

Role of *Aspergillus fumigatus*-Specific IgE in the Diagnosis of Allergic Bronchopulmonary Aspergillosis

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Keywords

Allergic bronchopulmonary aspergillosis · *Aspergillus fumigatus*-specific IgE · Asthma

Abstract

Introduction: Allergic bronchopulmonary aspergillosis (ABPA) has been regarded as a rare disease in China due to the lack of quantitative detection of *Aspergillus fumigatus*-specific IgE (sIgE). We compared the diagnostic rate of ABPA among asthma patients with or without *A. fumigatus*-sIgE screening tests to evaluate the benefit of the tests in diagnosing ABPA. **Methods:** We reviewed the detection rate of *A. fumigatus*-sIgE and the diagnostic rate of ABPA in 1842 asthma patients in the First Affiliated Hospital of Zhejiang University from 2014 to 2016. Additionally, we collected 144 asthma cases from November 2016 to March 2017 to detect the total serum IgE, *A. fumigatus*-sIgE and sIgE against mixed mold extract, the ABPA diagnostic rate of these patients was then compared with the total cohort. Total serum IgE, *A. fumigatus*-sIgE and sIgE against mixed mold extract were also

tested in 30 patients identified with *Aspergillus*-positive sputum culture to analyze the incidence of ABPA. **Results:** Among the 1,842 asthma cases, 566 were inspected for total IgE; 308 (55.40%) were total IgE-positive and 58 (10.43%) had total IgE >1,000 IU/mL. In contrast, only 126 cases were tested for *A. fumigatus*-sIgE (6.84%), and 28 had *A. fumigatus*-sIgE >0.35 kUA/L (22.22%). Eleven patients were finally diagnosed with ABPA. Of 1,842 asthma patients, only 0.6% were diagnosed with ABPA if the *A. fumigatus*-sIgE was not detected at first. Moreover, among the 144 asthma cases that were selected for total IgE, *A. fumigatus*-sIgE, and sIgE against mixed mold extract screening tests, 12 had total IgE >1,000 IU/mL (8.33%), 11 had *A. fumigatus*-sIgE >0.35 kUA/L (7.64%), and 14 had sIgE against mixed mold extract >0.35 (9.72%); 7 of these patients were confirmed as having ABPA according to the ISHAM guidelines (4.86%) but only 2 without *A. fumigatus*-sIgE screening test were diagnosed with ABPA (1.39%) ($p = 0.000$). Of the 30 *Aspergillus*-positive sputum culture cas-

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es, 4 had *A. fumigatus*-sIgE >0.35 kUA/L (13.33%), but none was diagnosed with ABPA. **Conclusions:** Routine *A. fumigatus*-sIgE screening for asthma patients can significantly improve the diagnostic rate of ABPA.

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Introduction

Allergic bronchopulmonary aspergillosis (ABPA) is an allergic reaction to the fungus *Aspergillus* in the trachea. *Aspergillus fumigatus* is the most common pathogen responsible for ABPA. Occasionally, *Aspergillus niger* and *Aspergillus flavus* are also implicated [1]. In China, ABPA has been regarded as a rare disease; its prevalence rate in adult patients with asthma has been reported as 2.5% [2]. In Ireland, the ABPA burden estimate is even lower (approx. 0.7%) [3]. However, the prevalence of ABPA is about 12.9% among outpatients in India, and the rate could be as high as 38.6% in intensive care unit (ICU) patients with severe asthma [4]. A majority of ABPA patients have symptoms of asthma, a common disease, so the rate of misdiagnosis could be 3.7–11.1% [4]. The overall prevalence of ABPA in patients with cystic fibrosis has been estimated at nearly 9% [5]. In 2013, the recommended diagnostic guidelines for ABPA were put forward by the ABPA expert group of the International Society for Human and Animal Mycology (ISHAM). In December 2016, Agarwal et al. [6, 7] revised the diagnostic criteria and proposed a new scoring system for the diagnosis of ABPA. It suggests that all patients with asthma should undergo screening for ABPA with *A. fumigatus*-specific IgE (sIgE). In China, however, diagnosis of ABPA is commonly missed due to the lack of quantitative detection of *A. fumigatus*-sIgE in most hospitals [1]. In this study, we have reviewed the detection rate of *A. fumigatus*-sIgE with the Phadia ImmunoCAP m3 and the diagnostic rate of ABPA in all asthma patients from the First Affiliated Hospital of Zhejiang University from 2014 to 2016. Total serum IgE, *A. fumigatus*-sIgE, and sIgE against mixed mold were measured in another 144 asthma cases, and their ABPA diagnosis rate was compared with the total cohort.

Methods

Study Subjects

All 1,842 patients with asthmatic symptoms admitted to the First Affiliated Hospital of Zhejiang University between 2014 and 2016 were included in the study to analyze the frequency of allergens detection and the diagnosis rate of ABPA.

A total of 144 patients with asthma, who had received treatment at the hospital from November 2016 to March 2017 were examined further. Patients were all in line with the Guidelines for the Prevention and Treatment of Bronchial Asthma (Diagnostic Criteria for Asthma) proposed by the Chinese Thoracic Society Asthma Group in 2008 [8], and they did not have other allergic diseases at the time. Patients who were pregnant, breastfeeding, or had malignancies were excluded. The selected 144 asthma patients included 76 males and 68 females with an average age of 50 years and a mean asthmatic history of 14 years.

Thirty patients with *Aspergillus*-positive sputum culture, including 24 males and 6 females of an average age of 60 years, were also examined. Among them, 26 cases were *A. fumigatus*-positive, 2 were *A. flavus*-positive, 1 was *A. terreus*-positive, and 1 was *A. niger*-positive.

Study Methods

A retrospective analysis was performed to examine the positive rate of serum allergen categories and the ABPA diagnostic rate of 1,842 asthma patients admitted during 2014–2016.

Furthermore, 144 asthma patients and 30 patients with *Aspergillus*-positive sputum culture were examined for levels of total serum IgE, *A. fumigatus*-sIgE, and sIgE against mixed mold. The significance of screening total IgE and m3 in improving the diagnostic rate of ABPA among patients with asthma was also analyzed.

The Phadia ImmunoCAP 1000 instrument (Pharmacia Diagnostics, Sweden) and its matching reagent kit were used in this study. *A. fumigatus*-sIgE was tested on ImmunoCAP m3, and sIgE against mixed mold on ImmunoCAP mx2.

Determination of total IgE, m3, and mx2:

- 1 total IgE: <100 IU/mL was negative; >100 IU/mL was positive.
- 2 m3 and mx2: negative: <0.35 kUA/L (grade 0); positive: 0.35–0.7 kUA/L (grade 1); 0.7–3.5 kUA/L (grade 2); 3.5–17.5 kUA/L (grade 3); 17.5–50.0 kUA/L (grade 4); 50.0–100.0 kUA/L (grade 5); >100.0 kUA/L (grade 6).

ABPA Diagnostic Criteria

According to the ISHAM-recommended diagnostic guidelines for ABPA:

- 1 Predisposing conditions: bronchial asthma or cystic fibrosis.
- 2 Essential criteria (both must be met): (i) serum *A. fumigatus*-sIgE levels >0.35 kUA/L or positive type I *Aspergillus* skin test; (ii) elevated serum total IgE levels >1,000 IU/mL.
- 3 Additional criteria (at least 2/3): (i) precipitating (or IgG) antibodies against *A. fumigatus* present in the serum; (ii) thoracic imaging findings consistent with ABPA; (iii) a peripheral blood eosinophil count of >500 cells/ μ L (may be historical) [6].

Statistical Analysis

SPSS v19.0 analysis software was used for statistical analysis. The comparison of the diagnostic rate of ABPA and the positivity rate of allergens between groups with or without m3 screening was performed using the χ^2 test. A *p* value <0.05 was considered statistically significant.

Table 1. Items for allergen examination and positive rate of 1,842 patients with asthma in the last 3 years

Item	Cases examined	Positive cases
Total IgE	556 (30.18)	308/556 (55.40)
m3	126 (6.84)	28/126 (22.22)
mx2	46 (2.50)	17/46 (36.96)
m5	6 (0.33)	3/6 (50)
hx2	260 (14.12)	90/260 (34.62)
d1	37 (2.01)	23/37 (62.16)
d2	88 (4.78)	46/88 (52.27)
h1	10 (0.54)	3/10 (33.33)
t11	11 (0.60)	0/11 (0)
Phadia	77 (4.18)	31/77 (40.25)
i6	10 (0.54)	2/10 (20)
Animal hair dander group	23 (1.25)	6/23 (26.09)
Food allergens	75 (4.07)	11/75 (14.67)
Examined patients	754 (40.93)	385/754 (51.06)

Values are expressed as *n* (%). mx2, *Penicillium notatum*, *Mycobacterium*, *Aspergillus fumigatus*, *Candida albicans*, *Alternaria*, *Bacillus* sp; hx2, dust mite mixed group; d1, household dust mites; d2, dust mites; h1, house dust; t11, sycamore pollen; Phadia, allergen inhalation screening tests; i6, cockroaches; m5, *Candida albicans*; Animal hair dander group, dog hair dander, cat hair dander, goose feathers, chicken feathers, duck feathers, cats, horses, dairy cows, and dog dander; Food allergens, egg white, milk, fish, wheat, soybeans, crab, and prawn.

Results

Allergen Examination and ABPA Ratio among Patients with Asthma in the Hospital in the Last 3 Years

The retrospective analysis of 1,842 patients with asthma showed that 754 cases (40.93%) were tested for various allergens; 566 (30.73%) inspected for total IgE, 308 of whom (55.40%) appeared total IgE-positive and 58 of whom (3.15%) had total IgE >1,000 IU/mL. In contrast, only 126 cases (6.84%) were tested for *A. fumigatus*-sIgE; 28 (22.22%) of these were found m3-positive (>0.35 kUA/L), and 11 were eventually diagnosed with ABPA which accounted for only 0.6% of all 1,842 asthma patients. The data for allergen examination positivity rate of 1,842 patients with asthma are shown in Table 1. The seasonal distribution of m3-positive patients with asthma in the last 3 years is shown in Figure 1.

Examination of *A. fumigatus*-sIgE, sIgE against Mixed Mold Extract, and Total IgE in 144 Patients with Asthma and the Diagnostic Rate of ABPA

Of the 144 asthma patients, 11 (7.64%) had *A. fumigatus*-sIgE >0.35 kUA/L, 12 (8.33%) had total IgE >1,000 IU/mL, and 14 (9.72%) had sIgE against mixed mold extract >0.35 kUA/L. Initially, only 2 cases (1.39%) were diagnosed with ABPA before the *A. fumigatus*-sIgE screening test. However, according to the ISHAM guide-

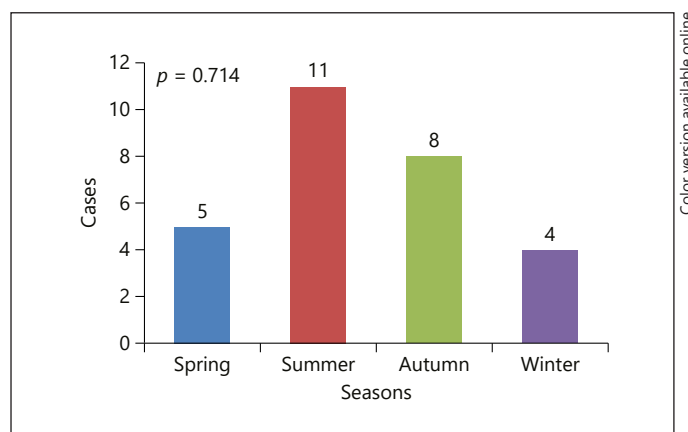


Fig. 1. Seasonal distribution of *A. fumigatus*-sIgE-positive cases in 1,842 patients with asthma in 2014–2016.

lines, 7 cases (4.86%) should have been diagnosed with ABPA, showing a significantly higher diagnostic rate when compared to those without m3 screening ($p = 0.000$), i.e., 5 cases (71.43%) were newly diagnosed with ABPA. The positivity rate of total IgE, m3, and mx2 and the diagnostic rate of ABPA in asthma patients with or without m3 screening are shown in Table 2. The laboratory examination results of the 7 patients diagnosed with ABPA are shown in Table 3. The laboratory examination

Table 2. Comparison of diagnostic rates of ABPA in patients with asthma with and without *A. fumigatus*-specific IgE screening

Group	Total IgE >1,000 IU/mL	m3 >0.35 kUA/L	mx2 >0.35 kUA/L	ABPA ratio
With <i>A. fumigatus</i> -sIgE screening	12/144 (8.33%)	11/144 (7.64%)	14/144 (9.72%)	7/144 (4.86%)
Without <i>A. fumigatus</i> -sIgE screening	58/566 (10.43%)	28/126 (22.22%)	17/46 (36.96%)	11/1,831 (0.60%)
<i>p</i> value	0.000			

Table 3. Laboratory examination results of 7 patients diagnosed with ABPA

Patient No.	Total IgE, IU/mL	<i>A. fumigatus</i> sIgE, kUA/L	Mixed mold sIgE, kUA/L	Eosinophils, cells/L	Imaging changes
1	>5,000	grade 2 (1.68)	grade 2 (1.57)	1.51	Part of the dilated bronchus in the right lung, multiple patchy, small glandular nodules with blurred boundaries, and heterogeneous lesions (some were hyperdense)
2	1,575	grade 3 (4.78)	grade 2 (1.90)	0.58	Both lungs had increased textures, without high-density lesions. Conclusion: bronchial lesions in both lungs
3	2,086	grade 3 (16.30)	grade 3 (5.60)	0.57	Both lungs had increased textures, without high-density lesions. Conclusion: bronchial lesions in both lungs
4	>5,000	grade 4 (29.7)	grade 3 (8.22)	0.75	Sporadic cystic and columnar dilation in segmental bronchi with speckled calcification and fibrosis adjacent to hyperdense bronchial lesions
5	>5,000	grade 3 (4.98)	grade 3 (10.00)	0.16	The dorsal pleura was thickened on both sides
6	2,157	grade 4 (33.80)	grade 3 (6.12)	0.47	Both lungs had a higher transmittance and showed sparsely grained, patchy, hyperdense nodules with no obvious edge; the adjacent airway was shaped like a column, with cystic changes
7	>5,000	grade 3 (5.45)	grade 3 (3.92)	0.74	Both lungs showed fibrosis and patchy hyperdense lesions with blurred boundaries, a marked margin, and calcification

results of the 4 m3-positive but non-ABPA patients are shown in Table 4.

Diagnosis of ABPA in 30 cases with *Aspergillus*-positive Sputum Culture

Among the 30 cases with *Aspergillus*-positive sputum culture, 1 (3.33%) had total IgE >1,000 IU/mL, 4 (13.33%) had m3 >0.35 kUA/L, and 4 (13.33%) had mx2 >0.35 kUA/L. No patients were clinically diagnosed with ABPA. The laboratory examination results of total IgE, m3, and mx2 in *Aspergillus*-positive patients are shown in Table 5.

Discussion

ABPA was first reported by Hinson et al. [9] in 1952. It is a type I and type III hypersensitivity-mediated allergic reaction to pulmonary parasitic *Aspergillus* [10], with the main clinical manifestations being shortness of breath

(or hardly controlled asthma), transient lung shadows, and recurrent bronchiectasis, sometimes accompanied by fever, fatigue, weight loss, or hemoptysis [7]. The hyphae formed by *Aspergillus* conidia release various inflammatory mediators, which further induce a Th2 immune response and result in inflammatory responses via the secretion of interleukin (IL)-4, IL-5, IL-13 and other cytokines, and the stimulation of inflammatory cells such as eosinophils [11]. If not diagnosed and treated in time, ABPA can develop into central bronchiectasis resulting in permanent lung injury, or even extensive bronchiectasis, pulmonary heart disease, and type II respiratory failure at the late stage of the disease [12]. ABPA results from an exaggerated allergic response to *Aspergillus*, with asthma as its most common clinical manifestation. Approximately 15–48% of patients with bronchial asthma are allergic to *Aspergillus*, 40% of whom progress to ABPA [13]. A study from India showed that 28% of asthma patients in the outpatient clinic were allergic to *Aspergillus*, and

Table 4. Laboratory examination results of 4 *A. fumigatus*-sIgE-positive but non-ABPA patients

Patient No.	Total IgE, IU/mL	<i>A. fumigatus</i> sIgE, kUA/L	Mixed mold sIgE, kUA/L	Eosinophils, cells/L	Imaging changes
1	2,820	grade 3 (4.36)	grade 3 (7.29)	0.15	Thoracic symmetry with the trachea located in the center, clear texture in both lungs, and no obvious abnormal dense lesions; normally shape and location of bilateral hilar lymph nodes
2	938	grade 2 (1.26)	grade 2 (3.26)	0.08	Thoracic symmetry with the trachea located in the center. Increased, thickened, and blurred texture in both lungs with no significant abnormal dense lesions; 2 hilar lymph nodes were clear. Conclusion: bronchial lesions in both lungs
3	534	grade 1 (0.38)	grade 2 (1.00)	0.1	Clear texture in both lungs, nodule shadow in the left lower lung, and nodular, cord-like, and patchy high-density shadow scattered in the other lung; the bronchial cavity of each leaf segment was smooth, without obvious stenosis and expansion, and no obvious lymph nodes were found in the mediastinum; extensive thickening on the 2 upper pleural surfaces
4	1,018	grade 1 (0.1)	grade 0 (0.18)	0.11	Thoracic symmetry with the trachea located in the center; slightly increased, thickened, and blurred texture in both lungs, but no significant abnormal density lesions; 2 hilar lymph nodes

Table 5. Laboratory examination results for 6 patients with serological *Aspergillus*-positive sputum culture

Patient No.	Diagnosis	Total IgE, IU/mL	<i>A. fumigatus</i> sIgE, kUA/L	Mixed mold sIgE, kUA/L	Eosinophils, cells/L	Imaging changes
1	pulmonary <i>Aspergillus</i> infection	49.2	grade 1 (0.04)	grade 0 (0.12)	0.01	Infectious lesions in the right lung and upper right lung cavity with inner nodule shadow; possibility of secondary <i>Aspergillus</i> infection
2	acute leukemia	261	grade 0 (0.06)	grade 2 (0.87)	0	Mild infection in both lungs, and pneumonocoele in the middle lobe of the right lung
3	renal insufficiency	55.8	grade 1 (0.61)	grade 1 (0.61)	0	Mild pleural effusion in both lungs; infectious lesions in both lower lungs
4	chronic bronchitis accompanied by emphysema	3,619	grade 0 (0.23)	grade 2 (1.00)	0.06	Chronic bronchitis, emphysema accompanied by infection, and bronchiectasis in the right lower lobe
5	<i>Aspergillus</i> pneumonia	487	grade 1 (0.38)	grade 1 (0.35)	0.05	Bronchial lesions in the right lung, right mid-lobe infection, and right pleural thickening with calcification
6	chronic bronchitis accompanied by a decline in lung function	344	grade 2 (0.84)	grade 0 (0.29)	0.04	Bronchial stenosis, segmental atrophy, and small nodules in the left lower lobe; possibility of proliferation of calcified lesions

the incidence among patients with severe asthma could be as high as 50% [4]. *Aspergillus* is known to be the main allergen in patients with severe asthma caused by allergies [14]. However, ABPA has been considered as a rare disease for a long time, with a reported incidence of only 2.5% among asthma patients in China [2].

ABPA should be differentially diagnosed from asthma as soon as possible to prevent further deterioration of the condition and avoid irreversible consequences. It is recommended that *A. fumigatus*-sIgE should be detected in all patients with asthma to reduce the misdiagnosis rate of ABPA [15].

In this study, we reviewed the detection rate of m3 and the diagnostic rate of ABPA in 1,842 asthma patients in the First Affiliated Hospital of Zhejiang University from 2014 to 2016. A total of 754 patients (40.93%) were tested for all kinds of allergens. Of these, 385 (20.91%) were tested for dust mite, mold, and other common inhalation allergens, but *A. fumigatus*-sIgE was detected only in 126 (6.84%); 28 of these were found to be m3-positive, and 11 were finally diagnosed with ABPA which accounted for only 0.6% of all 1,842 asthma patients.

In the second part of the study, a total of 144 asthma patients treated in the hospital were randomly selected, and their total serum IgE, *A. fumigatus*-sIgE, and sIgE against mixed mold levels were measured. Of these patients, 12 had total IgE >1,000 IU/mL, 11 were m3-positive, and 14 were mx2-positive. Finally, 7 patients (4.86%) were diagnosed with ABPA, and 5 of these (71.43%) were newly diagnosed after the screening. Thus, the detection rate of ABPA increased significantly (4.86 vs. 0.6%, $p = 0.000$) with *A. fumigatus*-sIgE screening in asthma patients. Of the 11 m3-positive patients, the remaining 4 were diagnosed with *Aspergillus*-induced asthma (AIA) instead of ABPA because their total IgE value was <1,000 IU/mL or their imaging results did not meet the diagnostic criteria of ABPA. However, approximately 25–50% of patients with AIA might progress to ABPA within 1–2 years. Hence, regular follow-up and early treatment should be performed to prevent disease progression [6].

Although total serum IgE is an important laboratory index, no uniform standard has specified its diagnostic threshold for ABPA. Currently, a value >1,000 IU/mL is the most recommended medical decision level of total IgE [6, 16]. However, total serum IgE has an advantage over m3 in disease monitoring during follow-up [17].

Among the 7 patients with ABPA in this study, 5 had an eosinophil count of <500 cells/ μ L, which might be related to the use of hormones before diagnosis [18]. The sensitivity of eosinophil examination is also low in the diagnosis of ABPA. It was reported that about 25% of patients have eosinophils <500 cells/ μ L [19].

The ISHAM expert group divides ABPA into the following 4 types according to the changes in lung imaging: ABPA serologic (ABPA-S), ABPA bronchiectasis, ABPA high-attenuation mucus, and ABPA chronic pulmonary aspergillosis [6]. Central bronchiectasis is a characteristic indicator for the diagnosis of ABPA, but lung lesions do not usually appear in patients in the early phase of ABPA; moreover, about 50% of patients with ABPA do not have significantly changes on imaging examination [20]. Of

the 7 patients with ABPA in this study, 5 were clinically misdiagnosed as having asthma instead of being diagnosed as having ABPA-S, which was the final accurate diagnosis. For now, ABPA-S is considered to be an early stage of ABPA and can cause related clinical manifestations [21]. Early treatment of ABPA-S can prevent further deterioration of the condition, thereby avoiding central bronchiectasis and other types of lung damage. Therefore, screening for total serum IgE and *A. fumigatus*-sIgE in asthma patients is particularly important for the diagnosis of patients with ABPA-S.

ABPA is often caused in asthma patients due to the allergy to *A. fumigatus*, but coinfection with other fungi is also considerable [22]. Of the 144 patients with asthma in our study, 14 (9.72%) were mx2-positive. Among them, 11 were both m3- and mx2-positive (78.57%); the other 3 cases were m3-negative. The latter were found to have other fungal infections. The allergic diseases caused by these other fungi, if not controlled, can develop into allergic bronchopulmonary mycosis (ABPM), whose clinical symptoms are similar to those of ABPA, but less common [23]. For patients with ABPA-S symptoms, it is recommended to simultaneously examine both m3 and mx2 to prevent a misdiagnosis of ABPA or ABPM.

In this study, 30 cases with *Aspergillus*-positive sputum culture were screened for total serum IgE, *A. fumigatus*-sIgE, and sIgE against mixed mold to investigate the incidence of ABPA in patients with pulmonary aspergillosis. Four cases (13.33%) were positive for either m3 or mx2, and 2 cases were positive for both (6.7%). The 4 m3-positive cases showed total IgE <1,000 IU/mL with no clinical manifestations of asthma. Therefore, they were diagnosed with pulmonary *Aspergillus* infection. One mx2-positive case had total IgE >1,000 IU/mL, and bronchiectasis on imaging, but was m3-negative, indicating that the patient had other fungal infections and ABPM should be considered. In this study, all 7 patients with ABPA had *Aspergillus*-negative sputum culture. The positive culture rate was lower than the reported rate of 39–60% [1], possibly due to the number of samples.

Among all the laboratory indicators for ABPA screening, *A. fumigatus*-sIgE is the most sensitive screening index [24]. At present in China, many hospitals are using the *Aspergillus* antigen intradermal test for ABPA screening. The sensitivity of using the criteria m3 >0.35 kUA/L to screen asthma patients for ABPA (100%) is higher than when using the *Aspergillus* antigen intradermal test (88–95%). This means that if the latter screening test is used, 5–12% of patients with ABPA may be misdiagnosed [25].

In summary, the screening of *A. fumigatus*-sIgE in patients with asthma can greatly improve the diagnostic rate of ABPA, especially in ABPA-S patients with normal imaging but positive for total serum IgE and *A. fumigatus*-sIgE. Early diagnosis and treatment of ABPA can greatly improve the quality of life and prognosis of patients, thereby preventing further deterioration of the condition and reducing the medical burden.

Statement of Ethics

This study was approved by the Ethics Committee of The First Affiliated Hospital, College of Medicine, Zhejiang University, and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from each participant prior to the study.

References

- 1 Zhao LH, Zheng H, Jiang P. A report of 5 cases of allergic bronchopulmonary aspergillosis and literature review. *Shandong Yiyao*. 2013; 53(48):95–6.
- 2 Ma YL, Zhang WB, Yu B, Chen YW, Mu S, Cui YL. [Prevalence of allergic bronchopulmonary aspergillosis in Chinese patients with bronchial asthma]. *Zhonghua Jie He He Hu Xi Za Zhi*. 2011 Dec;34(12):909–13.
- 3 Denning DW, Pleuvry A, Cole DC. Global burden of allergic bronchopulmonary aspergillosis with asthma and its complication chronic pulmonary aspergillosis in adults. *Med Mycol*. 2013 May;51(4):361–70.
- 4 Agarwal R, Nath A, Aggarwal AN, Gupta D, Chakrabarti A. Aspergillus, hypersensitivity and allergic bronchopulmonary aspergillosis in patients with acute severe asthma in a respiratory intensive care unit in North India. *Mycoses*. 2010;53(2):138–43.
- 5 Maturu VN, Agarwal R. Prevalence of Aspergillus sensitization and allergic bronchopulmonary aspergillosis in cystic fibrosis: systematic review and meta-analysis. *Clin Exp Allergy*. 2015 Dec;45(12):1765–78.
- 6 Agarwal R, Chakrabarti A, Shah A, Gupta D, Meis JF, Guleria R, et al; ABPA complicating asthma ISHAM working group. Allergic bronchopulmonary aspergillosis: review of literature and proposal of new diagnostic and classification criteria. *Clin Exp Allergy*. 2013;43(8):850–73.
- 7 Agarwal R, Sehgal IS, Dhooria S, Aggarwal AN. Developments in the diagnosis and treatment of allergic bronchopulmonary aspergillosis. *Expert Rev Respir Med*. 2016, 10(12): 1317–1334.
- 8 Chinese Thoracic Society Asthma Group. Guidelines for the prevention and treatment of bronchial asthma (definition, diagnosis, treatment and management of bronchial

asthma). *Zhonghua Jie He He Hu Xi Za Zhi*. 2008;31(3):177–85.

- 9 Hinson KF, Moon AJ, Plummer NS. Broncho-pulmonary aspergillosis; a review and a report of eight new cases. *Thorax*. 1952 Dec; 7(4):317–33.
- 10 Moss RB. Pathophysiology and immunology of allergic bronchopulmonary aspergillosis. *Med Mycol*. 2005;43(1):S203–6.
- 11 Qiao YN, Zhang SY, Li B. Research progress of severe asthma and fungi. *Chin J Lung Dis*. 2014;7(2):92–94.
- 12 Agarwal R, Khan A, Gupta D, Aggarwal AN, Saxena AK, Chakrabarti A. An alternate method of classifying allergic bronchopulmonary aspergillosis based on high-attenuation mucus. *PLoS One*. 2010 Dec;5(12):e15346.
- 13 Agarwal R, Aggarwal AN, Gupta D, Jindal SK. Aspergillus hypersensitivity and allergic bronchopulmonary aspergillosis in patients with bronchial asthma: systematic review and meta-analysis. *Int J Tuberc Lung Dis*. 2009 Aug;13(8):936–44.
- 14 Zou H, Su L, Fang QH, Ma YM, Wang XY. Specific IgE response to fungi and asthma severity. *Arch Otolaryngol Head Neck Surg*. 2012;17:1.
- 15 Chopra V, Patel K, Chahal A, Mascarenhas D, Kaur P. Allergic Bronchopulmonary Aspergillosis in Bronchial Asthma: A Prevalence Study. *Chest*. 2014;146(4):17A.
- 16 Agarwal R, Aggarwal AN, Garg M, Saikia B, Chakrabarti A. Cut-off values of serum IgE (total and *A. fumigatus* -specific) and eosinophil count in differentiating allergic bronchopulmonary aspergillosis from asthma. *Mycoses*. 2014 Nov;57(11):659–63.
- 17 Agarwal R, Aggarwal AN, Sehgal IS, Dhooria S, Behera D, Chakrabarti A. Utility of IgE (total and *Aspergillus fumigatus* specific) in monitoring for response and exacerbations in

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Author Contributions

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allergic bronchopulmonary aspergillosis. *Mycoses*. 2016 Jan;59(1):1–6.

- 18 Cao XP, Xie M, Liu XS. Recognition of allergic bronchopulmonary aspergillosis. *Zhongguo Shiyong Neike Zazhi*. 2016;36(8):625–8.
- 19 Agarwal R, Khan A, Aggarwal AN, Varma N, Garg M, Saikia B, Gupta D, Chakrabarti A. Clinical relevance of peripheral blood eosinophil count in allergic bronchopulmonary aspergillosis. *J Infect Public Health*. 2011;4(5-6):235–43.
- 20 Agarwal R, Khan A, Garg M, Aggarwal AN, Gupta D. Chest radiographic and computed tomographic manifestations in allergic bronchopulmonary aspergillosis. *World J Radiol*. 2012 Apr;4(4):141–50.
- 21 Agarwal R, Garg M, Aggarwal AN, Saikia B, Gupta D, Chakrabarti A. Serologic allergic bronchopulmonary aspergillosis (ABPA-S): long-term outcomes. *Respir Med*. 2012; 106(7):942–7.
- 22 Hu HS, Luo WT, Wu SQ, Wei NL, Liang XQ, Sun BQ. Correlations among serum specific IgE levels against several fungal species in patients with aspergillus fumigatus induced asthma or allergic bronchopulmonary aspergillosis. *Int J Respir*. 2016;36(10):721–5.
- 23 Chowdhary A, Agarwal K, Kathuria S, Gaur SN, Randhawa HS, Meis JF. Allergic bronchopulmonary mycosis due to fungi other than *Aspergillus*: a global overview. *Crit Rev Microbiol*. 2014 Feb;40(1):30–48.
- 24 Agarwal R, Maskey D, Aggarwal AN, Saikia B, Garg M, Gupta D, et al. Diagnostic performance of various tests and criteria employed in allergic bronchopulmonary aspergillosis: a latent class analysis. *PLoS One*. 2013 Apr;8(4):e61105.
- 25 Sehgal IS, Agarwal R. Specific IgE is better than skin testing for detecting *Aspergillus* sensitization and allergic bronchopulmonary aspergillosis in asthma. *Chest*. 2015 May;147(5):e194.