ORIGINAL ARTICLE

Prevalence, T2 Biomarkers, and Cost of Severe Asthma in the Era of Biologics: The BRAVO-1 Study

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Abstract

Background: The last decade has seen new classifications of the pathophysiology of asthma that have changed the treatment options available.
Objectives: To update data on the prevalence of T2 asthma, comorbidities, biomarker characterization, and costs of severe asthma in patients aged ≥12 years, taking into account new classifications and treatment options.
Methods: Retrospective, observational, nationwide study using a top-down approach. Data were obtained from BIG-PAC®, an electronic medical record database of 1.7 million patients in Spain. The study population comprised patients aged ≥12 years who had received medical care during the period 2016-2017 and been diagnosed with asthma at least 1 year prior to the index date. Patients were followed for 1 year.
Results: The prevalence of asthma was 5.5%. Asthma was severe in 3031 of these patients (7.7%), 81.2% of whom presented T2 asthma. Among patients with severe asthma, 64.1% had uncontrolled disease, 31.2% were oral corticosteroid–dependent (37% in the uncontrolled severe asthma group), and only 3.8% were receiving biologics. The most common T2 comorbidities were allergic rhinitis (66.1%), atopic dermatitis (29.1%), and chronic rhinosinusitis with nasal polyps (14.6%). Mortality rates in the total population and uncontrolled severe asthma groups were 4.2% and 5.5%, respectively. The total annual costs per patient with severe asthma were €5890 (uncontrolled) and €2841 (controlled).
Conclusions: In the era of biologics, most severe asthma patients present T2 asthma. Despite the availability of new treatments, rates of oral corticosteroid–dependent patients with uncontrolled severe asthma remain high, although biologics continue to be underused. The costs of uncontrolled severe asthma are twice as high as those of controlled severe asthma.

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 han 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 solo 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.

Summary box

- **What do we know about this topic?**
  The prevalence of asthma, severe asthma, and especially T2 asthma, as well as the percentage of oral corticosteroid–dependent patients and patients receiving biologic therapy, is not well established.
- **How does this study impact our current understanding and/or clinical management of this topic?**
  This study demonstrates that patients should be further phenotyped to proceed with appropriate biologic therapy and thus reduce corticosteroid consumption. Good asthma control saves economic resources.

Introduction

During the last 2 decades, the classification of asthma patients has progressed notably in parallel with advances in our understanding of the different pathophysiologic pathways, known as endotypes. First, the allergic cascade was renamed *adaptive immunity* or *T_H2 profile*, highlighting the role of T_H2 leukocytes [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]. Both types of immunity have the capacity to synthesize and release the same cytokines (IL-4, IL-5, and IL-13) and subsequently increase the number of eosinophils and fractional exhaled nitric oxide (FeNO). Given the involvement of ILC2s (from the innate arm) combined with T_H2 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/µL and/or FeNO value ≥20 ppb and/or be allergic (increased specific IgE or positive skin prick test results against an allergen, plus clinical symptoms of allergy). 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 knowledge of immunobiology renders currently available data on the disease obsolete. 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 nationwide study to update data on the prevalence of T2 asthma, comorbidities, biomarker characterization, and costs of severe asthma in patients aged ≥12 years in daily clinical practice.

Methods

Study Design and Data Source

Design: Retrospective, observational, nationwide study based on a top-down approach.

Data source: The BIG-PAC® database (Real Life Data; http://www.encepp.eu/encepp/search.htm) is an electronic medical records database containing the anonymized and dissociated data of 1.7 million patients from 7 Spanish regions chosen as representative of the whole country. Patient records were obtained using the *International Classification of Diseases, Tenth Revision, Clinical Modification* (*ICD-10-CM:* codes J45-J46).

Retrospective and prospective measurements were taken from the electronic medical records during a 1-year follow-up.

Clinical and laboratory data: The data collected were asthma diagnosis, exacerbation rate, biomarker levels (blood total immunoglobulin E [IgE], blood eosinophils, and FeNO), and spirometry values; the value closest to the date of inclusion was recorded. Findings from medical visits (primary care, specialist, emergency department), radiological tests, and other, additional tests were also recorded.

Medication administered: The active ingredients were obtained from drug dispensing records and classified according to the Anatomical Therapeutic Chemical classification

Table 1. Description of the Resources Use and Unit Costs (Year 2019).[a]

Health care and non–health care resources	Unit costs, €
Medical visits	
Primary care visits	23.19
Emergency care visits	117.53
Hospital admission (1 day)	420.90
Specialized care visit[b]	92.00
Additional tests	
Laboratory tests	22.30
Conventional radiology	18.50
Computed axial tomography	96.00
Magnetic resonance imaging	177.00
Diagnostic/therapeutic tests[c]	37.12
Drug prescription	PRP + VAT
Work productivity – indirect costs	
Cost per day off work	101.21

Abbreviation: PRP, public retail price; VAT, value added tax.
[a]Source of health care resources: proprietary analytical accounting and Spanish National Statistics Institute.
[b]Only in the pulmonology, allergy, and internal medicine departments.
[c]Asthma-related.

Table 2. Baseline Characteristics of Severe Asthma Patients According to Study Group.[a]

Study groups, No. of patients, %	Controlled n=1087 (35.9%)	Uncontrolled n=1944 (64.1%)	Total N=3031 (100%)	*P* Value
Sociodemographic characteristics				
Mean age, years	63.6 (18.5)	64.7 (17.2)	64.3 (17.7)	.116
Ranges: 12-17 y	1.1%	1.4%	1.3%	
18-44 y	16.3%	11.6%	13.3%	
45-65 y	29.7%	32.3%	31.3%	
65-74 y	21.7%	23.0%	22.5%	
≥75 y	31.2%	31.7%	31.5%	.006
Female sex	67.4%	67.3%	67.3%	.754
General comorbidity				
Mean diagnoses	3.7 (2.2)	4.3 (2.2)	4.1 (2.2)	<.001
Charlson index	1.3 (1.3)	1.5 (1.3)	1.4 (1.3)	<.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%	<.001
Associated comorbidities				
Hypertension	48.0%	53.8%	51.7%	.002
Diabetes mellitus	19.3%	23.2%	21.8%	.007
Dyslipidemia	43.3%	48.7%	46.8%	.003
Obesity	30.8%	45.4%	39.2%	<.001
Active smoker	8.2%	20.3%	15.9%	<.001
Ischemic heart disease	9.5%	11.5%	10.8%	.099
Cerebrovascular accident	7.7%	7.5%	7.6%	.440
Heart failure	14.1%	16.4%	15.6%	.049
Kidney failure	5.4%	7.0%	6.5%	.047
COPD	8.3%	14.1%	12.1%	.001
Arrhythmias	18.6%	18.5%	18.5%	.487
Dementia	13.2%	14.6%	14.1%	.147
Malignancy	8.3%	8.4%	8.3%	.490
Gastroesophageal reflux	11.0%	12.7%	12.1%	.105
Osteoporosis	18.9%	22.8%	21.4%	.006
Specific associated comorbidities				
Allergic rhinitis	60.7%	69.2%	66.1%	<.001
Atopic dermatitis	24.3%	31.8%	29.1%	<.001
Nasal polyposis	12.5%	15.8%	14.6%	.014
Other variables				
Death	1.8%	5.5%	4.2%	<.001
Time to diagnosis, years	34.3 (6.5)	34.7 (6.3)	34.6 (6.4)	.173
BMI, kg/m^2	28.9 (6.3)	30.0 (6.1)	29.7 (6.2)	<.001
Baseline FEV_1	52.9 (4.3)	53.6 (3.3)	53.4 (3.6)	.373

Abbreviation: BMI, body mass index; COPD, chronic obstructive pulmonary disease.
[a]Values reported as percentages or means (SD).

system [3]. The medications prescribed during the 1-year follow-up period were recorded, as follows: oral corticosteroids (OCS, H02AB), short-acting ß-agonists (SABA, R03AC), systemic ß-2 agonists (xanthine, R03), leukotriene antagonists (R03DC), anticholinergics (LAMA, R03BB04: tiotropium bromide), and biologics (R03DX05). OCS consumption was classified into 2 different categories: OCS-dependent patients (those receiving repeated prescriptions of OCS >6 months per year) and those receiving bursts of OCS for exacerbations.

Resource utilization: The use of resources during the follow-up period was recorded. The variables considered were health care costs (direct costs), which were related to health care activity (primary or specialized medical visits, days of hospital stay, emergencies, diagnostic or therapeutic needs, and/or medication), and non–health care costs (indirect costs), which were 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–health care 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–health care costs (ie, out-of-pocket costs [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 and diseases with a high prevalence are summarized in Table 2.

Specific comorbidities related to asthma such as allergic rhinitis, atopic dermatitis, and chronic rhinosinusitis with nasal polyps were also recorded.

To summarize general comorbidity for each patient we calculated the following: the Charlson comorbidity index [6] as a proxy of disease severity and mortality risk; and 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).

Inclusion and exclusion criteria

The study included all patients diagnosed with asthma (*ICD-10-CM*: codes J45-J46) requiring care between January 1, 2016 and December 31, 2017 who met the following characteristics: age ≥12 years; guaranteed follow-up (≥2 contacts) in the database for at least 12 months prior to the start of the study; enrolment in the prescription program (with documented daily dosage, time interval, and duration of each treatment provided); and asthma diagnosed at least 12 months before the inclusion date. The exclusion criteria were as follows: transfer to other centers or from outside the center's recruitment area; permanent institutionalization; a history of cystic fibrosis, lung cancer, bronchiectasis, or pulmonary fibrosis; actively treated or advanced cancer; and terminal illness or palliative care.

Definitions

Asthma severity was classified according to the International European Respiratory Society/American Thoracic Society guidelines [7] and assessed according to the recommendations of the Global Initiative for Asthma (GINA) [8] (high doses of inhaled corticosteroids and an additional controller medication [long-acting ß-2 agonists (LABAs), leukotriene antagonists, theophylline, OCS for more than 6 months] during the 12 months prior to the inclusion date).

Patients with uncontrolled severe asthma were defined as those presenting ≥2 exacerbations requiring OCS for more than 3 days and/or a hospital admission during the previous year [9]. Patients with controlled asthma were defined as those who did not fulfill the criteria for uncontrolled asthma.

Severe exacerbation was defined as the need for a burst of OCS, an increase in the daily maintenance dose for more than 3 days, and/or hospital admission.

OCS-dependent was defined as needing OCS on a regular basis for ≥6 months.

Allergy, for the purposes of this study, was defined as a positive skin prick test and total IgE >100 IU/mL, since it was impossible to obtain reliable information on specific IgE for every patient.

T2 asthma was defined as a peripheral blood eosinophil count ≥150/µL and/or FeNO ≥25 ppb, and/or previous allergy, or the need for OCS maintenance therapy.

The follow-up period was defined as 1 year from the index date and/or death from 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 were validated 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. Percentages and 95%CIs for parameters of interest were based on the total number of patients with no missing data. Means and standard deviations (SD), analysis of variance, and the χ^2 test were used for the bivariate analysis. For cost correction, an analysis of covariance (ANCOVA; generalized linear model) was carried out with sex, 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 health care costs (dependent variable; stepwise procedure). The analysis was performed using SPSS for Windows, Version 23.0 (IBM Corp.). Statistical significance was set at $P<.05$.

Data Confidentiality

Data confidentiality (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 an observational, postauthorization and retrospective study and was subsequently approved by the Clinical Research Ethics Committee of Terrassa Hospital (Barcelona).

Results

A total of 744 033 individuals aged ≥12 years 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).

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 comorbidity index score was 1.4 points. The most frequent comorbidities were allergic rhinitis (66.1%), hypertension (33.2%), and dyslipidemia (46.8%); the comorbidity burden was higher in patients with uncontrolled asthma. Moreover, the annual mortality rate was 4.2% for all patients with severe disease (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), LABAs, and short-acting ß-2 agonists (SABAs) as rescue therapy.

Among all patients aged ≥12 years with asthma, the prevalence of severe asthma was 7.7% (95%CI, 7.5%-7.9%). The 3031 patients who met the inclusion/exclusion criteria were analyzed and followed up during the study period. According to the criteria applied, 1944 (64.1%) of the severe asthma patients were classified as uncontrolled and 1087 (35.9%) 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% were considered OCS-dependent (37.0% in the uncontrolled group vs 21.0% in the controlled group; *P*<.001), representing 2.3% of all asthma patients. The uncontrolled group consumed a higher proportion of asthma-associated and concomitant medications (1.7 vs 1.5; *P*<.001).

Data for biomarkers are presented according to the study groups in Table 4. The percentage of patients with severe asthma presenting T2 inflammation was 81.2% (96% in uncontrolled severe asthma patients).

During the 1-year follow-up, mortality was 4.2% in the total severe asthma population and 5.5% in the uncontrolled severe asthma group. Patients with uncontrolled disease consumed more health care resources, particularly in terms of the number of primary care visits (13.4 vs 10.4; *P*<.001), days of hospital stay (6.1 vs 1.2; *P*<.001), and productivity loss in days off work (4.8 vs 2.4 days; *P*<.001) (Table 5). The total cost of the patients with controlled and uncontrolled severe asthma included in the

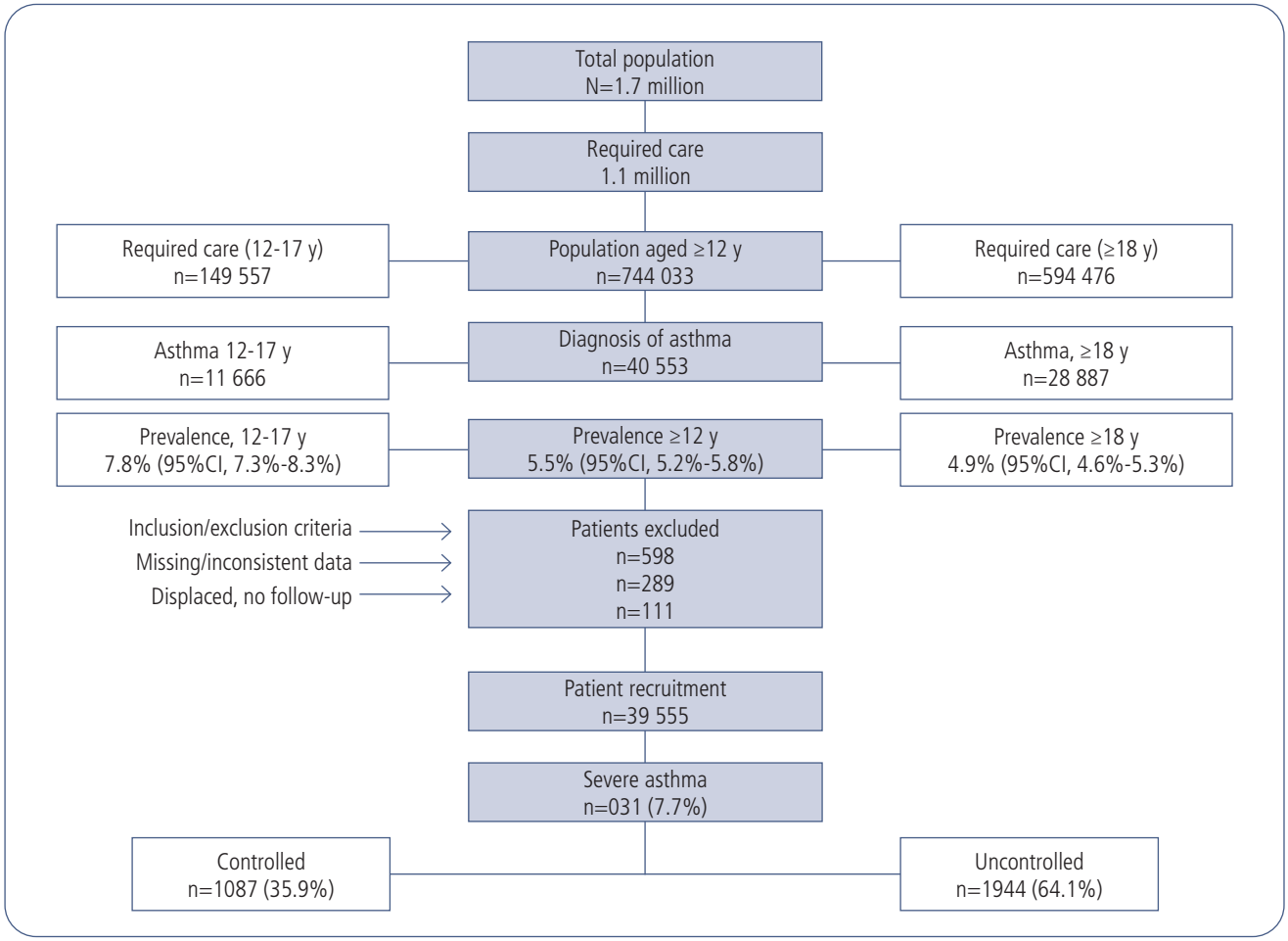

Figure. Study flow chart. A retrospective observational design was adopted based on a review of medical records (electronic databases containing anonymized and dissociated data) of patients with asthma.

study was €17 million per year, of which 91.8% corresponded to direct health care costs and 8.2% to indirect costs (productivity loss), with a mean total annual unit cost of €4856. The main components of this health care cost were hospital admissions (37.5%) and associated medications (34.4%). The average annual total unit cost corrected for covariates (ANCOVA) of uncontrolled and controlled disease was €5890 vs €2841 (P<.001), respectively. These differences were found in health

Table 3. Medication Administered, Adherence to Therapy, and Exacerbations During the Follow-up Period.

Study groups, No. of patients, %	Controlled n=1087 (35.9%)	Uncontrolled n=1944 (64.1%)	Total N=3031 (100%)	*P* Value
Medication used				
Oral/injectable corticosteroids	13.1%	68.5%	48.6%	<.001
Long-term oral corticosteroids[a]	21.0%	37.0%	31.2%	<.001
Systemic antibiotics	7.3%	36.2%	25.8%	<.001
Combined ICS/LABA	100.0%	100.0%	100.0%	.999
Leukotriene antagonists	3.0%	69.8%	45.9%	<.001
Methylxanthines	6.0%	9.7%	8.4%	<.001
Short-acting anticholinergic drugs	3.6%	20.7%	14.5%	<.001
Biological treatments	2.9%	4.3%	3.8%	.049
- Omalizumab	2.1%	3.2%	2.9%	.045
- Other	0.8%	1.1%	0.9%	.687
Nebulized treatments	9.9%	23.5%	17.3%	.022
Concomitant treatment				
Acetylsalicylic acid	14.9%	15.8%	15.5%	.264
Proton pump inhibitor	52.9%	62.6%	59.1%	<.001
ß-Blockers	13.2%	14.7%	14.2%	.268
Nonsteroidal anti-inflammatory drugs	34.9%	40.4%	38.4%	.002
Antihistamines	31.9%	33.9%	33.2%	.143
Mean (SD) no. of concomitant treatments	1.5 (1.1)	1.7 (1.1)	1.6 (1.1)	<.001
1	33.1%	30.8%	31.6%	
2	30.5%	33.0%	32.1%	
3+	16.8%	22.0%	20.1%	<.001

Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting ß$_2$-agonist.
[a]Defined as >6 months per year

Table 4. Biomarkers According to Study Groups.

Study groups, No. of patients, %	Controlled n=1087 (35.9%)	Uncontrolled n=1944 (64.1%)	Total N=3031 (100%)	*P* Value
Eosinophils/µL[a]	267 (119)	348 (154)	322 (148)	.031
FeNO, ppb	34.2 (16.2)	37.0 (14.1)	36.2 (14.8)	.462
IgE, IU/mL	187.9 (109.1)	271.6 (139.3)	245.6 (135.6)	.015
Eosinophils ≥150/µL	74.6%	85.9%	81.9%	<.001
FeNO ≥25 ppb	74.5%	86.8%	82.4%	<.001
Allergic (IgE >100 IU/mL + positive prick test)[b]	38.8%	59.9%	52.4%	<.001
Eosinophils ≥150/µL or FeNO ≥25 ppb or allergic or OCS intake[c]	54.8%	96%	81.2%	<.001

Abbreviations: FeNO, fractional exhaled nitric oxide; IgE, total immunoglobulin E; OCS, oral corticosteroid.
[a]Values reported as percentages or mean (SD).
[b]Patients are considered allergic when IgE >100 IU/L + positive allergic test (prick test).
[c]Long-term intake is defined as >6 months per year.

care costs (€5443 vs €2602, *P*<.001) and in non–health care costs (lost work productivity: €447 vs €239, *P*=.036).

In the binary correlation model, the exacerbations correlated moderately with eosinophil count (r=0.452) and highly with FEV_1 (r=–0.510) and health care costs (r=0.693). Uncontrolled severe asthma correlated mainly with exacerbations (r=0.625) and health care costs (r=0.513); *P*<.01 in all cases.

In the multiple linear regression model (stepwise approach), health care costs correlated positively with lack of asthma control (uncontrolled: β=0.068, t=3.5), number of exacerbations (β=0.486, t=24.2), eosinophil count (β=0.177, t=3.1), OCS use (>6 months per year: β=0.035, t=6.5), age (β=0.102, t=5.9), and Charlson comorbidity index (β=0.112, t=5.9) and negatively with FEV_1 (β=–0.038, t=–2.6); *P*<.01 in all cases. The coefficient of determination (R2) of the model was 66.8%.

Discussion

Asthma is a chronic respiratory disease with a variable prevalence depending on the series reviewed. Prevalence ranges between 5% and 10% of the adult population [10,11].

Severe asthma is a heterogeneous condition with multiple clinical phenotypes. Current data on the prevalence of severe asthma are inconclusive, particularly in adults [9,12,13], although it is generally accepted that severe disease affects 5%-10% of the general population of asthma patients [7,12]. In agreement with these data, the BRAVO-1 study found a prevalence of 5.5% for asthma and of 7.7% for severe asthma in the asthma population aged over 12 years.

Patients with severe asthma may have either controlled or uncontrolled disease [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]. A study carried out in Spain a decade ago found the prevalence of uncontrolled severe asthma in the asthmatic population to be 3.9% [13]. The authors classified patients based on medical criteria, with the result that severity was systematically underestimated with the GINA criteria, which 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 (ie, 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 patients with severe disease. Patient phenotyping plays a key role in appropriate or suboptimal use of 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" [16]. Others repeat the data reported in previous manuscripts, and even the GINA guidelines speak of "the majority of people with severe asthma", although they do not accompany this sentence with data or a quotation [8]. Other attempts to show prevalence have been made based on sputum interleukin analysis [17] and gene expression [18], reporting figures of 53% and 70%, respectively. These studies refer to T_H2 asthma and not to T2 asthma. In their study, Frøssing et al [19] discuss T2 patients and report a figure of 70% based on clinical and biomarker data combined. However, the number of patients is limited (116 out of 166 asthma patients included [70%]).

Our figure of 81.2% helps to clarify the prevalence of T2 asthma among severe asthma patients. As expected, it is higher than the rates obtained for T_H2 asthma patients in molecular studies (T2 includes T_H2), and our study has a much larger sample than that of Frøssing et al [19]. Finally, the prevalence of T2 asthma among uncontrolled severe asthma patients has not yet been recorded in the literature; therefore, 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 [20]. Furthermore, our study also showed that the percentage of comorbid T2 diseases is even higher in patients with uncontrolled severe asthma, indicating that comorbidities not only increase clinical and disease burden in affected patients, but also add to the difficulty of controlling asthma and make therapeutic management more complex [21].

Comorbidities were also recorded through the Charlson Comorbidity Index, which categorizes patients' comorbidities based on the ICD-10 diagnostic codes found in administrative data, such as hospital abstract 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 with comorbidities was generally low; in any case, the index was significantly higher in patients with uncontrolled disease. 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 reported 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 frequent 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. In line with our data, other authors concluded that many patients do not receive optimal therapy for asthma and that this is one of the reasons for the high rate of OCS consumption. These results draw attention to the need for new treatments in 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, although associated adverse effects should be borne in mind. A careful appraisal would show that a substantial number of patients taking long-term OCS may be candidates for biological treatments. Unfortunately, as the present study reflects, only 3.4% of severe asthma patients receive biologics.

Despite optimized standard treatment, quality of life is poor in severe asthma patients because of chronic symptoms (coughing, wheezing, and shortness of breath). They have a high risk of severe asthma attack that may require visits to the emergency department or hospitalization, which, in turn, can increase mortality. Although asthma mortality has decreased gradually in the last decade, the disease is still responsible for about 1000 deaths per year in Spain [26]. Mortality in BRAVO was 4.2% for severe asthma patients, rising to 5.5% in those whose disease was uncontrolled. One of the few literature reports on asthma mortality recorded a rate of 6.7% [27] and found that more severe asthma and poorer perceived asthma control were both associated with increased mortality risk in adults with severe asthma. Although it affects a small proportion of patients, severe asthma necessitates 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 of an asthma patient for the Spanish National Health System to be €1533 per patient-year, rising to €2635 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 €7472 per patient-year. The cost obtained was clearly higher than in the previous reports on the cost of asthma in Spanish patients; 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 €1100 in patients receiving nonbiological treatment). When indirect costs (the social perspective) were added, the total annual mean cost rose to €8554. Sicras-Mainar et al [31] recently found the mean total annual cost to be €5493 (health care cost, 68.2%; productivity losses, 31.8%).

Other international evaluations present similar results. In the US, Chastek et al [32] reported that patients with severe asthma required more hospitalizations, medication, and medical visits. The mean annual cost was $5174, and the cost for severely ill patients was 3 times higher than for those with mild-moderate asthma. In a French cohort of 155 patients followed for 1 year, Nordon et al [33] estimated the mean annual asthma-related cost to be €8222. These authors highlighted the high cost of medication.

In a 20-year follow-up study, Chen et al [34] found that the incremental cost of severe asthma compared with no asthma was $2779 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 €4856 per patient-year. Costs were higher for patients with uncontrolled severe asthma than for those whose disease was controlled (€5890 vs €2841). As shown above in the multiple regression model, higher health care costs were associated with lack of asthma control, number of exacerbations, eosinophilia, long-term OCS use, age, and comorbidities but not with FEV_1.

BRAVO-1 is subject to some of the limitations inherent to retrospective studies, mainly related to definitions of disease and data collection in the electronic records. In some cases, the differences may result in incorrect classifications of severity or underreporting of information and affect 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 could potentially lead to an underrepresentation of patients with milder asthma who do not usually require as much medical care and, therefore, to an overestimation of the prevalence of more severe asthma. 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.

To summarize, BRAVO-1 is the largest nationwide evaluation and the first study in the biologic era to provide 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 be characterized by high frequencies of uncontrolled disease (64.1%) and OCS-dependent disease (31.2%), despite the availability of new treatments. The percentage of patients receiving biologics is surprisingly low (3.8%). Comorbidities and consumption of health care resources were higher in the uncontrolled group.

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Conflicts of Interest

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, and Roxall. Clara Engroba is an employee of Sanofi and owns stock or stock options in Sanofi. The remaining authors declare that they have no conflicts of interest.

Previous Presentations

Christian Domingo Ribas, Ana Sogo Sagardia, Elena Prina, Antoni Sicras Mainar, Aram Sicras Navarro, Clara Engroba Teijeiro. "Prevalence, characterization and costs of severe asthma in Spain (BRAVO-1 study)". Oral Communication in ERS International Congress. Virtual, 5-9 September 2020. Available in European Respiratory Journal 2020 56: 4639.

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