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ORIGINAL RESEARCH

Evaluation of the Dynamiker Quantitative Anti-Aspergillus Fumigatus Specific Detection for the Diagnosis of Different Kinds of Chronic Pulmonary Aspergillosis

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Background: *Aspergillus*-specific IgG antibody test is considered to be the most reliable method for diagnosing chronic pulmonary aspergillosis (CPA), while its diagnostic roles in different kinds of CPA are still uncertain and it is a challenge of having a threshold to interpret the IgG levels.

Purpose: This study aimed to evaluate the diagnostic value of the Dynamiker quantitative *Aspergillus fumigatus*-specific IgG antibody in different types of CPA with the aim of providing a reference for clinical work.

Methods: This prospective study collected the clinical data of patients with suspected CPA admitted to the hospital from January 2020 to December 2022 and divided them into two groups: CPA and non-CPA. The study analyzed clinical characteristics and *Aspergillus*-specific IgG antibody test's diagnostic value, and a receiver operating characteristic (ROC) curve was used to evaluate diagnostic efficacy.

Results: We enrolled 54 CPA patients and 132 non-CPA patients. The average admission age of the CPA group was 61.0 (43.8, 70.0) years, and the sex ratio was 32/22 (male/female). The level of *Aspergillus fumigatus*-specific IgG antibody in the CPA group was significantly higher than the non-CPA group (95.2 (31.3, 213.3) vs 47.5 (34.0, 80.3) AU/mL, $p = 0.001$). The area under the ROC curve was 0.653 (95% confidence interval [CI]: 0.580–0.721, $p = 0.003$). The cutoff with the best diagnostic efficacy was 87 AU/mL, and the sensitivity and specificity were 57.4% and 77.3%, respectively. There was no significant difference in the level of specific IgG antibody among the five CPA types ($p = 0.543$); however, it was relatively higher in chronic cavitary pulmonary aspergillosis (CCPA).

Conclusion: *Aspergillus*-specific IgG antibody is valuable diagnostic marker for CPA, while its value in differential diagnosis among different types of CPA is limited.

Keywords: *Aspergillus*, chronic pulmonary aspergillosis, IgG, subtypes, diagnosis

Introduction

Aspergillus is a class of pathogenic saprophytic fungi that can cause systemic infections. To date, over 300 species of *Aspergillus* have been reported, and approximately 50 species are pathogenic to humans, most commonly *Aspergillus fumigatus (A. fumigatus)*.[1–3] Aspergillosis is defined as different kinds of diseases caused by *Aspergillus*, and pulmonary aspergillosis (PA) is the main clinical manifestation.[4]

The PA spectrum includes invasive pulmonary aspergillosis (IPA), allergic bronchopulmonary aspergillosis (ABPA) and chronic pulmonary aspergillosis (CPA). CPA is comprised of a series of progressive lung parenchymal diseases, including simple pulmonary aspergilloma, aspergillus nodules, chronic cavitary pulmonary aspergillosis (CCPA), chronic

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fibrosing pulmonary aspergillosis (CFPA) and chronic necrotizing pulmonary aspergillosis (CNPA), also known as subacute invasive aspergillosis (SAIA). CPA usually exists in immunocompetent individuals but is accompanied by underlying lung diseases; the most common ones are patients with cavitary lesions in the lungs caused by tuberculosis or nontuberculous mycobacterial infections.[5,6]

In recent years, the morbidity and mortality of PA have gradually increased, and approximately 3 million people worldwide suffer from CPA.[7] CPA has been regarded as an emerging fungal infectious disease with public health importance, therefore, early diagnosis and timely treatment are essential to reduce mortality and improve the prognosis of CPA. Owing to the complexity of the disease itself, the current diagnosis of CPA requires a systematic assessment of the relevant medical history, clinical manifestations, radiology, histopathology, immunology, microbiology, and other aspects. Among these diagnostic methods, immunological tests (specific antigen and antibody tests, including galactomannan (GM) test, 1.3-β-D-glucan (BDG) test (G test), *Aspergillus*-specific immunoglobulin M (IgM), IgG, IgE, IgA antibody tests, etc). have advantages of convenient operation, high sensitivity and specificity, short-time consuming and less trauma, which is of great value to improve the timely diagnosis rate of CPA.[8]

Among the biomarkers related to immunological tests for the diagnosis of CPA, specific antibodies, particularly IgG antibodies, are widely used. A meta-analysis reviewed and summarized the accuracy of various *Aspergillus*-specific antibodies for the diagnosis of CPA, and the results suggested that a specific IgG antibody was more valuable, especially in exclusionary diagnosis.[9] As an auxiliary indicator, previous study has proved that the serum detection of raised level of *Aspergillus*-specific IgG antibody is positive in over 90% of CPA, and it is considered to be the most reliable method for diagnosing CPA.[10] The sensitivity and specificity of serum specific IgG antibody can reach up to 96% and 99%, respectively.[11] The CPA disease itself is complex and has plenty of different subtypes, however, there is no research to clarify the difference in the level of specific IgG antibody between different subtypes of CPA.

Therefore, it is necessary to further explore specific IgG antibody for the diagnosis of different CPA subtypes. This study aimed to evaluate the diagnostic value of quantitative *A. fumigatus*-specific IgG antibody in CPA to provide more references for clinical work.

Materials and Methods

Materials and Data Collection

This prospective, single-center, controlled study included 186 patients with suspected CPA admitted to the First Affiliated Hospital, Zhejiang University School of Medicine, from January 2020 to December 2022 (Figure 1). Enrollment, diagnosis, and testing results were evaluated by experienced respiratory physicians at our hospital.

Patients with suspected CPA were recruited in the study, and the inclusion criteria were as follows: 1) age ≥18 years; 2) no or mild immune insufficiency (long-term smoking, diabetes, corticosteroid therapy, BMI<18, tuberculosis); 3) the time for appearance of suspected clinical symptoms (cough, expectoration, hemoptysis, weight loss, dyspnea) and abnormal imaging manifestations (single or multiple pulmonary nodules, pulmonary cavities, bronchiectasis, aspergilloma) of CPA is ≥3 months or lasting for 1–3 months, or persistent lung CT imaging abnormalities, which suggests the possibility of CPA.

The exclusion criteria were as follows: 1) receiving anti-*Aspergillus* treatment for ≥3 days in the past 3 months, 2) patients with a history of *Aspergillus* infection or colonization and 3) patients with infections caused by specific bacteria, viruses, tuberculosis, non-tuberculous mycobacteria, and fungi other than *Aspergillus spp.*

The patients were divided into two groups: CPA and non-CPA groups, and the diagnostic criteria of CPA were according to the guidelines of the European Respiratory Society (ERS) and European Confederation of Medical Mycology (ECCMID) in 2015.[10] Proven CPA should meet the inclusion criteria and histopathological evidence, or positive culture results from a sterile environment (excluding BALF), while probable CPA required mycological evidence such as galactomannan test (GM test), positive culture result (qualified specimen from sputum, BALF, and bronchial brush), *Aspergillus* PCR, etc. *A. fumigatus*-specific IgG antibody test was not used as a diagnostic criterion for CPA in this study.

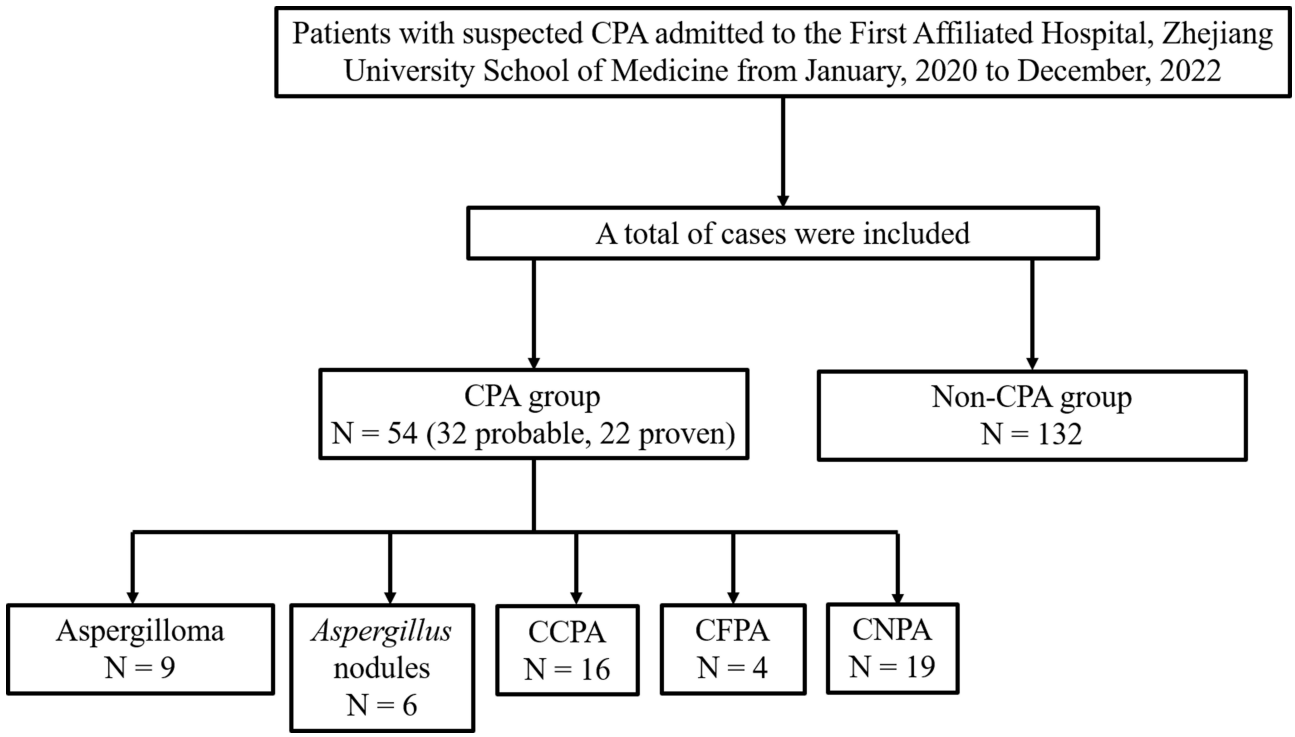

Figure 1 The flow chart of the study. Proven CPA should meet the inclusion criteria and histopathological evidence or positive culture results from a sterile environment. Probable CPA required inclusion criteria and mycological evidence, such as galactomannan test, positive culture results, *Aspergillus* PCR.
Abbreviations: CCPA, Chronic cavitary pulmonary aspergillosis; CFPA, chronic fibrosing pulmonary aspergillosis; CNPA, chronic necrotizing pulmonary aspergillosis.

Inpatient medical records were also recorded. The collected data included current medical history, medical history, personal history, and other laboratory test results (Tables 1 and 2).

Aspergillus Fumigatus-Specific IgG Antibody Test

The antibody used in this study was *Aspergillus fumigatus*-specific IgG antibody, which reflects people's immune response to spores and was detected using an enzyme-linked immunosorbent assay (ELISA) kit (Dynamiker, Tianjin, China). The optical density (OD) was measured using a microplate reader (Bio-Rad iMark, Hercules, California, USA).

Table 1 Clinical Baseline Information of CPA and Non-CPA Patients

Items	CPA (n=54) n (%)	Non-CPA (n=132) n (%)	*p* value
Admission age	61.0 (43.8,70.0)	60.0 (53.0,67.0)	0.780
Age range	18–78	26–78	/
Gender (Male/Female)	32/22	81/51	0.790
Smoking history	19 (35.2)	58 (43.9)	0.271
Allergic history	13 (24.1)	12 (9.1)	0.007
History of pulmonary diseases			
COPD	8 (14.8)	12 (9.1)	0.253
Bronchiectasis	14 (25.9)	14 (10.6)	0.008
Pulmonary tuberculosis	10 (18.5)	16 (12.1)	0.253
Lung cancer	3 (5.6)	31 (23.5)	0.004
Asthma	1 (1.97)	6 (4.5)	0.651
Others[a]	7 (13.0)	46 (34.8)	0.003

(*Continued*)

Table 1 (Continued).

Items	CPA (n=54) n (%)	Non-CPA (n=132) n (%)	*p* value
Other comorbidities			
Hypertension	16 (29.6)	35 (26.5)	0.666
Diabetes mellitus	6 (11.1)	21 (16.0)	0.389
Heart disease	5 (9.3)	14 (10.6)	0.783
Autoimmune disease	4 (7.4)	6 (4.5)	0.669
Liver cirrhosis	0	1 (0.8)	1.000
Other malignant tumor	1 (1.9)	7 (5.3)	0.512
Others[b]	17 (31.5)	53 (40.2)	0.268
Clinical symptoms			
Cough	49 (90.7)	119 (90.2)	0.902
Expectoration	42 (77.8)	96 (72.7)	0.475
Fever	19 (35.2)	39 (29.5)	0.451
Hemoptysis	22 (40.7)	27 (20.5)	0.004
Shortness of breath	13 (24.1)	37 (28.0)	0.581
Oppression in chest	16 (29.6)	40 (30.3)	0.928
Chest pain	5 (9.3)	24 (18.2)	0.128

Notes: a: pneumothorax, lung abscess, focal organizing pneumonia, etc. b: nervous system diseases, metabolic diseases, mental diseases, etc. COPD: Chronic obstructive pulmonary disease.

Other Laboratory Tests

Peripheral blood was used as the test specimen for the other laboratory tests. Serum *A. fumigatus*-specific IgG antibody levels were detected in all samples using the Dynamiker *A. fumigatus* IgG assay (Dynamiker, Tianjin, China). Plate enzyme-linked immunosorbent assays (ELISAs) were performed on all the samples in accordance with the manufacturer's instructions.

Table 2 Laboratory Testing Results of CPA and Non-CPA Patients

Items	CPA	non-CPA	*p* value
Cases	54	132	
Aspergillus-specific IgG antibody (AU/mL)	95.2 (31.3,213,3)	47.5 (34.0,80.3)	0.001
WBC (×109/L)	6.5 (4.6,8.7)	6.9 (5.2,8.6)	0.493
Neutrophils (×109/L)	4.4 (2.5,5.8)	4.6 (3.1,6.0)	0.519
Eosinophils (×109/L)	0.1 (0.1,0.2)	0.1 (0.1,0.3)	0.827
Monocytes (×109/L)	0.5 (0.4,0.8)	0.5 (0.4,0.7)	0.548
Lymphocytes (×109/L)	1.5 (1.2,2.0)	1.4 (1.1,1.8)	0.584
RBC ($\times 10^9$/L)	4.1 (3.9,4.5)	4.4 (4.0,4.6)	0.040
Hb (g/L)	125.0 (115.0,135.3)	128.5 (114.0,139.0)	0.265
PLT ($\times 10^9$/L)	253.0 (193.3,355.3)	252.0 (192.5,324.5)	0.602
ALT (U/L)	15.0 (11.0,29.0)	16.0 (10.0,26.8)	0.881
AST (U/L)	20.0 (17.0,24.5)	19.0 (16.0,23.8)	0.226
Albumin (g/L)	40.5 (36.4,44.3)	41.2 (37.1,44,4)	0.415
Creatine (μmol/L)	56.0 (50.0,68.0)	63.0 (51.3,73.0)	0.028
LDH (U/L)	200.0 (177.0,247.5)	211.0 (178.0,248.5)	0.595
CRP (mg/L)	9.7 (3.0,46.0)	6.9 (1.7,48.3)	0.441
ESR (mm/h)	27.0 (11.5,63.0)	21.5 (11.3,59.8)	0.840

Abbreviations: WBC, White blood cell; RBC, Red blood cell; Hb, Hemoglobulin; PLT, Platelets; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; LDH, Lactate dehydrogenase; CRP, C-reactive protein; ESR, Erythrocyte sedimentation rate.

Statistical Analysis

All data in this study were statistically analyzed using SPSS, version 20.0 software (IBM SPSS Inc., Chicago, Illinois, USA), GraphPad Prism, version 8.0 (GraphPad Software Inc., San Diego, CA, USA) and MedCalc, version 18.2 (MedCalc Software Ltd, Ostend, Belgium) software were also used to complete the figures. Continuous variables with normal distribution were expressed as mean ± standard deviation (SD), and continuous variables with abnormal distribution were presented as medians (interquartile range, p25-p75). The Kolmogorov–Smirnov test was used to determine whether the normal distribution condition was met. If $p > 0.05$, a normal distribution was met, and the *t*-test was used for comparisons between groups. If a normal distribution was not met, the non-parametric rank sum test was used for comparison between the groups. Count data were expressed in terms of frequency and percentage, and the chi-square test or Fisher's exact test was used for comparisons between groups.

The sensitivity, specificity, Youden's index, positive predictive value (PPV), and negative predictive value (NPV) were calculated. The receiver operating characteristic (ROC) curve was used to evaluate the diagnostic efficacy. The relationship between IgG antibody levels and other clinical factors in this study was investigated using multivariate linear regression models.

Results

Clinical Characteristics of Enrolled Patients

A total of 186 adult patients with suspected CPA were enrolled in this study between January 2020 and December 2022 (Figure 1, Table 1). There were 54 CPA cases (32 probable and 22 proven) and 132 non-CPA cases, whereas the specific diseases in the latter group included tuberculosis, pulmonary cryptococcosis, lung cancer, bacterial infection, and pulmonary actinomycosis. Meanwhile, CPA consisted of nine cases of simple pulmonary aspergilloma (16.7%), 16 cases of CCPA (29.6%), four cases of CFPA (7.4%), six cases of *Aspergillus* nodules (11.1%), and 19 cases of CNPA (35.2%).

The clinical baseline information and laboratory test results of CPA and non-CPA patients are shown in Tables 1 and 2. The average age of the CPA group was 61.0 (43.8, 70.0) years, the sex ratio was 32/22 (male/female), and the percentage of patients with a history of allergies and bronchiectasis was significantly higher than that in the non-CPA group (24.1% vs 9.1%, $p = 0.007$; 25.9% vs 10.6%, $p = 0.008$, respectively). Among the clinical symptoms, cough (90.7%), expectoration (77.8%), and hemoptysis (40.7%) were relatively common in CPA patients, whereas chest pain was less common (9.3%) and CPA patients were more likely to have hemoptysis than non-CPA patients (40.7% vs 20.5%, $p = 0.004$). The levels of red blood cells and creatine in the CPA group were significantly lower than those in the non-CPA group (4.1 (3.9,4.5) vs 4.4 (4.0,4.6), $p = 0.040$; 56.0 (50.0,68.0) vs 63.0 (51.3,73.0), $p = 0.028$, respectively); however, the median values were all within the normal range, which made little sense to the final conclusion.

Comparison

A. Fumigatus-Specific IgG Levels Between CPA and Non-CPA

The levels of *A. fumigatus*-specific IgG antibody in the CPA and non-CPA groups are shown in Figure 2. The level of specific IgG antibody in the CPA group was significantly higher than the non-CPA group (95.2 (31.3, 213.3) vs 47.5 (34.0, 80.3) AU/mL, $p = 0.001$, Figure 2A). In this study, the level of specific IgG antibody was significantly higher in the probable than the proven CPA group (131.3 (47.0, 250.8) vs 58.8 (31.3, 132.8), $p = 0.036$, Figure 2B, Table S1).

A. Fumigatus-Specific IgG Levels Between Different CPA Types

The levels of *A. fumigatus*-specific IgG antibody in the CPA groups are shown in Figure 2C. From the numerical point of view, the average level of antibody in the CCPA group (179.5 ± 152.6 AU/mL) was relatively higher, but there was no significant difference among the five groups ($p = 0.543$, Figure 2C, Table S2).

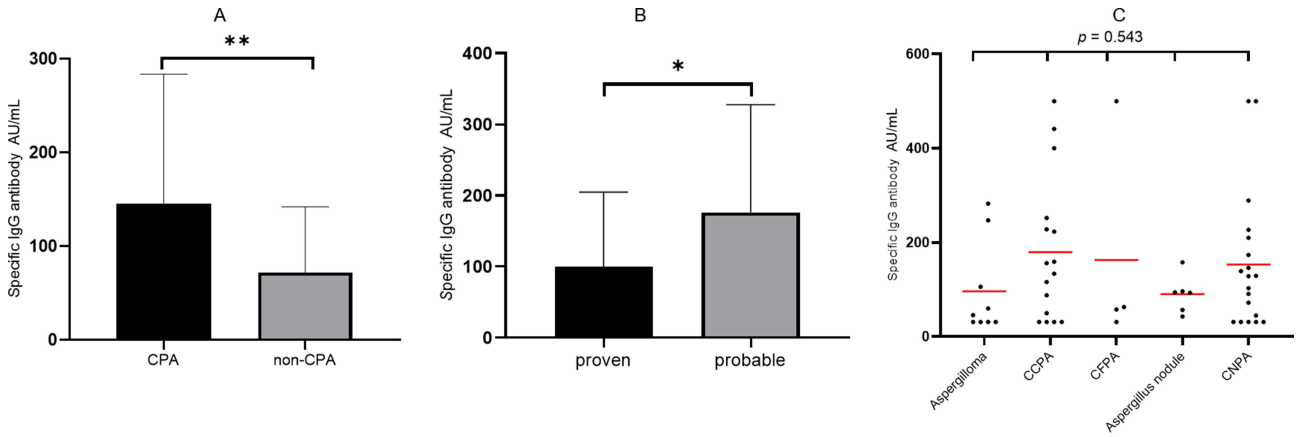

Figure 2 (**A**) The level of *Aspergillus fumigatus*-specific IgG antibody in CPA and non-CPA patients. (**B**) The level of *Aspergillus fumigatus*-specific IgG antibody in probable and proven CPA patients. (**C**) The level of *Aspergillus fumigatus*-specific IgG antibody among five subtypes of CPA patients. $^{**}p < 0.01$, $^{*}p = 0.036 < 0.05$.
Abbreviations: CCPA, Chronic cavitary pulmonary aspergillosis; CFPA, chronic fibrosing pulmonary aspergillosis; CNPA, chronic necrotizing pulmonary aspergillosis.

The Diagnostic Value and Cutoff of A. Fumigatus-Specific IgG for CPA

The ROC curve of the specific IgG antibody test for CPA diagnosis is shown in Figure 3, and the sensitivity, specificity, Youden's index, PPV, and NPV values under different cut-off values are listed in Table 3. In the ROC curve, the area

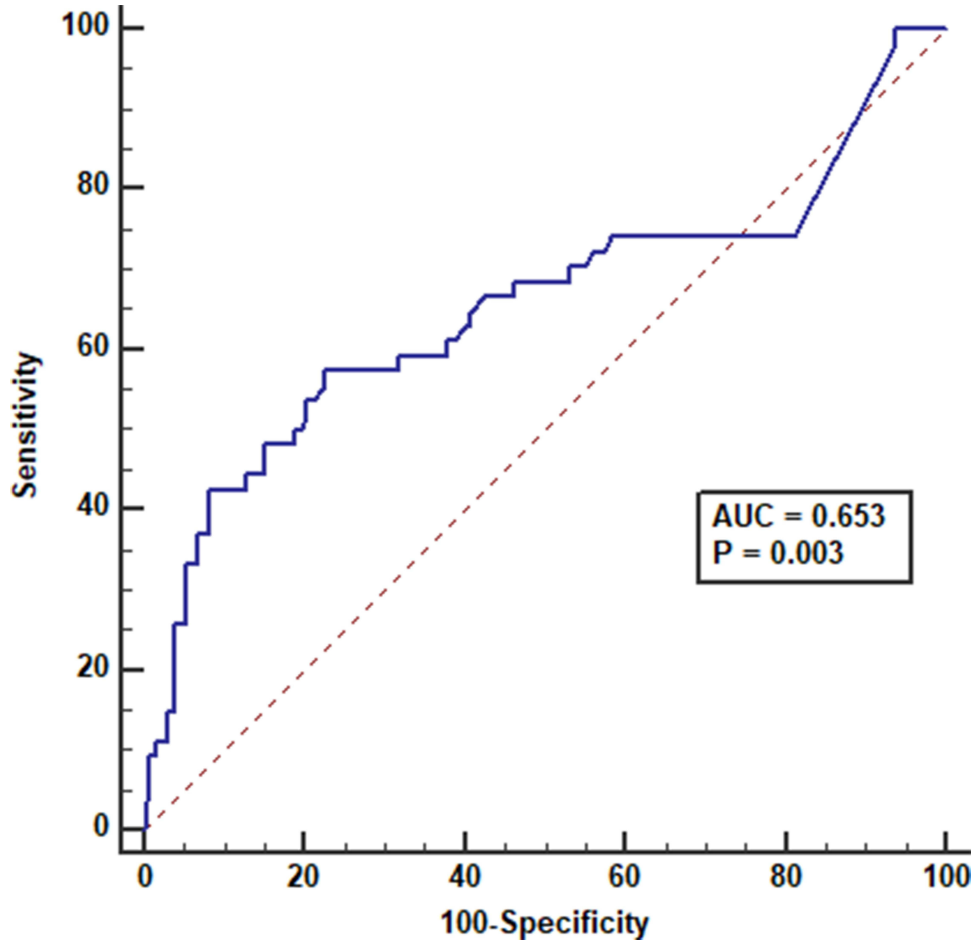

Figure 3 The ROC curve of *Aspergillus fumigatus*-specific IgG antibody test in the diagnosis of CPA.

Table 3 Sensitivity and Specificity of Aspergillus Fumigatus-Specific IgG Antibody Test at Different Cut-Offs in the Diagnosis of CPA

Cut-offs (AU/mL)	Results				
	Sensitivity	Specificity	Youden's index	PPV	NPV
70	0.593	0.674	0.267	0.600	0.802
80	0.574	0.750	0.324	0.484	0.811
87	0.574	0.773	0.347	0.508	0.816
100	0.482	0.841	0.323	0.620	0.799
120	0.426	0.886	0.312	0.605	0.791

Abbreviations: PPV, Positive predictive value; NPV, Negative predictive value.

under the ROC curve (AUROC) was 0.653 (95% CI: 0.580–0.721, $p = 0.003$), which indicated that the *A. fumigatus*-specific IgG antibody was a valuable marker for CPA diagnostic. The cutoff with the best diagnostic efficacy was 87 AU/mL, and the sensitivity and specificity were 57.4% and 77.3%, respectively. Youden's index was 0.347, and the PPV and NPV were 0.508 and 0.816, respectively, at this cut-off value.

A multivariate linear regression analysis is also performed to explore relationship between IgG antibody levels and other clinical factors in this study (Table S3). The results revealed IgG antibody levels were related with diagnosis of CPA, history of lung cancer, expectoration, platelets and albumin. Relatively, there was a significant positive relationship between specific IgG antibody levels and diagnosis of CPA ($\beta = 0.359$, $p < 0.001$).

Discussion

It is well known that the *A. fumigatus*-specific IgG antibody test occupies an essential position in the diagnosis of CPA, while its diagnostic roles in different types of CPA are still uncertain, and few data are available. Therefore, this study prospectively evaluated the diagnostic value of quantitative *A. fumigatus*-specific IgG antibody in various types of CPA.

The clinical characteristics of CPA and non-CPA patients in this study were also explored, and there was no significant difference between the two groups in terms of admission age, sex, or laboratory test results. CPA patients are prone to have a history of allergies and bronchiectasis, and hemoptysis is more likely to appear in CPA patients. These results verified that CPA patients were apparently immunocompetent or subtly immunocompromised with prior or current lung disease from another side.[1,8,12]

Our study further verified that specific IgG antibody tests play an important role in CPA diagnoses, and the result of multivariate regression analysis also supported this conclusion from another side. Several commercial specific kits are available for diagnosing CPA. Previous studies indicated that the specificity and sensitivity of *A. fumigatus*-specific IgG antibody kit varied depending on the manufacturer, and the preferred recommended sensitivities and specificities were 70.0%-90.0% and 82.8%-94.4%, respectively,[13–17] In this study, the specificity and sensitivity were lower than previously published data, which may be related to the sample size. It is also advised that the detection of other biomarkers such as galactomannan should be performed to improve diagnostic performance. Besides, it was worth mentioning that the level of specific IgG antibody was significantly higher in the probable than the proven CPA group in our study, which may be relevant to the missed diagnoses of other types of *Aspergillus* spp., different subtypes of CPA or sample size, and the above interesting findings could be deepen explored in the future.

Meanwhile, the cut-off value with the best diagnostic efficacy was 87 AU/mL, and a previous study found that the baseline *A. fumigatus*-specific IgG level in an Asian population with an intermediate TB burden could be higher than expected; thus, the optimal cut-off value of a specific kit in different geographic areas remains indeterminate.[18–20] The results of our study could deepen our understanding of the optimal cut-off value for this commercial kit, so as to broaden its application in clinical practice.

There are five subtypes of CPA, and in this study, there was no significant difference in the levels of specific IgG antibodies among the different types of CPA. However, levels of specific IgG antibody were higher in the CCPA group. Previously, Sehgal et al found that the sensitivity of a specific IgG antibody was lower in simple aspergilloma compared

with CCPA.[21] Besides, Lee et al reported that *A. fumigatus-specific* IgG level was higher in CCPA, CFPA and aspergilloma compared with CNPA and aspergillus nodule.[22] We have spent much more attention on specific IgG's diagnostic efficacy for CPA, but its diagnostic roles in different subtypes of CPA are still uncertain, and this study filled the subject with more research data, which could add to the understanding of *Aspergillus*-specific IgG antibody tests in CPA.

Although *Aspergillus*-specific IgG antibody test has been fully used in the diagnosis of CPA for years, researchers are still exploring ways to make the detection steps much more convenient. The above specific antibody tests mainly use the principles of ELISA, whereas the lateral flow assay (LFA) has been gradually applied to the diagnosis of CPA with point-of-care detection and limited equipment. LDBio LFA *Aspergillus* immunochromatographic technology is the only commercially available LFA for the diagnosis of CPA, which has comparable sensitivity and specificity with ELISA.[8] Previous studies showed sensitivities and specificities of LDBio LFA were 73.3%-91.6% and 70.0%-98.0%, for instance, Stucky et al found sensitivity and specificity for the LDBio *Aspergillus* immunochromatographic technology in proven CPA patients were 91.6% and 98.0%, while the routinely used kit of *A. fumigatus*-specific IgG exhibited 80.5% sensitivity for the same cohort.[23–25]

Beyond that, *Aspergillus*-specific IgG also has potential efficacy in monitoring the therapeutic response for CPA, but Sehgal et al evaluated the value of *Aspergillus*-specific IgG, GM, body weight change and pulmonary function in the follow-up of CPA, which indicated that the change of a specific IgG's level was not fully consistent with the therapeutic response, so it still needs more evidence to support a specific IgG's role in monitoring.[26,27] Meanwhile, researchers have also attempted to combine a specific IgG antibody with GM in diagnosis, and a previous study found that its combination could make sensitivity higher in simple aspergilloma.[28] Kosmidis et al found that *Aspergillus* IgG was a predictor of mortality in CPA.[29] Therefore, whether *Aspergillus*-specific IgG's diagnostic value in different subtypes of CPA or other aspects monitor, there are still more applications to discover and verify.

However, this study had some limitations. First, this was a single-center study with a limited sample size, which did not allow multivariate analysis. Second, the antibody kits used in this study were *A. fumigatus*-specific antibodies, which might have caused missed diagnoses of other types of *Aspergillus spp*. Third, we did not include healthy people as a control group. Furthermore, it is unclear whether the interference of colonization was completely eliminated. Finally, some of the correlations mentioned in the text can only provide references, and should be further explored with larger sample sizes in the future.

Conclusion

Aspergillus-specific IgG antibody is a valuable diagnostic marker for CPA, while its value in differential diagnosis among different types of CPA is limited.

Data Sharing Statement

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

Ethics Approval and Informed Consent

The Institutional Review Board of Clinical Research of the First Affiliated Hospital, School of Medicine, Zhejiang University approved the study protocol, and all methods were performed in accordance with the approved guidelines and regulations (IIT-2019-999). Written informed consent for the experiment and its publication was obtained from all patients. This study was conducted in accordance with the ethical standards of the Declaration of Helsinki.

Author Contributions

All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas, took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declared no conflict of interest.

References

1. Hayes GE, Novak-Frazer L. Chronic Pulmonary Aspergillosis-Where Are We? and Where Are We Going? *J Fung*. 2016;2(2). doi:10.3390/jof2020018
2. Samson RA, Visagie CM, Houbraken J, et al. Phylogeny, identification and nomenclature of the genus Aspergillus. *Studies in Mycology*. 2014;78:141–173. doi:10.1016/j.simyco.2014.07.004
3. Ullmann AJ, Aguado JM, Arikan-Akdagli S, et al. Diagnosis and management of Aspergillus diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline. *Clin Microbiol Infect*. 2018;24(1):e1–e38. doi:10.1016/j.cmi.2018.01.002
4. Hospenthal DR, Kwon-Chung KJ, Bennett JE. Concentrations of airborne Aspergillus compared to the incidence of invasive aspergillosis: lack of correlation. *Med Mycol*. 1998;36(3):165–168.
5. Richardson MD, Page ID. Aspergillus serology: have we arrived yet? *Med Mycol*. 2017;55(1):48–55. doi:10.1093/mmy/myw116
6. Kellett F, Redfern J, Niven RM. Evaluation of nebulised hypertonic saline (7%) as an adjunct to physiotherapy in patients with stable bronchiectasis. *Respir Med*. 2005;99(1):27–31. doi:10.1016/j.rmed.2004.05.006
7. Bongomin F, Gago S, Oladele RO, et al. Global and Multi-National Prevalence of Fungal Diseases-Estimate Precision. *J Fung*. 2017;3(4). doi:10.3390/jof3040057
8. Bongomin F, Asio LG, Baluku JB, et al. Chronic Pulmonary Aspergillosis: notes for a Clinician in a Resource-Limited Setting Where There Is No Mycologist. *J Fung*. 2020;6(2). doi:10.3390/jof6020075
9. Anan K, Kataoka Y, Okabayashi S, et al. Diagnostic accuracy of Aspergillus-specific antibodies for chronic pulmonary aspergillosis: a systematic review and meta-analysis. *Mycoses*. 2021;64(7):701–715. doi:10.1111/myc.13253
10. Denning DW, Cadranel J, Beigelman-Aubry C, et al. Chronic pulmonary aspergillosis: rationale and clinical guidelines for diagnosis and management. *Europ resp J*. 2016;47(1):45–68. doi:10.1183/13993003.00583-2015
11. Page ID, Richardson MD, Denning DW. Comparison of six Aspergillus-specific IgG assays for the diagnosis of chronic pulmonary aspergillosis (CPA). *The Journal of Infection*. 2016;72(2):240–249. doi:10.1016/j.jinf.2015.11.003
12. Wilopo B, Richardson MD, Denning DW. Diagnostic Aspects of Chronic Pulmonary Aspergillosis: present and New Direction. *Current Fungal Infection Reports*. 2019;13(4):292–300. doi:10.1007/s12281-019-00361-7
13. Denning DW, Page ID, Chakaya J, et al. Case Definition of Chronic Pulmonary Aspergillosis in Resource-Constrained Settings. *Emerg Infect Dise*. 2018;24(8). doi:10.3201/eid2408.171312
14. Dumollard C, Bailly S, Perriot S, et al. Prospective Evaluation of a New Aspergillus IgG Enzyme Immunoassay Kit for Diagnosis of Chronic and Allergic Pulmonary Aspergillosis. *Journal of Clinical Microbiology*. 2016;54(5):1236–1242. doi:10.1128/jcm.03261-15
15. Guo Y, Bai Y, Yang C, et al. Evaluation of Aspergillus IgG, IgM antibody for diagnosing in chronic pulmonary aspergillosis: a prospective study from a single center in China. *Medicine*. 2019;98(16):e15021. doi:10.1097/MD.0000000000015021
16. Li H, Rui Y, Zhou W, et al. Role of the Aspergillus-Specific IgG and IgM Test in the Diagnosis and Follow-Up of Chronic Pulmonary Aspergillosis. *Front Microbiol*. 2019;10:1438. doi:10.3389/fmicb.2019.01438
17. Ma X, Wang K, Zhao X, et al. Prospective study of the serum Aspergillus-specific IgG, IgA and IgM assays for chronic pulmonary aspergillosis diagnosis. *BMC Infect Dis*. 2019;19(1):694. doi:10.1186/s12879-019-4303-x
18. Lee MR, Huang HL, Chen LC, et al. Seroprevalence of Aspergillus IgG and disease prevalence of chronic pulmonary aspergillosis in a country with intermediate burden of tuberculosis: a prospective observational study. *Clin Microbiol Infect*. 2020;26(8):1091.e1–1091.e7. doi:10.1016/j.cmi.2019.12.009
19. Takazono T, Izumikawa K. Recent Advances in Diagnosing Chronic Pulmonary Aspergillosis. *Front Microbiol*. 2018;9:1810. doi:10.3389/fmicb.2018.01810
20. Page ID, Richardson MD, Denning DW. Siemens Immulite Aspergillus-specific IgG assay for chronic pulmonary aspergillosis diagnosis. *Med Mycol*. 2019;57(3):300–307. doi:10.1093/mmy/myy024
21. Sehgal IS, Choudhary H, Dhooria S, et al. Diagnostic cut-off of Aspergillus fumigatus-specific IgG in the diagnosis of chronic pulmonary aspergillosis. *Mycoses*. 2018;61(10):770–776. doi:10.1111/myc.12815
22. Lee MR, Huang HL, Keng LT, et al. Establishing Aspergillus-Specific IgG Cut-Off Level for Chronic Pulmonary Aspergillosis Diagnosis: multicenter Prospective Cohort Study. *J Fungi*. 7(6). doi:10.3390/jof7060480
23. Rozaliyani A, Rosianawati H, Handayani D, et al. Chronic Pulmonary Aspergillosis in Post Tuberculosis Patients in Indonesia and the Role of LDBio Aspergillus ICT as Part of the Diagnosis Scheme. *J Fung*. 2020;6(4). doi:10.3390/jof6040318
24. Ray A, Chowdhury M, Sachdev J, et al. Efficacy of LD Bio Aspergillus ICT Lateral Flow Assay for Serodiagnosis of Chronic Pulmonary Aspergillosis. *Journal of Fungi (Basel*. 8(4). doi:10.3390/jof8040400
25. Stucky Hunter E, Richardson MD, Denning DW. Evaluation of LDBio Aspergillus ICT Lateral Flow Assay for IgG and IgM Antibody Detection in Chronic Pulmonary Aspergillosis. *Journal of Clinical Microbiology*. 2019;57(9). doi:10.1128/jcm.00538-19
26. Lass-Flörl C, Samardzic E, Knoll M. Serology anno 2021-fungal infections: from invasive to chronic. *Clin Microbiol Infect*. 2021;27(9):1230–1241. doi:10.1016/j.cmi.2021.02.005

27. Sehgal IS, Dhooria S, Choudhary H, et al. Monitoring treatment response in chronic pulmonary aspergillosis: role of clinical, spirometric and immunological markers. *Clin Microbiol Infect*. 2019;25(9):1157.e1–1157.e7. doi:10.1016/j.cmi.2019.01.007
28. Sehgal IS, Dhooria S, Choudhary H, et al. Efficiency of A fumigatus-specific IgG and galactomannan testing in the diagnosis of simple aspergilloma. *Mycoses*. 2019;62(12):1108–1115. doi:10.1111/myc.12987
29. Kosmidis C, Smith H, Mollett G, Harris C, Akili S, Bazaz R. Predictive factors for treatment response and mortality in chronic pulmonary aspergillosis. *Mycoses*. 2023;66(11):960–968. doi:10.1111/myc.13641