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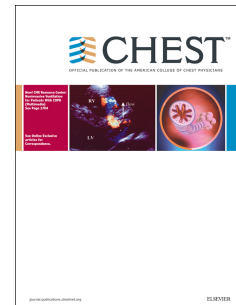
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Eosinophilic Granulomatosis with Polyangiitis: clinical predictors of long-term asthma severity.

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ABSTRACT

Background: The long-term clinical course of asthma in patients with Eosinophilic Granulomatosis with Polyangiitis (EGPA) remains unclear. We aimed to characterize long-term asthma in EGPA and to identify baseline predictors of long-term asthma severity.

Methods: Retrospective cohort study of patients who fulfilled standardized criteria for EGPA that were followed in a single referral center between 1990-2017. Baseline and 3 (± 1) years of follow-up clinical, laboratory and pulmonary function data were analyzed.

Results: Eighty-nine patients with EGPA, and a documented asthma assessment at baseline and at 3 years from diagnosis were included. Severe/uncontrolled asthma was observed in 42.7% of patients at diagnosis and was associated with previous history of respiratory allergy ($p < 0.01$), elevated serum total IgE levels ($p < 0.05$), increased use of high dose inhaled (ICS; $p < 0.05$) and oral corticosteroids (OCS; $p < 0.001$) for respiratory symptoms the year before the diagnosis of EGPA. During follow-up, an improvement or worsening in asthma severity was noted in 12.3% and 10.1% of patients, respectively. Severe/uncontrolled asthma was present in 40.5% of patients at 3 years, and was associated with increased airway resistance on pulmonary function testing ($p < 0.05$). Long-term PFTs did not improve during long-term follow-up regardless of ICS or OCS therapy. Using multivariate binary logistic regressions, severe rhinosinusitis ($p = 0.038$), pulmonary infiltrates ($p = 0.011$), overweight ($\text{BMI} > 25 \text{ kg/m}^2$; $p = 0.041$) and severe/uncontrolled asthma at vasculitis diagnosis ($p < 0.001$) independently predicted severe/uncontrolled asthma at the 3-year endpoint.

Conclusion: In asthmatic patients with EGPA, long-term severe/uncontrolled asthma is associated with baseline pulmonary and ENT manifestations, but not with clear-cut vasculitic features.

KEYWORDS: Severe/uncontrolled asthma; Asthma; eosinophilic granulomatosis with polyangiitis; EGPA; Churg-Strauss; ANCA-associated vasculitis;

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INTRODUCTION

Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare, small-vessel systemic necrotizing vasculitis, usually presenting with late-onset asthma and sustained peripheral blood eosinophilia (1–4). The clinical-pathologic spectrum ranges from hypereosinophilia driven manifestations, with eosinophilic organ infiltration, to vasculitic small vessel inflammation (5–7). Anti-neutrophil cytoplasmic antibodies (ANCA) are detected in about 40% of patients (7).

EGPA commonly presents with upper and lower airway involvement, including rhinosinusitis, asthma and migratory pulmonary infiltrates (8). An increase in asthma severity has been reported to occur in the months prior to the onset of eosinophilic manifestations (5), then systemic necrotizing vasculitis typically develops years later (5,8,9). After remission of vasculitis, severe refractory asthma tends to remain, associated with persistent airflow obstruction in up to 50% of EGPA patients (5,10). Thus, asthma management constitutes a major challenge, often requiring long-term oral corticosteroid (OCS) therapy (5,10)(11)(12)(13).

Early identification of patients likely to need long-term OCS therapy who would potentially benefit from early initiation of adjuvant OCS-sparing therapy would be clinically relevant. Therefore, we conducted the present study to: (i) characterize long-term asthma features in a cohort of EGPA patients and (ii) identify the baseline clinical and serological predictors of long-term severe/uncontrolled asthma.

MATERIAL AND METHODS

Study design and case ascertainment

Data were retrieved from January 1, 1990 to August 1, 2017. For inclusion, subjects needed to meet the criteria of at least one of three EGPA classification schemes: American College of Rheumatology (ACR) classification criteria (14), Chapel Hill Consensus Conference (CHCC) definition (1), or Lanham criteria (15). Subjects were included only if there was information that allowed the assessment of asthma severity at baseline and after 3 (± 1) years of follow-up. Those with allergic bronchopulmonary aspergillosis were excluded.

Information on patient demographics, clinical manifestations, laboratory findings, histopathology, pulmonary function tests, allergy testing, radiology, and disease activity at baseline and during follow-up were abstracted from the medical record. Baseline data for asthma and rhinosinusitis was taken from the closest time-point available in the year prior to diagnosis and initiation of treatment for EGPA. The long-term data was taken from the closest time-point to the 3rd year of follow-up after vasculitis diagnosis (range 2-4 years). Asthma assessment, pulmonary function tests (PFT), inhaled corticosteroids (ICS) and oral corticosteroids (OCS) dose were collected at baseline and at long-term follow-up evaluation. ICS doses were converted to standard beclomethasone dipropionate potency equivalents, and categorized for the purposes of statistical comparisons between groups, according to guidelines (16): low dose (200-500 daily micrograms), medium dose (500-1000 daily micrograms), and high dose (>1000 daily micrograms). All patients were followed until August 1, 2017, or death. Patients were treated according to the treating physician's assessment, as published by this group (3).

The study was conducted according to STROBE guidelines (STrengthening the Reporting of Observational Studies in Epidemiology) for cohort, case-control, and cross-sectional studies. This study

was conducted in compliance with the Good Clinical Practice protocol and the Declaration of Helsinki principles and was approved by the local Institutional Review Board (number 18-000486).

Definition of outcomes and variables

Severe/uncontrolled asthma - Subjects had to meet one major and two minor criteria as per the 2000 ATS Workshop on Refractory Asthma (17). Major criteria: 1/continuous or near-continuous OCS ($\geq 50\%$ of the previous year) or 2/high-dose ICS in the previous year. Minor criteria: requirement for an additional daily controller medication; asthma symptoms requiring SABA on daily or near daily basis; persistent airway obstruction (Forced expiratory volume in 1 second [FEV1] $< 80\%$ predicted, with FEV1/forced vital capacity [FVC] less than the lower limit of normal; diurnal peak expiratory flow variability $> 20\%$); three or more OCS bursts or prompt deterioration with less than 25% reduction in OCS or ICS dose in the previous year; one or more urgent care visits for asthma or, near fatal asthma event (≥ 1 hospitalization, intensive care unit stay or mechanical ventilation) in the previous year.

Allergic asthma and/or rhinitis/rhinosinusitis -at least one documented positive skin prick test and/or serum specific IgE for aeroallergens in association with a compatible clinical history (6), and/or the report in clinical notes of a previous documented allergic asthma or rhinitis/rhinosinusitis.

Asthma relapse -an increase or recurrence of asthma symptoms, based on the treating physician's documentation, requiring therapeutic adjustment (ICS, OCS or intravenous corticosteroids).

"*Vasculitis manifestations*" of EGPA were predefined definite vasculitis features or surrogates of vasculitis (18); manifestations likely related to eosinophilic organ infiltration without clear evidence of vascular inflammation were not included in this definition.

Vasculitis was defined as severe at diagnosis if *Five Factor score (FFS)* scored equal or greater than 1, (19). *Severe chronic rhinosinusitis* was rhinosinusitis lasting for ≥ 12 weeks and requiring sinus surgery to control nasal polyps and/or reduce symptoms (≥ 1 surgery).

Clinical vasculitis remission - Absence of vasculitic manifestations for at least three consecutive months.

Systemic/vasculitis relapse - Recurrence or worsening of a systemic/vasculitic manifestation following a remission of at least 3 months, and/or the need to resume/increase corticosteroid therapy (daily dose of oral or intravenous corticosteroids) or initiate immunosuppressive therapy for clinical manifestations of EGPA other than asthma.

Pulmonary function test measurements

Spirometry was performed in triplicate in accordance with ERS guidelines (20). The severity of pulmonary obstruction was graded according to the official ATS/ERS guidelines (21). When obstruction was present, bronchodilator responsiveness was tested with repeat spirometry after the inhalation of a short-acting bronchodilator (albuterol 180 mcg administered through a spacer) to test reversibility ($FEV_1 \geq 12\%$ and ≥ 200 ml) (21). Lung volumes (Total lung capacity, TLC, and Residual Volume, RV) and Diffusing capacity of lung for carbon monoxide (DLCO) were measured and interpreted according to international guidelines (20,21).

Statistical analysis

Data are presented as means with standard deviations (SD) if normally distributed, or medians with interquartile range (IQR) if skewed. Categorical data were analyzed using the X^2 test or Fisher exact

tests; continuous variables using t test or Mann–Whitney test, when appropriate. For the comparison among the asthma patterns, categorical characteristics were compared by using χ^2 or Fisher exact tests; continuous parametric data were analyzed with a two-way ANOVA; non parametric data were log-transformed for this analysis (z score). Bonferroni correction was used when more than 2 means were being compared.

A logistic regression model was used to establish the predictors of severe/uncontrolled long-term asthma. Variables that presented a p-value <0.20 in the univariate analysis were included in the multivariate model performed using a backward stepwise method. Continuous variables were dichotomized based on median values for compelling the criteria required for this analysis. The odds ratio (OR) with a 95% confidence interval (CI) was presented when appropriate. A p-value of <0.05 was considered statistically significant. Analyses were performed using JMP Pro package (SAS Institute Inc., Cary, North Carolina).

Cross-validation of the linear regression model

To cross-validate this model, we built an additional classifier, as previously described (22). We adopted the Scikit-learn (23), version 0.20.3 python library implementation of random forest (24) as implemented in the tool MetAML (25), a python framework for machine learning originally developed for metagenomics research. The ability of this model to predict long-term severe compared to non-severe asthma in patients with EGPA was therefore quantified by a 1000 times iterated 10-fold cross-validation, and the resulting receiver operating characteristic (ROC) curve was averaged. The MetAML (25) randomly stratifies the dataset in 10 groups (10-fold), automatically balanced by the main outcome (i.e. relative frequency of subjects with severe long-term asthma). We used 90% of the study population for training and the remaining 10% for testing at each cross-validation iteration (default).

The procedure of forming the folds and assessing the models was repeated 1000 times (22). The scoring index chosen was the area under the curve with standard deviation ($AUC \pm S.D.$; 10000-iterations averaged).

RESULTS

Patient characteristics

We identified 187 individuals with EGPA, evaluated at our institution from 1990-2017. Eighty-nine individuals (47.6%) had data assessing asthma at baseline and the 3 year follow-up, and were evaluated further (**e-Figure 1**). There were no asthma related deaths in this cohort during this time period. Two additional patients with complete baseline asthma assessment were excluded because of death, unrelated to EGPA at 8 and 19 months after diagnosis, respectively.

Baseline clinical, laboratory and pulmonary physiology features of this cohort are shown in **Table 1**. The mean age was 51.4 (± 15.9), 47% were female, and 97% were Caucasian. At baseline, 38 (42.7%) subjects had severe/uncontrolled asthma defined as per the 2000 ATS Workshop on Refractory Asthma (17). At the 3 year follow-up, 36 (40.5%) subjects had severe/uncontrolled asthma. A previous history of allergic rhinitis/rhinosinusitis and/or allergic asthma was associated with baseline severe asthma (63% versus 31%, $p=0.003$), and median serum IgE levels were approximately double in patients with severe asthma versus those without ($p=0.017$). Other baseline clinical and spirometry features were similar in both groups. Demographic, clinical features and asthma severity of subjects excluded for insufficient data were similar to those of subjects included (**e-Table 1**).

Asthma treatment at baseline

At baseline, the majority of patients received daily ICS for asthma (67/87, for 2 subjects this data was not reported), and over half received a LABA, with no significant difference between the two groups (**e-Figure 2**). High dose ICS were used more in the severe asthma group, compared to non-severe group (55% versus 30%, $p=0.025$), as expected. Forty-nine patients (57%) were on OCS in the year

before their diagnosis of vasculitis (85% in the severe asthma group and 38% in the non-severe group, $p<0.001$), although the mean dosage of OCS did not significantly differ between the two groups ($p=0.663$). No subjects were on immunosuppressants at the time of initial asthma assessment. During the year preceeding the EGPA diagnosis, two subjects received anticholinergic drugs, 5% received omalizumab, and 39% antileukotrienes, with no statistical difference between the two groups ($p>0.05$).

Vasculitis treatment during follow-up

The cumulative frequency of drugs used during the 3 years of follow-up are reported in **Table 2**. Treatment approach to vasculitis was standardized; all subjects received systemic corticosteroids for their vasculitis. Remission-induction treatment with cyclophosphamide and other disease modifying immunosuppressants was reserved for severe manifestations, and all with a FFS ≥ 1 at EGPA diagnosis were treated with an additional immunosuppressant. After vasculitis remission, OCS was reduced to the lowest dosage as soon as possible. Overall, no difference among the two asthma groups was observed ($p>0.05$ for all comparisons).

Asthma course and treatment during follow-up

Severe asthma was present in 42.7% subjects at baseline and in 40.5% at long-term follow-up. Although the overall proportion of subjects with severe/uncontrolled asthma remained approximately the same at baseline and follow-up, 22.4% of subjects had a change in asthma severity/control (**Figure 1**): 10.1% with non-severe asthma at baseline developed severe asthma, while 12.3% with severe/uncontrolled asthma at baseline improved. After correction for multiple comparisons, those with persistent non-severe asthma were less likely to have a history of respiratory allergy ($p=0.003$), and

higher baseline IgE levels correlated with severe asthma at baseline, which then improved ($p=0.013$). Neither vasculitic features (**e-Table-2**), nor systemic immunosuppressive treatments correlated with asthma clinical course (**e-Table 3**).

In the group with severe/uncontrolled asthma at baseline, no difference of inhaled therapy and OCS between baseline and long-term follow-up were observed (**e-Figure 3 A-B**). In the group that had non-severe asthma at baseline (**e-Figure 3 C-D**), a significantly higher proportion of subjects were on a LABA ($p=0.017$) and OCS at final follow-up versus baseline ($p<0.001$).

Serial pulmonary function data during follow-up

Forty-seven patients had pulmonary physiology data available at baseline, but only 36 had these data available for both baseline and long-term follow-up. Of those 36, 47.2% had severe/uncontrolled asthma at baseline. Overall, FEV1/FVC and FEV1 values did not significantly change over the study (**Figure 2**). In subjects with severe/uncontrolled asthma at baseline ($n=17/36$), there was a downward trend in FEV1/FVC ratio and FEV1 in follow up (Δ FEV1/FVC predicted (mean (SD): -8.79% (3.93), $p=0.040$) and of Δ FEV1% (-4.00% (2.99), $p=0.199$)), while they remained essentially stable in those without severe/uncontrolled asthma (**e-Table 4**). All patients required systemic corticosteroids for EGPA during the course of the disease. At long-term follow-up, 26/36 (72%) were on OCS for asthma, and 32/36 (89%) were on ICS with or without LABA, in fairly similar proportions in both groups ($p=1.000$). Although this analysis includes only a small subset of the whole cohort, it suggests that pulmonary function does not improve during long-term follow-up, regardless of OCS or ICS treatment.

Asthma characterization at final long-term follow-up

Pulmonary physiology measure were available for a greater number of patients at final follow-up (80%, n=71) (**Figure 3, panel A**). The distribution of asthma severity (based on ATS workshop criteria) was similar for those in whom we did and did not have PFT data available. Eighty-one % of the group with severe/uncontrolled asthma at long-term follow-up had bronchial obstruction on spirometry, compared to 50% of the non-severe/controlled asthma group ($p=0.008$; **Figure 3, panel B and C**). Fifty-two percent of patients with severe/uncontrolled asthma had mild or moderate bronchial obstruction, compared to 90% in non-severe/controlled asthma group ($p=0.009$; **Figure 3**). Bronchodilator responsiveness (in those patients with bronchial obstruction), static lung volumes (TLC, RV) and DLCO were not statistically different between the two categories ($p>0.05$ in all comparisons). In those with severe/uncontrolled asthma the mean BMI collected concomitantly with the spirometry tests was higher (30.7 kg/m² versus 26.1 kg/m², $p=0.003$) (**Table 3**). They also had higher airway resistance, and a lower mean FEV1/FVC ratio (x100) and mean FEV1 (% predicted) (both $p<0.05$).

Baseline predictors of long-term severe/uncontrolled asthma in EGPA

Variables that were associated ($p<0.20$) with severe/uncontrolled asthma after 3 years of follow-up in univariate analysis (**Table 4**) or recognized risk factors were included in the multiple binary logistic regression analysis. The independent predictors of long-term severe/uncontrolled asthma included: severe/uncontrolled asthma at baseline (OR 10.64, 95% CI: 3.43-39.08), pulmonary infiltrates (OR 5.16, 95% CI: 1.43-21.85, $p=0.011$), severe rhinosinusitis (OR 3.57, 95% CI: 1.07-13.55), and an overweight (BMI ≥ 25 kg/m²; OR 3.41, 95% CI: 1.05-12.90, $p=0.041$). In a sensitivity analysis, using a

higher BMI consistent with obesity (≥ 30 kg/m²); the model confirmed the relevance of the identified predictors (severe/uncontrolled asthma at baseline, pulmonary infiltrates, severe rhinosinusitis), while obesity showed a trend approaching statistical significance ($p=0.094$).

Validation analysis

The ability of this model (four predictor-model: baseline severe/uncontrolled asthma, pulmonary infiltrates, severe rhinosinusitis, and an overweight) to distinguish severe from non-severe long-term asthma in EGPA was cross-validated by random forest classification model, with the characteristic ROC curve (**Figure 4**). The model identifying the long-term predictors of asthma severity in EGPA showed an AUC $\pm$ SD of 0.85 ± 0.13 when trained and tested 1000 times in a 10-fold iterated cross-validation, consistently supporting the predictive power of the described baseline predictors.

DISCUSSION

Our findings show that severe/uncontrolled asthma is present in more than 40% of patients with EGPA at vasculitis diagnosis, and associates with a previous history of respiratory allergy, higher serum IgE levels, and increased use of high dose ICS and OCS for respiratory symptoms. During follow up, severe/uncontrolled asthma persists in about 40% of patients after 3 years from diagnosis. Approximately 12% of patients improve asthma severity during the course of the disease, while about 10% with non-severe/controlled asthma worsen; baseline features of these patients are substantially similar to those of patients whose asthma severity did not change. Overall, pulmonary function does not improve during long-term follow-up regardless of ICS and OCS therapy; subjects with long-term severe/uncontrolled asthma showed more frequent and more severe airflow obstruction, suggesting that either asthma treatment is not effective or airway remodeling has already occurred after the resolution of vasculitis. Finally, severe rhinosinusitis, pulmonary infiltrates, being overweight (i.e. defined as a baseline BMI > 30 kg/m²) and having severe/uncontrolled asthma at presentation are the only factors that are independently associated with severe/uncontrolled long-term asthma, while no other factors and particularly any of the characteristic manifestations of overt vasculitis associate with it. All of these findings highlight the importance of the question of how to optimize asthma treatment in EGPA patients, and the need to identify early predictors of long-term asthma severity.

Appropriate asthma management is one of the main clinical unmet needs of EGPA (5,10,16). Airway obstruction did not substantially improve despite corticosteroids in these patients during follow-up, while after 3 years from EGPA diagnosis the proportion of patients with detectable bronchial obstruction and severe obstruction were higher in those with severe/uncontrolled asthma. More than half of those patients with airway obstruction were not responsive to bronchodilator on spirometry. Overall, it is tempting to speculate that chronic damage induced by eosinophils is already established in

most of the patients when a diagnosis of EGPA is made, likely as the result of a long history of eosinophilic asthma. We analyzed the median time between asthma and EGPA diagnosis and did not observe any significant difference in the four asthma patterns. This theory may be further supported by the fact that bronchodilator reversibility (tested with PFTs) was overall quite low in the whole cohort, suggesting an advanced airway remodeling. Indeed, this irreversible structural change of bronchial trees may have increased airway obstruction and impacted long-term pulmonary function. Chronic airway changes in eosinophilic asthma are thought to be mediated primarily by eosinophils, infiltrating bronchial tissues and inducing subepithelial fibrosis, myofibroblast proliferation and mucous gland hyperplasia, while systemic vasculitis is thought to be the result of activation of a more broad inflammatory cascade (involving lymphocytes and neutrophils), ultimately leading to leukocytoclastic vascular inflammation. Hence, while systemic immunosuppressive treatments may be effective on the leukocytoclastic vasculitis component, improving the systemic manifestations of the diseases, they may not be effective in treating eosinophilic airway inflammation. This has been the rationale for the recent MIRRA trial, exploring the role of anti-IL-5 therapy in asthma. Of note, during the time-period of our study, only 1 patient received an anti-IL5 agent, mepolizumab, and thus the potential implications of mepolizumab treatment on longitudinal asthma severity in EGPA could not be assessed.

Early predictors of long-term severe asthma in EGPA were never systematically analyzed in any other study. Severe/uncontrolled asthma during the year before the diagnosis of vasculitis was the most important predictor of long-term asthma severity, confirming a small study showing that bronchial asthma of pre-EGPA patients was severe and frequently complicated by sinusitis at the first hospital visit before the onset of EGPA (26). Among the more traditional risk factors associated with eosinophilic asthma (16,27,28), we observed higher BMI higher baseline asthma severity and severe associated rhinosinusitis. A growing body of literature showed that obesity is a risk factor for asthma, found a positive correlation between baseline BMI and the subsequent development of asthma, and

found that weight loss improves asthma course (16,27,28). Several patients in our cohort were already on OCS at the time of baseline assessment, which could have contributed to their baseline BMI. However a growing body of literature has shown that obesity is a risk factor for asthma, finding a positive correlation between baseline BMI and the subsequent development of asthma, and finding that weight loss improves asthma course (16,27,28). Overall, obesity can reduce pulmonary compliance, lung volumes, and is associated with small airways disease (29) (30).

We found pulmonary infiltrates to be an independent predictor in our EGPA cohort. Similarly, a report of 31 asthmatic patients with EGPA showed that those with severe asthma had a significantly higher incidence of airway abnormalities than the group with mild to moderate asthma (31). Surprisingly, our findings indicate that some well-known risk factors of severity in the general asthma population such as smoking, female sex, older age and blood eosinophilia (16,27,28), did not predict asthma severity in EGPA. Thus, our results confirm and further expand on the published data on asthma severity derived from smaller EGPA cohorts (6,10,31). Respiratory allergy was not a predictor of long-term asthma severity/control, suggesting that the presence of atopy might influence the severity of asthma prior to and independently of the diagnosis of EGPA (6), while in the long term, when bronchial damage is already established, its impact is no longer significant. Finally, no disease manifestations or laboratory markers clearly attributable to vasculitis were identified as factors associated with asthma severity or prognosis. Taken altogether, this suggests that severe asthma in patients with EGPA shares several, but not all, predictors with severe asthma in patients without EGPA, and establishes that the severity and course of asthma are independent of the vasculitis of EGPA.

Of note, this model assessing long-term severe asthma predictors in EGPA showed a good AUC (0.85) when trained in cross-validation, highlighting the validity and reproducibility of the predictors identified by multivariable linear regression. The power for detecting the difference in the outcome was

high, while predicting long-term asthma severity in such cases is clinically challenging. EGPA is a rare disease in which the asthma component has been largely neglected, possibly because most of the published analyses have been conducted by rheumatologists or internists rather than by allergists or pulmonologists. As a consequence, data on asthma severity have not been collected consistently, and a different similar-size group of patients with EGPA and complete asthma assessments at baseline and during long-term follow-up that could serve as a validation cohort will be hard to find. Therefore, we decided to perform another well-accepted cross-validation approach (22). The tool we adopted was originally developed for the application of classification model to the shotgun metagenomics (i.e. up to thousands of features at the same time, in dozens to hundreds of samples), is adaptable to any set of features or clinical conditions, and has been used in cohorts of similar or smaller size than the one of the present study (22).

The strengths of this study assessing long-term asthma in EGPA include the fact that it is a monocentric cohort, and patients with EGPA were principally managed by pulmonologists, allowing for more robust collection of respiratory data and harmonization of the standard clinical management of patients' asthma. Second, all the patients included in this paper fulfilled at least one of the accepted classification criteria for EGPA vasculitis (1,14,15), allowing a more precise identification of the study population as opposed to previous studies assessing respiratory manifestations of EGPA, which included *forme fruste* disease (5). Third, all baseline asthma data was collected prior to a diagnosis of vasculitis, when corticosteroids were being prescribed for the diagnosis of asthma alone.

An additional strength of this study is that the findings were robust to the validation analysis, suggesting good reproducibility and accuracy as a prediction model for severe asthma in EGPA.

Our study has several limitations. There was a lack of data on treatment compliance and cumulative dosage of OCS used, a problem with most retrospective studies published on this topic. Although

ascertainment bias, classification error, survivor treatment selection and other biases cannot be completely excluded, clinical and asthma features of those patients that have been excluded for insufficient data were similar to those of the patients included, minimizing the possibility of a selection bias. Furthermore, asthma severity was assessed by the treating physician, in most –but not all cases– supported by PFT studies (80%), with the potential risk of over- or under-diagnosis. It can be difficult to firmly establish what symptoms corticosteroids are treating in EGPA cohorts, a concern in randomized control trials as well as retrospective studies.

The definition of asthma, per se, remains clinically based, dependent on appropriate symptoms and on the response to bronchodilators. This general definition of asthma makes precise definitions of severe asthma even more difficult. In the last 20 years, an important effort by international scientific societies has been made to classify asthma severity, to promote unified approaches to the disease in clinical practice and research (16,17,32–34). The latest, most precise criteria to classify severe/uncontrolled asthma from the ERS/ATS (European Respiratory Society/American Thoracic Society) (16), include variables that are not systematically collected by physicians in routine clinical practice, as for instance Asthma Control Questionnaire and the Asthma Control Test scores. Hence, for this study assessing the long-term asthma severity we utilized the fairly similar working definition of severe/uncontrolled asthma proposed by ATS Workshop (17), which is based on information usually reported in clinical charts, allowing a more exhaustive case detection of patients with severe/uncontrolled asthma and widely used in large multicentric international databases (32,35).

In conclusion, approximately 40% of EGPA patients had severe/uncontrolled asthma at baseline and during follow-up. Overall, pulmonary function did not improve during long-term follow-up regardless of ICS and OCS therapy, and patients with severe/uncontrolled asthma show a higher proportion of

bronchial obstruction and more severe airway resistance in the long-term follow-up. Severe rhinosinusitis, pulmonary infiltrates, being overweight and having severe/uncontrolled asthma at presentation, independently predicted severe/uncontrolled long-term asthma, but vasculitic disease manifestations did not.

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AUTHOR CONTRIBUTIONS:

The authors have no financial or non-financial potential conflicts of interest to declare related to this project. Dr. Berti, Dr. Casal Moura, Dr. Smith and Dr. Cornec acquired the data. Dr. Berti and Dr. Keogh conceived the study, while Dr. Berti, Dr. Cornec, Dr. Dagna and Dr. Sepcks designed the study. Dr. Berti and Dr. Keogh had full access to all of the data in the study and takes responsibility for the integrity of the data; Dr. Berti takes responsibility for the accuracy of the data analysis and drafted the article. All the authors were involved in the writing and editing of the manuscript, and approved the final version to be published

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FIGURE LEGENDS

Figure 1. Severe/uncontrolled asthma in subjects with eosinophilic granulomatosis with polyangiitis.

At baseline, 38 (42.7%) patients had severe/uncontrolled asthma, after 3 (± 1) years from diagnosis, 36 (40.5%) had severe/uncontrolled asthma. Four asthma patterns based on its clinical course during follow-up were identified: 30.4% of patients had persistent severe/uncontrolled asthma, 12.3% had an improving asthma pattern, 10.1% had a worsening asthma pattern, and 47.2% had persistent non-severe/controlled asthma.

Footnotes: Severe/uncontrolled asthma was defined as per the 2000 ATS Workshop on Refractory Asthma (22). These criteria were as follows: subjects had to have one of the following major criteria: 1/continuous or near-continuous OCS ($\geq 50\%$ of the previous year) or 2/high-dose ICS in the previous year and 2 of the following minor criteria: requirement for an additional daily controller medication; asthma symptoms requiring SABA on daily or near daily basis; persistent airway obstruction (Forced expiratory volume in 1 second [FEV1] $< 80\%$ predicted, in the face of reduced FEV1/forced vital capacity [FVC] defined as less than the lower limit of normal in the previous year; diurnal peak expiratory flow variability $> 20\%$ in the previous year); three or more OCS bursts in the previous year; prompt deterioration with less than 25% reduction in OCS or ICS dose in the previous year; one or more urgent care visits for asthma in the previous year or, near fatal asthma event (≥ 1 hospitalization, intensive care unit stay or mechanical ventilation) in the previous year.

Figure 2. Pulmonary function in subjects with eosinophilic granulomatosis with polyangiitis.

Forty-seven patients had had pulmonary physiology data available at baseline and 71 after 3 years of follow-up; of those, 36 had these data available for both time points (connected by solid lines in the figure). Forced expiratory volume in the first second (FEV1%) and FEV1/forced vital capacity (FVC) did not significantly change during follow-up.

Figure 3. Bronchial obstruction at long-term follow-up in all the subjects with eosinophilic granulomatosis with polyangiitis (A), in those with severe/uncontrolled asthma (B) and in those with non-severe/controlled asthma (C). Seventy-one patients had pulmonary physiology data available at after 3 years of follow-up. The % of subjects with bronchial obstruction

(FEV1/FVC<LLN) is represented on the left side of the figure; the severity of obstruction and the bronchodilator reversibility during PFT, among those who had bronchial obstruction, in the middle and in the right side of the figure, respectively.

Footnotes: The FEV1/FVC ratio was considered reduced when below the lower limit of normal (or <70% in case of old PFTs). Severity was classified based on FEV1% predicted according to ATS Workshop (17): mild obstruction if FEV1>70%, moderately severe obstruction if FEV1≥60% and <70%, moderately severe obstruction if FEV1≥50% and <60%; severe obstruction if FEV1≥35% and <50%; very severe obstruction if FEV1≤35%.

Figure 4. Receiver operating characteristic curve showing the ability of the model (four predictor-model: baseline severe/uncontrolled asthma, pulmonary infiltrates, severe rhinosinusitis, and an overweight) to distinguish severe from non-severe long-term asthma in EGPA, AUC±SD 0.85±0.13. The inside-dataset prediction capability was measured through 10-fold cross-validation, and the procedure of forming the folds and assessing the models was repeated 1000 times.

TABLES

Table 1. Features of subjects with Eosinophilic Granulomatosis with Polyangiitis with severe/uncontrolled asthma at baseline.

Baseline Characteristic	Baseline non-severe/controlled asthma [#] (N=51)	Baseline severe/uncontrolled asthma [#] (N=38)	Total (N=89)	p value
Age , years, mean (SD)	54.3 (14.2)	47.8 (17.5)	51.4 (15.9)	0.059
Sex, female, n (%)	26/51 (51%)	16/38 (42%)	42/89 (47%)	0.520
BMI (kg/m²), mean (SD)	26.10 (6.28)	26.30 (5.60)	26.18 (5.96)	0.889
Ethnicity, Caucasian, n (%)	50/51 (98%) [†]	36/38 (95%) [*]	86/89 (97%)	0.180
Smoking				0.655
Never, n (%)	37 (73%)	25 (66%)	62 (70%)	
Current, n (%)	11 (2%)	2 (5%)	3 (3%)	
Former, n (%)	13 (25%)	11 (29%)	24 (27%)	
Gastroesophageal reflux, n (%)	6/51 (12%)	8/38 (21%)	14/89 (16%)	0.256
Clinical manifestation of EGPA				
Peripheral Nervous System, n (%)	39/51 (76%)	24/38 (63%)	63/89 (71%)	0.239
Central Nervous System, n (%)	6/51 (12%)	1/38 (3%)	7/89 (8%)	0.231
Skin, n (%)	24/51 (47%)	15/38 (39%)	39/89 (44%)	0.522
Heart, n (%)	12/51 (24%)	7/38 (18%)	19/89 (21%)	0.611
Renal, n (%)	10/51 (20%)	5/38 (13%)	15/89 (17%)	0.569
Pulmonary infiltrate, n (%)	29/51 (57%)	28/38 (73%)	57/89 (64%)	0.122
Pleural Effusion, n (%)	12/48 (25%)	8/35 (23%)	20/83 (24%)	1.000
Gastrointestinal, n (%)	10/51 (20%)	7/38 (18%)	17/89 (19%)	1.000
Joints, n (%)	12/51 (24%)	8/38 (21%)	20/89 (22%)	1.000
Biopsy, performed, n (%)	40/51 (78%)	30/38 (79%)	70/89 (79%)	1.000
Biopsy[‡], positive, n (%)	29/40 (73%)	21/30 (70%)	50/70 (71%)	1.000
Five Factor Score (FFS)				0.156
FFS = 0, n (%)	28/51 (55%)	28/38 (74%)	56/89 (63%)	

FFS = 1, <i>n</i> (%)	18/51 (35%)	9/38 (24%)	27/89 (30%)	
FFS ≥ 2, <i>n</i> (%)	5/51 (10%)	1/38 (3%)	6/89 (7%)	
Respiratory manifestations				
Chronic rhinosinusitis [§] , <i>n</i> (%)	44/51 (86%)	36/38 (95%)	80/89 (90%)	0.291
Delay between rhinosinusitis and EGPA diagnosis, years, median [IQR]	8.3 [2.0-20.8]	6.2 [2.1-16.2]	7.5 [1.9-15.4]	0.721
Severe, chronic rhinosinusitis at baseline [§] , <i>n</i> (%)	26/51 (51%)	21/38 (55%)	47/84 (56%)	0.830
Asthma, <i>n</i> (%)	51/51 (100%)	38/38 (100%)	89/89 (100%)	1.000
Delay between asthma and EGPA diagnosis, years, median [IQR]	8.0 [2.0-15.8]	3.0 [1.1-14.9]	4.4 [1.9-15.4]	0.198
Severe/uncontrolled asthma at baseline, <i>n</i> (%) [#]	-	-	38/89 (43%)	-
History of respiratory allergy, <i>n</i> (%) ^{&}	16/51 (31%)	24/38 (63%)	40/89 (45%)	0.003
Abnormalities at chest imaging, <i>n</i> (%) [£]	33/51 (65%)	29/38 (76%)	62/89 (70%)	0.256
Treatment history before EGPA				
Previous/current Immunotherapy, <i>n</i> (%)	1/48 (2%)	3/36 (8%)	4/84 (5%)	0.309
Previous antileukotrienes, <i>n</i> (%)	16/49 (33%)	17/35 (49%)	33/84 (39%)	0.176
Previous Omalizumab therapy, <i>n</i> (%)	1/49 (2%)	3/35 (9%)	4/84 (5%)	0.303
Drug hypersensitivity, <i>n</i> (%)	26/51 (51%)	22/38 (58%)	48/89 (54%)	0.529
Baseline Pulmonary Function Tests[§]				
FEV1/FVC ratio, (x100), mean (SD)	65.4 (9.6)	67.0 (14.8)	66.2 (12.2)	0.650
FEV1/FVC ratio < LLN, <i>n</i> (%)	15/24 (63%)	13/23 (57%)	28/47 (60%)	0.676
FEV1, (% <i>predicted</i>), mean (SD)	78.0 (20.1)	67.6 (18.8)	72.9 (20.3)	0.079
Reversibility, <i>n</i> (%)	7/23 (30%)	7/20 (35%)	14/43 (33%)	1.000
Laboratory				
P-ANCA/MPO-ANCA at diagnosis, <i>n</i> (%)	24/51 (47%)	11/38 (29%)	35/89 (39%)	0.124
Eosinophils peak >10% of total WBC and/or >1.5 cells/10 ⁹ /L, <i>n</i> (%)	50/51 (98%)	34/36 (94%)	84/87 (97%)	0.567
Eosinophils peak, cells/10 ⁹ /L, median [IQR]	5.7 [3.2-16.2]	8.0 [2.8-12.7]	7.5 [3.2-14.5]	0.951
ESR, mm/h, mean (SD)	41 (34)	41 (36)	41 (34)	0.987

Total serum IgE, IU/mL, median [IQR] 85.3 [3.0-201.5] 150 [69.0-462.0] 107.0 [32.0-295.0] **0.017**

OCS: oral corticosteroids, ICS: inhaled corticosteroids, LABA: long acting beta2 agonist, SABA: short acting beta2 agonist, FEV1: forced expiratory volume in 1 s. FVC: Forced expiratory volume, LLN: lower limit of normality, Reversibility: bronchodilator responsiveness assessed during PFT, p-ANCA/MPO-ANCA: perinuclear anti-neutrophil cytoplasmic antibody/myeloperoxidase anti-neutrophil cytoplasmic antibody, FFS: Five Factor score, ESR: Erythrocyte sedimentation rate, SD: standard deviation, IQR: 25-75% interquartile range.

[†] All but one patient (Hispanic) were Caucasian

^{*} All but two patients (Native Indian or Alaskan) were Caucasian

[‡] Chest abnormalities at X-ray or CT scan: ground-glass opacities and consolidations, pulmonary infiltrates, pulmonary nodules and micronodules, interlobular septal thickening; bronchial wall thickening and/or bronchial dilatation; diffuse alveolar hemorrhage.

[¶] Histological confirmation of EGPA diagnosis in 71% of patients and with no difference between the two groups. Most frequent sites of biopsy were skin (31% of cases, 22/70), sural nerve (21% of cases, 15/70), lung (19% of cases, 13/70), paranasal sinuses and gastrointestinal tract (7% of cases each, 5/70), kidney (6% of cases, 4/70), myocardium (3% of cases, 2/70). Other sites of biopsy were bladder, testes, muscles (one each), and one was not accessible by chart review.

[&] Allergic asthma and/or rhinitis before the diagnosis of EGPA were defined if the patient had a documented positive skin prick test and/or serum specific IgE in conjunction with a compatible clinical history and/or the treated physician reported in the chart a previous documented allergic asthma or rhinitis

^{\$} Defined as rhinosinusitis that needed sinus surgery to control nasal polyps and/or reduce symptoms (≥ 1 surgery)

[§] Baseline spirometry data available for 47 patients only

[#] The definition from ATS Workshop was used to identify patients with severe/uncontrolled asthma

Table 2. Systemic Immunosuppressive Therapy and asthma and vasculitis relapses in subjects with Eosinophilic Granulomatosis with Polyangiitis during the 3 ($\pm$ 1) years of follow-up from diagnosis.

Prevalence of the variables	Long-term non-severe/controlled asthma [#] (N=53)	Long-term severe/uncontrolled asthma [#] (N=36)	Total (N=89)	p value
Immunosuppressive therapy				
Cyclophosphamide, <i>n</i> (%)	22/53 (42%)	18/36 (50%)	40/89 (45%)	0.516
Rituximab, <i>n</i> (%)	9/53 (17%)	2/36 (6%)	11/89 (12%)	0.188
Methotrexate, <i>n</i> (%)	11/53 (21%)	14/36 (38%)	25/89 (28%)	0.092
Azathioprine, <i>n</i> (%)	22/53 (42%)	18/36 (50%)	40/89 (45%)	0.516
Hydroxychloroquine, <i>n</i> (%)	1/53 (2%)	2/36 (6%)	3/89 (3%)	0.563
Hydroxyurea, <i>n</i> (%)	2/53 (4%)	1/36 (3%)	3/89 (3%)	1.000
Mycophenolate Mofetil, <i>n</i> (%)	6/53 (11%)	3/36 (8%)	9/89 (10%)	0.734
Mepolizumab, <i>n</i> (%)	-	1/36 (3%)	1/89 (1%)	-
Interferon-alpha, <i>n</i> (%)	-	1/36 (3%)	1/89 (1%)	-
IVIG, <i>n</i> (%)	-	1/36 (3%)	1/89 (1%)	-

IVIG: intravenous Immunoglobulin

[#] The definition from ATS Workshop was used to identify patients with severe/uncontrolled asthma

Table 3. Long-term pulmonary function testing, by asthma severity.

PFT Characteristic at 3rd year	Long-term non-severe/controlled asthma[#] (N=40)	Long-term severe/uncontrolled asthma[#] (N=31)	Total* (N=71)	p value
BMI (kg/m ²), mean (SD)	26.1 (4.3)	30.7 (8.0)	28.4 (7.0)	0.003
FEV1/FVC ratio (x100), mean (SD)	66.5 (12.3)	59.7 (15.3)	63.5 (13.9)	0.040
FEV1/FVC ratio < LLN, n (%)	20/20 (50%)	25/31 (81%)	45/71 (63%)	0.008
FEV1 (% predicted), mean (SD)	78.9 (17.6)	68.0 (22.0)	73.8 (20.3)	0.024
Reversibility (% predicted), mean (SD)	8.5 (9.8)	13.0 (12.4)	10.4 (11.1)	0.116
TLC (% predicted), mean (SD)	108.8 (18.1)	101.7 (24.8)	105.1 (21.9)	0.339
RV (% predicted), mean (SD)	121.8 (27.6)	136.6 (45.5)	131.0 (38.9)	0.234
DLCO (% predicted), mean (SD)	88.2 (21.9)	82.9 (21.4)	85.4 (21.7)	0.361

PFT: pulmonary function tests, BMI: body mass index, FEV1: forced expiratory volume in 1 s. FVC: Forced expiratory volume, FEV1/FVC (x100): Tiffaneu index, LLN: lower limit of normality, Reversibility: bronchodilator responsiveness assessed during PFT, TLC: total lung capacity, RV: residual volume, DLCO: lung diffusion capacity of carbon monoxide, SD: standard deviation.

*Pulmonary function tests at 3 (±1) years of follow-up available for 71 patients

[#] The definition from ATS Workshop was used to identify patients with severe/uncontrolled asthma

Table 4. Baseline predictors of long-term severe/uncontrolled asthma in patients with Eosinophilic Granulomatosis with Polyangiitis. Univariate analysis and multiple binary logistic regressions of baseline variables associated with severe/uncontrolled asthma at 3 ($\pm$ 1) years of follow-up.

Univariate Analysis				Multivariate Analysis		
Variables	Odds Ratio	95% Confidence of Interval	P value	Odds Ratio	95% Confidence of Interval	P value
Age, years	1.01	0.98-1.04	0.422	-	-	-
≥ 50 years old	0.84	0.34-2.04	0.693	-	-	-
Sex, female	1.45	0.29-1.61	0.389	-	-	-
BMI at baseline (kg/m ²)	1.08	0.99 -1.17	0.063	-	-	-
Overweight (>25 kg/m ²)	1.75	0.70-4.41	0.231	3.41	1.05-12.90	0.041
Obesity (>30 kg/m ²)†	1.69	0.57-4.99	0.341	-	-	-
Smoking, former or current	1.02	0.40-2.54	0.971	-	-	-
Gastroesophageal reflux	1.13	0.35-3.57	0.841	-	-	-
Rhinosinusitis	2.59	0.51-13.24	0.239	-	-	-
Severe Rhinosinusitis ^s	1.76	0.74-4.16	0.196	3.57	1.07-13.55	0.038
Severe/uncontrolled Asthma at baseline [#]	11.45	4.36-32.96	<0.001	10.64	3.43-39.08	<0.001
Drug hypersensitivity	1.12	0.48-2.63	0.800	-	-	-
Previous history of respiratory allergy*	3.75	1.56-9.37	0.003	-	-	-

Clinical manifestation of EGPA				-	-	-
Peripheral Nervous System	0.46	0.18-1.16	0.099	-	-	-
Central Nervous System	1.11	0.23-5.30	1.000	-	-	-
Skin	0.86	0.37-2.03	0.893	-	-	-
Heart	0.82	0.29-2.34	0.717	-	-	-
Renal	1.36	0.44-4.15	0.593	-	-	-
Pulmonary infiltrate	3.70	1.43-10.52	0.006	5.16	1.43-21.85	0.011
Pleural Effusion	0.57	0.19-1.68	0.309	-	-	-
Gastrointestinal	0.55	0.18-1.73	0.307	-	-	-
Joints	0.98	0.35-2.69	0.962	-	-	-
FFS, ≥ 1	0.93	0.38-2.24	0.876	-	-	-
OCS use at baseline	6.84	2.64-19.68	<0.001	-	-	-
High dose ICS use at baseline	2.31	0.97-5.64	0.059	-	-	-
LABA use at baseline	1.76	0.75-4.22	0.195	-	-	-
Baseline FEV1/FVC, <LLN	1.10	0.34-3.67	0.875	-	-	-
Baseline FEV1, <80% predicted	1.56	0.46-5.60	0.475	-	-	-

Baseline reversibility, $\geq 12\%$ predicted	1.06	0.28-3.87	0.927	-	-	-
Serum IgE at baseline, ≥ 100 IU/mL	1.94	0.82-4.67	0.131	-	-	-
Peripheral hypereosinophilia, peak $>10\%$ of total WBC	0.99	0.97-1.03	0.924	-	-	-
Detectable p-ANCA/MPO-ANCA at diagnosis	0.53	0.21-1.28	0.165	-	-	-
Baseline ESR, ≥ 20 mm/h	0.86	0.26-2.79	0.797	-	-	-

BMI: body mass index, FFS: Five Factor score, OCS: oral corticosteroids, ICS: inhaled corticosteroids, LABA: long acting beta2 agonist, FEV1: forced expiratory volume in 1 s. FVC: Forced expiratory volume, LLN: lower limit of normality, Reversibility: bronchodilator responsiveness assessed during PFT, p-ANCA/MPO-ANCA: perinuclear anti-neutrophil cytoplasmic antibody/myeloperoxidase anti-neutrophil cytoplasmic antibody, ESR: Erythrocyte sedimentation rate.

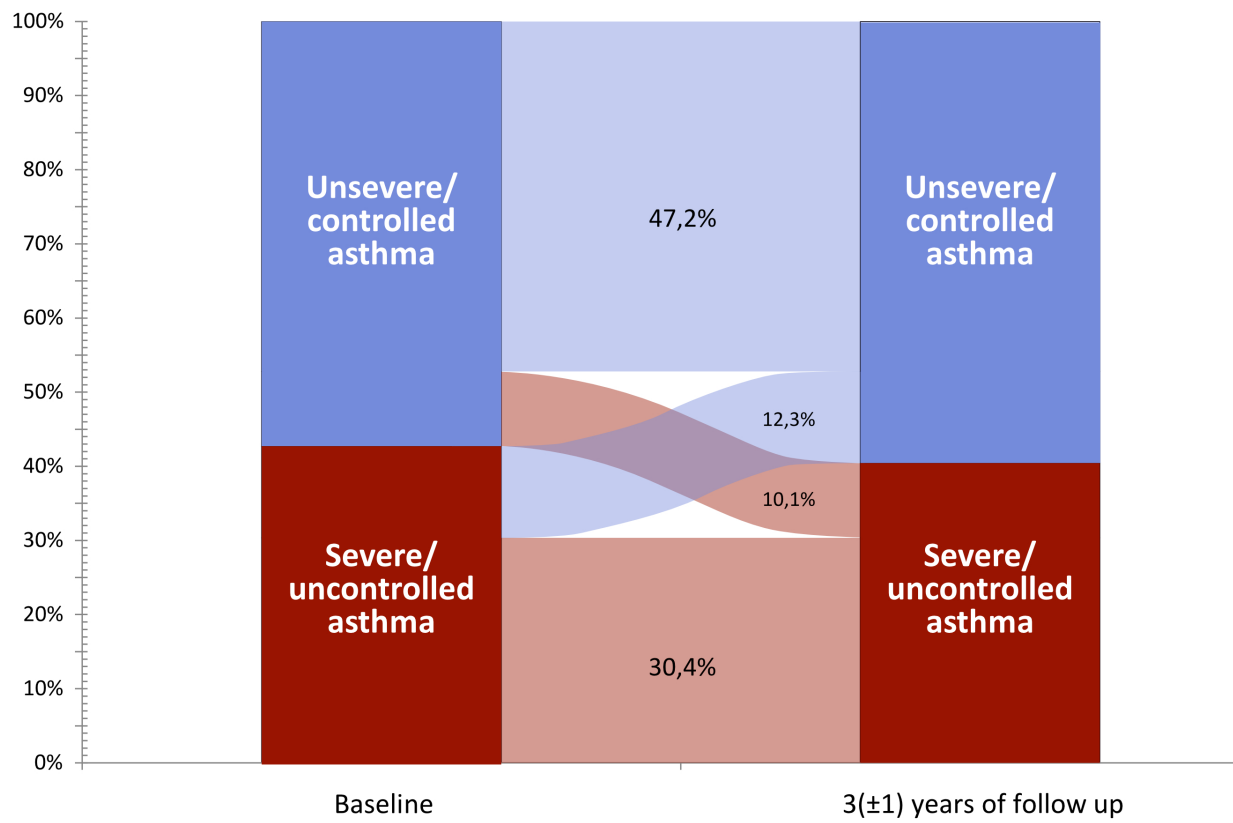
^{\$} Defined as rhinosinusitis that needed sinus surgery to control nasal polyps and/or reduce symptoms (≥ 1 surgery)

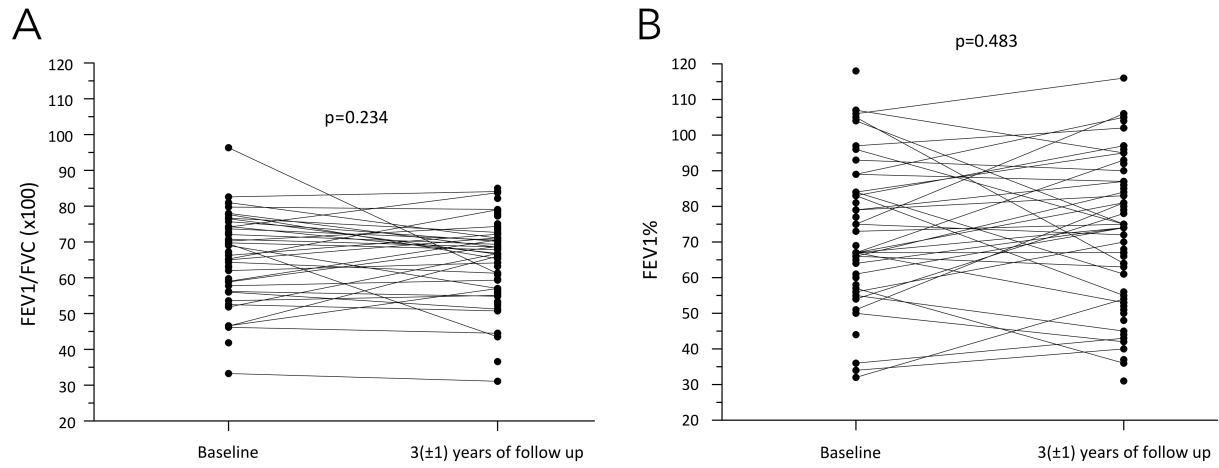
[#] The definition from ATS Workshop was used to identify patients with severe/uncontrolled asthma

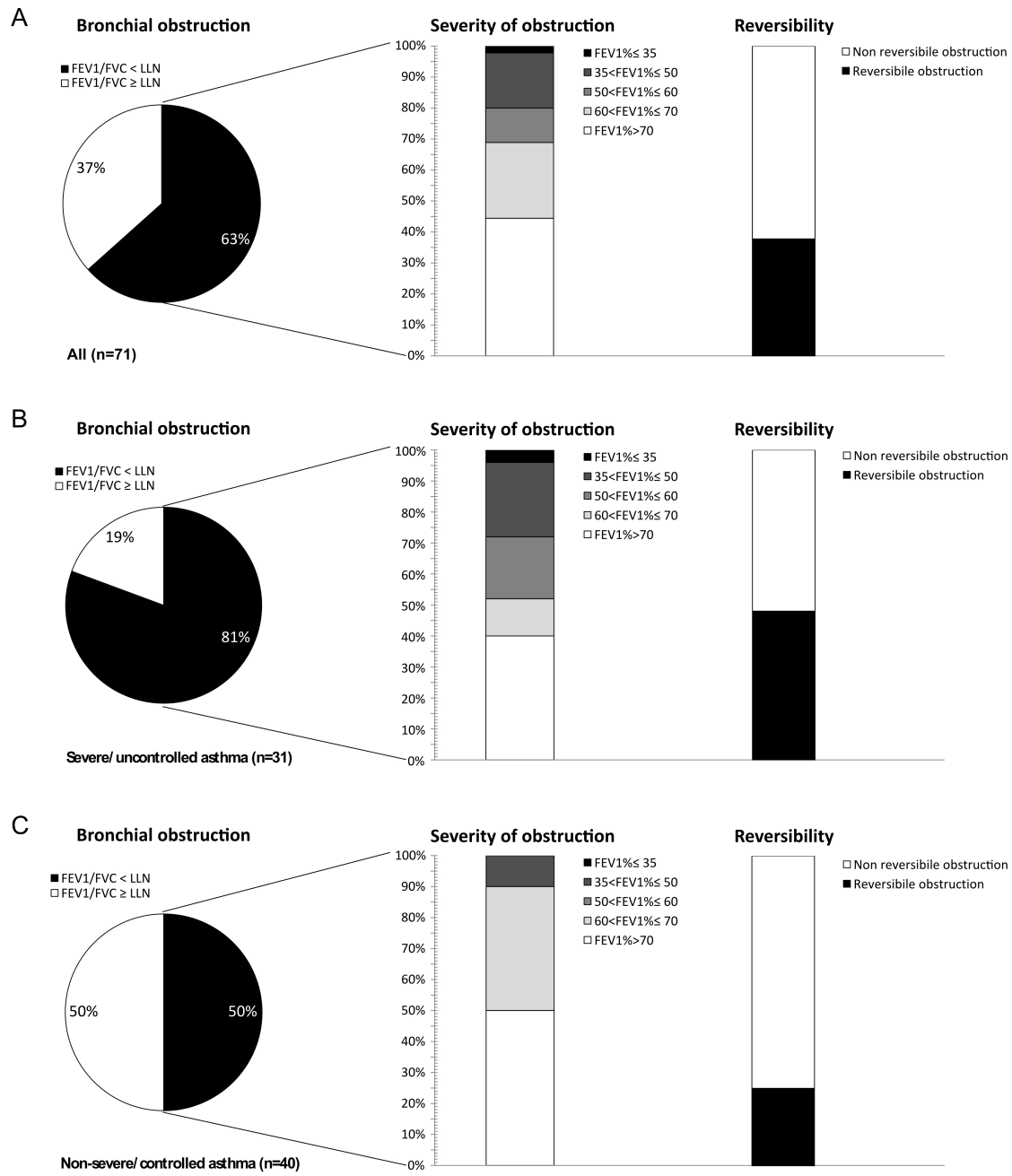
[&] Allergic asthma and/or rhinitis before the diagnosis of EGPA were defined if the patient had a documented positive skin prick test and/or serum specific IgE in conjunction with a compatible clinical history and/or the treated physician reported in the chart a previous documented allergic asthma or rhinitis

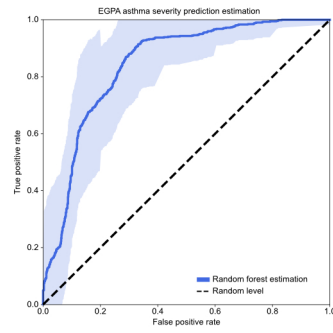
[†] When obesity at baseline ($\text{BMI} \geq 30 \text{ kg/m}^2$) was used in the same model instead of overweight ($\text{BMI} \geq 25 \text{ kg/m}^2$), the analysis identified the same predictors but obesity approached statistical significance ($p=0.094$)

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ABBREVIATIONS: ANCA=anti-neutrophil cytoplasmic antibody; EGPA=eosinophilic granulomatosis with polyangiitis; MPO-myeloperoxidase; OCS=oral corticosteroids; ICS=inhaled corticosteroids, LABA=long acting beta-2 agonist, SABA= short acting beta-2 agonist; FEV1=forced expiratory volume in 1 second; FVC=Forced expiratory volume; FFS=Five Factor score; TLC=total lung capacity; RV=residual volume; ACR=American College of Rheumatology; CHCC=Chapel Hill Consensus Conference; ERS=European Respiratory Society; ATS=American Thoracic Society.