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Frequency of *Aspergillus fumigatus* sensitization and its impact on longitudinal asthma control: a 12-week prospective cohort study

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Abstract

The role of fungi as the dominant allergen in asthma pathogenesis has been extensively explored. Most intriguing has been the relationship between asthma and *Aspergillus fumigatus*, given its ubiquitous presence and tendency to cause a wide spectrum of diseases in humans. Existing literature suggests that *Aspergillus* sensitization is associated with increased asthma severity, but prospective data comparing treatment outcomes between *Aspergillus*-sensitized and non-sensitized asthma patients remain limited. This study aimed to (i) determine the prevalence of *Aspergillus fumigatus* sensitization in an asthma cohort and (ii) prospectively compare longitudinal treatment outcomes, including symptom control, quality of life, and lung function, between sensitized and non-sensitized groups. A total of 124 patients with asthma were recruited. Patients were divided into two groups: *Aspergillus*-sensitized and non-sensitized, as determined by skin prick tests with *Aspergillus fumigatus* antigen. A total of 36 patients (29.03%) were found to be sensitive to *Aspergillus fumigatus*. *Aspergillus*-sensitized patients were evaluated for allergic bronchopulmonary aspergillosis, and 5 were identified and excluded from the study. The remaining 119 asthma patients, 31 sensitized and 88 non-sensitized, were included in the analysis. Baseline clinical characteristics, spirometry findings, and symptom questionnaire scores (Asthma Control Test and mini Asthma Quality of Life Questionnaire) were obtained. Asthma symptom control was assessed as per the Global Initiative for Asthma guidelines. All patients received standard asthma therapy and were followed up at a three-month interval. At baseline, both groups were similar in clinical characteristics, asthma symptom control, lung function, and symptom questionnaire scores. On follow-up, no differences were found between the two groups in asthma symptom control, symptom questionnaire scores, or exacerbation frequency. *Aspergillus fumigatus* sensitization was not associated with increased asthma severity or poorer treatment outcomes. Testing for *Aspergillus* sensitization may be reserved for patients with a poor therapeutic response or a strong clinical suspicion of allergic bronchopulmonary aspergillosis.

Key words: asthma, *Aspergillus fumigatus*, aspergillus sensitization, asthma control, Asthma Control Test, mini Asthma Quality of Life Questionnaire.

Introduction

Asthma affects millions of people worldwide, ranging from 1– 29% of the population in different countries [1]. Over the past few decades, extensive research has established fungi as a predominant allergen in the pathogenesis of asthma [2]. Various population-based studies conducted in different parts of the world have shown that fungal sensitization is associated with increased asthma severity [3-5]. Several fungi have been identified, including Aspergillus, Alternaria, Candida, Cladosporium, Penicillium, and Trichophyton.

Although ample evidence suggests that sensitization to moulds can increase asthma severity, the relationship is complex and influenced by multiple factors. Most of the data come from observational studies that assess asthma severity at a single point in time and relate it to fungal sensitization (as measured by skin prick tests or specific IgE levels). These studies do have inherent limitations, including potential biases. A definitive causal association between fungal sensitization and increased asthma severity is yet to be established through experimental testing. Additionally, several issues exist, including a lack of a unified definition of fungal sensitization and inconsistent performance of available tests. The diagnostic criteria for identifying severe asthma have evolved over time, further complicating the issue.

Among the fungi linked to asthma, Aspergillus stands out for its ability to colonize and its association with a wide spectrum of diseases. Aspergillus sensitization has been identified as a risk factor for increased airflow limitation and bronchiectasis in individuals with asthma [6,7]. However, this airflow limitation does not always translate into poor asthma control and worsened quality of life [8]. There is a lack of prospective evidence comparing treatment outcomes between Aspergillus-sensitized and non-sensitized patients with asthma.

To address these uncertainties, we conducted a prospective observational study. We hypothesized that asthma patients sensitized to *Aspergillus fumigatus* would exhibit poorer clinical control and a diminished response to standard therapy over time compared to non-sensitized patients. The primary objective was to determine the frequency of *Aspergillus fumigatus* sensitization in an asthma cohort. The secondary objective was to prospectively compare longitudinal treatment outcomes, specifically asthma control, quality of life, and lung function, between sensitized and non-sensitized groups over a 12-week period.

Materials and Methods

This study was conducted from July 2021 to December 2022 in the Department of Pulmonary Medicine at a tertiary care hospital in western India. The study was approved by the Institute Ethics Committee of All India Institute of Medical Sciences, Jodhpur, Rajasthan (AIIMS/IEC/2021/3685), and written informed consent was obtained from all subjects before

enrollment. The sample size for this study was calculated based on the primary objective of determining the prevalence of *Aspergillus* sensitization in asthma patients. Based on previous literature by Agarwal et al., which reported a sensitization rate of 52.5% in a similar population, we determined that at least 119 patients were required to achieve a 9% margin of error at a 5% level of significance (Type I error) [8]. To reduce the margin of error, the total sample size taken is 124. Because no prior data existed for longitudinal outcomes in this specific context, the sample size was determined by the primary objective (prevalence), and the longitudinal findings may serve as a pilot for future, larger-scale, powered trials.

The following formula was used:

$$N \quad (p(1-p))/(ME/z_{\alpha})^2$$

Where Z_{α} is the value of Z (normal variate) at two sided alpha error of 5%, ME is the margin of error, and p is the proportion of patients with A fumigatus sensitization.

Patients aged 18 years or older with a clinical diagnosis of asthma were included in this study. Exclusion criteria were pregnancy, immunosuppressive states such as chronic liver failure, chronic renal failure, patients on immunosuppressive medications, severe comorbidities in the form of malignancies, congestive heart failure, diagnosed cases of ABPA, and systemic corticosteroid use within the last six weeks.

A comprehensive clinical history was obtained from all the patients, after which they underwent a detailed physical examination. The following details were recorded: age, gender, body mass index (BMI), residence (rural or urban), tobacco smoking, symptoms (cough, wheeze, shortness of breath, chest tightness), frequency of daytime and night-time symptoms, and family history of asthma. Asthma symptom control was assessed as per the latest GINA guidelines [9]. The subjects were asked to complete two self-administered questionnaires: the Asthma Control Test (ACT) and the mini–Asthma Quality of Life Questionnaire (mAQLQ) [10,11]. All the patients were also asked to perform spirometry, and parameters were recorded both pre- and post-bronchodilator administration. The Aspergillus skin prick test (SPT) was performed using commercially prepared A. fumigatus antigen (All Cure Pharma Pvt Ltd, New Delhi, India). All subjects were divided into two groups based on Aspergillus SPT results: Aspergillus-sensitized and Aspergillus-non-sensitized (Figure 1). Aspergillus-sensitized patients were evaluated further for ABPA, and if diagnosed as having ABPA, they were excluded from the study.

The Aspergillus SPT was applied at the volar aspect of the forearm at least 2-3 cm from the wrist and antecubital fossa. All the emergency equipment for intubation, along with a crash tray, was kept ready during the test. For the positive control, 0.1% histamine was used; for the negative control, buffered normal saline was used. The test was read 15-20 minutes after application, and

a wheal greater than 3 mm in diameter than that of the negative control was taken as a positive result [12]. All subjects underwent spirometry on Cosmed microQuark spirometer as per the latest ATS spirometry standardization guidelines [13]. An increase in FEV1 of more than 12% and 200 mL was considered a positive bronchodilator response. Patients in both groups were treated and followed up for three months. All patients were prescribed an inhaled combination of Formoterol and Budesonide, either as maintenance and reliever therapy (MART) or as needed reliever (AIR) therapy, as per the principles of TRACK 1 treatment in GINA, and the dose of Budesonide was adjusted accordingly. The treatment outcome was assessed using spirometry, the ACT questionnaire, the mini AQLQ, and assessment of asthma symptom control (Well controlled, Uncontrolled, or Partly controlled) as per GINA guidelines 2021. A telephonic follow-up or an OPD visit was arranged between the initial visit and the 3-month follow-up to assess inhaler technique and treatment adherence.

Statistical analysis

The presentation of the Categorical variables was done as numbers and percentages (%). On the other hand, quantitative data with a normal distribution were presented as the mean ± SD, and data with a non-normal distribution as the median with 25th and 75th percentiles (interquartile range). Normality of the data was checked using the Shapiro-Wilk test. In cases where the data were not normally distributed, we used nonparametric tests. The comparison of the variables, which were quantitative and not normally distributed in nature, was analysed using the Mann-Whitney Test, and variables, which were quantitative and normally distributed in nature, were analysed using the independent t-test. The comparison of the variables, which were qualitative in nature, was analysed using the Chi-Square test. If any cell had an expected value of less than 5, then Fisher's exact test was used. A two-way repeated-measures analysis using a mixed-effects model was performed to compare the ACT Total Score and mAQLQ Total Score between sensitized and non-sensitized groups across time periods, with time (baseline and follow-up) as the within-subject factor and Aspergillus sensitization status as the between-subject factor. The data entry was done in the Microsoft Excel spreadsheet, and the final analysis was performed using the Statistical Package for the Social Sciences (SPSS) software, IBM, Chicago, USA, version 25.0. For statistical significance, p value of less than 0.05 was considered statistically significant.

Results

We screened 153 patients; 29 were excluded (6 had COPD, 5 had unstable cardiovascular status, 9 had a history of recent corticosteroid or antihistamine use, and 9 declined follow-up), leaving 124 to undergo SPT for *Aspergillus fumigatus*. Thirty-six patients (29.03%) were SPT-positive, and 88 (70.96%) were SPT-negative. Among the SPT-positive cohort, five were diagnosed with ABPA

and excluded per protocol, yielding 31 patients in the Aspergillus-sensitized group. The 88 SPT-negative patients comprised the Aspergillus-non-sensitized group (Figure 1). The mean age of the study cohort was 32.18 ± 12.3, ranging from 18 to 72 years. The distributions of age, gender, and BMI were comparable between Aspergillus-sensitized and non-sensitized subjects. Women comprised 51.14% of the Aspergillus non-sensitized group and 35.48% of the Aspergillus sensitized group, while Men comprised 48.86% and 64.52%, respectively. The median BMI of the cohort was 22.22 kg/m2. The distribution of residential areas was comparable between Aspergillus-sensitized and non-sensitized individuals. The history of smoking among the two groups was similar. Family history of asthma was present in 30.68% of Aspergillus non-sensitized vs 29.03% of Aspergillus-sensitized. (Table 1)

The most common complaint among the two groups was shortness of breath, followed by cough, wheezing, and chest tightness. The distribution of symptoms and the frequency of daytime and nighttime symptoms were comparable in both groups. The median duration of asthma in Aspergillus non-sensitized was 36 months, and in Aspergillus sensitized was 24 months, with no significant association between them. (Table 2)

Symptom control was assessed using the GINA symptom control tool. At baseline, 57.98% had uncontrolled disease, 42.02% had partially controlled disease. No statistically significant difference in symptom control was observed between the two groups. Spirometry was obtained at baseline in 117 patients. Two patients, one from each group, were unable to perform the spirometry manoeuvre. No significant association was observed between baseline pre-BD FEV1, FVC, and FEV1/FVC ratio and Aspergillus sensitization status. The presence of bronchodilator responsiveness was also similar between the two groups.

Questionnaires were made available to patients in both Hindi and English, whichever they preferred. On mAQLQ, no significant associations were observed for scores on symptoms, activity limitation, emotional function, environmental stimuli (dust, air pollution, and cigarette smoke), or mAQLQ total between Aspergillus-sensitized and non-sensitized groups. The distribution of ACT scores was also comparable. (Table 3)

After the initial assessment, all the patients were followed up for three months. At 3 months, asthma symptom control was assessed, questionnaires were obtained, and spirometry was advised. Spirometry could not be performed on all patients during follow-up due to issues with patient travel from home to the hospital. One patient from the Aspergillus non-sensitized group expired due to reasons unrelated to asthma (Figure 1). Of the total 118 patients, 105 (88.98%) were compliant with the treatment. Of the 13 non-compliant patients, 9 were from the Aspergillus non-sensitized group and 4 from the Aspergillus sensitized group; the difference was not statistically significant. In contrast to one patient in the sensitized group, five patients in the non-sensitized group experienced exacerbations during follow-up, which was not statistically

significant. The majority of patients, 74.71% in the Aspergillus non-sensitized group and 83.87% in the Aspergillus-sensitized group, had their asthma controlled on follow-up, and the difference was not statistically significant. (Table 4)

Since follow-up spirometry was not feasible in all patients, this parameter was excluded from our statistical analysis. No significant difference in mAQLQ and ACT scores was observed between the groups at follow-up. (Table 4) However, both groups showed a significant improvement in ACT and mAQLQ from baseline. (Table 5)

Discussion

Aspergillus species are ubiquitous and can cause a wide spectrum of respiratory disorders. Certain special abilities help them colonize the human airways, such as their small spore size and thermotolerant growth, which enable them to grow at human body temperatures [14].

The frequency of Aspergillus sensitisation in asthma patients ranges from 15% to 48% globally, exhibiting significant heterogeneity. In our study, 36 patients (29.03%) were sensitized to Aspergillus. Such variations can be attributed to differences in diagnostic methods, climatic conditions, and geographic factors, which result in varying Aspergillus exposures and differences in research populations with respect to atopy, asthma severity, and comorbidities [15]. A recent systematic review reported a pooled prevalence of Aspergillus sensitization in asthma of 25.1%, comparable to our finding [16].

Several studies have suggested that Aspergillus sensitization negatively impacts quality of life, associating it with prolonged symptom duration, increased nocturnal awakenings, and more frequent courses of oral corticosteroids [17,18]. However, our study does not support these findings, as the mean patient age and the duration of asthma symptoms were comparable between the two groups, suggesting similar patterns of symptom onset. Furthermore, the frequency of daytime and nighttime symptoms remained similar between the two groups. Another study of 318 asthma patients found that those with Aspergillus sensitization had longer asthma duration and required more frequent maintenance treatment with oral corticosteroids. However, this study focused exclusively on difficult-to-treat patients, thereby limiting the ability to extrapolate these findings to individuals with milder forms of asthma [19]. One more study from India involving 417 asthmatic patients reported a significantly higher incidence of nocturnal awakenings in the Aspergillus-sensitive group. At the same time, the remaining clinical characteristics were similar between the two groups [8]. The underlying reasons why some patients develop sensitization to Aspergillus while others do not remain unclear. The pathogenesis of fungal asthma remains incompletely understood, likely involving complex interactions among environmental, fungal, and genetic factors that may heighten severity in some patients [2].

Sensitization to Aspergillus has long been associated with diminished lung function in asthma [6-8,18-21]. Studies focusing on sputum fungal cultures have shown that Aspergillus sensitization is significantly associated with reduced FEV1 and a positive sputum culture for Aspergillus species [6,7,21]. These findings have led to the hypothesis that prolonged fungal colonization may result in airway damage, subsequent sensitization, and even fixed airflow obstruction. In contrast, our study did not reveal any significant differences in baseline spirometry between the Aspergillus-sensitized and non-sensitized groups. It is important to note that we did not perform sputum fungal cultures in our study. Consequently, we are unable to comment on the presence of Aspergillus colonization or its potential impact on lung function. It also raises the possibility that fungal sensitization may just reflect a heightened atopic response rather than a direct contributor to lung function.

At baseline, asthma severity was comparable between the two groups, with the majority of patients experiencing uncontrolled asthma [including partly controlled and uncontrolled cases]. Baseline miniAQLQ scores across all domains were similar between the groups, a finding that aligns with another north Indian study [8]. Likewise, baseline ACT scores showed no significant differences between groups, suggesting comparable frequencies of daytime and nocturnal symptoms, rescue medication use, and limitations in daily activities. On follow-up, these scores were also comparable, and the differences were statistically insignificant. Clinical assessments further confirmed improved asthma symptom control across both groups, with comparable distributions of control levels. The follow-up was scheduled at a 3-month interval, in line with international guidelines that recommend this interval for repeat spirometry and clinical reassessment. [9]

While previous studies have linked Aspergillus sensitization with increased asthma severity, our findings differ from these observations. Notably, the recently updated ISHAM-ABPA Working Group clinical practice guidelines underscore the importance of assessing Aspergillus fumigatus sensitization in all adult patients with asthma in tertiary care settings, highlighting its role in comprehensive asthma management [22]. Our results underscore the nuanced, multifaceted nature of the relationship between asthma and fungal sensitization, suggesting that additional factors warrant further exploration.

We utilized SPT to assess sensitivity to Aspergillus fumigatus. The outcome of SPT depends on multiple factors, such as the quality of allergen extracts, storage conditions for allergen solutions, and the technical expertise of the person performing the tests. While many researchers have employed specific IgE testing for fungal sensitization [6,7], current evidence does not definitively establish the superiority of one method over the other. To date, standard criteria have not been established to define the sensitivity and specificity of allergen skin tests or in vitro IgE assays. In general, SPTs have proven to be more sensitive but less specific than specific IgE tests [23]. Relying only on SPT may misclassify certain non-sensitized patients as sensitized. Also, in cases of

Aspergillus fumigatus sensitization, few studies have found that a notable proportion of IgE-positive individuals may test negative on SPT. One study reported only 54% concordance between SPT and specific IgE testing for Aspergillus sensitization in patients with severe asthma, recommending the use of both tests for a more comprehensive assessment [24]. Another study from north India reported a lower sensitivity of Intradermal testing for Aspergillus fumigatus sensitization compared to the specific IgE assay [25]. In our study setting, financial constraints among the patient population made specific IgE testing cost-prohibitive for most participants. While serum-specific IgE testing can provide confirmatory value, SPT is globally recognized as a primary diagnostic tool for allergic sensitization due to its high sensitivity, high negative predictive value, and direct correlation with mast cell-mediated clinical responses [26].

To the best of our knowledge, this is the first study to longitudinally follow asthma patients with and without Aspergillus sensitization to evaluate the impact on treatment outcomes, addressing a significant gap in previous research where such comparative follow-ups were not undertaken. We conducted a multidimensional assessment of asthma that included two questionnaires, spirometry, and clinical examination.

Our study has some limitations worth mentioning. As this is the first prospective study to evaluate longitudinal outcomes specifically comparing *Aspergillus*-sensitized and non-sensitized asthma patients over 12 weeks, a formal power calculation for the secondary objective was not possible. The longitudinal comparison of outcomes may have been limited by the study's power to detect smaller clinical differences between the two subgroups. Being a single-centre investigation, it may not have captured potential regional variations that could influence the relationship between asthma and fungal sensitization. Additionally, follow-up spirometry could be performed in only a limited number of patients; we were unable to compare values between the two groups. Planning a field-based study can overcome this challenge, allowing follow-up spirometry to be performed at patients' homes.

We acknowledge that the 3-month follow-up duration limits our ability to assess long-term outcomes, such as annual decline in lung function or the impact of seasonal peaks in fungal spore counts. Furthermore, the low number of exacerbations recorded (n=6) during this period means the study was likely underpowered to detect a difference in acute events. However, this duration was chosen in accordance with clinical guidelines for assessing treatment response. Though our findings regarding improved ACT and mini-AQLQ scores serve as a robust measure of short-term clinical control, future longer follow-up studies are needed to capture seasonal dynamics.

Asthma is a heterogeneous disease, and given the complex, incompletely understood role of fungal sensitisation in disease severity, further phenotyping and endotyping studies are required that may better identify subgroups in which fungal sensitisation has a differential contribution to clinical outcomes. Integrating molecular, genetic, and immunologic profiling with detailed

environmental exposure assessment could better clarify the biological pathways and immune responses that underlie these differences. Such work will ultimately support more personalized asthma management, in which antifungal or anti–type 2 pathway strategies may be deployed according to the relative importance of fungal sensitization in each patient's disease [2].

Conclusions

Aspergillus sensitization is relatively common among patients with asthma. It does not independently predict quality of life, asthma control, or treatment outcomes. Routine testing for Aspergillus sensitization should be reserved for patients with an inadequate response to standard therapy or with a strong clinical suspicion of allergic bronchopulmonary aspergillosis.

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Table 1. Association of demographic characteristics with Aspergillus non-sensitized and sensitized patients. Data are mean ± standard deviation or number of patients, n (%)

Demographic characteristics	Aspergillus non sensitized (n=88)	Aspergillus sensitized (n=31)	Total	p
Age(years)				
Mean ± SD	31.78±12.74	33.29±11.2	32.18±12.33	0.561
Gender				
Female	45 (51.14%)	11 (35.48%)	56 (47.06%)	0.133
Male	43 (48.86%)	20 (64.52%)	63 (52.94%)	
Body mass index(kg/m²)				
Median (25th-75th percentile)	21.63(18.712-26.127)	23.32 (20.04-25.454)	22.22 (18.89-25.985)	0.398
Area of residence				
Rural	25 (26.32%)	11 (33.33%)	36 (28.13%)	0.461
Urban	63 (71.59%)	20 (64.52%)	83 (69.75%)	
Smoking history				
Nonsmoker	85 (96.59%)	31 (100%)	116 (97.48%)	1
Ex-smoker	2 (2.27%)	0 (0%)	2 (1.68%)	
Current smoker	1 (1.14%)	0 (0%)	1 (0.84%)	
Family history of asthma	27 (30.68%)	9 (29.03%)	36 (30.25%)	0.863

SD, standard deviation.

Table 2. Association of symptomatology, duration of asthma, and frequency of symptoms with Aspergillus non-sensitized and sensitized patients. Data are mean ± standard deviation or number of patients, n (%).

	Aspergillus non sensitized(n=88)	Aspergillus sensitized(n=31)	Total	p
Cough	74 (84.09%)	27 (87.10%)	101 (84.87%)	0.779
Wheezing	68 (77.27%)	25 (80.65%)	93 (78.15%)	0.696
Shortness of breath	87 (98.86%)	30 (96.77%)	117 (98.32%)	0.455
Chest tightness	60 (68.18%)	21 (67.74%)	81 (68.07%)	0.964
Duration of asthma(months) Median(25th-75th percentile)	36(24-63)	24(12-66)	36(18-66)	0.354
Frequency of daytime symptoms				
Less than 2 per week	34 (38.64%)	18 (58.06%)	52 (43.70%)	0.172
More than 2 per week	29 (32.95%)	7 (22.58%)	36 (30.25%)	
Daily	25 (28.41%)	6 (19.35%)	31 (26.05%)	
Frequency of night time symptoms				
Nil	29 (32.95%)	10 (32.26%)	39 (32.77%)	0.799
Less than 2 per month	19 (21.59%)	10 (32.26%)	29 (24.37%)	
More than 2 per month but less than 1 per week	27 (30.68%)	8 (25.81%)	35 (29.41%)	
More than once a week	12 (13.64%)	3 (9.68%)	15 (12.61%)	
Most days a week	1 (1.14%)	0 (0%)	1 (0.84%)	

SD, standard deviation.

Table 3. Baseline assessment of symptom control, spirometry parameters, mAQLQ, and ACT questionnaires. Data are mean ± standard deviation or number of patients, n (%).

Baseline symptom control	**Aspergillus non sensitized (n=88)**	**Aspergillus sensitized (n=31)**	**Total**	**p**
Controlled	0	0	0	
Partly controlled	36 (40.91%)	14 (45.16%)	50 (42.02%)	0.68
Uncontrolled	52 (59.09%)	17 (54.84%)	69 (57.98%)	
Baseline spirometry parameters (mean± SD)	n=87	n=30		
Pre BD FEV1(% Pred)	78.45 ± 20.54	80.33 ± 23.82	78.93 ± 21.34	0.678
Pre BD FVC(% Pred)	85.95 ± 17.78	89.6 ± 19.7	86.88 ± 18.27	0.347
Pre BD FEV1/FVC ratio	75.88 ± 11.7	74.92 ± 12.89	75.64 ± 11.97	0.705
mAQLQ (Mean± SD)	n=88	n=31		
Symptoms	3.86 ± 1.28	4.1 ± 1.34	3.92 ± 1.3	0.377
Activity limitation	4.97 ± 1.5	4.87 ± 1.31	4.95 ± 1.45	0.728
Emotional function	4.51 ± 1.63	4.91 ± 1.64	4.61 ± 1.64	0.25
Environmental stimuli	3.98 ± 1.71	4.25 ± 1.72	4.05 ± 1.71	0.449
mAQLQ total	4.31 ± 1.18	4.5 ± 1.19	4.36 ± 1.18	0.445
ACT-1 (During the last 4 weeks, how much of the time has your asthma kept you from getting as much done at work, school or home?)				
All of the time	9 (10.23%)	3 (9.68%)	12 (10.08%)	
Most of the time	18 (20.45%)	6 (19.35%)	24 (20.17%)	
Some of the time	25 (28.41%)	10 (32.26%)	35 (29.41%)	0.992
A little of the time	23 (26.14%)	7 (22.58%)	30 (25.21%)	
None of the time	13 (14.77%)	5 (16.13%)	18 (15.13%)	
ACT-2 (During the last 4 weeks, how often have you had shortness of breath?)				
More than once a day	24 (25.26%)	4 (12.12%)	28 (21.88%)	
Once a day	10 (10.53%)	6 (18.18%)	16 (12.50%)	
3 to 6 times a week	21 (22.11%)	6 (18.18%)	27 (21.09%)	0.385
Once or twice a week	29 (30.53%)	15 (45.45%)	44 (34.38%)	
Not at all	8 (9.09%)	2 (6.45%)	10 (8.40%)	
ACT-3 (During the last 4 weeks, how often have your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) woken you up at night or earlier than usual in the morning?)				
4 or more nights a week	16 (18.18%)	4 (12.90%)	20 (16.81%)	
2 to 3 nights a week	28 (31.82%)	7 (22.58%)	35 (29.41%)	
Once a week	13 (14.77%)	5 (16.13%)	18 (15.13%)	0.547
Once or twice	18 (20.45%)	11 (35.48%)	29 (24.37%)	
Not at all	13 (14.77%)	4 (12.90%)	17 (14.29%)	
ACT-4 (During the last 4 weeks, how often have you used your rescue inhaler or nebulizer medication (such as Salbutamol)?)				
3 or more times a day	8 (9.09%)	1 (3.23%)	9 (7.56%)	0.741
1 or 2 times a day	25 (28.41%)	8 (25.81%)	33 (27.73%)	
2 or 3 times a week	18 (20.45%)	6 (19.35%)	24 (20.17%)	
Once a week or less	16 (18.18%)	5 (16.13%)	21 (17.65%)	
Not at all	21 (23.86%)	11 (35.48%)	32 (26.89%)	
ACT-5 (How would you rate your asthma control during the last 4 weeks?)				
Not controlled at all	4 (4.55%)	0 (0%)	4 (3.36%)	
Poorly controlled	22 (25%)	7 (22.58%)	29 (24.37%)	
Somewhat controlled	35 (39.77%)	12 (38.71%)	47 (39.50%)	0.858
Well-controlled	20 (22.73%)	9 (29.03%)	29 (24.37%)	
Completely controlled	7 (7.95%)	3 (9.68%)	10 (8.40%)	
ACT Total	15.03 ± 4.38	16.19 ± 3.93	15.34 ± 4.28	0.196

ACT, Asthma Control Test; FEV1,Forced Expiratory Volume in 1 second; FVC, Forced Vital Capacity; mAQLQ, mini Asthma Quality of Life questionnaire; Pre – BD, Pre Bronchodilator; SD, standard deviation.

Table 4. Assessment of symptom control, spirometry parameters, mAQLQ, and ACT questionnaires on follow-up. Data are mean ± standard deviation or number of patients, n (%).

Symptom control	Aspergillus non sensitized (n=87)	Aspergillus sensitized (n=31)	Total	p
Controlled	65 (74.71%)	26 (83.87%)	91 (77.12%)	
Partly controlled	14 (16.09%)	3 (9.68%)	17 (14.41%)	0.706
Uncontrolled	8 (9.20%)	2 (6.45%)	10 (8.47%)	
mAQLQ (Mean± SD)	N=87	N=31		
Symptoms	5.08 ± 1.46	5.31 ± 1.39	5.14 ± 1.44	0.458
Activity limitation	5.38 ± 1.39	5.69 ± 1.38	5.46 ± 1.38	0.297
Emotional function	5.33 ± 1.55	5.72 ± 1.43	5.44 ± 1.52	0.23
Environmental stimuli	4.77 ± 1.61	5.19 ± 1.81	4.88 ± 1.67	0.232
mAQLQ total	5.15 ± 1.29	5.5 ± 1.31	5.24 ± 1.3	0.212
ACT-1 (During the last 4 weeks, how much of the time has your asthma kept you from getting as much done at work, school or home?)				
All of the time	3 (3.45%)	0 (0%)	3 (2.54%)	
Most of the time	4 (4.60%)	1 (3.23%)	5 (4.24%)	
Some of the time	20 (22.99%)	6 (19.35%)	26 (22.03%)	0.92
A little of the time	37 (42.53%)	14 (45.16%)	51 (43.22%)	
None of the time	23 (26.44%)	10 (32.26%)	33 (27.97%)	
ACT-2 (During the last 4 weeks, how often have you had shortness of breath?)				
More than once a day	7 (8.05%)	0 (0%)	7 (5.93%)	
Once a day	6 (6.90%)	2 (6.45%)	8 (6.78%)	
3 to 6 times a week	11 (12.64%)	5 (16.13%)	16 (13.56%)	0.61
Once or twice a week	34 (39.08%)	14 (45.16%)	48 (40.68%)	
Not at all	29 (33.33%)	10 (32.26%)	39 (33.05%)	
ACT-3 (During the last 4 weeks, how often have your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) woken you up at night or earlier than usual in the morning?)				
4 or more nights a week	8 (9.20%)	1 (3.23%)	9 (7.63%)	
2 to 3 nights a week	7 (8.05%)	1 (3.23%)	8 (6.78%)	
Once a week	10 (11.49%)	0 (0%)	10 (8.47%)	0.136
Once or twice	15 (17.24%)	6 (19.35%)	21 (17.80%)	
Not at all	47 (54.02%)	23 (74.19%)	70 (59.32%)	
ACT-4 (During the last 4 weeks, how often have you used your rescue inhaler or nebulizer medication (such as Salbutamol)?)				
3 or more times a day	1 (1.15%)	0 (0%)	1 (0.85%)	
1 or 2 times a day	10 (11.49%)	1 (3.23%)	11 (9.32%)	
2 or 3 times a week	5 (5.75%)	2 (6.45%)	7 (5.93%)	0.658
Once a week or less	18 (20.69%)	5 (16.13%)	23 (19.49%)	
Not at all	53 (60.92%)	23 (74.19%)	76 (64.41%)	
ACT-5 (How would you rate your asthma control during the last 4 weeks?)				
Not controlled at all	2 (2.30%)	0 (0%)	2 (1.69%)	
Poorly controlled	4 (4.60%)	1 (3.23%)	5 (4.24%)	
Somewhat controlled	14 (16.09%)	3 (9.68%)	17 (14.41%)	0.565
Well-controlled	37 (42.53%)	11 (35.48%)	48 (40.68%)	
Completely controlled	30 (34.48%)	16 (51.61%)	46 (38.98%)	
ACT Total	19.94 ± 4.34	21.65 ± 3.4	20.39 ± 4.17	0.05

ACT, Asthma Control Test; FEV1, Forced Expiratory Volume in 1 second; FVC, Forced Vital Capacity; mAQLQ, mini Asthma Quality of Life questionnaire; Pre – BD, Pre-Bronchodilator; SD, standard deviation.

Table 5. Comparison of ACT total and mAQLQ total between baseline and follow-up in Aspergillus sensitized and Aspergillus non-sensitized patients.

Outcome	Time Effect (p-value)	Group Effect (p-value)	Time × Group Interaction (p value)
ACT Total	<0.0001	0.003	0.678
mAQLQ Total	<0.0001	<0.0001	0.681

A two-way repeated-measures analysis using a mixed-effects model was performed, with time (baseline and follow-up) as the within-subject factor and Aspergillus sensitization status as the between-subject factor. ACT, Asthma Control Test; mAQLQ, mini–Asthma Quality of Life questionnaire.

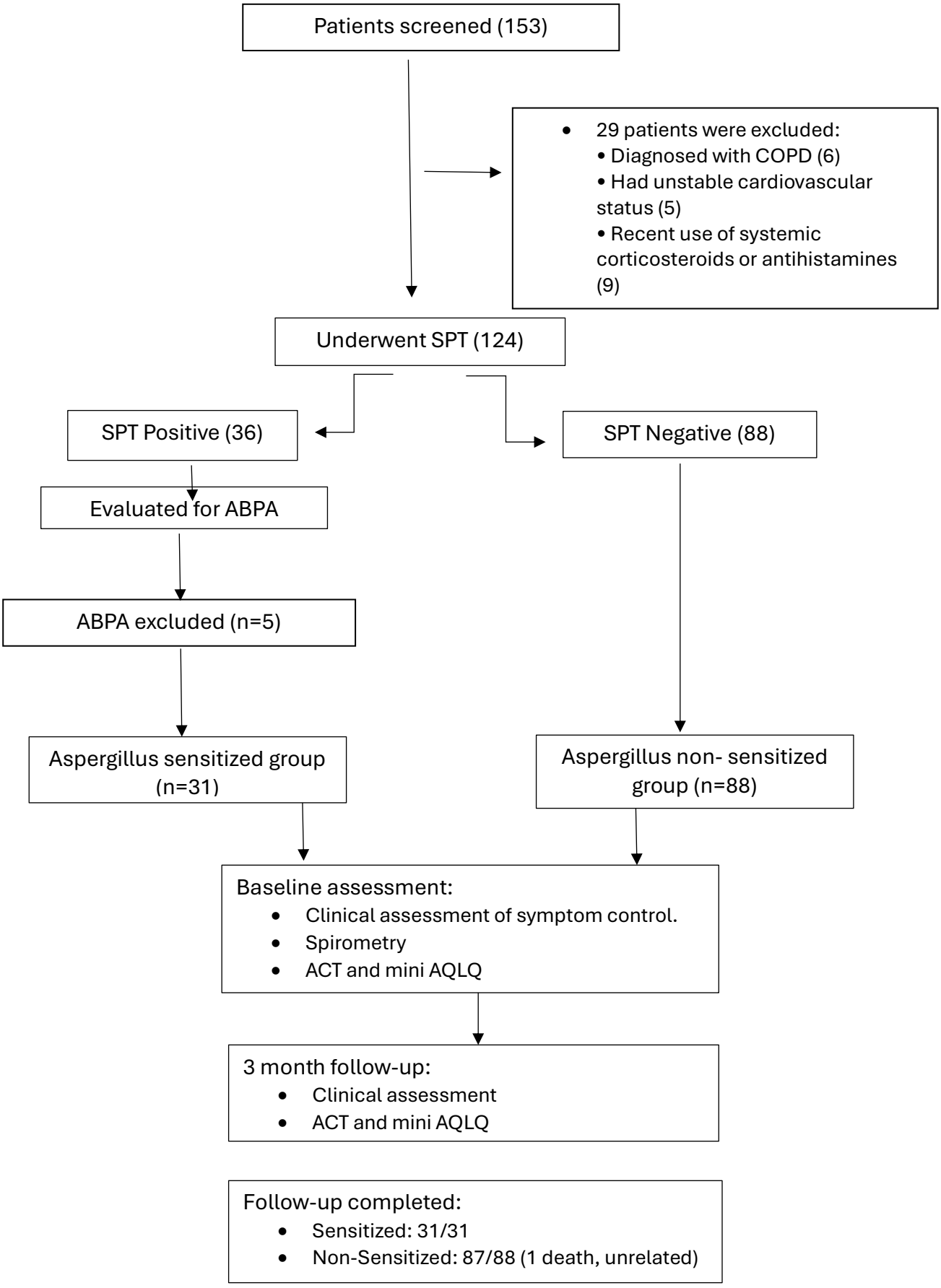

Figure 1. Flow chart of patients included in the study. Numbers in parentheses indicate the number of patients.