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Evaluation of the clinical performance of four fungus-specific immunoglobulin E detection systems in patients with Aspergillus allergy

Zhifeng Huang,[1] Wanjia Li,[1,2]* Hao Chen,[1] Huiqing Zhu,[1] Baoqing Sun[1]*

Abstract

Background: Allergic bronchopulmonary aspergillosis (ABPA) is an airway disease caused by Aspergillus (mainly *Aspergillus fumigatus*).

Objective: To evaluate the diagnostic performance of four fungal-related allergen-specific immunoglobulin E (sIgE) detection systems.

Methods: A total of 99 patients with ABPA and 30 control patients admitted to the First Affiliated Hospital of Guangzhou Medical University from 2017 to 2019 were included in the study. Four allergen detection systems were used to detect Aspergillus-related sIgE.

Results: The 99 patients were divided into two groups based on the total IgE. Fluorescence immunoassay for fungal mixtures detected positive rates of 100% and 81% in the Confirmed and Probable groups, respectively. For *Aspergillus fumigatus*, the positive rates were 90.2% and 87.9%, respectively. In the detection of sIgE of fungal mixtures in all ABPA patients, the sensitivity of System 1 was 90.9%, which was higher than for the other three systems (System 2, 38.4%; System 3, 44.4%; System 4, 52.5%), All four systems have excellent specificity (> 90.0%) and had higher consistency in the Confirmed group than in the Probable group ($P < 0.05$). Consistency for the Aspergillus mixture and *Aspergillus fumigatus* detected by fluorescence immunoassay was 90.2% and 86.2% in the Confirmed and Probable groups, respectively.

Conclusion: Despite the many methods used to detect fungal-related sIgE, the ImmunoCAP system has the best clinical diagnostic performance. It is recommended that this method be used to detect fungal (mixtures or *Aspergillus fumigatus*) sIgE in order to reduce the missed diagnosis rate of ABPA.

Key words: ABPA, methodology, *Aspergillus fumigatus*, IgE, fluorescence immunoassay

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Affiliations:
[1] Department of Allergy and Clinical Immunology, Guangzhou Institute of Respiratory health, State Key Laboratory of Respiratory Disease, National Clinical Research Center of Respiratory Disease, First Affiliated Hospital of Guangzhou Medical University, Guangzhou Medical University, Guangzhou, China
[2] Yichun University, Yuanzhou District, Yichun, China

*Zhifeng Huang and Wanjia Li contributed equally as co-first authors.

Corresponding author:
Baoqing Sun
151 Yan Jiang Rd. Guangzhou (Canton)
E-mail: sunbaoqing@vip.163.com

Introduction

Allergic bronchopulmonary aspergillosis (ABPA) is an airway disease characterized by increased peripheral blood eosinophil count, elevated serum immunoglobulin E (IgE) level, lung infiltration, bronchiectasis and central bronchiectasis with mucus embolism, caused by Aspergillus (mainly *Aspergillus fumigatus*). It was first described by Hinson et al. in 1952.[1] ABPA is common in China and its prevalence rate in adult patients with asthma is 2.5%.[2] Early diagnosis and treatment are warranted.

It has been reported that two-thirds of patients with ABPA or allergic bronchopulmonary mycosis (ABPM) worldwide are misdiagnosed.[3,4] Laboratory tests in the recently revised ABPA diagnostic criteria mainly rely on serological indicators,[5,6] including increased total IgE (tIgE) and *Aspergillus fumigatus*-specific IgE (sIgE) levels or skin prick test (SPT)-confirmed Aspergillus sensitization. In addition, the radiological features of ABPA, increased eosinophil level or increased serum *Aspergillus fumigatus* sIgG level must be observed. Although there are many methods on the market to detect the sIgE concentration of fungal allergens, the most recognized ImmunoCAP system is difficult to promote in low- and middle-level medical institutions due to its high cost, long detection time and high operator requirements. With other systems, although the sensitivity is relatively low, the advantages of low price, low serum consumption and less detection time make them more suitable for a wider range of primary medical institutions. This study systematically evaluated the clinical diagnostic efficiency of four fungal-related sIgE detection systems to provide reference values to aid in clinical diagnosis and laboratory testing, thus enabling the introduction of a suitable fungal allergen detection system.

Methods

Subjects

A total of 99 patients with ABPA from the First Affiliated Hospital of Guangzhou Medical University were enrolled in the study from June 2017 to June 2019. The diagnosis of ABPA was confirmed by experienced clinicians. The following inclusion criteria were used to enroll patients[7]: (1) presence of asthma or other upper respiratory tract diseases, including bronchiectasis, chronic obstructive pulmonary disease and cystic pulmonary fibrosis; (2) positive *Aspergillus fumigatus* SPT (wheal diameter ≥ 3 mm) or sIgE ≥ 0.35 kU_A/L detected by ImmunoCAP; (3) increased serum tIgE level of ≥ 1000 kU_A/L detected by ImmunoCAP and, if other conditions are met, tIgE < 1000 kU_A/L can also be considered; and (4) other criteria, including positive Aspergillus-related sIgG or precipitated protein, eosinophil level > 500 cells/μL and radiological features of ABPA. The patients were divided into two groups according to the tIgE level: ≥ 1000 kU_A/L, Confirmed group; 100–1000 kU_A/L, Probable group. Moreover, 30 patients with a negative SPT for *Aspergillus fumigatus* were included as the control group, with all of them meeting the following criteria: (1) clinical symptoms of upper respiratory disease, including rhinitis and/or asthma; (2) negative SPT of *Aspergillus fumigatus* (wheal < 3 mm); and (3) tIgE level < 100 kU_A/L.

Measurement of allergen sIgE and tIgE levels

During the clinical visit, *Aspergillus fumigatus* (SPT) and serum tIgE were detected in all patients and controls. Four systems were then used to detect the sIgE of the Aspergillus allergen; the fluorescence immune system (System 1, ImmunoCAP, Thermo Fisher, USA) was used to detect the serum sIgE levels of fungal mixtures (Penicillium chrysogenum, Cladosporium herbarum, *Aspergillus fumigatus*, Candida albicans, Alternaria alternata, Setomelanomma rostrata) and *Aspergillus fumigatus* in all serum samples; the microfluidic chip technique combined with chemiluminescence (System 2, BioIC, Agnitio, China Taiwan) was used to detect the allergen serum sIgE of *Aspergillus fumigatus* and Candida albicans; serum sIgE of fungal mixtures (Penicillium chrysogenum, Cladosporium herbarum, *Aspergillus fumigatus* and Alternaria alternata) was detected using the Western blotting system (System 3, EUROLine, EUROIMMUN, German); and serum sIgE of fungal mixtures (Penicillium chrysogenum, *Aspergillus fumigatus*, Cladosporium herbarum, Alternaria alternate, Rhizopus nigricans and Mucor racemosus) was detected using an enzyme-linked immune system (System 4, Ouboke, HOB, China). Among these methods, System 1 is a full quantitative detection system with a detection range of 0–100 kU_A/L, whereas the other three are semiquantitative detection systems.

sIgE levels of < 0.35 kU_A/L were defined as sIgE negative and ≥ 0.35kU_A/L as sIgE positive. sIgE-positive tests were categorized into the following six classes: class 1, ≥ 0.35 to < 0.70 kU_A/L; class 2, ≥ 0.70 to < 3.50 kU_A/L; class 3, ≥ 3.50 to < 17.50 kU_A/L; class 4, ≥ 17.50 to < 50 kU_A/L; class 5, ≥ 50 to < 100 kU_A/L; and class 6, ≥ 100 kU_A/L.

Data analysis

Statistical studies were performed using Excel 2016 (Microsoft Excel® 2016) and Statistical Package for the Social Sciences 22.0 (International Business Machines Corporation, Armonk, NY). Parametric quantitative data are presented as mean ± standard deviation. Nonparametric quantitative data are presented as median (interquartile range). A histogram was used to show the positive rate distribution of fungal allergens detected by the four systems. Clinical diagnosis was used to evaluate the clinical diagnostic performance of the four systems in terms of sensitivity, specificity and consistency. Consistency is calculated according to a four-grid table and the formula is (a + d)/(a + b + c + d). The consistency coefficient is distributed between 0 and 1, and the closer the value is to 1, the better the consistency. Pearson's chi-square test (χ^2) was used to compare the frequencies between subgroups and the Mann-Whitney U test was used to compare nonparametric quantitative data; $P < 0.05$ was considered to be statistically significant.

Results

Demographic characteristics of participants

Among the 99 patients with ABPA, 56 were male (56.6%) and 43 were female (43.4%). The mean age was 33 (23–50) years. The Phadiatop and tIgE levels detected by ImmunoCAP were 3.26 (0.66–36.91) kU_A/L and 920.65 (523.00–1654.25) kU_A/L, respectively. There were 41 patients in the Confirmed group, including 27 men (65.85%), and the mean age was 25 (23–50) years. There were 58 patients in the Probable group, including 29 men (50.00%), and the mean age was 32 (23–51) years. There was no significant difference in age and gender distribution between the two groups ($P > 0.05$). However, the Phadiatop level in the Confirmed group was higher than in the Probable group, and the difference was statistically significant (3.46 [1.21–86.62] vs. 2.18 [0.19–16.17], $P < 0.05$) (**Table 1**).

Distribution of positive rates of fungal allergens

For fungal mixtures, the positive rate in the Confirmed group detected by System 1 was 100% (41/41) and that in the Probable group was 81.0% (47/58). There was a statistically significant difference in the positive rate between the two groups ($P < 0.01$). For *Aspergillus fumigatus* allergen, the positive rate in the Confirmed group detected by System 1 was 90.2% (37/41) and that in the Probable group was 87.93% (51/58); there was no significant difference between the two groups ($P > 0.05$). The positive rate of System 1 was higher than that of other systems, regardless of whether the allergen was a fungal mixture or *Aspergillus fumigatus*. In addition, for other allergen detection systems (including Systems 2–4), patients in the Confirmed group had a higher positive rate than those in the Probable group (all $P < 0.05$) (**Figure 1**).

Evaluation of the validity of the four diagnostic systems in detecting fungal mixtures

A total of 99 patients with clinically diagnosed ABPA were included in this study, of which 90 were sIgE positive for fungal mixtures detected by System 1, with a sensitivity of 90.9% (83.0–95.5). The sensitivities of the Confirmed and Probable groups were 100% (89.3–100) and 81.0% (68.2–89.7), respectively, and the specificities were 90.0% (72.3–97.4) for both groups. For the other three detection systems, the sensitivity for fungal mixtures was relatively low. The sensitivity of System 2 was 38.4% (29.0–48.7), and the specificity was 96.7% (81.0–99.8). The sensitivity of System 3 was 44.4% (34.6–54.8), while the specificity was 100% (85.9–100). The sensitivity of System 4 was 52.5% (42.3–62.6), and the specificity was 90.0% (72.3–97.4). In this study, all four systems in the Confirmed group had higher consistency than those in the Probable group, and the difference was statistically significant (all $P < 0.05$) (**Table 2**).

Evaluation of the validity of System 1 and System 2 in detecting Aspergillus fumigatus

Of the 99 patients with ABPA, 89 were sIgE positive for *Aspergillus fumigatus* detected by System 1, with a sensitivity of 88.9% (80.6–94.1) and specificity of 100% (85.9–100). For the Confirmed and Probable groups, 90.24% (37/41) and 87.9% (51/58) of the samples, respectively, were positive for *Aspergillus fumigatus*. However, only 26 samples were positive for *Aspergillus fumigatus* allergen in System 2, with a sensitivity of 26.3% (18.16–36.2) and specificity of 96.7% (81.0–99.8). Of the 58 patients in the Probable group, only 5 (8.6%) were sIgE positive for *Aspergillus fumigatus* (**Table 3**).

Table 1. Patient Demographic Characteristics.

	ABPA (All)	ABPA (Confirmed)	ABPA (Probable)	Control	*P*-value*
N	99	41	58	30	-
Sex					0.12
Male, n (%)	56 (56.6)	27 (65.9)	29 (50.0)	13 (43.3)	
Female, n (%)	43 (43.4)	14 (34.2)	29 (50.0)	17 (56.7)	
Age					0.80
Median (IQR)	33 (23-50)	35 (23-50)	32 (23-51)	25 (24-3)	
Range	6-78	8-71	6-78	8-59	
Total IgE, kU_A/L	920.7 (523.0-1654.3)	1824.0 (1350.7-2974.8)	518.09 (373.0-811.3)	43.36 (18.11-67.0)	< 0.01
Phadiatop, kU_A/L	3.7 (0.66-36.9)	3.46 (1.2-86.6)	2.18 (0.2-16.2)	0.30 (0.0-2.7)	< 0.01

Note: *the *p* value refers to the comparison of the differences between Confirmed and Probable group. Pearson Chi-Square test (χ^2) was used to compare the frequencies between subgroup, and Mann-Whitney U test was used to compare the Nonparametric quantitative data. Phadiatop is an IgE screening item that measures a mixture of common aeroallergens, and the higher the level of IgE antibody (that is, the degree of atopy), the higher the risk of allergic symptoms.

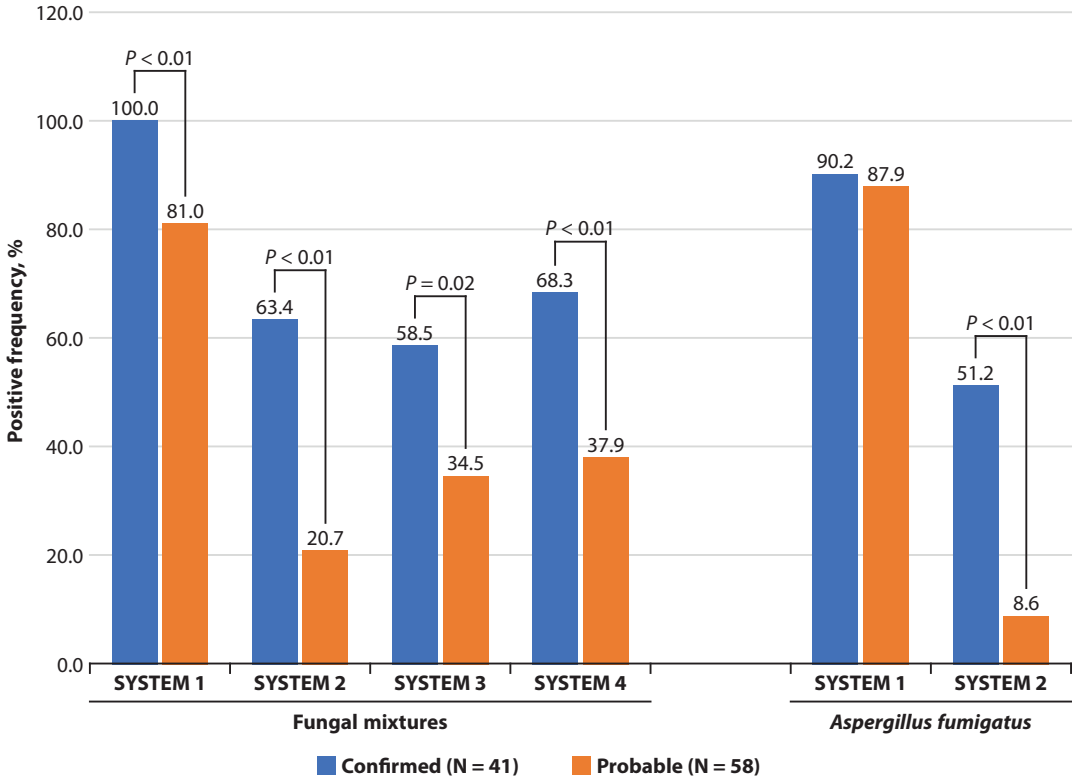

Figure 1. Distribution of allergen sIgE positive rates of fungal mixtures and *Aspergillus fumigatus* detected by the four systems. sIgE levels ≥ 0.35 kU_A/L were defined as sIgE positive, and Pearson chi-square test (χ^2) was used to compare the frequencies between subgroups.

Table 2. Evaluate the validity of the four diagnostic systems in detecting the fungal mixtures.

	Sensitivity (%, 95%CI)	Specificity (%, 95%CI)	Consistency
SYSTEM 1			
ABPA (All)	90.9 (83.0-95.5)	-	90.7
ABPA (Confirmed)	100 (89.3-100)	-	95.8
ABPA (Probable)	81.0 (68.2-89.7)	-	88.6
Control		90.0 (72.3-97.4)	
SYSTEM 2			
ABPA (All)	38.4 (29.0-48.7)	-	51.9
ABPA (Confirmed)	63.4 (46.92-77.4)	-	77.5
ABPA (Probable)	20.7 (11.6-33.7)	-	46.6
Control		96.7 (81.0-99.8)	

	Sensitivity (%, 95%CI)	Specificity (%, 95%CI)	Consistency
SYSTEM 3			
ABPA (All)	44.4 (34.6-54.8)	-	57.4
ABPA (Confirmed)	79.4 (61.6-90.7)	-	76.1
ABPA (Probable)	34.5 (22.8-48.2)	-	56.8
Control		100 (85.9-100)	
SYSTEM 4			
ABPA (All)	52.5 (42.3-62.6)	-	61.2
ABPA (Confirmed)	68.3 (51.8-81.4)	-	77.5
ABPA (Probable)	37.9 (25.8-51.7)	-	55.7
Control		90.0 (72.3-97.4)	

Table 3. Evaluate the validity of the system 1 and system 2 in detecting the *Aspergillus fumigatus*.

	Sensitivity (%, 95%CI)	Specificity (%, 95%CI)	Consistency
SYSTEM 1			
ABPA (All)	88.9 (80.6-94.1)	-	91.5
ABPA (Confirmed)	90.2 (75.7-96.8)	-	94.4
ABPA (Probable)	87.9 (76.1-94.6)	-	87.5
Control		100 (85.9-100)	

	Sensitivity (%, 95%CI)	Specificity (%, 95%CI)	Consistency
SYSTEM 2			
ABPA (All)	26.3 (18.3-36.3)	-	42.6
ABPA (Confirmed)	51.2 (35.4-66.9)	-	70.4
ABPA (Probable)	8.6 (3.2-19.7)	-	38.6
Control		96.7 (81.0-99.8)	

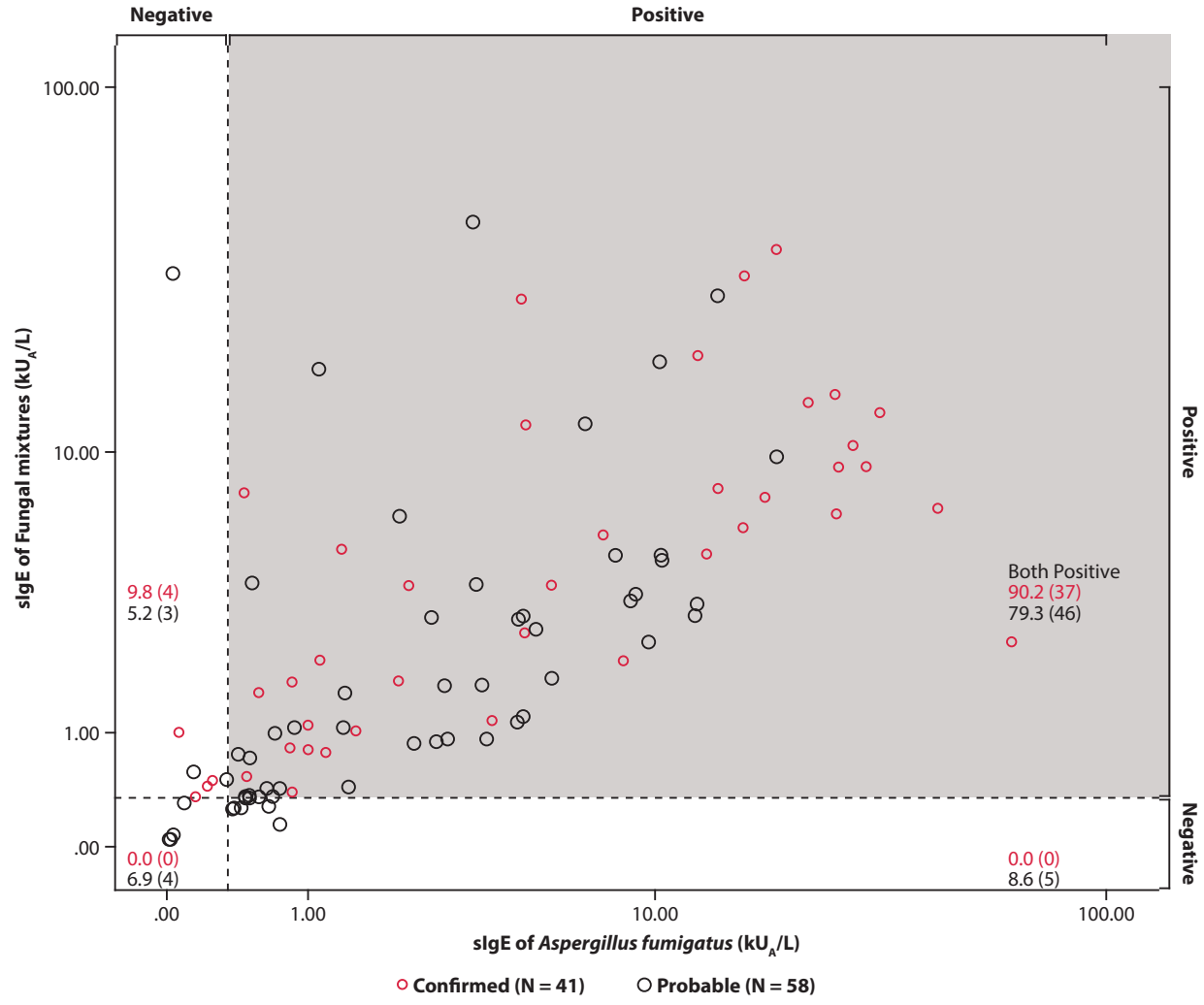

Figure 2. Comparison of consistencies between fungal mixtures and *Aspergillus fumigatus* detected by System 1. 0.35 kU$_A$/L as the cut-off value of sIgE of fungal mixtures and *Aspergillus fumigatus* allergen. The gray shadow indicates that both fungal mixtures and *Aspergillus fumigatus* allergens are positive, and the percentage is expressed in the form of % (N).

Consistency between fungal mixtures and Aspergillus fumigatus detected by System 1

In the Confirmed group, the consistency of fungal mixtures and *Aspergillus fumigatus* was 90.2% (37/41); the other four patients (9.8%) were positive for fungal mixtures and negative for *Aspergillus fumigatus*. In the Probable group, the consistency of fungal mixtures and *Aspergillus fumigatus* allergen was 86.2% (50/58), of which 79.3% (46/58) were positive and 6.9% (4/58) were negative for both fungal mixtures and *Aspergillus fumigatus*. Five patients (8.6%) were positive for *Aspergillus fumigatus* and negative for fungal mixtures. Considering that the *Aspergillus fumigatus* sensitization level of five patients was low, it may be insufficient to detect them in the Aspergillus mixture. We also noted that the sIgE of fungal mixtures for these five samples ranged from 0.15 to 0.28 kU_A/L, although they were all < 0.35 kU_A/L. In addition, three patients (5.2%) were positive for fungal mixtures and negative for *Aspergillus fumigatus* in this group (**Figure 2**).

Discussion

In December 2016, Agarwal et al.[8] revised the diagnostic criteria of ABPA, proposed a new ABPA diagnostic scoring system and suggested that all patients with asthma should be screened for *Aspergillus fumigatus* sIgE to reduce the rate of missed diagnosis and misdiagnosis of ABPA.[9]

Of the 99 patients with clinically confirmed ABPA included in this study, 58 (58.6%) had a tIgE level of < 1000 kU_A/L but all tIgE levels were >100 kU_A/L. In Japan and South Korea it has been reported[10,11] that the tIgE level in many patients with ABPA was < 1000 kU_A/L. A study focusing on the clinical characteristics of patients with ABPA in China identified that a quarter of patients had a tIgE level of < 1000 kU_A/L.[12]

The results showed that using the fluorescence immunoassay (System 1) in the detection of fungal mixtures led to positive rates of 100% in the Confirmed group and 81.0% in the Probable group. For *Aspergillus fumigatus* allergen, the positive rate in the Confirmed group was 90.2% and in the Probable group was 87.9%. The patients with ABPA included in this study all had a positive *Aspergillus fumigatus* SPT but the serum sIgE of 11 patients was negative for *Aspergillus fumigatus* allergen, suggesting that there is a difference between *in vivo* and *in vitro* allergen detection results, as has been repeatedly proposed in other studies.[13,14] In addition, for the four systems, the positive rate in the Confirmed group was higher than in the Probable group ($P < 0.05$), indicating that the positive rate of fungal allergen in ABPA patients with a tIgE level of < 1000 kU_A/L was more likely to be undetectable. Therefore, in clinical diagnosis, combined detection of tIgE, Aspergillus allergen SPT and *Aspergillus fumigatus* sIgE is recommended in patients with high suspicion of ABPA in order to reduce the missed diagnosis rate of ABPA.

We evaluated the clinical diagnostic performance of four allergen detection systems with different principles in this study. The sensitivity of System 1 for detecting sIgE of fungal mixtures was 90.9%, the sensitivity in the Confirmed and Probable groups was 100% and 81.0%, respectively, and the specificity in both groups was 90.0%. For *Aspergillus fumigatus*, the sensitivity was 88.9% (90.3% in the Confirmed group and 87.9% in the Probable group) and the specificity in both groups was 100%. Regardless of whether it was a fungal mixture or *Aspergillus fumigatus* allergen, System 1 showed better clinical diagnostic performance than the other systems. Presently, the ImmunoCAP automatic allergen detection system based on the principle of fluorescence immunoassay is an internationally recognized "reference method" for detecting allergen sIgE.[15] In addition, a large number of previous studies have reported that the system has good clinical consistency in the detection of common allergen sIgE.[16,17]

Twaroch et al.[18] found that, in addition to the sensitization to *Aspergillus fumigatus*, mixed infection of ABPA with other fungal allergens was also quite serious, and thus they recommended the detection of both fungal mixtures and *Aspergillus fumigatus* allergens simultaneously in patients with early clinical manifestations of ABPA. In our study, we used ImmunoCAP to detect fungal mixtures and *Aspergillus fumigatus*. The results showed that the consistency of fungal mixtures and *Aspergillus fumigatus* was > 90% in the Confirmed group and 86.2% in the Probable group. There were four (9.8%) and three (5.2%) patients who were positive for fungal mixtures and negative for *Aspergillus fumigatus* in the Confirmed and Probable groups, respectively. We noted that the *Aspergillus fumigatus* levels of these seven patients ranged from 0.15 to 0.35 kU_A/L, which were considered as low-level sIgE against *Aspergillus fumigatus* combined with other fungal allergens. In addition, in the Probable group, five patients (8.6%) were positive for *Aspergillus fumigatus* and negative for fungal mixtures. It was speculated that in these five patients, sIgE could not be detected in the mixture because the serum antibody level of *Aspergillus fumigatus* was low. A study from India[19] pointed out that the use of the same fixed reference threshold to explain the fungal allergen sIgE in all populations may lead to poor diagnostic efficacy and that the optimal threshold value for local trials should be established through large sample-size studies. ImmunoCAP, as the only quantitative detection system of allergen sIgE in this study, has important clinical significance in explaining the sIgE level of fungal allergens between 0.1 and 0.35 kU_A/L.

There are some limitations in this study. The main purpose of the study was to evaluate the clinical diagnostic performance of the four systems and to explain the connection between *Aspergillus fumigatus* and fungal mixture allergens. However, the accuracy and stability of instruments and reagents, the detection performance of different samples from the same patient and changes over time in the same patient were not verified.

Conclusions

Currently, there are many methods that can be used to detect the fungal allergen sIgE, among which the ImmunoCAP system has the best clinical diagnostic performance. It is recommended that this method be used to detect tIgE and fungal (mixture or Aspergillus fumigatus) allergen sIgE to reduce the missed diagnosis rate of ABPA.

Ethical considerations

This study and the use of human serum samples were approved by the ethics committee of the First Affiliated Hospital of Guangzhou Medical University (GYYY-2016-73).

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Conflict of interest

None of the authors have any conflict of interest to declare.

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Author contributions

- B.Q.S. and Z.F.H. conceived and designed the study and obtained approval.
- W.J.L. and Z.F.H. collected clinical information and serum samples from clinical patients.
- W.J.L., Z.F.H. and H.C. performed the detection of allergen-specific IgE for all samples.
- Z.F.H., H.C. and H.Q.Z. analyzed the data.
- B.Q.S., Z.F.H. and W.J.L. drafted the manuscript in close collaboration with all co-authors.
- All authors read and approved the final version.

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