Prevalence, T2-biomarkers and cost of severe asthma in the era of biologics: The BRAVO-1 study

Short Title: Prevalence and cost of T2 severe asthma

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ABSTRACT

Background. The last decade has seen a new era of classifications of asthma pathophysiology which have changed the treatment options available.

Objectives. To update the figures of prevalence of T2 asthma, comorbidities, biomarker characterization and costs of severe asthma in patients≥12-years-old adapted to this new situation.

Methods. Retroprospective, observational, nationwide study using a top-down approach. Data were obtained from the BIG-PAC®, an electronic medical record database of 1.7 million patients in Spain. Patients≥12-years-old who had received medical care during the period 2016-2017 and diagnosed with asthma at least one year prior to the index date were included and followed for one year.

Results. Prevalence of asthma was 5.5%. Of these patients, asthma was severe in 3.031 (7.7%), 81.2% of whom presented T2 asthma. Among severe asthma patients, 64·1% were uncontrolled, 31.2% were Oral corticosteroids-dependent (37% in the uncontrolled severe asthma group) and only 3.8% were on biologics. The most common T2 comorbidities were allergic rhinitis (66·1%), atopic dermatitis (29·1%) and chronic rhinositis with nasal polyps (14.6%). Mortality rates in the total and the uncontrolled severe asthma groups were 4.2% and 5.5% respectively. The total annual costs per patient with severe asthma were 5.890€ (uncontrolled) and 2.841€ (controlled).

Conclusions. In the era of biologics, most severe asthma patients present T2 asthma. Despite the availability of new treatments, the rates of uncontrolled and oral corticosteroids-dependent patients with severe asthma remain high, but biologics still underused. The costs of uncontrolled severe asthma are twice as high as those of controlled severe asthma.

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Key words: Asthma prevalence. Severe asthma. Type 2 asthma. Uncontrolled asthma. Asthma comorbidities. Asthma costs.

RESUMEN

Introducción. En la última década se han concadenado una serie de clasificaciones de la fisiopatología del asma que ha cambiado las opciones de tratamientos disponibles.

Objetivos. Actualizar los datos de prevalencia del asma T2, comorbilidades, caracterización de biomarcadores y costes del asma grave en pacientes ≥ 12 años en esta nueva situación.

Métodos. Estudio retrospectivo, observacional y de ámbito nacional con un enfoque descendente. Los datos se obtuvieron de BIG-PAC®, una base de datos de historias clínicas electrónicas de 1,7 millones de pacientes en España. Se incluyeron pacientes ≥ 12 años que habían recibido atención médica durante el periodo 2016-2017 y que habían sido diagnosticados de asma al menos un año antes de la fecha índice y fueron seguidos durante un año.

Resultados. La prevalencia del asma fue del 5.5%. De estos pacientes, 3.031 presentaban asma grave (7.7%), de los cuales el 81.2% presentaba asma T2. Entre los pacientes con asma grave, el 64.1% no estaban controlados, el 31.2% eran dependientes de corticosteroides orales (37% en el grupo de asma grave no controlada) y sólo el 3.8% estaban en tratamiento con biológicos. Las comorbilidades T2 más frecuentes fueron la rinitis alérgica (66.1%), la dermatitis atópica (29.1%) y la rinosinusitis crónica con poliposis nasal (14.6%). Las tasas de mortalidad en los grupos de asma grave total y no controlada fueron

del 4.2% y del 5.5% respectivamente. Los costes totales anuales por paciente con asma grave fueron de 5.890 euros (no controlado) y 2.841 euros (controlado).

Conclusiones. En la era de los biológicos, la mayoría de los pacientes con asma grave presentan asma T2. A pesar de la disponibilidad de nuevos tratamientos, las tasas de pacientes con asma grave no controlados y dependientes de corticosteroides orales siguen siendo altas, y los biológicos siguen estando infrautilizados. Los costes del asma grave no controlada duplican los del asma grave controlada.

Palabras clave: Prevalencia del asma. Asma grave. Asma Tipo 2. Asma no controlada. Comorbilidades del asma. Costes del asma.

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INTRODUCTION

During the last two decades, the classification of asthma patients has progressed notably in parallel with the advances in the understanding of the different pathophysiologic pathways, also named endotypes. First, the allergic cascade was renamed “adaptive immunity” or “Th2 profile” (the role of Th2 leukocytes was recognized as paramount) [1]. The next step was to identify the role of innate immunity triggered by the secretory function of the bronchial epithelium (and the release of alarmins) and its control over adaptive immunity [2]. The two arms of immunity have the capacity to synthesize and release the same cytokines (IL4, IL5 and IL13) and subsequently increase the number of eosinophils as well as the exhaled fraction of nitric oxide (FeNO). Given the involvement of ILC2s (from the innate arm) combined with Th2 lymphocytes (from the adaptive arm), this condition has been termed “T2 asthma”. To meet the criteria for T2 asthma, patients must have a peripheral blood eosinophil count≥150 and/or FeNO value≥20 ppb and/or be allergic (with increased specific IgE or positive skin prick test against an allergen, plus clinical symptoms of allergy: GINA 2021). The response to ICS and OCS is also characteristic of T2 asthma patients. Patients who do not meet the criteria for T2 asthma are defined as non-T2.

This new classification or redefinition of the types of asthma derived from new immunobiological knowledge renders obsolete the data currently available on the disease. It is now necessary to establish the prevalence of these new groups and of the most frequent comorbidities; to determine the rates of severe asthma (controlled and uncontrolled); to assess the adequacy of the treatments patients receive and to determine the costs of patient management.

The aim of our study is to fill this information gap by means of a country-wide study determining the prevalence, comorbidities, biomarkers characterization and costs of severe asthma in patients≥12-year-old in standard clinical practice.

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METHODS

Study design and data source

Design: Retroprospective, observational, nationwide study applying a top-down approach.

Data source: The BIG-PAC® database (Real Life Data; *http://www.encepp.eu/encepp/search.htm*) an electronic medical records database containing anonymized and dissociated data of 1.7 million patients from seven Spanish regions chosen as representative of the whole country. Patients records were obtained using the International Classification of Diseases (CIE-10-MC:J45-J46).

The electronic medical records provided retrospective and prospective measurements during a one-year follow-up.

Clinical and laboratory data: asthma diagnosis, exacerbation rate, biomarkers (blood total immunoglobulin E (IgE) levels, blood eosinophils (EOS) and FeNO) and spirometry data were obtained; the value closest to the date of inclusion was recorded. Medical visits (primary care, specialist, emergency department), radiological tests and other complementary tests were also compiled.

Medication administered: the active ingredients were obtained from drug dispensing records and classified according to the ATC (*Anatomical Therapeutic Chemical Classification System*) [3]. The medications prescribed during the one-year follow-up period were recorded: oral corticosteroids (OCS, H02AB), short-acting beta-agonists (SABA, R03AC), systemic beta-2 agonists (xanthine, R03), leukotriene antagonists (R03DC) anticholinergics (LAMA, R03BB04: tiotropium bromide) and biologics (R03DX05). OCS consumption was classified into two different categories: OCS-dependent patients (those receiving repeated prescriptions of OCS>6 month/year) and those receiving bursts of OCS for exacerbations.

Resource utilization: The use of resources during the follow-up period was recorded. The following variables were considered: healthcare costs (direct costs) relating to healthcare activity (primary or specialized medical visits, hospital days, emergencies, diagnostic or therapeutic needs and/or medication), and non-healthcare costs (indirect costs) were those related to lost work productivity (days off work).

Costs: Costs were expressed as the mean annual cost per patient. The different study concepts and their economic assessment are detailed in **Table 1**. The cost of prescriptions was quantified according to the price per package (public retail price + value added tax) at the time of prescription (source: Bot Plus database [4]). Non-healthcare costs comprised only the days off work or productivity loss based on the interprofessional minimum wage (source: Spanish National Statistics Institute, INE [5]); other direct non-healthcare costs (i.e., "out-of-pocket costs" or costs paid by the patient/family) were not included, since these data were not recorded in the database, and the study design precluded direct access to the patient. Patient resource use and costs referred only to asthma.

Population characteristics:

Sociodemographic variables and comorbidity

Demographic data as well as diseases with a high prevalence are summarized in **Table 2**.

Specific comorbidities related to asthma such as allergic rhinitis (AR), atopic dermatitis (AD), chronic rhinosinusitis with nasal polyps (CRSwNP) were also recorded.

To summarize general comorbidity for each patient we calculated: a) the Charlson comorbidity index [6] as a proxy of patient's severity and mortality risk and b) the total and mean number of chronic comorbidities. These data were obtained on the index date of the patient's inclusion (first record between January 1 2016 and December 31 2017).

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Inclusion and exclusion criteria

The study included all patients diagnosed with asthma (CIE-10-MC:J45-J46) requiring care between January 1 2016 and December 31 2017 who met the following characteristics: a) age≥12 years; b) guaranteed follow-up (≥2 contacts) in the database at least 12 months prior to the start of the study; c) enrolment in the prescription program (with documented daily dosage, time interval and duration of each treatment provided); d) asthma diagnosed at least 12 months before the inclusion date. The exclusion criteria were a) patients transferred to other centers or from outside the center's recruitment area; b) permanently institutionalized patients; c) patients with a history of cystic fibrosis, lung cancer, bronchiectasis, or pulmonary fibrosis; (d) patients with actively treated or advanced cancer; and d) terminally ill patients or patients receiving palliative care.

Definitions

Asthma severity was classified according to the International ERS/ATS guidelines [7] and assessed according to the recommendations of GINA [8] (high doses of inhaled corticosteroids and an additional controller medication [LABA, leukotriene antagonists, theophylline, OCS more than 6 month] during the 12 months prior to the inclusion date).

Uncontrolled severe asthma was defined as patients who presented≥2 exacerbations requiring OC use for more than three days, and/or a hospital admission during the previous year [9]. Controlled asthma patients are those who do not fulfill the criteria for uncontrolled asthma.

Severe exacerbation was defined when the patient received a burst of OCS, increased the daily maintenance dose for more than three days, and/or required hospital admission.

OCS-dependent: OCS intake on a regular basis for≥six months.

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Allergy: Since it was impossible to obtain reliable information on specific IgE for every patient, for the purposes of this study patients with a positive skin prick test and total IgE >100 UI/mL were considered to be allergic.

T2: T2 patients were defined as those with peripheral blood eosinophil count (EOS) ≥150/µl, and/or a fractional exhaled nitric oxide concentration (FeNO) ≥25 ppb, and/or were allergic or required OCS maintenance.

Follow-up: One year from the index date and/or death for any cause.

Outcomes

Prevalence of asthma, severe asthma, uncontrolled asthma, OCS-dependent asthma, T2 asthma and costs of asthma management were estimated.

Statistical analysis

Data validation was performed to ensure the quality of the results. A univariate descriptive statistical analysis was performed for the variables of interest. Absolute and relative frequencies were recorded for qualitative data. Proportions and 95% confidence intervals (CIs) for parameters of interest were based on the total number of subjects with no missing data. Means and standard deviations (SD), analysis of variance (ANOVA) and chi-squared test were used for the bivariate analysis. For cost correction, an analysis of covariance (ANCOVA; generalized linear model) was carried out with gender, age, Charlson index and time from diagnosis as covariates (procedure: estimation of marginal means; Bonferroni correction). Multiple linear regression analysis was used to obtain the variables associated with healthcare costs (dependent variable; stepwise procedure). The SPSSWIN version 23 statistical package was used, with statistical significance set at $p<0.05$.

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Confidentiality of the information

The confidentiality of the data (anonymized and dissociated) was respected in accordance with Spanish legislation on personal data protection. The study was classified by the Spanish Agency for Medicinal Products and Medical Devices as EPA-OD (observational, post-authorization and retrospective study) and was subsequently approved by the Clinical Research Ethics Committee of Terrassa Hospital (Barcelona).

RESULTS

A total of 744.033 individuals≥12 years of age required care during 2016-2017. Of these, 40.553 were diagnosed with asthma, resulting in a prevalence of 5.5% (95% CI: 5.2–5.8%). Regarding age distribution, 4.9% were adults and 7.8% were adolescents (**Figure 1**).

The baseline characteristics (demographic and morbidity) according to study group are shown in **Table 2**. The mean age was 64.3 years, 67.3% were female and the mean Charlson index score was 1.4 points. Allergic rhinitis (66.1%), hypertension (33.2%) and dyslipidemia (46.8%) were the most frequent comorbidities. The subjects with uncontrolled asthma presented a higher comorbidity burden. Moreover, annual mortality rate was 4.2% for all severe patients (5.5% in the uncontrolled group and 1.8% in the controlled group).

Table 3 displays the medication administered during the follow-up period. All patients in the study were being treated with inhaled corticosteroids (ICS), long-acting beta-2 agonists (LABAs) and short-acting beta-2 agonists (SABAs) as rescue therapy.

In the total of patients ≥12 years with asthma, the prevalence of severe asthma was 7.7% (95% CI 7.5-7.9%). The 3.031 patients who met the inclusion/exclusion criteria were analyzed and followed up during the study period. According to the criteria applied, 64.1% (N=1.944)

of the severe asthma patients were classified as uncontrolled and 35.9% (N=1.087) as controlled. The prevalence of severe uncontrolled asthma was 4.9% (95% CI: 4.1–5.7%) in the total asthma population.

Almost half the patients (48.6%) received OCS at some time; 31.2% of them were considered OCS-dependent (37.0% in the uncontrolled group vs. 21.0% in the controlled group; p<0.001) representing a 2.3% of total asthmatic patients. Uncontrolled patients consumed a higher proportion of asthma-associated and concomitant medications (1.7vs.1.5; p<0.001).

The relationship of biomarkers according to the study groups is detailed in **Table 4.** The percentage of patients with severe asthma presenting T2 inflammation was 81.2% (96% in uncontrolled severe asthma patients).

During the one-year follow-up, mortality in the total severe asthma population was 4.2% and in the uncontrolled severe asthma group 5.5%. Uncontrolled patients used more healthcare resources, particularly in terms of the number of primary care visits (13.4vs.10.4; p<0.001), days of hospital stay (6.1vs.1.2; p<0.001), and productivity loss in days off work (4.8vs.2.4 days; p<0.001) (**Table 5).** The total cost of the patients with controlled and uncontrolled severe asthma included in the study was 17€ million/year, of which 91.8% corresponded to direct healthcare costs and 8.2% to indirect costs (productivity loss), with a mean total annual unit cost of 4.856€. The main components of this healthcare cost were hospital admissions (37.5%) and associated medications (34.4%). The average annual total unit costs corrected for covariates (ANCOVA) of uncontrolled and controlled patients were 5.890€ vs 2.841€ (p<0.001) respectively. These differences were found in healthcare costs (5.443€ vs. 2.602€, p<0.001) and in non-health costs (lost work productivity: 447€ vs. 239€, p=0.036).

In the binary correlation model, the exacerbations correlated moderately with EOS (r=0.452) and higher with FEV_1 (r=-0.510) and health costs (r=0.693). Uncontrolled severe asthma was correlated largely with exacerbations (r=0.625) and health cost (r=0.513); p<0.01 in all cases.

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In the multiple linear regression model (stepwise approach), healthcare cost correlated positively with lack of asthma control (uncontrolled: β=0.068, t=3.5), number of exacerbations (β=0.486, t=24.2), EOS (β=0.177, t=3.1), OCS use (>six month/year: β=0.035, t=6.5), age (β=0.102, t=5.9), Charlson index (β=0.112, t=5.9) and negatively with FEV1 (β=-0.038, t=-2.6); p<0.01 in all cases. The coefficient of determination (R^2) of the model was 66.8%.

DISCUSSION

Asthma is a chronic respiratory disease with a variable prevalence depending on the series reviewed. It is considered to range between 5-10% of the adult population [10,11].

Severe asthma is a heterogeneous condition with multiple clinical phenotypes. The data on the prevalence of severe asthma that are currently available are variable, particularly in adults [9,12-13] but it is generally accepted that it accounts for 5-10% of the general population of asthmatics [7,12]. In agreement with these data, the BRAVO-1 study found a prevalence of asthma of 5.5% and of severe asthma of 7.7% in the asthmatic population aged over 12 years.

Patients with severe asthma may be either controlled or uncontrolled [8-9,12-13]. BRAVO-1 found that two-thirds of severe asthma patients (representing 4.9% of all asthma patients) met the definition of uncontrolled severe asthma. In other words, most patients with severe asthma have poor disease control [8-9,14]. In a study carried out in Spain a decade ago, the prevalence of uncontrolled severe asthma in the asthmatic population was 3.9% [13]. To classify patients, that study used medical criteria; therefore, as the authors noted, it systematically underestimated disease severity compared with the GINA criteria that we used in our study. As a result, we believe our data are more reliable.

When the data were evaluated according to the recent pathophysiological classification, (i.e., as T2 and non-T2 asthma), BRAVO-1 found that 81.2% of patients with severe asthma met the criteria for T2 inflammation. Among the uncontrolled severe asthma patients, the percentage was even higher (96%), showing a close association between T2 inflammation and lack of control in severe patients. The importance of proper patient phenotyping directly influences the appropriate or suboptimal use of the monoclonal antibodies [15].

In the literature, the information available on T2 prevalence is scarce. In one paper, T2 inflammation is described as occurring in “many but not all patients” (sic) [16]. Others repeat the data of previous manuscripts, and even GINA speaks of “the majority of people with severe asthma” (sic) but does not accompany this sentence with any data or a quotation [8]. Other attempts to show the prevalence have been made based on sputum interleukin analysis [17] or gene expression [18] reporting figures of 53% and 70% respectively. These studies refer to Th2 and not to T2 asthma. The most recent study, Frossing et al [19], refers to T2 patients and gives a figure of 70% combining clinical and biomarker data. However, the number of patients is limited (116 [70%] out of 166 asthma patients included).

Our figure of 81.2% thus contributes to clarifying the prevalence of T2 asthma among severe asthma patients. As expected, it is higher than the rates of Th2 patients obtained in molecular studies (T2 includes Th2) and our study has a much larger sample than Frossing’s study. Finally, the prevalence of T2 asthma among uncontrolled severe asthma patients has not yet been recorded in the literature, and so our figure of 96% breaks new ground.

T2 asthma is frequently associated with other T2 diseases. BRAVO-1 found that 66.1% of patients had associated allergic rhinitis, 29.1% atopic dermatitis and 14.6% nasal polyposis. These results are in line with the literature published [20]. Our study also found that the percentage of comorbid T2 diseases is even higher in patients with uncontrolled severe asthma, showing that comorbidities not only increase the clinical and disease burden in these

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patients but also add to the difficulty of controlling the asthma and make more complex the therapeutic management of these subjects [21].

Comorbidities were also recorded through the Charlson Comorbidity Index. This index categorizes patients' comorbidities based on the International Classification of Diseases diagnosis codes found in administrative data, such as hospital abstracts data. Each comorbidity category has an associated weight (1-6), based on the adjusted risk of mortality or resource use, and the sum of all the weights produces a single comorbidity score for a patient. A score of zero indicates that no comorbidities were found. The higher the score, the more likely the predicted outcome will result in mortality or higher resource use. According to this index, the mortality risk associated to comorbidities was in general low; in any case, the index was significantly higher in uncontrolled patients. Finally, mortality was also higher in uncontrolled severe asthma patients than in controls.

BRAVO-1 found that 31.2% of the patients met the criteria for OCS dependence (37.0% in uncontrolled severe asthma). Similar results have been found by other authors. In their narrative review, Chung et al [22], reported a range of 25.60% in developed countries. Taube et al [23], found a prevalence of severe asthma of 7.3%, among which 33.6% were OCS-dependent. Izquierdo et al [24] highlighted the frequently use of OCS in Spain (ranging from 31.4% in 2015 to 39.6% in 2019). BRAVO-1 also showed that 1 out of 43 asthma patients are corticodependent. Like us, other authors concluded that many patients do not receive optimal therapy for asthma, this is one of the reasons for the high rate of OCS consumption. These results drew attention to the need for new treatments for severe asthma, and in fact this view is increasingly reflected in current treatment guidelines that incorporate objective biomarker-based strategies [14,25]. Long-term use of OCS can improve asthma control, but its side effects should be borne in mind. A careful appraisal would show that a substantial number of these OCS patients may be candidates for biological treatments. Unfortunately, as the present study reflects, only 3.4% of severe asthma patients are administered biologics.

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Despite optimized standard treatment, quality of life in severe asthma patients is poor because of their chronic symptoms (coughing, wheezing, and shortness of breath). They have a high risk of severe asthma attack that may require emergency room visits or hospitalization, which in turn increase mortality. Although the trends in asthma mortality in the last decade shows a progressive decrease, it is still responsible of about 1.000 deaths/year in Spain at the present time [26]. The mortality found in BRAVO was 4.2% for severe asthma patients, rising to 5.5% in those in whom it was uncontrolled. One of the few literature reports on asthma mortality recorded a rate of 6.7% [27] and found that higher severity-of-asthma scores and poorer perceived asthma control scores were both associated with increased mortality risk in adults with severe asthma. Although it affects a small proportion of patients, severe asthma requires high resource use and represents a significant economic burden for health systems and for patients, their families and society in general [8,12,28].

Several economic studies of asthma have been performed in Spain. In 2009, the AsmaCost study estimated the annual cost for the Spanish NHS of an asthmatic patient to be 1,533€ per patient-year, rising to 2,635€ in patients with severe asthma [29]. The study was performed before biological treatments were marketed.

In 2018, Melero et al [30] calculated that the economic impact of severe asthma for the Spanish NHS was 7.472€ per patient-year. The cost obtained was clearly higher than the previous reports on the cost of Spanish patients with asthma, one reason for the increase in costs may have been the introduction of biological treatments (annual pharmacological costs for patients treated with biological treatment was 13.124€ vs 1.100€ in patients with non-biological treatment). When indirect costs (the social perspective) were added, the total annual mean cost rose to 8.554€. Recently, Sicras-Mainar et al [31], found the mean total annual cost to be 5.493€ (healthcare cost: 68.2%; productivity losses: 31.8%).

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Other international evaluations present similar results. In the US, Chastek et al [32], reported that patients with severe asthma required more hospitalizations, medication consumption and medical visits. The mean annual cost was 5.174$, and the cost for severe patients was three times higher than for those with mild/moderate asthma. In France, in a cohort of 155 patients followed during one year, Nordon et al [33], estimated the mean annual asthma-related cost to be 8.222€. These authors highlighted the high cost of medication.

In a 20-year follow-up study, Chen et al [34], found that the incremental costs of severe asthma compared to no asthma were 2.779$ per person/year, 54% of which was attributable to comorbidities. These results highlight the importance of considering the burden of multimorbidity in evidence-informed decision-making for patients with severe asthma.

In the BRAVO-1 study, the average/unit total cost was 4.856€ patient/year. Uncontrolled severe asthma patients presented a higher cost than controlled patients (5.890€ vs. 2.841€). As shown above in the multiple regression model, higher healthcare costs were associated with lack of asthma control, number of exacerbations, EOS, OCS chronic use, age, comorbidities and negatively with FEV1.

BRAVO-1 has some of the limitations inherent in retrospective studies, related to disease definitions and data collection in the electronic records. The differences may in some cases result in incorrect classifications of severity or the underreporting of information and may affect the outcomes (clinical as well as economic). A possible bias of the study lies in the fact that the patients studied were those who sought medical attention. This possibly led to an underrepresentation of patients with milder asthma who do not usually require as much medical attention and, therefore, to an overestimation of the prevalence of more severe asthmatics. However, to some extent at least, the large amount of information obtained from this study should counterbalance its limitations, especially since BRAVO-1 is the first study of its kind in the era of biologic treatments.

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To summarize, BRAVO-1 is the largest nation-wide evaluation and the first study in the era of biologics that provides updated information on the prevalence of asthma (5.5%) and of severe asthma among asthma patients (7.7%). Most severe asthma patients presented T2 asthma (81.2%). Severe asthma continues to have high rates of uncontrolled (64.1%) and OCS-dependent patients (31.2%), despite the availability of new treatments. The percentage of patients receiving biologics is surprisingly low (3.8%). Comorbidities and healthcare resources were higher in the uncontrolled group.

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Conflicts of interests

Christian Domingo has received honoraria or consultation fees from Novartis, Sanofi, GSK, TEVA, Boehringer Ingelheim, MSD, Esteve, Almirall, AstraZeneca, Chiesi, Menarini, Pfizer, Ferrer, Stallergenes, ALK-Abelló, Allergy therapeutics, Hall Allergy, Inmunotek, Roxall. Clara Engroba is an employee of Sanofi and owns stock or stock options in Sanofi. All other authors declare no competing interest.

Previous presentation

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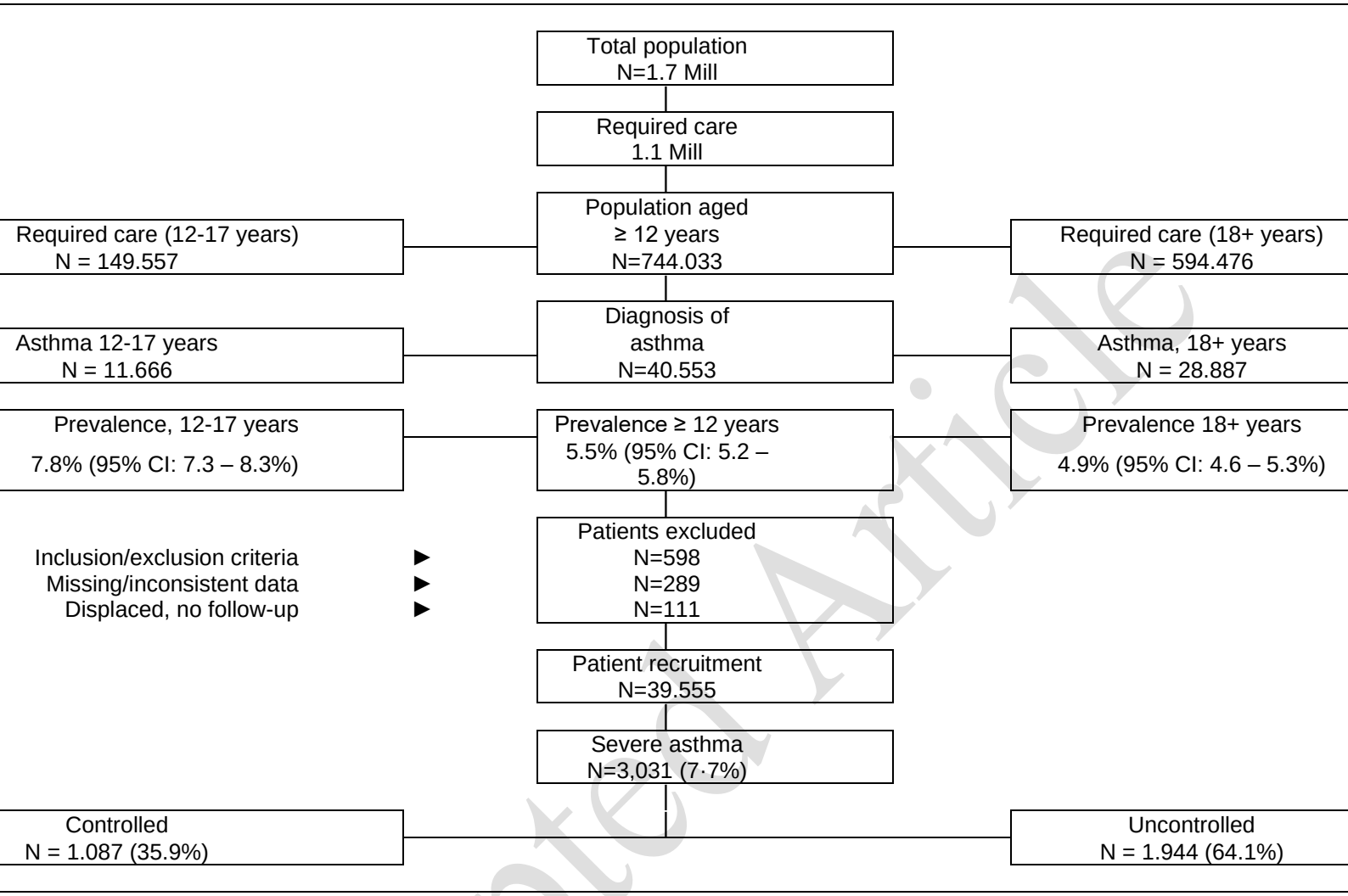
Figure 1. Study Flow chart. A retrospective observational design was adopted based on review of medical records (electronic databases containing anonymized and dissociated data) of patients with asthma.



Abbreviation: CI, confidence interval.

Table 1. Description of the resources use and unit costs (year 2019)

Healthcare and non-healthcare resources	Unit costs (€)
Medical visits	
Primary care visits	23.19
Emergency care visits	117.53
Hospital admission (one day)	420.90
Specialized care visit*	92.00
Complementary tests	
Laboratory tests	22.30
Conventional radiology	18.50
Computed axial tomography	96.00
Magnetic resonance imaging	177.00
Diagnostic/therapeutic tests**	37.12
Drug prescription	PRP + VAT
Work productivity – indirect costs	
Cost per day off work	101.21

Source of healthcare resources: proprietary analytical accounting and Spanish Statistics Institute.
Abbreviation: PRP, public retail price
*Only in pulmonology, allergy and internal medicine departments.
**Asthma-related.

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Table 2. Baseline characteristics of the severe asthma patients according to study group

Study groups,	Controlled	Uncontrolled	Total	
Nº of patients, %	N = 1.087 (35.9%)	N = 1.944 (64.1%)	N = 3.031 (100%)	p-value
Sociodemographic characteristics				
Mean age, years	63.6 (18.5)	64.7 (17·2)	64.3 (17·7)	0·116
Ranges: 12 - 17 years	1·1%	1·4%	1·3%	
18 - 44 years	16·3%	11·6%	13.3%	
45 - 65 years	29.7%	32.3%	31.3%	
65 - 74 years	21.7%	23.0%	22.5%	
≥ 75 years	31.2%	31.7%	31.5%	0.006
Gender (female)	67.4%	67.3%	67.3%	0.754
General comorbidity				
Mean diagnoses	3.7 (2.2)	4.3 (2.2)	4.1 (2.2)	<0.001
Charlson index	1.3 (1.3)	1.5 (1.3)	1.4 (1.3)	<0.001
0	31.0%	24.6%	26.9%	
1	32.3%	29.9%	30.7%	
2	20.9%	24.7%	23.4%	
3+	15.8%	20.7%	19.0%	<0.001
Associated comorbidities				
Hypertension	48.0%	53.8%	51.7%	0.002
Diabetes mellitus	19.3%	23.2%	21.8%	0.007
Dyslipidemia	43.3%	48.7%	46.8%	0.003
Obesity	30.8%	45.4%	39.2%	<0.001
Active smoker	8.2%	20.3%	15.9%	<0.001
Ischemic heart disease	9.5%	11.5%	10.8%	0.099
Cerebrovascular accident	7.7%	7.5%	7.6%	0.440
Heart failure	14.1%	16.4%	15.6%	0.049
Renal failure	5.4%	7.0%	6.5%	0.047
COPD	8.3%	14.1%	12.1%	0.001
Arrhythmias	18.6%	18.5%	18.5%	0.487
Dementia	13.2%	14.6%	14.1%	0.147

Malignancy	8.3%	8.4%	8.3%	0.490
Gastro-esophageal reflux	11.0%	12.7%	12.1%	0.105
Osteoporosis	18.9%	22.8%	21.4%	0.006
Specific associated comorbidities				
Allergic rhinitis	60.7%	69.2%	66.1%	<0.001
Atopic dermatitis	24.3%	31.8%	29.1%	<0.001
Nasal polyposis	12.5%	15.8%	14.6%	0.014
Other variables				
Death	1.8%	5.5%	4.2%	<0.001
Time to diagnosis, years	34.3 (6.5)	34.7 (6.3)	34.6 (6.4)	0.173
BMI, Kg/m^2	28.9 (6.3)	30.0 (6.1)	29.7 (6.2)	<0.001
Baseline FEV1	52.9 (4.3)	53.6 (3.3)	53.4 (3.6)	0.373

Values reported as percentages or means (standard deviation in brackets)
Abbreviations: p, statistical significance

Table 3. Medication administered, adherence to therapy and exacerbations during the follow-up period.

Study groups, Number of patients, %	Controlled N = 1.087 (35.9%)	Uncontrolled N = 1.944 (64.1%)	Total N = 3.031 (100%)	p-value
Medication used				
Oral/injectable corticosteroids	13.1%	68.5%	48.6%	<0.001
Chronic use oral corticosteroids	21.0%	37.0%	31.2%	<0.001
Systemic antibiotics	7.3%	36.2%	25.8%	<0.001
Combined ICS/LABA	100.0%	100.0%	100.0%	0.999
Leukotriene antagonists	3.0%	69.8%	45.9%	<0.001
Methylxanthines	6.0%	9.7%	8.4%	<0.001
Short.acting anticholinergic drugs	3.6%	20.7%	14.5%	<0.001
Biological treatments	2.9%	4.3%	3.8%	0.049
- Omalizumab	2.1%	3.2%	2.9%	0.045
- Others	0.8%	1.1%	0.9%	0.687
Nebulized treatments	9.9%	23.5%	17.3%	0.022
Concomitant treatment				
Acetylsalicylic acid	14.9%	15.8%	15.5%	0.264
Proton-pump inhibitor	52.9%	62.6%	59.1%	<0.001
Beta blockers	13.2%	14.7%	14.2%	0.268
Non-steroidal anti-inflammatories	34.9%	40.4%	38.4%	0.002
Antihistamines	31.9%	33.9%	33.2%	0.143
Mean nº of concomitant treatments	1.5 (1.1)	1.7 (1.1)	1.6 (1.1)	<0.001
1	33.1%	30.8%	31.6%	
2	30.5%	33.0%	32.1%	
3+	16.8%	22.0%	20.1%	<0.001

Values reported as percentages or means (standard deviation in brackets)
Chronic oral corticosteroid use defined as > 6 month/year
Abbreviations: p, statistical significance

Table 4. Biomarker characterization according to study groups

Study groups, Nº of patients, %	Controlled N = 1.087 (35-9%)	Uncontrolled N = 1.944 (64.1%)	Total N = 3.031 (100%)	p-value
Mean EOS, cel/mcL	267 (119)	348 (154)	322 (148)	0.031
Mean FeNO, ppb	34.2 (16.2)	37.0 (14.1)	36.2 (14.8)	0.462
Mean Ig E, UI/mL	187.9 (109.1)	271.6 (139.3)	245.6 (135.6)	0.015
EOS ≥ 150	74.6%	85.9%	81.9%	<0.001
FeNO ≥ 25	74.5%	86.8%	82.4%	<0.001
Allergic (Ig E > 100 UI/mL + positive prick test)	38.8%	59.9%	52.4%	<0.001
EOS ≥ 150 or FeNO ≥ 25 or Allergic or OC	54.8%	96%	81.2%	<0.001

Values reported as percentages or means (standard deviation in brackets)
Abbreviations: p, statistical significance; EOS: blood eosinophils; FeNO: Fractional exhaled nitric oxide; Ig E: Total immunoglobulin E
Patients are considered allergic when Ig E > 100 IU/L + positive allergic test (prick test)
Chronic oral corticosteroid use is defined as OCS intake > 6 month/year

Table 5. Resource utilization and associated costs (in EUR, 2019 costs) per study subgroup

Study groups, Nº of patients, %	Controlled N = 1.087 (35.9%)	Uncontrolled N = 1.944 (64.1%)	Total N = 3.031 (100%)	p-value
Medical visits				
Primary care	10.4 (12)	13.4 (13.5)	12.3 (13.1)	<0.001
Specialized care	0.8 (1.7)	3.3 (2.3)	2.4 (2.4)	<0.001
Hospital emergencies	0.4 (1.1)	1.6 (1.2)	1.2 (1.3)	<0.001
Hospitalization (days of hospital stay)	1.2 (3.1)	6.1 (4.9)	4.3 (4.9)	<0.001
Complementary tests	0.1 (0.4)	0.1 (0.5)	0.1 (0.5)	0.767
Laboratory tests	1.5 (1.9)	2.0 (2.1)	1.8 (2.1)	<0.001
Conventional radiology	0.1 (0.3)	0.4 (0.5)	0.3 (0.5)	<0.001
TAC/RNM	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0.555
Diagnostic/therapeutic tests	1.8 (1.0)	3.4 (1.4)	2.8 (1.5)	<0.001
Productivity loss (days off work)	2.4 (15.6)	4.8 (28.2)	4.0 (24.5)	<0.001
Gross costs (EUR)				
Primary care costs	241 (277)	311 (314)	286 (303)	<0.001
Specialized care costs	78 (155)	304 (209)	223 (220)	<0.001
Hospital emergencies	46 (133)	192 (146)	140 (158)	<0.001
Hospitalization (days of hospital stay)	497 (1315)	2560 (2049)	1820 (2072)	<0.001
Laboratory tests	33 (43)	46 (47)	41 (46)	<0.001
Conventional radiology	2 (5)	7 (10)	5 (9)	<0.001
TAC/RNM	7 (38)	12 (51)	10 (47)	0.001
Diagnostic/therapeutic tests	67 (38)	124 (53)	103 (55)	<0.001
Associated medications	1432 (876)	1803 (1073)	1670 (1022)	<0.001
Concomitant medications	145 (103)	165 (104)	158 (104)	<0.001
Costs groups (EUR)				
- Healthcare (direct costs)	2547 (2025)	5523 (2915)	4456 (2993)	<0.001
- Non-healthcare (productivity loss)	244 (1577)	487 (2856)	400 (2477)	0.010
- Total costs	2791 (2655)	6010 (4189)	4856 (4021)	<0.001
*Corrected cost model**			*Difference*	
Healthcare costs	2.602	5.443	2.841	<0.001
95 % CI	2.439 – 2.764	5.321 – 5.564		
Non-healthcare costs (productivity)	239	447	208	0.036
95 % CI	83 - 394	330 - 563		
Total costs	2.841	5.890	3.049	<0.001
95 % CI	2.608 – 3.073	5.715 – 6.034		

Values reported as percentages or means (standard deviation in brackets)
Abbreviations: p, statistical significance; CI: Confidence interval
*ANCOVA model (covariates: gender, age, comorbidity, and time from diagnosis; procedure: estimation of marginal means; Bonferroni correction).