Allergy Asthma Immunol Res. 2025 Jul;17(4):447-459
https://doi.org/10.4168/aair.2025.17.4.447
pISSN 2092-7355·eISSN 2092-7363

Allergy, Asthma & Immunology Research AAIR

Original Article

Prevalence and Clinical Characteristics of Severe Asthma With Fungal Sensitization in Korea

Hyo-In Rhyou,[1†] **Tae-Bum Kim**,[2†] **Sun-Young Yoon**,[3] **Jae-Woo Kwon**,[4] **Hye-Kyung Park**,[5] **Sung-Ryeol Kim**,[6] **Young-Hee Nam**,[7] **Joo-Hee Kim**,[8] **Young-Joo Cho**,[9] **Ho Joo Yoon**,[10] **Yoo Seob Shin**,[11] **Jae-Woo Jung**,[12] **Taehoon Lee**,[13] **Yoon-Seok Chang**,[14] **Sang-Heon Cho**,[15] **Seung-Eun Lee**,[16] **Byung-Jae Lee**,[17] **Hwa Young Lee**,[18] **Hyun Jung Jin**,[19] **So-Young Park**,[20] **Kyoung-Hee Sohn**,[21] **Byung Keun Kim**,[22] **Youngsoo Lee**,[11] **Woo-Jung Song**,[2] **Sang-Heon Kim**,[23*] **Chan Sun Park**[1*]

[1]Department of Internal Medicine, Haeundae Paik Hospital, Inje University College of Medicine, Busan, Korea
[2]Department of Allergy and Clinical Immunology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea
[3]Departments of Allergy and Pulmonology in Internal Medicine, Chungnam National University, Chungnam National University Sejong Hospital, Sejong, Korea
[4]Department of Internal Medicine, Kangwon National University School of Medicine, Chuncheon, Korea
[5]Department of Internal Medicine, Pusan National University School of Medicine, Busan, Korea
[6]Division of Pulmonology, Allergy and Critical Care Medicine, Department of Internal Medicine, Yongin Severance Hospital, Yonsei University College of Medicine, Seoul, Korea
[7]Department of Internal Medicine, Dong-A University School of Medicine, Busan, Korea
[8]Department of Internal Medicine, Hallym University College of Medicine, Anyang, Korea
[9]Department of Internal Medicine, Ewha Womans University College of Medicine, Seoul, Korea
[10]Department of Internal Medicine, Hanyang University College of Medicine, Seoul, Korea
[11]Department of Allergy and Clinical Immunology, Ajou University School of Medicine, Suwon, Korea
[12]Department of Internal Medicine, Chung-Ang University College of Medicine, Seoul, Korea
[13]Department of Internal Medicine, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, Korea
[14]Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Korea
[15]Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea
[16]Department of Internal Medicine, Pusan National University Yangsan Hospital, Yangsan, Korea
[17]Division of Allergy, Department of Medicine, Samsung Medical Center, Sungkyunkwan University College of Medicine, Seoul, Korea
[18]Division of Allergy, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea
[19]Department of Internal Medicine, Yeungnam University College of Medicine, Daegu, Korea
[20]Department of Internal Medicine, Chung-Ang University College of Medicine, Gwangmyeong, Korea
[21]Division of pulmonology and Allergy, Department of Internal Medicine, Kyung Hee University School of Medicine, Seoul, Korea
[22]Division of Pulmonology, Allergy and Critical Care Medicine, Department of Internal Medicine, Korea University College of Medicine, Seoul, Korea
[23]Department of Internal Medicine, Hanyang University Hospital, Hanyang University College of Medicine, Seoul, Korea

Received: Feb 6, 2025
Accepted: Apr 22, 2025
Published online: Jun 4, 2025

Correspondence to
Chan Sun Park
Department of Internal Medicine, Haeundae Paik Hospital, Inje University College of Medicine, 875 Haeun-daero, Haeundae-gu, Busan 48108, Korea.
Tel: +82-51-797-2211
Fax: +82-51-797-1341
Email: mdpcs00@hanmail.net

Sang-Heon Kim
Department of Internal Medicine, Hanyang University Hospital, Hanyang University College of Medicine, 222 Wangsimni-ro, Seongdong-gu, Seoul 04763, Korea.
Tel: +82-2-2298-9183
Fax: +82-2-2298-9183
Email: sangheonkim@hanyang.ac.kr

†Hyo-In Rhyou and Tae-Bum Kim share first co-authorship.

ORCID iDs
Hyo-In Rhyou
https://orcid.org/0000-0003-0905-4649

ABSTRACT

Purpose: Severe asthma with fungal sensitization (SAFS) is associated with life-threatening exacerbation and severe airflow limitation. We aimed to investigate the prevalence of fungal sensitization in asthma and clinical characteristics of SAFS.
Methods: This study analyzed data from the Cohort for Reality and Evolution of Adult Asthma in Korea and the Korean Severe Asthma Registry cohorts. Study subjects were

Tae-Bum Kim
https://orcid.org/0000-0001-5663-0640
Sun-Young Yoon
https://orcid.org/0000-0002-4205-1434
Jae-Woo Kwon
https://orcid.org/0000-0003-1639-3606
Hye-Kyung Park
https://orcid.org/0000-0003-4065-2962
Sung-Ryeol Kim
https://orcid.org/0000-0001-7418-0049
Young-Hee Nam
https://orcid.org/0000-0001-8759-2982
Joo-Hee Kim
https://orcid.org/0000-0002-1572-5149
Young-Joo Cho
https://orcid.org/0000-0002-9414-5934
Ho Joo Yoon
https://orcid.org/0000-0002-4645-4863
Yoo Seob Shin
https://orcid.org/0000-0002-9855-3185
Jae-Woo Jung
https://orcid.org/0000-0002-3411-735X
Taehoon Lee
https://orcid.org/0000-0002-9224-0866
Yoon-Seok Chang
https://orcid.org/0000-0003-3157-0447
Sang-Heon Cho
https://orcid.org/0000-0002-7644-6469
Seung-Eun Lee
https://orcid.org/0000-0002-4266-7722
Byung-Jae Lee
https://orcid.org/0000-0001-6940-0836
Hwa Young Lee
https://orcid.org/0000-0002-1582-2256
Hyun Jung Jin
https://orcid.org/0000-0003-2888-420X
So-Young Park
https://orcid.org/0000-0002-5224-3077
Kyoung-Hee Sohn
https://orcid.org/0000-0001-8407-8080
Byung Keun Kim
https://orcid.org/0000-0001-5147-6306
Youngsoo Lee
https://orcid.org/0000-0001-8918-9353
Woo-Jung Song
https://orcid.org/0000-0002-4630-9922
Sang-Heon Kim
https://orcid.org/0000-0001-8398-4444
Chan Sun Park
https://orcid.org/0000-0003-0113-8354

Disclosure

There are no financial or other issues that might lead to conflict of interest.

classified based on fungal sensitization and asthma severity. Clinical characteristics of patients with severe asthma were compared according to fungal sensitization status.

Results: The rate of skin test positivity to fungi was 14.1% and 7.1% in severe asthma (n = 270) and non-severe asthma (n = 2,605). Patients with SAFS were diagnosed with asthma earlier than those with severe asthma without fungal sensitization (SANFS) ($P = 0.019$), and had a lower body mass index compared to the SANFS group ($P = 0.044$). Factional exhaled nitric oxide levels and sputum eosinophilia/neutrophilia showed significant differences between the SAFS and SANFS groups (all $P < 0.05$). Patients with SAFS were more frequently treated with biologics (36.8% vs. 24.6%, $P = 0.116$) than those with SANFS. Multivariate analysis revealed that early diagnosed asthma was significantly associated with SAFS.

Conclusions: The prevalence of fungal sensitization in severe asthma is approximately twice as high as in non-severe asthma. Early diagnosed asthma may be a risk factor for SAFS, and patients with SAFS face a greater burden of additional treatment compared to those with SANFS. SAFS has a distinct airway inflammation profile that differentiates it from SANFS.

Keywords: Asthma; fungi; immunologic sensitization; eosinophils; neutrophils; biologics

INTRODUCTION

Asthma is a chronic inflammatory airway disease that affects approximately 300 million people worldwide. It is characterized by episodic symptoms, including cough, wheezing, and shortness of breath, variable airway obstruction and airway hyper-responsiveness.[1] The heterogeneous nature of asthma poses significant challenges for accurate diagnosis and treatment, particularly in patients with severe asthma.[2,3] Patients with severe asthma account for approximately 5% to 10% of the asthma population and are significantly associated with increased morbidity, mortality, and socioeconomic burdens.[4] The costs associated with severe asthma exceed 60% of the total costs for asthma management,[5] and ongoing efforts are focused on understanding the heterogeneous characteristics and mechanisms of severe asthma as well as identifying treatable traits to mitigate its impact.

In recent decades, the interplay between microbiome and asthma has been a topic of investigation aimed at unraveling the pathophysiologic mechanisms underlying asthma. Most previous studies on the respiratory microbiome have concentrated on bacterial communities, with comparatively little attention given to fungi.[6] However, airborne fungi are ubiquitous in the global environment and can contribute to respiratory diseases, allergies, and other health issues, despite the highly effective host defense mechanisms against them.[7,8] Notably, *Aspergillus fumigatus*, *Alternaria alternata*, and *Cladosporium herbarum* are recognized as important triggers in fungal allergy, although there are more than 2 million species of fungi globally. Fungal sensitization has been shown to correlate with asthma control and severity, with a higher prevalence of fungal sensitization observed in severe asthma compared to non-severe asthma.[9] Approximately 30% to 70% of patients with severe asthma are sensitized to fungi, which is referred to as severe asthma with fungal sensitization (SAFS), a newly identified phenotype.[10,11] SAFS is associated with reduced lung function, frequent exacerbations, and increased risk of asthma-related mortality. However, clinical characteristics, pathogenesis, and optimized treatment strategies for SAFS remain unclear, and to date, only limited research has been conducted on this topic worldwide. Therefore, this study aimed to investigate the prevalence of fungal sensitization in asthma according to the disease severity and explore the clinical characteristics of SAFS in Korea.

MATERIALS AND METHODS

Study population

The Cohort for Reality and Evolution of Adult Asthma in Korea (COREA) is a multicenter asthma cohort established in 2005, comprising 21 university hospitals. These patients were diagnosed with asthma by allergists and pulmonologists and exhibited symptoms such as dyspnea, cough, sputum or wheezing for more than 3 months. All subjects demonstrated significant airway hyper-responsiveness (the provocative concentration of methacholine that results in a 20% fall in forced expiratory volume in one second [FEV1] < 16 mg/mL) or positive bronchodilator responsiveness (improvement of FEV1 ≥ 12% after inhalation of 180 ug of salbutamol) and were in stable condition with regular medications at the time of enrollment.[12]

The Korean Severe Asthma Registry (KoSAR) cohort serves as a representative severe asthma registry established in 2010 by the Working Group on Severe Asthma, the Korean Academy of Asthma, Allergy, and Clinical Immunology, which includes adults with severe asthma (≥ 18 years). This cohort is a multicenter study of severe and non-severe asthmatics recruited from 39 university hospitals in Korea. All subjects had been treated by asthma specialists for at least 1 year (https://www.severeasthmawg.com/html/).[13]

This retrospective cross-sectional study enrolled a total of 2,874 asthmatics from the COREA and the KoSAR cohorts, all of whom underwent allergen skin prick testing (SPT). If any of the subjects were enrolled in both cohorts, their data were combined into a single entry, and patients with allergic bronchopulmonary aspergillosis (ABPA) were excluded from the study.

This study was approved by the Institutional Review Boards (IRBs) of Haeundae Paik Hospital (IRB number: HPIRB 2024-06-002), and the requirement for informed consent was waived due to the retrospective nature of the study.

Defining severe asthma and fungal sensitization

Severe asthma was defined as follows: patients with asthma who were not well-controlled despite receiving treatment at the Global Initiative of Asthma step 4 of 5; patients with asthma who were well-controlled but experienced more than one urgent care visit per year, received burst steroid treatment more than 3 times a year, had exacerbations following a reduction of 25% in oral or inhaled corticosteroids, or had ever experienced a near-fatal asthma exacerbation.

Patients who underwent allergen SPT were included in the present study, and the aeroallergens used in the SPT comprised a panel of 10 aeroallergens: *Dermatophagoides pteronyssinus*, *Dermatophagoides farina*, tree mix, birch, oak, grass mix, ragweed, mugwort, Japanese hop, *A. alternata*, *A. fumigatus*, cockroach, cat dander, dog hair. Fungal sensitization was defined as a positive SPT response to *A. alternata* and/or *A. fumigatus*. The results of the SPT were interpreted as positive if the mean diameter of the wheal was greater than or equal to 3 mm, or greater than or equal to the response to histamine.

Data collection

Baseline data from the COREA and KoSAR cohorts were retrospectively reviewed to obtain the following information: demographic information (sex, age, body mass index [BMI], smoking status, and pets); comorbidities (allergic rhinitis, chronic rhinosinusitis, nasal

polyp, atopic dermatitis, diabetes mellitus, hypertension); Asthma Control Test (ACT) scores; asthma exacerbation history (including emergency department [ED] visits, hospitalizations and admissions of intensive care unit [ICU], either ever or within the past year); medical treatment details (maintenance dose of inhaled corticosteroids [ICS]-expressed as the budesonide-equivalent dose in mcg/day; use of systemic corticosteroids, including maintenance systemic corticosteroids and total cumulative dosage over the last 6 months-expressed as the prednisolone-equivalent dose in mg; use of biologics; and use of leukotriene modifiers); lung function measurements (FEV1, FEV1/forced vital capacity [FVC], forced mid-expiratory flow ($FEF_{25-75\%}$), and △FEV1% of the initial FEV1); and laboratory test results (white blood cells [WBCs], blood eosinophil count [BEC], fractional exhaled nitric oxide [FeNO], sputum eosinophils, and sputum neutrophils). Participants enrolled in the study received standard medical care and pharmacological treatment, and data were collected at the time of enrollment regarding patient characteristics, medication use, and disease status.

Sputum eosinophilia and neutrophilia were defined as sputum eosinophil percentages of ≥ 3% and sputum neutrophil percentages of ≥ 70%, respectively.

Statistical analysis

Statistical analyses were conducted using SPSS version 22.0 (IBM Corp., Armonk, NY, USA). Continuous variables were presented as mean ± standard deviation, and categorical variables were reported as absolute numbers and percentages. The *t*-test was employed to compare continuous variables, while the χ^2 test was used to compare categorical variables between groups. Univariate and multivariate logistic regression were performed to assess the potential risk factors for SAFS, with variables achieving a *P* value of less than 0.05 in the univariate analysis being included in the multivariate analysis. Pearson correlation analysis or Point-Biserial correlation analysis were applied to evaluate the associations between inflammatory biomarkers (FeNO and sputum eosinophils/neutrophils) and medication use (daily budesonide dosage, total cumulative systemic corticosteroids dosage over last 6 months, biologic treatments, and leukotriene modifiers). A $P < 0.05$ was considered statistically significant, and significant *P* values were adjusted for multiple comparisons using the Bonferroni correction.

RESULTS

Prevalence of fungal sensitization in patients with non-severe and severe asthma

A total of 2,874 patients with asthma were enrolled in the present study (**Fig. 1**).
The participants were categorized in 2 steps. First, they were divided into two groups based on asthma severity: 270 patients with severe asthma and 2,605 with non-severe asthma. Subsequently, they were further stratified based on the presence or absence of fungal sensitization: 38 patients of SAFS and 232 severe asthmatics without fungal sensitization (SANFS); 185 non-severe asthmatics with fungal sensitization and 2,420 non-severe asthmatics without fungal sensitization. The prevalence of fungal sensitization was 14.1% in severe asthma and 7.1% in non-severe asthma.

Demographic and clinical characteristics of patients with severe asthma according to fungal sensitization

A total of 270 patients with severe asthma were included in the comparison, and demographic and clinical characteristics of the SAFS (n = 38) and SANFS (n = 232) groups

https://doi.org/10.4168/aair.2025.17.4.447

Allergy, Asthma & Immunology Research AAIR

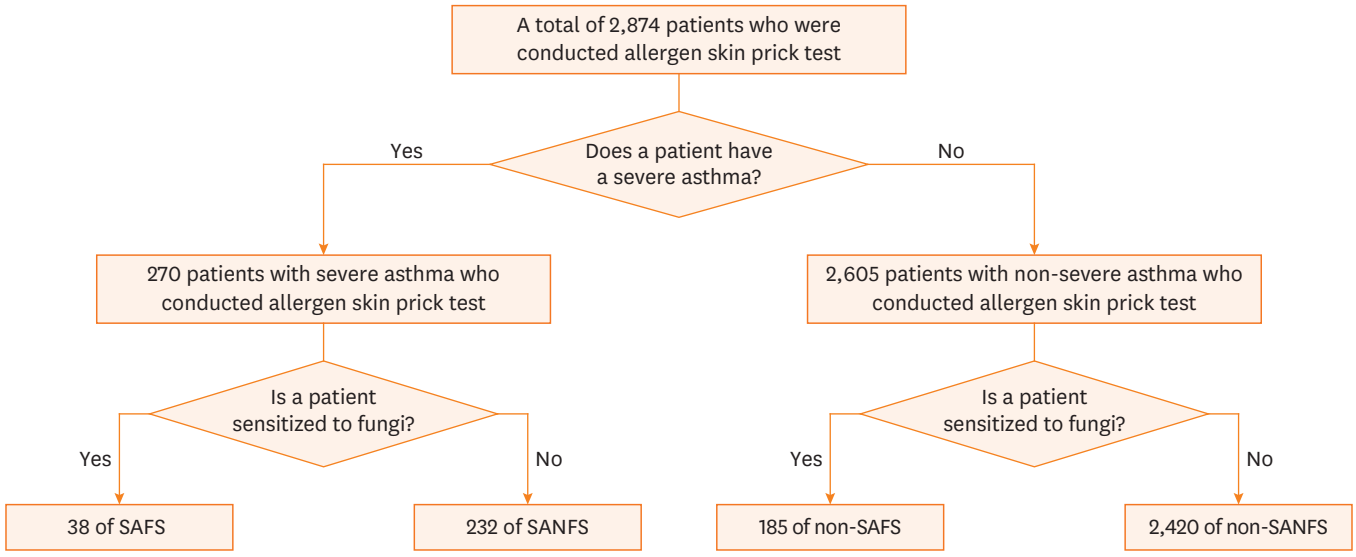

Fig. 1. A study flow diagram describing the selection of subjects.
SAFS, severe asthma with fungal sensitization; SANFS, severe asthma without fungal sensitization.

are presented in **Tables 1** and **2**. Among 38 patients with SAFS, four were sensitized to fungi alone, while the majority, 34 patients, were sensitized to other inhalant allergens in addition to fungi.

There were no significant differences in age or sex between the 2 groups (**Table 1**). Patients were diagnosed with asthma at a younger age in the SAFS group than in the SANFS group (38.5 ± 15.2 vs. 44.9 ± 15.3 years, $P = 0.019$). The BMI was significantly lower in the SAFS group than in the SANFS group (23.6 ± 4.2 vs. 25.1 ± 4.0 kg/m^2, $P = 0.044$).

There were no significant differences in ACT score, lung function, or bronchial responsiveness between the 2 groups. However, the ACT score, pre-FEV1/FVC, and pre-$FEF_{25-75\%}$ were lower in the SAFS group than in the SANFS group (**Table 2**).

In terms of inflammatory biomarkers, FeNO levels (50.3 ± 56.9 vs. 75.0 ± 51.9 ppb, $P = 0.036$) and proportion of sputum eosinophilia (50.0% vs. 85.7%, $P = 0.002$) were significantly higher

Table 1. Comparison of demographic characteristics between patients with SAFS and SANFS

Characteristics	SAFS (n = 38)	SANFS (n = 232)	*P* value
Sex, male	14 (36.8)	112 (48.3)	0.221
Age (yr)	52.2 ± 13.8	53.5 ± 14.8	0.595
Age at asthma diagnosis (yr) (n = 262)	38.5 ± 15.2	44.9 ± 15.3	0.019
Body mass index (kg/m^2)	23.6 ± 4.2	25.1 ± 4.0	0.044
Never smoker	15 (39.5)	105 (45.3)	0.506
Pet owner (current)	9 (23.7)	55 (23.8)	0.987
Comorbidities			
Allergic rhinitis	29/37 (78.4)	153/195 (78.5)	0.991
Chronic rhinosinusitis	17/35 (48.6)	73/170 (42.9)	0.578
Nasal polyp	9/34 (26.5)	30/172 (17.4)	0.234
Atopic dermatitis	4/34 (11.8)	14/179 (7.8)	0.499
Diabetes mellitus	4/35 (11.4)	20/172 (11.6)	0.973
Hypertension	7/34 (20.6)	46/171 (26.9)	0.443

Data are presented as mean ± standard deviation or number (%).
SAFS, severe asthma with fungal sensitization; SANFS, severe asthma without fungal sensitization.

https://doi.org/10.4168/aair.2025.17.4.447

Table 2. Comparison of clinical characteristics and laboratory findings between patients with SAFS and SANFS

Characteristics	SAFS (n = 38)	SANFS (n = 232)	*P* value
Asthma Control Test	17.5 ± 5.5	18.8 ± 4.6	0.098
Lung function			
Pre-FEV1 (%) (n = 258)	71.2 ± 18.6	68.1 ± 18.9	0.368
Pre-FEV1/FVC (n = 267)	62.6 ± 17.8	67.0 ± 13.5	0.079
Pre-$FEF_{25-75\%}$ (L/s) (n = 261)	1.3 ± 1.0	1.6 ± 1.1	0.223
△FEV1 % of the initial FEV1 (n = 83)	6.8 ± 11.8	7.4 ± 10.8	0.812
Inflammatory biomarker			
Total IgE (IU/mL) (n = 218)	578.3 ± 720.0	483.3 ± 716.4	0.468
WBC (*10^3 cells/uL) (n = 249)	8.1 ± 2.3	8.0 ± 2.9	0.748
BEC (cells/uL) (n = 239)	538.1 ± 531.4	525.8 ± 810.9	0.911
Sputum eosinophils ≥ 3%	7/14 (50.0)	60/70 (85.7)	0.002
Sputum neutrophils ≥ 70%	10/14 (71.4)	21/63 (33.3)	0.009
FeNO (ppb) (n = 160)	50.3 ± 56.9	75.0 ± 51.9	0.036
Treatments			
ICS* (n = 237)	716.5 ± 446.2	736.5 ± 511.7	0.828
SCS use (last 6 months)	22/37 (59.5)	109/223 (48.9)	0.287
Maintenance of OCS (last 6 months)	4/37 (10.8)	29/194 (14.9)	0.616
Total dosage of SCS (last 6 months)† (n = 120)	357.4 ± 416.4	341.9 ± 443.2	0.877
Biologics	14/38 (36.8)	57/232 (24.6)	0.116
Leukotriene modifiers	34/37 (91.9)	171/225 (76.0)	0.031
Asthma exacerbation related event			
ED visit (ever)	20/35 (57.1)	89/196 (45.4)	0.270
ED visit (a previous year)	8/34 (23.5)	33/183 (18.0)	0.476
Hospitalization (ever)	17/36 (47.2)	83/195 (42.6)	0.715
Hospitalization (a previous year)	5/34 (14.7)	31/184 (16.8)	0.810
ICU care (ever)	2/31 (6.5)	5/114 (4.4)	0.642
ICU care (a previous year)	1/31 (3.2)	1/113 (0.9)	0.385

Data are presented as mean ± standard deviation or number (%).
SAFS, severe asthma with fungal sensitization; SANFS, severe asthma without fungal sensitization; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; $FEF_{25-75\%}$, forced mid-expiratory flow; IgE, immunoglobulin E; WBC, white blood cell; BEC, blood eosinophil count; FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroid; SCS, systemic corticosteroid; OCS, oral corticosteroid; ED, emergency department; ICU, intensive care unit.
*Equivalent dose of budesonide, mcg/day; †Equivalent dose of prednisolone, mg.

in the SANFS group, whereas the SAFS group demonstrated a significantly higher proportion of sputum neutrophilia (71.4% vs. 33.3%, *P* = 0.009) (**Table 2**, **Fig. 2**).

No significant differences were observed between the two groups regarding the use of inhaled and systemic corticosteroids. However, patients with SAFS were more frequently treated with biologics (36.8% vs. 24.6%, *P* = 0.116) and leukotriene modifiers (91.9% vs. 76.0%, *P* = 0.031) compared to those with SANFS, with the latter difference reaching statistical significance. In both groups, the use of anti-immunoglobulin E (IgE) (SAFS, 3 [7.9%]; SANFS, 16 [6.9%]), anti-interleukin (IL)-5/5R (SAFS, 4 [10.6%]; SANFS, 17 [7.3%]), anti-IL-4R/IL-13 (SAFS, 5 [13.2%]; SANFS, 17 [7.3%]), and anti-TSLP (SANFS, 1 [0.4%]) was similar, with no statistically significant differences between the groups (*P* = 0.734) (**Supplementary Table S1**).

The history of ED visits (ever, 57.1% vs. 45.4%, *P* = 0.270; a previous year, 23.5% vs. 18.0%, *P* = 0.476) and ICU admissions (ever, 6.5% vs. 4.4%, *P* = 0.642; a previous year, 3.2% vs. 0.9%, *P* = 0.385) due to asthma exacerbation appeared to be more frequent in the SAFS group than in the SANFS group, although these differences were not statistically significant (**Table 2**).

https://doi.org/10.4168/aair.2025.17.4.447

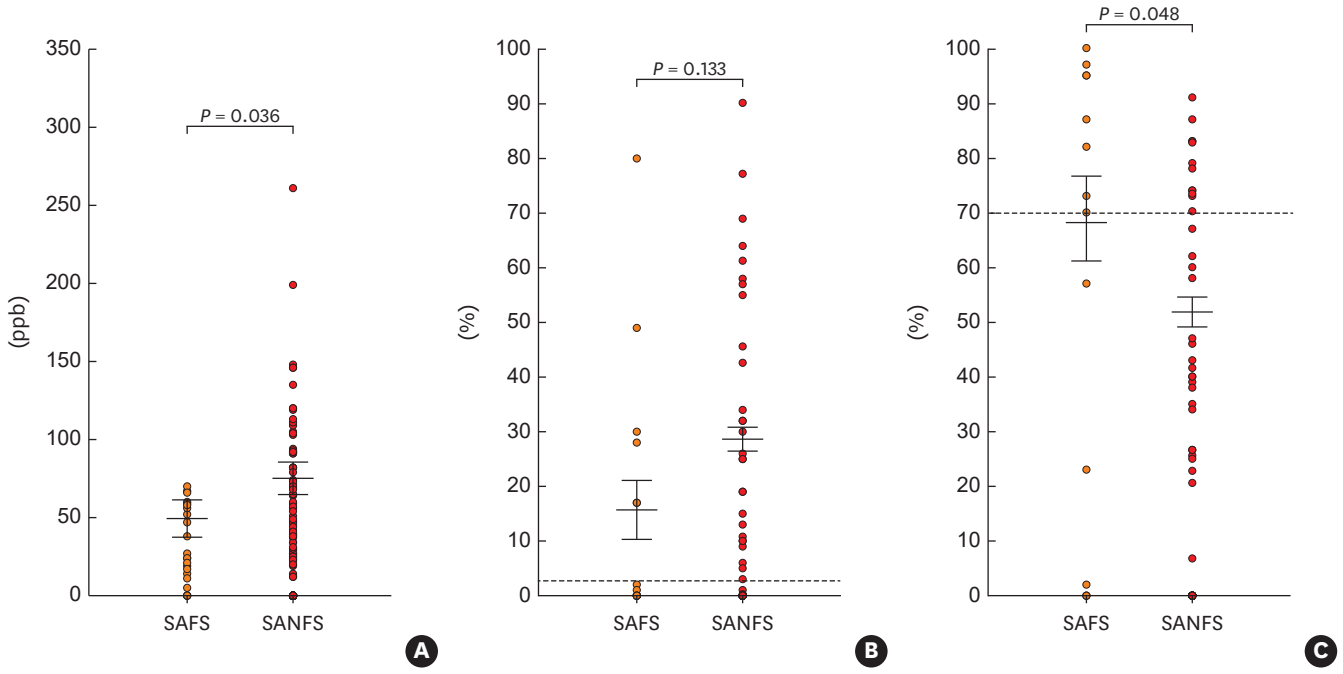

Fig. 2. Comparison of the inflammatory biomarkers between the SAFS and SANFS groups. Levels of (A) FeNO, (B) sputum eosinophils, and (C) sputum neutrophils between the SAFS and the SANFS groups were compared. The dotted lines represent the threshold that differentiates sputum eosinophilia in graph (B) and sputum neutrophilia in graph (C), respectively.
SAFS, severe asthma with fungal sensitization; SANFS, severe asthma without fungal sensitization; FeNO, fractional exhaled nitric oxide.

Demographic and clinical characteristics between patients with SAFS and SANFS according to atopic status

Most patients (89.5%, n = 34) in the SAFS group were also sensitized to allergens other than fungi. Therefore, they exhibited characteristics of allergic asthma as well. To account for this, the SANFS group was further stratified into 2 subgroups based on the presence or absence of sensitization to aeroallergens, excluding fungi, for comparison with the SAFS group. The subgroups included 73 patients with non-atopic severe asthma (non-atopic SANFS) and 159 with atopic severe asthma without fungal sensitization (atopic SANFS). Consequently, we compared the demographic and clinical characteristics of the SAFS group with both the non-atopic SANFS and atopic SANFS groups (**Supplementary Tables S2** and **S3**).

The age at asthma diagnosis was significantly lower in the SAFS group than in the non-atopic SANFS group (38.5 ± 14.3 vs. 48.5 ± 14.8 years, $P = 0.001$), though not significantly different when compared with the atopic SANFS group (43.3 ± 15.2 years, $P = 0.088$). BMI of the SAFS group was also lower compared with both the non-atopic SANFS (23.6 ± 4.2 vs. 25.4 ± 3.9 kg/m^2, $P = 0.032$) and atopic SANFS (25.0 ± 4.0 kg/m^2, $P = 0.072$) (**Supplementary Table S2**).

The ACT score was lower in the SAFS group than in the atopic SANFS group (17.5 ± 5.5 vs. 19.2 ± 4.6, $P = 0.048$), although there was no statistical significance when compared to the non-atopic SANFS (17.5 ± 5.5 vs. 18.1 ± 4.5, $P = 0.524$) (**Supplementary Table S3**).

No significant differences were observed in spirometry and bronchodilator test results between the SAFS and non-atopic SANFS groups (pre-FEV1, 71.2% ± 18.6% vs. 67.2% ± 19.5%, $P = 0.309$; pre-FEV1/FVC, 62.6% ± 17.8% vs. 64.0% ± 13.4%, $P = 0.642$; pre-$FEF_{25-75\%}$, 1.3 ± 1.0 vs. 1.3 ± 1.0 L/s, $P = 0.740$; △FEV1% of the initial FEV1, 6.8% ± 11.8% vs. 4.5% ± 4.2%, $P = 0.587$)

https://doi.org/10.4168/aair.2025.17.4.447

(**Supplementary Table S3**). On the contrary, the SAFS group demonstrated more severe airway obstruction compared to the atopic SANFS group (pre-FEV1, 68.6% ± 18.6%, $P = 0.455$; pre-FEV1/FVC, 68.3% ± 13.4%, $P = 0.027$; pre-$FEF_{25-75\%}$, 1.7 ± 1.2 L/s, $P = 0.067$).

FeNO levels trended lower in the SAFS group than in the non-atopic SANFS (50.3 ± 56.9 vs. 81.1 ± 55.0 ppb, $P = 0.044$) and also lower compared with atopic SANFS (73.0 ± 51.0 ppb, $P = 0.056$) (**Supplementary Table S3**). Additionally, significant differences in inflammatory sputum cell analysis were observed: the SAFS group exhibited a lower proportion of sputum eosinophilia and a higher proportion of sputum neutrophilia compared with the non-atopic SANFS (sputum eosinophilia, 50.0% vs. 94.1%, $P = 0.011$; sputum neutrophilia, 71.4% vs. 21.4%, $P = 0.021$) and the atopic SANFS groups (sputum eosinophilia, 83.0%, $P = 0.016$; sputum neutrophilia, 36.7%, $P = 0.032$).

There were no significant differences in corticosteroid treatment (inhaled or systemic) among the SAFS group and the other 2 groups (Table S3). However, biologic treatment and leukotriene modifiers were more frequently prescribed in the SAFS group than in the non-atopic SANFS (biologics, 36.8% vs. 16.4%, $P = 0.020$; leukotriene modifiers, 91.9% vs. 75.7%, $P = 0.033$) and atopic SANFS groups (biologics, 28.3%, $P = 0.327$; leukotriene modifiers, 76.1%, $P = 0.034$).

The frequency of asthma exacerbation-related events (ED visit/hospitalization/ICU care) among the SAFS and the other 2 groups did not show a significant difference.

Correlation analysis between airway inflammation parameters and treatments

A correlation analysis was performed to assess whether therapeutic agents such as corticosteroids, biologics, and leukotriene modifiers influenced the levels of inflammatory biomarkers. In the SANFS group, blood eosinophils and FeNO were not significantly correlated with the daily dosage of ICS, the total systemic corticosteroid dosage over the past 6 months, or treatment with biologics and leukotriene modifiers (**Table 3**). Sputum eosinophils showed a positive correlation with the daily ICS dosage ($r = 0.424$, $P < 0.05$). In contrast, sputum neutrophils were negatively correlated with the daily ICS dosage ($r = -0.304$, $P < 0.05$) and biologic treatments ($r = -0.303$, $P < 0.05$). There was no significant correlation between inflammatory biomarkers and treatments in the SAFS group.

Table 3. Correlation analysis between inflammatory biomarkers and treatments in the SANFS and SAFS groups

Variables	ICS*	Total systemic corticosteroids in last 6 months†	Biologics	Leukotriene modifiers
Blood eosinophils (cells/uL)	$r = 0.088$ $r' = -0.098$	$r = -0.128$ $r' = -0.037$	$r = 0.002$ $r' = 0.170$	$r = 0.041$ $r' = -0.238$
FeNO (ppb)	$r = 0.129$ $r' = -0.051$	$r = -0.032$ $r' = 0.078$	$r = 0.091$ $r' = 0.250$	$r = 0.031$ $r' = -0.210$
Sputum eosinophils (%)	$r = 0.424$‡ $r' = 0.207$	$r = -0.042$ $r' = 0.523$	$r = 0.190$ $r' = 0.173$	$r = -0.073$ $r' = -0.211$
Sputum neutrophils (%)	$r = -0.304$‡ $r' = -0.177$	$r = -0.086$ $r' = -0.223$	$r = -0.303$‡ $r' = -0.146$	$r = 0.137$ $r' = 0.273$

r and r' values represent Pearson correlation coefficient in the SANFS and SAFS groups, respectively.
SANFS, severe asthma without fungal sensitization; SAFS, severe asthma with fungal sensitization; ICS, inhaled corticosteroids; FeNO, fractional exhaled nitric oxide.
*Equivalent dose of budesonide, mcg/day; †Equivalent dose of prednisolone, mg.
‡$P < 0.05$.

https://doi.org/10.4168/aair.2025.17.4.447

Table 4. Potential associated factors for fungal sensitization in severe asthma

Variables	Univariate		Multivariate	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age at asthma diagnosis	0.972 (0.950–0.996)	0.021	0.933 (0.871–0.999)	0.048
Body mass index	0.897 (0.811–0.991)	0.033	0.779 (0.606–1.002)	0.052
FeNO	0.986 (0.974–0.999)	0.036	1.004 (0.990–1.019)	0.576
Sputum eosinophilia	0.167 (0.048–0.578)	0.005	0.244 (0.037–1.607)	0.142
Sputum neutrophilia	5.000 (1.401–17.846)	0.013	3.667 (0.613–21.938)	0.154

OR, odds ratio; CI, confidential interval; FeNO, fractional exhaled nitric oxide.

Analysis of factors associated with SAFS in severe asthma

In the univariate analysis, several factors were significantly associated with fungal sensitization in patients with severe asthma, including age at asthma diagnosis (odds ratio [OR], 0.972; 95% confidence interval [CI], 0.950–0.996; $P = 0.021$), BMI (OR, 0.897; 95% CI, 0.811–0.991; $P = 0.033$), FeNO (OR, 0.986; 95% CI, 0.974–0.999; $P = 0.036$), sputum eosinophilia (OR, 0.167; 95% CI, 0.048–0.578; $P = 0.005$), and sputum neutrophilia (OR, 5.000; 95% CI, 1.401–17.846; $P = 0.013$) (**Table 4**). However, in the multivariate analysis, age at asthma diagnosis emerged as the only significant factor associated with fungal sensitization in patients with severe asthma (OR, 0.933; 95% CI, 0.871–0.999; $P = 0.048$).

DISCUSSION

We identified the prevalence of fungal sensitization in severe and non-severe asthma from representative nationwide asthma cohorts in Korea and significant distinguishing inflammatory profiles as well as early diagnosed asthma as a potential risk factor of SAFS compared to severe asthma without fungal sensitization.

Fungal sensitization is associated with asthma severity and is more prevalent in severe asthma than in non-severe asthma. The prevalence of fungal sensitization varies based on environmental factors, including climate conditions and fungal exposure, ranging from 5% to 10% in the general population and up to 80% among asthmatics.[14] Additionally, the high variability and poor quality of fungal extracts used as diagnostic solutions contribute to inaccuracies in diagnosing fungal allergies. In severe asthma, over 70% of patients exhibit skin reactivity to at least one fungus (*e.g.*, *A. fumigatus*, *Penicillium notatum*, *C. herbarum*, *A. alternata*, or *Candida albicans*), while only 16%–19% of those with moderate or mild asthma in the UK show skin reactivity to molds.[9] A retrospective study in Korea revealed that 67 out of 551 children with asthma (12.2%) were sensitized to fungi (*A. fumigatus*, *A. alternata*)[15]; however, there is a lack of studies evaluating the prevalence of fungal sensitization in adults with asthma. In the present study, we confirmed skin test positivity to *A. fumigatus and A. alternata* in adults with asthma. Compared to previous results,[15] the rate of fungal sensitization is lower in adults than in children with asthma, which aligns with earlier studies evaluating the prevalence of fungal sensitization across age groups.[16,17] Additionally, the rate of fungal sensitization in severe asthma was approximately twice as high as in non-severe asthma.

We compared demographic characteristics between the SAFS and SANFS groups, revealing that patients with SAFS were diagnosed with asthma at a significantly younger age and had a lower BMI than those with SANFS. Notably, most patients with SAFS exhibited polysensitization to other aeroallergens in addition to fungi, rather than sensitization to fungi alone. Considering the impact of sensitization to other aeroallergens, we further divided the non-SAFS group into

https://doi.org/10.4168/aair.2025.17.4.447

those who were non-sensitized and those sensitized to any allergens other than fungi. Age at asthma diagnosis was significantly younger in the SAFS group than in the non-atopic SANFS group, while there was no significant difference between the SAFS and atopic SANFS groups. This suggests that an early diagnosis of asthma is more characteristic of atopic asthma rather than SAFS. However, the SAFS group exhibited the lowest age at asthma diagnosis, which was identified as a significant factor for SAFS development in the multivariate analysis. The prevalence of fungal sensitization is known to be highest during the teenage years and gradually decreases thereafter.[18] Additionally, fungal sensitization is associated with developing asthma in children.[19] It is also well established that asthma with coexisting fungal sensitization is related to severe asthma.[20] Taken together, a high prevalence of fungal sensitization in adolescents or young adults may be associated with a higher risk of development of SAFS. Conversely, the use of inhaled corticosteroids affects the airway microbiome in patients with asthma.[21,22] The potential for long-term use of inhaled corticosteroids to induce fungal colonization or sensitization exists, and further studies are needed.

Fungal sensitization is associated with a higher risk of life-threatening asthma exacerbation requiring ICU care, mortality, and severe airway obstruction compared to asthma sensitized to other aeroallergens or non-sensitized asthma.[23,24] In the present study, no significant differences were observed in lung function, asthma exacerbation-related outcomes, or ACT scores between the SAFS and SANFS groups. However, when comparing patients with SAFS to those with atopic SANFS, SAFS patients demonstrated more severe airway obstruction and lower ACT scores. Fungi have particularly a small size and distinct surface properties, such as fungal pattern recognition molecules, so they can mediate the activation of the respiratory barrier as a trigger for asthma.[7] The exposure concentration of fungal conidia is more than 1,000 times higher than that of grass and pollens.[9,25] Fungi also exhibit diverse antigenic signatures depending on different life cycle stages.[26] Taken together, fungal sensitization, unlike other inhalant allergens, may play a significant role in poor asthma control and severe airflow limitation. Notably, the SAFS group exhibited a higher frequency of biologic treatment and leukotriene modifier use than the other control groups, highlighting the substantial treatment burden associated with SAFS. Furthermore, although not statistically significant, asthma exacerbation-related events occurred more frequently in the SAFS group than in the SANFS group. Further research is warranted to assess the overall socioeconomic impact of SAFS and to explore optimized treatment strategies.

Asthmatics with fungal sensitization represent a subtype of atopic asthma, which is characterized by eosinophilic and type 2 inflammatory phenotypes.[7] A previous study involving 551 asthmatics indicated significantly higher levels of blood eosinophils, eosinophil cationic protein, and FeNO in groups sensitized to fungi and other aeroallergens compared to the non-sensitized group, although no significant differences were noted between the 2 atopic groups.[15] Twenty-eight patients with SAFS exhibited higher blood eosinophil counts and total IgE levels compared to 28 matched non-sensitized asthmatics.[24] The type 2/eosinophilic inflammation phenotype is a typical characteristic of SAFS, and clinical data have been accumulated that biologic agents such as anti-IgE, anti-IL-5, and anti-IL-4/13 showed a positive effect in SAFS.[27] Our results indicate that all three groups (non-atopic SANFS, atopic SANFS, and SAFS) displayed prominent eosinophilic inflammatory profiles (high BEC, sputum eosinophilia, elevated FeNO), reinforcing the notion of an eosinophilic/type 2 phenotype in severe asthmatics, despite variations in allergen sensitization. Interestingly, patients with SAFS exhibited significantly lower FeNO levels and a higher sputum neutrophil ratio compared to the other 2 groups, suggesting that in addition to eosinophilic inflammation, neutrophilic inflammation is also predominant

in SAFS compared to SANFS. We considered the possibility that treatment effects may influence inflammatory biomarkers and conducted correlation analyses. A positive correlation was found between sputum eosinophils and biologics treatment, while a negative correlation was noted between sputum neutrophils and biologic treatments (most commonly applied in the SAFS group). These findings suggest that the differences in inflammatory biomarkers between the SAFS group and the other control groups reflect the unique inflammatory profiles of SAFS. Previous data indicated that more sputum neutrophils were found in patients sensitized to *A. fumigatus* compared to non-sensitized patients in a cohort where approximately 90% were classified as severe asthma.[28] Moreover, *A. fumigatus*-sensitized asthmatics exhibited significantly higher positive culture rates of *A. fumigatus* in sputum, indicating fungal colonization. Indeed, fungal infections or exposures have been shown to induce T helper (Th)1- and Th17-type adaptive immunity in various animal models,[29-33] and interaction between *Candida albicans* and dendritic cells in mouse models have been shown to induce both Th1- and Th2-type responses.[34] Both Th1/Th17 and Th2 immune responses may be elicited following exposure to fungi,[35,36] and the neutrophil/eosinophil bi-dominant inflammation observed in this study may support these findings, highlighting the need for further research to elucidate the underlying inflammatory mechanism in SAFS. Reducing the burden of fungal exposure in the airways can be a treatment strategy for SAFS. Although antifungal treatment was not administered to patients with SAFS in this study, it may offer effectiveness. Antifungal treatment reduced the burden of fungi, showing effectiveness in controlled trials in ABPA,[37,38] and a prior controlled trials noted significant improvements in SAFS patients following 8 months of oral itraconazole treatment.[39] Collectively, these findings suggest that fungal colonization and ongoing exposure may play a role in SAFS, inducing both neutrophilic and eosinophilic/type 2 inflammation, leading to more complex inflammatory profiles.

The present study has several limitations. First, it is a retrospective cross-sectional study based on cohort data, which may limit the information available regarding asthma outcomes and changes in inflammatory biomarkers after treatments due to varying follow-up duration among individual subjects. However, this study includes the largest number of patients with SAFS reported to date and is significant as it relies on nationwide cohort data. Second, environmental factors such as living conditions and occupational exposures were not sufficiently considered. Third, there were many missing values in FeNO and sputum analyses, which could lower the statistical power. Nevertheless, our findings revealed statistically significant differences in inflammatory biomarkers, and further investigation is needed in the future.

In conclusion, the prevalence of fungal sensitization in severe asthma is approximately twice that observed in non-severe asthma. Early diagnosis of asthma with concurrent fungal sensitization may confer a higher risk for SAFS, necessitating long-term monitoring and proactive asthma management. Additionally, both neutrophilic and eosinophilic inflammation may serve as crucial mechanisms in SAFS, warranting the consideration of treatment strategies aimed at reducing this complex airway inflammation.

ACKNOWLEDGMENTS

This research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HI19C0481, HC20C0076) and the Korea National Institute of Health research project (project No.2025-ER1206-00). The authors

thank the investigators, clinical research coordinators, and participants for their time and efforts in the KoSAR.

SUPPLEMENTARY MATERIALS

Supplementary Table S1

Profiles of treated biologics in study subjects

Supplementary Table S2

Comparison of demographic characteristics between in patients with SAFS and non-atopic SANFS and atopic SANFS

Supplementary Table S3

Comparison of clinical characteristics and laboratory findings between patients with SAFS and non-atopic SANFS and atopic SANFS

REFERENCES

1. Holgate ST, Wenzel S, Postma DS, Weiss ST, Renz H, Sly PD. Asthma. Nat Rev Dis Primers 2015;1:15025. PUBMED | CROSSREF
2. Jones TL, Neville DM, Chauhan AJ. Diagnosis and treatment of severe asthma: a phenotype-based approach. Clin Med (Lond) 2018;18:s36-40. PUBMED | CROSSREF
3. Ricciardolo FLM, Guida G, Bertolini F, Di Stefano A, Carriero V. Phenotype overlap in the natural history of asthma. Eur Respir Rev 2023;32:220201. PUBMED | CROSSREF
4. Porsbjerg C, Melén E, Lehtimäki L, Shaw D. Asthma. Lancet 2023;401:858-73. PUBMED | CROSSREF
5. Sadatsafavi M, Lynd L, Marra C, Carleton B, Tan WC, Sullivan S, et al. Direct health care costs associated with asthma in British Columbia. Can Respir J 2010;17:74-80. PUBMED | CROSSREF
6. Campbell CD, Gleeson M, Sulaiman I. The role of the respiratory microbiome in asthma. Front Allergy 2023;4:1120999. PUBMED | CROSSREF
7. Tiwary M, Samarasinghe AE. Initiation and pathogenesis of severe asthma with fungal sensitization. Cells 2021;10:913. PUBMED | CROSSREF
8. Prasad R, Kazmi SAH, Kacker R, Nikhil G. Severe asthma with fungal sensitization. Indian J Allergy Asthma Immunol 2021;35:3-7. CROSSREF
9. Denning DW, O'Driscoll BR, Hogaboam CM, Bowyer P, Niven RM. The link between fungi and severe asthma: a summary of the evidence. Eur Respir J 2006;27:615-26. PUBMED | CROSSREF
10. Jain AK, Kumar A. Fungal sensitization and its impact on asthma control-a prospective study at allergy clinic. Indian J Allergy Asthma Immunol 2023;37:17-20. CROSSREF
11. Agarwal R, Muthu V, Sehgal IS. Relationship between *Aspergillus* and asthma. Allergol Int 2023;72:507-20. PUBMED | CROSSREF
12. Park SY, Jung HW, Lee JM, Shin B, Kim HJ, Kim MH, et al. Novel trajectories for identifying asthma phenotypes: a longitudinal study in Korean asthma cohort, COREA. J Allergy Clin Immunol Pract 2019;7:1850-1857.e4. PUBMED | CROSSREF
13. Kim SH, Lee H, Park SY, Park SY, Song WJ, Kim JH, et al. The Korean Severe Asthma Registry (KoSAR): real world research in severe asthma. Korean J Intern Med 2022;37:249-60. PUBMED | CROSSREF
14. Pfeiffer S, Swoboda I. Problems encountered using fungal extracts as test solutions for fungal allergy diagnosis. J Fungi (Basel) 2023;9:957. PUBMED | CROSSREF
15. Byeon JH, Ri S, Amarsaikhan O, Kim E, Ahn SH, Choi IS, et al. Association between sensitization to mold and impaired pulmonary function in children with asthma. Allergy Asthma Immunol Res 2017;9:509-16. PUBMED | CROSSREF
16. Twaroch TE, Curin M, Valenta R, Swoboda I. Mold allergens in respiratory allergy: from structure to therapy. Allergy Asthma Immunol Res 2015;7:205-20. PUBMED | CROSSREF

17. Forkel S, Beutner C, Schröder SS, Bader O, Gupta S, Fuchs T, et al. Sensitization against fungi in patients with airway allergies over 20 years in Germany. Int Arch Allergy Immunol 2021;182:515-23. PUBMED | CROSSREF
18. Kwong K, Robinson M, Sullivan A, Letovsky S, Liu AH, Valcour A. Fungal allergen sensitization: prevalence, risk factors, and geographic variation in the United States. J Allergy Clin Immunol 2023;152:1658-68. PUBMED | CROSSREF
19. Wen HJ, Wang SL, Li MC, Guo YL. *Aspergillus* sensitization associated with current asthma in children in the United States: an analysis of data from the 2005-2006 NHANES. Epidemiol Health 2022;44:e2022099. PUBMED | CROSSREF
20. Medrek SK, Kao CC, Yang DH, Hanania NA, Parulekar AD. Fungal sensitization is associated with increased risk of life-threatening asthma. J Allergy Clin Immunol Pract 2017;5:1025-1031.e2. PUBMED | CROSSREF
21. Huang C, Ni Y, Du W, Shi G. Effect of inhaled corticosteroids on microbiome and microbial correlations in asthma over a 9-month period. Clin Transl Sci 2022;15:1723-36. PUBMED | CROSSREF
22. Oğuzülgen K, Öztürk AB, Bacceoğlu A, Aydın Ö, Köycü Buhari G, Damadoğlu E, et al. Inhaler steroid use changes oral and airway bacterial and fungal microbiome profile in asthma patients. Int Arch Allergy Immunol 2024;185:10-9. PUBMED | CROSSREF
23. Goh KJ, Yii ACA, Lapperre TS, Chan AK, Chew FT, Chotirmall SH, et al. Sensitization to *Aspergillus* species is associated with frequent exacerbations in severe asthma. J Asthma Allergy 2017;10:131-40. PUBMED | CROSSREF
24. Chan R, Lipworth B. Severe asthma with fungal sensitization is associated with worse small airway dysfunction but similar symptom control. Ann Allergy Asthma Immunol 2023;130:518-20. PUBMED | CROSSREF
25. Knutsen AP, Bush RK, Demain JG, Denning DW, Dixit A, Fairs A, et al. Fungi and allergic lower respiratory tract diseases. J Allergy Clin Immunol 2012;129:280-91. PUBMED | CROSSREF
26. Green BJ, Tovey ER, Sercombe JK, Blachere FM, Beezhold DH, Schmechel D. Airborne fungal fragments and allergenicity. Med Mycol 2006;44 Suppl 1:S245-55. PUBMED | CROSSREF
27. Moss RB. Severe fungal asthma. A role for biologics and inhaled antifungals. J Fungi (Basel) 2023;9:85. PUBMED | CROSSREF
28. Fairs A, Agbetile J, Hargadon B, Bourne M, Monteiro WR, Brightling CE, et al. IgE sensitization to *Aspergillus fumigatus* is associated with reduced lung function in asthma. Am J Respir Crit Care Med 2010;182:1362-8. PUBMED | CROSSREF
29. Romani L. Immunity to fungal infections. Nat Rev Immunol 2011;11:275-88. PUBMED | CROSSREF
30. Szymczak WA, Deepe GS Jr. The CCL7-CCL2-CCR2 axis regulates IL-4 production in lungs and fungal immunity. J Immunol 2009;183:1964-74. PUBMED | CROSSREF
31. Osterholzer JJ, Curtis JL, Polak T, Ames T, Chen GH, McDonald R, et al. CCR2 mediates conventional dendritic cell recruitment and the formation of bronchovascular mononuclear cell infiltrates in the lungs of mice infected with Cryptococcus neoformans. J Immunol 2008;181:610-20. PUBMED | CROSSREF
32. Conti HR, Gaffen SL. Host responses to *Candida albicans*: Th17 cells and mucosal candidiasis. Microbes Infect 2010;12:518-27. PUBMED | CROSSREF
33. Huang W, Na L, Fidel PL, Schwarzenberger P. Requirement of interleukin-17A for systemic anti-*Candida albicans* host defense in mice. J Infect Dis 2004;190:624-31. PUBMED | CROSSREF
34. d'Ostiani CF, Del Sero G, Bacci A, Montagnoli C, Spreca A, Mencacci A, et al. Dendritic cells discriminate between yeasts and hyphae of the fungus *Candida albicans*. Implications for initiation of T helper cell immunity *in vitro* and *in vivo*. J Exp Med 2000;191:1661-74. PUBMED | CROSSREF
35. Brown GD. Innate antifungal immunity: the key role of phagocytes. Annu Rev Immunol 2011;29:1-21. PUBMED | CROSSREF
36. Remcho TP, Kolls JK. Unfolding the role of Th17 cells in neutrophilic lung inflammation. Am J Respir Cell Mol Biol 2024;71:137-8. PUBMED | CROSSREF
37. Agarwal R, Dhooria S, Singh Sehgal I, Aggarwal AN, Garg M, Saikia B, et al. A randomized trial of itraconazole vs prednisolone in acute-stage allergic bronchopulmonary aspergillosis complicating asthma. Chest 2018;153:656-64. PUBMED | CROSSREF
38. Stevens DA, Schwartz HJ, Lee JY, Moskovitz BL, Jerome DC, Catanzaro A, et al. A randomized trial of itraconazole in allergic bronchopulmonary aspergillosis. N Engl J Med 2000;342:756-62. PUBMED | CROSSREF
39. Denning DW, O'Driscoll BR, Powell G, Chew F, Atherton GT, Vyas A, et al. Randomized controlled trial of oral antifungal treatment for severe asthma with fungal sensitization: the Fungal Asthma Sensitization Trial (FAST) study. Am J Respir Crit Care Med 2009;179:11-8. PUBMED | CROSSREF