

Atopy Is Associated with Age at Asthma Onset in Elderly Patients



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What is already known about this topic? There are conflicting findings about the prevalence of allergic asthma in elderly patients.

What does this article add to our knowledge? Atopy, especially mite allergy, was observed in most elderly asthmatic patients. There was a negative correlation between duration of asthma and forced expiratory volume in 1 second values, independent of the presence of atopy.

How does this study impact current management guidelines? Atopy should be investigated in elderly asthmatic patients, because there are specific management approaches that can be applied to atopic asthmatic patients.

BACKGROUND: Asthma in the elderly population (60 years of age and older) is frequently underdiagnosed, as well as atopy.

Atopy, although more prevalent in younger patients, can be a major cause of asthma in the elderly. Chronic obstructive pulmonary disease (COPD) and cardiovascular disease are common differential diagnoses, especially in elderly smokers.

OBJECTIVE: The objective of this study was to assess atopy and comorbidities in elderly patients with asthma.

METHODS: This was an observational and retrospective study involving elderly asthmatic patients followed up at a tertiary center. Patients were assessed for severity of asthma, frequency of atopy, and frequency of comorbidities concomitant with asthma. Then, they were classified according to their age at asthma onset and the groups compared with each other for atopy, spirometric parameters, and comorbidities.

RESULTS: This study included 243 elderly asthmatic patients, 71.8% of them presenting severe disease and 82.3% forced expiratory volume in 1 second (FEV₁) < 80%. Gastroesophageal reflux disease, obesity, and asthma-COPD overlap syndrome were observed, respectively, in 64%, 37%, and 13% of these patients. Atopy was observed in 63%, mainly in those with early onset disease, and its frequency decreased as the age of asthma

onset increased ($P < .05$). Total serum IgE was higher for allergic patients and FEV₁ values were lower for patients with long-term asthma. Aspirin-exacerbated respiratory disease was more frequent in patients with nonallergic asthma.

CONCLUSIONS: Most elderly asthmatic patients followed up in our tertiary center were atopic and higher values of total serum IgE suggest atopy. Atopy was inversely correlated with age of asthma onset. The diagnosis of allergic asthma in the elderly population is essential to treat patients more properly, improving their quality of life and decreasing asthma morbidity and mortality. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:865-71)

Key words: Asthma; Allergic asthma; Elderly; Aeroallergens; Atopy; IgE; Asthma-COPD overlap syndrome (ACOS); Age of asthma onset

The forecast is that the number of elderly persons in the population will increase in the coming years throughout the world, and it will be around 20% by 2030 in Brazil.¹ Similarly, the prevalence of asthma and allergic disease is growing in some parts of the world, and in Brazil, the prevalence of asthma patients is 13% of the population.² Atopy affects individuals of all ages and its prevalence in elderly people is around 8% to 15%.^{3,4}

Asthma is a heterogeneous disease characterized by chronic inflammation of the respiratory tract. It is defined by the history of respiratory symptoms such as wheezing, shortness of breath, chest tightness, and cough that vary over time and in intensity, associated with variable expiratory airflow limitation.^{5,6} The prevalence of asthma in the elderly population (≥65 years of age), although difficult to establish because of its clinical heterogeneity, has been reported to be around 5% to 12%, being more frequent in women.⁷ The burden of asthma is more significant in the elderly than in younger asthmatic patients, particularly with respect to mortality, hospitalization, medical costs, and quality of life.⁷

Various factors are involved in asthma pathogenesis in the elderly, such as allergic sensitization and immunological

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Abbreviations used

ACOS- Asthma-COPD overlap syndrome
 AERD- Aspirin-exacerbated respiratory disease
 BMI- Body mass index
 COPD- Chronic obstructive pulmonary disease
 CT- Computed tomography
 FEV₁- Forced expiratory volume in 1 second
 FVC- Forced vital capacity
 GERD- Gastroesophageal reflux disease
 HDM- House dust mite
 ICS- Inhaled corticosteroids
 LABA- Long-acting β -agonist
 LTRA- Leukotriene receptor antagonist
 NSAID- Nonsteroidal anti-inflammatory drug
 SD- Standard deviation
 SPT- Skin prick tests

alterations of immunosenescence. The immunological and structural consequences of immunosenescence involved in asthma include impairment of the mucociliary clearance and impairment of high-affinity antibody production, leading to an increased risk of respiratory infections (these infections could exacerbate asthma or play a role in the pathogenesis of late onset asthma).^{8,9}

According to the data published in the literature, allergic sensitization in elderly asthmatic patients varies widely; 28% to 74% of them are sensitized to at least 1 allergen. The major aeroallergens related to allergic asthma in elderly patients are house dust mites (HDM) and cockroaches.^{10,11}

The investigation of allergic asthma in the elderly is a challenge to the clinician due to several reasons. Dyspnea is a common symptom of many respiratory diseases, and in the elderly, this symptom is often considered normal because of aging and deconditioning. Differential diagnoses or comorbidities, such as chronic obstructive pulmonary disease (COPD) and congestive heart failure, may mask the diagnosis of asthma in these population.^{7,12} COPD is a common preventable and treatable disease, characterized by persistent airflow limitation that is usually progressive and associated with enhanced chronic inflammatory responses in the airways and the lungs to noxious particles or gases.¹³

Asthma exacerbations and associated comorbidities contribute to the overall severity of the disease in elderly patients.⁶ Moreover, distinguishing asthma from COPD can be problematic, particularly in smokers and older adults. The presence of asthma and COPD symptoms in the same patient has recently been named asthma-COPD overlap syndrome (ACOS).¹⁴ There is no universally accepted definition of ACOS.^{15,16} Therefore, ACOS is identified in clinical practice by the features that it shares with both asthma and COPD. A specific definition for ACOS cannot be developed until more evidence is available regarding its clinical phenotypes and underlying mechanisms.¹⁴ Sin et al¹⁶ proposed a definition for ACOS that incorporated features such as persistent airflow limitation in symptomatic patients 40 years of age and older, a well-documented history of asthma in childhood or early adulthood, and a significant history of exposure to cigarette or biomass smoke. Tobacco smoking is the most important and preventable risk factor for the development and progression of COPD.^{17,18}

Asthma may be classified according to the age at onset of symptoms: (1) early-onset asthma, whose onset occurred before 12 years of age, that is, a long-term, more symptomatic, and severe asthma, with high prevalence of atopy and lower forced expiratory volume in 1 second (FEV₁); (2) late-onset asthma, whose symptoms and FEV₁ are, initially, less severe than the early-onset asthma, and atopy is less common.^{12,19,20} Forty-eight percent of elderly asthmatic patients presented asthma onset before 40 years of age, and around 30% had their disease onset before 20 years of age.^{12,19,21,22} It is important to characterize elderly asthmatic patients for the presence of atopy and/or ACOS to provide other therapeutic options to control their disease.

The major objective of this study was to assess atopy and comorbidities in elderly patients with asthma. These patients were also classified according to age at disease onset, which was correlated to the occurrence of atopy, lung function parameters, and comorbidities.

METHODS

This was an observational, retrospective study involving elderly asthmatic patients who have been followed up at the Asthma Outpatient Clinic of the Clinical Immunology and Allergy Division, University of São Paulo, Brazil. Patients 60 years of age or older were considered elderly (according to the Brazilian Institute of Geography and Statistics—IBGE's—definition for Brazil¹); the diagnosis of asthma was made according to Holgate et al,⁶ that is, a characteristic pattern of respiratory symptoms such as wheezing, dyspnea, chest tightness, or cough, besides the presence of reversibility and variability of these symptoms and reversibility and variability of expiratory airflow limitation.⁶ Patients were included sequentially in the study, in the order in which they were seen in the clinic, when they met the inclusion criteria.

Spirometry was performed using a Koko spirometer (PDS Instrumentation, Louisville, Colo), which provides flow-volume and volume-time curves. The techniques and interpretation of the results were those recommended by the 2005 American Thoracic Society consensus and the 2005 European Respiratory Society consensus.^{23,24} The reference values used were those established for Brazilians.²⁵ The tests were repeated 15 minutes after the inhalation of 400 mcg of salbutamol via a metered-dose inhaler with a spacer. The bronchodilator response was defined as an increase (over baseline) of at least 12% and 200 mL in FEV₁ and/or forced vital capacity (FVC).

To be considered asthmatic and included in the study, patients had to present a characteristic pattern of respiratory symptoms compatible with asthma and reversibility and variability of expiratory airflow limitation.⁶ Because many patients have been followed up in the clinic for a long time, only those who showed reversibility in at least 1 spirometry were included.

Cardiovascular disease is a common differential diagnosis or comorbidity in patients with asthma and/or COPD, particularly in elderly patients. In this study, asthma was diagnosed based on the presence of reversibility and variability of symptoms and lung function, during months or years of medical follow-up. Patients with uncontrolled cardiovascular disease were excluded.

Asthma severity was classified according to the treatment step prescribed, as suggested in GINA guidelines.^{5,6} Briefly, patients prescribed step 2 treatments (low-dose inhaled corticosteroids [ICS], or leukotriene receptor antagonist [LTRA], or low-dose theophylline) were defined as mild asthma cases; step 3 therapies (low-dose ICS/LTRA, or medium/high-dose ICS) were classified as moderate;

and step 4-5 (medium/high-dose ICS/long-acting β -agonist [LABA] with or without tiotropium, or medium/high-dose ICS/LTRA, or additional low-dose oral corticosteroid) as having severe asthma.⁶

Patients were classified as allergic and nonallergic asthma according to the presence of atopy.

The skin prick test (SPT) and/or serum-specific IgE analysis (ImmunoCAP; ThermoFisher Scientific, Uppsala, Sweden) for aeroallergens (HDM, molds, dander, cockroaches, and pollen) were performed to confirm or rule out atopy.^{26,27} SPT was performed by the application of a drop of each test solution to the volar face of the forearm, at least 2 to 3 cm from the wrist and the antecubital fossae. The distance between each drop was at least 2 cm. Skin prick testing is the standard method to assess IgE-mediated sensitization to aeroallergens. This test uses common standard extracts (International Pharmaceutical Immunology - IPI-ASAC, São Paulo, Brazil), including the use of positive and negative controls. Histamine dihydrochloride 10 mg/mL was used as positive control (provides wheal size of 6-8 mm) and glycerin 50.0% (v/v) as negative control (provides a wheal <3 mm).²⁷⁻²⁹

Standardized aeroallergen extracts were applied to the skin, and, immediately, the skin under each of these drops was pricked with a plastic lancet (Alergopricks Puntor; Neoflex Biotecnologia Ltda), using 1 lancet for each drop. The results were read 15 minutes after application. The largest diameter of the wheal of each specific allergen was measured and the test was considered positive for a wheal size of ≥ 3 mm.²⁷ The positive control should be positive and the negative control should be negative; when there were any controversial results, serum specific IgE was performed. SPT was not performed in patients who had extensive eczema, dermatographism, or urticaria, or who were taking antihistamines or other medications that interfere with the proper interpretation of the test results. The aeroallergens studied were HDM (*Dermatophagoides pteronyssinus*, *Blomia tropicalis*), *Canis familiaris*, *Felis domesticus*, molds (*Aspergillus fumigatus*, *Penicillium notatum*), cockroaches (*Blattella germanica*, *Periplaneta americana*), and grass pollen (*Lolium perenne*). Serum specific IgE was quantified by ImmunoCAP, and the test was considered positive when the value was 0.35 kU_A/L or higher.²⁶ Total serum IgE and peripheral eosinophils were also assessed.

Patients were assessed regarding their age at symptoms onset, duration of asthma, spirometric values, and comorbidities (gastroesophageal reflux disease [GERD], aspirin-exacerbated respiratory disease [AERD], obesity, and ACOS).

Patients were also grouped according to their age at the onset of asthma symptoms into the following subgroups: (A) 12 years of age and under (early-onset asthma); (B) 13 to 20 years of age (young-onset asthma); (C) 21 to 39 years of age (adult-onset asthma); (D) 40 to 54 years of age (late-onset asthma); and (E) 55 years of age or older (very late-onset asthma).

The patients presenting typical symptoms such as retrosternal burning (often labeled heartburn) and regurgitation were considered to have GERD, or endoscopic findings demonstrating the disease, according to "The Montreal definition and classification of gastroesophageal reflux disease."³⁰ AERD diagnosis was made according to the history of asthma exacerbation with nonsteroidal anti-inflammatory drugs (NSAIDs), and obesity when body mass index (BMI) was 30 kg/cm² or higher. Exposure to tobacco was considered when there was an exposition of at least 1 pack-year of cigarettes.³¹

The ACOS diagnosis was made according to the 2016 International Consensus.¹⁶ The patients who presented all 3 major criteria and at least 1 minor criterion¹⁶ were considered to have ACOS (Table I). The major criteria were: (1) persistent airflow limitation

TABLE I. Criteria for ACOS—asthma-chronic obstructive pulmonary disease (COPD) overlap syndrome diagnosis

Major criteria	Minor criteria
1. Persistent airflow limitation individuals ≥ 40 y	1. Documented history of atopy
2. At least 10 pack-years of tobacco smoking or equivalent indoor	2. Bronchodilator response of FEV ₁ ≥ 200 mL and 12% from baseline values on 2 or more visits.
3. Document history of asthma before 40 y of age	3. Peripheral blood eosinophil count of ≥ 300 cells/mm ³
4. Emphysema on chest CT*	

ACOS diagnose = 3 major (1, 2, and 3) + 1 minor (any: 1, 2, or 3) or major (criterion number 4 + 1, 2, or 3) + minor (at least criterion number 2).

ACOS, Asthma-COPD overlap syndrome; CT, computed tomography; FEV₁, forced expiratory volume in 1 s.

Modified from Sin et al.¹⁶

*Major criterion number 4 was included as an individual criterion for COPD, as many patients had chest CT images available and emphysema is not expected in asthma alone.

(postbronchodilator FEV₁/FVC < 0.70 or lower than the normal limit) in individuals 40 years of age or older; (2) at least 10 pack-years of tobacco smoking or equivalent indoor or outdoor air pollution exposure; and (3) documented history of asthma before 40 years of age, or a bronchodilator response with improvement of >400 mL in FEV₁ after administration of 400 mcg of salbutamol. The minor criteria were: (1) documented history of atopy or allergic rhinitis; (2) bronchodilator response with improvement of ≥ 200 mL and 12% in FEV₁ on 2 or more visits after administration of 400 mcg of salbutamol; and (3) peripheral blood eosinophil count of ≥ 300 cells/mm³. Beyond these criteria, we also considered emphysema at chest computed tomography (CT), which could replace the smoking major criterion, as a fourth major criterion for ACOS diagnosis, because emphysema is not expected in asthma alone. Therefore, in this study, ACOS was diagnosed when major criteria 1, 2, and 3 and at least 1 minor criterion were present; or when major criterion number 4 and 1, 2, or 3 and at least the minor criterion number 2 were present (Table I).

Statistical analysis

All data were analyzed using nonparametric tests. Fisher's exact test was used for comparison between allergic and nonallergic asthmatic patients, which included: female gender, patient's current treatment (step 4), and comorbidities (GERD, AERD, obesity, and ACOS). The Mann-Whitney test was used to compare allergic asthma or nonallergic asthma groups by current age, age at onset of asthma symptoms, duration of disease, and spirometric values. The χ^2 test was used to compare female prevalence, atopy, and comorbidities by age at onset of asthma. The Kruskal-Wallis test was used to compare current age, FEV₁, FVC, total IgE, and peripheral eosinophils in the different groups according to age at onset of asthma. The level of significance was set at 5% ($P < .05$) for all the tests, and 95% confidence intervals for the group comparisons.

RESULTS

The present study included 243 elderly asthmatic patients, and 200 of them (82.3%) were women. The mean age was 70.5 years (standard deviation [SD], 6.9 years), mean age at onset of symptoms was 28.9 years (SD, 19.1 years), and mean duration of disease was 41.6 years (SD, 18.9 years). Of these elderly

TABLE II. Normal or altered FEV₁ according to the history of exposure to tobacco

History of exposure to tobacco	FEV ₁ ≥ 80% predicted (%)	FEV ₁ < 80% predicted (%)
No exposure	19.0	81.0
Smoker or ex-smoker	12.0	84.0
Passive smoking	16.8	83.2

χ^2 test $P = .212$.

FEV₁, Forced expiratory volume in 1 s.

asthmatics, 63.3% had asthma symptom onset before 40 years of age, 40% had early onset asthma before 20 years of age, and 28% had early onset asthma before 12 years of age.

Of these patients, 74.1% were classified as having severe asthma (step 4 or 5), their average daily ICS dose being 1016.5 mcg, and 79.8% of them were under treatment with LABA associated with ICS. They presented a high frequency of comorbidities; GERD was present in 64.3% of them, and obesity in 37.2%.

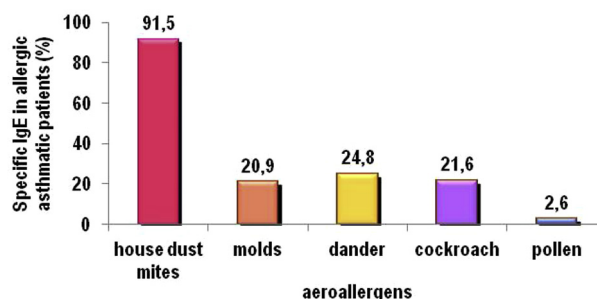
Spirometry was normal (FEV₁ ≥ 80% of the predicted value) in only 18.1% of all patients. All of them showed reversibility and variability on more than 1 occasion, during the period of follow-up. The average FEV₁ was 66.6% of the predicted value.

Only 5 patients (2.1%) were still active smokers and 70 patients were ex-smokers (28.8%). The average smoking history was 28.6 pack-years. The remaining patients, 25.1% had no exposure to tobacco and 44.0% were passive smokers. FEV₁ according to tobacco exposure is shown in Table II. More than 80% of the studied patients had low FEV₁, independent of the group to which they belonged (smokers and ex-smokers, passive smoking, and no exposure groups), suggesting that smoke exposure can be less relevant than long-standing asthma.

Thirty-two patients (13.2%) were considered to have ACOS, 13 of them (40.6%) being men. The mean age for this subgroup with ACOS was 71.0 years (SD, 7.0 years), and the mean duration of disease was 46.4 years (SD, 18.0 years). Of these patients, 16 (50%) were considered having ACOS because they met all defining criteria for ACOS (Table I). The remaining 16 patients (50%) partially met those criteria and were considered to have ACOS because of the presence of emphysema on chest CT.

Allergic asthma was observed in 62.9% of elderly patients, and these patients presented a longer duration of disease ($P = .005$). Sensitization to HDM was present in 91.5% of them, representing 57.6% of all patients (Fig 1). There was no mono-sensitization. Dander sensitization was more prevalent in patients with severe asthma than in those with nonsevere asthma, although there was no statistical difference (18.3% vs 7.9%, $P = .07$). Otherwise, cockroach sensitization was more prevalent in patients with nonsevere asthma than in those with severe asthma, with no statistical difference (17.5% vs 12.2%, $P = .29$).

When allergic patients were compared with nonallergic patients, total serum IgE values were found to be higher in allergic patients (429.6 IU/mL vs 220.3 IU/mL; $P < .001$), but mean peripheral eosinophils were similar in both groups (240.1 cells/mm³ vs 239.3 cells/mm³; $P > .05$) (Fig 2). Regarding the comorbidities, AERD diagnosis was more prevalent in patients with nonallergic asthma than those with allergic asthma (17.8% vs 8.5%; $P < .04$). Comparison between the groups, allergic and nonallergic asthma, is demonstrated in Table III.

**FIGURE 1.** Frequency of aeroallergens sensitization in elderly atopic asthmatic patients assessed through serum specific IgE or skin prick test.

When elderly asthmatic patients were classified according to the age at onset of asthma symptoms, FEV₁ showed lower values in group A (ie, age at onset of asthma symptoms ≤12 years) and higher values in the patients with shorter duration of disease (group E) ($P = .03$), that is, there was a correlation between long-standing asthma and loss of lung function (Fig 3). The frequency of ACOS in groups A, B, C, and D was similar, with respective frequency of 16.2%, 13.8%, 14.1%, and 13.5%. The frequency of ACOS in group E (age at asthma onset ≥55 years) was 3.4%; there was no statistical difference (χ^2 test $P > .05$) between all groups (Table IV). Atopy (or allergic asthma) prevalence gradually decreased as the age at onset of asthma symptoms increased, being statistically significant ($P = .037$) (Fig 4).

Patients' clinical and laboratory characteristics according to age of asthma onset may be seen in Table IV. The frequency of comorbidities, GERD, AERD, and obesity was similar in all groups, as well as total IgE levels and peripheral eosinophils.

DISCUSSION

Although asthma prevalence in elderly patients is not uncommon, it is customarily underestimated and, in consequence, under- or misdiagnosed and undertreated.^{8,19,32} Dyspnea is a common symptom in asthma; nevertheless, it is often confused with other diseases in the elderly and even considered normal.³³

The present study assessed 243 elderly asthmatic outpatients of a tertiary Clinical Immunology and Allergy Service, and early onset asthma, which started before 20 years of age, was observed in 40.0% of them, thus characterizing long-standing asthma in a large percentage of patients. Severe asthma (step 4 or 5) was observed in 74.1% of elderly asthmatic patients, spirometry was normal (FEV₁ ≥ 80% of the predicted value) in only 18.1%, and atopy was presented in more than 60% of them.

A high prevalence of abnormal lung function was observed in several studies in the literature, because elderly asthmatic patients show a significant loss of lung function because of long-standing asthma.¹² In an earlier study of our group, it was observed that there was an association between lung functional loss and higher BMI, but only in the adult asthmatics of 60 years of age and below. This association was not observed in elderly asthmatic patients (>60 years old), who had worse lung function than the younger ones, independent of BMI.³⁴ We can speculate that long-standing asthma has a higher impact in lung function than smoke exposure and BMI, and can mask the effect of these last two.

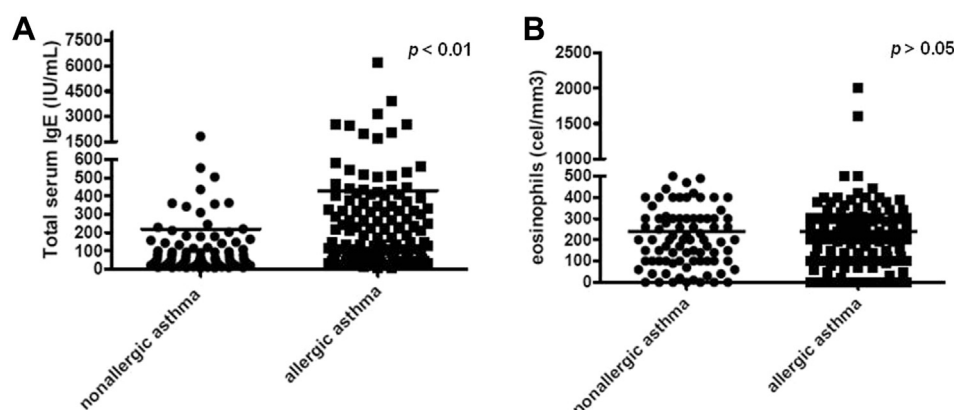


FIGURE 2. Total serum IgE and peripheral eosinophils in allergic or nonallergic elderly asthmatics. **A**, Total serum IgE (Mann-Whitney test, $P < .001$). **B**, Peripheral eosinophils (Mann-Whitney test, $P > .05$).

TABLE III. Demographic characteristics of allergic asthmatic elderly patients compared with nonallergic asthmatic elderly patients

Characteristics	Allergic asthma	Nonallergic asthma	P
Female (%)	81.0	84.4	NS
Current age (y), mean (SD)	70.2 (6.5)	71 (7.5)	NS
Age at onset of asthma (y), mean (SD)	26.0 (17.6)	33.8 (20.6)	NS
Duration of disease (y), mean (SD)**	44.2 (17.6)	37.1 (20.1)	<.001
FEV ₁ (%), mean (SD)	65.5 (13.7)	68.4 (15.4)	NS
FVC (%), mean (SD)	78.0 (12.9)	80.8 (13.7)	NS
Asthma step 4 or 5 (%)	86.9	77.8	.07
Inhaled corticosteroids, mean (SD)	1035.3 (457.2)	984.4 (469.7)	NS
Total serum IgE (IU/mL), mean (SD)**	429.6 (763.9)	220.3 (355.2)	<.001
Eosinophils (cells/mm ³), mean (SD)	240.1 (245.2)	239.3 (186.8)	NS
GERD (%)	65.1	62.9	NS
AERD (%)*	8.5	17.8	.04
Obesity (%)	36.6	38.2	NS
ACOS (%) (see Table I)	11.1	14.4	NS

Fisher's exact test for female, asthma severity (step 4 or 5), and comorbidities. The Mann-Whitney test for current age, age at onset of asthma, time of disease, inhaled corticosteroid, total serum IgE, peripheral eosinophils, and spirometric values. ACOS, Asthma-chronic obstructive pulmonary disease (COPD) overlap syndrome; AERD, aspirin-exacerbated respiratory disease; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; GERD, gastroesophageal reflux disease; NS, not significant; SD, standard deviation.

* $P < .05$; ** $P < .001$. NS: $P > .10$.

The prevalence of atopy in elderly asthmatic patients varies widely, and HDM and cockroaches are major aeroallergens for this population.^{10,11} We observed atopy in 62.9% of our patients, and HDM was the most prevalent aeroallergen observed (57.4% of 243 patients). There might be a bias as our service is an allergy outpatient clinic. Atopy was more prevalent in the group of patients whose asthma started at 12 years of age or below (72.1%), and atopy frequency showed a gradual reduction as the age at onset of asthma increased ($P < .05$). The

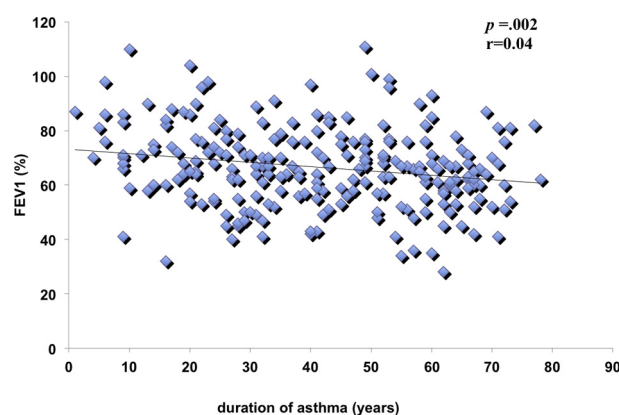


FIGURE 3. Correlation between duration of asthma and lung function. χ^2 test (* $P = .002$, $r = 0.04$). FEV₁, Forced expiratory volume in 1 second.

prevalence of atopy in group E (age at onset of asthma of 55 years or older) was 37.9%. It has already been suggested that there is a decline of allergen sensitization with age, probably related to immunosenescence.³² The lower prevalence of atopy in elderly asthmatic patients whose age at the onset of symptoms was greater may also be due to other triggers of asthma (NSAID, viral upper respiratory infection, between others) or the presence of local allergic rhinitis or asthma.^{9,35}

Of the atopic patients (62.9%), 91.5% were sensitized to HDM, 24.8% to dander (cat and/or dog), 21.6% to cockroaches, 20.9% to molds, and 2.6% to pollens. Severe asthma in elderly patients has been associated with cockroach sensitization.¹⁰ This association was not observed in our study, perhaps because we work in a tertiary center and 74.1% of our patients were classified as severe asthma cases (step 4 or 5). The National Asthma Education and Prevention Program Expert Panel guidelines for the management of asthma recommend that patients who require daily asthma medications have allergy testing for aeroallergens, including perennial indoor allergens. The diagnosis of allergic asthma in elderly patients allows several therapeutic options such as appropriate drug treatment, environmental control, monoclonal anti-IgE, and, occasionally, specific immunotherapy.^{19,36}

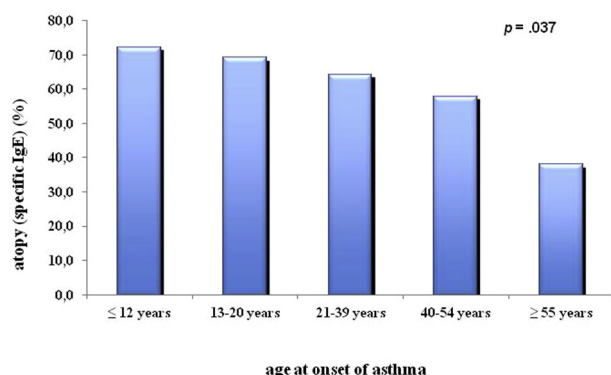
TABLE IV. Demographic characteristics of elderly asthmatic patients according to age at onset of asthma symptoms

Characteristics	≤12 y	13-20 y	21-39 y	40-54 y	≥55 y	P
Female (%)	85.3	86.2	79.7	80.8	79.3	NS
Current age (y), mean (SD)**	69.7 (5.8)	69.7 (6.0)	68.8 (6.7)	71.0 (7.8)	74.8 (7.3)	.003
Age of symptoms onset (y), mean (SD)	6.0 (3.5)	18.0 (2.0)	29.7 (4.7)	45.5 (4.3)	61.1 (6.5)	-
Time of disease (y), mean (SD)	63.7 (6.5)	51.7 (5.8)	39.1 (8.3)	25.5 (8.4)	13.8 (7.2)	-
FEV ₁ (%), mean (SD)*	63.3 (13.8)	67.9 (15.1)	65.8 (12.9)	66.4 (14.5)	74.3 (16.2)	.030
FVC (%), mean (SD)	78.4 (12.7)	77.6 (13.0)	79.6 (13.0)	76.8 (12.9)	84.4 (15.5)	NS
Atopy (%)*	72.1	69.0	64.1	57.7	37.9	.037
Total serum IgE (IU/mL), mean (SD)	379.7 (865.9)	359.8 (521.0)	306.4 (403.4)	370.2 (621.4)	287.7 (621.0)	NS
Eosinophil (cells/mm ³), mean (SD)	196.0 (153.5)	296.0 (379.3)	207.7 (162.7)	272.3 (281.2)	254.8 (172.7)	NS
GERD (%)	64.7	69.0	57.1	69.2	67.9	NS
AERD (%)	11.8	3.4	7.8	19.2	17.2	NS
Obesity (%)	40.3	37.9	39.1	32.7	34.5	NS
ACOS (%)	16.2	13.8	14.1	13.5	3.4	NS

χ^2 analysis for female, atopy, and comorbidities. The Kruskal-Wallis test for current age, total IgE and peripheral eosinophils, FEV₁, and FVC.

ACOS, Asthma-chronic obstructive pulmonary disease (COPD) overlap syndrome; AERD, aspirin-exacerbated respiratory disease; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; GERD, gastroesophageal reflux disease; NS, not significant; SD, standard deviation.

* $P < .05$; ** $P < .01$. NS: $P > .10$.

**FIGURE 4.** Frequency of atopy according to age at onset of asthma symptoms. χ^2 test (* $P = .037$).

Allergic asthma is characterized by chronic eosinophilic inflammation, which is induced by a Th2 immune response. The response mediated by Th2 cells is characterized by mast cell activation after IgE molecule crosslinking by an allergen, leading to the release of several mediators, which, together with activated Th2 cells, attract and activate eosinophils in the bronchial mucosa. However, asthma is a heterogeneous disease with many phenotypes, and other pathogenic mechanisms are involved beyond Th2-mediated immune response.^{37,38}

In the present study, peripheral eosinophils and total serum IgE were assessed; eosinophils ranged from 0 to 2000 cells/mm³, without statistical differences between allergic or nonallergic asthma, as well as between groups according to age of asthma onset. Regarding total serum IgE, there was a range from 6 to 6200 IU/mL, without any statistical differences between groups according to age of asthma onset; however, total serum IgE levels were significantly higher for allergic compared with nonallergic asthmatic elderly patients. These results show that higher levels of total serum IgE suggest atopy, and that eosinophilia is not a marker for atopy.

Comorbidities such as GERD and obesity are common in patients with severe asthma as well as in elderly asthmatic

patients.^{35,39,40} We observed GERD in 64.3% and obesity in 37.2% of our patients. These data reinforce that these comorbidities are prevalent in this age group of patients with asthma, which makes the diagnosis and treatment of asthma more difficult. There were no significant differences in the prevalence of GERD or obesity between allergic and nonallergic patients. However, AERD was statistically more frequent in nonallergic asthmatic patients.

The diagnosis of ACOS is complex and represents a clinical challenge because there is no worldwide consensus for the ACOS definition and it is difficult to distinguish between asthma and COPD, particularly in smoker elderly patients.^{34,41} Patients with ACOS may be asthmatics who smoke or heavy smokers with a genetic background for asthma.^{41,42} According to international trials, the prevalence of ACOS ranged from 12% to 55% of adult patients with obstructive airway disease.^{43,44}

In our study, ACOS prevalence in elderly asthmatic patients was 13.1%, and there was a higher frequency in male patients (25.5% for non-ACOS vs 34.4% for ACOS). Although FEV₁ was initially abnormal independent of exposure to tobacco, it was lower in the ACOS group (mean FEV₁ = 60.4% of the predicted value) compared with the non-ACOS group (mean FEV₁ = 67.6% of the predicted value), and this finding was compatible with the literature.⁴⁵ ACOS was not related to allergic status (Table III).

In conclusion, this study showed that atopy was prevalent in elderly asthmatic patients, and that atopy prevalence decreases with increasing age at onset of asthma. Comorbidities such as GERD, obesity, and COPD are relevant in elderly patients with asthma. FEV₁ assessment showed lower values for elderly asthmatic patients with long-term asthma, as well as for patients with ACOS. These findings highlight the need to diagnose allergic asthma in the elderly population, especially for those with childhood-onset asthma, to offer them additional specific therapy for disease control.

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