ECONOMICS

Economic impact of severe asthma in Spain: multicentre observational longitudinal study

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ABSTRACT

Objective: Estimate the economic impact of severe asthma from the Spanish social perspective through the estimation of the associated annual direct and indirect costs. Methods: Observational, longitudinal, retrospective study carried out in 20 Spanish secondary settings (Pulmonology and Allergy Services) among patients aged ≥18, diagnosed with severe asthma according to European Respiratory Society/American Thoracic Society consensus and who have not experienced an exacerbation in the previous 2 months. Asthma-related healthcare resource utilization as well as asthma-related days off work were collected over a retrospective 12-month period from medical records review (inclusion period: June to November 2016). Total costs were calculated by multiplying the natural resource units used within 1 year by the corresponding unit cost. Costs were expressed in Euros for 2018. Results: A total of 303 patients were included, mean age was 54 years old and 67% were women. There were 5.7 physician visits per patient (3.3 in secondary care). The most common pharmacologic treatment was fixed dose combination of inhaled corticosteroids/long-acting β2-adrenergic agonists (96.7%), followed by leukotriene receptor antagonists (57.1%). 134 patients (44.2%) had at least one severe asthma exacerbation (mean: 1.9 exacerbation/patient), of whom 22 patients required hospitalization, with a mean hospital stay of 10.9 days/patient. Mean sick leave due to severe asthma was 9.1 days per patient per year. Mean annual direct cost (confidence interval 95%) was €7472/patient (€6578–€8612). The cost per exacerbation was €1410/patient. When indirect costs were added (€1082/patient [€564–1987]), the total annual mean cost rose to €8554/patient (€7411–10199). Conclusions: Taking the social perspective, the economic impact of severe asthma in Spain was estimated to be €8554/patient/year.

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Introduction and objective

Severe asthma is a heterogeneous disease with multiple phenotypes whose identification has important diagnostic and therapeutic implications [1]. Various definitions of severe asthma have been proposed. The 2014 European Respiratory Society/American Thoracic Society (ERS/ATS) consensus defines severe asthma as that requiring treatment with high doses of inhaled corticosteroids (ICS), a second controller and/or systemic corticosteroids and which remains uncontrolled despite these therapies [2].

The ERS/ATS report on severe asthma states that the prevalence of severe asthma is unclear (especially when using a rigorous definition), although estimates indicate that 5–10% of the total asthma population have severe disease [3]. Currently, there are few treatment options available as add-on to standard of care for patients with severe asthma and there is a considerable portion of patients that remain uncontrolled. Despite afflicting a small proportion of patients, the management of severe asthma is associated with high and disproportional consumption of healthcare resources.
resources. Estimates suggest up to 40–50% of health care costs due to asthma are attributable to severe patients, owing to frequent hospital admissions, use of emergency services and drug consumption [4,5].

In Spain, the most relevant studies on costs and quality of life (QoL) in adult asthmatic patients are the AsmaCost and EUCOAST studies. The AsmaCost study [6] estimated that the mean annual cost of an asthmatic patient was €1726 from the social perspective. In patients with severe asthma, the total mean cost was €2635. The aim of the EUCOAST study [7] was to describe the costs and QoL in French and Spanish adult asthmatic patients according to the degree of asthma control. The mean direct health costs (€/3 months/patient) in Spanish patients with controlled, partially controlled or uncontrolled asthma, were €152.6, €241.2, and €556.8, respectively. Although both studies included varying proportions of patients with severe asthma, neither included a sample sufficient to characterize the specific economic and human burden of severe asthma, as they were not designed for this purpose.

The main objective of this study was to estimate the economic impact of severe asthma in adult patients in Spain through estimation of the associated direct and indirect annual costs. The secondary objectives were to estimate the QoL of patients with severe asthma and the degree of disease control.

Methods
Study design
A multicentre epidemiological, observational, longitudinal retrospective study was carried out in Pulmonology and Allergy Services of 20 Spanish hospitals (Supplementary Table SA1). Patients with severe asthma who attended a routine follow-up visit and fulfilled the selection criteria were invited by the investigator to participate in the study, until the number of patients needed was completed. All patients included gave written informed consent to participate in the study. Only one visit per patient was necessary and no follow-up visit was made.

The study inclusion period was from June to November 2016. The time horizon of the analysis was the 12 months before the inclusion visit.

According the information available in the medical records the corresponding sociodemographic, clinical and resource use data were collected and reviewed by the investigators and that provided by the patient in a specifically-designed case report form. Patients were invited to complete the Saint George’s Respiratory Questionnaire (SGRQ) [8] and the Asthma Control Questionnaire (ACQ-5) [9] at the inclusion visit. The economic evaluation was carried out from the Spanish social perspective.

The study was approved by the Clinical Research and Ethics Committee of Hospital Clinic (Barcelona, Spain) and all patients provided written informed consent prior to study participation. It was carried out in accordance with the principles of the Declaration of Helsinki and complied with the standards of Good Clinical Practice [10] as well as following the guidelines for Good Epidemiological Practice [11].

Study population
The study population consisted of patients aged ≥18 years diagnosed with severe asthma defined according to the ERS/ATS consensus [2] confirmed, at least, 12 months before the date of inclusion and in stable phase (without exacerbation in progress) for the last two months. Patients were excluded if they were diagnosed with chronic obstructive pulmonary disease, cystic fibrosis, lung cancer, or pulmonary fibrosis, patients with any oncological disease receiving treatment or at an advanced stage, or with cognitive impairment that would make them unable to understand or complete the informed consent and questionnaires or had participated in an interventional clinical trial during the 12 months prior to the inclusion visit.

To ensure the study population was representative of Spain, patients were recruited in hospitals from four geographical areas according to the total population of each area: central area (Aragón, Castilla-La Mancha, Castilla y León, Madrid and La Rioja), eastern area (Cataluña, Comunidad Valenciana and Islas Baleares), northern area (Asturias, Cantabria, Galicia, Navarra and País Vasco), and southern area (Andalucía, Islas Canarias, Ceuta, Extremadura, Melilla and Murcia). Recruitment was competitive by geographic area in order to adapt to the recruiting capacity of the participating centers without reducing the representativeness of the study population.

Data collection
Sociodemographic characteristics, including age, gender, employment status, and exposure to animals dander or feather, and clinical variables such as body mass index (BMI), smoking history, concomitant diseases related to asthma, and characteristics of severe asthma, such as the time from the diagnosis of severe asthma, pulmonary function (forced expiratory volume in one second (FEV₁), forced vital capacity (FVC)), blood eosinophil levels, total serum Immunoglobulin E (IgE)
levels, the fractional nitric oxide concentration in exhaled breath (FE\textsubscript{NO}), and skin prick tests (SPT) to common aeroallergens were collected.

In addition, the distribution of patients according to eosinophil count and SPT results was analyzed for the total population and for the patients with frequent exacerbations (\geq 2 severe exacerbations in previous 12 months).

Resource use in the stable phase during the 12 months prior to inclusion visit, including primary care (PC) physician and secondary care (SC) visits, outpatient tests and pharmacological treatments was collected. In addition, in patients with \geq 1 severe exacerbation, resource use for each severe exacerbation was collected (hospitalizations, intensive care unit [ICU] admission, pharmacological treatment, unscheduled visits to the emergency room, PC, and SC). The days of absenteeism attributable to severe asthma were also collected. Pharmacological treatment in the stable phase and during severe exacerbations was collected. The total dose was calculated for each active pharmaceutical ingredient during the last 12 months in the stable phase and during severe exacerbations. For this purpose, the dose was multiplied by the length of treatment. In cases of on-demand administration, the minimum dose according to the technical specifications was imputed.

A severe exacerbation was defined as an exacerbation requiring at least one hospitalization, emergency department visit, ICU admission, the need for noninvasive ventilation, or an exacerbation requiring oral/systemic corticosteroids (or an increase in the dose of maintenance oral corticosteroid) for at least three days [12].

Patients were invited to complete the SGRQ and ACQ-5 questionnaires.

The SGRQ [8] is a questionnaire developed to quantify the impact of the disease on the health and QoL perceived by patients with respiratory diseases. It consists of 50 items divided in three scales that include information on the frequency and severity of respiratory symptoms (symptoms), the limitation of activities due to dyspnea (activity) and the changes in psychological and social functioning caused by the disease (impact). A score for each scale (symptoms, activity, and impact) and a global score are calculated. The final score varies between 0 and 100, with 100 representing the worst possible health status and 0 the best.

The ACQ-5 [9] has been developed as a measure of subjects’ asthma control. It is a five-item questionnaire that evaluates symptoms in the last week. The answers to each question are based on a scale of 0 (no impairment) to 6 (maximum impairment). The total ACQ-5 score is obtained as the mean of the five responses and the degree of asthma control per patient is determined by categorizing the score obtained: controlled asthma (ACQ-5 score <0.5), partially controlled asthma (score ACQ-5 \geq 0.5 and <1) and uncontrolled asthma (ACQ-5 score \geq 1) [13].

**Costs**

To estimate the economic impact of severe asthma from the social perspective, direct healthcare costs (resource use in the stable phase and during severe exacerbations) and indirect costs (lost work productivity) were calculated.

Direct healthcare costs were calculated by multiplying the natural units of the resources used by the associated unit cost except for hospitalization and pharmacologic treatment.

The cost of hospitalizations was obtained by multiplying the days of stay by the unit cost corresponding to the Pulmonology Service. The cost of each pharmacological treatment was obtained by multiplying the total dose each patient received during the stable phase and during severe exacerbations by the unit cost of each treatment. For treatments dispensed in the pharmacy office, the unit costs for each treatment were calculated taking into account the retail price plus value added tax (VAT) without applying the deduction of the Spanish Royal Decree-Law 8/2010 [14]. For treatments dispensed in the hospital, the price to wholesaler without VAT was applied according to the presentation of the medicine.

The costs of lost productivity attributable to severe asthma were included as indirect costs. The calculation was made based on the human capital method, considering that the salary reflects the productivity of the worker [15]. Therefore, the number of days the patient was unable to work due to severe asthma was multiplied by the updated salary cost. With this method, the indirect cost of patients not actively employed during the study period (e.g., unemployed and retired workers) was 0.

The unit costs of the use of resources were obtained from the official tariffs of Spanish Autonomous regions (eSalud database) [16] (Supplementary Table SA2) and pharmacological treatments from the website of the General Council of Official Associations of Pharmacists (Bot PLUS) [17]. For lost productivity, salary costs were taken from the latest data published by the Spanish Statistics National Institute (INE) in the 2015 salary structure survey [18] (Supplementary Table SA2). All costs were expressed in 2018 euros.

Additionally, stratified analysis were made to estimate the direct, indirect and total cost according to the degree
of control of severe asthma (ACQ-5); and to estimate pharmacological cost according biological treatment.

**Statistical analysis**

A descriptive analysis of the variables collected was made. Quantitative variables were described using means, confidence intervals (CIs), medians, and interquartile range (IQR) and qualitative variables using absolute and relative frequencies.

The CI of the costs was calculated using bootstrapping techniques using replacement samples of the same size as the original sample [19,20]. In total 10 000 simulations were made and the 2.5 and 97.5 percentiles of the distribution were used to determine the 95% CI.

The analysis was made using the R (version 3.3.2) [21] statistical package.

**Results**

The initial cohort included 305 patients who met the selection criteria, of whom 303 were valid for the main analysis and 302 for the QoL analyses: 67% of patients were women, the mean age was 54-years old, and 34% were former smokers (mean 16.7 packets/year). The mean BMI was 28.5 kg/m2, and 41% of patients were in the range of obesity (BMI ≥30 kg/m2). Rhinitis (71%) was the most common concomitant disease (Table 1).

The median time from the diagnosis of severe asthma to the date of study inclusion was 5 years. The mean post-bronchodilator FEV1/FVC ratio was 68% (Table 2).

The mean eosinophil count was 346.6 cells/mm3 of which 149 (51%) patients had a level of ≥300 cells/mm3 and 16% of patients had a level of ≥150 cells/mm3 and two or more severe exacerbations (Table 2).

The SPT was positive in 66% of patients, with mites being the most frequent type of allergen (44%) and mean total IgE levels were 470.0 kU/L (Table 2).

The mean number of work days lost (95% CI) due to severe asthma was 9.1 (3.7–14.6) per patient. However, if only the 44 (15%) patients who had ≥1 sick leave were considered, the mean was (95% CI) 63.0 (28.4–97.5) days per patient.

### Table 1. Sociodemographic and clinical patient data.

| Variable                                                                 | Statistics     | N  |
|-------------------------------------------------------------------------|----------------|----|
| **Sociodemographic characteristics**                                     |                |    |
| Age (years)                                                             | Mean (95% CI)  | 54.3 (52.8–55.9) |
|                                                                     | Median (IQR)   | 56.0 (45.0–64.5) |
|                                                                     | Men—n (%)      | 101 (33.3%)      |
|                                                                     | Working—n (%)  | 150 (49.5%)      |
|                                                                     | Retired—n (%)  | 89 (29.4%)       |
|                                                                     | Unemployed—n (%)| 23 (7.6%)       |
|                                                                     | Other*—n (%)   | 41 (13.5%)       |
|                                                                     | Exposure to animal dander or feathers—n (%) | 83 (27.4%) |
|                                                                     | Smoking—n (%)  | 16 (5.3%)        |
|                                                                     | No—n (%)       | 184 (60.7%)      |
|                                                                     | Former smoker—n (%) | 103 (34.0%)       |
| Number of packages-year (Smoker)                                        |                | 16 |
|                                                                     | Mean (95% CI)  | 10.9 (5.7–16.1)  |
|                                                                     | Median (IQR)   | 10.0 (4.3–13.1)  |
| Number of packages-year (Former smoker)                                 |                | 103 |
|                                                                     | Mean (95% CI)  | 16.7 (13.4–19.9) |
|                                                                     | Median (IQR)   | 10.0 (4.5–22.5)  |
| BMI (kg/m²)                                                             |                | 302 |
|                                                                     | Mean (95% CI)  | 28.5 (27.9–29.1) |
|                                                                     | Median (IQR)   | 28.0 (24.5–32.4) |
| BMI—n (%)                                                               |                | 302 |
|                                                                     | Underweight (BMI <18.5 kg/m²) | 6 (2.0%) |
|                                                                     | Normal weight (18.5 kg/m² ≤ BMI < 25 kg/m²) | 84 (27.8%) |
|                                                                     | Overweight (25 kg/m² ≤ BMI < 30 kg/m²) | 89 (29.3%) |
|                                                                     | Obesity (BMI ≥30 kg/m²) | 123 (40.7%) |
| Comorbid diseases related to asthma—n (%)b                              |                | 303 |
|                                                                     | Rhinitis       | 215 (71.0%)      |
|                                                                     | Nasal polyposis | 91 (30.0%)      |
|                                                                     | Gastroesophageal reflux | 79 (26.1%)       |
|                                                                     | Anxiety or depression | 67 (22.1%) |
|                                                                     | Conjunctivitis | 67 (22.1%) |
|                                                                     | AERD           | 59 (19.5%)       |
|                                                                     | Sleep apnoea-hypopnea syndrome | 34 (11.2%) |
|                                                                     | Atopic dermatitis | 28 (9.2%)      |

AERD: aspirin-exacerbated respiratory disease; BMI: body mass index; CI: confidence interval; IQR: interquartile range; N: number of patients.

*Housewife (n = 28), student (n = 5), disability/invalidity (n = 5), unemployed (n = 2), non-remunerative work (n = 1).

1Non-exclusive categories.

The mean (95% CI) total score of SGRQ was 38.1 (35.9–40.4). Figure 2 compares the scores for the three SGRQ scales in 302 patients with valid data and in the healthy Spanish population (22).

The results of the ACQ-5 questionnaire [9] showed that 67.7% of patients had poor asthma control, 7.3% partially controlled asthma and 25.1% controlled asthma.

**Resource use**

**Resource use in the stable phase**

The mean number (95% CI) of medical visits related to severe asthma was 5.7 (5.1–6.4) visits/patient/year, of which 2.4 and 3.3 visits were to the PC and SC, respectively. The most frequent outpatient tests were spirometry (n = 293) and blood tests (n = 246) with a mean (95% CI) of 2.7 (2.4–3.0) and 1.5 (1.3–1.7) tests per patient, respectively.
Of the pharmacological treatments prescribed for severe asthma during the stable phase, the most common were fixed combinations of ICS with long-acting β2-adrenergic agonists (LABA) (96.7%), especially the budesonide/formoterol combination (33.3%) followed by leukotriene receptor antagonists (LTRA) (57.1%), specifically montelukast; short-acting β2-adrenergic agonists (SABA) (54.8%), mainly salbutamol (39.3%); anticholinergics (45.5%), especially tiotropium bromide (31.3%), and biological treatments (omalizumab, the only biological marketed at the time of the study) (39.3%). The remaining drugs were prescribed in <13% of patients (Table 3).

Resource use during severe exacerbations

Of the 303 patients valid for the main analysis, 134 (44.2%) had ≥1 severe exacerbation during the 12 months prior to the inclusion visit and 66 (21.8%) had ≥2 severe exacerbations. The mean number of severe exacerbations per patient was 1.9 (95% CI: 1.6–2.1).

The mean number of physician/emergency department unscheduled visits due to asthma severe exacerbations was 2.8 (95% CI: 2.4–3.2) per exacerbated patient, of which 1.1 were emergency department visits, 0.88 PC unscheduled visits and 0.78 SC unscheduled visits (Table 4). Of the 134 patients with severe exacerbations, 22 required hospitalization and the mean number of hospital admissions was 1.5 per patient. The mean hospital stay was 10.9 days (95% CI: 6.5–15.2) (Table 4). Only one patient was admitted to the ICU and had stay of 3 days.

The most common pharmacological treatments prescribed for severe exacerbations were systemic glucocorticoids (94.0%), including prednisone (67.2%) and methylprednisolone (17.2%). In 19.4% of patients with ≥1 severe exacerbation, antibiotics were prescribed, especially azithromycin. In 11.2% SABA (all

Table 2. Characteristics of severe asthma.

| Variables | Statistics | N |
|-----------|------------|---|
| Time from diagnosis of asthma [years]a | Mean (95% CI) 18.7 (17.0–20.4) | 303 |
| | Median (IQR) 15.0 (6.0–29.5) | 303 |
| Time from the diagnosis of severe asthma [years]a | Mean (95% CI) 7.5 (6.6–8.5) | 303 |
| | Median (IQR) 5.0 (2.0–10.0) | 303 |
| Severe exacerbations—n (%) | 0 169 (55.8%) | 303 |
| | 1 68 (22.4%) | 303 |
| | 2 39 (12.9%) | 303 |
| | 3 18 (5.9%) | 303 |
| | ≥4 9 (3.0%) | 303 |
| FEV1/FVC pre-bronchodilator [%] | Mean (95% CI) 66.0 (64.5–67.5) | 289 |
| | Median (IQR) 67.0 (59.0–75.0) | 289 |
| FEV1/FVC post-bronchodilator [%] | Mean (95% CI) 68.0 (66.6–69.5) | 274 |
| | Median (IQR) 70.0 (61.0–77.0) | 274 |
| FE(NO) (ppb) | Mean (95% CI) 40.0 (35.3–44.7) | 256 |
| | Median (IQR) 29.0 (16.7–49.0) | 256 |
| Eosinophil count (cell/mm3)—n (%) | <150 77 (26.5%) | 291 |
| | 150–300 65 (22.3%) | 291 |
| | 300–500 80 (27.5%) | 291 |
| | ≥500 69 (23.7%) | 291 |
| | Mean (95% CI) 436.6 (313.9–379.4) | 291 |
| | Median (IQR) 300.00 (135.00–485.00) | 291 |
| ≥2 severe exacerbations and > 150 cells/mm3—n (%) | Mean (95% CI) 470.0 (376.8–563.3) | 280 |
| | Median (IQR) 229.0 (94.6–542.0) | 280 |
| Total serum IgE levels (kU/L) | Mean (95% CI) 470.0 (376.8–563.3) | 280 |
| | Median (IQR) 229.0 (94.6–542.0) | 280 |
| SPT positive—n (%)b | 183 (65.8%) | 278 |
| Type of allergen—n (%)b | Mites 122 (43.9%) | 278 |
| | Pollens 106 (38.1%) | 278 |
| | Animal dander 90 (32.4%) | 278 |
| | Molds 27 (9.7%) | 278 |
| | Other 11 (4.0%) | 278 |

CI: confidence interval; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; FE(NO): fractional exhaled nitric oxide; IgE: immunoglobulin E; IQR: interquartile range; ppb: particles per billion; SPT: skin prick test; N: number of patients. FEV1/FVC (%): absolute ratio of FEV1 and FVC expressed as percentage.

aUntil inclusion visit.
bNon-exclusive categories.
Figure 1. Eosinophil count according to SPT in total population and population with ≥2 severe exacerbations.

Figure 2. Mean SGRQ score (95% CI) for each scale: comparison of study population and general healthy population. *According to data from the healthy Spanish general population (n = 862) [24]. SGRQ: Saint George's Respiratory Questionnaire.
than in those with partially controlled and controlled asthma (€3043 [1869–11327] and €3070 [1553–10578], respectively). Supplementary Table SA3 shows all costs according to the degree of asthma control (ACQ-5).

**Discussion**

This study evaluated the impact of severe asthma in adult Spanish patients by analysis of direct and indirect costs and QoL and asthma control questionnaires, providing information about the economic impact of the disease and the self-perceived health status of the patients. The mean annual cost of an adult patient with severe asthma in Spain was €8554 from the social perspective, of which approximately 13.0% corresponded to indirect costs. Pharmacological treatment represented 85.0% of direct costs in the stable phase.

The QoL results showed a notable difference between the mean total SGRQ score in the study population (38.1 points) and the mean total score of the healthy Spanish population (8.4 points) [22]. In addition, 67.7% of patients had poor asthma control despite medication and only 25.1% were controlled.

The cost of asthma is related to severity of the disease. The results described in others studies showed that the cost for patients with severe asthma were almost three times higher than for those with moderate asthma (€1196 vs €2782, for moderate and severe asthma, respectively) [4,5].

### Table 3. Pharmacological treatment in stable phase and during severe exacerbations.

| Group               | n (%) | Three groups prescribed to <2% of patients not shown |
|---------------------|-------|------------------------------------------------------|
| **Stable phase (N = 303)** |       |                                                      |
| Fixed combinations: ICS/LABA | 293 (96.7) |                                                      |
| LTRA                 | 173 (57.1) |                                                      |
| SABA                 | 166 (54.6) |                                                      |
| Anticholinergics     | 138 (45.5) |                                                      |
| Anti-IgE monoclonal antibodies | 119 (39.3) |                                                      |
| Systemic glucocorticoids | 37 (12.2)  |                                                      |
| Inhaled glucocorticoids | 31 (10.2)  |                                                      |
| **Severe exacerbations (N = 134)** |       |                                                      |
| Systemic glucocorticoids | 126 (94.0) |                                                      |
| Antibiotics          | 26 (19.4)  |                                                      |
| SABA                 | 15 (11.2)  |                                                      |
| Anticholinergic      | 6 (4.5)    |                                                      |
| ICS                  | 4 (3.0)    |                                                      |

ICS: inhaled corticosteroids; LABA: long-acting β2-adrenergic agonists; LTRA: leukotriene receptor antagonists; SABA: short-acting inhaled β2-adrenergic agonists.

### Table 4. Characteristics of asthma severe exacerbations.

| Variables                        | N = 134 |
|----------------------------------|---------|
| **Outpatient visits per patient** |         |
| Number of unscheduled visits due to severe exacerbations |         |
| Mean (95% CI)                    | 2.8 (2.4–3.2) |
| Median (IQR)                     | 2.0 (1.0–3.0) |
| **Number of PC unscheduled visits** |         |
| Mean (95% CI)                    | 0.88 (0.67–1.1) |
| Median (Min–Max)                 | 1.0 (0–10.0) |
| **Number of SC unscheduled visits** |         |
| Mean (95% CI)                    | 0.78 (0.60–0.95) |
| Median (Min–Max)                 | 1.0 (0–5.0) |
| **Number of emergency visits**   |         |
| Mean (95% CI)                    | 1.1 (0.90–1.4) |
| Median (Min–Max)                 | 1.0 (0–8.0) |

 rents included visits to PC physician and/or SC and/or emergency field.

| **Hospitalizations per patient (N = 22)** |         |
| Number of hospital admissions |         |
| Mean (95% CI)                  | 0.52 (0.37–0.68) |
| Median (IQR)                   | 0 (0–7.0) |
| Number of hospital emergency visits |         |
| Mean (95% CI)                  | 0.61 (0.43–0.79) |
| Median (IQR)                   | 0 (0–7.0) |
| **Length of hospital stay [days]** |         |
| Mean (95% CI)                  | 10.9 (6.5–15.2) |
| Median (IQR)                   | 8.0 (5.2–12.0) |

CI: confidence interval; IQR: interquartile range; Min: minimum; Max: maximum; PC: primary care; SC: secondary care.

**Costs**

**Direct healthcare costs**

The mean annual cost per patient during the stable phase was €6848 (n = 303), with pharmacological costs accounting for 85.0% of the total (Table 5). Mean annual pharmacological costs were higher for patients treated with a biological treatment (€13 124 [95% CI: 11 670–14938]) than those without (€1100 [95% CI: 1017–1193]). Of the 303 patients, 134 had ≥1 severe exacerbation whose mean annual cost per patient was €1410, with hospital admissions generating the highest cost (Table 5).

**Indirect costs**

The mean annual indirect cost per patient of lost work productivity due to severe asthma was €1081 (Table 5). However, if only the 150 workers were considered, the mean was (95% CI) €2072 (1050–3821) per patient.

**Total costs**

The mean (95% CI) direct annual direct cost was €7472 (6579–8612) per patient, of which €6848/patient corresponded to the total cost in the stable phase (91.6% of direct cost) and €623.5/patient to the total annual cost in severe exacerbations. From the social perspective, considering the indirect costs, which represent 12.6% of total costs, the mean total cost per patient was €8554 (Table 5).

**Costs according to the degree of asthma control**

The median (IQR) total annual cost was higher in patients with uncontrolled asthma (€3616 [1915–11485]) than in those with partially controlled and controlled asthma (€3043 [1869–11327] and €3070 [1553–10578], respectively). Supplementary Table SA3 shows all costs according to the degree of asthma control (ACQ-5).
The costs obtained are clearly higher than those of previous reports on the cost of Spanish patients with asthma. In the AsmaCost study [6], the mean annual cost per patient with severe asthma, defined according to the Global Initiative for Asthma/Spanish Guidelines for Asthma Management criteria [1,23], the mean estimated cost was €2635 (€2392 direct costs and €243 indirect costs), one third of the costs found in our study. In addition to the subtle differences in the definition of severe asthma in the two studies, one reason for the increase in costs may be the introduction into the Spanish market of the first biological drug for severe asthma, omalizumab, in 2011. In our study, the pharmacological costs obtained for patients treated with biological treatment was almost 12 times higher than for those with non-biological treatment (€13 124 vs €1100, respectively). All monoclonal antibody drugs have a high production cost, which impacts on their market price [24]. However, several studies have positively assessed the cost-effectiveness, since this biologic drug improve the QoL, decrease hospital admissions, prevent exacerbations, and allow reductions in oral glucocorticoids and, consequently, adverse events [25–32].

The results obtained in our study are close to a recent local study performed in two areas of Spain (La Roca del Vallés and Girona) that estimated the annual cost per patient with severe asthma between €5842 (patients with ≥2 exacerbations) and €3655 (patients with <2 exacerbations) [33]. Increasing costs due to rising pharmacological costs have also been observed in other countries such as the United Kingdom in which, in recently published studies, the pharmacological cost represented between 57.4 and 75.0% of the total direct cost [34,35].

Likewise, only 25.1% of our patients had controlled asthma. Patients with poor or partial asthma control had higher mean total costs (€9014 and €8840, respectively) than controlled patients (€7229), as described by other studies such as the EUCOAST study [7].

These results show the importance of therapeutic alternatives that decrease the rate of exacerbations and increase the percentage of patients with controlled asthma in reducing the costs of severe asthma.

The IDEAL study [36] described the eligibility and overlapping of severe asthmatic patients for treatment with the three biological drugs currently marketed in Spain: omalizumab (anti-IgE), mepolizumab (anti-IL-5) and reslizumab (anti-IL-5). According to the eligibility criteria for each drug, which were taken from the regulatory label of omalizumab and from clinical trial inclusion criteria in the case of mepolizumab and reslizumab, patients with severe asthma with a non-allergic phenotype could not benefit from omalizumab. Therefore, according to the eligibility criteria, at least 34.8% of the total population of this study lacked therapeutic alternatives at the time of the study, as they had a negative SPT and the only biological available was omalizumab.

The results obtained in our study are close to a recent local study performed in two areas of Spain (La Roca del Vallés and Girona) that estimated the annual cost per patient with severe asthma between €5842 (patients with ≥2 exacerbations) and €3655 (patients with <2 exacerbations) [33]. Increasing costs due to rising pharmacological costs have also been observed in other countries such as the United Kingdom in which, in recently published studies, the pharmacological cost represented between 57.4 and 75.0% of the total direct cost [34,35].

### Table 5. Costs per patient during the last 12 months.

| Variables | Cost (€) Mean (95% CI) |
|-----------|-----------------------|
| **Direct health cost** | |
| Total annual cost of resource use in stable phase (N = 303) | 6848.2 (6002.7–7884.6) |
| Annual pharmacological cost | 5822.6 (4996.6–6831.6) |
| Annual cost of total visits | 343.4 (311.9–384.3) |
| Annual cost of ambulatory tests | 682.2 (620.9–754.5) |
| Total cost of resource use during severe exacerbations (N = 134) | 14099.0 (947.7–2322.4) |
| Pharmacological cost | 9.8 (7.8–12.8) |
| Cost of PC physician unscheduled visits | 21.3 (17.0–27.8) |
| Cost of SC unscheduled visits | 67.1 (53.5–82.6) |
| Cost of PC emergency room visits | 39.6 (28.9–52.7) |
| Cost of hospital emergency room visits | 99.4 (73.9–133.3) |
| Cost of hospital admissions | 11583 (707.6–2031.8) |
| Cost of stay in ICU | 14.4 (0.04–43.2) |
| Total direct annual health cost (N = 303) | 7471.8 (6578.7–8612.4) |
| Total annual cost in stable phase | 6848.2 (6002.7–7884.6) |
| Total cost during severe exacerbations | 623.5 (406.9–1018.4) |
| **Indirect cost** | |
| Annual cost of lost productivity (N = 303) | 1081.8 (563.7–1987.4) |
| **Total costs** | |
| Total direct and indirect annual cost (N = 303) | 8553.6 (7411.0–10199.0) |

PC: primary care; SC: secondary care; 95% CI: 95% confidence interval; N: number of patients; ICU: intensive care unit.
variables. This subpopulation would correspond to the 19% of the IDEAL study patients eligible only to be treated with anti-IL-5 and, therefore, not included in the overlap with omalizumab [36].

Some limitations of the study may have influenced the results. First, due to the nature of retrospective observational studies, there was a lack of information on some clinically-relevant variables for patients with severe asthma (e.g., lung function, eosinophil count, total serum IgE levels and SPT results). Even so, data were obtained for >80% of the study population. However, complex analyses which studied the population affected by the interaction of two or more variables (eosinophilia, SPT, and/or severe exacerbations) may have had a small sample size.

Second, QoL is normally analyzed according to the evolution of the questionnaire score throughout the follow-up period. In our case, as it is a retrospective study, we did not obtain data on the progression of QoL and, therefore, we compared the score with that of the healthy population of another Spanish study [22].

Third, the stratified analysis of costs according to the degree of control of asthma was not proposed as the main objective and, therefore, the subgroups obtained were not balanced. However, it was estimated that the cost of controlled asthma was lower than that of uncontrolled asthma as shown in previous studies [7].

Fourth, the indirect costs in this study were approached by the human capital method. There were only included the costs associated with days of absenteeism attributable to severe asthma in actively employed patients and indirect cost of patients not actively employed during the study period was 0. Therefore, the indirect costs were probably underestimated by not taking into account the loss of productivity due to the days the patient attended work suffering from severe asthma (presenteeism). A 2013 Spanish study that considered the cost of presenteeism and absenteeism in patients with asthma estimated the indirect costs at €3430 [37], well above the €1082 estimated in our study.

Conclusions

Until now, no study has specifically evaluated the impact of severe asthma in real life with Spanish patients.

Despite the limitations of the study, the results show the high economic impact of severe asthma and its severe exacerbations in Spain. In addition, we found that most patients do not reach optimal asthma control despite medication, and it is precisely this poorly-controlled population that has a higher impact.

We found that, at the time of the study, some patients lacked a specific therapeutic alternative. It is hypothesized that in future studies a decrease in exacerbations in these patients may be observed due to the appearance of new, specific treatments, which could reduce total costs.

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Declarations of interests

AH is a GSK employee and shareholder. CM is now a GSK employee but was not associated with GSK at the time of this study. SQ has no relevant competing interest to disclose. EU and MC are employees of Oblikue Consulting, which received funds from GSK for the development and analysis of this study. AH, CM, SQ, EU, and MC contributed to the conception and design of the study, the acquisition and interpretation of data, and the drafting of the article. EU and MC contributed to the analysis of the study. Editorial support in the form of literature review and editing was provided by Maria Mallén at Oblikue Consulting and was funded by GSK. All authors have given final approval of this version to be published.

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