

The Difference in All-Cause Mortality Between Allergic Bronchopulmonary Aspergillosis with and without Chronic Obstructive Pulmonary Disease

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Background: Allergic bronchopulmonary aspergillosis (ABPA) primarily complicates the course of asthma, cystic fibrosis, and chronic obstructive pulmonary disease (COPD). Mortality data of ABPA and the difference in all-cause mortality between ABPA with and without COPD are not available.

Objective: We investigated the difference in all-cause mortality between ABPA with and without COPD.

Methods: A retrospective review was performed among patients with the diagnosis of ABPA at Peking University People's Hospital between January 2010 and March 2022. Logrank test was performed to investigate the difference between all-cause mortality for ABPA with and without COPD and Cox regression analysis was performed to investigate the independent risk factors for all-cause mortality in patients with ABPA.

Results: Sixty-one patients with ABPA were enrolled in this study. The follow-up duration was 50.38 months (3–143 months). In the COPD group, 7 patients died (7/10), while in the non-COPD group, 4 patients died (4/51). The 1-year survival rates of ABPA with and without COPD were 60% and 97.8%, respectively. The 5-year survival rates of ABPA with and without COPD were 40% and 94%, respectively. The Cox regression analysis showed that higher C-reactive protein (CRP) (HR = 1.017, 95% CI 1.004–1.031, $P = 0.013$) and complicating COPD (HR = 8.525, 95% CI 1.827–39.773, $P = 0.006$) were independent risk factors associated with mortality in patients with ABPA.

Conclusion: The all-cause mortality for ABPA with COPD is higher than that for ABPA without COPD. Higher CRP and complicating COPD are independent risk factor for mortality in patients with ABPA.

Keywords: allergic bronchopulmonary aspergillosis, pulmonary disease, mortality, risk factor, chronic obstructive pulmonary disease

Introduction

Allergic bronchopulmonary aspergillosis (ABPA) is an allergic pulmonary disease caused by a hypersensitivity reaction to *Aspergillus* species.^{1,2} A meta-analysis has shown that the prevalence of ABPA in adults with asthma worldwide ranges from 0.72% to 3.5%,³ and 2.5% of non-smoking adult asthma patients in China meet the diagnostic criteria for ABPA,⁴ which reveals that ABPA is not a rare disease in asthma patients. Chronic obstructive pulmonary disease (COPD),^{5–7} bronchiectasis,⁸ and cystic fibrosis⁹ can also be complicated by ABPA. Agarwal et al initially described the occurrence of ABPA in COPD in 2008.¹⁰ Its prevalence ranges from 2% to 15%, with a pooled prevalence of about 9.5%,¹¹ suggesting that ABPA is not a rare comorbidity of COPD. It is well known that COPD has high morbidity and mortality worldwide.¹² The presence of *Aspergillus* sensitization in COPD is associated with frequent exacerbations,¹³ bronchiectasis,⁷ and poor lung function.^{5,14} Considering the fact that the combination with COPD can significantly increase the mortality of patients with asthma,¹⁵ COPD may also have a similar impact on patients with ABPA. Most studies performed in patients with ABPA were case reports or cross-sectional studies with the follow-up duration ranging from 3 months to 43.7 months,^{16–20} and few studies focused on the long-term follow-up and prognosis, especially for

ABPA with COPD. Additionally, the mortality of ABPA and the difference between all-cause mortality for ABPA with and without COPD have never been reported.^{16–23} Hence, this study aimed to retrospectively analyze the follow-up data of patients with ABPA to explore the difference between all-cause mortality for ABPA with and without COPD and to promote early identification and intervention of severe and high-risk patients.

Methods

Study Design and Ethics Approval

This study was a retrospective clinical data analysis, and the research protocol was approved by the Ethics Committee of Peking University People's Hospital. The requirement for obtaining informed consent was waived due to the retrospective nature of the study, but all data were anonymized and data confidentiality was maintained.

Study Subjects

The medical records of patients diagnosed with ABPA in the outpatient or inpatient department of Respiratory and Critical Care Medicine from January 2010 to March 2022 in the information system of Peking University People's Hospital were reviewed using “allergic bronchopulmonary aspergillosis” as the search term.

Inclusion and Exclusion Criteria

Patients with ABPA who met the diagnostic criteria of the “Expert Consensus on the Diagnosis and Treatment of Allergic Bronchopulmonary Aspergillosis” (2017 edition) were included in the study,²⁴ and patients with insufficient diagnostic evidence and less than 3 months of follow-up were excluded from the study. The diagnosis of COPD complied with the diagnostic criteria of the Guidelines for the Diagnosis and Treatment of COPD (2013 Revised Edition).²⁵ The diagnosis of asthma complied with the diagnostic criteria of the Guidelines for the Prevention and Treatment of Bronchial Asthma (2016 Edition).²⁶ The diagnosis of bronchiectasis complied with the diagnostic criteria of the Expert Consensus on the Diagnosis and Treatment of Adult Bronchiectasis (2012 Edition).²⁷ Central bronchiectasis (CB) was defined using two different criteria, depending on whether bronchiectasis was confined to the medial half (point midway between the hilum and chest wall) or the medial two-thirds of the lung.²⁸

Data Collection

Data, including general information, clinical manifestations, laboratory tests, chest high-resolution computed tomography (HRCT), pulmonary function (Jaeger, Germany), diagnosis course, follow-up time, treatment medicine, and survival status, were collected from the medical records of patients. Serum total immunoglobulin E (IgE) was assessed using Roche Cobas e601 electrochemiluminescence instrument; *Aspergillus fumigatus* m3 allergen among Thermo Fisher Scientific detection reagents was used to assess *Aspergillus fumigatus* specific IgE (Sp-IgE). Results of laboratory tests, chest HRCT, and pulmonary function were obtained when the patients were diagnosed with ABPA for the first time in our hospital or in another hospital. An arterial blood gas test was performed in patients without oxygen uptake before treatment.

Statistical Analysis

Data were analyzed, and graphs were drawn with SPSS (version 26.0; SPSS, Chicago, IL, USA). Categorical variables were expressed as numbers and percentages. Continuous variables were expressed as mean \pm standard deviation or median with interquartile range (IQR; 25th to 75th percentile). Categorical variables were compared using Chi-square test, while Student's *t*-test or Mann–Whitney *U*-test was used for continuous variables. Kaplan–Meier analysis was used to compare the survival distribution among different groups and Kaplan–Meier survival curves for different groups of subjects were obtained and plotted. To identify variables independently associated with mortality, we conducted the Cox regression analysis by including the variables with $P \leq 0.05$ in the univariate analysis. $P < 0.05$ was considered to indicate statistical significance.

Results

Baseline Data of Patients with ABPA

Seventy-five inpatients and outpatients were retrieved, and 13 patients with an inadequate diagnosis and 1 patient with a follow-up period of less than 3 months were excluded. Among the 61 patients, 58 patients fully met the diagnostic criteria, and total IgE of three patients was not more than 1000 IU/mL (764.8–978.2 IU/mL). All of them were taking glucocorticoids while testing of total IgE, their clinical characteristics and imaging features met the diagnostic criteria of ABPA, and glucocorticoids and antifungal drugs were effective. Finally, 61 patients were included, including 29 males. All patients had stage I disease on admission. The follow-up time ranged from 3 to 143 months, with an average follow-up time of 50.38 months. Ten patients with COPD were identified; all of them had a long-term history of heavy smoking (32.5 [27.5–55.13] pack-years) and definite emphysema, and 4 of them were complicated with asthma. There were 11 deaths during 252 person-years of follow-up. Among the 11 patients who died, 7 died of respiratory disease, 2 died of colon cancer, 1 died of cardiovascular and cerebrovascular events, and 1 died due to an unknown cause. Seven of the 10 patients with COPD died (70%). Among the 50 patients without COPD, 4 patients died (7.84%). The mean survival time of ABPA with and without COPD was 37 months and 129.98 months, respectively. The mean age at the time of death for ABPA with and without COPD was 76 years and 74 years, respectively.

Comparison of Characteristics Between Patients Who Had ABPA with or Without COPD

Age (76.00 ± 9.64 years vs 52.78 ± 16.77 years, $P < 0.001$), proportion of male patients (10 [100%] vs 21 [41.18%], $P = 0.002$), smoking history (10 [100%] vs 11 [21.57%], $P < 0.001$), pack-years of smoking (0 [0–0] vs 32.5 [27.5–55.13], $P < 0.001$), death rate (7 [70%] vs 4 [7.84%], $P < 0.001$), neutrophil count ($7.45 \pm 2.64 \times 10^9/L$ vs $5.12 \pm 3.05 \times 10^9/L$, $P = 0.029$), neutrophil percentage ($69.04 \pm 25.5\%$ vs $55.08 \pm 15.73\%$, $P = 0.041$), neutrophil-to-lymphocyte ratio (NLR) ($8.68 [4.33–16.66]$ vs $1.90 [1.43–5.86]$, $P < 0.001$), and C-reactive protein (CRP) (15.10 mg/L [7.91–100.84 mg/L] vs 3.94 mg/L [1.00–15.40 mg/L], $P = 0.011$) at diagnosis were significantly higher in patients with COPD than in patients without COPD. Body mass index (BMI) (20.61 ± 2.59 kg/m² vs 23.07 ± 3.48 kg/m², $P = 0.040$), eosinophil count ($0.09 \times 10^9/L$ [0.03–0.65 $\times 10^9/L$] vs $0.62 \times 10^9/L$ [0.24–0.94 $\times 10^9/L$], $P = 0.026$), eosinophil percentage (1.45% [0.23–6.85%] vs 9.6 [2.61–13.5%], $P = 0.006$), proportion of patients with asthma (4 [40.00%] vs 48 [94.12%], $P < 0.001$) and with allergic rhinitis (1 [10.00%] vs 32 [60.78%], $P = 0.009$), forced expiratory volume in one second (FEV₁)/forced vital capacity (FVC) ($46.94 \pm 7.79\%$ vs $63.08 \pm 15.9\%$, $P < 0.001$), percentage of FEV₁ predicted (FEV₁%) ($37.17 \pm 8.59\%$ vs $64.82 \pm 26.25\%$, $P < 0.001$), peak expiratory flow percentage (PEF) (2.80 L/s [2.57–3.58 L/s] vs 4.70 L/s [3.21–6.55 L/s], $P = 0.012$), percentage of PEF predicted (PEF%) (40.30% [32.50–47.15%] vs 73.80 [49.50–95.30%], $P = 0.001$), percentage of the diffusing capacity of carbon monoxide predicted (DLCO%) ($56.56 \pm 14.66\%$ vs $75.68 \pm 22.74\%$, $P = 0.021$), and diffusing capacity divided by the alveolar volume (DLCO/VA) (0.85 mmol/min/kPa/L [0.64–1.04 mmol/min/kPa/L] vs 1.47 mmol/min/kPa/L [1.24–1.60 mmol/min/kPa/L], $P < 0.001$) were significantly lower in patients with COPD than in patients without COPD (Table 1).

Survival Time and Rate in Patients with ABPA

Kaplan-Meier curves showed the overall survival curve of all patients with ABPA. The average survival time was 114 months. The 1-year and 5-year survival rate was 91.3% and 83.8%, respectively (Figure 1).

Results of the Kaplan-Meier Analysis for Mortality of ABPA

Kaplan-Meier analysis demonstrated that COPD affected the survival time of patients with ABPA, and the all-cause mortality for ABPA with COPD was much higher than that for ABPA without COPD (Figure 1). According to the results of Kaplan-Meier analysis, male gender, smoking history, older age, higher CRP and NLR, lower PEF, PEF%, DLCO%, and DLCO/VA had a significantly higher risk for all-cause mortality (the cutoff value of continuous variables was calculated by the ROC curve) (Table 2 and Figure 2).

Table 1 Comparison of Characteristics Between Patients Who Had ABPA with or Without COPD

	All Patients (n=61)	With COPD		P value
		Yes (n=10)	No (n=51)	
Age, years	58.63±17.01	76.00±9.64	52.78±16.77	<0.001
Male	31 (50.82%)	10(100.00%)	21(41.18%)	0.002
Smokers	21(34.43%)	10(100.00%)	11(21.57%)	<0.001
Pack-years of smoking	0 (0–12.5)	0 (0–0)	32.5 (27.5–55.13)	<0.001
Dead	11(18.03%)	7(70.00%)	4(7.84%)	<0.001
Duration of ABPA, in months	249.00(85.00–592.00)	321(76.50–603.50)	165.00(85.00–592.00)	0.585
BMI (kg/m ²)	22.61±3.53	20.61±2.59	23.07±3.48	0.040
Peripheral blood cells				
Leukocyte, ×10 ⁹ /L	9.12±3.83	9.40±2.54	8.89±4.00	0.703
Neutrophil, ×10 ⁹ /L	5.63±3.10	7.45±2.64	5.12±3.05	0.029
Neutrophil, %	58.00±18.27	69.04±24.5	55.08±15.73	0.026
Eosinophil, ×10 ⁹ /L	0.49(0.07–0.90)	0.09(0.03–0.65)	0.62(0.24–0.94)	0.026
Eosinophil, %	6.90(0.9–13.00)	1.45(0.23–6.85)	9.60(2.61–13.50)	0.006
Inflammatory indicator				
NLR	2.65(1.49–6.65)	8.68(4.33–16.66)	1.90(1.43–5.86)	<0.001
CRP, mg/L	5.97(1.90–18.50)	15.1(7.91–100.84)	3.94(1.00–15.40)	0.011
ESR, mm/h	17.00(7.0–29.00)	20.5(7.50–43.25)	17(6.00–28.00)	0.477
Immunological tests				
Total IgE, IU/mL	2248.00(1256.00–2500.00)	2213.50(1260.50–2500.00)	2248.00(1256.00–2500.00)	0.968
Sp-IgE, kUA/L	2.82(0.68–12.80)	2.56(1.10–6.83)	2.82(0.53–13.30)	0.579
Comorbidity				
Asthma	52(85.25%)	4(40.00%)	48(94.12%)	<0.001
Allergic rhinitis	32(52.46%)	1(10.00%)	31(60.78%)	0.009
Spirometry				
FEV ₁ /FVC	59.45±15.80	46.94±7.79	63.08±15.90	<0.001
FEV ₁ /pred	57.79±27.06	37.17±8.59	64.82±26.25	<0.001
PEF, L/s	3.79(2.89–5.93)	2.80(2.57–3.58)	4.70(3.21–6.55)	0.012
PEF, %	57.50(41.00–87.00)	40.3(32.50–47.15)	73.8(49.5–95.30)	0.001
DLCO, %	71.94±22.68	56.56±14.66	75.68±22.74	0.021
DLCO/VA, mmol/min/kPa/L	1.29(1.05–1.55)	0.85(0.64–1.04)	1.47(1.24–1.60)	<0.001

(Continued)

Table 1 (Continued).

	All Patients (n=61)	With COPD		P value
		Yes (n=10)	No (n=51)	
Arterial blood gas				
PaO ₂ , mmHg	76.05±12.35	73.00±11.89	76.33±12.71	0.461
PaCO ₂ , mmHg	41.00(39.00–44.00)	40.00(40.00–4.75)	41.00(38.00–43.00)	0.566
SaO ₂ , %	96.00 (94.00–97.00)	95.00(91.50–96.75)	96.00(94.00–97.00)	0.182
Treatment				
Glucocorticoids	54(88.52%)	8(80.00%)	46(90.20%)	0.702
Antifungal Drugs	43(70.49%)	6(60.00%)	35(68.63%)	0.870

Abbreviations: BMI, Body mass index; CRP, C-reactive protein; DLCO, Diffusion capacity of carbon monoxide; VA, Alveolar volume; ESR, Erythrocyte sedimentation rate; FEV₁/FVC, Forced expiratory volume in one second (FEV₁)/forced vital capacity (FVC); FEV₁/pred, Percentage of FEV₁ predicted; IgE, Immunoglobulin E; NLR, Neutrophil-to-lymphocyte ratio; PEF, Peak expiratory flow percentage; PaO₂, Partial arterial oxygen pressure; PaCO₂, Partial arterial pressure of carbon dioxide; SaO₂, Oxygen saturation; Sp-IgE, *Aspergillus fumigatus* specific IgE.

Comparison of the Clinical Characteristics of All Patients with ABPA Between the Death and Survival Groups

Age (73.00 ± 10.02 years vs 52.98 ± 17.37 years, $P = 0.001$), proportion of male patients (9 [81.82%] vs 22 [44.00%], $P = 0.023$), smoking history (9 [81.82%] vs 12 [24.00%], $P = 0.001$), pack-years of smoking (0 [0–0] vs 30 [15–50], $P < 0.001$), neutrophil count ($7.33 \pm 2.85 \times 10^9/L$ vs $5.09 \pm 3.01 \times 10^9/L$, $P = 0.030$), NLR (6.50 [2.96–14.28] vs 1.97 [1.41–5.88], $P = 0.002$), CRP (48.16 mg/L [9.72–126.70 mg/L] vs 3.03 mg/L [0.98–10.96 mg/L], $P < 0.001$), erythrocyte sedimentation rate (ESR) (28.00 mm/h [15.00–67.50 mm/h] vs 13.50 [5.00–26.50 mm/h], $P = 0.030$), and proportion of patients with COPD (7 [63.64%] vs 3 [6.00%], $P < 0.001$) were significantly higher in the death group than in the survival group. Proportion of patients with allergic rhinitis (2 [18.18%] vs 30 [60.00%], $P = 0.012$),

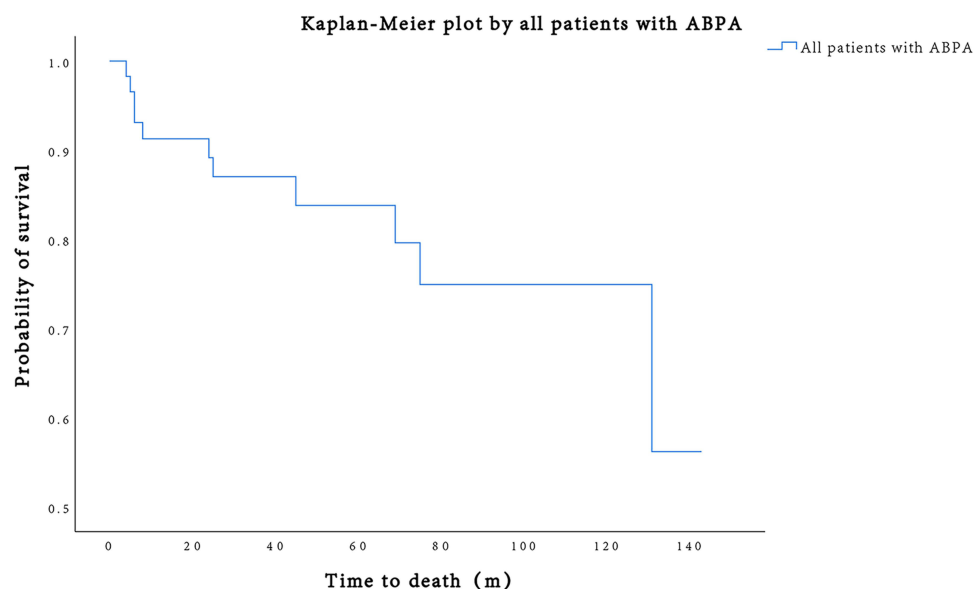
**Figure 1** Survival curves for all-cause mortality in all patients with ABPA.

Table 2 Results of the Kaplan-Meier Analysis for Mortality of ABPA

Variable		Log Rank Test		
		Mean Survival Time (Months)	χ^2	P value
COPD	Yes	37.00	34.94	<0.001
	No	129.98		
Age	≥ 60 years	80.84	14.75	<0.001
	< 60 years	137.31		
Gender	Male	91.85	6.73	0.009
	Female	134.00		
Smokers	Yes	72.21	15.77	<0.001
	No	134.63		
Neutrophil	≥4.4 × 10 ⁹ /L	92.00	7.06	0.008
	<4.4 × 10 ⁹ /L	134.78		
CRP	≥11.56mg/L	73.53	13.83	<0.001
	<11.56mg/L	133.33		
NLR	≥3.76	76.64	7.44	0.006
	<3.76	131.52		
PEF	≥2.91L/s	120.65	9.03	0.003
	<2.91L/s	71.06		
PEF%	≥41.55%	120.87	10.16	0.001
	<41.55%	68.25		
DLCO%	≥72.85%	-	7.97	0.005
	<72.85%	82.96		
DLCO/VA	≥1.235mmol/min/kPa/L	131.00	18.35	<0.001
	<1.235mmol/min/kPa/L	60.04		

Abbreviations: COPD, Chronic Obstructive Pulmonary Disease; CRP, C-reactive protein; DLCO, Diffusion capacity of carbon monoxide; VA, Alveolar volume; NLR, Neutrophil-to-lymphocyte ratio; PEF, Peak expiratory flow percentage.

PEF (2.71 L/s [2.35–3.67 L/s] vs 4.68 L/s [3.31–6.53 L/s], $P = 0.027$), PEF% (39.6% [30.55–56.90%] vs 73.50 [48.83–94.48%], $P = 0.024$), DLCO% ($57.57 \pm 10.62\%$ vs $76.41 \pm 23.51\%$, $P = 0.014$), and DLCO/VA (1.04 mmol/min/kPa/L [0.78–1.15 mmol/min/kPa/L] vs 1.48 mmol/min/kPa/L [1.24–1.61 mmol/min/kPa/L], $P < 0.001$) were significantly lower in patients in the death group than in patients in the survival group (Table 3). The detailed condition of the died patients was provided (Table 4).

Results of Cox Regression Analysis

Cox regression analysis showed that higher CRP (HR = 1.017, 95% CI 1.004–1.031, $P = 0.013$) and complicating COPD (HR = 8.525, 95% CI 1.827–39.773, $P = 0.006$) were independent risk factors associated with mortality in patients with ABPA.

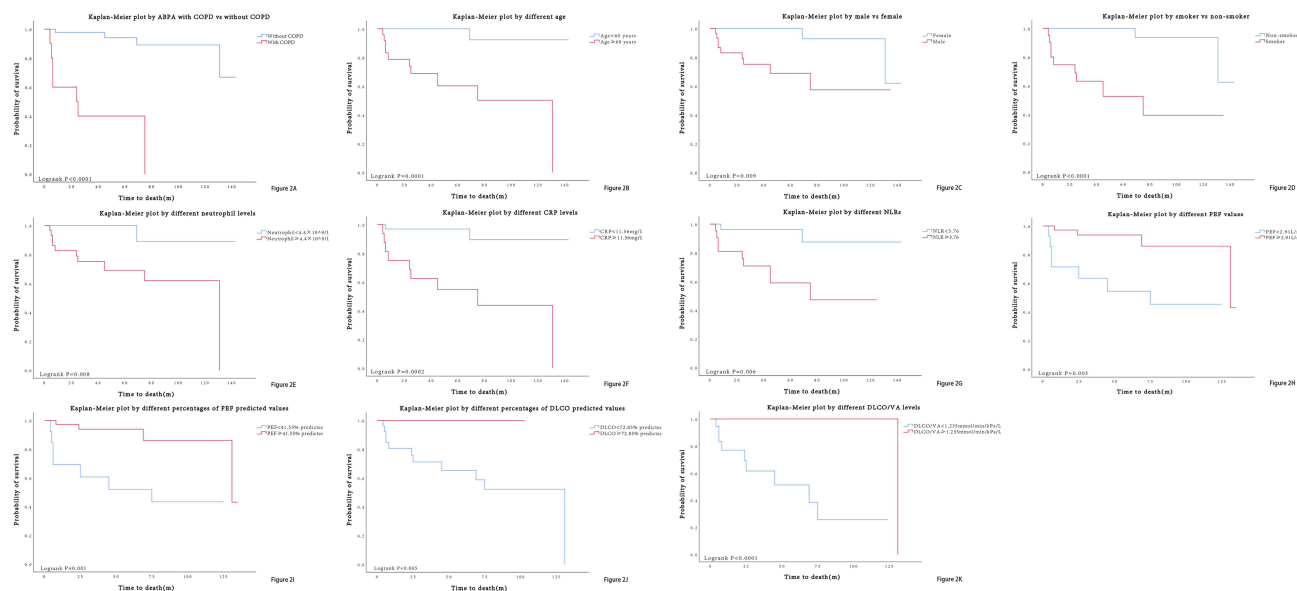


Figure 2 Survival curves for all-cause mortality in patients of different subgroups.

Comparison of Characteristics Between Patients Who Had ABPA with or Without CB

Smoking history (1 [6.25%] vs 20 [44.44%], $P = 0.006$), pack-years of smoking (0 [0–0] vs 0 [0–18.75], $P = 0.025$), and BMI ($20.75 \pm 3.29 \text{ kg/m}^2$ vs $23.38 \pm 3.27 \text{ kg/m}^2$, $P = 0.009$) were significantly lower in patients with CB than in patients without CB. Eosinophil count ($0.77 \times 10^9/\text{L}$ [$0.23\text{--}0.94 \times 10^9/\text{L}$] vs $0.48 \times 10^9/\text{L}$ [$0.05\text{--}0.71 \times 10^9/\text{L}$], $P = 0.029$) and Sp-IgE level (13.30 kUA/L [$3.50\text{--}25.90 \text{ kUA/L}$] vs 0.93 kUA/L [$0.54\text{--}6.10 \text{ kUA/L}$], $P = 0.001$) were significantly higher in patients who had ABPA with CB than in patients without CB (Table 5). And we showed several typical HRCT photographs of ABPA including 3 died patients (Figure 3).

Table 3 Comparison of Clinical Characteristics of All Patients with ABPA Between the Death and Survival Groups

	Survival		P value
	Yes (n=50)	No (n=11)	
Age, years	52.98±17.37	73.00±10.02	0.001
Male	22(44.00%)	9(81.82%)	0.023
Smokers	12(24.00%)	9(81.82%)	0.001
Pack-years of smoking	0(0–0)	30(15–50)	<0.001
Duration of ABPA, in months	262.50(89.00–610.75)	165.00(49.00–517.00)	0.800
BMI (kg/m^2)	23.00±3.54	21.13±2.73	0.107
Peripheral blood cells			
Leukocyte, $\times 10^9/\text{L}$	8.52±3.33	10.91±4.98	0.058
Neutrophil, $\times 10^9/\text{L}$	5.09±3.01	7.33±2.85	0.030
Neutrophil, %	56.68±16.52	61.23±24.4	0.461
Eosinophil, $\times 10^9/\text{L}$	0.48(0.09–0.80)	0.70(0.06–1.75)	0.968
Eosinophil, %	7.50(1.35–11.24)	6.90(0.60–15.85)	0.750

(Continued)

Table 3 (Continued).

	Survival		P value
	Yes (n=50)	No (n=11)	
Inflammatory indicator			
NLR	1.97(1.41–5.88)	6.50(2.96–14.28)	0.002
CRP, mg/L	3.03(0.98–10.96)	48.16(9.72–126.7)	<0.001
ESR, mm/h	13.50(5.00–26.50)	28.00(15.00–67.50)	0.030
Immunological tests			
Total IgE, IU/mL	2324.50(1276.25–2500.00)	1927.00(1101.00–2500.00)	0.526
Sp-IgE, kUA/L	2.22(0.55–14.03)	3.5(0.73–6.62)	0.219
Comorbidity			
Asthma	45(90.00%)	7(63.64%)	0.078
COPD	3(6.00%)	7(63.64%)	<0.001
Allergic rhinitis	30(60.00%)	2(18.18%)	0.012
Spirometry			
FEV ₁ /FVC	62.62±16.12	53.00±14.2	0.077
FEV ₁ /pred	63.11±25.60	48.07±26.27	0.095
PEF, L/s	4.68(3.31–6.53)	2.71(2.35–3.67)	0.027
PEF, %	73.50(48.83–94.48)	39.6(30.55–56.90)	0.024
DLCO, %	76.41±23.51	57.57±10.62	0.014
DLCO/VA, mmol/min/kPa/L	1.48(1.24–1.61)	1.04(0.78–1.15)	<0.001
Arterial blood gas			
PaO ₂ , mmHg	76.46±13.15	72.91±10.14	0.417
PaCO ₂ , mmHg	41.50(38.75–44.25)	40.00(39.00–42.5)	0.326
SaO ₂ , %	96.00(94.00–97.00)	95.00(93.50–97.00)	0.567
Treatment			
Glucocorticoids	43(86.00%)	11(100.00%)	0.426
Antifungal Drugs	34(68.00%)	7(63.64%)	1.000

Abbreviations: BMI, Body mass index; CRP, C-reactive protein; DLCO, Diffusion capacity of carbon monoxide; VA, Alveolar volume; ESR, Erythrocyte sedimentation rate; FEV₁/FVC, Forced expiratory volume in one second (FEV₁)/forced vital capacity (FVC); FEV₁/pred, Percentage of FEV₁ predicted; IgE, Immunoglobulin E; NLR, Neutrophil-to-lymphocyte ratio; PEF, Peak expiratory flow percentage; PaO₂, Partial arterial oxygen pressure; PaCO₂, Partial arterial pressure of carbon dioxide; SaO₂, Oxygen saturation; Sp-IgE, *Aspergillus fumigatus* specific IgE.

Discussion

ABPA presents with symptoms that are similar to those of asthma. They include coughing, wheezing, and shortness of breath. Chronic airway diseases, including asthma and COPD, which are the background diseases of ABPA, have a high incidence in the world. Various research studies were performed to assess the characteristics and prognosis of ABPA with asthma, but few studies paid attention to the characteristics and prognosis of ABPA with COPD, although some studies showed that *Aspergillus* was associated with frequent exacerbations and higher mortality in COPD.²⁹

Table 4 The Detailed Condition of the Death Group

Died Patients	Age (Years)	Gender	Predisposing Conditions	Comorbidity	Cause of Death
Case 1	64	Male	COPD Asthma	Coronary heart disease	Pneumomediastinum AECOPD Respiratory failure
Case 2	82	Male	COPD	Coronary heart disease	AECOPD NSTEMI Respiratory failure
Case 3	83	Male	COPD	Chronic pulmonary heart disease	AECOPD Respiratory failure
Case 4	74	Male	Asthma	Coronary heart disease Acute cerebral infarction	Coronary heart disease Acute cerebral infarction
Case 5	62	Male	COPD Asthma	Pulmonary tuberculosis	Pulmonary tuberculosis AECOPD Respiratory failure
Case 6	82	Male	COPD	Chronic pulmonary heart disease	AECOPD Respiratory failure
Case 7	81	Male	Asthma	Advanced colorectal cancer	Advanced colorectal cancer
Case 8	52	Female	Asthma	Depression	Unknown
Case 9	77	Male	COPD Asthma	NSCLC	NSCLC AECOPD Respiratory failure
Case 10	69	Female	Asthma	Advanced colorectal cancer	Advanced colorectal cancer
Case 11	76	Male	COPD	Chronic pulmonary heart disease	AECOPD Heart failure Respiratory failure

Abbreviations: AECOPD, Acute exacerbations of chronic obstructive pulmonary disease; NSTEMI, Non-ST Segment Elevation Myocardial Infarction; NSCLC, Non-small-cell lung cancer.

Table 5 Comparison of Characteristics Between Patients Who Had ABPA with or Without Central Bronchiectasis

	Central Bronchiectasis		P value
	Yes (n=16)	No (n=45)	
Age, years	50.94±19.06	58.60±17.35	0.145
Male	5(31.25%)	26(57.78%)	0.068
Smokers	1(6.25%)	20(44.44%)	0.006
Pack-years of smoking	0(0–0)	0(0–18.75)	0.025
Dead	1(6.25%)	10(22.22%)	0.294
Duration of ABPA, in months	592(105.00–631.00)	154.5(73.00–427.50)	0.018
BMI (kg/m ²)	20.75±3.29	23.38±3.27	0.009

(Continued)

Table 5 (Continued).

	Central Bronchiectasis		P value
	Yes (n=16)	No (n=45)	
Peripheral blood cells			
Leukocyte, $\times 10^9/L$	9.50 \pm 3.32	8.78 \pm 3.95	0.522
Neutrophil, $\times 10^9/L$	5.46 \pm 2.84	5.57 \pm 3.21	0.899
Neutrophil, %	54.82 \pm 18.72	58.58 \pm 18.09	0.498
Eosinophil, $\times 10^9/L$	0.77(0.23–0.94)	0.48(0.05–0.71)	0.029
Eosinophil, %	9.6(2.61–11.15)	6.4(0.45–13.97)	0.144
Inflammatory indicator			
NLR	1.90(1.21–3.99)	4.14(1.5–7.71)	0.375
CRP, mg/L	3.94(2.25–11.70)	8.09(1.23–41.37)	0.910
ESR, mm/h	26.00(17.00–29.00)	12.00(5.25–28.75)	0.160
Immunological tests			
Total IgE, IU/mL	2248.00(1011.00–2500.00)	2322.00(1262.75–2500.00)	0.398
Sp-IgE, kUA/L	13.30(3.50–25.9)	0.93(0.54–6.10)	0.001
Comorbidity			
Asthma	15(93.75%)	37(82.22%)	0.480
COPD	1(6.25%)	9(20.00%)	0.377
Allergic rhinitis	8(50.00%)	24(53.33%)	0.819
Spirometry			
FEV ₁ /FVC	54.44 \pm 18.95	62.64 \pm 14.77	0.112
FEV ₁ /pred	50.78 \pm 29.71	62.97 \pm 24.54	0.153
PEF, L/s	3.16(2.82–6.52)	3.90(3.16–5.75)	0.078
PEF, %	49.50(38.20–94.2)	65.25(43.33–87.08)	0.160
DLCO, %	66.68 \pm 31.97	74.10 \pm 18.19	0.317
DLCO/VA, mmol/min/kPa/L	1.48(1.17–1.60)	1.24(1.04–1.55)	0.616
Arterial blood gas			
PaO ₂ , mmHg	75.21 \pm 13.57	75.78 \pm 12.21	0.889
PaCO ₂ , mmHg	41.00(40.00–52.00)	41(38.00–43.00)	0.101
SaO ₂ , %	95.00(94.00–97.00)	96.00(94.00–97.00)	0.866
Treatment			
Glucocorticoids	15(93.75%)	39(86.67%)	0.759
Antifungal Drugs	13(81.25%)	28(62.22%)	0.164

Abbreviations: BMI, Body mass index; CRP, C-reactive protein; DLCO, Diffusion capacity of carbon monoxide; VA, Alveolar volume; ESR, Erythrocyte sedimentation rate; FEV₁/FVC, Forced expiratory volume in one second (FEV₁)/forced vital capacity (FVC); FEV₁/pred, Percentage of FEV₁ predicted; IgE, Immunoglobulin E; NLR, Neutrophil-to-lymphocyte ratio; PEF, Peak expiratory flow percentage; PaO₂, Partial arterial oxygen pressure; PaCO₂, Partial arterial pressure of carbon dioxide; SaO₂, Oxygen saturation; Sp-IgE, *Aspergillus fumigatus* specific IgE.

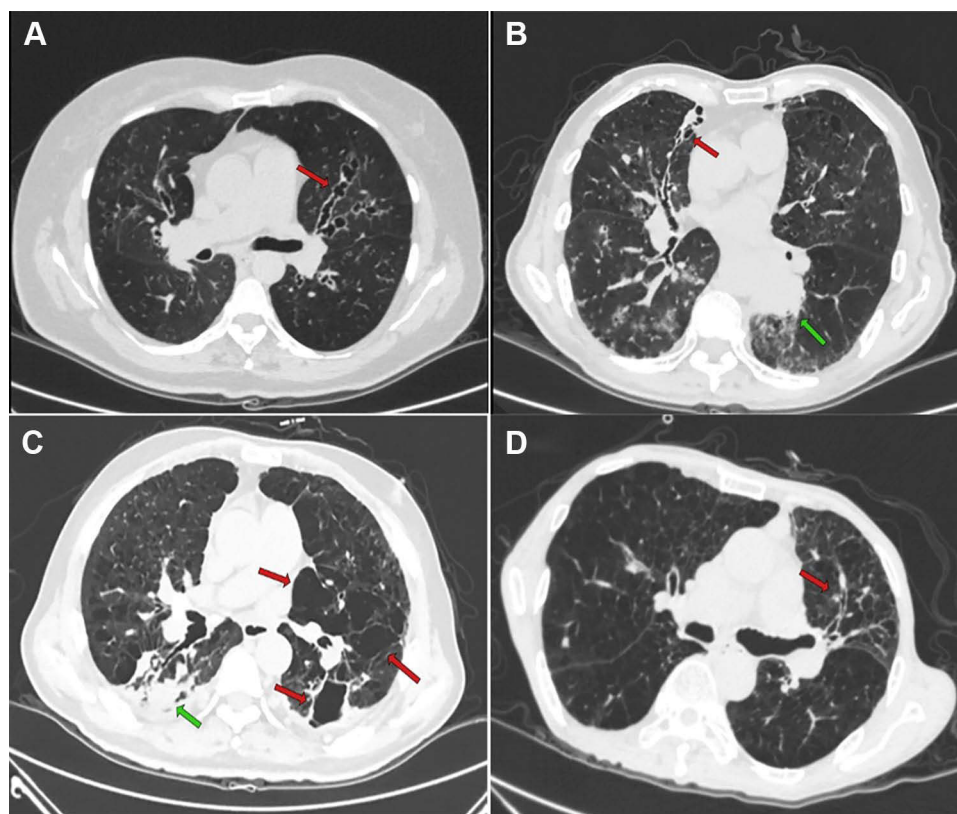


Figure 3 HRCT scans of patients with ABPA.

In this study, we retrospectively analyzed the long-term follow-up data of 61 patients who had ABPA with an average follow-up time of 50.38 months (range, 3–143 months), and we reported that the all-cause mortality rate of ABPA with COPD (70%) was significantly higher than that of ABPA without COPD (7.84%). The Log rank test showed that the mean survival time of ABPA with COPD was 37 months, which was much shorter than that of ABPA without COPD (129.98 months). The cause of death in patients who had ABPA with and without COPD was definitely different. Most patients with COPD and ABPA died of respiratory diseases, such as AECOPD, while death of patients without COPD was usually due to a malignant tumor, and cardiovascular and cerebrovascular events.

However, univariate analysis showed that old age, poor pulmonary function, and severe systemic inflammatory reaction were closely related to the higher mortality of ABPA. The Cox regression analysis showed that complicating COPD (HR = 8.525, 95% CI 1.827–39.773, $P = 0.006$) was one of the independent risk factors associated with mortality in patients with ABPA. We suppose that all these significant univariate factors are related to COPD.

The main reasons for the increased mortality in patients with COPD include the following: Firstly, the mean age of patients with ABPA and COPD in this study was 76 years, which was much higher than that of patients without COPD (53 years). The mean age of three patients with ABPA and COPD was 77 years in the study by Sun.⁶ Another study showed that the mean age of 10 patients with ABPA and COPD was 59 years,³⁰ which was in line with the age characteristic of patients with COPD in this study. Therefore, advanced age is a prominent feature of patients with ABPA and COPD, which is in accordance with the different onset age of patients with COPD and asthma. Asthma often occurs in childhood and usually before the age of 40 years, while COPD usually occurs after the age of 50 years in smokers. On the other hand, although the incidence of ABPA in COPD might not be lower than that in asthma,¹¹ the proportion of ABPA with COPD was much lower than that of ABPA with asthma in most of the current case studies. A previous study in China showed that none of the 77 patients with ABPA had COPD.³¹ In another study, 1 out of 46 patients with ABPA had COPD,³² and in a recent retrospective analysis by Zeng, 3 out of 193 patients with ABPA had COPD.¹⁸ It can be speculated that a large number of patients with COPD and ABPA are underdiagnosed or misdiagnosed, leading to

a higher age at the time of first diagnosis in these patients. These two aspects lead to the fact that the age of patients with ABPA and COPD is much higher than that of ABPA patients without COPD. A delayed diagnosis and treatment will lead to gradual aggravation of clinical symptoms, severe airflow obstruction, CB, and other structural lung damage, which seriously affect the quality of life and survival time of patients.

Secondly, patients with COPD have more severe airflow obstruction and significantly reduced diffusing function, which was significantly associated with increased mortality. The univariate analysis and Kaplan-Meier analysis showed that reduced pulmonary ventilation function and diffusing capacity were closely related to COPD and increased mortality. Smoking history was closely associated with genesis and development of COPD and worse pulmonary function, which was also demonstrated in this study. Although a retrospective study found that DLCO/VA was lower in patients who had ABPA with CB,¹⁸ CB had no significant association with DLCO/VA in this study. Thus, the important factor leading to the decline in pulmonary ventilation and diffusing capacity in our patients was coexisting COPD, and not CB. Therefore, COPD-induced decline in pulmonary function is an important cause of death in patients with ABPA.

In addition to the significant differences in age and pulmonary function, the inflammatory characteristics were significantly different between patients with COPD and without COPD. Univariate analysis showed that patients with COPD had significantly a higher neutrophil count, neutrophil percentage, CRP and NLR, but the indicators related to ABPA-characteristic allergic inflammation, such as blood eosinophil count and eosinophil percentage, were significantly lower. Agarwal et al found that elderly patients with ABPA had lower serum total IgE and Sp-IgE levels and less bronchiectasis,²¹ suggesting that patients with ABPA aged over 60 years and with COPD showed a hypoallergenic inflammatory reaction but a severe neutrophilic inflammatory reaction. NLR and CRP are sensitive indicators of systemic infection, and previous studies have found that these indicators are associated with an increased risk of acute exacerbation, hospitalization, and early death in patients with COPD.^{33–36} We also analyzed the impact of CB on mortality. ABPA with CB did not increase the risk of mortality. Besides, our study also showed that the inflammatory characteristics of patients with COPD were significantly different from those of patients with CB. The former was dominated by increased CRP and neutrophil count, while the latter was dominated by increased ABPA-characteristic allergic inflammation indicators, such as eosinophil count and Sp-IgE level. Previous studies suggested that patients with ABPA and CB have higher levels of total IgE and Sp-IgE, more severe immunoreactivity, more aggressive clinical form and symptoms, and more frequent exacerbations.^{17,37–39} The prominent inflammatory characteristic of patients with ABPA and COPD suggests that patients with COPD may have more severe airway infections and the type and mechanism of airway inflammation in COPD with ABPA are different from those in typical asthma with ABPA. Th2 inflammation reaction and fungal colonization of the airways are important mechanisms for the pathogenesis of ABPA.⁴⁰ There is an interaction and overlap between infection and Th2 inflammation of the airways caused by fungal colonization. Airway inflammation was more likely secondary to fungal colonization in patients who had COPD instead of persistent allergy. It remains to be determined whether there are different pathways of airway inflammation in patients with COPD and ABPA and patients with classic asthma and ABPA.

The clinical characteristics and pathogenesis of patients with ABPA and COPD may be different from those of patients with ABPA but without COPD, which can lead to significant differences in mortality. Thus, we should increase the screening of *Aspergillus* sensitization and ABPA in patients with COPD to reduce misdiagnosis, improve early detection and treatment, and lower mortality. In addition, due to the limited treatment methods for ABPA, glucocorticoids and antifungal drugs are the main medications, and a higher priority is given to glucocorticoids. However, physicians are usually more cautious when applying glucocorticoids in patients with COPD and ABPA, considering their advanced age, more underlying diseases, and worse immune status. Some patients often fail to take a sufficient amount of glucocorticoids and complete the full course of treatment with glucocorticoids. The mechanism of ABPA in COPD should be explored through more research studies to identify the differences from that of ABPA based on classic asthma. It is necessary to further optimize the treatment plan according to the pathogenesis and clinical characteristics of patients with COPD and ABPA to improve their compliance, thereby improving the treatment effect and reducing the mortality.

In summary, the all-cause mortality for ABPA with COPD was much higher than that for ABPA without COPD. Older age, poorer pulmonary function, and a more severe neutrophilic inflammatory reaction were closely related to higher mortality of ABPA with COPD. Higher CRP and complicating COPD were independent risk factors for mortality in patients with ABPA. Patients with COPD should be routinely evaluated for *Aspergillus* sensitization and ABPA to promote early identification and intervention of severe and high-risk patients and ultimately reduce mortality.

However, our study has some limitations that should be acknowledged. It was a single-center retrospective study with a small sample size. The mortality rate obtained in this study cannot be extrapolated to all patients with ABPA. The laboratory had set the upper limit of the total IgE detection value at 2500 IU/mL, which may have influenced the significance of total IgE. Further, some new biological targeted drugs, such as the anti-IgE antibody omalizumab, were not included in our study.⁴¹ Moreover, patients with COPD have a higher mortality rate versus age-matched controls. We did not compare the difference in mortality between COPD with and without ABPA in order to analyze how ABPA can contribute to mortality in patients with COPD and ABPA. Hence, a prospective large-scale research study with a longer follow-up time period is needed to explore the difference in all-cause mortality between ABPA with and without COPD and related risk factors.

Abbreviations

ABPA, Allergic Bronchopulmonary Aspergillosis;; AECOPD, Acute exacerbations of chronic obstructive pulmonary disease; BMI, Body mass index; CB, Central bronchiectasis; COPD, Chronic Obstructive Pulmonary Disease; CRP, C-reactive protein; DLCO, Diffusion capacity of carbon monoxide; VA, Alveolar volume; ESR, Erythrocyte sedimentation rate; FEV₁, Forced expiratory volume in one second; FEV₁/pred, Percentage of FEV₁ predicted; FVC, Forced vital capacity; HRCT, High-resolution computed tomography; IgE, Immunoglobulin E; NLR, Neutrophil-to-lymphocyte ratio; NSCLC, Non-small-cell lung cancer; NSTEMI, Non-ST Segment Elevation Myocardial Infarction; PEF, Peak expiratory flow percentage; PaO₂, Partial arterial oxygen pressure; PaCO₂, Partial arterial pressure of carbon dioxide; SaO₂, Oxygen saturation; Sp-IgE, *Aspergillus fumigatus* specific IgE; Th2, T helper cell type 2.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is 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 report no conflicts of interest in this work.

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