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Alternaria Alternata Sensitization in Asthma: A Cross-sectional Study of Prevalence and Demographic Risk Factors

Seyed Hesamodin Nabavizadeh[1], Aida Askarisarvestani[2], Elham Amini[2], Fardin Karbakhsh Ravari[3], and Golnoosh Karimi[4]

[1] Department of Immunology, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran
[2] Allergy Research Center, Shiraz University of Medical Sciences, Shiraz, Iran
[3] Student Research Committee, Shiraz University of Medical Sciences, Shiraz, Iran
[4] Department of Pediatric, Shiraz University of Medical Sciences, Shiraz, Iran

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ABSTRACT

Alternaria alternata is one of the most potent fungal allergens associated with allergic respiratory diseases, particularly asthma. Sensitization to *A alternata* has been linked to poor asthma control and increased morbidity, yet its prevalence varies widely across populations due to environmental and methodological differences. This study aimed to determine the prevalence and demographic predictors of *A alternata* sensitization among patients with moderate to severe asthma.

A cross-sectional study was conducted from March to September 2024 among 80 patients with physician-diagnosed moderate or severe asthma in Shiraz, Iran. Participants underwent skin prick testing (SPT) for *A. alternata*. Demographic and clinical data were collected and analyzed using descriptive statistics, χ^2 tests, and logistic regression.

Among the 80 patients (mean age 29.03 ± 20.45 years; 53.8% male), 28.8% tested positive for *Alternaria* sensitization. Sensitization was significantly more prevalent in patients younger than 18 years (44.1%) compared to adults (17.4%). No significant difference was observed based on sex. Although sensitization was more frequent in patients with severe asthma (40.6%) than moderate asthma (20.8%), this trend was not statistically significant. Logistic regression identified younger age as the only independent predictor of sensitization.

Alternaria alternata sensitization is common among individuals with moderate to severe asthma, particularly in younger patients. These findings underscore the importance of routine fungal allergen screening in asthmatics, especially children, to inform targeted management strategies and potentially reduce asthma-related morbidity.

Keywords: Age; *Alternaria*; Asthma; Fungal sensitization; Skin test

INTRODUCTION

Fungal spores are ubiquitous in the atmosphere, representing the most abundant category of aerobiological particles.[1] Only a limited number of more than 100 000 fungal species are implicated in respiratory diseases, with *Alternaria alternata* recognized as one of the most potent sensitizing molds.[2,3] Sensitization to *A*

Corresponding Author: Golnoosh Karimi, MD;
Department of Pediatric, Shiraz University of Medical Sciences, Shiraz, Iran. Tel: (+98 937) 2586 378, Fax: (+98 71) 3628 156, Email: karimi2807@yahoo.com

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alternata is strongly associated with allergic conditions such as rhinosinusitis, bronchopulmonary mycosis, and particularly asthma, which may lead to severe outcomes including hospitalizations and even asthma-related deaths.[4–6] Reported prevalence rates of *Alternaria* sensitization vary widely across regions, from 0.2% to 44.9%, reflecting geographic, environmental, and methodological differences.[7–9]

In parallel, asthma poses a significant public health challenge, affecting approximately 8.7% of the US population.[10] Among these individuals, nearly 10% experience severe disease, often requiring aggressive pharmacologic management.[11] Severe asthma leads to higher rates of illness, death, and increased healthcare expenses.[12] However, asthma is not uniform; it presents in diverse ways and can be divided into various clinical types.[13] One such type includes individuals sensitized to fungal allergens.[14] Sensitization to airborne allergens, especially fungi, has been linked to the onset of asthma and its severity.[15,16] In asthmatic patients, fungal sensitization has been associated with more severe disease, including poorer asthma control, reduced lung function, more frequent hospital and ICU admissions, respiratory arrest, and even asthma-related fatalities.[17,18]

This study aims to investigate the prevalence of sensitization to *Alternaria* in patients with moderate to severe asthma. Given the known links between fungal sensitization and asthma severity, this research addresses a crucial gap in our understanding of allergic disease burden in underserved and mobile populations.

MATERIALS AND METHODS

This cross-sectional study was conducted from March and September 2024. The study population included physician-diagnosed moderate to severe persistent asthma patients referred to our outpatient clinic. All patients presented with uncontrolled respiratory symptoms and were eligible for skin prick testing (SPT) to *Alternaria alternata*. Asthma severity was determined by a physician and classified as mild, moderate, or severe based on clinical symptoms and spirometric measurements, following the guidelines of the National Heart, Lung, and Blood Institute (NHLBI).[19] Eligibility criteria included a confirmed diagnosis of moderate or severe asthma and suitability for undergoing an *Alternaria alternata* skin prick test (SPT). Patients were excluded if they declined participation or demonstrated an invalid SPT response (negative histamine or positive saline control). Written informed consent was obtained from all participants or their legal guardians prior to enrollment. All eligible patients referred during the study period were systematically screened for inclusion.

Patient data were collected using a structured data form, including age, sex, date of asthma diagnosis, severity of asthma, current medications, and known exposure to allergens. A skin prick test using standardized *Alternaria alternata* extract was performed on the volar aspect of the forearm of all patients. The allergen extract used for SPT was a standardized glycerinated (50% glycerin) extract supplied by Greer (M1 *Alternaria alternata*, SPT 5 mL Glycerin Aqueous, USA). A drop of the allergen was placed on marked skin, and the area was gently pricked using a sterile lancet. Simultaneously, histamine and normal saline were applied as positive and negative controls. All participants were instructed to withhold oral antihistamines for at least 5 days and systemic or topical corticosteroids for at least 7 days prior to testing, as these medications can suppress SPT reactivity. Patients who showed a negative response to histamine or a positive response to saline were excluded from analysis. Test results were read after 15 minutes. A positive test was defined as a wheal diameter ≥3 mm greater than the negative control or a flare with redness exceeding 10 mm in diameter. Tests not meeting these thresholds were considered negative.

Data were entered and analyzed using IBM SPSS Statistics version 26 (IBM Corp, Armonk, NY, USA). Descriptive statistics were reported as range, mean, and standard deviation for quantitative variables and frequencies and percentages for qualitative variables. The χ^2 test (Fisher exact test when expected cell counts were small) was used for categorical comparisons. The independent samples *t* test or the Mann-Whitney *U* test (for nonnormally distributed data) was applied for continuous variables. Logistic regression analysis was used to identify independent predictors of *Alternaria* sensitization. A p value of <0.05 was considered statistically significant.

RESULTS

A total of 80 patients were enrolled in the study. The mean age of participants was 29.03 ± 20.45 years. Of these, 34 individuals (42.5%) were younger than 18, while 46 (57.5%) were aged 18 years or older.

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Regarding sex distribution, 43 patients (53.8%) were male and 37 (46.3%) were female. Regarding asthma severity, 48 patients (60%) were classified as having moderate asthma and 32 patients (40%) as having severe asthma. Skin prick testing for *Alternaria* showed positive results in 23 patients (28.8%) of the total sample (Table 1).

As shown in Table 2, the prevalence of sensitization to *Alternaria* was significantly higher in patients younger than 18 years (44.1%) compared with those aged 18 years or older (17.4%) (p=0.013). There was no statistically significant difference in the prevalence of sensitization between male (25.6%) and female patients (32.4%) (p=0.622). Sensitization to *Alternaria* was more frequently observed among patients with severe asthma (40.6%) than those with moderate asthma (20.8%); however, this difference did not reach statistical significance (p=0.078) (Table 2).

Logistic regression analysis revealed that age group was the only variable significantly associated with *Alternaria* sensitization. Patients younger than 18 years had 3.75 times higher odds of sensitization compared to those aged 18 years or older (odds ratio [OR], 3.75; 95% confidence interval [CI], 1.35–10.39; p=0.011). Neither sex nor asthma severity showed a significant predictive value for sensitization (Table 3). This finding is visually represented in the forest plot, where only the confidence interval for the age group variable does not cross the line of no effect (OR=1), confirming its statistical significance, while the intervals for sex and asthma severity encompass the null value (Figure 1).

Table 1. Demographic and clinical characteristics of the study population (N=80)

Characteristic	Number	Percentage (%)	Mean ± SD
Age, y	–	–	29.03 ± 20.45
Age group			
<18 years	34	42.5	–
≥18 years	46	57.5	–
Sex			
Male	43	53.8	–
Female	37	46.3	–
Asthma severity			
Moderate	48	60.0	–
Severe	32	40.0	–
Positive skin test for *Alternaria*	23	28.8	–

SD: standard deviation.

Table 2. Association between *Alternaria* sensitization and age group, sex, and asthma severity

Variable	Sensitization Positive, n (%)	Sensitization Negative, n (%)	*p*
Age group			
<18 years	15 (44.1)	19 (55.9)	0.013
≥18 years	8 (17.4)	38 (82.6)	
Sex			
Male	11 (25.6)	32 (74.4)	0.622
Female	12 (32.4)	25 (67.6)	
Asthma severity			
Moderate	10 (20.8)	38 (79.2)	0.078
Severe	13 (40.6)	19 (59.4)	

Table 3. Logistic regression analysis of predictors for *Alternaria* sensitization

Variable	Odds Ratio	95% Confidence Interval	*p*
Age <18 years	3.750	1.353–10.395	0.011
Female sex	0.716	0.271–1.891	0.500
Severe asthma	2.600	0.965–7.007	0.059

CI: confidence interval; OR: odds ratio.

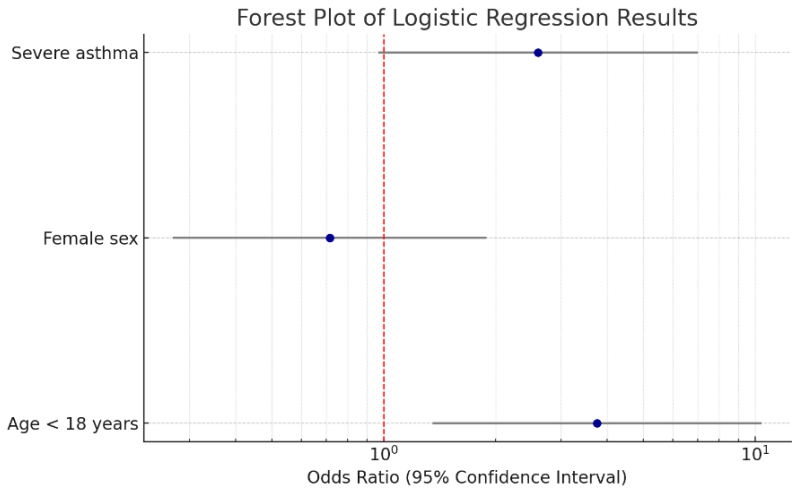

Figure 1. Predictors of *Alternaria* sensitization based on logistic regression analysis.

DISCUSSION

Fungal sensitization, particularly to *Alternaria* species, has emerged as a significant factor in asthma morbidity, especially in environments conducive to mold growth. In our study, the prevalence of *Alternaria* sensitization was 28.8% among patients with moderate to severe asthma, a rate that aligns closely with recent pediatric-focused studies such as Lehmann et al.[20] (15%–25%). This difference might reflect a recent increase in *Alternaria* sensitization over time, as suggested by Hernandez-Ramirez et al, potentially driven by environmental shifts favoring fungal proliferation or improved diagnostic sensitivity.[21] The inclusion of both pediatric and adult asthmatics in our cohort, compared to studies limited to nonasthmatic populations, likely further contributed to the higher prevalence, given the established link between asthma and fungal sensitization.[7,22] Notably, the observed prevalence underscores *Alternaria*'s relevance as a contributor to asthma morbidity, particularly in regions with climatic conditions conducive to mold growth.[21]

A striking finding was the significantly higher rate of sensitization in patients younger than 18 years (44.1%) compared to adults (17.4%), consistent with Guan et al's report of peak sensitization in children aged 6 to 11.[23] This age-related susceptibility may arise from developmental immune factors, such as T_H2-polarized responses in early life, combined with greater environmental exposure during outdoor activities.[24,25] While Lehmann et al documented increasing sensitization with age among children, their exclusion of adults limits direct comparison.[20] Our logistic regression analysis, which identified younger age as an independent predictor (OR, 3.75), suggests that age may be an important factor to consider when assessing sensitization patterns, but further studies with larger samples are needed before making formal recommendations for screening or management.

We found no significant differences in sensitization rates between males and females (p=0.622), a finding that contrasts with some reports indicating higher rates of fungal sensitization in males,[26] yet aligns with broader epidemiological studies that show inconsistent sex-

specific trends in mold allergy.[7,8] This result is also consistent with other investigations that similarly found no association between sex and sensitization to *Alternaria*.[20,27,28] Prior reports attributing higher sensitization rates in females to hormonal influences or airway anatomy may not generalize to asthmatic populations, where shared inflammatory pathways could mitigate sex-specific effects.[8]

Although our study did not find a statistically significant association between asthma severity and *Alternaria* sensitization (p=0.078), the observed trend toward higher sensitization in patients with severe asthma (40.6% vs 20.8% in moderate cases) supports the established role of *Alternaria* in exacerbating asthma morbidity.[4,29–32] Our findings therefore align with previous reports by Lyons et al and Denning et al, who implicated *Alternaria* in worsening asthma severity through protease-mediated epithelial damage and IgE-driven inflammation.[31,32] A study demonstrated that *Alternaria alternata* was the only allergen independently associated with asthma at 6 and 11 years of age, particularly among children with persistent asthma.[33] Similarly, Pezzanowski et al found that *Alternaria* sensitization was more frequent among asthmatics than controls in US cohorts, identifying it as an independent risk factor despite regional variability.[34] A US household study found that higher concentrations of *Alternaria* antigen in house dust were associated with increased risk of current asthma symptoms, especially recent exacerbations.[35]

Alternaria alternata plays a significant role in the pathogenesis of asthma through the induction of a strong type 2 immune response. Upon inhalation, its spores interact with airway epithelial cells and immune receptors, rapidly releasing proinflammatory cytokines and alarmins such as IL-25, IL-33, and TSLP.[36,37] This initiates a cascade involving innate lymphoid cells (ILC2s), eosinophils, and T_H2-related cytokines (IL-4, IL-5, IL-13), resulting in airway hyperreactivity, mucus hypersecretion, and eosinophilic infiltration, hallmarks of severe asthma.[21] The major allergen Alt a 1 is central to this process and may contribute to direct airway inflammation and sensitization.[38] While these mechanisms are well established in experimental models, our study primarily supports their clinical relevance rather than providing mechanistic evidence.

Beyond direct sensitization, *Alternaria* may also influence the broader allergic profile of patients. Studies have considered *Alternaria*'s role as a "Trojan horse" for cosensitization, highlighting its capacity to facilitate immune responses to other allergens. Literature review underscores that *Alternaria* spores can act as carriers for grass pollen allergens (e.g., Phl p 1)[39] and induce cross-reactivity with food allergens like kiwifruit Act-d-2.[40] However, this concept remains hypothetical and should be regarded as a hypothesis-generating framework rather than a demonstrated mechanism, since our study did not assess cosensitization or allergen cross-reactivity directly. Nevertheless, the high prevalence of *Alternaria* sensitization in younger asthmatics may indicate a potential gateway effect, predisposing individuals to polysensitization, a phenomenon that has been associated with greater asthma severity.[29,41] This aligns with murine models where *Alternaria* exposure enhances type 2 polarization of dendritic cells and $CD4^+$ T cells, amplifying responses to unrelated allergens.[42]

Limitations: The small sample size, limited environmental exposure data, and lack of information on certain background factors restrict the generalizability of our findings and the ability to fully assess contributors to *Alternaria* sensitization. Future studies should include larger cohorts, longitudinal designs, and comprehensive assessment of environmental and personal risk factors to better understand *Alternaria*'s role in asthma.

In conclusion, the study highlights a significant prevalence of *Alternaria alternata* sensitization in patients with moderate to severe asthma, particularly among younger individuals. The findings suggest a potential link between *Alternaria* sensitization and asthma severity, with age emerging as a key factor in susceptibility.

STATEMENT OF ETHICS

The study protocol was approved by the Ethics Committee of Shiraz University of Medical Sciences (Ethical Approval Code: IR.SUMS.MED.REC.1403.485). Written informed consent was obtained from all participants prior to enrollment.

FUNDING

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGMENTS

Not applicable.

DATA AVAILABILITY

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request

AI ASSISTANCE DISCLOSURE

Artificial intelligence–based tools (ChatGPT) were used only to improve language quality and readability. No AI tools were used in data analysis, interpretation, or decision-making processes. The authors retain full responsibility for the accuracy and integrity of the work

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