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CLINICAL FEATURE
ORIGINAL RESEARCH

Predictors of future exacerbation risk in patients with asthma

Andriana I. Papaioannou^{a*}, Konstantinos Kostikas^{a*}, Petros Bakakos^b, Anastasia Papaportfyriou^b, Elissavet Konstantellou^b, Georgios Hillas^c, Georgios Papatheodorou^d, Nikolaos G. Koulouris^b, Spyridon Papiris^a and Stelios Loukides^a

^a2nd Respiratory Medicine Department, Attikon Hospital, University of Athens, Athens, Greece; ^b1st Respiratory Medicine Department, Sotiria Hospital, University of Athens, Athens, Greece; ^cRespiratory Medicine Department, Evagelismos Hospital, Athens, Greece; ^dClinical Research unit, Athens Army General Hospital, Athens, Greece

ABSTRACT

Objectives: Although modern treatment of asthma improves asthma control, some patients still experience exacerbations. The aim of the present study was to detect predictors of asthmatic exacerbations

Methods: We included patients with asthma followed up in asthma clinics of 2 tertiary University hospitals. Demographic and functional characteristics, levels of exhaled NO, and inflammatory biomarkers (IL-13, ECP and IL-8) and cell counts in induced sputum were recorded at baseline. Measurements were performed with the patients in stability and were considered as their personal best. Patients received optimal treatment with good compliance and were followed up for 1 year for asthma exacerbations occurrence. Evaluation of the effect of recorded parameters on asthma exacerbations was performed with univariate and multivariate Poisson regression analysis.

Results: 171 patients (118 female) with bronchial asthma (mean age 51.6 ± 13.2 years) were included in the study. The mean number of exacerbations in 1 year of follow up was 0.4 ± 0.8 while the majority of patients (71.9%) did not experience any exacerbation. In multivariate Poisson Regression analysis only 3 characteristics were predictors of future exacerbations: FEV₁ [IRR(95% CI)], [0.970(0.954–0.987)], $p = 0.001$, high BMI [1.078(1.030–1.129)], $p = 0.001$, and the need for permanent treatment with oral corticosteroids for asthma control maintenance [2.542(1.083–5.964)], $p = 0.032$

Conclusion: Optimal guideline-based asthma management results in minimal occurrence of exacerbations in the majority of patients. Predictors of exacerbations are low FEV₁ levels in stability, high BMI and the need for permanent treatment with oral corticosteroids.

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Asthma; exacerbations; biomarkers; exhaled nitric oxide; pulmonary function; body mass index

Introduction

Asthma is a heterogeneous disease characterized by chronic airway inflammation. It is defined by a history of respiratory symptoms, such as wheeze, shortness of breath, chest tightness, and cough, that vary over time and in intensity together with variable expiratory flow limitation [1]. Asthma prevalence has increased worldwide over the past decades [2], and it represents a major cause of disability, health-care utilization, and impairment of the patient's quality of life [3]. Although modern treatment of asthma improves asthma control, some patients still experience exacerbations [4]. Asthma exacerbations are associated with an accelerated decline in lung function [5], increased costs for the health-care system [6], and are the main cause of mortality in patients with asthma.

Several studies have examined factors associated with asthma exacerbations and have shown that patients more prone to experience an exacerbation are patients with more severe asthma who have a previous history of an exacerbation within the last 3 months [7], suffer from comorbidities (including severe

nasal sinus disease, gastroesophageal reflux, psychiatric disease, and obstructive sleep apnea) [8], are current smokers [9], or have impaired lung function [10]. Several biomarkers have been also evaluated as predictors of asthmatic exacerbations [11]. The early identification of asthmatic patients who are prone to exacerbations may provide an opportunity for more intensive treatment in order to reduce the risk of the occurrence of an exacerbation and improve the patient's health status and quality of life.

The aim of this prospective cohort study of patients with asthma treated in tertiary asthma clinics was to investigate the possible predictors of future exacerbation risk.

Methods

Study design

We included patients with previously diagnosed bronchial asthma, followed up in asthma clinics of two tertiary hospitals (1st Respiratory Medicine Department, University of Athens, Sotiria Hospital, Athens, Greece, and 2nd Respiratory Medicine

Department, University of Athens, 'Attikon' Hospital, Chaidari, Greece). In all patients, we recorded demographic and functional characteristics, smoking status, body mass index (BMI), and medication. Spirometric values, bronchial hyperresponsiveness (BHR), levels of fractional exhaled nitric oxide (FeNO), as well as inflammatory biomarkers and cell counts in induced sputum were also measured and recorded. All measurements were performed with the patients in stable condition and were considered as their personal best according to their personal records in the asthma clinics which included pulmonary function tests and Asthma Control Tests (ACTs).

All patients included in this study were receiving optimal treatment and were adherent to therapy as evaluated by their treating physicians and prescriptions of maintenance medication. Optimization of treatment was based on clinical and functional criteria and on the results of ACT. Diagnosis and treatment of asthma was based on the Global Initiative for Asthma guidelines [12]. Patients were characterized as having severe asthma according to the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines [13]. Patients with diagnosis of other respiratory disease; concomitant malignancy; or severe heart, liver, renal, or collagen disease were not included in the study. Patients were followed up for 1 year and asthma exacerbations were recorded. During the follow-up period, the patients were asked to contact the study investigators in case they experienced any symptom deterioration. Furthermore, telephone contacts were performed monthly and exacerbations were recorded. Finally, patients were evaluated every 3 months and optimization of treatment was performed according to the level of asthma control [1]. Adherence to therapy was evaluated by prescriptions in their personal records that are mandatory for the Greek National Health system. The study protocol was approved by the ethics committees of both hospitals and all subjects provided written informed consent.

Study measurements

Lung function, atopy, and bronchial hyperresponsiveness

Forced expiratory volume in 1 s (FEV₁) and forced vital capacity (FVC) were measured using Master Screen Body (Viasys Healthcare, Jaeger, Hoechberg, Germany) according to the ATS guidelines and was evaluated by asthma specialists [14]. Atopy was defined as the presence of a positive skin prick test to at least 1 out of 20 common aeroallergens. BHR was measured as PD15 to methacholine using a commercially available system (APS; Viasys Healthcare, Jaeger, Hoechberg, Germany) according to the ATS guidelines [15].

Sputum induction and processing

Sputum induction was performed as previously described [16,17], using all the modifications for safe measurements according to the underlying asthma severity [18,19]. The process had a total duration of 15 min, where subjects inhaled 3% saline at room temperature by an ultrasonic nebulizer (DeVilbiss Co., Heston, UK). Sputum supernatant was removed with centrifugation and total cell count was evaluated with a hemocytometer using trypan blue

stain. Slides were prepared by cytopsin (Shandon, Runcorn, UK) and were stained with May–Grunwald and Giemsa for differential cell counts. A blind observer performed counting of a minimum 500 inflammatory cells in each sample. Sputum samples were considered acceptable if they had a volume of at least 2 ml after final expectoration and the percentage of squamous cells on the prepared slides was <10%. Total cell count was expressed as the number of cells $\times 10^6$ /ml and sputum inflammatory cells as percentage of non-squamous cells. Sputum supernatants were kept at -70°C until measurement of the mediators.

Measurement of FeNO

FeNO was measured using a portable NO analyzer (NIOX MINO, Aerocrine, Solna, Sweden) [20]. MINO measurements performed at a fixed flow rate of 50 ml/s are expressed as parts per billion (ppb) and are in clinically acceptable agreement with measurements provided by a stationary analyzer according to the ATS guidelines [20–22].

Measurement of biomarkers in induced sputum

Levels of interleukin (IL)-13, IL-8, and eosinophilic cationic protein (ECP) were assessed in sputum supernatant using commercially available kits. ECP was measured using Unicap ECP kit (detection limit 0.5 ng/ml, Pharmacia Diagnostics, Uppsala, Sweden), while IL-13 and IL-8 were measured using enzyme-linked immunosorbent assay (ELISA) kits (R&D systems, Minneapolis, MN, USA).

Definition and recognition of an asthmatic exacerbation

During follow-up, asthmatic exacerbations were defined according to the ATS and the ERS task force [23]. According to this task force, exacerbations of asthma were events that were characterized by any of the following: (1) deterioration of symptoms outside the patient's usual range of day-to-day variability, (2) deterioration of lung function, (3) increased use of rescue medication for at least 2 days, (4) use of systemic corticosteroids and an increase from a stable maintenance dose for at least 3 days, and (5) hospitalization and emergency department visit because of asthma symptoms requiring systemic corticosteroids.

Statistical analysis

Categorical variables are presented as n (%), whereas numerical variables are presented as mean $\pm$ standard deviation (SD) or median (interquartile ranges) for normally distributed and skewed data, respectively. Normality of distributions was checked with Kolmogorov–Smirnov test. Comparisons between patients with and without exacerbations during follow-up were performed using chi-square tests for categorical data, as well as unpaired t -tests or Mann–Whitney U -tests for normally distributed or skewed numerical data, respectively.

Poisson regression univariate and multivariate analyses were performed in order to account for variability in exacerbation rates between patients [24]. The results are presented as incidence rate ratios (IRRs) with 95% confidence intervals

(CIs). Statistically significant variables in the univariate analysis were included in the multivariate analysis. Skewed data were logarithmically transformed for regression analyses. All p -values <0.05 were considered statistically significant. Data were analyzed using Statistical Program for Social Sciences (SPSS) 17.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Demographic, clinical, and functional characteristics of the 171 patients included to the study are presented in Table 1. Patients were divided into two groups: those who did not experience any asthmatic exacerbation in the 1 year of follow-up ($n = 123$) and those who did experience one or more exacerbations of asthma during this period of time ($n = 48$). The mean number of exacerbations in 1 year of follow-up was 0.4 ± 0.8 while the majority of patients (71.9%) did not experience any exacerbation.

Patients who experienced exacerbations had a greater BMI and more impaired lung function as expressed by lower FEV₁ % pred and lower FEV₁/FVC ratio. Regarding the results in induced sputum, patients experiencing asthma exacerbations had a higher percentage of eosinophils (median 5.3 vs. 2.0 [$p = 0.006$]) and higher levels of IL-13 and ECP in induced sputum supernatant. Finally, patients who experienced asthma exacerbations received in a greater percentage high doses of inhaled corticosteroids (56.3% vs. 18.7%; $p < 0.001$) and needed regular treatment with oral corticosteroids (47.9% vs. 9.8%; $p < 0.001$).

As shown in Table 1, patients who experienced exacerbations were more often suffering from severe asthma compared to those not experiencing exacerbations. Furthermore, patients with severe asthma expressed higher levels of biomarkers compared to those with non-severe asthma (Table 2).

In the univariate analysis, predictors of future exacerbations were low FEV₁ (%pred), high BMI, increased percentage of eosinophils in induced sputum, need for treatment with high doses of inhaled corticosteroids, need for regular treatment with oral corticosteroids, treatment with omalizumab, high levels of IL-13 and ECP in induced sputum, and ACT score. In the multivariate Poisson regression analysis, only three characteristics were predictors of future exacerbations: FEV₁ (IRR [95% CI] 0.970 [0.954–0.987], $p = 0.001$), high BMI (1.078 [1.030–1.129], $p = 0.001$), and the need for regular treatment with oral corticosteroids for maintenance of asthma control (2.542 [1.083–5.964], $p = 0.032$). Univariate and multivariate Poisson regression analyses are presented in Table 3.

Discussion

In the present study, we evaluated the clinical, functional, and inflammatory characteristics of asthmatic patients according to the development or not of an asthmatic exacerbation in 1 year of follow-up. Our results have shown that the majority of asthmatic patients receiving appropriate treatment in tertiary centers do not experience exacerbations. In this specific population, patients more prone to have an exacerbation of asthma are patients with low FEV₁ in stability, high BMI, and patients with severe asthma who require continuous treatment with oral corticosteroids for maintenance of asthma control.

Our results are in agreement with previous studies [10,25] which have shown that both low FEV₁ and high BMI were predictors of asthmatic exacerbations. Modern asthma treatment has resulted in the improvement of asthma control and a great reduction of exacerbations for the majority of asthmatic patients [26–30]. However, some patients with asthma

Table 1. Demographic and functional characteristics of the study subjects.

	All <i>N</i> = 171	Patients without asthma exacerbation <i>N</i> = 123	Patients with asthma exacerbation(s) <i>N</i> = 48	<i>p</i> -Value
Gender (female) <i>N</i> (%)	118 (69)	82 (66.7)	36 (75)	0.359
Age (years)	51.6 $\pm$ 13.2	51.4 $\pm$ 13.9	52.2 $\pm$ 11.6	0.974
BMI (kg/m ²)	27.0 (24.6, 30.0)	26.4 (24.0, 29.8)	28.0 (26.6, 31.8)	0.002
Smoking status (never/ex/current)	119/7/45	86/31/6	33/14/1	0.647
Pack years	0.0 (0.0, 14.0)	0.0 (0.0, 11.5)	0.0 (0.0, 30.0)	0.971
AE/patient/year	0.4 $\pm$ 0.8	N/A	1.6 $\pm$ 0.8	N/A
FEV ₁ (%pred)	75.0 (64.0, 91.0)	78.0 (70.0, 96.0)	65.0 (50.3, 75.5)	<0.001
FVC (%pred)	91.0 (79.6, 102.0)	93.0 (82.0, 106.0)	86.5 (71.5, 94.0)	<0.001
FEV ₁ /FVC	68.0 (62.0, 76.0)	70.0 (66.0, 77.0)	61.6 (56.3, 71.0)	<0.001
Atopy <i>N</i> (%)	90 (52.6)	65 (52.8)	25 (52.1)	0.929
BHR (PD15 [mg of metacholine])	0.16 (0.08, 0.29)	0.17 (0.09, 0.32)	0.11 (0.07, 0.26)	0.148
FeNO (ppb)	22.0 (16.0, 35.0)	21.0 (16.0, 32.0)	23.0 (16.3, 56.5)	0.213
Sputum Eo (%)	3.0 (0.0, 8.0)	2.0 (0.0, 6.0)	5.3 (1.3, 13.3)	0.006
Sputum Ne (%)	32.0 (20.0, 44.0)	31.5 (20.0, 42.0)	37.0 (21.0, 46.8)	0.122
Disease duration (years)	23.0 (15.0, 35.0)	23.0 (14.0, 34.0)	26.5 (19.5, 40.0)	0.259
High doses of ICS, <i>N</i> (%)	50 (29.2)	23 (18.7)	27 (56.3)	<0.001
Corticosteroids per os <i>N</i> (%)	35 (20.5)	12 (9.8)	23 (47.9)	<0.001
Treatment with omalizumab <i>N</i> (%)	11 (11.4)	5 (4.1)	6 (12.5)	0.052
Sputum IL-13 (pg/ml)	87.0 (68.0, 21.0)	78.5 (66.0, 104.3)	110.5 (77.8, 205.8)	<0.001
Sputum ECP (ng/ml)	1.1 (0.8, 1.9)	0.98 (0.78, 1.6)	1.5 (0.8, 2.5)	0.015
Sputum IL-8 (ng/ml)	1.2 (0.7, 2.8)	1.03 (0.65, 2.5)	1.9 (0.6, 3.0)	0.259
Severe asthma <i>N</i> (%)	48 (28.1)	23 (18.7)	25 (52.1)	<0.001
ACT	23 (21, 24)	23 (21, 24)	21.5 (19, 23)	0.002

BMI: body mass index; AE: acute exacerbations; FEV₁: forced expiratory volume in 1 s; FVC: forced vital capacity; BHR: bronchial hyperresponsiveness; FeNO: fractional of exhaled nitric oxide; Eo: eosinophils; Ne: neutrophils; ICS: inhaled corticosteroids; IL-13: interleukin 13; ECP: eosinophilic cationic protein; IL-8: interleukin 8; ACT: asthma control test.

Table 2. Differences in inflammatory biomarkers in patients with severe and non-severe asthma.

	Severe asthma	Non-severe asthma	p-Value
IL-13 (pg/ml)	145.0 (80.5, 237.0)	78.0 (65.8, 104.0)	<0.001
ECP (ng/ml)	1.5 (0.8, 2.9)	1.02 (0.78, 1.60)	0.021
IL-8 (ng/ml)	1.88 (0.70, 3.03)	0.98 (0.60, 2.40)	0.095
Sputum Eo (%)	4.3 (22.2, 50.8)	2.0 (0.0, 6.3)	0.005
Sputum Ne (%)	41.0 (22.2, 50.8)	31.5 (19.0, 40.0)	0.020
FeNO (ppb)	27.0 (20.3, 62.5)	21.0 (14.0, 28.0)	0.001

FeNO: fractional of exhaled nitric oxide; Eo: eosinophils; Ne: neutrophils; ICS: inhaled corticosteroids; IL-13: interleukin 13; ECP: eosinophilic cationic protein; IL-8: interleukin 8.

continue to experience exacerbations despite optimal treatment.

Previous studies have also found that both children and adult patients with asthma with low FEV₁ were at greater risk of experiencing asthmatic exacerbations [10,31]. Our results are in accordance with this observation. Patients who experienced asthmatic exacerbations during the follow-up period had more impaired lung function, while FEV₁ was an independent predictor of a future exacerbation in the multivariate Poisson regression analysis. This finding underlines the importance of performing pulmonary function tests in an outpatient setting in order to identify asthmatic patients who might be more prone to experience exacerbations. Patients with asthma who experience exacerbations are known to have more rapid lung function decline [32], and some patients might also develop fixed airflow obstruction [33]. This increased loss of lung function may plausibly be the result of the activation of inflammatory pathways that occurs during acute exacerbations and lead to airway remodeling [34].

In our study, we have shown that asthmatic patients receiving oral corticosteroids at a regular basis in order to achieve asthma control were more prone to exacerbations. Patients requiring oral corticosteroids for the achievement of asthma control are most likely to have severe asthma [13], and

patients with severe asthma are more prone to exacerbations, especially when they suffer from comorbid diseases [13]. Although we have excluded patients with significant comorbidities, we did not take into account mild comorbid diseases in our study patients. Furthermore, our patients at the time of inclusion to the study (performance of pulmonary function tests, sputum induction, and measurement of exhaled NO) were on stable condition with their asthma being controlled and all measurements were their personal best. According to the above, we can come to the conclusion that patients with severe asthma requiring oral corticosteroids for the achievement of control are more prone to exacerbations even when they receive optimal treatment.

Previous studies have shown that asthma exacerbations are more common in females than in males and that female asthmatic patients are twice as likely to be hospitalized for asthma compared to male asthmatic patients [35]. In our study, no difference was observed in exacerbation risk between genders; this discrepancy could be possibly explained by the fact that the majority of patients in our cohort (69%) were female. Furthermore, smoking status has been also recognized as an important risk factor for future exacerbations in asthmatic patients [9]. However, in our study, smoking history was not related to exacerbations. This might be due to the fact that the majority of our patients were never smokers.

Several studies have shown that there is an association between asthma and obesity [36]. Obese asthmatic patients experience more exacerbations which often are severe and require treatment in the emergency department or require hospital admission [7]. In our study group, patients who experienced asthma exacerbations had significantly greater BMI and BMI itself was a predictive factor of the development of exacerbations during the 1-year follow-up. Several mechanisms have been proposed by which obesity could be associated to exacerbations of asthma, including the production of

Table 3. Univariate and multivariate Poisson regression analyses for predictors of future asthma exacerbations.

	Univariate analysis			Multivariate analysis		
	IRR	95% CI	p-Value	IRR	95% CI	p-Value
Gender (female)	1.176	0.712–1.945	0.527			
Age (years)	0.999	0.982–1.016	0.879			
Smoking habit (current smokers)	2.800	0.374–20.974	0.316			
Pack years	0.995	0.985–1.006	0.389			
FEV ₁ (%pred)	0.952	0.940–0.964	<0.001	0.9370	0.954–0.987	0.001
FeNO (ppb)	1.006	1.000–1.011	0.058			
BMI (kg/m ²)	1.060	1.018–1.104	0.005	1.078	1.030–1.129	0.001
BHR (PD15 [mg of metacholine])	1.181	0.011–3.074	0.237			
Atopy	1.054	0.672–1.653	0.818			
Sputum Eo (%)	1.025	1.009–1.040	0.001	1.010	0.978–1.043	0.541
Sputum Ne (%)	1.005	0.993–1.017	0.393			
Disease duration (years)	1.010	0.995–1.026	0.188			
High dose of ICS (No)	0.215	0.134–0.345	<0.001	0.699	0.225–1.169	0.537
Need for CS peros (Yes)	5.641	3.570–8.913	<0.001	2.542	1.083–5.964	0.032
Omalizumab (No)	0.454	0.233–0.882	0.020	1.014	0.486–2.117	0.970
Sputum IL-13 (pg/ml)	1.005	1.002–1.007	0.001	0.998	0.994–1.003	0.456
Sputum ECP (ng/ml)	1.346	1.168–1.551	<0.001	1.096	0.861–1.396	0.457
Sputum IL-8 (ng/ml)	1.083	0.933–1.257	0.294			
ACT	0.869	0.808–0.935	<0.001	0.923	0.812–1.049	0.220
Severe asthma	3.720	2.354–5.878	<0.001	1.515	0.606–3.792	0.374

FEV₁: forced expiratory volume in 1 s; FeNO: fractional of exhaled nitric oxide; BMI: body mass index; BHR: bronchial hyperresponsiveness; Eo: eosinophils; Ne: neutrophils; ICS: inhaled corticosteroids; CS: corticosteroids; IL-13: interleukin 13; ECP: eosinophilic cationic protein; IL-8: interleukin 8; ACT: asthma control test; IRR: incidence rate ratios.

pro-inflammatory cytokines and chemokines (i.e. eotaxin, leptin, IL-6, and TNF- α) [37]. Interestingly, and besides the fact that our patients who experienced exacerbations had increased biomarkers related to eosinophilic inflammation, no single biomarker was related to exacerbations in the multivariate Poisson regression analysis.

Patients prone to exacerbations had higher levels of eosinophils in induced sputum and higher levels of biomarkers indicating eosinophilic inflammation (such as ECP and IL-13), although neither the number of eosinophils nor IL-13 levels were independent predictors of future exacerbations. Both eosinophil and neutrophil numbers in induced sputum show wide variability in severe asthma and some patients continue to have high levels of eosinophils despite treatment with systemic corticosteroids [38]. Furthermore, in our study, patients with severe asthma had higher levels of inflammatory biomarkers including eosinophil levels in induced sputum compared to patients with non-severe asthma. Our results are generally in accordance with the findings of the U-BIOPRED (Unbiased BIOMarkers in PREdiction of respiratory disease outcomes) adult severe asthma cohort [39], in which patients with severe asthma expressed higher levels of sputum eosinophils. An important difference of our study is that sputum eosinophils were not an independent predictor of a future exacerbation and this finding was opposed to the findings of Price et al. showing that high blood eosinophil count increased the likelihood of two or more exacerbations in patients with asthma [40]. However, eosinophilic inflammation even in patients with severe asthma varies with time [41] and this may be the reason that it is not related to exacerbation susceptibility in our group of patients.

Although several studies have shown that FeNO might serve as a useful biomarker for the prediction of alterations in a patients' level of asthma control [42–44] and that sputum eosinophils are a useful tool for treatment guidance in order to achieve the asthma control and reduce exacerbation rate [45–47], in our study, neither FeNO level nor sputum eosinophil count was a predictor of future exacerbations. However, both measurements took place only at baseline and were not repeated during the patient's follow-up. It is known that when used for the guidance of therapy, measurements of both FeNO and sputum eosinophils should be repeated in several intervals in order to monitor the level of airway inflammation. Alterations of these biomarkers beyond what is known as the patient's personal best (for FeNO) [28,42,43] and a low level (usually <3%) for sputum eosinophils have been shown to be related to the level of asthma control. The absence of follow-up of our patients using repeated measurements of these biomarkers may be a reason for the fact that they were not predictors of an exacerbation in our study subjects. Furthermore, the single measurement of these biomarkers was performed upon their inclusion in the study when they were optimally treated.

Interestingly, although omalizumab is prescribed in patients with severe uncontrolled allergic asthma who usually experience exacerbations despite high doses of ICS [1,13], in our groups of patients, there was no difference between patients treated or not with omalizumab. A possible explanation for that is the fact that all patients were receiving optimal

treatment. Patients with severe asthma not treated with omalizumab were those who did not fulfill the criteria for this treatment or failed to show any improvement after drug initiation for at least 4 months [1]. The improvement of asthma control together with the reduction in asthmatic exacerbations in patients receiving treatment with omalizumab might be the reason why this treatment at baseline is no longer a predictor of future asthma exacerbations.

Our study has several limitations. First, our results are in line with previous literature, but this is a real life study confirming the clinical significance of some basic characteristics of asthmatic patients as predictors of future exacerbation and helps clinicians to identify patients at risk without the use of demanding, expensive, and difficult to obtain biomarkers. Furthermore, some of our patients were current or ex-smokers with a significant smoking history (i.e. > 10 pys). This, in combination with the low values of both FEV₁ and FEV₁/FVC (<70) in some patients, raises questions on whether these patients are asthmatic patients with fixed airway obstruction or patients with the so-called asthma-Chronic Obstructive Lung Disease (COPD) overlap syndrome (ACOS). However, in our study, the diagnosis of asthma was made in the asthma centers of two tertiary hospitals from experts with long-standing experience in asthma management who have excluded a diagnosis of COPD or a COPD component that would justify a diagnosis of ACOS.

Conclusion

In conclusion, the majority of patients with controlled asthma followed up in tertiary asthma clinics do not experience exacerbations in a 1-year follow-up. In this population, patients more prone to asthma exacerbations are those with low FEV₁, high BMI, and those who require systemic corticosteroids for the achievement of asthma control. The identification of such patients possibly represents a need for more intensive or additional treatments that might reduce the risk of future exacerbations and improve patients' health status and quality of life.

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Declaration of interest

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