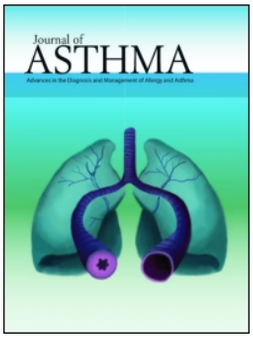

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Key factors associated with uncontrolled asthma – the Asthma Control in Latin America Study

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ABSTRACT

Objective: This study aimed to estimate asthma control at specialist treatment centers in four Latin American countries and assess factors influencing poor asthma control.

Methods: Patients aged ≥12 years with an asthma diagnosis and asthma medication prescription, followed at outpatient specialist centers in Argentina, Chile, Colombia, and Mexico, were included. The study received all applicable ethical approvals. The Asthma Control Test (ACT) was used to classify patients as having controlled (ACT 20–25) or uncontrolled (ACT ≤19) asthma. Frequency and statistical tests were used to assess the association between hospital admissions/exacerbations/emergency department (ED) visits and uncontrolled asthma; multivariate logistic regression was used to assess the association of uncontrolled asthma with clinical/demographic variables.

Results: A total of 594 patients were included. Overall controlled-asthma prevalence was 43.4% (95% confidence interval [CI]: 39.0, 47.4). Patients with uncontrolled asthma were more likely to be women (adjusted odds ratio [aOR]: 1.85; $p = 0.003$), non-white (aOR: 2.14; $p < 0.001$), obese (aOR: 1.71; $p = 0.036$), to have a low monthly family income (aOR: 1.75; $p = 0.004$), to have severe asthma (aOR:1.59; $p = 0.26$), and, compared with patients with controlled asthma, to have a higher likelihood of asthma exacerbations (34.5% vs. 15.9%; $p < 0.001$), hospital admissions (6.9% vs. 3.1%; $p = 0.042$), and ED visits (34.5% vs. 15.9%; $p < 0.001$) due to asthma.

Conclusions: Even in specialist ambulatory services, fewer than half of patients were classified as having controlled asthma. The proportion of uncontrolled patients varied according to clinical and demographic variables.

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Outpatient specialist centers; ACT; Latin American countries; hospital admissions; asthma exacerbations; emergency department visits

Introduction

Asthma is a chronic disease exhibiting different phenotypes. It is a disorder characterized by attacks of breathlessness and wheezing, of which the severity and frequency can vary from person to person. Asthma imposes a significant social and economic burden, and is associated with school and work absenteeism, limitation of physical activities, and high healthcare resource utilization [1].

It is estimated that 235 million people are affected with asthma worldwide [1]. Asthma is highly prevalent in most cities in Latin America [2,3]. A recent survey in Argentina in people aged 20–44 years notes the prevalence of asthma as 9.5%, –based by the diagnosis made by a physician [4]. Correct diagnosis and management remain the key challenges of the disease [5].

Poorly controlled or uncontrolled asthma contributes to increased disability, reduced productivity and

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Dr Rodriguez was a GSK employee at the time this study was conducted.

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health-related quality of life, and high morbidity and mortality [6,7]. Factors that may contribute to low rates of asthma control include errors in asthma medication use, poor drug adherence, low physician compliance with asthma treatment guidelines [8], and the presence of difficult-to-treat and treatment-resistant asthma in the patient population.

In Latin America, rates of asthma control do not meet the standards set by international guidelines. In 2003, the Asthma Insights and Reality in Latin America (AIRLA) survey, a population-based study including more than 2000 patients with asthma from 11 countries in Latin America, showed that only 2.4% of respondents had controlled asthma [9]. In the more recent Latin America Asthma Insights and Management (LA AIM) survey conducted in 2011, the proportion of respondents ($n = 2169$) with controlled asthma was 8% [10]. The study setting seems to have an impact on the observed frequency of asthma control; however, there is a paucity of data regarding rates of asthma control in patients followed in specialist centers in Latin America.

Improving patient management is an important element in achieving asthma control. Optimal management of patients with asthma includes good access to treatment, frequent medical visits, and high treatment adherence. In order to assess the status of asthma management in Latin America, comprehensive information relating to asthma control factors is needed. The aim of this study was to estimate asthma control at specialist treatment centers in four Latin American countries and to assess the factors that influence asthma control.

Materials and methods

Patients

Patients with asthma from 16 public and private outpatient specialist ambulatory centers in four Latin American countries (Argentina, Chile, Colombia, and Mexico) were enrolled in this study between December 2013 and December 2015. There were five centers each from Argentina and Chile, and three centers each from Colombia and Mexico. Eligibility criteria included: age (≥12 years), evidence in the medical record of an asthma diagnosis, prescription of an asthma medication, and at least one medical visit for asthma within the previous 6 months.

The study was approved by applicable institutional review boards/independent ethics committees and was conducted in accordance with the Declaration of Helsinki [11]. Prior to study participation, all patients aged ≥18 years provided written informed consent; parents or legal guardians (for emancipated minors) provided written informed consent for patients aged 12–18 years, in accordance with local requirements.

Study design

The Asthma Control in Latin America study (ASLA; www.gsk-clinicalstudyregister.com; GSK Registration Number 200087) was a multi-country, observational, cross-sectional study, with demographic and medical data collected by a participating physician via patient interview. Variables collected were: gender; age at study entry; age at asthma diagnosis; race/ethnicity; nutritional status; body mass index (BMI); height; weight; family monthly income; number of household members; presence/absence of at least one peak expiratory flow (PEF) test in the previous year; presence/absence of at least one spirometry test in the previous year; treatment access, that is, the last time the patient needed asthma medication (complete access *vs* no/partial access); medication used by the patient at the time of the interview; hospital admissions due to asthma and due to other causes; number of asthma exacerbations in the previous year; hospital admissions including intensive care unit (ICU) due to asthma and due to other causes; emergency department (ED) visits due to asthma and due to other causes; ED visits requiring systemic corticosteroids due to asthma and due to other causes.

An asthma exacerbation was defined as any ED visit or hospitalization due to asthma in the previous year. Patients' access to medication was determined based on questions that evaluated if the last time they required medication to treat asthma was all, part or not obtained for free and regarding the medications the patient did not get for free, if they needed to pay for all, part or none of the medication. Based on this, complete access was considered if all required medication was obtained for free, or paid for, or both (partly obtained for free and the rest paid for); any other answer was classified as partial/incomplete access to medication.

Patients were categorized as having high, medium, or low treatment adherence based on the Morisky Medication Adherence Scale (MMAS-8) [12–14]. All questions were scored from 0 to 1 and added to give a total score that ranged from 0 (lowest adherence) to 8 (highest adherence) points. A score of 8 on the scale indicated a highly adherent patient; a score of 6 to <8 indicated a medium adherent patient; and a score of <6 indicated a patient with low adherence.

The Asthma Control Test (ACT) questionnaire [15] was used to classify patients as having controlled or uncontrolled asthma. The ACT questionnaire is a validated, five-item, patient-completed assessment of their asthma control in the prior 4 weeks. An ACT total score of 20–25 was indicative of controlled asthma, whereas a total score of ≤19 indicated uncontrolled asthma.

Race was self-categorized as white (Caucasian) or non-white (Mestizo [mixed-race], African-Latin American, Native American, or other). Guidance for the questionnaire stated the following: "Patient to freely inform whether he/she considers himself/herself as White, Mestizo, African-Latin American, Native American, or Other. In case of doubt, let the patient know the available answer options in the questionnaire."

BMI was calculated based on patient self-reported height and weight at the time of the medical interview using the following formula: weight (kg)/height (m^2). BMI for adults was categorized as follows: underweight ≤18.5 kg/m^2; eutrophic 18.5–24.9 kg/m^2; overweight 25.0–29.9 kg/m^2; and obese ≥30.0 kg/m^2. The nutritional status of adolescents was based on reference curves from the World Health Organization using a BMI-for-age chart, according to gender [16]. The following cut-off points were adopted: Z-score < -3 (very low weight); Z-score ≥ -3 and < -2 (low weight); Z-score ≥ -2 and ≤ 1 (eutrophic); Z-score >1 and ≤ 2 (overweight); and Z-score >2 (obese). The groups "very low weight" and "low weight" were termed "underweight."

Asthma severity was defined using the ERS/ATS 2014 guidelines [17], that is, "asthma that required step four or five treatment" (i.e., high ICS doses plus a 2nd controller or use of OCS regardless of ICS doses). In cases where there was doubt about the best classification for the patient (i.e., severe asthma or non-severe asthma), three pulmonologists were consulted to adjudicate the classification. The pulmonologists' respective decisions about these patients' classifications and treatments are noted in Table 1. If specialists did not concur, the adjudication process called for consecutive rounds of discussion until a consensus was obtained.

Analysis

Descriptive analyses were conducted with continuous variables summarized as mean (standard deviation [SD]) or median (interquartile range [IQR]); categorical variables were summarized as frequencies and percentages. Analyses were conducted for the overall population and stratified by asthma control classification per ACT score. The Mann–Whitney test was used for comparisons of continuous variables. The Chi-square test was used for categorical variables; Fisher's exact test was applied for categorical variables with a frequency less than 5.

Univariate logistic regression analysis was used to assess the association of uncontrolled asthma with the following variables: age group (aged 12–19, 20–29, 30–39, 40–49, 50–59, or ≥60 years); sex (male, female); race (white, non-white); family income (≥ *vs* <median); number of household members (≥ *vs* <median); age at asthma diagnosis (quartiles); and BMI. Other variables included: PEF and spirometry tests in the previous year; use of long-acting β_2-agonists (LABA) + inhaled corticosteroids (ICS), access to asthma medication at the time it was last required (none/partial *vs* complete), severe asthma (severe *vs* non-severe) and adherence to treatment (high *vs* medium *vs* low adherence). Association of uncontrolled asthma with: number of exacerbations; asthma severity; hospital admissions and ED visit(s) due to asthma or other causes in the past 12 months; and medication class were assessed by frequency and the appropriate statistical test, as mentioned previously.

The medicines reported in the study were categorized by therapeutic class and are presented in **Appendix 1**.

Multiple logistic regression included the variables that presented with a p value <0.1 in the univariate analysis. To avoid the possibility of co-linearity, the

Table 1. Pulmonologists-adjudicated decisions about patients' asthma classifications and treatments, for cases where ERS/ATS 2014 guidelines were unclear.

Treatment Scheme Not Clearly Defined by ERS/ATS 2014	Classification Decision – Defined by 3 Pulmonologists
1: Patients using non-high dose of ICS + LAMA	Severe asthma
2: Patients using non-high dose of ICS + LABA + Anti-IgE	Severe asthma
3: Patients using OCS with other controllers that are not ICS	Severe asthma
4: Patients using non-high dose of ICS +2 or more controllers *(leukotrienes receptor antagonist OR LABA OR xanthines (theophylline OR aminophylline)*	Non-severe asthma

ICS: inhaled corticosteroids; LAMA: long-acting muscarinic receptor antagonist; LABA: long-acting β_2-agonist; Anti-IgE: anti-immunoglobulin E; OCS: oral corticosteroids.

variables "healthcare resources used" and "exacerbations in the last year" were not included in the regression analysis, as both variables were also evaluated in the ACT questionnaire to determine asthma control.

All analyses were performed using STATA v13 (StataCorp LP, College Station, TX, USA).

Results

A total of 594 patients met the eligibility criteria and were included in the study: 163 (27.4%) from Mexico, 154 (25.9%) from Argentina, 154 (25.9%) from Chile, and 123 (20.7%) from Colombia. All invited patients agreed to participate and all patients initially interviewed were included in our analysis, Mean age was 26.9 years, 72.7% were female, and 50.8% of the study population were white. More than 60% of patients with asthma were overweight or obese. The median monthly family income was $668.5 US, and the median number of household members was three. The overall prevalence of controlled asthma was 43.4% (95% confidence interval [95% CI]: 39.0,

Table 2. Characteristics of asthma patients by asthma control status in Argentina, Chile, Colombia and Mexico.

Independent Variables	Controlled		Uncontrolled		Total		Crude OR	95% CI	*p* value	Adjusted OR	95% CI	*p* value
	n = 258	(%)	*n* = 336	(%)	*n* = 594	(%)						
Gender												
Male	95	58.6	67	41.4	162	27.3	Reference			Reference		
Female	163	37.7	269	62.3	432	72.7	2.36	(1.63–3.42)	<0.001	1.85	(1.23-2.77)	0.003
Age at study entry, years												
12–19	31	50.8	30	49.2	61	10.3	Reference			Reference		
20–29	48	61.5	30	38.5	78	13.1	0.60	(0.30–1.20)	0.149	0.47	(0.22–0.98)	0.044
30–39	31	37.3	52	62.7	83	14.0	1.59	(0.81–3.13)	0.180	1.25	(0.60–2.59)	0.555
40–49	40	35.7	72	64.3	112	18.9	1.76	(0.92–3.35)	0.085	1.13	(0.56–2.28)	0.734
50–59	43	35.8	77	64.2	120	20.2	1.73	(0.92–3.26)	0.089	1.07	(0.53–2.16)	0.843
≥60	65	46.4	75	53.6	140	23.6	1.10	(0.60–2.02)	0.758	0.72	(0.37–1.39)	0.320
Age at asthma diagnosis, years												
≤9	71	47.0	80	53.0	151	25.4	Reference					
10–25	73	47.7	80	52.3	153	25.8	0.97	(0.62–1.53)	0.903			
26–41	55	37.7	91	62.3	146	24.6	1.44	(0.90–2.30)	0.124			
≥42	59	41.0	85	59.0	144	24.2	1.25	(0.78–1.98)	0.352			
*Race/ethnicity**												
White	165	54.8	136	45.2	301	50.8	Reference			Reference		
Non-white	93	31.8	199	68.1	292	49.2	2.60	(1.86–3.64)	<0.001	2.14	(1.47–3.11)	<0.001
*Nutritional status**												
Underweight	6	42.9	8	57.1	14	2.4	1.24	(0.42–3.71)	0.696	2.07	(0.61–6.94)	0.240
Normal	98	48.5	104	51.5	202	34.1	Reference			Reference		
Overweight	108	47.6	119	52.4	227	38.3	1.02	(0.70–1.49)	0.919	0.98	(0.64–1.51)	0.945
Obese	45	30.2	104	69.8	149	25.2	2.16	(1.38–3.37)	0.001	1.71	(1.04–2.84)	0.036
*Family monthly income, USD**												
≥668.5	162	54.4	136	45.6	298	50.2	Reference			Reference		
<668.5	95	32.2	200	67.8	295	49.7	2.58	(1.84–3.60)	<0.001	1.75	(1.20–2.56)	0.004
*Household members, n**												
<3	78	45.3	94	54.7	172	29.0	Reference					
≥3	180	42.8	241	57.2	421	70.9	1.14	(0.79–1.63)	0.482			
Had at least one PEF test												
Yes	66	49.3	68	50.7	134	22.6	Reference					
No	192	41.7	268	58.3	460	77.4	1.36	(0.92–2.00)	0.123			
Had at least one spirometry												
Yes	174	43.8	223	56.2	397	66.8	Reference					
No	84	42.6	113	57.4	197	33.2	1.05	(0.74–1.48)	0.800			
*Medication access level**												
Complete access	186	40.3	275	59.7	461	77.6	Reference			Reference		
No/Partial access	71	53.8	61	46.2	132	22.2	0.59	(0.40–0.88)	0.009	0.88	(0.57–1.37)	0.582
Treatment with ICS + LABA												
Yes	181	43.2	238	56.8	419	70.5	Reference					
No	77	44.0	98	56.0	175	29.5	0.98	(0.69–1.40)	0.921			
Asthma severity												
Non-severe	192	46.8	218	53.2	410	69.0						
Severe Asthma	66	35.9	118	64.1	184	31.0	1.51	(1.05–2.17)	0.025	1.59	(1.06–2.38)	0.026
*Treatment adherence**												
High	58	45.3	70	54.7	128	21.6	Reference					
Medium	98	48.3	105	51.7	203	34.2	0.89	(0.57–1.40)	0.623			
Low	102	38.9	160	61.1	262	44.2	1.30	(0.85–2.00)	0.232			

Note. Six patients were not included in the logistic model because they had missing information in at least 1 variable included in the model.
*One missing.
CI: confidence interval; ICS: inhaled corticosteroids; LABA: long-acting β_2-agonist; OR: odds ratio; PEF: peak expiratory flow; USD: United States dollars.

47.4); the highest frequency of patients with controlled asthma was found in Argentina (60.4%), followed by Chile (48.1%), Colombia (33.3%), and Mexico (30.7%).

Table 2 shows patient characteristics by asthma control status. In the univariate analysis, age, gender, race, obesity, family income, medication access, and asthma severity were associated with poor asthma control.

In the multivariate analysis, the association between uncontrolled asthma and medication access were not retained. Women remained more likely to have uncontrolled asthma compared with men (adjusted odds ratio [aOR]: 1.85; 95% CI: 1.23, 2.77; $p = 0.003$). Patients with obesity were more likely to have uncontrolled asthma than eutrophic patients, even after adjusting for other variables (aOR: 1.71; 95% CI: 1.04, 2.84; $p = 0.036$). Non-white patients and patients with a family income below the median were more likely to have uncontrolled asthma (aOR: 2.14; 95% CI: 1.47, 3.11; $p < 0.001$ and aOR: 1.75; 95% CI: 1.20, 2.54; $p = 0.004$, respectively). Patients with severe asthma were also more likely to have uncontrolled asthma (aOR: 1.59; 95% CI: 1.06, 2.38; $p = 0.026$).

Table 3 describes the healthcare resources used in the past year by asthma control status. Among patients classified as having uncontrolled asthma, 6.9% had at least one hospital visit due to asthma, and 34.5% had at least one asthma-related ED visit. Patients with uncontrolled asthma had more hospital admissions ($p < 0.05$) and ED visits ($p < 0.05$) due to asthma compared with those who had controlled asthma. The proportion of patients with a previous asthma exacerbation was also higher in patients with uncontrolled asthma (34.5%) compared to those with controlled asthma (15.9%; $p < 0.001$).

Table 4 presents the use of asthma-related medications by asthma control status. The reported use of ICS alone or in combination was 91.9% for patients

Table 3. Healthcare resources used in previous 12 months and exacerbation frequency by asthma control status.

	Controlled Asthma ($n = 258$)		Uncontrolled Asthma ($n = 336$)		Overall		
Clinical Characteristics	*n*	(%)	*n*	(%)	*n*	(%)	*p*-value
Hospital admissions due to asthma							
Yes	8	3.1	23	6.9	31	5.2	0.042
No	250	96.9	313	93.1	563	94.8	
Hospital admissions due to other causes							
Yes	6	2.3	16	4.8	22	3.7	0.119
No	252	9.7	320	95.2	572	96.3	
Hospital admissions							
Due to asthma: mean (SD); median (IQR)	0.1 (0.3); 0.0 (0.0)		0.2 (1.4); 0.0 (0.0)		0.1 (1.1); 0.0 (0.0)		0.041
Due to other causes: mean (SD); median (IQR)	0.0 (0.4); 0.0 (0.0)		0.1 (0.5); 0.0 (0.0)		0.1 (0.4); 0.0 (0.0)		0.117
Asthma exacerbation							
Yes	41	15.9	116	34.5	157	26.4	<0.001
No	217	84.1	220	65.5	437	73.6	
Hospital admissions including ICU due to asthma							
Yes	2	0.8	12	3.6	14	2.4	0.026
No	256	99.2	324	96.4	580	97.6	
Hospital admissions including ICU due to other causes							
Yes	3	1.2	9	2.7	12	2.0	0.193
No	255	98.8	327	97.3	582	97.9	
Hospital admissions including ICU							
Due to asthma: mean (SD); median (IQR)	0.0 (0.1); 0.0 (0.0)		0.1 (0.8); 0.0 (0.0)		0.1 (0.6); 0.0 (0.0)		0.025
Due to other causes: mean (SD); median (IQR)	0.0 (0.2); 0.0 (0.0)		0.0 (0.2); 0.0 (0.0)		0.0 (0.2); 0.0 (0.0)		0.196
ED visits due to asthma							
Yes	41	15.9	116	34.5	157	26.4	<0.001
No	217	84.1	220	65.5	437	73.6	
ED visits due to other causes							
Yes	15	5.8	41	12.2	56	9.4	0.008
No	243	94.2	295	87.8	538	90.6	
ED visits due to asthma requiring systemic (injectable) corticosteroid							
Yes	28	10.9	93	27.7	121	20.4	<0.001
No	230	89.1	243	72.3	473	79.6	
ED visits due to other causes requiring systemic (injectable) corticosteroid							
Yes	7	2.7	16	4.8	23	3.9	0.200
No	251	97.3	320	95.2	571	96.1	
ED visits							
Due to asthma: mean (SD); median (IQR)	0.3 (1.1); 0.0 (0.0)		1.2 (5.8); 0.0 (1.0)		0.8 (4.4); 0.0 (1.0)		<0.001
Due to other causes: mean (SD); median (IQR)	0.1 (0.3); 0.0 (0.0)		0.2 (0.7); 0.0 (0.0)		0.1 (0.6); 0.0 (0.0)		0.007

ED: Emergency department; ICU: intensive care unit; SD: Standard deviation; IQR: Interquartile range.

Table 4. Use of asthma medications at the time of the interview according to asthma control status.

Medication Class	Controlled Asthma *n* (%)	Uncontrolled Asthma *n* (%)	Total *n* (%)	*p* value
Anti-immunoglobulin E agents	7 (2.7)	8 (2.4)	15 (2.5)	0.798
Anticholinergics	20 (7.8)	84 (25.0)	104 (17.5)	<0.001
Antihistamines	19 (7.3)	24 (7.1)	43 (7.2)	0.918
Inhaled corticosteroids only or in combination with any other asthma medication	237 (91.9)	307 (91.4)	544 (91.6)	0.831
Inhaled corticosteroids + LABA	181 (70.2)	238 (70.8)	419 (70.5)	0.857
Leukotriene antagonists	27 (10.5)	65 (19.4)	92 (15.5)	0.003
Short-acting beta-agonists	154 (59.7)	207 (61.6)	361 (60.8)	0.635
Systemic corticosteroids	3 (1.2)	17 (5.1)	20 (3.4)	0.009
Xanthine and adrenergics	7 (2.7)	9 (2.7)	16 (2.7)	0.979
Other	3 (1.2)	1 (0.3)	4 (0.7)	0.201

ICS: inhaled corticosteroids; LABA: long-acting β_2-agonists.

with controlled asthma and 91.4% for those with uncontrolled asthma, with no significant differences based on asthma control status. No significant differences were observed between the two groups with regard to the use of rescue medications such as short-acting β-agonists (SABA) and xanthine. The frequencies of anticholinergics, leukotriene antagonists, and systemic corticoids were significantly higher in patients with uncontrolled asthma ($p < 0.001$, $p = 0.003$, and $p = 0.009$, respectively; Table 4).

Discussion

In this study, we identified the frequency of controlled asthma among patients from specialist ambulatory centers in four Latin American countries, with the expectation that these estimates would reflect the best practice in asthma management. The proportion of patients with asthma who had controlled disease was considerably higher in our analysis compared with survey results from other studies in Latin America [9,10]. Further, most patients in our study had no asthma-related hospitalizations (94.8%) or ED visits (73.6%) in the previous year. In contrast, the AIRLA study showed a hospitalization rate of 22% [9], and the LA AIM survey found that 23% of the asthma population analyzed had been hospitalized and 44% had at least one ED visit due to asthma in the past year [10]. These results suggest a positive impact of specialist care; however, it is important to note that, even in this setting, less than half of the population (43.4%) was classified as having controlled asthma. This proportion was similar to earlier estimates based on patients from asthma specialist centers in South Africa (47.2%) [18] and Turkey (51.5%) [19].

These combined results suggest that, despite the focused management of specialist centers that likely offer greater access to medication, attract patients within higher socioeconomic levels, and allow for more frequent physician visits compared with primary care, a considerable proportion of patients still had uncontrolled asthma.

As with findings from earlier studies, our results show greater healthcare utilization for patients with uncontrolled asthma, placing a higher burden on the healthcare system for this patient group. The proportion of patients with at least one asthma-related hospital admission in the previous year was more than twice as high among patients with uncontrolled asthma [19,20].

Approximately 56.0% of patients with asthma in our study had high or medium adherence to asthma medication; this result is similar to earlier reports using self-reported tools from the United States [21]. However, we found no significant difference in adherence for patients with or without controlled asthma in the multivariate analysis. This result differs from previous studies that have shown associations between poor therapeutic adherence and higher mortality, frequent asthma exacerbations, and poorer asthma control [20,22,23]. Indeed, other studies have demonstrated an association between medication adherence and asthma control [24,25]. Our finding may be related to the cross-sectional design of our study, limiting the ability to detect the temporal association of adherence. Although we have used a validated questionnaire for measuring adherence to treatment, as data were obtained from self-reported information, it is possible that information bias occurred in our study. Another possibility is that a greater number of patients with difficult-to-control or refractory asthma were included in our study sample.

Our study found that 33.2% of the patients had not experienced at least one spirometry in the previous year. A published study on the impact of asthma in Latin America showed that 54% of asthma patients in AIRLA [9] had no spirometry performed during the previous year, according to patient self-reported surveys. Of course, AIRLA and ASLA have different methodologies, as AIRLA was population-based and our study was conducted in specialist centers, but

these results certainly highlight that spirometry is not common in Latin America.

One of the sociodemographic factors most strongly associated with asthma control was gender in our study: men were more likely than women to have controlled asthma, as previously reported [19,26,27]. One possible explanation is that women are more prone to severe asthma than men [28].

Low income and non-white race were identified as factors associated with poorly controlled asthma, in alignment with previous investigations [29,30]. Possible explanations for this association between low income and poor asthma control may include a higher exposure to indoor allergens [31] and biomass [32], a lower ability to afford medicine, and reduced access to physician visits and other outpatient care [33]. However, the reason for higher rates of uncontrolled asthma in non-white patients even after controlling for socioeconomic status remains unclear [30].

In the multivariate analysis, obesity was associated with worse disease control, which aligns with other studies in which higher BMI was found to be associated with poor asthma control [6,27,34]. It should be noted that the "obese asthma" phenotype is complex and multifactorial; the two diseases act simultaneously and the mechanisms involved are not fully known [35]. Nevertheless, studies have shown the effects of weight loss on asthma symptoms [35,36]. Weight reduction programs can decrease the prevalence and severity of asthma in obese patients, as well as reduce medication use and hospitalization time as a result of improved control of the disease [36,37]. In contrast to our results, a cross-sectional study conducted in Spain with more than 2000 patients found a prevalence of 63.9% of uncontrolled asthma using the ACT tool, a result similar to ours, but neither gender nor obesity were associated with asthma control [24]. A major difference between this study and ASLA is that the González-Barcala study was performed in a primary care setting; only 4.22% patients were classified as having high persistent asthma [24].

Nearly all patients in our analysis used ICS, which aligned with another study conducted in specialist ambulatory centers [38]. When ICS and LABA usage was compared between controlled and uncontrolled asthma patients, there was no difference between the groups, contrary to results from another investigation [38]. In our study, we had a small number of patients who did not use controller medication, and the imbalance between the groups could have affected the results. Again, the cross-sectional design of our study may have influenced our results, if some patients had recently stepped up their asthma treatment due to uncontrolled asthma. It is also possible that some patients in our study population had refractory asthma. SABA use was similar between the controlled and uncontrolled asthma groups, while anticholinergics and systemic corticoids were more frequently used among patients with uncontrolled asthma. Other studies have also found a higher use of systemic corticoids within this uncontrolled population [19]. In the medical interview, we only asked patients to report what medications they were using and not the frequency of use. As SABA is a rescue medication and it is recommended to be used in all GINA treatment steps that may explain why no difference was found between the controlled and uncontrolled groups.

The current study found a higher use of anticholinergics in the uncontrolled group. A recent systematic review and meta-analysis reported that tiotropium, an anticholinergic, with low- to medium-dose ICS once daily could be an acceptable option in the treatment of adults with moderate uncontrolled asthma, with improvements in lung function noted. However, it is important to note that no statistically significant differences were found in the two studies analyzed that used the Asthma Control Questionnaire, with relevant heterogeneity detected [39]. Our study also considered long-acting muscarinic antagonists (LAMA) and SAMA in the anticholinergic drug class, while the systematic review considered tiotropium only.

Differences in asthma control related to asthma severity were found in our study. We considered the ERS/ATS 2014 criteria [17] to classify patients with severe asthma, defined as "asthma that requires treatment with high dose inhaled corticosteroids plus a second controller and/or systemic corticosteroids to prevent it from becoming 'uncontrolled' or that remains 'uncontrolled' despite this therapy." These criteria are more stringent versus the Global Initiative for Asthma (GINA) 2017 guidance [40]. Our study found that 31% of patients had severe asthma, and, of these, 64.1% were uncontrolled. This is consistent with another study, showing that patients with severe asthma had an increased number of exacerbations, higher rates of hospital admissions and ED room visits [41].

In our study, most patients reported complete access to asthma medication. Surprisingly, the proportion of patients with total access to asthma medications was higher among the patients with uncontrolled asthma. These findings suggest that the lack of asthma control observed in this population was not the result of poor medication access, but may be related to

other factors, such as inadequate patient education, appropriateness of therapy, treatment resistance, disease severity, adherence, and co-morbidities.

This study had some limitations. Firstly, because our study population was a convenience sample from specialist ambulatory centers, our results may not be representative of the general Latin American population. This study was not planned to be representative for each country, therefore selection bias could have occurred that could explain the large variation in the proportion of patients with controlled asthma between countries. Secondly, as data collection was based on questionnaire completion and analysis, recall bias may have occurred, especially regarding questions about events that occurred a long time ago and previous use of medication.

However, most of our findings were consistent with other studies investigating asthma at the tertiary level. As the ACT questionnaire assessed patients' perceptions of their asthma control in the prior 4 weeks only, it was not possible to know the starting point or duration of the uncontrolled asthma. Further, most variables were collected through participant interviews, which adds potential for information bias. The cross-sectional design of our study did not allow for analysis of the association between asthma control and time-dependent variables, leaving potential for reverse causality. The lack of inclusion of any assessment of the patient's inhaler technique should also be mentioned as a limitation of our study, as that could be an important confounding effect associated not only with explanatory variables, such as socioeconomic level and education, but also with the response to treatment and, consequently, control. This explanation should also be taken into consideration as a possible factor connected with the lack of association found in our study between the use of ICS, or adherence, and asthma control. In conclusion, asthma control was inadequate in more than half of the patients from specialist ambulatory centers in Latin America, although the overall control was better than had been reported in the general asthma population. Poor asthma control was associated with higher healthcare resource utilization. Some characteristics were associated with asthma control (including gender, race, obesity status, and family income), which corroborates the emerging role of social determinants in asthma burden. These data contribute to the identification of possible patients with uncontrolled asthma on specialist care. Our study reinforces the importance of improving patient management in specialist centers and emphasizes that there is still a high proportion of uncontrolled asthma at the tertiary level of care. Additional research is needed in order to better recognize factors associated with poor asthma control and to improve asthma management and a patient's quality of life. An important initiative could be the development of plans for health education in asthma patients, to stimulate confidence and adherence to asthma treatment regimens [42]. Educational programs targeting patients with asthma have been shown to produce positive achievements in clinical aspects of the disease and, consequently, in improving the quality of life [43].

Conclusions/key findings

Even in specialist ambulatory services, fewer than half of the patient population we analyzed could be classified as having controlled asthma.

Patients with uncontrolled asthma were more likely to be women, obese, and non-white, with a low monthly family income.

In this study, patients classified with uncontrolled asthma had more exacerbations, hospital admissions, and ED visits due to asthma compared with those who had controlled asthma.

Disclosure statement

No potential conflict of interest was reported by the authors.

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