

Is There an Overlap in Immune Response Between Allergic Bronchopulmonary and Chronic Pulmonary Aspergillosis?



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What is already known about this topic? Chronic pulmonary aspergillosis (CPA) and allergic bronchopulmonary aspergillosis (ABPA) are presumed to represent 2 distinct manifestations of *Aspergillus* species in the lung. Whether there is any overlap between these 2 entities is not known.

What does this article add to our knowledge? In this study, we systematically evaluated patients with CPA for allergic sensitization against *Aspergillus fumigatus*. We found that 5% of subjects with CPA fulfilled all the immunological criteria used for diagnosing ABPA, whereas 22% met the obligatory criteria for ABPA.

How does this study impact current management guidelines? This study raises the question whether patients of CPA with “ABPA overlap” represent a distinct category and require a different management protocol.

BACKGROUND: Chronic pulmonary aspergillosis (CPA) and allergic bronchopulmonary aspergillosis (ABPA) are presumed to represent 2 distinct manifestations of *Aspergillus* species in the lung.

OBJECTIVE: To investigate any possible overlap of the immunological tests used for diagnosing ABPA in proven cases of CPA.

METHODS: In consecutive subjects with CPA, we calculated the proportion of subjects who tested positive for all the immunological investigations used to diagnose ABPA (*Aspergillus fumigatus* specific IgE >0.35 kUA/L, total IgE ≥500 IU/mL, and eosinophil count ≥500 cells/μL) or obligatory criteria (*A. fumigatus* specific IgE >0.35 kUA/L and total IgE ≥500 IU/mL).

RESULTS: A total of 269 subjects (53.5% males) of CPA with the mean (standard deviation [SD]) age of 44.3 (14.7) years were

enrolled. The most common underlying disease was previously treated pulmonary tuberculosis (n = 230, 85.5%). Ninety-three (34.6%) subjects had total IgE ≥500 IU/mL, whereas *A. fumigatus* specific IgE >0.35 kUA/L was seen in 112 (41.6%) subjects. Thirteen (4.8%) subjects met all the immunological criteria for ABPA, whereas 59 (21.9%) subjects met the obligatory criteria. Subjects meeting the obligatory criteria had significantly higher eosinophil count ($P \leq .0001$), greater immediate cutaneous reactivity to *Aspergillus* antigen (CPA-others vs obligatory criteria, 9.8 ± 13.9 vs 13.9 ± 14.9 mm, P value = .048), higher *A. fumigatus* specific IgG (99.3 ± 61.9 vs 122 ± 66.6 mgA/L, $P = .015$), and greater number of fungal balls (0.9 ± 0.7 [range, 0-3] vs 1.1 ± 0.9 [range, 0-4], $P = .026$) compared with those without.

CONCLUSIONS: Approximately 5% of subjects with CPA fulfilled all the immunological criteria used for diagnosing ABPA, whereas 22% met the obligatory criteria for ABPA. Whether these patients would require a different management protocol requires further investigation. © 2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:969-74)

Key words: Chronic pulmonary aspergillosis; ABPA; Aspergillosis; CCPA; Aspergilloma; Tuberculosis

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No funding was received for this work.

Conflicts of interest: R. Agarwal has received consultancy fees from Pulmatrix Inc. and research support from Cipla Pharmaceuticals, India. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication June 12, 2018; revised August 25, 2018; accepted for publication August 30, 2018.

Available online September 8, 2018.

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2213-2198

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<https://doi.org/10.1016/j.jaip.2018.08.034>

Abbreviations used

ABPA- Allergic bronchopulmonary aspergillosis
BALF- Bronchoalveolar lavage fluid
BMI- Body mass index
CCPA- Chronic cavitary pulmonary aspergillosis
CFPA- Chronic fibrosing pulmonary aspergillosis
CPA- Chronic pulmonary aspergillosis
CT- Computed tomography
PNU- Protein nitrogen unit
SA- Simple aspergilloma
SD- Standard deviation

pulmonary disease, sarcoidosis, diffuse parenchymal lung disease, and others).¹⁻³ The diagnosis of CPA is based on the presence of clinical symptoms (low-grade fever, weight loss, malaise, chronic cough, recurrent hemoptysis, and others), radiological features (combination of 1 or more cavities and the presence of fungal ball or fibrosis, pericavitary infiltrates, consolidation, nodules, and pleural thickening), and the demonstration of either direct (growth of *Aspergillus* on sputum or bronchoalveolar lavage fluid [BALF] culture) or indirect (elevated serum or BALF galactomannan index or *Aspergillus fumigatus* specific IgG or precipitin in serum) evidence of *Aspergillus* infection.^{2,3} Primarily seen in patients with asthma and cystic fibrosis, the diagnosis of ABPA is currently made on the combination of clinical (low-grade fever, hemoptysis, and others), radiological (bronchiectasis, mucus impaction, centrilobular nodules, and others), and immunological (*A. fumigatus* specific IgE and IgG, total IgE, and elevated eosinophils) findings.⁴

Although ABPA and CPA represent 2 distinct manifestations of *Aspergillus*-related lung disease, there is an overlap of investigations that are currently used for the diagnosis of these entities. For example, *A. fumigatus* specific IgG and *Aspergillus* precipitins are used both in diagnosing ABPA and CPA. The culture of respiratory tract secretions can demonstrate the growth of *Aspergillus* in both these disorders. Limited evidence suggests that individuals with CPA could also demonstrate positive serological tests (*A. fumigatus* specific IgE, total IgE, and elevated eosinophils) used in the diagnosis of ABPA.⁵ This overlap can cause difficulty in differentiating between these 2 entities. No previous study has systematically evaluated the overlap of immunological tests for ABPA in subjects with CPA. Herein, we evaluate the occurrence of positive immunological tests used for diagnosing ABPA in subjects with CPA.

METHODS

This was a prospective study conducted between January 2017 and March 2018 in the Chest Clinic of this Institute. The Institute Ethics Committee approved the study protocol. We obtained written informed consent from all the subjects to use anonymized data.

Study participants

We included consecutive treatment-naïve subjects with CPA. The diagnosis of CPA was made by a multidisciplinary team (pulmonary physicians, radiologist, and microbiologist) based on a composite of clinical, radiological, and microbiological criteria.^{2,3,6} This included the presence of all of the following: (1) one or more clinical symptoms (persistent cough, recurrent hemoptysis, weight loss, malaise,

fever, and dyspnea) for at least 3 months; (2) slowly progressive or persistent radiological findings (1 or more cavities and surrounding fibrosis, infiltrates, consolidation, with or without fungal ball, or progressive pleural thickening) on computed tomography (CT) of the thorax; (3) *A. fumigatus* specific IgG >27 mgA/L or microbiological evidence of *Aspergillus* infection (growth of *Aspergillus* on sputum or BALF culture); and (4) exclusion of other pulmonary disorders with similar presentation. Patients with CPA were further characterized as simple aspergilloma (SA), chronic cavitary pulmonary aspergillosis (CCPA), and chronic fibrosing pulmonary aspergillosis (CFPA) based on the findings of CT thorax, as previously described.^{3,5,7} We excluded subjects with CPA complicating ABPA or those with prior history of asthma from the current analysis.

Study procedure

All study participants underwent the following investigations: *A. fumigatus* specific IgG, *Aspergillus* precipitins, sputum culture for fungus, mycobacteria, and bacteria, *A. fumigatus* specific IgE, *Aspergillus* skin test, eosinophil count, total IgE, spirometry, chest radiograph, and CT of the thorax.

A. fumigatus specific IgE and IgG levels were assayed using the M3 ImmunoCap with the commercial ImmunoCAP system (ThermoFisher Scientific, Uppsala, Sweden).^{8,9} *A. fumigatus* specific IgE and IgG values >0.35 kUA/L and >27 mgA/L, respectively, were considered as a positive result.^{4,9,10}

Aspergillus precipitins were detected for *A. fumigatus* using the Ouchterlony gel double-diffusion technique according to the method described by Longbottom and Pepys.

The *Aspergillus* skin test was carried out by injecting 0.2 mL of 100 protein nitrogen units (PNU)/mL of the *A. fumigatus* antigen (1 PNU = 0.00001 mg/mL) intradermally in the forearm, as previously described.¹¹ Phosphate buffer saline (0.2 mL) served as the control. The injection site was examined every 15 minutes for 1 hour. An immediate cutaneous hyperreactivity was defined if a wheal and erythema developed within 1 minute, reached a maximum after 10 to 20 minutes, and resolved within 1 hour. The antigen arm skin reaction diameter had to be at least 8 mm greater than the control arm.¹¹

Total IgE levels were estimated with automated fluorescent enzyme immunoassay using the ImmunoCAP system.¹²

Sputum and BALF examination: sputum and BALF were initially homogenized with N-acetyl-L-cysteine, treated with sodium citrate and neutralized with phosphate-buffered saline. The sample was centrifuged, and the pellet was used for microscopy (calcofluor dye with potassium hydroxide) and culture (Sabouraud glucose agar medium). After mycelial growth, it was subcultured on malt extract agar and Czapek-Dox agar. Morphological characteristics identified the *Aspergillus* species.

Definitions and outcomes

For the study, we categorized subjects as follows: (a) immunological ABPA: those with *A. fumigatus* specific IgE >0.35 kUA/L, total IgE ≥500 IU/mL, and eosinophil count ≥500 cells/μL; (b) obligatory ABPA criteria: those with *A. fumigatus* specific IgE >0.35 kUA/L and total IgE ≥500 IU/mL; (c) *Aspergillus* sensitization: defined as *A. fumigatus* specific IgE >0.35 kUA/L. We also calculated the proportion of subjects who had total IgE ≥1000 IU/mL or eosinophil count ≥500 cells/μL. We compared the clinical, serological, and radiological manifestations of subjects with or without the obligatory criteria for ABPA.

TABLE I. Demographics and clinical profile of the study population (n = 269)

Parameter	Value
Demographic	
Age, years	44.3 ± 14.7
Male gender	144 (53.5)
Body mass index, kg/m ²	19.4 ± 4.2
Body mass index <18.5 kg/m ²	110 (40.9)
Clinical findings	
Duration of symptoms, y	2.9 ± 4.4
Cough	235 (87.4)
Dyspnea	86 (32)
mMRC grade I	49 (18.2)
mMRC grade II	26 (9.6)
mMRC grade III	11 (4.1)
Recurrent hemoptysis	191 (71)
Fever	83 (30.9)
Malaise	62 (23)
Weight loss	150 (55.8)
No. of episodes of tuberculosis	1.2 ± 0.8
Spirometry	
FEV1, L	1.7 ± 0.7
FEV1/FVC ratio	73.1 ± 16.7
Underlying disease	
Tuberculosis	230 (85.5)
Chronic obstructive pulmonary disease	5 (1.9)
Chronic hypersensitivity pneumonitis	2 (0.7)
Sarcoidosis	2 (0.7)
Mycobacterium other than tuberculosis	1 (0.4)
Idiopathic pulmonary fibrosis	1 (0.4)
Type II diabetes mellitus	3 (1.1)
None	25 (9.3)
More than 1 risk factor	60 (22.3)
Category of chronic pulmonary aspergillosis	
Simple aspergilloma	17 (6.3)
Chronic cavitary pulmonary aspergillosis	215 (79.9)
Chronic fibrosing pulmonary aspergillosis	37 (13.8)

Values are described as mean ± standard deviation or number (percentage) unless specified.

FEV1, Forced expiratory volume in 1 s; FVC, forced vital capacity; mMRC, modified medical research council.

Statistical analysis

Data are presented descriptively as mean (SD) or number (percentage). The difference between continuous and categorical variables was analyzed using the Mann-Whitney *U* test and Fischer's exact test, respectively.

RESULTS

We enrolled 269 subjects (53.5% males) of CPA with a mean (SD) age of 44.3 (14.7) years during the study period. The baseline characteristics are described in Table I. The mean (SD) body mass index (BMI) of the study population was 19.4 (4.2) kg/m²; 41% of the subjects were underweight (BMI <18.5 kg/m²). The mean (SD) duration of symptoms in the study population was 2.9 (4.4) years. Long-standing cough (n = 235, 87.4%) and recurrent hemoptysis (n = 191, 71%) were the frequently encountered symptoms. Other common

TABLE II. Proportion of subjects with chronic pulmonary aspergillosis demonstrating positive immunological tests used in the diagnosis of allergic bronchopulmonary aspergillosis

Investigations	No. of subjects
Immunological ABPA*	13 (4.8)
Obligatory ABPA criteria†	59 (21.9)
<i>A. fumigatus</i> specific IgE >0.35 kUA/mL	112 (41.6)
Total IgE ≥1000 IU/mL	49 (18.2)
Total IgE ≥500 IU/mL	93 (34.6)
Total eosinophil count ≥1000 cells/μL	5 (1.9)
Total eosinophil count ≥500 cells/μL	30 (11.2)

All values are presented as number (percentage).

ABPA, Allergic bronchopulmonary aspergillosis.

**A. fumigatus* specific IgE >0.35 kUA/mL, total IgE ≥500 IU/mL, and total eosinophil count ≥500 cells/μL.

†*A. fumigatus* specific IgE >0.35 kUA/mL and total IgE ≥500 IU/mL.

features included progressive weight loss, low-grade fever, and dyspnea. The most common underlying disease was previously treated pulmonary tuberculosis (n = 230, 85.5%), with a mean (SD) number of previous episodes of tuberculosis being 1.2 (0.8). Other predisposing conditions were chronic obstructive pulmonary disease, chronic hypersensitivity pneumonitis, sarcoidosis, and idiopathic pulmonary fibrosis. In 9.3% (n = 25) subjects, no underlying disease could be identified. Sixty (22.3%) subjects had more than 1 risk factor for developing CPA (Table I). The most common category of CPA was CCPA (n = 215, 79.9%) followed by CFPA (n = 37, 13.8%); SA was seen in 17 (6.3%) subjects. The *A. fumigatus* specific IgG level >27 mgA/L was seen in 255 (94.8%) subjects, with a mean (SD) value being 104.3 (63.6) mgA/L. In the remaining 14 subjects, the diagnosis of CPA was made on the presence of serum or BALF galactomannan or the growth of *Aspergillus* on respiratory tract specimen culture.

Aspergillus sensitization was seen in 112 (41.6%) subjects. Thirteen (4.8%) subjects met all the immunological criteria of ABPA (Table II). The clinical and immunological findings of these 13 subjects are summarized in Table III. Importantly, none of these 13 subjects had bronchiectasis on CT of the thorax. Fifty-nine (21.9%) subjects demonstrated the obligatory criteria of ABPA. A total IgE ≥1000 and ≥500 IU/mL were seen in 49 (18.2%) and 93 (34.6%) subjects, respectively. Elevated eosinophil count ≥1000 and ≥500 cells/μL were seen in 5 (1.9%) and 30 (11.2%) subjects, respectively.

Subjects with the obligatory criteria had significantly higher eosinophil count ($P \leq .0001$), greater immediate cutaneous reactivity on the *Aspergillus* skin test (CPA-others vs obligatory criteria, 9.8 ± 13.9 mm vs 13.9 ± 14.9 mm; P value = .048), and higher *A. fumigatus* specific IgG (99.3 ± 61.9 mgA/L vs 122 ± 66.6 mgA/L; $P = .015$) compared with those without. There was, however, no difference in the other clinical and immunological findings between the 2 groups (Table IV). The subjects with obligatory ABPA criteria had a higher number of fungal balls (CPA-others vs obligatory criteria, 0.9 ± 0.7 [range, 0-3] vs 1.1 ± 0.9 [range, 0-4]; $P = .026$) on CT thorax. However, there was no difference in the number of segments with bronchiectasis or proportion of subjects with pleural thickening on CT thorax. We also did not observe any difference in the number of cavities, centrilobular nodules, random nodules, and consolidation on CT thorax, between the 2 groups (Table IV).

TABLE III. Characteristics of subjects with chronic pulmonary aspergillosis (CPA) fulfilling all serological criteria of allergic broncho-pulmonary aspergillosis

S. no.	Age, y/gender	Underlying disease	No. of previous ATT	Hemoptysis	CPA category	Sputum culture	BAL culture	No. of cavities	No. of fungal ball	TEC, cells/ μ L	Af IgE, kUA/mL	TIGE, IU/L	Af IgG, mgA/L
1	18/F	TB	1	No	CCPA	<i>A. fumigatus</i>	Not done	4	4	900	12.3	8970	200
2	21/F	TB	1	No	CFPA	Sterile	Not done	2	0	1080	0.52	6090	87.9
3	62/M	TB, COPD	1	Yes	CCPA	Sterile	Sterile	5	2	650	0.69	6000	85
4	50/M	TB, DM	1	Yes	SA	Sterile	<i>A. fumigatus</i>	1	1	500	0.81	4731	50.9
5	54/M	None	0	No	CFPA	Sterile	<i>A. fumigatus</i>	2	0	740	0.46	4350	200
6	24/M	TB	1	Yes	CCPA	Sterile	Not done	2	1	770	34.7	3619	30.7
7	67/M	TB, COPD	2	Yes	CFPA	Sterile	Not done	1	0	1700	1.7	3319	59
8	80/M	TB	1	Yes	CFPA	Sterile	Not done	1	0	1480	17.7	2357	200
9	24/F	TB	3	Yes	CCPA	Sterile	Sterile	4	0	600	1.7	2062	138
10	64/M	TB	1	No	CCPA	Sterile	Not done	1	1	1450	2.1	1693	81.3
11	52/F	None	0	Yes	CCPA	<i>Aspergillus flavus</i>	<i>A. fumigatus</i>	2	1	500	12.7	1627	127
12	34/M	TB	1	Yes	CCPA	Sterile	Sterile	2	0	600	0.41	855	123
13	64/F	TB, CHP	1	Yes	CCPA	Sterile	Sterile	2	2	747	1.2	528	128

Af, *Aspergillus fumigatus*; ATT, antituberculosis therapy; BAL, bronchoalveolar lavage; CCPA, chronic cavitary pulmonary aspergillosis; CFPA, chronic fibrosing pulmonary aspergillosis; CHP, chronic hypersensitivity pneumonitis; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; F, female; M, male; SA, simple aspergilloma; TB, tuberculosis; TEC, total eosinophil count; TIGE, total immunoglobulin E.

DISCUSSION

The results of this study indicate a possible immunological overlap between ABPA and CPA. In fact, 13 subjects fulfilled all the 3 immunological criteria for ABPA, whereas 22% of the subjects met the obligatory criteria of ABPA. A total IgE ≥ 500 IU/mL was seen in almost one-third of the subjects with CPA.

The diagnosis of ABPA and CPA relies on clinico-radiological findings and immunological investigations that are common to both. A raised *A. fumigatus* specific IgG is the diagnostic hallmark for CPA³; however, a high level is seen in almost 87% of patients with ABPA.⁹ In fact, the cutoff for *A. fumigatus* specific IgG used for diagnosing ABPA is similar (>27 mgA/L) in both ABPA and CPA, and there is no value of *A. fumigatus* IgG that can discriminate between the 2 disorders.^{9,10} On the other hand, *A. fumigatus* specific IgE and elevated total IgE are essential tests in the diagnosis and follow-up in ABPA.⁸ In the current study, we found that the obligatory criteria used for diagnosing ABPA were seen in up to 22% of the subjects, whereas 5% of subjects fulfilled all the immunological criteria needed to diagnose ABPA.

Few studies have evaluated for the positivity of immunological tests used in ABPA, in patients with CPA. In one study, 22 of the 407 asthmatic patients fulfilled all criteria for ABPA and CPA.¹³ However, apart from being retrospective with a small sample size, it included only subjects with CPA related to prior ABPA. In another study, 4% of subjects with ABPA had concomitant aspergilloma. These individuals had more extensive bronchiectasis and a higher risk of relapse.¹⁴ In a previous study in subjects with pulmonary tuberculosis—related fibrocavitary disease, we could demonstrate a significant relationship between airflow obstruction and *Aspergillus* sensitization.¹⁵ Even in the current study, subjects of CPA meeting the obligatory criteria for ABPA had a higher number of fungal balls with higher total IgE and *A. fumigatus* specific IgG. This suggests that the subset of individuals with “ABPA-CPA overlap” may have greater immunological activity with poorer outcomes.

What are the clinical implications of this study? Based on the host-pathogen interaction and host immunity, *Aspergillus* can cause either allergic or invasive disease. In immunocompetent hosts, it causes preponderant Th2 response (ABPA), whereas CPA is due to dysfunctional Th1 response in a mildly immunocompromised host. These entities are considered mutually exclusive; however, in some individuals, they may occur concomitantly. The preferable therapy in patients with ABPA is systemic glucocorticoids, whereas the primary therapy in CPA is oral triazoles. Generally, misclassifying CPA as ABPA using the immunological investigations could expose these individuals to glucocorticoids that may have detrimental effects. It has been previously shown that the use of glucocorticoids may increase the fungal burden and lead to a more severe invasive disease.^{16,17} However, the results of the current study suggest the possibility of a different management protocol in the “overlap group” with low doses of glucocorticoids and triazoles, which needs to be systematically explored.

Finally, our study is not without limitations. The limitation, apart from the being a single center study, is that most subjects in the current study had previously treated pulmonary tuberculosis as an underlying risk factor. Also, whether the subjects with CPA who had positive immunological tests for ABPA behave differently (with regard to treatment response) cannot be ascertained from this study and needs further evaluation. Finally, were patients who met all criteria of ABPA actually ABPA and not CPA? This appears unlikely as none of these subjects had asthma or bronchiectasis on CT thorax. The strength of the current study is the prospective collection of the data and the large sample size. The diagnosis of CPA was made by a multidisciplinary team, and all the radiology tests were reviewed independently by 2 investigators.

In conclusion, there is a high prevalence of positivity for immunological tests for ABPA in patients with CPA. Future studies should investigate whether the clinical outcomes and response to treatment are different in this subset of subjects with CPA.

TABLE IV. Comparison of clinical, immunological, and radiological findings in subjects with CPA with or without the obligatory criteria for allergic bronchopulmonary aspergillosis (*A. fumigatus* specific IgE >0.35 kUA/L and total IgE ≥500 IU/mL)

	CPA-others (n = 210)	Obligatory criteria (n = 59)	P value
Age, y	43.5 ± 14.3	46.9 ± 16	.117
Body mass index, kg/m ²	19.6 ± 4.3	18.8 ± 3.6	.247
Duration of symptoms, y	2.7 ± 3.9	3.5 ± 5.7	.227
FEV1, L	1.7 ± 0.7	1.6 ± 0.6	.355
FEV1:FVC ratio	73.9 ± 16.6	70.2 ± 16.9	.169
Immunological findings			
<i>A. fumigatus</i> specific IgG levels, mgA/L	99.3 ± 61.9	122 ± 66.6	.015
Total eosinophil count, cells/μL	223.7 ± 173.9	371.7 ± 355.6	<.0001
<i>Aspergillus</i> precipitins	46 (22)	13 (22)	.997
Type 1 <i>Aspergillus</i> skin test, mm	9.8 ± 13.9	13.9 ± 14.9	.048
Sputum fungal culture			.817
<i>A. fumigatus</i>	15 (7.1)	3 (5.1)	
<i>Aspergillus flavus</i>	10 (4.8)	4 (6.8)	
<i>Aspergillus terreus</i>	1 (0.5)	0	
BAL fungal culture (n = 74)			.736
<i>A. fumigatus</i>	20 (17.9)	6 (18.2)	
<i>A. flavus</i>	16 (14.3)	3 (9.1)	
HRCT chest findings			
Cavity	198 (94.3)	55 (93.2)	.758
No. of cavities	1.9 ± 1.1	2.1 ± 1.2	.340
Fungal ball	135 (64.3)	44 (74.6)	.161
Number of fungal balls*	0.9 ± 0.7 (0-3)	1.1 ± 0.9 (0-4)	.026
Bronchiectasis	10 (4.8)	3 (5.1)	.919
No. of segments with bronchiectasis	0.3 ± 1.4	0.2 ± 0.9	.655
Centrilobular nodules	36 (17.1)	15 (25.4)	.187
Random nodules	57 (27.1)	23 (39)	.106
Consolidation	52 (24.8)	15 (25.4)	1.000
Pleural thickening	160 (76.2)	46 (78)	.863
CPA category			.700
Simple aspergilloma	13 (6.2)	4 (6.8)	
CCPA	170 (81)	45 (76.3)	
CFPA	27 (12.9)	10 (16.9)	

All values are specified as mean ± standard deviation or number (percentage), unless specified otherwise. Bold indicates statistical significance ($P < .05$).

BAL, Bronchoalveolar lavage; CCPA, chronic cavitary pulmonary aspergillosis; CFPA, chronic fibrosing pulmonary aspergillosis; CPA, chronic pulmonary aspergillosis; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; HRCT, high-resolution computed tomography.

*The values in parenthesis represent the range.

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