J Bras Pneumol. 2020;46(3):e20180341
http://dx.doi.org/10.36416/1806-3756/e20180341

ORIGINAL ARTICLE

Clinical features and associated factors with severe asthma in Salvador, Brazil

Alexssandra Maia Alves[1], Luane Marques de Mello[2], Aline Silva Lima Matos[3], Álvaro Augusto Cruz[4]

1. Programa de Pós-Graduação em Ciências da Saúde, Universidade Federal da Bahia, Salvador (BA) Brasil.
2. Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto (SP) Brasil.
3. Núcleo de Excelência em Asma, Programa para o Controle da Asma na Bahia, Universidade Federal da Bahia, Salvador (BA) Brasil.
4. Faculdade de Medicina, Universidade Federal da Bahia, Salvador (BA) Brasil.

Submitted: 06 November 2018.
Accepted: 01 April 2019.

Study carried out in the Núcleo de Excelência em Asma, Programa para o Controle da Asma na Bahia, Salvador (BA) Brasil.

ABSTRACT

Objective: To describe the clinical features and to identify factors associated with significant severe asthma in samples of patients followed in a reference center in Salvador. **Methods:** A cross-sectional study of 473 adults, regularly followed in the "Asthma Control Program" in Bahia (*Programa de Controle da Asma e da Rinite Alérgica na Bahia* (ProAR)), reassessed systematically between 2013 and 2015. The patients were admitted for meeting previous criteria of severe asthma and were reclassified according to the most current definition proposed by a joint document of the "European Respiratory Society/American Thoracic Society" (ERS/ATS) (ERS/ATS 2014). **Results:** Only 88/473 (18%) were reclassified as having severe asthma by ERS/ATS criteria (SA-ERS/ATS). Among these patients, 87% were women, 48% obese, with a median Body Mass Index (BMI) of 29 kg·m^2 (IQ 26-34), furthermore, 99% had symptoms of chronic rhinitis and 83% had symptoms of Gastroesophageal Reflux Disease (GERD). None of the 88 patients claimed to be current smokers. The most frequently corticosteroids were beclomethasone dipropionate (BDP) (88%) and budesonide (BUD) (69%). The majority of the evaluations reported adequate adherence (77%), however, the minority (0,6%) detected serious errors in inhalation techniques. The median Forced Expiratory Volume (FEV_1) associated with post-bronchodilator test (post-BD) was 67% predicted (IQ 55-80). The median number of eosinophils in the peripheral blood was lower in patients with SA-ERS/ATS (258 cells/mm^3 (IQ 116-321) than in the other patients studied [258 cells/mm^3 (IQ 154-403)]. Gastroesophageal reflux symptoms were associated with a higher severity [OR = 2.2 95% CI (1.2-4.2)]. **Conclusion:** In this group of patients, symptoms of GERD were associated with SA-ERS/ATS and eosinophil count > 260 cells/mm^3 were associated 42% with less chance SA-ERS/ATS

Keywords: Asthma; Gastroesophageal reflux disease (GERD); Eosinophils; Biomarkers.

INTRODUCTION

Most asthmatics can achieve adequate control of symptoms with inhaled corticosteroids, but approximately 5% are unsuccessful, even with adequate treatment and good adherence.[1] In addition to high morbidity, this group is responsible for most health expenditures, which are higher than those of other chronic diseases such as diabetes and kidney disease.[2] In Brazil, the annual cost of severe asthma is estimated to exceed a thousand dollars/patient/year.[3]

Despite some recognized phenotypes, there is great variability in clinical presentation and biomarkers associated with asthma severity. The studies conducted by the National Heart, Lung and Blood Institute (NHLBI) of the National Institutes of Health (NIH) in Severe Asthma Research Program (SARP III) found that with advancing age, patients with severe asthma became more obese and less sensitive to allergens.[4] The study from the European Unbiased Biomarkers in Prediction of Respiratory Disease Outcomes (U-BIOPRED) found a higher frequency of nasal polyps and Gastroesophageal Reflux Disease (GERD)[5] in patients with severe asthma.

In Brazil, some studies have described the clinical and sociodemographic profile of adults and severe asthmatic children in different regions.[6-9] More recently, Kuschnir et al.[10] found a significant association between asthma severity and metabolic syndrome in a study on cardiovascular risk in adolescents.

Given the wide diversity of clinical manifestations of this disease, the negative impact on patients' quality of life and the high health costs, there is still a need to better understand the factors related to severe asthma in specific regions.

There has been no uniformity in the definition of severe asthma. A World Health Organization (WHO) expert meeting in 2009 proposed a classification that included three categories: untreated severe asthma; difficult to treat severe asthma and treatment-resistant severe

Correspondence to:
Alexssandra Maia Alves. Programa para o Controle da Asma na Bahia, Rua Carlos Gomes, 270, Centro de Saúde Carlos Gomes, 7º andar, Dois de Julho, CEP 40060-330, Salvador, BA, Brasil.
Tel.: 55 71 3013-8462. E-mail: alexssandra.maia@yahoo.com
Financial support: This study used data from a larger line of research entitled "Fatores de risco, biomarcadores e endofenótipos de asma grave" which receives financial support from Programa de Apoio a Núcleos de Excelência (PRONEX) of the Fundação de Amparo à Pesquisa do Estado da Bahia (FAPESB) and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), no. 6353, Edital 020/2009 (Núcleo de Excelência em Asma da Universidade Federal da Bahia). This study received financial support from the Conselho Nacional de Desenvolvimento Científico e Tecnológico (Process: 471057/2014-2) and GlaxoSmithKline, Trust in Science program, *investigator initiated grant* (2012-2015).

asthma.[11] In the Program for the Control of Asthma in Bahia, described in Portuguese as ProAR, there is a cohort of patients with severe asthma established from 2003,[12] using the severity criteria of that time, which coincide with the untreated severe asthma category proposed by WHO. In a study started in 2013, it was observed that most patients in this cohort can be considered as belonging to the severe asthma category that is difficult to treat.[13]

The aim of this study was to describe clinical, laboratory and functional characteristics of severe asthma, to assess the level of control and to identify factors associated with an expressive asthma severity in a group of patients, users of the Unified Health System (in Portuguese *Sistema Único de Saúde* (SUS)), followed at the ProAR referral outpatient clinic. These patients were also reclassified retrospectively according to the current criteria of the European Respiratory Society/American Thoracic Society (ERS/ATS) in 2014 (AG-ERS/ATS),[14] which were not known when the original study was started.

METHODS

This was a cross-sectional study, which was conducted through the analysis of secondary data from a larger project entitled "Risk factors, biomarkers and endophenotypes of severe asthma".

The study population consisted of adult patients, followed regularly since 2003 at the ProAR from the *Universidade Federal da Bahia* (UFBA) at Central Referral Outpatient Clinic for patients with severe asthma in Salvador. For admission to this outpatient clinic, the patients should meet at least one of the following severity criteria, based on the NIH-NHBLI Guidelines for Diagnosis and Management of Asthma[15] and Global Initiative for Asthma (GINA),[16] such as: daily symptoms; limitation of daily activities (symptoms with minimal effort); nocturnal symptoms > twice a week; use of bronchodilators > twice a day; Peak Expiratory Flow/Forced Expiratory Volume 1 (PEF/FEV1) < 60% of predicted.

At the beginning of the main study, each patient had their diagnosis confirmed and validated by two specialists, through a review of the medical records, when the presence of typical asthma and spirometry symptoms was verified, demonstrating significant reversible obstructive ventilatory disorder (increase of 12% and 200 ml in post-bronchodilator (post-BD FEV1). When there was a divergence in validation among experts, a third party was consulted.

For "inclusion" in this study, the following criteria were used: age ≥ 18 years; residency in Salvador or Lauro de Freitas in the state of Bahia (BA); validation of asthma diagnosis and a follow-up program for at least six months. Patients with conditions that could interfere with the interpretation of results, such as Chronic Obstructive Pulmonary Disease (COPD), sequelae in patients associated with extensive tuberculosis, structural changes in the lungs and pregnancy, were excluded.

After the selection of eligible individuals, telephone contact and invitation to participate in the study were made. On the scheduled date, the Informed Consent Form (ICF) was read and those who agreed and signed, were systematically evaluated in "face-to-face" visits, which were conducted between January 2013 and July 2015. A properly trained multidisciplinary team, composed of doctors, nurses, pharmacists, physiotherapists, nutritionists and psychologists, performed the research evaluations and procedures.

Blood collection and anthropometric measurements were performed with the fasting patient. Individuals with Body Mass Index (BMI) ≥ 30 kg/m^2 (WHO norm[17]) were considered obese.

Immediate-reading skin test was performed according to Global Allergy and Asthma European Network/ Allergic Rhinitis and its Impact on Asthma (GA2LEN/ARIA)[18] guidelines and evaluated the hypersensitivity to aeroallergens: *Dermatophagoides pteronyssinus*, *D. farinae*, *Aspergillus flavus*, *A. fumigatus*, *Alternaria alternata*, *Cladosporium herium*, *C. herio cat*, *Blatella germanica*, *Periplaneta americana*, *Paspalum notatum* Fluegge (Bahia *grass*), *Cynodon dactylon* (L.) Pers (Bermuda *grass*) *(GREER®)* and *Blomia tropicalis (FDA allergenics*. Positive responses were considered, papules ≥ 3mm when compared to the papule of the negative control. Testicle readings were interpreted by allergist.

Spirometry was performed by a trained technician or physiotherapist certified by the Brazilian Society of Pulmonology and Physiology (SBPT) using a Koko® spirometer (PDS Instrumentation Inc., Louisville, CO, USA) following the 1995 American Thoracic Society protocol.[19] Spirometer software was updated with Brazilian normal values.[20]

Stool samples were evaluated by the spontaneous sedimentation method to verify the presence of parasites.

The blood count was obtained by the automated Cell-Dyn Ruby method and the total IgE by the chemiluminescence method. For the evaluation of eosinophilia, the cutoff point was the peripheral blood eosinophil count of 260 cells/mm3, based on the work of Zhang et al.,[21] who found this value through Receiver Operating Characteristics (ROV) curve (ROC curve) analysis in a population with similar characteristics to the population of the present study.

The inhalation technique was systematically verified with each patient using the devices: pressurized inhaler with and without spacer; aerolizer; turbuhaler and diskus. Serious errors considered the absence of one of the following steps: "put between the lips"; inhale; hold the breath (all devices); trigger (pressurized inhaler); open the compartment and place the capsule inside; press the inhaler buttons (aerolizer) and rotate the device (turbuhaler). It is noteworthy that most patients used more than one device, which is why the number of evaluations was much larger than the sample size.

Adequate adherence was considered by subjective/self-reported assessment when the patient reported consumption of at least 70% of doses in the evaluation week. For objective evaluation, pharmaceutical dispensation records were used and adherence was considered adequate when the drug was withdrawn monthly by the patient within the last six months of the evaluation.

The Asthma Control Questionnaire-6 (ACQ-6) questionnaires for control,[22] Asthma Quality of Life Questionnaire (AQLQ) for quality of life[23] and QS-GERD questionnaires were also used to evaluate symptoms of GERD.[24] All questionnaires were translated into Brazilian Portuguese and validated in our population. In addition,the GINA classification was used to evaluate symptom control.[25]

The selection of ERS/ATS 2014[14] criteria for reclassification is justified as the most recent and widely accepted severity definition criteria. These criteria define severe asthma as requiring treatment according to GINA step 4 or 5 (high dose of inhaled corticosteroid associated with long-acting beta-agonist and/or leukotriene and/or theophylline modifier) in the last year, or corticosteroid ≥ 50% of the year in the last year to prevent it from becoming uncontrolled or remaining uncontrolled despite treatment.

The final sample, therefore, consisted of patients who used high doses of corticosteroids (equal to or greater than 1600 µg budesonide (BUD) or equivalent) associated with another controller (long acting bronchodilator) and/or systemic corticosteroids for 50% or more of the last year of the assessment.

Statistical Package for Social Sciences for Windows version 20.0 (SPSS Inc., Chicago, IL, USA) was used. Variables were described using the median and interquartile range. The tests used in the statistical analysis were Chi-square and Fisher's Exact for categorical variables and Mann-Withney for numerical variables. Binary logistic regression was performed for multivariate analysis to identify possible predictors for severity classification.

This study was approved by the *Comissão Nacional de Ética em Seres Humanos* (CONEP) statement no. 450/10.

RESULTS

Clinical features

Secondary data from 473 patients followed in ProAR were reclassified and analyzed. Eighty-eight were considered to have AG-ERS/ATS (Figure 1). The median age was 53 years (Intelligence Quotient (IQ) 45-62) and the age at onset of symptoms was nine years (IQ 1-25). Most of the sample, 77 (87%) were women. No patient declared as current smoker and 22 (25%) reported previous smoking history. Almost half of those studied patients [43 (49%)] were obese. The median BMI was 29 kg/m^2 (IQ 26-34). Most patients [73 (83%)] admitted GERD symptoms, with median QS-GERD scores of nine (IQ 4-15). Almost all cases [87 (99%)] had rhinitis symptoms. We found a significantly higher proportion of patients with obesity, GERD and rhinitis in the AG-ERS/ATS group than in the group without AG-ERS/ATS (Table 1).

Treatment features

The main inhaled corticosteroids used as control medication were beclomethasone dipropionate 78 (88%), budesonide (BUD) 69 (78%), fluticasone propionate 17 (19%), mometasone furoate monohydrate 1 (1%), nevertheless, the long-acting bronchodilators were formoterol 69 (78%) and salmeterol 17 (19%). Many patients used a combination of inhaled corticosteroids for maintaining a higher dose. Most patients had adequate adherence according to self-report [68 (77%)], but this proportion was lower when assessed through pharmacy records [50 (57%)]. A total of 977 inhalation device technique evaluations were performed, and only six (0.6%) cases showed severe errors involving the inhalation technique.

Functional features

The median absolute values and percentages of FEV_1 and Forced Expiratory Flow $(FEF)_{25-75}$ post-BD were slightly lower in patients with AG-ERS/ATS [$FEV_{1post-BD}$ = 1.7L (IQ 1.3-2.0) and $FEV_{1\ post-BD}$ = 67% (IQ 55-80); FEF_{25-75} = 0.9L/s (IQ 0.6-1.5) and FEF25-75 37% (IQ 26-64)] compared to those without AG-ERS/ATS [$FEV_{1\ post-BD}$ = 1.8L (1, 4-2.3) and $FEV_{1\ post-BD}$ = 69% (IQ 58-81) and FEF_{25-75} = 1.1L/s (IQ 0.7-1.8) and FEF_{25-75} = 41% (30-63) with statistically significant difference only in relation to the absolute value of FEV1 (Table 1).

Laboratory features

Absolute and relative peripheral blood eosinophil counts [209 cells/mm3 (IQ 16-321) and 3% [(IQ 1-5), respectively]) were significantly lower in AG-ERS/ATS patients compared to patients without AG-ERS/ATS [258 cells/mm3 (IQ154-403) and 4% (IQ3-7)]. The opposite was true for absolute and relative neutrophil count values [3988 cells/mm3 (IQ 2958-5191) and 58% (IQ 51-65), respectively], which was significantly higher in patients with ER-ERS./ATS, compared to those without severe asthma [3481 cells/mm3 (IQ 2409-4548) and 55% (48-61)].

The median total IgE concentration was 276 IU/mL (IQ 117-423) and 52 (69%) patients had positive skin test for aeroallergens (Table 1) among patients with AG-ERS/ATS.

A parasitological stool examination was performed on 446 patients. Only 10 (2%) presented parasites associated with eosinophilia (four infected with strongyloidiasis, three with ascariasis and three with schistosomiasis). Only two patients with AG-ERS/ATS had positive samples for stool parasitology and only one of these had peripheral blood eosinophil count > 260 cells/mm3. The low proportion of patients with positive samples for stool parasitology in this category rule out the influence of parasitosis on eosinophil count results.

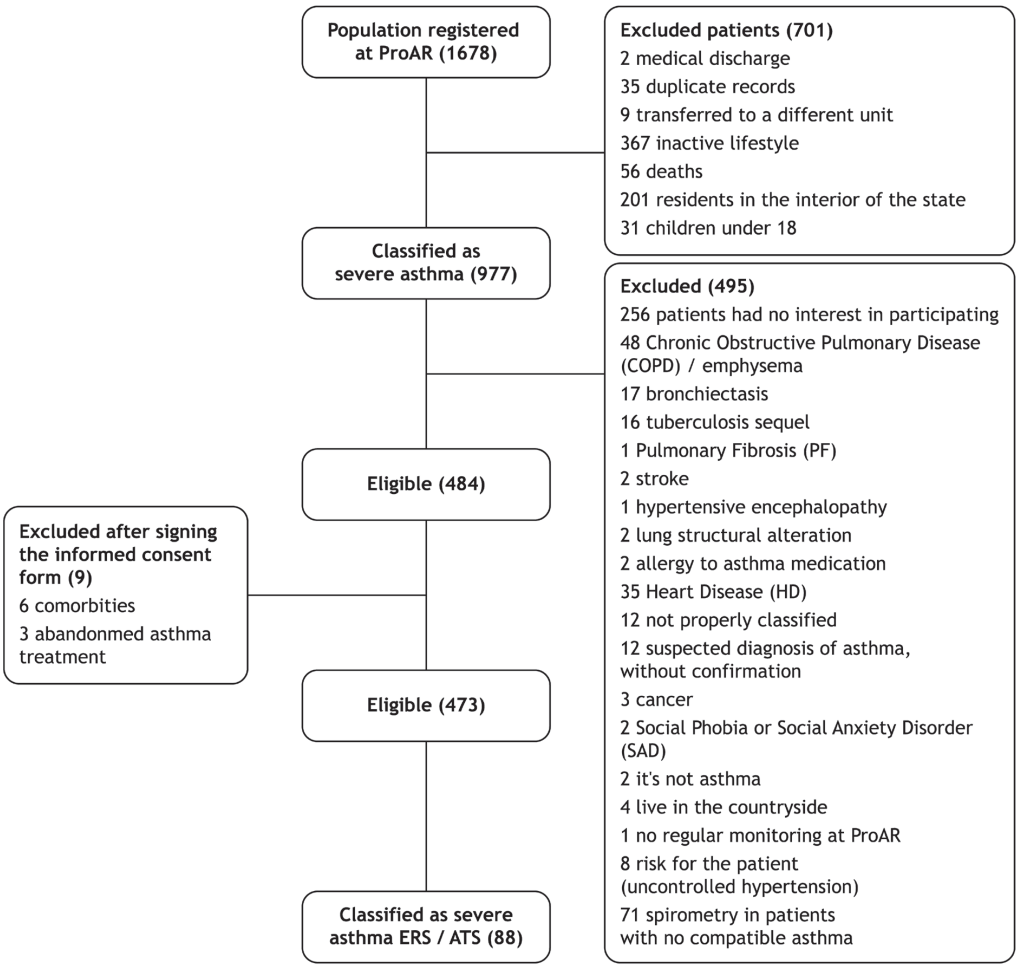

Figure 1. Inclusion and evaluation in the study. The eligibility criteria mentioned were in relation to the main study. The reclassification of patients according to the 2014 ERS/ATS criteria resulted in the final sample of 88 patients considered to have severe asthma (AG-ERS/ATS).

Adjusted analysis

Factors associated with AG-ERS/ATS were verified by multivariate logistic regression. Age, age at onset of symptoms, gender, obesity (BMI > 30 kg/m^2), rhinitis, GERD and eosinophil count > 260 cells/mm^3 were included in the model.

Analysis showed that patients with GERD symptoms were 2.28 times more likely to have AG-ERS/ATS than those without these complaints. Patients with eosinophil counts > 260 cells/mm^3 were 42% less likely to have AG-ERS/ATS than those with eosinophil counts ≤ 260 cells/mm^3 (Table 2).

Exacerbations in the last year

Patients with AG-ERS/ATS had significantly higher morbidity [sought emergency 1.5 times more (95% CI 1.09-2.32) and used oral corticosteroids last year 3.8 times (95% CI 2.40-6,16) when compared to patients without AG-ERS/ATS] (Table 3).

Control evaluation

In patients with AG-ERS/ATS, the median ACQ-6 score was 1.5 (IQ 0.8-2.3) and AQLQ was 3.4 (IQ 2.5-4.7) showing poor control and poor quality of life, respectively, with a statistically significant difference when compared to the scores of patients without severe asthma. By GINA categorical classification, 24 (27%) patients were controlled, 35 (39%) were partially controlled, and 29 (32%) were uncontrolled (Table 4).

DISCUSSION

In our study, the proportion of AG-ERS/ATS was higher than that presented in the general literature, in samples obtained from specialized services. This

Table 1. Sociodemographic, clinical, functional and laboratory features of patients with severe asthma according to the criteria of the ERS/ATS 2014 (AG-ERS/ATS) compared to the group without AG-ERS/ATS[a].

Feature	With AG-ERS/ATS n=88	Without AG-ERS/ATS n=385	*p* value
Female gender - n (%)	77(87)	303 (78)	0.61 [¥]
Age/Years - Md (IQ)	53 (45-62)	51 (42-61)	0.21 [T]
Asthma onset > 18 years - n (%)	39(44)	137 (35)	0.12 [¥]
Age at onset of symptoms (years) Md (IQ)	9 (1-25)	10 (2-25)	0.73 [T]
Current smoking - n (%)	0	5 (1)	0.53 [Ω]
Obesity (BMI ≥30 kg/m^2) - n (%)	43 (48)	140(36)	0.03 [¥]
BMI kg/m^2 - Md (IQ)	29 (26-34)	28 (24-31)	0.01 [T]
GERD symptoms - n (%)	73(83)	252 (65)	<0.01 [¥]
QS DRGE * in scores - Md (IQ)	9 (4-15)	7 (1-12)	0.01 [T]
Symptoms of chronic rhinitis - n (%)	87(99)	359 (93)	0.04 [¥]
Beclomethasone use - n (%)	78(88)	111(28)	<0.01 [¥]
Budesonide (BUD) use - n (%)	88(69)	299(77)	0.26 [¥]
Fluticasone use - n (%)	17(19)	67(17)	0.67 [¥]
Formoterol use - n (%)	69(78)	301(78)	0.14 [¥]
Salmeterol use - n (%)	17(19)	68(17)	0.71 [¥]
Treatment adherence (pharmacy records) - n (%)	50(57) [#]	178(46) [##]	0.07 [¥]
Treatment adherence (self-report) - n (%)	68(77)	310(80) [###]	0.46 [¥]
FEV1 $_{post\ BD}$ <60% - n (%)	41(46) [#]	163(42)	0.46 [¥]
FEV1 $_{post\ BD}$ L - Md (IQ)	1.7(1.3-2.0)	1.8(1.4-2.3)	0.32 [T]
FEV1 $_{post\ BD}$ % predicted - Md (IQ)	67(55-80)	69 (58-81)	0.22 [T]
Neutrophils % - Md (IQ)	58(51- 65)	55(48-61) [⊥]	<0.01[T]
Neutrophils cells/mm^3 - Md (IQ)	3988(2958-5191)	3481(2409-4548) [⊥]	<0.01[T]
Eosinophils % - Md (IQ)	3 (1-5)	4(3-7) [⊥]	<0.01[T]
Eosinophils cells/mm3 - Md (IQ)	209(116-321)	258(154-403) [⊥]	0.01[T]
Eosinophils> 260 cells/mm^3	32 (36) [⊥]	189(49) [⊥]	0.02 [¥]
IgE IU/ml - Md (IQ)	276 (117-423)	346 (149-517)	0.10 [T]
Positive skin test - n (%)	52 (69) [⊥⊥]	224 (63) [⊥⊥⊥]	0.34 [¥]

[a]Values expressed as *n* (%) for categorical variables and median (Md)/interquartile range (IQ) for continuous variables; [¥]Chi-square test; [Ω]Fisher Fisher's exact test; [T]Mann-Withney test; *QS GERD: Questionnaire on the severity of symptoms of Gastroesophageal Reflux Disease; [#]n: 87 patients; [##]n: 380 patients; [###]n: 384 patients; [⊥]n: 381 patients; [⊥⊥]n: 75 patients; [⊥⊥⊥]n: 352 patients. n (%): number of cases in absolute values and percentage; p: probability of significance.

Table 2. Multivariate logistic regression analysis model for the evaluation of possible factors associated with severe asthma by the criteria of the ERS/ATS 2014 (AG-ERS/ATS).

Variable	Gross effect (OR; CI95%)	Adjusted effect* (OR; CI95%)
Feminine gender	1.89 (0.96-3.73)	1.41 (0.71-2.59)
Age in years		1.00 (0.98-1.02)
Onset of asthma symptoms> 18 years	1.44 (0.90-2.3)	1.50 (0.89-2.52)
Obesity*	1.67 (1.05-2.67)	1.46 (0.89-2.39)
GERD symptoms	2.57 (1.42-4.65)	2.28 (1.22-4.23)
Rhinitis Symptoms	6.30 (0.84-47.7)	4.55 (0.58-35.4)
Eosinophils > 260 cells/mm3	0.58 (0.36-0.94)	0.58 (0.35-0.96)

*BMI> 30 (WHO). ERS: European Respiratory Society; ATS: American Thoracic Society; AG: Severe Asthma; OR: Odds Ratio; 95% CI: 95% Confidence Interval; GERD: Gastroesophageal Reflux Disease.

Table 3. Comparison between the proportion of patients with exacerbations in the last year according to the presence or absence of severe asthma concerning the ATS/ERS 2014 classification (AG-ERS/ATS)[12].

Feature	AG-ERS/ATS YES n=88	AG-ERS/ATS NO n=385	*p* value	PR (CI95%)
Visits to emergency services n (%)	35 (39)	104 (27)	<0.01[¥]	1.59 (1.09-2.32)
Oral corticosteroid use	68 (77)	198 (51)	0.01[¥]	3.85 (2.40-6.16)
n (%)	6 (6)	16 (4)	<0.28[¥]	1.50 (0.74-3.05)

Values expressed in n (%). [¥]Chi-square test; PR= Prevalence Ratio. CI95%: Confidence interval 95%; n (%): number of cases in absolute values and percentage; p: probability of significance.

Table 4. Evaluation of asthma symptom control among patients with severe asthma according to ATS/ERS 2014 classification (AG-ERS/ATS) and comparison with patients without AG-ERS/ATS[12].

Features	AG-ERS/ATS YES n=88	AG-ERS/ATS NO n=385	*p* value
ACQ-6 score - Md (IQ)	1.5 (0.8-2.3)	0.8 (0.3-1.6)	<0.01[T]
AQLQ score - Md (IQ)	3.4 (2.5-4.7)	4 .6 (3.5-5.6)	<0.01[T]
GINA Control Level - n (%)			<0.01[¥]
Controlled	24 (29)	184 (47)	
Partially Controlled	35 (39)	136 (35)	
Uncontrolled	29(32)	65 (16)	

Values expressed as median Md (IQ) and interquartile range. [¥]Chi-square test; [T]Mann-Withney test. n (%): number of cases in absolute values and percentage; p: probability of significance; ACQ-6: Asthma Control Questionnaire; AQLQ: Asthma Quality of Life Questionnaire; GINA: Global Initiative for Asthma; ERS: European Respiratory Society; ATS: American Thoracic Society.

result is justified because they are patients followed in a specific outpatient clinic for severe asthma. To be admitted to the program in the past, such patients would initially have to meet the current severity criteria from 2003 and have been reclassified to the most current severity criteria from 2015.

No patient claimed to be a smoker. Smoking is an exclusion condition for dispensing formoterol + budesonide according to a decree of the Ministry of Health. Some patients may have omitted this information during the interview. Some studies, using indirect measures of smoking such as urinary cotinine test, showed an omission of smoking among asthmatic patients. Pinheiro et al.,[26] in a study of 1341 individuals in Salvador-BA, including the sample evaluated in the present study, observed elevated urinary cotinine levels among some self-reported non-smokers and past smokers, especially in patients with severe asthma. Stelmach found 38% omission among asthmatic patients and patients with COPD in a study conducted at a referral outpatient clinic in São Paulo.[27]

Regarding treatment, patients received free of charge the drugs listed in *Relação Nacional de Medicamentos Essenciais* (RENAME) and/or the list of specialized components of the "Bahia State Health Department", standardized by SUS. The discrepancy between adherence declared and obtained by the pharmacy is explained, in part, by the shortage of public pharmacies that occurred in some periods throughout the main study, causing patients to purchase them with their own resources. Considering self-report, our rates are higher than those described in the literature.[28] The extremely low proportion of errors in inhalation technique results from the multiprofessional approach and continuing education applied to ProAR patients.

As for comorbidities, the patients with AG-ERS/ATS studied had more obesity, symptoms of GERD and rhinitis when compared to patients without severe asthma (Table 1).

The proportion of obese patients in this study was high, especially in the group with severe asthma. Studies show a higher prevalence of asthma among obese,[29] who tend to have worse control and greater impairment of lung function.[30] Heaney et al.[31] observed a median BMI similar to our study in patients with refractory asthma in a multicenter study in the United Kingdom (UK). Several pathophysiological mechanisms have been proposed to justify this association[32] but the causal relationship has not yet been clearly established.

The GERD symptoms were more frequent in AG-ERS/ATS patients, according to the median QS-GERD score. In addition, the association between severe asthma and GERD symptoms was found in both crude and adjusted analysis. The prevalence of GERD in the general population ranges from 8-33%[33] and in asthmatics, it exceeds 50%.[34] The "reflux and reflex theory"[35] proposes that both "reflux leads to asthma and asthma leads to reflux". Although the current study was based on self-report, the validated QS-DRGE[24] questionnaire was used, increasing the reliability of this information.

Our results also corroborated the "single airway disease" hypothesis.[36] The North American multicenter study TENOR II identified allergic rhinitis as the most common comorbidity among patients with severe/difficult to treat asthma.[37]

The inverse relationship between eosinophil count > 260 cells/mm^3 and higher asthma severity can be explained by the profile of our sample. The AG-ERS/ATS by definition, includes the need for high doses of corticosteroids, which are known to induce eosinophil apoptosis and inhibit neutrophil apoptosis.[38] Ortega et al.[39] observed in a real-life study a decrease in blood eosinophil count following corticosteroid use in patients with severe or persistent asthma. In addition, our sample consisted of mostly female and largely obese, a phenotype that may be associated with the non-TH2 profile. Furthermore, it is known that patients with eosinophilic asthma tend to respond better to corticosteroids, which would not generally qualify them for the AG-ERS/ATS criteria. It is important to highlight the study by Lima-Matos et al.,[13] which found an association between number of eosinophils in the blood > 260 cells/mm^3, lack of control and significant asthma severity. The authors evaluated a population from the same referral center and included the sample of patients with severe asthma used in our study. Patients

without asthma, from mild to moderate asthma and severe asthma were included, and in this last group, previous criteria of severity were used, which are included in the standardization proposal presented to the WHO.[11] The difference between the results of the two studies reflects how much the choice of severity criterion may influence the identification of groups with distinct clinical characteristics.

Patients with AG-ERS/ATS also had more visits to emergency services, poorer control and poorer quality of life. This, our results are as expected and agree with similar studies.[40]

In conclusion, the present study, by re-evaluating 473 patients classified as severe asthma according to previous criteria, found that only 88 (18%) patients fell into the severe asthma category according to the 2014 ERS/ATS classification. Gastroesophageal reflux symptoms were associated with AG-ERS/ATS and eosinophil count > 260 cells/mm^3, in contrast, was inversely associated with AG-ERS/ATS.

REFERENCES

1. Hekking PW, Wener RR, Amelink M, Zwinderman AH, Bouvy ML, Bel EH. The prevalence of severe refractory asthma. J Allergy Clin Immunol. 2015;135(4):896-902. http://dx.doi.org/10.1016/j.jaci.2014.08.042. PMid:25441637.
2. O'Neill S, Sweeney J, Patterson CC, Menzies-Gow A, Niven R, Mansur AH, et al. The coast of treating severe refractory asthma in the UK: an economic analysis from British Thoracic Society Difficult Asthma Registry. Thorax. 2015;70(4):376-8. http://dx.doi.org/10.1136/thoraxjnl-2013-204114. PMid:24917087.
3. Franco R, Santos AC, Nascimento HF, Souza-Machado C, Ponte E, Souza-Machado A, et al. Cost-effectiveness analysis of a state funded programme for control of severe asthma. BMC Public Health. 2007;7(1):82. http://dx.doi.org/10.1186/1471-2458-7-82. PMid:17509137.
4. Teague WG, Phillips BR, Fahy JV, Wenzel SE, Fitzpatrick AM, Moore WC, et al. Baseline Features of the Severe Asthma Research Program (SARP III) Cohort: differences with Age. J Allergy Clin Immunol Pract. 2018;6(2):545-54. http://dx.doi.org/10.1016/j.jaip.2017.05.032. PMid:28866107.
5. Shaw DE, Sousa AR, Fowler SJ, Fleming LJ, Roberts G, Corfield J, et al. Clinical and inflammatory characteristics of the European U-BIOPRED adult severe asthma cohort. Eur Respir J. 2015;46(5):1308-21. http://dx.doi.org/10.1183/13993003.00779-2015. PMid:26357963.
6. Pereira ED, Cavalcante AG, Pereira EN, Lucas P, Holanda MA. Controle da asma e qualidade de vida em pacientes com asma moderada ou grave. J Bras Pneumol. 2011;37(6):705-11. http://dx.doi.org/10.1590/S1806-37132011000600002. PMid:22241026.
7. Athanazio R, Carvalho-Pinto R, Fernandes FL, Rached S, Rabe K, Cukier A, et al. Can severe asthmatic patients achieve asthma control? A systematic approach in patients with difficult to control asthma followed in a specialized clinic. BMC Pulm Med. 2016;16(1):153. http://dx.doi.org/10.1186/s12890-016-0314-1. PMid:27852260.
8. Andrade WCC, Lasmar LMLBF, Ricci CAT, Camargos PAM, Cruz AA. Phenotypes of severe asthma among children and adolescents in Brazil: a prospective study. BMC Pulm Med. 2015;15(1):36. http://dx.doi.org/10.1186/s12890-015-0029-8. PMid:25912047.
9. Rodrigues AM, Roncada C, Santos G, Heinzmann-Filho JP, Souza RG, Vargas MHM, et al. Clinical characteristics of children and adolescents with severe therapy-resistant asthma in Brazil. J Bras Pneumol. 2015;41(4):343-50. http://dx.doi.org/10.1590/S1806-37132015000004462. PMid:26398754.
10. Kuschnir FC, Felix MMR, Kuschnir MCC, Bloch KV, Azevedo E, Solé D. LedoAJ.Severe asthma is associated with metabolic syndrome in Brazilian adolescents. J Allergy Clin Immunol. 2018;141(5):1947-9. http://dx.doi.org/10.1016/j.jaci.2018.01.026. PMid:29427644.
11. Bousquet J, Mantzouranis E, Cruz A, Aït-Khaled N, Baena-Cagnani CE, Bleecker ER, et al. Uniform definition of asthma severity, control, and exacerbations: document presented for the World Health Organization Consultation on Severe Asthma. J Allergy Clin Immunol. 2010;126(5):926-38. http://dx.doi.org/10.1016/j.jaci.2010.07.019. PMid:20926125.
12. Cruz AA, Souza-Machado A, Franco R, Souza-Machado C, Ponte EV, Santos PM, et al. The impact of a program for control of asthma in a low-income setting. World Allergy Organ J. 2010;3(4):167-74. http://dx.doi.org/10.1097/WOX.0b013e3181dc3383. PMid:23268428.
13. Lima-Matos A, Ponte EV, Jesus JPV, Almeida PCA, Lima VB, Kwon N, et al. Eosinophilic asthma, according to a blood eosinophilcriterion, is associated with disease severity and lack of control among underprivileged urban Brazilians. Respir Med. 2018;145:95-100. http://dx.doi.org/10.1016/j.rmed.2018.10.025. PMid:30509723.
14. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J. 2014;43(2):343-73. http://dx.doi.org/10.1183/09031936.00202013. PMid:24337046.
15. NAEPP: National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. J Allergy Clin Immunol. 2007;120(5, Suppl.):S94-138. PMid:17983880. http://dx.doi.org/10.1016/j.jaci.2007.09.029
16. GINA: Global Initiative for Asthma. Global strategy for asthma management and prevention. Fontana, WI; 2002.
17. WHO: World Health Organization. Obesity: preventing and managing the global epidemic. Report of WHO consultation. World Health Organ Tech Rep Ser. 2000;894:i-xii, 1-253. PMid:11234459.
18. Bousquet J, Heinzerling L, Bachert C, Papadopoulos NG, Bousquet PJ, Burney PG, et al. Practical guide to skin prick tests in allergy to aeroallergens. Allergy. 2012;67(1):18-24. http://dx.doi.org/10.1111/j.1398-9995.2011.02728.x. PMid:22050279.
19. ATS: American Thoracic Society. Standardization of Spirometry, 1994 Update. Am J Respir Crit Care Med. 1995;152(3):1107-36. http://dx.doi.org/10.1164/ajrccm.152.3.7663792. PMid:7663792.
20. Pereira CA, Sato T, Rodrigues SC. New reference values for forced spirometry in white adults in Brazil. J Bras Pneumol. 2007;33(4):397-406. http://dx.doi.org/10.1590/S1806-37132007000400008. PMid:17982531.
21. Zhang XY, Simpson JL, Powell H, Yang IA, Upham JW, Reynolds PN, et al. Full blood count parameters for the detection of asthma inflammatory phenotypes. Clin Exp Allergy. 2014;44(9):1137-45. http://dx.doi.org/10.1111/cea.12345. PMid:24849076.
22. Leite M, Ponte EV, Petroni J, D'Oliveira Júnior A, Pizzichini E, Cruz AA. Avaliação do questionário de controle da asma validado para uso no Brasil. J Bras Pneumol. 2008;34(10):756-63. http://dx.doi.org/10.1590/S1806-37132008001000002. PMid:19009207.
23. Silva LMC, Silva LCC. Validação do questionário de qualidade de vida em asma (Juniper) para o português brasileiro. Rev Assoc Med Rio Grande do Sul. 2007;51(1):31-7.
24. Fornari F, Gruber AC, Lopes AB, Cecchetti D, Barros SG. Questionário de sintomas na doença do refluxo gastroesofágico. Arq Gastroenterol. 2004;41(4):263-7. http://dx.doi.org/10.1590/S0004-28032004000400012. PMid:15806272.
25. GINA: Global Initiative for Asthma. Global strategy for asthma management and prevention. NHLB/Who Report. 2014;63(7):932-8.
26. Pinheiro GP, Souza-Machado C, Fernandes AGO, Mota RCL, Lima LL, Vasconcellos DS, et al. Tabagismo entre asmáticos: avaliação por autorrelato e dosagem de cotinina urinária. J Bras Pneumol. 2018;44(6):477-85. http://dx.doi.org/10.1590/s1806-37562017000000018. PMid:30304204.
27. Stelmach R, Fernandes FL, Carvalho-Pinto RM, Athanazio RA, Rached SZ, Prado GF, et al. Comparison between objective measures of smoking and self-reported smoking status in patients with asthma or COPD: are our patients telling us the truth? J Bras Pneumol. 2015;41(2):124-32. http://dx.doi.org/10.1590/S1806-37132015000004526. PMid:25972966.
28. Bårnes CB, Ulrik CS. Asthma and adherence to inhaled corticosteroids: current status and future perspectives. Respir Care. 2015;60(3):455-68. http://dx.doi.org/10.4187/respcare.03200. PMid:25118311.
29. Akinbami LJ, Fryar CD. Current asthma prevalence by weight status among adults: United States, 2001-2014 [Internet]. [cited 2017 Mar 13]. Atlanta: CDC; 2016. Available from: https://www.cdc.gov/nchs/products/databriefs/db239.htm
30. Jesus JPV, Lima-Matos AS, Almeida PCA, Lima VB, Mello LM, Souza-Machado A, et al. Obesidade e asma: caracterização clínica elaboratorial

de uma associação frequente. J Bras Pneumol. 2018;44(3):207-12. http://dx.doi.org/10.1590/s1806-37562017000000034. PMid:30043887.

31. Heaney LG, Brightling CE, Menzies-Gow A, Stevenson M, Niven RM. Refractory asthma in the UK: cross-sectional findings from a UK multicentre registry. Thorax. 2010;65(9):787-94. http://dx.doi.org/10.1136/thx.2010.137414. PMid:20805172.
32. Peters U, Dixon AE, Forno E. Obesity and asthma. J Allergy Clin Immunol. 2018;141(4):1169-79. http://dx.doi.org/10.1016/j.jaci.2018.02.004. PMid:29627041.
33. El-Serag HB, Sweet S, Winchester CC, Dent J. Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut. 2014;63(6):871-80. http://dx.doi.org/10.1136/gutjnl-2012-304269. PMid:23853213.
34. Havemann BD, Henderson CA, El-Serag HB. The association between gastro-oesophageal reflux disease and asthma: a systematic review. Gut. 2007;56(12):1654-64. http://dx.doi.org/10.1136/gut.2007.122465. PMid:17682001.
35. Ates F, Vaezi MF. Insight into the relationship between gastroesophageal reflux disease and asthma. Gastroenterol Hepatol. 2014;10(11):729-36. PMid:28435409.
36. Giavina-Bianchi P, Aun MV, Takejima P, Kalil J, Agondi RC. United airway disease: current perspectives. J Asthma Allergy. 2016;2016:93-100. http://dx.doi.org/10.2147/JAA.S81541. PMid:27257389.
37. Chipps BE, Haselkorn T, Paknis B, Ortiz B, Bleecker ER, Kianifard F, et al. More than a decade follow-up in patients with severe or difficult-to-treat asthma: the epidemiology and natural history of asthma: outcomes and Treatment Regimens (TENOR) II. J Allergy Clin Immunol. 2018;141(5):1590-7. http://dx.doi.org/10.1016/j.jaci.2017.07.014. PMid:28797732.
38. Dunican EM, Fahy JV. Asthma and corticosteroids: time for a more precise approach to treatment. Eur Respir J. 2017;49(6):1701167. http://dx.doi.org/10.1183/13993003.01167-2017. PMid:28663322.
39. Ortega H, Llanos JP, Lafeuille MH, Duh MS, Germain G, Lejeune D, et al. Effects of systemic corticosteroids on blood eosinophil counts in asthma: real-world data. J Asthma. 2018;16:1-8. http://dx.doi.org/10.1080/02770903.2018.1502301. PMid:30130418.
40. Suruki RY, Daugherty JB, Boudiaf N, Albers FC. The frequency of asthma exacerbations and healthcare utilization in patients with asthma from the UK and USA. BMC Pulm Med. 2017;17(1):74. http://dx.doi.org/10.1186/s12890-017-0409-3. PMid:28449686.