

Irreversible airway obstruction in asthma: a risk factor for severe exacerbations in spite of proper treatment.

Abstract

Objectives: To evaluate whether irreversible airway obstruction (IAO) related to asthma is a risk factor for lack of symptoms control, poor quality of life and exacerbations. **Methods:** We evaluated consecutive outpatients with asthma in a one-year cohort study. We excluded subjects with smoke history > 9 pack-years. Definition of IAO was post bronchodilator FEV₁/CVF ratio below the lower limit of normality. Subjects received high dose of inhaled medications for asthma. We used logistic regression models, adjusted for the treatment offered during the study, to evaluate whether IAO related to asthma is a risk factor for symptoms control, quality of life, any emergency room visit, number of emergency room visits and hospital admission. **Results:** We enrolled 248 subjects in the study. IAO was not a risk factor for poor symptoms control [OR 1.354, 95 CI (0.632–2.899)] or worse asthma related quality of life [OR 0.705, 95 CI (0.413–1.204)]. Subjects with IAO had higher odds of any emergency room visit [OR 2.214, 95 CI (1.300–3.768)] and hospital admission [OR 8.530, 95 CI (1.517–47.978)] and lower odds to reduce emergency room visits in the course of the follow up period [OR 0.452, 95 CI (0.265–0.769)]. IAO did not predict the number of emergency room visits [OR 1.53, 95 CI (0.71–3.30)]. **Conclusion:** IAO is not a risk factor for poor symptoms control or poor quality of life, in a setting of proper treatment. It is a risk factor for emergency room visit and hospital admission. Subjects with IAO have poor response to treatment.

Key words

- [Control/Management](#),
- [Morbidity and Mortality](#),
- [Pharmacotherapy](#),
- [Quality of Life](#),
- [Treatment](#)

Introduction

Airway obstruction persists in a subset of subjects with asthma in spite of proper treatment with corticosteroids and bronchodilators. This condition is acknowledged as irreversible airway obstruction from asthma. Irreversible airway obstruction is associated with non-inflammatory structural changes of the airway wall at bronchial biopsies [1]. Current airway inflammation seems to have a limited role in irreversible airway obstruction. Cross-sectional studies did not observe an association between irreversible airway obstruction and airway inflammation, as measured by induced sputum cytology or exhaled nitric oxide [2; 3; 4].

Jang et al found 8.4% of irreversible airway obstruction in a sample of 582 asthmatic subjects under regular treatment [5]. Cross sectional studies demonstrated that irreversible airway obstruction is associated with adult onset asthma [6], longer duration of symptoms [2; 7], male gender [2; 4], lower education [4], aspirin sensitivity [8], greater bronchial hyper-responsiveness [9; 6] and less chronic rhinitis diagnosis [10].

Longitudinal studies evaluated outcomes associated with irreversible airway obstruction. However, these studies enrolled subjects with Overlap Syndrome or Chronic Obstructive Pulmonary Disease (COPD), because heavy smoking history was common in the irreversible airway obstruction group [11; 12; 13]. Other studies did not provide treatment during follow up, rendering it difficult to establish whether irreversible airway obstruction or under-treatment determined outcomes [14; 15; 16]. Longitudinal studies are necessary to evaluate outcomes of irreversible airway obstruction in subjects with asthma. We hypothesized that asthmatic subjects with irreversible airway obstruction have worse outcomes. The aim of this study was to evaluate whether irreversible airway obstruction related to asthma is a risk factor for symptoms control, quality of life and exacerbations from asthma in a setting of proper treatment.

Methods

Study Population

Subjects were screened consecutively upon admission in the severe asthma clinic of the Program for Control of Asthma in Bahia (ProAR). Patients were from the low-income strata of Salvador City, Brazil, and were not in regular use of inhaled corticosteroids before enrollment. Enrollment period was from January 2004 to January 2006.

Inclusion criteria were: 1) Diagnosis of uncontrolled asthma; 2) Age >12 years old; 3) Informed consent signed by patients or guardians. Exclusion criteria were: 1) Smoking history > 9 pack/years; 2) Current smoking; 3) Other lung diseases or other disease that could possibly interfere in the evaluation of asthma control or severity.

Two physicians experienced in asthma care independently checked the diagnosis of asthma. A third physician decided in case of disagreement. The tools for asthma diagnosis were physician evaluation, spirometry and chest radiography. The physician looked for typical symptoms of asthma such as chronic and recurrent episodes of wheezing, cough or dyspnea. Lung function should be normal or have airway obstruction. Response to bronchodilator was not a criterion for enrollment. The chest radiography was important to exclude subjects with large lung scars, because this abnormality indicates a relevant concomitant pulmonary disease. The attending physician requested a high-resolution computerized tomography of the chest according to clinical judgment, to rule out bronchiectasis. Subjects with bronchiectasis observed at the CT were excluded.

Criteria for uncontrolled asthma at enrollment were: 1) daily symptoms of asthma; or 2) more than two night awakenings per week due to asthma symptoms; or 3) use of rescue medication for asthma more than twice a day. The Institutional Review Board of MCO - Federal University of Bahia approved the study.

Study design

This is an outpatient prospective cohort study. Subjects were followed during one year. The study comprised five visits at intervals of 3 months. In visit I inclusion and exclusion criteria were checked, subjects were evaluated by a multidisciplinary team (chest physician, nurse and pharmacist), reported emergency room visits and hospital admissions from asthma during the year before enrollment, performed lung function test and skin prick test to aeroallergens. In visits II to V a multidisciplinary team evaluated subjects and reported emergency room visits and hospital admissions from asthma since the last study visit. In visit V subjects repeated lung function test, answered symptoms questionnaire (*Asthma Control Questionnaire* - ACQ), quality of life questionnaire (*Asthma Quality of Life Questionnaire* - AQLQ) and a physician evaluated rhinitis symptoms. Two hundred and forty eight subjects fulfilled the inclusion/exclusion criteria and completed the follow up period.

At enrollment in the study, all subjects received an initial prescription of 800 µg/day of inhaled budesonide plus 24 µg/day of inhaled formoterol [17]. Subjects received inhaled short-acting β-2 agonist, to use on demand. The physician in charge evaluated asthma treatment every study visit. Subjects who reported hospital admission or emergency room visit from asthma since the last study visit or symptoms of asthma in the last 2 weeks had treatment up titrated. Subjects without hospital admission, emergency room visit and symptoms of asthma had treatment down titrated. A pharmacist supplied the medications for asthma free of charge and controlled adherence to treatment every month.

Lung function

A technician performed a lung function test at enrollment and at the last study visit (Koko® spirometer, software PDS Instrumentation, Inc., Louisville, Colorado, EUA), according to American Thoracic Society

recommendations [18]. The spirometer software was updated with Brazilian values of normality [19]. These values were used to calculate the percent of predicted of Forced Expiratory Volume in the first second (FEV₁) and Forced Vital Capacity (FVC).

The criterion of irreversible airway obstruction was post bronchodilator FEV₁/FVC ratio below the lower limit of normality in both pre and post treatment spirometry performed at study visits I and V, respectively. We obtained the equation to calculate the lower limit of normality from Cerveri et al [20].

Allergic skin prick-tests and rhinitis symptoms evaluation

The definition of atopy was a positive skin prick-test to any aeroallergen tested. The antigens were *Dermatophagoides pteronyssinus*, *Blomia tropicalis*, dog and cat dander allergens. We measured the wheal diameters 15 minutes after puncture. The test was positive when at least one antigen induced a reaction 3 mm greater than the negative control with saline solution.

A physician evaluated rhinitis at enrollment. At the last study visit a questionnaire was applied to evaluate the severity of rhinitis symptoms. The questionnaire measured nasal obstruction, sneezing, itching and runny nose in the preceding 7 days. Symptoms were classified as absent (0), mild (1), moderate (2) or severe (3). The sum of symptoms score defined a final score from zero to 12.

Asthma control and quality of life

At the last study visit we applied the ACQ questionnaire. The ACQ questionnaire measures the severity of asthma symptoms. Lower score indicates fewer symptoms. The Brazilian Portuguese version of the ACQ questionnaire was validated [21]. The cutoff of well-controlled asthma is 0.75 [21].

At the last study visit we also applied the AQLQ questionnaire. This is a 32-item questionnaire that measures asthma related quality of life. Higher score indicates better quality of life [22]. There is no cutoff to distinguish high from low quality of life. We used the 50th percentile to dichotomize the AQLQ score: high or low quality of life. The dichotomized AQLQ was the dependent variable of an adjusted binary logistic regression model.

Statistical analysis

Chi-Square and Mann Whitney tests were used to compare outcomes of asthma control between subjects with and without irreversible airway obstruction. We used the Chi-Square test to analyze nominal variables. We used the Mann Whitney test to analyze continuous and ordinal variables because the distribution was not normal. Hospital admission from asthma during the study was the primary endpoint of asthma control. Emergency room visit during the study, ACQ and AQLQ scores at visit V were secondary endpoints of asthma control.

We evaluated the response to treatment with inhaled corticosteroid and Long Acting Beta 2 Agonist. The study population was not under regular use of inhaled medications for asthma before the study. Therefore, the inhaled medications supplied during the study was the most likely reason for an important reduction in the number of emergency room visits. We classified subjects in two categories: $\geq 90\%$ or $<90\%$ reduction of emergency room visits. The number of emergency room visits in the year before the study, reported at visit I, was the baseline information to estimate reduction of emergency room visits during the study.

We performed four adjusted binary logistic regression models to evaluate whether irreversible airway obstruction (independent variable) was a risk factor for endpoints of asthma control (dependent variables). The endpoints of asthma control were emergency room visit during the follow up period, hospital admission during the follow up period, ACQ score below 0.75 and AQLQ score above the 50th percentile at the last study visit (*Statistical Package for the Social Sciences* - SPSS Inc., Chicago, IL, USA). The regression models were adjusted for the treatment offered in the course of the study (independent variable). We defined

high dose of inhaled medication for asthma the use of more than 800 µg/day of inhaled budesonide associated with 24 µg/day of inhaled formoterol [17]. The method of data entry in the adjusted binary logistic regression model was the Backward Likelihood Ratio. We used the Hosmer-Lemeshow test to measure goodness-of-fit and the Tolerance test and Variance Inflation Factor to measure collinearity.

We also performed a multivariate negative binomial regression model to evaluate whether irreversible airway obstruction was a risk factor for the number of emergency room visits during the follow up. This analysis was adjusted for the use of high dose of inhaled medication for asthma in the follow up and for the number of emergency room visits in the year before enrollment. We used the STATA software for this analysis.

Results

[Table 1](#) describes baseline characteristics of 248 subjects enrolled in the study. It depicts ordinal and continuous variables as median and 25–75 percentiles and nominal variables as absolute number and proportions. Female represents 82% of the sample, median age at enrollment was 47 (35–56) years old and median Body Mass Index (BMI) was 26 (23–31). The physician diagnosed chronic rhinitis in 207 (84%) subjects. The age of initial asthma symptoms was 10 (4–25) years old. The number of emergency room visits and hospital admissions from asthma per subject in the year before enrollment was 6 (2–20) and 0 (0–1), respectively. Skin prick tests to aeroallergens were positive in 127 (61%) subjects.

TABLE 1. Clinical characteristics of patients at enrollment in the study.

[Table 2](#) compares baseline characteristics of the study population according to lung function patterns. At that moment in time subjects were not using inhaled medications for asthma. Irreversible airway obstruction was not associated with gender, Body Mass Index, chronic rhinitis diagnosis, age of first asthma symptoms, duration of asthma, smoking history, number of emergency room visits in the year before the study, number of hospital admissions in the year before the study and frequency of positive skin prick test to aeroallergens. A trend toward association between older age at enrollment and irreversible airway obstruction was observed [median and 25–75th percentiles; 50 (39–57) versus 43 (34–54). $p = 0.05$].

TABLE 2 – Clinical characteristics of patients with asthma at enrollment, according to their lung function pattern.

[Table 3](#) compares follow up data of the study population according to lung function patterns. At that moment in time subjects were using inhaled medications for asthma during the last year. Irreversible airway obstruction was associated with higher number of emergency room visits per subject, higher frequency of subjects reporting any emergency room visit, higher number of hospital admissions per subject, higher frequency of subjects reporting any hospital admission and lower frequency of $\geq 90\%$ reduction of emergency room visits in the course of follow up. Groups were similar regarding the frequency of rhinitis treatment, the frequency of high dose of inhaled medication for asthma, the scores of the ACQ and AQLQ questionnaires. Lower rhinitis symptoms score had a borderline association with irreversible airway obstruction.

TABLE 3 – Asthma control and response to treatment during the follow up period, according to lung function pattern.

[Table 4](#) depicts adjusted binary logistic regression models to identify risk factors for higher symptoms scores, poor quality of life scores, emergency room visit, hospital admission and reduction of emergency room visits from asthma during the follow up period. Data are depicted as odds and 95% confidence intervals. Subjects with irreversible airway obstruction had higher odds of emergency room visit [OR 2.214, 95 CI (1.300–3.768)] and hospital admission [OR 8.530, 95 CI (1.517–47.978)] from asthma during the follow up. They had lower odds of $\geq 90\%$ reduction of emergency room visits from asthma in the course of follow up [OR 0.452, 95 CI (0.265–0.769)]. Subjects using high dose of inhaled medication for asthma during the study had

lower odds of emergency room visit [OR 0.416, 95 CI (0.189–0.911)] and higher odds of $\geq 90\%$ reduction of emergency room visits from asthma in the course of follow up [OR 2.407, 95 CI (1.097–5.279)]. Subjects using high dose of inhaled medication for asthma had higher odds of ACQ score < 0.75 [OR 1.002, 95 CI (1.001–1.004)] and of high AQLQ score at the last study visit [OR 1.002, 95 CI (1.001–1.003)].

TABLE 4 – Adjusted regression model to identify risk factors for asthma exacerbations and response to treatment during the follow up period.

The multivariate negative binomial regression model demonstrated that irreversible airway obstruction, adjusted for the dose of inhaled medication for asthma in the follow up and for the number of emergency room visits in the year before enrollment, did not predict the number of emergency room visits during the follow up [OR 1.53, 95 CI (0.71–3.30)].

Discussion

Our cohort study demonstrates that subjects with irreversible airway obstruction had increased odds of emergency room visit and hospital admission from asthma during the follow up period in spite of high dose of inhaled medications, however, irreversible airway obstruction did not predict the number of emergency room visits. Subjects with irreversible airway obstruction had lower odds to reduce emergency room visits during one year of treatment with inhaled corticosteroids plus Long Acting Beta 2 Agonist. In our study irreversible airway obstruction group was unlikely to include subjects with Asthma COPD Overlap Syndrome or COPD, because we excluded subjects with smoke history > 9 pack years and two chest physicians independently checked the diagnosis of asthma. Although we did not measure exposure to indoor wood smoke in this urban population, our strategy to avoid COPD related airway obstruction was probably successful as both study groups had baseline characteristics of asthma such as low age of first respiratory symptoms and high frequency of chronic rhinitis. Under treatment had little chance to bias the results since we monitored treatment, most subjects used high dose of inhaled medication for asthma and treatment was a co-variate in the adjusted regression models.

In our study irreversible airway obstruction was not a risk factor for uncontrolled symptoms of asthma or worse asthma related quality of life. Teeter et al demonstrated that lung function does not correlate well with asthma symptoms and symptoms improvement can occur without improvement of lung function in asthmatic subjects without irreversible airway obstruction [23]. Reduced perception of airway obstruction [24] and underrate respiratory symptoms [25] may contribute to the disconnection between airway obstruction and symptoms reported by subjects with asthma. These observations reinforce the need of proper characterization of lung function pattern in subjects with asthma to estimate the risk of future exacerbations.

We did not observe an association between the duration of asthma symptoms and irreversible airway obstruction. Memory bias may be the reason of this unexpected result. Previous studies indicate that the length of asthma symptoms is associated with irreversible airway obstruction [13; 16]. It is possible that long-term airway inflammation causes airway remodeling and subsequent irreversible airway obstruction. The protective effect of anti-inflammatory medications for asthma on the development of airway obstruction supports this hypothesis [12]. However, non-inflammatory mechanisms seem to participate in the physiopathology of airway remodeling and irreversible airway obstruction. Evidences demonstrate that *in vitro* mechanical strain of human airway smooth muscle cells [26] and *in vivo* induced bronchial spasm [27] can cause airway remodeling with no apparent inflammatory cell mediation.

Our study did not find association between atopy and irreversible airway obstruction. Previous survey did not find associations between atopy and symptoms control in adult subjects with asthma [28]. These observations suggest that atopy has only a partial role in the physiopathology of asthma in adult subjects.

Chronic rhinitis is often associated with more severe asthma and lower lung function [29]. Underlying systemic inflammation possibly leads to concomitant upper and lower airways abnormalities. In our study irreversible airway obstruction was not associated with chronic rhinitis diagnosis or severity of rhinitis symptoms. Jang et al observed an inverse association between irreversible airway obstruction and diagnosis of rhinitis [10]. These observations suggest a disconnection between upper and lower airway pathologies in asthmatic subjects with irreversible airway obstruction.

Jang et al estimated 8.4% of irreversible airway obstruction among asthmatic subjects [5]. We observed a much higher frequency in our study. This result is within the expectation for subjects with severe symptoms of asthma and no previous regular use of inhaled corticosteroids. Population based studies are needed to define unbiased prevalence of irreversible airway obstruction related to asthma across all severities. Our sample of severe asthmatics also explains the high rate of female gender, since severe asthma affects females more frequently [30].

A recent uncontrolled study suggests that Tiotropium improves symptoms and prevents exacerbations in subjects with irreversible airway obstruction related to asthma [31]. However, further studies are necessary to assure effectiveness and safety of Tiotropium for irreversible airway obstruction related to asthma.

Our criterion of irreversible airway obstruction was post-bronchodilator FEV_1/CVF ratio below the lower limit of normality before and after treatment. Post-bronchodilator FEV_1/CVF ratio below the lower limit of normality is an up to date criterion of airway obstruction [20]. Subjects used high dose of inhaled corticosteroids plus Long Acting Beta 2 agonist during one year to control airway inflammation and assure irreversibility of airway obstruction in the post-treatment lung function test. A trial with high dose of oral corticosteroids would have only a small additional effect on residual airway inflammation, eventually not controlled by the one year of high dose of inhaled medications for asthma. However, a trial with high dose of oral corticosteroids would demand additional exclusion criteria and many subjects might refuse to participate due to concerns regarding side effects. We suppose these are the reasons why most previous studies on this topic did not use a trial of oral corticosteroids to define irreversible airway obstruction [2; 3; 4; 9; 10; 12; 13; 14].

We conclude that irreversible airway obstruction is not a risk factor for poor control of asthma symptoms or asthma related quality of life, in a setting of proper treatment. It is a risk factor for emergency room visit and hospital admission from asthma, however, irreversible airway obstruction did not predict the number of emergency room visits. Subjects with irreversible airway obstruction have lower odds to reduce emergency room visits after treatment. These data emphasize the necessity to characterize irreversible airway obstruction related to asthma in clinical practice and to investigate new treatment options for these subjects.

Acknowledgements

We acknowledge CNPq/FAPESB for the financial support (Grant 020/2009 - PRONEX – 6353 – PNX0018/2009)

Conflict of interest

All authors declare no conflict of interest and no financial relationships with companies that have an interest in the subject matter of this manuscript.

References

- 1. Kim ES, Kim SH, Kim KW, et al. Basement membrane thickening and clinical features of children with asthma. *Allergy*.2007;62:635–640. [[CrossRef](#)], [[PubMed](#)], [[Web of Science ®](#)]

- **2.** Bumbacea D, Campbell D, Nguyen L, et al. Parameters associated with persistent airflow obstruction in chronic severe asthma. *Eur Respir J*. 2004;24:122–128. [\[CrossRef\]](#), [\[PubMed\]](#), [\[Web of Science ®\]](#)
- **3.** ten Brinke A, Zwinderman AH, Sterk PJ, et al. Factors associated with persistent airflow limitation in severe asthma. *Am J Respir Crit Care Med*. 2001;164:744–748. [\[CrossRef\]](#), [\[PubMed\]](#), [\[Web of Science ®\]](#)
- **4.** Lee JH, Haselkorn T, Borish L, et al. Risk factors associated with persistent airflow limitation in severe or difficult-to-treat asthma: insights from the TENOR study. *Chest*. 2007;132:1882–1889. [\[CrossRef\]](#), [\[PubMed\]](#), [\[Web of Science ®\]](#)
- **5.** Jang AS, Lee JH, Park SW, et al. Risk factors related to fixed airway obstruction in patients with asthma after antiasthma treatment. *Ann Allergy Asthma Immunol*. 2007;99:408–412. [\[CrossRef\]](#), [\[PubMed\]](#), [\[Web of Science ®\]](#)
- **6.** Ten Brinke A, Zwinderman AH, Sterk PJ, et al. Factors associated with persistent airflow limitation in severe asthma. *Am J Resp Crit Care Med* 2001;164:744–748. [\[CrossRef\]](#), [\[PubMed\]](#), [\[Web of Science ®\]](#)
- **7.** Sexton P, Black P, Wu L, et al. Fixed airflow obstruction among nonsmokers with asthma: a case-comparison study. *J Asthma* 2013;50:606–612. [\[Taylor & Francis Online\]](#), [\[PubMed\]](#), [\[Web of Science ®\]](#)
- **8.** Mascia K, Haselkorn T, Deniz YM, et al. Aspirin sensitivity and severity of asthma: evidence for irreversible airway obstruction in patients with severe or difficult-to-treat asthma. *J Allergy Clin Immunol*. 2005;116:970–975 [\[CrossRef\]](#), [\[PubMed\]](#), [\[Web of Science ®\]](#)
- **9.** Boulet L, B  langer M, Carrier G. Airway responsiveness and bronchial-wall thickness in asthma with or without fixed airflow obstruction. *Am J Respir Crit Care Med*. 1995;152:865–871. [\[CrossRef\]](#), [\[PubMed\]](#), [\[Web of Science ®\]](#)
- **10.** Jang AS, Park JS, Lee JH, et al. Asthmatics without rhinitis have more fixed airway obstruction than those with concurrent rhinitis. *Allergy Asthma Immunol Res*. 2010;2:108–113. [\[CrossRef\]](#), [\[PubMed\]](#), [\[Web of Science ®\]](#)
- **11.** Grol MH, Gerritsen J, Vonk JM, et al. Risk factors for growth and decline of lung function in asthmatic individuals up to age 42 years. A 30-year follow-up study. *Am J Respir Crit Care Med*. 1999;160:1830–1837. [\[CrossRef\]](#), [\[PubMed\]](#), [\[Web of Science ®\]](#)
- **12.** Vonk JM, Jongepier H, Panhuysen CIM, et al. Risk factors associated with the presence of irreversible airflow limitation and reduced transfer coefficient in patients with asthma after 26 years of follow up. *Thorax* 2003;58:322–327. [\[CrossRef\]](#), [\[PubMed\]](#), [\[Web of Science ®\]](#)
- **13.** Lee T, Lee YS, Bae YJ, et al. Smoking, longer disease duration and absence of rhinosinusitis are related to fixed airway obstruction in Koreans with severe asthma: findings from the COREA study. *Respir Res*. 2011;3:12
- **14.** Ulrik CS, Backer V. Nonreversible airflow obstruction in life-long nonsmokers with moderate to severe asthma. *Eur Respir J* 1999;14:892–896. [\[CrossRef\]](#), [\[PubMed\]](#), [\[Web of Science ®\]](#)
- **15.** Hansen EF, Phanareth K, Laursen LC, et al. Reversible and irreversible airflow obstruction as predictor of overall mortality in asthma and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 1999;159:1267–1271. [\[CrossRef\]](#), [\[PubMed\]](#), [\[Web of Science ®\]](#)
- **16.** Limb SL, Brown KC, Wood RA, et al. Irreversible lung function deficits in young adults with a history of childhood asthma. *J Allergy Clin Immunol*. 2005;116:1213–1219. [\[CrossRef\]](#), [\[PubMed\]](#), [\[Web of Science ®\]](#)
- **17.** Diretrizes da Sociedade Brasileira de Pneumologia e Tisiologia para Asma *Jornal Brasileiro de Pneumologia* 2012;38:S1–S46
- **18.** American Thoracic Society (ATS) Standardization of Spirometry 1994 Update. *Am J Respir Crit Care Med*. 1995;152:1107–1136. [\[Web of Science ®\]](#)
- **19.** Pereira CAC, Barreto SP, Sim  es JG, et al. Valores de refer  ncia para espirometria em uma amostra da popula  o brasileira adulta. *J Pneumol*. 1992;18:10–22.

- **20.** Cerveri I, Corsico AG, Accordini S, et al. Underestimation of airflow obstruction among young adults using FEV1/FVC <70% as a fixed cut-off: a longitudinal evaluation of clinical and functional outcomes. *Thorax*. 2008;63:1040–1045. [\[CrossRef\]](#), [\[PubMed\]](#), [\[Web of Science ®\]](#)
- **21.** Leite M, Ponte EV, Petroni J, et al. Evaluation of the Asthma Control Questionnaire validated for use in Brazil. *J Bras Pneumol* 2008;34:756–763. [\[CrossRef\]](#), [\[PubMed\]](#)
- **22.** Juniper EF, Guyatt GH, Cox FM, et al. Development validation of the Mini Asthma Quality of Life Questionnaire. *Eur Respir J* 1999;14:32–38. [\[CrossRef\]](#), [\[PubMed\]](#), [\[Web of Science ®\]](#)
- **23.** Teeter JG, Bleecker ER. Relationship between airway obstruction and respiratory symptoms in adult asthmatics. *Chest* 1998;113:272–277. [\[CrossRef\]](#), [\[PubMed\]](#), [\[Web of Science ®\]](#)
- **24.** Burdon JG, Juniper EF, Killian KJ, et al. The perception of breathlessness in asthma. *Am Rev Respir Dis*. 1982;126:825–828. [\[PubMed\]](#), [\[Web of Science ®\]](#)
- **25.** Ponte EV, Petroni J, Ramos DC, et al. Perception of asthma control in asthma patients. *J Bras Pneumol*. 2007;33:635–640 [\[CrossRef\]](#), [\[PubMed\]](#)
- **26.** Hasaneen NA1, Zucker S, Cao J, et al. Cyclic mechanical strain-induced proliferation and migration of human airway smooth muscle cells: role of EMMPRIN and MMPs. *FASEB J*. 2005;19:1507–1509. [\[PubMed\]](#), [\[Web of Science ®\]](#)
- **27.** Grainge CL, Lau LC, Ward JA, et al. Effect of bronchoconstriction on airway remodeling in asthma. *N Engl J Med*. 2011;364:2006–2015. [\[CrossRef\]](#), [\[PubMed\]](#), [\[Web of Science ®\]](#)
- **28.** Ponte EV, Souza-Machado A, Souza-Machado C, et al. Atopy is not associated with poor control of asthma. *J Asthma*. 2012;49:1021–1026. [\[Taylor & Francis Online\]](#), [\[PubMed\]](#), [\[Web of Science ®\]](#)
- **29.** Ponte EV, Franco R, Nascimento HF, et al. Lack of control of severe asthma is associated with co-existence of moderate-to-severe rhinitis. *Allergy*. 2008;63:564–569. [\[CrossRef\]](#), [\[PubMed\]](#), [\[Web of Science ®\]](#)
- **30.** Almqvist C, Worm M, Leynaert B. Impact of gender on asthma in childhood and adolescence: a GA2LEN review. *Allergy* 2008;63:47–57 [\[PubMed\]](#), [\[Web of Science ®\]](#)
- **31.** Abadoglu O, Berk S. Tiotropium may improve asthma symptoms and lung function in asthmatic patients with irreversible airway obstruction: the real-life data. *Clin Respir J*. 2014 doi: 10.1111/crj.12230 [\[CrossRef\]](#), [\[PubMed\]](#)

Table 1 of 4

TABLE 1. Clinical characteristics of patients at enrollment in the study.

	N = 248
Gender (%)	
Female	203 (82)
Male	45 (18)
Age at enrollment, in years	47 (35–56)
Body Mass Index	26 (23–31)
Chronic rhinitis (%)	
Present	207 (84)
Absent	41 (16)
Age of initial asthma symptoms	10 (4–25)
Duration of asthma, in years	28 (17–42)
Smoking history (pack years)	0 (0–0)
Number of emergency room visits per patient in the year before enrollment	6 (2–20)
Patients reporting emergency room visits in the year before enrollment (%)	
At least one emergency room visit	220 (89)
No emergency room visit	28 (11)
Number of hospital admissions per patient in the year before enrollment	0 (0–1)
Patients reporting hospital admission in the year before enrollment (%)	
At least one hospital admission	82 (33)
No hospital admission	166 (67)
Skin prick test to aeroallergens (%)	
Positive	127 (61)
Negative	79 (39)
FEV ₁ post-bronchodilator percent of predict at visit I	79 (64–95)
FVC post-bronchodilator percent of predict at visit I	96 (86–111)

* Data available for 206 patientsTable depicts categorical variables as absolute values and proportionTable depicts continuous and ordinal variables as median and inter quartile values

Table 2 of 4

TABLE 2 – Clinical characteristics of patients with asthma at enrollment, according to their lung function pattern.

	Irreversible airway obstruction (n = 124)	Reversible airway obstruction (n = 124)	P Value
Gender (%)			
Female	97 (78)	106 (85)	0.14
Male	27 (22)	18 (15)	
Age at enrollment, in years	50 (39–57)	43 (34–54)	0.05
Body Mass Index	26 (22–30)	27 (24–31)	0.07
Chronic rhinitis (%)			
Present	99 (80)	108 (87)	0.12
Absent	25 (20)	16 (13)	
Age of initial asthma symptoms	10 (3–26)	12 (5–24)	0.67
Duration of asthma	29 (18–43)	26 (16–38)	0.16
Smoking history (pack years)	0 (0–0)	0 (0–0)	0.45
N° of emergency room visits per patient in the year before enrollment	6 (2–20)	8 (2–24)	0.47
Patients reporting emergency room visit in the year before enrollment (%)			
At least one emergency room visit	107 (86)	113 (91)	0.23
No emergency room visit	17 (14)	11 (9)	
N° of hospital admissions per patient in the year before enrollment	0 (0–1)	0 (0–1)	0.76
Patients reporting hospital admission in the year before enrollment (%)			
At least one hospital admission	41 (33)	41 (33)	1
No hospital admission	83 (67)	83 (67)	
Skin prick test to aeroallergens (%)			
Positive	68 (66)	59 (57)	0.2
Negative	35 (34)	44 (43)	
FEV ₁ post-bronchodilator percent of predict at visit I	64 (55–77)	90 (79–104)	< 0.01
FVC post-bronchodilator percent of predict at visit I	94 (81–110)	91 (100–111)	0.09

* Data available for 206 patientsTable depicts categorical variables as absolute values and proportionTable depicts continuous and ordinal variables as median and inter quartile valuesStatistics with Chi-Square test for bina

Table 3 of 4

TABLE 3 – Asthma control and response to treatment during the follow up period, according to lung function pattern.

	Irreversible airway obstruction (n = 124)	Reversible airway obstruction (n = 124)	P Value
Use of nasal corticosteroids for rhinitis (%)			
Yes	49 (40)	55 (44)	0.47
No	75 (60)	69 (56)	
Rhinitis severity score at the last study visit	3 (0–6)	4 (1–8)	0.05
High dose of inhaled medication for asthma (%)			
Yes	112 (90)	111 (90)	0.59
No	12 (10)	13 (10)	
Asthma control according to the ACQ score < 0.75 at the last study visit (%)			
Well controlled asthma	14 (11)	19 (15)	0.35
Not well controlled asthma	110 (89)	105 (85)	
ACQ score at the last study visit	1.8 (1.3–2.8)	2.0 (1.1–2.7)	0.34
AQLQ score at the last study visit	4.0 (2.9–5.5)	3.7 (2.8–4.9)	0.4
Number of emergency room visits per patient in the year of follow up	1 (0–3)	0 (0–2)	0.02
Patients reporting emergency room visit in the year of follow up (%)			
At least one emergency room visit	67 (54)	48 (39)	0.02
No emergency room visit	57 (46)	76 (61)	
Number of hospital admissions per patient in the year of follow up	0 (0–1)	0 (0–0)	0.02
Patients reporting hospital admission in the year of follow up (%)			
At least one hospital admission	10 (8)	2 (2)	0.02
No hospital admission	114 (92)	122 (98)	
Patients with ≥ 90% reduction of emergency room visits (%)			
Yes	57 (46)	76 (61)	0.02
No	67 (54)	48 (39)	
FEV ₁ post-bronchodilator percent of predict at the last study visit	69 (55–82)	88 (76–98)	< 0.01
FVC post-bronchodilator percent of predict at the last study visit	97 (84–111)	96 (87–109)	0.85

* More than 800 µg/day of inhaled budesonide associated with 24 µg/day of inhaled formoterol ACQ = Asthma Control Questionnaire; AQLQ = Asthma Quality of Life Questionnaire Table depicts categorical variables as absolute values and proportion Table depicts continuous and ordinal variables as median and inter quartile values Statistics with Chi-Square test for binary variables and Mann-Whitney test for ordinal and continuous variables

Table 4 of 4

TABLE 4 – Adjusted regression model to identify risk factors for asthma exacerbations and response to treatment during the follow up period.

	OR (95 CI)
Emergency room visit in the follow up	
Irreversible airway obstruction	2.214 (1.300–3.768)
High dose of inhaled medication for asthma	0.416 (0.189–0.911)
Any emergency room visit in the year before enrollment	2.461 (1.012–5.988)
Hospital admission in the follow up	
Irreversible airway obstruction	8.530 (1.517–47.978)
High dose of inhaled medication for asthma	1.002 (0.999–1.004)
Any hospital admission in the year before enrollment	4.824 (1.289–18.058)
≥ 90% reduction of emergency room visits in the follow up	
Irreversible airway obstruction	0.452 (0.265–0.769)
High dose of inhaled medication for asthma	2.407 (1.097–5.279)
Any emergency room visit in the year before enrollment	0.406 (0.167–0.989)
ACQ score < 0.75 at the last study visit	
Irreversible airway obstruction	1.354 (0.632–2.899)
High dose of inhaled medication for asthma	1.002 (1.001–1.004)
High AQLQ score at the last study visit	
Irreversible airway obstruction	0.705 (0.413–1.204)
High dose of inhaled medication for asthma	1.002 (1.001–1.003)
High rhinitis symptoms score at the last study visit	
Irreversible airway obstruction	1.281 (0.766–2.144)
Use of nasal corticosteroids for rhinitis	0.995 (0.993–0.998)

* More than 800 µg/day of inhaled budesonide associated with 24 µg/day of inhaled formoterol ** Scores dichotomized according to the 50th percentile Table depicts values as odds and 95% Confidence Intervals