	135 (17.88)	175 (17.43)	0.947
Length of stay, (days), mean (SD)	9.22 (7.88)	8.59 (7.09)	8.31 (6.87)	0.045
Cost (euros), mean (SD)	3036.78 (1953.11)	3064.83 (3026.75)	3430.88 (3478.52)	0.01

p values for time trend comparing the three time periods shown in the table using chi square for trends except for age, length of stay and costs that ANOVA was used.

In all variables the proportions shown are for those that fulfill the condition.

Additionally, the proportion of readmission and cost was significantly higher in patients with bronchiectasis, as shown in Table 1.

We found that the IHM in patients with asthma and bronchiectasis was 2.07% and 1.2% in those without bronchiectasis ($p < 0.001$). However, after adjustments were made for age, gender and comorbidities, this difference became insignificant.

Tables 2 and 3 show the prevalence, clinical characteristics, diagnostic procedures and outcomes of male (Table 2) and female (Table 3) patients admitted to the hospital with asthma and suffering concomitant bronchiectasis in Spain from 2001 to 2015 in five-year periods. Detailed year-by-year data can be found in Supplementary Tables 1–4.

The prevalence of bronchiectasis increased from 2.16% in 2001 to 4.47% in 2015 ($p < 0.001$). This increase was significant over time in both genders, from 1.53% in 2001–2005 to 2.79% in 2011–2015 in males and from 2.89% in the first period to 4.43% in the last period in females. The Poisson regression models adjusted by age and CCI showed a significant increase in the prevalence of bronchiectasis for males (IRR 1.11, 95% CI 1.02–1.17) and females (IRR 1.08, 95% CI 1.01–1.14).

The mean age increased progressively over time in both genders, from 63.55 years in 2001–2005 to

67.64 years in 2011–2015 in men and from 67.85 years to 70.43 years in women ($p < 0.001$ in both cases). Comorbidity also increased significantly over time in males and females (percentage of patients with ≥ 2 comorbid conditions: 8.53% in men and 6.59% in women during the first period; 13.65% and 11.84% in the last; $p < 0.001$ in both cases).

The percentage of smokers increased gradually in both genders, from 31.56% in men and 6.45% in women during 2001–2005 to 37.95% and 14.01%, respectively, in 2011–2015 ($p = 0.01$ in males and $p < 0.001$ in females). However, obesity only increased significantly in females over time.

For the isolation of microorganisms, the frequency of infection by *P. aeruginosa* increased significantly over time in both genders.

The percentage of computerized axial tomography of the thorax and bronchoscopy increased over time only in women (from 9.95% and 1.12% in the first period to 13.84% and 2.2% in the last period, respectively, $p < 0.001$). The need for invasive mechanical ventilation decreased gradually in women (from 1.12% in 2001–2005 to 0.68% in 2011–2015, $p = 0.028$), whereas the use of noninvasive mechanical ventilation increased in both genders over time. Furthermore, the frequency of oxygen therapy and aerosol therapy increased significantly for both genders over time.

Table 3. Prevalence, clinical characteristics, diagnosis procedures and outcomes of female patients admitted to the hospital with asthma and suffering concomitant bronchiectasis in Spain from 2001 to 2015.

Factors	2001–2005	2006–2010	2011–2015	p-value trend
Prevalence, <i>n</i> (%)	2231 (2.89)	2405 (3.24)	3361 (4.43)	<0.001
Age (years), mean (SD)	67.85 (14.91)	70.86 (13.68)	70.43 (14.39)	<0.001
Age groups, <i>n</i> (%)				<0.001
< 65 years	668 (29.94)	610 (25.36)	888 (26.42)	
65–74 years	726 (32.54)	662 (27.53)	826 (24.58)	
≥75 years	837 (37.52)	1133 (47.11)	1647 (49)	
Charlson comorbidity index, <i>n</i> (%)				<0.001
0	1506 (67.5)	1493 (62.08)	1914 (56.95)	
1	578 (25.91)	724 (30.1)	1049 (31.21)	
≥2	147 (6.59)	188 (7.82)	398 (11.84)	
Tobacco use, <i>n</i> (%)	144 (6.45)	207 (8.61)	471 (14.01)	<0.001
Obesity, <i>n</i> (%)	138 (6.19)	238 (9.9)	435 (12.94)	<0.001
<i>Pseudomonas aeruginosa</i> infection, <i>n</i> (%)	147 (6.59)	232 (9.65)	256 (7.62)	<0.001
<i>S. Pneumoniae</i> infection, <i>n</i> (%)	3 (0.13)	5 (0.21)	2 (0.06)	0.287
Legionella infection, <i>n</i> (%)	0 (0)	0 (0)	0 (0)	
<i>S. Aureus</i> infection, <i>n</i> (%)	0 (0)	1 (0.04)	0 (0)	0.313
<i>H. Influenzae</i> infection, <i>n</i> (%)	0 (0)	0 (0)	0 (0)	
Virus infection, <i>n</i> (%)	0 (0)	1 (0.04)	1 (0.03)	0.653
Aspergilosis infection, <i>n</i> (%)	21 (0.94)	30 (1.25)	24 (0.71)	0.117
Thoracic computed tomography, <i>n</i> (%)	222 (9.95)	304 (12.64)	465 (13.84)	<0.001
Bronchoscopy, <i>n</i> (%)	25 (1.12)	42 (1.75)	74 (2.2)	0.011
Invasive mechanical ventilation, <i>n</i> (%)	25 (1.12)	11 (0.46)	23 (0.68)	0.028
Noninvasive mechanical ventilation, <i>n</i> (%)	34 (1.52)	53 (2.2)	120 (3.57)	<0.001
Eosinophilia, <i>n</i> (%)	4 (0.18)	5 (0.21)	10 (0.3)	0.632
Aerosol therapy, <i>n</i> (%)	251 (11.25)	321 (13.35)	777 (23.12)	<0.001
Oxygen therapy, <i>n</i> (%)	425 (19.05)	496 (20.62)	783 (23.3)	<0.001
In-hospital mortality, <i>n</i> (%)	55 (2.47)	55 (2.29)	62 (1.84)	0.252
Readmission, <i>n</i> (%)	378 (16.94)	412 (17.13)	553 (16.45)	0.775
Length of stay, (days), mean (SD)	10.51 (9.58)	9.81 (8.06)	8.9 (6.78)	<0.001
Cost (euros), mean (SD)	3026.11 (1587.84)	2951 (1564.85)	3158.62 (2019.6)	<0.001

p values for time trend comparing the three time periods shown in the table using chi square for trends except for age, length of stay and costs that ANOVA was used.

In all variables the proportions shown are for those that fulfill the condition.

Table 4. Predictor of in hospital mortality of patients admitted to the hospital with asthma and suffering concomitant bronchiectasis in Spain from 2001 to 2015.

Factors		Both gender OR (CI 95%)	Female	Male OR (CI 95%)
Gender	Female	1	NA	NA
	Male	1.08 (0.76–1.54)	NA	NA
Age groups	< 40 years	1	1	1
	40–64 years	3.25 (0.4–24.05)	2.82 (0.29–26.12)	3.78 (0.67–28.61)
	65–74 years	8.02 (1.09–59.16)	8.86 (1.39–61.03)	7.14 (1.01–68.45)
	≥ 75 years	12.24 (1.67–89.66)	11.03 (1.24–93.41)	14.82 (2.09–97.28)
Charlson comorbidity index	0	1	1	1
	1	1.76 (1.28–2.41)	1.62 (1.12–2.69)	1.90 (1.34–3.23)
	≥2	3.03 (2.09–4.45)	3.55 (1.89–5.09)	2.39 (1.36–4.99)
Tobacco use	No	1	1	1
	Yes	0.36 (0.18–0.73)	0.45 (0.22–0.84)	0.32 (0.10–0.86)
Aspergilosis infection	No	1	1	1
	Yes	3.11 (1.31–7.39)	2.53 (1.06–8.19)	4.01 (1.44–9.37)
Invasive mechanical ventilation	No	1	1	1
	Yes	11.51 (6.17–21.46)	13.21 (7.06–24.86)	8.02 (1.91–22.35)
Noninvasive mechanical ventilation	No	1	1	1
	Yes	3.54 (2.06–6.07)	3.20 (1.97–6.39)	3.96 (2.25–6.88)
Readmission	No	1	1	1
	Yes	2.8 (2.1–3.73)	2.9 (2.21–3.98)	2.5 (1.87–3.42)

IHM remained stable in both genders during the study period. Shown in [Supplementary Table 5](#) are the time trend analysis for males and females from 2001 to 2015 using Poisson regression adjusted by age and the CCI. As seen, none of the time trends analyzed showed significant change over time.

The mean LOHS decreased significantly in both men and women (from 9.22 and 10.51 days, respectively, in

2001–2005 to 8.31 and 8.9 days in 2011–2015; $p = 0.045$ for males and $p < 0.001$ for females). The mean hospital cost increased significantly for both genders over time.

[Table 4](#) summarizes the results of the multivariable analysis of factors associated with IHM among patients hospitalized with asthma and concomitant bronchiectasis according to gender. The predictors of IHM were the same for females and males.

For the entire population, the IHM was significantly higher in older subjects (vs. <40 years old, OR: 8.02, 95% CI 1.09–59.16 for those 65–74 years old; OR: 12.24, 95% CI 1.67–89.66 for those $\geq$ 75 years old) and in those with more comorbidities according to the CCI (vs. no comorbidities; OR: 1.76, 95% CI 1.28–2.41 for one comorbidity; OR: 3.03, 95% CI 2.09–4.45 for two or more comorbidities).

Patients with *Aspergillo*sis infection had a 3.11-fold higher probability of dying during their stay than did those without that pathogen.

The presence of invasive and noninvasive mechanical ventilation increased the probability of dying in patients with asthma and concomitant bronchiectasis (OR 11.51, 95% CI 6.17–21.46 and OR 3.54, 95% CI 2.06–6.07, respectively).

We found that patients with readmission were 2.82 (95% CI 2.1–3.73) times more likely to die than were patients without readmission.

The results of the multivariable logistic regression model to identify predictors of IHM among patients with asthma and without concomitant bronchiectasis are shown in [Supplementary Table 6](#).

The predictors of IHM were very similar to those found among patients suffering concomitant bronchiectasis. However, in this population, male gender (OR 1.14; 95% CI 1.05–1.24) and *Pseudomonas aeruginosa* infection (OR 1.67; 95% CI 1.35–2.06), increased the risk of death. Unlike those with bronchiectasis, among those without this disease, obesity (OR 0.80; 95% CI 0.72–0.89) and aerosol therapy (OR 0.75; 95% CI 0.68–0.82) showed a protective effect. We analyzed the existence of collinearity between variables in the final models, finding no variables with significant associations.

Discussion

In this study, we found the presence of bronchiectasis in 3.02% of patients admitted for asthma exacerbation, being more frequent in women, in older patients and in those with greater comorbidity. The prevalence of bronchiectasis in asthma patients has been analyzed previously, with highly variable results according to the methodology used (7–13), although in some works, similar values to ours have been found (10,17). In the study conducted by Kang et al. (10), 2,270 cases of asthma were reviewed, with a bronchiectasis prevalence of 2.2%. Similarly, Oguzulgen et al. (17) evaluated 1680 asthmatic patients and detected a prevalence of bronchiectasis of 3%. When assessing these results, it is important to take into account that

no computerized axial tomography of the thorax (CT) was performed on all patients, which could contribute to an underestimation of the diagnosis. A study with a methodology similar to ours conducted by Xie et al. (18) analyzed bronchial asthma admissions according to the presence or absence of bronchiectasis and found this condition in 19.7% of cases. In general, the prevalence is higher in studies in which a high-resolution CT was performed in all patients (9,13,22), although it should be noted that these studies had been carried out in patients with severe or uncontrolled asthma, in whom bronchiectasis appears to be more frequent.

Regarding microbiological isolates, a higher proportion of *Pseudomonas aeruginosa* and *Aspergillus* infections were observed in asthma exacerbations with associated bronchiectasis. These results are consistent with those obtained in other studies (23), which could be justified by the greater predisposition to infection in this patient group. When diagnostic tests were examined, we can see that more CT and more bronchoscopy were performed in the group with bronchiectasis. This finding could be partly due to the use of CT as the diagnostic method of choice and the higher frequency of hemoptysis or respiratory infections that require samples for culture when bronchiectasis exists.

Eosinophilia was more frequent in asthmatic patients with bronchiectasis. Similar results have been previously described by other authors, such as Coman et al. (22), raising the possibility of considering bronchiectasis as another criterion for severe eosinophilic asthma.

The LOHS, costs and number of readmissions were higher in patients with bronchiectasis. When analyzing the costs of hospitalizations for bronchiectasis in Spain, it has been observed that they decrease only when bronchiectasis is the main cause but increase when they constitute a secondary diagnosis (24), as we found in our study.

When analyzing the evolution of the prevalence and clinical characteristics, we observed that the prevalence increased significantly during the study period, as well as age and comorbidity. Similar results have been described by other authors, such as Xie et al. (18). This increase over time could be explained, at least in part, by the existence of greater knowledge of this pathology, by the greater longevity of the population and by the increase in the use of CT to diagnose bronchiectasis.

After adjusting for age, gender and comorbidities, we did not find differences in IHM in asthmatic patients with and without bronchiectasis. These results merit attention considering that previous studies have

shown that asthmatic patients hospitalized for acute exacerbation of bronchiectasis have more serious conditions and longer hospitalization times than do asthmatic patients hospitalized for acute asthmatic attack (18). The possible effect of bronchiectasis on IHM should be evaluated in prospective studies using clinical data and a larger sample size.

We did not detect significant variations in IHM over time, as described by other authors (25). There are few studies that evaluate general mortality rates in patients with bronchiectasis (26,27). In the study carried out by Roberts et al. (27), 5,700 bronchiectasis deaths in Wales and England were collected from 2001 to 2007. They detected an increase in mortality due to bronchiectasis at a rate of 3% per year. This finding is relevant and should lead us to consider that the prognosis of bronchiectasis is not negligible and that mortality could be increasing.

The determining factors of higher mortality among patients hospitalized with asthma and concomitant bronchiectasis in our study were age, comorbidity, *Aspergillus* infection, use of mechanical ventilation and readmissions. Active smoking was a protective factor, which seems contradictory since a history of smoking has been significantly associated with increased mortality in patients with bronchiectasis (28). We think that a survival bias can partly explain this contradictory result, with the heaviest smoker dying before developing bronchiectasis. Additionally, a selection bias could occur, as only those with mild asthma and bronchiectasis continue smoking, while those with more severe diseases (and a higher risk of dying) have stopped this unhealthy habit after many years but before their hospitalization, which may bias our results. However, these hypotheses require verification in additional studies.

In previous studies, other factors associated with increased mortality or poor prognoses have been identified in patients with bronchiectasis. They include male gender, low body mass index (29), isolation of *Pseudomonas* (30) and existence of airflow limitation (28,30).

This study has strengths and limitations that we should consider when interpreting the results. The main strength is the large sample size. In addition, the methodology is homogeneous and remains constant throughout the entire period analyzed. The main limitation and potential source of bias is the use of ICD-9-CM diagnostic codes to identify patients admitted for asthma and bronchiectasis, since we do not know the accuracy with which they have been applied. On the other hand, the reflected results are limited to the

coded variables, which means that there are relevant data that we cannot include, such as lung function, antecedents or symptomatology.

Despite these limitations, the SNHDD has the great advantage of being linked to the National Public Health System and of including almost 100% of hospital admissions in Spain. In turn, the Spanish health system is public, complete and free for the entire population, so the data collected include individuals in all socioeconomic categories, which improves the external validity of the results.

Conclusions

We found that the presence of bronchiectasis in asthma patients is more frequent in women, in older patients and in those with more comorbidities. In addition, it is related to a higher frequency of infection by *Pseudomonas aeruginosa* and leads to an increase in LOHS, costs and rate of readmissions. The prevalence of admissions for exacerbation of bronchial asthma with bronchiectasis is increasing over time, without striking differences observed between genders in this evolution. The results obtained are in favor of the presence of bronchiectasis being related to the existence of poorly controlled asthma, either as a risk factor or as a consequence of this fact. More studies are needed to corroborate and deepen the characteristics of this relationship.

Time periods were not included in the model since there was no significant association in the bivariate analysis for the entire sample, females or male patients.

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D. José Luis del Barrio Fernández, como Secretario del Comité de Ética de la Investigación de la Universidad Rey Juan Carlos

CERTIFICA que:

El Proyecto de Investigación con el título: **“INVESTIGACIÓN EPIDEMIOLÓGICA DE ENFERMEDADES CRÓNICAS DE ALTA PREVALENCIA, DIABETES Y EPOC, CON EL USO DEL CMBD Y LAS ENCUESTAS POBLACIONALES DE SALUD DE ESPAÑA”** y cuyo investigador principal es el doctor don Rodrigo Jiménez García, **NO NECESITA** certificado del Comité Ética de la Investigación dada la naturaleza de dicha investigación al encontrarse dentro de lo expuesto en el segundo párrafo del punto 5 de la Orden SAS /3470/2009 de 16 de diciembre y no hallarse dentro de los supuestos establecidos en el artículo 2.e) de la Ley 14/2007, de 3 de junio, de Investigación Biomédica.

Móstoles 17 de enero de 2018



Fdo.: José Luis del Barrio Fernández

Supplementary table 5. Time trend in the hospital mortality among patients admitted to hospital with asthma and with and without concomitant bronchiectasis in Spain from 2001 to 2015 according to gender.

	Without bronchiectasis		With bronchiectasis	
	Male	Female	Male	Female
2001	0.59	1.26	3.01	4.05
2002	0.92	1.65	2.38	2.34
2003	0.67	1.70	0.85	2.11
2004	0.78	1.62	3.92	2.55
2005	1.04	1.97	1.4	1.85
2006	0.58	1.29	0.67	1.93
2007	0.85	1.33	2.84	2.73
2008	0.63	1.34	1.52	2.59
2009	0.54	1.36	1.1	2.56
2010	0.47	1.14	3.97	1.58
2011	0.66	1.35	0.75	1.93
2012	0.69	1.51	1.66	2.6
2013	0.79	1.45	1.59	1.72
2014	0.81	1.36	1.33	1.29
2015	0.83	1.72	1.45	1.75
Total	0.72	1.48	2.03	2.40
IRR (95%CI)	0.98(0.87-1.14)	0.99(0.90-1.09)	0.97(0.88-1.04)	0.96(0.88-1.03)
P value	0.977	0.908	0.395	0.324

IRR: Incidence Rate Ratio. CI: Confidence Interval.

Poisson Regression models were adjusted by age and Charlson Comorbidity Index.

Supplementary table 6. Predictors of in hospital mortality of patients admitted to the hospital with asthma and NOT suffering concomitant bronchiectasis in Spain from 2001 to 2015.

	IHM	
		OR 95%CI
Gender	Female	1
	Male	1.14(1.05-1.24)
Age groups	<40	1
	40-64 years	4.24(3.38-5.32)
	65-74 years	9.50(7.69-11.7)
	75 o mas	2.81(2.30-3.43)
Charlson comorbidity index	0	1
	1	1.75(1.62-1.89)
	≥2	2.99(2.74-3.26)
Tobacco use		0.62(0.54-0.72)
Obesity		0.80(0.72-0.89)
<i>Pseudomonas aeruginosa</i> infection.		1.67(1.35-2.06)
Aspergilosis infection		4.26(3.08-5.89)
Invasive mechanical ventilation		1.70(1.50-1.93)
Non-invasive mechanical ventilation		2.67(2.30-3.11)
Aerosol therapy		0.75(0.68-0.82)
Readmission		2.21(2.04-2.39)

Supplementary table 1. Prevalence and clinical characteristics of men admitted to the hospital with asthma and suffering concomitant bronchiectasis in Spain from 2001 to 2015.

		2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	p-value
Prevalence. n (%)		133(1.69)	126(1.54)	117(1.39)	102(1.23)	143(1.82)	149(1.8)	141(1.84)	132(1.73)	182(2.4)	151(1.97)	134(2)	181(2.51)	189(2.61)	225(3.1)	275(3.64)	<0.001
Age(year).mean(SD)		62.66(18.2)	61.99(18.42)	63.64(17.08)	63.17(18.67)	65.95(15.9)	62.95(17.04)	65.47(16.73)	63.43(19.26)	64.96(17.03)	65.68(16.8)	63.04(17.48)	67.82(17.98)	67.94(16.29)	69.04(15.86)	68.42(15.3)	<0.001
Age groups. n (%)	< 40 years	16(12.03)	17(13.49)	10(8.55)	15(14.71)	9(6.29)	23(15.44)	15(10.64)	19(14.39)	20(10.99)	16(10.6)	15(11.19)	14(7.73)	16(8.47)	18(8)	17(6.18)	<0.001
	40-64 years	33(24.81)	31(24.6)	32(27.35)	23(22.55)	41(28.67)	35(23.49)	30(21.28)	31(23.48)	43(23.63)	42(27.81)	41(30.6)	42(23.2)	47(24.87)	44(19.56)	73(26.55)	
	65-74 years	50(37.59)	45(35.71)	39(33.33)	31(30.39)	45(31.47)	45(30.2)	51(36.17)	41(31.06)	53(29.12)	35(23.18)	37(27.61)	43(23.76)	43(22.75)	52(23.11)	46(16.73)	
	75 o mas	34(25.56)	33(26.19)	36(30.77)	33(32.35)	48(33.57)	46(30.87)	45(31.91)	41(31.06)	66(36.26)	58(38.41)	41(30.6)	82(45.3)	83(43.92)	111(49.33)	139(50.55)	
Charlson comorbidity index. n (%)	0	91(68.42)	97(76.98)	77(65.81)	75(73.53)	108(75.52)	98(65.77)	90(63.83)	90(68.18)	124(68.13)	88(58.28)	82(61.19)	94(51.93)	104(55.03)	135(60)	156(56.73)	<0.001
	1	33(24.81)	21(16.67)	26(22.22)	17(16.67)	23(16.08)	42(28.19)	45(31.91)	36(27.27)	50(27.47)	34(22.52)	41(30.6)	63(34.81)	57(30.16)	56(24.89)	79(28.73)	
	2 +	9(6.77)	8(6.35)	14(11.97)	10(9.8)	12(8.39)	9(6.04)	6(4.26)	6(4.55)	8(4.4)	29(19.21)	11(8.21)	24(13.26)	28(14.81)	34(15.11)	40(14.55)	
Tobacco use. n (%)		43(32.33)	33(26.19)	33(28.21)	34(33.33)	53(37.06)	42(28.19)	48(34.04)	43(32.58)	62(34.07)	49(32.45)	54(40.3)	55(30.39)	81(42.86)	98(43.56)	93(33.82)	0.01
Obesity . n (%)		5(3.76)	3(2.38)	8(6.84)	8(7.84)	10(6.99)	4(2.68)	10(7.09)	9(6.82)	10(5.49)	4(2.65)	13(9.7)	8(4.42)	9(4.76)	13(5.78)	25(9.09)	0.229
<i>Pseudomonas aeruginosa</i> infection. n (%)		7(5.26)	8(6.35)	6(5.13)	10(9.8)	9(6.29)	17(11.41)	15(10.64)	12(9.09)	15(8.24)	19(12.58)	12(8.96)	14(7.73)	19(10.05)	16(7.11)	16(5.82)	0.024
<i>S Pneumoniae</i> infection. n (%)		0(0)	0(0)	1(0.85)	0(0)	0(0)	0(0)	0(0)	0(0)	1(0.55)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0.474
Legionella infection. n (%)		133(100)	126(100)	117(100)	102(100)	143(100)	149(100)	141(100)	132(100)	182(100)	151(100)	134(100)	181(100)	189(100)	225(100)	275(100)	
<i>S. Aureus</i> infection. n (%)		0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	
<i>H. Influenzae</i> infection. n (%)		0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	1(0.71)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0.341
Virus infection. n (%)		0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	1(0.36)	0.504
Aspergillosis infection. n (%)		0(0)	1(0.79)	0(0)	2(1.96)	2(1.4)	0(0)	1(0.71)	1(0.76)	2(1.1)	1(0.66)	2(1.49)	3(1.66)	2(1.06)	2(0.89)	3(1.09)	0.48

P value for time trend using chi square for trends using every single year except for age, length of stay and costs that ANOVA was used.

Supplementary table 2. Prevalence and clinical characteristics of women admitted to the hospital with asthma and suffering concomitant bronchiectasis in Spain from 2001 to 2015.

		2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	p-value
Prevalence. n (%)		321(2.45)	427(2.79)	474(2.89)	471(2.99)	538(3.24)	415(2.8)	476(3.12)	501(3.36)	507(3.44)	506(3.52)	569(4.02)	655(4.37)	640(4.27)	697(4.56)	800(4.86)	<0.001
Age(year).mean(SD)		68.2(15.17)	66.45(16.19)	68.22(14.38)	66.78(15.59)	69.37(13.35)	69.76(14.04)	71.3(13.28)	71.46(14.05)	71.47(12.47)	70.17(14.47)	70.48(13.83)	70.03(14.6)	70.22(14.6)	70.63(13.99)	70.74(14.79)	<0.001
Age groups. n (%)	< 40 years	19(5.92)	39(9.13)	20(4.22)	29(6.16)	17(3.16)	19(4.58)	11(2.31)	19(3.79)	11(2.17)	19(3.75)	27(4.75)	32(4.89)	22(3.44)	19(2.73)	36(4.5)	<0.001
	40-64 years	73(22.74)	97(22.72)	119(25.11)	135(28.66)	120(22.3)	99(23.86)	107(22.48)	100(19.96)	106(20.91)	119(23.52)	110(19.33)	143(21.83)	156(24.38)	169(24.25)	174(21.75)	
	65-74 years	104(32.4)	142(33.26)	158(33.33)	143(30.36)	179(33.27)	126(30.36)	128(26.89)	134(26.75)	139(27.42)	135(26.68)	162(28.47)	166(25.34)	151(23.59)	175(25.11)	172(21.5)	
	75 o mas	125(38.94)	149(34.89)	177(37.34)	164(34.82)	222(41.26)	171(41.2)	230(48.32)	248(49.5)	251(49.51)	233(46.05)	270(47.45)	314(47.94)	311(48.59)	334(47.92)	418(52.25)	
Charlson comorbidity index. n (%)	0	220(68.54)	324(75.88)	315(66.46)	314(66.67)	333(61.9)	266(64.1)	283(59.45)	319(63.67)	322(63.51)	303(59.88)	332(58.35)	369(56.34)	366(57.19)	374(53.66)	473(59.13)	<0.001
	1	83(25.86)	93(21.78)	123(25.95)	124(26.33)	155(28.81)	123(29.64)	142(29.83)	150(29.94)	146(28.8)	163(32.21)	176(30.93)	205(31.3)	195(30.47)	232(33.29)	241(30.13)	
	2 +	18(5.61)	10(2.34)	36(7.59)	33(7.01)	50(9.29)	26(6.27)	51(10.71)	32(6.39)	39(7.69)	40(7.91)	61(10.72)	81(12.37)	79(12.34)	91(13.06)	86(10.75)	
Tobacco use. n (%)		14(4.36)	23(5.39)	30(6.33)	48(10.19)	29(5.39)	23(5.54)	35(7.35)	39(7.78)	44(8.68)	66(13.04)	64(11.25)	79(12.06)	99(15.47)	109(15.64)	120(15)	<0.001
Obesity . n (%)		13(4.05)	20(4.68)	39(8.23)	32(6.79)	34(6.32)	37(8.92)	45(9.45)	42(8.38)	55(10.85)	59(11.66)	64(11.25)	79(12.06)	96(15)	88(12.63)	108(13.5)	<0.001
<i>Pseudomonas aeruginosa</i> infection. n (%)		16(4.98)	18(4.22)	37(7.81)	37(7.86)	39(7.25)	32(7.71)	46(9.66)	51(10.18)	54(10.65)	49(9.68)	58(10.19)	55(8.4)	46(7.19)	41(5.88)	56(7)	<0.001
<i>S. Pneumoniae</i> infection. n (%)		1(0.31)	0(0)	0(0)	0(0)	2(0.37)	1(0.24)	1(0.21)	0(0)	3(0.59)	0(0)	0(0)	0(0)	1(0.16)	1(0.14)	0(0)	0.287
<i>Legionella</i> infection. n (%)		0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	
<i>S. Aureus</i> infection. n (%)		0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	1(0.2)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0.313
<i>H. Influenzae</i> infection. n (%)		0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	
Virus infection. n (%)		0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	1(0.2)	0(0)	0(0)	0(0)	0(0)	1(0.14)	0(0)	0.653
Aspergillosis infection. n (%)		4(1.25)	4(0.94)	5(1.05)	2(0.42)	6(1.12)	7(1.69)	4(0.84)	6(1.2)	8(1.58)	5(0.99)	5(0.88)	3(0.46)	3(0.47)	4(0.57)	9(1.13)	0.117

P value for time trend using chi square for trends using every single year except for age, length of stay and costs that ANOVA was used.

Supplementary table 3. Diagnosis procedures and outcomes of men admitted to the hospital with asthma and suffering concomitant bronchiectasis in Spain from 2001 to 2015.

	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	p-value
Thoracic computed tomography.. n (%)	11(8.27)	21(16.67)	15(12.82)	13(12.75)	24(16.78)	26(17.45)	21(14.89)	20(15.15)	30(16.48)	22(14.57)	25(18.66)	31(17.13)	23(12.17)	39(17.33)	34(12.36)	0.494
Bronchoscopy. n (%)	0(0)	3(2.38)	0(0)	4(3.92)	1(0.7)	3(2.01)	5(3.55)	3(2.27)	4(2.2)	7(4.64)	3(2.24)	5(2.76)	5(2.65)	5(2.22)	9(3.27)	0.106
Invasive mechanical ventilation. n (%)	2(1.5)	2(1.59)	1(0.85)	2(1.96)	3(2.1)	0(0)	2(1.42)	0(0)	1(0.55)	4(2.65)	1(0.75)	2(1.1)	1(0.53)	3(1.33)	1(0.36)	0.272
Non-invasive mechanical ventilation. n (%)	0(0)	2(1.59)	1(0.85)	1(0.98)	2(1.4)	2(1.34)	1(0.71)	1(0.76)	1(0.55)	5(3.31)	4(2.99)	2(1.1)	6(3.17)	11(4.89)	6(2.18)	0.008
Eosinophilia. n (%)	2(1.5)	0(0)	0(0)	0(0)	0(0)	1(0.67)	0(0)	1(0.76)	0(0)	0(0)	1(0.75)	0(0)	2(1.06)	1(0.44)	3(1.09)	0.348
Aerosol therapy. n (%)	12(9.02)	8(6.35)	8(6.84)	8(7.84)	11(7.69)	21(14.09)	16(11.35)	23(17.42)	20(10.99)	23(15.23)	20(14.93)	47(25.97)	40(21.16)	52(23.11)	85(30.91)	<0.001
Oxygen therapy. n (%)	18(13.53)	28(22.22)	17(14.53)	13(12.75)	26(18.18)	34(22.82)	18(12.77)	28(21.21)	37(20.33)	32(21.19)	30(22.39)	48(26.52)	45(23.81)	59(26.22)	65(23.64)	<0.001
In-hospital mortality. n (%)	4(3.01)	3(2.38)	1(0.85)	4(3.92)	2(1.4)	1(0.67)	4(2.84)	2(1.52)	2(1.1)	6(3.97)	1(0.75)	3(1.66)	3(1.59)	3(1.33)	4(1.45)	0.406
Readmission. n (%)	23(17.29)	23(18.25)	24(20.51)	15(14.71)	22(15.38)	30(20.13)	25(17.73)	17(12.88)	42(23.08)	21(13.91)	19(14.18)	31(17.13)	32(16.93)	45(20)	48(17.45)	0.947
Length of stay(days). Mean(SD)	10.39(9.53)	8.92(7.42)	9.07(6.99)	8.9(6.39)	8.74(8.21)	9.61(8.37)	8.64(7.07)	8.03(5.4)	7.95(6.39)	8.79(7.75)	8.39(6.94)	8.62(6.89)	9.4(9.81)	7.76(5.2)	7.75(5.33)	0.045
Cost(euros).mean(SD)	2821.26(631)	2774.62(821)	3319.65(406)	3236.99(126)	3094(923.26)	2537.07(116)	2658.61(973)	3156.09(103)	3288.89(117)	3615.07(635)	3467.81(293)	3251.76(568)	3441.37(900)	3511.88(466)	3457.29(698)	0.01

P value for time trend using chi square for trends using every single year except for age, length of stay and costs that ANOVA was used.

Supplementary table 4. Diagnosis procedures and outcomes of men and women admitted to the hospital with asthma and suffering concomitant bronchiectasis in Spain from 2001 to 2015.

	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	p-value
Thoracic computed tomography.. n (%)	29(9.03)	40(9.37)	51(10.76)	50(10.62)	52(9.67)	41(9.88)	44(9.24)	67(13.37)	69(13.61)	83(16.4)	71(12.48)	97(14.81)	95(14.84)	96(13.77)	106(13.25)	<0.001
Bronchoscopy. n (%)	5(1.56)	4(0.94)	6(1.27)	5(1.06)	5(0.93)	8(1.93)	8(1.68)	7(1.4)	8(1.58)	11(2.17)	10(1.76)	24(3.66)	9(1.41)	11(1.58)	20(2.5)	0.011
Invasive mechanical ventilation. n (%)	6(1.87)	3(0.7)	2(0.42)	6(1.27)	8(1.49)	1(0.24)	3(0.63)	2(0.4)	3(0.59)	2(0.4)	3(0.53)	10(1.53)	4(0.63)	3(0.43)	3(0.38)	0.028
Non-invasive mechanical ventilation. n (%)	2(0.62)	6(1.41)	8(1.69)	8(1.7)	10(1.86)	3(0.72)	6(1.26)	6(1.2)	18(3.55)	20(3.95)	18(3.16)	22(3.36)	18(2.81)	36(5.16)	26(3.25)	<0.001
Eosinophilia. n (%)	0(0)	1(0.23)	1(0.21)	2(0.42)	0(0)	2(0.48)	0(0)	2(0.4)	1(0.2)	0(0)	2(0.35)	4(0.61)	2(0.31)	0(0)	2(0.25)	0.632
Aerosol therapy. n (%)	32(9.97)	48(11.24)	45(9.49)	69(14.65)	57(10.59)	61(14.7)	46(9.66)	57(11.38)	61(12.03)	96(18.97)	115(20.21)	136(20.76)	147(22.97)	172(24.68)	207(25.88)	<0.001
Oxygen therapy. n (%)	66(20.56)	90(21.08)	79(16.67)	86(18.26)	104(19.33)	94(22.65)	88(18.49)	98(19.56)	114(22.49)	102(20.16)	111(19.51)	151(23.05)	151(23.59)	164(23.53)	206(25.75)	<0.001
In-hospital mortality. n (%)	13(4.05)	10(2.34)	10(2.11)	12(2.55)	10(1.86)	8(1.93)	13(2.73)	13(2.59)	13(2.56)	8(1.58)	11(1.93)	17(2.6)	11(1.72)	9(1.29)	14(1.75)	0.252
Readmission. n (%)	41(12.77)	71(16.63)	95(20.04)	72(15.29)	99(18.4)	68(16.39)	82(17.23)	92(18.36)	84(16.57)	86(17)	100(17.57)	114(17.4)	103(16.09)	107(15.35)	129(16.13)	0.775
Length of stay(days). Mean(SD)	10.49(8.88)	10.13(6.9)	11.55(27.02)	10.17(8.75)	10.2(9.29)	10.13(11.36)	9.51(9.99)	9.59(7.42)	10.46(9.47)	9.39(6.78)	9.11(8.08)	9.29(9.72)	8.8(7.17)	8.57(7.29)	8.79(6.57)	<0.001
Cost(euros).mean(SD)	2958.2(2243)	2805.99(936)	2904.94(993)	3240.21(2283)	3160.67(1108)	2573.8(1233)	2682.32(1065)	3287.71(2418)	3223.76(1474)	2906.45(995)	2999.31(1284)	2931.69(1524)	3442.51(3955)	3080.12(748)	3299(960.75)	<0.001

P value for time trend using chi square for trends using every single year except for age, length of stay and costs that ANOVA was used.