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Economic burden assessment for the management of asthma patients at Mexico's National Institute for Respiratory Diseases

Evaluación de la carga económica para el tratamiento de pacientes con asma en el Instituto Nacional de Enfermedades Respiratorias de México

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Abstract

Objective: Determine the annual economic burden of the disease from an institutional perspective and based on GINA's recommended classification in a retrospective cohort of adults treated at Instituto Nacional de Enfermedades Respiratorias (INER) of Mexico City.

Methods: A retrospective, longitudinal observational study comprised by data from 247 female asthma patients, annual direct costs were estimated including: visits, laboratory tests, pharmacological treatment and management of crisis or exacerbations, to determine the annual burden of the disease from an institutional perspective and according to Global Initiative for Asthma classification.

Results: The average annual cost was $43,813.92, which increased in relation to the need of inhaled corticosteroids and long-acting beta agonists dosage increase. The average doctor's appointment cost was $2,004.57, $982.82 for crisis management and $2,645.95 for laboratory testing. Pharmacological treatment represented the main economic burden with an annual average cost of $38,180.58.

Conclusions: The results highlight an economic burden of asthma estimated at an annual cost per patient of $43,813.92 MXN (SD=93,348.85) in the context of the third level of care in the Mexican public health system. The asthma severity and treatments such as biologics were the main factors that increased direct costs of care.

Keywords: Asthma; Burden of the disease; Costs; Economic burden.

Resumen

Objetivo: Determinar la carga económica anual del asma, desde una perspectiva institucional y con base en la clasificación recomendada por GINA, en una cohorte retrospectiva de adultos atendidos en el Instituto Nacional de Enfermedades Respiratorias (INER) de México.

Métodos: Estudio observacional, longitudinal y retrospectivo, llevado a cabo a partir de la información recabada de 247 pacientes femeninas con asma. Se estimaron los costos directos anuales: visitas, pruebas de laboratorio, tratamiento farmacológico y de las crisis o exacerbaciones, para determinar la carga anual de la enfermedad desde una perspectiva institucional, y según la clasificación de la Iniciativa Global para el Asma.

Resultados: El costo promedio anual fue de $43,813,92, que aumentó en relación con la necesidad de aumento de dosis de corticoides inhalados y beta-agonistas de acción prolongada. El costo promedio de la consulta médica fue de $2004.57, $982.82 por gestión de crisis y $2645.95 por pruebas de laboratorio. El tratamiento farmacológico representó la principal carga económica, con un costo promedio anual de $38,180.58.

Conclusiones: Los resultados resaltan una carga económica del asma estimada en un costo anual por paciente de $43,813.92 MXN (DE=93,348.85), en el contexto del tercer nivel de atención en el sistema de salud público mexicano. La gravedad del asma, los tratamientos y los biológicos fueron los principales factores que aumentaron los costos directos de la atención.

Palabras clave: Asma; Carga de la enfermedad; Costos; Carga económica.

INTRODUCTION

Asthma is one of the main non transmissible diseases that affects both children and adults. It's been estimated that in 2019, a total of 262 million people were affected by it and caused 461 deaths worldwide.[1] Other assessments have estimated the costs associated with the disease are now superior to the spending on tuberculosis and HIV/AIDS combined. The burden of the disease affects the health system in terms of direct costs through increases of both hospitalizations and treatment costs; as well as indirect costs such as school and work absences.[2]

Despite pharmacologic advances and the constant update of international guidelines for the diagnosis, treatment, and prevention of asthma; it remains a relevant disease worldwide with a complex and challenging treatment, where strategies focused on better health results are heterogenous, especially in developing countries.[3]

Asthma is at the top of twenty disease causes in Mexico, with 254,713 new cases reported in 2019 according to the International Study of Asthma and Allergies in Childhood (ISAAC) Phase 3, asthma prevalence ranged between 5 and 14% in 6 Mexican cities with varied geographic conditions.[4,5]

Current recommendations by the Global Initiative for Asthma (GINA) divide treatment in five steps according to patient requirements, starting with inhaled corticosteroids (ICS) and long-acting beta agonists (LABA), such as low-dose formoterol, that may require adjustments to higher maintenance dosages.[6]

Clinical trials and observational studies usually describe patients with mild, moderate, or severe asthma in relation to the prescribed treatment, classifying mild asthma as patients treated with steps 1 or 2; moderate for those in steps 3 and 4 and finally; moderate to severe asthma for patients that require steps 4 or 5.[6]

GINA guidelines do not recommend this approach, as it is based on the assumption that patients received adequate management and that those that are prescribed more intense treatment, received said management due to an underlying and more severe disease. Additionally, this method may cause confusion since asthma is a chronic disease and recommended treatment may vary overtime.[6]

Taking this into consideration, the present study classified patients in accordance with the 2021 GINA guidelines, based on relevant maintenance treatment and avoiding severity evaluation based on treatment prescription.[6]

The lack of control in these patients increases disability, generating a high burden of the disease, not only for them but also for the public health institutions where they received attention.[7] A previous study has reported that the direct costs in patients with asthma are generated mainly by hospitalizations and emergency services use.[8]

In Mexico, there is no current information on the costs of care for these patients. However, a study from 2007 estimated that the burden of asthma disease, derived from direct medical costs is between $3,700 and $4,500 MXN,7 while other from 2014 reported that the annual cost per patient ranged between $1,170 in controlled patients reaching up to $13,648 in uncontrolled patients.[8]

The Latin America Asthma Insights and Management (LA AIM) survey reported in 2014 is the precedent for resource utilization for asthma care and estimation of health outcomes. It confirmed that poorly controlled asthma generates a significant cost burden, however, Mexico's collaboration of controlled patients was 9%, additionally local information is required to estimate more accurately[10,11], in Latin American countries.

The main objective of the present study was to determine the annual economic burden of the disease from an institutional perspective and based on GINA's recommended classification in a retrospective cohort of adults diagnosed with asthma and treated at Mexico's National Institute for Respiratory Diseases (INER for the Spanish acronym).

METHODS

Patients

A retrospective, longitudinal observational study was performed on data from an institutional program focused on the analysis of women's health in Mexico. Female patients were included, aged 18 years or older, diagnosed with asthma, with or without comorbidities, who were under follow-up for a minimum period of one year at the National Institute of Respiratory Diseases (INER) during the period from 2015 to 2021. Data were excluded from patients who missed two or more of their quarterly scheduled visits as well as those patients who did not have at least 80% of information required for the estimation of resources.

Variables included socio-demographic data, clinical outcomes related to the disease and asthma control through the Asthma Control Test and Asthma Control Questionnaire, Quality of Life data through the Asthma Quality of Life Questionnaire (AQLQ) and the use of treatment resources, outpatient visits, admission to the emergency, intensive care units and laboratory testing. All data was obtained from clinical files entries for each outpatient visit during the first year of follow-up.

Classification

Study population was divided according to the preferred controller treatment to prevent exacerbations and control symptoms that were prescribed the longest during the year of follow-up. According to this, patients were assigned to one of three groups: Step 3: treated with a low dose of ICS-LABA; step 4; treated with medium dose of ICS-LABA and step 5 for those treated with a high dose ICS-LABA.

Cost analysis

The burden of the disease was determined from an institutional perspective through annual direct medical costs including outpatient visits, laboratory studies, pharmacologic treatment and management of crisis or exacerbations, (using unitary costs provided by INER for 2020) and reported in Mexican pesos (MXN). **Table 1**

Outpatient visits costs include the costs of first time and subsequent visits at INER, laboratory studies included those directly related to the disease, such as spirometry and determination of fractional exhaled nitric oxide (FeNO).

Table 1. Unitary costs for medical services at INER for 2020 in Mexican Pesos.

Service	Cost MXN 2020
Specialist outpatient visit	$472.00
Crisis management	
Outpatient visit	$472.00
Emergency admission**	$3,258.00
Hospitalization*	$36,823.00
Laboratory Studies	
Spirometry	$471.00
FeNO: determination of fractional exhaled nitric oxide	$1,363.00

Costs are expressed in Mexican Pesos (MXN) for 2020. *The cost for hospitalization was estimated as the product of one day of hospitalization and the average of days required for an asthma patient ($5,665.00 x 6.5). Unitary costs were provided by INER** Emergency admission cost was obtained from Mexico's Official National Diary.[9]

For treatment costs considerations we included pharmacologic treatment such as ICS, LABA, LAMA (long acting muscarinic or anticholinergics) prescribed as maintenance medication, anti-leukotrienes, theophylline, and biologic treatments. The total amount of required medication for each patient was estimated based on the prescribed daily dose prescribed each visit. Rescue medication was not considered as it was impossible to estimate dosages and costs. Exacerbation or crisis management included outpatient visits, emergency admission, hospitalization, and intensive care unit admission.

Total cost for each concept was estimated by multiplying unitary costs by the amount of resource required.

Statistical analysis

Quantitative variables were expressed through dispersion measurements: average and standard deviation (SD). Categoric variables were expressed through number of patients and percentages. Variables were compared among groups, for continuous quantitative variables with normal distribution, a one-way ANOVA test was performed and for those with a non-normal distribution, we used a non-parametric Kruskal–Wallis's test. For categorical variables, Pearson's Chi square test or Fisher's exact test was used in cases where the frequency in any cell of the contingency table was below 5.

A multivariate analysis was performed to analyze factors affecting the annual total cost. We considered basal characteristics that could have a potential effect on the cost, considering those that were statistically significant during our univariate analysis. We used a generalized linear model with a gamma distribution and a logarithmic link function, this model was considered adequate for cost analysis due to the fact that it takes into consideration that these analyses have a right-skewed distribution bias.[11]

The analysis was performed through the R programming language version 4.0.5. We considered a level of confidence of 0.05 for the entire analysis.

Ethics approval and consent to participate

The present study was a retrospective analysis that posed no clinical risks or risk on the identity of the patients, requiring no ethical committee review or written informed consent.

RESULTS

Analysis of sociodemographic and clinical characteristics of the population

A total of 247 female patients were included in the analysis, of which 20.2% (n=50) was classified to the low-dose ICS-LABA group, 71.7% (n=177) to the medium dose group and 8.1% (n=20) to the high dose group. Average age was 52.5 years (SD=±14.79), 87.8% of patients classified to a low or average socioeconomic level, 72.5% were homemakers and the group of high dose patients was the one with a larger proportion of working women (40%, p=0.037). The most common comorbidity was allergic rhinitis (45.3%), followed by Gastroesophageal Reflux Disease (GERD) in 34.1% of patients and the only comorbidity with statistically significant difference amongst groups was atopic dermatitis, with 1.2%, where the high-dose ICS-LABA group had the highest incidence (5.3%). Only 0.8% of patients declared themselves as smokers during the follow-up period and 17.3% had a history of smoking, with an average of 14.2 years since they quit smoking. **Table 2**

The average time elapsed since diagnosis was 14.5 years (SD=±12.2), with the longest time lapsed in the high-dose group (19.55 (SD=±15.31), p=0.010). Spirometry results indicate a statistically significant difference amongst groups with greater pulmonary function deterioration in patients who require larger ICS-LABA doses. 46% of patients had their activities limited, with a larger proportion amongst the high-dose group (64.7%, p=0.008). The average number of exacerbations in the last year was 0.67 (SD=±1.23), the increase in relation with the need to increase dosage to control symptoms (p=0.012). The ACQ test showed that 54.3% of patients were uncontrolled, with an increase of uncontrolled patients in parallel to ICS-LABA dose increase. As for quality of life, a higher dose of ICS-LABA correlated with a worsening of the activity area (p=0.037) and overall AQLQ score (p=0.046). **Table 3**

Use of resources

As seen on table 4, patients attended an average of 4.25 (SD=1.09) specialist appointments throughout the year, and where a spirometry test was performed. 34.4% of patients received a FeNO test with an average of 0.47 (SD=0.84) tests a year. 36% of patients had at least one crisis during the year and the most common management setting, in 32.4% of cases was through outpatient visit. 6.9% of patients required admission through emergen-

Table 2. Basal sociodemographic characteristics by treatment group.

Variable	Total (n=247)	Low-dose ICS-LABA (n=50)	Medium-dose ICS-LABA (n=177)	High-dose ICS-LABA (n=20)	p-value
Age average (SD)	52.56 (±14.79)	52.70 (±14.70)	53.04 (±14.47)	47.98 (±17.56)	0.461
Weight average (SD)	67.49 (±13.48)	64.04 (±12.22)	68.66 (±13.70)	65.75 (±13.46)	0.087
Size average (SD)	152.45 (±7.28)	151.14 (±7.62)	152.61 (±6.98)	154.35 (±8.83)	0.217
Body Mass Index average (SD)	29.05 (±5.51)	28.01 (±4.76)	29.51 (±5.70)	27.62 (±5.25)	0.224
Socioeconomic level n (%)					0.161
Low	109 (44.3)	26 (52.0)	79 (44.9)	4 (20.0)	
Medium	107 (43.5)	19 (38.0)	75 (42.6)	13 (65.0)	
High	30 (12.2)	5 (10.0)	22 (12.5)	3 (15.0)	
Occupation n (%)					**0.037**
Homemaker	179 (72.5)	35 (70.0)	134 (75.7)	10 (50.0)	
Workforce	63 (25.5)	14 (28.0)	41 (23.2)	8 (40.0)	
Student	4 (1.6)	1 (2.0)	1 (0.6)	2 (10.0)	
None	1 (0.4)	0 (0.0)	1 (0.6)	0 (0.0)	
Own pet with his n (%)	136 (55.1)	30 (60.0)	100 (56.5)	6 (30.0)	0.065
Comorbidities					
Allergic rhinitis n (%)	112 (45.3)	25 (50.0)	74 (41.8)	13 (65.0)	0.110
Gastroesophageal reflux disease n (%)	84 (34.1)	13 (26.0)	64 (36.2)	7 (36.8)	0.404
Hypertension n (%)	38 (15.4)	8 (16.0)	26 (14.7)	4 (20.0)	0.698
Type 2 diabetes n (%)	25 (10.1)	6 (12.0)	17 (9.6)	2 (10.0)	0.827
SAMTER syndrome n (%)	10 (4.0)	2 (4.0)	7 (4.0)	1 (5.0)	0.871
Atopic dermatitis n (%)	3 (1.2)	2 (4.0)	0 (0.0)	1 (5.3)	**0.021**

...continuation table 2.

Variable	Total (n=247)	Low-dose ICS-LABA (n=50)	Medium-dose ICS-LABA (n=177)	High-dose ICS-LABA (n=20)	p-value
Clinical variables					
Smokes n (%)	2 (0.8)	1 (2.0)	1 (0.6)	0 (0.0)	0.487
Used to smoke n (%)	42 (17.3)	9 (19.1)	30 (16.9)	3 (15.8)	0.957
Time since they stopped smoking	14.24 (±10.91)	12.76 (±15.24)	14.67 (±10.07)	14.33 (±5.13)	0.376
Wood smoke exposure average (SD)	5 (±2.0)	3 (±6.0)	1 (±0.6)	1 (±5.0)	**0.026**
Years since diagnosis average (SD)	14.55 (±12.18)	11.16 (10.70)	14.94 (12.00)	19.55 (15.31)	**0.010**
Total Immunoglobulin E (IgE) average (SD)	217.15 (±327.41)	225.33 (±251.81)	203.57 (±339.06)	374.39 (±312.73)	**0.015**

n: number of patients, SD: Standard deviation, Kg: Kilograms, cm: centimeters.

cy services, with the largest proportion within the high-dose ICS-LABA patients (30%, p=0.001). 100% of patients received pharmacologic treatment. The proportion of patients that required theophylline and LAMA increased in relation with the need to increase dosage to reach symptom control (p=0.001, p<0.001). 40% of patients in the high-dose ICS-LABA group received biologic treatment. **Table 4**

Costs

The average annual cost was $43,813.92 (SD=93,348.85), which increased in relation to the need to increase the ICS-LABA dose (p<0.001). The average cost for outpatient visits was $2,004.57 (SD=514.18), $982.82 (SD=4,608.77) for crisis management and $2,645.95 (1,246.73) for laboratory testing; none of these had a statistically significant difference amongst groups. Pharmacologic treatment represented the greatest economic burden with an annual average of $38,180.58 (SD=92,490.68), ranging from $17,562.06 (SD=21,060.76) for the low-dose group to $196,211.35 (SD=$282,684.53) in the high-dose group (p<0.001), where the rise in costs was derived from the inclusion of biologic, which had an average cost of $169,675.80 (SD=284,460.42). **Table 5**

Factors affecting costs

The results of the multivariate analysis showed that age, socioeconomic level, the presence of allergic rhinitis and asthma control expressed by the ACQ score, do not have a statistically significant effect on the annual cost of management. Some spirometry variables had statistical significance, finding that as lung function worsens, costs are increased. Lastly, there was an increase in costs related to the need of higher ICS-LABA doses. Therefore, we can conclude that as asthma severity is associates with an increase of the total annual management cost of the disease. **Table 6**

DISCUSSION

The present study was set up to quantify the economic burden of asthma at INER, in Mexico City. We used annual direct costs including outpatient visits, admissions to emergency services and intensive care units, laboratory testing, pharmacologic treatment and management of exacerbations or crisis.

The average annual management cost was $43,813.92 (SD=93,348.85), where pharmacologic treatment represented the largest burden with an annual cost of $38,180.58 (SD=92,490.68), our findings coincide with several studies report the main direct costs spending are those associated with hospitalization or medication and highlight that these two alone, represent a larger economic burden than indirect costs.[12]

The results by treatment groups based on ICS-LABA doses reflect that patients who required higher doses are those with a longer time since diagnosis, poorer lung function and patients who are uncontrolled despite receiving adequate treatment; considering these characteristics, they could be classified as “difficult to treat” patients with severe asthma based on GINA definitions.[6] The present study showed a statistically significant correlation between an increase in management costs and decreased pulmonary function as well as an increased cost based on ICS-LABA dosage.

Table 3. Clinical and quality of life characteristics by treatment group.

Variable	Total (n=247)	Low-dose ICS-LABA (n=50)	Medium-dose ICS-LABA (n=177)	High-dose ICS-LABA (n=20)	p-value
Spirometry					
FEV1/FVC preBD % average (SD)	87.67 (±11.46)	92.34 (±10.01)	87.31 (±10.17)	79.25 (±18.76)	**<0.001**
FEV1 pre % average (SD)	66.96 (±20.08)	81.92 (±19.07)	63.82 (±18.78)	57.25 (±15.29)	**<0.001**
FEV1 postBD % average (SD)	79.80 (±19.01)	90.96 (±14.82)	78.23 (±18.56)	65.75 (±18.97)	**<0.001**
FeNO					
FeNO average (SD)	35.16 (±31.60)	35.85 (±42.88)	35.81 (±30.12)	26.95 (±20.09)	0.668
FeNO high average (SD)	18 (22.2)	2 (15.4)	15 (24.2)	1 (16.7)	0.891
Asthma control					
Limits activity n (%)	99 (46.7)	14 (28.6)	74 (50.7)	11 (64.7)	**0.008**
Use of rescue medication (days a month) average (SD)	5.42 (±8.59)	5.43 (±9.00)	5.16 (±8.17)	7.59 (±10.90)	0.986
Exacerbations in the last year media (SD)	0.67 (±1.23)	0.27 (±0.64)	0.75 (±1.30)	1.05 (±1.51)	**0.012**
ACT n (%)					0.128
Uncontrolled	159 (64.9)	27 (54.0)	118 (66.7)	14 (77.8)	
Controlled	86 (35.1)	23 (46.0)	59 (33.3)	4 (22.2)	
ACQ n (%)					0.001
Uncontrolled	134 (54.3)	17 (34.0)	101 (57.1)	16 (80.0)	
Controlled	113 (45.7)	33 (66.0)	76 (42.9)	4 (20.0)	
Quality of life					
AQLQ symptoms average (SD)	61.53 (±16.50)	66.10 (±14.97)	60.61 (±16.89)	57.63 (±15.14)	0.050
AQLQ activities average (SD)	53.24 (±14.15)	57.82 (±12.82)	52.22 (±14.14)	50.26 (±15.70)	**0.037**
AQLQ total average (SD)	152.66 (±41.43)	165.04 (±38.26)	149.82 (±41.76)	145.32 (±42.16)	**0.046**

AQLQ: Asthma Quality of Life Questionnaire, ACT: Asthma Control Test, ACQ; Asthma Control Questionnaire, FeNO: Fractional exhaled nitric oxide, FEV: Forced Expiratory Volume in one second; FVC: Forced Vital Capacity, BD: Bronchodilator, n: number of patients SD: Standard deviation.

Table 4. Use of resources by treatment group.

Variable	Total (n=247)	Low-dose ICS-LABA (n=50)	Medium-dose ICS-LABA (n=177)	High-dose ICS-LABA (n=20)	p-value
Specialist consultation n (%)	247 (100)	50 (100)	177 (100)	20 (100)	
Average (SD)	4.25 (±1.09)	4.20 (±0.57)	4.18 (±0.93)	5.00 (±2.41)	0.603
Laboratory tests n (%)					
Spirometry	247 (100)	50 (100)	177 (100)	20 (100)	
Average (SD)	4.25 (±1.09)	4.20 (±0.57)	4.18 (±0.93)	5.00 (±2.41)	0.603
FeNO	85 (34.4)	14 (28.0)	64 (36.2)	7 (35.0)	0.562
Average (SD)	0.47 (±0.84)	0.30 ± (0.51)	0.46 (±0.72)	1.00 (±1.78)	0.380
Total	247 (100)	50 (100)	177 (100)	20 (100)	
Average (SD)	4.72 (±1.37)	4.50 (±0.74)	4.64 (±1.11)	6.00 (±3.09)	0.280
Crisis management n (%)					
Outpatient visit	80 (32.4)	15 (30.0)	58 (32.8)	7 (35.0)	0.903
Average (SD)	0.35 (±0.53)	0.34 (±0.56)	0.36 (±0.54)	0.35 (±0.49)	0.942
Emergency services	17 (6.9)	4 (8.0)	7 (4.0)	6 (30.0)	**0.001**
Average (SD)	0.11 (±0.54)	0.10 (±0.36)	0.05 (±0.23)	0.75 (±1.59)	**<0.001**
Hospitalization	3 (1.2)	0 (0.0)	2 (1.1)	1 (5.0)	0.320
Average (SD)	0.01 (±0.11)	0.00 (±0.00)	0.01 (±0.11)	0.05 (±0.22)	0.223
Total	89 (36.0)	18 (36.0)	61 (34.5)	10 (50.0)	0.390
Average (SD)	0.48 (±0.82)	0.44 (±0.67)	0.41 (±0.63)	1.15 (±1.79)	0.160

...continuation table 4.

Variable	Total (n=247)	Low-dose ICS-LABA (n=50)	Medium-dose ICS-LABA (n=177)	High-dose ICS-LABA (n=20)	p-value
Pharmacologic treatment n (%)					
Theophylline	19 (7.7)	0 (0.0)	13 (7.3)	6 (30.0)	**0.001**
Antileukotrienes	160 (64.8)	20 (40.0)	126 (71.2)	14 (70.0)	**<0.001**
ICS-LABA	247 (100)	50 (100)	177 (100)	20 (100)	
LAMA	32 (13.0)	1 (2.0)	19 (10.7)	12 (60.0)	**<0.001**
Biologics	8 (3.2)	0 (0.0)	0 (0.0)	8 (40.0)	**<0.001**
Total	247 (100)	50 (100)	177 (100)	20 (100)	

Relative frequency and average were estimated using the number of patients as denominator.
FeNO: Fractional exhaled nitric oxide. ICS: Inhaled corticosteroids LABA: long-acting beta agonists. LAMA: Long acting antimuscarinic or anticholinergics, n: number of patients SD: Standard deviation.

Table 5. Annual costs by treatment group.

Variable	Total (n=247)	Low-dose ICS-LABA (n=50)	Medium-dose ICS-LABA (n=177)	High-dose ICS-LABA (n=20)	p-value
Specialist consultation	$2,004.57 (±514.18)	$1,982.40 (±269.71)	$1,970.67 (±440.90)	$2,360.00 (±1,135.69)	0.603
Crisis management					
Outpatient visit	$166.25 (±252.42)	$160.48 (±263.06)	$168.00 (±253.02)	$165.20 (±230.98)	0.942
Emergency services	$369.33 (±1,772.66)	$325.80 (±1,186.61)	$147.25 (±762.43)	$2,443.50 (±5,164.89)	**<0.001**
Hospitalization	$447.24 (±4,041.59)	$0.00 (±0.00)	$416.07 (±3,903.05)	$1841.12 (±8,233.76)	0.223
Total	$982.82 (±4,608.77)	$486.28 (±1,223.15)	$731.33 (±4,151.04)	$4449.82 (±9,881.70)	0.121
Laboratory studies					
Spirometry	$2,000.32 (±513.09)	$1,978.20 (±269.14)	$1,966.49 (±439.97)	$2,355.00 (±1,133.29)	0.603
FeNO	$645.63 (±1,138.31)	$408.90 (±688.42)	$631.45 (±985.51)	$1,363.00 (±2,422.11)	0.380
Total	$2,645.95 (±1246.73)	$2,387.10 (±721.22)	$2,597.94 (±1,029.58)	$3,718.00 (±2,748.90)	0.270

...continuation table 5.

Variable	Total (n=247)	Low-dose ICS-LABA (n=50)	Medium-dose ICS-LABA (n=177)	High-dose ICS-LABA (n=20)	p-value
Pharmacologic treatment					
Theophylline	$223.27 (±972.47)	$0.00 (±0.00)	$172.28 (±731.20)	$1,232.70 (±2,462.46)	**<0.001**
Antileukotrienes	$6,397.67 (±5,999.96)	$3,023.74 (±4,819.21)	$7,209.51 (±5,935.99)	$7,647.75 (±6,485.87)	**<0.001**
ICS-LABA	$17,673.25 (±11,307.40)	$14,498.88 (±18)	$18,686.93 (±8,357.23)	$16,638.05 (±8,339.64)	**<0.001**
LAMA	$147.46 (±771.17)	$39.44 (±278.86)	$79.71 (±309.10)	$1,017 (±2,396.83)	**<0.001**
Biologics	$13,738.93 (±91656.20)	$0.00 (±0.00)	$0.00 (±0.00)	$169,675.80 (±28,4460.42)	**<0.001**
Total	$38,180.58 (±92,490.68)	$17,562.06 (±21,060.76)	$26,148.44 (±10,119.59)	$196,211.35 (±282,684.53)	**<0.001**
Total	$43,813.92 (±93,348.85)	$22,417.84 (±21,186.59)	$31,448.37 (±11,484.10)	$206,739.18 (±282,618.64)	**<0.001**

Relative frequency and average were estimated using the number of patients as denominator.
FeNO: Fractional exhaled nitric oxide. ICS: Inhaled corticosteroids LABA: Long-acting Beta agonist. LAMA: Long acting antimuscarinic or anticholinergics, n: number of patients SD: Standard deviation

Table 6. Multivariate analysis for total annual costs

Variable	Coefficient	Standard Error	p-value
Intercept	127,834	2.681	**< 0.001**
Age	1.001	1.003	0.734
Socioeconomic level (reference: 1)			
2	1.067	1.087	0.437
3	1.286	1.136	0.051
Allergic rhinitis	1.15	1.086	0.085
Spirometry			
FEV1/FVC prebd %	0.952	1.019	**0.009**
FEV1 pre %	1.003	1.003	0.376

...continuation table 6.

Variable	Coefficient	Standard Error	p-value
FVC prebd %	0.986	1.011	0.213
PEF prebd	1.022	1.032	0.487
Rel FEV1/FVC post	1.027	1.020	0.191
FEV1 postbd %	1.012	1.012	0.318
FEV1 change %	0.963	1.015	**0.015**
FVC change %	1.037	1.018	**0.037**
ACQ	1.079	1.050	0.121
Treatment Group (reference: low-dose ICS-LABA)			
Medium-dose ICS-LABA	1.329	1.109	**0.006**
High-dose ICS-LABA	5.639	1.189	**< 0.001**

Coefficients and standard errors are expressed exponentially this represents the ratio of cost increment per increase unit in continuous variables or the ratio of cost increment to the reference value in categoric variables.
FEV: Forced Expiratory Volume in one second; FVC: Forced Vital Capacity, PEF: Peak Expiratory Flow.

Amongst patients in the high-dose ICS-LABA group, the cost increased mainly in relation to pharmacologic treatment, more specifically, the inclusion of complementary treatment, mainly biologics, due to their high cost and the fact that they are currently only indicated for patients with severe asthma. In the analyzed cohort, 8% of patients were classified in the severe asthma group (high-dose ICS-LABA), yet they concentrated 38.2% of the total annual management cost, highlighting the importance of an analysis on the use of biologics, which comprised 82% of the annual management cost in this patient group and 86% of their pharmacologic treatment cost. Two studies performed in Spain in 2015 and 2016 on the introduction of the biologic treatment omalizumab for severe asthma have reported that this introduction can actually help reduce both direct and indirect costs with similar results on their Incremental Cost-Effectiveness Ratio (ICER), as well as the estimation of avoided exacerbations and their estimation of an increase of 3 points on the ACT test,[13,14] pointing towards an economic benefit in the proper use of these therapeutic options when administered based on the current recommendations to guarantee their use exclusively on the population who would benefit from the inclusion and to obtain the described budgetary benefits.

INER is a third level hospital with over 200 beds that focuses primarily on the treatment of patients with respiratory conditions, it provides medical attention to the public in general with over 3000 first time outpatient visits a year in the pulmonology department.[15,16]

In 2005, asthma represented 43% of the outpatient visits motives at INER, where a lower percentage included those referred to the emergency services, where patients are derived for crisis management, and an even lower portion is comprised by patients referred by their first-contact clinic physician.[15,16]

In 2018, INER reported that 14,783 of the visits to their outpatient clinic, emergency services and hospitalizations were related to the ten main respiratory conditions, with asthma leading the list with a total of 4,058 patients.[17] If we correlate these numbers with our findings, where the annual average cost of management for each asthma patient was $43,813.92, this would signify a spending of $177,796,887.36, which would represent 9.2% of the total annual budget for INER for 2022.[17]

This estimation represents an analysis on the behavior and budget allocation of a third level hospital such as INER, therefore it does not reflect the budget and management patterns in different institutions and care levels that comprise the Mexican health system, however it does open the possibility for comparative analysis in other scenarios. However, due to the volume and variability in severity of the cases analyzed, the results presented here do represent valuable information for the landscape of asthma management in Mexico.

Amongst limitations, we must mention the retrospective nature of the present study as well as the fact that data was obtained from clinical records and the record-keeping errors this could imply. The present study is also an analysis that

only considers direct costs of the disease, so results and conclusions do not consider the effects of indirect costs. We did find that quality of life was decreased as dosage increased, therefore we may speak of a disease that affects different aspects of a patient's life, and an analysis of the economic effects of asthma in indirect costs such as the time invested in seeking treatment, transfers and economic loss associated with work and school absenteeism would provide a broader landscape on the real burden of the disease.

Additionally, the present study only includes female patients, due to the nature of the selected database which originated as part of an institutional program focused on health care provision for women in Mexico. Asthma prevalence, its severity, number of exacerbations, hospitalizations and mortality are higher in the female population, even if emergency services visits and hospitalizations in pediatric patients are more frequent in male patients.[18] The causes of this difference in health outcomes for asthma patients is still being studied, however, a relationship between immunologic and hormonal factors has been established. Other differences in management and outcomes related to gender can be found in symptom perception and treatment adherence, where asthmatic women present more severe forms of the disease and use health services more frequently and they are more likely to carry their rescue inhaler with them versus men (61 vs 30%) and more male patients visit the emergency services because they ran out of their medication.[18]

CONCLUSIONS

The annual average total direct medical cost per patient was estimated at $43,813.92 MXN (DE=93,348.85), which corresponds to 9.18% of the INER budget in 2022. The present analysis showed that asthma severity and the use of complementary treatment through biologics, were the main relevant factors in the increase of direct treatment costs. Our results reflect a large economic burden for asthma within the context of the third level of care in the public health system in Mexico.

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Consent for publication

All authors have read and approved the present manuscript and are in agreement of its publication.

Availability of data and materials

All generated data and analysis performed for the present study is included in the manuscript. The database is available through the corresponding author based on reasonable requests.

Competing interests

MCCS, ECLE, JSH, ECLE, MEAR, MCV, MEP, KST, SGV, declare no conflict of interest for the present study. SGV, HSM and SRGG declare a paid work relationship with HS Pharmacoeconomic Research.

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REFERENCES

1. World Health Organization Asthma Fact Sheet. https://www.who.int. [Online]. https://www.who.int/es/news-room/fact-sheets/detail/asthma.
2. Del-Río-Navarro B, Berber A, Reyes-Noriega N, Navarrete-Rodríguez E, et al. Global Asthma Network Phase I study in Mexico: prevalence of asthma symptoms, risk factors and altitude associations-a cross-sectional study. BMJ Open Respir Res. 2020; 7 (1): e000658.
3. Flórez-Tanus Á, Parra D, Zakzuk J, Caraballo L, Alvis-Guzmán N. Health care costs and resource utilization for different asthma severity stages in Colombia: a claims data analysis. World Allergy Organ J 2018; 11 (1).
4. Mexico's Health Department. Morbidity Yearbook 1984 - 2019. 2021 https://epidemiologia.salud.gob.mx/anuario/html/morbilidad_nacional.html.
5. Ocampo J GRSJ. Prevalence of asthma in Latin America. Critical look at ISAAC and other studies. Rev Alerg Mex. 2017; 64 (2): 188-197.
6. Global Initiative for Asthma. 2021 https://ginasthma.org/pocket-guide-for-asthma-management-and-prevention/.
7. Secretaría de Salud. Specific Action Program for Chronic Respiratory Diseases. http://www.gob.mx. [Online]. 2022. http://www.gob.mx/salud/cenaprece
8. Gallardo-Martínez G, Arias-Crus A, González Díaz S, Galindo-Rodriguez G. Derived costs of medical care for asthma in a group of children from the Northeast of Mexico. Rev Alergia Méx 2007; 54 (3).
9. AGREEMENT number ACDO.AS3.HCT.301120/310.P.DF dictated by the H. Technical Council on their ordinary session on November 30th of 2020, related to the approval of Unitary Costs by Level updated to the year 2021. Official Federation Diary.
10. Janson C, Lisspers K, Ställberg B, Johansson G, et al. Health care resource utilization and cost for asthma patients regularly treated with oral corticosteroids - a Swedish observational cohort study (PACEHR). Respir Res 2018; 19 (1): 168.
11. Glick, Henry A. and others, Economic Evaluation in Clinical Trials, 2 edn, Handbooks in Health Economic Evaluation (Oxford, 2014; online edn, Oxford Academic, 1 Oct. 2014), https://doi.org/10.1093/med/9780199685028.001.0001
12. Bahadori K, Doyle-Waters MM, Marra C, Lynd L, et al. Economic burden of asthma: a systematic review. BMC Pulm Med. 2009; 19 (9): 24.
13. Martínez-Moragón E, Climent M, Chiner E, Fernández-Aracil C, et al. Effectivenes and pharmacoeconomic analysis of severe asthma treated with omalizumab in the clinical practice. Farm Hosp 2019; 43: 101-9.
14. Entrenas-Costa LM, Casas-Maldonado F, Soto-Campos JG, Padilla-Galo A, et al. Economic Impact and Clinical Outcomes of Omalizumab Add-On Therapy for Patients with Severe Persistent Asthma: A Real-World Study. Pharmacoecon Open 2019; 3: 333-42.
15. Fernández-Vega M, Vargas Mario H, Regalado-Pineda J, Chapela-Mendoza R, et al. Characteristics of the Mexican asthma patient in outpatient clinics. Rev invest Clín 2005; 57 (4): 513-521.
16. National Institute for Respiratory Diseases. Budget Reports. http://iner.salud.gob.mx/interna/armonizacioncontable_informacionpresupuestal.html.
17. Mexico's Superior Audit Department. Performance of Mexico´s National Institute of Respiratory Diseases Ismael Cosío Villegas. Performance audit 2018-1-12NCD-07-1590-2019. 1590-DS. https://www.asf.gob.mx/Trans/Informes/IR2020c/Documentos/Auditorias/2020_0248_a.pdf
18. Zein JG, Erzurum SC. Asthma is Different in Women. Curr Allergy Asthma Rep 2015; 15 (6): 28.